

## Rectal Complications After Modern Radiation for Prostate Cancer: A Colorectal Surgical Challenge

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The operative management of rectal complications after radiation for prostate cancer has been incompletely studied. Our aim was to determine a logical surgical approach to these severe rectal complications. From an institutional database, we identified 5719 patients who were evaluated between 1990 and 2003 with a history of prostate cancer that was treated with radiation. Fourteen patients were identified from this group who underwent operative intervention for complications stemming from radiation. Charts were retrospectively reviewed for demographics, prostate cancer treatment, rectal symptoms, diagnostic techniques, operative interventions, and outcome. Ten patients (71%) had documented rectourethral fistulas. An additional four patients (29%) had either transfusion-dependent rectal bleeding or intractable fecal incontinence. Using a surgical algorithm, we proceeded with fecal diversion alone (20%), urinary and fecal diversion alone (50%), and primary repair with or without a tissue flap and fecal diversion (29%) in the 14 affected patients. Symptomatic improvement and resolution of these three complications occurred in 12 (85%) of patients. However, only 2 (15%) were able to retain their intestinal continuity to achieve this outcome. The introduction of a step-wise approach to this problem has resulted in symptomatic resolution in the majority of patients. However, this is achieved at the cost of permanent fecal and sometimes urinary diversion. (*J GASTROINTEST SURG* 2005;9:461–466) © 2005 The Society for Surgery of the Alimentary Tract

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KEY WORDS: Rectourethral fistula, radiation, surgery

Prostate cancer is one of the most common cancers in men with approximately 180,000 new cases expected yearly. Treatment with external beam radiation therapy (EBRT) or interstitial brachytherapy (IB) has become increasingly more common. Operative management of rectal complications from radiation has been incompletely studied. Rectourethral fistula (RUF), transfusion-dependent rectal bleeding, and fecal incontinence are several of the surgical challenges that surgeons now face. RUF is known to affect up to 3% of those treated with IB therapy.<sup>1–5</sup> Current surgical literature lacks a standard treatment algorithm for these known radiation-induced rectal complications. Previous surgical series addressed

RUFs of all etiologies, focusing on primary repair with or without fecal or urinary diversion.<sup>3,5,6</sup> These studies lack significant numbers of patients treated with radiation. Therefore, the role of fecal diversion, urinary diversion, radical exenteration, and primary repair with or without tissue flaps has not been addressed in these patients. To better understand how to resolve symptoms in this population, we reviewed our surgical experience over the past 13 years. In this series, we present an algorithm for the management of patients presenting with rectal complications, including rectal bleeding, fecal incontinence, and RUF from radiation therapy for prostate cancer.

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## MATERIALS AND METHODS

The medical records of 36,232 patients seen between 1990 and 2003 at the Mayo Clinic Rochester with a diagnosis of prostate cancer were reviewed with the approval of the Mayo Clinic Institutional Review Board. Attention was focused on patients treated in the past decade in an attempt to better evaluate the side effects of more modern radiation therapy techniques; 5719 of these patients were treated at the Mayo Clinic or at outside institutions with radiation therapy (EBRT or IB). Of these, 22 patients were identified who required colorectal surgery for presumed complications of radiation therapy.

Patients were excluded if their complication could be linked to malignant disease progression (prostate or rectal cancer) ( $n = 6$ ), iatrogenic surgical complications ( $n = 1$ ), or inflammatory bowel disease ( $n = 1$ ). The remaining 14 patients were presumed to have radiation-induced rectal complications. We desired to evaluate this homogeneous patient subgroup to provide meaningful data. Individual prostate cancer history was reviewed, including grade, stage, treatment, and outcome. All charts were reviewed to determine presenting symptoms from suspected radiation-related complications as well as diagnostic modalities, operative interventions, and treatment outcomes.

Surgical procedures were categorized as (1) primary rectal repair including primary repair with or without a tissue flap as well as resection and reanastomosis; (2) fecal diversion (FD) including excisional procedures such as proctectomy or diversionary procedures such as an ileostomy or colostomy; and (3) urinary diversion (UD), which included cystoprostatectomy with ileal or colonic conduits. Surgical therapy aimed both to resolve symptoms and to eliminate rectal pathology. Our goal from a surgical perspective was to preserve intestinal and urinary continuity; however, given the extensive damage, this was a rare outcome. Overall, surgical therapy was considered successful if the patient's symptoms and pathology abated, even if a permanent FD or UD was needed to achieve this outcome.

## RESULTS

During the 13-year study period, 14 patients were treated with prostate radiation and developed rectal complications requiring operative intervention. The median age at the time of diagnosis of prostate cancer was 66 years (range, 51–78 years). The median follow-up from cancer diagnosis was 53.5 months (range, 25–302 months). Symptoms from complications appeared at a median of 19 months from completion of

radiation (range, 1.2–244 months). The median time from symptoms to definitive treatment was 8 months (range, 0–168 months). Our postoperative follow-up from definitive surgical intervention was a median of 22.7 months (range, 0.6–80 months). Only one of our patients had less than 6-month follow-up after definitive repair.

## Presentation and Treatment of Prostate Cancer

All patients received radiation therapy (EBRT, IB, or a combination). Radiation was the primary treatment in 64% and used as an adjuvant or as salvage therapy in 36% of patients. Initial treatment of the prostate cancer included androgen-deprivation therapy (7%), IB (43%), EBRT (7%), IB and EBRT (14%), and radical retropubic prostatectomy (29%). Seven (50%) of 14 patients had biochemical or localized recurrence of their prostate cancer. The treatment of recurrence for those seven patients included hormone deprivation (28%), IB (14%), EBRT (43%), and EBRT with IB (14%). At the time of definitive surgery for their rectal complication, no patients had evidence of recurrent prostate cancer. By the time of last follow-up, 2 (14%) of the 14 patients had evidence of biochemical recurrent prostate cancer. Of the patients treated with EBRT ( $n = 8$ ), five (63%) had known radiation doses, with a median treatment dose of 6000 cGy (range, 4500–6840 cGy). Four patients (29%) received EBRT alone, six had IB alone (42%), and four underwent both EBRT and IB (29%).

## Clinical Presentation and Diagnosis

All patients were symptomatic and presented with complaints to their local physician at a median time of 19 months (range, 1.2–243 months) from the end of radiation treatment (Table 1). Of the patients who presented with complaints of rectal bleeding or fecal incontinence, four had transfusion-dependent bleeding and/or intractable fecal incontinence. Ten patients presented with signs of RUF. The diagnosis of

**Table 1.** Signs and symptoms

| Sign                  | No. of Patients (%) | Symptoms     | No. of Patients (%) |
|-----------------------|---------------------|--------------|---------------------|
| Rectourethral fistula | 10 (71)             | Rectourea    | 10 (71)             |
|                       |                     | Pain         | 8 (57)              |
| Proctitis             | 7 (50)              | Bleeding     | 8 (57)              |
| Rectal ulcer          | 6 (43)              | Frequency    | 7 (50)              |
| Hematuria             | 2 (14)              | Incontinence | 7 (50)              |
| Cystitis              | 1 (7)               | Tenesmus     | 2 (14)              |
| Osteomyelitis         | 1 (7)               | Obstruction  | 1 (7)               |

RUF in particular was obtained by history and physical examination given the size of these fistulas. Diagnostic studies were useful in helping to define these fistulas and included colonoscopy (11%), cystoscopy (55%), voiding cystourethrogram (22%), and endoscopic ultrasound (22%). Given the extent of radiation injury, most patients did not undergo anal rectal manometry or cystometric studies, which may have been useful with a smaller fistula. The 10 patients with RUFs were diagnosed at an average of 35 months after radiation treatment. The median diameter of the RUFs diagnosed was 2.5 cm (range, 0.4–5 cm).

### Management

Individual operative treatment and outcome are given in Table 2. The treatment algorithm, which was followed in the majority of patients, is given in Fig. 1. Five (36%) patients had definitive simultaneous urinary and fecal diversion as their first operative intervention. These five patients had severe incontinence and large RUFs. The remaining nine patients (64%) had fecal diversion, which was later followed by urinary diversion in five patients (36%). Currently, symptomatic resolution has been achieved in 12 (85%) of the 14 patients. At last follow-up, only 2 of the 14 patients (15%) had a functioning rectum. Overall, an average of 2.3 operations were performed per patient (including those performed for postoperative complications). In those with RUF, the average number of operations was slightly higher at 2.7 per patient. Overall, definitive treatment occurred at a median of 8 months (range, 0–167 months) from the onset of symptoms. These patients have now been followed for an additional median of 22.7 months.

There were no postoperative deaths associated with any of the procedures.

Patients treated for fecal incontinence, transfusion-dependent rectal bleeding, and RUF were managed differently (Table 2). Of the patients with intractable fecal incontinence, one had FD alone and the other underwent FD and UD secondary to incontinence of both urine and stool. Both patients have had resolution of symptoms. Of the patients with transfusion-dependent rectal bleeding, one underwent multiple endoscopic argon beam ablations without success and finally we resorted to FD. The other underwent both UD and FD because, in addition to bleeding, he had incontinence of urine and stool. All patients in this group had resolution of their symptoms.

The most complex operations occurred in the RUF group. Five (50%) patients had UD and FD; all of these patients had symptomatic and fistula resolution. A single patient (10%) had a simple colostomy with fistula resolution but had continued pain. Another patient (10%) had fecal diversion with unsuccessful primary suture repair and muscle flap followed by a third unsuccessful repair with fibrin glue. The final three patients (30%) had primary repair with suture, FD, and UD in one patient and resection and anastomosis with FD and UD in two patients. As of today, none of these patients have had reversal of their UD. All of these patients had symptomatic resolution, and two of them eventually had bowel continuity restored.

### DISCUSSION

Radiation is commonly used for both primary and salvage therapy for prostate cancer. Long-term complications, although rare, can be debilitating and require major surgical intervention. Complications

**Table 2.** Surgical intervention and outcome

| Patient | Main Complaint          | EBRT, IB, or Both | Endoscopic Treatment | Fistula Resolution | P, FD, UD | Functional Rectum | Persistent Symptoms |
|---------|-------------------------|-------------------|----------------------|--------------------|-----------|-------------------|---------------------|
| 1       | RUF                     | IB                | No                   | Yes                | P, FD, UD | Yes               | No                  |
| 2       | Incontinence            | Both              | No                   | NA                 | FD, UD    | No                | No                  |
| 3       | Bleeding with proctitis | EBRT              | Yes                  | NA                 | FD        | No                | No                  |
| 4       | RUF                     | IB                | No                   | Yes                | P, FD, UD | No                | No                  |
| 5       | Incontinence            | EBRT              | No                   | NA                 | FD        | No                | No                  |
| 6       | RUF                     | IB                | No                   | Yes                | FD, UD    | No                | No                  |
| 7       | RUF                     | EBRT              | Yes                  | Yes                | P, FD, UD | Yes               | No                  |
| 8       | Bleeding with proctitis | EBRT              | No                   | NA                 | FD, UD    | No                | No                  |
| 9       | RUF                     | Both              | Yes                  | Yes                | FD, UD    | No                | No                  |
| 10      | RUF                     | Both              | No                   | Yes                | FD, UD    | No                | No                  |
| 11      | RUF                     | Both              | No                   | Yes                | FD, UD    | No                | No                  |
| 12      | RUF                     | IB                | Yes                  | No                 | TF, FD    | No                | Yes                 |
| 13      | RUF                     | IB                | No                   | Yes                | FD, UD    | No                | No                  |
| 14      | RUF                     | IB                | No                   | Yes                | FD        | No                | Yes                 |

P, primary repair or tissue flap; FD, fecal diversion; RUF, rectourethral fistula; IB, interstitial brachytherapy; EBRT, external beam radiation therapy; UD, urinary diversion; TF, tissue flap.

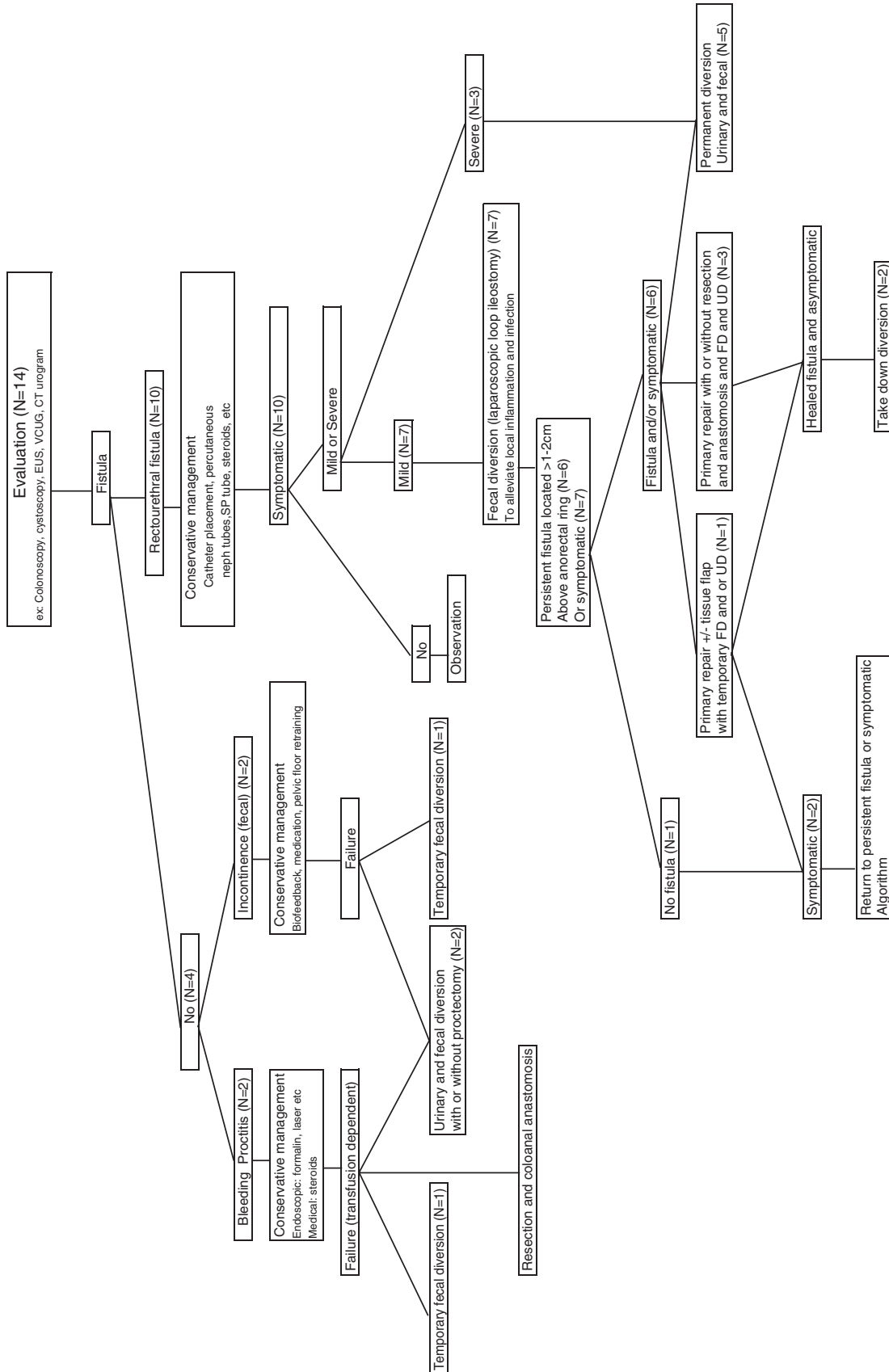


Fig. 1. Treatment algorithm.

requiring operative intervention occurred in our series from 1 month to over 20 years after radiation. In the era of PSA testing, approximately 77% of prostate cancers are localized at the time of diagnosis.<sup>2</sup> It has been estimated that by 2006, 50% of these localized cancers will be treated with radiation therapy.<sup>2</sup> The current literature suggests that the risk of RUF after IB varies from 0.4% to 3%; however, the largest series of radiation-induced RUF includes only seven patients.<sup>1,4,7-10</sup> However, in the future this complication may translate into 300 to 2000 potential RUFs each year.

The medical and endoscopic management of radiation-induced rectal complications is beyond the scope of this paper. Certainly conservative measures should be instituted first in an attempt to provide the patient with less invasive means to attain symptom resolution and retain intestinal and urinary continuity. However, patients with intractable fecal incontinence, transfusion-dependent rectal bleeding, or large RUFs require aggressive intervention. For these reasons we have adopted a stepwise approach to our current management of these complications.

Risk factors for severe rectal complications in our series included the presence of an anterior rectal ulcer (6 of 10 patients had a known ulcer prior to RUF formation). This seems to be the single most consistent sign prior to RUF formation. This finding is supported by the literature addressing RUF of various etiologies.<sup>3,5,6</sup> IB is also a significant risk factor, as 90% of our patients who developed RUF had received brachytherapy. EBRT, which was the sole cause of RUF in one patient, is more often associated with proctitis in our series.

The role of treatment or diagnostic procedures in the development of a RUF is still unknown. Shah and colleagues<sup>10</sup> reported that transurethral resection of the prostate does not seem to be a risk factor for this complication, and our data are in agreement; only one patient in our series had a previous transurethral resection of the prostate.<sup>10</sup> It is unknown whether endoscopic laser or argon beam ablation for rectal bleeding has the potential to promote fistula formation. Three of our patients (30%) with fistulas had prior endoscopic argon beam ablation for bleeding proctitis. However, there are multiple studies that maintain its utility and safety in the control of bleeding from radiation-induced proctitis.<sup>8,11-13</sup> We recommend that if endoscopic or medical management does not result in prompt resolution of transfusion requirements or if pelvic pain is poorly managed, then more aggressive measures need to be taken. Potential treatments in our patients included diversion, which has the potential for reversal or resection, and coloanal anastomosis, which to date we have not

used. Another potential management issue is whether a patient with a rectal ulcer after radiation should undergo a biopsy. In our group of patients, six presented with endoscopic evidence of an anterior rectal ulcer. Only one underwent a biopsy at an outside hospital. All of these patients went on to eventually have an RUF form. It is our belief that in the setting of an anterior ulcer with the known history of EBRT or IB, this ulcer should be observed, assuming a negligible PSA and no history of rectal cancer. Biopsy of these ulcers might theoretically contribute to the possibility of fistulization. It is impossible to tell if any of these interventions led to fistulization or if a fistula would have eventually developed regardless.

Diagnosis is relatively straightforward. The patient's presenting symptom usually guides the initial choice of diagnostic test. Because most patients will present with rectal bleeding or urinary symptoms, colonoscopy or cystoscopy is likely to be the first test that is obtained. We have found that history and physical examination are the most important predictors of RUF and surgical management. This management, however, is a complex issue. It is a decision arrived at jointly by the surgeon and patient, given the radical nature of diversionary procedures coupled with the knowledge that multiple operations may be required. Within our algorithm, the first step in the management of RUF is timely fecal diversion. Fecal diversion as definitive treatment for RUF is unlikely to result in permanent healing. Only one patient in our series with diversion without fistula repair achieved closure, but unfortunately, he continued to have unbearable pelvic pain. These results are supported by findings from previous studies.<sup>3,5,6</sup> The usual role of fecal diversion is to alleviate infection and inflammation and possibly achieve symptomatic relief prior to definitive repair.<sup>5</sup> Because the fistulized prostate is likely infected and poorly vascularized after radiation, diverting the fecal stream is paramount as the first of a series of staged treatments.

Muscle transposition flaps at the time of primary rectal repair, although ineffective in the one patient in our series, have been shown to be useful in other studies. Proper timing is imperative in order to maximize the chance of success. All inflammation and infection should be eradicated prior to a muscle flap transposition. A well-vascularized portion of tissue placed between the urethra and the rectum theoretically decreases the chance for refistulization. However, rectal tissue must be of sufficient quality to allow for primary closure. Once the fistula heals and symptoms abate, one may consider takedown of FD and/or UD after 6 months. Most patients in our series had extensive rectal damage from radiation and the

fistula, which eliminated them as possible candidates for repair or future diversion takedown.

Our experience confirms that there are no easy solutions for patients with severe postradiation rectal injury. These complications are uncommon, even at referral centers. Therefore, a stepwise approach is required. The surgical procedures are complex and technically demanding, given the presence of postradiation fibrosis and radiated bowel. This series is the largest of its type and illustrates the difficulty of maintaining fecal and urinary continence in the face of severe rectal complications after radiation. Our results are based upon our current treatment algorithm. Although preservation of bowel continuity is ideal, in our experience, primary repair or resection and reanastomosis are rarely technically possible. If this is undertaken, one must use sound intraoperative judgment and use nonradiated colon as the proximal portion of all anastomoses. If the patient is fortunate enough to have a fistula above the anorectal ring, which is repairable or resectable with a subsequent coloanal anastomosis, this provides the greatest potential for retaining intestinal continuity. Unfortunately, the majority of patients will have radiation change, distal fistulization, and necrotic and infected tissue, which require aggressive resection.

Although this study provides important data, bias does exist. The retrospective nature of the study and the tertiary referral pattern at this institution led to a higher-risk patient population. Therefore, less radical and more reconstructive surgery with a greater potential for retaining intestinal and urinary continuity may be a reasonable management strategy. The number of RUFs treated (nonsurgically) at our institution along with their resolution rate is currently unknown but anecdotally low. It is likely that even this number is significantly affected by selection bias. The final confounding factor centers on the fact that 86% of patients did not receive their radiation at our institution. Data regarding the details of their radiation are incomplete, and we are unable to comment on whether radiation dose or technique played a role in these complications.

## CONCLUSION

Radiation therapy with EBRT and/or IB is a common treatment for prostate cancer. Outcomes are excellent in terms of oncologic control, but the potential exists for devastating rectal complications in a small percentage of patients. These complications, unfortunately, may appear years after treatment. For patients who require radical surgical intervention,

most can expect resolution of symptoms. However, many of these patients will be burdened by permanent fecal and, often, urinary diversion. Colorectal surgeons across the country will likely face this problem more frequently as the number of irradiated men increases. Adopting a systematic approach to diagnosis and stepwise operative management is ideal. Initial surgical management of patients for whom endoscopic or medical therapy fails should include fecal diversion followed by fistula repair. Unfortunately, severe radiation-induced colorectal complications will often require permanent diversion in order to achieve symptomatic relief. We hope that improvements in radiation therapy technology and IB techniques will reduce the incidence of RUF, fecal incontinence, and transfusion-dependent rectal bleeding.

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# Fas/FasL Play a Central Role in Pancreatitis-Induced Hepatocyte Apoptosis

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Liver injury is a clinical prognostic indicator in acute pancreatitis (AP). We have demonstrated that Kupffer cell-derived FasL mediates liver injury during AP and sought to determine its role in AP-induced hepatocyte apoptosis. AP was induced in National Institutes of Health (NIH) Swiss mice, C57/C57, and Fas<sup>-/-</sup>, FasL<sup>-/-</sup> mice by a choline-deficient ethionine-supplement diet. Liver Fas, FasL, p38-mitogen activated phosphokinase (p38-MAPK), poly-ADP ribose polymerase (PARP), and cytochrome C were measured by immunoblotting. Apoptosis was assessed by terminal deoxynucleotidyl transferase biotin-dUTP nick end labeling (TUNEL) and DNA fragmentation (ELISA). AP upregulated liver FasL (4280 ± 580 vs. 733 ± 336), Fas (2866 ± 595 vs. 649 ± 111), cytochrome C (6980 ± 237 vs. 903 ± 156), and PARP (6393 ± 591 vs. 466 ± 261) as well as increased TUNEL staining (40 ± 2 vs. 14 ± 1) and DNA fragmentation (all *P* < 0.03 vs. control). In FasL<sup>-/-</sup> and Fas<sup>-/-</sup> mice, AP-induced upregulation of p38-MAPK, PARP, and cytochrome C was significantly attenuated (all *P* < 0.01 compared to C57/C57 control). In addition, AP-induced DNA fragmentation was reduced 60% in Fas<sup>-/-</sup> and FasL<sup>-/-</sup> mice (*P* < 0.01 vs. C57/C57). AP induces apoptosis by transcriptional activation of Fas/FasL. AP-induced apoptosis was significantly reduced in Fas and FasL knockout mice along with downregulation of p38-MAPK, PARP, and cytochrome C, thereby suggesting a central role for Fas/FasL in hepatocyte apoptosis. The manipulation of interactions between Kupffer cell-derived FasL and hepatocytes may have important therapeutic implications. (J GASTROINTEST SURG 2005;9:467–475) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Acute pancreatitis, Fas/FasL, liver injury, hepatocyte apoptosis, p38-MAPK, PARP, cytochrome C

## INTRODUCTION

Acute pancreatitis remains a unique and intriguing model of inflammation manifesting over a continuum from local peripancreatic inflammation to widespread systemic inflammatory response with distant organ injury.<sup>1</sup> Distant organ injury, including liver injury, ileus, and lung injury whether from acute pancreatitis, sepsis, or another source of systemic inflammation, has broad-reaching clinical implications. Specifically, liver injury is an important prognostic indicator; as such, it has been incorporated into multiple scoring systems used to predict the severity of illness, in this case acute pancreatitis.

The role of extrapancreatic, macrophage-derived, and organ-specific cytokine production is one likely

link between localized, peripancreatic inflammation and the systemic manifestations of pancreatitis, particularly in experimental models of pancreatitis-induced lung and liver injury.<sup>2–6</sup> The liver is unique, because its resident macrophages, the Kupffer cells, are the largest population of fixed tissue macrophages. We have recently demonstrated that pancreatic elastase, much like acute pancreatitis, upregulates Kupffer cell TNF, FasL, and Fas expression *in vitro* and *in vivo*.<sup>2,3</sup> Similarly, in the *in vitro* model of pancreatitis-induced liver injury, both upstream and downstream apoptosis effector pathways are upregulated.<sup>2,3</sup>

While FasL-induced apoptosis plays an important role in parenchymal cell damage in alcoholic liver

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disease,<sup>7</sup> there is very little information regarding the mechanistic relationship between Kupffer cell-derived Fas/FasL and the pathogenesis of the systemic manifestations associated with acute pancreatitis or any other systemic inflammatory disease. The purpose of this study was to characterize the role of Fas/FasL in hepatocyte apoptosis during acute pancreatitis.

## METHODS

Animal care was in accordance with the guidelines established by the Department of Laboratory Animal Medicine at the University of South Florida, a facility accredited by the American Association for Accreditation in Laboratory Animal Care. Studies were conducted with approval from the Institutional Animal Care and Use Committee as well.

### Animals

Female National Institutes of Health (NIH) Swiss mice (Harlan, Indianapolis, IN) were used for preliminary investigations including FasL and Fas measurements as well as apoptosis. Additionally, female C57 mice (Jax Mice, The Jackson Laboratory, Bar Harbor, ME) were purchased in three different genotypes: C57/C57 (C57BL/6J), FasL<sup>-/-</sup> (B6MnC3-TnFsf or C3H/HeJ-Tnfsf6), and Fas<sup>-/-</sup> (B6MRL-Tnfrsf6 or C3MRL-Tnfrsf6) for p38-mitogen activated phosphokinase (p38-MAPK), poly-ADP ribose polymerase (PARP), cytochrome C, and apoptosis experiments.

### Induction of Acute Pancreatitis

Acute pancreatitis was induced ( $n = 3$  for all experiments) in female NIH Swiss mice (10–15 g) or female C57 mice (10–15 g) using choline-deficient ethionine-supplement diet (CDE diet). The CDE diet induces severe acute hemorrhagic and necrotizing pancreatitis with approximately 70% mortality over 5 days. Briefly, the young mice were fasted overnight with free access to water before beginning the CDE diet. The special laboratory mouse food (Harlan Taklad, Madison, WI) mixed with 5% ethionine (Sigma, St. Louis, MO) was given to mice with a special “J” feeder. The feeder was changed every 4 to 6 hours or sooner if found to be contaminated by animal excrement to ensure sanitary conditions.

Livers were harvested 48 hours after initiation of the CDE diet for all experiments, processed with TRIzol Reagent (Invitrogen, Carlsbad, CA) for RNA isolation and protein isolation per the package insert instructions,<sup>8,9</sup> and stored at  $-80^{\circ}\text{C}$  prior to reverse

transcriptase-polymerase chain reaction and immunoblotting, respectively. In order to determine RNA and total protein under precisely the same experimental conditions and because of the small-scale nature of the experiments and sample sizes, RNA and total protein were isolated from the same samples; this method has been well established and validated in the literature.<sup>8,9</sup>

### Liver FasL, Fas, p38-MAPK, PARP, and Cytochrome C (Immunoblotting)

Using TRIzol Reagent, total protein was isolated from mice livers from the phenol-ethanol supernatant collected after DNA precipitation with ethanol,<sup>9</sup> separated by sodium dodecylsulfate-polyacrylamide gel electrophoresis, and transferred to a nitrocellulose membrane. Nonspecific binding was blocked with 5% bovine serum albumin (Sigma, St Louis, MO) or 5% instant nonfat dry milk for 2 hours at room temperature. The membranes were then incubated overnight at  $4^{\circ}\text{C}$  with 1:1000 dilution of anti-Fas Ligand/CD95L and 1:2500 dilution of anti-Fas/CD95APO-1 primary antibodies (BD Biosciences, San Diego, CA) or either 1:1000 dilution of polyclonal, phosphospecific p38-MAPK (Cell Signaling Technology, Beverly, MA), 1:1000 dilution of cleaved, monoclonal PARP (Cell Signaling Technology, Beverly, MA), or 1:1000 dilution of sheep polyclonal anticcytochrome C antibody (Stress Gen Biotechnologies, Victoria, British Columbia, Canada). Western immunoblots were completed individually for each protein in triplicate.

Subsequently, the membrane was washed and incubated with horseradish peroxidase-conjugated anti-mouse monoclonal antibody or polyclonal anti-rabbit antibody according to the matching requirement of the primary antibodies (New England Biolabs, Beverly, MA) for 2 hours at room temperature. The immunoblot was washed, the bands were detected with an enhanced chemiluminescence kit (LumiGlo, New England Biolabs, Beverly, MA), and each protein was quantified individually by densitometry using UVP Gel Documentation System (GDS) 8000 (UVP, Upland, CA). Immunoblots ( $n = 3$ ) were repeated in triplicate utilizing positive controls provided by the manufacturers (not shown in the selected gels). Western immunoblot band position was confirmed by the antibody molecular weight for each protein (FasL = 37kD, Fas = 45kD, p38-MAPK = 43kD, PARP = 89kD, and cytochrome C = 14kD).

### DNA Fragmentation

The DNA fragmentation was measured using Cell Death Detection ELISA<sup>PLUS</sup> (Roche, Mannheim,



Germany), which is a photometric enzyme immunoassay used for the qualitative and quantitative in vitro determination of cytoplasmic histone-associated-DNA-fragments (mono- and oligonucleosomes) after induced cell death. The manufacturer's protocol for ELISA was followed, and samples were measured at 405 nm against a 2,2-azino-di(3-ethylbenzthiazoline) sulfonic acid solution as a blank with a reference wavelength of 490 nm.

### TUNEL Staining

Terminal deoxynucleotidyl transferase biotin-dUTP nick end labeling (TUNEL) staining was completed using the ApopTag Fluorescein Apoptosis Detection Kit #S7110 (Serologicals Corp., Norcross, GA). The manufacturer's protocol for fluorescent staining of tissue cryosections or cells using a fluorescent-labeled antibody was followed. Mounting medium containing 0.5 to 1.0  $\mu\text{g/ml}$  of propidium iodide or 4',6-diamidino-2-phenylindole (DAPI) was applied followed by a glass coverslip for oil immersion. Slides were viewed by confocal fluorescence microscopy with a dual pass filter for fluorescein isothiocyanate using standard fluorescein excitation (490 nm) and emission (520 nm) filters. The number of positively stained cells was counted in 10 different high-power fields (HPF) and averaged.

### Statistical Analysis

All experiments were repeated in triplicate as noted above in the methods; results were averaged. All Western immunoblots were repeated in triplicate. Controls were measured for each experiment; however, controls are not shown in all figures. Data are mean  $\pm$  SEM. Student's *t* test was used to evaluate parametric data. Significance for alpha was set at  $P < 0.05$ .

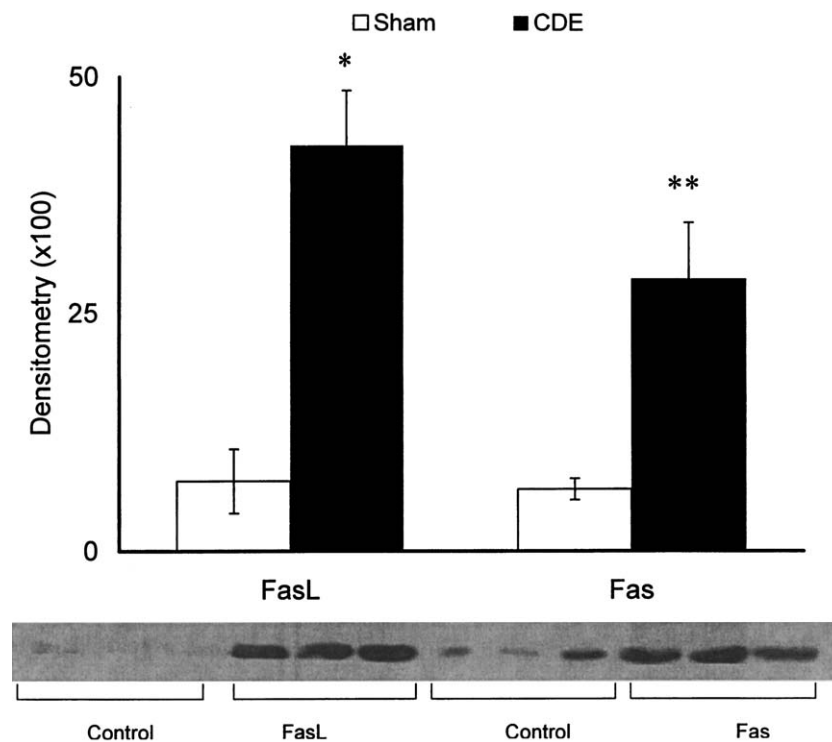
## RESULTS

### Acute Pancreatitis Upregulates FasL and Fas (Immunoblotting)

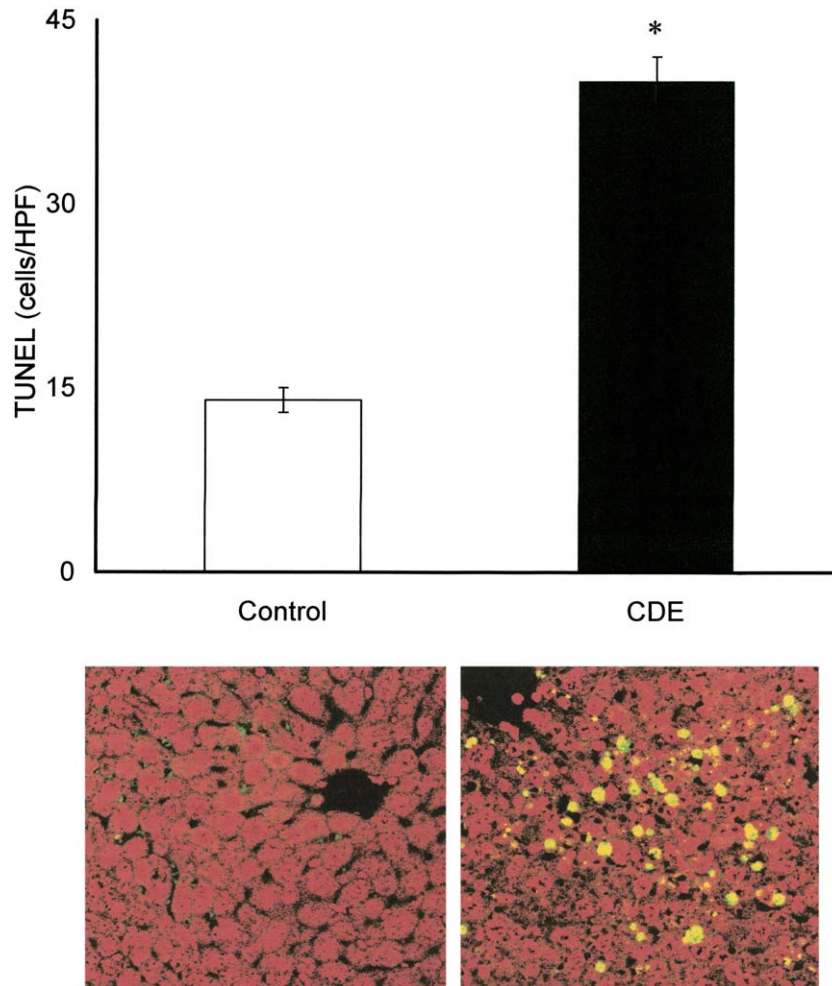
CDE-induced pancreatitis increased liver FasL ( $4280 \pm 580$  vs.  $733 \pm 336$ ,  $P = 0.01$  pancreatitis vs. sham) and Fas ( $2866 \pm 595$  vs.  $649 \pm 111$ ,  $P = 0.02$  pancreatitis vs. sham) in wild type NIH mice (Fig. 1).

### Acute Pancreatitis Induces Apoptosis (TUNEL Staining and DNA Fragmentation)

Apoptosis was measured by TUNEL staining and confirmed by DNA fragmentation. TUNEL staining was significantly increased during acute pancreatitis ( $40 \pm 2/\text{hpf}$  vs.  $14 \pm 1/\text{hpf}$ ,  $P < 0.01$  pancreatitis vs. sham, Fig. 2). Likewise, DNA fragmentation was increased significantly during acute pancreatitis



**Fig. 1.** Upregulation of FasL ( $4280 \pm 580$  vs.  $733 \pm 336$ ,  $*P = 0.01$  pancreatitis vs. sham) and Fas ( $2866 \pm 595$  vs.  $649 \pm 111$ ,  $**P = 0.02$ ) in mice livers during CDE diet-induced acute pancreatitis.



**Fig. 2.** Increased hepatocyte apoptosis ( $40 \pm 2/\text{hpf}$  vs.  $14 \pm 1/\text{hpf}$ ,  $*P < 0.01$  pancreatitis vs. sham) during CDE diet-induced acute pancreatitis as measured by TUNEL staining. Representative photomicrograph of liver sections with TUNEL staining; positively stained cells appear bright (40x).

( $0.36 \pm 0.04$  vs.  $0.05 \pm 0.01$ , optical density;  $P < 0.01$  vs. sham, Fig. 3).

#### Acute Pancreatitis Activates p38-MAPK, PARP, and Cytochrome C (Immunoblotting)

We investigated whether acute pancreatitis upregulates three proapoptotic cell signaling systems by measuring p38-MAPK phosphorylation, PARP cleavage, and cytochrome C. The CDE diet-induced acute pancreatitis significantly upregulated p38-MAPK phosphorylation ( $4894 \pm 388$  vs.  $1103 \pm 211$ ,  $P < 0.01$  vs. C57/C57 control), PARP ( $6393 \pm 591$  vs.  $466 \pm 261$ ,  $P < 0.01$  vs. C57/C57 control), and cytochrome C ( $6980 \pm 237$  vs.  $903 \pm 156$ ;  $P < 0.01$  vs. C57/C57 control).

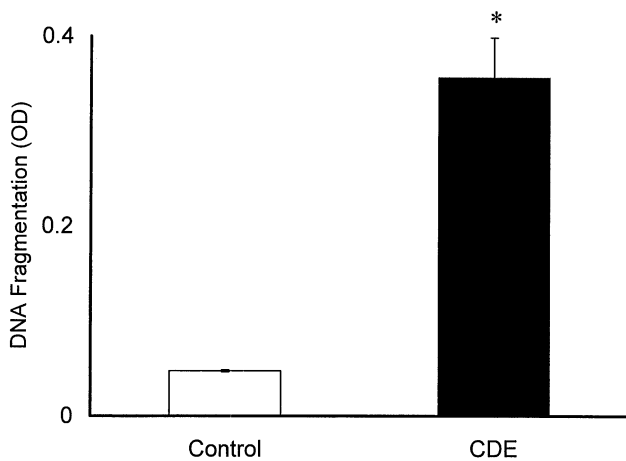
#### Acute Pancreatitis in FasL<sup>-/-</sup> and Fas<sup>-/-</sup> Mice (Immunoblotting)

Because it is already established that FasL and Fas (the receptor for FasL) are upregulated during acute

pancreatitis in vitro,<sup>2,3</sup> we sought to evaluate the effects of FasL and Fas on the transcriptional activity of p38-MAPK, PARP, and cytochrome C in genetically engineered mice. In FasL<sup>-/-</sup> mice, the pancreatitis-induced upregulation of p38-MAPK, PARP, and cytochrome C was significantly attenuated ( $1747 \pm 54$  vs.  $4894 \pm 388$ ,  $3594 \pm 107$  vs.  $6393 \pm 591$ ,  $3514 \pm 53$  vs.  $6980 \pm 237$ , all  $P < 0.01$  vs. C57/C57 CDE) as shown in Fig. 4. Similarly, in Fas<sup>-/-</sup> mice, p38-MAPK, PARP, and cytochrome C were significantly downregulated ( $1707 \pm 503$  vs.  $4894 \pm 388$ ,  $1988 \pm 510$  vs.  $6393 \pm 591$ , and  $1988 \pm 485$  vs.  $6980 \pm 237$ , all  $P < 0.01$  vs. C57/C57 CDE) as shown in Fig. 5. Representative gels are shown in Fig. 6.

#### Pancreatitis Induced Apoptosis in FasL<sup>-/-</sup> and Fas<sup>-/-</sup> Mice

Pancreatitis-induced apoptosis as measured by DNA fragmentation was significantly reduced by



**Fig. 3.** Increased hepatocyte apoptosis ( $0.36 \pm 0.04$  vs.  $0.05 \pm 0.01$ ,  $*P < 0.01$  vs. sham) during CDE diet-induced acute pancreatitis as measured by increased DNA fragmentation ELISA. DNA fragmentation is quantified by optical density (OD).

60% in FasL<sup>-/-</sup> mice ( $0.12 \pm 0.01$  vs.  $0.36 \pm 0.04$ ,  $P < 0.01$  vs C57/C57 CDE) as well as Fas<sup>-/-</sup> mice ( $0.14 \pm 0.01$  vs.  $0.36 \pm 0.04$ ,  $P < 0.01$  vs. C57/C57 CDE, Fig. 7).

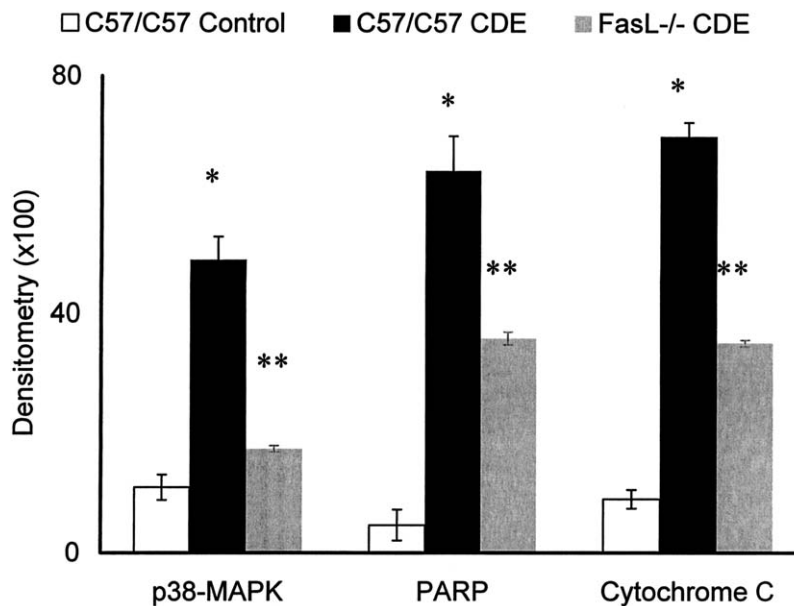
## DISCUSSION

Our understanding of the systemic manifestations of acute pancreatitis has expanded since elucidating

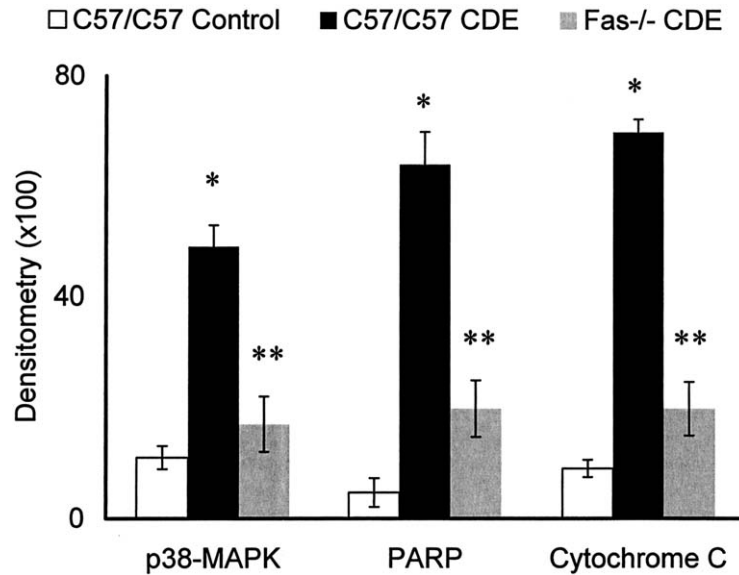
the role macrophage-derived cytokines and pancreatic enzymes in the systemic progression of acute pancreatitis. Pancreatic enzymes that are produced in large quantities during acute pancreatitis enter the systemic circulation via inflamed retroperitoneal lymphatics and subsequently stimulate the production of proinflammatory cytokines in distant organs, specifically in the lungs and liver.<sup>1,2,4,10</sup> Specifically, we have shown that pancreatic enzymes, most significantly elastase, stimulate the production of tumor necrosis factor from the resident macrophages in the lung and liver as well as FasL from the Kupffer cells.<sup>2-6</sup>

FasL plays a pivotal role in the pathogenesis of various diseases and cellular apoptosis.<sup>11</sup> We and others have shown that FasL is produced by Kupffer cells when treated with elastase, in vitro, and in mice livers during cerulein-induced acute pancreatitis.<sup>2,3,12</sup> Moreover, Kupffer cell-derived FasL induces hepatocyte apoptosis in vitro and in cocultures of hepatocytes and Kupffer cells.<sup>2,3</sup> Therefore, we sought to determine the role of FasL and Fas in the pathogenesis of pancreatitis-induced hepatocyte apoptosis in an experimental model of severe acute pancreatitis.

The CDE diet induces a severe, hemorrhagic, necrotizing, acute pancreatitis with nearly 70% 5-day mortality. The CDE diet-induced acute pancreatitis upregulates FasL and Fas gene expression in mice livers several fold and is consistent with our prior observations in an in vivo model.<sup>2,3</sup>



**Fig. 4.** The CDE diet induced upregulation of p38-MAPK, PARP, and cytochrome C ( $4894 \pm 388$  vs.  $1103 \pm 211$ ,  $6980 \pm 237$  vs.  $466 \pm 261$ , and  $6980 \pm 237$  vs.  $903 \pm 156$ , respectively; all  $*P < 0.01$  vs. C57/C57 control), which is significantly attenuated in FasL<sup>-/-</sup> mice (p38-MAPK:  $1747 \pm 54$  vs.  $4894 \pm 388$ , PARP:  $3594 \pm 107$  vs.  $6980 \pm 237$ , and cytochrome C:  $3514 \pm 53$  vs.  $6980 \pm 237$ ; all  $**P < 0.01$  vs. C57/C57 CDE).



**Fig. 5.** The CDE diet induced upregulation of p38-MAPK, PARP, and cytochrome C ( $4894 \pm 388$  vs.  $1103 \pm 211$ ,  $6393 \pm 591$  vs.  $466 \pm 261$ , and  $6980 \pm 237$  vs.  $903 \pm 156$ , respectively; all  $*P < 0.01$  vs. C57/C57 control), which are significantly attenuated in Fas<sup>-/-</sup> mice (p38-MAPK:  $1707 \pm 503$  vs.  $4894 \pm 388$ , PARP:  $1988 \pm 510$  vs.  $6393 \pm 591$ , and cytochrome C:  $1988 \pm 485$  vs.  $6980 \pm 237$ ; all  $**P < 0.01$  vs. C57/C57 CDE).

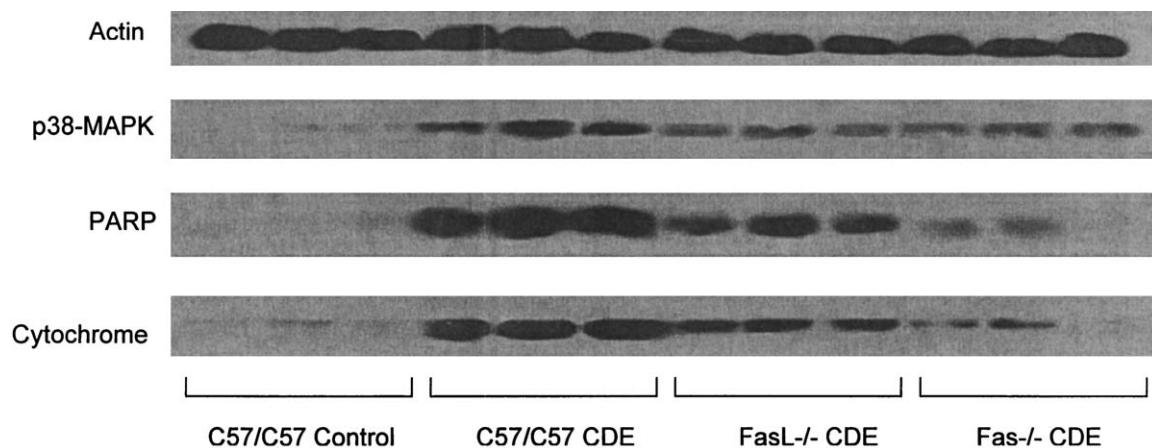
Additionally, CDE diet-induced pancreatitis significantly increased the number of apoptotic liver cells. These findings confirm our previous observations in a cerulein-induced pancreatitis model, in which pancreatitis-induced liver injury was manifested by an increase in apoptosis as well as increased serum levels of parenchymal liver enzymes.<sup>2,3</sup>

We further investigated apoptosis by studying upstream and downstream pro-apoptotic signaling pathways; the CDE diet-induced pancreatitis upregulates p38-MAPK, PARP, and cytochrome C in mice livers. These data corroborate our previous findings

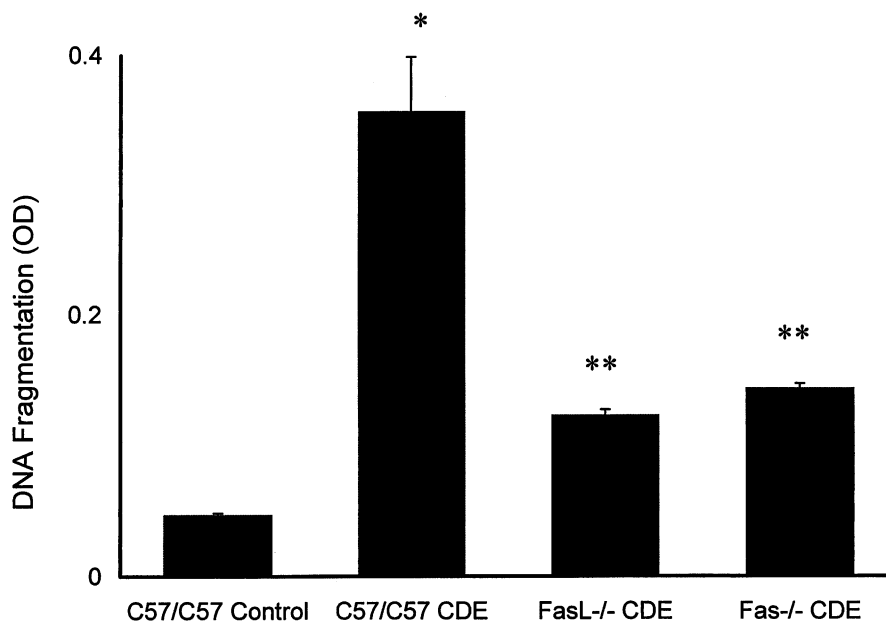
of p38-MAPK and caspase-3 upregulation in a cerulein-induced model of pancreatitis.<sup>2,3</sup>

We utilized genetically engineered mice to determine whether deletion of the FasL and Fas genes impact pancreatitis-induced apoptosis. Apoptosis was significantly reduced; in addition, all three cell signaling systems were significantly downregulated in FasL<sup>-/-</sup> and Fas<sup>-/-</sup> mice as compared to C57/C57 mice.

In an in vitro model, we previously demonstrated that antibodies to FasL reduced the severity of hepatocyte injury as well as the activation of p38-MAPK



**Fig. 6.** CDE diet-induced pancreatitis upregulates p38-MAPK (43kD), cleaved PARP (89kD), and cytochrome C (14kD) in C57/C57 fed CDE as compared to control mice; the activation of all signaling systems is attenuated in FasL<sup>-/-</sup> mice and Fas<sup>-/-</sup> mice fed the same CDE diet.



**Fig. 7.** Increased DNA fragmentation (ELISA) in the livers of C57/C57 mice fed CDE diet ( $0.36 \pm 0.04$  vs.  $0.05 \pm 0.01$ ,  $*P < 0.01$  vs. C57/C57 control mice fed regular chow); DNA fragmentation is significantly attenuated in FasL<sup>-/-</sup> ( $0.12 \pm 0.01$  vs.  $0.36 \pm 0.04$ ,  $**P < 0.01$  vs. C57/C57 CDE) as well as Fas<sup>-/-</sup> ( $0.14 \pm 0.01$  vs.  $0.36 \pm 0.04$ ,  $**P < 0.01$  vs. C57/C57 CDE).

and caspase-3.<sup>2,3</sup> Our current data further supports previous findings in the in vitro model and support our overall hypothesis that Fas/FasL play an important role in pancreatitis-induced apoptosis.

FasL was thought to be predominantly expressed in lymphocytes and natural killer cells; however, non-lymphoid cells such as macrophages also express FasL.<sup>13</sup> We have documented that FasL originates within Kupffer cells in both an in vitro model utilizing cell cultures as well as an in vivo model of cerulein-induced pancreatitis in which FasL production was manipulated with gadolinium chloride, a powerful Kupffer cell inhibitor.<sup>2,3,14</sup> In those models, macrophage-derived pancreatitis clearly induced liver injury and hepatocyte apoptosis.<sup>2,3</sup> Our current model of CDE diet-induced pancreatitis utilizes full liver sections to determine apoptosis by TUNEL and DNA fragmentation; therefore, nonparenchymal cells may be miscounted as apoptotic hepatocytes. Notwithstanding, the purpose of the current study was to determine which apoptotic pathways are activated by Fas/FasL during acute pancreatitis. To that end we surmise that Fas/FasL upregulates upstream and downstream pathways of cellular apoptosis.

FasL binds to Fas and activates the Fas-associated death domain, thereby unmasking the death effector domain.<sup>15</sup> Based on our current data, we propose that p38-MAPK is subsequently phosphorylated, thereby initiating a pro-apoptotic cascade that involves cleavage of PARP (a downstream regulator of apoptosis),

and mitochondrial pathways (cytochrome C), ultimately leading to DNA cleavage and cell apoptosis.<sup>16,17</sup>

## CONCLUSION

The novel finding that acute pancreatitis upregulates Kupffer cell-derived FasL and Fas transcriptional activity as well as pro-apoptotic pathways in the liver via upregulation of p38-MAPK, PARP, and cytochrome warrants further investigation and may shed light on regulatory mechanisms of immunocompetent cells as well as their role in sepsis and other systemic inflammatory conditions. Moreover, the ability to manipulate interactions between Kupffer cell-derived FasL, Fas receptor, and hepatocytes may have important therapeutic implications.

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*We thank the NIAAA-supported Non-Parenchymal Liver Cell Core (R24 AA12885) for providing Kupffer cells for tissue cultures.*

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## Discussion

**Dr. Kevin Behrns** (Chapel Hill, NC): Congratulations, Scott, on another fine study that was well presented, and also thanks for providing me with a copy of the manuscript. Your previous work has nicely demonstrated the importance of Fas and Fas ligand in a cerulein-induced pancreatitis model of liver injury. In this study you examined liver injury in a more severe necrotizing pancreatitis model that was induced by a choline-deficient diet. In this model the liver was harvested at 48 hours after the start of the diet, and you showed the results based on a 48-hour time point. My question is, what is the condition of the animals at that time? Are any of them near death, and where are they in the progression of the disease? Also, what are the histologic features of the pancreas and the liver at the time of organ harvest? If these animals have any evidence of severe organ injury by 48 hours, then some of these effects could be mediated by systemic inflammatory cells rather than the local Kupffer cells. So I think it is important to know where these animals are in the course of their disease.

Furthermore, do the histologic sections of the liver at 48 hours show any evidence of liver necrosis, that

is, is the liver cell death purely apoptotic or could it be both necrotic and apoptotic? In other words, is the cell death caspase-mediated, and have you used any caspase inhibitors to definitely determine that this is apoptotic cell death?

And then finally, you propose that the p38 MAP kinase cascade is an integral mediator of the Fas/Fas ligand signaling. Because there is substantial redundancy in inflammatory-induced cell-signaling pathways, could other pathways such as the stress-activated protein kinase pathway be involved, and have you used the p38 MAP kinase inhibitor and examined the effect on liver injury?

Thank you for allowing me to review this nice study and congratulations on furthering our insights about the mechanisms of pancreatitis-induced liver injury.

**Dr. Gallagher:** Dr. Behrns, thank you for your kind comments and your insightful questions. I will try and address them in order.

As far as the condition of the mice at 48 hours and were any of them near death, no, none of them were near death. They were ill-appearing, and that goes for the regular C57 CDE mice as well as the Fas Ligand

knockout mice and the Fas knockout mice. They exhibited the similar tendencies you would expect in ill mice, less activity, more burrowing, their urine was a little more concentrated, but we didn't quantify that, and so we didn't look at that specifically as far as a clinical evaluation of the severity of pancreatitis.

We picked 48 hours, because with giving mice CDE diet there is a variable intake. We fast them before we start the diet, but we wanted to make sure that all the mice actually had pancreatitis. By 96 hours, or 5 days, 70% of the mice die, and so we didn't want to start getting into the shock and the real big systemic manifestations to try and factor out that possibility. So that is the reason we picked 48 hours.

As far as the histology goes, like I said, I don't think the mice were in shock, but we didn't measure that. We did look at the histology; we have done that a long time ago in the pancreas and the liver. We haven't looked at it in this set of experiments. But we do plan to investigate using MPO and H&E staining in the future. We are working on a set of experi-

ments now, which I will talk about in the next question a little bit as part of that set of experiments.

As far as apoptosis and necrosis goes, that is really difficult to ferret out. We used TUNEL, we used DNA fragmentation (ELISA) to look at that, and as you could see in the pictures, those cells obviously weren't necrotic.

As far as looking at whether it is a caspase-mediated pathway or a p38-mediated pathway, we didn't look at that in this set of experiments, but we have done that before. In the last set, in the cerulein-induced, or the CCK-induced pancreatitis, we did look at caspase 3 and p38, and we did use gadolinium to try and inhibit those things in that as well as previous experiments *in vitro* where we were looking specifically at Kupffer cells and hepatocytes using gadolinium as kind of a global Kupffer cell inhibitor of cytokine production. And the current project we are working on is an NF $\kappa$ B-related project where we are looking at the cellular signaling and upregulation of Fas ligand and if we can block NF $\kappa$ B.

## The Utility of Laparoscopic Assessment in the Preoperative Staging of Suspected Hilar Cholangiocarcinoma

Saxon Connor, F.R.A.C.S., Emma Barron, B.Sc., Stephen J. Wigmore, M.D., F.R.C.S., Krishnakumar K. Madhavan, M.S., F.R.C.S., Rowan W. Parks, M.D., F.R.C.S., O. James Garden, M.D., F.R.C.S.

The aim of this study was to review the role of laparoscopic assessment in the staging algorithm of suspected hilar cholangiocarcinoma and to identify factors highly likely to be associated with unresectable disease. Data prospectively collected between 1992 and 2003 were analyzed. Demographics, symptoms, preoperative radiologic staging, laparoscopic assessment, and final outcome were recorded. Yield was defined as the number of unresectable patients detected by laparoscopic assessment divided by the total number of patients undergoing laparoscopic assessment. Accuracy was defined as the number of unresectable patients detected by laparoscopic assessment divided by the total number of unresectable cases. Eighty-four patients underwent laparoscopic assessment for suspected hilar cholangiocarcinoma, of which 20 (23.8%) underwent resection. The yield from laparoscopy alone was 24.3% (20 of 82), which increased to 41.5% (35 of 82) with the addition of intraoperative ultrasound. The overall accuracy was 53.1% (35 of 66). The use of a preoperative radiologic staging system predicted the likelihood of unresectable disease ( $P = 0.007$ ). The use of laparoscopic assessment in the preoperative staging of patients with suspected hilar cholangiocarcinoma is justified given it will spare 42.2% of patients an unnecessary laparotomy. Accurate staging of cholangiocarcinoma remains a challenge, but the use of a preoperative radiologic staging system may help to stratify a patient's risk of unresectable disease. (J GASTROINTEST SURG 2005;9:476-480) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Laparoscopy, biliary malignancy, laparoscopic ultrasound

Hilar cholangiocarcinoma is an uncommon tumor with an incidence that is increasing.<sup>1</sup> Its management involves a complex algorithm of preoperative staging investigations.<sup>2</sup> The majority of patients will require palliation,<sup>3</sup> and thus the avoidance of unnecessary laparotomy, from which there is significant morbidity, is an important goal of preoperative staging. Nonetheless, a significant number of patients are found to be incurable at the time of laparotomy,<sup>3</sup> despite the use of modern radiologic staging. Laparoscopy with or without laparoscopic ultrasound has been suggested as a way to minimize the incidence of unnecessary laparotomy in the management of suspected hepato-biliary-pancreatic malignancy, but its

low yield has meant that its routine use has not been accepted universally.<sup>4-7</sup> Furthermore, the accuracy of noninvasive radiologic imaging continues to improve, which is likely to result in a further reduction in the yield.

There is paucity of data on the effectiveness of laparoscopic assessment in the staging algorithm for patients with suspected hilar cholangiocarcinoma. The Memorial Sloan-Kettering Cancer Center (MSKCC) group proposed a radiologic staging system based on tumor position, involvement of surrounding vascular structures, and the presence of lobar atrophy.<sup>3</sup> This has been shown to predict resectability, likelihood of a clear resection margin, and survival.<sup>3</sup> It has been suggested that this same staging system may help

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identify those patients in whom laparoscopic assessment is likely to be beneficial.<sup>8</sup>

The aim of this study was to review the experience of laparoscopic ultrasound for suspected hilar cholangiocarcinoma in a large tertiary referral center and to identify factors that may help to select patients who are likely to have unresectable disease.

## METHODS

### Data Collection

All patients with suspected hilar cholangiocarcinoma undergoing laparoscopic assessment were identified from a prospectively collected database between 1992 and 2003. The database was validated by a retrospective case note review. Patients were excluded if they had intrahepatic cholangiocarcinoma or if the tumor arose from the distal third of the common bile duct. Demographics, year of presentation (pre- or post-2000), symptoms, details of preoperative radiologic imaging, findings at laparoscopic assessment, subsequent treatment, and outcome were recorded. The reason for unresectability was documented. This was classified as peritoneal disease (peritoneal metastases, including miliary-type nodules over Glisson's capsule, positive ascitic cytology), distant metastases (parenchymal liver lesions and distant nodal metastases outside the resection field), or locally advanced disease (main or bilateral portal vein involvement not amenable to resection, hepatic artery involvement, proximal extension of tumor such that resection would not leave sufficient volume of functioning liver). In the event of there being more than one contraindication to resection, the cause that was detected first was recorded; that is, peritoneal metastases detected by laparoscopy were recorded rather than intraparenchymal liver metastases detected by laparoscopic ultrasound. This allowed the usefulness of laparoscopic ultrasound compared with laparoscopy alone to be determined.

The preoperative radiologic imaging was consolidated to create a T-stage (1–3) based on that previously described by Jarnagin et al.<sup>3</sup> T1 tumors were defined as those arising from the confluence with or without unilateral extension into second-order biliary radicals. T2 tumors were defined as those meeting T1 criteria with ipsilateral portal vein involvement with or without ipsilateral hepatic lobar atrophy. T3 tumors were defined as either those tumors arising from the confluence with unilateral extension into secondary biliary radicals and contralateral involvement of either second-order biliary radicals, portal vein or hepatic lobar atrophy, or tumors arising from the confluence with bilateral or main portal vein involvement.

Due to the long period over which this study was conducted, the preoperative radiologic assessment evolved over time, but all patients underwent either abdominal ultrasound or contrast-enhanced computed tomography (CE-CT) and cholangiography, whereas 57 patients underwent additional angiography. Only a few of the most recent patients have undergone magnetic resonance imaging.

### Surgical Laparoscopic Technique

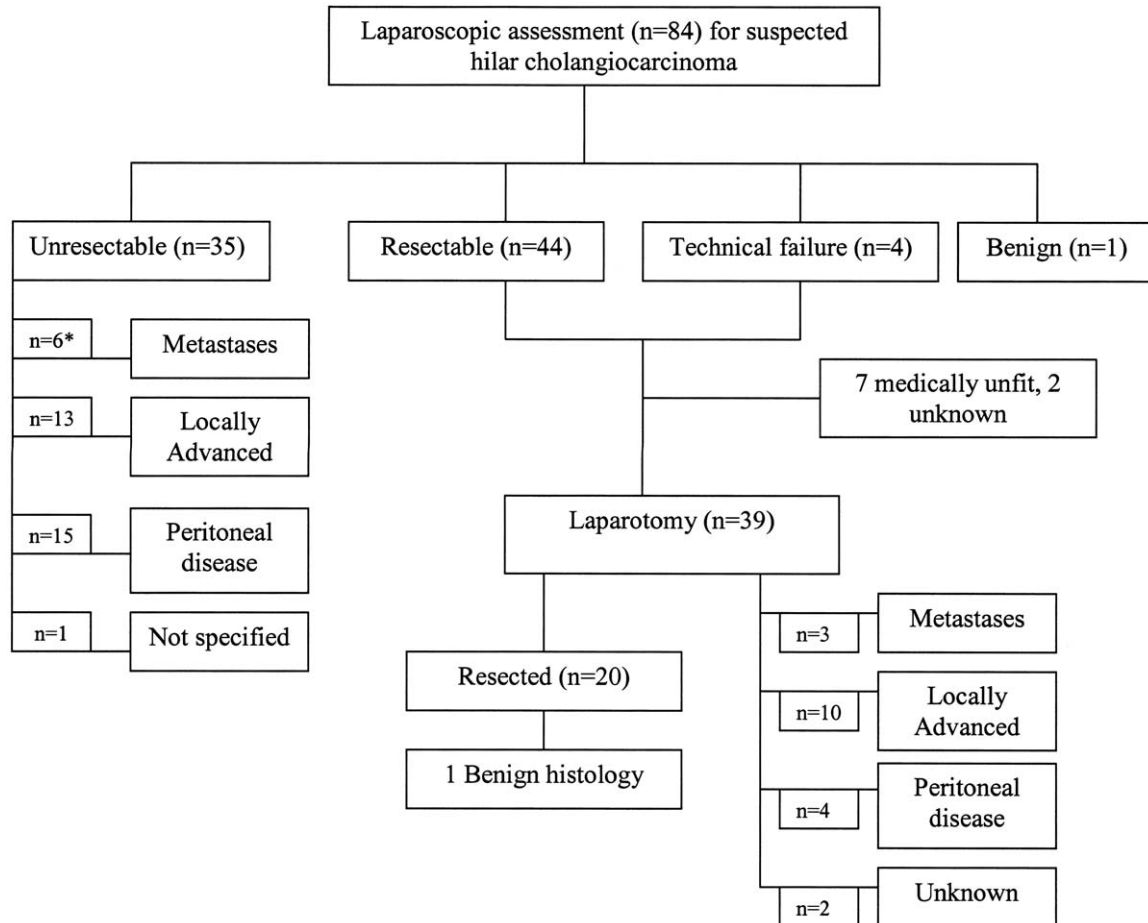
Standard laparoscopy was performed to assess the peritoneal cavity. In addition, intraoperative laparoscopic ultrasonography was used to assess the liver parenchyma and the local extent of the tumor to determine the presence of vascular invasion (arterial or venous) and the proximal extent of the tumor within the biliary tree. Routine nodal sampling was not undertaken unless there was evidence of macroscopic disease.

### Statistical Analysis

Continuous data are presented as median (95% confidence interval [CI]) and analyzed by Mann-Whitney *U*. Nominal data were compared by Fisher exact or  $\chi^2$  tests. Levels of significance were  $P < 0.05$ . Data were analyzed using StatView version 5 (SAS Institute, Cary, NC). Yield was defined as number of unresectable patients detected at laparoscopic assessment divided by the total number of patients who underwent laparoscopic assessment. Accuracy was defined as number of unresectable cases detected by laparoscopic assessment divided by the total number of unresectable cases. Unresectability was defined as metastatic disease, locally advanced disease precluding resection, the presence of a carcinoma in those being assessed for a liver transplant (given this is a contraindication to transplantation).

## RESULTS

Between March 1992 and November 2003, 235 patients were assessed with suspected hilar cholangiocarcinoma; following radiologic imaging, 122 patients (51.9%) were considered resectable. Eighty-four patients (68.9%) underwent laparoscopic assessment as part of their preoperative staging (Fig. 1). The median age was 62 years (range, 59–64 years), and 50 (59.5%) were male. Twenty patients (24.1%) were ultimately resected, of whom 2 underwent liver transplantation. Eight patients had negative resection margins, 10 patients had positive resection margins, in 1 there was no evidence of malignancy, and in the remaining patient it was unknown. In 12 patients with locally advanced disease, no histology was obtained.



**Fig. 1.** Outcome following laparoscopic assessment for suspected hilar cholangiocarcinoma. \*Only one patient had intraparenchymal liver metastases detected by laparoscopic ultrasound; five had microscopic nodal involvement outside the field of resection.

The results of the laparoscopic assessment and ultimate outcome are shown in Fig. 1. The overall yield (one patient, excluded as benign disease was diagnosed at laparoscopy) was 42.2% (35 of 83), and the accuracy was 53.1% (35 of 66). The yield from laparoscopy alone (a further patient was excluded as the cause of unresectability not specified) was 24.3% (20 of 82), which increased to 41.5% (34 of 82) with the addition of laparoscopic ultrasound. The yield of laparoscopic assessment did not differ when comparing those performed within the past 4 years (2000–2003) with those performed before 2000 (14 of 36 versus 19 of 38,  $P = 0.337$ ).

Twenty patients (23.8%) were staged by preoperative radiologic imaging as T1, 41 patients (48.8%) as T2, and 18 patients (21.4%) as T3, and 5 patients (6.0%) were unknown. The proportion of patients resectable by laparoscopic criteria and ultimately resectable by T stage is shown in Table 1. Those patients staged radiologically with preoperative T3 disease were more likely to be unresectable than those

with T1 (1 of 17 resectable versus 8 of 17 for T1 disease,  $P = 0.007$ ) and T2 (1 of 17 resectable versus 11 of 37 for T2 disease,  $P = 0.050$ ) disease. Similarly, laparoscopic assessment was more likely to detect unresectable disease in patients who were staged preoperatively as T3 disease compared with those with T1 (11 of 16 T3 unresectable versus 5 of 19 of T1,  $P = 0.012$ ) or T2 (11 of 16 T3 unresectable versus 15 of 40 of T2,  $P = 0.034$ ) disease. There was no difference in the frequency of unresectable disease at the time of laparoscopic assessment ( $P = 0.396$ ) or at laparotomy ( $P = 0.216$ ) between T1 and T2 staged disease. The reason for unresectability differed between patients staged with T3 tumors and those with T1-2 tumors in that there was a higher proportion of metastatic disease compared with locally advanced disease in the T1-2 tumors (22 of 32 had metastatic disease versus 4 of 15 for T3 tumors,  $P = 0.007$ ).

Neither symptoms (pain or weight loss) nor the presence of a mass on CE-CT correlated with either laparoscopically assessed resectability or ultimate resectability (Table 2).

**Table 1.** Numbers of patients resectable by laparoscopic criteria and ultimately resected by T stage

| Resectable                  | T1<br>(n = 19) | T2<br>(n = 41) | T3<br>(n = 18) |
|-----------------------------|----------------|----------------|----------------|
| By laparoscopic criteria*   | 14/19          | 25/40          | 5/16           |
| Number ultimately resected† | 8/17           | 11/37          | 1/17           |

\*Where denominator is less than total, it is due to exclusion of patients due to technical failure of laparoscopic assessment or due to identification of benign disease at the time of laparoscopy (one patient).

†Where denominator is less than total, it is due to patients being unfit to proceed to laparotomy despite resectable disease being suggested by the laparoscopic assessment.

A subgroup analysis of those who had locally advanced disease or were ultimately resected was conducted to determine whether the presence of a stent affected either laparoscopic assessment or ultimate resectability. There was no difference in the frequency of those assessed to be resectable at the time of laparoscopic assessment (9 of 13 with no stent versus 21 of 29 with stent,  $P = 0.999$ ) or resected at time of laparotomy (7 of 13 with no stent versus 13 of 29,  $P = 0.741$ ).

Of the 38 patients who did not undergo laparoscopy, 18 were ultimately resected, which was significantly greater than those undergoing laparoscopy ( $P = 0.012$ ). Eighteen were staged preoperatively as T1, 11 as T2, and 3 as T3, and in 6 cases, it was unknown. Those in whom laparoscopy was omitted had a higher proportion of T1 tumors by preoperative staging compared with those undergoing laparoscopy ( $P = 0.007$ ).

## DISCUSSION

Hilar cholangiocarcinoma remains a challenging condition to treat. The majority of patients will only

be suitable for palliative measures,<sup>3</sup> which in the main can be performed without the need for laparotomy, although there is a subgroup who may benefit from surgical biliary bypass.<sup>9</sup> Staging laparoscopic assessment has been shown to reduce hospital stay for those with incurable disease,<sup>8</sup> but studies regarding the benefit of laparoscopy for patients with suspected hilar cholangiocarcinoma is scarce.<sup>7,8,10-12</sup>

The current study has shown that the accuracy of laparoscopic assessment for suspected hilar cholangiocarcinoma was 53% and that the overall yield was 42%. Thus, the routine use of laparoscopic assessment for suspected hilar cholangiocarcinoma may spare up to 42% of patients an unnecessary laparotomy. These figures were considerably better than those reported by the only other large study of laparoscopic assessment for hilar cholangiocarcinoma,<sup>8</sup> in which the accuracy was 42% (14 of 33) and the yield was 25% (14 of 56). Possible reasons for this discrepancy include differences in the quality of preoperative imaging, selection criteria for laparoscopy, and criteria for determining unresectability. Certainly the MSKCC data were gathered over a shorter, more contemporary period of time; however, in the current study, there was no decrease in the yield from laparoscopic assessment in the two time periods analyzed. During this study period, 48% were thought to be unresectable following radiologic assessment, a rate much higher than that previously reported by the MSKCC group (29%).<sup>3</sup> The criteria for considering laparoscopy or resection will also affect the yield. Those undergoing laparoscopy had a significantly higher T stage, suggesting that a selective policy was in place. The overall percentage of patients (all patients coming forward for possible resection) with T3 tumors was greater in the current study (19%) compared with that reported by Weber et al<sup>8</sup> (7%). This may reflect differing referral patterns and criteria for nonresectability on preoperative imaging.

**Table 2.** Relationship of symptoms or presence of a mass on contrast-enhanced computed tomography at presentation to laparoscopically assessed resectability and ultimate resectability at time of laparotomy

| Symptom       | Laparoscopically assessed resectable |             |       | Ultimately resected |             |       |
|---------------|--------------------------------------|-------------|-------|---------------------|-------------|-------|
|               | Yes (n = 44)                         | No (n = 35) | P     | Yes (n = 20)        | No (n = 54) | P     |
| Pain          |                                      |             | 0.575 |                     |             | 0.555 |
| Yes           | 23                                   | 16          |       | 11                  | 26          |       |
| No            | 20                                   | 18          |       | 8                   | 26          |       |
| Weight loss   |                                      |             | 0.759 |                     |             | 0.612 |
| Yes           | 29                                   | 20          |       | 14                  | 30          |       |
| No            | 15                                   | 12          |       | 6                   | 20          |       |
| Mass on CE-CT |                                      |             | 0.537 |                     |             | 0.363 |
| Yes           | 25                                   | 20          |       | 11                  | 32          |       |
| No            | 17                                   | 10          |       | 9                   | 16          |       |

Where numbers are less than denominator, it is due to incomplete datasets.

The addition of intraoperative ultrasonography at the time of laparoscopy has been suggested as a means of increasing the yield by determining locally advanced disease or parenchymal liver metastases; however, its use remains to be fully elucidated. The MSKCC study<sup>8</sup> did not detect any patients who benefited from the addition of laparoscopic ultrasound, whereas others have reported benefit in only isolated cases.<sup>11,12</sup> The current study detected only one patient with an intraparenchymal liver metastasis in the absence of disease not detectable by laparoscopy, but it did detect 13 patients in whom the management was changed due to locally advanced disease (Fig. 1). Thus, laparoscopic ultrasound increased the yield from 24% to 42% compared with laparoscopy alone. Despite this, the major reason for unresectability at laparotomy following laparoscopic assessment was locally advanced disease; furthermore, 10 of the 19 patients undergoing resection had positive resection margins, indicating that in practice it is not easy to accurately assess local invasion. The presence of a stent did not seem to alter the accuracy of assessment of locally advanced disease. In two patients with primary sclerosing cholangitis who were under consideration for liver transplantation, it failed to detect underlying malignancy, and in one case, it failed to differentiate from benign disease.

The MSKCC-proposed preoperative radiologic T staging system<sup>3</sup> correlated well with an increased rate of unresectability with advancing T stage. Perhaps of greater interest was that metastatic disease was more likely to be the reason for unresectability in T1 and T2 tumors, whereas for T3 tumors, it was mainly as a result of locally advanced disease. This raises the possibility of diversity of biological behavior within these tumors. This pattern of spread may also allow targeted use of laparoscopic assessment. It has been shown that those patients with locally advanced disease have significantly longer median survival (17 months) compared with those with metastatic disease (3–5 months).<sup>8</sup> It has been also suggested that those with an expected survival of greater than 6 months may benefit from surgical palliation in the form of a segment III bypass because it provides better long-term palliation.<sup>8,9</sup> Those patients with T3 disease may benefit from a laparoscopy alone and in the absence of metastatic disease might directly proceed to laparotomy for trial dissection. A segment III bypass might be considered for unresectable tumors if this is considered feasible. Those patients with T1–2 tumors are more likely to benefit from staged laparoscopic ultrasound assessment. Although the yield will be lower, patients are less likely to proceed to laparotomy in the event of metastatic disease and this would enable better use of valuable operating time. The

presence of symptoms of advanced malignancy or the presence of a mass on CE-CT did not predict resectability or help in selecting patients who may benefit from laparoscopic assessment.

In conclusion, the use of laparoscopic assessment in preoperative staging of suspected hilar cholangiocarcinoma is justifiable, as it would spare 42.2% of patients an unnecessary laparotomy. The accuracy, however, remains only fair, particularly with regard to identifying locally advanced disease. Whether selective use based on preoperative radiologic staging can improve the efficiency of treatment for these patients may depend on individual institutions referral patterns, criteria for resection, preferred method of palliation, and operating theatre set-up. The accurate staging of cholangiocarcinoma remains a considerable challenge.

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# The Role of Ciprofloxacin in Prolonging Polyethylene Biliary Stent Patency: A MultiCenter, Double-Blinded Effectiveness Study

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Plastic stents are the mainstay of the palliation of malignant jaundice but are complicated by recurrent obstruction. Previous trials have failed to demonstrate any improvement in patency with the use of antibiotics. Patients with malignant jaundice were randomized in a double-blind fashion, after polyethylene stent insertion, to receive ciprofloxacin or placebo. After successful stent decompression, there were 50 patients in the treatment arm and 44 in the placebo. There were 14 (33%) episodes of stent occlusion in the ciprofloxacin group versus 23 (49%) in placebo ( $\chi^2$  test,  $P = 0.115$ ). There was no significant difference in patency (log-rank test,  $P = 0.17$ ). There were significantly fewer episodes of cholangitis with ciprofloxacin: 10 (23%) versus 21 (42%) in the placebo ( $P = 0.047$ ). The ciprofloxacin group also demonstrated a significant improvement in the Social Function domain of the SF-36 Quality of Life Survey at 1 month (paired T test,  $P = 0.03$ ). The other domains of the SF-36 were not different, nor was survival (log rank,  $P = 0.80$ ). There is insufficient evidence to show that prophylactic ciprofloxacin can prolong plastic biliary stent patency. The observed trends suggest that ciprofloxacin significantly decreases the incidence of cholangitis and results in improvements in certain aspects of quality of life. (J GASTROINTEST SURG 2005;9:481-488) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Stents, biliary, obstructive jaundice, ciprofloxacin, quality of life

Primary biliopancreatic cancers bear an ominous prognosis, even when diagnosed at an early stage. Pancreatic cancer is responsible for a significant burden of such disease: it is the fifth most deadly cancer despite being only the 11th most common.<sup>1</sup> This is in part attributable to the observation that most patients present for treatment at an unresectable stage. Almost half of patients already have liver or other distant metastases at diagnosis, and more than 80% of the remaining patients have locally advanced tumors.<sup>2</sup> The poor outlook for patients who present with biliary obstruction has thus focused therapeutic efforts at improving the palliation of symptoms. Malignant jaundice is associated with a number of

physiologic impairments,<sup>3</sup> including renal failure<sup>4</sup> and immunosuppression.<sup>5</sup> Yet, the jaundice, pruritus, anorexia, and pain cause the greatest loss of a patient's quality of life.<sup>6,7</sup> Pain and anorexia can be difficult to manage clinically, but decompression of an obstructed biliary tree results in improvements in pruritus and jaundice.<sup>6-10</sup> In fact, two groups, including our group, have shown that palliative biliary decompression is associated with significant improvements in the quality of life of such patients.<sup>8,11</sup>

Insertion of a plastic polyethylene stent endoscopically is the most widely practiced method of palliation for malignant biliary obstruction in North America, even though the use of metal stents has increased

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over the past few years (A.N. Barkun, personal communication). Metal stents have superior patency,<sup>10</sup> but direct cost, permanency, and increased expertise have limited their use. The main limitation of plastic stents is obstruction, and possibly cholangitis, which frequently antedates a patient's death.<sup>9,12-15</sup> Clinical and animal studies have examined the effect of altering the stent size, shape, or materials or prescribing adjuvant treatments such as an antibiotic and/or a choleric agent. Unfortunately, no change has been conclusively beneficial. The purpose of the current randomized trial was to examine a new strategy: we propose to sterilize bile with ciprofloxacin before stent insertion and thereafter continue a chronic maintenance ciprofloxacin therapy. The primary outcome is the duration of stent patency.

## METHODS

### Participating Centers

We report a placebo-controlled, double-masked, parallel-arm, randomized clinical trial conducted at the following Canadian centers: the Royal Victoria and Montreal General hospital sites of the McGill University Health Centre (Montreal, Quebec), the Sir Mortimer B. Davis-Jewish General Hospital (Montreal, Quebec), The Queen Elizabeth II Health Science Centre (Halifax, Nova Scotia), and St. Paul's Hospital (Vancouver, British Columbia).

### Selection Criteria

All patients who presented to one of the five participating hospitals were offered entry into the trial if they had met all of the following inclusion criteria: obstructive jaundice due to unresectable malignancy, absence of any previous biliary drainage procedure, and a signed informed consent. Patients were excluded if there was any contraindication to undergoing endoscopic retrograde cholangiopancreatography (ERCP), a known allergy to ciprofloxacin, significant renal failure (less than one third of estimated creatinine clearance), acute hepatic insufficiency, pregnancy, uncorrected coagulopathy, or concomitant use of theophylline, iron, sucralfate, glyburide, probenecid, cyclosporin, antacids, or calcium.

### Intervention and Randomization

All patients were administered ciprofloxacin 750 mg PO as prophylaxis within the 4 hours preceding the procedure. At the time of ERCP, a Cotton-Leung or Cotton-Huibregtse polyethylene stent (Wilson-Cook Medical, Winston-Salem, NC), size 10 French,

was inserted. Successful initial ERCP stent placement was defined as the demonstration of drainage of most of the injected contrast media from the biliary system into the duodenum within 5 minutes of placement. Patients were randomized in a 1:1 ratio to either ciprofloxacin 500 mg or placebo (of identical appearance) orally twice daily. All medications were administered until the patient ultimately developed stent blockage, died, could no longer take oral medication, or was lost to follow-up. Randomization was carried out by the use of concealed computer-generated random numbers and was stratified according to the location of malignant obstruction (lower two thirds versus upper third of the biliary tree) and by center. The medication was prepared by a third party to ensure masking.

### Patient Follow-up

Patients were followed in an outpatient clinic at 7 days after stent insertion and monthly thereafter, until stent occlusion, death, or loss to follow-up. A drop in bilirubin level of greater than 20% over the first week was considered to represent satisfactory drainage and was a criterion for maintenance in the trial, as previously suggested.<sup>10</sup> We postulated that patients not exhibiting a drop in bilirubin, despite adequate stent placement, might have been jaundiced because of the presence of clinically occult liver metastases rather than biliary obstruction or had experienced early stent dysfunction such as slippage or unsuspected inadequate initial placement—all situations that would make it impossible to validly assess the primary outcome. Thus, these cases were excluded from analysis. Patients who were lost to follow-up before the day-7 visit were also excluded as noncompliant. At each visit, recorded clinical data included symptoms, blood chemistry measurements, and the SF-36 Quality of Life questionnaire. Compliance was ensured by patient interviews and the return and pill counts of prepackaged medication bottles.

### Outcome Measures

The primary outcome measure was the development of stent occlusion. This was suspected if the patient presented with either jaundice (recurrent or worsening) or cholangitis (upper abdominal pain, jaundice, and fever or flu-like symptoms). Serum biochemistry tests and an abdominal ultrasound were also performed. An ERCP was performed to assess pneumobilia and bile flow into the duodenum. ERCP findings were used to establish the diagnosis of stent occlusion and the stent was changed. Patients were followed after they had reached the primary outcome to measure secondary outcomes, including

mortality and morbidity (infection, hemorrhage, obstruction, or perforation) and quality of life measurements, or were lost to follow-up. At this point, patients were treated according to the standard of care.

### Statistical Analyses

All inferential statistical analyses were carried out using the Student's *t* test for continuous variables and  $\chi^2$  test for categorical variables. Stent patency and patient survival were analyzed by the Kaplan-Meier method and compared by the log-rank test. For the analysis, patients were censored if they died with a patent stent or were lost to follow-up. Statistical significance was taken at  $P < 0.05$ . An intention-to-treat analysis was carried out.

Sample size calculation before start of the trial, allowing for a 20% dropout rate, had estimated that patient accrual of 150 patients in each group would be sufficient to detect a 20% difference in stent clogging for an  $\alpha$  of .05 and a power of 80%. We allowed for a dropout rate of 20%.

## RESULTS

### Patient Population

One-hundred thirty-five patients were ultimately recruited in this study with 70 patients randomized to the placebo group and 65 to the ciprofloxacin group. Ten patients subsequently underwent surgery after randomization in an attempt at tumor resection and were excluded. Four patients had a complication related to the ERCP, including one duodenal perforation, one hemorrhage, one dislodged stent, and one failure of cannulation after an invalid initial randomization. Thirteen patients were lost to follow-up, of whom four dropped out on the advice of the treating oncologist. Further, 14 patients had persistent or worsening jaundice 1 week after initial ERCP despite confirmed proper stent placement and thus were excluded from the rest of the analysis. These patients who did not respond to biliary decompression were assumed to have hepatic metastases.

In the final analysis, there were 50 patients in the placebo group and 44 in the ciprofloxacin group. The study was stopped due to a combination of study fatigue and competing trials that limited further accrual. Characteristics of the excluded patients were similar in both groups and are not discussed further. The CONSORT diagram is shown in Fig. 1.

The two groups were comparable in terms of baseline characteristics that included mean age, gender, American Society of Anesthesiologists classification, and the prevalence of symptoms such as fatigue,

nausea, vomiting, pruritis, weight loss, and abdominal pain. Upper gastrointestinal obstruction was uncommon in either group. The location of biliary obstruction in the majority of cases was in the distal two thirds (80% of placebo versus 88% of ciprofloxacin). Obstruction was secondary to pancreatic cancer in 56% and 60%, respectively. Blood chemistry values were similar in both groups at baseline, including total bilirubin, alkaline phosphatase, creatinine, AST, and ALT (Table 1).

### Outcomes

**Stent Occlusion.** There were 22 (49%) stent occlusion in the placebo group and 14 (33%) in the ciprofloxacin group ( $P = 0.115$ ). The median durations of stent patency were similar: 92 days in the placebo group and 101 days in the ciprofloxacin group (Table 2). Life-table analysis of the duration of stent patency failed to show any significant difference between the two groups (log-rank test,  $P = 0.17$ ) (Fig. 2).

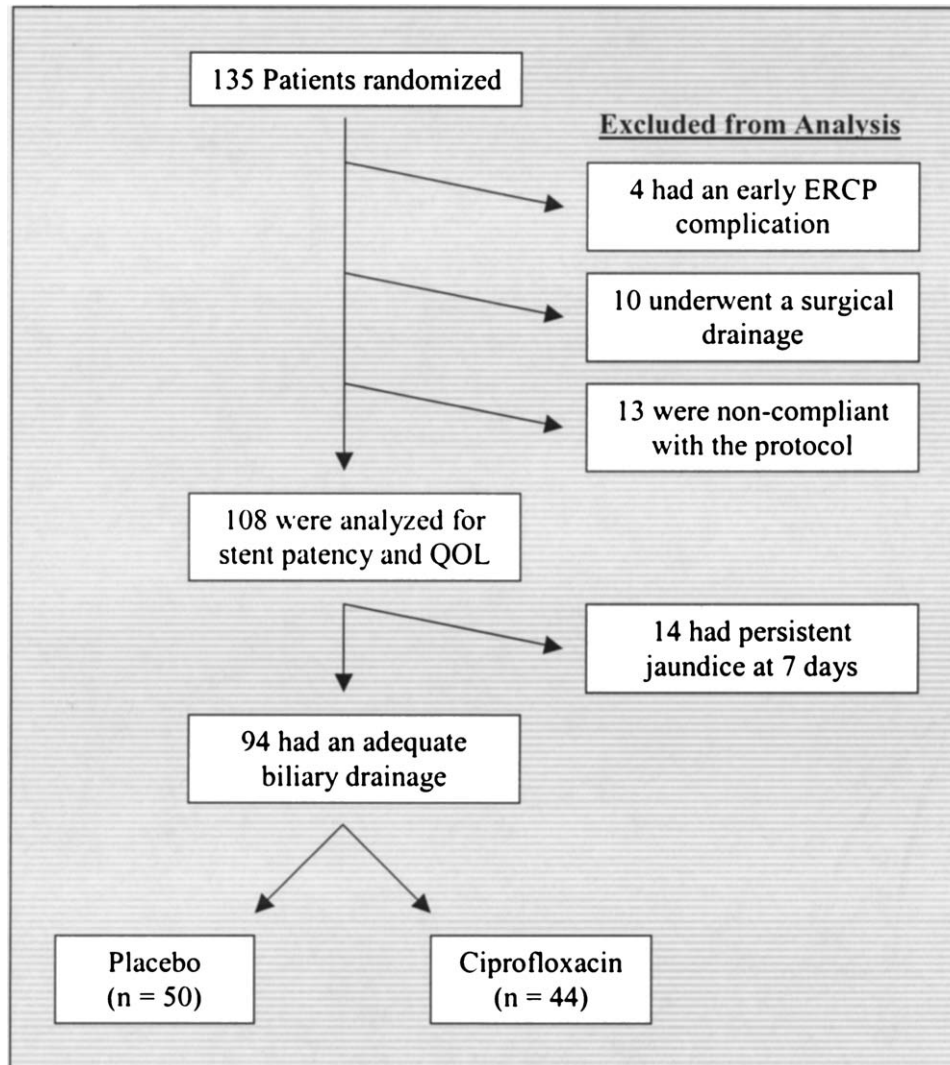
**Episodes of Cholangitis.** There was a statistically significant decrease in the number of episodes of cholangitis in the ciprofloxacin group (10 episodes [23%]) compared with placebo (21 episodes [42%]) (log-rank test,  $P = 0.047$ ) (Table 2).

**Survival.** The median patient survival was 126 days in the placebo group and 140 days in the ciprofloxacin group. Analysis of patient overall survival using the Kaplan-Meier method did not show any significant difference across groups (log-rank test,  $P = 0.80$ ) (Fig. 3).

**Quality of Life.** In total, 15 patients in the placebo group and 16 patients in the ciprofloxacin group adequately completed the questionnaire at baseline and at 1-month follow-up. There was no statistical difference between the two groups at baseline for any of the individual measures or the component summaries. After 1 month, the ciprofloxacin group demonstrated a significant improvement in Social Functioning compared with the placebo group ( $P = 0.031$ ). This was the only measure for which one group demonstrated an improvement while the other worsened. There was no statistical difference between the two groups for the other measures of Physical Functioning, Physical Role, Bodily Pain, General Health, Vitality, Emotional Role, and Mental Health. There also was no difference for the summary scores of the physical component summary or the mental component summary (Table 3).

## DISCUSSION

There are a limited number of treatment options to offer to patients with malignant obstructive jaundice,



**Fig. 1.** CONSORT diagram: a randomized clinical trial of the use of ciprofloxacin in prolonging plastic stent patency in malignant jaundice.

and palliation of symptoms remains the primary goal. Available methods of biliary decompression include surgical bypass, percutaneous drainage, and endoscopic drainage. In several randomized trials, surgery has been found to be associated with greater early morbidity and mortality, but more prolonged relief of jaundice. Consequently, operative management is reserved for a minority of patients who are expected to survive “longer” than 6 months.<sup>16-19</sup>

Biliary endoprosthesis insertion is thus the most common method of palliation, and an ERCP approach has been found to be superior to the transhepatic route.<sup>20</sup> Polyethylene (plastic) endobiliary stents are most commonly used<sup>9,21</sup> even though expandable metal stents are associated with a significantly longer patency.<sup>22,23</sup> The reason for this is that they are initially less expensive and easier to manipulate. Regardless of the type that is used, all biliary stents have a

significant risk of obstruction. This is a major cause of inadequate palliation and unwelcome hospital admission in a patient with a limited life expectancy.<sup>24</sup> For this reason, avoidance or delay of plastic stent blockage has been a principal focus of clinical research, particularly as it relates to quality of life.<sup>11,21</sup> Microscopic studies of occluded stents have demonstrated the formation of a bacterial biofilm that is adherent to the stent lumen.<sup>25-27</sup> It is composed of a matrix of fibrillar anionic products and bacterial cells for which bacterial enzymatic activity leads to a deposition of crystals and subsequently to the formation of biliary sludge, which obstructs the lumen. As a consequence, strategies for the prevention of stent blockage have addressed stent design, and bile composition or bacterial factors. The modification of stents, in terms of side holes, position, and texture, has yet to yield an appreciable and consistent clinical



**Table 1.** Patient characteristics

| Characteristic                        | No. (%) Assigned to Placebo (n = 50) | No. (%) Assigned to Ciprofloxacin (n = 44) |
|---------------------------------------|--------------------------------------|--|
| Age, mean [range] (yr)                | 73.4 [40–93]                         | 71.3 [52–94]                               |
| Male                                  | 23 (46)                              | 24 (55)                                    |
| Fatigue                               | 43 (86)                              | 37 (84)                                    |
| Nausea and Vomiting                   | 20 (40)                              | 18 (41)                                    |
| Pruritis                              | 32 (64)                              | 30 (68)                                    |
| Weight loss                           | 40 (80)                              | 39 (89)                                    |
| Abdominal pain/<br>tenderness         | 28 (56)                              | 27 (61)                                    |
| Upper gastrointestinal<br>obstruction | 2 (4)                                | 3 (7)                                      |
| Site of obstruction                   |                                      |  |
| Distal third                          | 33 (66)                              | 33 (75)                                    |
| Mid third                             | 8 (16)                               | 8 (18)                                     |
| Hilar                                 | 8 (16)                               | 2 (5)                                      |
| Intra hepatic                         | 1 (2)                                | 1 (2)                                      |
| Malignancy                            |                                      |  |
| Ampullary                             | 6 (12)                               | 2 (5)                                      |
| Pancreatic                            | 29 (58)                              | 27 (61)                                    |
| Metastases                            | 5 (10)                               | 8 (18)                                     |
| Klatskin's                            | 2 (4)                                | 0 (0)                                      |
| Cholangiocarcinoma                    | 5 (10)                               | 6 (14)                                     |
| Other                                 | 3 (6)                                | 1 (2)                                      |
| Total bilirubin (μmol/L)              | 265                                  | 294  |
| AST (U/L)                             | 160                                  | 198  |
| ALT (U/L)                             | 197                                  | 13   |
| ALKP (U/L)                            | 749                                  | 640  |
| Creatinine (μmol/L)                   | 93                                   | 83   |

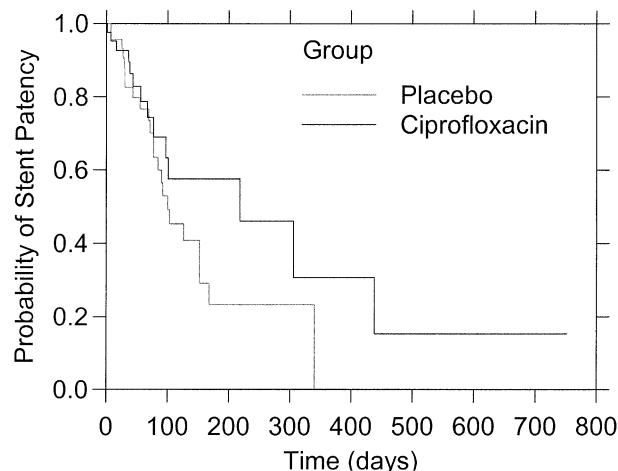
benefit.<sup>28–33</sup> A randomized trial comparing 10 F to 11.5 F stents found no statistical difference between a mean patency rate of 3 and 4 months, respectively. The length of the stent was found not to have any relationship with outcomes of obstruction, when comparing short (< 8 cm) and long (>9 cm) lengths.<sup>34</sup> Although UCDA can improve biliary flow in vitro,<sup>35</sup> it has been found to be clinically ineffective<sup>28</sup> in prolonging stent patency.

**Table 2.** Outcomes

|  | Placebo     | Ciprofloxacin | P                  |
|--|-------------|---------------|--------------------|
| Stent occlusion (%)                      | 23 (49)     | 14 (33)       | 0.115*             |
| Cholangitis (%)                          | 21 (42)     | 10 (23)       | 0.047*             |
| Median duration of<br>patency, days [SD] | 92 [72.8]   | 101 [134.9]   | 0.169 <sup>†</sup> |
| Median survival,<br>days [SD]            | 126 [167.7] | 140 [194.1]   | 0.803 <sup>†</sup> |

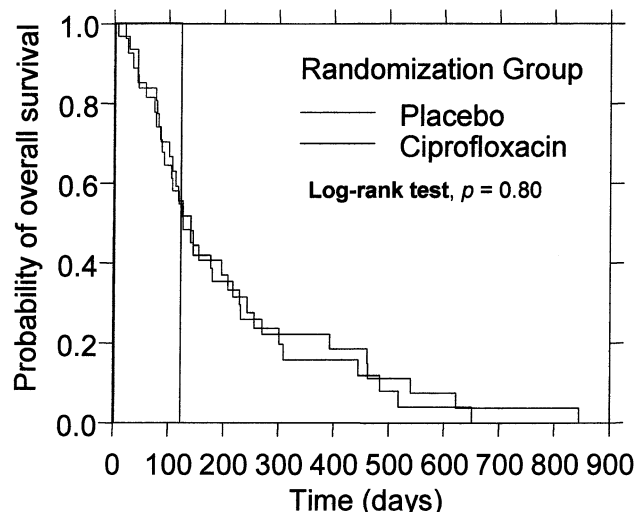
\* $\chi^2$  test.

<sup>†</sup>Log-rank test.



**Fig. 2.** Kaplan-Meier estimates of stent patency.

The addition of an antibiotic, norfloxacin, to ursodeoxycholic acid had initially demonstrated promising results in a trial by Barrioz et al.<sup>36</sup>: with respect to patency, 49 weeks (antibiotic and choleric treatment) versus 6 weeks (conservative treatment), and for median survival, 67 versus 18 weeks, respectively. However, in this trial, the characteristics of the patients in the two arms were not uniform, as there were more patients with cholangiocarcinoma in the drug group. Also, the limited small sample size (20 patients randomized) made the possibility of a type I error too great to ignore. Multiple subsequent studies have in fact failed to duplicate these results<sup>37–41</sup> while using a variety of protocols. These studies included another choleric agent, Rowachol,<sup>38</sup> and several antibiotics such as norfloxacin,<sup>36,41</sup> ofloxacin,<sup>37</sup> and ciprofloxacin.<sup>38–40</sup>



**Fig. 3.** Kaplan-Meier estimates of overall survival.

**Table 3.** SF-36 Quality of life questionnaire

| SF-36 Measure              | Mean Score | Placebo (n = 15) | Ciprofloxacin (n = 16) | P Value*     |
|----------------------------|------------|------------------|------------------------|--------------|
| Physical functioning       | Baseline   | 46.0             | 51.3                   | 0.784        |
|                            | Month 1    | 49.0             | 56.3                   |              |
|                            | Δ          | 3.00             | 5.07                   |              |
| Role physical              | Baseline   | 28.3             | 28.1                   | 0.898        |
|                            | Month 1    | 35.0             | 33.3                   |              |
|                            | Δ          | 6.67             | 5.00                   |              |
| Bodily pain                | Baseline   | 47.3             | 58.6                   | 0.811        |
|                            | Month 1    | 49.6             | 58.5                   |              |
|                            | Δ          | 2.33             | 0.00                   |              |
| General health             | Baseline   | 49.9             | 38.8                   | 0.747        |
|                            | Month 1    | 53.1             | 43.7                   |              |
|                            | Δ          | 3.17             | 4.92                   |              |
| Vitality                   | Baseline   | 46.3             | 42.8                   | 0.770        |
|                            | Month 1    | 35.7             | 34.1                   |              |
|                            | Δ          | -10.7            | -8.75                  |              |
| Social functioning         | Baseline   | 60.8             | 62.5                   | <b>0.031</b> |
|                            | Month 1    | 53.3             | 69.5                   |              |
|                            | Δ          | <b>-7.03</b>     | <b>7.50</b>            |              |
| Emotional role             | Baseline   | 44.4             | 33.3                   | 0.700        |
|                            | Month 1    | 54.4             | 45.6                   |              |
|                            | Δ          | 10.0             | 16.7                   |              |
| Mental health              | Baseline   | 53.3             | 53.3                   | 0.490        |
|                            | Month 1    | 56.3             | 53.8                   |              |
|                            | Δ          | 2.93             | 0.50                   |              |
| Physical component summary | Baseline   | 42.356           | 37.358                 | 0.892        |
|                            | Month 1    | 47.273           | 42.765                 |              |
|                            | Δ          | 4.917            | 5.406                  |              |
| Mental component summary   | Baseline   | 35.718           | 36.791                 | 0.898        |
|                            | Month 1    | 34.120           | 34.926                 |              |
|                            | Δ          | -1.599           | -1.866                 |              |

No significant difference between mean scores of the treatment and placebo groups at baseline by Student *t* test.

\*Student *t* test for separate variance (95% confidence interval, 1.46–27.60).

Numbers in bold indicate a statistically significant result.

Ciprofloxacin, a quinolone antibiotic, has excellent oral bioavailability, exhibits strong biliary penetration, and is bactericidal against bacterial flora commonly associated with cholangitis. A combination of ciprofloxacin and Rowachol did not find any benefit to preventing stent occlusion.<sup>38</sup> In a trial of ciprofloxacin alone versus placebo, no benefit in patency prolongation could be found.<sup>39</sup> On meta-analysis of these two trials examining ciprofloxacin, the pooled results of the two trials<sup>38,39,42</sup> did not demonstrate any advantage, but in each case, a type II error could not be excluded because of the small combined number of patients randomized (n = 106). No quality of life measurement has been reported previously.

Based on these studies, we derived the following trial strategy. First, we used an appropriate antibiotic before any biliary manipulation to sterilize the biliary system, thus possibly delaying early bacterial biofilm formation. All patients were thus given a large dose of

ciprofloxacin (750 mg), before the initial procedure and stent placement. Second, we monitored the incidence of cholangitis, in addition to stent blockage, and defined it pre-hoc, as a major end point. We thought this could represent a proxy measure of the clinical effectiveness of the antibiotics, although the primary outcome of our trial remained stent blockage. Third, an analysis was carried out of the effect of the antibiotic treatment on quality of life. The randomization scheme was stratified by center and, according to the location of the malignant obstruction, to minimize the likelihood of any possible sources of confounding.

We were unable to show a significant difference ( $P > 0.05$ ) in stent patency between the ciprofloxacin and placebo groups by log-rank analysis. This is partly explained by the observed duration of stent patency in the control group (92 days), which was much greater than anticipated. There may be a trend favoring the

treatment group beyond 200 days, but the number of patients surviving at this time is small and no conclusive statement is possible. The two previous trials<sup>38,39</sup> and a meta-analysis also did not show a significant difference in duration of stent patency.<sup>42</sup>

As with the previous trials, we were unable to reach the targeted sample size of 150 patients in both arms, despite the inclusion of multiple centers: although this study is the largest to date, it remains underpowered (40%) and is still not able to exclude the presence of a  $\beta$ -error.

We did observe a significant decrease in the incidence of cholangitis in patients receiving ciprofloxacin (23% versus 42% in the placebo,  $P = 0.047$ ). The fact that this benefit was not translated into prolonged stent patency may point to the multifactorial nature of stent occlusion.

The administration of prophylactic antibiotics had no effect on overall survival ( $P = 0.80$ ), and none had been expected since biliary drainage has never been shown to alter the progression of the cancer. Any survival advantage gained from a decreased incidence of cholangitis was thus minor in the face of terminal cancer, because an occluded stent can usually be successfully replaced.

Perhaps the most important patient-centered result of the trial relates to the analysis of quality of life, which was performed with a nonspecific, widely used score: the SF-36 health-related questionnaire. In a previous report based on 50 patients with advanced hepatobiliary cancer, we had already demonstrated that a successful decompression and improvement in the symptoms of biliary obstruction<sup>11</sup> were associated with improvement in the Social Functioning measure of the SF-36. This had been observed even though the physical and mental composite scores had not been sensitive to a change in biliary symptoms. Once again in this trial, there was no significant difference in the physical and mental composite scores and there was a significant benefit specific to the scale of Social Functioning (95% confidence interval, 1.46–27.60) favoring the ciprofloxacin group. This scale of the SF-36 is based on the patient's perception of their personal and public interactions. It can be hypothesized that a diminished level of acute or sub acute cholangitis may have contributed in making the treatment group patients more apt to feel comfortable socially. We understand, however, that this finding does not necessarily signify that the patients' overall quality of life was favorably affected.

The dismal prognosis of these patients, their rapidly deteriorating quality of life, and the aversion to long-term study follow-up will remain significant limitations to any future trials.

## CONCLUSION

There is insufficient evidence to show that prophylactic ciprofloxacin can prolong the duration of plastic biliary stent patency. The observed trends do suggest that ciprofloxacin can significantly decrease the incidence of cholangitis and result in improvements in certain aspects of quality of life.

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# Selective Portal Vein Clamping for Radiofrequency Ablation of Hepatocellular Carcinoma With Portal Vein Invasion

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Surgical resection provides potential cure for patients with hepatocellular carcinoma. Unfortunately, resection is suitable in only about 10–37% of patients because of the limited hepatic functional reserve from the underlying chronic liver disease in the majority of patients. Survival of patients with unresectable diseases, especially those with portal vein tumor invasion, remains very poor. Radiofrequency ablation (RFA) is a form of locoregional therapy that allows a selected group of previously inoperable patients to be treated. However, problems with RFA leading to induced portal vein thrombosis have been reported in the literature. Nevertheless, patients with portal vein tumor invasion may be considered for radiofrequency tumor ablation to improve survival. We report the case of a patient with hepatocellular carcinoma with left portal vein invasion. Complete tumor ablation was achieved after RFA with left portal vein clamping. He remained disease free both radiologically and biochemically 6 months after the operation. (*J GASTROINTEST SURG* 2005;9:489–493) © 2005 The Society for Surgery of the Alimentary Tract

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KEY WORDS: Hepatocellular carcinoma, portal vein invasion, radiofrequency ablation

Hepatocellular carcinoma (HCC) is the leading cause of death among patients with cirrhosis, and its incidence has increased over the past decade.<sup>1</sup> Despite the significant progress in diagnostic techniques and therapeutic methods, the prognosis for HCC remains poor. Surgical resection is suitable in only about 10–37% of patients because of the limited hepatic functional reserve from the underlying chronic liver disease in the majority of patients.<sup>2–4</sup> The median survival period for unresectable HCC is only a few months. The survival rate for patients with advanced HCC with portal vein tumor thrombosis is even worse.<sup>5–7</sup> It has been reported that patients with diffuse HCC complicated with portal vein tumor thrombosis survived for only 1–2 months if effective treatment could not be delivered.<sup>8</sup>

Advances in technology have enabled a selected group of patients, who were previously diagnosed as having unresectable diseases, to receive surgical treatments with local ablative procedures. Among the locoregional therapies that have been reported for

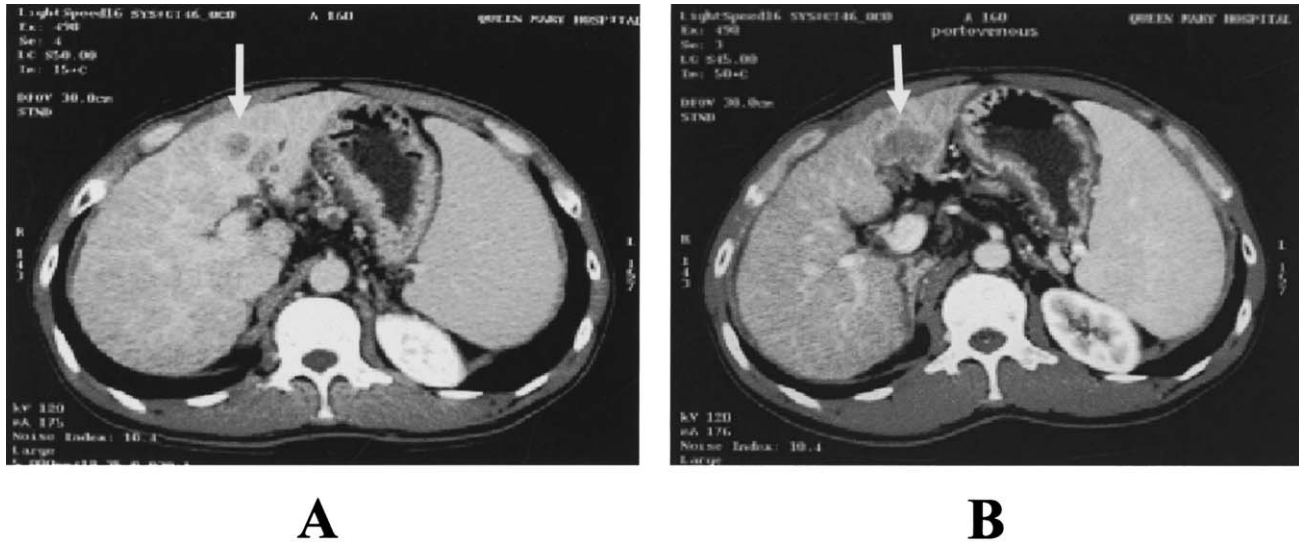
unresectable HCC, radiofrequency ablation (RFA) is the most promising one. It has been shown to be a safe, effective, predictable, and repeatable procedure with low morbidity (0–12%) and mortality (0–3%) rates.<sup>9–17</sup> However, the completeness of tumor ablation, especially when the tumor is located close to the major vasculature, is always in doubt as a result of the “heat-sink” effect. Tumor cells in close proximity to major vessels are protected from the radiofrequency by the cooling effect of the blood flow. Therefore, to ablate the tumor thrombus inside a major vessel is even more difficult, if not impossible.

We report the case of a patient with HCC with portal vein tumor thrombosis that was treated effectively with RFA of the tumor after portal vein clamping.

## CASE REPORT

The patient was a 45-year-old Chinese man with a history of hepatitis B virus-related Child’s B liver

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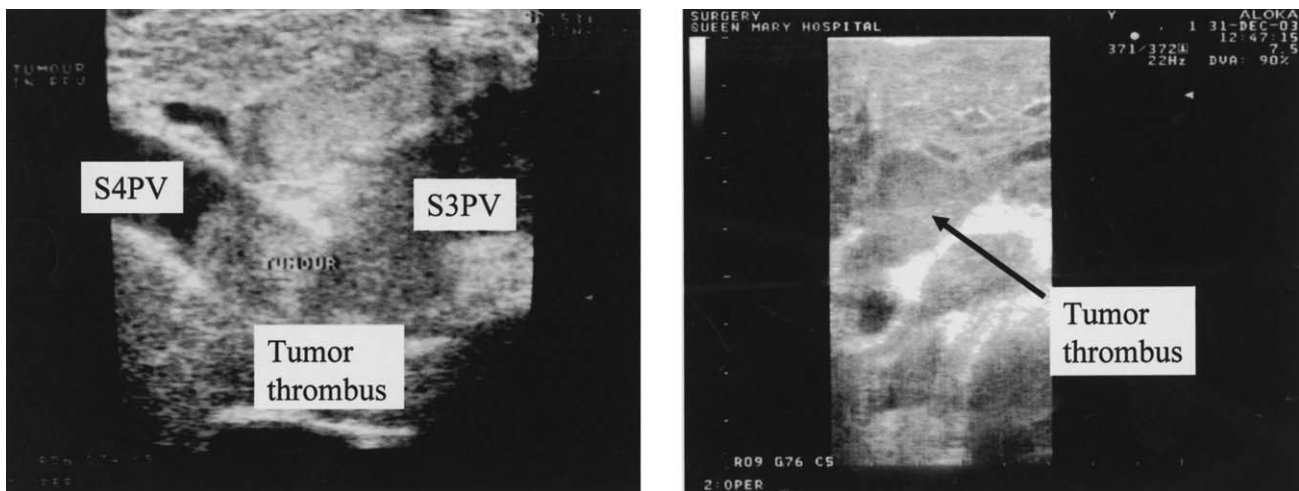


**Fig. 1.** Computed tomography scan of the abdomen showing a contrast-enhancing lesion in the arterial phase (A) (*arrow*) and early washout in the portovenous phase (B) (*arrow*).

cirrhosis. He was referred to us from the physicians for consideration for liver transplantation due to deteriorating liver function with repeated esophageal variceal bleeding and ascites. The patient neglected his illness and did not attend the outpatient clinic until 1 year after the initial referral, when he developed symptoms of right upper quadrant abdominal pain and increasing malaise. His serum  $\alpha$ -fetoprotein concentration was increased to 2137 ng/ml, and a computed tomography scan of the abdomen showed an HCC measuring  $3.5 \times 2.7$  cm in diameter at segment III of the liver in close proximity to the umbilical part of the left portal vein (Fig. 1). He had a normal hemoglobin concentration and white blood

cell count but had thrombocytopenia ( $45 \times 10^9/L$ ). His clotting profile was deranged with prolongation of prothrombin time (international standardized ratio, 1.4). Indocyanine green clearance test was also performed to estimate the functional liver reserve, and the retention value was 14.4% at 15 minutes. Because of the lack of cadaveric liver donors and because no volunteer live donor was available for the patient, a left lateral segmentectomy was offered to him.

Intraoperatively, he was found to have a large spleen plus a small shrunken liver with significant macronodular cirrhosis. The tumor was situated at segment III and measured  $3.5 \times 4$  cm in diameter.



**Fig. 2.** Intraoperative ultrasonography showing a tumor thrombus in the branch of left portal vein. S4PV = segment 4 portal vein; S3PV = segment 3 portal vein.

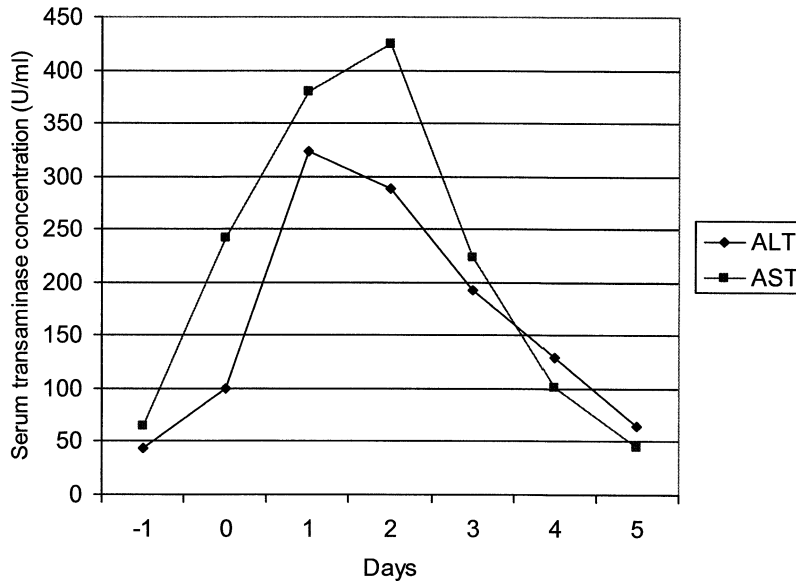
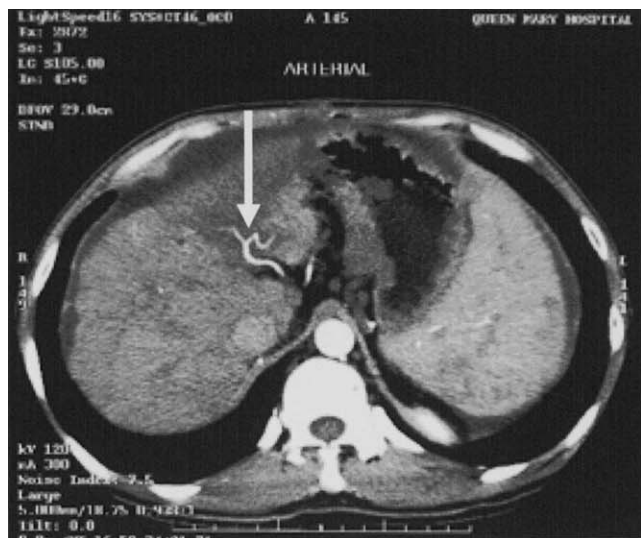


Fig. 3. Trend of serum transaminase concentration before and after the operation. ALT = alanine aminotransferase; AST = aspartate aminotransferase.

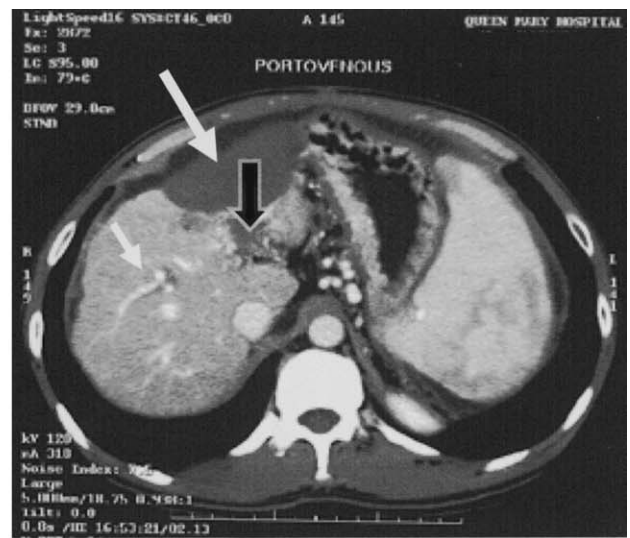
Intraoperative ultrasonography showed tumor invasion and thrombus inside the umbilical part of the left portal vein with Doppler flow signal indicating partial blockage (Fig. 2). As a left lateral segmentectomy was deemed inadequate for tumor control and a left hepatectomy was needed, RFA was performed instead.

To completely ablate the tumor and the portal vein tumor thrombus, RFA with left portal vein

clamping was performed. The origin of the left main portal vein was dissected and clamped. RFA with the use of the Cool-tip RF System (Radionics, Burlington, MA) was performed. The tumor was ablated with a cluster probe under ultrasonographic guidance for a total of 26 minutes. The RFA cluster probe was inserted into the center of the tumor, which was in close proximity to the portal vein. The umbilical part of the left portal vein was not punctured so

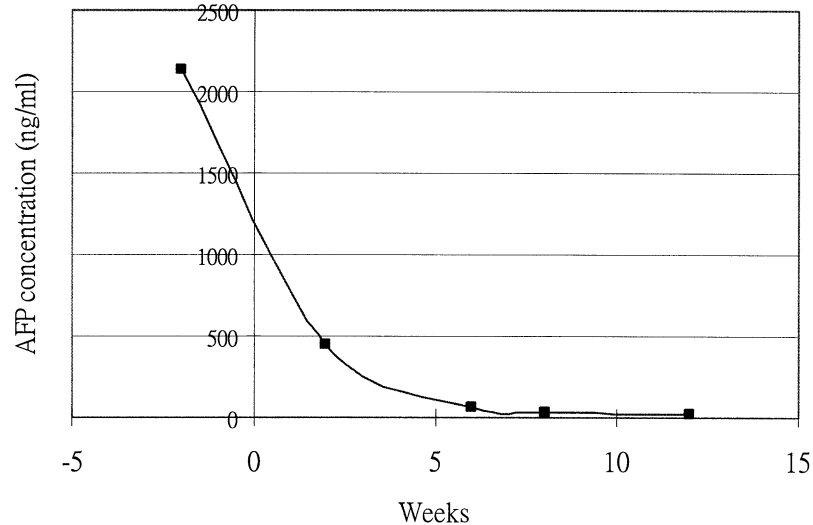


A



B

Fig. 4. Computed tomography scan of the liver 3 months after radiofrequency ablation showing (A) the patent left hepatic artery (arrow) and (B) the patent right portal vein (small arrow) and complete tumor ablation (large arrow) including the tumor thrombus (hollow arrow).



**Fig. 5.** Schematic diagram showing the trend of serum  $\alpha$ -fetoprotein (AFP) concentration before and after the operation.

as to not dislodge the tumor cell distally. In addition, the cystic duct was cannulated with a catheter for bile duct cooling using 4°C normal saline to prevent bile duct injury.<sup>18</sup>

The postoperative course was uneventful. Serum transaminase levels were found to be elevated initially (Fig. 3) but returned to their preoperative levels 5 days after the procedure. The patient was discharged home on day 7. Computed tomography scanning of the abdomen was performed 1 and 3 months postoperatively. Both studies showed no evidence of recurrence or residual tumor radiologically (Fig. 4). The serum  $\alpha$ -fetoprotein concentration dropped from more than 2000 ng/ml preoperatively to 4 ng/ml 3 months after the RFA (Fig. 5). The patient was disease free clinically, biochemically, and radiologically 6 months after the operation.

## DISCUSSION

RFA is an effective hyperthermic treatment for malignant liver tumors. The development of expandable and cooled-tip electrodes has enabled lesions of larger size to be effectively treated by RFA. Hepatic inflow occlusion using the Pringle maneuver has been used to increase the volume of RFA ablated tissue in animal studies.<sup>19-22</sup> The elimination of hepatic blood flow reduces the “heat-sink” effect against RFA. However, an animal study from our institution showed that this may increase the chance of delayed portal vein thrombosis.<sup>23</sup>

In our patient, tumor thrombus was unexpectedly found within the branches of the left portal vein extending into the left main branch. A left hepatectomy

was not feasible in view of the severe macronodular cirrhosis. Therefore, we proceeded to treat the lesion with local RFA. With portal venous blood flow within the left main portal vein, we had doubts about the effectiveness of RFA. A Pringle maneuver was contemplated, but taking into account the poor liver reserve of the patient, we opted to place a clamp on the left main portal vein to reduce the “heat-sink” effect on the tumor. This also allowed maximal penetration of the RFA thermoablative effect on the portal vein tumor thrombus in an attempt to achieve total ablation of the tumor bulk. The portal vein was not punctured directly to minimize the risk of dislodgment of the tumor thrombus.

To prove the success of RFA for this patient, a longer-term follow-up will be required to document any tumor recurrence or development of any delayed complications. The follow-up of our patient to date showed that RFA of portal vein tumor thrombus appeared to be an effective method for treating advanced HCC with portal vein invasion.

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# Xanthogranulomatous Cholecystitis in Laparoscopic Surgery

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Xanthogranulomatous cholecystitis (XGC) is one presentation of cholecystitis and can be a cause of difficulty in cholecystectomy. We reviewed the clinical files of 12,426 patients who had undergone cholecystectomy. In this group, there were 182 cases of XGC, and 41 of these patients had undergone laparoscopic surgery. Patients with XGC represented 1.46% of the cholecystectomies that were performed. Of the 41 patients who underwent laparoscopic surgery, 27 were men (66%) and 14 were women (34%) (average age, 52 years). A total of 36 patients (88%) presented with a chronic condition. XGC was found to be associated with lithiasis in 85%, with jaundice in 22%, and with cancer in 2.4% (one patient). A total of 33 patients (80%) required conversion to open surgery, because of technical difficulties; of these patients, 64% underwent partial cholecystectomy. We conclude that XGC creates difficulty at laparoscopy and therefore any preoperative suspicion of XGC should cause the clinician to consider open cholecystectomy. (*J GASTROINTEST SURG* 2005;9:494–497) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Cholecystitis, cholelithiasis, chronic cholecystitis, jaundice, cholecystectomy

Xanthogranulomatous cholecystitis (XGC) is a chronic inflammatory disease of the gallbladder.<sup>1,2</sup> The principal characteristic is thickening of the gallbladder wall with a tendency to adhere to neighboring organs, even leading to fistula formation.<sup>3,4</sup> The clinical presentation of XGC is similar to that of chronic or acute cholecystitis, and the findings on the imaging studies, (ultrasonography and abdominal computed tomography [CT]) may be mistaken for cancer.<sup>5,6</sup> Furthermore, the condition has been related to difficult cholecystectomy.<sup>2,7</sup>

The aim of the current study was to share the experience gained at a teaching hospital in the surgical treatment of XGC by means of laparoscopic cholecystectomy.

## PATIENTS AND METHODS

During the past 15 years, we reviewed the clinical files of 12,426 patients who had undergone cholecystectomy. This included 182 cases with a histopathologic diagnosis of XGC, arrived at according to the following criteria: focal or diffuse mural affectation with the presence of histiocytes, cholesterol deposits,

and lipids; giant multinucleated cells of the type that react to foreign bodies or of the Touton type; cells that phagocytize lipids and bile pigments, forming xanthomatous cells; and the presence of cells with acute and chronic inflammation. As of July 1996, laparoscopic surgery was performed on 41 patients, and this approach formed the basis for this study.

We analyzed the clinical characteristics, imaging study findings, surgical findings, incidence of conversion to open surgery, and postoperative evolution. Parametric data were evaluated by T Student *t* test analysis.

This review was approved by the Board Clinical Research Center at the General Hospital “Gabriel Mancera.”

## RESULTS

Of the 12,426 cholecystectomy cases reviewed, 182 were found to have a diagnosis of XGC (1.46%). Of these 182, 41 patients had undergone laparoscopic surgery (27 men [66%] and 14 women [34%]; male-to-female ratio, 2:1; average age, 52 years; age range, 35–75 years). Of the 41 patients, 13 (32%) presented

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with some form of concomitant illness (Table 1). Chronic symptoms of the disease were present in 88% of the cases, and acute symptoms were present in the remaining 12% (Table 2).

Of the 41 patients studied for XGC treated by means of laparoscopic cholecystectomy, 35 (85%) had stones in the gallbladder, indicating that the remaining 15% of cases were associated with alithiasic cholecystitis. Of the patients with alithiasic cholecystitis, 83% presented in an acute state, and the remaining 17% had chronic symptoms.

Of the 41 cases, 9 patients (22%) presented with jaundice. All patients undergo endoscopic cholangiography before cholecystectomy—the cause of the jaundice was choledolithiasis in only 3 cases (33%), calculus were removed endoscopically; the remaining patients (67%) developed jaundice as secondary to extrinsic compression of the gallbladder on the bile duct (Mirizzi syndrome).

Table 3 summarizes the findings on ultrasonography and abdominal CT, which demonstrate that in the case of five patients (12%), diffuse thickening of the wall noted on ultrasonography aroused the suspicion of gallbladder carcinoma. CT was carried out on all of these patients, showing thickening of the gallbladder wall, but without any evidence of hepatic infiltration or of metastases. One of these patients was found after cholecystectomy to have moderately differentiated adenocarcinoma, not associated with XGC.

Of the 41 cases reviewed, for 33 (80%) great technical difficulty was reported in carrying out the laparoscopic cholecystectomy, resulting in the need to convert to an open procedure. In the eight patients in whom minimally invasive surgery was possible, total cholecystectomy was performed. However, in 21 (64%) of those 33 patients whose procedure had to be converted to open surgery, the cholecystectomy performed was only partial; the remaining 12 patients underwent total extirpation of the gallbladder.

**Table 1.** Associated diseases in 41 patients with xanthogranulomatous cholecystitis undergoing laparoscopic cholecystectomy

| Disease                                    | No. (%) |
|--|---------|
| Arterial hypertension                      | 5 (12)  |
| Diabetes mellitus type 2                   | 4 (10)  |
| Hypertension plus diabetes mellitus type 2 | 2 (5)   |
| Ischemic cardiopathy                       | 1 (2)   |
| Obesity                                    | 1 (2)   |
| Total                                      | 13 (32) |

**Table 2.** Characteristics and clinical presentation of 41 patients with xanthogranulomatous cholecystitis

| Variable                          | No. (%)  |
|-----------------------------------|----------|
| Acute cholecystitis               | 27 (22)  |
| Chronic cholecystitis             | 134 (88) |
| Pain                              | 39 (95)  |
| Obstructive jaundice present      | 9 (22)   |
| Previous jaundice                 | 2 (5)    |
| Fever/pain/jaundice (cholangitis) | 1 (2)    |
| Palpable mass                     | 2 (5)    |

Postoperative complications are summarized in (Table 4); there were no deaths related to this condition. Statistically significant differences were present if all cases of complications were taken into account.

## DISCUSSION

XGC is a rare condition, representing about 0.7<sup>8</sup> to 13.2%<sup>9</sup> of all cases of cholecystitis. This review demonstrated an incidence of 1.46% among all of the cholecystectomies carried out during a 15-year period at a teaching hospital.

XGC is the cause of an acute or a chronic inflammatory process of the gallbladder, associated with the introduction of bile pigments and cholesterol into the gallbladder wall. The work carried out by Mori and collaborators<sup>10</sup> confirmed the presence of bacteria in the bile that are phagocytized by macrophages, thus playing a significant associated role in the genesis of this intense inflammatory process.

The clinical presentation of this condition is reported elsewhere as affecting men and women equally.<sup>7</sup> However, in this review, XGC presented predominantly in men, and we cannot account for this observation. The average age for presentation

**Table 3.** Radiological findings in 41 patients with xanthogranulomatous cholecystitis undergoing laparoscopic cholecystectomy

|   | Ultrasonography,<br>No. (%) | Abdominal<br>computed<br>tomography,<br>No. (%) |
|---|-----------------------------|---|
| Thickening of the wall  | 41 (100)                    | 5 (100)   |
| Cholelithiasis  | 33 (80)                     | 5 (100)   |
| Suspicion of carcinoma  | 5 (12)                      | 3 (7)   |
| Distention of the<br>gallbladder with<br>perivesicular liquid | 6 (15)                      | Not evaluated                                   |
| Alithiasic cholecystitis                                      | 4 (10)                      | None  |

**Table 4.** Postoperative complications in patients with xanthogranulomatous cholecystitis undergoing cholecystectomy

| Complication             | Total cholecystectomy (n = 8) | Partial cholecystectomy (n = 21) | Significance |
|--------------------------|-------------------------------|----------------------------------|--------------|
| Surgical wound infection | 2 (10%)                       | 2 (9.5%)                         | NS           |
| Controlled bile fistula  | 1 (5%)                        | 2 (9.5%)                         | NS           |
| Biliperitoneum           | 0                             | 2 (9.5%)*                        | NS           |
| Hemoperitoneum           | 0                             | 0                                | NS           |
| Bile tract lesion        | 0                             | 0                                | NS           |
| Death                    | None                          | None                             | NS           |
| Total                    | 3 (15%)                       | 6 (28.5%)                        | <0.05        |

\*Required reoperation.

was 52 years, similar to that reported in other series.<sup>7,11</sup> This suggests that time to evolve must be one of the significant factors in the development of the disease. The concomitant illnesses given in Table 1 demonstrated no direct relationship to XGC and illustrate only the type of population studied.

XGC presents mainly in chronic form, principally in association with the presence of calculi; this has even been suggested as part of the genesis of the condition.<sup>7,12</sup> The present study noted the presence of calculi in only 85% of the cases, which leads to the conclusion that the presence of calculi in the gallbladder is only an associated condition and not the cause of the inflammatory process. This study showed that six patients (15%) presented without calculi in the gallbladder (alithiasic cholecystitis), and these cases mainly presented with an acute picture, predominantly related to jaundice. The jaundice was due to compression of the bile tract occasioned by the intense inflammatory process in the gallbladder. This leads to the conclusion that almost 70% of XGC cases are associated with Mirizzi syndrome.

The radiologic findings given in Table 3 highlight both focal and diffuse thickening of the gallbladder wall. There was radiologic suspicion of carcinoma in 12% of the cases, but this was corroborated in only one case (2%). Diffuse thickening of the gallbladder wall suggested the possibility of cancer, and this fact is mentioned in the work of Balague et al.<sup>13</sup> and Guermazi et al.<sup>(14)</sup>

The intense chronic inflammatory process that characterizes XGC has caused it to be related to fistulas in neighboring organs.<sup>3,4</sup> This complication was not observed among the 41 patients who had undergone laparoscopic surgery, but it was noted in two of the open procedure cases.

After the option of laparoscopic cholecystectomy became part of hospital routine, the procedure had to be converted into an open procedure in 33 cases (80%) due to difficulty in dissecting a gallbladder with adherent organs or due to the suspicion of carcinoma.

This situation signifies that both XGC and carcinoma cause problems when electing to perform laparoscopic cholecystectomy. Histologic corroboration of the lesion during surgery is necessary, in the case of malignancy, to perform optimum surgery from the oncologic point of view.

The patients with XGC experienced a greater incidence of complications.<sup>2,15</sup> Table 4 shows that the complications occurred more readily among patients undergoing partial cholecystectomy. The complications are thus related more to the technical difficulty of gallbladder extirpation and the clinical condition of the patient than to the disease itself. In relating total or partial cholecystectomy with incidence of postoperative complications, no statistically significant difference was encountered, but there was a significant difference if all complications were taken into account.

XGC has been linked to adenocarcinoma, and this is thought to be due to structural changes in the cells brought on by the chronic inflammatory process.<sup>16</sup> In this review, however, no relationship was demonstrated; the only patient diagnosed with cancer did not have any xanthomatous cells in the gallbladder.

Given that there were no deaths related to this disease, XGC cannot be considered a direct cause of increased mortality.

## CONCLUSIONS

XGC is a rare condition of acute or chronic inflammation of the gallbladder, associated with a high incidence of conversion to open cholecystectomy. Any preoperative suspicion should therefore lead to consideration of open cholecystectomy as a possible means of approach. To ensure the performance of optimum surgery, transoperative study is recommended to preclude malignancy.

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# Gastric Cancer Developing in the Stomach After Pylorus-Preserving Pancreaticoduodenectomy With Pancreaticogastrostomy: Case Report and Review of the Literature

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A 59-year-old woman underwent surgery for uterine corpus cancer in March 1998. She also underwent pylorus-preserving pancreaticoduodenectomy with pancreaticogastrostomy for common bile duct cancer in November 1998. She was followed up at our outpatient clinic after pylorus-preserving pancreaticoduodenectomy. In November 2002, her carcinoembryonic antigen level became elevated and abdominal ultrasound revealed a huge tumor. Gastroscopy showed a Borrmann type 3 tumor at the anastomosis of the pancreaticogastrostomy, and a biopsy revealed adenocarcinoma. With a diagnosis of advanced gastric cancer, she underwent total gastrectomy, splenectomy, and residual pancreatectomy in January 2003. The pathologic findings revealed that the gastric cancer was separated from the pancreas, suggesting that the cancer had developed from the stomach. The present report describes a rare case of gastric cancer that had developed at the anastomosis of a pancreaticogastrostomy. (*J GASTROINTEST SURG* 2005;9:498–502) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Pylorus-preserving pancreaticoduodenectomy, pancreaticogastrostomy, gastric cancer

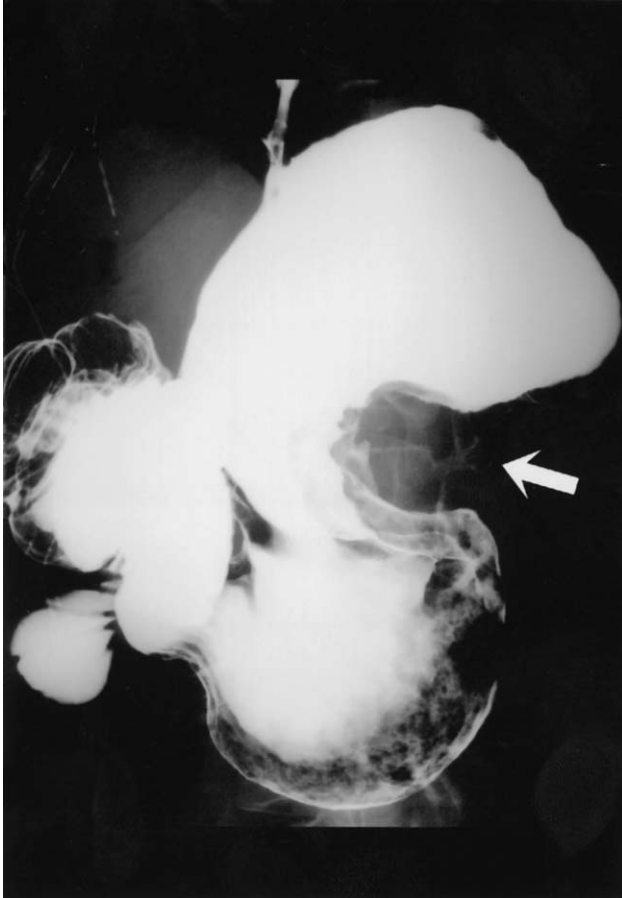
Pancreaticoduodenectomy (PD) is one of the surgical procedures used for treating patients with neoplasms of the peripancreatic head area. In this procedure, the remnant pancreas is usually anastomosed to either the jejunum or the stomach. When a pylorus-preserving pancreaticoduodenectomy (PpPD) is performed, pancreaticogastrostomy (PG) is also an alternative for draining the pancreatic juice,<sup>1,2</sup> but its influence on the gastric mucosa remains unclarified. This report describes a rare case in which gastric cancer developed at the anastomosis of the PG.

## CASE REPORT

A 59-year-old woman underwent abdominal total hysterectomy and adnexectomy because of uterine corpus cancer in March 1998. The histologic diagnosis was endometrioid adenocarcinoma with the clinical stage of stage IA (pT1a pN0 pM0) according to

the TMN classification proposed by the International Union Against Cancer (UICC).<sup>3</sup> She then underwent PpPD with PG for common bile duct cancer in November 1998. The histologic diagnosis was moderately differentiated tubular adenocarcinoma of the common bile duct invading to the muscularis propria. There were no malignant cells at the surgical margin. The clinical stage was stage IA (pT1 pN0 pM0). The remnant pancreas was anastomosed to the posterior wall of the stomach, and the pancreatic juice was drained into the gastric cavity via a stent tube. The patient was followed up at our outpatient clinic after PpPD. At the end of November 2002, her carcinoembryonic antigen level was found to be elevated to 24.7 ng/ml. Abdominal ultrasound revealed a tumor at the epigastric area. An upper gastrointestinal series showed a tumor at the site of the PG (Fig. 1). Abdominal computed tomography revealed a massive enhanced tumor in the stomach without any pancreatic

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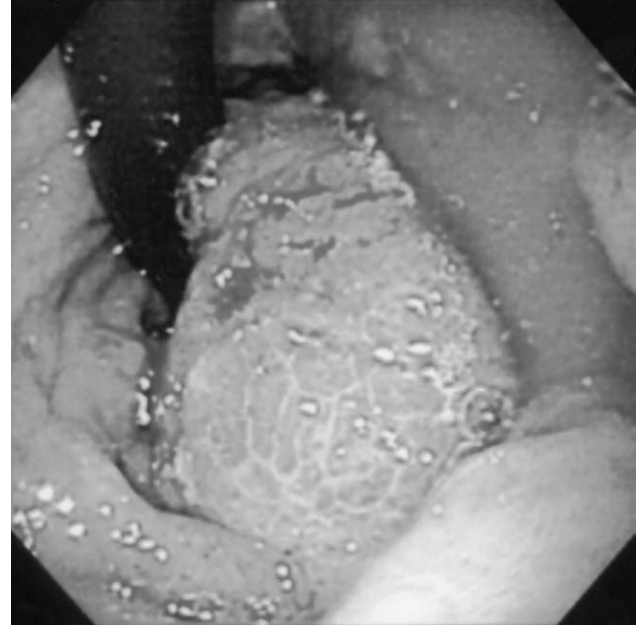


**Fig. 1.** An upper gastrointestinal series showing a tumor at the site of pancreaticogastrostomy (→) in December 2002.

duct dilatation (Fig. 2). Gastroscopy showed a Borrmann type 3 tumor at the site of the PG (Fig. 3). Biopsy revealed features consistent with a diagnosis of moderately differentiated tubular adenocarcinoma. Abdominal angiography revealed a tumor blush at



**Fig. 2.** Abdominal computed tomography scan showing an enhanced tumor (→) without any pancreatic duct dilatation in the stomach in December 2002.



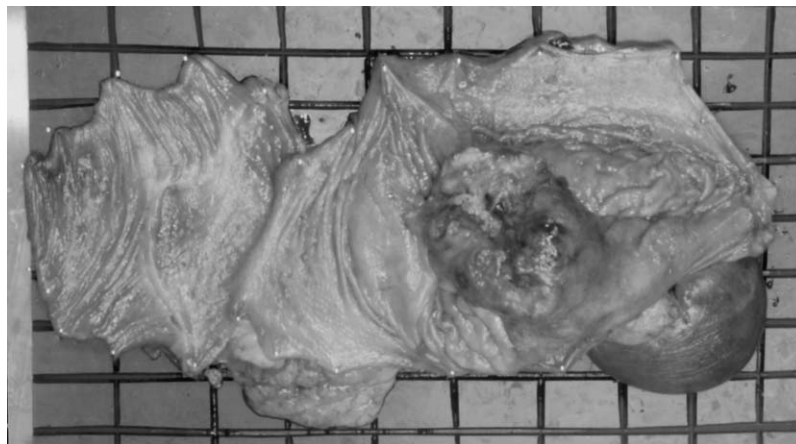
**Fig. 3.** Gastroscopy showing a Borrmann type 3 tumor at the site of the pancreaticogastrostomy in December 2002.

the body of the stomach. With a diagnosis of advanced gastric cancer developing at the site of PG, the patient underwent total gastrectomy, splenectomy, and residual pancreatectomy in January 2003. Macroscopically, an irregularly shaped tumor with an ulcer was found at the curvature ventriculi major. The tumor was 74 mm × 58 mm (Figs. 4, 5). The results of immunohistochemical study were summarized in Table 1. The cancer cells were positive for CK7, Muc5AC, and Muc6, but they were negative for AAT, indicating that the tumor was gastric cancer. The histologic diagnosis was moderately differentiated tubular adenocarcinoma of the stomach with the clinical stage of stage 1B (pT2b pN0 pM0) (Fig. 6). After surgery, her blood sugar level was controlled with insulin, and she was discharged in February 2003.

In August 2003, the patient was admitted to our department because of appetite loss and obstructive jaundice caused by the hepatic hilar enlarged lymph nodes. She underwent percutaneous transhepatic biliary drainage and radiotherapy at a total dose of 50 Gy. She improved and was discharged in October 2003. However, her condition deteriorated gradually and she died of cancerous pancreatitis in December 2003.

## DISCUSSION

A nonphysiologic condition whereby pancreatic juice is excreted into the gastric cavity is created when



**Fig. 4.** An irregularly shaped tumor with an ulcer was found at the curvature ventriculi major.

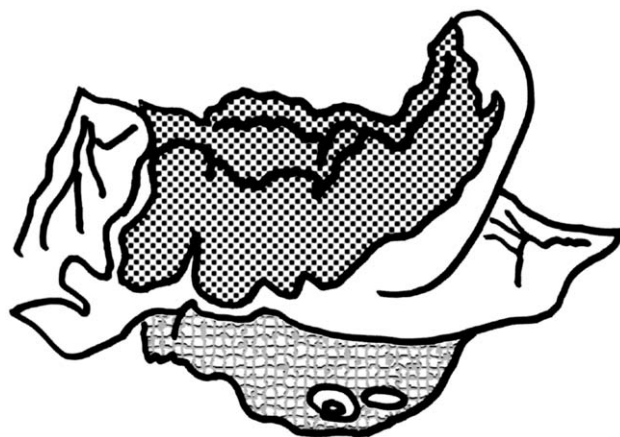
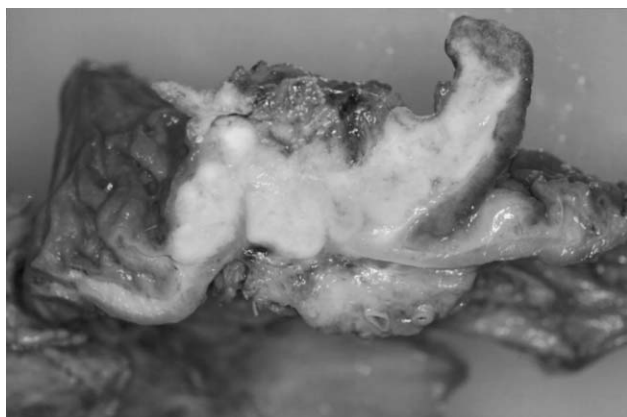
the pancreas is anastomosed to the stomach for pancreatic transplantation or after PD. Although this condition is considered to neutralize gastric acids, it has not been clarified how the directly excreted pancreatic juice damages the gastric mucosa.

Orthotopic pancreatic transplantation, in which the splenic vein is anastomosed to the portal venous system and the pancreatic juice is excreted into the stomach, was first described by Calne in 1984.<sup>4</sup> Since then, however, there have been no reports of the development of gastric cancer following this type of pancreas transplantation.

Including the present case, there have been six cases reported<sup>5-9</sup> in which gastric cancer developed after PD with PG (Table 2). All the patients underwent PpPD and were reported from Japan. Among these cases, the current report is the first to describe gastric cancer developing at the anastomosis of the

PG. The tumor was confirmed immunohistochemically to be gastric cancer.

The causal relationship between excretion of pancreatic juice into the stomach and the development of gastric cancer has not been clarified. Mason and colleagues<sup>10,11</sup> reported that duodenogastric reflux induces gastric cancer in rats. Schlag et al.<sup>12</sup> hypothesized that cytotoxic bile and pancreatoduodenal juice make gastric glands atrophic and increase the pH in the stomach. This pH elevation increases the number of bacteria such as *Escherichia coli*, which reduce dietary nitrate to nitrite and produce nitrosamine, a carcinogen.<sup>12</sup> Furthermore, in patients with anomalous junction of the pancreaticobiliary ductal system, a mixture of bile and refluxed pancreatic juice is considered to induce biliary cancers with a high incidence.<sup>13</sup> It can be speculated that the same phenomenon occurs in the stomach after PpPD with PG,



**Fig. 5.** **A,** The cut surface of the tumor showing that the tumor originated from the stomach. **B,** Distribution of gastric cancer (checked area at the top) and the pancreas (textured area at the bottom) in the cut surface shown in **A**.



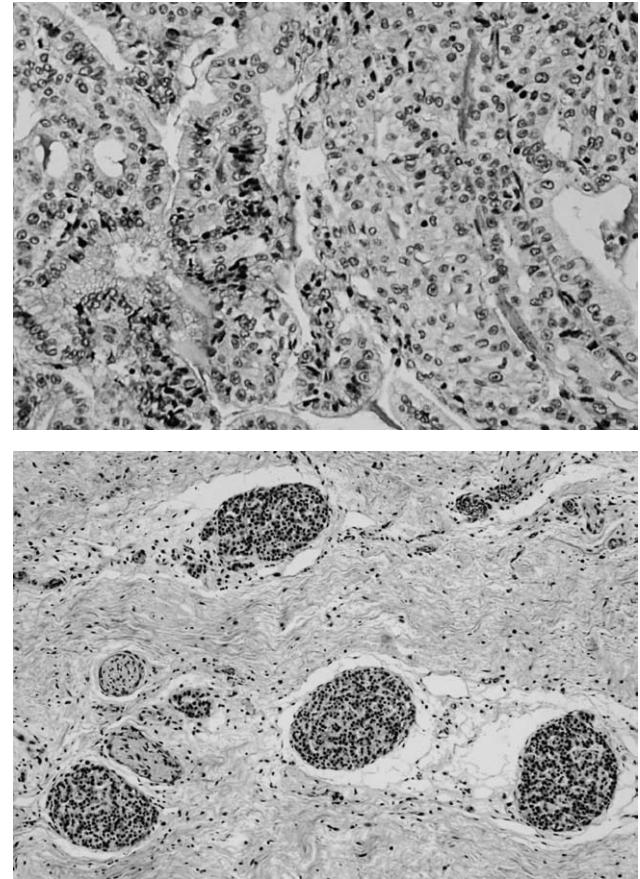
**Table 1.** Immunohistochemical stains

|            | CK7 | CK20 | Muc2 | Muc5AC | Muc6 | CD10 | AAT |
|------------|-----|------|------|--------|------|------|-----|
| Cancer     | ++  | -    | -    | ++     | +    | -    | -   |
| Langerhans | -   | -    | -    | -      | -    | -    | -   |
| Gastric    | +   | +    | -    | ++     | +    | +    | -   |

CK7 = cytokeratin7; CK20 = cytokeratin20; Muc2 = Muc-2 glycoprotein; Muc5AC = Muc-5AC glycoprotein; Muc6 = Muc-6 glycoprotein; CD10 = common acute lymphoblastic leukemia antigen (CALLA); AAT =  $\alpha_1$ -antitrypsin; cancer = cancer cell; Langerhans = Langerhans islet of pancreas; gastric = gastric mucosa.

possibly contributing to the development of gastric cancer.

The interval until the development of gastric cancer differed among the patients, with a median time of 47.6 months (range, 21–70 months). In our patient, the cancer was found 48 months after surgery. This suggests that long-term follow-up is necessary for patients with PG, even if the original diseases are benign. At our department, we try to perform follow-up gastroscopy once per year for 5 years in such patients. Once gastric cancer was found, the stomach was resected partially or totally according to the location and depth of the tumor. Four of the six patients had early gastric cancer, whereas the remaining two had advanced cancer. The five cases reported to date did not require resection of the remaining pancreas. In our patient, an advanced carcinoma was found at the site of the PG, requiring total gastrectomy with resection of the remaining pancreas and spleen.



**Fig. 6.** **A**, Pathologic finding of gastric cancer, diagnosed as moderately differentiated tubular adenocarcinoma. **B**, Pathologic findings for the pancreas. The pancreatic tissue was atrophic without any sign of malignancy.

**Table 2.** Reported cases of gastric carcinoma after pylorus-preserving pancreatoduodenectomy with pancreaticogastrostomy in Japan

| Year                | Patient age (yr)-gender | First Diagnosis                   | Second Diagnosis: surgical procedure  | Period (mo) | Prognosis (after second operation) |
|---------------------|-------------------------|-----------------------------------|---|-------------|------------------------------------|
| 1995 <sup>5</sup>   | 68 M                    | Pancreatic mucinous cyst adenoma  | Early gastric carcinoma: mucosal resection  | 49          | Alive (1 yr)                       |
| 1996 <sup>6</sup>   | 65 F                    | Chronic pancreatitis              | Early gastric carcinoma: wedge resection  | 21          | Alive (1 yr 4 mo)                  |
| 2001 <sup>7</sup>   | Not stated              | Not stated                        | Early gastric carcinoma: not stated   | Not stated  | Not stated                         |
| 2001 <sup>8</sup>   | 55 F                    | Carcinoma of the papilla of Vater | Advanced gastric carcinoma: distal gastrectomy  | 70          | Dead* (1 yr 10 mo)                 |
| 2002 <sup>9</sup>   | 72 M                    | Pancreatic carcinoma              | Early gastric carcinoma: distal gastrectomy   | 50          | Alive (3 yr 3 mo)                  |
| 2004 (present case) | 59 F                    | Carcinoma of the common bile duct | Advanced gastric carcinoma: total gastrectomy, splenectomy, and residual pancreatectomy | 48          | Dead* (10 mo)                      |

Period = period from first diagnosis to second diagnosis; prognosis = period of observation after second operation.

\*Patients 4 and 6 both died due to recurrence.

Although it is still unknown how the original diseases, which had required PpPD, influenced the prognosis of the patients, it appeared to depend on the advancement of gastric cancer. Three of the six patients with early gastric cancer were alive at the time of writing, whereas two with advanced gastric cancer, including our patient, died due to recurrence with cancerous peritonitis. Although our patient had bile duct cancer, her prognosis appeared to be determined by the advanced gastric cancer.

In summary, although the causal relationship between PG and the development of gastric cancer remains uncertain, patients who have undergone PD with PG should be followed up carefully, regardless of whether their original disease is benign or malignant, so that a gastric cancer is not overlooked.

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# Resection of the Celiac Axis for Invasive Pancreatic Cancer

*Martin A. Makary, M.D., M.P.H., Elliot K. Fishman, M.D., John L. Cameron, M.D.*

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Pancreatic cancer arising in the neck or body of the gland frequently presents at a more advanced stage compared with tumors arising in the pancreatic head. Vascular invasion into the celiac axis is a common contraindication to surgical resection. We report an en bloc pancreatectomy, splenectomy, and total gastrectomy with resection of the celiac axis for a pancreatic body adenocarcinoma invading the celiac axis and posterior stomach. Collateral blood flow to the liver via the gastroduodenal artery was initially identified on preoperative computed tomography (CT) imaging and confirmed intraoperatively with vascular testing before resection. One of 14 regional lymph nodes was positive for malignancy, and surgical margins were free of tumor. The patient's postoperative course was unremarkable. En bloc resection of the celiac axis and hepatic artery may be safely performed in select patients with localized pancreatic cancer invading these vessels. (*J GASTROINTEST SURG* 2005;9:503–507) © 2005 The Society for Surgery of the Alimentary Tract

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KEY WORDS: Pancreatic cancer, distal pancreatectomy, celiac axis, common hepatic artery

Local invasion of pancreatic cancer into vascular structures frequently precludes surgical resection. Vascular invasion into the celiac axis is a common occurrence in tumors arising in the neck or body of the gland. We describe a complete en bloc distal pancreatectomy, splenectomy, and total gastrectomy with resection of the celiac axis for a pancreatic body cancer invading the celiac axis and posterior stomach. Preoperative three-dimensional computed tomography (CT) imaging and intraoperative vascular testing were performed to confirm sufficient collateral blood flow to the liver before resection.

## CASE REPORT

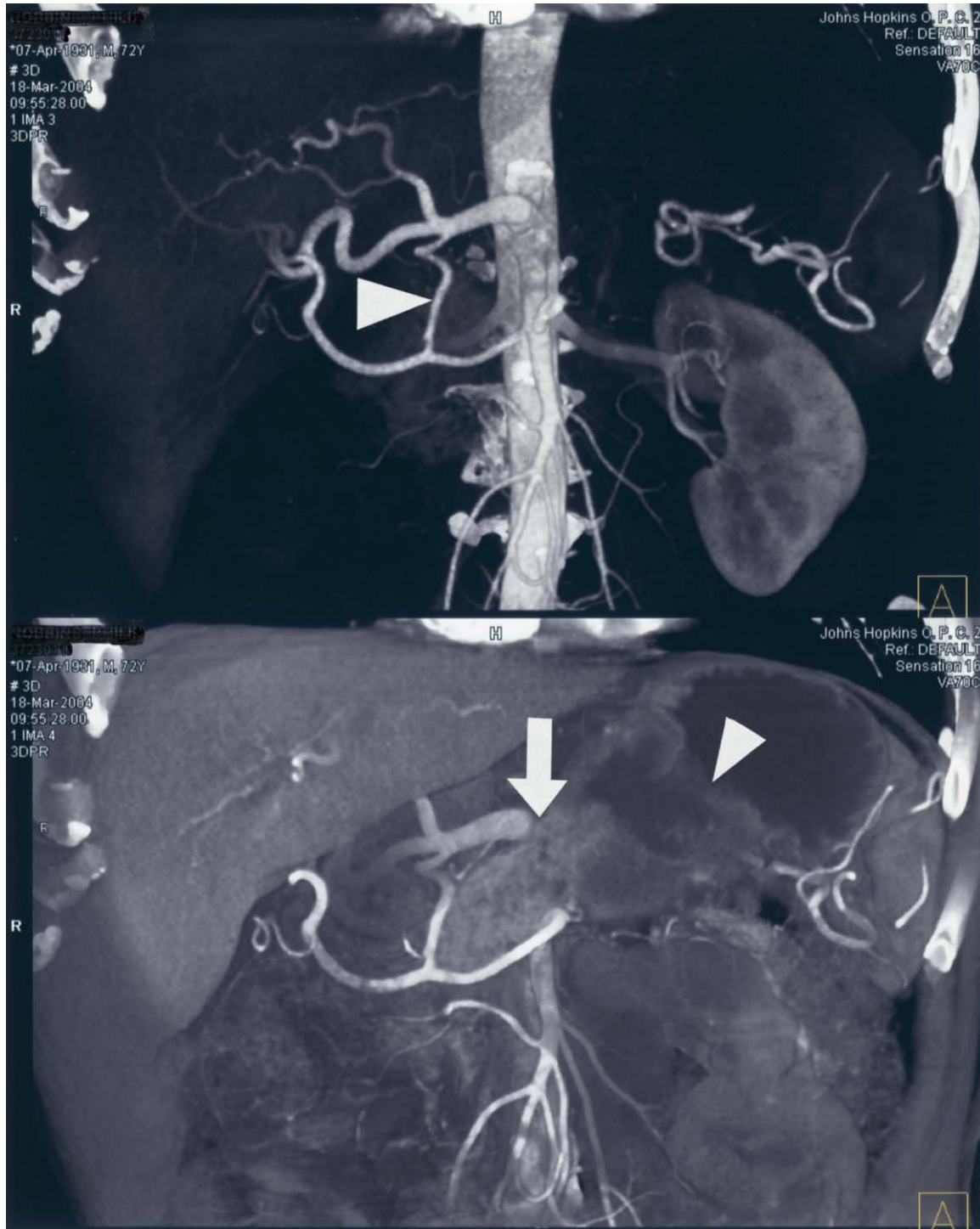
A 72-year-old man with no significant past medical history presented to the Johns Hopkins Hospital with a 15-pound weight loss. A CT scan revealed a large mass in the body of the pancreas, invading the posterior wall of the stomach, with no evidence of metastatic disease. Preoperative studies included an endoscopic biopsy of the pancreatic tumor that demonstrated poorly differentiated adenocarcinoma. A 16-slice multidetector row CT scan demonstrated

invasion of the pancreatic mass into the celiac axis (*Fig. 1, Top*). Using vascular reconstruction imaging techniques, the gastroduodenal artery was observed to provide excellent collateral blood flow to the liver (*Fig. 1, Bottom*). Our three-dimensional CT angiographic scan protocol uses cross-sectional images of 0.75 mm in thickness with 0.5-mm interscan spacing. Solid organ and angiographic images were constructed by post-processing data using volume rendering and maximum intensity projection (MIP) techniques.<sup>1</sup>

At the time of operative exploration, there was a large pancreatic mass that occupied most of the body and tail and extended into the posterior stomach (*Fig. 2*). A large posterior gastric ulcer was found to be continuous with an excavated cavity of the tumor. This ulcer was so large that the anterior wall of the stomach could be invaginated into the excavated cavity. The pancreatic neck was divided at the level of the superior mesenteric and portal veins. The spleen, body, and tail of the pancreas were mobilized out of the retroperitoneum. The first portion of the duodenum and the gastroesophageal junction were divided with a linear stapler and blade, and the entire stomach was mobilized. The tumor was adherent to the celiac

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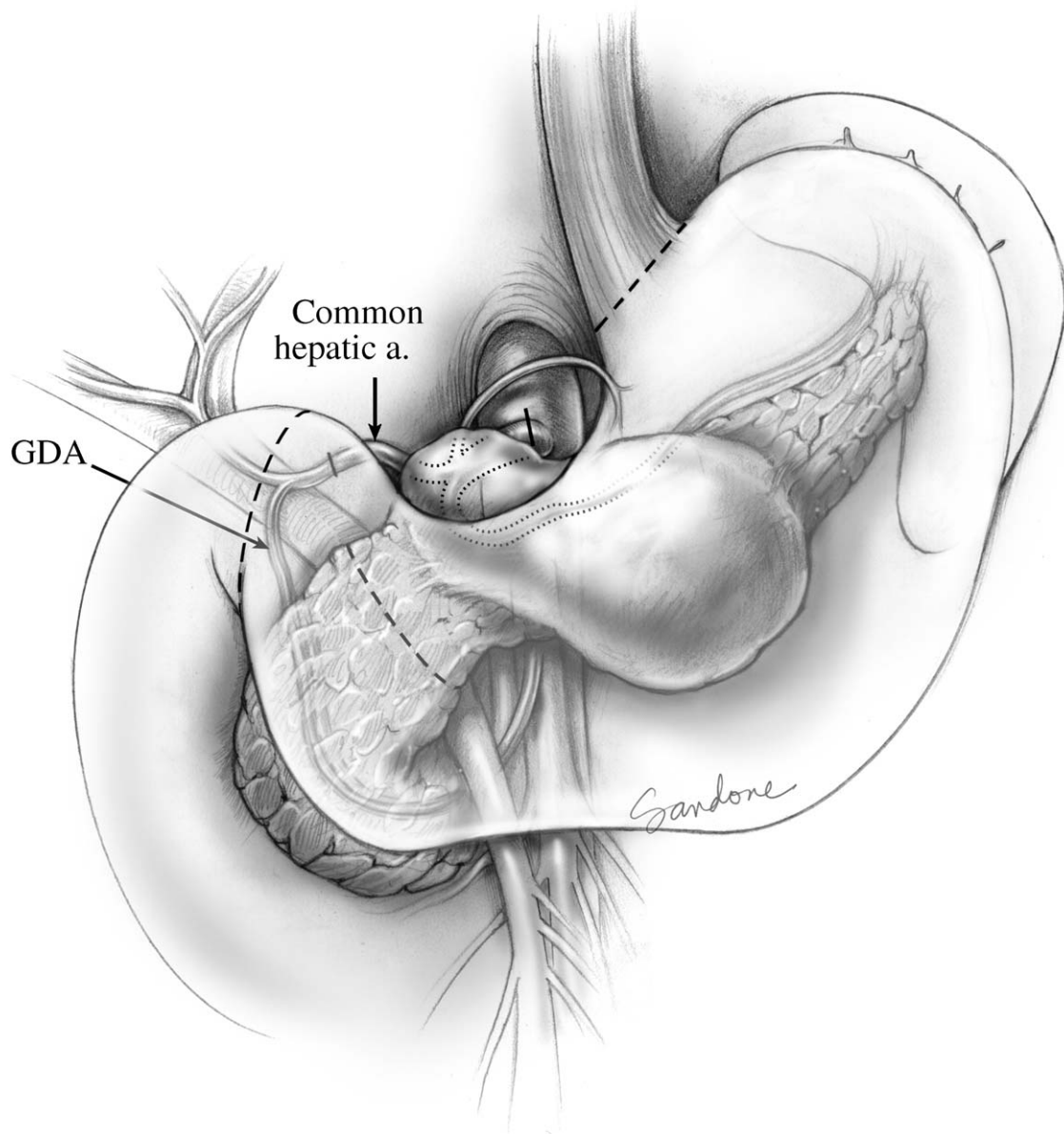
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**Fig. 1. (Top)** Three-dimensional computed tomography scan demonstrating collateral blood flow to the liver via the gastroduodenal artery (*arrowhead*). **(Bottom)** Three-dimensional computed tomography scan of the pancreatic head mass invading the celiac axis (*arrow*) and posterior stomach (*arrowhead*).

axis at the takeoff of the common hepatic, left gastric, and splenic arteries, involving a 2-cm segment. The celiac axis was cleaned for a 4-cm length down to the aorta. The celiac axis was occluded with a Cooley clamp at the aorta, and the common hepatic

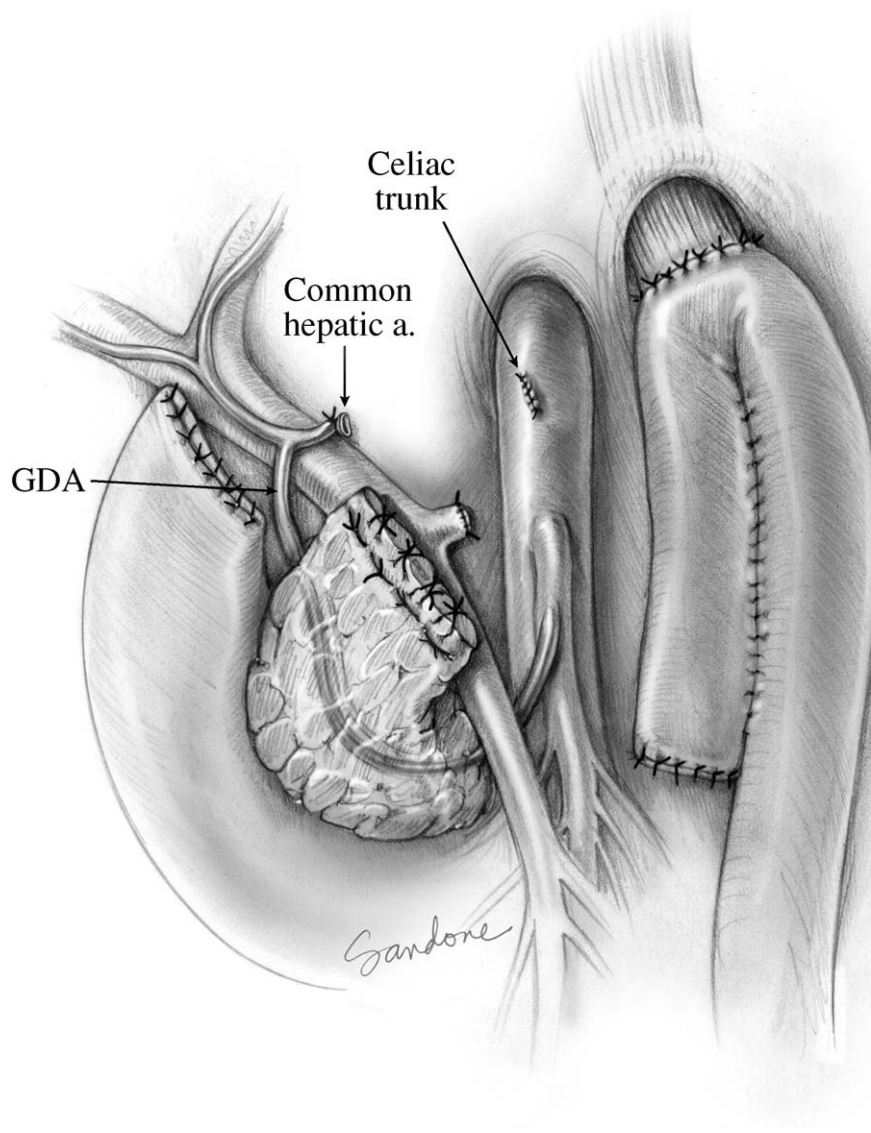
artery was occluded with a DeBakey bulldog clamp distal to the tumor involvement but proximal to the gastroduodenal artery. The pulses in the right and left hepatic arteries were diminished but were still present. The celiac axis was divided distal to the



**Fig. 2.** Drawing of the pancreatic cancer with local invasion; lines of resection are indicated. GDA = gastroduodenal artery; a. = artery.

Cooley clamp, and the hepatic artery was divided proximal to the Debakey bulldog clamp. Both were oversewn with 5-0 Prolene. The splenic artery and vein were then divided and ligated (Fig. 3). Approximately 85% of the pancreas was removed. A Roux-en-Y proximal jejunal limb was created 70 cm in length, and a Hunt-Lawrence pouch was created at its proximal end. An end-to-side esophagojejunostomy was performed. A closed-suction, Silastic drain was placed next to the pancreatic margin at the conclusion of the operation. All margins of resection were negative on frozen section.

The patient's postoperative hospital course was uncomplicated. Serial liver function tests were checked every 6 hours during the initial 24-hour postoperative period, then daily during the remainder of the hospitalization. All liver function test results remained normal. A nasogastric tube was used postoperatively and was removed on day 3. A liquid diet was initiated and advanced within 1 day. The patient's recovery was uneventful, and he was discharged on day 7 after the administration of post-splenectomy vaccines. The final pathology report revealed a moderately differentiated pancreatic adenocarcinoma



**Fig. 3.** Operative reconstruction demonstrating collateral flow via the gastroduodenal artery (GDA).  
a. = artery.

with 1 of 14 regional lymph nodes being positive for malignancy. Surgical margins were free of tumor.

## DISCUSSION

Pancreatic neck, body, and tail tumors rarely present with biliary obstruction. Often they present with back pain secondary to local invasion into the celiac plexus. Thus, given their anatomic location and natural history, malignancies of the neck, body, and tail often present at a more advanced stage, and the associated presence of back pain has traditionally been regarded as a predictor of unresectability and a poor prognosis.<sup>2</sup>

Celiac artery ligation with reliance on collateral blood flow to the liver from the gastroduodenal artery was first reported for trauma to the celiac artery. These reports describe ligation of the celiac or common hepatic arteries for major trauma to these vessels in the context of hemodynamic instability.<sup>3,4</sup> In addition, resection of the celiac artery has been reported for celiac artery aneurysms.<sup>5,6</sup> In the management of pancreatic cancer, distal pancreatectomy with en bloc resection of the celiac artery was first proposed in Japan.<sup>7-9</sup> In a series of six patients, Mayumi et al.<sup>7</sup> described an en bloc resection of the celiac axis for local vascular invasion of pancreatic cancer. They noted a 9.5-month median survival, with one patient

alive at 5 years. Kondo et al.<sup>9</sup> have subsequently reported a series of five patients who underwent a similar celiac axis resection and observed a median survival of 11 months. They concluded that such an “extended” distal pancreatectomy not only improved outcomes but also improved postoperative pain control because of the resection of the associated celiac plexus ganglion as recognized by others.<sup>8,10</sup>

Although local vascular involvement is generally considered to be a contraindication to surgical resection, the present case represents a novel approach to the management of pancreatic cancer invading the celiac or common hepatic arteries. Furthermore, this case is consistent with our experience that some lesions assessed by CT scan to be “unresectable” may in fact be resected with negative margins.<sup>11</sup> As evident in this patient, it is clear that hepatic blood flow can be successfully preserved with a resection of the celiac axis. Preoperative vascular imaging of the gastroduodenal artery, such as a three-dimensional CT with angiographic reconstruction, is important in assessing candidacy for this technique.

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*We wish to thank Corinne Sandone, who demonstrated the procedure through the drawings presented in this article.*

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# Effect of “White Diet” During Bile Monitoring With Bilitec 2000 on Esophageal pH-Metry in Patients With Gastroesophageal Reflux Disease

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With introduction of the Bilitec 2000 device, intraluminal bile monitoring has become a standard technique for evaluation of patients with gastroesophageal reflux disease and symptoms of bile reflux. A specific “white diet” excluding colored food is necessary to provide correct measurements. The influence of this specific diet on simultaneous esophageal pH monitoring is unknown. Forty patients with reflux symptoms were studied prospectively. Meal times and supine and erect phases of measurement were recorded in a standardized fashion using a patient protocol. Esophageal 24-hour pH monitoring with administration of a “colorless” diet (water, milk, potatoes, fish, chicken) was started on day 1, followed by esophageal 24-hour pH-metry with intake of a normal diet on day 2. Data from the two successive pH measurements were compared. The prevalence of a pathologic esophageal pH-metry was significantly higher during intake of a normal diet compared with a colorless diet ( $P = 0.025$ ). During total and upright phases, administration of a white diet led to significant reduction in the percentage of time with a pH less than 4 ( $P \leq 0.01$ ), the total number of reflux episodes ( $P \leq 0.001$ ), and the DeMeester’s score ( $P = 0.01$ ). This difference was exclusively found in patients with a normal pH-metry (group 1,  $n = 13$ ) and pathologic upright reflux (group 2,  $n = 12$ ). No change in reflux pattern was found in patients with isolated supine reflux (group 3,  $n = 7$ ) and combined upright and supine reflux (group 4,  $n = 8$ ). In patients with a pathologic upright reflux pattern, administration of a white diet results in a significant modification of esophageal pH-metry. Data derived from simultaneous esophageal pH and bile monitoring should be interpreted with care. (J GASTROINTEST SURG 2005;9:508–513) © 2005 The Society for Surgery of the Alimentary Tract

Mixed reflux of acid and duodenal juice through the lower esophageal sphincter (LES) has been linked to the development of Barrett’s esophagus and Barrett’s carcinoma.<sup>1</sup> However, the toxic effect of duodenogastroesophageal reflux (DGER) was discussed controversially for many years due to the lack of a precise diagnostic test. With the development of the Bilitec 2000 device (Medtronic Germany GmbH, Düsseldorf, Germany) using bilirubin as a marker for duodenal juice, a convenient method allowing continuous long-term monitoring of DGER over a 24-hour period is now available.<sup>2</sup> The device consists of a miniaturized fiberoptic probe connected to a portable optoelectronic unit equipped with a data recorder for bilirubin monitoring over a 24-hour period. The instrument measures absorbance of a

light beam whose wavelength (470 nm) is close to the absorbance peak of bilirubin (453 nm). Dark-colored food and drinks such as coffee or chocolate strongly interfere with the absorbance of bilirubin due to the optical properties of the instrument, resulting in false-positive readings. Therefore, intake of a specific colorless “white diet” (WD) is compulsory for exact interpretation of data.<sup>3,4</sup>

In many gastrointestinal function laboratories, simultaneous long-term monitoring of bile and acid is now implemented as standard diagnostic test for patients with suspected DGER. Further, combined esophageal pH and bile monitoring was used in several landmark studies to evaluate the impact of acidic, bilious, and mixed reflux on the development of Barrett’s esophagus.<sup>5–8</sup> In a recent report, we used

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simultaneous esophageal pH and bile monitoring to study the respective roles of truncal vagotomy, posture, pyloroplasty, and administration of erythromycin in the regulation of bile exposure of the transposed stomach after subtotal esophagectomy.<sup>9</sup> However, the influence of the modified WD on gastroesophageal reflux patterns has not been studied. Due to our personal clinical experience with patients presenting to our gastrointestinal function laboratory, our hypothesis was that the administration of a colorless diet substantially reduces reflux symptoms in a subset of patients. In this setting, it was challenging to analyze the impact of WD on esophageal 24-hour pH-metry.

## MATERIAL AND METHODS

### Study Protocol and Patient Characteristics

During an 8-month period, 40 consecutive patients (24 women and 16 men; age range, 18–77 years) who presented to the gastrointestinal function laboratory of our department were studied. Inclusion criteria were symptoms of gastroesophageal reflux (i.e., heartburn and regurgitation) for a period of longer than 1 year; exclusion criteria were a history of previous upper gastrointestinal surgery and lack of consent to participate in the study. Proton pump inhibitors were stopped for a period of longer than 1 week.

The standardized diagnostic work-up included solid-state esophageal manometry, upper gastrointestinal endoscopy, and barium meal radiography before pH-metry and bilimetry. *Esophagitis* was defined as macroscopically visible erosion within the distal esophagus during endoscopy with positive histologic proof of inflammation. An *hiatal hernia* was defined as a gastroesophageal junction located more than 1 cm above the diaphragm in the supine position on upper gastrointestinal contrast radiography. An insufficient *lower esophageal sphincter* was defined by manometric criteria established by Castell and Castell.<sup>10</sup>

Patients were subdivided according to four classic patterns of gastroesophageal reflux: no pathologic reflux during erect or supine phases (group 1,  $n = 13$ ), pathologic reflux during the upright phase (group 2,  $n = 12$ ), pathologic reflux during the supine phase (group 3,  $n = 7$ ), and pathologic reflux during both phases (i.e., bipositional or mixed reflux) (group 4,  $n = 8$ ). Data for subclassification of patients were derived from normal diet (ND) readings. Cutoff values were adapted from *Jamieson et al.*<sup>11</sup>: pathologic acid reflux during total, upright, and supine phases was considered pathologic if the percentage of time of esophageal exposure to pH less than 4 exceeded the 95th percentile of reference values obtained from

50 healthy volunteers (4.5%, 8.4%, and 3.5%, respectively).

### Esophageal pH and Bile Monitoring

For 24-hour pH monitoring, a portable datalogger (Digitrapper Mark III; Medtronic) connected to a multiuse antimony pH catheter (Medtronic) was used. The system was calibrated before each study in buffer solutions with a known pH of 4.0 and 7.0. The 24-hour bile monitoring was performed by using the Bilitec 2000 portable unit (Medtronic). The assembly consists of a memory component connected to a fiberoptic probe that was calibrated in water before each study.

From a practical standpoint, bile and pH probes were taped together and passed transnasally into the esophagus. The tips of both probes were positioned 5 cm above the upper border of the LES as defined by esophageal manometry. Patients were asked to follow a strict study protocol: they were instructed to take three meals per day, and no liquids were allowed between meals. Recumbent phases of recording were permitted only at night. Patients were asked to keep a diary with exact specification of meals, supine and erect phases of measurement, and sensations of heartburn and regurgitation.

In every patient, two successive measurements were made. On day 1, pH monitoring with administration of a colorless diet that included liquid and solid foods with a maximum in vitro bile absorbance of 0.25 (absorbance scale ranges from 0 [plain water] to 1 [total screen]) was performed. The meals included water, milk, potatoes, chicken, dry biscuits, fish, and Fresubin (Fresenius AG, Bad Homburg, Germany). On day 2, pH-metry with administration of a normal full diet at pH of 5 to 7 was performed.

### Data Acquisition and Interpretation

After completion of the measurements, probes were withdrawn from the patients, and data were stored via an interface on an IBM-compatible computer equipped with Polygram software (Medtronic). Statistical analysis was performed with Statistica software (StatSoft, Tulsa, OK). Wilcoxon matched pair,  $\chi^2$ , and Kruskal-Wallis tests were used as appropriate. A value of  $P < 0.05$  was considered statistically significant.

## RESULTS

### Patient Characteristics According to Reflux Pattern

There were no significant differences among the four groups concerning mean age, prevalence of hiatal

**Table 1.** Comparison of clinical data according to the pattern of reflux

| Patient Characteristic    | Mean age (yr) (range) | Gender (% female) | Esophagitis (%) | Hiatal hernia (%) | Incompetent lower esophageal sphincter (%) |
|---------------------------|-----------------------|-------------------|-----------------|-------------------|--|
| Total population (n = 40) | 48.2 (18–77)          | 60.0              | 80.0            | 72.5              | 45.0                                       |
| Normal pH-metry (n = 13)  | 48.7 (35–67)          | 92.3              | 69.2            | 76.9              | 23.1                                       |
| Upright reflux (n = 12)   | 52.3 (33–77)          | 50.0              | 66.7            | 66.7              | 58.3                                       |
| Supine reflux (n = 7)     | 45.4 (35–73)          | 57.1              | 100.0           | 85.7              | 42.9                                       |
| Mixed reflux (n = 8)      | 43.6 (18–69)          | 25.0              | 100.0           | 62.5              | 62.5                                       |
| <i>P</i>                  | NS                    | 0.004             | NS              | NS                | NS   |

hernia, presence of macroscopic esophagitis, and prevalence of incompetent LES as measured by stationary perfusion manometry (Table 1). However, most group 1 subjects were female. Patients with supine or bipositional reflux (combined groups 3 and 4) had a higher prevalence of macroscopic esophagitis than did patients without supine reflux pattern (combined groups 1 and 2) ( $P = .041$ ). An hiatal hernia or an incompetent LES was not found more frequently among group 3 and 4 subjects than in the combined groups 1 and 2 ( $P \geq 0.622$ ).

### Overall Analysis of pH Data

Ingestion of a WD caused dramatic modification of the classic parameters of esophageal pH-metry (Table 2): compared with ND measurements, the prevalence of a pathologic pH-metry was significantly lower. In total, 13 patients (32.5%) moved into the normal range of pH-metry. Accordingly, the DeMeester composite score significantly decreased after ingestion of a WD and the prevalence of a

pathologic score was significantly lower. In total, DeMeester score became normal in 12 patients (30%) after ingestion of a WD. Likewise, the percentage of time that pH was less than 4 was significantly reduced during total and upright phases in WD compared with ND monitoring. In contrast, measurements were similar in comparing WD with ND values during supine phases.

Intake of WD initiated a significant decrease of the number of reflux episodes during total and upright, but not during supine, phases of reading. The duration of the longest reflux period and the number of reflux episodes longer than 5 minutes were similar in comparing ND and WD recordings.

### Analysis of pH Data According to Reflux Patterns

Ingestion of a WD particularly changed parameters of esophageal pH-metry in patients with a normal pH-metry and in those with an upright reflux pattern (groups 1 and 2 patients): in both groups, a significant

**Table 2.** Comparison of pH data (n = 40) according to the diet ingested

|   | Period     | Normal diet         | White diet        | <i>P</i> |
|---|------------|---------------------|-------------------|----------|
| Percent time pH <4 (mean $\pm$ 95% CI)                | Total time | 9.14 (6.7–11.6)     | 7.03 (4.0–10.1)   | 0.012    |
|   | Upright    | 12.3 (8.9–15.6)     | 7.9 (4.4–11.3)    | 0.001    |
|   | Supine     | 3.6 (2.2–5.0)       | 5.9 (2.7–9.0)     | NS       |
| No. of reflux episodes (mean $\pm$ 95% CI)            | Total time | 152.5 (109.7–195.4) | 76.5 (49.2–103.7) | <0.0001  |
|   | Upright    | 130.1 (90.8–169.4)  | 55.2 (34.7–75.7)  | <0.0001  |
|   | Supine     | 22.8 (14.0–31.6)    | 21.7 (10.8–32.5)  | NS       |
| No. of reflux episodes >5 minutes (mean $\pm$ 95% CI) | Total time | 4.8 (3.1–6.5)       | 3.9 (2.1–5.7)     | NS       |
|   | Upright    | 3.9 (2.4–5.4)       | 2.7 (1.5–3.9)     | 0.058    |
|   | Supine     | 1.15 (0.5–1.8)      | 1.3 (0.6–2.0)     | NS       |
| Longest reflux period (mean $\pm$ 95% CI)             | Total time | 13.9 (10.6–17.1)    | 19.9 (12.2–27.5)  | NS       |
|   | Upright    | 12.3 (9.1–15.6)     | 11.9 (6.8–17.0)   | NS       |
|   | Supine     | 5.8 (3.2–8.4)       | 13.1 (5.8–20.4)   | NS       |
| Pathologic pH-metry (%)                               | Total time | 65.0                | 37.5              | 0.025    |
|   | Upright    | 50.0                | 30.0              | NS       |
|   | Supine     | 37.5                | 35.0              | NS       |
| Composite score (mean $\pm$ 95% CI)                   |            | 34.5 (26.3–42.7)    | 27.2 (16.5–38.0)  | 0.037    |
| Pathologic score (%)                                  |            | 72.5                | 45                | 0.023    |

CI = confidence interval.

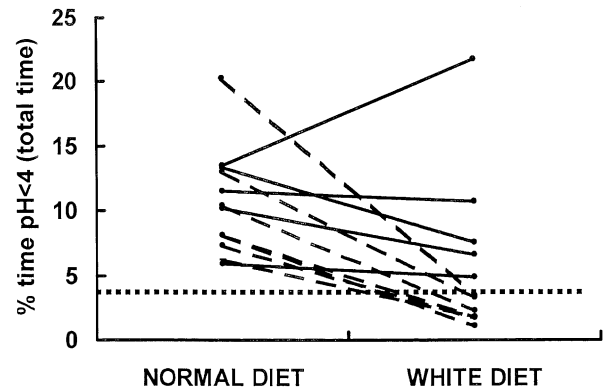
change was found in the percentage of time with a pH of less than 4 and in the number of reflux episodes during total and upright, but not during supine, phases. In addition, during ingestion of a WD, upright refluxers had a significantly lower number of long reflux episodes during the upright phase of measurement (Table 3).

Prevalence of a pathologic DeMeester composite score and that of a pathologic pH-metry decreased significantly only in patients with an upright reflux pattern (group 2). In total, seven patients (58.3%) were reclassified as being in the normal range of pH-metry. None of the group 2 patients moved from pathologic pH monitoring during WD measurement into the normal pH range during intake of the regular diet (Fig. 1). Likewise, the DeMeester composite score significantly decreased in patients with upright reflux after ingestion of a WD, and the prevalence of a pathologic score was significantly lower (Table 3). In total, the DeMeester score became normal in 6 patients (50%) while ingesting a WD. None of the group 2 patients had a pathologic DeMeester score during WD that became normal during intake of the regular diet.

In contrast, use of the WD did not change the results of esophageal pH-metry in subjects with a supine or bipositional reflux pattern (group 3 and 4 patients).

## DISCUSSION

The idea that diet modification influences reflux patterns has been investigated earlier by others for a



**Fig. 1.** Comparison of normal diet with white diet measurements in 12 patients with an upright reflux pattern (group 2). Percentage of total time pH is less than 4 is shown. *Dotted line*, threshold of normal values as adapted from Jamieson et al.<sup>11</sup> (pH < 4.5%). *Hatched lines*, seven patients reclassified from pathologic pH-metry on a regular diet to normal pH values on a white diet.

variety of foods. It is known that chili pepper,<sup>12</sup> raw onions,<sup>13</sup> chocolate,<sup>14</sup> white wine,<sup>15</sup> and high-caloric meals<sup>16</sup> do promote acid reflux and heartburn. However, our study is the first to demonstrate an influence on gastroesophageal reflux pattern due to intake of a specific diet used for intraluminal bile monitoring with the Bilitec 2000 device.

The major finding of this study is that acidic gastroesophageal reflux is significantly modified by the WD. In regard to the entire study group of 40 patients, about one third of patients (32.5%) moved from a normal pH test during WD into the pathologic range on a regular diet. Moreover, 58.3% of patients

**Table 3.** Comparison of pH data according to the pattern of reflux showing only p values

|                                   | Period     | Normal pH-metry (n = 13) | Upright reflux (n = 12) | Supine reflux (n = 7) | Mixed reflux (n = 8) |
|-----------------------------------|------------|--------------------------|-------------------------|-----------------------|----------------------|
| Percent time pH <4                | Total time | 0.033                    | 0.023                   | NS                    | NS                   |
|                                   | Upright    | 0.034                    | 0.004                   | NS                    | NS                   |
|                                   | Supine     | NS                       | NS                      | NS                    | NS                   |
| No. of reflux episodes            | Total time | 0.009                    | 0.041                   | NS                    | NS                   |
|                                   | Upright    | 0.009                    | 0.012                   | 0.017                 | NS                   |
|                                   | Supine     | NS                       | NS                      | NS                    | NS                   |
| No. of reflux episodes >5 minutes | Total      | NS                       | NS                      | NS                    | NS                   |
|                                   | Upright    | NS                       | 0.033                   | NS                    | NS                   |
|                                   | Supine     | —                        | NS                      | NS                    | NS                   |
| Longest reflux period             | Total      | NS                       | NS                      | NS                    | NS                   |
|                                   | Upright    | NS                       | NS                      | NS                    | NS                   |
|                                   | Supine     | NS                       | NS                      | NS                    | NS                   |
| Composite score                   |            | 0.046                    | 0.049                   | NS                    | NS                   |
| Pathologic composite score        |            | NS                       | 0.018                   | NS                    | NS                   |
| Pathologic pH-metry               |            | NS                       | 0.007                   | NS                    | NS                   |

with an upright reflux pattern showed false-negative pH monitoring during intake of WD.

Our first conclusion is that data obtained from synchronized esophageal pH and bile monitoring should be interpreted with care. Moreover, we believe that the additional risk, cost, and effort of a second nasal intubation does not outweigh the diagnostic benefits of an accurate measurement. As a consequence, we have omitted the practice of simultaneous esophageal pH-metry and bilimetry in our gastrointestinal function laboratory as a routine diagnostic test for patients with suspected DGER.

Furthermore, one may conclude from our study that the Bilitec test may not be suitable to accurately detect DGER in patients with upright reflux, as both frequency and duration of gastroesophageal reflux events, and therefore reflux of bile into the distal esophagus, are significantly influenced by the modified diet. Therefore, Bilitec data obtained from patients with a classic upright reflux pattern should be interpreted with caution.

The changing frequency of reflux episodes during upright and postprandial phases seen in our group 1 and 2 patients can be explained by transient losses of sphincter competence during the postprandial phase. It has been shown that transient loss of sphincter competence typically occurs during upright and postprandial phases in patients with an otherwise mechanically intact LES<sup>17</sup> and, like in our group 1 and 2 patients, with a lower prevalence of esophagitis and an upright reflux pattern.<sup>18</sup> In contrast, patients with a supine or bipositional reflux pattern are more likely to have permanent loss of the anatomic barrier function due to a structural defect of the LES.<sup>19</sup> Typically, they present with larger hiatal hernias<sup>17</sup> and a higher prevalence of esophagitis.<sup>20</sup> Accordingly, the best explanation for the phenomenon observed in our study is that diet modifications initiate vagal activation of brainstem circuits resulting in transient losses of sphincter competence in a subset of patients—those with an LES without major structural defect and an intact vagal supply.

Our findings suggest a classification of reflux patients into two basic groups according to their upright reflux pattern: those who show alteration of the number of reflux episodes in relation to diet changes (groups 1 and 2) and those who do not (groups 3 and 4). Diet suggestions such as avoiding refluxogenic foods, coffee, or high-caloric meals may be indicated only in patients with upright reflux. These suggestions, as mentioned in every textbook of medicine, are considered to be first-line treatment for patients with GERD regardless of its pattern, although they may be useless in patients with supine reflux. A similar

conclusion was recently made in a study that compared patients with complicated versus noncomplicated reflux esophagitis.<sup>18</sup> The authors questioned the usefulness of postural measures in patients with uncomplicated esophagitis due to the absence of supine reflux in this group.

In summary, our study confirms that gastroesophageal reflux must be seen and treated as a heterogeneous disease with different causes leading to different clinical appearances. The importance of an exact classification with the use of functional investigations such as endoscopy, manometry, radiography, pH monitoring, and bile monitoring must be emphasized. Although the pattern of reflux has been shown not to influence the outcome of antireflux surgery,<sup>20</sup> it should be taken into account that during first-line conservative treatment, patients with supine reflux may not profit from diet modifications, whereas those presenting with an upright reflux pattern may not benefit from postural measures.

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# Spontaneous Small Bowel Perforations Due to Intestinal Tuberculosis Should Not Be Repaired by Simple Closure

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Intestinal tuberculosis is a major problem in many regions of the world. The incidence of it is rising in Western countries due to immigration from Third World countries and human immunodeficiency virus infection. The difference between the simple closure and resection and anastomosis was evaluated in this study. Retrospectively, 12 patients with intestinal tuberculosis diagnosed histopathologically among 50 patients with free intestinal perforations operated on between 1995 and 2003 at Turgut Ozal Medical Center were evaluated. Each patient underwent routine laboratory tests and radiologic studies. The most common symptoms of patients were abdominal pain, night sweats, and weight loss. Sites of perforation were ileum in 10 patients (multiple perforation in 4) and jejunum in 2 patients (both had multiple perforations). The perforation was closed by primary closure in 7 patients. Resection-anastomosis was performed in 5 patients. Leaks occurred in overall 3 of 7 patients with primary closure. Three of the 7 patients with leaks due to septicemia died. The mortality rate among all patients was 25%. Intestinal tuberculosis should be kept in mind as a cause in free intestinal perforations. Because of high mortality rate, the resection of the affected area and anastomosis may be the treatment of choice rather than primary closure. (*J GASTROINTEST SURG* 2005;9:514–517) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Intestinal tuberculosis, perforation, treatment

Despite considerable progress made in therapy and prophylaxis, abdominal tuberculosis is still a major problem in many regions of the world.<sup>1,2</sup> Intestinal tuberculosis incidence is increasing in the West due to immigration from Third World countries, an aging population, and an increasing incidence of human immunodeficiency virus infection.<sup>3</sup> Free intestinal perforations occur in 1% to 15% of patients with abdominal tuberculosis.<sup>1,4,5</sup>

The present study summarizes retrospectively the outcome of treatment modalities of 12 patients diagnosed with intestinal tuberculosis.

## PATIENTS AND METHODS

We reviewed 50 patients operated on for free intestinal perforations due to various causes at Turgut Ozal Medical Center between February 1995 and

December 2003. Twelve (24%) of them were diagnosed with intestinal tuberculosis (other diagnoses were lymphoma in 7, Crohn's disease in 4, typhoid perforation in 2, foreign body in 4, Behçet disease in 3, intestinal tumor in 2, femoral hernia in 2, strangulated hernia in 4, ileus related to intestinal adhesion in 6, and delayed mesentery artery ischemia in 4 patients). Their clinical history, symptoms, and preoperative investigations and details of their management were analyzed. A complete blood cell count, liver and renal function tests, plain radiograph of the abdomen, chest radiograph, and abdominal ultrasonogram were performed. There was no previous tuberculosis history in 10 patients, but patient 6 had a history of operation due to intra-abdominal abscess 1 month earlier and the pathology of intestinal mesentery lymph node diagnosed as tuberculosis, and he received antituberculosis treatment for 25 days before perforation. Patient 12 also had a history of tuberculosis diagnosed

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pathologically from right cervical lymph nodes 4 months before perforation and treated with antituberculosis drugs. In addition, patient 3 had a history of Addison's disease, and patient 7 had a history of Crohn's disease by colonic biopsy. Steroid treatment was given to both of them.

## RESULTS

The median age of 12 patients with intestinal tuberculosis (6 females, 6 males) was 45 years (range, 19–75 years). The laboratory and operative findings and outcome of patients are summarized in Table 1. The most common symptoms were acute abdominal pain, night sweats, weight loss, diarrhea, and vomiting. Physical examinations showed abdominal tenderness and muscular rigidity. Chest radiograph of all patients was normal. In 9 patients, abdominal ultrasonography showed free fluid in the rectovesical or Douglas pouch and between intestinal segments. All patients underwent laparotomy after nasogastric suction and appropriate fluid replacement. In most of the patients, the serosa of the small bowel and peritoneum showed miliary tubercles and were presented with purulent peritonitis at the same time. Patient 2 had multiple perforations in an 80-cm-long intestinal segment from 10 cm proximal to the ileocecal valve. Perforations were primarily closed. At postoperative day 7, a leakage was noticed and patient underwent a reoperation and intestinal resection, right hemicolectomy, and end-ileostomy. During the postoperative period, wound infection and evisceration were realized. The patient died from sepsis. Patient 3, who had a history of Addison's disease, was admitted to the emergency department with intestinal perforation and primary closure of the perforated area

was performed; postoperatively, steroid treatment was given. On postoperative day 5, leakage was noticed and end-ileostomy was performed at the repeat laparotomy. He was lost due to leakage and sepsis. Patient 7 had a previous colonic biopsy of Crohn's disease for 1 year. When he was hospitalized due to acute abdomen, laparotomy was performed. There was ileocecal mass, ileal stricture, and ileal perforation. Right hemicolectomy, ileal stricturoplasty, and simple closure were performed. The intestinal specimen was examined by a pathologist and diagnosed as representing Crohn's disease, and steroid treatment was given after the first operation. The patient was not examined for tuberculosis in the first resection because of previous diagnosis history. The leakage was realized at postoperative day 11, and the resection and end-ileostomy were performed by repeat operation. The histopathologic examination of the terminal ileum excised in the second operation showed intestinal tuberculosis affecting all layers of the diseased segment. Reexamination of the first specimen was also diagnosed as intestinal tuberculosis. Despite maximal medical support, the patient died from sepsis.

Patient 6, who had a history of an operation due to intra-abdominal abscess 1 month earlier, was presented to our clinics with acute abdomen and operated on with simple closure. On postoperative day 13, an enterocutaneous fistula formed, the patient underwent repeat laparotomy, and repair of perforation and loop ileostomy were performed. In all patients, histopathologic examination of the specimen of resected bowel, material from the mesenteric edge of the perforation, or mesenteric lymph nodes revealed caseating granulomas surrounded by epithelial cells and Langerhans giant cells. Acid-fast bacilli

**Table 1.** Laboratory and operative findings and outcome of patients

| Patient                   | Age/gender | Radiology        | Perforation site/type | Reoperation | Outcome         |
|---------------------------|------------|------------------|-----------------------|-------------|-----------------|
| Simple closure            |            |                  |                       |             |                 |
| 1                         | 30/F       | Free air         | Ileum                 | No          | Discharged well |
| 2                         | 24/F       | Air-fluid levels | Ileum/multiple        | Yes         | Leak, died      |
| 3                         | 75/M       | Free air         | Ileum/multiple        | Yes         | Leak, died      |
| 4                         | 70/M       | Air-fluid levels | Ileum                 | No          | Discharged well |
| 5                         | 20/F       | Free air         | Ileum                 | No          | Discharged well |
| 6                         | 20/F       | Free air         | Ileum                 | Yes         | Discharged well |
| 7                         | 27/F       | Free air         | Ileum                 | Yes         | Leak, died      |
| Resection and anastomosis |            |                  |                       |             |                 |
| 8                         | 65/M       | Air-fluid levels | Jejunum/multiple      | No          | Discharged well |
| 9                         | 36/F       | Free air         | Jejunum/multiple      | No          | Discharged well |
| 10                        | 64/M       | Air-fluid levels | Ileum/multiple        | No          | Discharged well |
| 11                        | 64/M       | Air-fluid levels | Ileum/multiple        | No          | Discharged well |
| 12                        | 35/M       | Air-fluid levels | Ileum                 | No          | Discharged well |

were demonstrated by Ziehl-Nielsen staining in 12 patients. We treated all patients with isoniazid 300 mg/day and rifampin 600 mg/day for 12 months and pyrazinamide 1.5 g/day and ethambutol 1 g/day were added to treatment for the first 2 months. All patients were symptom free after 12 months of treatment.

## DISCUSSION

Although most patients with intestinal tuberculosis respond favorably to medical therapy,<sup>6</sup> surgery should be reserved for complications such as obstruction, free perforation, confined perforation with abscess fistula, and massive bleeding.<sup>5,7,8</sup>

As reported in previous studies, intestinal perforation may occur after antituberculosis treatment.<sup>9,10</sup> In our study, two patients had antituberculosis treatment before perforation. Free intestinal perforations occur in 1% to 15% of patients with abdominal tuberculosis.<sup>1,4,5</sup> Clinical diagnosis has been reported to be accurate in less than 50% of patients even in endemic countries like India.<sup>11</sup>

The main symptoms of intestinal tuberculosis are abdominal pain (85%), weight loss (66%), diarrhea (20%), and other symptoms, including nausea, vomiting, and melena.<sup>6,12</sup> Abdominal pain, night sweats, and weight loss were the main symptoms in our patients. Most radiologic images were not diagnostic. Subdiaphragmatic free air has been reported as occurring in 25% to 71% in the literature,<sup>1,2,13,14</sup> but it was detected as 50% in the present study. Usually, multiple air-fluid levels are seen with intestinal obstruction.<sup>1</sup> In our study, they were seen in six patients.

The majority of the perforations are solitary and occur proximal to the site of the stricture.<sup>15</sup> In 10 of our 12 patients, perforations were on the distal ileum, as mentioned in the other reports.<sup>4,14,15</sup> The multiple-perforation rate was reported as 10% to 40% in previous articles,<sup>15-17</sup> but it was 50% in our study. The most effective treatment of intestinal tuberculosis is resection of the diseased segment with end-to-end anastomosis.<sup>12,14</sup> We performed resection and end-to-end anastomosis in five patients. Simple closure may occasionally be attended successfully,<sup>12</sup> but Kakar et al.<sup>15</sup> did not recommend simple closure because of the high incidence of leak and fecal fistula formation. The overall mortality of perforation has ranged from 25% to 45%<sup>2,14,15</sup>; the mortality in our study was 25%.

Early diagnosis is very important. If surgical treatment is delayed, rapid progression of peritonitis and electrolyte imbalance and features of toxemia develop rapidly and worsen the prognosis. The important factors causing high morbidity and mortality in our

patients were delayed operation, presence of multiple perforations, primary closure of perforations, leak from operated area, and steroid treatment. When we compared patients according to surgical technique, the cause of death in the simple closure group was primary closure of multiple perforations in patients 2 and 3 and steroid treatment in patient 7 due to misdiagnosis with Crohn's disease.

The excised specimen should be sent for histologic examination, and a segment of diseased tissue or lymph node should be cultured for mycobacterium. This is particularly important in the elderly, in whom peritoneal tubercles may be diagnosed as disseminated malignant disease. Also, one should keep in mind that inflammatory bowel diseases (especially Crohn's disease) might interfere with intestinal tuberculosis in pathologic examination. Another important point for tuberculosis is the preventive measurements. Because the spread of intestinal tuberculosis is very low, classic preventive methods are sufficient to prevent the spread of tuberculosis to hospital and physician personnel during laparotomy and the treatment phase.

## CONCLUSION

Intestinal tuberculosis might be kept in mind as a cause of free intestinal perforations. Because of a high mortality rate, the resection of the affected area and anastomosis may be the treatment of choice as surgical modality rather than primary closure. Also, patients have to be examined for intestinal tuberculosis in addition to inflammatory bowel disease (especially Crohn's) to avert misdiagnosis.

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# 2005 AHPBA CONGRESS ABSTRACTS—FREE PAPERS AND VIDEOS

**1**

**NATIONAL STUDY OF BURNOUT AMONG  
TRANSPLANT SURGEONS IN NORTH AMERICA**

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This study provides an assessment of burnout in a national sample of transplant surgeons and examines critical relationship between burnout and personal, professional and organizational factors as well as the role of family support, coping strategies, and spousal perceptions. After two separate mailings of 734 questionnaires to members of the American Society for Transplant Surgeons, we received 259 responses; 50 responders were nonsurgeons and were excluded from analysis. Measures included a Demographic Survey, the Maslach Burnout Inventory, the Surgeon Coping Inventory, and the Spousal Version of the Maslach Burnout Inventory. The mean of age of the sample was  $48.7 \pm 7.69$  years. Eight percent of the primary responders (21/259) have left the field and 7.7% (20/259) were retired. Thirty-eight percent of surgeons scored high on the Emotional Exhaustion (EE) dimension of burnout, while 27% showed high levels of Depersonalization (DP; an impersonal response to patients), and 16% had low levels of Personal Accomplishment (PA). All these three dimensions were inversely correlated with "Age" and "Years of Practice", but only EE was inversely correlated with "Leisure Time" (days per month;  $r = -0.30, P < 0.0001$ ). It is noteworthy that 99% of surgeons found transplantation rewarding in terms of patient satisfaction. Twenty-six percent of surgeons reported that they often question their career choice in transplantation. Better overall level of coping was correlated with lower EE ( $r = -0.37, P < 0.0001$ ) and higher levels of PA ( $r = 0.52, P < 0.0001$ ). A stepwise multiple regression analysis showed significant predictors for each burnout dimension (Table 1). This study

suggests that surgeon burnout could be improved with 1, greater institutional support, 2, increasing opportunities for professional growth, and 3, greater surgeon control over services to facilitate efficient work. Many surgeons (26%) have questioned their career choice in transplantation although the overwhelming majority (99%) find it rewarding in terms of patient satisfaction.

**2**

**120 LAPAROSCOPIC LIVER RESECTIONS IN A SINGLE INSTITUTION**

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Minimally invasive techniques have revolutionized diagnosis and treatment in modern medicine, resulting in the reduction of patient morbidity while expanding surgical treatment options. Though in its infancy, minimally invasive (laparoscopic) hepatic surgery offers the same advantages, however, the feasibility, techniques, safety, and outcomes are largely undefined. We present our institutional experience in the minimally invasive treatment of hepatic neoplasms (benign and malignant), establishing the value of minimally invasive surgery in the armamentarium of liver-directed therapy. Between 7/01 and 10/04 we performed 120 laparoscopic hepatic resections, including: segmentectomy, left lateral segmentectomy (LLat. Seg), hepatic sectorectomy, caudate lobectomy, left lobectomy, right lobectomy, and trisegmentectomy (Triseg). Resection was performed for a wide variety of neoplastic lesions: adenoma, focal nodular hyperplasia, hemangioma, portal vein-hepatic vein venovenous malformation, polycystic liver disease, cystadenoma, adenocarcinoma, neuroendocrine tumor, hepatocellular carcinoma. Twelve patients had cirrhosis at the time of procedure. Operative time, blood loss, resection margin (malignant tumors), transfusion (tx), length of stay (LOS), bile leaks, infection, pulmonary complications, and tumor recurrence were assessed (Table 1). We find laparoscopic liver resection provides a minimally invasive

**Table 1.**

|                        |  | Standard Coefficient | T Value | P Value  |
|------------------------|--|----------------------|---------|----------|
| EE<br>( $R^2 = 0.43$ ) | 1) Questioning their career choice                       | 0.3994               | 6.6500  | 0.000000 |
|                        | 2) Give up important activities because of career choice | 0.3095               | 5.1115  | 0.000001 |
|                        | 3) Ability to control the delivery of medical services   | -0.1603              | -2.5923 | 0.01     |
| DP<br>( $R^2 = 0.15$ ) | 1) Question their career choice                          | 0.1997               | 2.7157  | 0.007    |
|                        | 2) Appreciated by patients                               | -0.2163              | -3.0939 | 0.002    |
|                        | 3) Ability to control the delivery of medical services   | -0.1460              | -2.0151 | 0.04     |
| PA<br>( $R^2 = 0.23$ ) | 1) Feeling limited in professional growth opportunities  | -0.2302              | -3.1838 | 0.001    |
|                        | 2) Appreciated by patients                               | 0.1782               | 2.6913  | 0.007    |
|                        | 3) Supporting of surgeon's needs by institution          | 0.1646               | 2.2963  | 0.02     |
|                        | 4) Question their career choice                          | -0.1515              | -2.0577 | 0.04     |

**Table 1.** Laparoscopic Resection: Results

| Procedure  | N  | OR time (min)* | Blood loss (ml)* | Tx | LOS (days) | Complications      | Recurrence     |
|------------|----|----------------|------------------|----|------------|--------------------|----------------|
| Segment    | 41 | 72             | minimal          | 0  | 1.0        | 1 bile leak        | none           |
| LLat Seg.  | 18 | 110            | 25               | 0  | 1.2        | none               | none           |
| Sector     | 9  | 142            | 100              | 0  | 1.5        | none               | 1, cystadenoma |
| Caudate    | 3  | 127            | 500              | 1  | 2.5        | 1 atelectasis      | none           |
| Left Lobe  | 16 | 159            | 250              | 0  | 1.8        | none               | none           |
| Right Lobe | 29 | 166            | 325              | 1  | 1.9        | 1 bile leak        | none           |
| Triseg.    | 4  | 194            | 125              | 0  | 2.2        | 1 suture granuloma | none           |

therapeutic option in the treatment of benign and malignant hepatic neoplasms. Although not yet directly compared to open resection, our initial review suggests this novel approach is safe and effective in 1) a variety of hepatic diseases and 2) the range of segmental to subtotal liver resection. Given these findings minimally invasive hepatic surgery will be a valuable addition to the management algorithm for hepatic neoplasms.

3

**VEGF EXPRESSION PREDICTS ADJUVANT THERAPY OUTCOMES IN RESECTED PANCREATIC CANCER**

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Angiogenesis is important for the progression of pancreatic cancer, but its predictive value is not known. We investigated the association of various angiogenic factors and microvessel density (MVD) with adjuvant therapy and prognosis in resected pancreatic cancer. Tissue cores from a multi-institutional retrospective series of 128 resected patients were used to build a pancreatic cancer tissue microarray. Vascular endothelial growth factor (VEGF), platelet-derived endothelial cell growth factor (PD-ECGF), CD31 (for MVD) and DPC4 expression were determined using immunohistochemistry. Expression of VEGF and PD-ECGF, both proangiogenic factors, was observed in 74 (58%) and 75 (59%) tumors, respectively. Expression of DPC4, an angiogenesis inhibitor, was observed in 59(46%) tumors. VEGF expression correlated significantly with increased MVD ( $P = 0.03$ ). Pancreatic cancers with loss of the angiogenesis inhibitor DPC4 also showed increased MVD ( $P = 0.05$ ). However, PD-ECGF expression did not correlate with MVD. Median survival in patients with VEGF-negative tumors was longer than in those with VEGF-positive tumors (20.2 versus 14.7 months; HR 0.71, 95% CI, 0.51–1.12;  $P = 0.16$ ). Use of adjuvant therapy was associated with increased survival in patients with VEGF-positive tumors (18.9 [treated] versus 11.2 [untreated] months; HR 0.38, 95% CI, 0.19–0.76;  $P = 0.005$ ). However, no survival benefit from adjuvant therapy was observed in patients with VEGF-negative tumors. Conversely, adjuvant therapy was associated with significantly increased survival in patients with loss of angiogenesis inhibitor DPC4 (20.3 [treated] versus 11.2 [untreated] months; HR 0.36, 95% CI, 0.14–0.94;  $P = 0.002$ ), but not in those with normal DPC4 expression. PD-ECGF expression and MVD were not associated with survival. VEGF (stimulator) and DPC4 (inhibitor) are important regulators of pancreatic tumor angiogenesis and predictive of benefit from adjuvant therapy in resected pancreatic cancer. This suggests that adjuvant therapy may be both anti-angiogenic and cytotoxic. Addition of anti-VEGF agents to adjuvant regimens may further improve outcomes.

4

**LONG-TERM RESULTS OF BILIARY DUCT RECONSTRUCTION AFTER PARTIAL SEGMENT IV RESECTION**

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Roux-en-Y hepatojejunostomy is the preferred operation for biliary reconstruction after complex iatrogenic injury. Complex injuries are defined as those that require a circumferential anastomosis as a presumed definitive repair. These lesions are usually associated with vascular injury and concomitant ischemia of the ducts. In order to avoid the ischemic component of the biliary injury, our group routinely performs a high repair to assure an anastomosis in noninflamed, non-scarred, and nonischemic ducts. If the duct bifurcation is preserved, the Hepp-Couinaud approach for reconstruction offers an excellent choice. Partial liver resection of segment IV and V, allows adequate exposure of the bile duct at its bifurcation with an anterior approach of the ducts (therefore not jeopardizing the circulation), allowing a tension-free anastomosis. In some cases with preserved bifurcation, section of the hilar plate allows exposure of the left duct, but in many cases the base of segment IV hangs over the duct, not allowing room for the jejunal limb. Long-term results of bile duct reconstruction using this approach are described. A total of 285 bile duct reconstruction

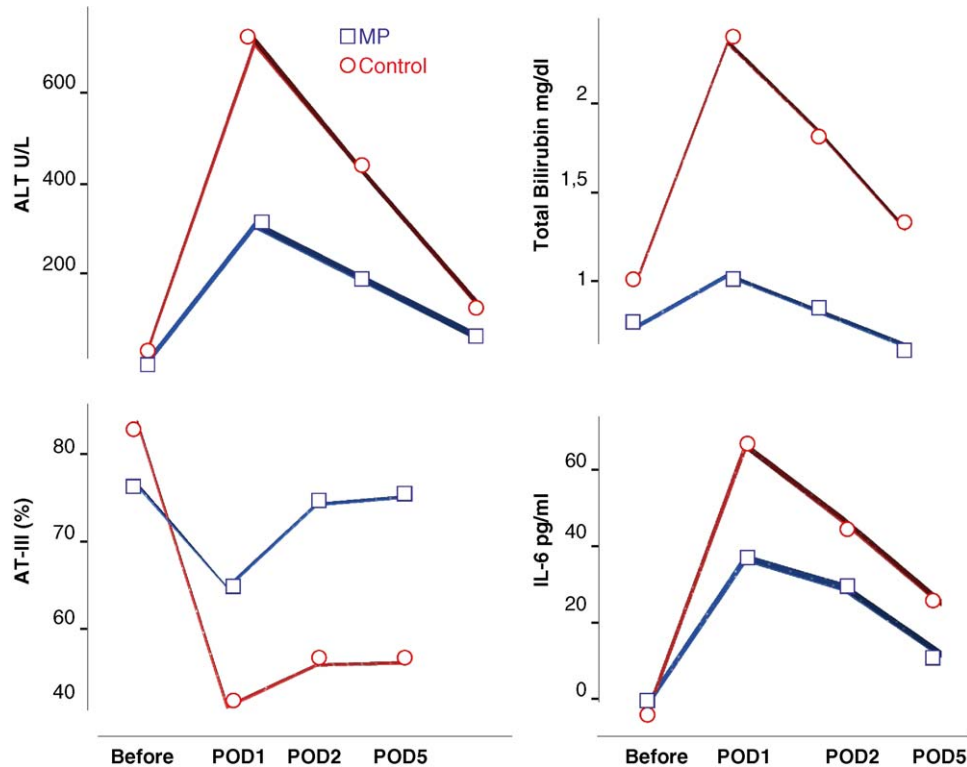
were done between 1989 and 2004 in a tertiary care university hospital. The first partial segment IV resection was done in 1994 and since that time 94 cases have been reconstructed using this approach. All of them had a complex injury (Strasberg E1-E5), and although in many cases the bifurcation was preserved (E1-E3), a high bilioenteric anastomosis was done, because of the technical advantage of the resection for reconstruction. In 70 cases the bifurcation was identified and in 24 cases, in which the confluence was not preserved, the right and left ducts were found, except in one case. In 3 cases, the right duct was found unsuitable for anastomosis and a liver resection was done. In the remaining 21 cases, an anastomosis was done, using a stent (transhepatic, transanastomotic) through the right duct. Results were considered good according to the Hopkins criteria in 86 cases (91%). In 4 of the 8 remaining cases a reoperation was done. Four of these cases have developed secondary biliary cirrhosis, two of which have died while waiting for a liver transplantation, four and six years after reconstruction. Partial segment IV and V resection allows adequate exposure of the confluence and the isolated left or right hepatic ducts. Anterior exposure of the ducts allows an anastomosis in well-preserved, nonischemic, nonscarred, or noninflamed ducts. Parenchymal removal allows also the free placement of the jejunal limb, without external compression and tension, obtaining a high-quality anastomosis with excellent long-term results.

5

**PROSPECTIVE RANDOMIZED STUDY OF THE BENEFITS OF PREOPERATIVE CORTICOSTEROID ADMINISTRATION ON THE HEPATIC ISCHEMIA-REPERFUSION INJURY AND CYTOKINE RESPONSE IN PATIENTS UNDERGOING HEPATIC RESECTION**

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Hepatic pedicle clamping is widely used in many institutions to reduce intraoperative bleeding during liver surgery. The major drawback of hepatic pedicle clamping is ischemia-reperfusion (I/R) injury, which is cause of liver injury and dysfunction. Preoperative steroid administration has been advocated to reduce ischemia-reperfusion injury and surgical stress following hepatic resection. The aim of this prospective, randomized study was to determine whether steroid administration may reduce liver injury and improve short-term outcome. Forty-three patients undergoing liver resection were randomized to a steroid group (MP group) or to a control group (control group); patients in MP group received 500 mg of methylprednisolone just before the surgery whereas those in control group did not. Serum liver levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (t-bil); anti-thrombin III (AT-III), prothrombin time (PT), interleukin-6 (IL-6), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) were measured before and immediately after the operation and on postoperative days (POD) 1, 2, and 5. Length of stay, and type and number of complications were recorded. Postoperative serum levels of ALT, AST, T-bil, were significantly lower in the MP group than in controls at POD 1, 2, and 5. The postoperative level of AT-III in the control group was significantly lower than in the steroid group at each time point measured after hepatic resection (ANOVA  $P < 0.01$ ). The values of inflammatory cytokine as IL-6 and TNF- $\alpha$  were significantly lower compared with the control group as well as the incidence of postoperative complications in the control group tended to be significantly higher than those in the steroid pulse group. CONCLUSION: Preoperative administration of methylprednisolone resulted in significantly lower hepatic enzyme elevation, inflammatory cytokine levels and attenuated the decrease in AT-III following hepatic resection. These results suggest that Steroid pretreatment represents a potentially



important biologic modifier of I/R injury and may improve the postoperative outcome (Fig. 1).

6

**COLD ISCHEMIA CAUSES INCREASED MITOCHONDRIAL  $Ca^{2+}$  UPTAKE VIA INCREASED EXPRESSION AND ACTIVITY OF MITOCHONDRIAL PHOSPHOLIPASE C**

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Primary graft nonfunction is a significant problem in liver transplantation and is related to cold ischemic (CI) damage. The mechanism of this injury involves increased cellular and mitochondrial  $Ca^{2+}$  ( $mCa^{2+}$ ) uptake, which leads to  $mCa^{2+}$  overload and release of proapoptotic factors from the mitochondria. We have shown that inhibition of  $mCa^{2+}$  uptake can attenuate cold ischemic (CI) damage and that phospholipase C- $\delta 1$  is a regulator of this pathway. We hypothesized that mitochondrial phospholipase C is upregulated or sensitized by CI which facilitates increased  $mCa^{2+}$  uptake. Rat livers were perfused with UW solution and harvested. Half was homogenized immediately; the other half was first subjected to 24 hour cold storage in UW. Mitochondria were isolated and incubated in a buffer containing 1 mM ATP and 0.1 or 0.2  $\mu M$   $^{45}Ca^{2+}$ . A selective PLC inhibitor, U-73122, and its inactive analog, U-73343, were added to determine their effects on  $mCa^{2+}$  uptake. Western blots were performed on mitochondrial membranes from both ischemic and nonischemic livers using anti-PLC- $\delta 1$  antibodies, and densitometric analyses were used to quantify protein expression. Mitochondrial transmembrane potential ( $m\Delta\psi$ ) was evaluated using Mito Tracker Red fluorescence. Experiments were performed on a minimum of 4 animals; Student *t* test determined significance. 1) Mitochondrial  $Ca^{2+}$  uptake increased significantly after 24 hour CI in UW in the presence of both 0.1  $\mu M$  ( $34 \pm 10\%$ ) and 0.2  $\mu M$   $Ca^{2+}$  ( $61 \pm 16\%$ ) ( $P < 0.01$  for both).

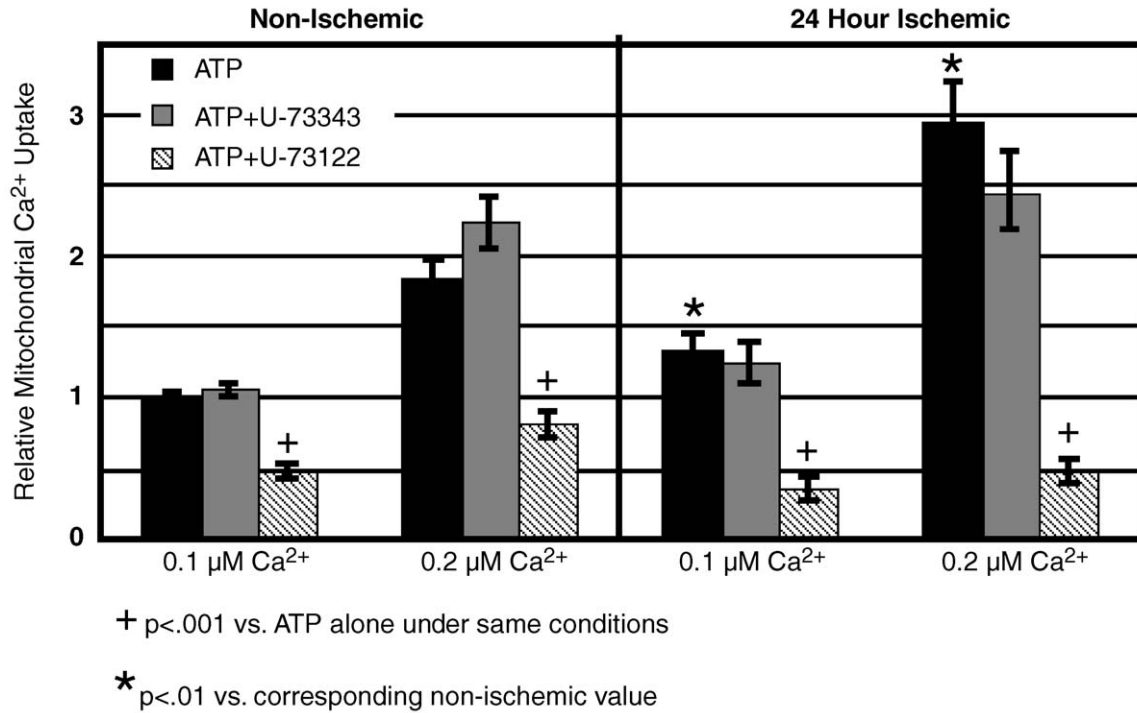
2) U-73122, but not U-73343, significantly and dose-dependently decreased  $mCa^{2+}$  uptake in mitochondria from both ischemic and nonischemic livers ( $P < 0.001$ ), without affecting  $m\Delta\psi$ . 3) U-73122 had a more pronounced effect following CI ( $72 \pm 4\%$  vs.  $51 \pm 5\%$  decrease in  $mCa^{2+}$  uptake,  $P < 0.01$ ). 4) Western blot and densitometry demonstrated that mitochondrial PLC- $\delta 1$  expression increased by  $175 \pm 75\%$  ( $P < 0.05$ ) following CI. These data demonstrate that PLC is essential for  $mCa^{2+}$  uptake during both physiologic and CI conditions. Mitochondrial PLC has increased expression and appears to be sensitized following CI, as U-73122 had a more profound effect post-CI. Inhibition of mitochondrial PLC therefore represents a novel target in the study of liver damage resulting from CI (Fig. 1).

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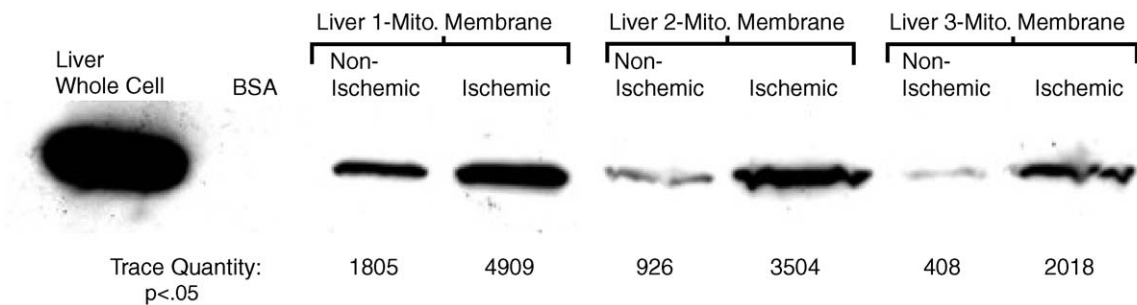
**CEACAM1 EXPRESSION IN INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS (IPMNs) OF THE PANCREAS: A FACTOR OF PROGNOSTIC SIGNIFICANCE IN INVASIVE IPM-CARCINOMAS**

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Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) is a member of the carcinoembryonic antigen (CEA) family, which belongs to the immunoglobulin supergene family. CEACAM1 is involved in intercellular adhesion, signal transduction, and tumor cell growth regulation. This study was performed to assess whether CEACAM1 expression in intraductal papillary mucinous neoplasms (IPMNs) is correlated to long-term survival. Immunohistochemical staining pattern of the monoclonal anti-CEACAM1



Western Blots for PLC-δ1 in Mito. Membranes Pre- and Post-Ischemia



antibody 4D1/D2 was evaluated in 32 IPMNs of the pancreas (4 IPM-adenomas [A], 15 IPM-borderlines [B], 2 noninvasive IPM-carcinomas [C], 11 invasive IPM-C). There are several distinctive staining pattern: cytoplasmatic and apical negative (-), apical positive (+), moderate cytoplasmatic and apical positive (++), strong cytoplasmatic and apical positive (+++). Kaplan-Meier analysis was performed with an up-to-80 month follow-up to assess the prognostic relevance of CEACAM1 expression; 27 tumors (84%) were classified as CEACAM1 positive. In IPM-A and IPMN-B a weak apical staining (+) was observed in 50% and 80%, respectively. Median follow-up in IPM-A was 58 months; in IPM-B, 49 months. No patient died of tumor-relapse. Noninvasive IPM-C showed both cytoplasmatic and apical positive staining (++). One patient died of tumor recurrence 49 months after initial diagnosis, the other patient is still disease-free after 56 months. The strongest CEACAM1 expression was observed in invasive IPM-C of relapse-free survivors (1x ++, 3x +++). The median follow-up for relapse-free survivors was 39 months. In patients with tumor-related death (median tumor related follow-up, 12 months), the CEACAM1 expression was significantly lower (4x +, 1x ++). Kaplan-Meier analysis revealed a highly significant association between CEACAM1 overexpression and long-term survival ( $P < 0.033$ ) in invasive IPMN-C. Moderate to high cytoplasmatic

and apical expression of CEACAM1 in invasive IPM-C of the pancreas is highly associated with a long-term survival ( $P < 0.033$ ). This raises the possibility to stratify patients with invasive IPM-C into low-risk and high-risk groups.

8

MIDDLE HEPATIC VEIN PRESERVATION WITH SPLENIC ARTERY GRAFT IN RIGHT LOBE LIVING DONOR

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We herein present a case with the use of a right lobe of the liver with the inclusion of the middle hepatic vein (IMHV) in the graft as well as a splenic artery vascular graft in a living related liver transplantation. The IMHV have been applied by the groups from Asia with large experience and good results, although it is not routine in the Western countries. The donor was a 19-year-woman who donated part of her liver to her mother, a 52-year-old woman who suffered from hepatitis C cirrhosis and a one single 3-cm hepatocellular carcinoma nodule

with no evidence of extrahepatic spread and MELD score of 11. The donor had no evidence of diseases and was evaluated based on our group living donor protocol. The arterial reconstruction during the reperfusion sometimes is complicated because of the presence of a small and short arterial stump and because of the proximity of the biliary structures in the graft-cutting surface. The current literature has demonstrated that in patients with portal hypertension and high flow in the portal vein, the hyperflux to the graft can be avoided by splenic artery ligation or even temporary portocaval shunt. We decided to apply in this case a 4 cm long arterial graft that came from the recipient and the proximal hepatic artery reconstruction was done in the back table. This maneuver made the arterial reconstruction at the recipient easier and faster because we were then able to make the distal anastomosis in a larger part of the hepatic artery near the celiac trunk. In the other hand, the inclusion of the middle hepatic vein offers to the patient a graft with optimal outflow and less blood congestion that can facilitate the organ regeneration and recovery of its functions. The donor was discharged from the hospital 5 days after surgery and the recipient in the 9<sup>th</sup> postoperative day with no evidence of any complication related to the surgery. Based in our growing experience with the IMHV in the right donor grafts we can concluded that this technique is safe and can offer to the recipient a better chance of recovery during the post operative period. The use of splenic artery graft can represent a new technical option to the arterial reconstruction besides its utilities in the cases of portal hyperflux.

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**SPLIT LIVER TRANSPLANT FOR TWO ADULT RECIPIENTS—SURGICAL TECHNIQUE**

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This video demonstrates our technique for division of a single donor liver for two adult recipients. Split liver transplant for two adult recipients is a procedure that is slowly developing as issues such as donor

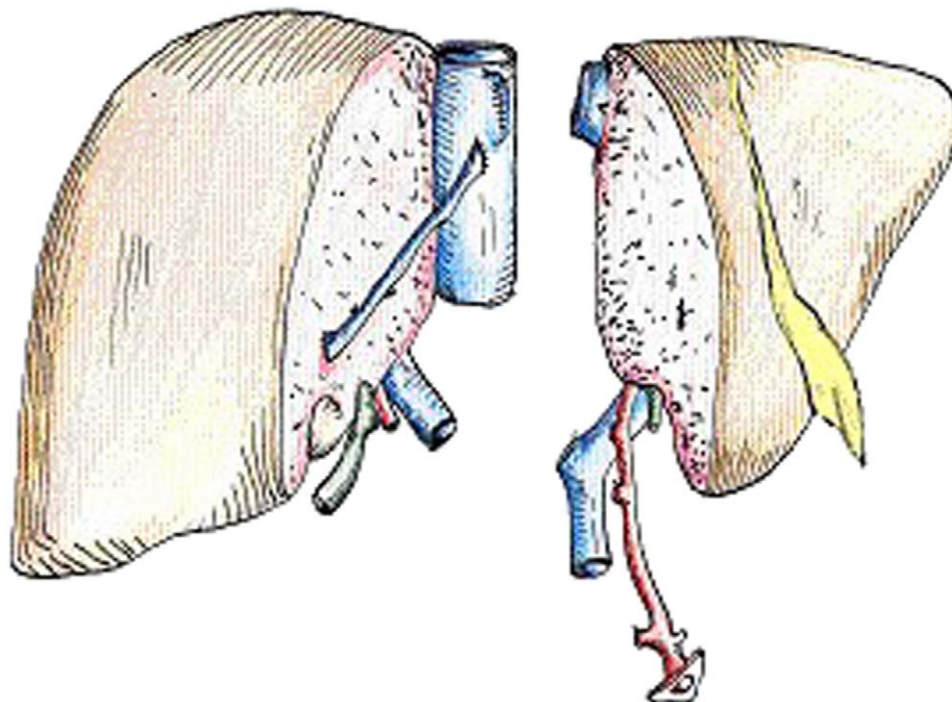
and recipient selection are better defined. It remains a technically demanding procedure and optimizing the surgical technique of the split will play an important role in its success and ability to expand the donor pool. Since 1999, we have performed 32 right lobe/left lobe splits from 16 deceased donors. The split is performed in the mid-plane of the liver, dividing it into its anatomic right and left lobe. The inferior vena cava is preserved with the right lobe, thus maximizing outflow of the right lobe graft (by preserving all short hepatic veins draining into the vena cava) and allowing back-table reconstruction of large middle hepatic vein tributaries using vein grafts from the donor. The outflow for the left graft is based on the common confluence of the left and middle hepatic vein. The main hilar vascular structures are preserved with the left lobe graft while the common bile duct is preserved with the right lobe graft. Biliary drainage of both grafts is then possible with a single anastomosis in both recipients (right graft via CBD, left graft via single left hepatic duct). The actual parenchymal transection is performed in situ, thus minimizing the amount of cold ischemia to the grafts. A diagram of the surgical procedure is shown (Fig. 1).

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**EXTRACORPOREAL EXTENDED RIGHT LOBECTOMY WITH VENA CAVA RESECTION**

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The majority of major liver resections can be performed with conventional techniques of vascular control and normothermic ischemia. In very selected cases as tumoral invasion of hepatocaval confluence, resection is not possible. The period of vascular clamping and resulting ischemia can be too short to allow for major and complex liver resections and vascular reconstruction. In an attempt to offer new options to increase the resectability rate for these extreme cases, has been



developed different procedures in which hypothermic protection of the remnant liver was added to hepatic vascular exclusion. The video details the presentation of a patient with cholangiocellular carcinoma occupying the right lobe and segment IV of the liver. The right and middle hepatic veins and the inferior vena cava were markedly compressed and invaded by the tumor. No evidence of distant spread was observed.

Preoperative percutaneous transhepatic right trisegment portal vein embolization was performed to initiate compensatory hypertrophy in the remnant segments II and III. Extracorporeal extended right hepatic lobectomy (ex situ in vivo procedure) combined with resection of inferior vena cava was performed. An ePTE graft, 20 mm in diameter was interposed in the defect of the inferior vena cava, avoiding the use of venous extracorporeal bypass. The left hepatic vein was reimplanted into graft replacement. A groin arteriovenous fistula was created between superficial femoral artery and saphenous vein.

## 11

### HAND-ASSISTED LAPAROSCOPIC LEFT SECTIONECTOMY

Eduardo de Santibañes, Juan Pekolj, Rodrigo Sánchez Clariá, Gustavo Stork, Martín Palavecino, Christian Bertona, Hospital Italiano, Buenos Aires, Argentina

Indications for laparoscopic liver resections are: benign liver tumors located in anterior segments. Nowadays, according to the technological advances, these indications are increasing. The purpose of this video is to show the surgical technique to resect a benign hepatic tumor, using a hand-assisted method in a left trisectionectomy. We report the case of a 32-year-old female patient with a giant liver mass in segments II, III and IV of Couinaud, without previous illness and a history of medication with contraceptives. Four months before, she began with epigastric pain and early satiety. Laboratory test showed a normal CA 19-9. The CT scan showed an image located in the left liver, hypervascularized, with a central hypodensity. The mass was near the middle hepatic vein, pushing it to the right. As the patient was symptomatic, a surgical treatment was decided. In the procedure the maneuvers that we used in open surgery were reproduced: left liver mobilization, left pedicle isolation, Pringle maneuver, isolated ligation of vascular structures, CUSA, and US. The patient was discharged at day 5, without postoperative complications. Hand-assisted laparoscopic liver resections are procedures that can be performed safely, if specific indications and the same tips used in open surgery are followed.

## 12

### LIVER RESECTION AND IVC RECONSTRUCTION UTILIZING LIVER HANGING TECHNIQUE

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We have successfully performed right hepatectomy with intrahepatic IVC resection followed by IVC reconstruction for a case of giant right adrenal malignant tumor with extensive direct invasion to the liver and IVC. A 58-year-old male patient was admitted with diagnosis of advanced right adrenal malignant tumor (10 cm in diameter) with extensive direct invasion to the right liver and a wide area of surrounding tissues (including IVC, diaphragm, and retroperitoneum) associated with a marked tumor thrombus in IVC. Because of extensive tumor invasion to the surrounding tissues, mobilization of the right liver was not possible at all. Consequently, anterior approach with

“Liver Hanging Technique” was employed for right hepatectomy. Following careful placement of a tape between the anterior wall of IVC and the posterior surface of the caudate lobe of the liver for the “Hanging Technique,” the liver parenchyma was transected at the level of “Cantlie’s line” utilizing forceps fracture method, CUSA, and bipolar scissors. After liver transaction was completed, the exposed anterior wall of IVC was carefully examined with intraoperative ultrasonography (IOUS). IOUS revealed an extensive tumor invasion to the right-posterior wall of IVC (7 cm in length) and a marked tumor thrombus protruded inside the IVC cavity. Finally, the intrahepatic-intrahepatic IVC (a segment of 9 cm long), immediately caudal to the origin of middle and left hepatic veins, was resected together with right liver (en bloc). Following the segmental resection, the IVC was replaced with a PTFE graft (15 mm in diameter) with end-to-end anastomosis for both ends of the graft. Postoperative course was uneventful. Since the pathology of the tumor turned out to be malignant (diffuse large B cell) lymphoma, the patient subsequently underwent chemotherapy. For the safe resection of giant liver tumors with extensive direct invasion to surrounding tissues (or right adrenal tumors with liver invasion) with or without IVC reconstruction, anterior approach utilizing “Liver Hanging Technique” appears to be extremely useful.

## 13

### THE EFFECT OF NEOADJUVANT CHEMOTHERAPY FOR HEPATIC COLORECTAL METASTASES ON THE ACCURACY OF FDG-PET SCAN

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FDG-PET scan improves the therapeutic management of patients with colorectal liver metastases, including better patient selection for surgery. Neoadjuvant chemotherapy before hepatic resection of colorectal metastases may also improve patient selection and overall outcome. The accuracy of FDG-PET scan following neoadjuvant chemotherapy is not established. Patients with colorectal hepatic metastases were assigned to either neoadjuvant treatment or immediate hepatic resection according to the resectability, the risk of recurrence (MSKCC clinical score 2 or more) and the oncologist’s preference. Neoadjuvant regimens were based on Irinotecan or Oxaliplatin. Most patients were evaluated with FDG-PET before neoadjuvant treatment and all were evaluated with CT and FDG-PET before surgery. In the absence of extensive extrahepatic disease they underwent open exploration, intra-operative ultrasound and resection of all metastatic sites by either anatomic or nonanatomic hepatic resection. In case of complete clinical response, the metastatic sites were resected as guided by original imaging. Operative and pathological findings were compared to the CT and FDG-PET; 51 patients were studied. Twenty-three patients, with 23 liver lesions, underwent immediate hepatic resection (group 1), and 27 patients, with 54 lesions, received neoadjuvant chemotherapy before surgery (group 2). For group 1, FDG-PET was true positive (TP) in 20 lesions, false negative (FN) in 3 lesions, and false positive (FP) in 1 case. Sensitivity was 87% and accuracy 83%. For group 2, FDG-PET was TP in 23 lesions, true negative (TN-complete FDG-PET and complete pathological response) in 18 lesions, it was FP in 3 lesions, and FN in 12 lesions (FN-complete FDG-PET response but not complete pathological response). The sensitivity, specificity, and accuracy in the evaluation of intrahepatic metastases were therefore 66%, 86%, and 73%, respectively, significantly inferior to the results in the first group ( $P = 0.03$ ). Sensitivity of FDG-PET in detecting colorectal hepatic metastases following neoadjuvant chemotherapy decreases significantly. In candidates for potential curative hepatic resection following neoadjuvant chemotherapy, the extent of resection should be guided by additional

imaging modalities (intraoperative ultrasound and CT) and by the original imaging.

14

**ONCOSURGE: A COMPUTER-BASED DECISION MODEL TO OPTIMIZE THERAPEUTIC STRATEGIES IN THE MANAGEMENT OF PATIENTS WITH COLORECTAL LIVER METASTASES (CLM)**

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Surgery is the only potentially curative treatment for CLM, with 5-year survival of 20–35%. Only 20% of patients are initially resectable. Oxaliplatin (OXA) chemotherapy renders an additional 10–20% for resection with curative intent. No consensus exists on appropriate treatment strategies. Following a comprehensive literature review, an expert panel of 16 surgeons and oncologists rated the appropriateness of different strategies (resection, chemotherapy, local destruction, and their combination) for 1,500 hypothetical CLM cases. Using the statistically validated RAND/UCLA Appropriateness Method, a computer based decision model was constructed. Treatments are appropriate if the benefits outweigh the harms on a scale of 1 (inappropriate) to 9 (appropriate). Overall agreement rates between experts ranged from 93.4% to 99.1%. Absolute contraindications for resection included nonresectable extra-hepatic disease, unfit for surgery, metastatic involvement of >70% liver. Age, primary tumor stage, timing of detection, blood transfusion, resection type, CEA levels and previous hepatectomy are known prognostic factors but did not influence the decision making strategy. With regard to appropriate pre-operative chemotherapy regimen ratings: 5-FU + FA was inappropriate; 5-FU + FA + OXA 75%, 5-FU + FA + irinotecan (IRI) 65%; 5-FU + FA + IRI + OXA 33%. The appropriateness ratings of postoperative chemotherapy post R0 resection: 5-FU + FA inappropriate, 5-FU + FA + OXA 55%, 5-FU + FA + IRI 43%, 5-FU + FA + OXA + IRI 10%, and post R1-resection: 5-FU + FA inappropriate; 5-FU + FA + OXA 80%, 5-FU + FA + IRI 75%; 5-FU + FA + OXA + IRI 55% (Table 1). In the absence of prior consensus, a high degree of agreement between experts was detected, making the

**Table 1.** Appropriateness of Preoperative Chemotherapy If Surgery or Ablation Intended

| Determinants of Preoperative Chemotherapy | Appropriateness of Treatment Rating (%) |
|---|---|
| Adequate radiological resection margins   | 33                                      |
| Inadequate radiological resection margins | 67                                      |
| No portal lymph node involvement          | 11                                      |
| Possible portal lymphadenopathy           | 89                                      |
| 1 metastasis                              | 35                                      |
| 2–4 metastases                            | 80                                      |
| >4 metastases                             | 85                                      |
| Largest metastasis <4 cm                  | 30                                      |
| Largest metastasis >4 cm                  | 70                                      |
| Unilobar involvement                      | 30                                      |
| Bilobar involvement                       | 70                                      |
| No extrahepatic disease                   | 11                                      |
| Resectable extrahepatic disease           | 89                                      |

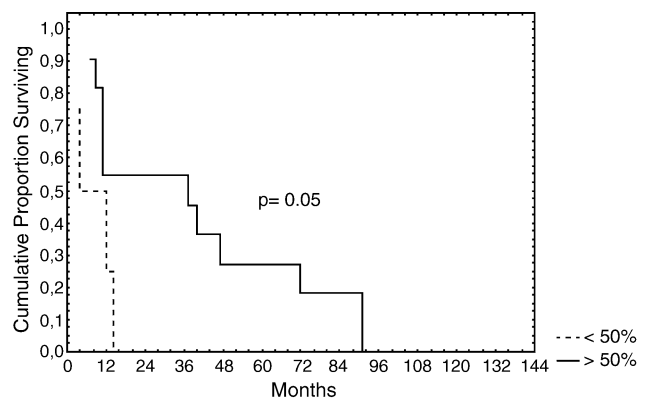
model a useful tool to assist treatment decisions. The model will be available for distribution to interested medical practitioners as an interactive CD-ROM.

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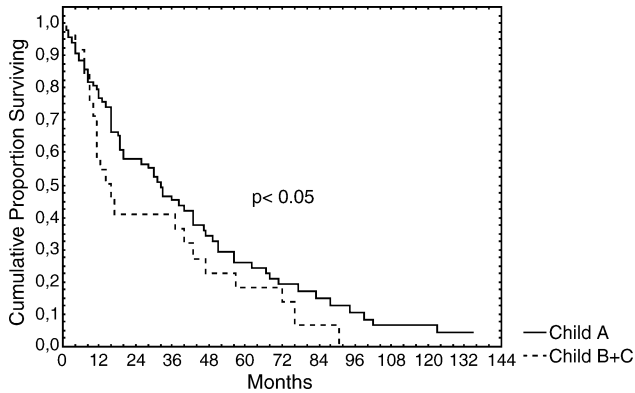
**PREOPERATIVE CT VOLUMETRIC ANALYSIS TO PLAN LIVER RESECTION FOR HEPATOCELLULAR CARCINOMA ON CIRRHOSIS**

Enrico Benzioni, MD, Marta Mozzon, MD, Alessandro Favero, MD, Roberta Molaro, MD, Alessandro Uzzau, MD, University of Udine, Udine, Italy

The purpose of this study was to evaluate the influence of liver function and liver's volumetric parameters on liver resection for hepatocellular carcinoma on cirrhosis. We used CT images in 66 consecutive patients, affected by HCC on cirrhosis, to evaluate the liver's and tumor's volume and to plan preoperatively the surgical procedure to perform, calculating the estimated liver remnant volume (ELRV). The 50 (75.7%) patients belonged to Child-Pugh class A, 16 (24.3%) to class B and C. The areas of the liver, of the lesion, and of the planned resection were delineated consecutively on the screen: ELRV was calculated by subtraction of Total Liver Volume (TLV) and Resection Volume (RV). In-hospital mortality rate was 4.6%, 66% of these cases were Child-Pugh B patients, morbidity rate was 25.8%. The 1-, 3-, 5-, and 7-year survival rates for Child-Pugh class A vs. B + C were 74.5%, 37.6%, 26.2%, 12.6% vs. 50%, 27.3%, 18.2%, and 6.5%, respectively ( $P < 0.05$ ). Analyzing results on the basis of %ELRV in Child-Pugh class A 1-, 3-, 5-, and 7-year survival rate of 72.5%, 50%, 29.2%, and 11.6% is reported when ELRV was over 50%, and 62.5%, 50%, 22.5%, and 0% when ELRV was under 50% ( $P = n.s.$ ). A 1-, 3-, 5-, and 7-year survival rate calculated for Child-Pugh class B + C group was 54.5%, 36.4%, 27.3%, 16.3% vs. 25%, 0%, 0% and 0%, >50% vs. <50% ELRV, respectively ( $P < 0.05$ ). This study shows that the selection of patients with HCC on cirrhosis needs more than a technical and oncological evaluation: the %ELRV could be a good preoperative parameter to plan the surgical procedure when it could be performed. In our series for Child-Pugh B + C, an ELRV <50% is associated with high mortality in the first year and no survival after the third year compared with ELRV >50%, while the threshold of 50% ELRV is not so critical for Child-Pugh class A. Child-Pugh class combined with %ELRV could give the surgeon more information about the safely procedure to perform to obtain the more radical resection according to patient's clinical condition (Figs. 1 and 2).







## 16

### SIMPLIFIED STAGING SYSTEM FOR PREDICTING PROGNOSIS OF PATIENTS WITH COLORECTAL LIVER METASTASIS

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To make a simplified staging system which will reflect the prognosis of patients with liver metastases from colorectal cancer. Until now, some staging systems have been proposed, although no one gained worldwide acceptance. From 1980 to 2002, 369 patients underwent curative resection for liver metastasis from colorectal cancer. The effects of 22 clinicopathological factors on long-term prognosis were analyzed in mono- and multivariate fashion. Using the independent prognostic factors, simplified scoring staging system was constructed. The 3-, 5-, and 10-year survival rates in the 369 patients were 52%, 38%, and 26%. There was no in-hospital death. Factors that significantly affected the prognosis were number of lymph node metastases around the primary cancer ( $P < 0.0001$ ), carcinoembryonic antigen level ( $P < 0.001$ ), resection margin of the liver nodule  $< 5$  mm ( $P < 0.0001$ ), multiple liver metastases ( $P < 0.0001$ ), distribution of liver nodules ( $P = 0.0006$ ), hepatic lymph node metastases ( $P = 0.0059$ ), diameter of liver metastasis  $\geq 5$  cm ( $P = 0.0167$ ), depth of wall invasion (pT4) ( $P = 0.0229$ ) and lymphatic duct invasion ( $P = 0.026$ ) of primary cancer, extrahepatic metastasis

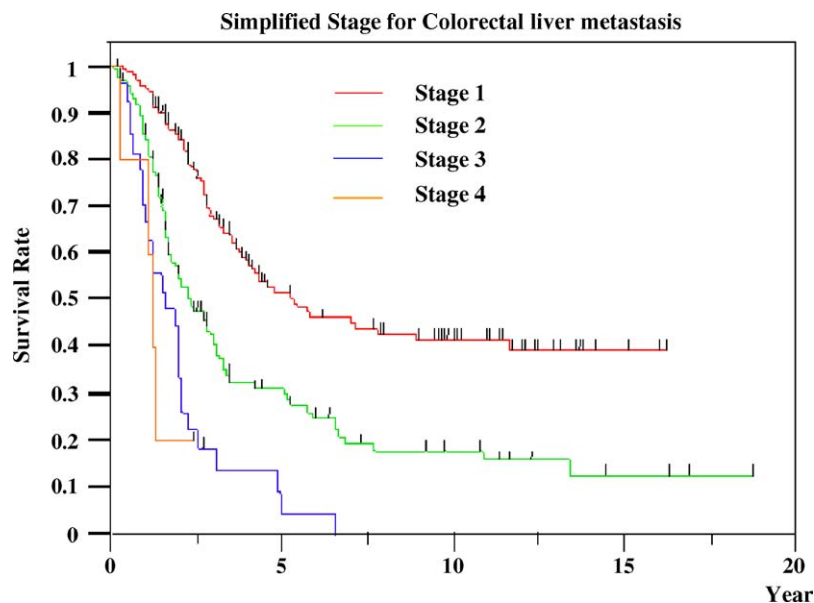
( $P = 0.0273$ ), extrahepatic invasion ( $P = 0.0284$ ), less than 6 months interval between primary and hepatic resection ( $P = 0.0361$ ). In a multivariate analysis, 4 or more lymph node metastases around the primary cancer ( $P < 0.0001$ ) and 50 ng/ml or more carcinoembryonic antigen level ( $P < 0.0001$ ) were independent poor prognostic factors. The patients with hepatic lymph node metastases, who had shortest median survival time of 1.3 years, were assigned to Stage 4. In the rest of the instances, the patients without the independent poor prognostic factors were assigned to Stage 1, those with the either factor to Stage 2, and those with both of the factors to Stage 3. The median survival time (95% confidential interval for median) of each stage were Stage 1, 5.4 years (4.0~11.6), Stage 2, 2.4 years (1.8~3.1), Stage 3, 1.6 years (1.0~2.1), Stage 4, 1.3 years (0.4~). Prognosis of patients with liver metastases can simply be predicted by nodal status of the liver, the number of mesenteric lymph node metastases, and the serum level of carcinoembryonic antigen, if all the hepatic and extrahepatic nodules can be removed (Fig. 1).

## 17

### EVALUATION OF INTERACTION BETWEEN CHEMOTHERAPY AND RADIOFREQUENCY ABLATION (RFA) IN TREATING COLORECTAL LIVER METASTASES USING CELL CULTURE MODEL

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RFA for the treatment of unresectable colorectal liver metastases is associated with up to 45% local/regional recurrence. One mechanism of failure is sublethal temperature in the heat zone of RFA. Combination of chemotherapy is being investigated to reduce recurrence and increase survival. To design a rational chemotherapy strategy, we evaluated the cytotoxicity of three chemotherapeutic agents, 5-FU, oxaliplatin and irinotecan, combined with sublethal heat treatment at different scheduling sequences in two human colon cancer cell lines HT29 (p53 mutant) and HCT116 (p53 wild type). Cell survivals, determined by MTT assays, at varying drug concentrations and different temperatures of 37°, 42°, and 45°C were plotted. We identified that HCT116 cells, but not HT29 cells, became significantly less sensitive to these drugs after pre-exposure to heat shock at 45°C for



**Table 1.** Cell Survival\* of Colon Cancer Cells Preexposure to Heat Shock Followed by Various Drug Treatments

| Cell Line | 5-FU        |               | Oxaliplatin  |             | Irinotecan  |             |
|-----------|-------------|---------------|--------------|-------------|-------------|-------------|
|           | 37°C        | 45°C          | 37°C         | 45°C        | 37°C        | 45°C        |
| HT29      | 77.6 ± 4.4% | 76.1 ± 17.6%  | 61.2 ± 14.1% | 55.2 ± 7.8% | 67.5 ± 6.1% | 71.2 ± 4.1% |
| HCT116    | 68.5 ± 3.1% | 104.8 ± 13.1% | 54.9 ± 1.7%  | 68.3 ± 3.4% | 63.4 ± 3.3% | 87.7 ± 7.3% |

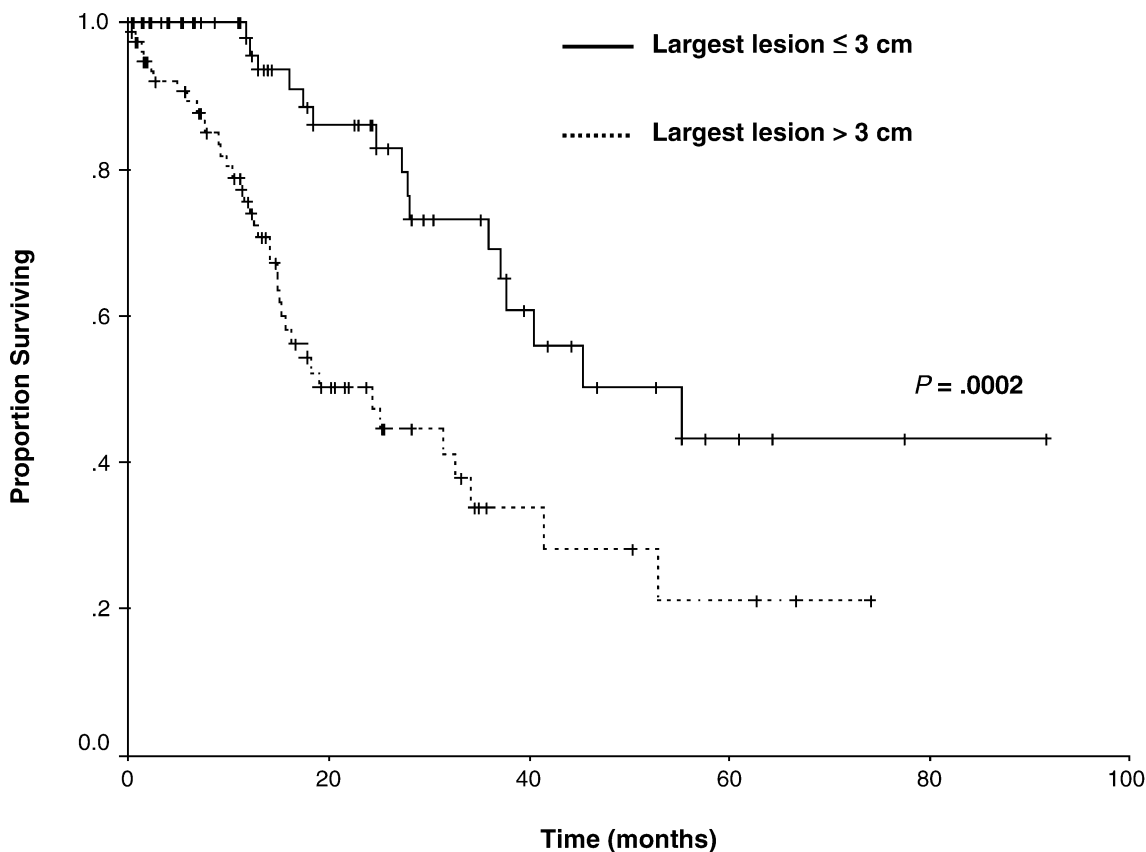
15 min in comparison to 37C ( $P < 0.05$  by Student's  $t$  test; Table 1). With synchronous heat shock and drug exposure, resistance was observed only with irinotecan in HCT116 cells at 45°C in comparison to 37°C (cell survival\* 47.4 ± 7.9% vs. 30.5 ± 2.3%,  $P < 0.05$ , at 10 μM). With pre-exposure to drug followed by heat shock, we also observed a decrease of heat sensitivity at 45°C in comparison to 37°C in irinotecan-treated HCT116 cells (cell survival\* 45.3 ± 8.1% vs. 27.5 ± 2.6%,  $P < 0.05$ , at 10 μM). We further demonstrated a prolong delay of cell cycle transition induced by heat shock at 45°C in HCT116 cells in comparison to HT29 cells using flow cytometry analysis. Furthermore, heat shock protein 27 (HSP27) is highly induced after heat shock at 45°C in HCT116 cells, but not in HT29 cells, analyzed by Western blot. These results implicate the heterogeneity of cancer cells in responding to chemotherapy plus heat treatment. These in vitro data also provide valuable information on selecting chemotherapeutic agents when considering the combination of RFA and chemotherapy in the clinical setting. (\*Cell survival for each temperature was corrected for heat cytotoxicity.)

18

**DEBUNKING DOGMA: SURGERY FOR MORE THAN FOUR COLORECTAL LIVER METASTASES IS JUSTIFIED**

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The efficacy of surgical resection of one to three hepatic colorectal metastases (CRM) is well established. Treatment of four or more CRM, however, is controversial and remains a relative contraindication to surgery at some institutions. We sought to examine patients treated with resection, radiofrequency ablation (RFA), or combined resection plus RFA to assess their overall prognosis, as well as to determine factors impacting on survival. Between 1996 and 2004, 159 patients with four or more CRM were treated surgically at a single institution. All patients were followed in a prospective database. Prognostic factors were evaluated by univariate and multivariate analysis. The study included 107 men and 52 women with a median age of 56 years. The median number of treated lesions was 5 (range: 4 to 14) and the median size of the largest lesion was 3.5 cm (range: 0.3 to 15 cm). The majority of patients ( $n = 117$ , 74%) had bilobar disease. One hundred and one (64%) patients underwent resection plus RFA, 46 (28%) underwent resection only, and 12 (8%) underwent RFA only. The perioperative complication rate was 26% and the 90-day mortality rate was 2.0%. At a median follow-up of 15 months, the median actuarial survival was 35.9 months and the 5-year survival rate was 31%. Unilobar disease and a maximal tumor size less than 3 cm were associated with better 5-year survival rates (57.6% vs. 21.3%,  $P = .06$  and 43.2% vs. 21.3%,  $P = .0002$ , respectively). Patients who underwent resection only (55.3 months) tended to have a longer median survival compared with patients who also had RFA (28.1 months) ( $P = .05$ ). On multivariate analysis, maximal tumor size less



than 3 cm remained a significant predictor of survival (HR = 2.5,  $P = .01$ ) (Fig. 1). Patients with four or more CRM should be considered for liver resection, RFA, or both in order to achieve complete surgical treatment. Surgical treatment is associated with a low perioperative mortality rate and a 5-year survival rate exceeding 30%. Certain clinicopathologic factors, including large tumor size and bilobar disease, are associated with a worse prognosis.

## 19

#### LIVING DONOR LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA IN ADULTS

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Living donor liver transplantation offers the possibility to extend the eligibility criteria of patients suffering from hepatocellular carcinoma (HCC) without penalizing patients waiting for a graft from a deceased donor. From 1988 to 2003, surgical treatment of HCC was performed in 489 patients (transplantation:  $n = 161$ ; resection:  $n = 328$ ). In the transplantation group, all patients were suffering from HCC in liver cirrhosis except for 2 patients with noncirrhotic livers. Among the transplantation group, 17 patients underwent living related liver transplantation of the right lobe (11% of all liver transplantations for HCC; 25% off all living related liver transplantation of the right lobe:  $n = 68$ ). The primary diagnoses in these 17 patients were hepatitis C. ( $n = 10$ ), hepatitis B ( $n = 3$ ), alcohol-toxic ( $n = 2$ ), and cryptogenic liver cirrhosis ( $n = 1$ ). In 1 patient, the HCC had developed in a noncirrhotic liver. The tumor stages were pT1 N0 M0 ( $n = 7$ ), pT2 N0 M0 ( $n = 2$ ), pT3 N0 M0 ( $n = 4$ ), and pT4 N0 M0 ( $n = 4$ ). The HCCs were well-differentiated in 4 patients, moderately differentiated in 10 patients and poorly differentiated in 3 patients. The median tumor diameter was 5.0 cm (1–12 cm). Vascular invasion had occurred in 8 patients (47%; macroscopic invasion  $n = 4$ ; macroscopic invasion:  $n = 4$ ). After a median follow-up of 32 months (1–53 months), tumor recurrence was observed in 3 patients (in 2 patients with a macroscopic vascular invasion and in 1 patient with a microscopic infiltration). Two patients with tumor recurrence died 8 and 26 months postoperatively, respectively. Two more patients died within the first month posttransplant from intracranial bleeding and sepsis. The postoperative mortality was significantly higher when compared to our previously reported experience with full-size liver transplantation. However, the overall results warrant a careful extension of the current eligibility criteria. Interestingly, this extension did not result in an increased rate of HCC with vascular infiltration.

## 20

#### ARE NEOADJUVANT APPROACHES SUPERIOR TO ADJUVANT THERAPIES IN THE TREATMENT OF RESECTABLE PANCREATIC CANCER?

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We sought to compare the effects on survival of adjuvant and neoadjuvant 5-FU based chemotherapy protocols for the treatment of patients with resectable pancreatic carcinoma. An individual-level comparison of prospectively collected primary data from two large institutional series was undertaken. Intent-to-treat neoadjuvant cases were compared to patients following pancreaticoduodenectomy as initial therapy. The results of each study were compared to the existing literature

and determined to be representative of the published literature with regard to outcomes. A pooled sample size of 232 patients (53 surgery only, 120 surgery and adjuvant therapy, 59 neoadjuvant therapy) was examined. Patient cohorts appear similar with a median age of 66 years, range of 37–81 years, and 55% male in the adjuvant group and a median age of 64 years, range of 31–80, and 57% male in the neoadjuvant group. Comparison of Kaplan-Meier survival curves of all patients who initiated therapy demonstrated an improved survival for those who underwent a neoadjuvant approach ( $\chi^2 = 5.474$ ,  $P = 0.02$ ) with median survivals of 19 months in the adjuvant group versus 23 months in the neoadjuvant group. Limiting the comparison to only those patients who underwent postoperative adjuvant therapy, a median overall survival of 20 months was noted in the adjuvant group and 23 months in the neoadjuvant group (NS). Amongst patients who successfully completed both surgery and either adjuvant or neoadjuvant chemotherapy a trend of increased late survival was observed in the neoadjuvant group ( $\chi^2 = 3.339$ ,  $P = 0.07$ ) with a median survival of 39 months in the neoadjuvant group versus 20 months for the adjuvant group. These data suggest a small overall benefit from the application of a neoadjuvant approach in the treatment of pancreatic cancer. Among patients who complete a neoadjuvant protocol, including surgery, a late improvement of survival is suggested versus those who undergo standard surgery followed by adjuvant therapy. These data support the continued use of neoadjuvant therapy, suggesting a benefit to the early application of chemotherapy. These data also suggest that as more effective chemotherapies are identified it may be better to administer them as part of a neoadjuvant protocol as overall survival is not decreased and clinical response can be evaluated.

## 21

#### A NOVEL PANCREATIC CANCER GENETIC SUSCEPTIBILITY FACTOR

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Pancreatic cancer is the fifth leading cause of death due to malignancy in North America representing a major public health problem. The study of individuals with chromosomal translocations and pancreatic cancer will provide clues to where in the genome causative genes might reside. We have identified a patient with early onset pancreatic cancer (age 42) and a familial germline balanced translocation t(2;6)(p25;p22). We hypothesize that by characterizing the translocation breakpoints on chromosome 2 or 6 we will identify a novel gene of importance in the pathogenesis of pancreatic cancer and possibly other human cancers. The chromosome 6p breakpoint is being characterized first because of high frequency of non-random chromosomal rearrangements in this region. The breakpoint has been refined using FISH to within 3 kb, bisecting a predicted gene. RT-PCR and Northern blot hybridizations using primers designed from various portions of the predicted gene demonstrate the presence of as many as 3 isoforms of a novel gene in multiple tissues including pancreas and colon. RT-PCR has shown variable expression of this novel gene in pancreatic and colorectal cancer cell lines. RACE data and EST analyses resulted in identification of a novel gene with 13 exons with a large open-reading frame (495 amino acids) as well as its 3'UTR. Northern blot analysis of the full length of this novel gene demonstrates the presence of a 3 kb and a 5 kb mRNA in multiple tissues. The protein is predicted to have 6 transmembrane domains. A portion of this new protein has high sequence homology to a membrane-bound O-acyltransferase motif. A Myc-epitope was conjugated to this novel protein in a mammalian expression vector used to transfect COS-7 cells. Immunofluorescence using anti-Myc antibodies demonstrates perinuclear localization of this protein. When used in conjunction with endoplasmic reticulum (ER)-specific anti-GRP94 antibodies,

this protein co-localizes to the ER in COS-7 cells. Western blot analysis of Myc-conjugated protein identified the protein in the insoluble fraction. Loss of heterozygosity (LOH) was studied in a cohort of patients with history of pancreatic cancer. We detected over 40% rate of LOH using an intragenic microsatellite marker. We have demonstrated a novel gene that is disrupted by chromosomal rearrangement in a pancreatic cancer patient. The protein product has a motif important in cancer-related pathways. We have observed the loss of this gene in cancer cell lines and in over 40% of pancreatic cancer patients. Further characterization of the gene and its isoforms to confirm the potential tumor suppresser activity and mutation screening is currently ongoing.

## 22

### **Bcl-XL DEPLETION SENSITIZES PANCREATIC CANCER CELLS TO LIGAND-MEDIATED APOPTOSIS**

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To identify potential molecular mechanisms underlying the profound chemoresistance of pancreatic cancer, we examined the expression and potency of three major death receptors, TNF-R, TRAIL-R, and Fas, in mediating cytotoxicity in four invasive pancreatic cancer cell lines. In addition, we analyzed the expression of major anti-apoptotic factors, cell cycle regulators, and death receptor decoys (DcRs) in comparison with normal pancreas tissues and five other human malignant tumor cell lines. Different pancreatic cancer cell lines coexpressed high-levels of TRAIL-R, Fas, and TNF-R1, but were strongly resistant to apoptosis triggered by those death receptors. DcR2 and DcR3 were overexpressed and this coincided with the resistance of pancreatic cancer cells to TRAIL-R and Fas-mediated cytotoxicity. Bcl-XL was predominantly overexpressed in certain pancreatic cancer cell lines, and was also overexpressed in prostate, colorectal and intestinal cancer cells. To determine whether targeted downregulation of Bcl-XL could disable anti-apoptotic mechanisms responsible for chemoresistance, we used RNA interference (RNAi) to knockdown its expression. Bcl-XL knockdown significantly reduced the viability of pancreatic cancer cells to TNF- $\alpha$  and TRAIL-mediated apoptosis. Furthermore, this cytotoxicity was significantly potentiated when Bcl-XL knockdown cells were exposed to novel sublethal-dose antitumor regimens that included geldanamycin (GA), PS-341, Trichostatin A, and Doxorubicin. Geldanamycin and PS-341, in particular, synergistically blocked NF- $\kappa$ B activation, suppressed the Akt/PKB pathway, and downregulated Bcl-2, cIAP-1 and cyclin D1 expression. These alterations of anti-apoptotic and cell cycle checkpoints are likely critical in ligand-mediated cytotoxicity, since GA and PS-341 combined dramatically enhanced the cytotoxic effects of TRAIL and fully broke through chemoresistance. Bcl-XL plays a vital role in pancreatic cancer chemoresistance, and its selective depletion may contribute to novel drug design strategies for the treatment of pancreatic cancer.

## 23

### **MICROVESSEL DENSITY CORRELATES WITH LYMPH NODE METASTASIS, BUT NOT WITH PROGNOSIS, IN HUMAN PANCREATIC CANCER**

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Microvessel density (MVD) has been described as a poor prognostic marker in many malignant diseases. We compared the quantitative

expression of the MVD and vascular endothelial growth factor (VEGF) in normal, inflamed and malignantly transformed pancreatic tissue and determined the prognostic relevance. In 47 tissue samples from patients with adenocarcinoma of the pancreas, 18 of these with non-transformed pancreatic tissue at the resection margins, 11 samples from patients with chronic pancreatitis, who all underwent the Whipple procedure, VEGF and MVD were determined after immunostaining with a CD31 specific monoclonal antibody according to the method of Weidner et al. MVD was correlated with WHO classification, histopathologic grading, lymph node status, tumor size and survival. MVD ranged from 28 to 189 vessels/field. MVD was significantly higher in transformed compared to nontransformed pancreatic tissue ( $P \leq 0.01$ ). Lymph node positive pancreatic tumor specimen showed a higher MVD than lymph node negative tumors ( $P \leq 0.001$ ). No correlation between MVD and survival, tumor size or histopathological grading was found. In a multivariate analysis no prognostic factors for survival were identified. VEGF was expressed in transformed as well as in nontransformed pancreatic tissue and no significant differences were observed. MVD does not provide a useful prognostic marker for patients suffering from pancreatic cancer. The correlation between MVD and lymph node status suggests a role for angiogenesis in early lymphatic metastasis. MVD is significantly higher in transformed compared to nontransformed pancreatic tissue and may serve as an additional diagnostic marker to differentiate chronic pancreatitis from pancreatic cancer.

## 24

### **PREDICTIVE FACTORS FOR MALIGNANCY OR INVASIVE CARCINOMA IN INTRADUCTAL PAPILLARY-MUCINOUS NEOPLASMS (IPMN) OF THE PANCREAS**

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Recently, organ-preserving pancreatic resections for intraductal papillary-mucinous neoplasms (IPMNs) have been reported. Preoperative differential diagnosis between benign and malignant IPMNs, or between non-invasive and invasive IPMNs is crucial for these procedures. The purpose of present study was to identify useful predictive factors for malignant or invasive IPMNs of pancreas by univariate and multivariate analysis. Sixty-two patients with IPMNs of pancreas treated surgically at Hiroshima University Hospital from 1990 to 2003 were reviewed. These patients consisted of 29 patients with adenoma, 10 patients with borderline lesion, 11 patients with noninvasive carcinoma, and 12 patients with invasive carcinoma (according to WHO classification of tumors). Preoperative predictive factors of malignant or invasive IPMNs were analyzed among 10 factors by univariate and multivariate analysis. Size of cystic mass ( $\geq 28$  mm), diameter of main pancreatic duct ( $\geq 6$  mm), presence of patulous papilla, and cytological examinations of pancreatic juice (the presence of malignant cells) were associated with malignancy by univariate analysis ( $P < 0.05$ ). Diameter of main pancreatic duct ( $\geq 6$  mm) and cytological examination of pancreatic juice were identified as independent predictive factors of malignant IPMNs by multivariate analysis ( $P < 0.05$ ). Size of cystic mass ( $\geq 28$  mm), diameter of main pancreatic duct ( $\geq 6$  mm), presence of patulous papilla, mural nodule, and malignant cells in pancreatic juice were associated with invasive IPMNs by univariate analysis ( $P < 0.05$ ). Only presence of malignant cells in pancreatic juice by cytological examination was identified as an independent predictor of invasive IPMNs by multivariate analysis ( $P < 0.05$ ). Carried out single-institution analysis showed predictive factors for malignant or invasive IPMNs of pancreas. These factors should be considered in the preoperative diagnosis of IPMNs to facilitate appropriate surgical management.

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### ARE ANTISENSE OLIGONUCLEOTIDES TARGETED *K-ras* POINT MUTATION EFFECTIVE IN THE TREATMENT OF HAMSTER PANCREATIC CANCER MODEL?

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Pancreatic ductal adenocarcinoma is a complex genetic disease. About >80% of this type of cancer carries *K-ras* point mutation. Oligonucleotides have shown an ability to target specific oncogene transcripts and inhibit their expression in cells. Thus, antisense oligonucleotides (ASO) may be a good therapeutic approach. We sought to elucidate the effectiveness of this gene therapy in hamster experimental pancreatic cancer model. HaP-T1, a cell culture derived from BHP-induced hamster pancreatic cancer was used. MTT, MTT-Agarose were performed using ASO specific to *K-ras* gene. For in vivo experiments, orthotopic tissue implantation was performed. Hamsters were divided in 3 groups: Positive control (PC), Sense treated hamsters (STH), and Antisense treated hamsters (ATH). Oligonucleotides were administered for 2 weeks. Follow up was done by evaluation of the tumor growth by palpation, "general state," weight, and side effects. Five animals of each group were sacrificed at days 10, 17, 24, 31, and 38 to study the local response and metastatic sites. Five animals of each group were left to study the survival time. Necropsy was performed and specimens were fixed in formalin for histopathological study. Antisense oligonucleotides could inhibit the tumoral growth in vitro. It could also inhibit the invasiveness. All tumors were palpable. Positive controls, STH, and ATH survived in average 72.7, 73.8, and 79.6 days, respectively. Side effects were noted in both oligonucleotide-injected groups. Tumor sizes were in average smaller in ATH throughout the study. Spontaneous lymph node metastases were found from 31 days in ATH group, while PC and STH groups showed metastases and direct invasion to adjacent organs from 17 days. After death, metastatic sites were similar in the 3 groups. Liver metastasis has an incidence higher in PC. Moreover, only PC group showed ascites. Antisense oligonucleotides targeted *K-ras* gene may be a good choice in the management of pancreatic cancer because of the suppression of tumor growth in vitro and in vivo.

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### LAPAROSCOPIC PALLIATION OF PANCREATIC CANCER

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Palliation is especially relevant to pancreatic cancer as most patients who present to the surgeon do so with irresectable disease, either locally advanced or with metastatic disease or due to patient factors that preclude them from a potentially morbid operation. It has been claimed that the palliation of symptoms of jaundice and malignant gastric outlet obstruction improve quality of life and may even prolong life. Laparoscopic palliation is achievable and appropriate for selected patients. It has the inherent advantages of laparoscopic surgery and the durability that only surgical palliation can achieve. Since 1991 laparoscopic biliary and gastric bypass has been performed on selected patients. The most common indications are failure of ERCP to relieve biliary obstruction and gastric outlet obstruction that develops following endoscopic decompression of the biliary tree. Since 1991, 27

patients have had laparoscopic bypass operations. There was one post operative death and complications occurred in 3 patients, namely one postoperative cerebrovascular accident, one episode of gastroparesis, and one bile leak that was managed with re-laparoscopy and suture. Median hospital stay was 4 days and operative time ranged from 36 minutes to 240 minutes. This reflects the varying complexity of the operations that were completed. No patient required re-intervention for recurrent jaundice or gastric outlet obstruction. Laparoscopic biliary and gastric bypass is feasible in selected patients. It is technically demanding but provides the patient with the benefit of durable palliation achieved with a surgical bypass with the added benefits of minimal access surgery that are universally accepted such as less post operative pain, fewer wound complications and shorter inpatient stays.

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### INCREASED HEPATIC EXPRESSION OF TUMOR NECROSIS FACTOR-ALPHA-CONVERTING ENZYME (TACE) AND TNF- $\alpha$ AFTER ISCHEMIA REPERFUSION INJURY IN RAT MODEL

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Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) plays a critical role in the inflammatory cascade that follows hepatic ischemia/reperfusion injury. TNF- $\alpha$  converting enzyme (TACE or ADAM17) is a metalloproteinase disintegrin that specifically cleaves precursor TNF- $\alpha$  to its mature form and is involved in the ectodomain shedding of TNF receptors. The regulation of TACE is poorly understood and its role in liver injury and/or regeneration has not been described. Male Wistar rats were subjected to 10 or 30 minutes of partial warm hepatic ischemia followed by zero to 24 hours of reperfusion. Hepatic TACE, TNF- $\alpha$ , and TNF- $\alpha$  receptor levels were assessed by RT-PCR and western blot. Hepatic TACE levels were confirmed with real-time RT-PCR. Serum TNF- $\alpha$  and IL-6 levels were measured by ELISAs. Low levels of TACE were detected in normal liver tissue by both RT-PCR and Western blot. Ten minutes of warm ischemia resulted in a logarithmic rise in TACE mRNA levels, which peaked 6 hours after hepatic reperfusion. At 24 hours, TACE mRNA levels remained overexpressed compared to baseline, but had declined from the 6-hour peak. Real-time RT-PCR of hepatic TACE confirmed this pattern of expression. Western blot analysis demonstrated a strong increase in TACE protein levels 6 hours after the ischemic injury. Following 30 minutes of ischemia, hepatic TACE mRNA levels demonstrated a similar up-regulated pattern of expression, though each time point had an increase when compared to its 10-minute ischemia counterpart. At 10 and 30 minutes of ischemia followed by reperfusion, TNF- $\alpha$  and TNF- $\alpha$  receptor mRNA levels were up-regulated in a pattern similar to TACE mRNA levels. Serum TNF- $\alpha$  and IL-6 levels correlated with the observed increases in mRNA levels in the liver (Table 1). This is the first study to document the presence of TACE in normal liver tissue. Moreover, TACE expression by RT-PCR and western blot is increased following ischemia/reperfusion injury to the liver. This increase in TACE activity, as measured by increases in liver TNF- $\alpha$ , TNF- $\alpha$  receptor and serum TNF- $\alpha$  and IL-6 levels, suggests that TACE plays an important role in liver ischemia/reperfusion injury. Further study to define its role and to determine whether specific TACE inhibitors can change the course of hepatic ischemia/reperfusion injury.

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### VITAMIN E A DAY KEEPS THE PNF AWAY: A NOVEL LINK BETWEEN ENERGY AND ROS IN THE SETTING OF STEATOSIS AND ISCHEMIA/REPERFUSION

**Table 1.** Serum Levels of TNF- $\alpha$  and IL-6 Following Liver Ischemia-Reperfusion Injury

| Groups (n = 4/group)                      | TNF- $\alpha$ (pg/ml) | IL-6 (pg/ml)       | TACE mRNA (fg/ $\mu$ g total liver RNA) |
|---|-----------------------|--------------------|---|
| Control                                   | 56.29 $\pm$ 7.27      | 29.24 $\pm$ 2.13   | 100 $\pm$ 31.11*                        |
| 10 minutes ischemia, 3 hours reperfusion  | 77.70 $\pm$ 6.81      | 70.27 $\pm$ 10.28* | 151.67 $\pm$ 34.16*                     |
| 10 minutes ischemia, 6 hours reperfusion  | 90.61 $\pm$ 8.87*     | 40.33 $\pm$ 2.52*  | 176.67 $\pm$ 26.94*                     |
| 10 minutes ischemia, 24 hours reperfusion | 56.53 $\pm$ 5.20      | 40.33 $\pm$ 6.54   | 110 $\pm$ 8.61*                         |
| Control                                   | 56.29 $\pm$ 7.27      | 29.24 $\pm$ 2.13   | 241.67 $\pm$ 30.97**                    |
| 30 minutes ischemia, 3 hours reperfusion  | 86.30 $\pm$ 1.80*     | 56.96 $\pm$ 5.28** | 275 $\pm$ 50.30**                       |
| 30 minutes ischemia, 6 hours reperfusion  | 106.11 $\pm$ 3.81**   | 72.47 $\pm$ 1.21** | 588.33 $\pm$ 39.02**                    |
| 30 minutes ischemia, 24 hours reperfusion | 44.67 $\pm$ 5.54      | 27.40 $\pm$ 2.45   | 138.33 $\pm$ 22.03*                     |

Data are mean  $\pm$  1 SE. \* $P < 0.05$ ,  $P < 0.01$  vs. Control.

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Hepatic steatosis is an increasingly frequent clinical condition associated with complex and detrimental pathophysiologies. Hepatocytes of steatotic livers overexpress mitochondrial uncoupling-protein 2 (UCP2) in response to elevated levels of reactive oxygen species (ROS) and energy substrate. This expression causes the depolarization of the inner-mitochondrial membrane resulting in ATP depletion at rest and especially after stresses such as ischemia and reperfusion (I/R). This ultimately leads to increased susceptibility to primary nonfunction (PNF). In this study, we evaluated the ability of vitamin E acetate, a potent intramitochondrial ROS scavenger, to downregulate UCP2 in order to determine if this would improve cellular energy status at baseline and following I/R. Twelve-week-old male ob/ob mice were fed a control or vitamin E acetate enriched diet for 7 days and hepatic tissue was measured for markers of energy status, ROS, and ROS damage at baseline and 1, 24, and 48 hours following 15 min of total hepatic ischemia.  $P < 0.05$  was considered significant. Prior to I/R, vitamin E acetate resulted in a significant increase in concentration of ATP per gram of protein and was 79% greater than the control

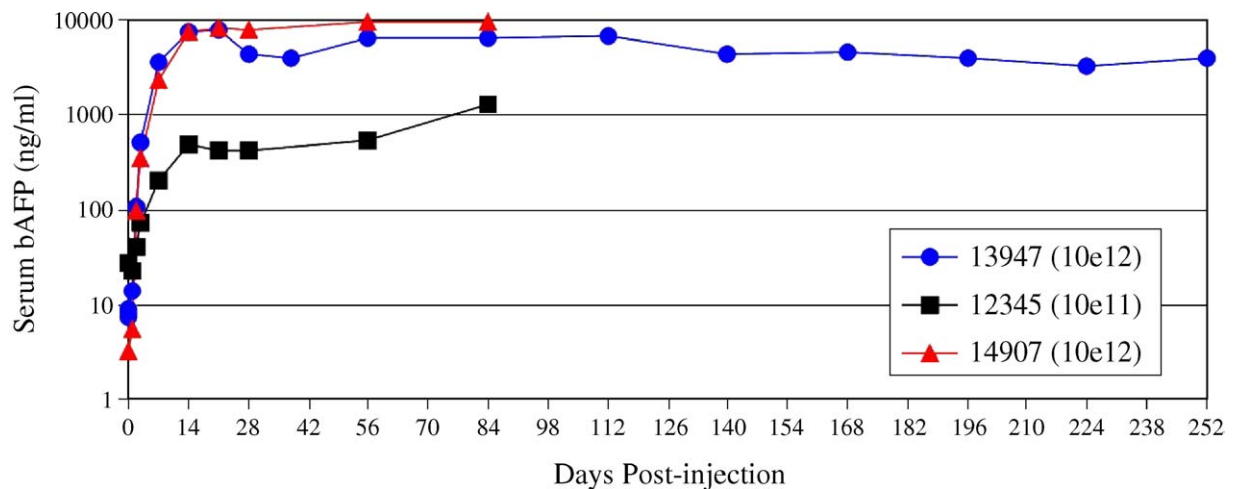
value. This correlated with a significant decrease in UCP2 mRNA expression, which was 58% of that found in control animals. These trends were consistent following I/R in which vitamin E induced a fold decrease in UCP2 content at the early timepoint, while increasing the ATP concentration by nearly 60%. These differences leveled off by 24 hours of reperfusion as animals recovered from the insult. In addition, vitamin E acetate supplementation significantly increased GSH levels, supporting the role of vitamin E acetate as an ROS scavenger at baseline and following I/R. It also was protective against I/R associated ROS resulting in significantly elevated levels of intact mitochondrial DNA, a common marker of ROS damage. Given the reduced baseline energy status of the steatotic liver, administration of vitamin E acetate is functional before and during I/R by scavenging ROS thereby downregulating UCP2. Vitamin E administration results in increased ATP levels and decreased ROS damage following I/R, correcting the inherent weaknesses of these livers. Vitamin E therefore offers a multipotent agent that could be used to protect steatotic livers from PNF.

29

**ISOLATED HEPATIC PERFUSION OF HELPER-DEPENDENT ADENOVIRUS RESULTS IN LONG-TERM GENE EXPRESSION IN THE PRIMATE MODEL**

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Helper-dependent adenoviral vectors (HDAd) are vectors for liver-directed gene therapy since they mediate sustained, high-level transgene expression with negligible long-term toxicity. However, high vector doses are required to achieve efficient hepatic transduction by peripheral intravenous injection. High systemic doses result in wide spread vector dissemination and dose-dependent activation of the acute inflammatory response which can result in severe toxicity. This problem can be surmounted by delivering the vector to the liver via isolated hepatic perfusion. This results in efficient hepatic transduction using low vector doses with minimal systemic dissemination. Three primates were treated with HDAd expressing AFP via the portal vein into the vascularly isolated liver. Two animals received  $1 \times 10^{12}$  vp/kg and the third  $1 \times 10^{11}$  vp/kg. Total hepatic isolation was achieved by Pringle maneuver and suprahepatic and suprarenal vena cava occlusion. Prior to total hepatic isolation, saline was infused into the portal vein to flush blood out of the liver. The vector was then injected



directly into the isolated liver via a portal vein cannula. Hepatic inflow and outflow remained clamped for 30 min to prolong exposure to the virus. Following the 30-min dwell time, unabsorbed vector was flushed from the liver to minimize systemic dissemination. Postoperatively serum AFP levels were measured weekly for the first month, then monthly thereafter. Liver biopsies were performed at 28 days. All three animals tolerated the procedures well with no clinical evidence of vector related systemic inflammatory response. Serum AFP reached a peak at 14 days and has been sustained at high levels for the duration of the observation period (see Fig. 1). Postoperative liver biopsies demonstrated no histologic abnormalities. Isolated hepatic perfusion with subsequent hepatic vascular flushing and drainage results in long-term gene expression of AFP in the primate model. This approach increases the safety and efficacy of HDAd-mediated, liver-directed gene therapy by minimizing the dose required to achieve efficient hepatic transduction and by minimizing systemic vector dissemination. This approach may have clinical applications for gene therapy.

## 30

### OUTCOME OF 1,000 PATIENTS EVALUATED AT THE UPMC LIVER CANCER CENTER

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We evaluated 1,000 consecutive patients with liver tumors at the University of Pittsburgh Liver Cancer Center over the 4-year period from August 2000 to August 2004. Of the 1,000 patients seen, 573 had primary liver cancer and 427 had metastatic cancer to the liver. The liver cancers are categorized in Table 1. Of the 1,000 patients

**Table 1.**

| Tumor Type         | Number | %    |
|--------------------|--------|------|
| HCC                | 464    | 46.4 |
| Cholangiocarcinoma | 109    | 10.9 |
| Neuroendocrine CA  | 74     | 7.4  |
| Colorectal mets    | 171    | 17.1 |
| Other mets         | 182    | 18.2 |

evaluated, 61% were male and 39% female. Mean age was 62.2 years. Treatment consisted of a liver surgical procedure (resection or RFA) in 369 cases (36.9%), hepatic intra-arterial regional therapy (TACE or <sup>90</sup>yttrium microspheres) in 524 cases (52.4%), systemic chemotherapy in 35 cases (3.5%), and palliative care in 72 patients (7.2%). For treated patients, 1, 2, and 3-year actuarial survival is shown in Table 2: These data indicate that over 90% of patients with liver

**Table 2.**

| Procedure              | 1 yr  | 2 yr  | 3 yr  | Median (days) |
|------------------------|-------|-------|-------|---------------|
| Resection/RFA          | 70.8% | 59.4% | 37.9% | 884           |
| Intra-arterial therapy | 44.8% | 23.3% | 8.5%  | 295           |
| Overall survival       | 52.9% | 33.2% | 24.7% | 426           |

cancer evaluated at a tertiary referral center can be offered some form of therapy. Survival rates are superior with a liver resection or ablation procedure ( $P < 0.0001$ ) vs. intra-arterial therapy, which is likely consistent with selection bias. HCC was the most common tumor seen due to referral pattern and screening of hepatitis patients at a major

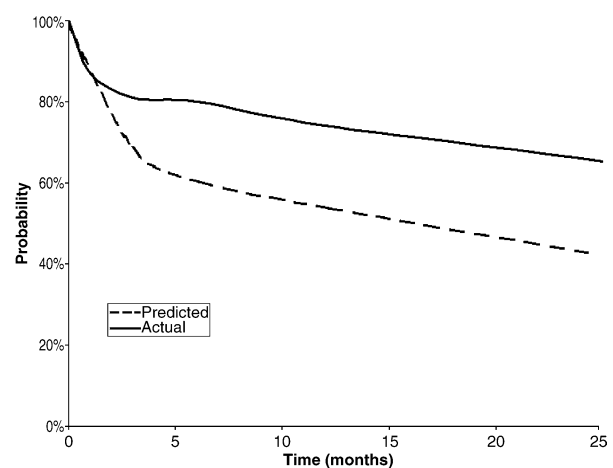
liver transplant center. The most common reason for offering palliative care was hepatic insufficiency (T Bili  $>3.0$ ) usually associated with cirrhosis.

## 31

### LONG-TERM OUTCOME WITH NONSELECTIVE PARTIAL PORTAL DECOMPRESSION FOR PORTAL HYPERTENSION ENCOURAGES APPLICATION

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Operative portal decompression is infrequently undertaken and is generally no longer considered for patients with complicated portal hypertension. This study was undertaken to report outcomes with operative portal decompression attained through small (8 mm) diameter prosthetic H-graft portacaval shunts (HGPCS) and to compare survival to that predicted by MELD. Since 1988 we have prospectively followed patients after undergoing HGPCS to treat bleeding varices failing/not amenable to sclerotherapy/banding. One hundred seventy patients, 115 males and 55 females, of average age of 55 years  $\pm$  13.2 underwent shunting. Cirrhosis was due to alcohol in 56%, hepatitis in 10%, and both in 11%; 17 (10%) were of Child's class A, 47 (28%) of class B, and 106 (62%) of class C. Median, mean  $\pm$  SD of preshunt MELD scores was 13, 14  $\pm$  5.48. Shunting decreased portal vein-IVC pressure gradients from 17  $\pm$  5.0 to 6  $\pm$  3.0 mm Hg (paired Student's *t* test,  $P < 0.001$ ). Thirty-three (20%) patients died by 6 months, 54 (34%) by 24 months, and 87 (62%) by 60 months, generally because of liver failure. Five patients are lost to follow-up and 51 are alive at 48.3, 76  $\pm$  57.8 months (median, mean  $\pm$  SD). Variceal rehemorrhage occurred in 3 (2%) patients after shunting. The 5/10-year survival for patients of Child's class A was 66.7%/33.3%, class B was 48.6%/15.6%, and class C was 29.2%/7.0%. Actual survival was superior to predicted survival (MELD) (Mantel-Haenszel  $\chi^2 P < 0.001$ ) (Fig. 1). Patients undergoing partial portal decompression by small diameter prosthetic H-graft portacaval shunting were generally middle-aged males with advanced alcoholic cirrhosis. After shunting, variceal rehemorrhage was very uncommon. Actual survival was superior to predicted survival by MELD. Long-term survival correlated with degree of hepatic function, though even with very advanced cirrhosis long-term survival was possible. Application of HGPCS for patients with bleeding varices due to cirrhosis and portal hypertension is encouraged.



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**MORTALITY FOLLOWING PORTAL DECOMPRESSION FOR BLEEDING VARICES DEPENDENT ON HOSPITAL VOLUME FOR SURGICAL BUT NOT RADIOLOGIC SHUNTS**

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Mortality following complex surgical procedures has been shown to be inversely related to hospital volume. The purpose of this study

was to determine whether these findings are applicable to radiologic and surgical procedures for complicated portal hypertension. The Agency for Healthcare Administration for the State of Florida database was queried to determine outcomes following TIPS or surgical shunts for 4 years (2000–2003 inclusive). Hospitals were segregated by average number of procedures undertaken per year, and mortality, length of stay, and costs were correlated with hospital volume. Results were compared using Fisher’s exact test; 1,486 patients underwent either TIPS (1,321) or surgical shunts (165) in the state of Florida for the calendar years encompassing 2000–2003. Natural breakpoints

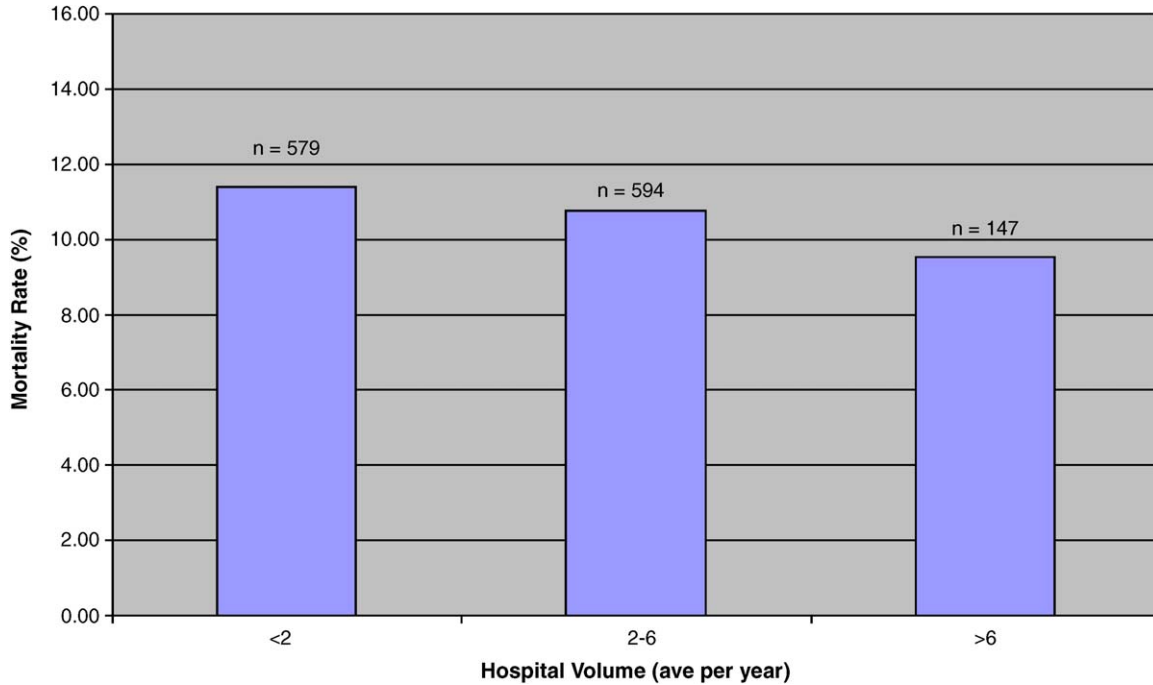
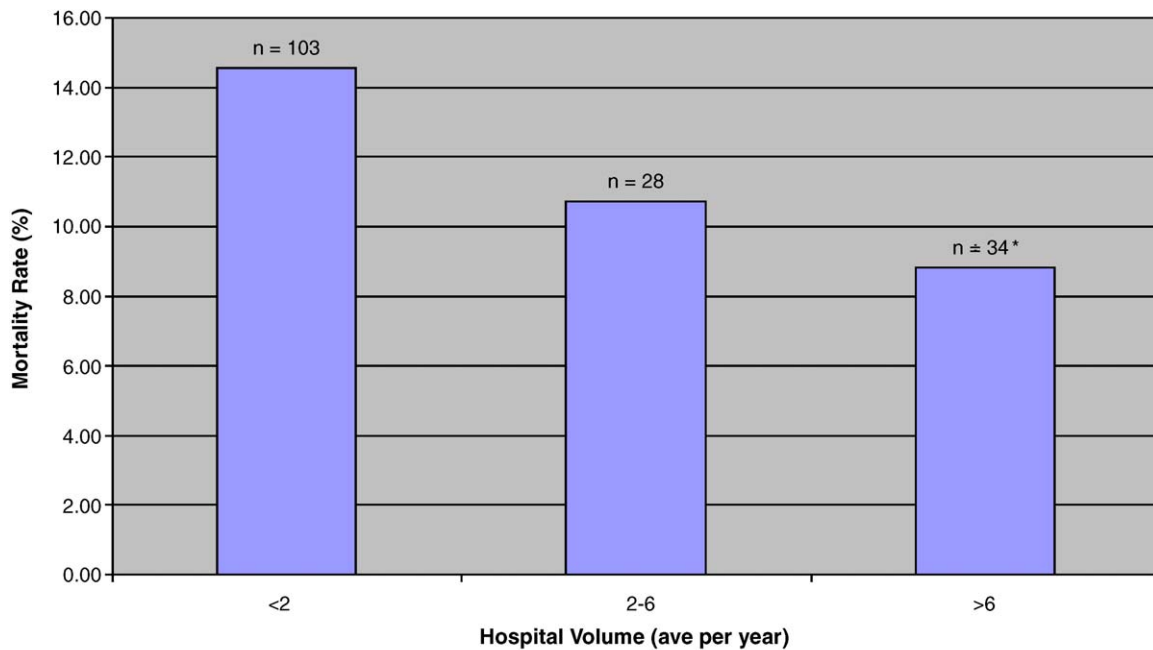


Fig. 1.



\* = significantly less than low volume centers

Fig. 2.



in mortality occurred at 2 and 6 procedures per year and such volumes were significantly correlated with survival for surgical shunts but not TIPS (see Figs. 1 and 2). Overall mortality was not different between TIPS and surgical shunts (10.98% v. 12.73%,  $P = 0.51$ ); however the cost of TIPS when compared with shunting was significant ( $44K \pm 21$  v.  $59K \pm 22$ ,  $P < 0.0001$ ) as well as length of hospitalization ( $8.8$  days  $\pm 9.0$  v.  $15.0$  days  $\pm 12.6$ ,  $P = <0.0001$ ). Surgical procedures for complicated portal hypertension are utilized infrequently when compared to TIPS. Index admission hospital costs and length of stay were less following TIPS, but these findings do not take into account the cost and resources necessary to maintain TIPS patency. Surgical shunts should only be undertaken in high volume centers.

## 33

### PANCREATICODUODENECTOMY OUTCOMES IN A GENERAL SURGERY TRAINING PROGRAM

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The purpose of this study was to compare surgical outcomes after pancreaticoduodenectomy (PD) as a function of the status of the primary operating surgeon (attending surgeon or trainee), within a general surgery training program. The future of the Whipple operation or PD performed in a general surgery residency program may be in doubt. Data support the centralization of PD to high volume centers, many of which are locations for postgraduate fellowship training. We examine surgical outcomes for operations performed by attending staff and resident staff (with supervision). From January 2001 to October 2004, 164 PDs were performed for periampullary disease. These were performed by a single fellowship trained attending in a general surgery training program. Data were prospectively entered into a computerized database, including resident participation. Criteria for performance by the chief resident were established; the operation was considered to have been performed by the chief resident when the trainee performed the entire resection and reconstruction. When these criteria were not met, the operation was considered to have been performed by the attending surgeon. The 30-day inpatient mortality and morbidity were analyzed and compared; 138 Whipple operations were performed with a chief resident as the primary surgeon, and 26 operations were performed with the attending surgeon as the primary surgeon, primarily involving vascular resection and reconstruction (hepatic artery 7/26, portal vein 14/26, IVC 1/26, and superior mesenteric vein 4/26). The 30-day mortality and morbidity were similar between the two groups, including pathologic results; slightly higher mortality was noted in patients where the attending was the primary surgeon. PD can be performed with acceptable morbidity and mortality within the teaching structure of a general surgery training program. Surgical outcomes were similar between attending surgeons and residents, with slightly higher mortality when the attending was the primary surgeon, reflecting higher surgical complexity. This procedure is an important teaching operation for surgical trainees during general surgery training and can be performed with good results by surgical chief residents under supervision (Table 1).

**Table 1.** Outcomes and Surgeon Status

|                           | Number of Operations | Mortality | Delayed Gastric Emptying | Wound Infection | Pancreatic Fistula | Number of Vascular Resections | R0 Pathologic Margin |
|---------------------------|----------------------|-----------|--------------------------|-----------------|--------------------|-------------------------------|----------------------|
| PPPD by resident surgeon  | 138                  | 1.83%     | 33.8%                    | 12.5%           | 6.1%               | 12                            | 82.6%                |
| PPPD by attending surgeon | 26                   | 7.7%      | 15.4%                    | 11.5%           | 7.7%               | 26                            | 88.5%                |

## 34

### PANCREAS-SPARING DUODENECTOMY: EFFECTIVE MANAGEMENT FOR FAMILIAL ADENOMATOUS POLYPOSIS

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Duodenal adenocarcinoma remains a leading cause of death in familial adenomatous polyposis (FAP) patients who have previously undergone colectomy. Upper gastrointestinal surveillance and Spigelman classification system is being used to guide which patients may benefit from a duodenal resection prior to the development of invasive cancer. A retrospective review was done to evaluate the effectiveness of pancreas-sparing duodenectomy (PSD) for the management of duodenal polyps in FAP. There were 21 patients with FAP who underwent successful PSD between 1992–2004 at the Cleveland Clinic Foundation. There were 15 men and 6 women with a mean age of  $55.3 \pm 10.6$  years. All patients were in an endoscopic surveillance program (range 1–7 years). Nineteen patients were Spigelman IV, one III, and one II at the time of operation. No patient had a preoperative biopsy of invasive cancer. The mean time from diagnosis of FAP to duodenectomy was  $26.7 \pm 12.5$  years. Operative times averaged  $327 \pm 61$  minutes with mean estimated blood loss (EBL) of  $503 \pm 266$  ml. There was no mortality and eight patients (38%) had 12 complications; 6 patients (29%) had delayed gastric emptying, 4 patients (19%) had biliary/pancreatic anastomotic leak, 1 patient had pancreatitis, and 1 had a wound infection. There were two re-operations; a gastrojejunostomy was performed for persistent delayed gastric emptying and re-exploration was performed for an early biliary leak requiring t-tube placement. The mean length of stay (LOS) was  $13.1 \pm 10.8$  days. Only one patient (4%) was upstaged with their pathology, finding invasive cancer in both the duodenal specimen and one lymph node. The remaining 16 patients were cancer free. All patients have been followed with serial endoscopies for a mean of 79 months (range 3–152 months). Two patients developed recurrent polyps; one patient at the neoduodenal ampulla and a 4-cm polyp in the advanced jejunum at 68 months and the second developed a 1-cm polyp in the duodenal cuff at 96 months, both have been endoscopically treated. Two patients had late complications of a stomal ulcer at 48 months and intestinal obstruction at 24 months. PSD represents a definitive treatment for duodenal involvement from FAP, and can obviate the need for pancreaticoduodenectomy.

## 35

### PANCREATIC NECROSECTOMY THROUGH A CYST-GASTROSTOMY IMPROVES PATIENT OUTCOME COMPARED TO OPEN NECROSECTOMY IN PATIENTS WITH NECTROTIZING PANCREATITIS

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Roughly 20% of acute pancreatitis cases will be complicated by necrotizing pancreatitis, and more than 80% of deaths associated with acute pancreatitis are associated with the presence of necrosis. Recent guidelines and the practice of our institution have been to operate for pancreatic necrosis if infection is present upon aspiration or if there is continued clinical deterioration. Current surgical techniques carry significant morbidity and mortality and frequently require reoperation. We suggest a novel technique using a mini-laparotomy for pancreatic necrosectomy through a mini-cyst-gastrostomy and continuous retroperitoneal lavage as an alternative to open necrosectomy with multiple reoperations. Twenty-six patients undergoing cyst-gastrostomy (Grp A) with continuous retroperitoneal lavage (5 days) for infected necrosis or worsening clinical parameters were analyzed from a prospective database. Comparisons were made to a cohort receiving a traditional open necrosectomy (Grp B). Etiology of pancreatitis was biliary (Grp A 58% vs Grp B 74%), alcoholic (8% vs 21%), and unknown (34% vs 5%). Indications for surgery were infection (50% vs 100%), clinical deterioration (15% vs 0%), and pseudocyst (35% vs 0%). Using univariate linear regression, the cyst-gastrostomy cohort had a significant improvement ( $P < 0.001$ ) in length of stay (LOS) ( $19d \pm 13$  vs  $57d \pm 42$ ), ICU LOS ( $4d \pm 7$  vs  $37d \pm 40d$ ), complications (bleeding, fistula formation, and pseudocyst), total hospital charges ( $\$105,269 \pm 101,957$  vs  $\$355,651 \pm 338,234$ ), readmission, and reoperation rates. When adjusted for all patient and disease specific variables, including APACHE II score, the differences remained significant ( $P < 0.05$ ), except for total hospital charges. ICU LOS, significantly impacted by procedure, represents the majority of costs in the multivariate model, and therefore accounts for loss in significance from univariate analysis. Based upon improvements in LOS, costs, and complications, we suggest that mini-cyst-gastrostomy is a reasonable alternative to open necrosectomy in selected patients with necrotizing pancreatitis (Table 1).

**Table 1.** Univariate and Multivariate Linear Regression Analysis Outcomes

|   | Cyst Gastrostomy                  | Open Necrosectomy                  |
|---|-----------------------------------|------------------------------------|
| N                                       | 26                                | 19                                 |
| Mean APACHE II Score ( $\pm$ SD)        | 8.2 ( $\pm 3.5$ )                 | 13.5 ( $\pm 3.7$ )                 |
| Complications (%)                       | 5 (18.5)*                         | 18 (94.7)*                         |
| Reoperation (%)                         | 2 (7.7)*                          | 19 (100)*                          |
| Mean length of stay ( $\pm$ SD)         | 19 ( $\pm 13$ )*                  | 57 ( $\pm 41.7$ )*                 |
| Mean ICU length of stay ( $\pm$ SD)     | 4 ( $\pm 6.9$ )*                  | 37 ( $\pm 40.4$ )*                 |
| Mean total hospital charges ( $\pm$ SD) | $\$105,269 (\pm 101,957)^\dagger$ | $\$355,651 (\pm 338,234)^\ddagger$ |

\*Significant at  $P \leq 0.001$  in univariate analysis;  $P \leq 0.05$  in multivariate analysis.

†Significant at  $P \leq 0.001$  in univariate analysis.

**36**

**FACTORS ASSOCIATED WITH CLINICAL FAILURE FOLLOWING PANCREATECTOMY AND AUTOLOGOUS ISLET CELL TRANSPLANTATION**

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For patients with chronic pancreatitis (CP), total pancreatectomy and islet auto-transplantation (IAT) often alleviates debilitating abdominal pain. However, a small percentage of patients in our series have demonstrated clinical failure as evidenced by persistent narcotic-dependence. The factors associated with clinical IAT failures are not well

understood. During the period of 2000-2004, 47 total or near-total pancreatectomies with IAT were performed. Preoperative patient characteristics, metabolic studies, narcotic and insulin usage, and pain scores were recorded at routine clinic follow-up. Failure was defined by continued high narcotic usage and inability to be weaned off preoperative narcotic dosages. Narcotic usage was converted to morphine equivalents (MEQs) so that standard statistical calculations (Student's *t* test and  $\chi^2$  analysis) could be performed. Forty-seven patients with a median age of 39 (range, 16-63) underwent total ( $n = 43$ ) or near total ( $n = 4$ ) pancreatectomies with IAT. In the subset of patients considered failures, the etiology of CP was idiopathic ( $n = 8$ ), hereditary ( $n = 1$ ), and alcohol ( $n = 2$ ) induced pancreatitis. These patients postoperative MEQs were significantly greater ( $P = 0.03$ ) than the other 36 patients (263 mg vs. 99 mg). There was no significant difference ( $P = 0.73$ ) between preoperative MEQs (298 mg) and postoperative MEQs (263 mg) in the failure subset. A review of these patients identified several factors that may be associated with poor outcome; 4 patients were found to have minimal fibrosis of the pancreatic specimen despite a preoperative diagnosis of CP, suggesting an extrapancreatic cause of abdominal pain. Six patients were deemed to be drug seeking and noncompliant with their postoperative regimen, and finally one patient was found to have colonic changes associated with cystic fibrosis (visceral pain syndrome). A significantly greater proportion of failure patients are insulin-dependent ( $\chi^2 P < 0.05$ ) in comparison to the successful patients. Clinical failure following IAT is most likely due to multiple factors. In this subset of patients, other causes of abdominal pain need to be excluded before performing pancreatectomy and IAT. Preoperative evaluation should also include a comprehensive psychiatric profile to exclude a drug addiction.

**37**

**NATURAL HISTORY OF INDETERMINATE PANCREATIC CYSTS**

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The optimal treatment of asymptomatic and incidental pancreatic cysts is not clearly known. Surgical resection should be reserved for patients that harbor a mucinous neoplasm to prevent eventual symptoms and /or invasive carcinoma. Patients have been entered in a treatment protocol that advises resection of symptomatic or suspected mucinous neoplasms based on aspirate analysis. This follow up report focuses on the natural history of observed patients with an asymptomatic and indeterminate cyst. Initiated in September 1999, 172 consecutive patients have been evaluated for a suspected pancreatic cystic neoplasm. Seventy-one patients (41%) were initially resected for symptoms or cyst aspirates showing extracellular mucin or elevated CEA. One hundred one patients (59%) had an indeterminate cyst based on lack of symptoms, and/or aspirate lacking mucin, CEA <300 ng/ml, CA15-3 and CA125 <100 U/ml. Levels of amylase and CA 19-9 did not directly influence management. Ninety-five patients have been followed with an interval CT scan and symptoms for a minimum of 12 months and are here reported. There were 60 women and 35 men with a mean age of 62 (23-86) years. At enrollment the mean serum CA19-9 was 33 (range: <2-250) U/ml, and median maximal cyst diameter was 2.3 (0.4-8.7) cm. An endosonographic guided FNA was performed in 78 (82%), and the median volume of fluid aspirated was 4 (0.5-31) ml. The median aspirate results were CA19-9 = 1976 U/ml; CEA = 22.6 ng/ml; CA 15-3 = 3.1 U/ml; CA125 = 14 U/ml. In the 28 patients who had cyst aspirate analyzed for amylase, the value in eighteen patients was >1000 U/L, and <500 U/L in ten. At a mean follow up of 23 months, four patients (4%) required resection. The indication and pathology were: one for size increase (6.6 to 7.8 cm) at 18 months, lymphoepithelial; two for symptoms (abdominal

pain and obstructive jaundice) at 24 and 72 months respectively, mucinous and serous cystadenoma; and one for both abdominal pain and increase in size (2.0 to 3.7 cm) at 41 months, pseudocyst. In patients that continue to be observed, four expired (4%) due to an unrelated cause, twelve showed decrease in cyst size (13%) and four increased in size (18%, 27%, 30%, and 48% change). Initial follow-up indicates that asymptomatic patients without evidence of a mucinous neoplasm by cyst aspiration can be safely followed. Approximately 1% will harbor an unsuspected mucinous neoplasm.

## 38

#### LONG-TERM SURVIVAL AND QUALITY OF LIFE AFTER TOTAL PANCREATECTOMY

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In the past, total pancreatectomy has been an operation associated with high complication rates and long-term morbidity due to difficulty in controlling postoperative diabetes. With the development of new forms of insulin, the control of diabetes and its associated long-term complications in patients after total pancreatectomy has greatly improved. In this study, we examine quality of life in patients treated with total pancreatectomy to that in a matched cohort of patients who have undergone a Whipple procedure. We retrospectively reviewed records of 18 patients who had undergone total pancreatectomy at Barnes-Jewish Hospital between 1998 and 2004. Resections were performed for adenocarcinoma in 10 (55%), intraductal papillary mucinous tumor in 5 (28%), neuroendocrine tumors in 2 (11%), and for mucinous cystic neoplasm in one patient (6%). Eleven of 18 patients were alive at a median follow-up of 24 months (range, 5 months-6 years). Two of these 11 patients were lost to follow-up. The remaining nine patients were interviewed and their quality of life was assessed using the SF-36v2 Health Survey Questionnaire, and compared with age- and sex-matched patients who had undergone a Whipple procedure during the same time period. Complications occurred in 33% of patients. Intra-abdominal complications (abscess, hemorrhage) resulted in 3 reoperations. Median length of stay was 15 days, with 30-day mortality of 0%. For diabetic control, patients were placed on an intensive insulin regime using either an insulin pump or a combination of long- and short-acting injectable insulin. Quality of life across all SF-36v2 domains was excellent. There was no difference between total pancreatectomy and Whipple patients in terms of physical and mental summary measures or in specific physical outcome measures (physical functioning, role-physical, bodily pain, general health, or vitality). Though associated with a high rate of postoperative complications, total pancreatectomy is a well-tolerated procedure and quality of life at long-term follow-up is excellent.

## 39

#### PROTECTION FROM COLD ISCHEMIA-INDUCED APOPTOSIS DESPITE CYTOPLASMIC ATP DEPLETION BY PURINERGIC RECEPTOR ANTAGONISM

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Ruthenium Red (RR) and Reactive Blue 2 (RB2) inhibit mitochondrial calcium ( $mCa^{2+}$ ) uptake: RR through direct antagonism of the uniporter and RB2 through indirect antagonism of the uniporter as

mediated through mitochondrial purinergic-like receptors.  $mCa^{2+}$  uptake regulates mitochondrial ATP production via a feedback mechanism. Maintenance of cytosolic ATP level may be cytoprotective during IR injury. Both RR and RB2 are cytoprotective following cold-ischemic storage, but their effect on cellular ATP levels is unknown. We hypothesized that  $mCa^{2+}$  uptake antagonism during cold storage is cytoprotective, independent of intracellular ATP levels. HepG2 cells were transfected with a cDNA construct coding for luciferase targeted either to the mitochondrial membrane or to the cytoplasm. Cells were then stored in UW with or without RR (30  $\mu$ M) or RB2 (300  $\mu$ M). Storage conditions were either normoxic-hypothermic (4°C) (NH) or hypoxic (<0.1%  $O_2$ )-hypothermic (HH) storage for 6 hours. Untreated (no UW storage) cells served as a control. Following storage,  $2 \times 10^5$  cells were resuspended in tricine buffer with 10  $\mu$ l beetle luciferin. Luminescence was measured for 30 seconds and peak values were used for analysis (N = 6 for each group). Apoptosis was quantified by TUNEL staining. The 2-tailed Student *t* test ( $P \leq 0.05$ ) determined significance. Luminescence curves were standardized to control for interference from RR or RB2. 1) HH storage decreased *cytoplasmic* ATP levels when compared to NH storage (16%,  $P = 0.05$ ). 2) NH and HH storage with RB2 resulted in lower *cytoplasmic* ATP levels (28%,  $P = 0.003$ ; 25%,  $P = 0.005$ ) than in cells stored without RB2 treatment. RB2 decreased the rate of apoptosis following HH storage from 45% to 21% ( $P = 0.004$ ). 3) NH and HH storage with RR resulted in lower *cytoplasmic* ATP levels (16%,  $P = 0.028$ ; 17%,  $P = 0.032$ ) than cells in stored without RR treatment. RR decreased the fraction of apoptotic cells following HH storage from 45% to 16% ( $P = 0.001$ ). *Mitochondrial* ATP levels were not significantly affected by RR or RB2 treatment. RR and RB2 are similar in their effects on cellular apoptosis and cytoplasmic ATP levels; both RR and RB2 decrease cellular apoptosis, despite continued decreases in *cytoplasmic* ATP levels. These results suggest the involvement purinergic receptors in the regulation of  $mCa^{2+}$  uptake during cold storage. Further, prevention of apoptosis by RB2 despite ongoing decreases in cellular ATP implicates purinergic receptors in the regulation of cellular apoptosis during cold preservation via the modulation of  $mCa^{2+}$  uptake.

## 40

#### SHORT-TERM ADMINISTRATION OF (-)-EPIGALLOCATECHIN GALLATE REDUCES HEPATIC STEATOSIS AND PROTECTS AGAINST HEPATIC ISCHEMIA/REPERFUSION INJURY IN STEATOTIC MICE

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Hepatic steatosis increases the extent of cellular injury incurred during ischemia/reperfusion (I/R) injury. (-)-Epigallocatechin gallate (EGCG), the major flavonoid component of green tea (*Camellia sinensis*) is a potent antioxidant that inhibits fatty acid synthase (FAS) in vitro. This study investigated the effects of EGCG on hepatic steatosis and markers of cellular damage at baseline and following I/R injury in ob/ob mice. Animals were pretreated with 85 mg/kg EGCG via i.p. injection for 2 days or oral consumption in the drinking water for 5 days prior to 15 minutes of warm ischemia and 24 hours of reperfusion. After EGCG administration, total baseline hepatic fat content decreased from baseline ( $P < 0.05$ ). Palmitic acid and linoleic acid levels were also substantially reduced in all EGCG treated animals prior to ischemia/reperfusion (I/R) ( $P < 0.05$ ). ALT levels decreased in all EGCG treated animals compared to control animals following I/R ( $P < 0.05$ ). Histologic analysis demonstrated an average decrease of 65% necrosis after EGCG administration ( $P < 0.05$ ). EGCG,

administration also increased resting hepatic energy stores as determined by an increase in cellular ATP ( $P < 0.05$ ) with a concomitant decrease in uncoupling protein 2 (UCP2) prior to I/R ( $P < 0.05$ ). Finally, there was an increased level of glutathione (GSH) in the EGCG treated mice as compared to the vehicle treated mice both at baseline and following I/R. Taken together, this study demonstrates that treatment with EGCG by either oral or i.p. administration, significantly protects the liver following I/R possibly by reducing hepatic fat content, increasing hepatic energy status and functioning as an antioxidant.

**41****ONE LIVER FOR TWO: LIVER REGENERATION IN LIVING DONORS AND RECIPIENTS**

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Apart from balancing risk versus benefit, the principle of living donor liver transplantation is to split one liver, and to maintain sufficient liver mass and function for two patients—the donor and the recipient. For long-term survival, adequate regeneration of both liver lobes is essential. Published data on volume restoration after living donor liver resection and transplantation are limited and inconclusive. To investigate and compare the recovery of residual left lobes, and right lobe grafts, a consecutive series of adults—22 donors and 22 recipients—were included in a prospective analysis with serial volumetry by magnetic resonance imaging before and 3, 7, 14, 28, 60, 90, 180, and 360 days following right hemihepatectomy or partial liver transplantation. Actual donor and recipient liver volumes were measured (ALV), and calculated in relation to preoperative total donor liver volume (RLV), liver volume at the time of surgery (LVI), and body weight (LBR). Liver regeneration rates (LRR) were determined within the first 28 days. Immunosuppression was tacrolimus based, and completely steroid free in most cases. Overall, the kinetics of liver volume restoration after resection and transplantation of right lobes showed three phases: a rapid early increase within 28 days, an intermediate phase, and slow adaptation tending towards preoperative data. Liver regeneration was not completed after 1 year. There was a significant difference between donors and recipients. In donors, volume of residual left lobes increased continuously within one year after resection, from 45% to 93% RLV after 360 days. Recipients showed a 2-3-fold faster and stronger response with an overshoot reaction beyond 100% RLV within the first week after transplantation, and subsequent volume decrease of right lobe grafts. In conclusion, liver volume restoration after resection and transplantation seems to be regulated and controlled by different liver and host factors. In live donors, this process is comparable to liver regeneration, whereas the volume changes in recipients are multifactorial. Further studies are needed to assess the long-term results in these patients.

**42****LONG-TERM FOLLOW-UP OF LIVING DONOR LIVER TRANSPLANTATION: 12 YEARS OF EXPERIENCE**

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Our aim was to evaluate the long-term results of living donor liver transplantation (LDLT) in an experienced center; 186 patients (103 adults and 83 pediatrics) underwent LDLT in our center from June 1993 to March 2004. We retrospectively analyzed the indications for transplant, type of graft, recurrence of hepatitis C, outcome in

hepatocellular carcinoma (HCC), biliary complications, and patient and graft survival. Donor age was 35.8 (range 19-64). Recipient age was 52.8 (19-74) in adults and 2.7 (4 months-18 years) in pediatrics. Liver grafts consisted in 93 (90.3%) right lobes, and 10 (9.7%) left lobes in the adults; in pediatrics, 68 (81.9%) received a left lateral segment graft, 10 (12%) a left lobe and 5 (6%) a right lobe. The most common indication for transplant in the adult was Hepatitis C. in 47 (45.6%). In the pediatrics 42 (40.7%) had diagnosis of biliary atresia, followed by acute liver failure 19 (22.9%). Of the 47 patients with hepatitis C, 3(6.4%) died early in their postoperative course, 1(2.1%) patient required retransplantation within the first week of transplant for primary graft non-function. Of the 43 long-term survivors, 29 (67.4%) have evidence of recurrent Hepatitis C, 2(6.9%) required retransplantation. 38(36.9%) patients had HCC, 19 (50%) exceeded Milan criteria. Among the long-term survivors, freedom of recurrence is 82.2% at 1 year and 63.9% at 2 years. Incidence of overall biliary complications were 45.6% in adults and 14.5% in pediatrics. Incidence of biliary complications in the left lobe grafts were higher than the right lobe grafts (60% vs 15.1%). Biliary leak occurred early postoperative period and resulted in significant morbidity and mortality: 19% of patients with bile leak died secondary to infectious complications. On the other hand, bile duct strictures occurred in late postoperative period and mainly treated by interventional radiology without increasing mortality. In children underwent LDLT with the diagnosis of fulminant hepatic failure, overall survival was 80%. The 5-year patient and graft survival were 90%-82% in pediatrics and 67-63% in adults. Living donor liver transplantation is a viable option for patients waiting for liver transplantation. Selected patients with hepatocellular carcinoma exceeding Milan criteria may benefit from living donor liver transplantation. Biliary complications are still the Achilles' heel of living donor liver transplantation. Early biliary complications have higher incidence of morbidity and mortality. Living donor liver transplantation is a life saving procedure in pediatric patients with fulminant hepatic failure.

**43****PREDICTING POST-TRANSPLANT GRAFT SURVIVAL IN LIVER TRANSPLANT RECIPIENTS USING PERIOPERATIVE CHARACTERISTICS UNDER THE NEW MELD SYSTEM**

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The ever widening gap between donor organs and the number of liver transplant candidates requires optimization of post-transplant outcomes by matching donors and recipients on perioperative factors that maximize graft survival. The aim of this study was to evaluate graft survival based on preoperative donor, "situational," and recipient characteristics under the new MELD allocation system and devise a practical model with which to predict posttransplant survival. Demographic, clinical, and survival data were extracted from the UNOS Standard Transplant Analysis and Research files for adult, cadaveric liver transplants. Potential risk factors influencing outcomes included donor age, cold ischemia time (CIT), recipient age, MELD score, and previous transplant. Data were analyzed via Kaplan-Meier and Cox proportional hazards regression methods. There were 8,000 grafts transplanted between February 2002 and May 2004. The mean follow up was 8 + 3 months. One-year graft survival for recipients of donors <60 vs. >60 years old was 83% and 75%, respectively ( $P < .001$ ). Recipients of grafts with <12 vs. >12 hours of CIT had 1-year survivals of 83% and 75%, respectively ( $P < .001$ ). Recipients with MELD scores <30 had 1-year survivals of 84% compared to 77% for those with MELD scores >30 ( $P < .001$ ). Multivariate analysis with Cox

**Table 1.**

|               | B    | Relative Risk | 95% CI      | P Value |
|---------------|------|---------------|-------------|---------|
| Recipient age | .008 | 1.009         | 1.002–1.015 | 0.007   |
| Donor age     | .009 | 1.009         | 1.006–1.012 | <0.001  |
| CIT           | .020 | 1.020         | 1.005–1.036 | <0.01   |
| MELD ≥ 30     | .398 | 1.489         | 1.304–1.699 | <0.001  |
| Previous Tx   | .795 | 3.543         | 3.301–4.125 | <0.0001 |

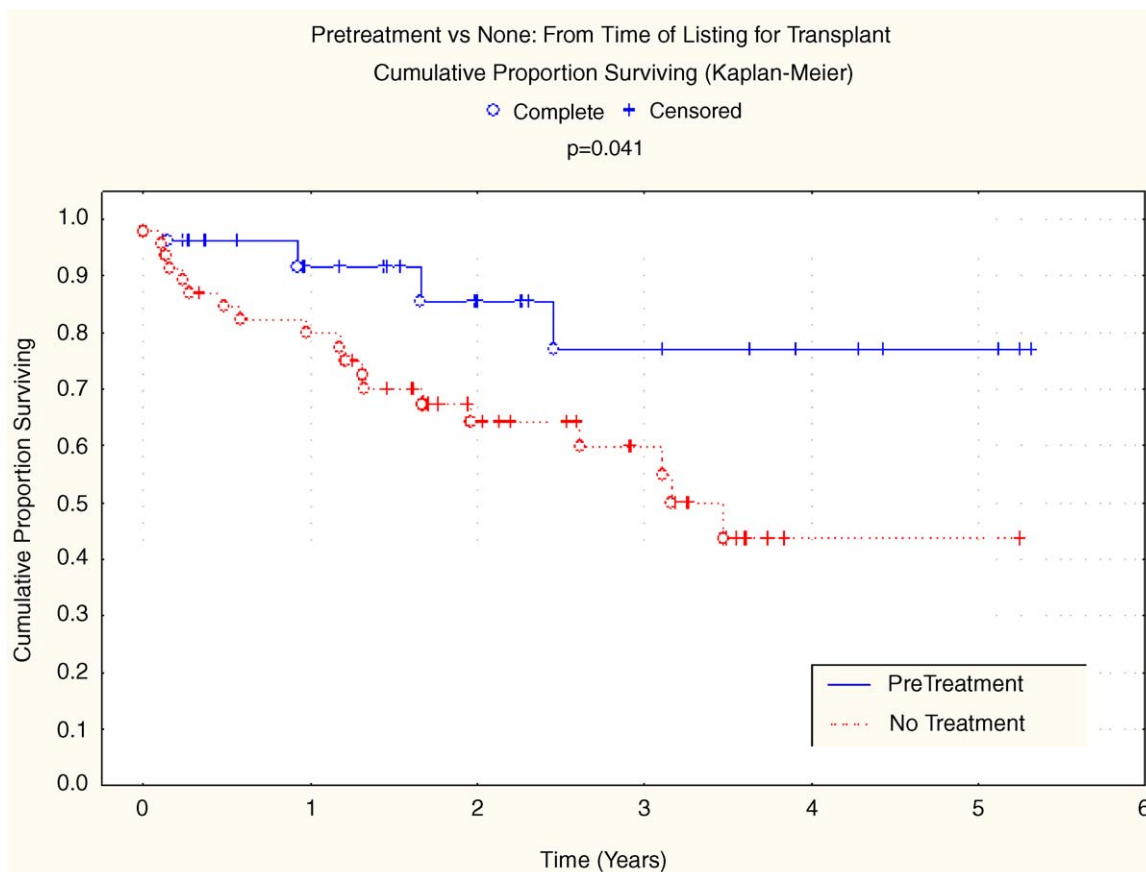
regression yielded the following (see Table 1). Using these five easily attainable perioperative risk factors a predictive risk score can be developed that adequately predicts 1-year graft survival. The C statistic is 0.7. Recipient age, donor age, cold ischemia time, MELD score, and previous transplant independently influence post-transplant graft survival. Therefore, the relative risks of these pre-transplant characteristics can be used to develop a practical model with which to match donors and recipients in order to improve post-transplant survival.

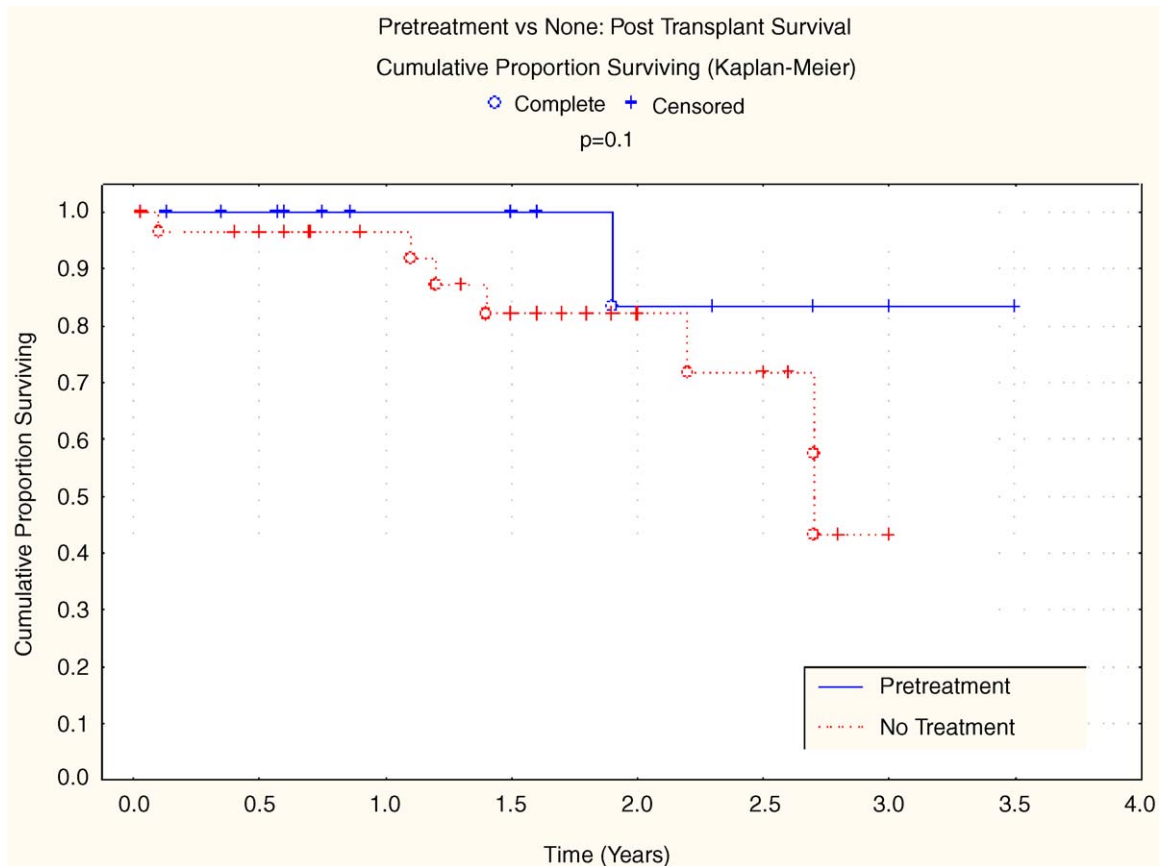
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**PRETRANSPLANT THERAPIES IMPROVE SURVIVAL IN PATIENTS WITH HEPATOCELLULAR CARCINOMA BUT FAIL TO ALTER POST-TRANSPLANT OUTCOME**

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Liver transplantation (LT) is the optimal treatment for early hepatocellular carcinoma (HCC). Ablative techniques prior to LT have been used as a form of tumor control; however, little data exist as to their overall effectiveness. We reviewed the records of patients evaluated at our center for LT with the diagnosis of HCC over the past 5 years. Patients with stage I and II HCC were considered for LT, based on preoperative imaging with CT or MRI. Continuous variables were analyzed with Student's *t* test, and categorical variables were analyzed with the Fisher's exact test. Survival curves were determined using the Kaplan-Meier method. Between 1999 and 2004, 88 patients were evaluated for LT with the diagnosis of HCC. Of these, 72 patients were accepted and listed for LT. Forty-four were transplanted, 7 died waiting, 10 were removed from the list, and 11 are still waiting for LT. Seven of the 10 patients removed from the list had progression of their HCC beyond Milan criteria. Twenty-four patients (33%) received some form of pretransplant therapy. Therapies included RFA in 17 patients, ethanol injection in 3 patients, surgical resection in 3 patients, chemoembolization in 1 patient, 1 patient had resection and RFA, and 1 patient received cryotherapy. When pretreated and untreated patients were compared, there was no significant difference in the number of patients who were transplanted, removed from the list, or died waiting. There were a significantly larger percentage of survivors in patients who received pretransplant therapy (85% vs 59%; *P* = 0.03) Five-year survival was improved in patients who received some form of pretransplant therapy (78% vs 42%; *P* = 0.04) (Fig. 1). However, the difference in post transplant survival was not significant (Fig. 2). Ablative therapies for HCC prior to LT do not alter the odds of being transplanted, or change post transplant survival.





However, in patients waiting and eventually transplanted for HCC pretransplant therapies may offer a survival advantage.

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**ACCESS TO PEDIATRIC LIVER TRANSPLANTATION: DOES REGIONAL VARIATION PLAY A ROLE?**

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Our purpose was to assess regional variability in access to liver transplantation for pediatric patients with end-stage liver disease as determined by variances in wait list mortality and time to transplantation. Using Organ Procurement and Transplantation Network (OPTN) liver wait list and transplantation data for all pediatric (age  $\leq 17$  years) candidates listed between January 2000 and July 2004, 1-, 3-, 6-, and 12-month wait list mortality rates were calculated. The effect of region on wait list mortality and time to transplant was determined using Kaplan-Meier and Cox proportional hazards methods. The proportion of cadaveric whole, cadaveric split/reduced, and living donor pediatric transplant recipients were compared between the regions using  $\chi^2$ . The 1-month regional mortality rates ranged from 2.5% to 7.2%. Kaplan-Meier analysis showed a significant effect of region on wait list mortality (model  $P = 0.01$ ). A Cox model demonstrated that both region and urgency status exerted independent effects on wait list mortality (model  $P < 0.001$ ) with the urgent patients and those removed from the wait list for reasons other than receiving a transplant or death having increased odds of death compared to

nonurgent candidates (both  $P < 0.001$ ). Kaplan-Meier analysis of time from listing to transplant also revealed significant regional variation (model  $P < 0.001$ ). In the Cox model, which controlled for urgency status, the effect of region on wait list time was again evident (model  $P < 0.001$ ). Since only transplant recipients have data on organ type, it was not included in the previous models. However, a separate  $\chi^2$  analysis of pediatric transplant recipients revealed that significant regional variation also existed with regard to the proportion of cadaveric whole, cadaveric split/reduced, and living donor organs used ( $P < 0.001$ ). Similar to the adult experience, wait list mortality and pretransplantation waiting times for pediatric patients with end-stage liver disease vary considerably within the 11 U.S. regions. Regional differences in utilization of cadaveric split and living donor organs may contribute to this variability.

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**SCINTIGRAPHY-GUIDED LAPAROSCOPIC RESECTION OF A PARA-AORTIC PRIMARY LYMPH NODE GASTRINOMA**

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We present a video case presentation of a 61-year-old man with peptic ulcer disease refractory to medical management who was found to have Zollinger-Ellison syndrome with a serum gastrin level of 2,600 pg/ml. An indium-111 labeled octreotide scan revealed a focal accumulation at an uncharacteristic location to the left of midline and caudal

to the bed of the pancreas. This corresponded to a small 12 × 9 mm retroperitoneal mass identifiable on CT scan that demonstrated marked enhancement in the arterial phase. Preoperative planning was facilitated by CT scan-generated three-dimensional imaging of the lesion and the surrounding vascular structures. The patient received 4.6 μCi of radiolabeled octreotide preoperatively. He was explored laparoscopically, and the suspected gastrinoma was localized using a laparoscopic scintigraphy probe. On histologic examination, the nodule contained a small glandular tumor embedded within lymphatic tissue. It consisted of tightly clustered, small, regular glands of tumor cells with an appearance characteristic of islet cell tumors. Immunohistochemically the tissue stained positive for synaptophysin, a marker for neuroendocrine differentiation. Postoperatively, the patient was discharged to home the following day. A serum gastrin level obtained at four weeks was found to be 36 pg/ml. He remained comfortable and asymptomatic without any further dyspepsia or diarrhea.

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#### **CENTRAL PANCREATECTOMY. A CONSERVATIVE TECHNIQUE PRESERVING FUNCTIONAL PANCREATIC PARENCHYMA**

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Central pancreatectomy (CP) is an operation that allows to resect benign or low malignant tumor located in the pancreatic isthmus that are not suitable for enucleation. The main advantage of this operation compared with major resections as pancreaticoduodenectomy and distal pancreatectomy is that it permits to spare normal pancreatic parenchyma and therefore the exocrine and endocrine functions are preserved. The video shows the technique: the operation is carried out by exposition of the pancreatic neck involved by the lesion and incision of the peritoneum along the superior and inferior margin of the part of the gland to be resected. Thereafter the gland is dissected from the splenic artery and portomesenteric axis and divided with a 1-cm clear margin on either sides of the lesion. The cephalic stump is sutured and the distal stump is anastomosed end-to-end with a Roux-en-Y jejunal loop. We treated 20 patients with this technique. Three patients were male and 17 female, mean age was 50 years. The indications for CP were serous cystadenoma in 7, mucinous in 3, solid cystic papillary tumor in 1, metastasis from renal cancer in 1, and endocrine tumor in 8 patients. Mean operative time was 235 min (range 180–300). Mean size of the lesions was 2.9 cm (range 1.2–5). Mortality rate was 0% and morbidity rate was 35%, pancreatic fistula occurred in 25% of the cases and was treated conservatively in all the cases. Mean postoperative hospital stay was 18 days (range 9–38). Postoperative endocrine and exocrine functional tests were normal in all controlled patients. All the patients are alive without clinical and imaging evidence of disease. We can conclude that CP is a safe technique for benign or low malignant tumor of the pancreatic neck that allows a cure of the tumor with evident functional results without increasing the risk for the patient.

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#### **ISOLATED UNCINATE RESECTION FOR PANCREATIC CYSTIC NEOPLASM**

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Lesions in the uncinata process of the pancreas typically require pancreaticoduodenectomy. This is to ensure a curative resection for the difficult to expose area. Local resection of some pancreatic neoplasms, such as cystic neoplasms and neuroendocrine lesions is the preferred

treatment when accessible. The surgical technique of resection of a solitary uncinata mass is demonstrated on this video.

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#### **COMBINED RESECTION OF PANCREATIC HEAD TUMOR WITH SUPERIOR MESENTERIC VEIN AND RIGHT HEPATIC ARTERY**

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Solid cystic tumors of the pancreas are a relatively rare type of cystic disease. These tumors usually present as a large asymptomatic mass of about 15 cm in diameter involving regional vascular structures. Recent advances in surgical techniques have contributed to an increased respectability rate in hepatobiliary and pancreatic benign and malignant tumors with vascular involvement. An acceptable early and late morbidity and mortality has been obtained. A huge pancreatic head tumor of more of 15 cm of diameter occurred on a 51-year-old woman. The complete resection was possible by a pancreatoduodenectomy associated to mesenteric vein and right hepatic artery resection. Vascular reconstruction was performed with an end-to-end anastomosis of the superior mesenteric vein and right hepatic artery, respectively. Microsurgery technique was performed in the arterial reconstruction. The video demonstrates the preoperative diagnostic procedures to evaluate the extent of tumor growth and the vascular invasion or compression as well as the surgical procedure.

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#### **LAPAROSCOPIC ROUX-EN-Y CYST-JEJUNOSTOMY FOR DRAINAGE OF PANCREATIC PSEUDOCYST**

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The video depicts the operative management of a pancreatic pseudocyst using minimally invasive techniques to establish enteric drainage. The patient is a 25-year-old woman who suffered an attack of severe, necrotizing gallstone pancreatitis during the third trimester of pregnancy. She underwent laparoscopic cholecystectomy and subsequently delivered her baby. In the ensuing months, she developed an enlarging pseudocyst involving the tail of her pancreas. She experienced intermittent left upper quadrant abdominal pain associated with the development of the cyst. It was situated inferior to the stomach and contained heterogeneous enhancement on CT scan consistent with residual necrosis. A laparoscopic, transmesocolic approach allowed debridement of the cyst cavity and enteric drainage using a Roux-En-Y limb. She was discharged home without drains in the early postoperative period without any complications. This case demonstrates the feasibility of using laparoscopic techniques, as an alternative to open or endoscopic techniques, in the drainage of dependent pancreatic pseudocysts.

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#### **LAPAROSCOPIC MAJOR HEPATIC RESECTION: ANALYSIS OF LOBECTOMY AND TRISEGMENTECTOMY**

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Laparoscopic liver resection is gaining popularity in many centers, resulting in increased case frequency and technical complexity. While segmental resection has become routine in many hepatobiliary centers, major laparoscopic hepatic resection (lobectomy, extended lobectomy, trisegmentectomy) remains largely undefined with regard to indications, technique, safety and outcome. We review our experience in laparoscopic major hepatic resection and compare this novel surgical strategy with open resection. We retrospectively reviewed those patients who underwent major laparoscopic liver resection (hepatic lobectomy or greater) at our institutions, specifically evaluating operative time, blood loss, transfusion requirement (Tx), length of stay (LOS), and complications (infection, bile leak, tumor recurrence, etc). These cases were compared to contemporaneous open procedures matched for patient demographics (age, diagnosis, tumor size) and extent of resection (Table 1). The laparoscopic resection patients experienced an overall complication rate of 17%. This compared favorably with open controls (16%) and did not include hepatic insufficiency or mortality. Bile leak and infection rates were similar in both groups. Mean follow-up time 12 months. Complication rates seem similar in laparoscopic vs. open major hepatic resection. While the cohort numbers are small, this initial experience suggests a trend toward shorter operative time, blood loss and LOS in the laparoscopic group. This study exhibits the potential value of laparoscopic major hepatic resection. Long-term follow-up and additional studies are necessary to confirm these findings.

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**SAFETY OF LAPAROSCOPIC HEPATIC RESECTION**

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Laparoscopic hepatic resection is a new and innovative operative strategy. As with any new procedure complications and technical difficulties are anticipated. Few series have examined the complications associated with hepatic resection. A two-institution experience from two surgeons was examined to identify the incidence of complications associated with the performance of laparoscopic hepatic surgery. During a three-year time frame, over 130 hepatic resections were performed at two institutions. The distribution of these cases was 56 segmental resections, 34 right lobes and 18 left lobes, 22 left lateral segmentectomies. Thirty-eight (29%) operations were performed for malignant disease. There were no operative conversions to open procedures. A total of 18 complications were encountered for a rate of 13.8%. Those complications encountered included bile leak n = 5, atelectasis/pneumonia n = 3, re-operation for bleeding n = 2, ascites n = 2, recurrent cyst n = 2, port site infection n = 1, intra abdominal abscess n = 1, hepatic insufficiency n = 1, and death n = 1. The rate of bile duct leak was 3.8% and mortality less than 1%. When complications were analyzed by resection type no significant difference was identified. Two recurrences were noted in the cystic lesion group. In the malignant group no tumor recurrences were documented after a median

time of 15 months. Laparoscopic hepatic resection appears extremely safe and efficacious. The complication and mortality rate of laparoscopic hepatic resection appears to be in the range of most reported modern series of open hepatic resections (Table 1).

**Table 1.**

| Resection | Number | Complications |
|-----------|--------|---------------|
| L lateral | 22     | 1 (4.5%)      |
| L lobe    | 18     | 4 (22%)       |
| R lobe    | 34     | 6 (17%)       |
| Segmental | 56     | 7 (12.5%)     |
|           | 130    | 18 (13.8%)    |

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**A PROSPECTIVE RANDOMIZED TRIAL OF PERIOPERATIVE PARENTERAL TRANEXAMIC ACID IN LIVER TUMOR RESECTION TOWARD A "BLOOD TRANSFUSION"-FREE LIVER RESECTION**

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Bleeding and homogeneous blood transfusion (HBT) remains detrimental in liver resection. The influence of antifibrinolytic agent, tranexamic acid (TA) on HBT in liver resection was unknown. A prospective double-blinded randomized trial was performed on elective liver tumor resections. In group A, TA 500 mg was intravenously administered just before operation and 250 mg, every 6 h, for 3 days. In group B, only placebo was given. The patients' background, HBT rates and early operative results between the two groups were compared. Factors that influenced HBT rates were analyzed. There were 108 hepatectomies in group A and 106 hepatectomies in group B. No significant differences were found in patients' background, operative procedures, hepatectomy extent, and liver transection area between the two groups. Although no significant difference regarding the operative morbidity and postoperative stay between both groups, the hepatectomies in group A had a significant less amount of operative blood loss, less HBT rate, shorter operative time and less hospital costs than group B. No patient in group A required HBT. Adverse effect of TA was not observed in any patient. The tumor size and the use of TA were independent factors that influenced HBT in liver tumor resection. Perioperative parenteral TA reduced the amount of operative blood loss, and make the HBT-free liver resection feasible.

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**IMAGE-GUIDED LIVER SURGERY: CONCEPTS AND INITIAL CLINICAL EXPERIENCES**

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**Table 1.** Laparoscopic vs. Open Major Resection (\*mean values)

| Procedure       | N  | OR Time (min)* | Blood Loss (ml)* | Tx | LOS (days)* | Complications                     | Recurrence |
|-----------------|----|----------------|------------------|----|-------------|-----------------------------------|------------|
| Lap. left lobe  | 22 | 140            | 250              | 0  | 1.9         | 2 bile leak, 2 infection          | none       |
| Lap. right lobe | 37 | 150            | 375              | 1  | 2.0         | 2 bile leak, 2 infection, 2 other | none       |
| Lap. triseg.    | 5  | 200            | 225              | 0  | 3.25        | 1 suture granuloma                | none       |
| Open left lobe  | 22 | 230            | 425              | 0  | 3.5         | 1 bile leak, 3 other              | none       |
| Open right lobe | 37 | 270            | 550              | 2  | 4.2         | 3 bile leak, 1 infection          | 1 HCC      |
| Open triseg.    | 5  | 310            | 650              | 2  | 5.0         | 2 bile leak                       | 1 HCC      |



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The purpose of this study was to determine intraoperative factors that will affect the utilization of image-guided surgical techniques during open liver resections. Image-guided surgery (IGS) provides navigational aids to the surgeon by displaying the position of a tracked surgical probe on preoperative tomograms in real time. The ability to link intraoperative presentation to preoperative imaging is achieved through a mapping process known as registration. The registration is established using features on the liver surface. In this study, intraoperative surface data of the liver was acquired from 8 patients undergoing resection for hepatic tumors. Individual points on the liver were digitized over repeated respiratory cycles in order to quantify the motion of the liver while breathing. Shape data was acquired either by sweeping an optically tracked probe across the liver surface, or by using a laser range scanner to rapidly acquire a dense point cloud. Registration was performed between the surface data and preoperative tomograms using the Iterative Closest Point (ICP) methods. Since soft tissue deformation occurs during surgery, the final step was to use a finite element model (FEM) to account for non-rigid components of the registration. Motion in the liver due to respiration was quantified as repeatable and cyclical, primarily along the cranial-caudal axis. Rigid surface registrations resulted in mean residual errors from 2–6 mm. Range scan data provided more robust results compared to the tracked probe. Less error also resulted from capturing feature-rich regions such as the inferior liver edge. The registration was able to provide target region errors of less than 1 cm. From visual inspection of the registration data, it appears that the largest source of error was due to deformation of the liver during intraoperative mobilization. Results from FEM studies indicate the model compensates for deformation by warping preoperative tomograms to match intraoperative data. IGS techniques have been developed to improve navigation during liver resection. Liver motion due to respiration has been quantified so that it can be accounted for in future procedures. Laser range scanning provides a rapid means of acquiring intraoperative surface data, necessary for an accurate and robust surface registration. Finite element modeling compensates for non-rigid discrepancies that arise during surgery. Applying IGS concepts will facilitate complex hepatic resections, including living donor transplantations.

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#### INLINE MULTIELECTRODE RADIOFREQUENCY ABLATION: A NEW TECHNIQUE TO MINIMIZE BLOOD LOSS IN HEPATIC PARENCHYMAL TRANSECTION

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InLine Radiofrequency Ablation (IL-RFA) is a novel modality which aims to reduce blood loss during hepatic resections. We conducted a prospective trial of hepatic resections using IL-RFA. The results of this trial are presented here. The ethics committee of SESAHS approved this study (approval no. 02/07). The InLine RFA device is a 5-cm-long plastic device with 6 electrodes, spaced along the device, each 10 cm long, which can be deployed to varying depths in the hepatic parenchyma. It is then connected to a standard RFA generator. No attempt was made to produce a low CVP and no Pringle inflow inclusion maneuver was performed. The resection plane was ablated with IL-RFA and then resected using the ultrasonic aspirator. Estimated blood loss, resection area, and the time taken for resection were recorded. The volume of intra-operative blood loss was as the

sum of the blood aspirated with the suckers and the blood loss as calculated by weighing the sponges. The surface area for each plane of resection was then measured to allow calculation of the blood loss per  $\text{cm}^2$  of liver resection. Similar results were seen in cirrhotic vs non-cirrhotic livers. Twenty-six patients have so far undergone liver resection using IL-RFA (13 men, 13 women; mean age: 60 years; range 35–84). Mean area resected was  $39 \text{ cm}^2$  (SD:  $9 \text{ cm}^2$ ). Mean blood loss was 227 ml (SD: 278 ml, range: 12–1220 ml). Average blood loss per  $\text{cm}^2$  was  $6 \text{ ml/cm}^2$  while average time taken per  $\text{cm}^2$  was 58 seconds/ $\text{cm}^2$ . InLine RFA significantly reduces bleeding during hepatic parenchymal resections. In comparison to current techniques of hepatic resection, i.e. the jet-cutter (which has been shown to be associated with an average blood loss of  $18 \text{ ml/cm}^2$ ) or the CUSA (average blood loss  $24 \text{ ml/cm}^2$ ), blood loss using IL-RFA is far superior. Furthermore, IL-RFA as a tool for resection does not result in a significantly increased time of resection.

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#### LIVER SURGERY IN OBESE AND OVERWEIGHT PATIENTS

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Obesity is associated with an increased risk of diabetes, systemic arterial hypertension, and malignancies. Also, obese patients are penalized by a higher risk of postoperative complications (although recently questioned in the context of abdominal surgery) and reluctance of some surgeons to operate on them. This might especially be the case in the context of liver surgery as obesity is also associated with NAFLD. We analyzed the characteristics of patients undergoing hepatectomies and the influence of the Body Mass Index (BMI) on the postoperative course. The 683 patients undergoing elective hepatectomies between 1999 and 2003 were stratified according to their BMI (in  $\text{kg/m}^2$ , range 15–44) into lean (BMI  $<25$ ), overweight (BMI 25 to 29) and obese (BMI  $\geq 30$ ). Minor (38%) and major hepatectomies (62%, including 271 right hepatectomies) were compared separately. Intraoperative ventilation parameters of obese patients undergoing major resections were in addition compared to those of patients with a BMI  $<30$ . Overweight (34%) and obesity (14%) were somewhat more frequent than in the general population and were associated with an increased risk of diabetes (15 and 14 vs. 7%), systemic arterial hypertension (39 and 34 vs. 16%), malignancies, steatosis, and liver fibrosis. Fibrosis in obese patients was more frequent than steatosis (58 vs. 39%). The BMI had no influence on in-hospital mortality (overall 3%), the incidence of postoperative liver failure, or the kinetics of bilirubin or prothrombin time. In contrast, morbidity (notably pulmonary complications) was increased in overweight patients following major hepatectomies (OR: 2.4) and in obese patients following both minor and major resections (OR: 2.5 and 3). This resulted in an increase of in-hospital stay. Intraoperative transfusion in major hepatectomies was more frequent in obese than in lean or overweight patients (45 vs. 17 and 23%,  $P < .01$ ), despite higher preoperative hemoglobin levels and both more frequent and more prolonged use of portal clamping. Despite greater intraoperative peak inspiratory airway pressures (18 vs. 15 mmHg,  $P < .05$ ), obese patients had smaller respiratory volumes (6 vs. 9 ml/kg,  $P < .001$ ). Almost half of the patients undergoing liver resections are either overweight or obese. Neither increased the mortality of the procedure and the BMI should therefore not interfere with the indication for, or extent of the resection. Patients with increased BMI are however at increased risk of pulmonary complications and intraoperative bleeding; both are partly explained by the inability to achieve adequate intraoperative respiratory volumes despite increased ventilation (and therefore hepatic vein) pressure, respectively.

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**POSTISCHEMIC ADMINISTRATION OF 2-APB PREVENTS REPERFUSION INJURY IN RAT LIVER**

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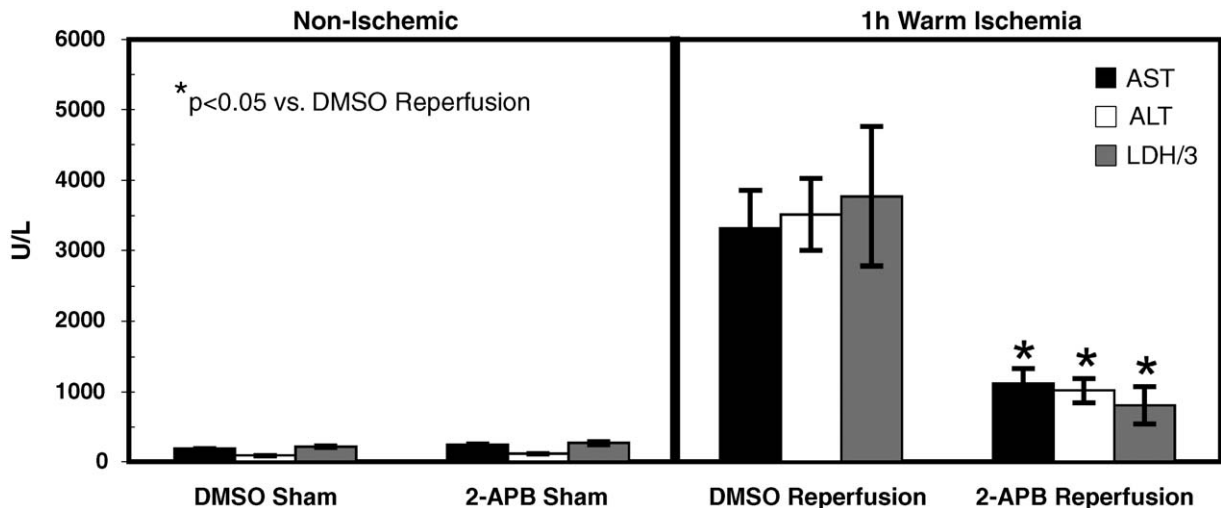
Mitochondrial calcium ( $mCa^{2+}$ ) regulation plays an important role in ischemia-reperfusion (I/R) injury in the liver, which is a significant problem in hepatic surgery. We have shown that 2-aminoethoxydiphenyl borate (2-APB) blocks  $mCa^{2+}$  uptake and prevents ischemic liver injury when administered prior to warm I/R. We hypothesized that post-ischemic administration of 2-APB would attenuate hepatic reperfusion injury in a rat model. Under isoflurane anesthesia, 18 rats underwent sham operation or 1 hour of warm ischemia to the superior 70% of the liver via atraumatic portal venous and hepatic arterial clamping. 2-APB (2mg/kg), or vehicle (DMSO) was injected into the portal vein following 1 hour of ischemia, concurrent with removal of the vascular clamp. Animals were sacrificed after 3 hours of reperfusion ( $n = 6$  per group). Serum AST, ALT, and LDH levels were measured, and liver samples were evaluated histologically using HandE and TUNEL staining. To investigate the effect of 2-APB at the cellular level, an I/R model in HepG2 cells transfected with GFP-tagged cytochrome c was used. Statistical significance was assessed using Student  $t$  test. 1) 1 hour of ischemia followed by 3 hours of reperfusion with DMSO significantly increased serum AST, ALT, and LDH levels by  $1,682 \pm 293\%$ ,  $4,030 \pm 603\%$ , and  $1,640 \pm 459\%$ , respectively compared to DMSO shams ( $P < 0.05$  for all). 2) Administration of 2-APB at the onset of reperfusion significantly inhibited this elevation of AST, ALT, and LDH ( $P < 0.05$  for all). 3) HandE histology demonstrated little evidence of hepatocyte necrosis when 2-APB was administered during reperfusion. 4) TUNEL assay demonstrated  $\leq 2\%$  hepatocellular apoptosis in tissue sections from animals receiving 2-APB during reperfusion. 5) Cytochrome c translocated from mitochondria to HepG2 cell periphery after 6 hours of hypoxia followed by reperfusion with DMSO, whereas reperfusion with  $100 \mu M$  2-APB reduced mitochondrial release of cytochrome c. 2-APB administration at the onset of reperfusion protects the liver against reperfusion injury. The mechanism of action involves limiting mitochondrial cytochrome c release, which prevents hepatocytes from apoptotic and necrotic cell death. 2-APB is a novel agent for administration following an ischemic insult to prevent reperfusion injury to the liver (Fig. 1).

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**LIVER RESECTION FOR PRIMARILY "UNRESECTABLE" COLORECTAL METASTASES DOWNSTAGED BY CHEMOTHERAPY**

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Liver resection is the only available treatment offering a possibility of long-term survival in patients with metastases of colorectal cancer (CRLM). However, the resectability rate of metastases at the time of diagnosis is low (10–20%). In this study we evaluated the impact of neoadjuvant systemic chemotherapy in the surgical treatment of primarily unresectable CRLM in our unit. From June 2000 to June 2004, 42 consecutive patients with unresectable CRLM were evaluated. These patients were treated by neoadjuvant systemic chemotherapy using FOLFIRI protocol (5-fluorouracil with folinic acid, combined with irinotecan). Among the 42 initially unresectable patients, 18 whose metastases were significantly downstaged after chemotherapy, underwent surgical exploration. Fifteen (36%) of these 18 patients underwent hepatic resection and the other 3 patients were considered unresectable after laparotomy because of the presence of multiple peritoneal nodules. The 15 patients who underwent liver resection were 10 men and 5 women with a mean age of 59 years (32–75). At diagnosis metastases were synchronous in 12 patients (80%). Their main causes of unresectability were: multinodularity ( $n = 3$ ; 20%); ill location ( $n = 5$ ; 33%); size  $> 5$  cm ( $n = 7$ ; 47%). These patients received an average of 9 courses of chemotherapy and the response to this treatment was evaluated by CT every 2 months. A complete response was observed in one patient (7%), a partial response (50% or more decrease in tumor size) was observed in 12 cases (80%) and a minor response ( $< 50\%$  decrease in tumor size) in 2 cases (13%). We performed surgery as soon as resectability was possible, with 2–3 weeks interval from the last course of chemotherapy. A major hepatectomy was performed in 3 (20%) of the 15 patients (3 right hepatectomies) and limited resections in 12 patients (80%). Operative mortality was nil. Three patients (20%) had postoperative complications. The median survival was 46 months and the median disease-free survival was 32 months. After a mean follow-up of 26 months



(range 4-52), eight patients (53%) developed tumor recurrence, 2 only hepatic and 6 both hepatic and extrahepatic. At the last follow-up 3 patients had died and the other 12 patients were alive, of whom 7 (58%) were disease-free and 5 (42%) had recurrence. In conclusion in this study neoadjuvant systemic chemotherapy with a combination of 5-FU/FA and irinotecan allowed to perform a liver resection in 36% of patients with primarily unresectable CRLM.

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### OUTCOME FOLLOWING MAJOR LIVER RESECTIONS IN PATIENTS OVER 70 YEARS

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Liver resection has become a safe operation in the last decade. This has allowed us to undertake major resections in the elderly population. We aimed to study the early and long-term outcome of patients'  $\geq 70$  years undergoing major liver resections and compare the results with patients below the age of 70. Data were retrieved from a prospective database for all patients undergoing major liver resection (defined as  $\geq 3$  segments) from January 1993 until June 2004. Patients were studied in two groups: Group A  $\geq 70$ , Group B  $< 70$  years of age and they were well matched in terms of patient characteristics. Operative mortality, morbidity, need for Intensive Care Unit (ICU), Length of Hospital Stay (LOS) and long term survival were analyzed. RESULT: A total of 519 patients underwent major liver resection. Group A: 128 and Group B: 391 patients. There was no significant difference in operative mortality between the two groups: Group A, 9%; Group B, 7% (log rank test,  $P$  value = 0.76, hazard ratio 1.1). There was no significant difference in both the ICU and hospital stay between the two groups ( $P = 0.55$  and  $P = 0.93$  respectively). There was also no significant difference postoperative morbidity ( $P = 0.634$ ). Five-year survival for both groups was not statistically significant: Group A, 32%; Group B, 38.8% (log rank test,  $P = 0.350$ ). Major liver resections can be safely performed in patients'  $\geq 70$  years of age with short-term results equivalent to  $< 70$  group undergoing a similar resection. In addition, five-year survival was not significantly different in both groups.

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### COMPARISON BETWEEN HEPATIC WEDGE RESECTION AND ANATOMIC RESECTION FOR COLORECTAL LIVER METASTASES

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Hepatic resection of colorectal liver metastases (CLM) with a negative microscopic surgical margin provides the best chance for long-term survival. Some investigators have suggested that wedge resection (WR) has a higher incidence of positive margin compared with anatomic resection (AR). We sought to investigate the margin status, pattern of recurrence and overall survival of patients with CLM treated with WR vs AR. We identified 253 consecutive patients with CLM who underwent either WR or AR between March 1991 and May 2004. WR was defined as a nonanatomic resection of the CLM to include a rim of macroscopically normal tissue, while AR was defined as single or multiple resections of one or two contiguous Couinaud segments. Patients who underwent hemihepatectomy or combined WR and AR were excluded from analysis. Clinicopathologic factors were

analyzed with regard to pattern of recurrence and survival. A total of 106 WRs were performed in 72 patients and 194 ARs in 181 patients. Primary tumor site, primary nodal status, preoperative CEA level, and number of CLM were comparable between each group (all  $P > 0.5$ ). Patients who underwent WR were more likely to have a disease-free interval from primary to CLM of less than 12 months (49% vs 30%;  $P = .02$ ) and size of largest metastasis less than 5 cm (94% vs 80%;  $P = .004$ ). On final pathologic analysis, patients treated with WR vs AR had no difference in the rate of positive surgical margin (8.3% vs 8.3%;  $P = .9$ ). With a median follow-up of 25 months, 100 patients (39.5%) recurred. Patients who underwent WR vs AR had comparable overall recurrence rates (37.5% vs 40.3%;  $P = .4$ ) and patterns of recurrence (Table 1). Patients who had a

**Table 1.** No. (%) of Patients Who Recurred by Type of Resection

| Site of Recurrence | WR (n = 72) | AR (n = 181) | P value |
|--------------------|-------------|--------------|---------|
| Surgical margin    | 2 (2.8)     | 7 (3.9)      | 0.5     |
| Other intrahepatic | 10 (13.9)   | 17 (9.4)     | 0.2     |
| Extrahepatic       | 8 (11.1)    | 25 (13.8)    | 0.4     |
| Intra-extrahepatic | 7 (9.7)     | 24 (13.2)    | 0.3     |
| Any recurrence     | 27 (37.5)   | 73 (40.3)    | 0.4     |

positive microscopic margin were more likely to recur at the surgical margin (14.3% vs 2.6%;  $P = .03$ ) regardless of whether they underwent WR or AR. The median survival was 76.6 months for WR and 80.8 months for AR ( $P = .2$ ) with 5-year actuarial survival rates of 61% and 60% ( $P = .15$ ), respectively. AR is not superior to WR in terms of surgical margin clearance, site of recurrence or survival. Resection with a clear surgical margin is the goal of surgical treatment for CLM.

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### ARE THERE RACIAL OR GENDER DISPARITIES IN HOW GALLBLADDER DISEASE IS SURGICALLY MANAGED?

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Racial and gender disparities in diagnosis, treatment, and outcome have been demonstrated for heart disease and cancer. Despite the high prevalence of gallstones in the US population, the effect of demographics on the surgical management of cholecystolithiasis in an urban population is unclear. Our hypothesis was that the surgical management of gallbladder disease in an urban hospital is influenced by race and gender. We reviewed all cases of cholecystectomy performed for symptomatic gallstones at our institution from July 1999 to June 2004 ( $N = 655$ ). Data collected included the independent variables race, gender, diagnosis (acute or chronic cholecystolithiasis), insurance type, and Zip code; and the dependent variables procedure type (laparoscopic or open; cholangiogram or no cholangiogram) and length of stay. The effect of the independent variables on the dependent variables

**Table 1.**

|                           | Open No. | Cholang. No. |
|---------------------------|----------|--------------|
| Black male (n = 72)       | 26 (36%) | 12 (17%)     |
| Black female (n = 259)    | 49 (19%) | 33 (13%)     |
| White male (n = 55)       | 15 (27%) | 9 (16%)      |
| White female (n = 109)    | 16 (15%) | 13 (12%)     |
| Hispanic male (n = 22)    | 7 (32%)  | 0 (0%)       |
| Hispanic female (n = 106) | 16 (15%) | 12 (11%)     |
| Other male (n = 9)        | 4 (44%)  | 2 (22%)      |
| Other female (n = 23)     | 2 (9%)   | 14 (56%)     |

was evaluated using standard nonparametric analysis. There were 2 perioperative deaths (0.3%). Similar percentages of blacks (21%), whites (16%), and Hispanics (17%) were treated by open cholecystectomy ( $P = NS$ ); and similar percentages had a cholangiogram ( $P = NS$ ). Males of all races were more likely than females to get open cholecystectomy ( $P < 0.05$ ), but males and females were equally likely to get intraoperative cholangiogram ( $P < 0.05$ ). Surgical management of symptomatic gallstones in an urban hospital is influenced by patient gender, but not patient race (Table 1).

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**REPAIR OF LAPAROSCOPIC CHOLECYSTECTOMY BILE DUCT INJURIES: A TEN-YEAR EXPERIENCE AT THE UNIVERSITY OF TORONTO**

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Bile duct injuries are a well-documented complication of laparoscopic cholecystectomy. Debates regarding timing of repair still exist. To address this question further, we reviewed all repairs of laparoscopic cholecystectomy associated bile duct injuries performed at two major referral centers affiliated with the University of Toronto over a ten-year period. The study period was from January 1st, 1993 to December 31st, 2004. Fifty-four patients were reviewed, 15 males and 39 females. Median age was 50 years. 32 early repairs (<3 weeks) and 19 late repairs (>3 weeks) were performed. 47 injuries were referred from community hospitals and 4 from academic institutions; 37% (20) had Bismuth type 1 injuries, 19% (10) had Bismuth type 2 injuries, 36% (19) had Bismuth type 3 injuries, 6% (3) had Bismuth type 4, and 2% (1) Bismuth type 5. Bile leakage was the most common presentation (52%). Sepsis was present in 9% of patients. Peak bilirubin at presentation was 114 mg/dl (mean 27 mg/dl). Thirty-two hepaticojejunostomies were performed, and 21 choledocojejunostomies. Right hepatic lobectomy was required in 2 patients. Overall complication rate was 35% (19). The most common postoperative complication was biliary stricture (17% or 9 patients). Post repair cholangitis occurred in 7 patients (13%). Stricture rate was not significantly associated with timing of repair (early vs late;  $P = 0.33$ ), repair type ( $P = 0.53$ ) or, location by Bismuth class ( $P = 0.26$ ). There was a trend towards preoperative bile leak predicting postoperative stricture ( $P = 0.06$ ). Postoperative complications were not significantly correlated with timing of repair ( $P = 0.69$ ), nor was location of injury by Bismuth class ( $P = 0.50$ ). Preoperative bile leak again showed a trend towards significance in predicting postoperative complications ( $P = 0.11$ ). In conclusion, our results suggest that the timing of repair (early vs late) and the Bismuth class location of injury were not significantly related to postoperative complication or stricture. Preoperative bile leak appears to influence postoperative morbidity perhaps as a marker of the difficulty of the repair.

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**CHOLECYSTITIS ON MARS: REMOTE GUIDANCE OF BILARY DRAINAGE FOR EXPLORATORY CLASS MISSIONS**

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Long-duration space flight may cause alterations in biliary motility increasing the risk of biliary stone disease and cholecystitis. Treating

acute cholecystitis in space is hampered by a lack of diagnostic procedures, surgical capabilities and limited training of the crew medical officer (CMO). We report percutaneous catheter drainage of the gallbladder in a microgravity animal model using remote mini-laparoscopy or ultrasound guidance. Adult female pigs were used for 1g:ground (n = 4), and 0g:microgravity (NASA KC-135, n = 4) studies. Nonphysician, CMO analogs, that had no previous training in ultrasound, catheter placement, or mini-laparoscopy, performed biliary ultrasound via remote expert verbal guidance. All procedures were viewed in real-time and facilitated by the remote expert. A percutaneous catheter was placed into the gallbladder under ultrasound visualization in both experiment groups. The abdomen was then insufflated and a 3-mm mini-laparoscope was inserted by the CMO followed by percutaneous biliary catheter placement during microgravity flight. Catheter placement was verified by ultrasound image, bile aspiration, or visualization during mini-laparoscopy. Ultrasonic and mini-laparoscopic visualization of the liver and gallbladder was achieved in the 1g and 0g animals by all operators within 1 minute using remote expert guidance. Percutaneous ultrasound guided placement of a biliary catheter was accomplished in 75% of all animals (avg time 2 min) and 100% of animals using mini-laparoscopy (avg time 2 min) allowing drainage of the gallbladder. There were no significant differences noted between 0g and 1g experiments, except microgravity aided laparoscopic visualization and catheter placement. No false catheter placements or complications were noted. Nonphysician crewmembers, with minimal or no training, can successfully visualize the gallbladder to facilitate diagnosis and treatment of acute cholecystitis. Remote expert guidance of ultrasound or mini-laparoscopic abdominal examination and percutaneous gallbladder catheter placement is readily accomplished in 0g. The technique of remote expert guidance can significantly reduce medical training requirements for CMOs while enhancing medical capabilities during exploratory class spaceflight. This model can be extrapolated to other environments (i.e., rural or military) where there is limited or delayed access to a tertiary care center.

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**ELDERLY PATIENTS HAVE MORE SEVERE BILARY INFECTIONS: INFLUENCE OF COMPLEMENT-KILLING AND INDUCTION OF TNF- $\alpha$  PRODUCTION**

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Biliary bacteria and choledocholithiasis are more common with advancing age, but even among patients with biliary bacteria, infectious manifestations (IF) are more common in the elderly. The reason for this is unclear. We previously identified factors associated with severe biliary infections including bacterial serum-sensitivity (SS), as opposed to serum-resistance (SR); and bacterial induction of TNF production in sera (iTNFsera). In this study we examined the influence of patient age on severity of biliary infections and these virulence factors. Clinical data, sera, bile, and gallstones were obtained from 281 patients. Gallstones and bile were cultured. Illness severity was staged as none (no clinical infection), moderate (fever, leukocytosis), or severe (cholangitis, bacteremia, abscess, hypotension, organ failure). Bacterial serum-sensitivity and in-vitro TNF- $\alpha$  production were determined. Patients <70 (young) or >70 (elderly) years were compared (Table 1). Biliary

Table 1.

|                                      | Young     | Elderly   | P Value  |
|--------------------------------------|-----------|-----------|----------|
| Biliary bacteria                     | 41%       | 64%       | < 0.0001 |
| Bacteria-laden CBD stones            | 68%       | 88%       | 0.042    |
| Complement-killing (patient's serum) | 45%       | 54%       | 0.615    |
| IF with biliary bacteria             | 54%       | 78%       | 0.006    |
| IF bacteria-laden CBD stones         | 66%       | 93%       | 0.018    |
| IF with SS bacteria                  | 87%       | 100%      | 0.500    |
| IF with SR bacteria                  | 10%       | 70%       | 0.008    |
| iTNFsera SS bacteria                 | 609 pg/ml | 827 pg/ml | 0.218    |
| iTNFsera SR bacteria                 | 52 pg/ml  | 422 pg/ml | 0.017    |

bacteria were more common among elderly patients, but even among patients with biliary bacteria, the elderly had more severe infections: young: 46% none, 17% moderate, 37% severe; vs elderly: none 22%, moderate 25%, severe 53%, ( $P = 0.012$ ). Sera from either group equally killed the bacteria. Bacteria from elderly patients induced more iTNFsera overall (584 vs 294 pg/ml,  $P = 0.015$ ). In both groups, SS bacteria caused IF and similar iTNFsera. But SR bacteria from elderly patients usually caused IF and large iTNFsera, while SR bacteria from young patients rarely caused IF and induced minimal iTNFsera. Biliary bacteria were more common in elderly patients, and produced more severe IF when present. In contrast, many (46%) young patients tolerated biliary bacteria without IF. SR bacteria rarely (10%) caused IF in young, but usually (70%) caused IF in elderly patients. Bacteria from elderly patients induced greater iTNFsera irrespective of serum-sensitivity. In contrast, SR bacteria from young patients induced minimal iTNFsera. This suggests that elderly patients are susceptible to colonization by more virulent bacterial species and/or have a heightened response to bacteria largely tolerated by younger patients. This is the first study to examine mechanisms of increased severity of biliary infections in elderly patients.

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#### HOSPITAL COST OF RIGHT HEPATECTOMY: ADULT-TO-ADULT LIVING DONOR VS. BENIGN AND MALIGNANT INDICATIONS

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Adult-to-adult living donor right hepatectomy is a very resource intensive surgical procedure. Our aim was to compare the hospital resources utilized as accounted by costs for right hepatectomies, comparing living donor surgeries to those where right hepatectomies were performed for other indications. We reviewed all of our adult-to-adult living donor surgeries as well as right hepatectomies performed for other indications at our institution from 1/1/1999 to 12/31/2003. Hospital costs and charges for the surgical hospitalization were obtained from our Decision Support Services, utilizing a full cost accounting methodology. Hospital costs and charges were expressed in relative units with living donor costs and charges serving as a common denominator to arrive at a relative value for the other indications.  $P$  values were calculated using either an unpaired, equal variance Student's  $t$  test or Fisher exact test as appropriate. During this time period we performed 26 right hepatectomies on adult-to-adult living donors and 36 right hepatectomies for other indications. Of the 36 other indications, 15 were performed for symptomatic benign disease (7 giant cavernous hemangiomas, 2 focal nodular hyperplasias, 2 adenomas, 1 angiomyolipoma, 1 inflammatory cyst, 1 mucinous cyst, and 1 hepatolithiasis). Twenty-one cases were performed

for malignancy (11 metastatic adenocarcinomas, 3 hepatomas, 2 liposarcomas, 1 metastatic renal cell carcinoma, 1 metastatic ovarian cancer, 1 neuroendocrine tumor, 1 melanoma, and 1 cholangiocarcinoma). None of these patients had significant hepatic fibrosis and all had good hepatic function prior to surgery. As depicted in the table below: mean age, mean length of stay (LOS), and hospital costs for living donor right hepatectomies were significantly lower than right hepatectomies performed for either benign or malignant indications. Readmission rates were similar among all three groups. Adult-to-adult living donor right hepatectomies can be performed with less hospital resource utilization as evidenced by a significantly shorter LOS, less hospital costs, and subsequent charges than right hepatectomies performed for either benign or malignant indications (Table 1).

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#### DEVELOPMENT OF A DEDICATED HEPATOPANCREATICOBILIARY (HPB) PROGRAM IN A UNIVERSITY HOSPITAL SYSTEM

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In 2001, a dedicated HPB program was established at a large, university hospital. Changes included recruitment of specialized HPB faculty, standardization of patient protocols and postoperative orders, development of coordinated multidisciplinary research and clinical efforts, and construction of a dedicated cancer hospital. The aim of this study was to evaluate the impact of this program on a university health system including effects on patient volume, surgical volume, outcomes, and costs. From January 1999 through September 2004, hospital and departmental databases were reviewed for all records pertaining to HPB surgical cases (by CPT codes), diagnoses (by ICD-9 codes), and financial information (by DRG codes). Since October 2001, all surgical outcomes data have been collected in a standardized, prospective way by a trained nurse reviewer. We compared HPB surgical volume to that of appendectomy as a control for any overall referral and volume changes at our institution. In 1999 HPB surgical volume was 24% that of appendectomy. By 2003 this increased to 65%, a 171% increase in HPB surgical volume. Increases in the number of distinct patients who had HPB diagnoses were seen across all pertinent departments in the system. A multidisciplinary approach to care was implemented, leading to increases in sharing of patients across departments (Table 1). Thirty-day mortality for HPB surgery was 11% in 1999-2000 and decreased to 3% in 2001-2003. HPB related research studies increased from 1 in 1999 to 8 in 2004. Hospital contribution margin per case increased from \$9,013 in fiscal year 2000 to \$13,600 in fiscal year 2003. Conclusions: Implementation of a dedicated HPB program with coordinated and standardized research and clinical efforts resulted in a significant increase in the number of HPB patients and operations in this system. Other beneficial effects included decreased patient

**Table 1.** Right Hepatectomy Indications

|                         | Living Donor (A) | Benign Disease (B) | Malignant Disease (C) | $P$ Value (A vs B) | $P$ Value (A vs C) | $P$ Value (B vs C) |
|-------------------------|------------------|--------------------|-----------------------|--------------------|--------------------|--------------------|
| N                       | 26               | 15                 | 21                    | NS                 | NS                 | NS                 |
| Mean age (yr)           | 37.2             | 46.4               | 63.0                  | 0.023              | < 0.001            | 0.002              |
| Mean LOS (days)         | 5.3              | 6.3                | 7.8                   | 0.027              | < 0.001            | NS                 |
| Relative costs          | 1.00             | 1.27               | 1.81                  | < 0.001            | < 0.001            | 0.049              |
| Relative charges        | 1.00             | 1.08               | 1.46                  | NS                 | 0.023              | NS                 |
| Readmission pts. (rate) | 1 (3.8%)         | 0 (0%)             | 2 (9.5%)              | NS                 | NS                 | NS                 |

**Table 1.** HPB Patient Volume by ICD-9 Codes for 1999 Through 2004

|                              | 1999 | 2000 | 2001 | 2002 | 2003 | 2004<br>(annualized) | % Increase |
|------------------------------|------|------|------|------|------|----------------------|------------|
| Gen surg/surg onc            | 13   | 16   | 53   | 76   | 94   | 88                   | 576%       |
| Int med/med onc              | 69   | 58   | 82   | 131  | 153  | 201                  | 191%       |
| Diagnostic rad               | 57   | 64   | 88   | 104  | 109  | 131                  | 130%       |
| Rad onc                      | 11   | 8    | 14   | 28   | 25   | 44                   | 300%       |
| Total system<br>(unique pts) | 133  | 135  | 208  | 224  | 246  | 299                  | 125%       |
| Shared patients              | 17   | 11   | 29   | 115  | 135  | 165                  | 870%       |

mortality, improved contribution margin, and increased research productivity. Establishment of this HPB program has had measurable institutional benefit.

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**SURGICAL RESECTION OF HEPATIC AND PULMONARY METASTASES FROM COLORECTAL CANCER**

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Patients with hepatic and pulmonary metastases from colorectal cancer (CRC) may benefit from aggressive surgical therapy. We examined the long-term outcomes of patients who underwent both lung and liver resections for colorectal metastases over a 10-year period. All patients who underwent liver and lung resections for metastatic colorectal cancer between 1992 and 2002 at two university-affiliated hospitals were identified. Demographic, perioperative and survival data were evaluated by retrospective chart review. Disease free survival (DFS) and overall survival (OS) were evaluated by Kaplan-Meier analysis. A total of 423 hepatectomies were performed for CRC between 1992-2002. Thirty-nine of these patients also underwent pulmonary resection for metastases from CRC. During hepatic resection, the average number of lesions resected was 1.9, average size was 5.1 cm, and 7/39 (18%) tumors were bilobar. Median follow-up time after hepatectomy was 54 months. Eleven patients (28%) underwent staged hepatic and pulmonary metastasectomy due to synchronously identified metastases. Twenty-eight (72%) patients underwent sequential metastasectomy due to recurrent disease. Median DFS and OS after initial hepatectomy was 19.8 and 87 months, respectively. Interestingly, serial metastasectomy was common in this patient population. The average number of metastectomies performed was 2.6 per patient (range 1-4). There was no difference in survival for patients with synchronous vs. metachronous hepatic and pulmonary metastases. The site of first recurrence after hepatectomy was most commonly the lung (19/39; 49%), followed by the liver (8/39; 20%). Nineteen patients (49%) underwent subsequent resections for recurrences. Ten (25%) patients underwent 2 or more hepatic resections for recurrent disease while sixteen (41%) underwent multiple pulmonary resections. The 5-year OS after hepatic metastasectomy with subsequent resections for recurrence was 74% compared to 42% for those who did not undergo pulmonary resection for lung metastases. An aggressive multi-disciplinary surgical approach should be undertaken for recurrent CRC metastases. In selected patients, serial metastasectomy for recurrent metastatic disease is safe and results in excellent long-term survival.

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**THE UTILITY AND COST OF DIAGNOSTIC LAPAROSCOPY WITH LIVER ULTRASOUND IN PATIENTS WITH HEPATIC METASTASES OF COLORECTAL CANCER**

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Diagnostic laparoscopy with liver ultrasound (DxLS) in patients with resectable liver metastases of colorectal cancer must be accurate, of low morbidity, and cost effective in order to be efficacious. This study tests the utility of DxLS by hypothesizing that DxLS reduces the rate of nontherapeutic laparotomy and the associated morbidities when compared with primary laparotomy in resectable hepatic metastases. A retrospective, IRB approved study over 4 years ending in 2003. Eighty patients undergoing planned resection (planned ablation patients were excluded) of liver metastases of colorectal cancer were identified: DxLS was performed in 36 patients, while laparotomy and liver ultrasound (Open) was performed in 44 patients. Data were collected regarding demographics, surgical outcomes and hospital cost. All patients underwent a complete preoperative evaluation to rule out extrahepatic metastatic disease. PET scans were used after the year 2000. The level of statistical significance for parametric and nonparametric tests was set at  $P < 0.05$ . There were no demographic differences between the two groups. A historical bias for Open patients in the first 1.5 years of the study was present. Diagnostic laparoscopy was technically feasible in 97% of patients. The overall rate of unresectability in the study was 29%: DxLS 36% (13/36) and Open 23% (10/44;  $P = 0.036$ ). Combining both groups, the reasons for unresectability included carcinomatosis (22%), miliary liver disease (48%), and technical inability to achieve a negative margin (22%). No patient from Group DxLS went on to have a nontherapeutic laparotomy. Focusing on unresectable patients (nontherapeutic, NT), the operating room time trended to be longer, the median length of stay (LOS) was significantly shorter and costs not significantly different comparing the NT-Open and NT-DxLS patients (Table 1). Diagnostic laparoscopy and liver ultrasound can significantly reduce the rate of

**Table 1.**

| Group   | Median OR Time (min) | Mean Total Cost (\$) | OR Cost (\$) | Median LOS (days) |
|---------|----------------------|----------------------|--------------|-------------------|
| NT-DxLS | 70                   | 8092                 | 3751         | 1                 |
| NT-Open | 142                  | 7196                 | 1421         | 2.5               |
| P value | 0.41                 | 0.70                 | 0.21         | <0.005            |

non-therapeutic laparotomy in liver surgery for metastatic colorectal cancer. Diagnostic laparoscopy is also associated with a significantly reduced hospital LOS and is cost neutral. Diagnostic laparoscopy with liver ultrasound is recommended as "the last diagnostic test" in the surgical care of patients with colorectal metastasis to the liver.

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**EFFECT OF INHIBITION OF TNF- $\alpha$  IN EXPERIMENTAL ACUTE PANCREATITIS: A STUDY OF SYSTEMIC INFLAMMATORY PROCESS, PANCREATIC INFECTION, AND MORTALITY RATE**

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Acute pancreatitis (AP) is considered one of the typical conditions causing systemic inflammatory response (SIRS). Levels of pro-inflammatory cytokines increase during the course of AP, and these

levels appear to be correlated with the severity of pancreatic inflammation. TNF- $\alpha$  may be an initiator of inflammatory process in AP. Previous studies using pentoxifylline to block TNF- $\alpha$  production has showed good benefits in experimental models of sepsis and shock. To determinate the effects of inhibition of TNF- $\alpha$  on the pancreatic and systemic inflammatory response, pancreatic infection, and mortality rate in necrotizing acute pancreatitis in rats. An experimental model of severe AP by injection of 0.5 ml of 2.5% sodium taurocholate into the pancreatic duct was utilized. Ninety male Wistar rats were divided in 3 groups: Sham (surgical procedure without AP induction), Pancreatitis (AP Induction), and Pentoxifylline (AP induction plus administration of 25 mg/kg pentoxifylline). Pancreatic inflammatory response was measured by histological studies and systemic inflammatory response was analyzed measuring the production of inflammatory cytokines (IL-6, IL-10, and TNF- $\alpha$ ). Pancreatic infection was evaluated with bacterial cultures performed 24 h after the AP induction. The numbers of organisms were expressed in colony forming units (CFU) per gram. The occurrence of pancreatic infection was also analyzed and considered positive when the CFU/g was  $> 10^5$ . The animals were kept alive for 7 days to study the mortality rate. Inhibition of TNF- $\alpha$  by pentoxifylline shows beneficial effects in this experimental model. The Pentoxifylline group had a statistically significant reduction of histological damage in the pancreas, inflammatory cytokines levels (IL-6, IL-10, and TNF- $\alpha$ ), and occurrence of pancreatic infection ( $P < 0.05$ ). These changes were associated with a significant reduction of mortality rate. Inhibition of TNF- $\alpha$  reduced local and systemic inflammatory response, reduced systemic complication as pancreatic infection, and decrease mortality rate in this model. These findings provide a possible improvement in treatment of acute pancreatitis. Supported by Grant: FAPESP 02/03773-6.

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**MAXIMIZING EFFICIENCY OF MICROWAVE ABLATION IN NORMAL HEPATIC PARENCHYMA AND HEPATIC COLORECTAL METASTASES: SELECTION OF THE OPTIMUM MICROWAVE FREQUENCY**

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Microwave ablation is one of a number of ablative techniques for the treatment of unresectable colorectal liver metastases. The volume of ablation that can be induced by a single treatment, however, restricts the success of all ablative modalities, particularly for the treatment of larger tumors. Microwave tissue penetration and, therefore, ablation volume are partly dependent on the frequency of microwaves used. To date microwave applicators currently use waves at a frequency that is based on assumptive rather than measured data. The aim of the study was to investigate the in vivo interaction between normal liver parenchyma and hepatic colorectal metastases over a range of microwave frequencies allowing the selection of the optimum frequency for use in the ablative equipment. At laparotomy, an open-ended co-axial sensor was placed into the liver parenchyma and colorectal metastasis(es) of nine patients with eleven tumors. Following successful calibration, 400 low energy microwave signals ranging from 0.5 to 10 GHz were passed into the tissue and the reflected waves were analyzed by a vector network analyzer. Using computer software, the magnitude and phase change for each of the microwaves from the 400 different frequencies were calculated and compared for each tissue type. Potential ablation efficiency was determined by calculating the uptake of energy by the tissue and the total energy losses experienced by the wave as it passed through the target tissue. Following successful calibration, readings were obtained from all the tissues investigated. Uptake of energy by the tissue and total energy losses experienced by the wave (known as the tissue's permittivity) were shown to vary dramatically with different microwave frequencies. Results for each tissue type were very similar, and the frequency of 2.45 GHz was demonstrated to allow the most efficient interaction for potential ablative techniques. The interaction between human liver parenchyma and hepatic colorectal metastases with microwave energy was demonstrated to be highly dependent on the frequency of the waves employed. The optimum microwave frequency for maximizing the efficacy of ablation equipment in the in vivo situation has been established. These data have not previously demonstrated in the in vivo situation and have now been used in the production of newer, more efficient, microwave ablation equipment.

## 2005 AHPBA CONGRESS ABSTRACTS—POSTERS

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### IMPACT OF BILE DUCT LIGATION ON PORTAL VENOUS INFECTION WITH *E. coli*: ROLE OF INTERLEUKIN 10

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Patients with jaundice are at greater risk for infection, especially with gram-negative organisms. Our previous data has demonstrated that bile duct ligation (BDL) prior to portal venous (PV) infection with *E. coli* results in greater mortality and bacterial growth. We investigate the role of a key cytokine, interleukin 10, in hepatic infection. C56BL/6 mice were subjected to BDL and infection with  $2 \times 10^5$  *E. coli* delivered concurrently via the PV (PV/BDL). Control animals received PV infection without BDL (PV/sham). Interleukin 10 levels were measured by RNase protection assay (RPA) and ELISA in systemic blood. The effect of interleukin 10 was examined by injecting *E. coli* into the PV of interleukin 10<sup>-/-</sup> mice with BDL, compared with wildtype (WT) mice subjected to the same manipulation. Liver tissue was cultured 36 hours after infection in interleukin 10<sup>-/-</sup> and WT mice, to examine the effect of interleukin 10 absence on bacterial growth. Presence of BDL increased mortality in animals infected via the PV compared with PV/sham: 18% compared with 100% survival. PV/BDL animals had greater interleukin 10 production by RPA and ELISA. However, absence of interleukin 10 resulted in greater, delayed (days 4–5) mortality compared with WT controls: 20% survival in interleukin 10<sup>-/-</sup> compared with 80% in WT. This was associated with an increase in bacterial growth in interleukin 10<sup>-/-</sup> mice. BDL impairs survival in a murine model of hepatic infection. Interleukin 10 appears to impact the late events that occur after hepatic infection with *E. coli*. Absence of this key cytokine results in increased late mortality and a late increase in bacterial growth.

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### LIVER ABSCESS ULTRASOUND-GUIDED DRAINAGE BY A SURGEON

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We sought to evaluate the outcome of patients who underwent ultrasound (U/S)-guided percutaneous drainage of liver abscess. A retrospective review of patients who underwent percutaneous drainage of liver abscess under U/S guidance was done over a period of 10 years, from 1992 to 2002 at Alexandra Hospital, Singapore. This study involved data only from the Department of General Surgery, where drainage was performed by the surgeon himself. The primary aim of the study was to evaluate the outcome of this procedure; 27 cases of liver abscess underwent U/S-guided drainage during this period. All of these patients had concomitant treatment with antibiotics; 24 (89%) of the patients had pyogenic abscesses and 3 (11%) had amoebic liver abscesses. The commonest underlying condition associated with pyogenic liver abscess was diabetes mellitus, seen in 13 (54%) patients. Biliary sepsis was found in 4 (17%) patients. Underlying malignancy was found in 3 (12%) patients. These included 2 with primary lung carcinoma and 1 with a colonic carcinoma. The predominant causative microorganism in the pyogenic abscess group was *Klebsiella* sp. (41%). The abscesses were predominantly in the right lobe in 16 patients, in the left lobe in 6 patients, and in both lobes in 2 patients. Fifteen patients had single abscesses and 6 patients had multiple abscesses.

Seventy-four percent (20 cases) had complete resolution of the abscesses following percutaneous drainage and antibiotic therapy. The remaining 5 patients (18.5%) had no change in size of the abscess. The time for complete resolution ranged between 6 and 10 weeks in duration. The mean length of stay was 26 days. Two patients died with causes that are not related or associated with the drainage procedure. The main morbidity was a right-sided pleural effusion. Antibiotic therapy and drainage remains the mainstay of treatment in liver abscess. U/S-guided percutaneous drainage is a safe and effective procedure, which can be done by an experienced surgeon who is trained in performing ultrasonography.

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### SURGICAL TREATMENT OF HEPATIC HEMANGIOMAS: A PERSONAL EXPERIENCE

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The conservative versus surgical approach of hepatic hemangiomas (HH) is still debated. These benign tumors of the liver, increasingly recognized by routine ultrasound scans (US), sometime show a rapid increase of size. Infrequently large, bilateral lesions cause a Kasabach-Merritt syndrome and must undergo resective surgery or even lead to hepatic failure, which in the most advanced cases has been treated by liver transplantation (OLT). Since February 1985, 41 patients (17 males and 24 women; mean age: 41.8 years) with HH with a mean diameter of 8.7 cm (ranging from 4.8 to 42 cm) underwent surgical treatment due to 1) uncertain diagnosis (1 case), 2) severe symptoms (26 cases), 3) size increase over 8 cm after 3 US (12 cases), and 4) liver failure (2 cases). Two patients underwent OLT, 19 patients underwent hepatectomy (HT), and 20 patients underwent segmental or atypical resections (RS). There was no mortality and an 8.5% (3 cases) incidence of minor morbidity; only OLT patients required blood transfusions. The mean in-hospital stay was 6.5 days for RS cases and 15 days for OLT patients. In our opinion, symptomatic or rapidly increasing HH should undergo surgical treatment, which, in selected institutions, is associated with an extremely low morbidity and mortality.

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### MULTIDISCIPLINARY MANAGEMENT OF RUPTURED HEPATOCELLULAR CARCINOMA

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Spontaneous rupture of hepatocellular carcinoma (HCC) is a rare but dramatic presentation of the disease. Current management of ruptured HCC, apart from resuscitation, is debated. Most of the studies are from Asian centers, and principally due to the low incidence, North American experience on this subject is limited. This study was undertaken to review the experience of ruptured HCC at a North American multidisciplinary unit and to compare the clinical outcome between the emergency resection and delayed resection of ruptured HCC. Thirty patients presenting with ruptured HCC at the Vancouver Hospital and Health Sciences Center Hepatopancreatobiliary Unit from 1985



to 2004 were studied retrospectively and analyzed according to the demographics, clinical presentation, tumor characteristics, treatment, and outcome in treatment groups of emergency resection, delayed resection (resection after angiographic embolization), transarterial catheter embolization (TACE), and conservative management. Pearson  $\chi^2$ , Fisher's exact test, two-tailed *t* test, and the Kaplan-Meier plot were used for statistical analysis. Ten, 10, 7, and 3 patients underwent emergency resection, delayed resection, TACE, and conservative treatment, respectively. Mean age was 57 years, mean Child-Pugh score was  $7 \pm 2$ , 67% of patients had comorbidities and cirrhosis was present in 57% of patients. Most common clinical presentation was sudden abdominal pain (82%) and the most common imaging modality for diagnosis was the CT scan. Spontaneous cessation of bleeding occurred in 23% of patients. 63% of tumors were greater than 5 cm, and 68% of them were multifocal. The 1-month mortality was significantly higher in the emergency resection group (40%) than in delayed resection group (0%); however, the 12-month and 24-month survival rates were similar in the two groups. The multidisciplinary approach of angiographic embolization, stabilization, and delayed resection results in better short-term survival than emergency resection of ruptured HCC in selected patients.

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#### A REVOLUTION IN RESECTIONAL THERAPY FOR BENIGN TUMORS OF THE LIVER

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Hepatic resection has been utilized sparingly for the treatment of benign liver disease. This conservative approach is based on the morbidity and potential mortality related to hepatic resections. We compared two consecutive periods of hepatic surgery. The period from 1991 to 2001 was compared with 2001 to the present. The number of resections, tumor types, operative outcomes, and complications were compared. During the 10-year period from 1991 to 2001, 100 resections were performed for 100 benign tumors: hemangiomas, *n* = 43; cysts, *n* = 19; adenomas, *n* = 17; FNH, *n* = 13; and other, *n* = 8. During the subsequent 3-year period, 55 benign lesions were resected including cysts, *n* = 15; hemangiomas, *n* = 15; FNH, *n* = 9; adenoma, *n* = 7; and other, *n* = 8. In the initial series, 20% of patients underwent lobectomy versus 27% in the most recent series. Complications encountered in the first series were reoperation, *n* = 3; ileus, *n* = 2; bile leak, *n* = 1; PE, *n* = 1, infections, *n* = 3; and death secondary to HELP syndrome, *n* = 1. In the second era there were re-operation, *n* = 1; pneumonia, *n* = 2; bile leak, *n* = 3; and infection, *n* = 1. In the first era there were two patients who need re-operation for recurrence or missed lesion. In the subsequent era there were no patients who needed re-excision. Hepatic resection for benign liver disease is safe and efficacious. The need for transfusion is around 10% as is the complication rate for these procedures. Only a single mortality was observed over the last decade associated with resection for benign disease (Table 1).

Table 1.

|     | Lap      | EBL | Transfuse | Comps    | Mortality |
|-----|----------|-----|-----------|----------|-----------|
| 100 | 3 (2%)   | 426 | 14 (14%)  | 11 (11%) | 1 (1%)    |
| 55  | 32 (58%) | 337 | 5 (9%)    | 7 (12%)  | 0 (0%)    |
| 155 | 35 (23%) |     | 19 (12%)  | 18 (11%) | 1 (1%)    |

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#### HEPATOBIILIARY PRACTICE GROWTH WITH THE INTRODUCTION OF LAPAROSCOPIC LIVER SURGERY

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As technology advances so does the approach to what has traditionally been deemed open hepatic surgical problems. With the introduction of laparoscopic procedures the disability and morbidity associated with major hepatic and biliary procedures has decreased. This fact has increased the referral of patients to a single surgeon. This paper examines the effect and growth patterns of a single surgeon introducing laparoscopic hepatic surgery to his practice. All cases performed by a single surgeon during three successive years 2002 to 2004 were examined and correlated with the addition of laparoscopic hepatic surgery. All hepatic and biliary cases were included while pancreatic cases were excluded. During 2001 laparoscopic radiofrequency ablation was first introduced to our practice. Later in 2002 laparoscopic hepatic resection was added. During this time period steady growth was observed in the case load increasing from 68 to 103 and currently to 121. This represents a 34% and 44% growth over the baseline year of 2002. During this same time frame the number of hepatic resections performed dramatically rose from 29 to 41 and finally to 60. This increase in cases correlated with an increase in the performance of laparoscopic hepatic resection. During the first two years the percentage of cases done laparoscopically was 37% and 34%, respectively. Most recently this percentage has risen to 50%. This introduction correlates with a 30% rise in hepatic resections per year. A similar trend was observed after the introduction of laparoscopic RFA. During the last year a second partner has joined the practice and is performing laparoscopic RFA. This study would conclude that introduction of technology has stimulated the growth of a large volume practice. It also underscores the high percentage of cases that can be performed laparoscopically. This may also indicate the willingness of referring doctors to send their patient to undergo a minimally invasive procedure rather than a traditionally open procedure (Table 1).

Table 1.

| Total | Biliary | Hepatic Rx | Lap Rx   | RFA |
|-------|---------|------------|----------|-----|
| 68    | 15      | 29         | 11 (37%) | 15  |
| 103   | 17      | 41         | 13 (34%) | 35  |
| 121   | 23      | 60         | 30 (50%) | 16  |
| 292   | 55      | 130        | 55 (43%) | 66  |

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#### HEPATIC ADENOMA: A SURGICAL TREATMENT

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Hepatic adenoma (HA) is a rare benign tumor of the liver. Tumor resection has been recommended for symptomatic or enlarging HA because of the risk of intraperitoneal, intrahepatic hemorrhage or even the development of hepatocellular carcinoma. From 1989 to 2003 we reviewed the medical records and radiology files of 28 patients with a proved diagnosis of HA. This article summarizes a single-center experience with surgical treatment of HA; 24 patients were female and 4 were male. Twenty-two patients had a history of oral contraceptive use. Abdominal pain was presented in 19 patients, and 3 of them have had an acute episode. The mean age was 36.3 years. Preoperative assessment included liver test, ultrasonography, and computed tomography in all patients plus technetium ( $^{99m}\text{Tc}$ )-sulfur colloid and  $^{99m}\text{Tc}$ -labeled DISIDA (dimethyliminoacetic acid) liver scintigraphy

(n = 19) and magnetic resonance imaging (n = 22). Operative procedures included enucleation in 3 patients, two of them associated with hepatic segmentectomy; resection of one or two segments in 14 patients; left and right hemihepatectomy, respectively, in 7 and 3 patients; right extended hepatectomy in one patient, and nonanatomic resection in one patient. There was no postoperative death and the complications were bile leakage (re-operation), one patient; intraperitoneal abscess (re-operation); one patient, pleural effusion, two patients; venous thrombosis, one patient; and wound infection, one patient. We recommend that since the diagnosis has been well established, both enucleation or anatomically based resections of HA should be performed in all cases mainly in female patients taking oral contraceptives with tumors greater than 3 cm for the risk of hepatic hemorrhage or even when malignancy cannot be excluded.

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### COMPARISON OF LAPAROSCOPIC AND OPEN SURGICAL TREATMENT OF NONPARASITIC HEPATIC CYSTS

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The outcomes of laparoscopic hepatic cyst surgery for symptomatic benign nonparasitic hepatic cysts have not been clearly evaluated to date. For this reason, our experience with laparoscopic therapy for this disease was compared with a contemporaneous group of patients who underwent open surgical therapy via laparotomy. Between March 1993 and March 2004, 42 patients were surgically treated for benign nonparasitic hepatic cysts at our single institution. Of these, 22 were performed or attempted laparoscopically, while 20 were done with an open laparotomy. Patients were treated primarily for symptoms in 80% of cases, and 70% were female. Histologic evaluation of the cyst wall confirmed benign simple cyst in all cases. Patients undergoing laparoscopic surgery were more likely to have solitary cysts (59% vs. 25%,  $P < 0.01$ ) and larger sized cysts (median of 12 cm vs. 8 cm,  $P = 0.02$ ). Open procedures were more common in patients with recurrent symptomatic cysts, multiple cysts, and polycystic liver disease. Surgical therapy consisted of cyst fenestration and partial resection in all patients, and greater than 50% of the cyst wall circumference was resected in all cases. There was no cyst location in which a laparoscopic approach was precluded preoperatively, although, in two cases, conversion from laparoscopic to open procedure required (9%), both due to an inability to successfully access and complete the resection with the minimal approach. There was no difference in the operative time, extent of cyst wall resection possible, or complication rate between groups. Hospital length of stay was significantly less in the laparoscopic group (2 days vs. 5 days,  $P = 0.02$ ). In long-term follow-up, all patients undergoing laparoscopy remained free of symptoms compared to only 85% in the open surgery group. Laparoscopic surgical therapy for benign nonparasitic hepatic cysts is a safe and effective approach for most patients with uncomplicated symptomatic disease. In our experience, open procedures are more often performed for complex, recurrent cystic disease and in those with polycystic liver disease.

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### LAPAROSCOPIC RADIOFREQUENCY-ASSISTED LIVER RESECTION (LRR): A NEW TECHNIQUE FOR MINIMALLY INVASIVE LIVER RESECTION IN CIRRHOTIC PATIENTS

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InLine radiofrequency ablation is a newly described technique to achieve hemostatic parenchymal transection of the liver. We describe a

laparoscopic-assisted application of this technology to resect liver tumors from cirrhotic patients. Resection is accomplished using a laparoscopic-assisted technique, utilizing the InLine radiofrequency coagulation (ILRFC) device (Resect Medical, Fremont, CA). A 7-cm right subcostal hand port is placed to deploy the device, as well as an infraumbilical 12-mm port and a left upper quadrant 10-mm port. A nonanatomic resection plane is identified around the liver mass to achieve a greater than 1-cm margin. Probes are placed full-thickness through liver parenchyma along the intended resection line. Intraoperative ultrasound is used if necessary. Using a standard RFA generator (Rita, Sunnyvale, CA), radiofrequency energy is applied for three minutes in an amount proportional to the volume (depth) of tissue to be coagulated. This technique results in a coagulated plane of tissue approximately 1 cm wide by 5 cm long by 1 to 6 cm deep depending on the depth of the electrode placement. This procedure is repeated to fully coagulate the entire length of the intended resection margin. Following coagulation, parenchymal division is accomplished with blunt dissection, cautery, or the harmonic scalpel. No transfusions have been required, and patients have tolerated a regular diet 24 hours postoperatively. Technological advances have facilitated increasingly complex laparoscopic liver resections, although hemostatic parenchymal transection remains a challenge in cirrhotic patients. Using InLine radiofrequency coagulation, multiple RFA electrodes are simultaneously deployed to rapidly coagulate a resection plane. We have used this technology to perform laparoscopic liver resection in cirrhotic patients with excellent results. Advantages include minimizing blood loss and minimizing the physiologic impact of surgery in cirrhotics. In addition, the use of radiofrequency energy along the entire resection line creates a border of coagulated tissue approximately 1 cm wide, which may further ensure negative surgical margins if the tumor is close to or at the resection line. Laparoscopic radiofrequency-assisted resection may also be combined with laparoscopic radiofrequency ablation of synchronous unresectable liver lesions.

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### SIMULTANEOUS COLORECTAL AND HEPATIC RESECTION FOR COLORECTAL CANCER: SHORT- AND LONG-TERM OUTCOMES

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We sought to analyze the results of simultaneous colorectal cancer and liver metastases resection for colorectal cancer. Between June 1982 and February 2003, 750 patients underwent liver resection for colorectal metastases. Liver resection was performed simultaneously with a colorectal resection in 137 cases, representing the population of this study. Mortality rate, morbidity rate, and overall and disease-free survival times were analyzed. Median follow-up was 30 months (range: 11 to 162). Prognostic factors and their influence on outcomes were analyzed. Median hospital stay was 8 days (range: 4 to 24). Morbidity rate was 21%, including 18 cases of pleural effusion, 14 cases of wound abscesses, 8 hepatic failures, 3 systemic infections, 3 abdominal abscesses, and 1 colonic anastomotic leakage. Operative mortality rate was 2.1%. Recurrence rate was 64%. Overall and disease-free survival at 1, 3, and 5 years were 91%, 39%, and 24% and 69%, 34%, and 21%, respectively. Prognostic factors with notable influence on patient outcomes were nodal stage, number of liver metastases, diameter (smaller or larger than 5 cm), and CEA level more than 20 ng/dl. Simultaneous resection of colorectal cancer and liver metastases can be performed with low morbidity and mortality rates, thus avoiding a second surgical procedure.

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**SAFETY OF SIMULTANEOUS TREATMENT WITH RADIOFREQUENCY ABLATION AND ETHANOL INJECTION FOR HEPATIC TUMORS**

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Radiofrequency ablation (RFA) of malignant tumors is a liver-directed treatment modality in patients who are not candidates for hepatic resection. It has garnered widespread acceptance predominantly because it is associated with low morbidity rates. Experimental data suggest that injection of small volumes of absolute ethanol into hepatic tumors prior to RFA acts as an intratumoral vascular sclerosant, reducing the RFA treatment time and increasing the size of the zone of coagulative necrosis. We report on the safety of dual modality therapy using simultaneous RFA and absolute ethanol injection. Retrospective review of a prospective database collected from 1997 to the present was performed. All patients treated during exploratory laparotomy with simultaneous ethanol injection and RFA for unresectable primary or metastatic liver tumors were identified. Ethanol injection was performed under real-time intraoperative ultrasound guidance immediately prior to RFA of the lesion. Perioperative complications were defined as those that occurred within 30 days of the procedure. Seventy-one tumors in 45 patients were treated with this approach. Twenty-one patients had colorectal metastases, 11 had hepatocellular carcinoma, 5 had neuroendocrine tumors, 4 had gastrointestinal stromal tumors, and 4 had metastases from tumors of other histologies. Median volume of ethanol injected was 40 ml (range, 2-60). There were no deaths following treatment and 11 patients (24%) had perioperative complications (Table 1). Five of these patients had concurrent resection in addition to RFA. One patient (2%) required ICU admission. Median length of stay was 5 days. No patient had a local recurrence in a tumor treated with ethanol injection and RFA. RFA with simultaneous ethanol injection is safe. Morbidity and mortality rates are not increased over that seen with RFA alone. This combined treatment approach warrants further evaluation of therapeutic benefit to reduce local recurrence rates in unresectable liver tumors treated with RFA.

**Table 1.**

| Complication                 | Incidence |
|------------------------------|-----------|
| Perihepatic fluid collection | 1         |
| Empyema                      | 1         |
| Pneumonia                    | 2         |
| Atrial fibrillation          | 1         |
| Ascites                      | 2         |
| Wound infection              | 2         |
| Urinary tract infection      | 1         |
| Mental status changes        | 1         |

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**MORTALITY FOLLOWING LIVER RESECTION IN U.S. MEDICARE PATIENTS—DOES THE PRESENCE OF A LIVER TRANSPLANT PROGRAM AFFECT OUTCOME?**

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Our goal was to determine if the presence of a liver transplant program at a center improves outcomes following hepatic resection when compared to centers without an associated liver transplant program. Hepatic resection is a complicated procedure, at times associated with

significant morbidity. Liver transplantation programs may improve outcomes following resective liver surgery at the institutional level by a number of means, including availability of ancillary services and personnel, specialized critical care, and added surgical expertise. Using data from the national Medicare claims database, 30-day mortality following all hepatic resections performed over a two-year period (1999, 2000) were studied. Regression techniques were used to assess the relationship between mortality at centers with an associated liver transplant program in comparison to those without, while controlling for potential confounding factors. The proportion of patients dying within 30 days among 4661 patients who underwent hepatic resection was 6.65%. Factors that did increase the risk of dying after hepatic resection included urgent or emergent surgery (vs. elective), primary liver cancer (vs. metastatic), male sex, increasing comorbidity score, low hospital volume, and extent of surgery. The presence of a liver transplant program within a center was not associated with any improvement in mortality. At an institutional level, the presence of a liver transplant program was not associated with decreased 30-day mortality following hepatic resection.

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**HISTOLOGICAL, CT, AND INTRAOPERATIVE ULTRASOUND APPEARANCE OF HEPATIC TUMORS PREVIOUSLY TREATED BY LAPAROSCOPIC RADIOFREQUENCY ABLATION**

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Local tumor control after radiofrequency ablation (RFA) is traditionally followed with serial CT or MR scans. There are little data regarding the biopsy of previously ablated foci to confirm necrosis in follow-up. The purpose of this paper is to compare biopsy results of previously ablated lesions with their preoperative CT and intraoperative laparoscopic ultrasound (LUS) appearances in patients undergoing repeat RFA. From 1996-2004, 461 patients underwent laparoscopic RFA for primary and metastatic liver tumors. Seventy repeat ablation procedures were performed in 59 (13%) patients. Previously ablated foci were biopsied using an 18-G biopsy gun. Preoperative CT and laparoscopic ultrasound appearances of the previously ablated lesions were compared with core biopsy results. There were 33 patients with colorectal cancer, 11 with hepatocellular cancer, 8 with neuroendocrine tumors, and 7 with other tumor types. Mean  $\pm$  SEM time to repeat RFA was  $12 \pm 1$  months. Two hundred lesions were treated by RFA in these 70 repeat ablations. Suspected recurrent tumor foci were enhancing on CT and produced a more finely stippled echo pattern on LUS. Biopsy confirmed recurrent tumor in 72 of 84 such lesions. Previously ablated foci had a CT appearance of a hypodense, nonenhancing lesion without evidence of adjacent enhancing foci. Laparoscopic ultrasound was of a hypoechoic lesion with a coarse internal pattern with the tracks of the ablation catheter probes often still visible. Biopsy found necrotic tissue in 21 of 22 such lesions appearing radiologically to be without recurrence. Biopsy of an ablated focus adjacent to an area of suspected recurrence showed necrotic tissue in 17 of 22 lesions and viable cancer in 5. CT and laparoscopic ultrasound appearance of previously ablated foci showed good correlation with core biopsies. We therefore feel that CT scan is reliable in following RFA lesions, without the need for routine biopsy. Laparoscopic ultrasound reliably distinguished recurrent from ablated lesions in patients undergoing repeat ablation.

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**NOVEL APPROACH FOR RESECTION OF HEPATIC LESIONS SITUATED BETWEEN THE MIDDLE HEPATIC VEIN AND VENA CAVA, PRESERVING THE MIDDLE HEPATIC VEIN**

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Lesions situated between the origin of the middle hepatic vein (MHV) and the vena cava (IVC) are in an awkward position with respect to resection. Currently excision requires a right or left hepatectomy resulting in sacrifice of the MHV and one other hepatic vein (HV). We highlight two case reports where a novel two-step liver resection technique allowed removal of all the lesions. The approach permitted conservation of liver mass and preservation of both the MHV and RHV. Case 1 was a 25-year-old man who presented with bilateral CRC hepatic metastases. Segments II/III contained large volume disease and all segments had metastatic deposits, one between the MHV and IVC. Step 1: A left lateral segmentectomy combined with resection of segment I was performed. Step 2: Resection of the segment VIII/IV lesion was performed, approaching the lesion from the lateral aspect, through the cut liver surface. A subcutaneous continuous infusion pump for postoperative intra-arterial chemotherapy to the liver was implanted. Two months later, a nonanatomical resection of the metastases in segments V–VIII was carried out at the expense of the RHV. The remaining liver depended on the preserved MHV for venous drainage. The patient is disease free five months later. Case 2 was a 67-year-old man who presented with CRC liver metastasis. He had a segment I/IV lesion, situated between the MHV and the IVC. Other lesions were in segment IV, VIII, and VI/VII. Step 1: A left lateral segmentectomy was performed and the caudate lobe resected. Step 2: The metastasis was approached from the lateral aspect, through the cut liver surface. The metastasis was dissected free from segment IV but was adherent to IVC. The tumor and a portion of IVC were resected. Resection margins were free of tumor. Two days later, lesions in segments IV, VIII, and VI/VII were resected. The patient is free from recurrence ten months postoperatively. Conservation of liver mass and preservation of more than one hepatic vein during liver resection increases the options available to the surgeon with respect to the patient's management. It would not have been possible to clear the first patient's liver of disease if the MHV had had to be divided at the first operation. The exposure created by resection of segments II/III, whether they are involved by tumor or not, as a first step to gain access to the area between the MHV and the IVC is even sufficient to allow safe resection of the wall of the IVC. The approach increases the chances of preserving the MHV and conserving liver mass and thereby reduces the size of the liver resection that the patient has to withstand.

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**EN BLOC LIVER AND INFERIOR VENA CAVA RESECTION FOR COLORECTAL METASTASES**

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Surgical resection continues to offer the only hope for cure of colorectal cancer metastatic to the liver. Forty percent 5-year survival can be attained for resected hepatic metastases compared to a median survival of up to 20 months in patients treated with chemotherapy alone. Tumor involvement of the inferior vena cava (IVC) has traditionally been a contraindication to surgical resection. While proven technically feasible, the survival advantages of en bloc liver and IVC resection remain unclear. We reviewed all patients at a tertiary care center who had resection of colorectal liver metastases involving the IVC. These

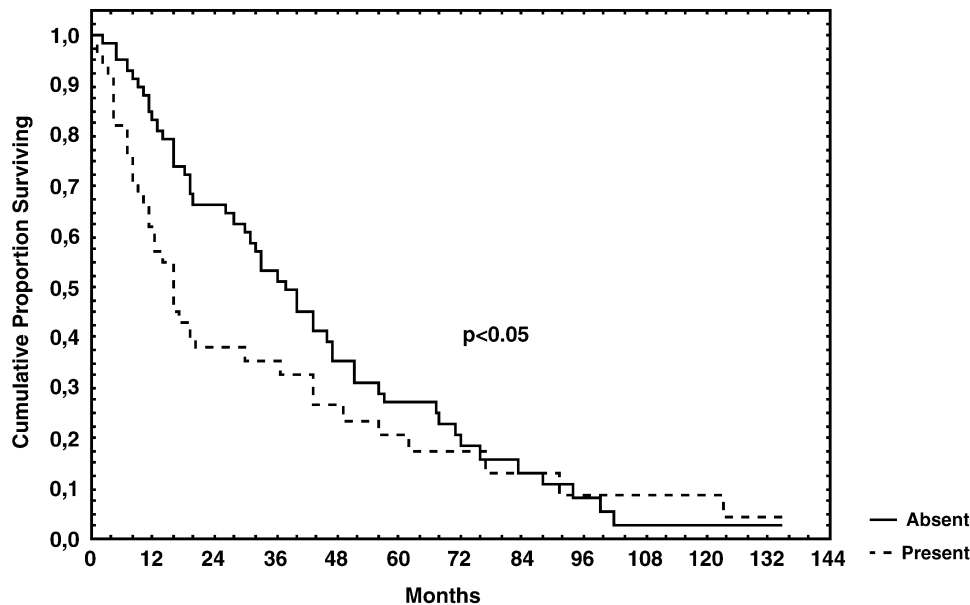
patients were compared to a cohort of patients who underwent isolated hepatic resection for colorectal metastases. Eleven patients had en bloc liver and IVC resection between 1988 and 2002; during the same time period 97 patients underwent isolated liver resection. The median age of the caval resection group was 61 years. One of the 11 patients had neoadjuvant chemotherapy. Mean operative time was 331 minutes (range, 238 to 446). A solitary metastasis was resected in 7 patients; greater than one metastasis was resected in 4. There were no perioperative deaths in the 11 patients. All resections had negative histologic margins. Perioperative transfusion was required in 7 patients (median 1 unit, range 1–4). Five patients received 5-fluorouracil-based adjuvant chemotherapy. Mean follow-up was 33 months (range, 11 to 71 months) from the date of surgery. Median disease-free survival of the group having caval resections was 9 months, while median survival was 34 months. When compared to the contemporary cohort of hepatic resections for colorectal cancer, the group undergoing caval resections experienced a significantly reduced disease-free survival 18.9 (95% CI: 10.5–27.2) vs. 9.2 (95% CI: 5.9–12.4) months, respectively, log rank  $P = 0.03$ , while there was no difference in overall survival between the two groups 55.2 (95% CI: 39.1–65.4) vs. 34.3 months (95% CI: 9.5 = 59.2), respectively, log rank  $P = 0.16$ . Tumor involvement of the IVC should not be a contraindication for surgical metastatectomy. Resection of hepatic colorectal metastasis involving the IVC provides similar benefit in terms of improved overall survival when compared to patients who did not need caval resections and resulted in longer survival than could be expected with chemotherapy alone (Fig 1).

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**ENHANCEMENT OF IN SITU MARGIN BY THERMAL DESTRUCTION (HEAT ZONE EFFECT) AFTER LOCAL APPLICATION OF THE SALINE-RADIOFREQUENCY DEVICE (TL) FOLLOWING LIVER RESECTION FOR TUMOR**

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Section, coagulation, and/or destruction of the liver parenchyma represent the main thermal properties of the TL device upon the type, power, and period of its application on the liver parenchyma. The aim of this experimental study was to evaluate the destructive thermal effect of TL device on the "in situ margin" after its application on the surrounding tumoral bed after limited resection for tumor. Five adult woodchucks infected with a hepatitis B virus (with 70% homology to the human HBV) and all presenting hepatocellular carcinoma were laparotomized upon institutional rules. The number and location of all of the tumors were assessed. Supracentimetric tumors were resected by local excision (tumorectomy) using conventional techniques (crush clamping and bipolar for hemostasis). After tumor resection, alternatively and upon tumor location from each other, TL have been applied on the liver parenchyma surrounding the resected tumor (power = 100 W, mean application time  $72 \pm 41$  sec). The main judgment criteria were (i) macroscopic margin analysis with special attention for the presence or absence involved margin and measurements of the thermal demarcation zone (heat zone), and (ii) microscopic analysis after H&E staining and viability studies by NADPH technique on frozen samples. The median tumor number per animal was 6 (1–20). The mean largest tumor diameter was 22 mm (3–53). Fifty tumors were resected and 84 samples prepared for final analysis. Among them, 34 did not have TL margin application (TL–, control group), while 50 had TL application (TL+ group). In 37% of the samples, the margin was considered as invaded (visible tumor  $\geq 1$  mm). TL application provoked a heat zone effect of  $12.1 \pm 3$  mm in



TL+ group versus  $0.7 \pm 1$  mm in TL- group ( $P < 0.05$ ). The NADPH viability test showed  $88 \pm 15\%$  of tissue and cellular necrosis (hepatocytes and/or tumor cell when noted in the in situ margin) in the TL+ group versus  $1 \pm 13\%$  in the TL- group ( $P < 0.05$ ). In conclusion, this experimental result strongly suggests that local application of TL device on the tumoral bed after resection can induce a heat zone with highly percentage of tissue necrosis on at least 10 mm of depth. This destructive thermal property of TL could therefore be interesting to use for the enhancement of the in situ margin after difficult limited or complex extended liver resections for tumor.

Postoperative recovery was uneventful, and the patient was discharged on the second postoperative day. Laparoscopic fenestration of multiple liver cysts has been used as an alternative approach to open surgery. Potential advantages of this approach include rapid recovery and few postoperative adhesions with good documented early clinical improvement. However, a high incidence of delayed recurrence of symptoms has been documented. Fear of injury to the inter-cystic structures including injury to the branches of the portal vein has to be borne in mind. Complications include hypothermia, hypercapnia, and cardiac failure.

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### LAPAROSCOPIC FENESTRATION OF SYMPTOMATIC POLYCYSTIC LIVER

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Adult polycystic liver disease (APLD) is a rare condition that usually occurs in association with polycystic kidney disease. Rarely symptomatic, a few patients have worsening symptoms, most commonly pain, needing intervention. Percutaneous drainage with sclerotherapy, fenestration, hepatic resection, and liver transplantation have been documented modes of surgical therapy. Laparoscopic fenestration recently has been reported as a technique for symptomatic cysts. We describe a case of laparoscopic fenestration of multiple liver cysts for symptomatic APLD. Our patient is a 57-year-old female who was known to have polycystic liver disease and developed increasing right upper quadrant pain. She had undergone a percutaneous aspiration of a large symptomatic cyst with minimal relief of symptoms. Her past history was remarkable for polycystic kidney disease and hyperthyroidism. Liver enzymes were remarkable for an elevated alkaline phosphatase. The patient had a computerized tomography scan of the abdomen that demonstrated multiple cysts in both lobes of the liver. A HIDA scan did not demonstrate gallbladder pathology. After adequate discussion, the patient was prepared for a laparoscopic fenestration of liver cysts. The patient underwent a successful laparoscopic fenestration of multiple liver cysts combined with an intraoperative cholangiogram and an antegrade cholecystectomy. An infraumbilical camera port and 3 other working ports, one 10-mm trocar in the left lower quadrant, two 5-mm trocar in the right upper and lower quadrant were used.

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### NORMOTHERMIA DURING PARTIAL HEPATIC ISCHEMIA INCREASES HEPATIC INJURY

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The protective effects of profound hypothermia on ischemia/reperfusion injury are well known. However, the effects of very moderate decreases in body temperature have not been addressed to date and a critical temperature threshold has not been established. We therefore assessed hepatic injury in rats undergoing partial hepatic ischemia that where either allowed to cool down to  $31^\circ$  or  $34^\circ\text{C}$  or maintained at  $37^\circ\text{C}$ . In 18 isoflurane-anesthetized male Wistar rats (300-400 grams) vascular supply to the left and medial lobe (70% of the liver) was clamped for 45 minutes. One group of rats were exposed to ambient temperature and allowed to cool down without intervention during ischemia, reaching  $31.3 \pm 0.8^\circ\text{C}$  (group 1,  $n = 6$ ), whereas a heating lamp was used to maintain body temperature at  $34.0 \pm 0.1^\circ\text{C}$  in the second group ( $n = 6$ ) and at  $37.1 \pm 0.3^\circ\text{C}$  in the third group ( $n = 6$ ). Following 24 hours of reperfusion, blood and liver samples were harvested. After 24 of reperfusion, ALT and AST increased to  $5101 \pm 2378$  and  $6409 \pm 4202$  U/L in group 3, respectively. Rats in group 2 demonstrated ALT and AST serum concentrations of  $99 \pm 87$  and  $171 \pm 38$  U/L, and in group 1  $136 \pm 45$  and  $175 \pm 38$  U/L, respectively ( $P < 0.01$  vs. T37). Macroscopic and histological assessment confirmed more severe liver injury in group 3. Very moderate hypothermia of  $34^\circ\text{C}$  resulted in a significant reduction of ischemia/reperfusion injury following 45 min of partial hepatic ischemia, when

compared to normothermic conditions. Decreasing body temperature further to 31°C had no additional protective effect. Such moderate hyperthermia is applicable in the clinical setting and is frequently seen in cardiac, neurosurgical, and ophthalmologic procedures. Maintaining normothermia appears to be detrimental in procedures that may result in hepatic ischemia/reperfusion.

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### GLUTAMINE DOES NOT AMELIORATE HEPATIC ISCHEMIA/REPERFUSION INJURY IN RATS

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Glutamine administration prior to ischemia-reperfusion (I/R) has been shown to be protective in experimental models of intestinal and myocardial I/R injury. Protection seems to result from induction of heat shock proteins (HSP). We investigated whether pretreatment with the supposed HSP inducers glutamine and herbimycin-A reduces hepatic injury in a model of warm liver ischemia in rats. Male lean Zucker rats were pretreated according to protocols that have been proven protective in other experimental settings.<sup>1,2</sup> Rats received either 2 doses glutamine (each 0.75 g/kg, GLU, n = 6) or saline (CON, n = 6) 24 and 6 h before ischemia. The third group was pretreated with herbimycin-A (10 µg/kg) 18 h prior to warm ischemia (HERB, n = 6). Seventy percent partial hepatic warm ischemia for 75 minutes was followed by 24 h reperfusion. In the CON- and GLU- groups, 5 of 6 animals survived 24 h reperfusion; in the HERB- group, 3 of 6 animals. There was no difference in liver morphology and transaminase serum concentrations in the surviving animals. ALT and AST serum concentrations at 24 h reperfusion were 5884 ± 2063 and 15,113 ± 4336 U/L (CON), 7763 ± 2524 and 17,695 ± 8531 U/L (GLU), and 6532 ± 544 and 23,291 ± 8662 U/L (HERB), respectively (all *P* > 0.05). Applying a protocol that has been previously shown to be protective against ischemia, pretreatment with glutamine or herbimycin did not reduce hepatic ischemia/reperfusion injury. Organ-specific differences in the characteristics of HSP induction seem to be responsible for differences in organ protection.

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### MILD HYPOTHERMIA SIGNIFICANTLY IMPROVES SURVIVAL IN RATS UNDERGOING HEPATECTOMY

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The goal of this study was to determine whether mild and clinically relevant hypothermia could provide a protective effect in rats undergoing warm ischemia and hepatectomy. Lean Zucker rats (10-12 weeks old) were subject to 75 minutes of ischemia by clamping the left and median lobe under isoflurane anesthesia under either normothermic or mild hypothermic conditions. At the end of ischemia, the right

lobe (nonischemic) was excised with subsequent reperfusion for either 4 (n = 4 each group) or 24 hr (n = 5 each group). Normothermic animals were carefully maintained with a body temperature of 37 ± 0.07°C using heat lamps and warming pads. Mildly hypothermic animals were exposed to ambient temperature and allowed to cool to a core temperature of 34.1 ± 0.2°C at the end of ischemia and surviving animals were sacrificed. Blood and liver tissue were harvested for histological and biochemical analysis at 4 hr and survival was noted after 24 hr. All mildly hypothermic animals (n = 5) survived in good general condition. In contrast, all normothermic rats (n = 5) died within 24 hours (*P* < 0.05). Serum AST and ALT levels at approximately 4 hr of reperfusion were significantly higher in the normothermic animals compared to the mildly hypothermic animals (mean ± SEM; AST: 15,280 ± 2456 vs. 6041 ± 659, ALT: 8963 ± 1720 vs. 3272 ± 506, *P* = 0.01 and *P* = 0.02, respectively). Macroscopic and histological analysis of liver tissue revealed more necrosis in the normothermic animals when compared to mildly hypothermic animals. Clinically relevant mild hypothermia achieved by exposure to ambient temperatures during surgery was sufficient to provide a significant survival benefit in rats undergoing warm ischemia and hepatectomy.

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### ISCHEMIC PRECONDITIONING IMPROVES BILE FLOW AFTER ISCHEMIA AND REPERFUSION INJURY TO THE LIVER IN RATS

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Ischemia and reperfusion (IR) injury to the liver is a well-known phenomenon in liver transplant and major liver resections and trauma. Ischemic preconditioning (IPC) potentially attenuates IR injury. While there are many proposed mechanisms to explain damage caused by IR and how this may be alleviated by IPC, these are generally not well understood. The reduction of bile flow following IR injury may lead to intrahepatic cholestasis and secondary liver failure. There have been few studies of the effects of an IPC regimen on bile flow in liver models reflecting the clinical situation. To elucidate the effect of IPC on bile flow after IR injury in an intact rat liver model and to investigate the intracellular mechanisms involved. Three groups of Hooded Wistar rats were studied. Group 1 (n = 5) were controls (selective bile duct cannulation (BDC) of the left lateral and median lobes, 2 hour measurement of bile flow). Group 2 (n = 7) received IR injury (BDC; 45 min clamping of portal vein (PV) and hepatic artery (HA) to the left lateral and the median lobes followed by 60 min of reperfusion). Group 3 (n = 7) were pretreated with IPC (BDC; 10 min of PV and HA clamping followed by 10 min of reperfusion prior to 45 min ischemia and 60 min reperfusion). Bile flow was measured at 5 min intervals. Serum AST, ALT, and LDH levels were measured at the beginning and at the end of the experiment. Liver histology was examined by H&E staining. F-actin distribution was measured using confocal fluorescence microscopy after staining with Texas Red-X phalloidin. Ischemia reduced bile flow to nil and bile flow did not recover after reperfusion (*P* < 0.001 group 2 vs. controls). IPC significantly improved bile flow during reperfusion (*P* < 0.05 group 3 vs. group 2). IPC did not significantly reduce ALT, AST, and LDH levels. Light microscopy showed mild portal inflammation and hepatocyte damage in group 2. This was less obvious in group 3. Cellular F-actin distribution did not differ between groups. F-actin was located around the peripheral cell membrane and the bile canaliculus. IPC

significantly improves bile flow after warm ischemia to the liver in rats. F-actin distribution was not significantly altered by IR or IPC. Future experiments are directed at elucidation of the mechanisms, including the roles of F-actin, cytoplasmic  $Ca^{2+}$ , and  $Ca^{2+}$  regulatory enzymes.

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### SHORT- AND LONG-TERM RESULTS OF INTRAOPERATIVE RADIOFREQUENCY ABLATION OF LIVER METASTASES

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Surgical resection is the only therapeutic option with curative effect on malignant liver tumors, but in over 70% of cases this is not a feasible option. A prospective study was performed to assess short and long term effects of intraoperative radiofrequency ablation on unresectable liver metastases. Between 1997 and 2001, 57 patients (mean age 61.9 years; range 31–83 years) with 297 unresectable liver metastases (colorectal adenocarcinoma  $n = 38$ ; carcinoid tumor  $n = 4$ ; malignant melanoma  $n = 3$ ; other metastases  $n = 12$ ) underwent intraoperative radiofrequency ablation. No mortality was observed in patients managed solely with radiofrequency ablation. Eight postoperative complications occurred in 8 patients (14%). Three occurred when radiofrequency ablation was combined with resection. Of the 33 patients completely ablated 30 patients are still alive and 21 are disease free after a median follow-up of 18.1 months (range 2–43). Ten patients underwent more than one intraoperative radiofrequency ablation episode. Overall survival was 72.5% at one year and 52.5% at 3 years. Complete ablation and number of lesions were significant independent prognostic factors for survival with  $P < 0.001$  and  $P < 0.0001$ , respectively. Radiofrequency ablation is a safe and effective option for patients with inoperable liver metastases without extra hepatic disease. Prospective controlled trials comparing results of different treatments are required to assess which patients will benefit best from this emerging new treatment.

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### RADIOFREQUENCY-ASSISTED LAPAROSCOPIC LIVER RESECTION

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Laparoscopic liver resection has become easier and safer. A number of patients underwent laparoscopic liver resection with radiofrequency in our units. Thirteen patients underwent a laparoscopic liver resection for liver tumors consisting of one hemangioma, 2 FNH, 5 HCC and 5 colorectal liver metastases. The liver resection was performed with an established technique in our units assisted with radiofrequency energy (RF). A 'cooled-tip' RF probe with a 500-kHz RF generator was used for induction of coagulative necrosis along an intended line of division of liver parenchyma without vascular clamping of either portal triads or major vessels. Then, the liver tissue was transected with scissors. The median age of patients was 56 years old. Three patients had a tumorectomy and 10 a segmentectomy. Of these segmentectomies, one patient had an additional tumorectomy and two patients two segments removed. There were one left lateral, 5 segment III, one segment IV, one segment V, 2 segment VI, and 2 segment VII resections. The median operative time was 200 min. There was no per- or postoperative blood transfusion or transfusion of blood products. All resections were achieved without vascular clamping or conversion to

open. There was one intraoperative pneumothorax caused by radiofrequency probe which was managed with a chest drain. There was no postoperative morbidity or mortality. The median length of hospital stay was 5 days. Laparoscopic liver resection assisted with RF can be safely performed with no blood transfusion and a short hospital stay.

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### HEPATIC TRISEGMENTECTOMY SHOULD BE PRECEDED BY PORTAL VEIN EMBOLIZATION TO DECREASE THE RISK OF POSTOPERATIVE LIVER FAILURE

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In patients being considered for hepatic trisegmentectomy, the remnant liver may be inadequate to prevent postoperative liver failure. Portal vein embolization (PVE) results in hypertrophy of the contralateral lobe of the liver and may result in a lower risk of liver failure. From December 1992 to September 2001, 19 patients had planned hepatic trisegmentectomy for primary and secondary malignancies. PVE was not considered in 11 patients prior to April 1999 but was routinely used after this time in 8 patients in whom liver volumetric measurements were performed by CT and the volume of the future hepatic remnant was less than 25% of the total hepatic volume. The records of these 19 patients (11 non-PVE group and 8 PVE group) were reviewed for demographics, diagnosis, tumor characteristics (primary vs metastatic, location, number of tumors, size), liver volume before and after PVE, postoperative complications, and survival. The mean volume of the left lateral segment prior to PVE was  $374.6 \pm 67.8 \text{ cm}^3$ , and after PVE was  $525.3 \pm 123.3 \text{ cm}^3$  ( $P$  value = 0.038). This was equivalent to a  $40.8 + 23.6\%$  increase in the volume of the left lateral segment with a hypertrophy ratio of 12.5%. Of the 19 patients, 17 underwent extended hepatic resections and 2 had segmental resections as PVE failed to cause sufficient hypertrophy. In the PVE group, there was one intraoperative death, no perioperative deaths and four (50%) had postoperative complications. There were no intraoperative deaths, 5 perioperative deaths (45.5%), and four (36.37%) had postoperative complications in the non-PVE group. Overall one-year survival was 68.42% compared to 87.5% in the PVE group and 54.5% in the non-PVE group ( $P = 0.18$ ). Mean survival was  $27.66 \pm 15.1$  vs  $34.5 \pm 49.5$  months in the PVE and non-PVE groups, respectively ( $P = 0.78$ ). Recurrence was seen in 10/19 (52.6%) patients overall after 24.6 months of follow-up compared to 5/8 (62.5%) patients in the PVE group and 5/11 (45.5%) in the non-PVE group ( $P = 0.65$ ). PVE induces sufficient hypertrophy of the contralateral liver lobe and permits safe and curative resection of the embolized liver in patients who otherwise would not be candidates for liver resection due to inadequate size future remnant. It reduces perioperative deaths related to hepatic insufficiency. Long-term survival is comparable to that of patients who undergo major hepatic resection without PVE. PVE should be considered in all patients undergoing hepatic trisegmentectomy.

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### SURGICAL TREATMENT OF HEPATOCELLULAR CARCINOMA ORIGINATING FROM CAUDATE LOBE

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Our aim was to explore the significance of surgical treatment of HCC originating from caudate lobe. From 1995 to 2003, caudate lobectomy, including 19 cases of isolated lobectomy (group 1) and 20 cases of combined lobectomy (group 2) were performed in 39 patients with HCC originating from caudate lobe. The factors which might influence postoperative liver function were compared between the two groups. All tumors were resected successfully. The mean operative time, blood loss, mean blood transfusions, and the time of inflow occlusion were  $296.26 \pm 99.32$  (min)  $1236.84 \pm 892.99$  (ml),  $1000.00 \pm 789.63$  (ml),  $52.05 \pm 8.85$  (min) in group 1; in group 2, the data were  $247.70 \pm 96.32$  (min),  $1107.50 \pm 969.65$  (ml),  $840.00 \pm 639.40$  (ml),  $48.00 \pm 7.96$  (min), the *P* value were not significant between the two groups. One patient died of postoperative renal failure. Hydrothorax occurred in 3 patients, and ascites in 4 patients, and bile leakage in 1 patient. The time for postoperative liver function restoring to normal range in group 1 is less than group 2 ( $P < 0.05$ ). The survival rates of 1, 3, 5 years were 53%, 50%, 39%, respectively. Caudate lobectomy is an effective method of treatment for HCC originating from caudate lobe. Isolated lobectomy does not have much risk than combined lobectomy.

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### LAPAROSCOPIC LIVER RESECTION FOR BENIGN AND MALIGNANT LESIONS: A FEASIBILITY AND SAFETY STUDY IN 35 PATIENTS

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During last years, development of laparoscopic surgery allowed carrying out more interventions such as liver resections. The aim of this study was to assess feasibility, safety, and morbidity of laparoscopic liver resections. A retrospective study of laparoscopic liver resections was undertaken. Each patient underwent surgical resection for preoperative diagnosis of benign or malignant lesions. Hepatic lesions had to be located in the left or peripheral right segments (II, III, IV, V, VI). Clinical data, type, and characteristics of the tumor and technical details of the procedure were collected. From September 1999 to January 2004, 36 laparoscopic liver resections were performed on 35 patients (13 men, 22 women, mean age 51 years) in our departments. There were 27 benign lesions (5 adenomas, 1 angiomyolipoma, 1 hemangioma, 1 cholangioma, 1 mucinous cystadenoma, 1 preneoplastic lesion, 4 biliary cysts, 2 polycystosis, and 11 nodular focal hyperplasia suspected to be adenomas or being painful) and 9 malignant tumors including 6 hepatocellular carcinomas and 3 metastasis (gastric sarcoma, colorectal cancer, and pulmonary neuroendocrine tumor). Mean tumor size was 50.6 mm. The resection included 7 left hepatectomies, 3 bisegmentectomies V/VI, 9 segmentectomies, and 20 atypical resections. Radiofrequency was associated with atypical resection of a left-sided tumor in one patient, for 2 right posterior lesions (VII and VIII). Parenchymal section was done using dissection, ultrasonic scalpel, ligature, floating ball, or endo-GIA. Conversion rate was 5.5% ( $n = 2$ ) for bleeding. Two patients needed perioperative transfusion. There were no postoperative deaths. Postoperative complications occurred in 2 patients (5.5%): wound of left biliary tract requiring opened left hepatectomy and ascites. Mean surgical time was 190 minutes. The median length of stay was 8 days. Liver laparoscopic resections are feasible and safe in selected patients with tumors located in the left-sided and right peripheral segments requiring limited resection, without increasing mortality and morbidity.

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### HEMORRHAGIC SHOCK IN A SCHISTOSOMIOTIC PATIENT SUBMITTED TO ENDOSCOPIC BIOPSY OF A GASTRIC FUNDUS VARICES CONFUSED WITH A POLYPOID LESION

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We herein present a case of a 40-year-old man, from endemic zone and known to have schistosomiasis since 1990 when he had a unique episode of upper digestive tract hemorrhage presented by melena that was found to be a esophageal variceal treated by endoscopic approach. He was submitted to a routine endoscopy requested by his gastroenterologist 6 months ago when the endoscopist found an elevated nonbleeding lesion that was supposed to be a polypoid lesion that was treated by biopsy. Immediately after the biopsy the patient had important bleeding from the site of it, and was taken to the ER at our institution. He was admitted clinically stable, with grade I shock, and initially after blood tests and samples with a admission hemoglobin level of 10.5 g/dL, platelet count of  $65,000/\text{mm}^3$ , normal liver function tests, vascular access and volume infusion he was taken to the in-hospital endoscopy to confirm the diagnostic and try to treat the hole in the gastric vessel. After several attempts of sclerotherapy and band ligation the endoscopist decided to locate a Sengstaken-Blakemore tube and then call the liver surgeons. After the clinical m evaluation, we decided to operate the patient since that there was a failure in the endoscopic treatment and the patient was still bleeding. The surgery performed was a splenectomy with azygo-portal desconnection and gastrotomy with continuous direct suture of the damaged gastric vein that had a hole with active bleeding even after the desconnection. The patient recovered uneventfully and was discharged from the hospital six days after surgery. Now he is followed by our team and so far with no evidence of recurrence of the portal hypertension. In conclusion, the endoscopists must keep in mind that in patients with portal hypertension any lesion in the gastric fundus must be very well analysed before a biopsy be done and if it so, the procedure need to be perform inside of the hospital with a surgical team capable to take care of emergency liver and portal hypertension surgery.

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### TRIPLE STAPLED HEPATECTOMY

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During the past two decades, hepatic resections have become feasible for widening indications because of a low operative mortality rate (ranging between 1% and 2% in noncirrhotic livers). Due to this low mortality rate, hepatic resections are now considered to be an effective therapy for patients with a wide array of benign and malignant hepatobiliary diseases. One of the major improvements in surgical technique has been the wider employment of stapling devices. Vascular and endoscopic staplers have become indispensable in gastrointestinal surgery. This study is the first to describe the use of a linear stapling device to dissect the (1) liver parenchyma, staple the hepatic (2) inflow and (3) outflow, referred to as a triple stapled hepatectomy (TRISH) technique. A total of 100 consecutive hepatectomies [right hepatectomy ( $n = 32$ ), extended right hepatectomy ( $n = 11$ ) and left hepatectomy ( $n = 57$ )] between April 2002 and November 2003 performed at the Vancouver General Hospital were included in the study. A GIA 100 was used to transect the parenchyma, while a vascular stapler was applied to staple the hepatic inflow and outflow. The mean operative time was 189 min (79 to 395), the mean operative blood loss accounted to 407 ml and the mean cross-clamp time was 19 min (6 to 42). There



was no hospital mortality; early postoperative complications included pneumonia, intra-abdominal fluid collection, fever longer than 48 h, and one minor bile leak. The overall complication rate was measured to be 27%. In the authors' experience, it is useful to employ stapling devices in dissecting the hepatic parenchyma, in order to simplify hepatic lobectomies. In this study, the operative time and the intraoperative blood loss were less, when compared to other major studies. The TRISH approach facilitates and simplifies major hepatectomies and has become the method of choice in our institution.

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### TOTAL VASCULAR EXCLUSION FOR COLORECTAL METASTASIS TO THE LIVER

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Resection of colorectal metastasis has been shown to improve survival. Complete removal of disease and transfusion requirements have been shown to be prognostic indicators for survival. Total vascular exclusion (TVE) of the liver can be used to provide optimal conditions for resection with low transfusion requirements and achievement of negative margins. We retrospectively reviewed hepatic resections performed for colorectal metastasis from September 1990 to July 2003. Patient and database records were reviewed. 107 patients were identified to have undergone hepatic resection for colorectal metastasis. Sixty-three patients from this group had resection under TVE. The remainder had other methods of inflow occlusion or no vascular control during resection. Of the patients who had TVE, there were 35 males (56%) and 28 females (44%). Average age was 60 (range 33–81). Eighty-four percent of patients had a major hepatectomy including 39 right hepatectomies, 6 left hepatectomies, and 8 trisegmentectomies. Sixteen percent (10) had segmental resections. Median blood loss was 900 ml. Average transfusion requirement was 1.1 units of packed red blood cells (range 2–9 units) with only 31% of patients requiring a transfusion. Average vascular exclusion time was 24 minutes (range 10–43), and the average operating time was 247 minutes (range 148–491). Seventeen patients had complications, which included 8 bile leaks, 6 abscesses, 4 pleural effusions that required drainage, 1 wound infection, and 1 portal vein thrombosis. There was 1 mortality (1.6%). Median length of stay was 8 days (range 4–31). Negative margin was achieved in 95% of patients. Total vascular exclusion of the liver can safely provide optimal conditions for complete resection of colorectal metastasis.

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### A ROLE FOR RADIOFREQUENCY ABLATION OF UNRESECTABLE LIVER MALIGNANCIES

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To review our experience with radiofrequency ablation (RFA) with or without liver resection, and to determine which patients may benefit from RFA based on tumor location, size, or type. Between October 1999 and July 2004, a total of 27 patients with 101 liver tumors underwent RFA at our institution. All patients were considered otherwise unresectable due to tumor location, liver function or comorbid conditions. The median number of liver tumors per patient was 3 (1–14) with a median size of 2.3 cm (0.2–12.5). Primary disease type was colorectal (n = 16), hepatocellular carcinoma (n = 5), neuroendocrine (n = 2), breast (n = 2), gastrointestinal stromal tumor (n = 1), and cholangiocarcinoma (n = 1). Colorectal metastasis was analyzed

**Table 1.** Overall Analysis of Risk Factors for Colorectal Patients

| Prognostic Variable  | N  | 3-Year Survival | P Value |
|----------------------|----|-----------------|---------|
| Whole group          | 16 | 64%             | N/A     |
| Extrahepatic disease |    |                 |         |
| Yes                  | 3  | 0%              | .0428   |
| No                   | 13 | 83%             |         |
| Bilobar disease      |    |                 |         |
| Yes                  | 10 | 27%             | .0131   |
| No                   | 6  | 100%            |         |
| ≤3 Tumors            |    |                 |         |
| Yes                  | 8  | 67%             | .8900   |
| No                   | 8  | 50%             |         |
| ≤3 cm                |    |                 |         |
| Yes                  | 12 | 80%             | .0018   |
| No                   | 4  | 0%              |         |

separately, with survival estimated using Kaplan-Meier analysis. The median length for overall follow-up was 15 months. Six patients were treated with RFA alone, 21 with RFA+Resection. All but two of the colorectal patients had chemotherapy to maximum response prior to RFA. The two not receiving preoperative chemotherapy had single, small tumors with long disease-free intervals. The colorectal results are represented in Table 1. Of the five hepatocellular carcinoma patients, three are NED at 10, 13, and 30 months, and two went on to transplant. Of the two patients with neuroendocrine tumor, one is NED, while the other patient has DOD at 15 months. One breast patient has DOD at 26 months and the other remains NED at 20 months. The patient with gastrointestinal stromal tumor had failed Gleevac treatment and is alive with extrahepatic disease after RFA and resection at 21 months. The patient with cholangiocarcinoma has DOD at 17 months. The patients in this study would have been deemed unresectable without the aid of RFA. With RFA, these patients were able to become surgical candidates. The size of the colorectal tumors, but not the number, impacted survival. Preoperative chemotherapy with the goal of reducing the colorectal tumors to ≤3 cm followed by RFA with or without resection may be associated with a prolonged survival. Patients with >3 tumors had equivalent survival as those with 3 or less, and therefore should be considered for aggressive combined modality treatment with RFA. RFA with or without resection in otherwise unresectable cases, appears beneficial to the treatment of liver malignancies in select cases.

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### EXPERIENCE WITH INTRAHEPATIC CHOLANGIOCARCINOMA

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Intrahepatic cholangiocarcinoma is uncommon malignant lesion with a known poor prognosis. Patients often present with advanced disease and are not amenable to curative resection and those that do undergo resection with curative intent have high recurrence rates. We retrospectively investigated our experience with intrahepatic cholangiocarcinoma to determine factors that may predict longer survival. We investigated 28 patients with intrahepatic cholangiocarcinoma who presented to our institution for treatment from January 1994 to September 2004. Variables were analyzed including age, sex, race, presenting symptoms, presence of cirrhosis, preoperative alkaline phosphatase, preoperative tumor markers, tumor size and number, tumor location, operation, proximal margin, tumor pathology, lymph node and vascular spread, and TNM staging. The accumulative 1-, 3-, 5-year survival rates of the 28 patients were 65.3%, 41.6%, and 16%, respectively. The average age of our 28 patient series was 58.6 years (range 39 to 76). Only 6 (21.4%) patients underwent operative

resection with curative intent. Seven (25%) underwent palliative procedures and 7 (25%) had diagnostic explorations. Analysis of all variables revealed that the only factors with statistically significant relationship to survival were TNM staging and operative resection with curative intent. Our experience with intrahepatic cholangiocarcinoma demonstrated a dismal prognosis. The survival benefit from operative resection demonstrates the need for early diagnosis and hepatectomy in these patients.

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#### VASCULAR RESECTION (PORTAL VEIN, SUPERIOR MESENTERIC VEIN, AND HEPATIC ARTERY) IN HPB SURGERY

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Vascular resection for cases of advanced tumors remains controversial, because of the high risk of postoperative complications and extremely poor long-term survival. Recent advances in surgical technique have contributed to an increased resectability rate and to an improved prognosis and outcome with respect to early morbidity and mortality rates, as well as vascular reconstruction patency. 13 patients (14 vascular resections) required a concomitant resection of a major vascular structure and vascular reconstruction in an attempt to achieve complete tumor resection. Six males and 7 females. Ages ranging from 32 to 79 years (mean age: 51 years). Superior mesenteric vein and portal vein was resected in 9 cases: portal vein (7), portal vein and left portal vein (1) and superior mesenteric vein and right hepatic artery (1). The primary disease was pancreas cancer (3), solid tumor pancreatic head (1), gallbladder cancer (2), cholangiocarcinoma (2), and recurrent liver metastasis from colon cancer (1). Multivisceral resection was performed: pancreatoduodenectomy (4), pancreatoduodenectomy + central hepatectomy (2), right hepatectomy extended to segment IV + extrahepatic biliary duct resection (1), liver segmentectomy (S IV) + partial gastroduodenectomy + extra and intrahepatic biliary duct resection (1), and extrahepatic biliary duct resection (1). Hepatic artery was resected in 4 cases: main (1) and right hepatic artery (3). The surgical technique was pancreatoduodenectomy (3) and left hepatectomy + biliary duct confluence (1). The morbidity and mortality related to vascular reconstruction was 14% (2/14) and 7% (1/13), respectively. The early and late patency vascular reconstruction was 100%. The 1-year survival was 100%, 66%, and 33% for patients operated by liver metastasis, gallbladder cancer, and cholangiocarcinoma, respectively. Our initial experience suggests that vascular resections in advanced HPB tumors can be performed in selected cases safely with acceptable morbidity and mortality. Multivisceral resection associated to vascular resection can be offer a good palliation for patients with advanced tumors.

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#### INFERIOR VENA CAVA RESECTION IN HPB SURGERY

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Due its proximity to a number of important regional vascular structures, tumors of the liver, biliary tract, pancreas, retroperitoneum area, and kidney are often associated with regional invasion or compression of the inferior vena cava (IVC). We describe the personal experience and policy concerning technical considerations for inferior

vena cava resection in selected cases of advanced tumors. Twelve patients required a concomitant resection of IVC with and without reconstruction in order to obtain a complete tumor resection with free margin. Five males and 7 females. Ages ranging from 32 to 54 years (mean age, 45 years). The primary disease was: Liver metastasis from colon cancer (4), ruptured hydatid cyst into IVC with hydatid thrombus in IVC and atrium and pulmonary dissemination (2), Intrahepatic cholangiocarcinoma (1), renal cancer + tumoral thrombus into IVC (2), tumoral thrombus into IVC (2) and tumoral thrombus into IVC + liver infiltration (segment V) (1). Total (3) and retrohepatic (3) IVC was performed in 6 patients. In 2 and 4 patients, we resected IVC with renal veins and hepatic vein bifurcation, respectively. Multivisceral resection was performed: Right hepatectomy extended to segment IV (4), hepatic segmentectomy (segment V) (1), total excision hydatid cyst (2) one of them with IVC and atrium thrombectomy, nephrectomy (3), and tumor thrombus resection (2). The general morbidity of the procedures was 29%, related to the vascular resection (8%). The early and late patency vascular reconstruction was 91%. One patient has a graft thrombosis after IVC resection and graft replacement. One patient died in the postoperative period due to liver failure. The 1-year survival was 100% for patients operated by liver metastasis and tumoral thrombus secondary to renal cancer, respectively. Our initial experience suggest that the IVC resection can be performed in selected cases with a low risk of morbidity and mortality. Long-term patient outcome is not determined by the need to perform a concomitant vascular resection but rather by the biological behavior of the resected malignancy.

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#### HEPATIC NEOPLASMS: ROLE OF HELICAL CT AND INTRAOPERATIVE ULTRASOUND (IOUS)

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Several studies have shown that IOUS is a more sensitive imaging tool than CT for staging hepatic neoplasms. The purpose of this study is to evaluate the role of IOUS in the management of hepatic neoplasms and to compare intraoperative findings to preoperative helical CT staging. The study was a retrospective review. From 1993-2004, 77 cases were identified with IOUS evaluation of presumed surgically treatable hepatic neoplasms. We reviewed preoperative helical CT scans for number of lesions seen and medical records for planned procedure. Pathology reports were reviewed. Operative notes were reviewed for number of lesions found on IOUS and procedure performed. Preoperative staging and planned procedure were compared to IOUS findings and actual procedure performed. Of 77 patients, 34 (44%) were male and 43 (56%) female, with an average age of 54 years. The most common cancers were metastatic colon cancer (n = 45; 58%), hepatocellular carcinoma (n = 9; 12%), and metastatic testicular cancer (n = 4; 5%). In 7 cases (9%), intraoperative inspection/palpation revealed lesions not seen on CT and changed planned procedure; 5 procedures were aborted. In 16 cases (21%) IOUS changed the planned procedure; 7 procedures were aborted and in 9 cases, the planned procedure was changed. In all cases in which an IOUS-guided resection was performed, the presence or absence of neoplasia identified by IOUS was confirmed by pathology. Other changes included the addition of RFA to resection (n = 3), addition of wedge resection to RFA (n = 2), conversion from RFA to wedge resection (n = 2), conversion from bilobar resection to segmentectomy (n = 1), and conversion from RFA to bilobar resection (n = 1). In only 12 cases (16%) was attempted surgical treatment aborted because of intraoperative findings not identified by helical CT. IOUS is an important imaging modality for surgical management of hepatic neoplasms. IOUS changed the management in 21% of

cases, but only 9% were aborted. Although IOUS changed the surgical management in a significant number of patients in this study, preoperative helical CT correctly identified 84% of surgically treatable hepatic neoplasms.

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#### LIVER RESECTION FOR HEPATOCELLULAR CARCINOMA (HCC) WITH DIRECT REMOVAL OF TUMOR THROMBUS IN THE MAIN PORTAL VEIN

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The prognosis of far advanced hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT) is extremely poor. The development of tumor thrombus in the main portal vein trunk is considered to be the terminal stage of this disease process and is associated with rupture of esophageal varices or hepatic failure. Herein we present two cases of HCC with tumor thrombus in the main portal vein trunk. We show our technique for surgery and discuss the indication of the surgery for these cases. Case 1 was a 60-year-old man with a tumor occupying S7 and S8 of the liver. PVTT was observed originating from right branch of the portal vein and extended to the main and left side. A right hepatectomy and removal of the tumor thrombus was performed. To reduce the bleeding from collateral veins, we inserted a bypass tube between superior mesenteric vein and falciform ligament. We used color Doppler ultrasonography intraoperatively following removal of involved segment. Approximately one month following surgery patient presented with recurrence of PVTT in the main portal trunk and superior mesenteric vein. Intrahepatic arterial infusion of 5-fluorouracil with interferon beta was performed. The patient died of liver failure secondary to multiple intra hepatic metastasis 6 months postoperatively. Case 2 was a 59-year-old man with HCC occupying the lateral and median segment of the liver. PVTT was observed originating from left branch of the portal vein and extending to the main and right side. A left hepatectomy with removal of the PVTT was performed. To avoid a massive hemorrhage, we inserted a bypass tube between superior mesenteric vein and great saphenous vein. One month after surgery, follow-up percutaneous Doppler ultrasound of the portal vein showed good blood flow without compromise. However, approximately 2 months postoperatively, the patient had progressive development of hepatic coma. Enhanced computed tomography revealed no blood flow in the portal vein without hypertrophic changes in the residual liver. The surgery for PVTT with collateral cavernous venous change is always difficult to perform, as it accompanies with massive bleeding during the surgery. To reduce the risk of intraoperative bleeding, we are using a bypass tube without any special equipment. Although we performed complete removal at the time of initial surgery, our two patients had tumor recurrences in the portal vein. To expect better result, we need to utilize other effective surgical or nonsurgical methods. Furthermore investigations are needed to evaluate these techniques and study their benefits.

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#### AN ELECTROPHYSIOLOGICAL STUDY OF PROTECTING EFFECTS OF 2-AMINOETHOXYDIPHENYL BORATE ON HEPATOCYTES OF HEPATIC ISCHEMIA/REPERFUSION INJURY IN RATS

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We sought to study the effects of hepatic ischemia/reperfusion (I/R) injury on store-operated calcium currents (Isoc) in freshly isolated

hepatocytes of rats and the effects of 2-aminoethoxydiphenyl borate (2-APB) on Isoc in hepatocytes of hepatic ischemia/reperfusion injury in rats. Established rat hepatic ischemia and reperfusion injury model, whole-cell patch-clamp technique was used to investigate the properties of Isoc and effects of 2-APB on it in freshly isolated hepatocytes of rats. Ischemia/reperfusion injury could significantly increase Isoc in rat hepatocytes, at the holding potential of  $-100$  mV, ischemia/reperfusion group increased the peak amplitude of Isoc up to  $-1058 \pm 223.34$  pA compared with sham-operated control,  $-664.52 \pm 140.43$  pA ( $P < 0.05$ ,  $n = 8$ ). 2-APB at the concentration of 20, 40, 60, 80, 100  $\mu$ M inhibited Isoc in a dose-dependent potentiation way with  $IC_{50}$  of  $64.63 \pm 10.56$   $\mu$ M ( $n = 8$ ), with the inhibiting rate of  $74.17 \pm 16.47\%$  at 100  $\mu$ M 2-APB. Ischemia/reperfusion injury obviously increases Isoc in rat hepatocytes. 2-APB has a protective effect on hepatocytes of hepatic ischemia/reperfusion injury, probably through inhibiting the Isoc.

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#### TECHNIQUES AND TECHNOLOGIES FOR LAPAROSCOPIC LIVER TRANSPLANTATION

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Laparoscopic surgery has evolved over the last two decades, leaving solid organ resection as the final frontier for this approach. Hepatic surgery is recognized as the most challenging and controversial of these resections. Retrospective review of surgical techniques employed during the first 100 hepatic resections performed by two surgeons at their respective institutions. One hundred laparoscopic hepatic resections were performed in a patient population with a mean age of 52 years (28–84 years). Thirty-five percent were performed for malignant disease and 19% in cirrhotics. Mean tumor size was 8 cm (1–25 cm). Thirty percent had formal lobectomies (20 right and 11 left). No operative conversions were encountered with a mean operative time of 2.2 hours. Two patients were reexplored for hemorrhage. Mean length of stay was 3 days. To achieve these results, several techniques were adopted: supine positioning for left-sided lesions, and lateral positioning for right lobe and right posterior tumors, two-person operative teams, and hand-assisted laparoscopy for lobar resections. Techniques evolved included high peritoneal pressures, steep reverse Trendelenburg, avoidance of vascular pedicle control, and hepatic parenchymal transection through vascular stapling. Technologies employed include ultrasonic dissection, Tissuelink hook cautery, and articulating 60 mm 2.5 mm load vascular stapler (TYCO). Hemostasis was modified employing argon beam, clip application, Floseal, and Tisseel. With careful and thoughtful planning, laparoscopic hepatic resection can be performed safely for a wide variety of lesions. This must be done with the use of appropriate techniques and technologies.

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#### USE OF THE RECIPIENT'S OWN SPLENIC ARTERY GRAFT TO HEPATIC ARTERY RECONSTRUCTION IN THE LIVING DONOR LIVER TRANSPLANTATION

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The recipient arterial reconstruction in the living donor liver transplantation (LDLT) represents one of the major problems in this modality of transplant. Besides these technical difficulties, the portal hyperflux due to high portal hypertension also represents another serious problem in the management of these patients in the immediate postoperative period. Nowadays there are an increasing number of

papers proposing new insights and solutions to create a rationale in this matter. In patients with portal hypertension we propose a new approach to solve these two major problems at the same time, first, by the dissection and section of the splenic artery (SA) as near as possible to the celiac trunk in the recipient, taking a 3- to 5-cm graft to be anastomosed to the right or left hepatic artery (HA) at the bench during the back table period. This approach brings a solution to these two problems because it eases the complex hepatic arterial anastomoses in the recipient after reperfusion at the surgical recipient operative field and, as a consequence, reduction in the portal blood flow to the liver decreasing the hyperflux syndrome, since the splenic ligature importantly decreases the splenic blood component to the portal flow. We applied this vascular reconstruction technique to the LDLT of right lobe in three patients. Case 1 was a 54-year-old woman with hepatocellular carcinoma (CHC), hepatitis C, and portal hypertension (HP). Case 2 was a 28-year-old man with sclerosing cholangitis presenting with a severe acute crisis of cholangitis and presenting with a huge spleen and HP. Case 3 was a 52-year-old man with hepatitis C, CHC, and HP. All donors were first-degree relatives and approved by the Hospital Ethics Committee. All patients (donors and recipients) had an uneventful evolution, being discharged between 1 and 2 weeks. The procedure is done by opening the greater gastric curvature between the stomach and colon, finding the splenic artery at the upper pancreatic border, and then dissecting it for an extension of 5 cm, beginning at the celiac trunk. After a sufficient length of splenic graft is obtained, the SA is ligated and resected. This segment is then offered to the donor surgical team, who at the back table performs the anastomoses between the SA graft and the donor right HA with a 6-0 running suture with 3.5 mag. lenses. After the reperfusion the arterial graft HA reconstruction in situ is much easier to perform since it is exactly the same anastomoses that we are used to do in cadaver LT, with a safer distance from the biliary duct.

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#### MORBIDITY AND MORTALITY ANALYSIS IN LIVING RELATED DONOR HEPATECTOMY

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Morbidity and mortality in hepatectomy are about 30–50% and 1–3%, respectively. Hepatic resection in living related donors for liver transplantation is a complex procedure for a healthy patient. Our goal was to retrospectively evaluate the results of hepatectomies in living related donors for liver transplantation. 80 hepatectomies in living related donors for 50 pediatric recipients and 30 for adult recipients. Forty-five left lateral sectionectomies, 5 monosegmentectomies, 29 right hepatectomies, and 1 left hepatectomy was performed. STROC score (Clavien et al.) was used to classify complications. No vascular exclusions were used. There were 3 intraoperative accidents (3.75%). Donors for pediatric recipients: ICU mean stay was 2 days, and in-hospital stay was 7.3 days (range: 6–9). At the beginning of the program, 6 patients received 1.2 red blood units. Morbidity was 12% (6/50): 3 biliary complications (6%), 1 biloma, and 1 patient with a biliary fistula (all patients were treated percutaneously) (STROC IIIa). One parietal abscess (STROC I) followed by an eventration (3.3%). One patient presented a gastric perforated ulcer who needed a surgical treatment (STROC IVa). Donors for adult recipients: mean ICU stay was 1.4 days and in-hospital stay was 7 days (range: 6–10). No blood transfusion in this group. Morbidity 16.7% (5/30). Three biliary complications (10%), 1 biloma (percutaneous drainage, STROC IIb), 1 biliary fistula spontaneously closed, and 1 choleperitoneum (with laparoscopic exploration, STROC IIIb). One patient with a parietal abscess (3.3%, STROC I) and 1 patient with a hepatic failure (solved

with medical treatment). No mortality in this series. All patients returned to normal life. Mean follow-up was 30 months in donors for adult recipients (range: 1–72) and 78 months (range: 3–144) in donors for pediatric recipients (range: 3–144). Low rate of transfusions and reoperations, a short hospitalization, low morbidity rate, and no mortality in donors, as well as good results in the recipients, confirm that living related donor liver transplantation is a good option for the treatment of end-stage hepatic disease.

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#### STRATEGIES TO KEEP PATIENTS WITH MALIGNANT TUMORS ON LIVER TRANSPLANTATION WAITING LIST

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Patients with malignant tumors in waiting list for liver transplantation have reduced therapeutic options: present inclusion criteria, poor pool of organs and tumoral progression. We sought to show our results with different therapeutic options in those patients with malignant tumors on the waiting list for liver transplantation. Between January 1988 and December 2003, we performed 37 liver transplantations in patients with malignant tumors. Twenty-two were diagnosed before the transplant. Eighteen were male (86.4%) with a mean age of 39 years old (1–65). Twenty-one (95.5%) were hepatocarcinomas and the remaining one was a hepatoblastoma. Nineteen patients presented with associated cirrhosis, of which 16 (72.7%) were viral. Mean stay on waiting list was 18 months (12–36) for those patients transplanted with cadaveric donors and 3.5 months for those undergoing liver transplantation with living related donors. Nine patients underwent chemoembolization; 3, surgical resections; 1, systemic chemotherapy; and 2, radiofrequency (1 associated with chemoembolization). Mean follow-up was 51 months. At present, chemoembolization is the gold standard treatment for patients with malignant tumors on the waiting list for liver transplantation. Thermal ablation, surgical resection, and systemic chemotherapy (alone or associated with other treatments) are useful with specific indications.

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#### T4? WHAT FOR? HEPATIC ISCHEMIA/REPERFUSION INJURY INCREASED WITH T4 PROTOCOL

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Hormonal resuscitation of hemodynamically unstable organ donors via protocols utilizing levothyroxine and methylprednisolone (T4 protocol) has become increasingly common in donor management. Since these levels diminish after neural-hormonal axis failure, restoring endogenous circulating levels should prove beneficial. In some studies, however, thyroid hormone has been shown to increase mitochondrial uncoupling protein levels, which may lead to depletion of energy stores in the donor tissues. In addition, our previous clinical data suggest that steatotic organs handled under the T4 protocol have an increased incidence of primary nonfunction (PNF). These data have led us to hypothesize that these agents are detrimental to steatotic liver allografts because of their heightened susceptibility to ischemia/reperfusion (I/R) injury. Modeling the T4 protocol, male 6-week-old lean and ob/ob C57BL/6 mice were pretreated once daily for 48 hours with levothyroxine (T4) and/or methylprednisolone (steroid) in parallel with age-matched controls receiving vehicle alone. All animals were subjected to 20 minutes of ischemia and 24 hours of reperfusion. End points assessed included survival, histology, serum AST/ALT, tissue

uncoupling protein 2 (UCP2) expression, and ATP content. Survival following I/R was decreased in the group receiving T4 and steroid (40%) as compared to vehicle-treated animals (80%). Histological analysis showed an increase in necrosis in the T4/steroid-treated group in both lean and ob/ob animals ( $P < 0.05$ ). We have also seen increased AST and ALT levels in animals treated with T4 and steroid compared to control or individual pretreatments alone. UCP2 expression levels, as shown by Northern analysis, were significantly elevated in ob/ob mice treated with T4 and T4/steroid as compared to controls. Finally, ATP content was significantly reduced in the ob/ob mice treated with T4 and T4/steroid, correlating with the increase in UCP2 expression. The "T4 protocol" appears to cause increased hepatocyte injury, possibly due to a decrease of energy stores and production. Although some previous data show that the T4 protocol is potentially beneficial in terms of hemodynamic stability and cardiac injury, we believe that the results of this study suggest this may not be true for all organs and its administration may be detrimental to steatotic donor livers prior to transplantation.

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##### SPONTANEOUS RUPTURE OF HEPATOCELLULAR CARCINOMA: DIFFERENT THERAPEUTIC OPTIONS

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Spontaneous rupture of hepatocellular carcinoma (HCC) is a potentially life-threatening complication. Different treatment modalities have been proposed; yet it is still uncertain which procedure is the best treatment option. We sought to analyze the results of different therapeutic options for the management of such complication. Twenty-four patients with rupture HCC treated at our Institution from January 2000 to December 2002 were divided according to the initial treatment modality into 3 groups: group I (10 patients) underwent emergency surgery; group II (8 patients) treated by transarterial embolization (TAE), and group III (6 patients) were treated conservatively. In group I, nonanatomical limited resection was done in 5 patients, suture plication in 2, enucleation of the ruptured tumor in 2, and pressure gauze packing in one. Three patients died within one month from liver failure. In group II, initial hemostasis was successful in all patients. Thereafter, one of them underwent delayed liver resection and 3 had received transarterial chemoembolization (TACE). Hospital mortality consisted of 2 patients. In group III, patients were treated conservatively; two of them received additional octreotide drip infusion for 5 days. Thereafter, one patient had received TACE 3 weeks later. Two patients of this group died within one week. Treatment options should be individualized according to the patient's general condition, hepatic reserve, experience of the surgeon, and the availability of interventional radiologist. Staged approach with noninvasive initial hemostatic techniques followed by delayed liver resection or TACE was an effective modality. The administration of octreotide in such patients carries a new promise but awaits a larger group of patients to reach a conclusion.

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##### LIVING RELATED LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA: THE EXPANDED CRITERIA

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The most widely accepted criteria to manage patients with hepatocellular carcinoma (HCC) and cirrhosis for liver transplantation are

the Milano criteria, but there is no universal consensus on this issue. Another difference of opinion exists in donor type: is it reliable for HCC patients to wait for a cadaver donor or is it logical to search for a living donor? Some centers justified taking a living donor into consideration if the waiting time for cadaveric OLT is expected to exceed 7 months. Despite every effort to increase the cadaveric donation rate in Turkey, it is still very far beyond the desired. For this reason, our liver transplantation program is mainly based on living donors for both the pediatric and adult recipients. For HCC patients, for whom the only chance of treatment is liver transplantation, we not only accept living related donors but also have expanded criteria for being a transplantation candidate. If there is no evidence of extrahepatic dissemination with advanced imaging studies, no major vascular invasion, negative cytopathology of intraperitoneal fluid, and negative surgical exploration including hilar lymph node frozen section, then the patient is considered as convenient for a liver transplantation. In this study, we evaluate our early results of liver transplantations for the HCC patients. Between January 2003 and September 2004, seven patients with HCC, aged between 1 and 64 years, underwent liver transplantation in our unit. Two of the tumors were diagnosed incidentally in the hepatectomy specimens. These were solitary occult carcinomas, one in an adult recipient with cryptogenic cirrhosis and the other in a pediatric 1-year-old recipient with PFIC-2 disease. The remaining tumors were beyond the Milano criteria except one. For preoperatively diagnosed HCCs, the donors were 3 siblings, 1 daughter, and 1 spouse, and for the incidental tumors, one donor was the mother and the other was a cadaveric liver. All patients received tacrolimus monotherapy and low-dose corticosteroid with early withdrawal as immunosuppression. In 2-11 months of follow-up period (mean, 5.5 months), all patients are doing well with excellent graft function and without tumor recurrence. The patients with advanced disease had neoadjuvant chemoembolization with farmorubicine, cisplatin, mitomycin-C, and polyvinyl alcohol. No patient had received adjuvant chemotherapy. We believe that the selection criteria of the HCC patients for liver transplantation should be expanded and living donor option should be discussed with the family members of the patient.

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##### ANALYSIS OF POSTSURGICAL COMPLICATIONS IN 65 LIVING-RELATED LIVER DONORS

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Sixty-five living donor liver transplantations have been performed in our transplantation center between April 1990 and September 2004. For each case, we collected the following list of data from patient charts and files and from the Baskent University Liver Registry data. There were 35 male and 30 female donors. Fifty-two (80%) of the donors were first-degree relatives of the recipient, 8 (12.3%) were second-degree relatives, and 5 (7.6%) were spouses. Mean age was  $35.2 \pm 9.3$  (range, 20 to 56 years). We have performed 26 (40%) left hepatic lobectomies, 20 (30.8%) left lateral segmentectomies, and 17 (26.1%) right hepatic lobectomies, and 2 (3.4%) donors had simultaneous living related donor nephrectomy + left liver lobectomies. Graft liver volume to donor body weight ratio was  $1.4 \pm 0.4\%$  (range, 0.8% to 2.5%). The mean percentage of the remnant liver to donor's total liver volume for right and left lobectomies was 41.7% and 67.8%, respectively. Patients' mean postoperative hospital stay was  $10 \pm 4.4$  (range, 3 to 29 days). There were no postoperative mortality or morbidity requiring re-operation. A total of 13 postsurgical complications have been observed in 12 donors (20%). Pleural effusion has developed in 2 patients (3%). Intra-abdominal collection was seen in 5 (7.6%) and biliary leak in 3 (4.6%) patients. These were treated with radiologic interventions. In 1 patient minor wound infection developed. Donor

safety should be the primary focus in living-donor liver transplantation. These donors face significant risks, including substantial morbidity and even death. More experience, improved surgical techniques, and meticulous donor evaluation will help to minimize morbidity and mortality for both living liver donors and their recipients.

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**MODELING LIVER TRANSPLANT SURVIVAL: COMPARING TECHNIQUES OF DERIVING PREDICTOR SETS**

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Selecting variables for predicting liver transplant survival has traditionally been an art form of statistics and clinical judgment. Computational techniques for feature selection may be used to obtain the minimal set of variables required for optimal prediction, called the "Markov blanket." The goal of this study was to compare the performance of survival models made from factors chosen using traditional methods versus those selected by an automated technique that approximates the Markov blanket. We evaluated the performance of these predictor sets across several types of models. Four different sets of predictors from the UNOS liver transplant dataset were used to model short-term graft survival. The variables identified by Desai (2004), Ghobrial (2002), and Thuluvath (2003) were used as baselines derived via well-established methods. Our feature selection technique used repeated tests of conditional independence to identify key features in the full set of 148 sufficiently populated pretransplant variables from the UNOS dataset. Various types of classifier models were built to predict 90-day graft survival, and their c-statistics were evaluated by cross- and prospective validation. The automated technique selected 21 survival predictors, all of which were clinically justifiable, and some of which had not been used in the other models. The linear regression, naive Bayes, and support vector machine showed more consistent performance than the neural network. For these model types, our feature set outperformed all other datasets by cross-validation. Similar trends were seen by prospective validation except for the Ghobrial dataset, which performed similarly to our feature set. Moreover, when increasing numbers of items were randomly removed from our predictor set, a gradual decline in model performance was seen. Key predictive factors for liver transplant survival may be found using fully automated methods, and our feature set was mostly a superset of others in the literature. Validation showed that our technique built models with statistically better performance than two out of three baseline datasets. This predictor set does not depend on a specific type of model to perform well. Our current work focuses on using heuristic search techniques to reduce further the size of the predictor set while maintaining predictive power (Table 1).

**Table 1.** Performance by c-Statistic, by Cross (Prospective) Validation

|                        | Desai        | Ghobrial     | Thuluvath    | Automated   |
|------------------------|--------------|--------------|--------------|-------------|
| Naive Bayes            | 0.62* (0.60) | 0.64* (0.61) | 0.63* (0.60) | 0.67 (0.63) |
| Neural network         | 0.58 (0.56)  | 0.64 (0.60)  | 0.61 (0.59)  | 0.63 (0.62) |
| Support vector machine | 0.63* (0.62) | 0.65* (0.65) | 0.63* (0.62) | 0.68 (0.65) |
| Linear regression      | 0.63* (0.62) | 0.65* (0.65) | 0.64* (0.63) | 0.67 (0.64) |

\*P < 0.0001 vs. Automated set.

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**ANTITHYMOCYTE GLOBULIN INDUCTION THERAPY IN HEPATITIS C POSITIVE LIVER TRANSPLANT RECIPIENTS**

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The use of antibody-based induction therapy in HCV+ liver transplant (LTx) recipients is controversial. We reviewed the outcome of ATG in HCV+ LTx recipients at our institution. There have been 468 adult cadaveric LTx performed at our institution between 1990 and 2004. Induction immunosuppression (IS) using antithymocyte globulin (ATG) has been used since the program began. All 148 patients with HCV receiving LTx were included in the analysis, 320 HCV- recipients were used as a control group. LTx recipients who died or lost their grafts within three months or undergoing re-transplantation were excluded. Recipients who had stage III or IV hepatocellular carcinoma (HCC) pretransplant, and those who died from HCC recurrence, were excluded. The first dose of ATG is on postop day 1. The ATG dose infused is 25 mg/10 kg body wt. The max total ATG dose is usually 6 mg/kg. All patients take a calcineurin inhibitor. Azathioprine or mycophenolate is also used along with steroids. Since 1992, 468 adult cadaveric LTx have been performed, and 148 recipients (31.6%) were HCV+ of which 47 LTx were excluded. Recipients were analyzed on the basis of IS. There were 101 HCV+ recipients (68.2%) included in the study and 81 (80.2%) had ATG induction. The median age of recipients was 54 years (ATG) vs 58 (No ATG). HCV-related disease ATG induction therapy did not change the time between LTx and HCV-related graft hepatitis. The time for 50% of recipients to develop hepatitis was 230 days (ATG induction) compared to 249 days (No ATG). TG did not alter the risk of graft loss for HCV-related disease (P = 1.0). The patients given ATG were less likely to have lost their graft from HCV-related disease after five years. Ten-year graft survival for HCV+ recipients was 72.4% (ATG) vs 62.9% (No ATG). The incidence of biopsy proven acute rejection (AR) was less in patients who received ATG (25.6%) vs No ATG (61.1%) (P = 0.0088). HC+ recipients given ATG had a worse graft survival than HCV- recipients who had not had ATG (P = 0.03). There was no difference in graft survival between HCV+ recipients given ATG and those not. Graft survival at ten years was 55.8% (ATG) vs 62.2% (No ATG) in HCV+ recipients. ATG induction does not increase the risk of HCV-related graft hepatitis, graft loss, or patient death. The excellent long-term graft and patient survival rates at 10 years of follow-up in HCV+ patients given ATG goes against conventional wisdom. ATG induction therapy is safe and effective in HCV+ recipients.

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**BILIARY COMPLICATIONS OF RIGHT LOBE SPLIT LIVER TRANSPLANTS**

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Biliary complications continue to be the Achilles' heel of partial liver grafts. Right lobe ex vivo split liver grafts are often considered marginal with frequent border-line size matching, longer ischemic time, and rewarming at the bench; therefore, external biliary drainage might be beneficial. Biliary reconstruction may be by duct-to-duct anastomosis (DD) or Roux-en-Y hepaticojejunostomy (RYHJ). From August 1994 to April 2003, 54 adult recipients received right lobe split liver transplants with RYHJ in 12 (22%), DD without T-tube in 27 (50%), and

DD over a T-tube in 15 (28%) most recently transplanted patients. We retrospectively analyzed the incidence, treatment, and outcome of biliary tract complications. The incidence of ischaemic biliary complications from hepatic artery thrombosis was 3.7% (n = 2); there was one death from biliary peritonitis and one successful retransplant for biliary necrosis. In the DD/non-T-tube group, 5 (18.5%) patients had anastomotic leaks. Treatment was by immediate RYHJ (1), endoscopic stenting (2), and delayed RYHJ for subsequent stricture formation after endoscopic failure (2). DD/T-tube anastomosis resulted in 2 strictures (13%) that were managed endoscopically and 1 leak (6.7%) that resolved spontaneously. There were no complications noted from primary RYHJ. One patient with DD/non-T-tube anastomosis died from a bile leak at the cut liver surface and one DD/T-tube recipient died from biliary peritonitis following T-tube removal. (i) Biliary peritonitis is associated with high mortality. (ii) Biliary complications requiring surgical repair may be more common when no T-tube is used. (iii) Hepaticojejunostomy results in fewest biliary complications in right lobe split liver transplantation.

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#### SUCCESSFUL LIVER TRANSPLANTATION AFTER EMBOLIZATION OF HEPATOCELLULAR CARCINOMA WITH THERASPHERES

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Liver transplantation (OLT) for hepatocellular carcinoma (HCC) in the setting of cirrhosis has been associated with favorable outcomes in select patients with small tumors. Downsizing of large tumors (>5 cm), which normally do not meet standard transplant criteria, may offer an opportunity for OLT and favorable outcome. We describe a previously unpublished unique approach of downsizing a large HCC with Theraspheres followed by OLT. The patient was a 51-year-old Caucasian man with HCV cirrhosis. Upon screening, his AFP was 1272 ng/ml, and MRI confirmed a 7.5 cm × 7.5 cm lesion consistent with HCC in the posterior right lobe, adjacent to hepatic veins and posterior to hilar structures. Selective embolization with PVA sponges resulted in an AFP drop to 124 ng/ml within 6 weeks. AFP went up to 144 ng/ml 2 1/2 months later. Due to anatomical reasons, re-embolization was not possible. Hence, embolization of the tumor-bearing region was performed on 2 occasions with Theraspheres (yttrium-90 glass microspheres). AFP surprisingly went down to 10 ng/ml, and follow-up MRI showed tumor size reduction to 6.2 cm × 5.4 cm 3 months after initiation of therapy. OLT was performed from a deceased donor 5 1/2 months after Therasphere therapy. The liver pathology showed a moderately differentiated HCC, 4.8 cm in maximal diameter with near total necrosis, and glass beads within necrotic tumor. Currently, patient is 11 1/2 months after OLT doing well with AFP of 5 ng/ml and negative imaging studies. 1. This is the first report of OLT for HCC after tumor downsizing with Therapshere embolization. 2. Therapshere embolization offers a good option for HCC therapy prior to OLT especially when selective embolization has failed. 3. Downsizing of HCC with Therasphere was safe in our experience and evaluation of this technology for wider application is indicated.

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#### PIVKA-II IS A DEFINITE INDICATOR OF VASCULAR INVASIVENESS IN HEPATOCELLULAR CARCINOMA PATIENTS

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Vascular tumor invasion is one of the factors predicting poor prognosis after liver transplantation for hepatocellular carcinoma. In this study, we analyzed whether PIVKA-II (protein induced by vitamin K absence or antagonist II) is an indicator for vascular invasiveness and recurrence after hepatectomy for hepatocellular carcinoma. Four hundred 35 patients operated between 1976 and 2004 at our institute were included in this study. Logistic regression analysis revealed that preoperative high PIVKA-II levels (> or = 37 mAU/ml) and portal flow defects on image studies were significant predictors of microscopic vascular invasiveness of the tumor ( $P < 0.05$ ). However, both univariate and multivariate Cox regression analyses could not show that PIVKA-II was an indicator for poor prognosis after hepatectomy. PIVKA-II was a definite indicator of microscopic vascular invasiveness. However, PIVKA-II failed to predict tumor recurrence after hepatectomy for hepatocellular carcinoma. The role of PIVKA-II in liver transplantation should be analyzed because even a low degree of vascular invasiveness may affect the prognosis in an immunosuppressive condition.

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#### DIC COMBINED CT-ANGIOGRAPHY FOR DONOR'S PREOPERATIVE ASSESSMENT IN LRLTX

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The complications of bile duct have the highest frequency at a donor's postoperative complications. In order to decrease complications, intensely examination of a bile duct is required. We were performing DIC-CT before. But because of remarkable progress of the technology of CT, especially multidetector computed tomography, a high-resolution image came to be obtained. This study was performed to determine the diagnostic value of DIC combined CT-angiography as the preoperative assessment method of a donor's biliary system and vascular anatomy. Between December 2002 and December 2003, 10 consecutive potential living donors were examined with DIC combined CT-angiography. CT imaging was performed using an 8-row MDCT Scanner. Systemic drip infusion was performed using iotroxate meglumine 100 ml in 30 minutes. The iohexol was used 10 minutes after the end of the DIC intravenous drip. The iohexol was bloused in 5 ml/s; the amount of contrast medium was 2 ml/kg. No severe complication was observed. The rubefaction by contrast media was observed in only one case. In this case, she was given steroids and finished the examination because most of contrast medium had dripped out and she accepted finishing the examination using steroids. In all 10 donors, the biliary tree and vessels were clearly visualized. DIC combined CT-angiography findings were correlated with intraoperative findings. Anatomical anomalies were found in two cases. These anomalies were thought to be hard to found with MRCP. A bile duct, the intersection part of an artery and the portal vein within a liver, and the physical relationship of a bile duct were also described clearly. Before an operation of donor harvesting, although inspection should fully be conducted for enforcement of a safe operation, we should avoid an invasive test as much as possible. Moreover, there is a limitation in CT test and, as for the number of times of a test, lessening as much as possible is desirable. DIC combined CT-angiography not only obtains a donor's detailed information but also simplifies preoperative examinations.

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**IMPACT OF REPEATED STEROID PULSE THERAPIES ON OUTCOME IN HCV-POSITIVE PATIENTS AFTER OLT**

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The optimal immunosuppressive regimen for HCV-positive liver transplant recipients has not been established. Treatment for acute rejection with steroids is associated with increased viral replication and graft hepatitis. We retrospectively analyzed 232 patients after orthotopic liver transplantation (OLT) for HCV cirrhosis to determine the influence of methylprednisolone pulse therapy on long-term outcome after OLT. Two hundred thirty-two liver transplants in HCV recipients between 1989 and 2001 were analyzed. Median follow-up was 4.4 years, and median age of patients was 53 years (15–72 years). Immunosuppression consisted of tacrolimus (Tac) or cyclosporine A (CyA) in different protocols. All rejection episodes were histologically proven. Of 232 graft losses, 28 occurred due to severe hepatitis C reinfection (12.06%); 105 of 232 patients showed a minimum of one episode of acute rejection (45.25%); 71 of 86 patients received methylprednisolone pulse therapy for one time (82.55%); 15 of 86 required treatment with OKT3 for steroid-resistant rejection (17.44%); and 19 of 232 patients required repeated steroid pulse therapy due to more than one episode of acute rejection (8.1%). In patients with more than one episode of acute rejection, the risk of HCV-related graft loss was significantly enhanced (6/19,  $P < 0.017$ ). The primary immunosuppression had no influence of the outcome in our data. Our data show that outcome of HCV-positive patients with repeated steroid pulse therapy for acute rejection is significantly worse compared to patients with single pulse therapy. Therefore, repeated steroid pulse therapies should be avoided in HCV-positive transplant recipients. New strategies in managing acute rejection in these patients are required.

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**A PROSPECTIVE RANDOMIZED TRIAL COMPARING TACROLIMUS AND MMF VERSUS TACROLIMUS AND STEROIDS AS PRIMARY IMMUNOSUPPRESSION FOR HCV-RELATED LIVER TRANSPLANTATION**

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End-stage hepatitis C virus (HCV) infection is a frequent indication for orthotopic liver transplantation (OLT). Recurrence of HCV is almost universal, and up to 30% of the patients will develop severe graft hepatitis and cirrhosis again after OLT. HCV genotype and steroid administration after OLT are known to play a major role in the severity of reinfection. The aim of the study was to examine whether a steroid-free immunosuppressive induction regimen is safe and possibly beneficial for the course of recurrent hepatitis and outcome. In a prospective analysis 59 consecutive patients with end-stage HCV hepatitis were randomly assigned to receive either tacrolimus (Tac)/mycophenolate mofetil (MMF) or tacrolimus/prednisolone (Pred). The groups consisted of 29 and 30 patients, respectively. Follow-up ranged from 14 to 60 months. The 1-year patient survival was 89.7% in the Tac/MMF-group compared to 83.3% with 5 of 30 in the Tac/Pred-group. The 1-year graft survival was 79.3% in the Tac/MMF-group and 83.3% in the Tac/Pred-group. The incidence of rejection was 31% in the Tac/MMF-group suffered from an episode of acute rejection (31%), whereas 6 of 30 patients in the Tac/Pred-group and 20% in the Tac/Pred-group (not statistically different). However, two of the patients in the Tac/Pred-group had

a steroid-resistant rejection with the need for OKT3-therapy. Viral load after two months was significantly lower for patients in the Tac/MMF-group ( $P = 0.004$ ). Biopsy-proven necroinflammatory activity and graft fibrosis after 1 year were similar in both groups as well as the incidence for re-transplantation or death because of severe recurrence of hepatitis (2 patients in the Tac/MMF-group and 3 patients in the Tac/Pred-group). Our data demonstrate that a steroid-free immunosuppressive induction protocol with Tac/MMF after OLT for HCV is safe and effective, reaching a similar risk for rejection compared to treatment with Tac/Pred. Biopsy-proven reinfection as well as HCV-related graft loss were equally low in both groups. The lower viral load after 2 months in the Tac/MMF-group indicates a milder course of reinfection and favours immunosuppression with MMF. However, longer follow-up is needed to show a beneficial effect of a steroid free immunosuppressive protocol on the course of recurrent HCV after OLT.

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**LIVING RELATED LIVER TRANSPLANTATION IN PEDIATRIC AGE GROUP: EARLY TWO CENTERS' EXPERIENCE**

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Living related liver transplantation (LRLT) is known to be an established acceptable therapeutic modality for end stage liver diseases, especially for children when cadaveric liver transplantation is not available. We present the early experience of pediatric LRLT in two centers in Egypt. Twenty-three cases of pediatric LRLT were done from October 2001 through March 2004. There were 12 girls and 11 boys with an age range from 9 months to 15 years with a mean of 7.3 years. The body weight of the recipients ranged from 7.8 to 45 kg with a mean of 22.5 kg. All recipients received left-lateral segment, extended left-lateral segment, or left lobe grafts. The donors were 21 parents (15 mother and 6 fathers), one sister, and one unrelated with mean body weight of 72.5 kg. The pretransplant primary diseases were biliary atresia in 6 patients, Budd-Chiari in 4 cases, metabolic liver disease in 3 cases, Byler's disease in 2 cases, congenital hepatic fibrosis in 2 cases, and cryptogenic cirrhosis in 2 patients. The remaining four patients were hepatoblastoma in one case, a case of fulminant hepatitis, one case of primary sclerosing cholangitis, and a case of autoimmune hepatitis. There was no donor mortality. Chest infection and wound seroma were observed in 2 donors, pleural effusion in two, and bile leak in one, which was treated successfully by endoscopic stenting. Recipients' postoperative morbidity was observed in the form of biliary leakage in two, burst abdomen in one, hematemesis in one, and chest infection in four cases. There was no operative mortality in recipients. Four recipients died postoperatively on days 20, 23, 92, and 127, with survival of 82.6%. Pediatric LRLT is a potentially safe procedure, especially in centers where there is no cadaveric liver transplantation. The initial results are encouraging and that progress in this field is remarkable, especially for children.

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**CAN WE SEE THE TUMOR?**

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It is a well-known fact that many of the patients on the waiting list for liver transplantation also have liver tumors. In fact, patients with Stage II HCC may receive extra priority on the waiting list. For this



group of patients it becomes vitally important to correctly identify the presence and size of the tumor. The assessment of such patients according to UNOS recommendations should include ultrasound of the patient's liver, a CT or MRI of the abdomen that documents the tumors, a CT of the chest that rules out metastatic disease, and the alpha-fetoprotein level. We used the database of our Liver Transplant Center to analyze the relationship between the preoperative diagnosis and results of the pathological examination of explanted liver. We also used our data to assess the impact of the tumor on the transplant outcome. We realize the limitations of this study due to small number of patients and short follow-up time (average 421 days, SD 297 days). Our Liver Transplant Program is young, having started in 2002. Of 36 liver transplants performed at our center by 10/12/2004, 19 patients had liver tumor diagnosis before or after transplant. One had angiosarcoma, one had leiomyosarcoma, three had CCC, and 14 had HCC; 11 patients were diagnosed with HCC preoperatively and 10 of them received UNOS priority status; and 7 of 14 patients had elevated AFP. MRI was most sensitive tool in our hands (11 of 14), far better than conventional CT (3 of 14) or ultrasound (4 of 14). Three of 14 patients had HCC detected only after transplant (incidental). In 9 of 14 patients HCC diagnosis was documented by pathology of explanted liver or by preoperative biopsy. Average MELD score for this group of patients was 22.5 (mean 24, ST 7.4). Average time on waiting list was 151 day (median 130, ST 98). Six of 14 patients received preoperative treatment for HCC. One patient died after transplant from sepsis. No recurrences were detected so far. Preoperative detection of the liver tumors in liver transplant candidate has important implications on the priority status of the patient and on the postoperative prognosis. Preoperative MRI in our hands appears to be the best test to detect the HCC in liver transplant candidates. The correlation of preoperative and postoperative staging is poor (5 of 11 preoperative HCC diagnoses were not conformed by pathology or biopsy, 3 of 7 explanted liver HCC diagnoses were not detected preoperatively). Further follow-up studies will be necessary to determine the clinical significance of these findings. Perhaps newer more sensitive and more specific diagnostic modalities will help to improve the detection and staging of the liver tumors in liver transplant candidates in the future.

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#### CUTANEOUS SCEDOSPORIASIS AFTER LIVER TRANSPLANTATION: REPORT OF A SUCCESSFULLY TREATED CASE

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Long-term immunosuppression places transplant recipients at an increased risk of acquiring opportunistic infections. *Scedosporium apiospermum* (SA), the asexual form of the fungus *Pseudallescheria boydii*, has been sporadically reported as the cause of both cutaneous and disseminated infections in transplant recipients, often with fatal consequences. A 68-year-old white male presented with an asymptomatic 17-mm red plaque on the dorsum of his right foot 5 months after liver transplantation for Stage 2 hepatocellular carcinoma in the setting of hepatitis C. The borders of the lesion were well demarcated and slightly elevated. There was no pain to palpation or increased temperature. The patient was a farmer in central Pennsylvania and denied any trauma or barefoot walking. His immunosuppression consisted of tacrolimus and prednisone. Punch biopsy reported the presence of hifae and spores, and the culture grew SA. Management consisted on temporary reduction of tacrolimus as well as oral itraconazole. The lesion was then excised surgically with 1-mm margins and the patient continued antifungal treatment for 21 days. The specimen contained dark spores and hifae. The culture confirmed SA, susceptible to itraconazole. One

year later the patient is doing well, without evidence of recurrent fungal disease and with excellent graft function. SA infection after liver transplantation has been shown to progress to invasive disease when opportune and appropriate therapy is not instituted. This case illustrates that aggressive treatment of SA infection after liver transplant can lead to successful eradication of this potentially fatal pathogen.

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#### EXPERIENCE WITH 151 SUPRACELIAC AORTIC ANASTOMOSIS FOR ARTERIAL REVASCULARIZATION IN LIVER TRANSPLANTATION

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Between 1991 and , the aortic anastomosis for arterial reconstruction was encouraged at our institution to achieve high perfusion pressures for the liver allograft and to avoid technical problems in case of anatomical variations or small sizes of the hepatic artery. The aim of this study was to analyze the experience with the supraceliac aortic anastomosis for arterial revascularization during liver transplantation in this time period. Between January 1991 and January 1996, 367 liver transplantations were performed. Pediatric patients and patients receiving split-livers or auxiliary transplants were excluded from this study; 151 adult patients receiving a new liver with aortic anastomoses were analyzed. The 1-year survival rate was 59% (79/133). After 3 years 69 (52%) patients were alive. The causes of death were sepsis (n = 38), recurrent diseases (n = 11), pneumonia and respiratory failure (n = 6), and brain death (n = 3). The overall rate of hepatic artery-related complications was 28 complications in 17 transplants (17/151; 11%). The most frequent artery related complications were 12 arterial occlusions in 11 transplants (12/28; 43%). Stenosis was observed in 6 of 28 complications (6/28; 21%) Bleeding from the side of the anastomosis occurred at the same rate (6/28; 21%). Kinking of the hepatic artery was observed in 3 cases (3/28; 11%). The rate of re-transplantation after hepatic artery complication was 40% (6/15) and the 1-year survival after arterial complication was 47% (7/15). Arterial occlusion of the hepatic artery occurred in the early postoperative phase as well as in the later course. The presence of variations of arterial anatomy of the transplanted liver and the need for arterial reconstruction have no statistically significant impact on the rate of arterial occlusion. The only significant risk factor for arterial occlusion was the re-use of vascular graft from the first transplantation if re-transplantation was performed. If there is any doubt about a sufficient arterial blood supply or the possibility of a perfect arterial anastomosis, an aortic anastomosis should be used for re-vascularisation. As demonstrated in this study, this is an equivalent way of arterial reconstruction, it is a well-known treatment for arterial complications, and it is advantageous in cases of anatomical variations of the graft's arterial supply as complex arterial reconstruction can be avoided in most cases.

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#### THE INCLUSION OF THE MIDDLE HEPATIC VEIN IN PARTIAL LIVER GRAFTS

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In Brazil, the living related liver transplantation (LRLT) has increased in the last few years due to the insufficiency number of organ donors as well as to the exponential increase in the number of patients in the waiting list. Nearly 25% of the liver transplant cases performed

are LRLT, with 250 cases to be done by the end of 2004. We report our experience with the use of right lobes of the liver with the inclusion of the middle hepatic vein (IMHV). Besides all hemodynamics and technical considerations, the results of this procedure are related to the size of the grafts and its drainage. In our series we report the use of the MHV in 08 partial liver donors in a total number of 37 LRLT. In all cases the evaluation before donation includes complete biochemical, serological, and tumoral marker evaluation, and imaging studies includes ultrasound and multislice computed tomography with vascular, biliary reconstruction, and hepatic volumetry. Cardiac, pulmonary, renal, as well as psychological evaluations were performed routinely before donation. During the donor surgery, the surgeons performed intraoperative ultrasound to confirm the vascular anatomy of the hepatic veins and cholangiography. Based on its anatomy, aspect of the vascular outflow as well as size of the remnant left size of the liver, we performed a right lobe hepatectomy including the MHV. The mean operative time was 420 minutes, the mean weight of the graft stimulated by CT volumetry was 860 g, and soon after harvesting, 785 g. The mean blood loss was 310 ml and the cell saver was used in all cases; it was also used the 300 ml of autologous blood saved in the preoperative period. There was no mortality in this current series, and the complications to the donors were intraoperative complications (none); until 7th POD we had 2 biliary fistulas (one treated by papilotomy and another resolved spontaneously) and one case of ascites. No long-term complications have occurred so far. The recipients presented good graft function in 6 cases, the liver function tests were within normal range after 10 days and the complications related to the graft were the following: 2 cases of arterial complications (one death before re-transplant and another submitted to new transplant and alive); 1 case of biliary complication resolved by percutaneous drainage; 4 other complications, 1 liver disfunction with jaundice, 1 recurrence of tumor, 1 bleeding on the cutting surface and one case of refractory ascites. The overall graft survival is 75% (6 of 8). The use of the MHV is feasible and safe, its use can improve the venous outflow, providing a gain in the hepatic "functional" mass of the graft and in consequence its faster recovery from surgery.

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### TECHNICAL VARIATION IN THE USE OF THE SPLENIC ARTERY TO THE GRAFT ARTERIAL REVASCLARIZATION IN THE RETRANSPLANTATION

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The most common approach during the arterial graft revascularization in the liver retransplantation is either the anastomosis directly in the aorta or the use of the splenic artery in the celiac trunk. One of the main challenges in this kind of procedure is the number and intensity of adjacent organs adherences, especially in the hepatic hilum, lesser gastric curvature, and celiac trunk, making the surgical dissection a hard procedure. The aim of this report is to present a different and unusual approach to the splenic artery to the reperfusion of the graft. The description of the technique is the following: opening of the greater gastric curvature between the stomach and transverse colon and careful dissection of the splenic artery in the upper pancreatic border from the head of the pancreas until we obtain a arterial segment of 5 cm. Then this part of the artery is carefully cut and prepared to be anastomosed. The splenic artery of the receptor is passed by a 1-cm hole in the lesser curvature, making the anastomosis with the donor hepatic artery at the level of the celiac trunk in a conventional end-to-end continuous suture using a 6-0 Prolene suture. We have used this approach in the cases of retransplantation and it seems to be an easy and fast way to perform the reconstruction of the artery

avoiding an extensive dissection of the adherent tissues around the hilum.

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### ROLE OF LIVER TRANSPLANTATION IN MANAGEMENT OF HEPATOCELLULAR CARCINOMA

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Liver resection has been the standard therapy for patients with HCC provided they have good hepatic reserve and complete tumor resection is technically feasible. Five-year survival rates after liver resection have ranged from 30-40%. The majority of these patients subsequently develop recurrent cancer in the liver remnant after resection. Adjuvant therapy has not been proven to be effective. Radiofrequency ablations, cryosurgery, alcohol injection, and chemoembolization of the tumor in the cirrhotic liver all have the same shortcoming of leaving behind a cirrhotic liver which can be the source of tumor recurrence. These techniques also can leave behind some tumor tissue at the site of treatment. Liver transplantation is the most effective treatment for patients with small hepatocellular carcinoma. In selected patients, it cures HCC and the underlying cirrhosis at the same time, though liver transplantation for large tumors (>5 cm or more than 3-4 lesions) has been associated with very poor results and is not recommended except under special study protocols when combinations of chemoembolization, transplant and chemotherapy is used. Since January 1993 to September 2004, a total of 415 adult patients received liver transplants at University of Tennessee in Memphis, TN, USA for different liver diseases. Thirty (7.6%) of the patients had malignant liver tumors (HCC). There were 25 males (83%) with a median age of  $51.43 \pm 12.88$  years in this category. Two patients (7%) had a tumor >5 cm in diameter and 60% had tumors <3 cm. Six (20%) patients had Stage IVa, 16 (53%) had Stage III, 2 patients (7%) had Stage II, and 6 (20%) had Stage I disease. The 1-, 3-, and 5-year survival of patients with HCC who received liver transplant is 80%, 63%, and 61%, respectively. Overall and disease-free survival for patients having tumors  $\leq 3$  cm is 68%. The tumor size >5 cm in diameter is independently associated with high recurrence rate ( $P < 0.05$ ). Also, patients with HCC with Stage I and II (AJCC Classifications) undergoing liver transplantation has significantly better survival shown in our multivariate analysis of prognostic factors ( $P < 0.05$ ). Among the patients who died after liver transplant, only 3 patients had recurrence and the cause of death in the rest of the patients was not related to tumor recurrence. Two patients are alive (53 and 74 months) after transplant with recurrent HCC diagnosed at 40 and 62 months after transplantation. Sixteen patients are living without tumor recurrence up to 8 years of follow-up. Liver transplantation in selected patients with HCC who have cirrhosis will result in very good patient and disease-free survival.

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### BILIARY STRICTURE AFTER LIVER TRANSPLANTATION

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Biliary stricture is a common complication in post-liver transplant patients. It occurs in 9% to 15% of cases. We present our experience at the University of Tennessee Liver Transplant Program with the endoscopic diagnosis and management of biliary strictures after orthotopic liver transplant (OLT). The aim of this study was to describe

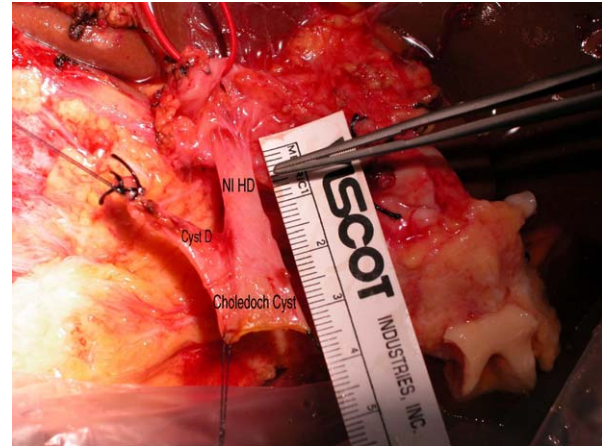
the incidence of biliary strictures in those liver transplantation recipients who underwent Endoscopic retrograde cholangiopancreatography (ERCP) due to the clinical and laboratory suspicion of biliary stricture. Our population included consecutive patients who had an OLT in the period of October 2001 and August 2004; we also included patients who were transplanted before October 2001 who developed signs of biliary stricture and were referred for ERCP during the previously mentioned period of time. All patients were followed for 3 months to 3 years. During October 2001 and August 2004, there were 104 OLTs. Fourteen patients underwent ERCP. ERCP was successful in all patients (100%). Biliary stricture was found in 9 (9%) patients. In 7 (77%) patients the stricture was found at the site of anastomosis. There were no post-ERCP complications. Treatment of the strictures consisted of balloon dilatation and placement of 1 to 3 stents. The number of procedures performed per patient was between 1 and 4 (average: 1.5). After endoscopic treatment, 7 of 9 patients improved, 6 of them with complete resolution of the stricture and 1 is still on treatment with stent exchange. Two patients died for causes unrelated to the stricture. In our study the most common site of biliary stricture in the post OLT patients was found to be at the anastomosis (77%). In this series, most post-transplantation biliary strictures were successfully corrected with endoscopic treatment.

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### PRESENCE OF TYPE 1 CHOLEDOCHAL CYST IN DONOR GRAFT AND LIVER TRANSPLANTATION

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Choledochal cysts are rare congenital dilatations of the biliary tract. The presence of certain choledochal cysts and their attendant complications are indications for transplantation. We present a case where a cadaveric donor liver was found to have a type 1 choledochal cyst and was used for orthotopic transplantation. Very little information is found in the literature concerning transplantation of choledochal cysts found in the donor liver and the long-term outcomes in the recipient patient. A 46 year-old male with hepatitis C and liver cirrhosis was evaluated for liver transplantation. The cadaveric donor liver was found to have a type 1 choledochal cyst, which was confirmed by IOC. The choledochal cyst was later excised during back table preparation. Orthotopic liver transplantation was performed and postoperatively a duplex ultrasound and a CT scan verified a normal common bile duct without intrahepatic dilatation. The patient's hospital course was uncomplicated and he was discharged. This case raises the question of concern for potential sequelae of choledochal cysts in the liver



recipient. These include intrahepatic hepatolithiasis, recurrent cholangitis, recurrent abscesses, and sepsis. More importantly it raises the question of cholangiocarcinoma which can occur in up to 30% of patients with choledochal cysts. Long-term follow-up will be needed to continue surveillance of any complications arising from transplanting a donor liver with a choledochal cyst (Figs. 1 and 2).

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### EARLY TRANSECTION OF THE HEPATIC DUCT AND BILE PROBE TECHNIQUE IN LIVING DONOR RIGHT HEPATECTOMY

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Transection of the hepatic duct (HD) is a delicate time of the right hepatectomy (RH) in the living donor. In most centers the HD is transected after the parenchymal transection and mapping of the HD confluence is obtained with intraoperative cholangiogram. We present our experience with early transection of the HD under bile probe guidance, which allows precise mapping of the confluence and totally avoids thermal dissection next to the biliary system. Donors undergoing RH, seg 5-8, underwent a minimal choledocotomy and probing of the HD confluence. Under probe guidance the right HD was transected, prior to parenchymal transection, after placing an Anderson clamp behind the hilar plate. Choledocotomy and HD stump were closed with absorbable sutures. HD orifice/s yield, donor and recipient complications and outcome were analyzed. From 2/02 to 9/04, 30 donors, 9 female, 21 male, age 34 years (range 20-56), underwent RH. Median follow-up is 13.5 months, range 1-33. A single HD was obtained in 20 cases, 66.6%; and 2 ducts in 10, 33.3%. In 3 cases with 2 ducts a single orifice was obtained after ductoplasty. Overall a single anastomosis was possible in 77% of the cases. Nineteen anastomoses were duct to duct and 11 hepaticojejunostomy. Two donors, 6%, suffered a resection surface bile leak. Overall recipient biliary complication incidence was 20%, 1 anastomotic and 1 resection surface leak and 4 stenoses. Actuarial 1-year patient and graft survival is 87%. Probing of the HD through a choledocotomy is a safe and effective method of assessing in a 3-D fashion the exact position of the confluence. Transection of the HD prior to parenchymal transection has an excellent yield of a single orifice for the biliary anastomosis and avoids thermal injury to the HD.

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**CAN HYALURONAN PREDICT ENDOTHELIAL DYSFUNCTION AFTER LIVER TRANSPLANTATION?**

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Traditional liver function tests underestimate the importance of the sinusoidal endothelial cells, which are important in liver preservation and early graft function. Hyaluronic acid (HA) is a ubiquitous glycosaminoglycan that is a major extracellular matrix protein. Greater than 90% of the serum HA is degraded via receptors in Ito cells and hepatic sinusoidal endothelial cells. Degradation normally takes 2–5 minutes. Our hypothesis is that serum HA level may be a predictor of allograft endothelial cell dysfunction after liver transplantation. A prospective inception cohort study of 28 liver transplant patients was analyzed. The eight variables considered were serum HA, age, sex, Etiology of liver disease, AST, ALT, bilirubin, and creatinine. Serum HA levels were obtained by ELISAs. Concomitant liver function tests and liver biopsies were performed as indicated. Allograft dysfunction leads to endothelial cell dysfunction (ECD) was mainly due to primary non-function, vascular thromboses, or rejection. This (ECD) was seen in 13 patients: 9 with biopsy proven rejection, 3 with vascular thromboses, and one with primary nondysfunction. This group was compared with the remaining 15 patients. Data were expressed as mean + SEM. Statistical analysis was performed by independent samples *t* test. *P* value < 0.05 was considered significant. The allograft dysfunction group had serum HA levels of 1932.80 + 450.26 ng/ml compared to 341.85 + 61.85 in the nondysfunction group (–ECD), *P* < 0.001. In those patients who had evidence of rejection, HA significantly decreased and correlated with successful treatment. Similarly in the patient who underwent retransplantation for portal vein thromboses, Serum HA normalized to <300 ng/ml on the fifth postoperative day. Serum HA can detect endothelial cell dysfunction following liver transplantation in patients with rejection, primary nonfunction or vascular thromboses. Serum HA may provide a noninvasive measure for early graft function.

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**LIVING DONOR ADULT-ADULT LIVER TRANSPLANT FOR HEPATOCELLULAR CARCINOMA WITH VENA CAVA RECONSTRUCTION FROM A DECEASED DONOR**

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Liver transplantation (OLT) has been accepted as treatment for patients with early hepatocellular cancer (HCC) in the setting of cirrhosis. Select patients who exceed current size criteria may still be good candidates for OLT and hence resort to living donor liver transplantation. This presents a technical problem if HCC is adherent to, or wraps around, the vena cava. We present a case where the HCC was adherent to the vena cava with partial encasement requiring en bloc excision and reconstruction with deceased donor vena cava. This is a 48-year-old Caucasian male diagnosed with a liver mass by ultrasound after complaint of abdominal pain. MRI showed 8.1-cm tumor consistent with HCC, confirmed on biopsy, and probable early cirrhosis. Serology was positive for HCV. Tumor was in the posterior right lobe and involved the caudate and was adherent and partially encasing the vena cava. An aggressive strategy for size reduction included confocal radiation therapy followed by selective arterial embolization with PVA sponges and coils. His AFP went from 207 ng/ml to 7 ng/ml over the course of 2½ months. MRI showed significant tumor necrosis and gradual reduction in size to 6.4 cm × 6.0 cm. He was then evaluated and accepted for living donor liver transplantation. During OLT the vena cava was included with the hepatectomy specimen with

a good margin that was confirmed as negative for HCC. An infrarenal vena cava segment from a deceased donor was then utilized to reconstruct the recipient vena cava. The donor right lobe right hepatic vein was then implanted into the native vena cava remnant. Two accessory donor hepatic veins were sutured directly into the implanted vena cava segment. Graft flow was excellent and patient recovered uneventfully. Currently he is 8 months following OLT with excellent graft function and AFP <3 ng/ml. Ultrasound performed recently showed excellent flow in the hepatic veins and infra-hepatic vena cava. 1) Living donor liver transplantation is an option for select candidates with HCC exceeding current criteria for OLT. 2) Multimodality therapy for HCC can effectively result in tumor downsizing. 3) Deceased donor vena cava grafting expands the technical armamentarium for situations where the native recipient inferior vena cava has to be excised.

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**ACUTE LUNG INFLAMMATION FOLLOWING HEPATIC ABLATION—A COMPARISON OF DIFFERENT ABLATIVE MODALITIES**

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Multi-organ dysfunction syndrome (MODS) resulting from an exaggerated systemic inflammatory response (SIRS) has been observed following cryotherapy. Acute lung injury is one of the features of this syndrome and is associated with a high mortality. Alternative techniques such as radiofrequency ablation (RFA) and microwave tissue ablation (MTA) have been developed, although their effect on the pulmonary system following large volume ablation remains unknown. This study compares lung injury induced by each of these modalities of treatment at three increasing volumes of ablation. Following laparotomy, adult rats underwent ablation or resection of 15%, 33%, or 66% of the total liver volume. Control rats received a sham laparotomy. At 48 hours postprocedure, the animals underwent terminal anaesthesia; the left main bronchus was ligated and the left lung removed to determine the wet/dry lung ratio. The trachea was cannulated and a bronchoalveolar lavage (BAL) performed on the right lung. BAL fluid was examined for the presence of inflammatory cells and the total protein content measured as a marker of alveolar permeability. In addition, the protein concentration in the BAL fluid and the serum was expressed as a ratio. This ratio was used to determine the cause of the pulmonary oedema either as a result of increased permeability or hydrostatic pressure. Lung sections were taken for histological assessment. All animals survived to 48 hours except those in the 66% cryoablation and RFA groups, which all died within 6 hours. Significantly increased wet/dry lung ratios were only found in the 33% and the 66% cryoablation groups and 66% RFA group. Inflammatory cells were not found in the BAL in any of the control, resection, or MTA group. However, these cells were present in the 33% and 66% cryoablation groups and also the 66% RFA group. These three groups also exhibited an increase in the BAL total protein content. The BAL/serum protein ratio indicated that the presence of protein in BAL was due to increased permeability, as a result of an inflammatory response. Histology revealed multiple foci of inflammatory cells in the lung following 66% cryoablation and RFA, but these were absent in the 66% resection and MTA groups. At lower volumes of hepatic ablation by cryotherapy, RFA or MTA, the lung does not appear to be significantly affected by an inflammatory response. At larger volumes of ablation cryotherapy and RFA induce significant lung injury, which was not seen following microwave ablation or surgical resection.

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### PROINFLAMMATORY CYTOKINE INDUCTION FOLLOWING LARGE VOLUME HEPATIC CRYOTHERAPY, RADIOFREQUENCY ABLATION, MICROWAVE TISSUE ABLATION, AND STANDARD HEPATIC RESECTION

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Several local ablative techniques have been developed for the treatment of liver tumors. Cryoablation has been complicated by cryoshock, a variant of an exaggerated systemic inflammatory response syndrome (SIRS). Proinflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 have been implicated as important mediators of this response. This study investigates the inflammatory response following liver ablation by different modalities and conventional surgical resection using markers of systemic inflammation. Following laparotomy, adult rats underwent cryoablation, radiofrequency ablation (RFA), microwave tissue ablation (MTA) or resection of 15%, 33%, or 66% of the total liver volume. Control rats underwent a sham laparotomy. Blood samples were taken preoperatively, and at 1, 3, 6, 24, and 48 hours postprocedure. The levels of the proinflammatory cytokines TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 were measured using standard enzyme-linked immunosorbent assay techniques. Following 15% and 33% ablation or resection, the animals in all treatment groups tolerated the procedures well. All animals undergoing 66% hepatic resection or MTA survived to the 48-hour timepoint. However, there was a 100% mortality rate at 6 hours following 66% cryoablation and 66% RFA. No significant difference in cytokine levels was observed in any group following 15% ablation or resection, compared to controls. Following 33% resection or ablation using MTA and RFA, cytokine levels peaked at 6 hours and dropped to baseline levels within 24 hours. Significantly raised cytokine levels were noted in the 33% and 66% cryoablation groups, the 66% RFA group and the 66% resection group. These elevated cytokine levels remained high for at least 24 hours. The 66% MTA group did not show a significantly elevated cytokine response. Large volume hepatic ablation using cryotherapy and RFA results in a significant proinflammatory cytokine response and high mortality. Microwave ablation, however, did not induce a similar cytokine response and was less than that observed following surgical resection.

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### DOES HEPATIC MICROWAVE TISSUE ABLATION INDUCE A SYSTEMIC INFLAMMATORY RESPONSE? AN INVESTIGATION WITH A NOVEL MICROWAVE SYSTEM

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Several ablative techniques have been developed for the treatment of liver tumors. Cryoablation has been complicated by cryoshock, a variant of an exaggerated systemic inflammatory response syndrome (SIRS). A novel microwave tissue ablation (MTA) system has been developed at our institution capable of producing large volume ablations (>8-cm diameter) within a few minutes with a single insertion of the applicator. This study examined the SIRS response to MTA by assessing systemic and organ-specific markers of inflammation. Following laparotomy, adult rats underwent ablation or resection of 15%, 33%, or 66% of the total liver volume. Control rats underwent a sham laparotomy. Blood samples were taken at 0, 1, 3, 6, 24, and 48 hours postprocedure and the levels of the proinflammatory cytokines

TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 were measured. At 48 hours the animals were culled and the left lung removed to assess the wet/dry lung ratio. Bronchoalveolar lavage (BAL) was performed to quantify the protein content and the presence of neutrophils in pulmonary oedema fluid as indicators of acute lung injury. Urine was collected to assess the presence of retinol binding protein (RBP), a urinary marker of renal damage. Lung, liver, and kidney sections were also examined histologically using routine and electron microscopic techniques. All animals survived to 48 hours. No significant elevation in proinflammatory cytokines was found following any of the MTA treatments. Protein content in BAL was not elevated, and no inflammatory cells were observed on cytology. There was no significant difference in the wet/dry lung ratio, compared to controls. Urinary RBP was also not significantly raised. There was no evidence of acute inflammation in the lungs or kidneys following any of the MTA treatments. Systemic and organ-specific markers of inflammation are not raised as a result of MTA, suggesting that MTA is a safe procedure for liver ablation, even when large volumes of ablation are performed.

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### LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA: EVALUATION OF SELECTION CRITERIA

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Hepatocellular carcinoma (HCC) is a well-established indication for orthotopic liver transplantation (OLT). Patient selection is often based on Milan criteria. Since Mazzaferro et al's report there have been conflicting reports questioning these criteria based on patient survival. The aim of this study was to compare the authors' experience of 81 consecutive patients having OLT for HCC based on different criteria for transplantation. These included Milan, UCSF and the Pittsburgh modified TNM criteria. Survival analysis was performed using Kaplan-Meier and Cox proportional hazards regression methods. During a seven-year period 852 OLT were performed; 81 patients (9.5%) underwent OLT for HCC. Preoperatively all patients were assessed by radiological cross-sectional imaging, to evaluate the number, size and presence of vascular invasion. The explanted specimens were histologically evaluated in terms of size, number, distribution, pathological grade, and vascular invasion (macro and micro). There was no significant difference in 5-year survival rates between patients with HCC exceeding Milan criteria ( $n = 30$ ) versus those meeting Milan criteria ( $n = 51$ ), 52% versus 58.6%, respectively. In comparison 5-year survival according to the UCSF criteria ( $n = 59$ ) was 59% versus 47% for those outside UCSF criteria ( $n = 22$ ) ( $P = 0.7$ ). However patients with stage I & II Pittsburgh criteria had significantly higher 5-year survival compared to patients with stage III&IV disease (69% versus 34%;  $P = 0.01$ ). In conclusion this study demonstrates that the Pittsburgh modified TNM criteria is a more useful predictor of long-term survival for patients with HCC treated by OLT.

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### CASES OF COLORECTAL CANCER AND GASTRIC CANCER WITH LIVER INVOLVEMENT—IS RESECTION OF LIVER METASTASIS AN EFFECTIVE APPROACH?

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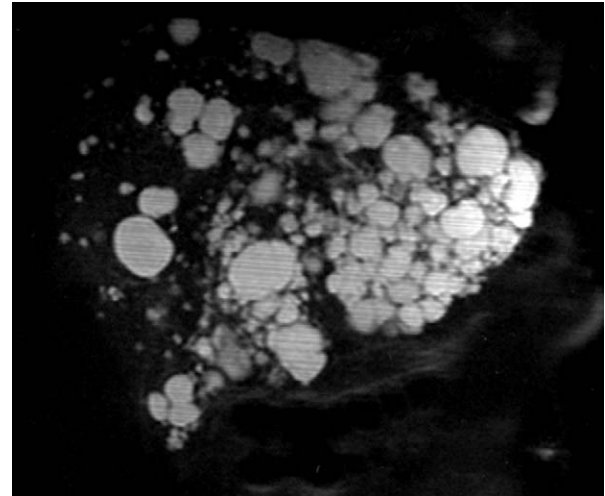
The cases of colorectal cancer and gastric cancer with liver involvement that were detected for the past 14 years were reviewed. The subjects were 74 patients with colorectal cancer with liver involvement

and 15 patients with gastric cancer with liver involvement treated during the period from 1990 to 2004. The patients with colorectal cancer with liver involvement were divided into two groups, hepatectomy group and nonhepatectomy group. There was a significant difference in survival period between these two groups. The patients were classified into two subgroups according to the timing of development of metastasis. A subgroup of patients who experienced metastasis seven months after the resection of the primary lesion or later showed significant extension of survival period when compared with a subgroup of patients who experienced metastasis simultaneously or within six months after the resection. A different subgroup of patients who had a single metastatic lesion showed significant extension of survival period when compared with a subgroup of patients who had multiple metastatic lesions. No efficacy of hepatectomy was recognized in a subgroup of patients who had 3 or more tumors. The maximum tumor diameter was not an important determinant of survival period. In the cases of gastric cancer with liver involvement, the hepatectomy group showed better outcome than the nonhepatectomy group although no significant difference was recognized between the two groups. The relationship between the survival period and the number of metastatic lesions was assessed and the results showed significant extension of survival period in the patients who had a single metastatic lesion. The results of assessment of the timing of development of liver metastasis showed no significant intergroup differences. In the cases of colorectal cancer with liver involvement, hepatectomy should be employed as long as this radical treatment can be tolerated. In the cases of colorectal cancer with three or more metastatic lesions, however, further evaluation of prognosis is needed. In the cases of gastric cancer with a single metastatic lesion in the liver, hepatectomy probably ensures a good prognosis for life as long as the local factors can be sufficiently controlled.

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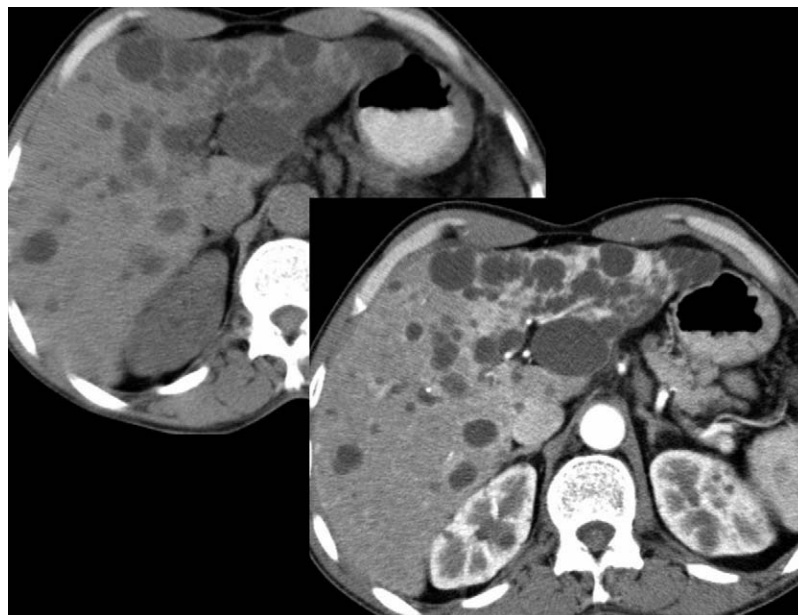
**ADULT POLYCYSTIC LIVER DISEASE**

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Adult polycystic liver disease (APLD) is a rare and benign inherited condition. At autopsy, the prevalence of APLD appears to be 0.13-0.6%. Most patients with APLD have no symptoms. Sometimes, symptoms arise from the enlargement of liver parenchyma and cyst, provoking compression of the adjacent organ. Abdominal distention and chronic pain are common clinical findings. The rate of complications arise from APLD is less than 5%, hemorrhage, rupture, infection, cholestasis, portal hypertension, but no hepatic insufficiency, have been reported. A 56-year-old man admitted to hospital with abdominal pain and distention. Patient examination showed an enlargement liver from subcostal line. Abdominal US showed increased liver volume caused by numerous hepatic cysts of various sizes. Initial noncontrast abdominal CT scan shows multiple hypodense cystic lesions. Contrast-enhanced CT scan shows nonenhancement of the same lesions. On coronal spin-echo T2-weighted MR imaging, the liver shows marked multiple hypointense cystic lesions. A laparoscopic fenestration was scheduled but the patient had not accepted the operation. For



this reason superficial and large cysts were treated with percutaneous drainage and alcohol sclerotherapy. There have been no recurrences at these cysts for last 10 months period. An asymptomatic, low-sized cyst does not require surgery and should be carefully evaluated on a yearly basis with an ultrasonographic follow-up. Open and laparoscopic fenestration, hepatic resection, and even liver transplantation are carried out in this disease. Cyst aspiration and sclerosis with alcohol, in selected cases, might represent a suitable and less invasive alternative to surgery. However, sclerosing cholangitis could be observed after an alcohol sclerotherapy, because of undiagnosed communication between the cyst wall and the biliary tract (Figs. 1 and 2).

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**HEPATIC ALVEOLAR ECHINOCOCCOSIS: SINGLE CENTER EXPERIENCE**

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Between February 1987 and June 2004, 63 patients with alveolar echinococcosis (AE) were evaluated in terms of results of medical and surgical treatment. The mean age was 47.1 years (range 14-80 years). Initial clinical symptoms in our cases were mainly cholestatic jaundice in 28 (44.4%) patients, dyspepsia in 20 (31.7%), and epigastric pain in 17 (27.0%) patients; 23 patients (36.5%) were incidentally determined during checkup. Fine needle aspiration or true cut biopsy was used for histopathological diagnosis. Hematologic examination, liver function tests, serologic tests (ELISA Em2 antigen), ultrasound (US), computed tomography (CT), and magnetic rezonans imaging (MRI) were carried out for diagnosis and for data for follow-up. According to Nakajima staging system, Type IIIa was mostly determined. There were distant metastasis in 14 patients; 5 had pulmonary, 5 regional lymph node, 3 brain, and 1 left adrenal metastasis. Curative surgical resection was performed in 23 patients (36.5%). (7 right hepatectomy, 4 left hepatectomy, 3 left lateral segmentectomy, 6 nonanatomical resection,

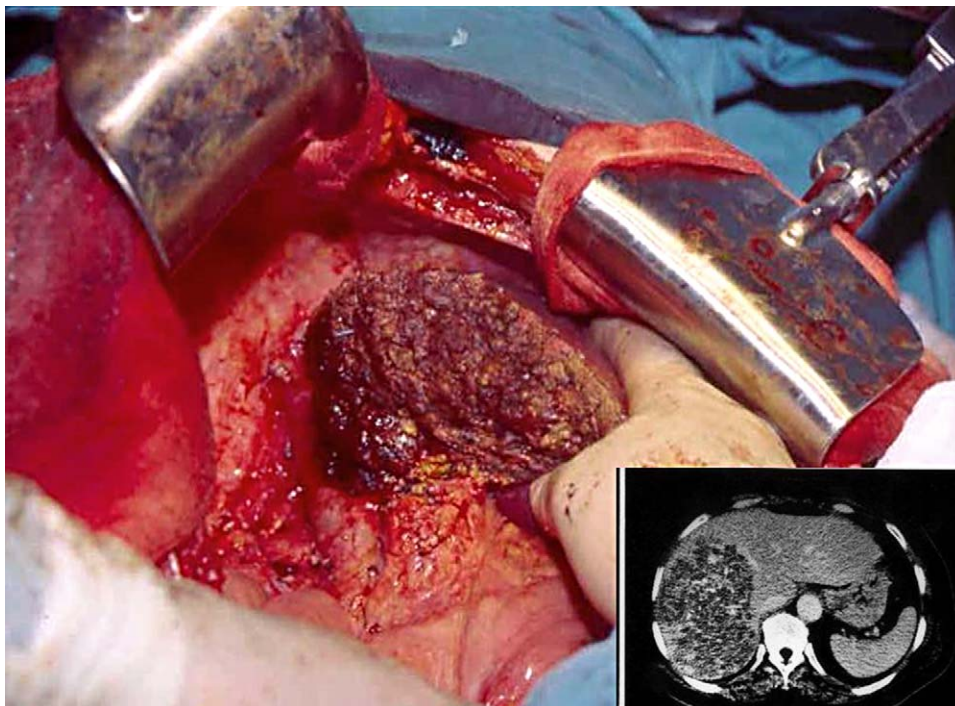
and 3 right extended hepatectomy). After curative surgical resection one patient showed controlled biliary leakage. There was no operative mortality. The average follow-up period was 4.5 years after curative resection; one patient showed recurrence. In patients with nonresectable AE, palliative procedures such as biliary diversion or external drainage was performed. Albendazole was used as chemotherapeutic agent. The chemotherapy protocol was 10 mg/kg/d orally in a treatment cycle 30 days with 10-day drug-free intervals. After curative resection, the average period of chemotherapy was 2 years. For nonresectable cases, this period was 6.5 years on average (8 months-15 years). There were no adverse reactions to discontinue chemotherapy. Five patients with nonresectable lesion died in follow-up period. The causes of death were liver failure and its complication in all patients. The other patients are alive. Five patients were listed for liver transplantation because of advanced AE with chronic liver failure (Fig. 1).

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**CHEMOTHERAPY DOES NOT IMPAIR COMPENSATORY LIVER HYPERTROPHY AFTER RIGHT PORTAL VEIN OBSTRUCTION**

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In patients with multiple colorectal liver metastases, the technical limits of curative surgery can be overcome by both reducing tumor volume with preoperative chemotherapy and by increasing the future remnant volume with portal vein embolization (PVE). Chemotherapy is generally discontinued before PVE and until the surgery, because is alleged to impair hypertrophy of the future remnant liver. To assess the rationale for chemotherapy discontinuation, we have compared the liver compensatory hypertrophy after right portal vein obstruction (RPO) in 2 groups of patients with and without chemotherapy. From 1999 to 2003, 20 patients with colorectal liver metastases underwent



a RPO before resection with volumetric helicoidal CT estimation of the liver volumes before RPO and before surgery (mean time of  $39 \pm 14$  days). In this group of RPO, including 11 PVE and 9 portal vein ligation during a two-stage hepatectomy, 10 received at least one course of chemotherapy (5-FU-oxaliplatin or 5-FU-irinotecan) during the interval between RPO and liver surgery. The two groups of patients with and without chemotherapy were similar concerning age ( $60 \pm 9$  vs  $61 \pm 9$  years), the number of metastases ( $7.7 \pm 3$  vs  $6.2 \pm 3$ ) and the volume of the future remnant liver ( $292 \pm 110$  vs  $355 \pm 94$  ml). After RPO, the increase of the future remnant liver volume ( $30 \pm 18\%$  vs  $25 \pm 21\%$ ) and the mean ratio between the left liver volume and the whole liver volume ( $39.3 \pm 8.8\%$  vs  $34.1 \pm 4.3\%$ ) was similar between the two groups. After liver resection, which was performed in 14 (70%) patients, 7 in each group, one patient in the group without chemotherapy died. Postoperative morbidity was similar in the two groups (20% vs 30%) including the rate of postoperative liver failure (0% vs 10%). In this study, the continuation of chemotherapy after portal occlusion did not impair the hypertrophy of the future remnant volume, nor the risk of liver resection. Therefore, when PVE is indicated chemotherapy can be safely continued until liver surgery.

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**LIVER RESECTION IN HEPATOCELLULAR CARCINOMA: OUTCOME, LONG-TERM RESULTS, AND PROGNOSTIC FACTORS**

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The purpose of this study, based on data prospectively collected, was to evaluate prognostic factors that influence outcome and long-term survival of liver resection for HCC. From September 1989 to March 2004, 124 consecutive patients had liver resection for HCC at our department. 94 patients belonged to Child-Pugh class A, 26 (20.9%) to class B. and 4 to class C. (3.2%). We performed 53 major liver resections (right hepatectomy, left hepatectomy, trisegmentectomy) and 71 limited resections (segmentectomy, wedge). In-hospital mortality rate was 8.1%, morbidity rate was 48.3%, caused by the rising of

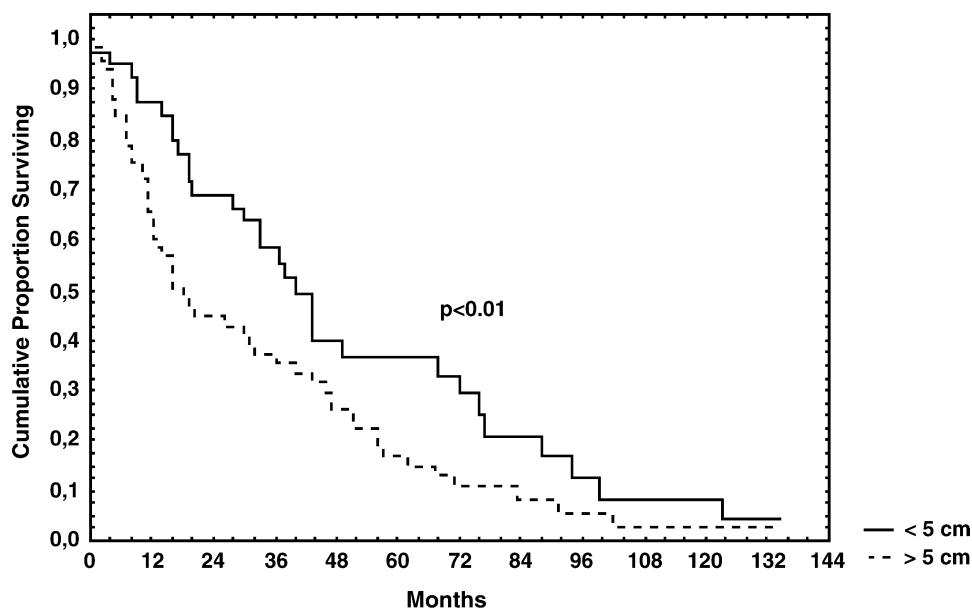
ascites (10%), hepatic insufficiency (19%), biliary fistula (6%), hepatic abscess (25%), hemoperitoneum (10%) and pleural effusion (30%). At preoperative evaluation 81 lesions were unifocal, tumor size measured before resection was over 5 cm in 61% of the cases. The preservation of 1 cm or greater tumor free margins has obtained in 77% of cases, and the histopathological examination revealed the presence of a capsule in 68.5% of lesions. Cumulative 1-, 3-, 5-, and 7-year survival rate were 73.7%, 44.2%, 22.8%, and 12.9%. The prognostic factors correlated with overall survival were lesion diameter (<5 cm vs. >5 cm,  $P < 0.01$ ), number of lesions (1 vs. >1,  $P < 0.01$ ), the presence of a capsule ( $P < 0.05$ ), Child-Pugh class (A vs. B. and C,  $P < 0.05$ ), Pringle's maneuver time (<20' vs. >20',  $P < 0.05$ ), type of resection (limited vs. major,  $P < 0.05$ ), postoperative complications ( $P < 0.05$ ), Okamoto-Child Index (<20% vs. >20%,  $P < 0.01$ ), and relapse of HCC ( $P < 0.05$ ). Liver resection is still the best practice against hepatocellular carcinoma. Surgical procedure should be encouraged in case of single lesion, diameter <5 cm, in patients of Child-Pugh class A, when the lesion is encapsulated and the surgical procedure could be limited rather than major Figure 1 shows cumulative survival: the influence of lesion's diameter on survival, and Figure 2 shows cumulative survival: the influence of postoperative complications on survival.

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**HEPATIC RESECTION FOR NONCOLORECTAL HEPATIC METASTASES**

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Since January 1997, 190 cases of hepatic resections have been performed at our center: 26 for noncolorectal metastases: 7 for breast cancer, 6 for renal cancer, 2 for endometrial cancer, 1 for adrenal cancer, 1 for gastric cancer, 1 for thymoma, 1 for neuroendocrine tumor, 1 for bladder cancer, 3 for gallbladder cancer, 2 for ampullary cancer, and 1 for lung cancer. We performed 2 right hepatectomies for metastases from renal and mammary cancer, 2 extended right hepatectomies: 1 case of metastases from thymoma and 1 case of metastases from breast carcinoma 12 years after mastectomy, 2 central hepatectomies:





1 case of metastases from breast cancer and 1 case of metastase from kidney cancer (together with caval thrombectomy), 3 left lobectomies, 9 bisegmentectomies, and 8 "wedge resections." There was neither perioperative mortality nor morbidity (incidence of wound infection: 3.5%; incidence of biliary leakage: 0%). Intraoperative blood losses ranged from 200 to 800 ml, while mean postoperative hospital stay was 8.5 days. One patient died 3 months after adrenalectomy and bisegmentectomy for recurrent adrenal cancer, 1 patient died of peritoneal carcinosis 1 year after "wedge resections" for metastases from uterine cancer, 1 patient died of recurrent breast cancer 3.5 years after hepatic resection, 1 patient died 11 months after central hepatectomy for metastatic renal cancer, 1 patient died with lung metastases 2 months after "wedge resections" and adrenalectomy for metastatic renal cancer, 1 patient with ampullary cancer died of peritoneal carcinosis 6 months after surgery, and 1 patient had bilateral hepatic metastases 24 months after extended right hepatectomy for metastases from breast cancer treated 12 years before. Although we have initially observed an incidence of cancer-related deaths after resective surgery of noncolorectal hepatic metastases higher than reported by other authors, it is not yet possible to draw statistically significant conclusions from our limited experience, due to the short follow-up period.

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#### OUTCOMES OF HEPATIC RESECTION FOR COLORECTAL METASTASIS FOLLOWING NEOADJUVANT CHEMOTHERAPY

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The use of systemic chemotherapy prior to resection of colorectal cancer (CRC) metastasis to the liver is becoming more and more prevalent. Despite this, many surgeons remain concerned about potentially increased morbidity and mortality associated with neoadjuvant therapy. The purpose of this study was to review our perioperative complications in patients receiving neoadjuvant systemic chemotherapy within 6 months of liver resection. Chemotherapy consisted of 5-fluoracil (5-FU), leucovorin (LCV), with or without irinotecan (CPT-11) or oxaliplatin. A retrospective chart review of consecutive patients undergoing liver resection for CRC metastasis from January 2002 to July 2004 was performed. 120 patients were identified. Perioperative parameters, patient demographics, tumor characteristics, and details of chemotherapy were measured in addition to morbidity and mortality. The analysis of the first 40 patients is presented here; 40 patients were identified and their charts reviewed. Sixteen patients (40%) received no chemotherapy, 12 (30%) received 5-FU/LCV, and 12 (30%) received 5-FU/LCV/CPT-11 or oxaliplatin. Patients receiving 5-FU/LCV/CPT-11 or oxaliplatin tended to have larger and more numerous tumors. Overall complication rates between groups were not significantly different. Hospital length of stay was similar for both groups. Intraoperative blood loss was also similar for both groups. There was a trend towards an increased rate of wound infection in the group receiving neoadjuvant chemotherapy (16% vs. 21%) but this did not reach statistical significance. There was no perioperative mortality in either group. From this analysis, we conclude that an aggressive use of neoadjuvant chemotherapy (5-FU/LCV ± CPT-11 or oxaliplatin) prior to liver resection does not result in increased morbidity or mortality. This strategy offers several potential advantages. Neoadjuvant chemotherapy may downstage tumors making unresectable lesions resectable. It may also allow more appropriate selection of patients for surgery: those who progress to extrahepatic disease during a short course of chemotherapy were unlikely to benefit from liver resection in the first place. The analysis of the remaining 80 patients will be presented at the meeting.

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#### RADIOFREQUENCY: NEW TECHNOLOGY FOR THE TREATMENT OF LIVER TUMORS

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Only 30-40% of patients with malignant hepatic tumors (primary or secondary) are candidates to a resection with curative intention. This stimulates the development of new technologies to perform a local ablation to modify the evolution. We sought to evaluate the results of the thermoablation with radiofrequency (RF) in the treatment of malignant liver tumors, even primary and secondary. The design was retrospective and observational. Between January 1999 and December 2003, 54 patients were treated with RF. Population was divided according to the original tumor: primary hepatic tumor (PHT), colorectal metastasis (CRM) and nonprimary noncolorectal metastasis (NPNCM). RF was applied alone or associated with another ablative procedure. RF was performed by laparotomy, laparoscopy or using percutaneous puncture. Mean age was 64 (range: 45-80). The tumors were CRM in 32 patients (60%), PHT in 14 (26%), and NPNCM in 8 (14%). RF was percutaneous in 8 (14%), laparoscopic in 4 (9%) and applied by laparotomy in 42 patients (77%). In 31 patients (57%) RF was the only therapy and in 23 (43%) it was associated with another resective or local ablative procedure. Mean hospital stay was 4 days (range: 3-10). Complication rate was 11%. There was no mortality. No reoperations were needed. Mean survival in PHT was 16.5 months, and the global overall survival rate was 47% at 4 years. In CRM mean survival was 16.3 months and overall survival rate was 27%. In NPNCM mean survival was 16.8 months and overall survival rate was 53%. Thermoablation with RF should be considered in patients with no chances of resection. This procedure can be associated with other resective procedures. Laparotomy is the safest way to perform it. The RF has a low rate of complications and it is safe in selected patients.

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#### NODULAR REGENERATIVE HYPERPLASIA ASSOCIATED WITH APLASIC ANEMIA: CASE REPORT

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Nodular regenerative hyperplasia (NRH) is a rare condition associated with immune, neoplastic, and vascular disorders, as well as with drugs and toxins. Pathogenesis is related to abnormal hepatic blood flow. Portal hypertension is the main complication. We report the case of a woman with NRH and aplastic anemia, association not previously described. A 31-year-old Hispanic female presented with pancytopenia and cholestasis. PMH was relevant for epilepsy treated with phenytoin for 5 years, which was discontinued 7 years before presentation. At admission she was pale and slightly jaundiced with diffuse petechiae. Lab report was as follows: CBC: leukocytes 2700/μl (with 500 total PMN cells); platelets 35,000/μl; Hb 6.7 g/dl; reticulocytes 0%. LFT: ALT 61 U/L, AST 70 U/L, Tot. Bil. 3.3 g/dl, Dir. Bil. 1.0 g/dl, Alk. Phos. 203 U/L, Alb 3.7 g/dl, globulins 3.9 g/dl, INR 1.4. Bone marrow biopsy was diagnostic of aplastic anemia. Abdominal ultrasound revealed multiple liver nodules, without hepato-splenomegaly. No abnormalities were noted in hepatic vessels. Serology for HBV and HCV was negative. Antimitochondrial (AMAs) and antinuclear antibodies were positive. Coagulation tests, antiphospholipid antibodies, C and S proteins, antithrombin III and factor V Leiden were normal. Liver biopsy showed hepatocyte nodules with central atrophy and sinusoidal dilatation in the absence of significant fibrosis. No arteritis, thrombosis or bile duct damage was found. Anti-thymocyte antiglobulin and cyclosporine were started with partial response at 5 weeks. Pathogenesis of NRH remains unclear. The most accepted theory was developed

by Wanless 24 years ago, and reinforced in 1997. It states that alterations in hepatic blood flow (portal obliterative venopathy) originate a specific response, initially consisting of apoptosis secondary to acute ischemia, with ensuing parenchymal atrophy and surrounding areas of liver regeneration and chronic ischemia. The common pathologic mechanism in all the associated diseases in NRH involves liver flow abnormalities secondary to microthromboses, vascular congestion, or vasculitis. In the current case we were unable to document evidence of liver flow abnormalities. Noteworthy there are previous descriptions of the association of NRH with primary biliary cirrhosis, and this patient was AMA positive, but without bile duct damage in the biopsy. Uncommonly, the only laboratory abnormality in NRH can be cholestasis. This case is relevant because we cannot sustain Wanless' theory and because it is the first description of the association of NRH with aplastic anemia.

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#### A CASE OF PSEUDOLYMPHOMA OF THE LIVER

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Pseudolymphoma (reactive lymphoid hyperplasia) of the liver is an extremely rare entity, with a few cases reported so far. We encountered a 50-year-old Japanese female with pseudolymphoma of the liver. A tumor-like lesion was discovered incidentally as a hypoechoic mass with a hyperechoic rim during clinical follow-up of endometriosis. Radiological studies, such as contrast-enhanced computed tomography (CT) and angiography demonstrated a hypervascular lesion. The hepatic lesion was resected because hepatocellular carcinoma was suspected after a needle biopsy. Grossly, the lesion was well defined and measured  $1.0 \times 1.5$  cm. Microscopically, the lesion consisted of hyperplastic lymphoid follicles with distinctive germinal centers and interfollicular areas consisting of mature lymphocytes and plasma cells. An immunohistological study revealed that the lymphoid cells of the lesion were polyclonal in immunophenotypes. These histological and immunohistochemical findings strongly suggested a pseudolymphoma of the liver. The following features have characterized the images in past cases, as well as ours: hypoechoic mass, occasionally with a rim, in ultrasonography and hypervascularity, shown by angiography and enhanced CT.

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#### TOO MANY COOKS SPOIL THE BROTH: THE DILEMMA OF SELECTING PATIENTS WITH HEPATOCELLULAR CARCINOMA FOR LIVER TRANSPLANTATION

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Criteria for liver transplantation in patients with hepatocellular carcinoma (HCC) differ amongst staging systems and amongst transplant centers. Originally used staging systems, e.g., TNM/UICC, are replaced by selection criteria described by Mazzaferro and the Milan criteria. The latter, however, are too tight and might breed the dilemma to falsely withhold an organ. Examining different selection criteria, it becomes obvious that a potential risk is that selected criteria may be used as one pleases in order to achieve improved results or in order to expand patient selection. This in return poses the risk of wasting an organ. Furthermore, established staging criteria (e.g., Milan criteria, Barcelona criteria) are conflicting as they use postoperative data, e.g., histological results, in order to select therapy. Thus, a comparison of results and outcome amongst transplant centers following liver transplantation and an outlook on prognosis is difficult if not impossible. The aim of this study was to analyze currently used

selection criteria for liver transplantation and to determine their reliability related to patient selection, therapy selection, and prognosis. We have reviewed the medical literature since 1954 to identify criteria published for the staging of HCC. To evaluate and compare the reliability of these criteria we focused on two questions: (1) Can the criteria be used in the decision making process for liver transplantation before and for treatment, and (2) How accurately can these criteria predict prognosis? As a tool we used the certainty factor (C factor) defining the level of diagnostic judgment and reliability: C1 clinical, C2 radiological, C3 biopsy, C4 resection, C5 autopsy. As an additional criterion liver function parameters were selected. Twenty-one staging systems were used for this comparative analysis. 1) Five staging systems can be used for therapy selection (C1-C3). 2) Three systems provided prognosis assessment only (C4-C5). 3) Thirteen staging systems allowed to both assist in decision making for therapy based on clinical criteria as well as the assessment of a prognosis based on pathological criteria (C1-C5). 4) Only five staging systems assessed tumor factors as well as liver function (C1-C5, LF). The ideal staging system should 1) facilitate the selection of transplant candidates based on tumor factors and clinical parameters and 2) predict long term prognosis as indicated by pathological tumor extent. It would be desirable to use a uniform staging system as suggested by the AHPBA consensus statement of 2003.

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#### RADIOFREQUENCY ABLATION IN THE PORCINE MODEL: COMPARISON OF MULTIPLE COOL TIP PROBES AND A SWITCHING CONTROLLER WITH A STANDARD THREE-PROBE CLUSTER

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Evaluation of the Switching Controller with multiple, combined cool tip probes for an output-based radiofrequency device. Radiofrequency (RF) ablation was performed in three randomly selected segments of the liver in 12 pigs. Half of the ablations were performed with a Pringle maneuver and half without. Ablations were performed with three 3.0 cm active tip, cooled RF probes spaced 2.0 cm apart and a 200 watt RF generator. Ablations using the standard cluster of probes were performed for 12 minutes in the non-Pringle subgroup and 6 minutes in the Pringle subgroup. Ablations using the Switching Controller with multiple, combined cool tip probes were performed for 16 minutes in the non-Pringle subgroup and 8 minutes in the Pringle subgroup. The Switching Controller delivered current that alternated among the probes, based on impedance (to 30 Ohms above baseline) and time (30 seconds maximum). The ablation dimensions, volume, temperature, current delivery parameters, and postablation histology were evaluated. A total of 34 successful ablations were performed. The minimum ablation diameter ( $D_{min}$ ) in the standard cluster group was  $40.3 \pm 4.3$  mm ( $42.5 \pm 4.1$  mm for the Pringle group and  $38.1 \pm 3.6$  mm for the non-Pringle group). The maximum ablation surface area ( $SA_{max}$ ) in this group was  $16.0 \pm 3.3$  cm<sup>2</sup> ( $17.6 \pm 2.2$  sqcm for the Pringle group and  $14.2 \pm 3.5$  cm<sup>2</sup> for the non-Pringle group). The ablation volume in the cluster group was  $36.9 \pm 9.5$  ml ( $40.1 \pm 8.1$  ml for the Pringle group and  $33.7 \pm 10.4$  ml for the non-Pringle group). In the Switching Controller Multiprobe group, the ablation  $D_{min}$  was  $51.4 \pm 7.4$  mm ( $54.5 \pm 8.5$  mm for the Pringle group and  $48.2 \pm 4.8$  mm for the non-Pringle group). The ablation  $SA_{max}$  in this group was  $22.4 \pm 4.7$  cm<sup>2</sup> ( $23.9 \pm 4.9$  cm<sup>2</sup> for the Pringle group and  $20.8 \pm 4.1$  cm<sup>2</sup> for the non-Pringle group). The ablation volume in the multiprobe group was  $66.1 \pm 17.9$  ml ( $68 \pm 16.8$  ml for the Pringle group and  $64.3 \pm 19.6$  ml for the non-Pringle group). Technology to increase the size of ablated areas and shorten the procedural time continues to evolve. The use of the

Switching Controller consistently resulted in ablation lesions with larger  $D_{min}$ ,  $SA_{max}$  and volume than ablations with the standard cool tip cluster. Furthermore, the Pringle maneuver allowed for the creation of an equally sized lesion in half of the time (Table 1).

**Table 1.** Cluster vs Switcher Multiprobe Ablation Outcomes

|                | $D_{min}$ (mm) | $SA_{max}$ (cm <sup>2</sup> ) | Volume (ml) |
|----------------|----------------|-------------------------------|-------------|
| Cluster        | 40.3           | 16.0                          | 36.9        |
| Switcher       | 51.4           | 22.4                          | 66.1        |
| <i>P</i> value | <0.0001        | 0.0002                        | <0.0001     |

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### SIMULTANEOUS RESECTION OF A DUODENAL VILLOUS ADENOMA, HEPATOCELLULAR CARCINOMA, AND COLON CARCINOMA

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Synchronous neoplasms of the gastrointestinal tract are uncommon. The presence of multiple distinctly different carcinomas is rare and often associated with an underlying syndrome or genetic aberrancy. Herein, we present a case of three primary neoplasms that included hepatocellular carcinoma, duodenal villous adenoma, and metachronous colon carcinoma. An 83-year-old male who was a former professional athlete presented for acute blood loss anemia. The past medical and surgical history were significant for a right hemicolectomy 20 years prior secondary to carcinoma. Endoscopic workup and preoperative imaging demonstrated a villous adenoma of the second portion of the duodenum, metachronous carcinoma of the transverse colon, and a liver mass. The patient underwent simultaneous resection of the villous adenoma, transverse colon, and segment V liver mass. The liver mass pathology was consistent with a 4.5-cm well-differentiated hepatocellular carcinoma. The transverse colon pathology revealed a moderately differentiated adenocarcinoma that measured  $4 \times 5 \times 1$  cm. The duodenal lesion was a large villous adenoma from the distal second portion of the duodenum that did not have invasive disease. The patient had an R0 resection of the malignant lesions and was discharged on postoperative day six without morbidity.

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### MULTIMODAL CYTOREDUCTION RESULTS IN SYMPTOM ALLEVIATION OF PATIENTS WITH ADVANCED CARCINOID LIVER METASTASES

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The objective of our study is to outline the efficacy of multimodal hepatic cytorreduction in the amelioration of symptoms in patients with advanced hepatic carcinoid metastases. Retrospective analysis of data collected on consecutive patients with metastatic carcinoid tumor to liver between October 1996 and October 2004. All the patients underwent hepatic cytorreduction with chemoembolization, resection, and/or radiofrequency ablation. Fifteen patients, mean age 61 (SD 11) years, underwent cytorreduction; 12 (80%) of the patients had extensive bilobular disease and 3 (20%) had solitary lesions. The average maximum tumor size was 4.04 cm (SD 3). 12 patients (80%) had specific preoperative carcinoid related symptoms and 10 (66.6%) had extrahepatic metastatic disease at the time of surgery. 13 patients

underwent a palliative debulking procedure. Hepatic cytorreduction included laparoscopic radiofrequency ablation on 10 patients, ethanol injections on 9, chemoembolization on 7, laparoscopic resections on 2, open resection on 1, and a multimodal approach was used on 9. At a postoperative mean follow-up after 29 months (SD 22.1), 6 patients (40%) had stable disease, 8 (53.3%) had progression of disease [hepatic only  $n = 2$  (25%), hepatic and extrahepatic  $n = 3$  (37.5%)] and 1 (6.6%) had no disease. Deaths occurred in 4 patients of which 2 were due to progression of disease. The mean and median symptom relief period was for 15 and 12 months, respectively. Aggressive cytorreductive hepatic therapy in patients with advanced metastatic disease is efficient in achieving symptom relief and disease control. The timing of combined treatment modalities and its role in prolonging survival warrant future studies.

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### EARLY RECURRENCE OF HCC AFTER CURATIVE HEPATECTOMY

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Hepatectomy has been established as major treatment of hepatocellular carcinoma (HCC). However, it is highly recurrence rate after curative resection: 5-year cumulative recurrence rates have been reported 80–100%. The purpose of this study, we have evaluated prognostic factors in patients with recurrence after undergoing curative resection of HCC, especially early type (within 6 months).

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### MICROWAVE HEPATIC ABLATION LEADS TO A MORE EFFICIENT AND EFFECTIVE HEPATIC ABLATION

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Hepatic tumor ablation has become an accepted and effective method of controlling both primary and secondary malignancies in combination with surgery or as the primary therapy. Radiofrequency ablation (RF) has been demonstrated to have a lower complication rate than cryoablation, however, the recurrence rate has been highly variable, from 9% to 50% depending on technique. Recent evidence has demonstrated that RF ablation may lose its effectiveness at the peripheral portion of the lesion. In addition tumors near blood vessels may be protected by the cooling effect of blood flow. Microwave ablation has been demonstrated to effectively treatment of hepatic tumors in multiple treat and resect studies. This study represents the first report of microwave ablation as the primary therapy in patients with hepatic malignancies. a prospective multi-institutional trial and retrospective study of microwave ablation of hepatic tumors from 1/2004 until 10/2004 was reviewed. A standard bracketed technique of placing multiple (maximum 3) probes around the periphery of the tumor was utilized. In all cases multiple ablations of hepatic lesions was performed simultaneously. Fifty-eight hepatic tumors were ablated in 18 patients (7 colorectal, 11 noncolorectal). The median tumor number was 3 (range 1-13) with a median size of 3 cm (range 1.5 to 4.0 cm). Multiple types of microwave probes (Surgical straight, Atom, and laparoscopic) were utilized depending on location and size. Nine patients underwent additional procedures including partial hepatectomies, colectomy, and gastrectomy. Total median ablation time was 10 minutes (range 5 to 22.5). There were no perioperative mortalities, with perioperative morbidity occurring in 5 patients, none of them related to hepatic ablation. After a median follow-up of 6 months there have been no ablation recurrences. Microwave ablation represents a faster and safer way to perform hepatic ablations in patients. The ability to perform bracketed ablations in tumors that are not perfectly spherical

will result in more complete initial ablations and fewer ablation recurrences. The ability to perform multiple ablations simultaneously allows for a more efficient surgical procedure, especially in patients with multiple lesions.

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**184****MAJOR LIVER RESECTION FOR GIANT HEPATIC TUMORS IN PEDIATRIC AGE GROUP**

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Successful formal or extended hepatectomy for giant liver tumors is a golden therapeutic modality for giant hepatic tumors with or without adjuvant therapy. Also is a mandatory step for living related liver transplantation (LRLT) in pediatric age group. Eleven patients with giant liver tumors were included from December 1994 to July 2003. There were four girls and eight boys and their ages ranged from 2.5 months to 13 years with mean age of 34.88 months. The tumor diameter ranged from 8 cm to 28 cm. Eight cases had hepatoblastoma, one case had malignant mesenchymoma (undifferentiated embryonal sarcoma). Two cases had liver cell adenoma. Right or extended right hepatectomy was done in 4 patients. Left or extended left hepatectomy was done in 3 cases. Quadrectomy (resection of segment IV) was done in one case. Hepatectomy was done in one case with hepatoblastoma who received LRLT. Ultrasonic dissector and bipolar coagulation irrigation was used in 6 cases. Post operative complications were, minor biliary leak in two cases, wound infection in three cases and hepatic recurrence in one case after two years. Hospital mortality was three cases, two of them died before surgery and after chemotherapy one with lung metastasis and the second with tumor thrombus occluding the IVC. One case lost in the follow-up. Major liver resection is a safe procedure, especially when performed on normal liver under elective conditions. Experience gained in hepatectomies is needed as in any program for liver transplantation from a living donor. Liver transplantation in case of hepatoblastoma needs long-term evaluation.

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**185****TAMOXIFEN VS. TAMOXIFEN-THALIDOMIDE FOR ADVANCED HEPATOCELLULAR CARCINOMA**

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Hepatocellular carcinoma is a common neoplasm that is usually diagnosed in an advanced stage when surgical resection or ablative therapies are not indicated. Several treatments have been investigated. However, there is no consensus for the treatment of these lesions. To analyze the results with tamoxifen alone compared with tamoxifen-thalidomide in patients with advanced hepatocellular carcinomas treated in two Institutions in Mexico. A retrospective review of the clinical files and the prospective database of patients with hepatocellular carcinoma who were treated with both forms of treatment were analyzed. All patients were studied and treated by the same group of surgeons under the same protocol. Two hundred eleven patients with hepatocellular carcinoma were treated in the last 14 years, 34 (16%) patients were included for analysis. Eighteen patients received tamoxifen 40 mg/day (Group I) and 16 patients received tamoxifen 40 mg/day plus thalidomide 100 mg/day (Group II). Both groups were similar in terms of gender, age, baseline performance status, and tumor size and stage. Alpha-fetoprotein mean levels at the time of diagnosis

were 26,424 mg/dL (range 0.3 to 343,700), the mean size of the tumor was 9.5 cm (range 1-16 cm). Of the patients treated with tamoxifen in five patients (27.7%), the disease did not progress and the rest of the group (72.3%) did not respond to the treatment. In the group treated with tamoxifen-thalidomide six patients (37.5%) presented with tumor progression, five patients (31.2%) presented with no disease progression, and two patients (12.5%) presented with tumor regression. Two patients in group II presented with dermal lesions that precluded the continuation of treatment. In this group a dramatic improvement in status performance and quality of life was observed in seven patients who respond to treatment. Tamoxifen-thalidomide is well tolerated, has minimal secondary effects, and seems to be more effective than tamoxifen alone in patients with advanced hepatocellular carcinoma. However, a prospective randomized double-blind study has to be performed in order to confirm our results.

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**186****RADIOFREQUENCY ABLATION FOR UNRESECTABLE LIVER LESIONS**

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Liver resection is the best form of treatment for most of the primary and secondary liver tumors. Unfortunately, the majority of patients are considered unresectable at the time of diagnosis. In recent years, a number of different ablative such as percutaneous ethanol injection, cryotherapy ablation and radiofrequency ablation have been described in the literature. We sought to evaluate preliminary results of radiofrequency ablation for primary and secondary liver tumors. A retrospective review of the clinical files of patients treated with radiofrequency ablation in two different hospitals was performed. Epidemiological data, methods of diagnosis, and results of treatment including morbidity and mortality were analyzed. From September 2002 to August 2004, 35 procedures were performed in 30 patients. Eighteen were female and twelve males. The median age at the time of treatment was 62 years (range 41-83 years); 53 lesions were treated and included 18 patients with hepatocellular carcinomas, four patients with breast metastases, four with colorectal metastases, two neuroendocrine liver metastases, one gallbladder carcinoma and one peripheral cholangiocarcinoma. Nineteen patients were performed by laparotomy, seven were percutaneous and four by a laparoscopic approach. The size of the lesion range from 2 to 20 cm (mean, 5.6 cm). In 26, a single ablative session was performed in three patients in two sessions, and in one patient three sessions were performed. Medium time of ablative therapy was 30.2 minutes (range, 5-50 min). Ambulatory procedure was performed in eight patients. In those operated the medium hospital stay was three days (range, 2-5 days). Indications for ablative procedure was the presence of cirrhosis in 18 patients, bilobular disease in six that was an adjuvant to liver resection, due to a difficult locations in patients with an increased operative risk, a palliative procedure was performed in one patient. Two patients presented operative complications (6.6%) that included fever and abdominal pain, and liver failure and fever in another patient. No mortality was recorded. Twenty-three patients are still alive at a medium follow-up of one year and seven patients died with tumor progression. Radiofrequency ablation can be performed with low morbidity and mortality. Three different approaches can be performed.

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**A COMPARATIVE STUDY OF RESECTION OF COLORECTAL AND NONCOLORECTAL LIVER METASTASES**

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Liver resection is a well-known procedure in colorectal metastases. The experience for noncolorectal metastases is scarce. We sought to compare results of surgical treatment of colorectal and noncolorectal liver metastases. A retrospective review of the clinical files of patients with colorectal and noncolorectal liver metastases was performed. Epidemiological data and results of treatment including morbidity and mortality were analyzed. From July 1995 to August 2004, 25 liver resections in 23 patients with colorectal metastases were performed. And 39 liver resections in 37 patients with noncolorectal metastases were performed. The median age for this group was 42 years (range from 15 to 70 years) of whom 15 were males and 22 females. The primary tumor was breast cancer in eight, testis in six, carcinoid in five, ovarian in four, gastric in four, and miscellaneous in 12. In the group of colorectal metastases, nine procedures were right hepatectomies, five segmentectomies, four left hepatectomies, three left lateral segmentectomies, two left trisegmentectomies and two right trisegmentectomies. Intraoperative ultrasound (IOUS) was used in six patients (24%), the main time of liver ischemia was 41 minutes (range from 20 to 100 minutes), the main trasoperative bleeding was 1272.6 ml (range from 20 to 4000 ml), the morbidity rate was 28% (n = 7), and mortality rate was 4% (n = 1). The main follow-up was 26 months (range from 4 to 68 months). In the group of non colorectal metastases 11 procedures were right hepatectomies, nine left hepatectomies, eight segmentectomies, six right trisegmentectomies and five left lateral segmentectomies. IOUS was used in 9 patients (23%), the main time of liver ischemia was 39 minutes (range from 20 to 76 minutes), the main trasoperative bleeding was 1289.4 ml (range from 30 to 4000 ml), the morbidity rate was 20.5% (n = 8), and mortality rate was 2.5% (n = 1). The main follow-up was 30 months (range from 4 to 104 months). Liver resection is a safe for metastatic disease. Survival observed in these series is similar in both groups; however, prognostic factors should be investigated in noncolorectal metastases in order to do a better selection of cases.

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**TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION WITH DEGRADABLE STARCH MICROSPHERES, IRINOTECAN, AND MITOMYCIN-C IN PATIENTS WITH LIVER METASTASES**

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Degradable starch microspheres (DSM) provide transient occlusion of small arteries and are thought to improve the therapeutic effect of anticancer drug. Irinotecan (CPT-11) is one of the most effective anticancer agents for adenocarcinoma, especially colorectal cancer (CRC). We herein report cases with liver metastases treated with transcatheter arterial chemoembolization with DSM, CPT-11, and mitomycin-c (MMC) (DSM-CPT therapy). Five patients underwent DSM-CPT therapy for the liver metastases originated from CRC for 4 and gastric cancer for 1. They all have advanced diseases which are out of the indication for surgery initially (all have multiple liver

metastases spread out in the whole liver and three have distant metastases outside the liver). They were all male in the range of 42-78 (mean, 55.2) years old. Three of them had pretreatment histories with 5-FU or related agents and 4 of them had combined systemic chemotherapy at the period of DSM-CPT therapy. From 300 to 1200 mg (required doses for stasis of whole blood flow of hepatic artery) of DSM, 80 mg of CPT-11, and 8 mg of MMC were used for single injection. After 1-6 injections, 4 of them with CRC origin acquired partial response (PR), which persisted more than 2 months, and the disease made progression in 1 patient with gastric cancer origin. Two of the PR patients underwent surgery after 2 months of the PR period. CEA levels in 3 patients with PR (the other patient had a normal CEA level) and CA19-9 levels in 4 patients with PR decreased to 16.1 and 19.3% of the level before treatment, respectively. DSM-CPT therapy is a potential therapy for advanced liver metastases, especially as neoadjuvant chemotherapy for the patients with CRC origin.

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**COMBINATION STUDY WITH ERK EXPRESSION EVALUATED PROPERTIES AND TREATMENT OF HEPATOCELLULAR CARCINOMA**

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The aim of this study is to evaluate the properties of hepatocellular carcinoma (HCC) from the combination study of extracellular signal regulated kinase (ERK) with the other factors related to hepatocyte growth factor (HGF) in tumor tissue. In the specimens of 30 HCC patients, who were operated at our department for the most recent two years, the induction values of HGF, c-Met, ERK and cyclin D1 were estimated by Western blot. 1) The expression values of ERK and cyclin D1 proteins were significantly higher in the cases with progressive tumors, such as histological type or the presence of intrahepatic metastasis (IM). And the ERK expression in tumor tissue was correlated clearly with both tumor size and serum levels of HGF by simple linear regression analysis. 2) The nontumor tissue level of cyclin D1 was significantly higher in poor functional liver evaluating due to ICGR15. 3) In the cases with overexpression level of ERK in tumor compared with nontumor tissue, the histological finding was noted more progressively; however, there was no similar tendency with cyclin D1. In the cases with overexpression of HGF and c-Met, the detection level of ERK was significantly higher, but not for cyclin D1. The detected level of cyclin D1 was significantly higher in the cases with overexpressed ERK in tumor tissue. 4. The relationship between the values of ERK and c-Met was correlated, and IM presence was detected more frequently in cases with high expression of ERK and c-Met protein. And even after complete removal for visible IM tumor, recurrence tumors were detected within 6 months in 7 cases with both high expressions of ERK and c-Met protein. Under this concept, the anatomical hepatectomy may be the preferred treatment to avoid recurrence. The combination study of tumor expression of ERK might be useful to estimate the properties of HCC, especially for the presence of IM.

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**A CASE OF MUCINOUS CHOLANGIOCARCINOMA**

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Mucinous cholangiocarcinoma (CC) is a rare histological type of CC, with a few cases reported so far. We encountered a 56-year-old Japanese man with mucinous CC. He was hospitalized due to an abdominal tumor. His medical history included rectal carcinoma at the age of 48. Computed tomography (CT) showed multilocular low density

area in the left hepatic lobe. Magnetic resonance imaging (MRI) showed low intensity on T1-weighted images and very high intensity on T2-weighted images. Celiac angiography demonstrated that the hepatic tumor was marginally hypervascular. We underwent the extended left lobectomy of the liver. The hepatic tumor grossly appeared multicystic, but there were no apparent cysts. Histologically, it consisted of adenocarcinoma cell nests floating in a mucinous lake and it produced a large amount of mucin, but did not secrete mucin into the bile duct. Mucinous carcinoma is seen in both cholangiocarcinoma and rectal carcinoma. However, the pathologic diagnosis of his rectal carcinoma was well-differentiated adenocarcinoma, so the diagnosis of this hepatic tumor was mucinous cholangiocarcinoma.

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**191****THE RELATIONSHIP BETWEEN INVASIVE PHENOTYPE AND MICROVESSEL DENSITY (MVD) IN COLORECTAL CANCERS AND THEIR LIVER METASTASES**

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Colorectal cancers can be classified into infiltrative/pushing and liver metastases into capsulated/noncapsulated based on their invasive growth pattern. This study aimed to determine i) the relationship between the invasive phenotypes of primary cancers and their metastases and ii) the association between invasive phenotype and tissue microvessel density (MVD). Twenty-one matched pairs of primary colorectal cancer and liver metastases (ethical committee approved) were subjected to H&E histochemistry and classified as infiltrative/pushing (primary cancers) and capsulated/noncapsulated (liver metastases). MVD in 2 defined areas (tumor center, invasive margin) was analyzed by CD31 immunohistochemistry using the Lucia image capture system. Seven of 21 (33%) primary cancers were infiltrative and 14/21 (67%) pushing. Infiltrative cancers tended to form noncapsulated and pushing cancers capsulated metastases. There was no difference in MVD between infiltrative/pushing cancers at the tumor center, but infiltrative cancers had a higher mean MVD at the invasive margin (152 [SEM 17.8] vs 102 [SEM 15.9];  $P = 0.05$ ). Similarly there was no difference in MVD between capsulated/noncapsulated metastases at the tumor center, but noncapsulated metastases had a higher mean MVD at the invasive margin (138 [SEM 17.2] vs 76 [SEM 12.9];  $P = 0.01$ ). Colorectal cancers and their liver metastases have invasive phenotypes with differing MVD patterns, with the more aggressive infiltrative tumor characterised by a higher MVD at the invasive margin.

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**192****KASABACH-MERRITT SYNDROME IN GIANT HEMANGIOMA OF THE LIVER—A CASE REPORT**

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Kasabach-Merritt syndrome is a rare coagulation disorder with consumption coagulopathy caused by vascular malformations. This rare condition form of intravascular coagulation that can progress to a secondary systemic fibrinolysis with fatal outcome for 20% to 30% of the patients. Usually there is a thrombocytopenia secondary to platelet trapping within the hemangioma. Surgical resection provides the only consistently effective method of treatment and is indicated for symptomatic lesions in patients with an acceptable surgical risk and in lesions for which a diagnosis is equivocal despite appropriate

preoperative evaluation. A 37-year-old woman had a 7-year history of abdominal distention and pain with a large mass in the right upper quadrant also presenting peripheral edema and post prandial sensation of fullness. Physical examination showed an upper-abdominal mass extending from right hypocondrium to 20 cm below the umbilicus. Laboratory studies disclosed thrombocytopenia (platelet count, 110,000 per cubic millimeter); prolongation of the prothrombin time (42%) and decrease in the fibrinogen level. A computed tomography scan showed a large, low-density mass in the right lobe of the liver with compression of the inferior vena cava measuring  $21 \times 8 \times 13$  cm and the smaller lesion  $10 \times 6$  cm in the left lobe. The patient underwent to a right hepatic lobectomy with no postoperative complication been discharged after 5 days. The mass was a cavernous hemangioma weighing 5 kg. In conclusion, this kind of disease is a rare condition and when the Kasabach-Merritt syndrome is present in association with abdominal discomfort the surgical resection or even a liver transplantation can be indicated with safe results and improvement of quality of life.

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**193****RADIOFREQUENCY ABLATION OF PRIMARY AND METASTATIC LIVER TUMORS—THE 4-YEAR EXPERIENCE**

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Radiofrequency ablation of primary and metastatic liver tumors has been shown to be one of the promising new modalities to treat or palliate liver tumors. It has been used as a bridge to liver transplantation as well as an approach to recurrent tumors after resection. We present a series of 78 cases, 39 females and 39 males with a mean age of 61 years. RFA has been used either by laparotomy or percutaneously to treat 117 lesions. There were 32 cases of hepatocellular carcinoma, 35 metastases of colorectal cancer and 11 cases of other tumors. The mean number of lesions treated were 1.5 per case with an average size of 3.6 cm per lesion. All liver segments were compromised specially IV, VII, VIII. The morbidity was 28% and the mortality was 2.5%. In 20,5% of the cases we were able to find recurrence after the procedure, with a mean time of 10.5 months. The RFA procedure is safe, can be performed by different ways and in the group of patients who are candidates to liver transplantation, while waiting for the organ. For the metastatic diseases it does not substitute surgery but can be used in patients who cannot be operated.

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**194****LIVER METASTASES FROM LEIOMYOSARCOMA: AN INDICATION FOR LIVER TRANSPLANTATION?**

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The discussion about liver transplantation (LTx) for malignancies has remained a hot topic and is as controversial today as compared to some 25 years ago, when total hepatectomy was considered an ideal treatment for nonresectable hepatobiliary tumors. Following periods of overwhelming enthusiasm, and disappointment, most transplant centers have learned that patient selection is crucial for tumor-free long-term survival, despite the fact that most criteria used for selection and assessment of prognosis are far from being uniform. With the exception of neuroendocrine tumors, liver metastases have almost never been accepted as indication for liver replacement.

This is a review of three of our own patients who had a liver transplantation for nonresectable metastases from various mesenchymal

Table 1.

|                                       | Patient 1  | Patient 2   | Patient 3  |
|---------------------------------------|--|---|--|
| Age at LTx (yr)                       | 38   | 43  | 46   |
| Gender                                | Female   | Male  | Female   |
| Previous medical/<br>surgical history | 02/89 gastric resection choriocarcinoma<br>05/91 neck tumor resection paraganglioma<br>05/97 liver tumors: biopsy epitheloid<br>hemangioendothelioma<br>10/98 lung tumor resection chondroma<br>01/99 (standard technique) | 09/96 gastric resection leiomyosarcoma<br>07/00 liver metastases<br>09/00 chemo, TACE | 08/03 Budd-Chiari syndrome<br>03/04 liver tumors: biopsy leiomyosarcoma<br>of the inferior vena cava |
| LTx                                   | 01/99 (standard technique)   | 11/00 (living donor, right lobe)  | 08/04 (cardiopulmonary bypass)   |
| Preoperative diagnosis                | Epitheloid hemangioendothelioma  | liver metastases leiomyosarcoma   | liver metastases leiomyosarcoma  |
| Postoperative diagnosis               | Gastrointestinal stroma tumor, Carney's triad  | gastrointestinal stroma tumor   | same as preoperative   |
| Status                                | Alive, tumor-free  | alive, tumor free   | alive, tumor free  |

primary tumors within the last five years. What can be learned from these cases? There are no large series of LTx for similar tumor entities, so that the experience per se is interesting, especially since all three patients had an obvious benefit from radical tumor removal. Although the final diagnosis was different, there are a number of common features: like younger age, unusual long previous medical histories indicating specific tumor biology, difficulty to establish a clear diagnosis before transplantation, and total hepatectomy as the only chance for long-term cure. Essential prerequisite for our decision in these cases was assessment of the individual case as well as exclusion of any extrahepatic malignant disease. In conclusion, presentation of a patient with liver metastases alone does not always justify the principle exclusion from transplantation (Table 1).

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#### CURRENT RADIOFREQUENCY TECHNOLOGIES IN LIVER ABLATIONS: WHICH IS THE BEST?

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Surgical removal of hepatic malignancy has been the treatment of choice for liver malignancies. With advent of interstitial therapies the indications for tumor treatment have been extended. The most recent advances in radiofrequency technology improved short- and long-term outcomes in patients with liver malignancy previously considered unresectable. RF is considered to be reliable, reproducible and relatively safe method of ablation. Direct comparison has been attempted to improve indications regarding the choice of RF technology. Six adult pigs (mean weight 220 lbs) were used in this study. Three currently available RF (Tyco Healthcare Group, Boston Scientific, and RITA Medical) probes were used in the study. Each of the probes was used in three different positions in the liver on the rotation base. Each of the ablations was repeated in the same place twice. The probes were used according to the user manual at all times. The efficacy of the ablation was evaluated by contrast enhanced biphasic liver CT with 3-D reconstruction and volume rendering for each of the ablations. Volumetric results were compared to gross pathology findings. Each ablation area was identified, removed from the surrounding tissue and then volumetric measurements utilizing Archimedes principles were conducted. In total 18 ablations were performed. Each technology was used six times. All CT and pathology findings are currently being calculated and will be available in November 2004. This is first North American study focusing on direct evaluation and comparison of available RF technologies and their efficacy in any model.

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#### PREDICTORS AND OUTCOMES FOR EARLY RECURRENCE AFTER LIVER RESECTION FOR HCC

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Early recurrence (<1 year) after liver resection is one of the most important factors that impact the prognosis of patients with hepatocellular carcinoma (HCC). We sought to determine factors that predict for early recurrence (ER) of HCC and examine the outcomes thereafter. From March 2001 to June 2003, 56 patients underwent liver resection for HCC at our institution and were prospectively followed for 24 months. Preoperatively, all patients underwent viral serologies, triple-phase CT and ultrasound to evaluate for cirrhosis and tumor characteristics, and ICG clearance to assess hepatic function. Patients who developed ER were compared with those who remained disease free >1 year. Patient, tumor, operative, and treatment characteristics were evaluated and tested for their prognostic significance by univariate and multivariate analysis using the log rank, *t* test, and Cox proportional hazards models. Time to recurrence and survival were determined by Kaplan-Meier analysis. The initial procedure undertaken in all patients was surgical hepatectomy; 21 patients (38%) developed ER, 31 (55%) remained disease free for more than 1 year, and 4 (7%) were omitted from evaluation due to early death. Median survival after initial hepatic resection for those with early recurrence was 27 months and two-year survival was 54%. There were no deaths in the same time period in the disease-free group (100% 2-year survival, *P* 5 cm, cirrhosis, pathologic vascular invasion and microscopic positive margins (*P* < 0.05). Operative factors including blood loss, use of the Pringle maneuver, and operative resection were not predictive. Only vascular invasion and microscopic margins on final pathology were significant by multivariate analysis (*P* < 0.05), with a positive predictive value of 77% and 73%, respectively. A retrospective review of preoperative imaging showed vascular invasion in only 1 of 10 patients with microscopic venous invasion. After ER, 11 patients (52%) underwent additional therapy (4 salvage resection, 3 RFA, 2 TACE, 2 transplantation) with significant prolongation of median survival compared to chemotherapy alone (2-year survival 73% vs. 37%; *P* < 0.05). Early recurrence after liver resection for HCC occurs frequently and is the leading cause of death within two years. Aggressive adjuvant treatment may prolong survival. The high rates of recurrence in patients with vascular invasion and/or positive margins suggest this group should be targeted for clinical trials of adjuvant therapies.

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**CLINICAL AND HORMONAL CHARACTERISTICS OF BILIARY CYSTADENOMAS**

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Biliary cystadenomas are rare cystic neoplasms of the liver. A premalignant potential is cited as a reason for resection, but the biological behavior is unclear. The purpose of this study is to elucidate the clinical characteristics, surgical management and histopathology of these tumors (including comparison with cystadenomas of other organs). Twelve patients with resected biliary cystadenomas (BCA) were identified (10 F:0 M; median: age 48 years; size: 10 cm; all mucinous-type). Preoperative imaging included ultrasound, CT and/or MRI. The principal surgical approach was enucleation. For histopathological comparison, 10 pancreatic cystadenomas (PCA; 7 F:3 M; median age: 60 years; size: 6 cm; 7 mucinous and 3 serous-type) and 10 matched ovarian cystadenofibromas (OCA; median age: 51 years; size: 8 cm; 3 mucinous and 7 serous-type) were also stained with a panel of immunohistochemical probes including estrogen (ER) and progesterone receptors (PR) and CD-117 (c-kit). The majority of patients were symptomatic and 25% had a previous failed drainage attempt. Concurrent hormonal therapy was noted in 75% of patients. Rapid growth was seen in one patient receiving hormonal infertility therapy. Complete excision was found to be curative. Enucleation in the plane of compressed liver tissue was associated with fewer complications than resection. Histopathology demonstrated no evidence of severe dysplasia or carcinoma in any of the 12 patients. Epithelial and stromal staining characteristics are shown in the Table 1. BCA epithelia were all negative for estrogen and progesterone receptors, while the stroma was positive: ER 70%, PR 60%. The BCA and PCA stroma additionally had myofibroblastic features with uniform SMA positivity and approximately one-third expressing CD10. A strong role for a hormonal pathogenesis of biliary cystadenomas, with growth mediated through stromal, rather than the epithelial proliferation, is suggested. Management remains complete surgical resection.

**Table 1.** Stromal Staining (%)

|     | Epithelium<br>ER + | Epithelium<br>PR + | Stroma<br>ER + | Stroma<br>PR + | c-kit |
|-----|--------------------|--------------------|----------------|----------------|-------|
| BCA | 0                  | 0                  | 70             | 60             | 0     |
| PCA | 0                  | 0                  | 80             | 40             | 40    |
| OCA | 0                  | 0                  | 100            | 60             | 0     |

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**ONCOLYTIC HERPES SIMPLEX VIRAL THERAPY IS EFFECTIVE IN THE TREATMENT OF HEPATOCELLULAR CARCINOMA CELL LINES**

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The rising incidence of hepatocellular carcinoma (HCC) in western countries, in combination with the poor prognosis offered by present-day treatment modalities, necessitates novel therapies. Oncolytic herpes simplex type-1 viruses (HSV-1) are replication-competent, attenuated viruses that selectively replicate within cancer cells and have been shown to be effective in the treatment of a wide variety of experimental human malignancies. We sought to investigate the

potential use of an oncolytic herpes virus in the treatment of primary hepatocellular carcinoma. All known commercially available sixteen human HCC cell lines from western and eastern origin were studied. Twelve of the sixteen cell lines are positive for hepatitis Bx protein. G207 is an attenuated, replication-competent, second-generation oncolytic herpes simplex virus genetically engineered to selectively replicate within cancer cells and is currently in clinical trials. All HCC cell lines were infected with G207 at multiplicities of infection (MOI) of 0.01, 0.1, and 1. Lactate dehydrogenase cytotoxicity assay was used to determine cell line viral sensitivity to G207. Further, cell lines were examined for their ability to support viral replication in vitro via viral plaque assay. By day 7, three of four cell lines of western origin (Hep3B, PLC5, and HepG2) were highly sensitive to G207 viral oncolysis ( $95 \pm 3\%$ ,  $P < 0.01$ ) at an MOI of 1. Eight of twelve cell lines of Asian origin (SNU-182, SNU-387, SNU-886, SNU-878, SNU-368, SNU-449, SNU-739, and SNU-761) demonstrated moderate-to-high sensitivity to viral oncolysis ( $65 \pm 21\%$ ,  $P < 0.01$ ) at an MOI of 1. In the highly sensitive cell line Hep3B, there is a 2500-fold increase in viral titer even when infected at an MOI of 0.01 ( $P < 0.01$ ). Human hepatocellular carcinoma cell lines are effectively lysed and support viral replication of the oncolytic herpes virus G207 at a clinically achievable infective dose. Our data suggest that oncolytic HSV therapy may have a role in the future treatment of hepatocellular carcinoma.

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**LESS THAN ONE-THIRD U.K. HEPATOMA (HCC) PATIENTS PRESENT WITH POTENTIALLY RESECTABLE DISEASE, AND DIAGNOSTIC BIOPSY COMPROMISES LONG-TERM SURVIVAL FOR THOSE WITH RESECTABLE TUMORS**

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HCC accounts for 90% of all primary liver cancers, 80% arising against a background of chronic liver disease (usually cirrhosis); 90% of HCC patients have elevated serum alpha-fetoprotein (AFP). Non-specialist centres biopsy liver lesions in high risk patients to establish a diagnosis. The aims of this study were to 1) assess the percent of UK patients presenting with incurable disease and 2) examine the impact of preoperative biopsy on survival in patients with resectable HCC. We conducted a retrospective analysis of a single cohort of 72 HCC patients presenting to a single tertiary center. Patients were considered unresectable because of multifocal disease, nonresectable tumor, Childs grade B and C cirrhosis, distant metastases, unfit for or declined surgery. In patients undergoing curative treatment (hepatectomy, RFA, cryosurgery and transplant) preoperative biopsy was noted. Mean age was 64 (41-85) years. Twenty-seven underwent potentially curative treatment. Of the 45 unresectable patients, 15 received chemotherapy  $\pm$  chemo-embolization, 30 received best supportive care. Reasons for unresectability: multifocal disease confined to the liver: 32, 3 presented with spontaneous HCC rupture and peritoneal tumor spillage, 1 was unfit for surgery because of poor ASA status, 7 had more than 1 reason. In 2 patients R0 resection was not possible because of vascular invasion. Of 27 patients (all with elevated AFP) considered potentially curable, 14 underwent preoperative biopsy. Survival of patients undergoing potentially curative treatment with or without preoperative biopsy is as follows (Table 1). Unlike most Far East series, the majority of HCC cases in our practice are idiopathic in etiology. Although screening programmes exist for patients at high risk of developing HCC, most tumors are unresectable at presentation



for reasons other than technical inability to achieve R0 resection. Preoperative diagnostic biopsy significantly compromises the survival of the small number (<33%) of patients who are considered potentially curable. We strongly recommend that suspected HCC should not be biopsied before referral to specialist center.

**Table 1.**

| Survival | No Biopsy % | Biopsy % |
|----------|-------------|----------|
| 1 year   | 85          | 65       |
| 2 years  | 82          | 57*      |
| 3 years  | 78          | 41*      |
| 4 years  | 76          | 27*      |
| 5 years  | 71          | 23*      |

\* $P < 0.05$ .

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### PRIMARY MYXOID LEIOMYOSARCOMA OF THE LIVER BY SURGICAL TREATMENT IN ADULT: REPORT OF A CASE

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An 83-year-old woman was admitted because of right hypochondralgia. Close examination revealed giant liver tumor mainly in the right lobe composed of solid and cystic lesion. At first liver metastasis of rectal carcinoma was suspected by her past history. However, cytology and needle biopsy did not show malignant findings. The size of the tumor increased and tumor resection was performed. Microscopic findings revealed that the tumor was leiomyosarcoma mainly composed of myxomatous stroma. This is the third case of myxoid type of primary hepatic leiomyosarcoma and we experienced the first surgical treatment of hepatic myxoid leiomyosarcoma on English literature.

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### SMALL HEPATOCELLULAR CARCINOMA: DIAGNOSIS, SURGICAL OUTCOME, AND PROGNOSTIC FACTORS CORRELATED WITH POSTOPERATIVE SURVIVAL

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Early detection and resection of hepatocellular carcinoma (HCC) are key measures to prolong survival of patients. However, these patients often have a risk of tumor recurrence or death from liver dysfunction. Therefore it is important to determine which clinicopathologic factors are related to the long-term prognosis after resection of small HCC. This study was designed to summarize the experience of diagnosis and surgical resection for small HCC, analyze the prognostic factors affecting postoperative survival in patients with small HCC. 105 patients undergoing resection for small HCC between 1986 and 2003 were followed up for more than half a year and reviewed retrospectively. Diagnostic value of preoperative image examinations was evaluated. Nine clinicopathologic factors: preoperative  $\alpha$ -fetoprotein (AFP)

level, liver cirrhosis, Child-Paugh score, tumor size (>2 cm vs.  $\leq$ 2 cm) and number (single vs. multiple), capsula formation, portal vein tumor thrombi (PVTT), Edmondson tumor grade and surgical margin, correlated with survival were analyzed by log-rank and Cox regression tests. The overall cumulative 1-, 3-, 5-, 7-, and 10-year survival rate was 86.5%, 70.3%, 55.2%, 51.8%, and 36.3%, respectively. The median overall survival was 113 months. Up to the time of follow-up, 36 patients had intrahepatic recurrence, 2 distant metastases postoperatively and 34 died. The causes leading these patients to death were hemorrhage from esophagogastric varices in 4, liver failure in 1, distant metastases in 2, intrahepatic recurrences or metastases in others. Twelve patients of the recurrent HCC underwent repeated tumor resection, of which, one died of hemorrhage from esophagogastric varices on 2 weeks postoperatively, the cumulative 1-, 3-, and 5-year survival rate of other 11 patients was 78.7%, 45%, and 33.8%, respectively, and median overall survival 31 months after the re-operation. Kaplan-Meier and multivariate Cox regression tests indicated that Child-Paugh score B and C, tumor more than 2 cm in diameter, PVTT and multiple lesions (including satellitic lesions) were adverse factors affecting postoperative survival. Limited hepatectomy with a margin width of at least 1 cm is an appropriate surgical approach. Arverse preoperative Child-Paugh score and intrahepatic recurrences postoperatively are main factors resulting in death of patients with small HCC.

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### A B16 MELANOMA CELL LINE THAT EXCLUSIVELY METASTASIZES TO THE LIVER

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B16 is a melanoma cell line derived from B6 mice. We have developed a hepatic metastasis model in which mice develop hepatic metastases after tumor challenge into the spleen. However, when we use a B16 F0 melanoma cell line in this model, the mice develop metastases throughout the body in addition to the liver. In this set of experiments, we have selected a substrain with a high affinity to metastasize to the liver. We are trying to define the differences between the substrain with high affinity to the liver and the parental strain. A murine model of tumor liver metastases was created by anesthetizing C57BL/6 mice, dividing their spleens into two hemispleens, injecting  $10^5$  B16 cells into one of the hemispleens, and then removing the injected hemispleen, leaving a remnant uncontaminated functional hemispleen. Two weeks later, the mice were sacrificed and tumor was harvested from their livers and cultured. These cells were then used to challenge mice again in the above hepatic metastasis model. Substrains were passaged up to 8 times in this fashion to yield B16 KY8 that had a high affinity to metastasize to the liver. Strain B16 KY8 (which had been previously passaged 8 times in the hepatic metastasis model) would only metastasize to the liver, and never into the peritoneal cavity or lungs, as the parental strain commonly did (Fig. 1). In a hepatocyte attachment assay, the B16 KY8 cells densely adhered to a monolayer of hepatocytes, whereas the parental B16 F0 strain did not. Flow cytometry analysis did not demonstrate differences in ICAM-1, VCAM-1, LECAM-1, PECAM-1, LFA-1, CXCR4, and CCR5 adhesion and chemokine receptor surface molecules. We have established a strain of B16 melanoma cells that has a high affinity to metastasize to the liver. This strain densely adheres to hepatocytes, whereas the parental strain does not. We have not detected differences in cell surface markers that are involved in the metastatic process. We will compare the two strains using gene chip technology focusing on genes involved in metastases.



**B16 F0**

**B16 KY8**

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**HISTOLOGIC CLASSIFICATION OF REMNANTS OF HEPATIC METASTASES FROM COLORECTAL CANCER FOLLOWING CHEMOTHERAPY**

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Accepted management for colorectal cancer (CRC) involves resection of the primary tumor followed by adjuvant therapy. Debate continues over the ideal order of chemotherapy and hepatic metastatectomy. While chemotherapy is intended to minimize tumor bulk, information about local histologic change is lacking. We sought to determine if preoperative chemotherapy aimed at CRC liver metastases can result in complete pathologic response and replacement with scar tissue. The Hepatobiliary Database at the Royal Victoria Hospital, McGill University, was searched for patients with CRC liver metastases treated between December 2003 and September 2004. Forty-one patients were identified and their charts reviewed. Those who received chemotherapy prior to liver resection (oxaliplatin or irinotecan) were further evaluated. Resected liver specimens were re-examined by pathologists (SH, JJ, VM) and categorized according to histologic changes seen. Of 41 patients (mean age  $59 \pm 13$  years), 13 did not receive the preoperative chemotherapy protocol, 5 were unresectable, and 2 had no available specimen. The remaining twenty specimens were classified based on the proportion of viable tumor, dirty necrosis, mucin and fibrosis. Calcification and granuloma formation were graded (0 to 3). Forty-three tumor nodules were identified, giving an average number of 2.15 tumor foci per patient. Seventy percent were moderately differentiated and the average size was  $1.8 \pm 1.7$  cm. The mean composition of these nodules was dirty necrosis  $27.8 \pm 37.4\%$ , mucin  $17.0 \pm 34.0\%$  and fibrosis  $31.9 \pm 34.4\%$ , with viable

tumor only  $23.3 \pm 28.2\%$ . The average grades of calcification and granuloma were  $0.4 \pm 0.8$  and  $0.3 \pm 0.7$ , respectively. In some patients, lesions seen on imaging were not identified on pathologic review. One patient with four lesions on the preoperative CT-scan had none identified on pathology. In another, one focus of adenocarcinoma was found from 11 lesions seen on pretreatment imaging, along with multiple areas of mucin pooling. Oxaliplatin and irinotecan demonstrate benefit for CRC hepatic metastases and should be offered to all patients prior to liver resection. In some patients metastases are obliterated completely, but in others remnants of uncertain malignant potential (RUMP) remain. Further investigation is required to determine the natural history of these RUMP lesions, and the ability to predict the subtype of a given RUMP lesion from the histology of the primary tumor.

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**MANAGEMENT OF TYPE III AND IV MIRIZZI SYNDROME**

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Mirizzi syndrome, first described in 1948, is an uncommon complication of longstanding cholelithiasis. Many cases have been reported presenting earlier in the course of the disease as Mirizzi Type I\* (external compression of common bile duct without cholecystobiliary fistula) or Type II (with cholecystobiliary fistula involving less than one-third of the circumference of the common bile duct). However, little data exists regarding later presentation of the disease, described as Mirizzi Type III (erosion involving up to two-thirds of the circumference of the common bile duct) or IV (complete destruction of the entire wall of the common bile duct). We reviewed 1104 total cases

of open and laparoscopic cholecystectomies performed at a single university institute in the last six years. We report 3 cases of Type III Mirizzi syndrome and one case of Type IV, all occurring in the last two years. All patients were female with an average age of 70.3 at the time of surgery. All had a previous diagnosis of uncomplicated cholelithiasis, the earliest diagnosis made 27 months prior to the operation. All patients presented with obstructive jaundice and underwent an endoscopic retrograde cholangiopancreatogram (ERCP), which demonstrated impacted stones in the biliary system. Laparoscopic cholecystectomy was initially attempted, then converted to open with the realization of the extent of the disease and confirmation of Type III or IV Mirizzi syndrome. Treatment consisted of either hepaticojejunostomy or choledochojejunostomy. All Type III patients were discharged from the hospital in approximately one week with no major complications. The single Type IV patient remained in the hospital for two weeks with a small anastomotic leak and also required a second ERCP to release an impacted stone in the ampulla of Vater, which was causing ongoing pancreatitis. There have been no late complications. In cases such as these with later presentation and extensive involvement of the common bile duct, we adhere to the practice that Mirizzi syndrome Types III and IV should be treated with open exploration of the effected area with a bilioenteric anastomosis. \*Staging based on the "unifying classification" for Mirizzi syndrome published by A. Csendes et al. in *Br J Surg*, 1989.

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### LAPAROSCOPIC COMMON BILE DUCT EXPLORATION (LCBDE) FOR DIFFICULT STONES

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A retrospective analysis of LCBDE patients was done from 1998 to 2004. A total of 52 patients who underwent LCBDE were analyzed. The patients were divided into two groups: Group A, from 1998 to December 2001, and Group B, from January 2002 to present. In group A 18 patients underwent LCBDE. There were 3 conversions to the open procedure. One patient had a post-LCBDE retained stone and had "T" tube track extraction. All patients had latex "T" tubes placed in this period. Six patients had post "T" tube removal bile leakage, which settled on its own. Since January 2002 (group B) a new policy of taking out large stones (>1.5 cm) electively by LCBDE, placement of nasobiliary drain (NBD), and primary closure of duct was adapted. In this period 34 patients underwent LCBDE. All patients had their bile ducts cleared of stones. All but two patients had preoperative NBD placed. The CBD was primarily closed in these patients. Three patients underwent laparoscopic choledochoduodenostomy. The group B. had no conversions but one patient had hand-assisted choledochoduodenostomy (CD). One patient after CD had postoperative bile leak which settled down. One patient died of acute myocardial infarction on third postoperative day. The NBD helped by achieving a water-type closure of CBD. It was removed after 24-48 hours following NBDgram. The patients did not need a second ERCP for stent removal. It is our belief that elective LCBDE for difficult stones with preoperative NBD placement is a safe and effective management.

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### BOUVERET'S SYNDROME: A RARE COMPLICATION OF GALLSTONES

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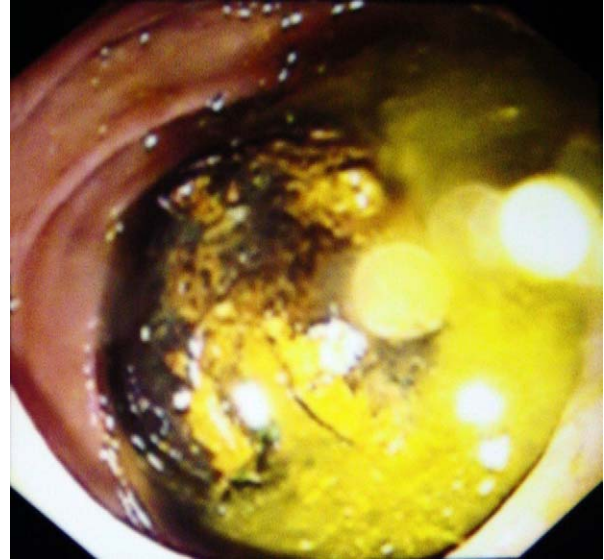


Fig. 1.

Bouveret's syndrome is an unusual presentation of duodenal obstruction caused by the passage of a large gallstone through a cholecystoduodenal fistula. The symptomatology of patients with Bouveret's syndrome can be nonspecific. Physical signs are consistent with those found in patients with gastric outlet obstruction. Plain radiography, abdominal ultrasound, and CT scan can be helpful, but endoscopy remains the mainstay of diagnosis and moreover, has added advantage of being therapeutic in some instances, especially in patients with high surgical risk. Surgical intervention, however, is generally the most accepted form of treatment. Controversy still exists between simple enterolithotomy and enterolithotomy in association with cholecystectomy and correction of the internal fistula as a one- or two-stage procedure. We reported the case of 72-year-old woman with Bouveret's syndrome who underwent a one-stage surgical management after unsuccessful endoscopic retrieval (Fig. 1).

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### NONALCOHOLIC FATTY GALLBLADDER DISEASE: THE INFLUENCE OF DIET

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The obesity epidemic has contributed to an increased prevalence of gallstones and a higher percentage of chronic acalculous cholecystitis. In addition, obesity is associated with Type II diabetes and hyperlipidemia. We have previously reported an inverse relationship between gallbladder contractility and serum glucose, insulin, cholesterol, and triglycerides in murine models of obesity. However, the relative role of insulin resistance and gallbladder fat infiltration in this phenomenon remains unclear. Therefore, we tested the hypothesis that gallbladder wall lipids are related to obesity and diet and are inversely correlated with gallbladder contractility. One hundred lean control and 36 obese leptin-deficient 8-week-old female mice were fed either a trace cholesterol, low fat chow diet or a 1.0% cholesterol (XOL), 15% butterfat diet for four weeks. After an overnight fast, a cholecystectomy was performed. Gallbladders were frozen, pooled into groups of 3-10, and subsequently analyzed for free fatty acids (FFA), phospholipids (PL),

total cholesterol (TC) and triglycerides (TG). Gallbladder wall lipids in  $\mu\text{g}/\text{mg}$  are as in Table 1. These data suggest that 1) obese mice have markedly increased gallbladder lipids and that a high cholesterol, high fat diet 2) increases gallbladder lipids in lean mice but 3) decreases gallbladder fatty acids, phospholipids and cholesterol in obese mice. Prior studies have documented similarly decreased gallbladder response to neurotransmitters in obese mice on a chow diet as well as lean and obese mice on a high cholesterol, high fat diet. Therefore, we conclude that leptin-deficient obesity and/or a high fat diet causes nonalcoholic fatty gallbladder disease (NAFGD) which is manifested by diminished gallbladder contractility.

**Table 1.**

| Strain | Lean Chow      | Lean XOL       | Obese Chow       | Obese XOL        |
|--------|----------------|----------------|------------------|------------------|
| FFA    | 18.5 $\pm$ 2.3 | 14.5 $\pm$ 2.1 | 76.9 $\pm$ 21.8* | 16.7 $\pm$ 1.5†  |
| PL     | 13.8 $\pm$ 2.7 | 10.5 $\pm$ 0.7 | 38.9 $\pm$ 5.5*  | 18.9 $\pm$ 2.4†§ |
| TC     | 3.0 $\pm$ 0.8* | 10.2 $\pm$ 0.3 | 9.8 $\pm$ 1.8    | 5.9 $\pm$ 1.0†   |
| TG     | 2.8 $\pm$ 0.8  | 4.3 $\pm$ 1.0  | 42.3 $\pm$ 16.5# | 40.5 $\pm$ 11.0# |

\* $P < 0.01$  vs Other Groups.  
 † $P < 0.05$  vs Lean XOL.  
 ‡ $P < 0.01$  vs Obese Chow.  
 § $P < 0.01$  vs Lean Chow and XOL.

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**PIOGLITAZONE DOES NOT IMPROVE GALLBLADDER MOTILITY IN LEPTIN-DEFICIENT OBESE DIABETIC MICE**

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Obesity and diabetes are major risk factors for the development of cholesterol gallstones. Pioglitazone (PGZ) is an oral PPAR $\gamma$  agonist that increases insulin sensitization in diabetes. PGZ has been shown to reduce hepatic fat in leptin-deficient (Lep<sup>ob</sup>) mice and improve NASH in humans. PGZ redistributes fat from central organs to the periphery, but a side effect is weight gain. Previous studies from our laboratory have shown that both leptin-deficient (Lep<sup>ob</sup>) and leptin-resistant (Lep<sup>dr</sup>) obese diabetic mice and leptin-normal nonobese diabetic (NOD) mice have decreased in vitro gallbladder motility compared to lean, nondiabetic mice. We have also shown that administration of leptin to leptin-deficient (Lep<sup>ob</sup>) and ciliary neurotrophic factor to leptin-resistant (Lep<sup>dr</sup>) mice reverses obesity and hyperglycemia and restores gallbladder motility. Therefore, we hypothesize that pioglitazone would cause weight gain, lower serum glucose, and restore gallbladder contractility in leptin-deficient (Lep<sup>ob</sup>) mice. 25 Lep<sup>ob</sup> 8-week-old mice were fed an AIN-93M (n = 13) or a 0.03% PGZ added AIN-93M diet (n = 12) for 4 weeks. Food intake was measured weekly. At 12 weeks, mice were weighed, underwent cholecystectomy, and glucose levels were measured. Intact gallbladders were mounted in a 3 ml muscle bath and stimulated with acetylcholine (ACh) and cholecystokinin (CCK). Data were analyzed by 2-way ANOVA and Student-Newman-Kuels t-tests. These data suggest that pioglitazone given to obese diabetic mice causes 1) significant weight gain, 2) no significant reduction in serum glucose, and 3) no improvement of gallbladder motility. Weight gain in the obese mice suggests an adequate dose of pioglitazone. However, failure to improve diabetes and/or a motility defect that is not related to gallbladder fat may explain why pioglitazone did not improve gallbladder function (Table 1).

**Table 1.**

| Group                   | Wt (g)      | Glucose (mg/dl) | ACh 10 <sup>-5</sup> M (N/cm <sup>2</sup> ) | CCK 10 <sup>-8</sup> M (N/cm <sup>2</sup> ) |
|-------------------------|-------------|-----------------|---|---|
| Lep <sup>ob</sup>       | 46 $\pm$ 0  | 407 $\pm$ 23    | .40 $\pm$ 0.07                              | 0.97 $\pm$ 0.14                             |
| Lep <sup>ob</sup> + PGZ | 52 $\pm$ 1* | 351 $\pm$ 37    | .29 $\pm$ 0.06                              | 0.78 $\pm$ 0.10                             |

\* $P < 0.01$  vs Lep<sup>ob</sup>.

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**TWO-STAGE VERSUS SINGLE STAGE MANAGEMENT OF CHOLELITHIASIS AND COMMON BILE DUCT STONES: A PROSPECTIVE, RANDOMIZED TRIAL**

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While laparoscopic cholecistectomy (LC) is widely accepted as the treatment of choice for symptomatic gallstones, the management of patients with associated common bile duct (CBD) stones is still controversial. Following magnetic resonance colangio-pancreatography (MRCP) confirmation of the presence of CBD stones and cholelithiasis, 39 patients were recruited to a prospective randomized clinical study. The patients were randomized to two groups. Group A (21 cases) had a preoperative endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES) followed by LC in the same hospital admission. Group B. (18 cases) had a one stage, rendezvous technique with simultaneous LC and ERCP facilitated by a guide wire passed down the cystic duct. The primary end point was hospital stay. Secondary end points included the rate of CBD clearance as well as morbidity and mortality rate. Hospital stay was significantly shorter in group B. than in group A: 9.6  $\pm$  2.9 days in group A vs 5.4  $\pm$  2.4 in group B ( $P < 0.0001$ ). The rate of CBD clearance after one ERCP was 90.4% (95% CI = 69.6-98.9) for group A and 100% (95% CI = 81.5-100) for group B. Morbidity rate was 4.7% in group A and 16.6% in group B. ( $P = \text{NS}$ , OR = 3.09). No deaths occurred in either group. The management of CBD stones is currently still under evaluation. The rendezvous technique provides an effective treatment because it offers the advantages of a greater patient's compliance and shorter postoperative hospitalisation, while the main disadvantage of this approach may be the prompt availability of an endoscopic team. Furthermore, an accurate standardization of the surgical technique is mandatory when this procedure is chosen: the positioning of the transcystic wire reduces the number of unsuccessful attempts in cannulation of the papilla, thus minimizing the risk of complications, and the positioning of an enterostate on the first jejunal loop eliminates the risk of conversion due to excessive bowel insufflation.

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**PREOPERATIVE ENDOSCOPIC SPHINCTEROTOMY AND LAPAROSCOPIC CHOLECYSTECTOMY FOR THE MANAGEMENT OF CHOLECYSTOCHOLEDOCHOLITHIASIS**

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Preoperative common bile duct clearance with endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (ES) is routinely performed in many centers where laparoscopic cholecystectomy (LC) is the procedure of choice for the treatment of patients with cholecystocholedocholithiasis. The purpose of this study was to evaluate the difficulty and efficacy of LC after ES with cholecystocholedocholithiasis. From January 2000 to March 2004, 291 patients with cholecystolithiasis were performed LC including 21 conversion cases to open laparotomy. Sixty-two patients with symptomatic cholecystocholedocholithiasis were performed LC after ES. Among them, 6 cases were converted into open laparotomy because of difficulty with dissection of cystic duct. The operation time was compared for an index of difficulty of operation. The LC after ES group needed

longer operation time compared with LC group. The cases after more than 3 weeks after ES had high conversion rate to open laparotomy. Appropriating clinical pathway to LC after ES group, the length of the postoperative stay was shortened from  $6.6 \pm 5.8$  days to  $3.2 \pm 6.3$  days. In conclusions, LC after ES has higher conversion rate into open laparotomy than conventional LC for cholecystolithiasis, but this rate decreases when operated on in early after common bile duct clearance with ES. The combination therapy of ES and LC will be recommended for this kind of patient as a minimally invasive procedure.

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### EVALUATION OF THE STRATEGY FOR TREATING ACUTE CHOLECYSTITIS—USEFULNESS OF EARLY LAPAROSCOPIC CHOLECYSTECTOMY

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In order to evaluate the strategy for treating acute cholecystitis and examine the possibility that laparoscopic cholecystectomy (LC) could be the treatment of first choice for acute cholecystitis, we made a comparative study by classifying the patients with acute cholecystitis into two groups: the emergency/early LC group and the elective LC group. From 955 patients who were treated in this department and underwent LC by September 2004, 103 patients who underwent LC as a surgical treatment for acute cholecystitis were selected as the subjects of the present study. They were classified into the emergency/early LC group and the elective LC group for intergroup study. According to the result of the assessment of patients' background, the incidence of preoperative complications in the elective LC group was significantly higher than that in the emergency/early LC group. The operation time was significantly shorter in the early LC group. The amount of bleeding was relatively small in the early LC group although no significant difference was recognized between the two groups. The hospitalization period was significantly longer in the elective LC group because of introduction of preoperative conservative therapy. The postoperative hospital stay was also significantly longer in the elective LC group. There was no significant difference in the incidence of postoperative complications between the two groups. All the patients who suffered postoperative complications proved to be convert cases. The patients, who tolerated LC well, experienced no postoperative complications. These results demonstrated that LC was a safe and effective surgical procedure for the early stage of acute cholecystitis characterized by congestion and edema.

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### PREOPERATIVE DRAINAGE OF MALIGNANT OBSTRUCTIVE JAUNDICE IS ASSOCIATED WITH INCREASED RATES OF BACTEROBILIA

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It is unclear whether there is an improvement in surgical outcome for patients who undergo preoperative ERCP. We therefore sought to establish if the use of preoperative ERCP for biliary decompression is associated with an alteration in bile bacteriology and highlight the

potential morbidity. A retrospective analysis was performed of 206 patients who had undergone HPB resection in our unit. The use of preoperative ERCP was established and a microbiological comparison made between those cases that underwent surgery alone and those who underwent preoperative ERCP with or without stent placement. Of the 206 patients 89 had ERCP prior to surgery and 117 had surgery only (Table 1). The incidence of bacteraemia and fungaemia was significantly higher in the ERCP with stent group by comparison to those who had only surgery ( $P < 0.001$ ). The most common organism cultured were coliforms and enterococcus, with an equal incidence of candida in those undergoing ERCP. ERCP for preoperative drainage of obstructed biliary systems is associated with both a high incidence of bile bacteraemia and fungal colonisation. ERCP should be reserved for those patients with cholangitis preoperatively and should not be used routinely until thorough staging has been completed.

**Table 1.** Bile Bacteriology After Surgery with or without Drainage

|                                 | Bile Bacteraemia | Fungal Colonization |
|---------------------------------|------------------|---------------------|
| Surgery alone (n = 117)         | 58 (50%)         | 9 (7.7%)            |
| ERCP + surgery (n = 35)         | 30 (86%)         | 0                   |
| ERCP + stent + surgery (n = 54) | 53 (98%)         | 36 (66.7%)          |

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### BILE DUCT INSTRUMENTATION PREDISPOSES TO BILIARY INFECTION AND ITS RELATED COMPLICATIONS BUT NOT MORTALITY

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We sought to analyze risk factors for bile colonization and to determine the relationship between bile duct instrumentation and positive intraoperative bile culture, morbidity and mortality rate in patients with obstructive jaundice. Controversy exists regarding the impact of preoperative factors in predicting accurately intraoperative bactibilia and positive intraoperative bile culture on postoperative morbidity and mortality rate after pancreaticobiliary surgery. Perioperative morbidity and mortality rate was evaluated in patients who presented with obstructive jaundice and underwent a pancreaticobiliary operation. Univariate and multivariate analyses were performed to determine risk factors for bactibilia; pre-, intra-, and post-operative factors to evaluate postoperative morbidity and mortality including infectious complications, leak rate, sepsis and death. A total of 220 patients were evaluated. One hundred thirteen patients (51.4%) had a positive intraoperative bile culture (IBC). One hundred-one patients (45.9%) developed one or more complications. Death occurred in 10 patients (4.5%). The overall infectious complications were significantly higher in patients with positive IBC ( $P = 0.03$ ) which was directly related to bile duct drainage (PBD) ( $P = .037$ ). The risk factors for bactibilia were age over 70 years ( $P = 0.007$ ), history of coronary artery disease ( $P = 0.006$ ), diagnosis of neoplasia ( $P = 0.01$ ), preoperative ALP > 100 IU/L ( $P = 0.038$ ), and preoperative PBD ( $P = 0.03$ ). A preoperative leukocyte count in excess of  $10 \times 10^9/L$  ( $WBC > 10$ ) also significantly contributed to wound infection ( $P = .018$ ). A preoperative leukocyte count in excess of  $12 \times 10^9/L$  ( $WBC > 12$ ) ( $P = 0.02$ ) and creatinine greater than 1.3 mg/100 ml ( $P = 0.03$ ) greatly increased the risk for pancreatic leak. Patients with a history of arrhythmia ( $P = 0.009$ ), a low preoperative albumin level  $\leq 30$  g/dL ( $P = 0.007$ ), and postoperative biliary leak ( $P = 0.003$ ) were more likely to develop postoperative sepsis.

Patients over 75 years of age ( $P = 0.001$ ) and with a low preoperative hemoglobin level  $\leq 10$  g/dL ( $P = 0.05$ ) and postoperative sepsis ( $P = 0.01$ ) were more likely to die. Preoperative bile duct instrumentation significantly increases the risk of bactibilia, which in turn increases the postoperative infection rate but not the mortality.

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### **SURGISIS-ASSISTED DELAYED REPAIR COMPLEX BILE DUCT INJURY AFTER LAPAROSCOPIC CHOLECYSTECTOMY**

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While laparoscopic cholecystectomy has successfully improved several patient outcome parameters; there has also been a marked increase in the incidence of complex and serious bile duct injuries. Herein, we present the case of a 74-year-old male who sustained a significant biliary injury subsequent to elective laparoscopic cholecystectomy. Transection of the immediate extrahepatic bile duct (at the hilar plate) inclusive of the posterior sectoral duct across the anterior system and up to, but not including the medial most wall of the left system occurred. Additionally, the right hepatic artery was clipped off. The adverse event was not recognized for 72 hours, after which laparotomy was performed and a T-tube was placed into the residual left system and distally into the distal CBD. Additionally, several penrose drains were placed and the patient transferred to our institution. Given the more than 1 week delay in therapy, immediate reconstruction was not an option; however conversion to controlled external biliary drainage was required. The initial operative management included intraoperative cholangiography and selective cannulation of the right posterior and anterior sectors with 8 french foley catheters for external drainage (Figure 1, right). The medial wall from where the left system entered the hilar plate was used to anastomose a C-shaped piece of 4-ply SURGISIS biomaterial forming a 360° tube to encase the multiple catheters and in order to facilitate return to the site in 6 months time for definitive repair. Interestingly, 3 months after our procedure the patient developed competent biliary drainage into the duodenum, radiographically appearing to flow through the SURGISIS channel. After 6 months, the patient underwent re-operation with partial resection of segments IVB and V followed by a high hepaticojejunostomy (Figure 1, left). At the time of his definitive biliary reconstruction it was noted that the SURGISIS material was completely incorporated. 1-year later the patient has normal LFTs and has returned to his pre-morbid quality of life. The case presented highlights the importance of timely referral to the experienced center for the repair of a

bile duct injury. Finally, this case represents the first report of the use of SURGISIS material as an adjunct in the treatment of a complex bile duct injury.

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### **CASE REPORT: AN UNUSUAL HEPATIC ARTERY COMPLICATION FOLLOWING A FOREIGN BODY INGESTION**

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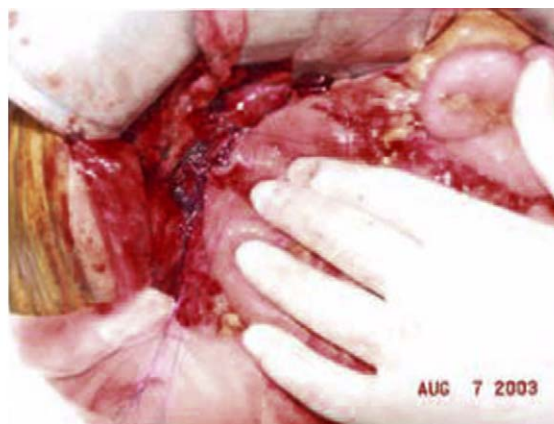
A 34-year-old man presented with repeated upper gastrointestinal (GI) bleeding after having an impacted toothbrush removed from duodenum by open surgery before. CT abdomen and hepatic angiogram revealed a pseudoaneurysm arising from the left hepatic artery and it connected to the left hepatic duct. Active contrast extravasation was noted. Bleeding was arrested by embolizing a segmental branch of the left hepatic artery.

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### **LAPAROSCOPIC BALLOON DILATATION AND BRUSH BIOPSY OF BENIGN COMMON BILE DUCT STRICTURE**

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Laparoscopic common bile duct (CBD) exploration is a well-established treatment option for patients with choledocholithiasis. We present a case where we use the laparoscopic approach for balloon dilatation of a benign CBD stricture. A 31-year-old male was referred to us with history of recurrent episodes of pancreatitis. Our work up included ultrasound, which showed a large gallbladder with sludge and a dilated CBD up to 1.5 cm. No evidence of a pancreatic mass was noted on a CT scan. A magnetic resonance cholangiopancreatography (MRCP) demonstrated a smooth distal CBD stricture. There was no evidence of CBD stones or pancreatic duct dilatation. Multiple attempts to dilate this stricture via endoscopic retrograde cholangiopancreatography (ERCP) approach were unsuccessful. Patient was taken to OR for a laparoscopic cholecystectomy. Transcystic access to the CBD was obtained. Intraoperative cholangiogram showed no evidence of choledocholithiasis and a smooth stricture in the mid to distal CBD. The common bile duct stricture was successively dilated using 4, 6, and



8 mm balloon angioplasty catheters with an excellent cholangiographic result. A brush biopsy was obtained at the end of the procedure and it showed no evidence of malignancy. There were no complications. The patient was discharged home the next day. The technique described combines laparoscopic cholecystectomy with laparoscopic balloon dilatation and brush biopsy using a transcystic approach. This allowed us to manage simultaneously the cholelithiasis and the benign CBD stricture without the morbidity of additional procedures. We are not aware of any description of this technique in surgical literature.

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### SURGICAL INDICATION FOR GALLBLADDER CANCER

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There are still controversies for adequate lymph node dissection for advanced gallbladder cancer. The aim of this study is to evaluate the long-term results in patients who had undergone various surgical procedures against gallbladder cancer from the standpoint of lymph node metastases. 144 patients who were diagnosed as gallbladder cancer from July 1975 to May 2001 at Tokyo Metropolitan Komagome Hospital were briefly reviewed. Lymph node dissection was carried out in every surgical procedure. Extended cholecystectomy was defined as cholecystectomy with liver resection of any volume. Modified extended cholecystectomy was defined as cholecystectomy without liver resection. 81 patients underwent surgery and the total number of extended cholecystectomy was 65. Dissected lymph nodes were examined according to the TNM classification (sixth edition, 2002) and number of positive nodes was counted. There were 22 males and 59 females, with the average age of 68. Extended cholecystectomy group included 8 cases of hepatopancreatoduodenectomies. Modified extended cholecystectomy group consist of 12 cholecystectomies and 4 pancreaticoduodenectomies. Average number of dissected lymph nodes were  $15.1 \pm 11.4$ . There were 36 node positive cases and the average positive nodes were  $2.9 \pm 2.5$ . Significant prognostic factors according to the Cox-hazard model were number of involved nodes (node negative group vs. 4 or more node positive group; HR 0.059,  $P < 0.0001$ , 95% CI: 0.024-0.143, 1 to 3 node positive group vs. 4 or more node positive group; HR 0.189,  $P = 0.0001$ , 95% CI: 0.080-0.445) and operative procedure (extended cholecystectomy group vs. modified extended cholecystectomy group; HR 0.507,  $P = 0.0366$ , 95% CI: 0.268-0.959). When the involved lymph nodes were within the regional nodes (pN1), survival curve was significantly better than cases with extensive node involvement (M1: LYM) ( $P = 0.0001$ ). However, even in pN1 group, when the number of involved nodes was 4 or more, the survival did not differ from M1: LYM group. Liver resection included 25 partial resections, 26 segmentectomies, and 14 lobectomies. Liver resection method did not influence the survival ( $P = 0.1216$ ); 79% of pathologically liver invasion positive cases showed node involvement ( $P = 0.0005$ ). Survival ratio did not differ among none, one or two involved organs, which may encourage radical resection. Regional lymph node dissection and liver resection can be concluded as a standard procedure for gallbladder cancer. Regional lymph node dissection is indispensable but sufficient, although the number of involved nodes is a prognostic factor.

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### BILE DUCT INJURIES: RESULTS OF 44 CASES IN A SINGLE UNIT

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The aim of this study was to evaluate how the moment of diagnosis, the severity of injury (classification), and the different kinds of repair affect outcome of the patients treated with iatrogenic bile duct injuries. There were 4077 elective cholecystectomies (2497 open and 1580 laparoscopic) performed in our service between March 1984 and August 2004. Forty-four patients sustained biliary tract injury, and 21 among them were referred from other hospitals. There were 39 women (88.6%) and 5 men (11.4%) with a mean age of 46.7 years. They were evaluated for the moment of the injury: during-operation, precocious (until 30th day after surgery), and later. The injuries were separated under Strasberg and Bismuth classification, and their surgical repair results were evaluated as well. The data of cholangiography results during operation time were collected. The injury rates in open and laparoscopic cholecystectomies were 0.6% and 0.5%, respectively ( $P = 0.861$ ). The injury diagnosis was established during operation in 28 patients, precocious in 7 and later in 9. There were 19 (43.2%) cholangiographic studies performed with 10.5% of missed injuries during operation ( $P = 0.290$ ). The rates of success of bile duct injury treatment were 67.9%, 14.3%, and 88.9% for the three different moments evaluated. The patients treated in the precocious period of time had worse outcome compared with those treated during and later after surgery ( $P = 0.027$  and 0.01). When the modalities of surgical repair were analyzed, the results about success rates showed single suture, 69.2%; suture with T-tube, 83.3%; duct-to-duct anastomosis, 33.3%; and biliary bypass, 63.2% ( $P = 0.686$ ). There were no statistical differences between outcomes of patients submitted to one- or two-layer biliary bypass and the severity of injury did not influence outcome. The mean follow-up period of time was 26.9 months (1-192 months). For patients with bile duct injuries treated in our institution: the moment of treatment had influenced the outcome; the modality of repair and the severity of injury did not change the outcome, and the cholangiography had no significance in the final results.

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### MANAGEMENT OF COMPLEX BILE DUCT INJURIES

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Laparoscopic cholecystectomy (LC) is the treatment of choice for gallbladder stones. This approach was associated with a higher incidence of biliary injuries (BDI). These injuries seem to be more complex. We considered complex injuries those 1) that involve the confluence; 2) with a previous failed repair; 3) associated with a vascular injury; or 4) with portal hypertension or secondary biliary cirrhosis. Between 1989 and 2003, 166 patients with BCI were treated in our Unit. 91 patients were female. The mean age of the patients was 46.2 years (range: 6-74). 21 BDIs were inflicted in our institution and 133 were referred from other institutions. Injuries were diagnosed during the surgical procedure in 39 cases (25.3%). In our own series of 5084 LCs, the incidence of BDI was 0.15% (8 patients) whereas in the open procedure it was 0.18%. 115 were produced during the open procedure and 51 occurred during LC. 107 patients (64.4%) were complex BDIs, 10 of which met more than one criterium. 54 involved the hepatic confluence, 38 were high stenoses with unsuccessful repair attempts, 7 had associated vascular injuries, and 18 had associated portal hypertension or secondary biliary cirrhosis. Percutaneous trans-hepatic biliary drainage (PTBD) was employed in 30 patients. Balloon dilatation was used in 12 patients and auto-expandable metallic prosthesis in 1 patient. Hepaticojejunostomy (HJ) as initial treatment was performed in 87 cases. HJ was also carried out for biliary stenosis

with previous repair failures in 38 patients. Hepatic resection was performed in seven patients, 5 right hepatectomies and 2 left hepatectomies. 18 patients were included in the liver transplantation (LT) waiting list, 12 were transplanted while 4 died waiting for an organ. The mean follow-up was 77.8 months (range: 4-168). The mortality rate for the whole series was 4.8% (8/166). 4 out of these 8 patients died in the waiting LT list. The surgical treatment success rate was 85%. The effectiveness for the treatment of primary stenosis was 93%. Hepatic resection had 100% success rate. The actuarial survival for LT at one year was 91.7%. Percutaneous dilatation of biliary stenosis had 58% success rate. Complex BDI should be treated in tertiary centers with HPB specialists. LT has to be considered for treatment of these complex lesions when no other therapeutic option is available.

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### **THE OUTCOME OF SURGERY FOR 97 CASES OF BILIARY ATRESIA: A SINGLE INSTITUTIONAL EXPERIENCE**

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Retrospective evaluation of the outcome for 97 patients with biliary atresia who underwent surgical treatment. Between June 1995 and June 2004, 97 cases of biliary atresia were treated in 47 females and 50 males. The mean age at surgery was 101 days for 37 cases done from June 1995 to June 2000 and 78 days for 60 cases done from July 2000 to June 2004, respectively. Hepatectomy was done for type I (5 cases). Hepatic portocholecystostomy was performed for type II (13 cases). For type III, Kasai operation was done in 53 cases, interposition jejunal loop with an intussusceptive anti-reflux valve for 16 cases, and hepatic portojejunostomy with valve for 10 cases. The mean age for type I was 111 days (range: 80-155 days); all are still alive, two for 7.5 years, two for 5 years, and one for 3.7 years. Type II was observed in 13 cases with a mean age of 78.58 days (range: 45-102 days); two of them were identical twins. The procedure was failed in four and converted to portoenterostomy, seven of them are alive, two for 4 years, two for 3 years, one for 2 years, and 2 for 1 year. The remaining 79 cases were type III with mean age of 76 days (range: 43-149 days). Thirteen patients underwent the operation below the age of 60 days, between age 61-90 days for 57 cases and above the age of 91 days for 27 cases. The overall survivors are 47 cases (48.45%), 21 of them are clinically jaundice free, hospital mortality was 31 cases, and 19 were lost in the follow-up. Five cases from the survivors received LRLT, one jaundice-free case because of hematemesis 5.5 years after Kasai operation and four due to recurrent attacks of cholangitis and liver failure. Close long-term care, follow-up, and elevation of the medical awareness of the family are essential to achieve good results especially in centers where liver transplantation has not started yet.

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### **IMPACT OF CONCOMITANT VASCULAR INJURIES, SPECIALITY OF SURGEON PERFORMING THE REPAIR, AND SUBSEQUENT PATIENT PSYCHOLOGICAL CONCERNS IN THE MANAGEMENT OF IATROGENIC BILE DUCT INJURIES**

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Of laparoscopic cholecystectomies, 0.3% of open and 0.8% continue to result in serious biliary injury (BI). While data suggest that the outcome

of repair is better in expert hands, little is known of the incidence and impact of associated vascular injuries (VI), nor the effect of BI on quality of life after seemingly successful repair. We conducted a retrospective study to address these issues. Case note review of 27 BI patients managed at a single center with an additional 17 medicolegal cases (all Strasburg grade E). VIs were detected following visceral angiography or documentation in the operative notes. 24 patients also completed The Hospital Anxiety and Depression Scale (HADS) and The Concerns Checklist. Median age: 47 (20-77) years; Median time to recognition of injury: 7 (0-730) days. Median duration of follow-up: 69 (8-168) months. BI occurred following laparoscopic cholecystectomy in 37, open cholecystectomy in 8 and right hemicolectomy in one patient. 17/44 had associated VI. Vessels involved: right hepatic artery (RHA) 10; common hepatic artery (CHA) 3; RHA with right branch of portal vein (PV) 2; PV injury 1; CHA plus PV 1. Six underwent immediate hepaticojejunostomy (HJ), while 38 had delayed primary/secondary HJ. Stricture development following immediate HJ: 1/4 (25%) without VI; 2/2 (100%) in the group with VI ( $P < 0.05$ ). Twenty-seven underwent repair by HPB surgeons and 17 by non HPB surgeons. Six (22%) strictures occurred following repair by HPB surgeons while 13 (77%) strictured when repaired by non HPB surgeons ( $P < 0.001$ ). The patients completing HADS and Concerns checklist reported an average 5 (0-11) concerns. Association between concerns number and psychological distress was not dependent on injury severity or repair type. Concerns about disabling effects of cholangitis and unresolved issues (referral delay, anger) were linked with depressive mood in 6. Strategies to reduce concerns included speedy referral to an HPB team; open access to HPB team; self-start protocol for treatment when cholangitis occurred. Imaging to exclude VI is necessary in the management of bile duct injury, since if detected, definitive surgery should be delayed to allow time for re-vascularisation of the biliary system. The complications of BI, even after seemingly successful repair, can have a significant psychological impact. Suitable strategies referred to above should be implemented early on to limit this negative effect. These outcomes, even in expert hands mandate early referral (as soon as BI is evident) to an HPB center.

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### **INTRAOPERATIVE BILE DUCT INJURY AND ITS MANAGEMENT**

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We introduced preoperative DIC-CT to evaluate an anatomy of bile duct, and intraoperative cholangiography (IOC) to avoid intraoperative bile duct injury. Intraoperative bile duct injury (IBDI) and its management were investigated. During recent two and half years, we performed laparoscopic cholecystectomy (LC) for 280 patients in our hospital. DIC-CT revealed anatomical anomaly on 15 patients of 280. IOC was performed completely on 96% patients. One patient out of 280 patients who underwent LC, encountered IBDI due to marked inflammation around the cystic duct, and she was treated with T-tube drainage under laparoscopic guidance and postoperative course was uneventful. IOC is still controversial; however, it is reported to be useful for intraoperative Examination of CBD stones, and also to be useful to avoid injury of bile duct. Routine IOC during LC including skeletonization of cystic duct and catheterization into cystic duct could improve skill of laparoscopic surgical procedures such as CBD exploration, colorectal surgery, and gastric surgery.



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**TREATMENT OF BILE DUCT INJURY DURING LAPAROSCOPIC AND OPEN CHOLECYSTECTOMY**

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Although laparoscopic cholecystectomy remains one of the more common surgical procedures performed, unrecognized and recognized bile duct injuries do occur. These injuries can be severe and lead to long-term disability if not recognized and treated appropriately. Likewise prompt recognition and active management can lead to improved morbidity and mortality. We retrospectively reviewed our experience of 80 patients referred to our institution sustaining biliary tree injuries during laparoscopic and open cholecystectomy between January 1994 and July 2004. From January 1994 to July 2004, 80 patients had common bile duct injuries evaluated at our institution. Sixty-nine (86.3%) were following laparoscopic cholecystectomy, while the remaining 11 (13.7) were during open cholecystectomy. Fifty-five (68.8%) of the patients were female and 25 (31.2%) were male. The average age of presenting patients was 48.2 years (range 16 to 78 years). The level of injury was evaluated and 45 (56.3%) patients were found to have a Bismuth I or II injury, while 35 (43.7%) were noted to have Bismuth II, IV, or V injuries. Four (5.0%) were found to have concomitant arterial injuries. The recognition of the injury did occur intraoperatively in 22 (27.5%) patients resulting in conversion to open procedures. A majority of patients had diagnosis of their injury by cholangiogram (56 or 70%), while 2 (2.5%) were diagnosed by MRI. Of the patients who did not have their injury discovered intraoperatively, the time from surgery to diagnosis of injury ranged between 1 day and 10 years. A majority (44 or 55%) of patients were referred to our facility had some form of repair ranging from hepaticojejunostomy to interventional radiology stenting, while the remaining 36 (45%) were without repair of their injury. Definitive surgical repair performed at our institution included 1 (1.2) right hepatic lobectomy, 1 (1.2) revision hepaticojejunostomy and stricturoplasty, 3 (3.8%) choledochojejunostomies, 3 (3.8%) Kasai procedures, 15 (18.7%) ERCPs with stent placement and 57 (71.3%) hepaticojejunostomies. The injuries that occur to the biliary tree during open and laparoscopic cholecystectomy are severe, but prompt recognition and definitive repair at an experienced facility can result in good outcomes.

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**HEPATOPANCREATODUODENECTOMY FOR ADVANCED BILE DUCT CANCER: REPORT OF 2 CASES**

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In bile duct cancer, the surgical indication for hepatopancreatoduodenectomy (HPD) is direct invasion to the duodenum or the presence of lymph node metastasis around the pancreas head. The prognosis even after HPD remains poor, so HPD has rarely been performed. Here, report 2 cases of HPD and discuss the outcome on prognosis. We present the case of a 53-year-old woman who presented with jaundice. She received percutaneous transhepatic biliary drainage after admission. Bile duct cancer with invasion to the duodenum and gallbladder was diagnosed using CT scan and MRI. Right lobectomy of the liver, pancreatoduodenectomy and lymph nodes dissection were performed. At 4 months after the operation, she died by local recurrence of bile duct cancer. The other case was also of a 53-year-old woman presenting with general fatigue, weight loss, and epigastralgia. After admission, hilar bile duct cancer was diagnosed. Moreover, lymph nodes swelling near the common hepatic artery and the proper hepatic artery were discovered on the CT scan. Pre-operative chemotherapy was administered consisting of CDDP and 5-FU for 2 months. Then

left lobectomy of the liver, pancreatoduodenectomy and lymph nodes dissection were performed. At 2 years to date after the operation, she is alive and free from tumor recurrence. The different outcomes suggest that HPD after chemotherapy may be a more effective treatment for advanced bile duct cancer patients.

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**CONCOMITANT ADENOSQUAMOUS CARCINOMA AND ADENOCARCINOMA OF THE COMMON BILE DUCT: A CASE REPORT**

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We describe a rare case of a concomitant adenosquamous carcinoma and an adenocarcinoma, both primary from the common bile duct. A 48-year-old male presented with a two months' history of jaundice, choloria, pruritus, weight loss (8 kg), and occasional acholia. At physical examination, significant jaundice was seen in a good performance status black man. There was no significant hepatomegaly or palpable abdominal masses. The tumor marker CA19.9 was 262 U/ml, the total bilirubin was 9.8 mg/dL, and the alkaline phosphatase was 2831 IU/L. The chest X-ray film was normal. Upper endoscopy revealed extrinsic compression of the duodenal bulb, with normal Vater papilla. The abdominal ultrasound revealed a 2.6-cm common bile duct, with intra and extra hepatic enlarged ducts. The CT scan showed a homogeneous liver, with a dilation of the whole biliary tree, including the common bile duct, though the obstructing lesion could not be identified. At celiotomy, a distended gallbladder, without stones, a normal sized liver, with cholestatic aspects, and two endurated nodules inside the common bile duct, with biliary tree enlargement distally. The biliary duct was free of disease in its insertion at the duodenum. There was no evidence of metastatic disease. The surgical option included resection of as much as possible common bile duct, including the gallbladder and the cystic duct, associated to hepatic hilum lymphadenectomy. All margins were free of disease at frozen sections. The reconstruction was made with a Roux-en-Y type hepatico-jejunostomy. The extrahepatic bile duct had two tumors: one, smaller, polypoid, with deep penetration into the wall, without invading the serosa, and its histopathology indicates a moderately differentiated adenocarcinoma. The second tumor was bigger and also a moderately differentiated adenocarcinoma of polypoid type, with poorly differentiated squamous metaplasia (adenosquamous carcinoma). This tumor is deeply invasive but confined to the bile duct. The patient remained asymptomatic for five months, when the CT scan showed an enlarged liver, with 11 nodules. The nodule fine needle aspiration was positive for metastatic disease. The patient presented a rapidly progressive worsening, dying 8 months after the surgery. A concomitant adenosquamous carcinoma with an adenocarcinoma has not been previously reported, to the best of our knowledge. We could experience the poor prognosis of this kind of lesion with this case.

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**MORBIDITY, SURVIVAL, AND MORTALITY IN PATIENTS SUBMITTED TO PANCREATODUODENECTOMY (PD) FOR VATER PAPILLA ADENOCARCINOMA**

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This study analyzed the survival, surgical morbidity, and mortality of the patients submitted to PD for papilla adenocarcinoma. Retrospective analysis of 29 patients submitted to PD due to papilla adenocarcinoma between 1995 and 2003 at INCA-Brazil. The statistical analysis used was the Fisher test and the Kaplan-Meier method. Fifteen men and 14 women, with mean age of 60 years old, had their records reviewed. The pathologic stage was I (n = 2), II (n = 5), III (n = 9), and IVa (n = 13). Twenty-one had a duct-to-mucosa pancreatojejunostomy anastomosis, with a mean operative time of 410 minutes, mean blood loss of 800 ml (21 patients required blood transfusion). The postoperative complications included 3 patients with late gastric emptying, one death, and two with pancreatic fistula. The mean hospital stay was 13 days, mean free disease interval of 29 months, with an overall survival period of 40 months (overall survival curve of 33% in 5 years). Our surgical results and overall survival in PD for papilla adenocarcinoma is comparable to the literature, though the advanced pathological staging in our experience.

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**AN ANALYSIS OF THE EXTENT OF HEPATECTOMY FOR ADENOCARCINOMA OF THE GALLBLADDER**

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The optimal extent of liver resection for adenocarcinoma of the gallbladder is unknown. We carried out a retrospective analysis of patients undergoing surgery for adenocarcinoma of the gallbladder and compared patients who underwent a major hepatectomy (MAJ, ≥lobe) to those who underwent lesser hepatic resections. From 5/90 through 4/02, 109 patients underwent resection. Sixty-three patients (61%) had T3/T4 tumors and 34 patients (33%) had lymph node metastases. At operation, the inflow pedicle was clinically involved in 21 patients (20%) mandating MAJ; an additional 15 patients underwent MAJ but did not have pedicle involvement. Neither inflow pedicle involvement nor the performance of MAJ was associated with advanced stage disease. There were 5 postoperative deaths, all of which occurred in the MAJ group (P = 0.006). Major postoperative morbidity was significantly higher in the MAJ group (Table 1). Actuarial 5-year survival for the whole group was 45%. T, N, and overall stage were significant predictors of survival. Survival was similar between patients with and without MAJ and between patients in whom a clinically involved inflow pedicle mandated MAJ (Table 1). Tumor proximity to the hepatic inflow pedicle mandating MAJ does not necessarily imply advanced stage disease. MAJ should be performed when necessary to clear all disease; however, when the inflow pedicle is not involved a more limited liver resection is preferred as this does not compromise survival and limits postoperative morbidity and mortality.

**Table 1.** Outcome With and Without Major Hepatectomy

|                            | n  | 5 Year Survival (%) | Major Morbidity (%) |
|----------------------------|----|---------------------|---------------------|
| Major hepatectomy          |    |                     |                     |
| Yes                        | 36 | 40                  | 41                  |
| No                         | 68 | 47 (P = 0.02)       | 19 (P = 0.009)      |
| Major hepatectomy mandated |    |                     |                     |
| Yes                        | 21 | 47                  | 48                  |
| No                         | 83 | 44 (P = 0.8)        | 21 (P = 0.05)       |

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**GALLBLADDER CANCER: A COHORT STUDY OF T2 PATIENTS**

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Gallbladder cancer (GC) is common in countries such as Chile. A majority of patients with a potentially curable disease are detected after the exam of the cholecystectomy specimen. Of these patients, those with a T2 (invasion restricted to the subserosal layer) are an especially group characterized by an intermediate prognosis. Since 1989 a prospective protocol of pathological diagnosis and treatment has been conducted by the main author. We analyze a prospective series of 139 patients, harboring a potentially resectable T2 GC. diagnosed after the exam of the cholecystectomy specimen. Significance of variables for survival were examined by the Kaplan-Meier method and log-rank test followed by a multivariate analysis using Cox's proportional hazard model for their potential relationship to risk of death. Of the patients, GC was suspected before the cholecystectomy in only 7 (5.03%) patients while in 16 (11.5%) was suspected during the operation. Majority of patients 120 (86%) underwent an open procedure. Among the patients 74 (53.2%) underwent reoperation with the aim of performing an extended cholecystectomy (EC). Of the patients who underwent reoperation, 51 (68.9%) underwent an EC. Lymph nodes metastasis were found in 10 (19.6%) while liver infiltration was found in 7 (13.7%) patients. Overall survival of all series was 51.8% while those who could be resected had a survival of 66.6%. Of the ten patients with lymph node compromise, only four are alive while three with hepatic compromise are alive. Among the patients who underwent EC, the following factors related to prognosis were studied by univariate analysis: a) poor differentiation of tumor (OR: 0.67, IC 0.23-1.79); b) unapparent type of tumor (OR: 2.17, IC 0.90-5.37); c) lymph node compromise (OR: 18.5, IC 2.36-209.04); d) liver infiltration (OR: 5.83, IC 0.77-46.0); and e) age older than 50 (OR: 0.78, IC 0.16-4.33). Finally in the Cox's proportional hazard model the following factors were studied: lymph node compromise (hazard ratio: 5.80, IC 1.52-22.06, P value: 0.010), liver infiltration (hazard ratio: 3.12, IC 0.77-12.60, P value: 0.110), unapparent type of tumor (hazard ratio: 1.24, IC 0.25-6.16, P value: 0.78). The feasibility of performing an EC in patients with GC allows them to obtain a good survival rate. The presence of lymph node compromise represents the main poor prognosis factor and some type of adjuvant therapy should be studied to improve the prognosis in this group of patients.

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**DETECTION OF MICROMETASTASIS IN BONE MARROW OF PATIENTS WITH GALLBLADDER CANCER**

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Gallbladder cancer is very common in Chile, being the leading cause of cancer deaths in women over 40 years. It seems to be a strong correlation between the appearance of cancer cells in blood and the occurrence of metastasis in gastrointestinal cancer. In this study, 38 bone marrow samples from patients with gallbladder carcinomas, 20 blood samples from healthy volunteers, and 10 frozen samples of gallbladder cancer were analyzed for the determination of MUC1, CK19, CK20 and CEA mRNA expression. Nested reverse transcriptase-polymerase chain reaction (nested RT-PCR) was used to analyze

mRNA expression. Of the 38 bone marrow samples from patients with gallbladder cancer, the expression of MUC1, CK19, CK20, and CEA, mRNA was 60.5% (23/38), 31.6% (12/38), 7.9% (3/38), and 7.9% (3/38), respectively. 63.5% (24/38) were positive for at least one marker. Ten gallbladder tumor tissues were all positive for CEA, CK19, and MUC1 mRNA and positive in 70% for CK20. 17 out of 20 samples from donors were positive with MUC1 and only one sample from donors was positive for both CK20 and CK19 mRNA. Our results indicate that the molecular detection of tumor cells in the bone marrow of patients with gallbladder carcinoma is feasible. This analysis could be useful to evaluate the prognosis and the selection of the treatment. Larger series with a longer follow-up should be studied.

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### TWENTY YEARS OF EXPERIENCE IN THE TREATMENT OF KLATSKIN TUMOR

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The purpose of this study was to evaluate the results of the treatment of hilar cholangiocarcinoma in our institution regarding to resective and palliative procedures, surgical morbidity, mortality, and follow-up. In a period of 20 years, 73 patients with extrahepatic biliary malignant obstruction were referred to our hospital for treatment. Forty-two patients with obstruction of the hepatic ducts confluence (Klatskin tumors) were studied retrospectively. The patients were separated under Bismuth classification and those with Bismuth I tumors were excluded. There were 19 men and 23 women with median age of 58.3 years. There were 22 (52.4%) Bismuth II, 3 (7.1%) Bismuth IIIA, 78 (16.7%) Bismuth IIIB, and 1 (10%) Bismuth IV, respectively. There were 9 local resections, with 4 (44.5%) positive margins at histopathological examination. There were 2 major resections (1 left hepatectomy and 1 parenchyma-preserving-hepatectomy ("Taj Mahal" procedure), both of them with negative surgical margins. Six patients (14.3%) were submitted to a peripheral biliary bypass (Couinaud-Soupault procedure) and 9 (21.4%) to a surgical stenting. Four patients (9.5%) were submitted to an endoscopic and percutaneous stenting procedures to relieve their jaundice. Twelve patients (28.6%) had no chances of treat their jaundice. No adjuvant therapy as radiotherapy or chemotherapy was done. The mortality in resective group was 9.1% and in the palliative group was 20%. The overall morbidity in the surgical patients was 45.8%. The survival time for the local resective group varied from 4 to 5 months. In this group, there are 3 patients alive with 4, 8, and 50 months of follow-up. The patients submitted to major resections were alive with 8 and 60 months of outcome with no evidence of tumor recurrence. The survival rate for patients with palliative treatment varied from 1 to 29 months with mean follow-up of 11.8 months. The positive surgical margins and lymph node metastasis are associated with poor prognosis. The hepatectomy has major probability to achieve radical treatment for hilar cholangiocarcinoma with better chances of long-term survival.

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### EPIDEMIOLOGY AND PROGNOSTIC FACTORS OF GALLBLADDER CANCER IN MÉXICO

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Gallbladder carcinoma is a rare neoplasm with a poor prognosis. At the time of diagnosis, only 10% of these tumors are candidates for

resection. We sought to analyze epidemiological and prognostic factors in a Mexican population. A retrospective review of the clinical files of patients with gallbladder carcinoma diagnosed and treated in two hospitals in Mexico between January 1989 and May 2004 was performed. Epidemiologic data, clinical presentation, forms of diagnosis and treatment were analyzed. One hundred fifty patients with diagnosis of gallbladder carcinoma were registered in this period in both institutions. One hundred thirty five (90%) patients were woman and 15 (10%) were men. The median age at the time of diagnosis was 56.5 years (range from 19 to 86 years). The symptoms were abdominal pain in 143 patients (96.6%), weight loss in 47 (31.3%), palpable mass in 41 (31.3%), jaundice in 37 (24.6%), nausea and vomiting in 16 (10.6%). Sixty-six (44%) patients had abdominal CT scan, and 38 (25%) had ultrasound. Six patients (4%) presented stage I of Nevin classification, 17 (11.3%) Nevin II, 31 (20.6%) Nevin III, 13 (8.6%) Nevin IV, 70 (46.6%) Nevin V and in 13 (8.6%) patients were not classified. Ninety-three (62%) had a previous operation out of our institutions and after cancer diagnosis were referred for specific treatment. Seventy-seven (44.6%) were operated in our institution of whom 12 (8%) had a palliative intent, 29 (19.3%) radical cholecistectomies with lymphadenectomy and 20 (13.3%) biopsies of the lesion only. Thirty-seven (24.6%) patients received adjuvant radiotherapy, ten (6.6%) patients received chemotherapy alone, nine (6%) received chemotherapy plus radiotherapy. The most common histology type was adenocarcinoma in 109 patients (75.6%). Global survival was 13.5 months (range from 6 days to 99 months), with a better survival for those patients with radical cholecistectomy with a mean survival of 27 months (range 1 to 99 months) and the mean survival for patients with palliative surgery was 4.8 months (range 6 days to 23 months). The actuarial 5-year survival rate of the patients according to the Nevin stage I, II, III, IV, and V was 100%, 60%, 45%, 17%, and 5%, respectively. Gallbladder cancer is a rare neoplasm with a bad prognosis. Radical resection is the better option for patients with stage II and III disease. For more advanced stages none of the treatments used in this study modified the natural history of the disease.

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### SUPPRESSION OF N-NITROSOBIS (2-OXOPROPYL)AMINE (BOP)-INDUCED BILIARY CARCINOGENESIS IN BILIOENTEROSTOMIZED HAMSTERS BY ETODOLAC, A SELECTIVE CYCLOOXYGENASE 2 INHIBITOR

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This study was designed to determine whether etodolac, a selective cyclooxygenase2 inhibitor, would prevent chemical induction of biliary carcinogenesis in bilioenterostomized hamsters. Syrian golden hamsters were subjected to choledochojejunostomy and then received subcutaneous injections of *N*-nitrosobis(2-oxopropyl)amine (BOP) every 2 weeks. The administration of BOP was started 4 week after surgery and continued up to 22 weeks, at a dose of 10 mg/kg body weight. The animals were simultaneously provided with an oral administration of etodolac 3 times per week at a dose of 10 mg/kg body weight in 10 ml/kg body weight of 0.5% methylcellulose solution (etodolac group; n = 18) for 18 weeks. The hamsters in the control group (n = 17) were provided with the same dose of methylcellulose without etodolac. At 22 weeks after surgery, the surviving hamsters were sacrificed and occurrence of neoplastic lesions in the biliary tree was histologically examined. The presence and degree of cholangitis and cell kinetic status of the biliary epithelium were also evaluated with special reference to the biliary carcinogenesis. The occurrence rates of adenoma were 88% and 61% of the hamsters in the control and

etodolac groups, respectively, and there was no significant difference in the incidence of adenoma between the two groups. Biliary carcinomas developed in 15 of 17 (88%) hamsters in control group, and only 6 of 18 (33%) in etodolac group ( $P < 0.05$ ). Severe cholangitis was evident in control hamsters, and the number and incidence of developing biliary carcinomas was well correlated with the degree of cholangitis. The cell kinetic study demonstrated that the average of proliferating cell nuclear antigen labeling index (PCNA LI) of the biliary epithelium was 9.67% and 5.14% in control and etodolac groups, respectively ( $P < 0.05$ ). Selective COX-2 inhibitor suppressed the occurrence of persistent cholangitis and acceleration of cell kinetic activity of the biliary epithelium after biliary reconstruction, resulting in a prevention of BOP-induced biliary carcinogenesis in hamsters.

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#### ENDOSCOPIC RESECTION OF AMPULLARY NEOPLASIA

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Ampullary neoplasia has a well-established malignant potential. Pancreaticoduodenectomy (Whipple) is standard therapy; however, some patients are not fit or refuse that procedure. This series reports our experience with endoscopic resection in such patients; 41 patients with ampullary neoplasia underwent endoscopic resection with snares. In one case a hook-shaped needle-knife was used after saline lift injections. Dual sphincterotomy and protective dual stenting were performed in all but one patient. Thermal ablation with Nd-YAG laser or argon plasma coagulator was utilized for incomplete resections. Further therapy, if needed, was performed at 1-2 mo until completion. Of 41 patients (mean age 66.5 y, r 31-90 y) 7 (mean age 43.3 y) had familial adenomatous polyposis; 8 (mean age 70.4 y) had adenocarcinoma (CA) or high-grade dysplasia (HGD) in the resection specimen and were reconsidered for surgery. Three of 8 with CA/HGD underwent Whipple. Five were treated with endoscopic debulking, stenting, and/or thermal ablation (2 with complete CA/HGD resection). An average of 4.5 endoscopic procedures were required for 24 patients diagnosed prior to 2000, or with CA/HGD, and/or with complications; 2.1 were required for the other 17. Fifteen of the 24 (62.5%) and only 3 of the 17 (17.6%) underwent thermal ablation ( $P \leq 0.0035$ ). One (without CA/HGD) had residual adenoma, treated to completion over 48 mo and remained free of disease 12 mo later. Three (without CA/HGD) had recurrent adenoma at mean follow-up of 40 mo (r 19-60 mo); one had a second recurrence. All were re-treated and no recurrence occurred at mean follow-up of 6.3 mo. Four of 41 developed complications. The very first patient underwent protective pancreatic but not biliary stenting and developed cholangitis, resolved after subsequent stenting. Two developed delayed bleeding requiring 2 and 4 transfusions. Hemostasis was attained with bipolar electrocautery. One developed duodenal perforation with abscess and was treated with surgical abscess evacuation and duodenal T-tube. (1) Endoscopic management of ampullary adenomas is safe and often effective therapy for poor surgical candidates, however further experience and longer follow-up are necessary. (2) Addition of thermal therapy after resection appears to be useful to ablate residual adenomatous tissue (3) Such therapy should not be used in place of Whipple resection in patients with CA/HGD who are fit for surgery. (4) Resection attains highly adequate histologic specimens. (5) It is important during therapy to preserve biliary and pancreatic drainage and to conduct careful endoscopic follow-up to detect recurrences.

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#### LIVER CYST OF ECHINOCOCCUS GRANULOSUS WITH RUPTURE INTO THE BILIARY TREE—SUCCESSFUL ENDOSCOPIC AND PHARMACEUTICAL TREATMENT

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Rupture of hepatic cysts into the biliary tree with biliary obstruction is a common complication of hepatic hydatid disease (HHD) occurring in 5-10% of patients. Established treatment options include surgical resection, percutaneous drainage, diagnostic and therapeutic ERCP and adjuvant medical therapy. In the literature, there are only a few case reports about successful treatment of complicated HHD by a combination of endoscopic techniques and pharmaceutical therapy. A 28-year-old Serbian man was admitted to our hospital with jaundice, fever, and right-sided abdominal pain. He had a 2-year history of uncomplicated HHD. Abnormal laboratory results included elevation of liver function tests and CRP. Abdominal ultrasound and CT scan showed a 5 × 4 cm hydatid liver cyst in the right lobe of the liver. Endosonography revealed amorph material obstructing the common bile duct (CBD). After ERCP with endoscopic sphincterotomy daughter cysts drained into the duodenum spontaneously. During ERCP no direct communication of the cyst with the biliary tree could be demonstrated. After extraction of cyst material from the CBD a nasobiliary tube was inserted into the intrahepatic bile duct next to the cyst. Examination of extracted material revealed characteristic hooklets of *Echinococcus granulosus*. For 14 days 15 ml of 23% hypertonic saline solution were installed into the cyst three times a day. The patient received antibiotics and albendazole 400 mg bid. Clinical symptoms and liver function tests improved. However, there was no significant shrinking of the hydatid cyst. Two months later, the patient was admitted once again with jaundice. ERCP was performed and cyst material was removed from the CBD. This time a direct communication between cyst and biliary tree could be demonstrated and a nasobiliary tube could be placed directly into the cyst cavity. The cyst was irrigated with 15 ml of 23% hypertonic saline solution three times a day for two weeks. The patient improved rapidly. One month later, a CT scan showed disappearance of the liver cyst with calcification. Nine months after the procedure the patient is completely asymptomatic. Our case shows that the combination of pharmaceutical therapy and ERCP with local lavage of the cyst with hypertonic saline solution via a nasobiliary tube is a safe and effective method for treatment of complicated HHD. However, placement of the nasobiliary tube directly into the cyst seems to be essential for the success of the method.

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#### METAL VS PLASTIC STENTS FOR MALIGNANT DISTAL COMMON BILE DUCT STENOSIS: A PROSPECTIVE, CONTROLLED, RANDOMIZED CLINICAL TRIAL

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Only about 20% of patients with pancreatic head cancer are suitable for curative resection. Palliation of jaundice by placement of a polyethylene (PE) stent with ERC technique is well established. Stent occlusion typically occurs in 3-5 months, while wide bore metal (ME) stents are reported to remain open twice as long. The initial higher cost of the ME-stent might thus be balanced by less need for reintervention. Our aim was to compare the patency of endoscopically inserted 10F plastic PE stents vs. covered steel stents (Wallstent, Boston Scientific Nordic AB) in a RCT, in patients with malignant distal bile duct

strictures not suitable for radical surgery. Endpoints were uneventful follow-up for 10 months, death or "failure," defined as proven occluded stent at reintervention. Inclusion was terminated at 100 patients. Currently 97 patients are evaluable, 49 in the PE-group and 48 ME-patients. 54 patients died without (proven) stent failure within 10 months, after a median of 2.6 months. 35 patients had hepatic or pulmonary metastasis at inclusion, with a median survival of 2.5 months. 21 PE-patients and 10 ME-patients ( $P < 0.05$ ) experienced proven stent failure, 8 more (6 PE, 2 ME) had clinical (no ERC) failure. Failure appeared after a median of 1.1 and 3.2 months, respectively. Overall median survival was 4.3 months, 40 patients did not survive 3 months. 9 patients (2 PE, 7 ME) survived 10 months without stent failure. This is the first RCT to compare plastic PE stents and covered steel stents. Our results indicate fewer patients with stent failure in the ME-group, and longer patency time in those ME-patients in which occlusion occurred. These results were significant despite a remarkably short overall survival.

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#### METALLIC STENT FOR TREATMENT OF DORSAL DUCT STRICTURE IN PANCREAS DIVISUM: REPORT OF A CASE

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We report the first case of a stent of the dorsal pancreatic duct with a metallic stent for treatment of a patient with symptomatic pancreas divisum and secondary chronic pancreatitis. A 72-year-old patient, with medical history of lymphoma, was referred for recurrent acute pancreatitis. In 1999, an endoscopic retrograde cholangio-pancreatography (ERCP) revealed a pancreas divisum with a short cephalic dorsal duct stricture and in 2001, a double endoscopic sphincterotomy of the major and minor papilla was done. An endoscopic ultrasound showed a moderate chronic pancreatitis with a predominant dorsal duct. In January 2003, after a new bout of acute pancreatitis, an ERCP showed a short persistent cephalic stricture of the dorsal duct. A plastic stent (10 fr  $\times$  5 cm) was successfully inserted through the minor papilla with adequate decompression of the dorsal duct. No subsequent procedure was needed until June 2003, when the patient had a new episode of acute pancreatitis. At the same time, a recurrent lymphoma of the right breast was diagnosed. Chemotherapy was re-instituted. ERCP showed a stable stricture of the dorsal duct. The pancreatic stent was changed for an uncovered metallic stent (8 mm  $\times$  4 cm) (Wallstent endoprosthesis endoscopic biliary with unistep plus delivery system; Boston Scientific, Natick - USA) allowing drainage of side pancreatic branches. We decided to use a metallic stent in the context of his recurrent lymphoma in order to avoid a radical surgery, delay the patient's treatment for his lymphoma and prevent any further acute pancreatitis. The patient has since then been symptom-free in regard to his pancreas divisum. He also had a complete response after chemotherapy for his lymphoma without any recurrence. In our patient's situation, there was a persistent stricture of the dorsal duct. Treatment of this stricture could not be achieved by sphincteroplasty alone and surgical drainage procedures were not indicated because of the absence of significant duct dilatation and the general condition of the patient. Thus, insertion of a wallstent for correction of the dorsal duct stricture was then considered a good option. In conclusion, the use of metallic stent for correction of a dorsal pancreatic duct stricture in the context of a pancreas divisum is an effective procedure. This treatment can be a valuable alternative to surgical procedures in selected cases.

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#### TREATMENT OF BILIARY STENOSIS AFTER LIVER TRANSPLANTATION USING WALLSTENTS

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Biliary stenosis are common after orthotopic liver transplantation (OLT), with a 15% reported incidence. Endoscopic treatment with dilatation and plastic stent is now a valuable therapeutic option. However, the use of metallic stents (Wallstents) to treat this condition is debated. The aim of this study was to report our experience using Wallstents to treat biliary stenosis after OLT. From January 1999 to July 2004, 279 patients underwent 306 whole-liver transplantations in our center. Among the 222 (73%) OLT performed with choledocholithotomy, 100 (45%) biliary stenosis were diagnosed and treated by endoscopic retrograde cholangio-pancreatography (ERCP) or percutaneous procedures. Primary hepaticojejunostomy (HJ) were excluded. Twenty-one patients (mean age  $57.0 \pm 5.6$  years) treated by a Wallstent were retrospectively studied. Stent was considered obstructed when insertion of a plastic or a second metallic stent was required or when surgical HJ was needed. The operative time, cold and warm ischemic time for the 21 studied cases were, respectively,  $225 \pm 60$ ,  $460 \pm 158$ , and  $40 \pm 9$  minutes. Mean blood losses were  $1420 \pm 1100$  (400-3500) ml. Donors mean age was  $45.5 \pm 16.2$  (17-70) years. Proximal and anastomotic stenosis were diagnosed in 4 and 17 patients and a Wallstent was placed by ERCP or percutaneous approach in 18 and 3 patients, respectively. A bile leak was identified in 4 (19%) patients. The mean interval between diagnosis and Wallstent insertion was  $179.7 \pm 292.8$  (0-1113) days. Total number of procedures for treatment was  $7.4 \pm 5.5$ , with  $3.7 \pm 3.9$  and  $2.7 \pm 3.4$  procedures before and after Wallstent insertion. The mean duration of patency was  $10.8 \pm 7.8$  (0.9-25.1) months with 12, 18, and 24 month-patency rates of 64%, 51%, and 26%, respectively, after a mean follow-up of  $37.8 \pm 17.2$  months. An HJ was performed in 5 (24%) patients and two (10%) patients underwent a second transplant for ischemic cholangitis and chronic rejection after a mean interval of  $782.1 \pm 638.2$  days after diagnosis. No graft was lost because of the use of a Wallstent. Overall complication rate was 29% including 3 pancreatitis, 2 cholangitis and one case of aeroportia. Treatment of post-transplant biliary stenosis using a Wallstent is a valuable option allowing to delay or to avoid surgery in 70% of patients. Endoscopic cleaning of the stent is simple with a low complication rate. Proximal stenosis can be treated this way in selected patients with major comorbidities. No technical problem was encountered during the removal of the stent when HJ was needed. The use of a temporary Wallstent in order to dilate post-transplant stenosis can also be considered and is actually under study.

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#### HEPATOBIILIARY AND PANCREATIC SURGICAL PUBLISHING IN TEN LEADING SURGICAL JOURNALS

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A rapidly growing knowledge base about recently developed diagnostic and therapeutic modalities in the management of hepatic-pancreatic-biliary (HPB) disease has emerged. With such advancement it is expected that the literature of the current day should reflect the emerging and evolving field of HPB surgery. We sought to review the surgical literature in the past 4 years to examine the predominance and scope of HPB topics in publication. Ten leading surgical journals over two

separate years (1998 and 2002) were identified for review. One reviewer using a combination of hand searching and MEDLINE searching using the PubMed search engine reviewed each journal. Data abstracted included: total number of separate publications in the given year, number of hepatobiliary or pancreatic publications, the type of publication, the category (hepatic, biliary, pancreatic), article focus (benign/malignant), and comment on surgical technique. Univariate comparisons were performed using the Fisher exact test or  $\chi^2$  test for dichotomous covariates, and the t test for continuous variables. A total of 807 articles were reviewed (376 in 1998, 431 in 2002). Fifty percent of journals reviewed showed an absolute increase in the number of articles; the largest increase for *Surgery* (14.8%; 2002: 64/431; 1998: 0/376). The *British Journal of Surgery* displayed the largest decrease in absolute HPB articles published (12.1%; 2002: 56/431; 1998: 94/376). An analysis of the nature of disease publication revealed that 90.9% (10/11) of articles published by the *Canadian Journal of Surgery* were for benign disease while 96.6% (28/29) of articles published by the *Annals of Surgical Oncology* were for malignant disease. There was a difference in the disease focus of each category published in the journals reviewed. Sixty-four percent (149/230) of the articles on hepatic disease focused on malignancy, as compared with 57.3% (122/213) on pancreatic disease and 29.1% (44/195) on biliary disease. A comment on surgical technique, though, was uniform across all categories (47.7%: 142/298 hepatic, 48.1%: 129/268 pancreas, 43.1%: 90/209 biliary). Articles dealing with HPB topics are published widely across all 10 journals reviewed. Although the absolute number of articles published increased over a 4-year period, there is significant variability in overall HPB publication and realm of focus between journals. Across all journals reviewed, there was a paucity of basic science articles, evidence-based reviews, and/or meta-analyses.

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### PREDICTORS OF FAILURE FOLLOWING PANCREATODUODENECTOMY FOR AMPULLARY CARCINOMA

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Although complete resection offers the only potential cure for ampullary carcinoma (AC), treatment failure (recurrence and metastasis) remains the major cause of death. We analyzed predictors of treatment failure in patients who underwent pancreaticoduodenectomy (PD) for ampullary carcinoma. We retrospectively reviewed all patients who underwent PD between August 1994 and August 2003 for ampullary carcinoma. Demographic (ie. age, gender) clinical (ie. symptoms, diagnostic tests), and pathologic data were collected using standardized forms.  $\chi^2$  analysis was used for categorical data and t-test was used for continuous variables. A significance level of 0.05 was used for both univariate and multivariate analysis. Forty-three patients (24 M) aged  $63.7 \pm 11.4$  years were followed for a mean of 2.1 years. Jaundice ( $n = 33$ ) and weight loss ( $n = 13$ ) were the most common presenting symptoms. Stage ( $P < 0.01$ ) and degree of differentiation ( $P < 0.05$ ) were significant predictors of failure by univariate analysis. However, only stage ( $P < 0.05$ ) was a significant predictor by multivariate analysis. Further analysis revealed that nodal status ( $P < 0.001$ ) but not tumor grade was a significant predictor of treatment failure. Neither demographic nor clinical variables were significant predictors. Tumor stage predicts failure after resection. Specifically, nodal status but not tumor grade is the significant variable that determines treatment failure following PD for ampullary carcinoma.

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### PERCUTANEOUS TRANSHEPATIC CHOLANGIODRAINAGE AS OPTIONAL THERAPY FOR SYMPTOMATIC BILIARY LEAKAGE WITHOUT BILIARY TRACT DILATION FOLLOWING UPPER ABDOMINAL SURGERY

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Symptomatic biliary leakage following upper abdominal surgery (e.g. pancreas surgery) usually requires surgical revision. Endoscopic biliary drainage is an optional therapy in cases with preserved gastroduodenal passage. If this is not possible (e.g., Whipple's operation) only relaparotomy or, alternatively, percutaneous transhepatic cholangiodrainage (PTCD) remains. In general, biliary tract dilation is compulsory for the feasibility of PTCD. In this study we observed a consecutive series of patients with symptomatic intraabdominal leakage of bile following upper abdominal surgery and without dilation of the biliary system on whom PTCD was performed. We evaluated if PTCD in this patient is a reasonable alternative to reoperation. During August 2000 and July 2004 a total of 18 patients (age 35-67) with symptomatic biliary leakage following surgery of the upper abdomen and without dilation of the biliary system underwent PTCD. Diagnosis leading to hospital admission and surgery were chronic pancreatitis ( $n = 6$ ), pancreatic cancer ( $n = 2$ ), ulcer perforations ( $n = 2$ ), oesophageal, gastric and duodenal cancer, choledocholithiasis and acute haemorrhagic necrotising pancreatitis ( $n = 1$  each). Operations were performed as follows: 6 duodenum-preserving pancreatic head resections, 2 total duodenosplenopancreatectomies, 2 partial gastric resections, one transhiatal oesophagectomy, one gastrectomy, one Whipple procedure, one subtotal splenopancreatectomy and one necrosectomy with partial resection of duodenum and jejunum. PTCD was feasible in 15 of 18 patients (83.3%) without complications. In 10 of these 15 patients (66.6%) biliary leakage was definitely controlled by PTCD, 5 had to be eventually reoperated due to persistence of biliary leakage. Three patients died perioperatively in the group of reoperated patients ( $n = 5$ ), whereas in the group of 10 patients treated successfully by PTCD 1 patient died of multiorgan failure. Mean postoperative days in hospital were  $56 \pm 28.4$  (range 21-113). Mean days with PTCD were  $37.6 \pm 35.6$  (range 3-147). PTCD in patients with biliary leakage and nondilated biliary tract following complex upper abdominal surgery is a reliable optional therapy with low incidence of complications. In our study this technique prevented a relaparotomy in 2 of 3 cases. Depending on patient's clinical condition PTCD should be considered as first-line therapy instead of immediate reoperation.

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### HEPATIC RESECTION VERSUS RADIOFREQUENCY ABLATION FOR SINGLE HEPATOCELLULAR CARCINOMAS MEASURING LESS THAN 5 CENTIMETERS. A MARKOV DECISION ANALYSIS MODEL

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Hepatocellular carcinoma (HCC) commonly arises in cirrhotic patients. Surgery is considered the only potential cure. However, observational studies suggested that radiofrequency ablation (RFA) may have survival benefit similar to surgery. Randomized controlled trials are necessary to confirm this. In the absence of randomized trials, Markov models are useful to assess the best therapeutic strategy.

A Markov model compared the quality of life expectancy for 65 years old individuals undergoing hepatic resection versus RFA for single 5 cm or smaller HCCs. Patients with negative margins were considered cured. Individuals with microscopic invasion had persistent disease and did not undergo further surgery. Patients undergoing RFA were cured if post treatment imaging were negative for viable HCC. Individuals with persistent tumor underwent a second ablation. If viable tumor was present after the second ablation, RFA failed. The probability of tumor seeding stayed constant for each RFA. Patients with tumor seeding transitioned to a state of tumor progression. Recurrent disease after hepatic resection or RFA was treated by RFA unless size or tumor locations were contraindications. When recurrent disease was not ablated, the patient experienced progression of HCC. Survival was measured in quality adjusted years. Quality of life (QOL) was 0.88 for compensated cirrhosis, 0.55 for HCC, 0.5 for the hospital stay after resection and 0.72 after RFA and 0.4 for all complications leading to death. The survival was simulated using the exponential function capturing the mortality rate associated with cirrhosis, age, HCC, and each therapeutic intervention. Hepatic resection was the best therapeutic option with 5.33 (SD +0.42) versus 3.91 (SD +0.38) quality-adjusted life years for RFA. Surgery was the best strategy for all the categories of patients stratified by age. One way sensitivity analysis showed that RFA was the preferred strategy if 1) perioperative mortality of hepatic resection was more than 30%, 2) radical resection was obtained less than 60% and 3) RFA was performed 60% or more for patients with recurrent disease after a previous ablation. Hepatic resection provided superior quality adjusted survival in comparison to RFA. RFA was a valid alternative to surgery if feasible at least in 60% of the patients with recurrent disease after previous ablation. The quality of life associated with both procedures did not influence the results of this model.

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#### CO<sub>2</sub>-3DCT CHOLANGIOGRAPHY: NEW FEASIBLE TECHNIQUE PROVIDING VIRTUAL CHOLANGIOSCOPY

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The authors investigated the feasibility of a new software system employing 3-dimensional (3D) virtual anatomic reconstruction using 3D computed tomography (3DCT) with carbon dioxide (CO<sub>2</sub>) gas as a negative contrast agent, and intraluminal virtual exploration for detection of preoperative visualization of the biliary anatomy. A total of 8 patients with pancreato-biliary disease (four patients with cholelithiasis, two with pancreatic malignancies, and one with gallbladder tumor, and one with hilar bile duct malignancy were suspected preoperatively) were included in this study. All patients demonstrated by cholangiography with iodinated contrast medium, CO<sub>2</sub> cholangiography using 3DCT was performed by manual injection of 5-20 ml CO<sub>2</sub> using through the endoscopic nasobiliary drainage or percutaneous approach. The data were downloaded to a workstation for interactive intraluminal navigation. The digital data from CO<sub>2</sub> 3DCT were incorporated into an original virtual reality software system to generate a 3D reconstruction. In five patients, CO<sub>2</sub> injection through the ENBD visualised cystic duct and intracholecystic mucosa without intervention into the gallbladder. In one patient 20 mm of protruding lesion of the gallbladder xantogranuloma was visualized. In one hilar bile duct cancer patient CO<sub>2</sub> visualised additional segments of the occluded bile duct. In 2 patients the poststenotic bile duct and pancreatic duct

were demonstrated with CO<sub>2</sub>. In two pancreatic tumor patients the stenosis of main pancreatic duct were demonstrated with CO<sub>2</sub>. Virtual CT cholangioscopy using CO<sub>2</sub>-3DCT revealed excellent and moderate endoluminal visualization to detect stenosis, obstruction, and detailed protruding lesion of the common bile duct and pancreatic duct. Our preliminary results indicate that CO<sub>2</sub>-3DCT cholangiography and cholangioscopy provided visualization of biliopancreatic duct disorder and detailed preoperative reconstruction of biliary anatomy. Newer software developments may further enhance its accuracy, so that virtual cholangioscopy might challenge or replace more invasive diagnostic measures in the near future.

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#### DEVELOPMENT OF A PLATFORM FOR ULTRASOUND IMAGE-GUIDED LIVER ABLATION AND RESECTION

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Only approximately 20% of metastatic and primary liver tumors are resectable with standard open surgery either because tumor location and burden prohibit safe resection or because the patient cannot tolerate a major operative procedure. Alternate therapeutic options have thus been developed either in the form of different techniques, such as laparoscopy, or different modalities, such as radiofrequency ablation. Critical to the success of both procedures is intraoperative imaging to identify tumor location and guide placement of the ablation probes. This imaging is currently performed with handheld ultrasound. The purpose of this work is to develop a platform for interactive image guidance during liver surgery that will assist the surgeon performing laparoscopic liver procedures. An optically tracked 7.5 MHz laparoscopic ultrasound probe was constructed and calibrated to a tracking accuracy of approximately 5 mm. The ultrasound beam may be swept over a target and individual two-dimensional images recorded to a computer at a rate of about 5 images per second. Using the tracking system record of the positions of the ultrasound beam as the images are acquired, the images are reconstructed into a three-dimensional volume similar to conventional computed tomography (CT). These three-dimensional volumes can be interactively visualized to reveal the target of interest, and because their actual positions in physical space are known, they can be used to direct other tracked instruments such as an ablation probe. Phantom studies using silicone polymer tumor targets were performed with the tracked ultrasound system. Several hundred images can be acquired and reconstructed into a volume within minutes. To assess the accuracy of the system, we simulated RFA probe placement by inserting a tracked needle into the center of the target and compared its position to the actual center as determined by a formal CT scan of the phantom. We have also used this system in the operating room to image 12 tumors in 7 patients. Intraoperative three-dimensional ultrasound volume reconstruction is feasible. We are continuing to develop interactive image guidance for minimally invasive liver procedures with the long-term goal of improving the effectiveness and safety of such procedures available to a larger set of patients. Image-guided technology merits further research as a means of assisting surgeons particularly during laparoscopy.

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#### SPLEEN PRESERVATION SURGERY WITH RADIOFREQUENCY ABLATION

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Traditionally the management of splenic trauma, tumors, and staging biopsies have necessitated total splenectomy. The significant mortality rate associated with overwhelming post splenectomy sepsis, however, has led to the current emphasis on splenic preservation in order to preserve immune function. Partial splenectomy remains technically challenging because of the rich blood supply and fragile parenchyma of the spleen. Radiofrequency ablation (RFA) has previously been reported for liver resection, we describe its application for splenic preservation surgery. Either partial splenectomy or local hemostasis was performed in 6 patients with tumors or trauma using RFA between 2001 and 2004 and the initial outcome reviewed. The procedure entails mobilisation of the spleen and either application of the RFA probe to the chosen resection margin to cause coagulative desiccation with subsequent division with a scalpel or application to splenic parenchyma adjacent to bleeding points. There were 3 men and 3 women of median age 49 years (range 29-74). There was one malignant neoplasm (ovarian adenocarcinoma metastasis), two benign neoplasms (angioma 1, infarctus lienis 1) and three patients with splenic trauma (road traffic accident {RTA} 2, iatrogenic 1). Three patients required a partial splenectomy (malignant neoplasm 1, benign neoplasm 1, RTA 1), one patient a wedge resection (benign neoplasm) and two patients local application of RFA. Two patients had concomitant liver procedure. Median length of ablation for resection was 15 min (range 4.5-25) and for local hemostasis 40.5 min (range 36-45). All patients had an uneventful recovery with a median length of stay of 7 days (range 4-14). Partial splenectomy should be considered the best surgical option in benign neoplasms and selected cases of trauma; its role in malignant neoplasms needs to be further evaluated. The use of RFA in conservative splenic surgery makes the procedure less technically difficult, allows nonanatomical resection and results in minimal blood loss from the resection margin.

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##### THE EFFECT OF MICROWAVE ABLATION ON WAVE PENETRATION THROUGH HEPATIC PARENCHYMA AND COLORECTAL METASTASES

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Use of ablative modalities for treatment of liver tumors is increasing. Ablative techniques are limited by the size of lesion that can be effectively treated. These limits are mainly due to increasing resistance of the target tissue to the energy applied as the ablation progresses (particularly radiofrequency ablation) and the consequent reduction in energy transfer from source to target tissue. Microwaves induce tissue destruction by heating cells within a field radiated from the applicator rather than via passage of a current or conduction used in alternative ablative modalities. The aim of this study was to investigate the relationship between the changes induced by microwave ablation on the penetration of microwaves through the tissue being treated. The relationship between the change in microwave resistance and the distance from the applicator was investigated. Normal bovine hepatic parenchyma and resected human hepatic colorectal metastases were investigated. Following calibration, an open ended, co-axial sensor was placed into the specimen and a microwave signal passed into it. The reflected signal was collected by the sensor and delivered to a vector network analyser where, using computer software, the microwave penetration was calculated. A microwave ablation was performed and the tissue sectioned. Once tissue temperature had equilibrated with room temperature, readings were taken using the sensor at increasing

distances from the ablation epicentre. Microwave penetration was expressed as 'skin depths' which defines the distance at which the wave loses 66% of its energy. Successful, highly accurate sensor calibration was obtained prior to each reading.

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##### ASYMPTOMATIC CAROLI'S DISEASE IN A SEPTUGENARIAN

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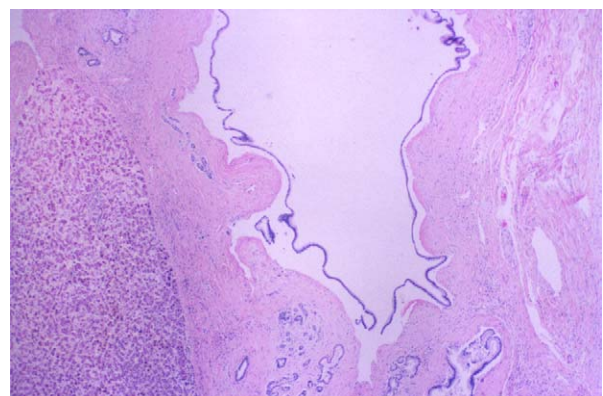
Caroli's disease is uncommon. It more often occurs with hepatic fibrosis constituting Caroli's syndrome. The natural history is variable as spontaneous regression has been reported. More commonly patients have been found to be symptomatic starting most often in early adulthood, less commonly in childhood. It is quite rare to have an asymptomatic course. We present the case of a septuagenarian who was discovered incidentally to have Caroli's disease. The patient was a 71-year-old male with end stage chronic obstructive pulmonary disease and recurrent episodes of hypercarbic respiratory failure and cor pulmonale. Ultrasonography to evaluate worsened bilateral lower extremity edema revealed incidental findings of a heterogeneous left lobe of the liver and cholelithiasis. His liver function tests were normal. Further evaluation with a computed tomography scan revealed a periportal hypodensity in the left lobe of the liver suggestive of biliary dilatation. He however continued to deteriorate and in keeping with his wishes comfort measures were instituted. He expired shortly thereafter. An autopsy was performed. Sections of the liver showed bile duct dilatation and lithiasis in the left lobe consistent with Caroli's disease (Fig. 1). Other autopsy findings were in keeping with his clinical diagnosis-panacinar emphysema and bronchopneumonia in his lungs, biventricular hypertrophy of his heart and cholelithiasis. Figure 1 shows cystically dilated intrahepatic bile ducts with periductal fibrosis.

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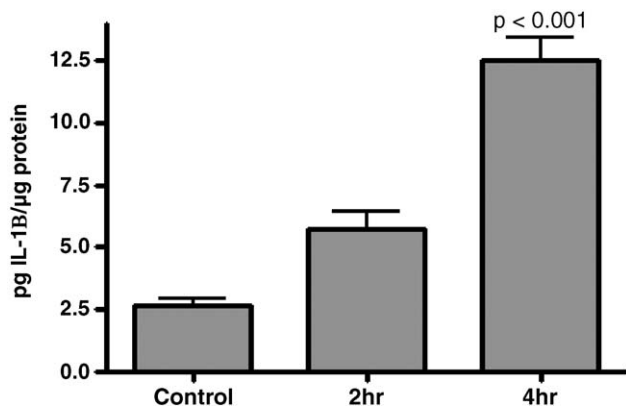
##### INTERLEUKIN-1 (IL-1) IS PROMINENT IN EARLY ACUTE LUNG INJURY CAUSED BY HEPATIC CRYOABLATION

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The etiology of acute pulmonary injury ("cryo-shock") resulting from hepatic cryoablation remains unknown. To further elucidate possible causative factors, gene expression profiling of pulmonary cytokines was performed in a murine model of large-volume hepatic cryoablation.







Midline laparotomy and 35% hepatic cryoablation with a commercial system utilizing a recirculating liquid nitrogen probe was performed in eight C57Bl/6 mice. Six unoperated mice served as controls. Lung tissue was removed four hours postablation. Total RNA was isolated by Trizol extraction, reverse transcribed,  $^{32}$ P-labelled, and hybridized to GEArray Q microarrays containing cDNA sequences of 96 genes mediating inflammatory response. Microarray data was analyzed with hierarchical clustering by Ward's method with complete linkage. Confirmatory cytokine quantification performed using cytokine-specific ELISA on serum and total lung protein. Unpaired t-tests and ANOVA used as appropriate; data depicted as mean  $\pm$  standard error. Inter-array data were standardized with  $\beta$ -actin and log normalized. Fifty-two genes demonstrated undetectable expression in half of either controls or experimental subjects and were thus excluded from further analysis. Using variation filtration and clustering techniques, a 35-gene signature was created which fully distinguished control mice from those with hepatic cryo-injury. The IL-1 family figured prominently in this signature, and expression of IL-1-related genes alone fully characterized all cryo-injured mice, prompting further investigation by ELISA. IL-1 $\beta$  was present in serum within two hours postcryoablation (0 at baseline vs.  $218.8 \pm 88.5$  pg/ml;  $P = 0.01$ ). Likewise, IL-1 $\beta$  levels in pulmonary tissue increased significantly following hepatic cryoablation (Fig. 1). Cryoablation of the liver produces a distinct proinflammatory pattern of gene expression in the lung. Pulmonary IL-1 expression at both the mRNA and protein level was shown to be significantly upregulated within four hours. Although likely multifactorial, acute lung injury following hepatic cryoablation may respond to targeted intervention directed against IL-1.

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#### A NOVEL MICROWAVE APPLICATOR PRODUCES LARGE VOLUME ABLATION IN LIVER

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We sought to characterize and optimize power and treatment duration on the extent of tissue coagulation in ex vivo and in vivo liver using a novel microwave applicator. Multiple tissue ablations were performed in ex vivo bovine liver ( $n = 128$ ) and in vivo swine liver ( $n = 40$ ) using a 5-mm diameter 2.45-GHz microwave applicator. In ex vivo trials, power was varied from 50 to 150 W in 25-W increments while treatment duration was varied from 2 to 20 minutes in 2-min increments. For in vivo trials, power was varied at 50, 100, and 150 W while treatment duration was varied from 2 to 20 minutes. Three-dimensional contour maps of the resultant short-axis and long-axis coagulation diameters were constructed to identify the optimal power

and duration necessary to achieve maximum coagulation. Multivariate analysis was performed to characterize the relationship between power and treatment duration using this high frequency microwave applicator and to compare ex vivo and in vivo results. In both ex vivo and in vivo liver, power and treatment duration were associated with coagulation ( $R^2 .78$ , all comparisons). For ex vivo tissues  $\leq 75$  W, coagulation and time were associated in sigmoidal fashion with nearly 100% of the maximum short coagulation diameter achieved in 8 minutes duration ( $4.8 \pm 0.4$  cm by  $6.3 \pm 0.3$  cm). However, for ex vivo  $\geq 100$  W, coagulation increased linearly, with the resultant coagulation measuring  $7.6 \pm 0.2$  cm by  $12.6 \pm 0.3$  cm for 150 W after 20 minutes duration. By contrast, for in vivo tissues, greater coagulation was achieved at shorter durations of energy application. For example, at 4 minutes,  $4.2 \pm 1.1$  cm and  $4.9 \pm 0.3$  cm were seen in vivo for the 100 and 150 Watt applicators, compared to  $3.7 \pm 0.3$  cm and  $4.1 \pm 0.1$  cm for ex vivo ( $P < 0.01$ , both comparisons). Nevertheless, maximum coagulation in vivo ( $4.2 \pm 0.3$ ,  $4.4 \pm 0.4$ , and  $6.0 \pm 0.3$  cm for 50, 100, and 150 W) was less than ex vivo as in vivo coagulation reached a plateau more rapidly than ex vivo (at 4-8 minutes). Large volumes of ablation can be achieved rapidly with this novel microwave applicator. Greater ablation size can be achieved with this device for short application times when used in vivo, suggesting possible differences in efficacy compared to RF ablation. Given these intriguing findings, further study of this device is warranted.

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#### SIMPLE MESOTHELIAL CYST OF THE RETROPERITONEUM WITH ELEVATED CA 125 AND CA 19-9

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Simple mesothelial cysts are benign abdominal masses, characterized by an inner surface of one or multiple layers of cubic mesothelial epithelium. We present a case of a rare mesothelial cyst located in retroperitoneum that expressed high Ca 19-9 and Ca 125. A 55-year-old man that presented abdominal and thoracic pain. Physical examination and laboratory tests were all normal, except for a marked elevation of Ca 125 and Ca 19-9 (538.5 U/ml and 315 U/L, respectively). Both abdominal sonography and CT scan suggested the presence of hepatic cyst (Fig. 1). It was close to the aorta and surrounded by the hepatic artery, therefore guided biopsy was ruled out. The cyst was surgically excised, noting that it was located in retroperitoneum, adjacent but without involving the hepatic left lobe and pancreatic head. Microscopic examination revealed an inner layer of mesothelial cells that contained fluid of inflammatory characteristics without neoplastic changes. The patient was discharged 5 days later and returned at 1 month for follow-up presenting no further complains. Retroperitoneal cysts can be considered benign tumors. Abdominal pain and distention are the most frequent manifestations. The diagnosis can usually be made with ultrasound or CT scan, but preoperative biopsy is useful to determine other causes or presence of malignancy. Total surgical excision is the treatment of choice in order to improve symptoms and avoid complications or recurrence. Ca 125 may raise as an expression of stimulated mesothelial cells, but there is no reported association with elevated Ca 19-9 titers. We highlight the rarity of its location, and the expression of tumor markers.

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**250****THERAPEUTIC APPLICATION OF MOLECULAR ADSORBENTS RECIRCULATING SYSTEM (MARS) IN CHRONIC SEVERE HEPATITIS PATIENTS COMPLICATED WITH MULTIORGAN FAILURE**

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The aim of this study is to evaluate the therapeutic effectiveness of Molecular Adsorbents Recirculating System (MARS) in patients of chronic severe hepatitis complicated with multiorgan failure. The present study randomized 82 patients of chronic severe hepatitis complicated with multiorgan failure into MARS therapy group of 40 patients and rests of 42 patients of the control group, respectively, 110 sessions of MARS treatments were performed with average of 2.75 sessions per patient, all were evaluated clinically by Model for End-stage Liver Diseases (MELD) and liver function, hemogram, ammonia lever, coagulopathy, BUN, and creatinine levels before and after treatments. MARS therapy resulted in remarkable improvement of prognosis assessment model of MELD ( $27.1 \pm 2.81$  to  $19.5 \pm 3.66$ ,  $P < 0.01$ ) and finally benefited the improved survival in the MARS group (19/40, 47.5% vs 10/42, 23.8% of control group,  $P < 0.05$ ), clinically presented in significant therapeutic effectiveness in hepatic encephalopathy or brain edema, renal dysfunction, obstinate ascites as well as reversal development of systematic inflammatory response syndrome (SIRS) and improvement of hemodynamic and respiratory function by selective elimination of accumulated metabolic toxins and management of electrolyte, fluid, and acid-base balance with nicer safe record. MARS therapy can be applied safely as preferable liver support for liver failure patients in therapeutic management for complications and multi organ failure.

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**251****LOCALLY ADVANCED HEPATIC GASTROINTESTINAL STROMAL TUMOR OF THE STOMACH**

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The standard treatment for gastrointestinal stromal tumors (GIST) has been surgical resection. Imatinib mesylate (Gleevec; ST1571) may be used as adjuvant therapy for tumor reduction, provided the tumor harbors a pathogenic mutation of the *c-Kit* (CD117) proto-oncogene. Herein, we report a case of massive tumor reduction following Gleevec therapy in a nonsurgical candidate with a locally advanced hepatic GIST of the stomach. The patient is an 84-year old African-American female who presented with syncope secondary to an upper gastrointestinal bleed. The past medical history was significant for postbypass coronary artery disease with an ejection fraction less than 20%, hypertension, hyperlipidemia, and mild dementia. After appropriate resuscitative measures, an upper endoscopy was performed that revealed a large proximal gastric mass along the cardia and lesser curvature. No further gastrointestinal bleeding was encountered. A computerized tomography (CT) scan of the abdomen demonstrated a 4-cm  $\times$  5-cm hypodense mass located along the proximal lesser curvature of the stomach that was inseparable from the left lateral hepatic sector. A CT-guided biopsy of the mass revealed a gastric GIST that was strongly positive for *c-Kit*. Surgical resection was not advised secondary to the substantial comorbidities and hence, a treatment plan was started that included single-agent Gleevec 400-mg po q day. A surveillance CT scan was performed four months status post initiation of treatment that revealed a 70% relative reduction in tumor size. At seven months status post initiation of treatment the tumor had decreased to 2.5  $\times$  1.5 cm, which corresponded to a 96% relative reduction and 99% overall reduction in size. The patient has not had recurrent gastrointestinal hemorrhage or symptoms related to the therapy. The aforementioned case scenario has outlined the remarkable independent effect of Gleevec on a GIST in a nonsurgical candidate. Although standard surgical treatment would include *en bloc* resection, inoperable patients with a *c-Kit* positive GIST may benefit from Gleevec therapy alone. Further data is necessary to ascertain the role of Gleevec in such instances.

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**252****RELATIONSHIP BETWEEN CYP2E1 GENE POLYMORPHISM AND ALCOHOLIC LIVER DISEASE**

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Genetic variations of ethanol-metabolizing enzymes can affect alcohol drinking behavior. The aim of this study was to investigate genetic polymorphism of CYP2E1 in alcoholic liver diseases and evaluation of association between this polymorphism and alcoholism. 59 patients were admitted to this study: 29 with alcoholic liver cirrhosis and 30 nondrinkers as a control group. Genotypes of CYP2E1 were identified by PCR and RFLP methods using PstI and RsaI as the restriction endonucleases. Genomic DNA was extracted from peripheral leukocytes. We investigate the frequency of c1 and c2 allele occurring in these two groups. In all nondrinkers only the c1 allele was observed. All patients of control group were homozygotic c1/c1. Frequency of c2 allele in alcohol liver cirrhosis group was 11%, and was higher than in the control group. Two alcohol liver cirrhotic patients were found homozygotic c2/c2, two were heterozygotic c1/c2. These results suggest that allele c2 may be a risk factor for the developing alcoholic liver diseases, and allele c1 can protect against alcoholism.

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**253****ALCOHOLIC HEPATITIS WITH LEUKEMOID REACTION AFTER SURGERY**

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Alcoholic hepatitis (AH) is a clinicopathological syndrome resulting from an excessive intake of alcohol. Leukemoid reactions (LRs) are characterized by a strikingly elevated granulocyte count over 40,000-50,000. Although a leukocytosis of 15-18,000/mm<sup>3</sup> is frequently seen in AH, LR is rare in this context. AH-associated LR is a sign of poor prognosis and has a high mortality. A 64-year-old male with a history of heavy alcohol intake underwent a right hemicolectomy for cecal carcinoma. Preoperative laboratory data was normal with the exception of an albumin of 2.1 g/dl. Liver biopsies, which were taken because of a nodular appearance, revealed micronodular cirrhosis, steatohepatitis, and Mallory bodies. Postoperatively, the patient developed a leukocytosis that progressively increased to 72.6/mm<sup>3</sup>. He also developed signs of impaired hepatic and renal function. Extensive workup failed to reveal a source of infection. A trial of IV antibiotics had no impact on the WBC. Methylprednisolone at a dose of 40 mg IV daily was started on postoperative day 9. The patient experienced a progressive decline in WBC, which reached 25.2 on postoperative day 14. However, he died on postoperative day 16. There have been 15 cases, including ours, of AH-associated LR. The pathophysiology of LR in AH is not clear. It is postulated that increased IL-18 levels in AH produce increased IL-1 $\beta$ , which along with increased IL-8, produce neutrophilia. In this setting, steroids may play a role in the treatment of LR by their reported inhibition of IL-1 $\beta$  transcription. LR in the presence of AH appears to carry an ominous prognosis. Among the reported cases, 12 did not receive steroids, and only one survived, constituting a mortality of 91%. Death was caused by hepatorenal syndrome in all cases. Of the three patients who received steroids, all of them showed an improvement in their WBC count, with only one death (our patient). To the best of our knowledge, this is the first reported patient with AH-associated LR in the postoperative period and also the first report of death despite successful treatment of the LR with steroids.

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#### COMMON PERONEAL NERVE PALSY: AN UNEXPECTED COMPLICATION OF LIVER SURGERY

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Common peroneal nerve palsy is a well-recognized complication following surgery in lithotomy position particularly colorectal and gynecological surgery. But it is quite rare complication after liver surgery which patients usually placed in supine position. There were 3 cases of common peroneal nerve palsy after liver surgery in the past 10 years, which 2 cases of liver transplantation and 1 case of extended right hepatectomy, 2 cases were bilateral and 1 case was unilateral. They were placed in supine position and the mean operative time was 8 hours. Patients complained symptom of foot drop within 1 week after operation. Electromyographic examinations showed evidences compatible with common peroneal nerve palsy. All of them were improved with conservative treatment within 6 months. Common peroneal nerve palsy could develop after liver surgery even in supine position. Injury to common peroneal nerve should be aware and concerned before and during operation. This complication could be managed conservatively with uneventful result.

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#### ESTROGEN ATTENUATES HEPATIC ISCHEMIA-REPERFUSION INJURY

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Tissue ischemia-reperfusion injury impacts many areas of surgical care with research directed at limiting or preventing reperfusion injury. Previous studies have shown that in mice, female gender resulted in increased survival versus male counterparts, possibly due to the effect of estrogen. We hypothesized that exogenous administration of estrogen to male mice would attenuate hepatic ischemia-reperfusion injury. Male C5BL/6 mice were divided into two groups. The control group received no estrogen and the experimental group received estrogen twenty-four hours prior to surgery. In both groups ischemia was accomplished by midline laparotomy with ligation of the vascular pedicle of the left lateral lobe of the liver for 45 minutes and followed by a reperfusion period of five hours. At that time 0.5 ml of blood was taken for measurement of AST and ALT as an indicator of hepatic dysfunction. We also directly visualized leukocyte dynamics in both control and experimental animals using intravital microscopy. Among the parameters of leukocyte dynamics, there was a significant difference in all measured parameters (rolling, salting [data not shown], and adhesion) between the two groups. AST, but not ALT, was significantly higher in the control group than the group receiving estrogen (265.3  $\pm$  72\* vs. 204  $\pm$  51\*). These data suggest that estrogen attenuates hepatic ischemia-reperfusion injury in mice possibly by contributing to inhibition of leukocyte activation and/or adhesion in the microcapillaries (Table 1).

**Table 1.** Neutrophil Dynamics

|                  | Rolling         | Adhesion (n)    | Adhesion (n/mm <sup>2</sup> ) |
|------------------|-----------------|-----------------|-------------------------------|
| Control (n = 7)  | 35.5 $\pm$ 3.7  | 5.5 $\pm$ 0.5   | 207 $\pm$ 16                  |
| Estrogen (n = 7) | 26.1 $\pm$ 2.1* | 2.7 $\pm$ 0.6** | 143 $\pm$ 25*                 |

\* $P < 0.05$ , \*\* $P < 0.01$ , Mean  $\pm$  SEM; statistical analysis with unpaired  $t$ -test;  $P < 0.05$  considered significant.

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#### APPLICATION OF MOLECULAR ADSORBENT RECIRCULATING SYSTEM (MARS) IN SEVERE VIRAL HEPATITIS PATIENTS AND THE PROGNOSIS ASSESSMENT BY MELD SCORE

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Liver failure of severe viral hepatitis is associated with multiple organ dysfunction and high short-term mortality. The aim of this trial is to evaluate the therapeutic effectiveness of MARS (Molecular Adsorbents Recirculation System) in patients with severe viral hepatitis, and to assess clinic outcome by using MELD (Mayo End-stage Liver Disease) prognosis model. Forty-nine single MARS treatments combined with standard medical treatment were performed on 27 patients with severe viral hepatitis from March 2002 to March 2004. They were evaluated biochemically, haemodynamically and clinically with MELD before and after the treatment, while the observed 3-month mortality was studied and compared to what MELD predicted. Data are given in mean  $\pm$  SD and are compared using Student's  $t$  test for related sample. MARS treatments result in significant improvement of multiple organ function including liver, renal, cerebral, coagulopathy, which proven by decreasing of bilirubin, INR, and creatinine significantly. Overall observed 3-month in hospital mortality is 51.8% (14/27), it was comparable to after-therapy MELD predicted mortality (MELD 27.4  $\pm$  10.7; predicted of 38.5% (range from 29% to 44%), which was better than the average predicted 3-month-mortality of 80.7% according to its before-therapy-MELD (32.37  $\pm$  11). The subgroup of 13 patients with MELD score between 20-29 most contributed the improvement of mortality statistically, however, the other two subgroups with

MELD score 30-39 and higher than 40 were observed of insignificant surgical improvement, respectively, which was supposed to be of scant scale (see Table 1). MARS can be regarded as a valid treatment option for said patients with safely effective improvement on multiple organ function and their in-hospital survival. MELD model is useful to assess and predict severity and mortality in patients with end stage liver disease, this findings should be confirmed by a larger number of patients in ongoing clinical studies (Table 1, breakdown of scoring MELD and the mortality analysis).

**Table 1.**

| MELD  | Case | Predicted Mortality | Observed Mortality | P Value |
|-------|------|---------------------|--------------------|---------|
| 10-19 | 2    | 27%                 | 0                  | <0.001  |
| 20-29 | 13   | 76%                 | 23%                | <0.01   |
| 30-39 | 5    | 83%                 | 80%                | >0.05   |
| ≥40   | 7    | 100%                | 100%               | >0.05   |
| Total | 27   | 80.7%               | 51.8%              | <0.001  |

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### INHIBITORY EFFECTS OF ANISODAMINE ON STORE-OPERATED CALCIUM CURRENTS INDUCED BY OXYGEN FREE RADICAL IN HUMAN HEPATOCYTE LINE HL-7702

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To evaluate the properties of store-operated  $Ca^{2+}$  currents ( $I_{SOC}$ ) of human hepatocyte line HL-7702, we studied the influences of oxygen free radical (OFR), one known hepatocyte injury ingredient, generated by hypoxanthine-xanthine oxidase (HX-OX) system, on  $I_{SOC}$  and the inhibitory effects of Anisodamine on OFR-induced  $I_{SOC}$  in HL-7702 hepatocytes. The  $I_{SOC}$  in the cultured HL-7702 hepatocytes were recorded by whole-cell patch-clamp technique. The HL-7702 hepatocytes were, respectively stimulated by  $10^{-4}$ ,  $10^{-3}$ ,  $10^{-2}$ ,  $10^{-1}$ , and 1.0 mM OFR or absence. 0.5, 1.0, and 1.5 mM Anisodamine were, respectively used after the stimulation with 0.1 mM OFR. OFR at the concentration of  $10^{-4}$  to 1.0 mM increased  $I_{SOC}$  in the HL-7702 hepatocytes in a concentration-dependent potentiation manner. At the holding potential of  $-100$  mV,  $10^{-4}$  mM OFR increased the peak amplitude of  $I_{SOC}$  from  $-341.65 \pm 48.99$  pA to  $-380.34 \pm 58.99$  pA, with the increasing rate of  $11.79 \pm 13.01\%$ ; 1.0 mM OFR from  $-341.65 \pm 48.99$  pA to  $-587.51 \pm 66.30$  pA, with the increasing rate of  $69.59 \pm 20.15\%$  ( $P < 0.0001$ ,  $n = 10$ ). There are significant differences among those groups besides the  $10^{-4}$  OFR group. Anisodamine could inhibit the  $I_{SOC}$ , after stimulation with 0.1 mM OFR, the peak amplitude of  $I_{SOC}$  in the HL-7702 hepatocytes was decreased from  $-577.04 \pm 93.69$  pA to  $-302.38 \pm 35.13$  pA by 1.5 mM Anisodamine at the holding potential of  $-100$  mV, with the inhibition rate of  $47.24 \pm 3.82\%$  ( $P < 0.0001$ ,  $n = 6$ ). There are significant differences among these groups, without affecting the reversal potential of  $I_{SOC}$  in all hepatocytes. It was concluded that the OFR generated by HX-OX system could obviously increase the store-operated  $Ca^{2+}$  currents of the HL-7702 hepatocytes in a dose-dependent potentiation way, and the increasing effects could be one of the mechanisms that OFR exerts injury effect on hepatocytes. Anisodamine significantly inhibited OFR-induced  $I_{SOC}$ , maybe play an important role of protecting hepatocytes from OFR injury.

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### EMERGENCY REPAIR OF COMPLICATED UMBILICAL HERNIA IN PATIENTS WITH LIVER CIRRHOSIS AND ASCITES: MESH OR NOT

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Repair of umbilical hernia (UH) in liver patients with ascites has received little attention in comparison to other problems of cirrhosis. The timing and methods of UH repair continues to be a matter of debate. To compare herniorrhaphy (primary suture) with hernioplasty (polypropylene mesh) in patients with a primary complicated UH in the setting of liver cirrhosis and ascites. The study was a randomized clinical trial included 40 consecutive adult cirrhotic patients, admitted to the Department of Emergency of the National Liver Institute with complicated UH. Patients with recurrent UH, malignant ascites or evident liver failure were excluded. Patients were randomly allocated into two groups: group A underwent direct suture repair whereas group B underwent hernioplasty with polypropylene mesh (on-lay technique). The population studied included 26 men and 14 women with a mean age at presentation 51 years. Patients presented with complicated UH in the form of incarceration (40%), obstruction (30%), strangulation (22.5%), and rupture (27.5%). The majority of patients ( $n = 36$ ) had surgery under general anaesthesia, while local anaesthesia was administered for only 4 cases. The in-hospital morbidity and mortality were reported. The mean postoperative follow-up was 24 months. Patients were followed for late mortality and hernia recurrence. There were no significant anaesthetic complications or surgical procedure-related deaths. The mean duration of surgery was greater for mesh than for suture repair (58.3 versus 40 min). The mean postoperative stay was longer for the mesh group (11.2 versus 9.2 days). Rates of early complications such as seroma, haematoma, wound infection, fever, and ascitic fluid leak were similar in the two groups. Postoperative hematemeses occurred in 2 (10%) patients of group B, while none of group A patients suffered this complication. Hospital mortality reported in 4 (10%) patients, distributed equally between the 2 groups. The hernia recurrence rate (11%) was similar after both methods of repair. Umbilical hernia exposes cirrhotic patients to potentially life-threatening complications such as rupture and strangulation. Emergency surgery should be considered cautiously and preferably in specialized centers for such decompensated patients. Mesh hernioplasty is not superior method concerning the mortality and hernia recurrence rates in such group of patients. The direct suture procedure has the advantage of shorter operative time and lower cost.

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### EXPERIMENTAL MODEL OF ACUTE PANCREATITIS IN SYRIAN GOLDEN HAMSTERS

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Severe acute pancreatitis (AP) continues to be a challenge for physicians according with the high mortality rates, no specific treatment, and difficulties to clarify the entire pathophysiology of the disease. Experimental models of AP are an important tool to establish new concepts in treatments, pathophysiology, and management. Then, an experimental model that resembles to human pancreas is desirable. Hamster pancreas is comparable to human pancreas phylogenetically, topographically, anatomically, and immunologically, in spite of this, there are no models of acute pancreatitis reported in these animals. The aim of the present study was to establish a model of acute pancreatitis injecting taurocholic acid into the pancreatic duct of Syrian Golden Hamsters. The animals were divided in 3 groups: Control (negative control  $n = 6$ ), Sham (laparotomy with duodenal manipulation  $n = 6$ ), and intraductal injection (ID  $n = 6$ ). Common bile duct was clamped and taurocholic acid 2.5% was injected into the pancreatic

duct. 24 hours later, animals were sacrificed to evaluate ascites, adhesions, sentinel loop, and gross appearance of the pancreas, liver, spleen, and lung. Blood sample was collected for biochemical study. Specimens of the pancreas, liver, spleen, and lung were sent for pathological study. Ascites was found in 50% of the cases, adhesions in 66.6%, and pulmonary changes, such as edema and local erythema in 16.6%. Concerning pancreas, edema was found in 83.3%, erythema in 83.3%, and necrosis in 50% of the cases. Increase in aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin, respectively, were observed. There were no changes in gamma-glutamyltranspeptidase, amylase, and glycemia levels. Histopathological examinations showed an extensive inflammatory process, edema, fat necrosis, and hemorrhagic areas in the pancreas, as well as, pulmonary edema. No histopathological changes were found in hepatic and splenic specimens. The model showed to be easily replicable and effective to produce AP. It could be used to the development of treatment and pathophysiology of AP.

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### PANCREATICOINTESTINAL FISTULA AFTER ENDOSCOPIC NASOPANCREATIC CYST DRAINAGE (ENPCD) IN PANCREATITIS

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Pseudocyst is a common complication of pancreatitis, may rupture into the surrounding organs. Fistulization of pancreatic pseudocysts into surrounding viscera is a well-known phenomenon and usually requires surgical management. We report here the pancreatic pseudocysts that developed spontaneous fistulas to the duodenum and jejunum, successfully treated nonoperatively with the management of endoscopic nasopancreatic cyst drainage (ENPCD). The patient was a 28-year-old male admitted with epigastric pain. After hospitalization, he was diagnosed as severe acute pancreatitis. An abdominal CT revealed that his pancreas was swollen contained pseudocysts and pancreatic fluid infiltration extended to the pelvic cavity, we treated with continuous arterial infusion therapy (CAI). After recovering from severe form, pancreatic pseudocysts developed at the maximum size of 13 × 9 cm, he complaint high fever with upper abdominal pain and distension. The patient was managed nonoperatively with ENPCD tube inserted through the papilla of Vater. The pancreatic cyst-duodenal and cyst-jejunal fistulas were radiologically evident. After 21 days from the procedure, the abdominal symptoms and signs subsided and resolution of the pseudocysts and cyst-intestinal fistulas were resolved, the tube was pulled out. For curing this disease, elimination of this potential toxic mediators was essential, our intensive IVR based therapy improved the patient's prognosis. ENPCD is an effective method for the drainage of pancreatic fluid caused resolution of the pseudocysts and cyst-intestinal fistulas, might have an important role in the treatment of complications with pancreatitis.

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### LYMPHOPLASMACYTIC SCLEROSING PANCREATITIS: A CASE REPORT AND REVIEW OF 240 CASES

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We describe a case of lymphoplasmacytic sclerosing pancreatitis (LPSP), initially thought to be pancreatic carcinoma, and review the

world literature on LPSP. A 24-year-old man with a past history of paratesticular rhabdomyosarcoma presented with obstructive jaundice, weight loss, and elevated liver function tests and amylase. Abdominal CT showed a 4-cm mass in the head of the pancreas with a double duct sign. On exploratory laparotomy, the mass was found to be densely adherent to the superior mesenteric and distal portal vein. A pancreaticoduodenectomy with a portal vein resection and reverse internal jugular vein reconstruction was performed. The patient recovered uneventfully. Pathologic analysis revealed diffuse fibrosis with a patchy inflammatory infiltrate of lymphocytes, plasma cells, and eosinophils consistent with LPSP. We reviewed the world literature on LPSP through a Medline search under the keywords "LPSP," "autoimmune pancreatitis," "autoimmune-related pancreatitis," "chronic sclerosing pancreatitis," and "duct-destructive pancreatitis." A review of literature showed that LPSP is characterized by a diffusely enlarged pancreas without a discrete mass on CT, a diffuse irregular narrowing of the main pancreatic duct on ERCP, and an elevated serum IgG4. We identified 240 cases of LPSP, with 118 cases (49.2%) from Japan or Korea, 89 cases (37.1%) from the United States, and 33 cases (13.3%) from Europe. 146 cases were treated with surgical resection alone, 76 cases with corticosteroids alone, 2 cases with surgical resection plus postoperative corticosteroids, and 9 cases were not reportedly treated. Treatment information was unavailable on 8 cases. Recurrence was reported in 14/104 (13.5%) cases treated with surgery alone and in 11/61 (18.0%) cases treated with corticosteroids alone. Autoimmune disease was reported in 26/201 (12.9%) cases, with Sjogren's and inflammatory bowel disease being reported in 11 and 7 cases, respectively. LPSP mimics pancreatic carcinoma clinically and radiographically. A review of literature shows subtle radiologic and serologic differences that favor the diagnosis of LPSP. Despite these differences, surgical resection is often undertaken due to diagnostic uncertainty. Reported rates of recurrence seem to be similar between surgical resection and corticosteroid therapy. A minority of LPSP cases are associated with Sjogren's and inflammatory bowel disease.

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### CYP2E1 GENE POLYMORPHISM AND ALCOHOLIC CHRONIC PANCREATITIS

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Alcohol abuse is being regarded as the main cause of chronic pancreatitis. The aim of this study was to investigate genetic polymorphism of CYP2E1 in alcoholic chronic pancreatitis and evaluation of relationship between this polymorphism and alcoholism. Thirty-nine patients were admitted to this study: 17 with alcoholic chronic pancreatitis and 22 nondrinkers as a control group. Genotypes of CYP2E1 were identified by PCR and RFLP methods using *PstI* and *RsaI* as the restriction endonucleases. Genomic DNA was extracted from peripheral leukocytes. We investigate the frequency of c1 and c2 allele occurring in these two groups. In all nondrinkers only the c1 allele was observed. All patients of control group were homozygotic c1/c1. Frequency of c2 allele in alcohol chronic pancreatitis group was 12%, and was higher than in the control group. In any patients were found homozygotic c2/c2, two of them were heterozygotic c1/c2. These results may suggest that allele c2 may be a risk factor for the developing alcoholic chronic pancreatitis.

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### EFFICACY OF FEEDING TUBE PLACEMENT DURING PANCREATICOUDODENECTOMY FOR CHRONIC PANCREATITIS

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The frequent finding of delayed gastric emptying after pancreaticoduodenectomy for chronic pancreatitis and the associated inability to tolerate nutrition by mouth has led to a common practice of prophylactic placement of enteral feeding tubes during the procedure. This is supposed to maximize enteral nutrition and avoid or minimize the use of parenteral nutrition in postoperative care. The purpose of this study is to examine the efficacy of feeding tubes placed during pancreatic head resection. The records of 78 consecutive patients who underwent pancreaticoduodenectomy for chronic pancreatitis were retrospectively reviewed and analyzed. Forty-nine patients received feeding tubes at time of operation in form of jejunostomy tube (42 patients) and/or gastrostomy tube (40 patients). This group was compared to 29 patients without feeding tube available for postoperative care. Both groups had a similar disease progress measured by degree of pancreatic fibrosis and preoperative nutritional status measured by serum albumin level, body mass index, and Subjective Global Assessment. Preoperative symptom of anorexia was more common in the feeding tube group (no tube 3% vs. tube 18%,  $P < 0.05$ ). During the time observed there was a trend towards not placing simultaneous feeding tubes (first 6 years 84% vs. last 2 years 33%). The overall complication rate after pancreaticoduodenectomy was 54% (no tube 41% vs. tube 61%,  $P < 0.05$ ). Placement of a feeding tube was associated with an increase in intra-abdominal morbidity from 34% to 57% ( $P < 0.03$ ). Delayed gastric emptying (7% vs. 22%), intra-abdominal abscess (10% vs. 16%), and anastomotic leak (7% vs. 16%) were more frequent in the feeding tube group but not significantly different in group comparison. None of the patients had a complication directly related to placement of the feeding tube. Eighty-eight percent of the placed feeding tubes were actually used. Despite of feeding tube placement 49% of patients required postoperative use of total parenteral nutrition compared to 55% of patients without feeding tube ( $P > 0.05$ ). Length of hospital stay and hospital readmission during the first postoperative year was not affected by placement of feeding tube. Simultaneous feeding tube placement along with pancreatic head resection for chronic pancreatitis can be performed safely but increases the risk for postoperative intra-abdominal complications. The majority of the placed tubes are being used in postoperative care but they do not prevent the use of total parenteral nutrition and do not shorten length of hospital stay.

**264****PANCREATICOPLURAL FISTULA: THE ROLE OF MAGNETIC RESONANCE CHOLANGIOPANCREATOGRAPHY IN DIAGNOSIS AND TREATMENT**

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Pancreaticopleural fistula is an uncommon entity and it results from pancreatic duct disruption or pancreatic pseudocyst extension into the pleural cavity. We present two cases of pancreaticopleural fistula in which the diagnosis was confirmed by magnetic resonance cholangiopancreatography (MRCP) and treatment accomplished by endoscopic transpapillary pancreatic duct stent placement and/or open surgery. A 34-year-old man with a 16-year history of alcohol intake developed a pancreatic pseudocyst and amylase-rich pleural effusion following acute pancreatitis. MRCP demonstrated a fistulous tract originating from the disrupted pancreatic duct in the mid-portion of the pancreas and extending to the mediastinum, being consistent with a diagnosis of pancreaticopleural fistula. Subsequently, endoscopic transpapillary implantation of a plastic stent into the main pancreatic duct was performed. Stent placement was effective, and the patient recovered without complications. A 48-year-old man with a long his-

tory of alcohol abuse and recurrent pleural effusion developed a mediastinal pseudocyst following acute pancreatitis. MRCP demonstrated a fistulous tract extending from the pancreas head to the mediastinal pseudocyst and a stenosis in the distal bile duct. After temporary pancreatic drainage with an endoscopic transpapillary pancreatic duct stent, longitudinal pancreaticojejunostomy, resection of the fistula, and choledochoduodenostomy were performed. The postoperative course was uneventful, and he has been well without recurrent pancreatic disease. Detection of a pancreaticopleural fistula by conventional radiologic techniques is often difficult. While diagnosis can be confirmed with ERP, it is invasive. MRCP is a reliable noninvasive tool for detecting a pancreaticopleural fistula and for planning the treatment strategy.

**265****FECAL ELASTASE-1 CONCENTRATION AS A SCREENING TOOL FOR CHRONICITY IN ACUTE PANCREATITIS ADMISSIONS**

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Acute and chronic pancreatitis are different pathological entities, although patients presenting with acute pain and elevated serum lipase may also have underlying chronic disease. Determining the presence of chronic pancreatitis in acute clinical presentations would be useful in guiding appropriate short- and long-term management. However accepted gold standard tests for chronic pancreatitis tend to be invasive, costly or time-consuming. The relatively new fecal elastase-1 assay has been shown to have acceptable diagnostic accuracy for moderate and severe exocrine deficiency when compared to the other tests (1). The aim of this study was to evaluate fecal elastase-1 concentration [FE-1] against clinical criteria for chronicity in an acute hospital setting. [FE-1] was performed on patients admitted to a surgical unit with a provisional diagnosis of acute pancreatitis based on the acute onset of epigastric pain and a serum lipase at least twice the upper limit of normal. Suspicion of chronic disease was defined by the presence of specific clinical, pathological or radiological criteria. A  $2 \times 2$  table comparing [FE-1] and clinical diagnosis was constructed. 117 stool specimens from 95 patients were suitable for [FE-1] determination. Values were compared to clinical case definition criteria of chronicity, after exclusion of liquid stool specimens and cases of moderate or severe acute pancreatitis (Ranson's score  $>2$ ). Using a threshold for exocrine insufficiency of 200 mcg/g, [FE-1] yielded the following results as a screening tool for chronic pancreatitis in the study cohort: positive predictive value = 96.9%, negative predictive value = 86.0%, sensitivity = 79.5% specificity = 98.0%. [FE-1] is an accurate screening tool for chronicity in pancreatitis patients when taken in the course of an acute hospital admission for mild pancreatitis. Since such cases represent the majority of pancreatitis admissions, the application of the assay to determine appropriate ongoing management protocols is justified. REFERENCE: 1. Löser C, Möllgaard A, Fölsch UR. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. *Gut* 1996; 39:580-586.

**266****CYSTIC DEGENERATION OF THE DUODENUM AND GROOVE PANCREATITIS: TWO NAMES FOR THE SAME CONDITION?**

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Cystic dystrophy of the duodenal wall (CD) is a rare lesion characterized by cyst formation in ectopic pancreatic tissue localized in the

duodenal wall. Groove pancreatitis (GP) is a form of segmental pancreatitis affecting the pancreatic head at the interface ("groove") with the duodenum. The clinical findings, imaging and histology in 8 cases (7 male, 1 female; aged 36-56 yr) were compared. All presented with epigastric pain, vomiting and weight loss. Imaging, usually based on CT and EUS, suggested CD in 5 cases. Duodenal wall thickening, mucosal irregularity and Brunner's glands hyperplasia were present in all cases with duodenal stenosis in 3. All showed plate-like scarring of the supra-ampullary duodenal wall, soft tissue at the pancreaticoduodenal interface and adjacent pancreatic parenchyma as described in GP. Cysts varying in number (2-15), size (0.3-2 cm), epithelial lining and content (inflammatory debris, protein plugs, concrement) were present in the duodenal wall of 6 patients. Ectopic pancreatic tissue was found in the duodenal wall (6 cases) and gastric antrum (1 case). Most patients show combined features of CD and GP. The significance of ectopic pancreatic tissue and alcohol as common aetiopathogenetic factors is discussed.

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#### GLUTAMINE TREATMENT OF ISLETS DURING PANCREAS PERFUSION AND ITS INFLUENCE ON OXIDATIVE STRESS AND TRANSPLANTATION

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The purpose of this study is to show a protective effect of intraductal glutamine administration on recovery of isolated islets of Langerhans from pancreata subjected to variable periods of ischemia prior to islet isolation and transplantation. Human pancreata were treated with either a 5 mM solution of L-glutamine through the main pancreatic duct ( $n = 6$ ) or perfused with collagenase enzyme alone ( $n = 6$ ), followed by standard islet isolation. The evaluation of isolation outcomes was performed *in vitro* by determining islet yield in Equivalent Islet Number (EIN), viability, and function through static glucose incubation. Levels of malondialdehyde (MDA) and Glutathione (GSH) were used as markers of oxidative stress to islets. *In vivo* analysis was performed through transplantation into diabetic "Nude" mice. Islet yields from human pancreata were significantly increased in the treatment group compared to controls; mean  $\pm$  SEM ( $305,243 \pm 39,744$  EIN vs.  $167,463 \pm 42,511$  EIN, respectively)  $P < 0.05$ . Although we did not observe the viability immediately postisolation to be significantly different ( $87\% \pm 3$  in treatment group vs.  $82\% \pm 2$  in control), *in vitro* islet function was improved by glutamine administration compared to control, stimulation index (S.I.) ( $9.80 \pm 3$  vs.  $6.93 \pm 2$ , respectively). The percentage of mice cured with glutamine treated islets was significantly increased when compared to controls ( $83\% n = 12$  vs  $26\% n = 23$ , respectively)  $P < 0.05$ , and in cured mice

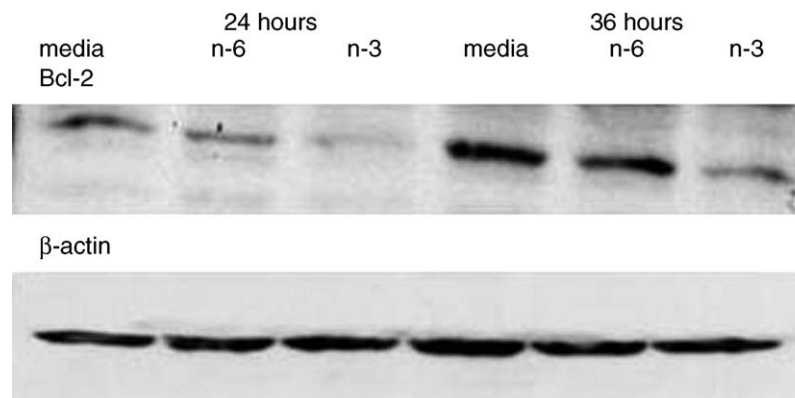
from both groups, the time to reach normoglycemia was significantly decreased in the glutamine group ( $1.83 \pm 0.4$  vs.  $7.3 \pm 3$  days)  $P < 0.05$ . Glutathione levels were increased in glutamine treated pancreata ( $n = 6$ ) vs control ( $n = 2$ ); ( $7.51 \pm 2.5$  nmol/mg of protein vs.  $5.25 \pm 0.2$  nmol/mg of protein), respectively, and MDA was slightly lower in glutamine groups when compared to the nontreated group. Current results (supporting previous studies) show that in human pancreata procured after a variable period of ischemia, intraductal administration of glutamine can decrease oxidative stress and improve islet yield, viability, and islet function after transplantation.

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#### DECREASED TOTAL Bcl-2 ANTI-APOPTOTIC PROTEIN LEVEL IN PANCREATIC CANCER (MIA PACA-2) CELLS INCUBATED WITH N-3 FATTY ACID ENHANCED MEDIA SUGGESTS MITOCHONDRIAL DIRECTED APOPTOSIS

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As previously reported, MiaPaCa-2 pancreatic cancer cells respond with a greater apoptotic response when incubated with an n-3 lipid emulsion than with n-6 lipid emulsion or media alone. What remains unknown, however, is the mechanism of the production of this cellular response. Bcl-2 protein acts in the cell to prevent the release of cytochrome-C from the mitochondrion, thus preventing the activation of the caspase system and cell death. The presence of Bcl-2 in larger amounts in the cell suggests a resistance to apoptosis, which contributes to the total anti- versus pro-apoptotic balance in the cell. The opposite has also been shown to be true. MiaPaCa-2 cells made prone to apoptosis by incubation with n-3 lipids exhibit a lower concentration of Bcl-2 anti-apoptotic than n-6 and media incubated cells. MiaPaCa-2 pancreatic adenocarcinoma cells were seeded in 100 mm<sup>2</sup> dishes and treated with media alone, media with 100  $\mu$ M n-6 lipid emulsion or 100  $\mu$ M n-3 lipid emulsion for 24 and 36 hours. The total protein from the cells was then extracted using an Active Motif extraction kit. After protein concentration measurement, a standard Western blotting protocol was performed with a specific anti human Bcl-2 antibody from Cell Signaling Technologies.  $\beta$ -Actin control and densitometry were also performed. The total Bcl-2 levels in the MiaPaCa-2 cells incubated with n-3 enhanced media show a marked decrease as compared to cells incubated with n-6 lipid enhanced media and media alone.  $\beta$ -Actin control and band densitometry confirms equal protein loading. MiaPaCa-2 pancreatic cells show a decrease in the level of Bcl-2 anti-apoptotic protein only when exposed to n-3 lipid enhanced media. In previous experiments, I $\kappa$ B phosphorylation was not shown to be altered in the presence of n-3 lipids, suggesting a mitochondrially controlled progression toward apoptosis. Further



experiments elucidating the mechanisms of these processes are needed. Increased knowledge of the intricacies of cell death in this model may help to promote n-3 supplementation as an adjunct to chemotherapy in pancreatic cancer treatment.

**269****CYSTS IN THE PANCREAS: HOW GOOD IS COMPUTED TOMOGRAPHY IN DIAGNOSIS?**

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There are two main cystic lesions in the pancreas: cystic pancreatic neoplasm (CPN) and pancreatic pseudocyst (PP). Differentiating between these two entities is critical to treatment, as PPs are drained while CPNs are resected. The efficacy of computed tomography (CT) in differentiating CPNs from PP has not been studied and is the purpose of this study. A retrospective review over a five-year period of all patients undergoing pancreatic surgery at a single institution was made. Of these, 32 patients met the inclusion criteria which required preoperative CT and surgical pathology of CPN or PP. The CT interpretation was then compared to the final surgical pathology. Of the 32 patients, 15 had CPN and 17 PP. Of the 15 patients with CPN, 13 were correctly diagnosed with the CT. Of the 17 patients with PP, 2 patients were incorrectly diagnosed by CT as having a CPN. The positive predictive value (PPV) for differentiating between these two entities is 87%. The sensitivity and specificity for CT in diagnosing CPN or PP is 87% and 88%, respectively. Although certain pancreatic lesions are not clearly defined by CT and require other studies, we found computed tomography to be a good method to differentiate between PP and CPN. Specifically, the PPV of CT in differentiating CPN from PP is comparable to published reports of endoscopic ultrasound, another popular diagnostic mode. Our data suggest that the work-up of pancreatic cystic lesions may involve simply a dedicated pancreatic CT.

**270****QUALITY OF LIFE AFTER SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTATION**

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Forty-eight simultaneous pancreas-kidney transplantations (SPKTx) were performed in our department between 1988 and 2004. Mean patient age was 34 years mean length of diabetes treatment was 23 years. Prior to SPKTx all patients were on maintenance haemodialysis. It is not well established whether SPKTx improves quality of life of these patients. The aim of this study was to assess the progress of diabetic complication after SPKTx and psycho-social status of these patients. By the end of June 2004, 37 patients were alive. 26 had functioning pancreas and kidney grafts. A questionnaire was sent and received from 26 patients with functioning pancreas grafts. 19 of them consented to take part in the study. We investigated ophthalmological status, presence of macroangiopathy and assessed quality of life. 4 of 19 patients had lower limb amputations after SPKTx. Seven of 19 patients were totally blind, 13 had retinopathy. Nineteen regarded their quality of life as improved compared to pretransplant status. This was mainly attributed to being dialysis and insulin-free. Fourteen

of 19 reported controlling their glycaemia regularly which was associated with fear of losing the pancreas graft. Seven of 19 persons returned to work after transplantation. Patients should be qualified to SPKTx before occurrence of diabetic complications, which can make the return to normal life after SPKTx difficult. Patients after SPKTx experience an improvement in the quality of life and, in some cases, return to professional life.

**271****SURGICAL COMPLICATIONS OBSERVED IN SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTATION (SPKTX)—16 YEARS' EXPERIENCE OF ONE CENTRE**

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Forty-eight SPKTx were performed in our department between 1988 and 2004. Mean patient age was 34 years and length of diabetes treatment, 23 years. All kidney and pancreas recipients were on maintenance hemodialysis therapy prior to SPKTx. The pancreas with duodenal segment and the kidneys were harvested from cadaveric heart beating donors. Cold Ischemia Time in UW solution varied from 4 to 14 hours. 20 patients had duodenal segment sutured to the urinary bladder while the remaining 28 grafts were drained to an isolated ileal loop. Quadruple immunosuppression was administered as well as anticoagulant and antibiotic prophylaxis; 46 patients (46/48, 95%) regained insulin-independence in the immediate postoperative period, and 41 (86%) recipients had immediate function of the kidney graft. Remaining patients underwent ATN during postoperative period. The longest ATN was 18 days. Of 48, 37 (77%) patients are alive (follow-up 6 up to 180 months); 26 of them (70%) with good pancreas function, 33 (89%) with good kidney function. Nineteen patients regarded their quality of life as improved compared to pretransplant status. This was mainly attributed to being dialysis and insulin-free. Fourteen of 19 reported controlling their glycaemia regularly which was associated with fear of losing the pancreas graft. Seven of 19 persons returned to work after transplantation. Four (8.3%) patients lost their kidney graft due to 2 of vascular complication, 2 of rejection. Four pancreas grafts with bladder drainage required conversion to enteric drainage due to persistent urinary infection or urinary fistula. 11 (23%) patients lost their pancreatic grafts within 1 year posttransplant due to the following: vascular complications: 8, septic complications, 1, rejection, 2. 11 patients died within one year after transplantation: 5 of septic complications, 4 of neuroinfection, 1 of pulmonary embolism, and 1 of myocardial infarction. Simultaneous pancreas-kidney transplantation is a successful treatment of diabetic nephropathy, burdened however by the possibility of serious complications.

**272****ISLET TRANSPLANTATION UNDER HEPATIC REGENERATION PROMOTES AMELIORATION OF HYPERGLYCEMIA AND INSULIN SECRETION IN STREPTOZOTOCIN-DIABETIC RATS**

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With the current donor shortage, future success with islet transplantation is incumbent on the ability to use single donor islets. Manipulating



the recipient graft environment may allow the use of fewer islets to achieve insulin-independence. We examined the impact of hepatic regeneration on engraftment of intraportally transplanted islet cells in the immediate postoperative period. Isolated pancreatic islets from a single-donor were intraportally transplanted to streptozotocin-diabetic rats immediately after 70% partial hepatectomy (HxPIT1;  $n = 12$ ). Plasma glucose levels and body weight were monitored for 30 days; intravenous glucose tolerance tests and serum insulin levels were obtained at the second and fourth weeks after transplantation; and morphological studies were performed on insulin immunostained sections of the liver. Results from HxPIT1 rats were compared to those from rats transplanted with single-donor islet grafts (PIT1;  $n = 10$ ) and those from rats transplanted with double-donor islet grafts (PIT2;  $n = 7$ ). Hyperglycemia was ameliorated in HxPIT1 and PIT2 rats after transplantation but not in PIT1 rats. Body weight gain of the HxPIT1 rats was more than that of the PIT1 rats. Glucose tolerance and insulin secretion in the HxPIT1 group were superior to the PIT1 group and equivalent to those in the PIT2 group. There were no significant differences comparing the glucose tolerance and insulin levels at the second week to those at the fourth week after transplantation. Morphologically, grafted islets from HxPIT1 rats were large and granulated by hypertrophic beta cells. The sizes of the grafted islets and individual insulin-stained islet cells were larger than those from PIT1 rats. In streptozotocin-diabetic rats, islet transplantation performed in regenerating liver results in improved insulin secretion and serum glucose control, even in the face of a limited number of islets. Hepatic regeneration might act both to induce hypertrophy of islet cells and to protect these cells from acute injuries during the immediate post-transplant period.

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#### PANCREATECTOMY WITH VASCULAR RESECTION AND RECONSTRUCTION: A SINGLE INSTITUTION 10-YEAR EXPERIENCE

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Pancreatic adenocarcinoma invading the portal or superior mesenteric vein is unresectable by traditional criteria. However, several reports have suggested that vascular resection and reconstruction can be performed safely, with a favorable oncologic outcome. The purpose of this study is to review a single institution's 10-year experience with vascular resection during pancreatectomy. The operative records of 471 patients who underwent pancreatectomy over the past 10 years at our institution were reviewed. Vascular resection was undertaken in 47 (10%). The morbidity, mortality, and survival of these patients were reviewed retrospectively. Portal/SMV resection was performed in 46 patients. Partial resection ( $n = 16$ ) was reconstructed primarily ( $n = 10$ ) or with a saphenous vein patch ( $n = 6$ ). Segmental resection ( $n = 30$ ) was reconstructed by primary end-to-end anastomosis ( $n = 14$ ) or with a vein interposition graft ( $n = 15$ ). One patient required caval resection. Approximately half of the patients had undergone neoadjuvant chemoradiation for initially unresectable disease ( $n = 24$ ), while the remainder underwent resection at initial exploration ( $n = 23$ ). Four patients had benign disease. Pancreatectomy included Whipple ( $n = 42$ ), total ( $n = 3$ ), and distal ( $n = 2$ ). Arterial reconstruction was performed in 3 patients. Postoperative mortality was 4.25%. The overall complication rate was 40%; PVT occurred in 15%, reoperation was required in 12%, and 8% had delayed gastric emptying. Arterial reconstruction was an independent risk factor for increased morbidity and mortality. Of the patients with invasive pancreatic adenocarcinoma ( $n = 41$ ), mean follow-up was 16.8 months (range 1.8 to 45.6 months). Median survival is at least 14 months and may be as high as 25 months as the data set matures. Pancreatectomy with vascular resection can

be performed with acceptable morbidity and mortality. Oncologic outcomes are similar to series limited to patients considered resectable by traditional criteria.

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#### DOES PRESERVATION OF THE RIGHT GASTRIC ARTERY AFFECT RETURN OF GASTRIC FUNCTION AFTER PYLORUS-PRESERVING PANCREATICODUODENECTOMY?

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Delayed gastric emptying is the most frequent complication after pylorus-preserving pancreaticoduodenectomy (PPPD). The maintenance of the pyloro duodenal blood supply has been proposed to decrease this complication by reducing ischemia to the duodenal cuff. There are little data in the literature about the value of preserving the right gastric artery (RGA) during PPPD for the postoperative return of gastric function. This was a retrospective study using an established database at our institution between 1994 and 2004. The patients who developed an anastomotic leak and/or intra-abdominal abscess were excluded leaving 100 patients undergoing PPPD with preservation of the RGA (Group 1) and 50 patients with division of the RGA (Group 2) based on individual surgeon preference. The two groups were comparable regarding age, gender, and histopathology (benign versus malignant). Statistical analysis was performed using Student *t* test and  $\chi^2$  test. All data are expressed as mean  $\pm$  SEM. The mean estimated blood loss was greater in cases that the RGA was preserved compared to those where the RGA was divided ( $552 \pm 35$  ml versus  $444 \pm 35$  ml, respectively,  $P < 0.05$ ). There was no difference in the time to removal of the nasogastric tube ( $5.3 \pm 0.3$  versus  $4.6 \pm 0.4$  days,  $P > 0.05$ ), the time to regular diet ( $8.4 \pm 0.4$  versus  $9.5 \pm 1.5$  days,  $P > 0.05$ ), the ICU stay ( $0.9 \pm 0.4$  versus  $1.3 \pm 0.8$  days,  $P > 0.05$ ) or the overall hospital stay ( $11.9 \pm 0.7$  versus  $13.9 \pm 1.5$  days,  $P > 0.05$ ) when the patients who had the RGA preserved were compared to those who had the RGA divided, respectively. Preservation of the right gastric artery does not appear to improve early gastric function or length of operative recovery after pylorus-preserving pancreaticoduodenectomy.

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#### THE EFFECT OF NEOADJUVANT THERAPY FOR PANCREATIC CANCER ON POSTOPERATIVE COMPLICATIONS

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Multimodal therapy for pancreatic cancer has long been known to be superior to surgery or chemotherapy and radiation alone, and more and more physicians are turning to neoadjuvant therapy as a preferred form of treatment. Many studies have shown an improvement in survival with neoadjuvant therapy; however, there are very little data comparing surgical complications in these groups. The goal of our study was to identify potential excess postoperative complications that might derive from administering neoadjuvant therapy. We did an exhaustive chart review of all patients diagnosed with pancreatic cancer from 1997-2003 in a major metropolitan health system. Of those we identified all patients who underwent any surgery with an anastomosis (112) including patients who underwent pancreaticoduodenectomy, choledochojejunostomy and gastrojejunostomy, choledochojejunostomy alone or gastrojejunostomy alone. We sorted them into two groups, those who had neoadjuvant therapy (NAT,  $n = 21$ ) and those who did not (control,  $n = 91$ ). We compared the rates of anastomotic

leaks (defined either by elevated drain amylase or bilirubin, or as reported by the physician) and infectious complication (wound infections, intra-abdominal abscesses, pneumonias, urinary tract infections). We analyzed our data using the Fisher exact test and the Mann-Whitney *U* test. We found 3 anastomotic leaks (14%) in the NAT group and 16 leaks in the control group (17%). Wound infection rate was 24% (*n* = 5) in the NAT group and 16% (*n* = 15) in the controls. Intra-abdominal abscesses were found in 14% (*n* = 3) of the NAT group and 15% (*n* = 14) in the controls. Pneumonias occurred in 10% (*n* = 2) of the NAT group and 6.6% (*n* = 6) of the controls. Urinary tract infections were found in 10% (*n* = 2) of the NAT group and 10% (*n* = 9) of the controls. Length of stay in the hospital was median 11 days (range 5-24) in the NAT group and median 12 days (range 4-86) in the controls. None of these data represented statistically significant differences between the two groups. Our conclusions are that in the pancreatic cancer patient, neoadjuvant therapy poses no increase risk of anastomotic leak, nor does neoadjuvant therapy pose increased risk of infectious complication. Postoperative length of stay is not impacted by neoadjuvant therapy.

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### A MATCHED COHORT STUDY OF EN BLOC VENOUS RESECTION DURING PANCREATICOUDENECTOMY FOR ADENOCARCINOMA OF THE PANCREATIC HEAD

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Incomplete resection of pancreatic head adenocarcinoma may lead to early recurrence and shorter duration of survival. Portal vein-superior mesenteric vein resection may be necessary to achieve an R0 resection. Prior studies have made comparisons with historical controls and have shown that duration of survival is no different following pancreaticoduodenectomy (PD) for adenocarcinoma of the pancreatic head with or without venous resection. A matched cohort has not been used to study survival after PD with venous resection. To compare operative and survival characteristics for patients undergoing PD for adenocarcinoma of the pancreatic head with or without venous resection. Fifty-two patients (venous resection (VR)) were matched to 52 patients (no venous resection (NVR)) such that year of operation, age, N stage, and tumor size were similar for the two cohorts. PD for adenocarcinoma of the pancreatic head was performed on these 104 patients from 1988-2003. The two groups were compared for clinicopathologic factors, along with survival. There was one (2%) operative mortality in the VR group as well as one (2%) in the NVR group. The groups were similar regarding sex (*P* = 0.11), length of stay (*P* = 0.23), surgical site infection (*P* = 0.72), abscess (*P* = 0.12), delayed gastric emptying (*P* = 0.09), and reoperation rate (*P* = 1.0). The VR patients had significantly higher rates of R1 resection (*P* = 0.02), intensive care admission (*P* < 0.01), operative time (*P* < 0.01), and blood loss (*P* < 0.01); however, the rate of pancreatic leak (*P* = 0.03) was significantly less. Survival was not significantly different between VR patients and NVR patients (*P* = 0.07), with five-year estimates of 12% and 16%, respectively. Histopathologic examination was performed on 40 (77%) of the resected venous specimens. Of these patients, the 24 (60%) with malignant invasion of the vein segment had significantly worse survival (*P* = 0.03). En bloc venous resection during PD for adenocarcinoma of the pancreatic head can be performed safely with morbidity and mortality rates similar to PD without venous resection. No significant difference in survival was demonstrated between the two groups. Finally, a surgeon should have a strategy to perform venous resection during PD when required to obtain negative surgical margins.

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### PYLORIC DILATATION REDUCES DELAYED GASTRIC EMPTYING AND DECREASES HOSPITAL STAY FOLLOWING PYLORUS-PRESERVING PANCREATICOUDENECTOMY

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The purpose of this study was to determine the effect of pyloric dilatation on delayed gastric emptying following pylorus-preserving pancreaticoduodenectomy. Delayed gastric emptying (DGE) occurs in 25% to 49% of patients following pylorus-preserving pancreaticoduodenectomy (PPPD). This has hampered the adoption of this procedure for the surgical treatment of periampullary disease due to prolonged hospital stay when compared to the classical Whipple operation, which involves gastrectomy. Multiple reports, however, have demonstrated that patients undergoing PPPD have a significantly improved quality of life and fewer post gastrectomy complications. We describe the novel use of pyloric dilation (PD), which appears to greatly decrease the incidence of delayed gastric emptying and facilitates earlier discharge. From January 2001 to June 2004, 46 consecutive operations were performed in the traditional manner (PPPD) with a duct to mucosa, two layered pancreaticojejunostomy, and end to side hepaticojejunostomy, and an antecolic, infracolic end to side duodenojejunosomy. 46 consecutive operations were then reconstructed in an identical manner, with mechanical dilation of the pylorus to 29 mm using a stainless steel tapered sizing device prior to the performance of the duodenojejunosomy (PPPD + PD). Delayed gastric emptying was defined as nasogastric suction beyond 10 days. Patient data were prospectively entered into a computerized database. Ninety-two patients were analyzed and the two groups (PPPD and PPPD + PD) were comparable regarding age, indication for surgery, final pathology, mean operating time and estimated blood loss (NS). The incidence of major complications was not statistically significant between the two groups (11% PPPD, 9% PPPD + PD, NS). The incidence of pancreatic fistula was also equivalent (4.4% PPPD, 4.4% PPPD + PD, NS). The incidence of delayed gastric emptying was greater in the PPPD vs. the PPPD + PD group (22% PPPD vs. 6.5% PPPD + PD, *P* < 0.05). Average length of stay was longer in the PPPD group vs. the PPPD + PD group (16.4 days PPPD vs. 10.3 days PPPD + PD, *P* < 0.05). PD decreases the incidence of delayed gastric emptying and length of hospital stay in patients undergoing PPPD.

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### EASY PANCREATICOJEJUNOSTOMY FOR THE SOFT PANCREAS USING A FAST-ABSORBABLE SUTURE

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Pancreaticojejunostomy for the soft pancreas with a small ductal size is known to be a risk factor for anastomotic leakage and is one of the major technical hurdles to complete pancreaticoduodenectomy. We developed a new, simple technique, by using an absorbable suture and a temporary stent tube. Two hundred fifty-six consecutive patients who underwent pancreaticojejunostomy at our institute until August 2004 were included in this study. Among them, recent 35 patients received the new technique of "easy pancreaticojejunostomy." Briefly, 5 or 6 Fr stent tube with a notch near the tip to prevent dislodging was inserted into the lumen of the main pancreatic duct. After exflow of the pancreatic juice was ascertained, the stent tube was fixed to the pancreatic duct near the cut end with a 4-0 fast-absorbable suture. Then, seromuscular layer of the jejunal limb was cut and

the submucosa was exposed the same width with the pancreatic cut surface. At the center of the submucosa, purse string suture was performed by a 4-0 fast-absorbable suture. Another tip of the stent tube described above was inserted into the intestinal lumen at the center of the purse string suture, where the stent tube was ligated and fixed. Then, both fast absorbable sutures, which fixed pancreatic duct and the jejunal submucosa, were approximated to contact each other and ligated. No other sutures were added to duct-to-mucosa approximation. Then, the pancreatic parenchyma was anastomosed to the wall of the seromuscular layer of the jejunum. Pancreatic juice flows through the lumen of the stent tube and then drained externally. Postoperative management was done by using a clinical path. Pancreatography was performed in all cases on the postoperative day 14. The duct was pulled out if there was no extravasation of the contrast medium. The average time to perform this technique was about 12 min which was significantly shorter than 30 min of the conventional duct-to-duct anastomosis. There were no significant differences in occurrence of anastomotic leakage (14% vs. 6%, NS) and hospital stay (25 d vs. 24 d, NS). This new technique allows even a beginner to perform pancreaticojejunostomy safely with minimum time requirement.

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**RECONSTRUCTION AFTER  
PANCREATICODUODENECTOMY**

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Pancreatic fistula is one of the most serious complications after pancreaticoduodenectomy (PD). However, this operation is recommended for operable cases of periampullary carcinomas because those who undergo resection live longer than who do not, palliation is better with successful resection and lastly there is the possibility for cure. We sought to retrospectively evaluate the methods of pancreatic stump management after pancreaticoduodenectomy (PD); pancreaticogastrostomy (PG), and pancreaticojejunostomy (PJ). Thirty patients (17 males and 13 females) with a median age of 52 (age range 35-70) undergoing standard Whipple's resection were evaluated over 42 months. The patients included 15 pancreatic head adenocarcinomas, 10 ampullary tumors, 3 lower end common bile duct tumors, and 2 duodenal carcinomas. Patients were randomly assigned to study groups as follows: Group 1 (n = 15) included PJ patients, group 2 included PG patients (n = 15). Prophylactic octreotide was administered for all patients postoperatively for 7 days in a dose of 0.1 mg/8 hr subcutaneously. Finally, the results were analyzed statistically. The presence of pancreatic leakage was 10%, and primary haemorrhage from the pancreatic stump was 3.33%. In group 1, there were two patients with pancreatic leakage and fistula with incidence of 6.66%, which ended fatally in one case (3.33%). In group 2, there was one patient (3.33%) who developed primary haemorrhage from the pancreatic stump, and another patient with pancreatic leakage, which ended fatally in the two patients. On statistical comparison, there was no significant difference between both pancreaticogastrostomy and pancreaticojejunostomy groups,  $P > 0.001$ . Both pancreaticogastrostomy and pancreaticojejunostomy groups show no difference on the incidence of pancreatic leakage and fistula.

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**LAPAROSCOPIC PANCREATICODUODENECTOMY**

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Despite the explosion of minimally invasive surgery, very limited experience has been gained into laparoscopic pancreatic surgery. A

recent review of laparoscopic treatment of pancreatic tumors revealed that 14 laparoscopic pancreaticoduodenectomy (PD), 93 pancreatic resections, 43 enucleations (2 hand-assisted) and 4 left-sided pancreatectomies have been reported since 1994. The reason for such a limited diffusion of the laparoscopic approach are complex: it is certainly a technically difficult procedure and it requires a long operating time but also it requires a surgeon who must be very experienced both in pancreatic and in laparoscopic procedures. We retrospectively analyzed 42 patients underwent laparoscopic PD from November 1999 to July 2004. 32 patients were operated for malignant and 10 for benign disease. In 21 cases a laparoscopic pylorus-preserving PD with Wirsung-jejunosomy was performed, while in 19 patients a Whipple procedure was performed and the main pancreatic duct was embolized with cyanoacrylate glue, and in two cases a laparoscopic pylorus-preserving PD without pancreaticojejunal anastomosis were performed. In 11 cases (26.2%) the operation was converted to open surgery. In 3 cases the operation was converted to open surgery during the realisation of the pancreatic tunnel for adhesion between the tumor and the portal vein. In 4 cases the procedure was converted to open surgery during the final phase of the detachment of the uncinate process for tumor extension (all were T3 cancer with positive nodes). In two benign cases the operation was converted for sclerosis due to pancreatitis. In one further patient the procedure was converted for a diffuse bleeding attributable to a prolonged prothrombin time and I.N.R. (International Normalised Ratio). The last patient was the only "emergency required" conversion due to the rupture of the portal vein in a patient with severe chronic pancreatitis. Average operative time was  $388.6 \pm 81.2$  (range from 240 to 560) minutes. Postoperative complications requiring re-operation occurred in 12 patients: 4 bile leaks, 7 bleeds, 1 bowel occlusion. Overall pancreatic fistula rate was 38% (16/42 patients). The incidence of pancreatic fistula was greater in the group without pancreaticojejunal anastomosis: 12/21 (57%) than in the group of patients with pancreaticojejunal anastomosis 6/21 (28.6%). The 60 days postoperative mortality was 7.1% (3/42). Laparoscopic PD is technically feasible. Short-term results favorably compare to open surgery. The theoretical benefits of a better quality of life and improved immune response are not yet proven.

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**PANCREATICODUODENECTOMY FOR CANCER IN  
THE PRESENCE OF NEAR OR COMPLETE SUPERIOR  
MESENTERIC VENOUS OBSTRUCTION: TECHNICAL  
FEASIBILITY AND OUTCOMES**

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Complete superior mesenteric venous (SMV) obstruction or extensive anterior portal venous invasion remains classic contraindication to the performance of a pancreaticoduodenectomy. This is in spite of the fact that resection theoretically could result in negative surgical margins (R0 resection). Given our increased experience in pancreaticoduodenectomy that includes resection of malignancies involving the portal confluence, we have begun to perform pancreaticoduodenectomy in select cases of periampullary malignancies with high grade (>80%) to complete (100%) SMV obstruction. The procedure is technically feasible, and our approach and outcomes are presented in 10 cases. No thirty-day mortalities were observed. Apparent palliation and cases of survival beyond one year have been observed. Based upon this initial series such resection is feasible and may be beneficial in select cases particularly following completion of neoadjuvant therapy without systemic progression. Further studies and more long-term follow-up are required, however, to determine the indications and potential benefit of such an undertaking.

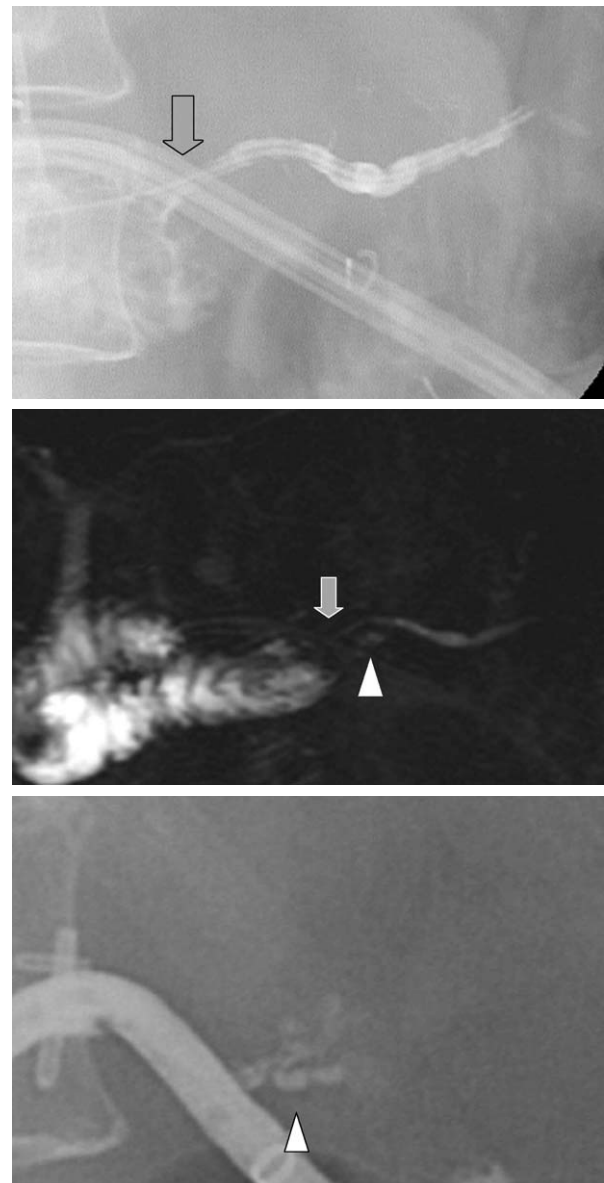
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### DEVELOPMENT OF POSTOPERATIVE PANCREATIC FISTULA DEPENDING ON THE PROCEDURES FOR DISSECTION OF PANCREAS

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In the present study, we reviewed the patients who were treated in this department and underwent pancreatic dissection for the past 15 years and evaluated development of postoperative pancreatic fistula depending on dissecting procedures. The subjects included 106 patients who underwent pancreaticoduodenectomy (PD) and 84 patients who underwent distal pancreatectomy (DP) in this department. The data on the patients' background, incidence of pancreatic fistula, incidence of postoperative complications and period of hospital stay after surgery were obtained from the two groups to make a comparison from the aspect of procedures of pancreatic dissection. In the statistic analysis, a value less than 0.05 was considered significant. There was no significant difference in the patients' background between PD group and DP group. The surgical procedures adopted in PD group were surgical treatment using a cavitron ultrasonic surgical aspirator (CUSA) (n = 17), conventional surgical treatment using a scalpel (n = 34) and electrocautery (n = 56). The number of patients who suffered pancreatic fistula after surgery was 1 (5.5%) in CUSA group, 9 (26.5%) in the scalpel group and 14 (25%) in the electrocautery group. Although no significant difference was recognized, the incidence of postoperative pancreatic fistula was lower in CUSA group. There was no significant difference in the incidence of postoperative complications and period of hospital stay after surgery. The surgical procedures adopted in DP group were CUSA (n = 4), conventional surgical treatment using a scalpel (n = 13), electrocautery (n = 58) and surgical treatment using laparoscopic coagulating shears (LCS) (n = 8). The number of patients who suffered pancreatic fistula after surgery was 1 (25%) in CUSA group, 2 (15.4%) in the scalpel group, 19 (32.5%) in the electrocautery group and 3 (37.5%) in LCS group. There was no significant difference in the incidence of postoperative complications and period of hospital stay after surgery. **DISCUSSION:** Use of CUSA, which enables exposure of the main pancreatic duct, branch ducts and blood vessels, ensures ligation and dissection and requires no closure of stumps. This surgical technique seems to be effective especially in dissecting the normal pancreas. Although the number of reported cases is limited, CUSA is considered a useful instrument that contributes to prevention of development of pancreatic fistula after pancreatectomy.

examination revealed evidence of chronic pancreatitis with hyperechoic stranding. Pancreatic cystic fluid obtained via FNA had a CEA level of 404 ng/ml and mucin. Patient underwent a classical pancreaticoduodenectomy with end-to-side mucosa-to-duct pancreatojejunostomy (PJ). An externalized pancreatic stent was placed. A J-P drain was placed beneath the PJ anastomosis. Final pathology showed IPMT of 2.5 × 1.5 × 1.0 cm with negative margins. The postoperative course was remarkable for elevated amylase in the J-P drain ranging from 1200 to 74,580 IU/ml. Serial pancreatograms did not demonstrate a leak at the PJ anastomosis (arrow in Fig. 1). MRCP confirmed a patent PJ anastomosis (arrow in Fig. 2) and probably a leak from a prominent pancreatic side-branch duct (arrowhead in Fig. 2). Subsequently, the sinogram successfully showed a patent pancreatic side-branch duct (arrowhead in Fig. 3). Tessel fibrin sealant was injected obliterating completely the patent pancreatic side-branch duct. J-P drain was removed. Patient has remained stable and continued to do well. In conclusion, a pancreatic leak can result from an anastomotic failure or parenchymal duct patency. Exact definition of the anatomy of the pancreatic leak can lead to definitive successful treatment.



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### NONANASTOMOTIC PANCREATIC LEAK AFTER A PANCREATODUODENECTOMY

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Pancreatic leakage remains a significant problem after pancreaticoduodenectomy. However, the exact anatomical nature of the pancreatic leak is usually not known. This study reports a case of a nonanastomotic leakage following pancreaticoduodenectomy. Case material involves a 67-year-old woman with 4-year history of chronic pancreatitis. MRI study demonstrated a cystic and nonenhancing lesion in the head of the pancreas measuring 2.3 cm × 1.8 cm. Endoscopic ultrasound

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**PANCREATICOJEJUNAL ANASTOMOSIS IS PREFERABLE TO PANCREATICOGASTROSTOMY AFTER PANCREATODUODENECTOMY IN TERMS OF THE LONG-TERM OUTCOME OF PANCREATIC EXOCRINE FUNCTION**

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The aim of this study was to evaluate pancreatic exocrine and endocrine function after pancreatoduodenectomy (PDD). Fifty-two patients underwent pancreatoduodenectomy for benign and malignant diseases (chronic pancreatitis and previous digestive surgery were excluded) in a delay of more than 24 months before the study. Pancreatic exocrine function was evaluated by a patient questionnaire and medical examination of stools and fecal output after discontinuing pancreatic enzyme supplements at least 10 days. Severe steatorrhea was defined as frequent stools, nauseating smell, yellow and pasty stools, fecal output >200 g/d. To evaluate endocrine function, fasting blood sugar level was measured. Association between severe steatorrhea and age, indication for surgery, histological obstructive pancreatitis, type of pancreatic anastomosis (pancreaticojejunal anastomosis (PJA) pancreaticogastric anastomosis (PGA)), and morbidity was studied. Median age was 61 year old and median follow-up was 75 months (range 25-166). Pancreatic and ampullary adenocarcinomas were the most frequent indications for resection. Complications occurred in 17 patients (33%) (12 pancreatic leakages). PJA was performed in 41 patients (79%), PGA in 11 patients (21%). At a median follow-up of 75 months (24-156 months), 65% of the patients of the study received enteric-coated pancreatic supplements. Nearly 50% of patients presented weight loss. Severe steatorrhea was observed in 22 patients (38%). Incidence of postoperative diabetes was 14.6%. Patients age (>60 years old), postoperative complication, obstructive pancreatitis were not associated with postoperative severe steatorrhea. In case of nonhistological obstructive pancreatitis, PGA was most frequently associated with severe steatorrhea than PJA (70% vs 21.7%,  $P < 0.025$ ). None of these factors significantly influenced the incidence of postoperative diabetes. After PDD, 40% of patients presented severe steatorrhea. PJA allows better pancreatic exocrine function preservation than PGA and should be recommended. The type of anastomosis didn't influence the endocrine function.

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**LAPAROSCOPIC PANCREATIC RESECTION: A SINGLE INSTITUTION EXPERIENCE WITH 42 PATIENTS**

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Potential applications of laparoscopy in pancreatic surgery include pancreatic resection for benign disease: cystic lesions and insulinomas. We report a single institution serial of 42 patients who presented pancreatic benign tumor treated by laparoscopy. All patients were operated at the Bordeaux University Hospital between 03/1999 and 10/2004. The median age was 37 (between 26 and 72). Our conversion rate was 14% (6 cases: one undetectable cephalic insulinoma, one undetectable corporeal insulinoma, bleeding, device problem, one for associated gastric resection, one for splenectomy). In 35 patients (83%), the entire procedure was performed by laparoscopy. 18 enucleations were performed (in 17 patients) (13 insulinomas or endocrine tumors, 5 cystic tumors: serous or mucinous cystadenomas, bronchogenic cysts, lymphangioma), 4 patients had a distal pancreatectomy (2 insulinomas, 1 included spleen, 1 congenital cyst), 11 patients underwent a left pancreatectomy (7 mucinous cyatadenoma, 1

serous cystadenoma, 1 pseudo papillary tumor and 1 insulinoma, 1 gastrinoma), 4 patients had a spleno-pancreatectomy (1 malignant insulinoma, 1 malignant endocrine tumor, 1 serous cystadenoma, 1 cystadenocarcinoma associated with a partial gastric resection), and 1 patient had a total duodeno-pancreatectomy (mucinous polycystadenomatosis). Two other patients underwent a median pancreatectomy with pancreatico-gastric anastomosis (mucinous cystadenoma, mucinous polycystadenomatosis). Two pancreatoduodenectomies were performed (one converted to laparotomy for insulinoma, one for ampullary adenocarcinoma). The median operating time was 140 minutes (60-480 minutes) and median intraoperative blood loss was 250 ml. Morbidity rate was represented by 4 pancreatic leakages (9.5%), a post operative bleeding (reoperation) and a partial splenic ischemia (no reoperation). One patient died (2.4%) from a superior mesenteric ischemia following enucleation. Mean hospital stay was 12 days. Laparoscopic surgery for benign lesion, specially left pancreatectomies, appears to be a safe procedure.

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**RESULTS OF TREATMENT OF CANCER OF THE PAPANILLA OF VATER**

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Kausch-Whipple technique of resection or pylorus-preserving pancreato-duodenectomy (PPPD) are the methods of choice in treatment of cancer of the papilla of Vater. Five-year survival after such operations varies between 45% and 65%. We sought to analyse the results of pancreatoduodenectomy in patients with carcinoma of the papilla of Vater. From 1987, 34 patients with cancer of the ampulla of Vater underwent pancreatoduodenectomy. There were 15 males and 19 females, mean age 51.9 years (range 29-72 years). Decompression of the bile ducts was performed in 22 patients. 12 patients with obstructive jaundice were operated. In 3 cases papillectomy was done. Most of the patients had II (58.8%) and III (32.4%) stages of disease. Morphologic study revealed lymph node metastasis in 11 patients. Postoperative complications occurred in 13 (38.2%) patients. More frequent complications were either pancreatojejunosotomy (3) or hepaticojejunosotomy (4) leak. 2 patients from this group had gastrojejunosotomy leak. Delayed gastric emptying observed in 6 (17.6%) patients who underwent PPPD. Mortality was 8.8% (3 patients). The cause of death was peritonitis (n = 1), pancreonecrosis (n = 1) and shock with DIC (n = 1). There were no deaths in last 19 pancreatoduodenal resections. Long-term results were studied in 25 (83.3%) patients: 1-, 3-, 5-, and 10-year survival was 90.4, 71.4, 61.2, and 51%, respectively. Univariate analysis revealed that only lymph node metastases ( $P = 0.012$ ) and tumor stage ( $P = 0.007$ ), independently influenced prognosis in patients with cancer of the papilla of Vater. Sex, tumor diameter, lymphadenectomy, and pylorus-preserving variant of surgery did not influence the long-term results. pancreatoduodenal resection must be surgery of choice in the treatment of resectable cancer of the papilla of Vater. The low mortality and complications rate could be achieved only if such surgery is undertaken in centers capable of carrying out careful case selection and sufficient surgical and intensive care experience.

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**PANCREATOBILIARY SURGERY WITHOUT INTRAPERITONEAL DRAINAGE**

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The use of intraperitoneal drains in pancreato-biliary surgery has been considered mandatory. However, recent evidence suggests that these

drains may not improve outcome and may be harmful. Routine placement of intraperitoneal drains was discontinued 3 years ago by a single surgeon at a tertiary referral center. Data on the outcome of these patients has been collected prospectively. One hundred five patients have been operated without drain placement: 35 pancreaticoduodenectomies, 23 palliative biliary and gastric bypass procedures, 18 hepaticojejunostomies, 15 distal pancreatectomies, 6 pancreaticojejunostomies, 5 pancreatic cyst gastrostomies and 3 ampullectomies. All anastomoses were performed with extramucosal 5.0 PDS sutures. Four patients required reoperation (1 bleed, 1 ileocolostomy leak, 1 pancreaticojejunostomy leak, 1 small bowel obstruction). Two patients required percutaneous drain placement for fluid collections (distal pancreatectomies). Five further patients with peripancreatic fluid collections were treated successfully with antibiotic therapy alone. There was one in-hospital death of a palliative bypass patient. Over this time period 4 patients received an intraperitoneal drain (2 pancreaticoduodenectomies, 2 hepaticojejunostomies) because of either extensive contamination or a tenuous anastomosis. Routine drainage of the peritoneal cavity after pancreatobiliary surgery is not necessary.

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**288****AN EVALUATION OF THE POSSUM SCORING SYSTEM IN PANCREATICODUODENECTOMY**

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No useful indicator is available for preoperative risk evaluation when considering treatment with pancreaticoduodenectomy (PD). The aim of this study was to clarify a usefulness of the POSSUM surgical scoring system for PD. From May 1996 to April 2004, 141 patients underwent PD. Postoperative complications were seen in 43 cases (30.5%). The subjects were divided into two groups by the presence or absence of postoperative complications. Twelve preoperative factors and 4 operative factors, and POSSUM parameters were compared between these two groups. In terms of the 12 preoperative factors and 4 operative factors, there was no significant difference between the complicated group and the noncomplicated group. Of the POSSUM parameters analyzed, the physiological score (PS,  $P = 0.0001$ ), the operative score ( $P = 0.0307$ ), the predicted mortality rate ( $P = 0.0001$ ), and the predicted morbidity rate ( $P = 0.0001$ ) differed significantly between the two groups. POSSUM is useful as a means of risk assessment in individuals scheduled to undergo PD.

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**289****CASE-CONTROL COMPARISON OF LAPAROSCOPIC VS. OPEN DISTAL PANCREATECTOMY**

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Laparoscopic distal pancreatectomy with or without splenectomy is become an increasingly used modality in the surgical treatment of pancreatic disease. Like with other laparoscopic surgery, the assumption is that this will lead to shorter hospital stay and faster returned to normal activities. However, actual comparative data between open and laparoscopic distal pancreatectomies is lacking. The purpose of this study is to compare these surgical procedures. All patients who underwent either laparoscopic or open distal pancreatectomies were eligible. 11 patients underwent laparoscopic distal pancreatectomy/splenectomy through a 4 trocar approach; while 38 underwent open distal pancreatectomy/splenectomy through either an upper, midline or left subcostal incision. The 11 laparoscopic patients were matched to 11 open patients for age, gender, and pancreatic pathology. Data

gathered included length of stay, pancreatic leak, postoperative complications, and return to normal activities (as reported by the patient). Data was analyzed using the paired signed rank test, and Fisher's exact test. Of the 11 laparoscopic patients, 2 were converted to open operations (they are still analyzed in the laparoscopic group). There were 7 females, 4 males, avg. age  $65 \pm 14$  years. Pathology distribution: 2 (18%) ductal adenocarcinoma, 5 (45%) cystic neoplasm, 2 (18%) neuroendocrine tumor, 2 (18%) chronic pancreatitis. Pathology distribution for all open cases: 13 (34%) ductal or cystic adenocarcinoma, 6 (15%) cystic neoplasm, 4 (11%) neuroendocrine tumor, 11 (29%) chronic pancreatitis, 4 (11%) other. All 11 laparoscopic cases were successfully matched to open controls. Length of stay: laparoscopic 6 days (range 3-9), open 8 days (range 6-23) ( $P = 0.02$ ). Pancreatic leak: both 18%. Postoperative complications: both 27%. Return to normal activity: laparoscopic 3 weeks (range 2-7), open 6 weeks (range 4-8) ( $P = 0.03$ ). Laparoscopic distal pancreatectomy/splenectomy does lead to shorter hospital stay and faster return to normal activity compared to open distal pancreatectomy/splenectomy. Pancreatic leak and complications are similar.

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**290****PANCREATICODUODENECTOMY FOR NONPERIAMPULLARY PRIMARY TUMORS**

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The role of extended resections for locally advanced carcinomas or isolated metastasis infiltrating duodenum and pancreas remains unclear. This review was performed to evaluate the outcome of patients undergoing pancreaticoduodenectomy (PD) for isolated metastasis or locally advanced nonperiampullary tumors (NPAP). Between 1992 and 2003, patients with NPAP invading duodenum and pancreas managed by a single surgical team at INCA-Brazil had their medical records reviewed. The clinical, pathological, and outcome details were analyzed. Thirteen patients were submitted to PD for NPAP. The primary tumor histopathology included colon ( $n = 8$ ), stomach ( $n = 3$ ), jejunum ( $n = 1$ ), and renal cell ( $n = 1$ ). Six patients presented with right upper quadrant pain as the first symptom, three with epigastric pain, one with anemia, one with palpable mass, one with jaundice, and one with weight loss. No operative deaths occurred. Ten had locally advanced tumors, while two had local recurrence and one had an isolated metastasis. The median length of hospital stay was 15 days (10 to 35 days). The median follow-up was 26 months. Four patients died for metastatic disease from 8 to 73 months after surgery. Seven patients are alive and free of locally recurrent disease, 3 to 38 months after the operation, but two have actual metastatic disease (23 and 29 months after surgery). PD for NPAP malignancy can be safely performed in locally advanced disease or isolated metastatic tumors, and is associated with a prolonged survival period.

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**291****DEVELOPING NOVEL BIOLOGICAL THERAPIES THAT DRIVE APOPTOSIS AND OVERCOME****CHEMORESISTANCE IN PANCREATIC CANCER CELLS**

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Today's typical fluorouracil or gemcitabine based chemoradiation protocols only marginally improve survival in patients with pancreatic cancer. Furthermore, not everyone agrees this to be true. To test novel concepts for biological therapies, we tested the cytotoxic effects of five anti-tumor drugs and their combinations in four invasive pancreatic cancer cell lines. The proposed drugs targeted specific pathways implicated in apoptosis control. These included the heat shock protein 90 (Hsp90) inhibitor geldanamycin (GA), proteasome inhibitor PS-341, histone deacetylase inhibitor (HDAC) trichostatin A (TSA), and the transcription inhibitor doxorubicin (Dox). We found that the cell lines had varying sensitivities to GA, PS-341, TSA and Dox in dose-dependent manners. By comparison, Gemcitabine (Gem) displayed no significant cytotoxic effects even at millimolar concentrations. We next determined the efficacies of GA (500 nM), PS-341 (50 nM) and TSA (500 nM) or Dox (250 nM), either alone or in combinations, in inducing apoptosis. TSA or PS-341 alone induced approximately 50% cell death, whereas GA or Dox alone caused 54% and 74% cell death, respectively. PS-341 combined with GA or TSA, reduced the viability of pancreatic cancer cells by 61% and 79%, respectively. TSA and GA together induced 50% of cell death, while Dox and PS-341 led to 58% cell death. This demonstrated that PS-341, combined with either GA or TSA, synergistically induced apoptosis in most pancreatic cancer cell lines. In particular, the combination of TSA and PS-341 induced apoptosis more effectively than any other combinatorial biological therapies. Dox and PS-341 synergistically induced apoptosis in Mia PaCa-2 (81% cell death), but not in the other cell lines. The combinations of Gem and either PS-341 or GA showed no significant cytotoxic effects on pancreatic cancer cells. To evaluate potential molecular aberrations resulting from these therapies, immunoblot assays were conducted interrogating the Akt/PKB and MAP kinase pathways. TSA and PS-341 together caused HDAC-2 degradation, and depletion of total Akt/PKB, ERK1/2 and MEK1/2 as well as activated phosphorylated MEK1/2. Furthermore, TSA inhibited NF- $\kappa$ B activation, presumably through HDAC-2 degradation. The efficacy of the proteasome inhibitor PS-341 against pancreatic cancer can be dramatically potentiated by combinatorial (GA or TSA) therapies that inhibit distinct anti-apoptotic pathways.

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**IMPACT OF ANGIOLYMPHATIC INVASION IN SURVIVAL OF PANCREATIC CANCER PATIENTS**

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The aim of this study was to assess the impact of angiolymphatic invasion in patients with resected pancreatic cancer. We retrospectively reviewed 40 patients with pancreatic cancer surgically treated, concerning histological type, degree of cellular differentiation, presence of angiolymphatic invasion, tumor size and survival rate. Patients with distant metastasis and per operative death were excluded. Among these patients we encountered 13 patients with Stage I (TNM classification), moderately differentiated adenocarcinoma of the head of the pancreas to assess the presence of angiolymphatic invasion. The group was composed of 13 patients, 7 men and 6 women, median age of 56.4 years (range 36-74). The angiolymphatic invasion was present in 46.2% of cases. The median survival rate of the patients with and without angiolymphatic invasion was 246 and 900 days, respectively. According to Kaplan-Meier curve it reached a difference statistically significant with  $P = 0.027$ , odds ratio 0.27 (IC 0.0048-0.54). The angiolymphatic invasion was associated with lower survival rate in patients with Stage I moderately differentiated adenocarcinoma of the head of the pancreas.

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**RACIAL VARIATION IN PANCREATIC ADENOCARCINOMA—AN URBAN UNIVERSITY EXPERIENCE**

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Pancreatic adenocarcinoma is 50-90% more common among blacks than whites in the United States. In addition, it has been demonstrated that the overall survival of black patients with pancreatic cancer is lower than in whites. The purpose of our study was to investigate demographics, tumor characteristics, treatment, and survival patterns in patients diagnosed with pancreatic cancer in an urban teaching hospital setting. A retrospective analysis using the hospital tumor registry data for pancreatic adenocarcinoma in black, white, and Hispanic patients from 1994-2003 was performed. Hispanic patients were included with whites, as per our state Tumor Registry board. Patients of other ethnicity or pathologies other than adenocarcinoma were excluded. Statistical analyses were performed using the Fishers Exact Test and the Cochran-Mantel-Haenszel analysis. A total of 182 patients (94 black, 88 white) met the criteria over the 10-year period. There was no difference in gender distribution between the 2 groups. Black patients were noted to present at a later AJCC stage than whites ( $P = 0.01$ ), were less likely to be resected (5% vs. 17%,  $P = 0.002$ ), were more likely to have no treatment (69% vs. 49%,  $P = 0.005$ ) and had an overall inferior survival (4 mos. vs. 8 mos. median survival, 40% vs. 20% 1-year survival). In addition, when controlled for the stage of the tumor, blacks were still less likely to receive treatment as compared to whites ( $P = 0.002$ ). This study demonstrates that there are significant racial discrepancies in the presentation, treatment and survival of patients with pancreatic cancer in an urban hospital setting. Further studies are warranted investigating the reasons for these differences and potential ways to improve and standardize care for patients of all races.

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**MUCINOUS CYSTIC TUMOR OF THE PANCREAS WITH OVARIAN-LIKE STROMA EXPRESSING ESTROGEN AND PROGESTERONE RECEPTORS IN A MALE PATIENT**

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The diagnostic criteria of mucinous cystic tumors (MCT) of the pancreas occur remains controversial. According to World Health Organization and Armed Forces Institute of Pathology, all MCTs must have ovarian-like stroma and occurs invariably in females. We report only the second case in the literature of a MCT demonstrating ovarian-type stroma with positive staining for vimentin, estrogen receptors and progesterone receptors in a 28-year-old male patient. This is a case report. A 28-year-old Chinese male presented with left iliac fossa pain of 2-weeks duration and was found on CT to have a 3-cm mass in the body of the pancreas with solid and cystic areas and calcification consistent with a mucinous cystadenoma. All the laboratory investigations including the liver functions tests, carbohydrate antigen 19-9 and carcinoembryonic antigen were within normal limits. The patient underwent spleen-preserving distal pancreatectomy and the patient's postoperative recovery was uneventful. Final histology revealed a pancreatic cystic neoplasm with features consistent with a mucinous cystadenoma. Grossly, there was a 2-cm unilocular cyst in the tail of the pancreas not communicating with the native pancreatic ducts. The cyst was lined by columnar epithelium with basal nuclei and abundant pale

mucous cystoplasm. The cyst wall demonstrated areas of hyaline collagenous thickening, focal calcification and subepithelial foci resembling ovarian stroma with parallel-orientated wavy fibroblasts. There were areas of metaplasia but no dysplasia or frank malignancy. The margins of resection were uninvolved. Immunohistochemistry demonstrated positive staining of the stromal cells for vimentin, estrogen and progesterone receptors. This case demonstrates that mucinous cystadenoma with ovarian-like stroma can occur in males.

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**SYNCHRONOUS SEROUS CYSTADENOMA AND PANCREATIC ENDOCRINE TUMOR: A CASE REPORT AND LITERATURE REVIEW**

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The coexistence of serous cystic tumors and islet cell tumors in the pancreas are extremely rare and may occur independently or combined within the same tumor mass. We report a case of a 52-year-old Chinese male with synchronous serous cystadenoma in the head of pancreas and pancreatic endocrine tumor (PET) in the tail. To the best of our knowledge, this is the first reported case in the English literature of synchronous serous cystic tumor and pancreatic tumor occurring separately and also only the second reported case of coexistent serous and endocrine tumor of the pancreas occurring in a male patient. This is a case report. A 52-year-old Chinese male was found incidentally to have a 14-mm hypoechoic nodule in the head of pancreas during screening US. The patient was asymptomatic and had no family history of von Hippel-Lindau syndrome. CT and MRI confirmed the presence of a 1.5 × 1.0 cm hypervascular mass in the ventral aspect of the head of pancreas suggestive of a PET. All the laboratory investigations including the serum concentrations of insulin, glucose, insulin/glucose ratio, C-peptide, calcium, phosphate, parathyroid hormone and 24-hour urinary metanephrine and normetanephrine excretion rates were within normal limits thus excluding the presence of insulinoma, pheochromocytoma or hyperparathyroidism. The liver function tests and tumor markers including carbohydrate 19-9, carcinoembryonic antigen and alphafetoprotein levels were also within normal limits. The patient underwent exploratory laparotomy during which a 2-cm cystic mass was found encroaching the head of the pancreas. Subtotal pancreatectomy with splenectomy was performed and the patient's postoperative recovery was uneventful. Final histology revealed a 1.5-cm serous microcystic adenoma in the head of pancreas and an incidental 0.3-cm benign nonfunctioning glucagonoma at the tail. At a follow-up of 2 years, the patient remained well and disease-free. This case emphasizes the importance of careful intraoperative examination for the occurrence of synchronous tumors during surgical resection of pancreatic tumors. The use of intraoperative ultrasound routinely may be helpful in detecting small synchronous tumors which may be difficult to detect via gross palpation. It also illustrates the importance of a thorough pathological examination and sampling of pancreatic tumors as grossly apparent benign pancreatic tumors may coexist and draw attention away from a synchronous neoplasm with malignant potential.

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**ZOLLINGER-ELLISON SYNDROME WITH SYNCHRONOUS ADENOCARCINOMA OF THE PANCREAS: A CASE REPORT**

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We report a rare case of a patient presenting with Zollinger-Ellison syndrome and an incidental finding of a synchronous pancreatic adenocarcinoma. A positive secretin stimulation test confirmed the diagnosis of Zollinger-Ellison syndrome. Localization studies including CT, MRI and endoscopic ultrasound revealed a pancreatic mass. Pancreatoduodenectomy revealed severely scarred and inflamed duodenum with a 3 × 3 cm pancreatic adenocarcinoma and a 2-mm duodenal gastrinoma with collision metastasis of both tumors in peripancreatic lymph nodes. To our knowledge, this is the first case report describing a primary gastrinoma with an incidental finding of a synchronous pancreatic adenocarcinoma with a collision metastatic lymph node.

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**PREVENTION AGAINST LIVER METASTASIS BY COMBINATION OF GEMCITABINE AND WHOLE LIVER IRRADIATION AFTER PANCREATIC CANCER SURGERY**

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The recurrence sites after pancreatic cancer excision are mainly local, peritoneum and liver. Extended operation and/or intraoperative irradiation are performed for the prevention of local or peritoneum recurrence. On the other hand, an effective prevention for metastases to the liver is not obscure. Radiation to the whole liver with simultaneous 5-FU IV administration, which is a radiation sensitizer, is an ongoing trial to kill minute liver metastasis, which is not visualized by CT or MRI at surgery (personal communication). Gemcitabine hydrochloride (GEM), which is also a radiation sensitizer, is utilized for patients with advanced pancreatic cancer in Japan since April 2001. We will report the effect of whole liver irradiation and simultaneous GEM administration comparing with those without GEM, retrospectively. Twenty-three patients with pancreatic cancer were operated to date since August 2001. Eight cases were withdrawn from the study (unresectable: 2, declined to participate: 1, death within 30-day: 1). GEM (1000 mg/body/wk × 3 wks) was given to the remaining 15 patients starting from two weeks after the curative intended surgery, and whole liver irradiation (2 × 10 Gy) was performed simultaneously. GEM (400-600 mg/body/2 wk) was continued as long as possible after discharge from hospital (Group A). Sixty-one patients undergone curative operation before 2001 (Group B) were compared as control on patients' background, survival, and liver metastases rate, retrospectively. Survival rates in Group A (100% at 1-year and 58% at 2-year) were significantly higher than that in Group B. (65% at 1-year and 58% at 2-year;  $P = 0.034$ ). Two of 3 patients died in Group A developed liver metastases. On the other hand, 30% of the patients in Group B. were confirmed to have liver metastases at the time of death. Simultaneous administration of GEM and whole liver irradiation improved survival rate after pancreas cancer surgery.

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**THE IMPACT OF SURGICAL COMPLICATIONS ON SURVIVAL OF PATIENTS WITH HPB MALIGNANCIES**

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There are numerous prognostic factors that affect surgical outcome for patients with hepato-pancreato-biliary (HPB) malignancies. The impact of surgical complications, however, has not been adequately studied. Herein, we describe the impact of postsurgical complications



on patient survival for HPB malignancies. Over a ten-year period (1993 to 2003), 86 patients underwent surgical resection for cancers of the liver, bile duct, and pancreas. The association between surgical complications and patient survival was examined through proportional hazards regression, adjusting for patient and tumor characteristics. Kaplan-Meier survival analyses were performed. Surgery-related readmission was defined as "admission within 30 days after initial discharge." Of 86 patients included in the study, 22 (25.5%) had complications. Patient data were adjusted for age; gender; tumor location; tumor size; stage; grade; type of operation; and comorbidities. Calculation of the proportional hazards regression demonstrated that surgical complications were an independent negative association with overall survival; hazard ratio (HR) 1.6 [CI-1.2-2.0] and HR 1.8 [CI-1.2-2.6], respectively. The mean survival for patients with surgical complications was 29.4 months (19.5-39.4 months, 95% CI) compared to 42.8 months (36.7-49.0 months, 95% CI) for patients without complications (log rank test,  $P = 0.0014$ ). Apart from the immediate clinical consequences, surgery-related complications have an independent negative association with survival for patients with HPB malignancies.

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#### L1 CELL ADHESION MOLECULE EXPRESSION AS A PROGNOSTIC MARKER FOR NEUROENDOCRINE PANCREATIC TUMORS

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Cell adhesion molecules have an essential function in tumor progression and metastasis. Recently this was shown for neuronal L1 cell adhesion molecule (L1CAM; CD117). In our study we determined expression of L1CAM in specimen of neuroendocrine pancreatic tumors and metastases. Expression was correlated with overall and tumor-specific survival. We retrospectively analyzed L1CAM expression by immunohistochemistry in neuroendocrine pancreatic tumors or metastatic lesions of 62 patients by peroxidase method on paraffin sections. Presence of L1CAM on the tumor cells was compared with clinical follow-up data. L1CAM was detectable in 14 out of 62 (22.6%) neuroendocrine pancreatic tumor specimen. Patients with positive immunostaining for L1CAM had a significantly worse overall and tumor-specific survival analyzed by Kaplan-Meier method ( $P = 0.038$  and  $P = 0.043$ ; log-rank test). Multivariate Cox regression analysis adjusted for age, sex, tumor stage, and metastasis identified L1CAM as an independent prognostic factor ( $P = 0.015$ ). L1CAM is expressed in a subgroup of neuroendocrine pancreatic tumors and is associated with a significantly worse outcome. Therefore it is a prognostic marker and could be a potential target molecule for immunotherapy for patients suffering of neuroendocrine tumors of the pancreas.

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#### HYPERMETHYLATION OF MULTIPLE GENES IN PANCREATIC CANCER

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Hypermethylation of CpG islands in the promoter regions is known to affect functional inactivation in several genes. The purpose of this study was to delineate more precisely its role in pancreatic cancer. EXPERIMENTAL DESIGN: We analyzed 7 pancreatic cancer cell lines for promoter hypermethylation in 8 tumor-related genes (3-OS-2, RAR-beta, RASSF1A, SEMA3B, FHIT, p16, SLIT2, MINT32) by methylation specific PCR (MSP). SLIT2 and MINT32 were methylated in 100% of cell lines. Hypermethylation was detected frequently in 3-OS-2 (86%), RASSF1A (71%), RAR-beta (57%), SEMA3B (57%), FHIT (57%), p16 (29%). In addition, we selected SLIT2 for functional analysis. Demethylating analysis demonstrated an increase in expression of SLIT2 in Panc1 cell line. Transcripts missing SLIT2 exons were detected in 5 (71%) cell lines. These results indicate that the hypermethylation of several genes may play an important role in pancreatic tumor development. Detection of hypermethylation in several clinical samples by a panel of 8 tumor-related genes may be a useful diagnostic tool for pancreatic cancer.

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#### A STRUCTURALLY OPTIMIZED CELECOXIB DERIVATIVE INHIBITS HUMAN PANCREATIC CANCER CELL GROWTH

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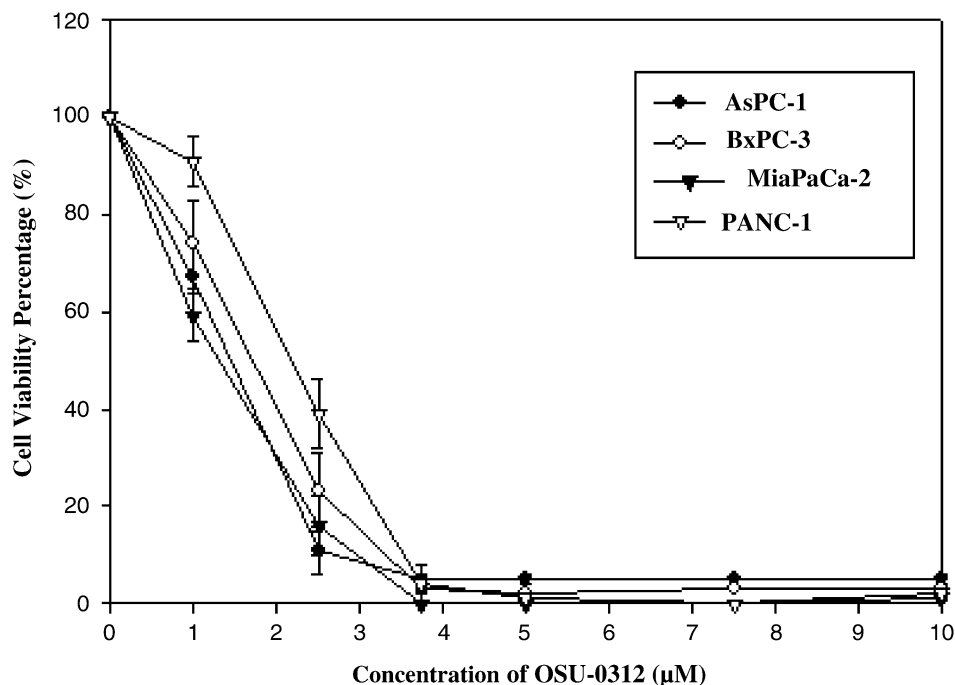
Dysregulation of the phosphatidylinositol 3-kinase (PI-3K)/PDK-1/Akt signaling cascade is associated with pancreatic cancer tumor invasion, angiogenesis, and tumor progression. It has been proposed that PDK-1/Akt signaling inhibitors may hold promise as novel therapeutic agents for pancreatic cancer. Disadvantages of currently available Akt inhibitors include tumor resistance, poor specificity, potential toxicity, and poor bioavailability. Previous studies demonstrate that OSU-03012, a celecoxib derivative, specifically inhibits PDK-1 mediated phosphorylation of Akt with  $IC_{50}$  values in the low  $\mu$ M range. Human pancreatic cancer cell lines AsPC-1, BxPC-3, MIA-PaCa-2, and PANC-1 were cultured in media containing varying concentrations of OSU-03012 and 5-Fluorouracil (5-FU), and cell viability was measured using an MTT assay. OSU-03012 demonstrated potent growth inhibition of all cell lines with  $IC_{50}$  values ranging between 1.0 and 2.5  $\mu$ M. In contrast, the  $IC_{50}$  values for 5-FU were higher than 25  $\mu$ M. These data suggest that OSU-03012 has potential value as a novel therapy for pancreatic cancer (Fig. 1).

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#### HSP90 INHIBITION SYNERGISM WITH CHEMOTHERAPEUTIC AGENTS MAY ACT THROUGH APAF-1 MODULATION IN PANCREATIC CANCER

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The novel anticancer therapeutic geldanamycin (GA) targets the chaperone protein Hsp90. Hsp90 holds client proteins in an inactive state before release or targeted destruction, thus maintaining a constant pool of protein ready for activation. Functional Apaf-1 is responsible for caspase-9 cleavage and stimulating apoptosis. Apoptosis was induced using 5-FU or TPA and measured by caspase-3/9 cleavage and increase in sub-G1 cells. Proteins were examined using immunohistochemistry, immunofluorescence, and Westerns. Viability was measured using MTT and Trypan Blue assays. Combination of GA and 5-FU synergize to kill pancreatic cell lines after 24 hours ( $P < 0.001$ ). Synergy is lost after 48 hours, 5-FU pretreatment sensitises cells to



GA, but pretreated cells are significantly more resistant to GA + 5-FU ( $P < 0.001$ ). GA pretreatment sensitises cells to 5-FU and GA + 5-FU. Serum-starvation (SS) for 16 h sensitises to apoptosis. Further SS has no effect. SS induces nuclear Hsp90 localization. Apaf-1 isoforms were modulated by GA treatment. In vivo nuclear Hsp90 is seen in PC but not normal pancreas, and is associated with larger tumors ( $P < 0.001$ ). Alteration of Hsp90-protein interactions sensitises PC cells to apoptosis. Hsp90 inhibition after 5-FU increases sensitivity but may reduce the induction of further damage by 5-FU. This may be mediated by alteration of Apaf-1 isoforms. In-vivo localization of Hsp90 may lead to resistance to apoptotic stimuli (equivalent to prolonged SS).

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#### THE VALUE OF CT ASSESSMENT OF REGIONAL LYMPH NODES IN PREDICTING NODAL METASTASIS, RESECTABILITY, AND SURVIVAL FOR PERIAMPULLARY TUMORS

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The prognostic value of lymph nodes  $>10$  mm on short-axis measurement by helical CT for periampullary tumors is debated; no criteria for long-axis measurements exist. Two distinct lymph nodes reproducibly assessed by CT are 1) the “common bile duct” (CBD) node, located supero-postero-lateral to the pancreatic head, and 2) the “celiac” node, located anterior to the origin of the gastroduodenal artery. We examined if radiographic enlargement of either lymph node predicts nodal metastasis, tumor resectability, or survival in patients with presumed periampullary malignancy. A single radiologist prospectively recorded short and long-axis measurements of the CBD and celiac nodes for 94 patients with periampullary tumors. Measurements were categorized using 10 mm for short-axis and the mean of the long-axis as cutoff values. All patients underwent attempted curative resection at one institution between Sep ‘01 and Jun ‘03. When feasible, the

aforementioned nodes were excised.  $\chi^2$  and logistic regression were used for statistical analysis. 42 CBD and 49 celiac nodes were retrieved for pathologic review; 61% ( $n = 57$ ) of tumors were resectable by pancreaticoduodenectomy; 77% of tumors in patients from whom either node was obtained ( $n = 60$ ) were resectable. Enlarged radiographic nodal size by either axis was not associated with the presence of metastasis to these lymph nodes. Only CBD node short-axis size  $>10$  mm, as confirmed by multivariate regression (OR: 3.2,  $P = 0.036$ ), predicted unresectability (Table 1). There was no association between the presence of a biliary stent ( $n = 60$ ) and enlarged CBD short-axis measurements. Overall, 6 month and one year survival was 87% and 68%, respectively. Enlarged radiographic size of either lymph node did not predict mortality at the above time points. Subset analysis of primary tumors confirmed to be pancreatic adenocarcinoma ( $n = 48$ ) did not reveal significant associations between nodal size and the above three outcomes. For presumed periampullary malignancy, CBD and celiac lymph node size as measured by CT does not predict the presence of nodal metastasis or survival. However, CBD node short-axis size  $>10$  mm predicts unresectability; this may influence preoperative decision making.

**Table 1.** Lymph Node Size and Resectability

| Lymph Node Size                              | Percent Resectable | P value |
|--|--------------------|---------|
| CBD node short-axis $\leq 10$ mm (N = 74)    | 67.6%              | 0.017   |
| CBD node short-axis $>10$ mm (N = 20)        | 35.0%              |         |
| CBD node long-axis $\leq 20$ mm (N = 57)     | 45.6%              | 0.786   |
| CBD node long-axis $>20$ mm (N = 37)         | 40.5%              |         |
| Celiac node short-axis $\leq 10$ mm (N = 74) | 60.8%              | 0.947   |
| Celiac node short-axis $>10$ mm (N = 20)     | 60.0%              |         |
| Celiac node long-axis $\leq 15$ mm (N = 57)  | 54.4%              | 0.271   |
| Celiac node long-axis $>15$ mm (N = 37)      | 40.5%              |         |

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#### CLINICAL EXPERIENCE WITH GEMCITABINE AS POSTOPERATIVE ADJUVANT THERAPY IN

**LOCALIZED ADVANCED PANCREATIC CANCER—  
A PRELIMINARY REPORT**

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Although clinical efficacy of gemcitabine hydrochloride (GEM) for unresectable pancreatic cancer has been documented, the efficacy of GEM as adjuvant therapy after surgical resection has not been thoroughly investigated. The present study examined the efficacy of GEM in preventing recurrence of pancreatic cancer after surgical resection. Among 138 patients who had undergone pancreatectomy for invasive ductal carcinoma of the pancreas, 16 (pancreatoduodenectomy, 13; distal pancreatectomy, 3) received GEM as postoperative adjuvant therapy. Prognosis was compared to a historical control group of 108 patients who had undergone pancreatectomy for pancreatic cancer prior to the introduction of GEM. Dosage of GEM was 1000 mg/m<sup>2</sup>/week, given iv, on three consecutive weeks with one week off. Adverse events were either grade 2 (leukopenia, 3; infection, 2; vomiting, 2; diarrhea, 1) or grade 3 (leukopenia, 4; anemia, 2), and no grade 4 events were observed. Tumor recurrence occurred in 9 patients, (local recurrence, 5; liver metastases, 3; lung metastases, 1). In GEM-treated patients, median postoperative survival was 19.1 ± 3.6 months, which was significantly longer than that of the control group (10.0 ± 1.9 months, *P* < 0.01). Systemic administration of GEM as a postoperative adjuvant therapy significantly improves survival after pancreatectomy in patients with pancreatic cancer.

**305****FARNESYLTRANSFERASE INHIBITOR IN HAMSTER  
EXPERIMENTAL PANCREATIC CANCER MODEL—  
IS IT EFFECTIVE AS NEOADJUVANT AND ADJUVANT  
THERAPY?**

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p21-Ras, the protein product of the proto-oncogene Ras is overactivated in pancreatic cancer. Signal transduction inhibition by targeting against Ras may be a promising therapeutic strategy. Farnesyl transferase inhibitors (FTI) could be a good choice. A curative resection model of hamster experimental pancreatic cancer has been developed previously. AIMS: To clarify the effectiveness of FTI (B956) as adjuvant or neoadjuvant therapy. HaP-T1, a hamster pancreatic adenocarcinoma cell line was used. MTT and MTT-agarose assays were done. Orthotopic tissue implantation was performed. At day 7 or day 14, partial pancreatectomy and splenectomy were done. Hamsters were divided into 7 groups: positive control (PC, n = 5), only FTI (FT, n = 5), neoadjuvant therapy after surgical resection at day 7 (NT-S7, n = 10), adjuvant therapy after resection at day 7 (AT-S7, n = 10), neoadjuvant therapy after surgical resection at day 14 (NT-14, n = 10), adjuvant therapy after resection at day 14 (AT-S14, n = 10), Only surgery at day 14 (SR, n = 5). FTI was administered for one week. Fourteen days after surgical resection, sacrifice was done. Four animals of each group were left to study the survival. After 180 days, living hamsters were sacrificed. Resected and necropsied specimens were sent for histopathological analysis. Inhibition was achieved in a dose dependent manner in vitro. Successful rate of implantation was 100%. PC, FT, NT-S7, AT-S7, NT-S14, AT-S14, and SR survived in average 82, 103, 119, 134, 123, 132, and 139 days. Two hamsters

of AT-S7, 2 of AT-S14, and 3 of SR were alive until 180 days. Intraoperative bleeding was higher in NT groups. Loss of body weight was present in all FTI treated groups. Farnesyltransferase inhibitor showed not to increase curative resection rate of orthotopically implanted tumors. However, compared to positive control the administration of the drug alone may be used to increase the survival.

**306****ARE ANTISENSE OLIGONUCLEOTIDES TARGETED  
TO K-ras GENE EFFECTIVE IN THE TREATMENT OF  
PARENTAL, METASTATIC, AND REMETASTATIC 5-FU  
AND MMC-RESISTANT HAMSTER PANCREATIC  
CANCER CELL LINES?**

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K-ras point mutation at codon 12 has a relationship greater than 80% with pancreatic cancer. Cancer therapy should also include the treatment of metastatic disease because it is known that the properties of metastatic cells may vary considerably from those of the primary tumor. To elucidate if the same drugs, which can inhibit the tumor growth in the parental cell line, can inhibit the pancreatic metastatic and remetastatic cell lines at the same concentrations and to compare the inhibition with antisense oligonucleotides mismatched to K-ras gene, in Syrian golden hamsters. HaP-T1, a BHP-induced hamster pancreatic cancer cell line, MS-PaS-1 (a metastatic cell line established from "return trip" metastases from the liver to the pancreas) and MS-PaS-2 named as a "remetastatic cell line", i.e., metastases from MS-PaS-1 were used. MTT and MTT-agarose assays were performed, using 5-fluorouracil (5-FU), Mitomycin C. (MMC) and antisense oligonucleotide specific to K-ras oncogene. The inhibitory concentration (IC<sub>50</sub>) of 5-FU, which inhibited HaP-T1, had to be increased by 50-fold to inhibit MS-PaS-1 and 100-fold to inhibit MS-PaS-2. MMC had to be increased by 10-fold to inhibit MS-PaS-1 and 50-fold to inhibit MS-PaS-2. However, IC<sub>50</sub> was the same when antisense oligonucleotide was tried in these 3 cell lines. Antisense oligonucleotide-targeted K-ras gene may be a good choice for therapy because it could inhibit the growth in metastatic and remetastatic cells as well as in primary tumor cells.

**307****SOLID-PSEUDOPAPILLARY TUMOR OF THE  
PANCREAS: REPORT OF FOUR CASES IN A  
BRAZILIAN INSTITUTION**

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Solid-pseudopapillary (SPT) tumor of the pancreas is a rare neoplasia of pancreas, with a rate varying from 0.17-2.7% of nonendocrine tumors of the pancreas. Recently there has been a steady increase in the number of SPTs of the pancreas, with more than two thirds of the total cases described in the last 10 years. We sought to evaluate 4 patients with Frantz's tumor in a Brazilian institution. Four patients with diagnosis of SPT tumor were analyzed in a retrospective analysis from December 2000 to February 2003, clinically and histopathologically. Therapeutic approach and prognosis were also studied.

There were 3 females and 1 male with a median age of 27 years (range, 17-42). Dyspeptic symptoms and abdominal palpable mass represented the initial clinical findings. The main localization of the tumor was the pancreatic head (3 of 4 cases). Enucleation was performed in one case, Whipple's surgery in 2 cases, and distal pancreatectomy in one case. Curative resection was possible in all cases confirmed by free margins. Two cases showed venous invasion histopathologically. Immunohistochemical analysis was done in 3 cases to confirm the diagnosis. In an average of 15-month follow-up, no recurrence has been observed. Our casuistics showed the preference of the tumor to the head of the pancreas, controversial to literature. However, other characteristics were similar to literature reports (clinical, histopathological, immunohistochemical, and therapeutics). In addition, a longer postoperative follow-up will be necessary to affirm about prognosis.

**308****COULD GREEN TEA EXTRACT INHIBIT THE TUMOR GROWTH AND INVASIVENESS IN A HAMSTER PANCREATIC CANCER MODEL?**

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Polyphenolic compounds present in tea may reduce the risk of a variety of illnesses, including cancer. Most studies have shown that tea consumption protects against lung, forestomach, esophagus, duodenum, pancreas, liver, breast, colon, and skin cancers induced by chemical carcinogens. Research findings in laboratory animals have shown the chemopreventive potential of tea polyphenols in cancer, the usefulness of tea polyphenols for humans should be evaluated in clinical trials. Inhibitory effect of green tea extract on the process of pancreatic carcinogenesis induced by nitrosamine and on tumor promotion after transplantation of nitrosamine induced pancreatic cancer in Syrian hamsters. However, there have been no reports using tissue culture to study the effectiveness of this therapy in cancer cells. To verify the anti-invasive activity of green tea extract in hamster pancreatic cancer. HaP-T1, a cell culture derived from BHP-induced hamster pancreatic cancer was used. After treatment with green tea extract, cell proliferation was studied by MTT and MTT-Agarose methods. In vitro chemoinvasion assay with the reconstitution of a matrix of basement membrane onto a filter in a Boyden chamber was used. Migrating cells of the lower chamber were studied by MTT assay. Green tea extract inhibited the tumor growth and invasiveness of HaP-T1 in a dose dependent manner. Green tea extract may be a new anticancer strategy for pancreatic cancer because it could not inhibit only the tumor growth and invasiveness. However, further studies *in vivo* will be necessary.

**309****THE PROPROTEIN CONVERTASE CHAPERONE PROTEIN 7B2 IS A NEW IMMUNOHISTOCHEMISTRY MARKER FOR PRIMARY AND METASTATIC NEUROENDOCRINE TUMORS OF THE PANCREAS AND GI TRACT**

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7B2 is a 21-kDa protein known as proprotein convertase PC2 chaperone protein. It escorts the PC2 protein through the secretory pathway

and prevents its premature activation. Substrates of PC2 include proinsulin, proglucagon and pro-CCK. We have previously observed that 7B2 mRNA and protein levels are high in functioning neuroendocrine tumors (NET) of the pancreas when compared with 7B2 mRNA and protein levels in nonfunctioning (NF) NET tumors, unaffected pancreas, normal pancreas and normal islet cells. The objective of this study was to determine if 7B2 could be used as a practical diagnostic marker of neuroendocrine tumors via immunohistochemistry. After appropriate patient consent, primary and metastatic neuroendocrine tumor biopsies from the pancreas, the small bowel, the colon and the liver were snap frozen in the operating room at the time of surgery. The biopsies to be studied via immunohistochemistry were covered in OCT before immersion in liquid nitrogen. Serial 4 micron thick cryostat sections of each neuroendocrine tumor were prepared and fixed in acetone on gelatin coated slides. The slides were blocked in PBS 1% donkey serum and incubated with rabbit anti-human 7B2 antibodies overnight followed by incubation with secondary donkey anti-rabbit fluorescent antibody. Sections were analyzed under fluoromicroscopy. A negative control was also prepared for each section by omitting incubation with the primary antibody. The immunohistochemistry revealed strongly positive results for 7B2 in secreting neuroendocrine tumors (glucagonomas, vipomas, insulinomas, and carcinoid tumors) and negative results for nonfunctioning neuroendocrine tumors. These results are in concordance with the intracellular protein profile of neuroendocrine tumors that we previously established. 7B2 is likely to become another immuno-marker for neuroendocrine tumors in addition to neuron-specific enolase and chromogranin A. While its diagnostic potential is becoming very clear, it is still too early to know what the prognostic implications of tumor 7B2 immunohistochemical positivity will be. So far, there is no difference between primary and metastatic tumors but our tissue biopsy pool is still preliminary. Our patient cohort is being followed so that the implications of 7B2 positivity can be assessed.

**310****UNDERSTAGING PANCREATIC CANCER: RESULTS OF COMPREHENSIVE PATHOLOGIC ASSESSMENT OF PANCREATICODUODENECTOMY SPECIMENS**

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Optimal management of localized adenocarcinoma of the head of the pancreas is pancreaticoduodenectomy with microscopically negative resection margins (R0). Multiple studies have demonstrated the adverse impact of positive resection margins (R1) on patient outcome. Assessment of surgical margins is often limited to the pancreatic cut surface, common bile duct (CBD) and posterior margin (pancreatic tissue overlying the inferior vena cava). Tumor extension to the superior mesenteric artery (SMA) and portal and superior mesenteric veins (PV/SMV) is often the limiting factor preventing complete surgical extirpation, yet this area is seldom assessed microscopically. The purpose of the study was to evaluate a comprehensive examination protocol of pancreaticoduodenectomy specimens to determine the frequency of microscopically positive SMA and PV/SMV margins, collectively referred to as mesenteric margin. Between 2001 and 2004, 27 patients underwent pancreaticoduodenectomy for pancreatic adenocarcinoma, with removal of all gross tumor (R0, R1). Following resection, the surgeon, in the presence of the pathologist, oriented the specimens and placed marking sutures denoting the following margins: pancreatic cut margin, CBD, posterior margin (pancreatic tissue overlying the inferior vena cava), SMA and PV/SMV. Margins were considered positive if tumor was present within 1 mm of inked surfaces. Of the 27 specimens analyzed, 12 (44%) had microscopically positive resection margins. The frequency of positive margins was: PV/SMV (6), SMA (5), posterior (3), pancreatic (2), and CBD (1).

Five specimens (19%) had multiple positive margins. In 7 specimens (26%), the only positive resection margins were the SMA or SMV/PV. More limited pathologic assessment of only the pancreatic, CBD and posterior margins would have resulted in a positive margin rate of 19%. In this series, a total of 135 margins were evaluated of which 17 (13%) of them were positive, with the mesenteric margin (SMA or SMV/PV) accounting for 65% of microscopically positive margins. The mesenteric tissue is the most frequently positive resection margin in patients with pancreatic cancer undergoing pancreaticoduodenectomy. Furthermore, a limited examination would have failed to detect a positive SMA or SMV/PV margin in as many as 26% of patients. Due to the prognostic significance of microscopically involved margins (R1 resection) on clinical outcome, comprehensive examination to include the mesenteric margins is recommended.

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#### THE EFFECT OF CISPLATIN INTRA-ARTERIAL INFUSION WITH RADIOTHERAPY AS A TREATMENT FOR UNRESECTABLE ADVANCED PANCREATIC CARCINOMA

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Cisplatin has been reported to enhance the cell-killing effect of radiation. The purpose of this study was to evaluate the feasibility and effectiveness of radiotherapy combined with cisplatin arterial infusion in patients with unresectable advanced pancreatic carcinoma. Between June 1999 and December 2003, thirty-three patients (Stage IVa without distant metastasis: n = 19, Stage IVb with distant metastasis: n = 14, Japan Pancreas Society: the fifth edition) from our facility were enrolled in this study. Pretreatment staging included chest X-ray, ultrasonography, dynamic computed tomography, and angiography of the abdomen. Causes of unresectability consisted of local invasion (obstruction or extensive invasion of the portal vein and/or tumor encasement of the celiac or superior mesenteric artery) and liver metastasis. The patients studied were treated with external beam radiation (1.8-2.0 Gy/fraction, 5 fractions/week, total: 40-50 Gy), cisplatin intra-arterial infusion (5 mg/m<sup>2</sup>/day intra-arterial infusion just before each radiation fraction) and 5-FU intravenous infusion (250 mg/m<sup>2</sup>/day). Prognosis was compared with a control group of 63 patients who had undergone pancreatectomy for stage IVa and stage IVb of pancreatic carcinoma. The major toxicity of cisplatin intra-arterial infusion with radiotherapy was nausea (2/33, 6%). In patients treated by intra-arterial infusion with radiotherapy, the median survival time of the stage IVa group and the stage IVb group was

12.9 ± 4.1 months (M) and 5.9 ± 0.8 M, respectively, which was not statistical by different from the control groups (13.6 ± 6.3 M and 6.0 ± 1.1 M, respectively). The 1-year survival rate was 42% (8/19) and 21% (3/14), respectively, which was comparable to the control groups (42% [21/50] and 15% [2/13], respectively). This arterial chemo-radiation regimen is effective for locally advanced pancreatic carcinoma with acceptable toxicity.

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#### SURGICAL TREATMENT OF TUMORS OF THE AMPULLA OF VATER

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Tumors of the ampulla of Vater are rare. Ampullary carcinoma have a significantly higher resectability rate and better prognosis than other carcinoma originating in the periampullary area. The most authors suggest radical resection as treatment of choice for carcinoma of the ampulla. Alternatively some investigators have recommended local resection to reduce treatment related mortality and morbidity rates. Adequate treatment of benign tumors of the ampulla is still a matter of debate. Due to a suspected adenoma-carcinoma sequence some argue that partial pancreaticoduodenectomy is mandatory. Others believe that local excision is sufficient in these patients. The purpose of this prospective study was to evaluate clinical course, surgical management, and outcome of patients operated for malignant and benign tumors of the ampulla of Vater; 202 consecutive patients undergoing surgical treatment for ampullary tumors between 1983 and 2003 were observed; 69% of all tumors were malignant, the remaining were benign neoplasm (n = 64); and 138 patients with ampullary adenocarcinoma were treated by classical pancreaticoduodenectomy (PR) in 36% and pylorus-preserving resection (PPPR) in 31%. Ampullectomy was performed in elderly patients with high cardiac risk (8%). Palliative bypass procedures were performed in 25%. 58 patients suffering from a benign tumor underwent ampullectomy. Due to macroscopical appearance suspicious for a malignant tumor, PPPR was performed in 6 cases for benign lesions. 72% of all patients with benign neoplasm exhibited a tubulovillous or villous adenoma with medium or severe degree of dysplasia. Hospital mortality for all resected patients was 2.6%. The 1-, 3-, and 5-year survival after radical resection for patients with adenocarcinoma was 83.1%, 62.2%, and 53.8%, respectively. 62 patients with benign neoplasm are still alive without evidence of recurrent disease (97%). Radical resection for ampullary cancer can be performed with a low mortality and morbidity. PPPR is the surgical treatment of choice for carcinomas of the ampulla of vater. Ampullectomy is an adequate procedure in treating benign ampullary lesions. The decision-making should be based on pre- and even more eminent intraoperative frozen section histology. If the histology is uncertain PPPR should be performed