1443 POSTER

Missed abdominal oncological diseases during laparoscopic cholecystectomy

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Background: One of lacks of videolaparoscopic cholecystectomy is the absence of manual exploration of abdominal cavity with the purpose of revealing of a possible concomitant pathology. The opportunities of the visual control and palpation of organs by manipulators for diagnostics of oncological diseases are limited.
Methods: Follow-up of 3000 laparoscopic cholecystectomies has shown 10 cases (0.3%) of missed oncological diseases, when the patients were operated on after laparoscopic cholecystectomy in terms from 4 months till 1 year. Among observed were 3 men and 7 women in the age from 42 till 80 years. The stenosing cancer of a stomach was revealed in 1 patient, the tumour of hepatic flexure of the colon in 2, the tumor of the head of the pancreas in 2, tumor of common bile duct in 1, cancer of endometrium in 1, cancer of the caecum in 2, cancer of the low third of the rectum in 1 patient. Retrospective study of case reports revealed that all the patients were subjected only to the ultrasonic research of abdominal cavity. However, analysis of the complaints of the patients exposed that in 8 of 10 cases there were symptoms of abdominal discomfort characteristical to stomach and colon ailment and not typical to clinical picture of gallstone desease.
Results: All patients were operated on by using laparotomy. Partial distal gastrectomy was carried out in 1 patient, right gemycolectomy in 4, gysterectomy in 1, abdomino-perineal extirpation of the recrum in 1, biliodigestive shunt in 3. Postoperative course in all patients was uneventful.
Conclusion: The prophilaxis of missed oncological pathology during laparoscopic cholecystectomy consist in more thorough preoperative investigation of the patients with gallstone desease. In patients senior than 40 years, it is advisable alongside with ultrasonic research of abdominal cavity to carry out endoscopic exploration of a stomach and colon and in women it is highly recommended to perform complete gynecological inspection.

1444 POSTER

Surgical treatment of bilobar hepatic metastases

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Background: Bilobar hepatic metastases represent one of the greatest challenges in surgical treatment of metastatic disease20% of patients with hepatic metastases have bilobar hepatic metastases. During the last decade significant technical achievements made radical surgical procedures safer In R0 resection 5-year survival is between 13% and 28% depending on various prognostic factors.
Surgical strategy for hepatic resection must satisfy two contradictory goals:
1. To accomplish metastases free resectional margins
2. To preserve as much as possible hepatic parenchyma for normal liver function and maybe for future resections

Material and methods: Combining hepatic resection (CUSA) and radio-frequent ablation (RADIONIX) we managed to satisfy both oncological radicality and preservation of sufficient amount of healthy liver parenchyma. We use this technique if there is a large metastatic lesion in one of the lobes needed to be resected and one or more lesions in the opposite lobe which if resected would compromise function of spared liver. During the period 2002 till the August 2004, we had 57 patients with bilobar hepatic metastases where we performed combine treatment –**resection + ablation**. 30 patients had colon and rectum metastases; 27 patients with metastases from other origin.
Results: There were no intra- and postoperative mortalities. 5 patients were febrile on the 4th postoperative day. Two patients died in the period of 6 to 8 months after surgery. Three patients died year after resection. Two patients have died from extra hepatic disease and three from multiple liver recurrence. Two patients had recurrent liver disease after one year and were reoperated radically once again and they are still alive. Till now all other patients are still alive without recurrence on the liver
Conclusion: Surgical treatment of metastases should be applied whenever possible. Combined approach allows removal of metastases with preservation of sufficient amount of liver parenchyma. Combined approach represents a safe method in the treatment of metastatic liver disease

1445 POSTER

The safe and reliable method of duct to mucosa pancreaticojejunostomy and extremely favorable results of 50 consecutive cases.

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Background: There is a high risk of anastomotic leakage after pancreaticojejunostomy. Pancreatic anastomotic leakage often results in severe complications of sepsis, intra-abdominal bleeding, pancreatic fistula, and is a significant cause of morbidity and mortality. An appropriate technique to minimize pancreatic leakage is very important. Recently we have performed duct to mucosapancreaticojejunostomy with resection of jejunal serosa and obtained positive results.
Patients and methods: During 1999–2005, 50 patients (24 female, 26 male) underwent duct to mucosa pancreaticojejunostomy with resection of jejunal serosa after pancreatic head resections for benign (n = 5) and malignant disease (n = 45). The mean age was 64.1 years (range 33–80).
Results: Mean post-operative hospital stay was 32.2 days. Morbidity rate due to early postoperative complication was 4% (pulmonary embolism in 1, pneumothorax in 1), with no pancreatic leakage.
Conclusions: There were low complication rate and an absence of pancreatic anastomotic leakage that occurred with 50 consecutive patients who underwent duct to mucosa pancreaticojejunostomy with resection of jejunal serosa. We consider that this pancreatic anastomotic technique is extremely favorable for pancreaticojejunostomy.

1446 POSTER

Factors influencing breath functions of oncology patients after thoracoscopic surgery

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The purpose of the research was to study the factors influencing breath of oncology patients who underwent thoracoscopic surgical procedure.
We evaluated breath functions of 30 patients before and 3 days after thoracoscopic surgery (21 lung resections, 9 tumour biopsies) using Flowscreen Pro spiroanalyser (Jager, Germany) and ABL-520 blood gas analyser (Radiometr, Denmark). On average, procedures lasted 34±8 minutes under general anaesthesia with pneumothorax on the side of the surgery. Generally, breath characteristics of all the patients before the procedure were at the lowest level but after the procedures VC and FVC reduced by 18.7%, PEF – by 24.2%, MEF_{50} – by 16.9%, MVV – by 18.25%. Other breath parameters and blood gas concentration did not change. Age and invasion level (lung resection, biopsy) did not affect breath functions. However, reduction of the indicated parameters in the patients with initially disturbed breath functions (n = 9) resulted in shortness of breath (II degree). Breath functions of patients with initially normal breath functions (n = 21) were low but still within normal range. Thus, shortness of breath does not develop in the patients with initially normal breath after thoracoscopic surgery. At the same time, the risk of getting shortness of breath raises dramatically for the patients with initially low breath characteristics irrespective of age and invasion scale.

1447 POSTER

The greater omentum in surgical treatment of radionecrosis in breast cancer patients

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The indications and techniques for surgical treatment of radionecrosis in breast cancer patients are presented. Surgical excision of radionecrotic tissues with reconstruction by well vascularised tissues is an effective mode of treatment. The flaps from neighbourhood (rotation or transposed) are good methods for wound covering after resection of ulceration. In case of breast cancer the thoracic wall defect may be covered by a flap of the opposite breast or latissinmus dorsi (LD) flap. In case of large and deep radionecrosis involving whole thickness of thoracic wall the greater omentum flap is an optimal solution for reconstruction of the defect created after excision of postradiation necrotic tissues. The greater omentum has a very good blood supply, produces an angiogenic factor promoting proliferation of vessels to underlying tissues, is resistant to infection and skin flaps or free skin grafts heals on it very well.
The greater omentum can be transposed on the chest wall after dissection from transverse colon and stomach, leaving a pedicle containing the left or right gastroepiploic vessels.

The clinical course of five patients after accidental overexposure of radiotherapy is presented. On February 27th 2001 in Bia3ystok Oncology Center (BOC) five patients treated by radiotherapy for breast cancer were accidentally overexposed. All patients developed necrotic ulcerations involving chest wall structures, and were qualified to surgical treatment. Three patients were operated in HCC and two at IC. The patients has been locally cured and followed up two years after operation. Surgical excision of necrotic tissues with reconstruction by well vascularised tissues is an effective mode of treatment of postradiation injures. The use of greater omentum flap is an optimal solution for this purpose.

Translational Research

Oral presentations (Tue, 1 Nov, 9.15–11.15)
Translational research

1448 ORAL

Molecular pharmacodynamic (MPD) phase I study with serial tumor and skin biopsies of the oral mTOR inhibitor Everolimus (E, RAD001) at different doses and schedules in patients (pts) with advanced solid tumors

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Background: E is an orally active derivative of rapamycin with antiproliferative effect shown in several human tumor models, *in vitro* and *in vivo*. E inhibits mTOR, a serine/threonine protein kinase downstream of PI3K and AKT, involved in the regulation of cell growth, proliferation and survival. In preclinical models, the administration of E is associated with reduction in downstream phosphorylated(p)-S6 (p-S6) and p-4EBP1, and increased upstream AKT phosphorylation (p-AKT). This study explores safety, drug levels and MPD changes in serial tumor and skin biopsies at different doses and schedules of E to help to define the recommended dose for further development.
Methods: Pts were treated in successive cohorts of E: weekly (WK) 20, 50 and 70 mg or daily (D) 5 and 10 mg. Dose escalation depended on dose limiting toxicity (DLT) rate during the first 4 weeks of treatment. Pre- and on-treatment steady-state (week 4 or 5: 24hr post-dose and, for the WK schedule, 5 days post-dose) tumor and skin biopsies were obtained from each pt. Biopsies were evaluated by immunohistochemistry for total and p-S6, p-4EBP1, p-eIF4G, p-AKT and Ki67 expression.
Results: 55 pts were treated with 6–8 fully evaluable pts in each cohort. Grade 3 DLT in 5 pts included stomatitis (1 pt at 10 mg/d, 2 at 70 mg/wk), neutropenia and hyperglycemia (1 pt each at 70 mg/wk). There was one partial response (colon cancer) and 4 stabilizations of >4 months (renal cell, melanoma, breast cancer in 2 pts). MPD studies demonstrated a dose and schedule-dependent inhibition of the mTOR pathway in tumor and skin after E treatment. In the D schedule, p-S6 and p-eIF4G were highly inhibited at 5 mg and completely inhibited at 10 mg, whereas p-AKT was upregulated in some patients in both cohorts. In the WK schedule p-S6 inhibition was complete and sustained at all levels, p-eIF4G only at doses *50 mg, whereas p-AKT was upregulated although unsustained, at doses *50 mg. No MPD distinction was evident between pts with clinical benefit and those without. Preliminary PK/MPD modeling shows a moderate correlation between trough concentration in blood and certain MPD effects in the D schedule.
Conclusions: This phase I study shows that E, at the doses and schedules studied, results in similar mTOR signaling inhibition in tumor and skin. Based on the safety and MPD findings, a dosage of 10 mg/d can be recommended for further phase II-III studies with E as a single agent.

1449 ORAL

A phase I/II trial to assess tolerability and efficacy of RAD-001 with gefitinib in patients with glioblastoma multiforme and castrate metastatic prostate cancer

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Background: This trial tested the hypothesis that simultaneous inhibition of both the EGFR and mTOR pathways will have antitumor efficacy in patients with PTEN deficient tumors, specifically advanced prostate cancer (PC) and glioblastoma multiforme (GBM). RAD-001 (RAD) is an orally available inhibitor of mTOR, a serine-threonine kinase located downstream of Akt that regulates cellular growth. Animal models have shown that markers for RAD activity include p70 S6 kinase, and that FDG-PET uptake intensity may reflect mTOR inhibition. While previous data suggest that EGFR inhibition alone will be ineffective in patients with PTEN deficient tumors, combination therapy with mTOR and EGFR inhibitors may be synergistic.
Methods: Patients with progressive castrate metastatic PC or GBM were eligible. Phase I was designed to determine safety and pharmacokinetics (PK) of an escalating dose of RAD (30/ 50/ 70 mg po weekly) and a fixed dose of gefitinib (250 mg po qd). A 3-week lead-in period allowed for toxicity and PK assessment of each drug alone. Patients initiated combination therapy at week 4. Immunohistochemical (IHC) staining of markers for drug activity was performed. Phase II evaluated the efficacy of the combination. PET scans and p70 S6 kinase assays were evaluated pre- and post-therapy in both phases.
Results: 12 patients (2 GBM, 10 PC) were treated in phase I, 6 patients at the highest dose level. No dose-limiting toxicities were observed. Grade 3 or 4 events possibly related to treatment were limited to grade 3 lymphopenia (25%). No patient had a PSA decline of $\geqslant$50% and no patient showed an objective radiographic response. PET scans showed decreased FDG uptake in some patients. PK parameters (tmax, Cmax and AUC) estimated by non-compartmental analyses suggested no clinically relevant PK interaction between RAD and gefitinib. Results from phase I suggested a phase II dose of RAD of 70 mg weekly with gefitinib 250 mg qd. Phase II accrual is ongoing with 16 patients (7 GBM, 9 PC) treated. An insufficient number of phase II outcomes are available to assess activity.
Conclusions: Combination therapy with RAD 70 mg weekly and gefitinib 250 mg daily appears to be safe. Antitumor activity with the drug combination on this schedule was not observed in the phase I portion of the study. A decrease in SUV FDG-PET imaging may correlate with RAD activity. IHC staining of tumor biopsies are pending.
Support: Novartis Pharmaceuticals, AstraZeneca Pharmaceuticals

1450 ORAL

Clinical synergism from combinatorial VEGF signal transduction inhibition in patients with advanced solid tumors – early results from a phase I study of sorafenib (BAY 43–9006) and bevacizumab

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Background: A number of signal transduction inhibitors (STIs) have come to clinical trials and have yielded mixed results. The majority of these agents appear to be cytostatic despite cytoxicity in preclinical models. We hypothesized that the combination a VEGF inhibitor and a tyrosine kinase inhibitor with activity against VEGFR2 will produce supra-additive effects in patients.
Methods: We have opened a phase I study of sorafenib (BAY) and bevacizumab (BEV) for patients with refractory solid tumors. This study is designed to both determine the maximum tolerated dose and a biologically effective dose of this combination. All patients have initiated treatment with BAY 200 mg bid. BEV was given at 5 mg/kg every 2 weeks at dose level (DL) 1; at DL2, 10 mg/kg was administered every 2 weeks. These are doses below those used in phase II clinical studies. Dose reductions were applied for drug-related toxicity. A 6-week delay was required between DL1 and DL2.
Results: Twelve patients have been enrolled since the trial opened in December 2004: 7 ovarian cancers (EOC), 2 renal cell carcinoma (RCCA), 2 melanoma, and 1 colon cancer. A synergy between the two agents was observed in both toxicity and clinical response. No grade 4 toxicities have been observed. Dose limiting toxicities have been seen at DL2 including hypertension, hand–foot syndrome, fatigue, diarrhea, elevated lipase, proteinuria, and thrombocytopenia. Other observed toxicities have been grade 1 and 2 and include neuropathy, rhinorrhea, weight loss, and anorexia. The maximum tolerated dose for continuously administered BAY with q2week BEV was determined to be 200 mg bid + 5 mg/kg, respectively. A cytotoxic clinical effect was seen in both dose levels with partial responses (5+ mos.; 3+ mos. – figure) in 2 of 7 heavily pretreated chemo-refractory ovarian cancer patients. Nine of the remaining patients have stable disease to minor tumor shrinkage. All 12 patients treated have experienced clinical benefit and disproportionately greater toxicity than would be predicted based on individual agent activity.
Conclusions: A clinical synergy was observed with the administration of BAY-BEV. This synergy is reflected in both anti-tumor effect and toxicity. We are proceeding to examine the individual contributions of the agents using sequential biopsies with proteomic analysis, biological imaging including PET and DCE-MRI, and pharmacokinetic/pharmacogenomics analysis.