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COPE GUIDELINES

Consensus Statement on the Adoption of the COPE Guidelines

We, the undersigned editors of the member journals of the Surgery Journal Editors Group (SJEG), in the furtherance of integrity in surgical and scientific publication, agree to adopt the guidelines established by the Committee on Publication Ethics (COPE)[1]. The COPE guidelines represent a means of addressing a variety of ethical concerns, including duplicate publication and authorship misconduct issues, which have, unfortunately, become more prevalent.

This statement is being simultaneously published in the respective journals of the members of the Surgery Journal Editors Group, as follows:

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2009 SSAT POSTER PRESENTATION MANUSCRIPT

Esophageal Replacement Following Gastric Devascularization Is Safe, Feasible, and May Decrease Anastomotic Complications

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Abstract
Background Gastric transposition is the most common reconstruction after esophagectomy. Despite technical improvements, the incidence of anastomotic complications remains high. Gastric devascularization followed by esophageal resection and reconstruction has been proposed to minimize these complications.
Methods Thirty-two patients underwent minimally invasive esophagectomy, and seven high-risk patients were selected for laparoscopic gastric devascularization performed either 1 week (n=5) or 12 weeks (n=2) before esophageal resection. Primary outcomes included anastomotic leak and stricture.
Results Each patient underwent successful laparoscopic devascularization and subsequent esophagectomy. Devascularization required an average of 134 minutes with minimal operative blood loss. There were no complications following gastric devascularization or directly attributable to delay. None of the delay patients developed an anastomotic leak, compared to 16% of patients after immediate reconstruction (p=0.258). One patient (14%) developed an anastomotic stricture that required endoscopic dilatation within the first year after surgery, compared to 12% of immediate reconstruction patients (p=0.872).
Conclusion In this series, all patients underwent successful delayed reconstruction following gastric devascularization without anastomotic leak. The absence of anastomotic leak in the delay group suggests that delayed conduit preparation can be accomplished safely while potentially reducing the morbidity associated with esophagectomy, but larger prospective studies are required to prove this definitively.

Keywords Esophageal replacement · Gastric conduit · Anastomotic complications

Introduction

Gastric pull-up reconstruction following esophagectomy is the most common method of esophageal replacement following resection for malignant or end-stage benign esophageal disease. However, this procedure carries a high postoperative morbidity, with anastomotic leakage occurring in up to 20% of cases.[1–8] Ischemic changes within the anastomosed gastric fundus, resulting from altered arterial inflow and venous drainage, have been implicated in the development of anastomotic complications.[9–14] Studies quantifying gastric vascularization have demonstrated impaired perfusion resulting from decreased capillary density in the proximal aspect of the gastric conduit.[9,10] It is postulated that this leads directly to distal end-organ ischemia and, subsequently, anastomotic leak and stricture.

These data were presented in poster form at the Annual Meeting of the Society for Surgery of the Alimentary Tract in Chicago, IL, on June 2, 2009.

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Human and animal studies have shown that devascularization of the stomach, followed by delayed resection and gastroesophageal reconstruction, may allow neovascularization of this portion of the stomach and improve wound healing at this tenuous anastomosis.[15–22] This study describes our surgical technique and early experience with laparoscopic gastric devascularization (LGD) and delayed minimally invasive gastric tube reconstruction following esophagectomy in the context of existing experimental and clinical literature.

Methods

Patients

Between July 2005 and June 2008, 32 patients underwent minimally invasive esophagectomy (MIE) for cancer using combined thoracoscopic–laparoscopic esophagectomy (TLE) with cervical esophagogastrostomy, as previously described.[23] Seven patients deemed high risk for esophagectomy due to poor cardiopulmonary performance status were selected for LGD with delayed esophageal resection and reconstruction. All patients had a tubularized gastric conduit for esophageal replacement.

LGD was performed 1 week before surgical resection in patients undergoing primary surgical resection (n=5) or 12 weeks (n = 2) before esophageal resection in patients receiving neoadjuvant radiochemotherapy. The primary outcome measure for this study was clinically significant cervical anastomotic leak defined by the presence of clinical signs of anastomotic breakdown with radiographic confirmation. Secondary outcome measures included the presence of an symptomatic anastomotic stricture requiring endoscopic therapy and operative morbidity related to LGD. Patient data are maintained in a prospective database approved by the Institutional Review Board of the Oregon Health and Science University. Specific informed consent was obtained from all patients for each surgical procedure, as was consent for data collection.

Technique of LGD

LGD is performed with the patient in supine split-leg position. The surgeon stands between the patient's legs, with the first assistant on the patient's left side. A five-port technique (two 5-mm ports, one 11-mm port, and two 12-mm ports) is used. The primary access point is an 11-mm camera port placed approximately 17 cm caudal to the xyphoid process and 2–3 cm to the left of the midline. The surgeon's right-hand port is placed along the left costal margin 12 cm from the tip of the xyphoid process. The primary assistant port is a 5-mm trocar placed in the anterior axillary line along the left costal margin. A Nathenson liver retractor (Cook Surgical, Bloomington, IN) is placed to the left of the xyphoid process and used to retract the left lobe of the liver upwards and to expose the esophageal hiatus. The surgeon's left-hand port is placed inferior to the right costal margin and through the falciform ligament with a slightly cephalad trajectory.

The operation begins with a complete abdominal exploration to evaluate the presence of metastatic disease. If no metastasis is encountered, attention is directed to the greater curvature of the stomach at the level of the inferior pole of the spleen. Care is taken to identify and preserve the terminal branches of the right gastroepiploic artery, and all of the short gastric vessels are divided using ultrasound dissection. A more extensive posterior gastric mobilization is not performed at this time in order to preserve tissue planes and to facilitate complete lymphadenectomy at the time of esophagectomy. The pars flacida of the gastrohepatic omentum is then opened to expose the left gastric artery and coronary vein. These vessels are skeletonized and divided near the origin of the left gastric artery using a vascular stapler. Next, a feeding jejunostomy tube is placed in the proximal jejunum using a percutaneous overwire technique.

Technique of Esophagectomy

All esophageal resections in this series were performed using combined TLE with cervical esophagogastrostomy, as previously reported.[21] Briefly, TLE begins with thoracoscopic esophageal mobilization performed with the patient in left lateral decubitus position. The mediastinal pleura overlying the esophagus is opened, and circumferential dissection of the esophagus and its surrounding lymphatic tissue is performed en bloc from the azygous vein to the level of the diaphragmatic hiatus. After the thoracic dissection is completed, two chest tubes are inserted, and the patient is placed in supine split-leg position. Gastric mobilization begins with the hiatal dissection and division of the left gastric artery at its base (unless previously performed in the LGD group), with care taken to maintain all periesophageal lymphatic tissues en bloc with the operative specimen. For patients who had undergone prior gastric devascularization, lymphadenectomy was completed at the time of esophageal resection, with care taken to identify the previously divided left gastric artery and coronary vein. The greater curvature and posterior stomach are completely mobilized, and Kocher maneuver is performed. A stapled gastric tube (3–5 cm) is created beginning on the lesser curve 5 cm proximal to the pylorus. The distal esophagus is mobilized with its accompanying lymphatic tissue until the thoracic dissection is reached. The cervical esophagus is exposed through a transverse left

lateral neck incision and divided. The esophageal specimen is removed through the cervical incision after suturing the conduit to the distal portion of the specimen. Gastroesophageal anastomosis is created using the linear stapled technique described by Orringer et al.[24]

Data Analysis

Data are presented as mean (± standard deviation) or median (range), where appropriate. Statistical analyses were performed using Stata 10 software (StataCorp. LP, College Station, TX). Comparisons between dichotomous variables were performed using chi-square test.

Results

All selected patients underwent successful LGD and subsequent esophagectomy. LGD required an average of 134 (± 44) min to complete, and the median blood loss was 50 (5–125) ml. There were no postoperative complications, and each patient was discharged on the following day after overnight observation. Five patients subsequently underwent MIE with reconstruction at a median of 8 (6–9) days following LGD, and two underwent esophagectomy after completing neoadjuvant radiochemotherapy (105 and 196 days after LGD). None of the LGD patients developed a cervical anastomotic leak compared to 16% (n=4) of patients who underwent immediate reconstruction (p=0.258). One (14%) patient who underwent delayed reconstruction developed an anastomotic stricture that required endoscopic dilatation within the first year of surgery, compared to three (12%) patients who underwent immediate reconstruction (p = 0.872). Following esophagectomy, two patients in the ischemic conditioning group developed atrial fibrillation, two developed postoperative pneumonia, and one of them developed acute respiratory distress syndrome. These complication rates are consistent with the rates seen following MIE with immediate reconstruction in our experience.[23]

Discussion

Dehiscence of esophagogastric anastomosis remains a dreaded and common complication of esophagectomy, occurring in up to 20% of cases.[1–8] Creation of the gastric conduit for esophageal replacement requires interruption of three of the five vessels that provide blood flow to the gastric fundus. Anatomic studies have demonstrated that division of the left gastric artery, left gastroepiploic artery, and short gastric artery renders the gastric conduit almost solely dependent on blood flow from the right gastroepiploic artery via a network of intramural capillaries.[9] Decreased perfusion in the area of the anastomosis produces a state of relative ischemia that has been implicated in the high incidence of gastroesophageal anastomotic leaks. It has been postulated that gastric devascularization, followed by a delay period prior to esophageal resection and reconstruction, allows the gastric fundus to recover from this ischemic insult prior to the creation of an anastomosis. Enhanced perfusion of the gastric fundus improves anastomotic healing and may decrease the morbidity associated with esophageal resection.

Several animal models have been used to examine the role of gastric devascularization in improving blood flow and anastomotic healing. Urschel[15] performed gastric devascularization in rats and found an 81% relative increase in blood flow after 14 days. Subsequently, Urschel demonstrated decreased anastomotic leak rates and increased anastomotic burst strength when esophagogastric anastomosis was performed 3 weeks after gastric devascularization.[16] In an opossum model of esophagogastrostomy, Reavis et al.[17] showed a marked decrease in fundic blood flow following gastric devascularization and a threefold increase in blood flow at the level of anastomosis following a 28-day delay compared to immediately reconstructed animals. The authors also demonstrated increased angiogenesis and decreased collagen deposition following devascularization and delay.

In the clinical arena, Akiyama et al.[18] sought to increase blood flow to the tip of the gastric conduit via preoperative embolization of the right gastric artery, left gastric artery, and splenic artery. Patients who underwent successful embolization followed by esophagectomy had an anastomotic leak rate of 2%, compared to 8% of patients who underwent reconstruction without gastric devascularization. Despite the apparent improvement in gastric perfusion, this approach was associated with complications including abdominal pain, nausea, vomiting, splenic infarction, and pancreatitis. Recently, Hölscher et al.[19] performed LGD followed 4 days later by transthoracic esophagectomy and demonstrated that LGD can be performed safely with an intrathoracic anastomotic leak rate of 6%. Another series demonstrated that ischemic conditioning performed 2 weeks prior to esophagectomy reduced conduit-related morbidity from 20% to 10% compared to immediate reconstruction.[20]

The results of our series are similar to those reported by Nguyen et al.[21] who reported nine successful laparoscopic devascularizations without complications, and suggest that this procedure may be performed in a timely manner with minimal complications during the staging of laparoscopy and may be coupled with placement of a feeding jejunostomy as dictated by patient symptoms. Although LGD appears safe and reasonable, several issues require further study, including which vessels must be divided to achieve a demonstrable clinical benefit, identifying the optimal duration of delay, and quantifying the effects of devascula-

rization on tumor angiogenesis and delivery of chemotherapeutic agents.

It remains unclear which vessels must be divided to create a degree of fundic ischemia that is sufficient to generate significant clinical benefit. Some authors advocate dividing only the left gastric vessels, whereas other human and animal studies have employed more extensive devascularizations.[15–20,25,26] Anatomic studies have suggested that the gastric conduit created for esophageal replacement is dependent almost entirely on flow from the right gastroepiploic artery, and that the left gastric artery and short gastric artery provide significant blood flow to the gastric fundus in the native stomach.[9] Our group has demonstrated that during gastric conduit creation, division of the short gastric vessels alone produces no significant decrease in mixed arterial–venous oxygen saturation at the tip of the gastric conduit, but a marked decrease occurs with the addition of left gastric artery and coronary vein division.[24] These data suggest that generating significant gastric ischemic changes in the region of the proposed anastomosis requires interruption of both the left gastric vessel and the short gastric vessel.

While the division of the left gastric artery and coronary vein may lead to a more effective gastric ischemic conditioning, there are concerns about the effect of this procedure on subsequent lymphadenectomy at the time of esophageal resection. In our institution, complete celiac lymph node dissection is performed in all cases. Celiac dissection following a 7-day delay, although more difficult than that performed after immediate reconstruction, was not significantly impacted by the presence of adhesions. In patients with longer delay periods, however, scarring around the staple line at the left gastric artery division made the dissection much more difficult. One possible way to alleviate this concern is to divide the left gastric artery at a more distal location during ischemic conditioning in order to preserve the planes of dissection for celiac lymphadenectomy at the time of esophageal resection.

The optimal duration of delay prior to esophagectomy and reconstruction is unknown. Most clinical studies published to date have utilized short delays ranging from 4 to 9 days, but with questionable clinical benefit.[18–20] The only large series published to date showed an anastomotic leak rate similar to that reported in the literature.[19] Veeramootoo et al.[22] however, showed that LGD performed 2 weeks prior to esophagectomy resulted in a significant reduction in gastric conduit ischemia compared to LGD performed 5 days before resection, indicating a time-dependent influence of ischemic conditioning. Animal studies reporting objective evidence of improved gastric perfusion and anastomotic wound healing have used longer delay periods of 3–4 weeks.[15–17] The rationale for shorter periods of delay in human studies centers around the potential for difficult dissections following longer delays due to postoperative adhesions. Two patients in this series underwent esophagectomy approximately 12 weeks after LGD. In these patients, we found minimal scarring in the area of the mobilized greater curve; however, significant adhesions were present in the area of the left gastric artery transection, making celiac lymph node dissection difficult. Further studies are required to quantify the optimal duration of delay following gastric devascularization. Should longer delay periods prove beneficial, technical refinements may allow interruption of left gastric artery flow with preservation of the tissue planes utilized for celiac lymphadenectomy.

Experimental and clinical studies performed to date have not examined the impact of additional surgical stress on tumor angiogenesis, or the potential influence of gastric devascularization on the delivery of neoadjuvant chemotherapeutic agents to gastroesophageal junction tumors. Although the delay phenomenon appears to have the potential to improve gastric perfusion and anastomotic healing, prospective comparative studies are required to evaluate the technique of gastric devascularization, the duration of delay, and its effects on anastomotic complications, tumor angiogenesis, chemotherapy delivery, and overall survival.

Conclusion

LGD with delayed esophageal resection and reconstruction can be safely performed with minimal morbidity, even in high-risk patients. The absence of anastomotic leaks in this small group of patients suggests that LGD may prove to reduce the incidence of anastomotic complications after esophagectomy. However, larger comparative studies are required to quantify the benefits and to determine the optimal timing of esophagectomy following gastric devascularization.

References

1. Orringer MB, Marshall B, Jannettoni MD. Transhiatal esophagectomy: clinical experience and refinements. Ann Surg 1999;230:392–403.
2. Ando N, Ozawa S, Kitagawa Y, et al. Improvement in the results of surgical treatment of advanced squamous cell esophageal carcinoma during 15 consecutive years. Ann Surg 2000;232:225–230.
3. Siewert JR, Stein HJ, Feith M, et al. Histologic tumor type is an independent prognostic parameter in esophageal cancer: lessons from more than 1,000 consecutive resections at a single center in the western world. Ann Surg 2001;234:360–369.
4. Holscher AH, Schroder W, Bollschweiler E, et al. How safe is high intrathoracic esophagogastrostomy? Chirurg 2003;74:726–733.
5. McCulloch P, Ward J, Tekkis PP. Mortality and morbidity in gastrooesophageal cancer surgery: initial results of ASCOT

multicenter prospective cohort study. BMJ 2003;327:1192–1197.
6. Rentz J, Bull D, Harpole D, et al. Transthoracic versus transhiatal esophagectomy: a prospective study of 945 patients. J Thorac Cardiovasc Surg 2003;125:1114–1120.
7. Valverde A, Hay JM, Fingerhut A, et al. Manual versus mechanical esophagogastric anastomosis after resection for carcinoma: a controlled trial. Surgery 1996;120:476–483.
8. Briel JW, Tamhankar AP, Hagen JA, et al. Prevalence and risk factors for ischemia, leak and stricture of esophageal anastomosis: gastric pull-up versus colon interposition. J Am Coll Surg 2004;198:536–541.
9. Liebermann-Meffert DMI, Meier R, Siewert JR. Vascular anatomy of the gastric tube used for esophageal reconstruction. Ann Thorac Surg 1992;54:1110–1115.
10. Pierie JP, De Graaf PW, Poen H, et al. Impaired healing of cervical esophagogastrostomies can be predicted by estimation of gastric serosal blood perfusion by laser Doppler flowmetry. Eur J Surg 1994;160:599–603.
11. Urschel JD. Esophagogastrostomy anastomotic leaks complicating esophagectomy: a review. Am J Surg 1995;169:634–640.
12. Boyle NH, Pearce A, Hunter D, et al. Scanning laser Doppler flowmetry and intraluminal recirculating gas tonometry in the assessment of gastric and jejunal perfusion during oesophageal resection. Br J Surg 1998;85:1407–1411.
13. Schroder W, Stippel D, Lacher M, et al. Intraoperative changes of mucosal pCO_2 during gastric tube formation. Langenbecks Arch Surg 2001;386:324–327.
14. Schroder W, Beckurts KTE, Stähler D, et al. Microcirculatory changes associated with gastric tube formation in the pig. Eur Surg Res 2002;34:411–417.
15. Urschel JD. Esophagogastric anastomotic leaks: the importance of gastric ischemia and therapeutic applications of gastric conditioning. J Invest Surg 1998;11:245–250.
16. Urschel JD, Antkowiak JG, Delacure MD, Takita H. Ischemic conditioning (delay phenomenon) improves esophagogastric anastomotic wound healing in the rat. J Surg Oncol 1997;66:254–256.
17. Reavis KM, Chang EY, Hunter JG, Jobe BA. Utilization of the delay phenomenon improves blood flow and reduces collagen deposition in esophagogastric anastomoses. Ann Surg 2005;241:736–745.
18. Akiyama S, Ito S, Sekiguchi H, et al. Preoperative embolization of gastric arteries for esophageal cancer. Surgery 1996;120:542–546.
19. Hölscher AH, Schneider PM, Gutschow C, Schröder W. Laparoscopic ischemic conditioning of the stomach for esophageal replacement. Ann Surg 2007;245:241–246.
20. Berrisford RG, Veeramootoo D, Parameswaran R, et al. Laparoscopic ischaemic conditioning of the stomach may reduce gastric-conduit morbidity following total minimally invasive oesophagectomy. Eur J Cardiothorac Surg 2009;36:888–893.
21. Nguyen NT, Longoria M, Sabio A, et al. Preoperative laparoscopic ligation of the left gastric vessels in preparation for esophagectomy. Ann Thorac Surg 2006;81:2318–2320.
22. Veeramootoo D, Shore AC, Shields B, et al. Ischemic conditioning shows a timedependent influence on the fate of the gastric conduit after minimally invasive esophagectomy. Surg Endosc 2010;24:1126–1131.
23. Perry KA, Enestvedt CK, Diggs BS, Jobe BA, Hunter JG. Perioperative outcomes of laparoscopic transhiatal inversion esophagectomy compare favorably to those of combined thoracoscopic–laparoscopic esophagectomy. Surg Endosc 2009; E-pub ahead of print. doi:10.1007/s00464-008-0249-6.
24. Orringer MB, Marshall B, Iannettoni MD (2000) Eliminating the cervical esophagogastric anastomotic leak with a side-to-side stapled anastomosis. J Thorac Cardiovasc Surg 119:277–288.
25. Varela E, Reavis KM, Hinojosa MW, Nguyen NT. Laparoscopic gastric ischemic conditioning prior to esophagogastrectomy: technique and review. Surg Innov 2007;15:132–135.
26. Perry KA, Enestvedt CK, Gareau D, Pham TH, Truffer F, Dolan JP, Jacques SL, Hunter JG. Measuring acute changes in gastric conduit perfusion during minimally invasive esophagectomy (MIE) using optical fiber spectroscopy. Presented at the annual meeting of the Society of American Gastrointestinal and Endoscopic Surgeons, Phoenix, AZ, April 2009.

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ORIGINAL ARTICLE

Lymphovascular or Perineural Invasion May Predict Lymph Node Metastasis in Patients With T1 and T2 Colorectal Cancer

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Abstract
Background The aim of the study was to evaluate factors for predicting lymph node metastasis in patients who had T1 and T2 colorectal cancer.
Methods A total of 224 patients with T1 or T2 colorectal cancers who underwent radical surgery with regional lymphadenectomy from January 1999 to January 2008 were analyzed.
Results Predictive factors for lymph node metastasis and prognostic factors were analyzed. Tumor stage was classified as T1 in 69 (30.8%) and T2 in 155 (69.2%) of patients. The overall incidence of lymph node metastasis was 21.0% (14.5% for T1 cancer and 23.9% for T2 cancer; $P=0.112$). The node positive and negative groups were similar with regard to patient demographics, except that the former contained a significantly higher number of lymphovascular invasion and perineural invasion cases. During the median follow-up period of 49 months, the 5-year overall and disease-free survival rates for patients without lymph node metastasis were 97.1% and 94.6%, which were significantly higher than the rates for those with lymph node metastasis (85.5%, $P=0.008$, and 82.0%, $P=0.007$, respectively). A multivariate analysis revealed that lymph node status was the only significant independent prognostic factor for both overall survival ($P=0.025$) and disease-free survival ($P=0.040$). Moreover, the presence of lymphovascular invasion ($P<0.001$) or perineural invasion ($P=0.004$) was an independent predictor for lymph node metastasis.
Conclusion Lymph node metastasis was the most powerful predictor for poorer survival in patients with T1 or T2 colorectal cancer. For patients with positive lymphovascular or perineural invasion, radical surgery should be recommended because of a greater chance for lymph node metastasis.

Keywords Early colorectal cancer · Lymph node metastasis · Lymphovascular invasion · Perineural invasion

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Introduction

The prognosis of colorectal cancer is related to the tumor-node-metastasis stage of the disease, and the depth of tumor invasion into the bowel wall is an essential component of colorectal cancer staging systems. Tumors within the muscularis propria (T1 and T2) are usually considered early lesions and can potentially be cured by complete tumor resection. Because of advances in noninvasive surgical techniques by endoscopy, it has recently become possible to perform resection of many early colon and rectal lesions, particularly those with peduncules.

However, lymph node metastasis occurs in approximately 8%–20% of patients with early carcinomas of the colon and rectum.[1–5] Despite the fact that the depth of tumor invasion into the bowel wall is limited, the prognosis for patients with

lymph node metastasis may be worse than that of those without. Therefore, we analyzed the prognostic factors for T1 and T2 colorectal cancer and evaluated factors for predicting lymph node metastasis in patients who had T1 and T2 colorectal cancer treated with radical surgery.

Methods

From a prospective database, in which data on all patients with colorectal cancers at our institution were collected, patients with T1 or T2 colorectal adenocarcinoma who underwent radical surgery and who operated on from January 1999 to January 2008 were reviewed and analyzed. Patients with synchronous tumors, recurrent diseases, familial adenomatous polyposis, palliative resections, or no radical surgery such as local excision or polypectomy were excluded. Patients with rectal cancer undergoing neoadjuvant chemoradiotherapy were also excluded because chemoradiotherapy may alter the number of lymph nodes and their metastatic pattern.[6] Ultimately, 224 patients were eligible for this retrospective review of prospectively collected data.

Table 1 Comparison of Patients with Colon and Rectal Cancer (n=224)

	Colon cancer (n=66)	Rectal cancer (n=158)	P
Age, y			
<61	27 (40.9)	72 (45.6)	0.522
≥61	39 (59.1)	86 (54.4)	
Sex			
Male	38 (57.6)	87 (55.1)	0.730
Female	28 (42.4)	71 (44.9)	
Tumor diameter, cm			
<3.5	45 (68.2)	83 (52.5)	0.031
≥3.5	21 (31.8)	75 (47.5)	
Differentiation			
Well+moderate	62 (93.9)	154 (97.5)	0.215
Poor+mucinous	4 (6.1)	4 (2.5)	
Macroscopic ulceration			
No	46 (69.7)	86 (54.4)	0.034
Yes	20 (30.3)	72 (45.6)	
Depth of tumor invasion (T)			
T1	35 (53.0)	34 (21.5)	<0.001
T2	31 (47.0)	124 (78.5)	
Lymph node metastasis			
Negative	51 (77.3)	126 (79.7)	0.678
Positive	15 (22.7)	32 (20.3)	
Lymphovascular invasion			
Negative	60 (90.9)	143 (90.5)	0.925
Positive	6 (9.1)	15 (9.5)	
Perineural invasion			
Negative	64 (97.0)	150 (94.9)	0.486
Positive	2 (3.0)	8 (5.1)	
No. of lymph nodes retrieved			
<12	35 (53.0)	85 (53.8)	0.916
≥12	31 (47.0)	73 (46.2)	
Operative method			
Open	39 (59.1)	116 (73.4)	0.034
Laparoscopic	27 (40.9)	42 (26.6)	
Preoperative CEA, ng/ml			
<5	53 (80.3)	105 (66.5)	0.084
≥5	7 (10.6)	21 (13.2)	
Not available	6 (9.1)	32 (20.3)	

CEA carcinoembryonic antigen

All patients underwent a standard colectomy and regional lymphadenectomy according to tumor location. For rectal cancer, total mesorectal excision was performed for lesions below the peritoneal reflexion, and the mesorectum was divided at 5 cm distal to the tumor for upper rectal lesions:[7,8] operations included 128 low anterior resection, 28 abdominoperineal resection, and 2 Hartmann's procedure. After the final histopathologic examination, the tumor was staged according to the sixth International Union Against Cancer (UICC) TNM staging system. Resected specimens were evaluated for depth of tumor invasion, macroscopic ulceration, differentiation, number of lymph nodes retrieved, number of lymph node metastases, lymphovascular invasion, and perineural invasion. Postoperative adjuvant chemotherapy using the Mayo Clinic regimen was our standard protocol for patients with stage III disease. Of the 47 patients with node-positive tumors, 44 (95.7%) received adjuvant chemotherapy and 1 (2.1%) received adjuvant chemoradiotherapy. The patients were followed at 3-month intervals for 2 years, at 6-month intervals for the next 3 years, and annually

Table 2 Comparison of Patients with and Without Lymph Node Metastasis (n=224)

	Negative nodes (n=177)	Positive nodes (n=47)	P
Age, y			
<61	73 (41.2)	26 (55.3)	0.084
≥61	104 (58.8)	21 (44.7)	
Sex			
Male	98 (55.4)	27 (57.4)	0.799
Female	79 (44.6)	20 (42.6)	
Location			
Colon	51 (28.8)	15 (31.9)	0.678
Rectum	126 (71.2)	32 (68.1)	
Tumor diameter, cm			
<3.5	99 (55.9)	29 (61.7)	0.477
≥3.5	78 (44.1)	18 (38.3)	
Differentiation			
Well+moderate	170 (96.0)	46 (97.9)	0.525
Poor+mucinous	7 (4.0)	1 (2.1)	
Macroscopic ulceration			
No	105 (59.3)	27 (57.4)	0.816
Yes	72 (40.7)	20 (42.6)	
Depth of tumor invasion (T)			
T1	59 (33.3)	10 (21.3)	0.112
T2	118 (66.7)	37 (78.7)	
Lymphovascular invasion			
Negative	171 (96.6)	32 (68.1)	<0.001
Positive	6 (3.4)	15 (31.9)	
Perineural invasion			
Negative	173 (97.7)	41 (87.2)	0.006
Positive	4 (2.3)	6 (12.8)	
No. of lymph nodes retrieved			
<12	92 (52.0)	28 (59.6)	0.353
≥12	85 (48.0)	19 (40.4)	
Operative method			
Open	122 (68.9)	33 (70.2)	0.865
Laparoscopic	55 (31.1)	14 (29.8)	
Preoperative CEA, ng/ml			
<5	129 (72.9)	29 (61.8)	0.231
≥5	19 (10.7)	9 (19.1)	
Not available	29 (16.4)	9 (19.1)	

CEA carcinoembryonic antigen

thereafter. On a semiannual basis or when there was a suspicion of recurrence, follow-up examinations included a clinical history, physical examination, serum carcinoembryonic antigen (CEA) assay, chest x-ray, abdominopelvic computed tomography or magnetic resonance imaging, colonoscopy, and positron emission tomography scanning, if available. Recurrence was determined by clinical and radiologic examinations or by histologic confirmation. The main pattern of recurrence was considered to be the first site of detectable failure during the follow-up period.

Statistical Analysis

Statistical analyses were conducted using SPSS software (SPSS for Windows, version 14.0; SPSS, Chicago, IL). Differences between groups were tested using the chi-square test. Variables with a statistical P value <0.10 were entered into a Cox model multivariate analysis. Survival rates were calculated using the Kaplan–Meier method, and prognostic factors and survival curves were compared using the log-rank test. A P value ≤0.05 was considered statistically significant.

Results

This analysis included 125 (55.8%) male and 99 (44.2%) female patients with a median age of 61 years (range, 29–92 years). The median tumor diameter was 3.5 cm (range, 0.3–11 cm). Of the 224 patients, 66 (29.5%) had colon cancer and 158 (70.5%) had rectal cancer. Tumor stage was classified as T1 in 69 (30.8%) and T2 in 155 (69.2%) of these patients. Forty-seven patients (21.0%) had evidence of lymph node metastasis with a median of 11 resected nodes (range, 2–55). Comparisons of patients with colon and rectal cancer are shown in Table 1. The gender distribution, age, differentiation, number of examined lymph nodes, and incidence of lymph node metastasis were comparable in the two groups. Comparisons of patients with and without lymph node metastasis are shown in Table 2. The node positive and negative groups were similar with regard to patient demographics except that the former contained a significantly higher number with lymphovascular invasion (P<0.001) and perineural invasion (P=0.006).

During the median follow-up period of 49 months (range, 1–130 months), the 5-year overall and disease-free survival rates for patients without lymph node metastasis were 97.1% and 94.6%, which were significantly higher than the rates for those with lymph node metastasis (85.5%, P=0.008 [Fig. 1a], and 82.0%, P=0.007 [Fig. 1b], respectively). In a univariate analysis (Table 3), factors associated with poorer overall survival were age and lymph node metastasis; factors associated with poorer disease-free survival were age, lymph node metastasis, and perineural invasion. In a multivariate analysis (Table 4), only lymph node metastasis was an independent prognostic factor for both overall and disease-free survival in patients with T1 and T2 colorectal cancer.

Given the importance of lymph node metastasis to both overall and disease-free survival, we performed a multivariate analysis to identify factors independently associated with lymph node mestastasis (Table 5). The presence of lymphovascular invasion (P<0.001) or perineural invasion (P=0.004) was an independent predictor of lymph node metastasis.

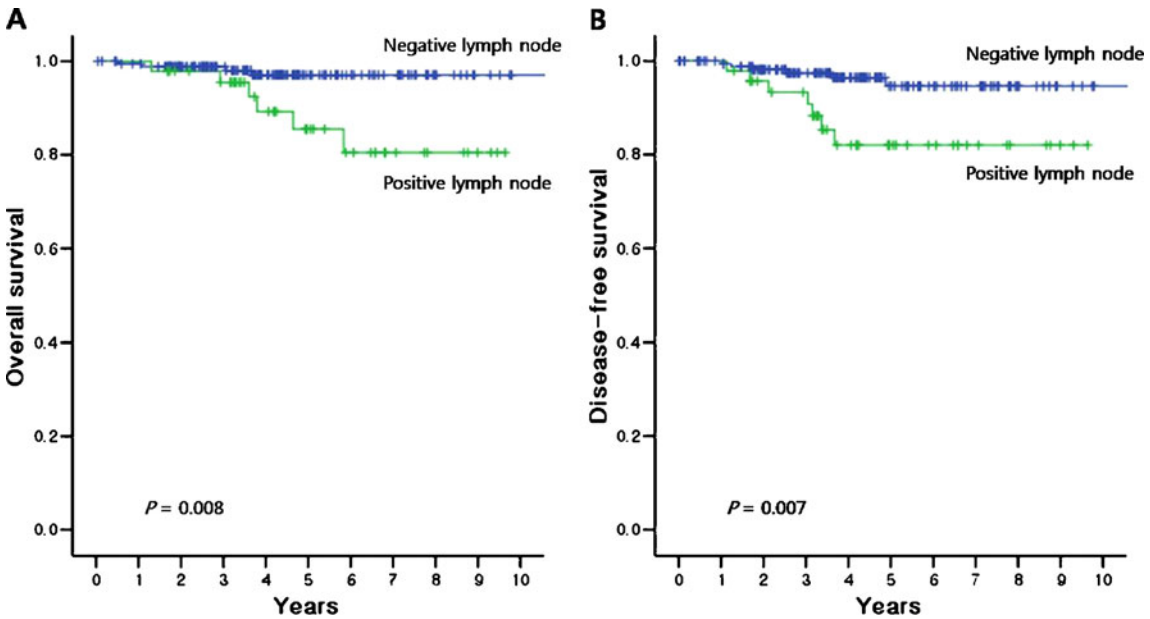

Figure 1 Survival curves of patients with T1–2 colorectal cancer according to lymph node metastasis. **a** Overall survival. **b** Disease-free survival.

Table 3 Univariate Analyses of Factors for 5-Year Overall Survival (OS) and Disease-Free Survival (DFS)

	No.	5-y OS (%)	*P*	5-y DFS (%)	*P*
Age, y					
<61	99	90.0	0.042	86.1	0.028
≥61	125	98.3		97.4	
Sex					
Male	125	92.0	0.086	89.4	0.274
Female	99	96.8		94.6	
Location					
Colon	66	92.3	0.614	98.0	0.150
Rectum	158	94.7		90.0	
Tumor diameter, cm					
<3.5	128	92.0	0.128	88.3	0.133
≥3.5	96	96.9		96.1	
Differentiation					
Well+moderate	216	93.9	0.507	91.4	0.472
Poor+mucinous	8	100		100	
Macroscopic ulceration					
No	132	91.9	0.123	94.3	0.450
Yes	92	96.9		89.1	
Depth of tumor invasion (T)					
T1	69	94.1	0.816	94.7	0.099
T2	155	94.3		90.4	
Lymph node metastasis					
Negative	177	97.1	0.008	94.6	0.007
Positive	47	85.5		82.0	
Lymphovascular invasion					
Negative	203	94.2	0.936	91.5	0.812
Positive	21	93.3		93.8	
Perineural invasion					
Negative	214	94.5	0.340	92.8	0.036
Positive	10	85.7		68.6	
No. of lymph nodes retrieved					
<12	120	94.0	0.741	92.4	0.528
≥12	104	94.3		91.1	
Operative method					
Open	155	95.4	0.403	91.6	0.981
Laparoscopic	69	92.8		94.6	
Preoperative CEA, ng/ml					
<5	158	94.7	0.928	94.6	0.146
≥5	28	95.8		89.1	
Not available	38	92.1		84.9	

CEA carcinoembryonic antigen

Discussion

Due to recent advances in endoscopic techniques, tumors within the muscularis propria (T1 and T2) are usually considered less advanced and may potentially be cured by noninvasive resection of the tumor with appropriate selection of patients. However, lymph node metastasis occurs in approximately 8%–20% of patients with early carcinomas of the colon and rectum.[1–5] It is therefore prudent to identify this high-risk group of patients.[2,9–11] Unfortunately, recent imaging modalities are inadequate to define metastatic lymph nodes, with an overall accuracy at detecting malignant lymphadenopathy of 60%–70%.[12–14] We demonstrated that the incidence of lymph node

Table 4 Multivariate Analyses of Factors for 5-Year Overall Survival (OS) and Disease-Free Survival (DFS)

	Hazard ratio (CI)	*P*
OS		
Age (<61 y vs. ≥61 y)	4.062 (0.856–19.266)	0.078
Sex (male vs. female)	3.839 (0.809–18.211)	0.090
Lymph node metastasis (positive vs. negative)	4.269 (1.199–15.192)	0.025
DFS		
Age (<61 y vs. ≥61 y)	3.219 (0.864–11.995)	0.082
Depth of tumor invasion (T2 vs. T1)	4.052 (0.517–31.791)	0.183
Perineural invasion (positive vs. negative)	1.476 (0.298–7.302)	0.633
Lymph node metastasis (positive vs. negative)	3.317 (1.059–10.388)	0.040

CI *confidence interval*

metastasis for all patients with an intramural tumor was 21.0% (14.5% in T1 and 23.9% in T2), which appears to be slightly high when compared with the results of other studies.[1–5] This may be due, at least in part, to the higher median number of lymph nodes examined in our study (10 in T1 and 12 in T2) than in other reports.[1,2] Moreover, the number of metastatic lymph nodes identified in this cohort was significant (up to 9), and this showed that a more extensive lymphadenectomy might be needed in this group of patients.

Several studies have attempted to evaluate predictive factors of lymph node metastasis.[1–4,15,16] In the present study, the presence of lymphovascular or perineural invasion was the only significant predictive factor. Lymphovascular invasion has been consistently reported in early colorectal cancers.[1–4,15–17] Chok et al.[2] suggested that half of patients with lymphovascular invasion had lymph node metastasis. However, the predictive role of perineural invasion in early colorectal cancer is still unknown. While perineural invasion has become an increasingly relevant yet understudied aspect of tumor biology in colorectal cancers, several studies have reported a role for perineural invasion as an independent predictor of outcome in patients with colorectal cancer.[18–20] We have recently observed a significant role for perineural invasion as a prognostic factor in node-negative colorectal cancer.[20] In our study, although the incidence of perineural invasion was only 4.5%, the odds ratio of lymph node metastasis increased 10-fold for patients who had perineural invasion, as compared with those who did not. This further supports a role for perineural invasion not only in disease progression but in tumor metastasis, despite intramural tumor invasion. To our knowledge, this is the first study demonstrating a predictive role for perineural invasion of lymph node metastasis in early colorectal cancer.

In our study, with a median follow-up period of 49 months, the 5-year overall and disease-free survival rates were 94.1% and 91.8%, respectively. There were no differences in survival between patients with T1 disease and those with T2 diseases. The depth of intramural tumor invasion did not appear to have an impact on the oncologic outcomes. The presence of lymph node metastasis was the only significant independent predictor for both poor overall and disease-free survival in this cohort of patients. Other adverse pathologic variables, such as differentiation, lymphovascular invasion, perineural invasion, or the number of lymph nodes examined, were not associated with poorer survival. This may be due to the low incidence of these factors in patients with early colorectal cancer and the small sample size in this analysis. Due to the inherent limitations of a retrospective study and the small sample size of this analysis, this result requires further investigation in order to reach a firm conclusion.

In conclusion, the presence of lymphovascular or perineural invasion was associated with lymph node metastasis, and the latter was the only significant independent factor predicting both overall and disease-free survival in patients with T1 and T2 colorectal cancer. This suggests that the presence of lymphovascular or perineural invasion in early colorectal cancer may provide valuable information from which to determine which patients would benefit from radical surgery, adjuvant chemotherapy, or radiotherapy after surgery due to the increased risk of lymph node metastasis.

Table 5 Multivariate Predictors of Lymph Node Metastasis in Patients with T1–2 Colorectal Cancer

	Odds ratio (CI)	*P*
Lymphovascular invasion (positive vs. negative)	15.792 (4.970–50.178)	<0.001
Perineural invasion (positive vs. negative)	10.745 (2.100–54.974)	0.004

CI *confidence interval*

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References

1. Rasheed S, Bowley DM, Aziz O, Tekkis PP, Sadat AE, Guenther T, Boello ML, McDonald PJ, Talbot IC, Northover JM. Can depth of tumour invasion predict lymph node positivity in patients undergoing resection for early rectal cancer? A comparative study between T1 and T2 cancers. Colorectal Dis 2008;10:231-238.
2. Chok KS, Law WL. Prognostic factors affecting survival and recurrence of patients with pT1 and pT2 colorectal cancer. World J Surg 2007;31:1485-1490.
3. Fang WL, Chang SC, Lin JK, Wang HS, Yang SH, Jiang JK Chen WC, Lin TC. Metastatic potential in T1 and T2 colorectal cancer. Hepatogastroenterology 2005;52:1688-1691.
4. Bayar S, Saxena R, Emir B, Salem RR. Venous invasion may predict lymph node metastasis in early rectal cancer. Eur J Surg Oncol 2002;28:413-417.
5. Sitzler PJ, Seow-Choen F, Ho YH, Leong AP. Lymph node involvement and tumor depth in rectal cancers: an analysis of 805 patients. Dis Colon Rectum 1997;40:1472-1476.
6. Baxter NN, Morris AM, Rothenberger DA, Tepper JE. Impact of preoperative radiation for rectal cancer on subsequent lymph node evaluation: a population-based analysis. Int J Radiat Oncol Biol Phys 2005;61:426-431.
7. Huh JW, Kim HR, Kim YJ. Anastomotic leakage after laparoscopic resection of rectal cancer: the impact of fibrin glue. Am J Surg 2010;199:435-441.
8. Huh JW, Kim HR, Kim YJ. Proliferating cell nuclear antigen as a prognostic factor after total mesorectal excision of stage II-III rectal cancer. Ann Surg Oncol 2009;16:1494-1500.
9. Huh JW, Park YA, Lee KY, Kim SA, Sohn SK. Recurrences after local excision for early rectal adenocarcinoma. Yonsei Med J 2009;50:704-708.
10. Lee HS, Lee S, Seo JH, Kwack KK, Kim JS, Jung HC, Song IS. Follow-up results of endoscopic mucosal resection for early colorectal cancer. J Korean Soc Coloproctol 2006; 22:103-112.
11. Huh JW, Jung EJ, Park YA, Lee KY, Sohn SK. Sphincter-preserving operations following preoperative chemoradiation: an alternative to abdominoperineal resection for lower rectal cancer? World J Surg 2008;32:1116-1123.
12. Norton SA, Thomas MG. Staging of rectosigmoid neoplasia with colonoscopic endoluminal ultrasonography. Br J Surg 1999;86:942-946.
13. Heneghan JP, Salem RR, Lange RC, Taylor KJ, Hammers LW. Transrectal sonography in staging rectal carcinoma: the role of gray-scale, color-flow, and Doppler imaging analysis. AJR Am J Roentgenol 1997;169:1247-1252.
14. Huh JW, Park YA, Jung EJ, Lee KY, Sohn SK. Accuracy of endorectal ultrasonography and computed tomography for restaging rectal cancer after preoperative chemoradiation. J Am Coll Surg 2008;207:7-12.
15. Nascimbeni R, Burgart LJ, Nivatvongs S, Larson DR. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. Dis Colon Rectum 2002;45:200-206.
16. Goldstein NS, Hart J. Histologic features associated with lymph node metastasis in stage T1 and superficial T2 rectal adenocarcinomas in abdominoperineal resection specimens. Identifying a subset of patients for whom treatment with adjuvant therapy or completion abdominoperineal resection should be considered after local excision. Am J Clin Pathol 1999;111:51-58.
17. Huh JW, Oh BR, Kim HR, Kim YJ. Preoperative carcinoembryonic antigen level as an independent prognostic factor in potentially curative colon cancer. J Surg Oncol 2010;101:396-400.
18. Liebig C, Ayala G, Wilks JA, Berger DH, Albo D. Perineural invasion in cancer: a review of the literature. Cancer 2009;115:3379-3391.
19. Quah HM, Chou JF, Gonen M, Shia J, Schrag D, Landmann RG, Guillem JG, Paty PB, Temple LK, Wong WD, Weiser MR. Identification of patients with high-risk stage II colon cancer for adjuvant therapy. Dis Colon Rectum 2008;51:503-507.
20. Huh JW, Kim YJ, Kim HR. Prognostic value of perineural invasion in patients with stage II colorectal cancer. Ann Surg Oncol 2010. doi:10.1245/S10434-010-0982-7

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2009 SSAT PLENARY PRESENTATION

Infection Rates in a Large Investigational Trial of Sacral Nerve Stimulation for Fecal Incontinence

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Abstract
Introduction Treatment options for patients with fecal incontinence (FI) are limited, and surgical treatments can be associated with high rates of infection and other complications. One treatment, sacral nerve stimulation (SNS), is approved for FI in Europe. A large multicenter trial was conducted in North America and Australia to assess the efficacy of SNS in patients with chronic fecal incontinence. The aim of this report was to analyze the infectious complication rates in that trial.
Methods Adult patients with a history of chronic fecal incontinence were enrolled into this study. Those patients who fulfilled study inclusion/exclusion criteria and demonstrated greater than two FI episodes per week underwent a 2-week test phase of SNS. Patients who showed a ≥50% reduction in incontinent episodes and/or days per week underwent chronic stimulator implantation. Adverse events were reported to the sponsor by investigators at each study site and then coded. All events coded as implant site infection were included in this analysis.
Results One hundred twenty subjects (92% female, 60.5±12.5 years old) received a chronically implanted InterStim® Therapy device (Medtronic, Minneapolis, MN, USA). Patients were followed for an average of 28 months (range 2.2-69.5). Thirteen of the 120 implanted subjects (10.8%) reported infection after the chronic system implant. One infection spontaneously resolved and five were successfully treated with antibiotics. Seven infections (5.8%) required surgical intervention, with infections in six patients requiring full permanent device explantation. The duration of the test stimulation implant procedure was similar between the infected group (74 min) and the non-infected group (74 min). The average duration of the chronic neurostimulator implant procedure was also similar between the infected (39 min) and non-infected group (37 min). Nine infections occurred within a month of chronic system implant and the remaining four infections

Study was presented as a podium presentation at the annual meeting of Society for Surgery of the Alimentary Tract/Digestive Disease Week in Chicago IL, USA, June 3, 2009.

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occurred more than a year from implantation. While the majority (7/9) of the early infections was successfully treated with observation, antibiotics, or system replacement, all four of the late infections resulted in permanent system explantation.

Conclusion SNS for FI resulted in a relatively low infection rate. This finding is especially important because the only other Food and Drug Administration-approved treatment for end-stage FI, the artificial bowel sphincter, reports a much higher rate. Combined with its published high therapeutic success rate, this treatment has a positive risk/benefit profile.

Keywords Infection rates · Sacral nerve stimulation · Fecal incontinence

Introduction

Adequate fecal continence mandates independent function of various systems as well as anatomic structures and optimal communication among them. Not surprisingly, fecal incontinence (FI) is also multifactorial.[1–4] Patients with FI will often undergo a thorough evaluation to try to determine the etiology and to also try to optimize the best therapeutic option. Conservative treatment including behavioral changes, medical management, and biofeedback are usually considered as initial treatment. When these measures fail or in patients who have sustained a sphincter injury, consideration is given to surgical repair.[4]

Some patients with an intact anal sphincter or a surgically repaired anal sphincter continue to experience the devastating effects of severe FI. These individuals have few surgical options to improve their situation. Stimulated graciloplasty (SG) or implantation of an artificial bowel sphincter (ABS) may be considered prior to colostomy construction. Since SG is not available in the USA, using an unstimulated gracilis muscle to encircle the anus as an alternative to the failing continence mechanism is the only viable option.[3] However, in the absence of chronic low voltage stimulation, it is not an ideal option. The ABS is still considered as an option for patients seeking to avoid a permanent stoma but technical issues including a high infection rate with a subsequently high explantation rate has limited adoption of the ABS.[5]

Sacral nerve stimulation (SNS) has been shown to improve both urinary incontinence and FI utilizing an implanted nerve stimulator to directly stimulate the sacral nerve roots.[2] Outside the USA, SNS has become a popular alternative for many patients with end stage FI. In order to attain Food and Drug Administration (FDA) approval to use SNS as a treatment for FI in the USA, a multicenter trial was conducted. The results of this study were recently presented, and subsequently published concluding that SNS therapy is safe and effective in treating subjects with chronic FI.[6,7]

The aim of the current report was to analyze the infectious complication rates in patients treated during this trial.

Methods

Adults (≥18 years) with greater than two episodes of FI per week for at least 6 months were enrolled in a prospective non-randomized trial undertaken at 16 institutions in North America and Australia. In the USA, this study was approved by each center's Institutional Review Board. Centers outside the United States utilized an Independent Ethics Committee that was governed by

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country-specific regulations and/or requirements. Voluntary informed consent was obtained from all enrolled patients. All patients had failed conservative treatment; patients were excluded if they had congenital anal malformations, anorectal surgery within the last 12 months (rectopexy, rectal resection, and anal sphincter repair), anorectal cancer surgery within the past 24 months, a defect in the external anal sphincter greater than 60°, inflammatory bowel disease, pelvic organ radiation damage, suppurative anorectal disease, significant peripheral neuropathy, or a spinal cord injury which would have prevented electrode placement. Also excluded were patients who planned to become pregnant, required an magnetic resonance imaging (MRI) to evaluate or follow a known disease, had life expectancy less than 12 months, or were unable to understand the study.

Patients were assessed with a bowel diary to determine the degree of their FI and qualifying patients then completed forms to assess the severity of FI and its impact on their quality of life. A quadripolar electrode (Medtronic Inc., Minneapolis, MN, USA Models 3886, 3966, 3889, or 3093) was placed in the operating room into the sacral foramen of S2, S3, or S4. This electrode was attached to an external test stimulator (Medtronic Inc. Model 3625), and patients recorded their incontinent bowel episodes for 10-14 days. If there was a ≥50% reduction of incontinent episodes and/or days per week, a neurostimulation device was implanted. To accomplish this goal, a temporary extension electrode (Medtronic Inc. Model 3550-05) which had initially been placed was removed and a shorter connecting electrode was placed from the quadripolar electrode to the pulse generator (Medtronic Inc. Model 3023 InterStim Neurostimulator). The pulse generator was implanted in a pocket created in the adipose tissue in contralateral gluteal region.

Both phases of implantation were done in the operating room under strict sterile conditions. The study protocol did not dictate a specific bowel preparation or antibiotic regimen; these decisions were separately made in each center by the respective principal investigator (PI). All adverse events including infections were reported to the sponsor by each institution's PI. Events were then classified by the sponsor using the Medical Dictionary for Regulatory Activities. All events coded as implant site infection were included in this analysis. Follow-up data were obtained to further investigate treatment and outcome for these patients. The functional results and outcome of the study were presented at the ASCRS annual meeting May 3, 2009 and subsequently published.[7,8]

Results

Two hundred eighty-five patients were enrolled at 14 sites in the USA, one in Canada and one in Australia, from 2002 to 2006. One hundred thirty-three patients met the inclusion criteria and underwent initial test stimulation. One hundred twenty of these 133 patients (90%) met the defined improvement criteria and had implantation of the chronic stimulating device. The mean age was 60.5 (range 30-88) years, and there were 110 females (92%). As previously reported, 73% of subjects showed ≥50% reduction in the number of incontinent episodes per week at 12 months compared to baseline, using a worst case analysis (where subjects missing study endpoints were assumed to have no improvement in symptoms).[8] The average follow-up was 28 (range 2.2-69.5) months.

Thirteen of the 120 (10.8%) patients experienced an event coded as implant site infection. These infections are detailed in Table 1. Infections were reported in eight centers where a range of three to 26 devices had been implanted during the study. Five incidents occurred in one center in which 26 patients were implanted, two in another institution in which 19 patients were implanted, and one each in six other centers. Two patients were the first to be implanted in their centers, three were the second to be implanted, two were the third to be implanted, and six patients were implanted later, ranging from the 13th to the 23rd.

Nine patients experienced an early infectious episode which was diagnosed between 0 and 21 days after the chronic device was implanted. One of this group of patients had a superficial yeast infection which spontaneously resolved; five infections were successfully treated with various antibiotics without compromising the SNS device, one infection required system explantation with a successful reimplantation, and two infections led to permanent system explantation. Thus seven of nine early infections were treated without permanent device explantation. In the remaining four patients with infection, the events occurred later; between 13 and 41 months after chronic implantation. These infectious complications necessitated permanent surgical explantation of the system. Positive bacterial cultures revealed *Staphylococcus aureus* in two cases. Comparing those patients who had infections with the remainder of the implanted patients, there was no difference in surgical procedure duration between the two groups for test stimulation implant (74 min for infected and 74 min for non-infected) or chronic neurostimulator implant (39 min for infected and 37 min for non-infected).

Two of the seven ultimate device explantations performed for infection were undertaken on an inpatient basis whereas the remaining five devices were explanted in the outpatient setting.

Discussion

Published studies of SNS for FI and urinary incontinence have uniformly revealed few infectious complications.

Table 1 Infection Events Details

Infection onset group	Time from implant to infection onset	Intervention	Outcome
Early onset (range 0-21 days, average 9 days)	Same day	Entire system explanted 2004-05-06 Patient hospitalized 5-7 May 04 for explant. Patient presented for explant on 5 May 04, but due to high blood pressure (pre-existing condition) was unable to have explant completed that day. Blood pressure controlled by 6May04 and explant procedure completed that day Post-op, patient continued to have pain at neurostimulator site and was given Vicodin (AE closed 14 May 04)	Infection AE closed on 14 May 04 (8 days after explant). Subject exited study after explant
	Same day	Diflucan medication was given, Levaquin antibiotic given at discharge	Infection AE resolved 7 Sept 05. Revision/ explant for infection not necessary
	Same day	Gentamicin sulfate 80 mg Q8h/Ampicillin 1 g/day Vancomycin 1 g	Infection AE resolved 16 Jan 06. Revision/ explant for infection not necessary
	6 days	Antibiotic-levaquin 500 mg po QD	Infection AE resolved 23 May 06. Revision/ explant for infection not necessary
	7 days	Neurostimulator replaced and lead revised 2004-02-02; Entire system explanted 2004-02-13 Patient hospitalized >24 h (02-03 Feb 04) for the device replacement and lead revision. Patient reported dizziness with position change at home, but this was resolved within 1 day After the device replacement, a new seroma developed rapidly. Patient was hospitalized <24 h for the 13 Feb 04 full system explant. Patient had condition of increased depression day prior to this procedure, and it resolved 25 Feb 04 with new anti-depressant medication	Infection AE closed on 5 Mar 04 (21 days after final explant). Subject exited study after explant
	13 days	Antibiotics	Infection AE resolved on 22 Jun 06. Revision/ explant for infection not necessary
	15 days	None	Infection AE resolved on 19 Aug 04. Revision/ explant for infection not necessary
	17 days	Ultrasound of insertion site R/O Abscess Keflex 500 mg po q 6 h × 2 weeks	Infection AE resolved on 18 Aug 06. Revision/ explant for infection not necessary
	21 days	Entire system explanted 2002-12-18; Lead re-implanted 2003-05-16; Neurostimulator and extension re-implanted 2003-06-06 All above procedures were completed in <24-h stay in hospital. No procedural related AEs reported during explant	Infection AE resolved on 22 Apr 03 (125 days after explant). Subject later successfully reimplanted

Late onset (range 13-41 months, average 22 months)	13.4 months	Entire system explanted 2007-11-16. Patient was hospitalized 16-20 Nov 07. No procedural related AEs reported during explant	Infection AE remained open when subject exited study post-explant. Do not have further information on infection
	16.3 months	Entire system explanted 2007-07-23. The procedure was completed in <24-h stay in hospital. No procedural related AEs reported during explant	Infection AE closed on 23Jul07 (0 days after final explant). Subject was later lost to follow-up and exited study
	16.8 months	Entire system explanted 2008-01-09. The procedure was completed in <24-h stay in hospital. No procedural related AEs reported during explant	Infection AE closed on 09 Jan 08 (0 days after final explant). Subject exited study after explant
	41.1 months	Lead tip in distal sigmoid colon explanted 2007-12-11 (infection onset: 4 Jan 08); Remaining proximal portion of lead explanted 2008-01-28; explant of entire device 2008-11-06. Patient is currently waiting to be re-implanted Procedure on 28 Jan 08 (removal of proximal portion of lead) required >24-h stay (28-29 Jan08). All other procedures listed for patient required <24-h stay at hospital During device explant on 06 Nov 08, patient experienced dislocation of TMJ (resolved during procedure). Patient had a history of previous TMJ dislocation with intubation	Infection AE closed on 21 Nov 08 (15 days after final explant). Subject is currently still waiting to be re-implanted

Tjandra et al. reported no septic complications in the 53 patients enrolled in their randomized study comparing SNS to optimal medical therapy for severe FI.[9] In a review article focusing on the published literature for FI by Tan et al., the infection rates for SNS ranged from 3% to 17%. These studies included from two to 30 patients and most of the reported infections were superficial.[2]

While analyzing the adverse infectious episodes reported in this study, no local or systemic risk factors could be isolated among the 13 patients who presented with infectious complication [Table 2]. Interestingly, the infectious complications could be divided into two groups: early and late. Nine of the 13 documented infectious complications occurred within an average of 9 (range 0-21) days following the chronic implant procedure. These infections successfully resolved in all but two patients with observation, oral antibiotics, or system replacement. However, the outcome was different in the other group of four patients, who presented with late onset infections, an average of 22 (range 13-41) months following chronic implantation. In this group, permanent system explant was necessary in all patients despite utilization of intravenous antibiotics. It appears that late infectious events do not respond to medical or surgical treatment and ultimately require complete explantation of the device. Table 3 and Fig. 1 show the Kaplan-Meier probability of wound infection.

The overall low rate of infectious complications in this study is reassuring compared to other available treatment. The data show that infections occurred in both high and low volume centers. These findings suggest the potential safety of implanting SNS in low volume centers without compromising patient safety.

Since SNS implantation for urinary dysfunction involves test stimulation and placement of the chronic device with essentially the same protocol, examination of infectious complications should provide data comparable to FI results. Washington and Hines specifically studied infections after both stages of SNS implantation for urinary incontinence. Five of 37 (13.5%) patients required device explantation following a culture- positive wound infection. Although slightly higher, these results are generally within the same range of this report. Infections occurred at a median of 76 (range 33-461) days after chronic stimulator implant. The authors did not detect a difference in the time elapsed from device implantation to the occurrence of the infectious episode and conservative treatment always failed leading to surgical explantation.[10] Therefore, when implanted for urinary incontinence, all reported infections resembled the infections which occurred in the late group of the present study. However, Washington and Hines noted no early infections in the first days following the chronic implantation. After device removal, infections resolved in all five patients, two of whom underwent successful reimplantation.

Table 2 Comparison of Possible Risk Factors Between Patients With and Without Infection

Risk factor	Mean (SD) in patients with infection (n=13)	Mean (SD) in patients without infection (n=107)	p value (t test)
Age	54.3 (16.6)	61.3 (11.7)	0.056
BMI	26.4 (6.7)	28.4 (5.3)	0.217
Test stimulation procedure duration	73.8 (28.4)	74.1 (40.7)	0.978
Chronic implant procedure duration	38.8 (12.6)	36.9 (19.4)	0.747

Figure 1 Kaplan-Meier plot of the survival probability without infection.

Specifically studying characteristics of infection in stimulation devices implanted for voiding dysfunction, Guralnick et al. reviewed charts of 76 patients. Lead infection occurred in nine of the 76 patients (12%). All were culture-positive for *S. aureus*. Six of these nine cultures revealed organisms sensitive to the antibiotics they had preoperatively received. Forty-five of 76 had the chronic pulse generator implanted and five of these (11%) experienced infections. Four of these five had cultures positive for *S. aureus*, all sensitive to the administered perioperative antibiotics. The only difference between patients who experienced an infection versus those who did not was a longer operative time for stage 2 in the infected group. Three patients in the infected group had identifiable risk factors for infection (steroid use, severe psoriasis, and recurrent skin abscesses).[11]

Matzel et al. recently reported what is now the longest available follow-up after SNS implantation—12 patients at a mean of 9.8 (range 7-14) years.[12] No immediate postoperative complications were observed although during this follow-up. Four therapy-related complications developed; no infectious complications were reported.

As previously mentioned, ABS is the only currently available alternative treatment option in the USA for patients with end-stage FI wishing to avoid a stoma. In the same review article mentioned above by Tan et al., the authors found the infectious complication rate for ABS in the published literature ranged from 4% to 60%. These authors echo views of many surgeons who care for FI patients, that results are favorable for patients with successful ABS implantation, but the high morbidity prohibits general adaptation of the ABS.[13–20] Most likely, there will never be a randomized study comparing ABS and SNS because of the difference in patient populations. Whereas SNS may be successful in patients with a sphincter defect, it does require the presence of an anal sphincter muscle. Conversely, the ABS can be successfully implanted in patients with absence of an anal sphincter.[21] Both ABS and SNS have favorable functional results if the final implanted device is free of complications.

One limitation when considering infectious complications in the present study was the lack of standardization of the peri-

Table 3 Kaplan-Meier Estimates of the Survival Probability Without Infection

Years from implant to infection onset	Number left	Number failed	Number censored	Survival probability (%)	Survival probability 95% CI
0.00	120	0	0	100.0	100%, 100%
0.00	117	3	0	97.5	92.5%, 99.2%
0.02	115	5	0	95.8	90.3%, 98.2%
0.04	113	7	0	94.2	88.2%, 97.2%
0.05	112	8	0	93.3	87.1%, 96.6%
0.06	111	9	0	92.5	86.1%, 96.0%
1.11	96	10	14	91.5	84.8%, 95.4%
1.35	86	11	23	90.5	83.4%, 94.6%
1.39	85	12	23	89.4	82.1%, 93.9%
3.40	17	13	90	84.5	69.6%, 92.4%

operative antibiotic and bowel preparation regimes. Prophylactic antibiotics and bowel preparation were given according to the PI preferences; in some centers antibiotic or bowel preparation were routinely given whereas in others they were not. When adverse infectious events did occur, each center consulted their own infectious diseases specialists who recommended different antibiotics. There were no suggested or required therapeutic algorithms for either prevention or treatment of infectious complications. A second limitation was the lack of standardized definition for infection and therefore the rate may have been either erroneously low or erroneously high depending upon the individual investigators' threshold for defining implant site infection. Moreover, patient comorbidity may have varied among centers affecting both efficacy and postoperative morbidity including infection. Interestingly, the recently published multicenter position paper on SNS did not include any discussion of morbidity which highlights the relative safety of the procedure.[22] A third limitation was that this study did not assess either the economic or the financial burdens of explantation were assessed. A fourth study limitation is that based upon these results, no specific inclusion or exclusion criteria can be recommended. However, logically significant spinal structural abnormalities may preclude lead placement. Active infection including skin infection is a general contraindication to the percutaneous implantation of any device. Neurologic conditions may preclude nerve stimulation and patients for whom routine MRI testing is required should not undergo device implantation.

Conclusion

SNS for FI resulted in a relatively low infection rate, especially considering the only other FDA-approved treatment for end-stage FI is the ABS with its higher infection rate. Episodes of infection occurring in the first 3 weeks following chronic device implantation appear to respond fairly well to oral antibiotics and close observation. This finding was not noted when late infectious adverse events occurred. In these cases, the best approach was device explantation with future consideration for reimplantation. The incidence and severity of these complications did not appear to relate either to surgeon's volume or to any identifiable patient risk factors. Unfortunately no specific inclusion or exclusion criteria can be enunciated based upon the results of this study.

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References

1. Jorge JM, Wexner SD. Etiology and management of fecal incontinence. *Dis Colon Rectum*. 1993;36(1):77–97.
2. Tan JJ, Chan M, Tjandra JJ. Evolving therapy for fecal incontinence. *Dis Colon Rectum*. 2007;50(11):1950–1967.
3. Person B, Wexner SD. Advances in the surgical treatment of fecal incontinence. *Surg Innov*. 2005;12(1):7–21.
4. Wald A. Clinical practice. Fecal incontinence in adults. N Engl J Med. 2007;356(16):1648–1655.
5. Edden Y, Wexner SD. Therapeutic devices for fecal incontinence: dynamic graciloplasty, artificial bowel sphincter and sacral nerve stimulation. Expert Rev Med Devices. 2009;6 (3):307–312.
6. S. Wexner, J. Coller, G. Devroede, T. Hull, R. McCallum, A. Mellgren, et al. Sacral nerve stimulation for fecal incontinence: results of a 120-patient prospective multi-center study. Dis Colon Rectum. 2009 April; Vol. 52 (4): P59.
7. Wexner SD, Coller JA, Devroede G, Hull T, McCallum R, Chan M, Ayscue JM. Sacral nerve stimulation for fecal incontinence: results of a 120-patient prospective multi-center study. Annals of Surgery 2010 Mar;251(3):441–449.
8. Wexner SD, Coller J, Devroede G, Hull T, McCallum R, Mellgren A, et al. Sacral nerve stimulation for fecal incontinence: results of a 120-patient prospective multi-center study. Dis Colon Rectum, 2009;71.
9. Tjandra JJ, Chan MK, Yeh CH, Murray-Green C. Sacral nerve stimulation is more effective than optimal medical therapy for severe fecal incontinence: a randomized, controlled study. Dis Colon Rectum. 2008;51(5):494–502.
10. Washington BB, Hines BJ. Implant infection after two-stage sacral nerve stimulator placement. Int Urogynecol J Pelvic Floor Dysfunct. 2007;18(12):1477–1480.
11. Guralnick ML, Benouni S, O'Connor RC, Edmiston C. Characteristics of infections in patients undergoing staged implantation for sacral nerve stimulation. Urology. 2007;69 (6):1073–1076.
12. Matzel, K. E.; Lux, P.; Heuer, S.; Besendorfer, M.; Zhang, W. Sacral nerve stimulation for faecal incontinence: long-term outcome. Colorectal Disease. 2009;11(6):636–641.
13. Lehur PA, Glemain P, Bruley des Varannes S, Buzelin JM, Leborgne J. Outcome of patients with an implanted artificial anal sphincter for severe faecal incontinence. A single institution report. Int J Colorectal Dis. 1998;13(2):88–92.
14. Altomare DF, Dodi G, La Torre F, Romano G, Melega E, Rinaldi M. Multicentre retrospective analysis of the outcome of artificial anal sphincter implantation for severe faecal incontinence. Br J Surg. 2001;88(11):1481–1486.
15. Casal E, San Ildefonso A, Carracedo R, Facal C, Sánchez JA. Artificial bowel sphincter in severe anal incontinence. Colorectal Dis. 2004;6(3):180–184.
16. Christiansen J, Rasmussen OO, Lindorff-Larsen K. Long-term results of artificial anal sphincter implantation for severe anal incontinence. Ann Surg. 1999;230(1):45–48.
17. Devesa JM, Rey A, Hervas PL, Halawa KS, Larrañaga I, Svidler L, Abraira V, Muriel A. Artificial anal sphincter: complications and functional results of a large personal series. Dis Colon Rectum. 2002;45(9):1154–1163.
18. Wong WD, Congliosi SM, Spencer MP, Corman ML, Tan P, Opelka FG, Burnstein M, Nogueras JJ, Bailey HR, Devesa JM, Fry RD, Cagir B, Birnbaum E, Fleshman JW, Lawrence MA, Buie WD, Heine J, Edelstein PS, Gregorcyk S, Lehur PA, Michot F, Phang PT, Schoetz DJ, Potenti F, Tsai JY. The safety and efficacy of the artificial bowel sphincter for fecal incontinence: results

from a multicenter cohort study. Dis Colon Rectum. 2002;45 (9):1139–1153.
19. Ortiz H, Armendariz P, DeMiguel M, Ruiz MD, Alós R, Roig JV. Complications and functional outcome following artificial anal sphincter implantation. Br J Surg. 2002;89(7):877–881.
20. Malouf AJ, Vaizey CJ, Kamm MA, Nicholls RJ. Reassessing artificial bowel sphincters. Lancet. 2000;355(9222):2219–2220.
21. da Silva GM, Jorge JM, Belin B, Nogueras JJ, Weiss EG, Vernava AM 3rd, Habr-Gama A, Wexner SD. New surgical options for fecal incontinence in patients with imperforate anus. Dis Colon Rectum. 2004;47(2):204–209.
22. Leroi AM, Damon H, Faucheron JL, Lehur PA, Siproudhis L, Slim, K, Barbieux JP, Barth, X, Borie, F, Bresler, L, Desfourneaux, V, Goudet, P, Huten, N, Lebreton, G, Mathieu, P, Meurette, G, Mathonnet, M, Mion, F,Orsoni, P, Parc, Y, Portier, G, Rullier, E, Sielezneff, I, Zerbib, F, Michot, F. Sacral nerve stimulation in faecal incontinence: position statement based on a collective experience. Colorectal Disease. 2009;11(6):572–583.

Discussant

Dr. James Fleshman (St. Louis): I want to thank Dr. Wexner for providing me with the manuscript and the presentation prior to today.

I also want to congratulate Dr. Wexner and his colleagues on an excellent effort to finally bring a reliable method of treating almost all types of fecal incontinence to the United States. As Dr. Wexner mentioned, other methods of treatment of incontinence or sphincter replacement have been plagued by infection-related complications. The infection rate of 10.8% is actually very commendable.

I have several questions that I would like to ask Dr. Wexner regarding the study. The exclusion criteria of the study eliminated women of child-bearing potential, larger sphincter defects, and patients with failed, recent, anal sphincter repairs.

Number one, can we assume that these patients will be benefited and eventually considered candidates? Dr. Joe Chandra, before he died, showed that the mechanism of action is probably levator plate lift, and, therefore, should probably be successful even in patients with large sphincter defects.

Number two, the infection documentation was left to the investigator at each institution and there was no real definition. Could this have biased the result? And would a third-party evaluation or audit be better to define the infection rate?

Number three, the infection rates varied by institution and may have been affected by the lack of standardization, but can you give us an idea of the methods you would now propose to prevent infection? And could they include antibiotic impregnated leads, prophylactic long-term antibiotics, and staphaureous skin colony reduction?

Number four, what is the cost of explantation, both in terms of resource consumption or dollars, as well as psyche and detriment to defunction? Are these patients any worse for wear after this procedure?

Thank you very much for the opportunity to comment on this excellent study.

Closing discussant

Dr. Steve Wexner: Thanks very much, Dr. Fleshman. I very much appreciate you having taking the time to review the manuscript and to review the slides on short notice, I might add, and I am very appreciative of the insight you've given to us.

I'll try to answer those couple of questions. First, in terms of the potential benefit to multiparous women who have had some sphincter injury, Joe Tjandra reported good success in patients with defects of up to 120 degrees. The study that I just reported included patients with defects of up to 60 degrees of whom I believe there were 13 out of 120 patients.

Although we can't tell from this current study about the anticipated results with larger defects, Joe was an excellent investigator and much missed and certainly by his work it appears that up to 120 degrees is satisfactory and perhaps even more. The SNS may work by more of a pelvic bellows pulling up, plus some type of sensory augmentation through neuromodulation that we absolutely don't yet understand.

So through the combination of a better early warning system, and better sensation and pelvic floor lifting, patients do seem to be able to gain some augmentation to their continence even if those patients have large defects. That issue will be worked out I'm sure, in this country, hopefully, once the device is FDA approved.

Second, in terms of infection, absolutely, that was one of the major limitations of the study. The definition was rather nebulous, and was individually determined at each site.

Having said that, I think the natural trepidation every surgeon has in implanting a foreign body anywhere near the anus, or spinal cord in this case, leads to assuming and treating infection at a very low threshold. And if anything, in this FDA scrutininzed data set, the investigators were probably overdiagnosing rather than underdiagnosing and therefore overtreating rather than undertreating, just because of the fear of a problem in the CNS with implantation of the stimulator.

Also, as you alluded to, if we look at infection rates for artificial bowel sphincter, 25% are explanted for infection. Stimulated graciloplasty infection rates were not that high, but that therapy is not available in this country anymore. That's not the case here. In the current study six devices out of 120 were explanted due to infection. A much lower rate was observed than with other therapies using the most stringent objective, definable end point - explantation. So I

absolutely agree with you, it was poorly defined at the beginning. There was a lack of standardization as you correctly mentioned.

To answer your third question, currently, I would use short-term prophylactic antibiotics, not long-term; which would include, as you mentioned, staph coverage. The leads are not impregnated with antibiotics, but I absolutely would soak them in antibiotics before implanting them. I would soak the device as well as long as you are not using something that's going to corrode the actual device, but soak in antibiotics.

To answer your fourth and final question, in terms of the explantation, the study allowed a reimbursement of $6,000 per revision or explantation. So how your hospital comes in, relative to that $6,000, one would guess how much does it cost to bring a patient to the operating room, and explant the device, and treat them with parenteral antibiotics. It could be $6,000 but it could be $10,000. It is absolutely costly but, again, fortunately it is relatively rare. And yes, you are correct, it does have a major detrimental toll on patients' psyche when this procedure fails because these patients don't have much more to go to. They could consider an artificial bowel sphincter, or they could be looking at a Malone antegrade colonic enema procedure, or stoma, or in this country a nonstimulated graciloplasty. None of which are particularly palatable to many patients.

I recently explanted somebody, not for infection, but just because of efficacy failure. And she's quite devastated by the loss of her stimulator even though her result was suboptimal. She was not one of the star pupils, still she was devastated. Patients feel they have lost hope for a relatively, noninvasive method compared to an ABS or graciloplasty and certainly compared to a stoma. Thanks again Dr Fleshman for your thoughtful insights and excellent questions.

Author disclosures

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ORIGINAL ARTICLE

Prophylaxis and Management of Wound Infections after Elective Colorectal Surgery: A Survey of the American Society of Colon and Rectal Surgeons Membership

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Abstract
Background Postoperative wound infections are a widespread and costly problem, especially in colorectal surgery. Despite their prevalence, there are few data regarding appropriate management and prevention strategies.
Materials and Methods In order to assess current attitudes and practices about this subject, and as a guide to designing a randomized trial to gather evidence in order to support data-driven protocol development, an e-mail survey was sent to the membership of the American Society of Colorectal Surgeons to assess current attitudes and practices pertaining to prevention and management of wound infections.
Results Most respondents estimated that the wound infection rate in their own patients was much lower than commonly reported in the literature. Use of evidence-based perioperative strategies for reducing wound infection, such as the use of a wound protector, hyperoxygenation, and implementation of the Surgical Care Improvement Project guidelines, were far from universal. Management strategies varied widely, without apparent rational basis.
Conclusion Based on the practices and beliefs in the surgical community, it is our hope that a multi-institutional study can be carried out to objectify best practices in both the effective and cost-effective management of this common condition and to reduce the wide variation in the treatment of surgical site infections.

Keywords Prophylaxis · Wound infections · Elective colorectal surgery

Introduction

Postoperative wound infections affect approximately 2% of the 30 million patients undergoing surgery annually in the United States.[1] Incisional surgical site infections complicate 20%–30% of elective colorectal surgical cases.[2] Although attitudes vary with regard to the significance or impact of their development, yearly costs associated with surgical site infections have been estimated to be 1 to 1.8 billion USD in the United States.[1] Surgical site infections are classified as incisional or organ/space infections. Incisional infections are located in the subcutaneous tissues above the abdominal fascia, and organ/space infections are located within the abdominal cavity below the abdominal fascia. According to the Center for Disease Control guidelines, an incisional surgical site infection can be diagnosed by any one of the following criteria: purulent drainage, organisms isolated from an aseptically obtained wound culture, signs/symptoms of infection, an incision that spontaneously dehisces or requires opening due to purulence, or diagnosis of surgical site infection by a surgeon or attending.[2] This study focuses on incisional surgical site infections, most commonly called superficial wound infections.

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Accepted patient-related factors that increase the risk of wound infections include obesity, smoking, malnutrition, diabetes, immunosuppression, and other medical comorbidities. Surgery-related factors associated with surgical site infections include clipping versus shaving, transfusion requirements, as well as emergency surgery and type of surgery (clean, clean contaminated, contaminated, and dirty). In colorectal resections, additional factors independently associated with wound infections involve the creation/revision and/or closure of an ostomy, increased body mass index, and intraoperative hypotension.[3]

With the prevalence of wound infections and the tremendous costs associated with their development, it is surprising to find a dearth of studies regarding management of wound infections. Furthermore, much of the available literature involves single-institution or limited multicenter trials detailing their experience, in contrast to knowledge of a cross-section from various practices ranging from private practice, academic, rural, urban, and across nations. Therefore, in anticipation of designing one or more randomized controlled studies of this subject, we conducted a survey of the American Society of Colorectal Surgeons membership to assess current attitudes and practices regarding the incidence, perioperative prophylaxis, and management of wound infections following colorectal surgical procedures.

Material and Methods

A survey was developed to assess opinions and common practices regarding the incidence, perioperative prophylaxis, and management of wound infections following elective colorectal resection. A questionnaire consisting of 47 separate scenarios was distributed electronically to all members of the American Society of Colon and Rectal Surgeons (Fig. 1). A spectrum of answers to each question was provided, as well as the opportunity for narrative answers for some questions. Where applicable, respondents were encouraged to select more than one answer to reflect their personal practice.

Results

We electronically distributed surveys to the entire membership of the American Society of Colon and Rectal Surgeons. Three hundred thirty-six members responded to the survey.

Demographics

The majority of respondents (62%) had been in practice for 10 or more years (Fig. 2). Eighty-two percent of respondents reported that >90% of their practice is limited to colorectal surgery. The rest of the respondents divided their time between general and colorectal surgery, though all respondents spent >50% of their time practicing colorectal surgery. The global distribution of surgeons was 84% from North America, 10% from Europe, and 6% from Asia, Australia, and Africa (Fig. 3).

Wound Infection Survey

At least 75% of those participating in our survey believed the wound infection rate in their abdominal surgical patients to be "<10%" after elective colorectal surgery, with a majority of those estimating their personal rate as "<5%" (Table 1). Mechanical bowel preparation (MBP) prior to colectomy was used routinely by 76%, selectively by an additional 19%, and omitted by only 4% of respondents. Thirty-six percent used an oral antibiotic preparation, in addition to perioperative parenteral antibiotics, for elective bowel resections. Ninety percent of respondents believed their hospitals to be in compliance with Surgical Care Improvement Project (SCIP) guidelines[4] (Table 2).

Intraoperative measures employed to minimize wound infections were as follows: wound protectors were used "always" in 33% and "selectively" in 36%. A drain was placed in the subcutaneous tissue "always" in 1% and "sometimes" in 21%. Choice of skin closure was staples in 67% and subcuticular sutures in 24% for routine elective cases. The most frequent responses to use of skin closure in contaminated cases, defined as gross spillage from the gastrointestinal tract or nonpurulent inflammation, were "loosely approximate skin" in 41%, "primary closure" in 30%, and "primary closure + drain" in 13%. Leaving the skin open to heal later by secondary intention, or delayed primary closure, was performed by only 6% and 9%, respectively. A negative pressure wound vacuum dressing was applied in contaminated cases in only 2%. The most frequent approach to skin closure after dirty cases, defined as gross intra-abdominal purulence or abscess, was to leave the skin open to heal by secondary intention or delayed primary closure in 42%, loosely approximate the skin in 34%, and apply a wound vacuum dressing in 10%. Of note, 7% of respondents would close the skin primarily in cases with frank intra-abdominal contamination (Table 3).

Once diagnosed, postoperative wound infections are opened at the bedside by 91% of our respondents. Wound infections were cultured by 56%, although the routine use of antibiotics in all patients is employed by only 10% of respondents (Table 4). In addition, we queried factors that may influence antibiotic use by providing four associated conditions, with instructions to select all choices that applied. Selective factors such as cellulitis (89%), immunocompromised state (56%), and fever (34%) influenced

1. How long have you been in practice?	
2. Is your practice >90% colorectal surgery?	25. What are your criteria for discharge from home health?
3. What is the location of your practice?	26. What is your preferred approach to skin closure in contaminated bowel cases?
4. What percentage of your patients develop wound infections after colorectal surgery?	27. What is your preferred approach to skin closure in dirty bowel cases?
5. Does your hospital adhere to SCIP guidelines for the prevention of SSI?	28. Does your approach to closure change from contaminated to dirty cases?
6. Do you use mechanical bowel prep for colon surgery?	29. What percentage of your patients require surgical wound revisions after complete healing from wound infections?
7. Do use an oral antibiotic prep prior to colon surgery?	30. Do you perform delayed primary closure in any wound that was opened for infection?
8. Do you place a wound protector in the operative field to protect the subcutaneous tissue?	31. What is your typical timing of delayed primary closure?
9. Do you use subcutaneous sutures?	32. Where do you perform delayed primary closure?
10. How do you close the skin?	33. What percentage of wounds that you have opened for a postop infection do you use delayed primary closure?
11. Do you prophylactically place a drain in the subcutaneous tissue prior to skin closure?	34. How often, in your practice, does delayed primary closure fail (infection requiring re-opening, dehiscence?)
12. Do you use perioperative oxygen (FiO2 0.80) to diminish the risk of wound infection?	35. Which method, in your opinion, is most successful in managing wound infections after colon surgery?
13. In a postoperative wound infection where do you prefer to open the incision?	36. In a postop wound infection where do you prefer to open the incision?
14. Do you culture the wound?	37. Do you culture the wound?
15. If you do routinely culture the wound, what describes best your rationale?	38. If you routinely culture the wound, what describes best your rationale?
16. When would you use antibiotics in managing a wound infection?	39. Which patients do you usually use antibiotics?
17. If you use antibiotics, which empiric coverage do you select?	40. If you use antibiotics, which empiric coverage do you select?
18. If you give antibiotics, do you cover for MRSA empirically?	41. If you give antibiotics, do you cover for MRSA empirically?
19. How do you manage the wound?	42. How do you manage the wound?
20. Do you involve ET/WOCN nurses in wound care of these patients?	43. Do you involve ET/WOCT nurses in wound care of outpatients?
21. Do you typically recommend SNF placement for patients with postop wound infections?	44. Do you consult home health nursing for patients seen in the E.R. or office?
22. If you don't recommend SNF placement, do you typically recommend Home Health Nursing?	45. What is/are your criterion/a for admission to the hospital?
23. How many days does a wound infection typically delay discharge?	46. What are your criteria for discharge from home health?
24. In general, what is your most important criterion for discharge from the hospital for patients with a postop wound infection after colon surgery?	47. Do you perform delayed primary closure on wound infections, diagnosed as an outpatient?

Fig. 1 Survey questions. *ET* Enterostomal Therapist; *WOCN* Wound, Ostomy and Continence Nurse; *WOCT* Wound, Ostomy and Continence Therapist; *SNF* Skilled Nursing Facility.

the respondents most to prescribe antibiotics. As an independent risk factor, age greater than 65 years did not appear to influence antibiotic use for treatment of these infections. Finally, when choosing antibiotics, 92% of respondents do not empirically cover methicillin-resistant *Staphylococcus aureus* (MRSA).

Preference for the management of the opened, infected wound was solicited by again providing four possible choices (packing, wet to dry; wound vacuum; packing, dry, other), and respondents were encouraged to select all that applied. The most preferred method was "packing, wet to dry" (75%), followed by wound vacuum dressing (50%), and

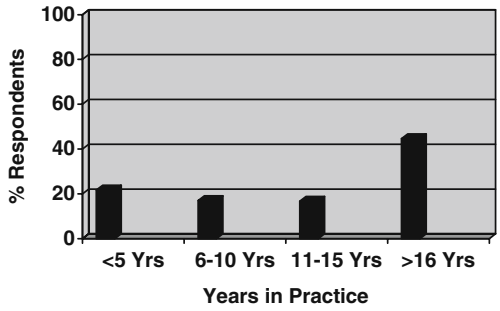

Fig. 2 Respondents average years in practice.

"packing, dry" (20%) (Table 5). Enterostomal therapists/wound-certified nurse specialists were utilized "sometimes," "rarely," and "never" by 44%, 17%, and 5% of respondents, respectively. However, home health nursing was perceived to be necessary "most of the time" by 51% of respondents and "always" by 13%. When queried about the impact of wound infection development on length of stay, the most frequent answer choice for "delay in discharge due to wound infection" was 2 days in 40%, followed by 1 day in 29% and 3 or more days in 19%.

Discussion

Despite the unfortunately high occurrence of infectious wound complications, there remains a lack of studies regarding their postoperative management. This is even more surprising given the annual cost to the healthcare system of a postoperative wound infection. This is emphasized by Ueno and colleagues,[6] who report a prevalence of 300,000 surgical infections per year in the United States at an annual cost in excess of 1 billion US dollars. Review of the literature was conducted by each of the authors independently, as well as with the assistance of two professional medical librarians. We encountered, at best, only a small number of level II evidence (Table 6) regarding management of wound infections. For example, a

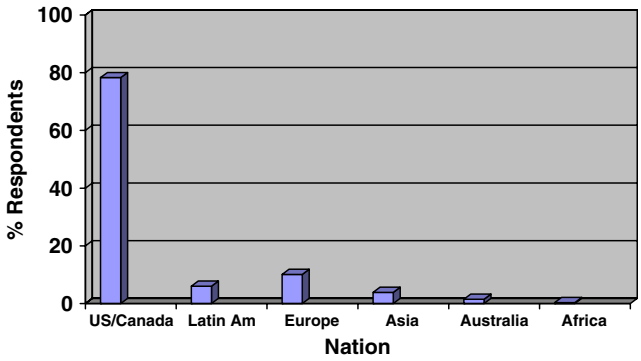

Fig. 3 Global distribution of survey respondents.

Table 1 Most Frequent Responses to Questions Regarding Preoperative Prophylaxis of Wound Infection

Question	Answer	% Respondents
Incidence of wound infection?	<5%	39
	6%–10%	36
	10%–15%	15
	16%–20%	9
	20%–30%	1
	>31%	0
Mechanical bowel prep?	Always	76
	Selectively	19
Oral antibiotic prep?	Never	55
	Always	36
Hospital adherence to SCIP?	Yes	90
	No	10

Prep preparation; *SCIP* Surgical Care Improvement Project

recent Cochrane review of surgical wound debridement found five small, conflicting randomized trials comparing various wound debridement methods (saline-soaked gauze, enzymatic debridement, dextranomer beads/paste, etc.). The authors concluded, "There is a complete absence of adequately powered, methodologically robust RCTs evaluating contemporary debridement interventions for surgical wounds.[6]" Furthermore, most of the agents tested in the cited randomized controlled trials (RCTs) are no longer manufactured. Though we found that 50% of our respondents used wound vacuum therapy for infected wounds, the Cochrane reviews of negative pressure wound therapy only evaluated chronic wounds,[7] and we could not locate any randomized studies of negative pressure therapy specifically in surgical site infections. The Cochrane review of surgical wounds healing by secondary intention cites 13 small RCTs, making it difficult to interpret the data.[8] This dearth of literature is also cited in the United Kingdom National Health Service guidelines, which conclude that there is insufficient evidence to make any recommendations for how to treat postsurgical wounds healing by secondary intention.[9]

In the current study, we distributed surveys to the entire membership of the American Society of Colon and Rectal Surgeons. Our focus was primarily to assess surgeons' practice patterns with regard to preoperative and intraoperative prophylaxis, as well as management of postoperative wound infections in both the inpatient and outpatient settings. With 334 member responses, this is the largest such survey of this type.

The majority (82%) of surgeons responding are primarily colorectal surgeons, meaning >90% of their practice consists of colorectal surgery. Interestingly, 75% of respondents estimated their own incidence of wound

Table 2 Surgical Care Improvement Project (SCIP) [4]

Prophylactic antibiotic received within 1 h prior to surgical incision
Appropriate antibiotic selection for surgical patients
Prophylactic antibiotics discontinued within 24 h after surgery end time (48 h for cardiac patients)
Cardiac surgery patients with controlled 6 AM postoperative serum glucose
Surgery patients with appropriate hair removal
Colorectal surgery patients with immediate postoperative normothermia

infection as <10%, and the most frequent response overall was <5% (39% of the survey participants). These figures are much lower than those published in the literature on this subject and most likely illustrate the recall bias associated with questionnaires. The National Institute for Clinical Excellence[10] reported an overall wound infection incidence of 26% for a single surgeon performing elective colorectal resections, and according to Hedrick et al.[11], the incidence of surgical site infection ranges from 5% to 30%. Similarly, Horan *et al*.[3] reported an overall surgical site infection of 25% following colorectal resection, of which 92% were clean-contaminated cases. In our survey, only 10% of respondents estimated their incidence of wound infection rate to be 16% or greater. This suggests that there is a tendency for surgeons to significantly underestimate and underreport the incidence of wound infection after colorectal resection. It also highlights the need for accurate reporting and data collection not only on the hospital, regional, and national levels, but also for the individual surgeon.

Ninety percent of respondents believed their hospitals to be in compliance with SCIP guidelines (Table 5). Adoption and implementation of these guidelines have recently proven beneficial in reducing the incidence of wound infections. Hedrick *et al*. showed a 39% reduction in the incidence of surgical site infection when his group implemented a multidisciplinary system protocol targeting five main process measures: antibiotic administration within 0–60 min before incision, proper antibiotic selection, discontinuation of perioperative antibiotics within 24 h of operation, maintenance of normothermia, and maintenance of normoglycemia. Interestingly, they also began placing Penrose drains into the subcutaneous space in patients who had a body mass index of >25 kg/m^2, contrasted with only ~20% of our cohort.[11] We are unable to find any studies that corroborate the efficacy of this practice.

Two thirds of respondents in our study used preoperative MBP, despite recent multicenter randomized trials demonstrating no difference in wound infection rates for patients undergoing elective colorectal resection receiving MBP compared with those not receiving bowel preparation.[12] According to a 2009 Cochrane Review, which included all randomized controlled trials comparing MBP to no MBP, there is no statistically significant evidence that MBP improves outcomes for patients including risk of anastomotic leak, mortality, wound infection, peritonitis, and need for reoperation.[13] Likely, this response from our respondents represents the surgical dogma associated with the perceived benefit of bowel preparations for colorectal surgery that is ingrained with most surgeons. Studies such as this survey will allow us to track practice patterns over time and to evaluate how surgeons respond to results in the literature.

We also attempted to identify the use of a variety of perioperative measures that have been found in the surgical

Table 3 Most Frequent Responses to Questions Regarding Intraoperative Prophylaxis of Wound Infection

Question	Answer	% Respondents
Wound protector?	Selectively	36
	Always	33
Close the subcutaneous tissue with sutures?	Never	61
	Selectively	28
Drain the subcutaneous layer?	Never	78
	Sometimes	21
Method of skin closure, clean-contaminated cases?	Staples	67
	Subcuticular	24
Method of skin closure, contaminated cases?	Loosely approximate	41
	Primary closure	30
	Primary closure + drain	13
Method of skin closure, dirty cases?	Loosely approximate	34
	Secondary intention	28
	Delayed primary closure	14

Table 4 Attitudes Regarding the Use of Antibiotics after the Diagnosis of a Wound Infection

Question	Answer	% Respondents
Routinely culture wound?	Yes	56
	No	44
Antibiotics for All patients?	Yes	10
What factors determine that you will use antibiotics?	Selective (e.g., cellulitis)	89
	Immunocompromised State	56
	Fever	34
	Age >65 y	7
If prescribing an antibiotic, empirically cover MRSA?	No	92
	Yes	8

literature to decrease the rate of wound infection. For example, two thirds of our respondents either "always" or "selectively" used a wound protector. In one randomized trial, Sookhai et al.[14] and Horiuchi et al.[15] reported an 84% reduction in postoperative wound infections after laparotomy over a 1-year period with the use of a wound protector, translating to a hospital savings of $319,000 USD over this same interval. In addition, the prophylactic placement of wound drains is "never" used after elective colorectal resection by 78% of surgeons in our survey. In the study by Gallup *et al.*[16], the prophylactic use of drains in the subcutaneous tissue of obese patients, defined as >30% over ideal body weight, resulted in decreasing all wound complications from 31% to 20%. Again, our study is somewhat limited by the questionnaire not specifying which patients would receive drains, but the high response rate of "never" again may reflect a recall bias, difference in patient population from the Gallup survey, or lack of knowledge regarding the successful use of drains in select patients. Finally, in our survey, only 28% of respondents used perioperative hyperoxygenation. The perioperative administration of 80% FiO2 (compared with 30%) during and for at least 6 h after surgery has been reported in two randomized trials to decrease surgical site infections from 24%–28% to 13%–15% following elective colorectal resection.[17, 18] The results of the present survey can therefore be used to highlight certain topics that may require additional education on a regional or national level.

Although this is primarily a survey of practice with elective colorectal cases, we took the opportunity to probe attitudes regarding skin closure for "contaminated" and "dirty" cases as well. Commonly accepted rates of wound infection for clean-contaminated, contaminated, and dirty cases are 10%, 20%, and 40%, respectively.[19] Not surprisingly, approaches to skin closure did change across these different scenarios. For contaminated cases, the most frequent response was "loosely approximate skin" (41%). Yet, if the responses to "primary closure" (30%) and "primary closure + drain" (13%) are combined (43%), "primary closure" would be the most frequent response. On the other hand, for dirty cases, the most frequent response type was still "loosely approximate skin" (34%), although we began to see a shift away from primary closure with or without a drain from contaminated (43%) to dirty cases (14%).

In our survey, slightly more than half of all surgeons cultured infected wounds, and only 10% treated all patients with antibiotics initially, relying more on opening the wound. Furthermore, when choosing antibiotics, only 8% select empiric coverage of MRSA. In a recent study of the

Table 5 Most Frequent Responses to the Management of the Opened, Infected Surgical Site

Question	Answer	% Respondents
Preferred approach to wound?	Packing, wet-to-dry	75
	Vacuum dressing	50
	Packing, dry	20
Involve enterostomal/wound nurse?	No (sometimes, rarely, never)	70
	Yes (always, most of the time)	30
Involve home health nursing?	Yes (always, most of the time)	63
	No (sometimes, rarely, never)	37
Average delay in discharge	2 d	40
	1 d	29
	>3 d	19
	No delay	12

Table 6 Levels of Evidence and Grade Recommendation

Level source of evidence
I. Meta-analysis of multiple well-designed, controlled studies, randomized trials with low false-positive and low false-negative errors (high power)
II. At least one well-designed experimental study; randomized trials with high false-positive or high false-negative errors or both (low power)
III. Well-designed, quasi-experimental studies, such as nonrandomized, controlled, single-group, preoperative–postoperative comparison, cohort, time, or matched case-control series
IV. Well-designed, nonexperimental studies, such as comparative and correlational descriptive and case studies
V. Case reports and clinical examples
Grade of recommendation
A. Evidence of type I or consistent findings from multiple studies of type II, III, or IV
B. Evidence of type II, III, or IV and generally consistent findings
C. Evidence of type II, III, or IV but inconsistent findings
D. Little or no systematic empirical evidence

Adapted from Gregor et al.[23] and Cook et al.[24]

microbiology of wound infections, the most frequent pathogen isolated in wounds was *S. aureus,* and approximately 60% were methicillin-resistant.[5]] Ueno and colleagues[6] found that factors associated with increased risk for MRSA are prolonged use of prophylactic antibiotics, use of drains for >24 h, and number of procedures performed on a patient. Other studies have also demonstrated a significant rate (14%) of MRSA in surgical site infections.[3] The Infectious Disease Society of America is currently updating their practice guidelines for both antimicrobial prophylaxis for surgery and MRSA. However, according to the "Guidelines for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the UK" the authors recommend prophylaxis with a glycopeptide (Vancomycin) in any patient requiring surgery who has a history of MRSA colonization or infection or in patients coming from facilities with a high prevalence of MRSA.[20] It is not clear if our respondents are following these current guidelines. According to the "Guidelines for Skin and Soft-Tissue Infections" published by the Infectious Disease Society, the primary treatment for an skin and soft-tissue infection is to open the incision, evacuate the purulent debris, and perform local wound care until healing occurs by secondary intention. As long as there is "minimal surrounding evidence of invasive infection" (<5 cm of erythema and induration), and if the patient has minimal systemic signs of infection (a temperature of <38.5°C and a pulse rate of <100 beats/min), antibiotics are unnecessary. If the above findings are noted, then a short course of antibiotics may be warranted along with opening the incision and local wound care.[21]

In contrast to the large number of studies on perioperative factors to prevent or decrease the incidence of wound infection, there are virtually no papers comparing different techniques to manage the opened incisional surgical site infection. In our survey, when a wound infection was diagnosed during the inpatient stay, the most frequent modalities used for management included packing of the wound with wet-to-dry (75%), negative pressure vacuum dressings (50%), and packing with dry dressing (20%). When a wound infection was diagnosed in the outpatient setting, packing with wet-to-dry remained the most common modality used (63%) followed by packing with dry dressing (16%). Interestingly, negative pressure vacuum dressings were much less utilized in the outpatient setting (8%). Regrettably, we are unaware of any data that suggest that any of these practices are either helpful or detrimental, when judged against alternative management strategies for comparative purposes.

Although there is widespread utilization of vacuum dressings, there is only equivocal data, at best, to support them. Braakenberg and colleagues[22] in a randomized, controlled trial found no significant difference in the healing time or amount of granulation tissue of wounds treated with vacuum dressing compared with conventional therapy (defined as hydrocolloid, alginate, acetic acid, or other dressings. Gregor and associates performed a meta-analysis of all RCTs evaluating the effect of negative pressure vacuum dressings compared with conventional dressings. They found a significant difference favoring negative pressure vacuum dressings in only two of five randomized controlled trials.[23] Most studies included in the meta-analysis were diabetic, pressure, venous stasis, and burn wounds and may not be generalizable to postoperative wound infections. The authors concluded that there is insufficient data to support the rampant use of this modality, especially when weighing the financial costs of such a measure.[24] Data are lacking regarding the use of negative pressure wound therapy specifically in postoperative wound infections and especially in colorectal surgery. This serves to provide even more impetus on gathering accurate data with regard to wound infection rates, severity, and management to provide guidelines to clinicians for proper

use of management tools such as the Wound VAC. This topic is in need of further prospective evaluation.

Much of the cost incurred by a postoperative wound infection is related to prolongation of the hospital stay for the patient with an infected wound, and the use, or perceived need, of ancillary services following discharge. Most respondents in our study felt that patients with wound infections required home health nursing, but not necessarily care by a specialized enterostomal/wound care nurse. National Institute for Clinical Excellence,[10] in its retrospective review of wound infections after elective colorectal resections by a single surgeon, found that 44% of patients were recommended to have home health nursing for wound care management. This group calculated the cost per patient for wound care management provided by home health care to range from $913 to $24,100 USD, with a mean cost per patient of $6,200 USD. The occurrence of an incisional surgical site infection was perceived by most respondents to delay discharge by at least 2 days, though reasons for this practice are not clear. This is in accordance with Horan et al. [3], who in their retrospective review of colorectal surgical patients reported a median length of stay for patients with an incisional surgical site infection to be 8 days. This was significantly longer than the 7-day length of stay for those patients without wound infection, which along with dressing supplies, antibiotics, and nursing care account for the rising costs. Thus, all efforts to prevent the onset of these infections should be employed to avoid additional costs, both for the individual patient and the healthcare system.

Conclusion

This survey represents the first attempt to gauge widespread attitudes regarding both the prophylaxis and management of postoperative wound infection following elective colorectal surgery. We found that most surgeons believe that they have significantly fewer patients with wound infections than the literature consensus reports. The use of antibiotics is generally reserved for specific wound and patient-related factors, such as fever or marked cellulitis. For the treatment of established wound infections, a large percentage of respondents believe that wound packing and/or vacuum dressings are helpful, despite the lack of supporting evidence. Furthermore, prolonged hospitalization and the frequent use of home health nurses after discharge are major determinates of the cost and resource expenditure in the treatment of these wounds.

We intend to use the results of this survey to serve as a springboard for controlled, prospective studies on wound infection management strategies in colorectal surgery patients. This survey also serves as a benchmark for future surveys to identify changes in practice patterns for surgeons managing these complications.

References

1. Bratzler DW, Houck PM, Richards C, Steele L, Dellinger EP, Fry DE, Wright C, Ma A, Carr K, Red L. Use of antimicrobial prophylaxis for major surgery: baseline results from the National Surgical Infection Prevention Project. Arch Surg 2005;140:174-182.
2. Smith RL, Bohl JK, McElearney ST, Friel CM, Barclay MM, Sawyer RG, Foley EF. Wound infection after elective colorectal resection. Ann Surg 2004;239:599-605.
3. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol 1992;13:606-608.
4. Blumetti J, Luu M, Sarosi G, Hartless K, McFarlin J, Parker B, Dineen S, Huerta S, Asolati M, Varela E, Anthony T . Surgical site infections after colorectal surgery: do risk factors vary depending on the type of infection considered? Surgery 2007;142:704-711.
5. Surgical Care Improvement Project. SCIP guidelines are available at www.medqic.org/scip. Accessed 7 February 2009.
6. Ueno C, Hunt TK, Hopf HW. Using physiology to improve surgical wound outcomes. Plast Recon Surg 2006;117:59S-71S.
7. Dryburgh N. Debridement for surgical wounds. Cochrane Database of Systematic Reviews. 2008;(4).
8. Ubbink D. Topical negative pressure for treating chronic wounds. Cochrane Database of Systematic Reviews. 2009;(4).
9. Vermeulen H, Ubbink DT, Goossens A, de Vos R, Legemate DA. Dressings and topical agents for surgical wounds healing by secondary intention. Cochrane Database of Systematic Reviews. 2009;(4).
10. National Institute for Clinical Excellence. Guidance on the use of debriding agents and specialist wound care clinics for difficult to heal surgical wounds October 2008. http://www.nice.org.uk/nicemedia/pdf/CG74.
11. Hedrick TL, Heckman JA, Smith RL, Sawyer RG, Friel CM, Foley EF. Efficacy of Protocol Implementation on Incidence of Wound Infection in Colorectal Operations. J Am Coll Surg 2007;205:432-438.
12. Contant CM, Hop WC, van Sant HP, Oostvogel HJ, Smeets HJ, Stassen LP, Neijenhuis PA, Idenburg FJ, Dijkhuis CM, Heres P, van Tets WF, Gerritsen JJ, Weidema WF. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomized trial. Lancet 2007;370:2112-2117.
13. Guenaga KK, Matos D, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev 2009;1:CD001544.
14. Sookhai S, Recmond HP, Deasy JM. Impervious wound-edge protector to reduce postoperative wound infection: a randomized, controlled trial. Lancet 1999;353:1585.
15. Horiuchi T, Tanishema H, Tamagawa K, et al. Randomized, controlled investigation of the anti-infective properties of the Alexis retractor/protector of incision sites. J Trauma 2007;62:212-215
16. Gallup DC, Gallup DG, Nolan TE, Smith RP, Messing MF, Kline KL. Use of a subcutaneous closed drainage system and antibiotics in obese gynecologic patients. Am J Obstet Gynecol 1996;175:358-361.
17. Grief R, Akca O, Horn EP, Kurz A, Sessler DI. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. NEJM 2000;342:161-167.
18. Belda FJ, Aguilera L, García de la Asunción J, Alberti J, Vicente R, Ferrándiz L, Rodríguez R, Company R, Sessler DI, Aguilar G,

Botello SG, Ortí R; Spanish Reduccion de la Tasa de Infeccion Quirurgica Group. Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. JAMA 2005;294:2035-2042.
19. National Nosocomial Infections Surveillance (NNIS) report, data summary from October 1986-April 1996, issued May 1996. A report from the National Nosocomial Infections Surveillance (NNIS System). Am J Infect Control 1996;24:380-388.
20. Gemmell CG, Edwards DI, Fraise AP, Gould FK, Ridgway GL, Warren RE. Guidelines for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the UK. J Antimicrob Chemother 2006;57:589-608.
21. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan EL, Montoya JG, Wade JC; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis 2005; 41:1373-1406
22. Braakenberg A, Obdeijn MC, Feitz R, van Rooij IALM, van Griethuysen AJ, Klinkenbijl JHG. The clinical efficacy and cost effectiveness of the vacuum-assisted closure technique in the management of acute and chronic wounds: a randomized controlled trial. Plast Reconstr Surg 2006;118:390-397.
23. Gregor S, Maegele M, Sauerland S, Krahn JF, Peinemann F, Lange S. Negative pressure wound therapy: a vacuum of evidence? Arch Surg 2008;143:189-196.
24. Cook DJ, Guyatt GH, Laupacis A, Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 1992;102(4 Suppl):305S–311S.

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ORIGINAL ARTICLE

Primary Sclerosing Cholangitis and Extraintestinal Manifestations in Patients with Ulcerative Colitis and Ileal Pouch–Anal Anastomosis

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Abstract
Objective The aim of this study was to assess complications and functional outcomes in patients having ileal pouch–anal anastomosis for ulcerative colitis with or without primary sclerosing cholangitis or extraintestinal manifestations and to assess if primary sclerosing cholangitis is a risk factor for pouchitis.
Materials and methods From 1984 to 2007, 289 patients underwent proctocolectomy with ileal pouch–anal anastomosis for ulcerative colitis. Mean follow-up time was 12 years and data was recorded prospectively. Eleven patients had primary sclerosing cholangitis, six had pyoderma gangrenosum, and 12 had arthritis or ankylosing spondylitis.
Results Early complications were similar for patients with or without extraintestinal manifestations. Functional outcomes were similar, but more incontinence among patients with sclerosing cholangitis was found. These patients had more frequent pouchitis, 5.25 vs. 2.72 average episodes of pouchitis ($p=0.048$), and more chronic pouchitis, 4/11 vs. 17/260 ($p<0.001$) compared to patients without adjunct disease. Neoplasm of the colon was more frequent in patients with primary sclerosing cholangitis, 4/11 vs. 4/260 in ulcerative colitis patients ($p<0.001$).
Conclusion An association between primary sclerosing cholangitis and chronic/severe pouchitis was found, but not with other extraintestinal manifestations. Functional results were good and alike in patients with and without primary sclerosing cholangitis. Primary sclerosing cholangitis is a risk factor for chronic pouchitis and is associated with neoplasia.

Keywords Ileal pouch–anal anastomosis · Ulcerative colitis · Pouchitis · Primary sclerosing cholangitis · Extraintestinal manifestations

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Introduction

The prevalence of primary sclerosing cholangitis (PSC) in patients with ulcerative colitis (UC) and ileal pouch–anal anastomosis (IPAA) varies between 1% and 6%[1–4] when the diagnosis is based on clinical symptoms and signs alone. When liver biopsies are taken perioperatively in UC patients undergoing IPAA, the prevalence increases to 10–11.8%,[2,5] indicating a substantial proportion of subclinical PSC. Pyoderma gangrenosum (PG) has been reported in 0.5–5% of UC patients.[4,6,7] Arthritis and ankylosing spondylitis have been reported among 12–23% of UC patients, whereas arthralgia has been reported as high as 55%.[4,8,9] Eye manifestations occur in about 3%.[10,11]

Reports of surgical and functional outcomes in UC patients with PSC or other extraintestinal manifestations (EIM) who underwent IPAA are limited and the results are conflicting. Several authors[1,2,5,12,13] have reported PSC to be a risk factor for pouchitis, whereas others have not found

this association.[3,14] Increased rates of pouchitis in patients with EIM have been reported by some authors[6,15,16] but not by others.[3,13,14,17] It seems, however, that pouchitis can provoke and exacerbate arthralgia.[18,19] The pathogenesis of the possible association between pouchitis and PSC/EIM remains unclear.

The aim of this study was to assess the association between PSC/EIM and pouchitis and to evaluate differences in long-term functional outcomes and complications in patients with UC with or without PSC and EIM operated with restorative proctocolectomy.

Materials and Methods

During the period 1984 to 2007, 289 patients with UC underwent IPAA at St Olavs Hospital, Trondheim, Norway. When elevated liver functional tests were found, PSC was suspected, and the diagnosis was confirmed by characteristic imaging features on magnetic resonance imaging, computed tomography cholangiogram and/or endoscopic retrograde cholangiogram, and occasionally liver biopsies. Liver biopsy was not a perioperative routine during IPAA construction.

PG was diagnosed by dermatologists by biopsies and arthritis or ankylosing spondylitis by rheumatologists. Patients with arthralgia without confirmed arthritis were not included in the analyses of arthritis. Five patients had uveitis/episcleritis, two of whom also suffered from ankylosing spondylitis; one had arthritis and one had PG. These patients are included in the respective diagnostic groups. One patient with isolated uveitis was not included in any EIM group.

Pouchitis was suspected when symptoms were typical and confirmed by endoscopy. Biopsies were not routinely taken. Patients with 15 or more episodes of pouchitis and made use of self-administration of antibiotics or patients with continuous antibiotic therapy were classified as having chronic pouchitis.

Each patient was offered a regular, annual follow-up at the outpatient clinic. Intervals were increased over time in agreement with the patients. Mean interval was 34 months. All patients were encouraged to contact the hospital if problems related to their IPAA occurred.

At the outpatient clinic, all patients were interviewed on functional outcomes according to a standardized questionnaire and had a clinical examination including endoscopy. Information on diagnosis, surgical complications, and long-term outcomes were collected and included in a database. No patients were lost to follow-up.

Statistical Analysis

Pearson chi-square test and Fischer exact test were used to analyze associations between categorical variables. Student's *t* test and Mann–Whitney test were used to compare means and medians between two groups. One-way ANOVA was used to compare differences in means between groups. Statistical significance was set to $p<0.05$. The statistical package SPSS v. 16 was used.

Results

The patients were divided into four different observational groups; UC without PSC or EIM (260), UC with PSC (11), UC with PG (6), and UC with joint affections (12). Nine patients had arthritis and three had ankylosing spondylitis. The patients' characteristics are given in Table 1. Time with UC before surgery was longer in patients with PSC than those without; 13 vs. 7 years ($p=0.004$). The numbers of visits at the outpatient clinic were similar for all groups. The rate of mucosectomy and use of temporary covering loop ileostomy was similar among patients with or without PSC/EIM. There were no differences between the groups with regard to gender, age at IPAA construction, or duration of the pouch. Five of the PSC patients had the diagnosis of PSC established more than 5 years before IPAA construction; six had the diagnosis in the first 4 years after IPAA.

The incidence of anastomotic dehiscence ($p=0.47$), pelvic sepsis ($p=0.84$), and overall fistula formations ($p=0.32$) were similar in the different groups (Table 2). Four patients developed postoperative hematomas; three patients without PSC and one with PSC. Four patients developed postoperative DVT; three UC patients without PSC/EIM and one patient with arthritis. No anastomotic varicoses or perianastomotic bleeding were recorded in medical charts or diagnosed at the outpatient visits in patients with PSC.

Table 3 shows the frequency of neoplasia. Four out of 11 patients with PSC had neoplasia compared to 4/260 patients with solely UC ($p<0.001$). There were no neoplasms diagnosed among UC patients with other EIM. Three patients died during the follow-up period, none of whom had PSC or EIM. Causes of death were metastatic adenocarcinoma of the prostate, uterus, and liver, respectively. Seven out of 260 UC patients without PSC/EIM were diagnosed with malignancies during the follow-up period: prostate (2), breast (2), urinary bladder (1), metastatic adenocarcinoma of the liver (1), endometrial cancer (1), and malignant melanoma (1).

Twelve patients with IPAA had short observational times partly due to early failures and were excluded from long-term analyses. Thus, 277 patients were eligible for analyses. Of these, 100 (36%) had chronic or episodic pouchitis. UC patients with PSC had more pouchitis (8/11) than patients without PSC (88/260) ($p=0.038$). Mean

Table 1 Ileal Pouch–Anal Anastomosis Operated 1984–2007 (n=289): Patient Characteristics. Number of Patients

	Ulcerative colitis (n=260)	Primary sclerosing cholangitis (n=11)	Pyoderma gangrenosum (n=6)	Arthritis (n=12)	p value
Male	163 (62%)	7 (63%)	2 (33%)	6 (50%)	0.41
Age (years)	34.5±11.2	38.6±11.6	31.5±10.6	38.0±15.0	0.42
Mean number of planned visits	5.7±3.9	6.2±4.5	7.3±3.0	8.7±3.8	0.06
Stapled anastomosis	159 (61%)	8 (72%)	4 (66%)	3 (33%)	0.87
Protective stoma	222 (85%)	9 (81%)	4 (67%)	9 (83%)	0.47
Mucosectomy	95 (36%)	3 (27%)	2 (33%)	5 (42%)	0.90
Duration (years) of UC before colectomy	6.58±6.77	12.73±9.55	2.83±3.7	5.0±4.6	0.004[b]
Pouch duration (years)	10.4±6.1	8.6±3.9	13.0±3.5	14.7±6.2	0.048[a]
Pouch failure	20 (8.3%)	1 (10%)	0	0	0.67

[a] Significant difference between patients with PSC and arthritis

[b] Significant difference between patients with ulcerative colitis with PSC and ulcerative colitis without PSC or EIM

number of episodic pouchitis was 5.25 for patients with PSC compared to 2.72 among UC patients without any EIM. Four out of 11 patients with PSC had chronic pouchitis in contrast to 17 of 260 patients without EIM (p<0.001) (Table 3). Two of the patients with PSC and chronic pouchitis had the diagnosis of PSC established before IPAA. Increased frequency of episodic pouchitis or chronic pouchitis was not found in patients with PG or joint affections.

Patients in the four diagnostic groups had similar frequencies of bowel movement. Patients with PSC had mean 0.55±0.5 episodes of daytime incontinence per week, which was significantly more frequent than for other patients (0.07±0.03 per week) (p=0.007). Functional outcomes are shown in Table 4.

Discussion

Chronic and frequent episodes of pouchitis were more common in UC patients with PSC than without PSC. These findings are in accordance with other studies, although the study design and clinical definitions of pouchitis vary, which complicate interpretations and comparison between studies.[1–4,12,13,16] The majority of studies have limited numbers of patients with PSC and/or EIM. Small patient numbers and the unknown etiology of the poorly defined entities of diseases make statistical analysis and interpretation difficult, and valid conclusions cannot easily be drawn. The strength of this study is the extensive follow-up program with more than 1,500 planned visits at the outpatient clinic and the long observational times. However,

Table 2 Complications and Rates of Pouchitis in Patients Operated with Restorative Proctocolectomy with or without Extraintestinal Manifestations (n=289): Number of Patients

	Ulcerative colitis (n=260)	Primary sclerosing cholangitis (n=11)	Pyoderma gangrenosum (n=6)	Arthritis (n=12)	p value
Early anastomotic separation	25	0	0	2	0.47
Early anastomotic leakage	10	0	0	1	0.72
Early pelvic sepsis	7	0	0	0	0.84
Late anastomotic complication	25	1	1	0	0.57
Patients with pouch fistula	19	2	1	0	0.32
Pouchitis[a]	88	8	2	2	0.038
Chronic pouchitis	17	4	0	0	0.0001
Episodic pouchitis	71	4	2	2	0.33
Mean pouchitis episodes	2.72	5.25			0.048[b]

[a] Twelve patients of 260 with only UC were excluded in the analyses of pouchitis due to early failure and very short observational time

[b] Student's t test equal variance assumed, Mann–Whitney test p=0.086

Table 3 Neoplasia in Ulcerative Colitis Patients with Primary Sclerosing Cholangitis and without any Extraintestinal Manifestations

	Ulcerative colitis (n=260)	Ulcerative colitis with primary sclerosing cholangitis (n=11)	
Malignancy	1	2	
Mucosal dysplasia	3	2	
Sum	4	4	$p<0.001$

the small number of patients makes statistical analysis weak. Missing patients and data weakens this even further and creates a potential bias. In the present study, no patients were lost to follow-up.

Among patients with UC, a reported incidence of pouchitis between 30% and 40% is common, and in the present study it was 36%. In the study by Abdelrazeq et al., 32% of the patients experienced pouchitis, and a strong association between PSC and chronic pouchitis was found[13] which are in accordance with the present study. Their study had more patients with PSC (16/198) and EIM (20/198) vs. 11/260 PSC and 18/260 EIM in the present study. Abdelrazeq et al. reported no association between PSC and episodic pouchitis.[13] However, the definition of chronic pouchitis in the present study is stricter, classifying patients with a high frequency of pouchitis in the acute/episodic pouchitis group rather than in the chronic pouchitis group. The association between PSC and acute pouchitis in the present study was based on the increased number of episodes of acute pouchitis in patients with UC and PSC as opposed to patients without UC and PSC; mean 5.25 vs. 2.72 episodes. This result supports the conclusion of Abdelrazeq et al.[13]

The prevalence of PSC in the studies by Aitola et al. and Lepistø et al. were high, 10% and 11.8%, respectively, which is explained by the routinely performed liver biopsies at operation.[2,5] A strong correlation between PSC, both clinical and subclinical, and pouchitis was reported. Their results indicate that subclinical PSC may be an additional risk factor for severe/chronic pouchitis. In a recently published follow-up study by Lepistø et al., it was, however, concluded that progression of PSC with minor ductal changes at the time of IPAA construction is unlikely.[20] However, in the study by Kartheuser et al. only advanced PSC was found to be significantly associated with pouchitis.[12]

A matched controlled study from the Cleveland Clinic[3] showed that chronic pouchitis was equally distributed between UC patients with PSC compared to UC and indeterminate colitis patients without PSC. The concept of chronic pouchitis is, however, not a universally recognized and distinct entity and the differences in study design could explain the diverting results in studies. We believe our data support the conclusions in many studies that an association between PSC and chronic and frequent pouchitis is likely.

The pathogenetic association between the mucosal affection (pouchitis/colitis) and PSC/EIM is not clear. There is no firm evidence showing that pouchitis aggravates PSC in UC patients,[10] but UC patients with PSC do have an increased risk of pouchitis.

Patients with other EIM are reported to have a higher risk of pouchitis.[15,16] Other reports, including the present study do not confirm this.[3,13,14] Therapeutic immunomodulation in PG and arthritis could possibly suppress pouchitis manifestations, giving an apparently low rate of pouchitis. In the present study, pouchitis was diagnosed in

Table 4 Functional Outcomes Assessed at Planned Visits (n=Patients/Number of Visits)

	Ulcerative colitis (n=260/1,483)	Primary sclerosing cholangitis (n=11/68)	Pyoderma gangrenosum (n=6/44)	Arthritis (n=12/104)	p value
Stool frequency (mean/patient)					
Day	5.93±1.8	5.89±1.9	4.18±1.1	5.12±1.3	0.28
Night	0.57±0.7	0.84±0.6	0.25±0.17	0.51±0.46	0.36
Incontinence N patients					
Day	39	4	1	2	0.33
Night	84	7	3	6	0.1
Weekly leakage rate:					
Day	0.07±0.3	0.55±0.5	0.03±0.07	0.06±0.3	0.007
Night	0.25±0.7	0.65±1.4	0.19±0.3	0.34±0.7	0.39
Rate of Loperamid per day	2.15±2.3	2.67±2.8	2.41±1.7	3.97±3.2	0.07
					0.5[a]

[a] Difference between patients with ulcerative colitis with PSC and ulcerative colitis without PSC or EIM

periods with or without anti-EIM medication. Pouchitis seems to exacerbate joint symptoms.[15] In a case report by Borg et al., the joint symptoms were eliminated after removal of the pouch.[21] No reports have documented that pouchitis provokes or exacerbates PG, which is in accordance with our results.

In the study from Cleveland Clinic[3], an increased rate of pelvic sepsis among patients with PSC was reported. A lower level of anastomosis when performing mucosectomy in PSC patients was suggested to explain this observation. In the present study, mucosectomies were not more frequently performed in the PSC patients nor did they suffer more early anastomotic or pouch complications compared to other UC patients. In a previous study[22] of the same population of patients, no association between early pelvic sepsis and stapled or hand-sewn low anastomosis was found which is in accordance with the study of Lovegrove et al.[23] Increased bleeding peri- and postoperatively may be related to the seriousness of liver affection. Bleeding and postoperative hematomas were not more frequently observed in our study. The differences in results between studies may be due to discrepancy in age at operation and the extent of liver disease at surgery. In PSC patients of the present study, there were no recorded anastomotic or anal bleeding events in the follow-up period. Some patients with PSC and conventional ileostomy develop peristomal varices and bleedings.[24] PSC patients with IPAA are spared this complication.

Neoplasia of the colon was more frequent among UC patients with PSC. One explanation may be that the duration of UC before colectomy was two times longer in the PSC group than in the group without PSC. These findings are consistent with those of the Cleveland Clinic study[3] and probably relate to a de facto higher risk for neoplasm in UC patients with PSC. In the Cleveland Clinic study, the PSC patients had an increased mortality rate which was not found in present study. This may be explained by the difference in mean ages as the patients in the present study were on average 10 years younger.

Except for the possible influence of pouchitis on functional outcome, the surgical and functional outcomes were similar in all groups. The patients with PSC/EIM can thus be offered the same surgical options as UC patients without PSC/EIM. The higher incidence of neoplasm in PSC patients having UC may call for an earlier proctocolectomy, including an oncological resection procedure.

We support the view of a distinct division of chronic and acute/episodic pouchitis and regard them as different biological entities.[13,25] The idea that chronic pouchitis and PSC share a common underlying cause is supported by the association observed in the present study and that documented by others.[12,13] The link between PSC and pouchitis may be associated with the duration of PSC, but this study cannot confirm this hypothesis. It is reasonable to differentiate between PSC and the other EIM in UC patients. Therefore, to cluster the many varieties of EIM including PSC in clinical studies makes this field troublesome.

Conclusion

The results of the present study indicate that PSC is a risk factor for frequent/chronic pouchitis. The increased risk of chronic pouchitis in PSC has to be communicated to the patients in need of surgery. Functional results were excellent and alike in patients with or without PSC. Patients with PSC had more neoplasm, but the mortality rate was not increased. There is no substantial evidence to exclude patients with PSC or EIM from undergoing IPAA. The risk of neoplasm calls for a thorough surveillance and early surgery when indicated.

References

1. Penna C, Dozois R, Tremaine W, Sandborn W, LaRusso N, Schleck C, Ilstrup D. Pouchitis after ileal pouch–anal anastomosis for ulcerative colitis occurs with increased frequency in patients with associated primary sclerosing cholangitis. Gut 1996;38:234–239.
2. Lepistö A, Kärkkäinen P, Järvinen HJ. Prevalence of primary sclerosing cholangitis in ulcerative colitis patients undergoing proctocolectomy and ileal pouch–anal anastomosis. Inflamm Bowel Dis 2008;14:775–779.
3. Gorgun E, Remzi FH, Manilich E, Preen M, Shen B, Fazio VW. Surgical outcome in patients with primary sclerosing cholangitis undergoing ileal pouch–anal anastomosis: a case–control study. Surgery 2005;138:631–639.
4. Lohmuller JL, Pemberton JH, Dozois RR, Ilstrup D, van Heerden J. Pouchitis and extraintestinal manifestations of inflammatory bowel disease after ileal pouch–anal anastomosis. Ann Surg 1990;211:622–627.
5. Aitola P, Matikainen M, Mattila T, Tomminen T, Hiltunen KM. Chronic inflammatory changes in the pouch mucosa are associated with cholangitis found on preoperative liver biopsy specimens at restorative proctocolectomy for ulcerative colitis. Scand J Gastroenterol 1998; 33: 289–293.
6. Monsen U, Sorstad J, Hellers G, Johansson C. Extracolonic diagnosis in ulcerative colitis: An epidemiological study. Am J Gastroenterol 1990;85:711–716.
7. Menachem Y, Gottsman I. Clinical manifestations of Pyoderma gangrenosum associated with inflammatory bowel disease. Isr Med Assoc J 2004;6:88–90
8. Dekker-Saeys BJ, Meuwissen SGM, Van Den Berg-Loonen EM, De Haas WHD, Agenant D, Tytgat GNJ. Prevalence of peripheral arthritis, and ankylosing spondylitis in patients suffering from inflammatory bowel disease. Ann Rheum Dis 1978;37:36–41.
9. Andreyev HJ, Kamm MA, Forbes A, Nicholls RJ. Joint symptoms after restorative proctocolectomy in ulcerative colitis and familial polyposis coli. Clin Gastroenterol 1996;23:35–39.
10. Goudet P, Dozois RR, Kelly KA, Ilstrup DM, Phillips SF. Characteristics and evolution of extraintestinal manifestations

associated with ulcerative colitis and proctocolectomy. Dig Surg 2001;18:51–55.
11. Bernstein CN, Blanchard JF, Rawsthorne, Yu N. The prevalence of extraintestinal diseases in inflammatory bowel disease: A population-based study. Am J Gastroenterol 2001;96:1116–1122.
12. Kartheuser AH, Dozois RR, Wiesner RH, LaRusso NF, Ilstrup DM, Schleck CD. Complications and risk factors after ileal pouch–anal anastomosis for ulcerative colitis associated with primary sclerosing cholangitis. Ann Surg 1993;217:314–320.
13. Abdelrazeq AS, Kandiyil N, Botterill ID, Lund JN, Reynolds JR, Holdsworth PJ, Leveson SH. Predictors for acute and chronic pouchitis following restorative proctocolectomy for ulcerative colitis. Colorectal Dis 2008;10:805–813.
14. Hoda MK, Collins JF, Knigge KL, Deveney KE. Predicators of pouchitis after ileal pouch–anal anastomosis: A retrospective review. Dis Colon Rectum 2008;51:554–560.
15. Hata K, Watanabe M, Shinozaki M, Nagawa H. Patients with extraintestinal manifestations have a higher risk of developing pouchitis in ulcerative colitis: multivariate analysis. Scand J Gastroenterol 2003;38:1055–1058.
16. Karlbom U, Raab Y, Ejerblad S, Graf W, Thörn M, Påhlman L. Factors influencing the functional outcome of restorative proctocolectomy in ulcerative colitis. Br J Surg 2000;87:1401–1408.
17. Shen B, Fazio VW, Remzi FH, Delaney CP, Bennet AE, Achkar JP, Brzezinski A, Khandwala F, Liu W, Bambrick ML, Bast J, Lashner B. Comprehensive evaluation of inflammatory and noninflamatory sequelae of ileal pouch anal anastomosis. Am J Gastroenterol 2005;100:93–101.
18. Nakamura M, Ikeuchi H, Nakano H, Uchino M, Noda M, Yanagi H, Yamamura T. Postoperative joint symptoms: A risk factor for pouchitis in ulcerative colitis patients. Dig Surg 2006;23:60–64.
19. Kuisma J, Järvinen H, Kahri A, Färkkilä M. Factors associated with disease activity of pouchitis after surgery for ulcerative colitis. Scand J Gastroenterol 2004;39:544–548
20. Lepisö A, Kivistö S, Kivisaari L, Arola J, Järvinen HJ. Primary sclerosing cholangitis: outcome of patients undergoing restorative proctocolectomy for ulcerative colitis. Int J Colorectal Dis 2009;20:1169–1174.
21. ter Borg EJ, Nadorp JHSM, Elbers JRJ: Ileal pouch arthritis: A case report. Eur J Gastroenterol Hepatol 1996;8:957–959.
22. Wasmuth HH, Tranø G, Endreseth B, Rydning A, Wibe A, Myrvold HE. Long term surgical load in patients with ileal pouch–anal anastomosis. Colorectal Dis 2009;11:711–718.
23. Lovegrove RE, Constantinidis V, Heriot AG, Athansiou T, Darzi A, Remzi FH, Nicholls AG, Fazio VW, Tekkis PP. A comparison of hand-sewn vs stapled ileal-pouch anal anastomosis (IPAA) following proctocolectomy. Ann Surg 2006;244:18–26.
24. Kartheuser AH, Dozois RR, LaRusso NF, Wiesner RH, Ilstrup DM, Schleck CD. Comparison of surgical treatment of ulcerative colitis associated with primary sclerosing cholangitis: ileal pouch–anal anastomosis versus Brook ileostomy. Mayo Clin Proc 1996;71:748–756.
25. Fleshner P, Ippoliti A, Dubinsky M, Ognibene S, Vasiliaukas E, Chelly M, Mei L, Papadakis KA, Landers C, Targan S. A prospective multivariate analysis of clinical factors associated with pouchitis after Ileal pouch–anal anastomosis. Clin Gastroenterol Hepatol 2007;5:952–958.

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ORIGINAL ARTICLE

Choledochal Cysts: Differences Between Pediatric and Adult Patients

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Abstract Choledochal cysts in children and adults are believed to be different, but direct comparison between them is lacking in the literature. This study was aimed to identify the clinicopathological differences between 42 children and 59 adults with choledochal cyst treated by same surgeons at the Cathay General Hospital. The mean follow-up period was 8.9 years. The result showed that the female-to-male ratios were 1.5:1 in pediatric patients and 4.9:1 in adult patients. Compared with adults with choledochal cyst, the pediatric patients presented more abdominal mass (52.4% vs 21.2%, P=0.002) and less abdominal pain (76.2% vs. 98.0%, P=0.002), are more frequently associated with anomalous pancreaticobiliary ductal union (85.7% vs. 59.6%, P=0.005) and sudden severe stenosis of terminal choledochus (76.2% vs. 42.3%, P=0.001), are less commonly associated with choledocholithiasis, are not associated with malignant transformation (0% vs 21.2%), and have fewer perioperative and long-term complications. Nevertheless, patients who received total excision had fewer surgical complications in both groups. This result shows that choledochal cysts in pediatric and adult patients are different in clinicopathological manifestations, prognosis, and the underlying abnormalities of the pancreaticobiliary system, suggesting that patients with choledochal cyst should be managed according to these differences.

Keywords Choledochal cyst · Difference between pediatric and adult patients · Anomalous pancreaticobiliary ductal union

Introduction

Choledochal cysts are uncommon and often diagnosed in the first decade of life.[1–3] Prevalence is higher in Asian than in western countries; most cases are reported in Japan, where they occur in one of every 1,000 live births.[4–6] Although choledochal cysts are described as a disease of childhood, more and more adult series have been reported.[7–14] Females are at higher risk for this disease.[4,5] The importance of choledochal cysts lies in the lethal complications such as biliary stasis, cholangitis, cholelithiasis, pancreatitis,[15–17] and malignant transformation.[18–22] To date, total excision of the cyst remains the choice of treatment.[4–7]

In patients with choledochal cyst, an anomalous junction between the common bile duct and pancreatic duct is often seen in both pediatric and adult patients.[23–25] The abnormal junction causes pressure gradient and results in a reflux of pancreatic secretion to the common bile duct, where the activated pancreatic enzymes damage the bile duct wall and result in cystic formation. Other etiologies include sphincter dysfunction, innervation deficit, and obstruction of distal choledochus of either congenital or acquired in nature.[5,26–29]. Todani's classification of the anomalous junctions, a modified version of the original proposal of Alonso-Lej et al.,[30] is currently

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employed by most authors in spite of being criticized by Way et al. as being misleading and nonpractical.[9]

Although previous studies suggest that presenting symptoms and clinical outcomes are different between pediatric and adult patients,[15,16] direct comparison of patients treated in one single institution has been rarely reported.[7] The aim of this study is, therefore, to determine the clinicopathological differences between pediatric and adult patients with choledochal cysts treated at the same surgical department of a single institute.

Patients and Methods

This study was approved by the institutional review board of the Cathay General Hospital. We retrieved all records on patients with choledochal cyst who had been diagnosed and treated at the Cathay General Hospital from March 1981 to August 2006. The demographic data, presenting symptoms, diagnostic images, surgical procedures, intraoperative cholangiographies, photographies of resected specimens, pathology micrographies, perioperative complications, and follow-up data were collected. Choledochal cysts were classified according to Todani's classification. A total of 101 cases were analyzed in this study. Among them, 94 had complete treatment and follow-up records for analysis, whereas in seven adult patients, only initial diagnostic informations were available for analysis. Ninety patients had received surgical treatment. The mean follow-up period was 8.9 years, ranging from 2 to 26 years. Statistical analysis of data from 42 pediatric patients (age <16) and 52 adult patients (age ≥16) were performed using statistical package for social sciences (SPSS 10.0). Statistical significance was set at $P<0.05$.

Results

There were 42 pediatric patients (14 days to 14 years, mean 3.7 years) and 59 adult patients (16 to 82 years, mean 43.6 years). There is a higher female predominance in adult patients ($P=0.01$) as the ratio of female to male was 1.5:1 in children and 4.9:1 in adults. Clinical symptoms, operative findings, and the Todani's classification are listed in Table 1. As a whole group, the most common symptom was abdominal pain (88.3%), followed by jaundice (79.8%) and abdominal mass (34.2%). Abdominal pain was more often experienced by adult patients (98.0% vs. 76.2%, $P=0.002$), whereas abdominal mass was more commonly found in pediatric patients (52.4% vs 21.2%, $P=0.002$). However, expression of jaundice was not different between the two groups.

Based on the Todani's classification, the distribution of types were as follows: Ia, 63.8%; Ib, 3.2%; Ic, 18.1%; II, 2.1%; IVa, 10.6%; and V, 2.1%. Most of our patients (85.1%) had type I cysts. Among the analyzed clinical symptoms, only biliary stone formation was statistically associated with the Todani's classification (Table 2). Fewer patients with type I cysts developed stones (35.0%), compared to the patients with other types (71.4%). In addition, biliary stone was more common in the cysts of adult patients than those of pediatric patients (50.0% vs 28.6%, $P=0.035$).

Anomalous pancreaticobiliary ductal union (APBDU) was found in 71.3% of the whole group. Pediatric patients were statistically more frequently associated with APBDU than adult patients (85.7% vs 59.6%, $P=0.005$). Sudden and severe narrowing of terminal choledochus (Fig. 1) was more common in pediatric patients (76.2%, $n=32$) than adult patients (42.3%, $n=22$; $P=0.001$). Among the 32 pediatric patients with sudden severe narrowing of terminal choledochus, two had distal atresia and three showed draining of the distal choledochus into the dorsal pancreatic duct.

Forty pediatric patients and 50 adult patients received surgical operation (Fig. 2). Among them, 81 patients (40 children and 41 adults) were treated by total excision of the cyst with hepaticoenterostomy reconstruction, and nine adult patients received nontotal excision procedure. More specifically, four patients with advanced malignant choledochocyst (types Ia, Ib, Ic, Ic) were treated by T-tube external drainage ($n=3$), T-tube drainage, and cystoduodenostomy ($n=1$); four patients who had severe comorbidities (types Ia, IVa, IVa, V) were treated by internal drainage ($n=1$), internal drainage followed by lobectomy ($n=1$), lobectomy with T-tube drainage ($n=1$), and abdominal drainage ($n=1$), and a patient with type V patient received left lobectomy. Approximately 17.8% of surgically treated patients (5% pediatric and 28% adult patients) experienced early postoperative complications (Table 3). Cholangitis was the most common early complication ($n=5$), followed by septicemia ($n=4$). Four (8.0%) adult patients died of operative complication while all pediatric patients survived the surgery. Nine adult patients who received nontotal excision surgical procedure had a higher rate of operative complication (55.6%) compared to 41 who received total excision (22.0%).

After a mean follow-up period of 8.9 years (2 to 26 years), 17 (34%) adult patients had late complications (Table 4), including seven adult patients who died of cancer recurrence ($n=3$) or progression ($n=4$) within 2 years after surgery, and a patient with type IVa cyst had malignant transformation of the extrahepatic cyst 2 years after left lobectomy. Chronic abdominal pain with cholangitis was found in four patients. Other late complications included biliary cirrhosis with jaundice or ascites ($n=3$) and biliary stricture with intrahepatic duct stone ($n=3$). Five (12.5%)

Table 1 Clinicopathological Characteristics of 94 Patients with Choledochal Cysts

Total	No. of total patients, 94 (100%)	Pediatric group, 42 (44.7%)	Adult group, 52 (55.3%)	*P* value
Symptoms				
Jaundice	75 (79.8%)	35 (83.3%)	40 (76.9%)	0.442
Abdominal pain	83 (88.3%)	32 (76.2%)	51 (98.1%)	0.002*
Abdominal mass	33 (35.1%)	22 (52.4%)	11 (21.2%)	0.002*
Operative findings				
AJPBDS	67 (71.3%)	36 (85.7%)	31 (59.6%)	0.005*
Sudden severe distal stenosis	54 (57.4%)	32 (76.2%)	22 (42.3%)	0.001*
Stone formation	38 (40.4%)	12 (28.6%)	26 (50.0%)	0.035*
Malignant transformation	11 (11.7%)	0 (0%)	11 (21.2%)	0.001*
Todani's classification				
Ia	60 (63.8%)	28 (66.7%)	32 (61.5%)	0.095
Ib	3 (3.2%)	0 (0%)	3 (5.8%)	
Ic	17 (18.1%)	11 (26.2%)	6 (11.5%)	
II	2 (2.1%)	0 (0%)	2 (3.8%)	
IVa	10 (10.6%)	3 (7.1%)	7 (13.5%)	
V	2 (2.1%)	0 (0%)	2 (3.8%)	

*$P<0.05$

pediatric patients had late complications including chronic abdominal pain with ileus ($n=3$) and intrahepatic stricture with stone ($n=2$). In addition, none of the 81 patients (40 pediatric and 41 adults) treated by total excision had newly developed malignancy on their pancreaticobiliary system.

Pediatric choledocal cysts were significantly unassociated with malignant transformation ($P=0.002$). On the contrary, 11 of 52 adult patients (21.2%) had malignant transformation of the biliary or pancreatic epithelium. These malignancies arose from extrahepatic dilated cyst wall ($n=8$), intrahepatic duct cyst ($n=1$), pancreatic duct ($n=1$), and gallbladder ($n=1$). The mean age of patients with malignant transformation was 57.1 years (range 32–82 years), higher than that of the whole adult group (43.6 years, range 18–82 years). By analyzing the correlation of malignant transformation with the clinical features of patients, we found age was the only significant factor (Table 5). All these malignant choledocal cysts were surgically treated, including four palliative and seven curative surgeries. The outcomes are shown in Table 6.

Discussion

We report the clinicopathological differences between pediatric and adult patients with choledochal cysts treated at one single institution. Previous studies showed that the classic triad of jaundice, abdominal pain, and abdominal mass was often seen in pediatric patients than in adults.[4,5] More specifically, adult patients were prone to have the symptom of abdominal pain, while pediatric patients tended to have jaundice.[7] In this study, we found that children tend to have the symptom of palpable abdominal mass, whereas adult patients tend to experience abdominal pain. However, we found no difference in the frequency of jaundice between the two groups as opposed to the previous

Table 2 The Correlation of Todani's Types with Clinical Manifestation

	No. of cases	Type I (Ia, Ib, Ic)	Types II, IVa, V	*P* value
Age <16	42 (44.7%)	39 (48.8%)	3 (21.4%)	0.058
Jaundice	75 (79.8%)	66 (82.5%)	9 (64.3%)	0.149
Abdominal pain	83 (88.3%)	69 (86.3%)	14 (100%)	0.208
Abdominal mass	33 (35.1%)	29 (36.3%)	4 (28.6%)	0.764
Pancreatitis	19 (20.2%)	17 (21.3%)	2 (14.3%)	0.728
AJPBDS	67 (71.3%)	60 (75.0%)	7 (50.0%)	0.079
Distal stenosis	54 (57.4%)	48 (60.0%)	6 (42.9%)	0.296
Stone formation	38 (40.4%)	28 (35.0%)	10 (71.4%)	0.012*

*$P<0.05$

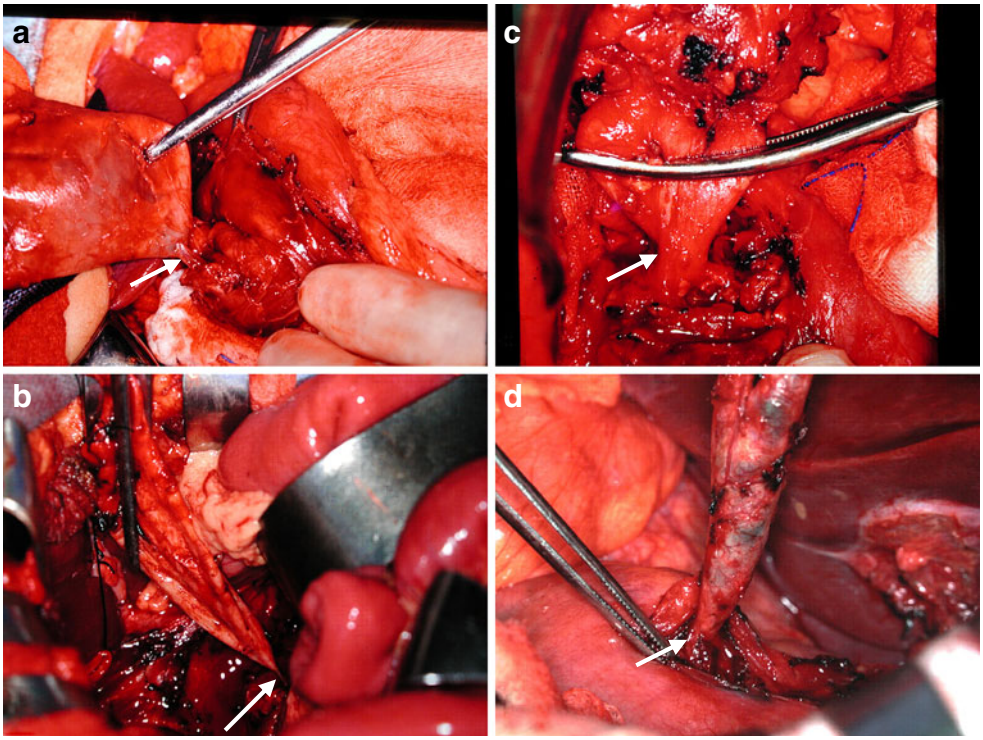

Figure 1 Morphological patterns of distal connection of choledochus; **a**, **b** Sudden severe narrowing of distal choledochus (*arrows*) before draining into pancreatic duct or common channel. **c**, **d** Gradual narrowing of distal choledochus (*arrows*) before draining into pancreatic duct or common channel.

observation.[7] Our speculation for this discrepancy is that adult patients in Taiwan tend not to seek for medical help until much symptomatic.

Although choledochal cysts have long been diagnosed in pediatric patients, a number of adult case series have recently been reported,[7,12,16] suggesting that choledochal cysts can remain clinically silent for quite a long time [31] or may develop as a slowly progressive disease.[29] The later suggests the acquired nature of some choledochal cysts. This notion was supported by our observation in that more than 50% (59/101) of choledochal cysts in our series were diagnosed in adult patients. Although it is well documented that females are at higher risk of having this disease,[7,9,11,13] our study particularly points out that the female predominance is higher in adult group. This observation further suggests that the acquired cases of choledochal cysts are more commonly developed in female while the congenital choledochal cyst has less female sex predilection.

Most of our patients (85.1%) had type I cysts. We found no difference in the distribution of various types between

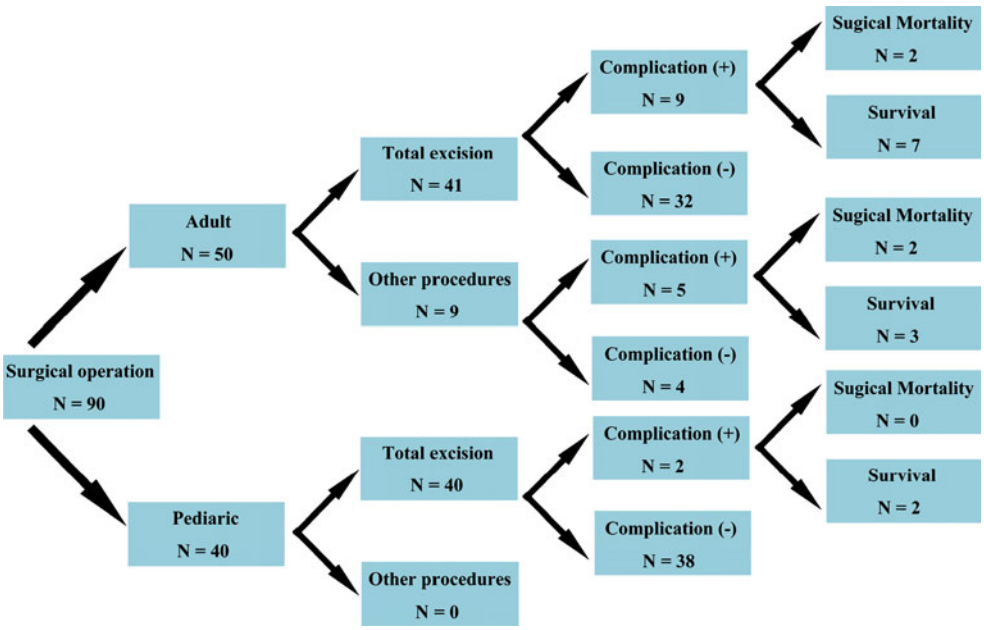

Figure 2 Schematic presentation of surgical management and clinical outcome of 90 patients with choledochal cyst.

Table 3 Perioperative Complications and Mortality of 90 Patients with Choledochal Cysts

	Pediatric group (n=40)	Adult group (n=50)
Complications	2/40 (5.0%)	14/50 (28.0%)
Surgical mortality	0/40 (0.0%)	4/50 (8.0%)

pediatric and adult patients as opposed to the previous observation that type IVa was predominant in adults.[7,8,12] We believed the difference is not only because the intrahepatic dilatation of IVa is poorly defined,[9] but also it may reverse to type Ic after total excision of extrahepatic cyst and hepaticojejunostomy as some of our cases demonstrated. We also showed that patients with type II, IV, or V cysts are at higher risk of stone formation than those with type I cyst. Stone formation more frequently occurred in adult patients. We speculated that the predilection of stone formation is related to the duration and severity of biliary stasis. Other than stone formation, none of the clinical manifestations were specifically associated with cystic type.

Since Babbitt et al. proposed that APBDU is an etiology of choledochal cyst,[23] a number of authors have reported the finding of APBDU in their series with frequency ranging from 29% to 96%.[6,16,24,25,31] In this study, APBDU was found in 71.3% of our patients and was more likely to be associated with pediatric patients (85.7%) than adult patients (59.6%). Although this difference is rarely reported in the literature,[8,16] it appears that the etiology in adult cases is probably having some differences from that in pediatric cases. Sudden severe narrowing of distal choledochus was more commonly found in pediatric patients than in adult patients. APBDU and distal choledochal narrowing together is thought to be a fundamental cause of pancreaticobiliary reflux and stasis, leading to a proximal choledochal dilatation [26–29,32] as these abnormalities allow pancreatic secretion reflux into bile ducts and cause ineffective bile flow, thus resulting in increased intraductal pressure and chemical and bacteria inflammation.[6,12] Taken together, the higher prevalence of APBDU and the sudden severe distal narrowing of the distal choledochus in pediatric patients may explain, at least in part, their early onset.[33,34]

Table 4 Late Complications of 90 Patients with Choledocal Cyst

	Incidence	Late complications
Adult (n=50)	17 (34%)	Stricture with IHD stone (n=3), cancer death (n=7), cholangitis (n=4), cirrhosis (n=3)
Pediatric (n=40)	5 (12.5%)	Abdominal pain and ileus (n=3), stricture and IHD stone (n=2)

Table 5 The Correlation of Malignancies in Choledochal Cyst with Clinical Features of Patients

	Case number			P value
	Total	With malignant transformation	Without malignant transformation	
Age (adult only)	52 (43.6%)	11 (57.1%)	41 (39.5%)	0.002*
Jaundice	75 (79.8%)	10 (90.9%)	65 (78.3%)	0.452
Abdominal pain	83 (88.3%)	11 (100%)	72 (86.7%)	0.351
Abdominal mass	33 (35.1%)	2 (18.2%)	31 (37.3%)	0.318
Pancreatitis	19 (20.2%)	1 (9.1%)	18 (21.7%)	0.452
AJPBDS	67 (71.3%)	6 (54.5%)	61 (73.5%)	0.255
Distal stenosis	54 (57.4%)	4 (36.4%)	50 (60.2%)	0.114
Stone formation	38 (40.4%)	4 (36.4%)	34 (41.0%)	NS

NS nonsignificant

*P<0.05

The choice of treatment for choledochal cysts is total excision when patients' general and local conditions allow. In contrast, palliative procedures are indicated when complications are present and patients' comorbidities and general conditions are not suitable for a total excision. In addition, the type of cyst and the presence of malignant transformation may influence the choice of produre.[7] Of importance, patients who received total excision experienced less complication than those treated by nontotal excision surgery in this study. Similar to other authors,[7,10,13] we also found that resectabilities, surgical complications, mortality, and long-term results of choledochal cysts in adult group were compromised by malignant transformation, the complicated hepatobiliary complications, and other systemic comorbidities. Because of no mortality and very low perioperative and long-term complications in our pediatric patients, we confirmed the safety and benefits of total excision in the treatment of choledochal cysts for pediatric patients. In this series, malignant transformation on the biliary epithelium was found in adult patients only (21.2%), not unlike other reports.[9,13] Except for the age, the patients with malignant transformation were not clinically different from those

Table 6 Surgical Procedure and Outcomes of 11 Patients of Choledochal Cyst with Malignant Transformation

Surgical procedure	Outcome
Surgery with curative intension (total excision, Whipple's, hepatic lobectomy), n=7	Operative mortality (n=1)
	Died of recurrence within 1 year (n=3)
	Survival longer than 1 year (n=3)
Palliative surgery, n=4	Died of disease progression within 1 year (n=4)

without (Table 5). However, early diagnosis of malignant transformation is difficult, and the prognosis of surgical treatment is poor. All these findings confirmed previous reports that the risk of developing carcinoma is associated with age,[10,11,15,35] and total excision of the choledochal cyst before malignant transformation greatly reduces the risk of developing malignancy [9,10,13] and may be the only effective way to reduce mortality associated with malignant transformation.

From the same department of a single institution, we directly compared and confirmed the differences between pediatric and adult patients with choledochal cysts. Adult patients are more likely to be associated with female predominance, malignant transformation, choledocholithiasis, complication, and mortality, whereas pediatric patients are more often associated with APBDU and sudden severe stenosis of distal choledochus, accounting for onset of choledochocyst in this age group. More importantly, total excision is a very safe procedure for pediatric patient with good long-term prognosis.

References

1. Miyano T, Yamataka A, Kato Y, Segawa O, Lane G, Takamizawa S, Kohno S, Fujiwara T. Hepaticoenterostomy after excision of choledochal cyst in children: a 30-year experience with 180 cases. J Pediatr Surg 1996;31:1417–1421.
2. Saing H, Han H, Chan KL, Lam W, Chan FL, Cheng W, Tam PK. Early and late results of excision of choledochal cysts. J Pediatr Surg 1997;32:1563–1566.
3. Joseph VT. Surgical techniques and long-term results in the treatment of choledochal cyst. J Pediatr Surg 1990;25:782–787.
4. Yamaguchi M. Congenital choledochal cyst. Analysis of 1,433 patients in the Japanese literature. Am J Surg 1980;140:653–657.
5. Lipsett PA, Pitt HA. Surgical treatment of choledochal cysts. J Hepatobiliary Pancreat Surg 2003;10:352–359.
6. Metcalfe MS, Wemyss-Holden SA, Maddern GJ. Management dilemmas with choledochal cysts. Arch Surg 2003;138:333–339.
7. Edil BH, Cameron JL, Reddy S, Lum Y, Lipsett PA, Nathan H, Pawlik TM, Choti MA, Wolfgang CL, Schulick RD. Choledochal cyst disease in children and adults: a 30-year single-institution experience. J Am Coll Surg 2008; 206:1000–1006.
8. Hewitt PM, Krige JE, Bornman PC, Terblanche J. Choledochal cysts in adults. Br J Surg 1995;82:382–385.
9. Visser BC, Suh I, Way LW, Kang SM. Congenital choledochal cysts in adults. Arch Surg 2004;139:855–860.
10. Liu CL, Fan ST, Lo CM, Lam CM, Poon RT, Wong J. Choledochal cysts in adults. Arch Surg 2002;137:465–468.
11. Lenriot JP, Gigot JF, Ségol P, Fagniez PL, Fingerhut A, Adloff M. Bile duct cysts in adults: a multi-institutional retrospective study. French Associations for Surgical Research. Ann Surg 1998;228:159–166.
12. Söreide K, Körner H, Havnen J, Söreide JA. Bile duct cysts in adults. Br J Surg 2004;91:1538–1548.
13. Lee KF, Lai EC, Lai PB. Adult choledochal cyst. Asian J Surg 2005;28:29–33.
14. Cheng SP, Yang TL, Jeng KS, Liu CL, Lee JJ, Liu TP. Choledochal cyst in adults: etiological considerations to intrahepatic involvement. ANZ J Surg 2004;74:964–967.
15. de Vries JS, de Vries S, Aronson DC, Bosman DK, Rauws EA, Bosma A, Heij HA, Gouma DJ, van Gulik TM. Choledochal cysts: age of presentation, symptoms, and late complications related to Todani's classification. J Pediatr Surg 2002;37:1568–1573.
16. Chaudhary A, Dhar P, Sachdev A, Kumar N, Vij JC, Sarin SK, Broor SL, Sharma SS. Choledochal cysts—differences in children and adults. Br J Surg 1996; 83:186–188.
17. Tsuchida Y, Takahashi A, Suzuki N, Kuroiwa M, Murai H, Toki F, Kawarasaki H, Hashizume K, Honna T. Development of intrahepatic biliary stones after excision of choledochal cysts. J Pediatr Surg 2002;37:165–167.
18. Wu GS, Zou SQ, Luo XW, Wu JH, Liu ZR. Proliferative activity of bile from congenital choledochal cyst patients. World J Gastroenterol 2003;9:184–187.
19. Komi N, Tamura T, Tsuge S, Miyoshi Y, Udaka H, Takehara H. Relation of patient age to premalignant alterations in choledochal cyst epithelium: histochemical and immunohistochemical studies. J Pediatr Surg 1986;21:430–433.
20. Komi N, Tamura T, Miyoshi Y, Kunitomo K, Udaka H, Takehara H. Nationwide survey of cases of choledochal cyst. Analysis of coexistent anomalies, complications and surgical treatment in 645 cases. Surg Gastroenterol 1984;3:69–73.
21. Tan SS, Tan NC, Ibrahim S, Tay KH. Management of adult choledochal cyst. Singapore Med J 2007;48:524–527.
22. Stain SC, Guthrie CR, Yellin AE, Donovan AJ. Choledochal cyst in the adult. Ann Surg 1995;222:128–133.
23. Babbitt DP, Starshak RJ, Clemett AR. Choledochal cyst: a concept of etiology. Am J Roentgenol Radium Ther Nucl Med 1973;119:57–62.
24. Ono J, Sakoda K, Akita H. Surgical aspect of cystic dilatation of the bile duct. An anomalous junction of the pancreaticobiliary tract in adults. Ann Surg 1982;195:203–208.
25. Shi LB, Peng SY, Meng XK, Peng CH, Liu YB, Chen XP, Ji ZL, Yang DT, Chen HR. Diagnosis and treatment of congenital choledochal cyst: 20 years' experience in China. World J Gastroenterol 2001;7:732–734.
26. Craig AG, Chen LD, Saccone GT, Chen J, Padbury RT, Toouli J. Sphincter of Oddi dysfunction associated with choledochal cyst. J Gastroenterol Hepatol 2001;16:230–234.
27. Davenport M, Basu R. Under pressure: choledochal malformation manometry. J Pediatr Surg 2005;40:331–335.
28. Matsufuji H, Araki Y, Nakamura A, Ohigashi S, Watanabe F. Dynamic study of pancreaticobiliary reflux using secretin-stimulated magnetic resonance cholangiopancreatography in patients with choledochal cysts. J Pediatr Surg 2006;41:1652–1656.
29. Han SJ, Hwang EH, Chung KS, Kim MJ, Kim H. Acquired choledochal cyst from anomalous pancreatobiliary duct union. J Pediatr Surg 1997;32:1735–1738.
30. Todani T, Watanabe Y, Narusue M, Tabuchi K, Okajima K. Congenital bile duct cysts: Classification, operative procedures, and review of thirty-seven cases including cancer arising from choledochal cyst. Am J Surg 1977;134:263–269.
31. Ramage AA, Tedesco FJ, Schuman BM. Asymptomatic choledochal cyst. Am J Gastroenterol 1985;80:816–818.
32. Tanaka M, Ikeda S, Kawakami K, Nakayama F. The presence of a positive pressure gradient from pancreatic duct to choledochal cyst demonstrated by duodenoscopic microtransducer manometry: clue to pancreaticobiliary reflux. Endoscopy 1982;14:45–47.
33. Ford EG, Jennings LM, Gleason W, Andrassy RJ. Efficacy of anomalous pancreatic drainage in choledochal cysts correlates with age of presentation and suggests etiology. Am Surg 1987;53:641–646.
34. Nomura T, Shirai Y, Wakai T, Yokoyama N, Sakata J, Hatakeyama K. Narrow portion of the terminal choledochus is a cause of upstream biliary dilatation in patients with anomalous union of the pancreatic and biliary ducts. World J Gastroenterol 2005;11:6503–6507.
35. Kusunoki M, Saitoh N, Yamamura T, Fujita S, Takahashi T, Utsunomiya J. Choledochal cysts. Oligoganglionosis in the narrow portion of the choledochus. Arch Surg 1988;123:984–986.

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ORIGINAL ARTICLE

High Hepatitis B Viral Load Predicts Recurrence of Small Hepatocellular Carcinoma after Curative Resection

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Abstract A retrospective cohort study was conducted to identify risk factors for recurrence of hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) after curative resection. A total of 317 patients who had received curative resection of pathologically proven small HCC (≤3 cm in diameter) were analyzed to ascertain the factors affecting recurrence. The median follow-up period was 33.7 months. Cumulative recurrence rates at 1, 3, and 5 years after resection were 23.5%, 49.5%, and 65.5%, respectively. Male sex, alpha-fetoprotein (AFP) ≥400 ng/mL, HBV DNA level ≥4 $\log_{10}$ copies/mL, prolonged prothrombin time, tumor size ≥2 cm, microvascular invasion, absence of capsular formation, moderate/poor tumor differentiation, and absence of postoperative interferon-alpha (IFN-α) treatment were associated with increased cumulative risk of HCC recurrence. By multivariate analysis, HBV DNA level ≥4 $\log_{10}$ copies/mL ($P<0.001$, hazard ratio (HR) 2.110), AFP ≥400 ng/mL ($P=0.011$, HR 1.574), microvascular invasion ($P<0.001$, HR 1.767), and postoperative IFN-α treatment ($P=0.022$, HR 0.562) remained to be independently associated with HCC recurrence. Those contributing to late recurrence (>2 years) were older age and HBV DNA level ≥4 $\log_{10}$ copies/mL. Patients with persistent HBV DNA level ≥4 $\log_{10}$ copies/mL at resection and follow-up had the highest recurrence risk ($P<0.001$, HR 4.129). HBV DNA level ≥4 $\log_{10}$ copies/mL at the time of resection was the most important risk factor for recurrence. Postoperative IFN-α treatment significantly decreased the recurrence risk after resection.

Keywords Hepatocellular carcinoma · Recurrence · Hepatitis B viral load

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer-related death in the world.[1] Etiologically, majority of HCC develops in chronic hepatitis B virus (HBV) carriers, especially in East Asia and sub-Saharan Africa, where HBV is endemic. During the past decades, with periodic serum alpha-fetoprotein (AFP) assays and the development of modern imaging systems, such as ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI), more and more small HCCs of diameter ≤3 cm can be detected and diagnosed early. For these patients, curative resection is considered the most effective treatment and the prognosis of HCC was greatly improved.[2,3] However, high possibility of intrahepatic recurrence remains one major obstacle for further improving the survival and prognosis of HCC patients after curative resection.[4] For patients who undergo tumor resection for hepatitis B-related HCC, the cumulative recurrence rate at 3 years after surgery is estimated to be as high as 50%.[5,6] It has been reported that tumor size, macroscopic vascular invasion, and intrahepatic metastasis were related significantly to HCC recurrence.[7–10] However, recurrence is also common in cases with small HCC having neither macroscopic vascular invasion nor intrahepatic metastasis.

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Recently, a significant association between high hepatitis B viral load and increased risk of HCC and liver cirrhosis was observed in several studies.[11,12] But only a few studies have evaluated the viral replicative status of subjects as a predictor of postoperative recurrence of HCC. In two case series studies on the recurrence of HCC after surgical resection, patients with high serum HBV DNA level at study entry had a significantly higher risk of HCC recurrence than those with low level.[13,14] However, in previous studies, the relation between hepatitis B viral load and the recurrence of HCC after resection may be confounded by other major risk factors for recurrence, such as macroscopic vascular invasion or noncurative resection. And these were limited in that most investigators evaluated the serum HBV DNA level at one time only (usually at the time of surgery) as a risk factor. To our knowledge, no reports published to date have demonstrated a relation between fluctuated hepatitis B viral load and recurrence risk in small HCC patients after curative resection. The goal of the present study was to assess the significance of hepatitis B viral load with other demographic, biochemical, tumor factors in the recurrence of small HCC patients after curative resection.

Patients and Methods

Patients

Between 2002 and 2005, 1,462 patients with hepatitis B-related HCC underwent tumor resection in the Department of Liver Surgery, Zhongshan Hospital, Fudan University. Of these, 354 patients who had received curative resection of pathologically proven small HCC (≤3 cm) were retrieved from a prospectively collected database. A total of 317 were finally entered into the analyses and 37 patients were excluded for the following reasons; seven patients died in hospital due to postoperative hepatic failure, 11 patients had early recurrence within 3 months after surgery (suggesting preexisting metastases before HCC resection), and data were lacking for 19 patients. No patients received antiviral drugs or adjuvant anti-tumor therapy before surgery. All patients had confirmed HCC in the surgical specimen from tumor resection. Curative resection was defined as (1) complete resection of all tumor nodules and the surgical free margin of more than 5 mm by pathological examination; (2) no cancerous thrombus found in the portal vein (main trunk or two major branches), hepatic veins, or bile duct; (3) the number of tumor nodules not exceeding three; and (4) no extrahepatic metastasis found. Histological grade proposed by Edmondson and Steiner with little modification,[15] maximal tumor size, nodule number, capsular formation around the tumor, microvascular invasion, and liver cirrhosis were also determined. Various surgical procedures were classified as wedge resection, segmentectomy, and two or more segmentectomies. This study was approved by the research ethics committee at Zhongshan Hospital, Fudan University, Shanghai, China.

Follow-up and End Point

After surgery, 36 patients received interferon-alpha1b (Sinogen, Kexing Bioproducts Co., Shenzhen, P. R. China) treatment, which was started at a pilot dose of 3 million units (mu) two times a week by intramuscular injection for 2 weeks, then 5 mu three times a week for 18 months. The interferon-alpha (IFN-α) treatment was terminated when recurrence was confirmed. No further anti-tumor treatment was given to 317 patients until recurrence was confirmed. All patients were followed up by determination of monthly AFP and US, as well as three monthly CT or MRI scan for 1 year. Then, all patients were screened by AFP and US every 3 months and helical CT or MRI every 6 months thereafter, and hepatic angiography when recurrence was suspected. The diagnosis of intrahepatic recurrence was based on histopathologic findings of tumor tissue in 47 patients undergoing repeat hepatic resection and on the characteristic appearance on US, CT, MRI, and hepatic angiography in 136 patients. The primary end point was tumor recurrence. Time to recurrence was defined as the period between surgery and the diagnosis of recurrence. If recurrence was not diagnosed at the time of study, the cases were censored on the date of death or the last date of follow-up. All follow-up data were summarized as of the end of October 2007.

Statistical Analysis

Virological data were analyzed with conventional clinical variables at the time of resection to identify factors that influenced recurrence via the Cox proportional hazards model. Risk factors contributing to late recurrence (>2 years) were investigated by stratified Cox regression analysis. Cumulative recurrence rate was calculated by the Kaplan-Meier method and differences were compared by the logrank test. Multivariate analysis was performed by the Cox proportional hazards regression model. Statistical significance was defined by a P value of less than 0.05. Statistical analyses were performed using the Statistical Program for Social Sciences (SPSS 11.5 for Windows; SPSS, Inc., Chicago, IL, USA).

Result

During the observation period (3-66.5 months), intrahepatic recurrence was detected in 183 patients (57.7%). The

cumulative recurrence rates at 1, 2, 3, 4, and 5 years after curative resection were 23.5%, 39.4%, 49.5%, 55.1%, and 65.5%, respectively. The baseline demographic, biochemical, tumor, and viral factors of the whole study population were depicted in Table 1.

Demographic Profile and HCC Recurrence

Male patients had a higher cumulative risk of developing HCC recurrence after resection when compared to female patients (P=0.034). Age at the time of curative resection did not have a significant effect on HCC recurrence (P=0.429; Table 2).

Prognostic Effect of Clinical Factors and HCC Recurrence

High serum AFP level and prolonged prothrombin time (PT) at the time of resection were the significant risk factors for recurrence in univariate analyses. AFP ≥400 ng/mL was associated with a higher cumulative risk of developing HCC recurrence after resection (Fig. 1). Among 183 recurrence patients, 141 (77.0%) had HBV DNA level ≥4 $\log_{10}$ copies/mL at the time of tumor resection. While, 70 (52.2%) of 134 nonrecurrence patients had HBV DNA level ≥4 $\log_{10}$ copies/mL (P<0.001). A significant biological gradient of recurrence risk by HBV DNA level from less than 4-6 $\log_{10}$ copies/mL or greater was observed. In

Table 1 Patient Characteristics

Characteristics	No. (%)	Values
No. of patients	317 (100)	
Median age, years (range)		51 (26-82)
Male/female ratio	270:47 (85.2:14.8)	
HBeAg seropositivity	106 (33.4)	
HBV DNA level ≥4 $\log_{10}$ copies/mL	211 (66.6)	
Alpha-fetoprotein ≥400 ng/mL	60 (18.9)	
Presence of cirrhosis	244 (77.0)	
Co-existing HCV infection	9 (2.8)	
Median baseline biochemistry and hematology (range)		
Total bilirubilin, μM		15.9 (5.3-40.1)
Albumin, g/L		42 (27-54)
Aminotransferase, IU/L		42 (10-398)
Prothrombin time, s		11.6 (9.2-19.6)
Tumor size (<2 cm: ≥2 cm)	132:185 (41.6:58.4)	
Tumor number (Single/multiple)	272:45 (85.8:14.2)	
Microvascular invasion	80 (25.2)	
Capsular formation	165 (52.1)	
Differentiation of tumor		
Well-differentiated	95 (30.0)	
Moderate	177 (55.8)	
Poor	45 (14.2)	
Child-Turcotte-Pugh grade		
A	304 (95.9)	
B	13 (4.1)	
Okuda stage		
I	301 (95.0)	
II	16 (5.0)	
Type of surgical procedure		
Wedge resection	225 (71.0)	
Segmentectomy	71 (22.4)	
Two or more segmentectomies	21 (6.6)	
Postoperative IFN-α treatment	36 (11.4)	
Median follow-up time (months)		33.7 (3-66.5)
Median time of recurrence (months)		16 (3-65)

Table 2 Factors Identified on Univariate Cox Regression Analysis that Influenced Recurrence in Small HCC Patients Undergoing Curative Resection

Factors	*P* value	Hazard ratio	95% CI
Sex (male vs. female)	0.034	1.655	1.040-2.633
Age, years	0.429	1.006	0.992-1.020
HBeAg seropositivity	0.293	1.177	0.869-1.593
HBV DNA level 4-5.99 $\log_{10}$ copies/mL	<0.001	1.981	1.366-2.872
≥6 $\log_{10}$ copies/mL	<0.001	3.086	2.054-4.634
Alpha-fetoprotein ≥400 ng/mL	0.005	1.626	1.155-2.291
Co-existing HCV infection	0.422	1.363	0.640-2.902
Total bilirubilin	0.690	0.996	0.976-1.016
Albumin	0.260	0.981	0.947-1.015
Aminotransferase	0.521	1.001	0.998-1.004
Prothrombin time	0.032	1.113	1.009-1.228
Presence of cirrhosis	0.138	1.318	0.915-1.899
Tumor size (≥2 cm vs. <2 cm)	0.011	1.487	1.097-2.015
Tumor number (multiple vs. single)	0.386	1.192	0.801-1.773
Microvascular invasion	<0.001	2.017	1.473-2.762
Capsular formation	0.030	0.724	0.541-0.970
Differentiation (moderate or poor differentiated vs. well differentiated)	0.038	1.424	1.020-1.989
Child-Turcotte-Pugh grade (A vs. B)	0.172	1.698	0.794-3.631
Okuda stage (I vs. II)	0.816	1.088	0.535-2.214
Postoperative IFN-α treatment	0.044	0.606	0.373-0.987

Fig. 2, there was a stepwise increase in the cumulative risk of recurrence with increasing hepatitis viral load starting from HBV DNA level ≥4 $\log_{10}$ copies/mL. The relationship between pathological factors and recurrence was also demonstrated by the univariate Cox regression analyses. Tumor size ≥2 cm, moderate/poor tumor differentiation, presence of microvascular invasion, and absence of capsular formation were significantly associated with intrahepatic recurrence. Figure 3 depicted the presence of microvascular invasion was associated with a significantly higher cumulative risk of tumor recurrence. Other clinical factors including serum albumin, total bilirubilin, aminotransferase, HBeAg statue, co-existing hepatitis C virus (HCV) infection, presence of cirrhosis, tumor number,

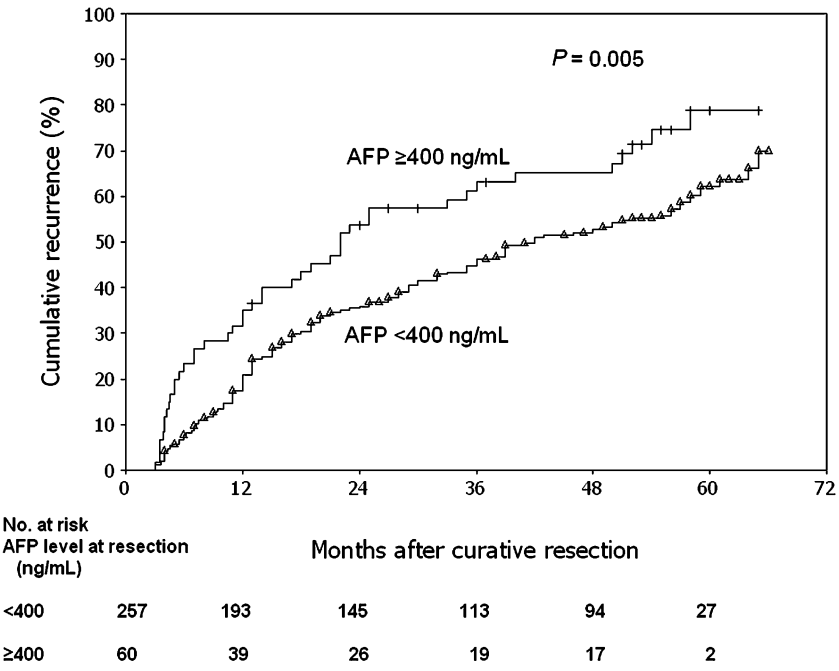

Figure 1 Cumulative HCC recurrence related to AFP level at the time of tumor resection (=0.005, logrank test).

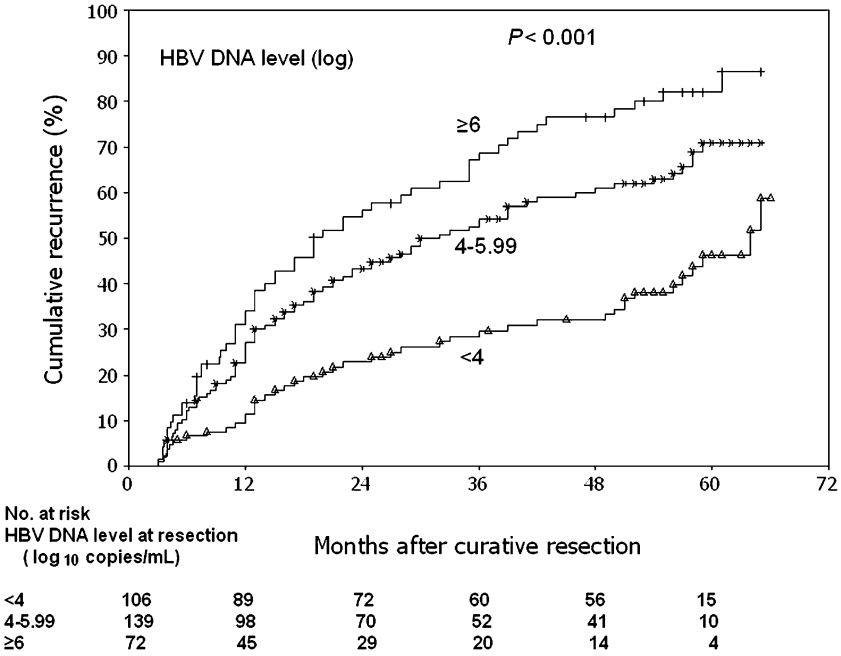

Figure 2 Cumulative HCC recurrence related to serum HBV DNA level at the time of tumor resection ($P<0.001$, logrank test).

Child-Turcotte-Pugh grade, and Okuda stage were not associated with HCC recurrence (Table 2).

Postoperative IFN-α Treatment and HCC Recurrence

A total of 36 patients received IFN-α treatment after curative resection. No other anti-tumor treatment was given to 317 patients until the recurrence was confirmed. Treatment with IFN-α after tumor resection was associated with significantly lower cumulative risk of recurrence compared to patients without IFN-α treatment (Fig. 4).

Multivariate Analysis of Risk Factors for HCC Recurrence

Univariate analysis revealed that the following factors had a significant effect on recurrence: male sex, AFP ≥400 ng/mL, HBV DNA level ≥4 $\log_{10}$ copies/mL, prolonged PT, tumor size ≥2 cm, microvascular invasion, absence of capsular formation, moderate/poor tumor differentiation, and patients without postoperative IFN-α treatment. All these variables were entered into the multivariate analysis by the Cox proportional hazards regression model. AFP ≥400 ng/mL, HBV DNA level ≥4 $\log_{10}$ copies/mL, microvascular

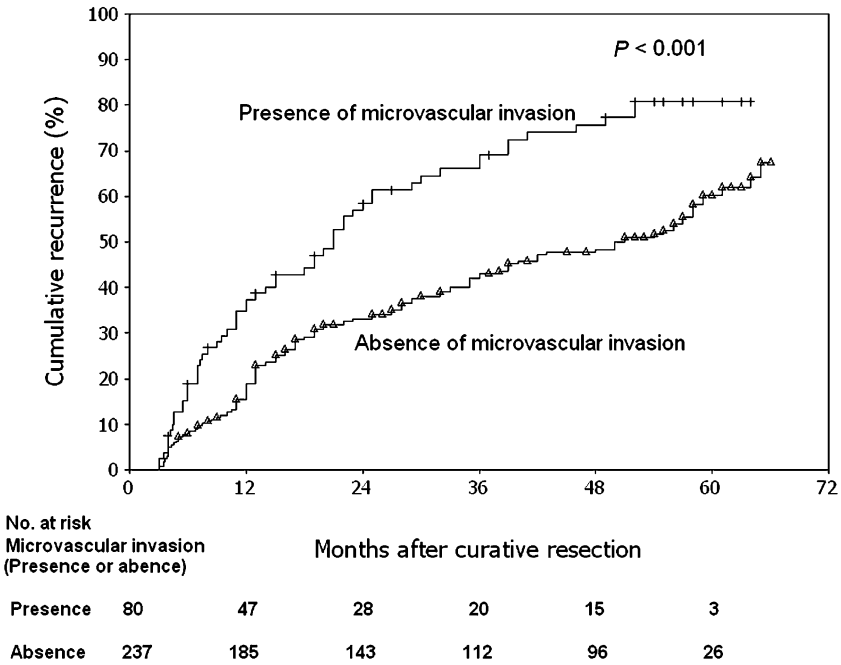

Figure 3 Cumulative HCC recurrence related to the presence of microvascular invasion in the resected tumor ($P<0.001$, logrank test).

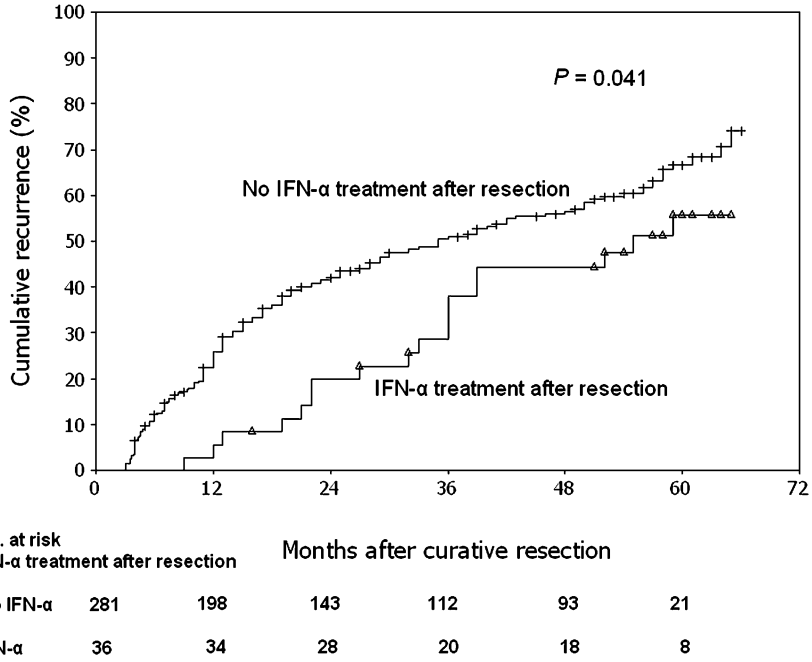

Figure 4 Cumulative HCC recurrence related to the IFN-α treatment after curative resection (P=0.041, logrank test).

invasion, and absence of postoperative IFN-α treatment were independent risk factors of HCC recurrence after curative resection (Table 3).

Factors Contributing to Late Recurrence (>2 years)

Factors related to late recurrence (>2 years) were investigated in 171 patients who were recurrence-free at first 2 years, as suggested by Imamura's study.[16] Recurrence was detected in 63 patients within follow-up. Stratified Cox regression analysis identified three factors contributing to late recurrence: male sex (P=0.043; hazard ratio [HR] 2.565, 95%CI 1.028-6.396), older age (P=0.028; HR 1.028, 95% CI 1.003-1.054), and HBV DNA level ≥4 $\log_{10}$ copies/mL (P=0.009; HR 2.047, 95% CI 1.193-3.512). By multivariate analysis, older age and HBV DNA level≥4 $\log_{10}$ copies/mL were independently associated with risk of late recurrence (Table 4). Patients with HBV DNA level ≥4 $\log_{10}$ copies/mL at resection had a significantly higher cumulative late recurrence rate than those with HBV DNA level <4 $\log_{10}$ copies/mL (Fig. 5).

Table 3 Multivariate Analysis of Independent Risk Factors Associated with Recurrence

Factors	P value	Hazard ratio	95% CI
HBV DNA level ≥4 $\log_{10}$ copies/mL	<0.001	2.110	1.483-3.002
Alpha-fetoprotein ≥400 ng/mL	0.011	1.574	1.109-2.234
Microvascular invasion	<0.001	1.767	1.286-2.429
Postoperative IFN-α treatment	0.022	0.562	0.343-0.921

Recurrence Risk by HBV DNA Level at the Time of Resection and Follow-up in Combination

We further examined the association between recurrence risk and persistently elevated serum HBV DNA level at resection and follow-up. Among 317 patients, 224 (70.7%) had received at least once time HBV DNA examination during follow-up (before the detection of recurrence). The median interval between the time of resection and last HBV DNA examination was 23 months (range from 6-55 months). We then evaluated the recurrence risk with HBV DNA level at the time of resection and follow-up in combination. Compared with subjects who had HBV DNA level <4 $\log_{10}$ copies/mL both at the time of resection and follow-up, the HR was 2.233 (95%CI 1.051-4.743) for subjects with HBV DNA level <4 $\log_{10}$ copies/mL at resection and ≥4 $\log_{10}$ copies/mL at follow-up. Subjects who had persistent HBV DNA level ≥4 $\log_{10}$ copies/mL both at the time of resection and follow-up were expected to have the highest recurrence risk (Table 5). Cumulative recurrence rate of respective groups are shown in Fig. 6.

Table 4 Multivariate Analysis of Independent Risk Factors Associated with Late Recurrence (>2 years) in 171 HCC Patients

Factors	P value	Hazard ratio	95% CI
Older age	0.017	1.031	1.005-1.057
HBV DNA level ≥4 $\log_{10}$ copies/mL	0.009	2.053	1.192-3.534

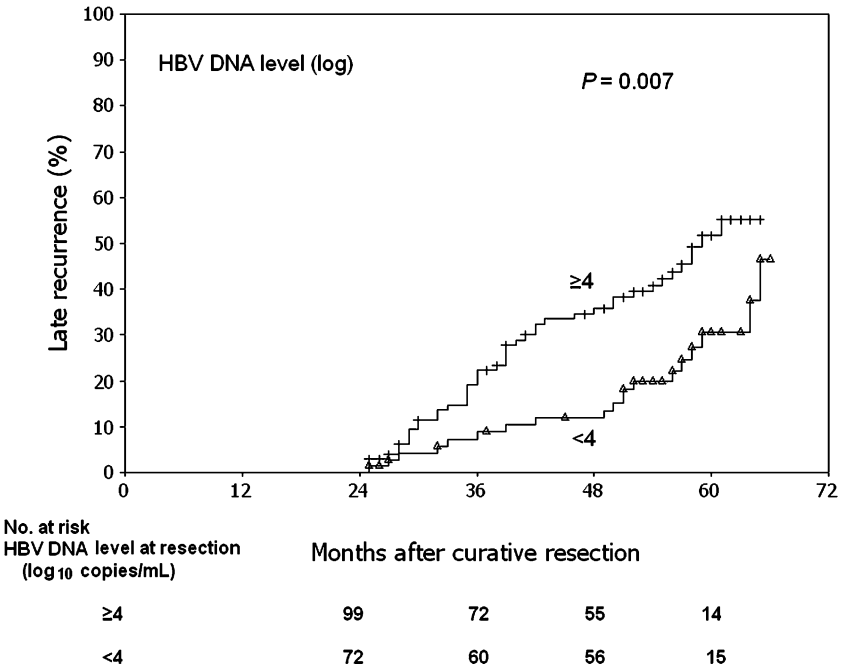

Figure 5 Cumulative late recurrence (>2 years) related to the initial HBV DNA level at the time of tumor resection (P=0.007, logrank test).

Discussion

The prognosis of HCC remains unsatisfactory although it has been improved much in the past decades. Even after curative resection, recurrence of hepatitis B-related HCC is extremely high.[17] Previous studies have shown that tumor size, nodule number, vascular invasion, high AFP level, a positive surgical margin, and Edmondson's grade are prognostic factors predicting recurrence.[6,7,9,13,18–20] The current study focused primarily on the correlation between hepatitis B viral load and recurrence of small HCC after curative resection.

Multivariate analysis demonstrated that HBV DNA level ≥4 $\log_{10}$ copies/mL, AFP ≥400 ng/mL, microvascular invasion, and absence of IFN-α treatment after curative resection were four independent factors associated with higher cumulative risk of tumor recurrence. According to our statistical analysis, the study revealed that HBV DNA level ≥4 $\log_{10}$ copies/mL at resection was the most important risk factors for recurrence of small HCC after surgery. Hung et al. have reported a similar finding in a study of 72 hepatitis B-related HCC patients after surgery.[13] Previous studies hypothesized that early and late intrahepatic recurrence of HCC was attributable to two different mechanisms: intrahepatic metastasis and de novo multicentric carcinogenicity.[16,18] The latter is clonally independent from the primary tumor.[21] Imamura et al. proposed a convenient framework to clinically differentiate each type of recurrence as "early" or "late" recurrence based on a cutoff of 2 years after surgery.[16] With the successful implementation of HCC surveillance and curative treatment, more patients avoid the risk of early recurrence and thus survive longer enough to acquire late recurrence. But risk factors contributing to late recurrence after surgery had not been investigated on a comprehensive basis. As the impact of viral factors on the recurrence of HCC after resection may be overshadowed by tumor-related factors during the early recurrence, we then investigated factors possibly contributing to late recurrence separately. In a subgroup of 171 patients who were recurrence-free at first 2 years, HBV DNA level ≥4 $\log_{10}$ copies/mL and older age

Table 5 Recurrence Risk by HBV DNA Level at the Time of Resection and Follow-Up in Combination

HBV DNA Level ($\log_{10}$ Copies/mL) at Resection at Follow-up[a]	No. of Participants (n=224) (%)[b]	No. of Recurrence (n=117) (%)	Hazard Ratio (95% CI)	P value
<4 <4	55 (24.6)	16 (13.7)	1.0 (reference)	-
<4 ≥4	24 (10.7)	12 (10.3)	2.233 (1.051-4.743)	0.037
≥4 <4	49 (21.9)	21 (17.9)	1.749 (0.911-3.358)	0.093
≥4 ≥4	96 (42.9)	68 (58.1)	4.129 (2.364-7.211)	<0.001

[a] Data of last HBV DNA examination during follow-up before the detection of recurrence

[b] Because of rounding, percentages do not always total 100

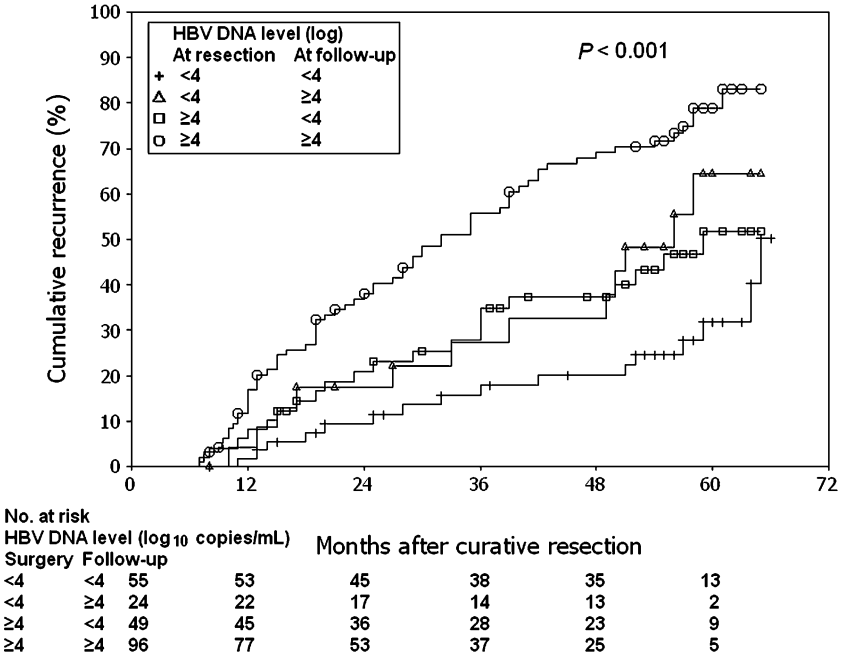

Figure 6 Cumulative HCC recurrence risk by HBV DNA level at the time of resection and follow-up in combination in 224 patients ($P<0.001$, logrank test).

were independent risk factors for late recurrence. However, tumor factors, such as AFP ≥400 ng/mL and microvascular invasion were not associated with late recurrence. Our finding supported that late recurrence was attributable to de novo HCC and the key role of high viral load on the development of late recurrence. Additionally, serum HBV DNA level may fluctuate during the course of chronic infection.[22] Previous studies were limited in that they measured only the high HBV DNA level at the time of resection as a risk factor. The fluctuation of HBV DNA level after resection has seldom been evaluated. In this study, we further examined the relationship between recurrence risk and serum HBV DNA level at resection and follow-up (before the detection of recurrence) in combination. Compared to those with instantaneous high HBV DNA level at the time of resection, patients who had persistent HBV DNA level ≥4 $\log_{10}$ copies/mL during follow-up were expected to have the highest risk of recurrence. It is likely that these patients who had ongoing active viral replication were more prone to recurrence. In theory, treating high viral load patients with antiviral drugs both pre- and post-operatively is reasonable.

Although the precise mechanism for recurrent carcinogenesis associated with HBV in the remaining liver in patients who have undergone curative resection is unclear, it is possible that sustained viremia and subsequent active viral replication may contribute to the carcinogenic process. Firstly, integration of subgenomic HBV DNA fragments into the host liver cell may activate cellular genes directly to allow selective growth advantage, while production of HBV X protein can act as a transactivator on various cellular genes for tumor development.[23] Secondly, continuing HBV replication can induce chronic liver inflammation and fibrosis and mediate alteration in transforming growth factor-beta1 and alpha2-macroglobulin production, thereby leading to carcinogenesis.[24,25] Thirdly, the upregulation of adhesion molecules on the cells lining the sinusoids may enhance tumor development and spread.[26]

IFNs are cytokines possessing a variety of biologic properties, including antiviral, immunomodulatory, antiproliferative, and antiangiogenic effects.[27,28] Many studies confirmed that postoperative IFN-α treatment can decrease HCC recurrence after resection. However, most trials included predominantly HCV infections. Whether such treatment will also benefit HBV-related HCC remains to be elucidated. In this study, multivariate analysis showed that IFN-α treatment decreased the recurrence rate: the HR of postoperative IFN-α treatment was 0.562 (95% CI, 0.343-0.921), indicating that such IFN-α treatment could decrease the hazard of HCC recurrence rate to approximately 44% of that with untreated patients. However, in a subgroup of 171 patients who were recurrence-free at first 2 years, both univariate and multivariate analysis did not show that initial 18 months IFN-α treatment after resection could decrease late recurrence. Based on this disaccording, we hypothesized that during the 18 months treatment with IFN-α, the recurrence rate was lower than that untreated patients, whereas, when IFN-α treatment stopped, the recurrence rate was similar between the two groups, which may imply that tumor growth was suppressed by IFN-α treatment, but became clinically evident after IFN-α treatment was stopped. Since the current study was a retrospective cohort study and the number of patients in the present study was too small to reach a firm conclusion, a prospective randomized controlled study should be conducted in the future.

Other independent risk factors associated with HCC recurrence after curative resection that were identified in this study included preoperative AFP ≥400 ng/mL and the presence of microvascular invasion. These findings were similar to that described previously.[13,29,30] Patients with high AFP level tended to have greater tumor size, bilobar involvement, massive or diffuse types, and tumor vascular invasion.[31] The presence of microvascular invasion was consistently reported as strongly predictive of intrahepatic metastasis.

There is strong evidence linking elevations in serum HBV DNA level and HCC progression in chronic hepatitis B.[12] In the present study, we further proved that HBV DNA level ≥4 $\log_{10}$ copies/mL was associated with a higher recurrence rate after tumor resection. At study entry, no patients received antiviral treatments with nucleoside analogs. During follow-up, seven patients received lamivudine treatment after resection. The median interval between resection and lamivudine treatment was 19 months (range from 11 to 37 months). Although we could not evaluate the effect of lamivudine treatment in preventing recurrence, postoperative IFN-α treatment showed a beneficial effect in reducing HCC recurrence. It might support the antiviral treatment in the prevention of recurrence after curative resection. The present data did not suggest that concurrent HBV and HCV infection have a deleterious effect on the prognosis of HCC patients, probably due to the relatively small number of patients with co-existing HCV infection.

Conclusion

In conclusion, HBV DNA level ≥4 $\log_{10}$ copies/mL, AFP ≥400 ng/mL, microvascular invasion, and postoperative IFN-α treatment were independently associated with HCC recurrence after surgery. Patients with persistent HBV DNA level ≥4 $\log_{10}$ copies/mL during follow-up were expected to have the highest recurrence risk. Elevations in serum HBV DNA level is not only a major risk factor for HCC recurrence, but the risk factor most amenable to modification. This may support prioritized use of anti-HBV treatment as adjuvant therapy after the resection of HCC for the patients with a high HBV DNA level to prevent recurrence. A potential limitation of the present study is that the data were based on a retrospective cohort of small HCC patients, large-scale prospective trials are necessary to elucidate the effects of sustained viremia on recurrence after surgery and the protective roles of antiviral treatment.

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Potential competing interests None.

References

1. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907-1917.
2. Takayama T, Makuuchi M, Hirohashi S, Sakamoto M, Yamamoto J, Shimada K, Kosuge T, Okada S, Takayasu K, Yamasaki S. Early hepatocellular carcinoma as an entity with a high rate of surgical cure. Hepatology 1998;28:1241-1246.
3. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004;130:417-422.
4. Adachi E, Maeda T, Matsumata T, Shirabe K, Kinukawa N, Sugimachi K, Tsuneyoshi M. Risk factors for intrahepatic recurrence in human small hepatocellular carcinoma. Gastroenterology 1995;108:768-775.
5. Takayama T, Sekine T, Makuuchi M, Yamasaki S, Kosuge T, Yamamoto J, Shimada K, Sakamoto M, Hirohashi S, Ohashi Y, Kakizoe T. Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: a randomised trial. Lancet 2000;356:802-807.
6. Shah SA, Cleary SP, Wei AC, Yang I, Taylor BR, Hemming AW, Langer B, Grant DR, Greig PD, Gallinger S. Recurrence after liver resection for hepatocellular carcinoma: risk factors, treatment, and outcomes. Surgery 2007;141:330-339.
7. Ohkubo T, Yamamoto J, Sugawara Y, Shimada K, Yamasaki S, Makuuchi M, Kosuge T. Surgical results for hepatocellular carcinoma with macroscopic portal vein tumor thrombosis. J Am Coll Surg 2000;191:657-660.
8. Schoniger-Hekele M, Muller C, Kutilek M, Oesterreicher C, Ferenci P, Gangl A. Hepatocellular carcinoma in Central Europe: prognostic features and survival. Gut 2001;48:103-109.
9. Tung-Ping Poon R, Fan ST, Wong J. Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. Ann Surg 2000;232:10-24
10. Utsunomiya T, Shimada M, Taguchi KI, Hasegawa H, Yamashita Y, Hamatsu T, Aishima SI, Sugimachi K. Clinicopathologic features and postoperative prognosis of multicentric small hepatocellular carcinoma. J Am Coll Surg 2000;190:331-335.
11. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology 2006;130:678-686.
12. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. Jama 2006;295:65-73.
13. Hung IF, Poon RT, Lai CL, Fung J, Fan ST, Yuen MF. Recurrence of hepatitis B-related hepatocellular carcinoma is associated with high viral load at the time of resection. Am J Gastroenterol 2008;103:1663-1673.
14. Wu JC, Huang YH, Chau GY, Su CW, Lai CR, Lee PC, Huo TI, Sheen IJ, Lee SD, Lui WY. Risk factors for early and late recurrence in hepatitis B-related hepatocellular carcinoma. J Hepatol 2009;51:890-897.
15. Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer 1954;7:462-503.
16. Imamura H, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S, Sugawara Y, Minagawa M, Takayama T, Kawasaki S, Makuuchi M. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol 2003;38:200-207.
17. Poon RT, Fan ST, Lo CM, Liu CL, Ng IO, Wong J. Long-term prognosis after resection of hepatocellular carcinoma associated with hepatitis B-related cirrhosis. J Clin Oncol 2000;18:1094-1101.

18. Poon RT, Fan ST, Ng IO, Lo CM, Liu CL, Wong J. Different risk factors and prognosis for early and late intrahepatic recurrence after resection of hepatocellular carcinoma. Cancer 2000;89:500-507.
19. Kubo S, Hirohashi K, Tanaka H, Tsukamoto T, Shuto T, Higaki I, Takemura S, Yamamoto T, Nishiguchi S, Kinoshita H. Virologic and biochemical changes and prognosis after liver resection for hepatitis B virus-related hepatocellular carcinoma. Dig Surg 2001;18:26-33.
20. Wang ZL, Liang P, Dong BW, Yu XL, Yu de J. Prognostic factors and recurrence of small hepatocellular carcinoma after hepatic resection or microwave ablation: a retrospective study. J Gastrointest Surg 2008;12:327-337.
21. Chen YJ, Yeh SH, Chen JT, Wu CC, Hsu MT, Tsai SF, Chen PJ, Lin CH. Chromosomal changes and clonality relationship between primary and recurrent hepatocellular carcinoma. Gastroenterology 2000;119:431-440.
22. Chu CJ, Hussain M, Lok AS. Quantitative serum HBV DNA levels during different stages of chronic hepatitis B infection. Hepatology 2002;36:1408-1415.
23. Chan HL, Sung JJ. Hepatocellular carcinoma and hepatitis B virus. Semin Liver Dis 2006;26:153-161.
24. Colombo M, Sangiovanni A. Etiology, natural history and treatment of hepatocellular carcinoma. Antiviral Res 2003;60:145-150.
25. Pan J, Clayton M, Feitelson MA. Hepatitis B virus X antigen promotes transforming growth factor-beta1 (TGF-beta1) activity by up-regulation of TGF-beta1 and down-regulation of alpha2-macroglobulin. J Gen Virol 2004;85:275-282.
26. Volpes R, Van Den Oord JJ, Desmet VJ. Vascular adhesion molecules in acute and chronic liver inflammation. Hepatology 1992;15:269-275.
27. von Marschall Z, Scholz A, Cramer T, Schafer G, Schirner M, Oberg K, Wiedenmann B, Hocker M, Rosewicz S. Effects of interferon alpha on vascular endothelial growth factor gene transcription and tumor angiogenesis. J Natl Cancer Inst 2003;95:437-448.
28. Wang L, Wu WZ, Sun HC, Wu XF, Qin LX, Liu YK, Liu KD, Tang ZY. Mechanism of interferon alpha on inhibition of metastasis and angiogenesis of hepatocellular carcinoma after curative resection in nude mice. J Gastrointest Surg 2003;7:587-594.
29. Ikai I, Arii S, Kojiro M, Ichida T, Makuuchi M, Matsuyama Y, Nakanuma Y, Okita K, Omata M, Takayasu K, Yamaoka Y. Reevaluation of prognostic factors for survival after liver resection in patients with hepatocellular carcinoma in a Japanese nationwide survey. Cancer 2004;101:796-802.
30. Sumie S, Kuromatsu R, Okuda K, Ando E, Takata A, Fukushima N, Watanabe Y, Kojiro M, Sata M. Microvascular invasion in patients with hepatocellular carcinoma and its predictable clinicopathological factors. Ann Surg Oncol 2008;15:1375-1382.
31. Tangkijvanich P, Anukulkarnkusol N, Suwangool P, Lertmaharit S, Hanvivatvong O, Kullavanijaya P, Poovorawan Y. Clinical characteristics and prognosis of hepatocellular carcinoma: analysis based on serum alpha-fetoprotein levels. J Clin Gastroenterol 2000;31:302-308.

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ORIGINAL ARTICLE

Does Primary Surgical Management of Liver Hydatid Cyst Influence Recurrence?

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Abstract
Background and aims Hydatid disease is still a major health problem in sheep-raising areas. Surgery remains the basic treatment for liver hydatid cyst (LHC). However, recurrences can occur after all therapies. Surgery for recurrence of LHC becomes technically more difficult with higher rate of morbidity and mortality. The aim of this study was to determine perfective factors associated to hepatic recurrence after LHC surgery and to propose and discuss postoperative follow-up schedules.
Methods It is a retrospective cohort study of 672 patients with LHC treated at the surgery department "A" at Ibn Sina University Hospital, Rabat, Morocco, from January 1990 to December 2004. Recurrence rates have been analyzed by the Kaplan–Meier method for patients undergoing surgery.
Results Fifty-six patients (8.5%) had LHC recurrence after surgery. There were 34 females (60.7%) and 22 males (39.3%). Median duration of recurrence's diagnosis was 24 months (interquartile range: 10–48 months). Recurrence's risk was 2.3%± 0.6% at 1 year and 9.1%±1.3% at the 10th year. The history of LHC (hazard ratio, 2; 95% confidential interval, 1.13–3.59) and three cysts or more (hazard ratio, 3.8; 95% confidential interval, 2.07–6.98) was an independent risk factor for recurrence.
Conclusion We think that the surgeon's practice and experience are the most important to success the surgical treatment. It prevents complications and recurrences.

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Keywords Liver · Hydatid cyst · Predictive factors · Recurrence · Surgery

Abbreviations
LHC liver hydatid cyst

Introduction

Despite recent advances in medical treatment, hydatid disease remains a major health problem in sheep-raising areas. Nowadays, even in nonendemic areas, due to the increase of travelling and immigration, many physicians present more interest to this zoonotic disease. In Morocco, surgical incidence of hydatidosis is 5.6/100,000 inhabitant (ranges

from 0.4 to 24.14).[1,2] Hydatid cyst grows in the liver in 77% of cases.[1,2] Surgery remains the basic treatment for liver hydatid cyst (LHC). The intended goals of this surgical treatment are to ensure complete elimination of the parasite and prevention of recurrent disease with lower morbidity and mortality. Recurrences can occur after all therapeutic methods including percutaneous treatment,[3,4] chemotherapy with benzimidazole compounds,[5] or surgery.[6–23] Most of the recurrent cysts are asymptomatic.[22] Ultrasonography (US) and/or computed tomography (CT) seems to be the best method to diagnose recurrent parasitic cysts.[2,16,17,24] In some equivocal cases, fine-needle aspiration cytology (FNAC) helps to distinguish between recurrence and residual cavity for patients with initial LHC surgery.[25] Surgery for recurrence of LHC is technically more difficult due to adhesions arising from previous surgeries,[26] which increase considerably the morbidity and mortality rate of this procedure.[11,18] In English literature, few authors tried to discuss recurrent disease problems and their predictive factors.[11–13,15,16,26] Only two studies focused on hepatic recurrences.[11,12] The aim of this retrospective study was to assess predictive factors associated to hepatic recurrence after LHC surgery and to discuss postoperative follow-up schedules.

Materials and Methods

We evaluated retrospectively all patients with LHC treated surgically and followed afterward at the surgery department "A" at Ibn Sina University Hospital, Rabat, Morocco, between January 1990 and December 2004. We included 672 patients, either referred with initial diagnosis of LHC or a recurrent disease. Diagnosis tools of LHC at admission to our unit and different surgical procedures used were previously developed in other studies.[2,25,27] After surgery, all patients underwent abdominal US surveillance, at the first month after discharge, every 6 months during the first 4 years and then annually, to detect recurrences. In the case of highly suspected LHC recurrence on the US, abdominal CT scan was performed. In uncertain cases, FNAC was used to confirm this recurrence.[25] Immunological tests were not routinely used for assessing the diagnosis in this study because they seem to be less sensitive and specific compared with radiologic explorations.[15,17]

Recurrence was defined as the appearance of a growing new cyst, undetected by radiologic exploration before the first surgery or by the surgeon during the first procedure, whether in the first location of the hydatid cyst in the liver or in another liver's segment. During the follow-up, cysts areas at US without change in size and without evidence of daughter cysts have not been considered as recurrence after negative CT scan and negative FNAC.

Nonoperated patients or the ones with missing data were excluded. Medical records of remained patients were analyzed according to the following parameters: age, sex, medical history of hydatid disease (surgery for LHC elsewhere before including in the study), weight loss more than 10% of initial weight, main symptoms and delay of their onset, physical examination findings, abdominal US cyst's characteristics (number of cyst: single or multiple, presence or absence of other organs involved with the disease), chest x-rays, presence or absence of preoperative complications and number of these factors (jaundice, fever: a temperature ≥38°C, dilatation of biliary tract, intraperitoneal rupture, Budd-Chiari syndrome, intrathoracic rupture), type of surgical procedure performed (radical procedures include pericystectomy and hepatic resection; conservative treatment includes unroofing associated to various residual cavity management procedures as omentoplasty, capitonage, drainage),[2,9] thickness of the pericyst, associated extrahepatic biliary tract surgery, concomitant treatment of other cysts (lung, spleen, kidney, and peritoneum), both postoperative mortality and morbidity, duration of stay after surgery, and follow up.

During this period, none of the patients took a preoperative or postoperative antiparasitic chemotherapy. In the last 5 years, a therapeutic cycle of 4 to 6 weeks of benzimidazole compounds was given only to the few patients with a disseminate hydatidosis.

Statistical methods Continuous variables were presented as mean value ± standard deviation or median interquartile range (IQR) and categorical variables were expressed as frequency and percentage. A cutoff 10-cm cyst's diameter was chosen for more commodities and also to compare our data to other studies.[2,12,19,23,24,27] We have conducted an univariate association between each liable factors and the recurrence occurrences with the χ^2 test. A Student's *t*-test was used to compare nonnormally distributed continuous variable, and Mann–Whitney *U*-test was used otherwise. Tests were always two-sided, and significance was considered from a P value less than 0.05.

Recurrence rates have been analyzed by the Kaplan–Meier method for patients undergoing surgery and apparently disease-free at the time of discharge from the hospital. Differences in recurrence between subgroups of patients were evaluated using the log-rank test. Univariate and multivariate analysis was performed by using the Cox proportional hazard method to identify independent predictors of 2-, 5-, and 10-year recurrence. The stepwise selection of variables and estimation of significant probabilities were computed by means of maximal likelihood ration test. The Statistical Package for the Social Sciences statistical software package (version 13.0; SPSS Inc, Chicago, IL) was used.

Results

Six hundred fifty-seven patients were eligible for this study. Fifty-six patients (8.5%) had LHC recurrence after surgery represented by 34 females (60.7%) and 22 males (39.3%). Mean (SD) age was 36.2 (14.4) years. Median duration of recurrence diagnosis was 24 months (IQR: 10–48 months) with a longest delay of recurrence as 156 months. Recurrence's risk was 2.3%±0.6% at the first year, 3.8%±0.8% at the second year, 5%±0.9% at the third year, 6.3%±1% at the fourth year, 8%±1.1% at the fifth year, and 9.1%±1.3% at the tenth year. The median duration of the follow-up was 75 months (IQR: 40–119 months). Fifty nine patients (9%) were lost to follow-up. Seventeen patients (30.4%) had previously undergone surgical therapy for LHC. Three patients (5.4%) were asymptomatic. The most common symptom was pain on the right-upper quadrant in 43 patients (76.8%), and the most common finding on the physical examination was a palpable mass at this location in 28 patients (50%). Jaundice was seen in 4 patients (7.1%) as well as fever in 4 patients (7.1%). All details of operative findings and procedures of patients with recurrent LHC after surgery are reported in Table 1.

On univariate analysis, we found six clinical factors associated to recurrence of LHC after surgery and one factor associated to our therapeutic attitude. In this study, 15.9% of patients (n=17) who developed recurrences had a history of surgical treatment of LHC compared with 7.1% of patients with recurrences (n=39) with free history (p=0.003). Recurrences occurred in 20.2% of cases (n=19) with three or more cyst on the liver compared with 7.1% of cases (n=37) who had two or one cyst (p<0.001). When cyst grew on liver's cephalad segments, recurrence occurs in 10.2% of patients (n=42) versus 5.7% of patients (n=14) with cysts located in caudal segment's cyst (p=0.047). Recurrences occurred in 10.5% of patients (n=45) with cyst's size ≥10 cm, in 12.7% of patients (n=28) with palpable abdominal mass, and in 19.7% of patients (n=13) with other cysts present outside the liver compared with 4.8% of patients (n=11) with cyst <10 cm (p=0.014), to 6.5% of patients (n=28) with no palpable abdominal mass (p=0.007), and to 7.4% of patients (n=43) with no cyst outside the liver (p=0.001), respectively.

Our data shows that the type of surgical procedure (radical/conservative), pericyst aspect, and obliteration management of the remained cavity do not have any influence on the occurrence of recurrence. However, recurrences occurred in 17.6% of patients (n=15) who underwent surgical management of other cysts during the same intervention compared with 7.2% of patients (n=41) who was treated only for liver's cysts (p=0.001).

Recurrence risk factors after LHC surgery for late mortality identified with univariate analyses were included into the multivariate Cox regression model. History of LHC and number of cyst were independent risk factors for recurrence. Results of Cox regression analyses for risk factors for recurrence are shown in Table 2. In Figs. 1 and 2, we expose the long-term recurrence rate after surgery using Kaplan–

Table 1 Cyst's Characteristics, Surgical Procedures, and Operative Findings on 56 Patients with Recurrent LHC After Surgery

Variables	No. of subject	%
History of LHC	17	30.3
No. of cysts		
1	25	44.7
2	12	21.4
3 and more	19	33.9
Localization of the cyst in the liver		
Caudal segments: III, IVb, V, VI	14	25
Cephalad segments: I, II, IVa, VII, VIII	42	75
Maaouni's distribution of the cyst[28]		
Cyst in the segment IV and /or I	4	7.1
Cyst in the segment II and /or III	7	12.5
Cyst in the segment V and /or VI	1	1.8
Cyst in the segment VII and /or VIII	19	33.9
Multiple cysts	25	44.7
Diameter of the cyst (cm)		
≤10	11	19.6
>10	45	80.4
Gharbi's morphologic type of the cyst		
Type I	9	16.1
Type II	6	10.7
Type III	25	44.7
Type IV	13	23.2
Type V	3	5.3
Biliary duct dilatation	1	1.8
Surgical treatment		
Conservative	47	83.9
Radical	9	16.1
Cyst wall (pericyst)		
Soft	9	16.1
Fibrotic or calcified	47	83.9
Biliary fistula	11	19.6
Biliary fistula's management		
Suture	8	72.7
Catheterization	2	18.2
Drainage	1	9.1
Residual cavity's management		
Capitonage	6	10.7
Omentoplasty	6	10.7
Drainage	25	44.7
Capitonnage + drainage	19	33.9

Table 2 Predictors of Recurrences at 2, 5, and 10 years by Univariate and Multivariate Cox Regression Analyses

Variables	Recurrence at 2y *n* (rate %)	Recurrence at 5y *n* (rate %)	Recurrence at 10y *n* (rate %)	Univariate analysis		Multivariate analysis	
				HR (95% CI)	*p*	HR (95% CI)	*p*
History of LHC					0.006		0.018
No	21 (3.2)	33 (6.9)	37 (8.6)	1		1	
Yes	8 (7.7)	13 (13.1)	15 (18.3)	2.226 (1.259–3.934)		2.01 (1.130–3.588)	
Abdominal mass					0.083		–
No	14 (3.4)	23 (6.3)	27 (10)	1		–	
Yes	15 (5.1)	23 (11.1)	25 (12.4)	1.599 (0.941–2.717)		–	
No. of cysts					<0.001		–
1	9 (1.2)	19 (5)	23 (7.5)	1		1	–
2	8 (8.1)	11 (12.2)	12 (14.1)	2.264 (1.137–4.507)		2.306 (1.153–4.612)	0.018
3 or more	12 (13.1)	16 (18.3)	17 (20.2)	3.938 (2.168–7.152)		3.801 (2.071–6.976)	<0.001
Localization of the cyst in the liver				0.064		–	
Caudal seg,	9 (3)	12 (5.5)	14 (7)	1		–	
Cephalad seg.	20 (4.3)	34 (9.5)	38 (12.2)	1.771 (0.967–3.244)		–	
Maaouni's distribution of the cyst[28]				0.006		–	
Seg. IV and /or I	2 (3.8)	3 (6.1)	4 (9.9)	1		–	
Seg. II and /or III	5 (5.8%)	5 (5.8)	7 (10.2)	1.038 (0.304–3.546)		–	
Seg. V and /or VI	0	1 (1.6)	1 (1.6)	0.190 (0.021–1.703)		–	
Seg. VII and /or VIII	7 (1.5)	16 (6.8)	18 (9.6)	0.864 (0.294–2.540)		–	
Multiple cysts	15 (10.1)	21 (15)	22 (16.1)	2.191 (0.762–6.297)		–	
Diameter of the cyst (cm)					0.021		–
≤10	3 (0.4)	7 (3.7)	10 (7.3)	1		–	
>10	26 (5.6)	39 (10.3)	42 (12)	2.172 (1.123–4.200)		–	
Management of other hydatid cysts outside the liver			0.002		–		
No	18 (2.5)	33 (6.8)	38 (9.1)	1		–	
Yes	11 (13.6)	13 (16.3)	14 (18.4)	2.546 (1.409–4.601)		–	
Cyst wall (pericyst)					0.058		–
Soft	3 (1.8)	7 (4.6)	9 (7.9)	1		–	
Fibrotic or calcified.	26 (4.9)	39 (9.6)	42 (11.2)	1.996 (0.977–4.080)		–	
Type of surgery					0.246	–	–
Radical methods	5 (3.9)	6 (4.9)	8 (7.9)	1			
Conservative methods	24 (3.8)	40 (9)	44 (11)	1.527 (0.747–3.125)			

n number of patients; *HR* hazard ratio; *CI* confidential interval; *LHC* liver hydatid cyst; *Seg* segment.

Meier curve and log-rank test adjusted on history of LHC and number of cyst, respectively.

Discussion

In the present retrospective analysis of 672 patients who underwent surgery for LHC in a single center, we found that both history of LHC (surgery for LHC before including into the study) and number of cysts in the liver are independent risk factors for recurrence.

Until now, frequency and circumstances of recurrence have never been the first preoccupation of authors. Some of them claim that recurrence rate greater than 10% would clearly call for a reassessment of the operative approach.[26] In literature, recurrence rate of LHC after surgery range from 4% to 25%.[4,6–9,11–13,15,17,18,21–23,26] However, the number of reported cases, the study period, the follow-up median, and the surgical team skill are very different in these studies, and no conclusion could be assessed.

The major factor of LHC recurrence reported in literature is the type of surgery: either conservative method (unroofing,

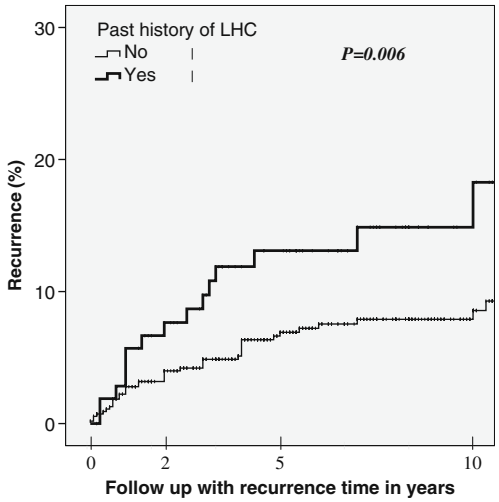

Fig. 1 Comparison of recurrence rates of LHC after surgery in patients with and without history of LHC after univariate analysis using Kaplan–Meier estimation and log-rank test.

drainage) or radical surgery (pericystectomy and hepatectomy). In our study, surgical procedures at the first intervention had no influence on the occurrence of recurrence. Some authors reported a higher recurrence rate of disease in patients undergoing an incomplete resection compared with those undergoing complete surgical resection of LHC.[6,14,16,23,29] They suggested that recurrences with conservative procedures are possible by leaving viable material on the outer surface of the pericyst (exogenous vesiculations).[4,6,8,13,14,16] In our practice, we proceed to meticulous operative inspection of the inner surface of the remaining cavity, pilling the laminated membrane to reduce pericyst's thickness and remove daughter cysts hidden in the pericyst layer. Using hydrogen peroxide to flush the remained cavity during at least 10 min may play a role to sterilize remained exogenous cysts exposed by the pilling procedure. Exogenous vesiculation appears when pericyst becomes thicker.[14] Our data failed to demonstrate the role of pericyst's aspect in occurrence of recurrence, even if the p value was near to significance (p=0.058). We keep defending that conservative surgery is safe and efficient since radical procedures may be very invasive for such benign disease especially in endemic areas.

Cyst's size over than 10 cm was a predictive factor for recurrence in univariate analysis (p=0.021), but not in the multivariate model. Some authors demonstrated that there is no correlation between cyst's size and recurrence's risk.[26] The expansion of LHC may cause various reactions in the surrounding parenchyma leading to fibrosis and thickening. These data support that pericyst's aspect does not influence on the occurrence of recurrence.

In our study, we can clearly assess that LHC recurrence has two independent risk factors: history of LHC and the number of cyst in the liver. Recurrence risk is 3.8-fold when number of cysts are three or more (p<0.001). This agree with the data reporting that 50% patients with LHC recurrence have usually multiple liver cysts.[11] After ingestion of eggs, numerous embryos can be trapped in the liver. If there is more than one, different growth of cysts can be observed. For this reason, multiple LHCs seem to have different sizes and different Gharbi's classification. During surgical procedure, small cysts or deepest ones may not appear on liver surface and then be misdiagnosed. In our practice, abdominal CT was performed on patients showing multiple cysts at US to add further morphologic details. Moreover, intraoperative ultrasound can detect small cysts and may help to choose the right procedure and adjust the treatment to a radical one.[11] In our opinion, this kind of liver hydatidosis represents one of the rare indications of hepatectomy for LHC.[16] Moreover, cysts should be limited to an anatomic liver territory, and the remained liver parenchyma should be sufficient for normal postoperative hepatic function. However, in some rare situations, nonresection of centimetrics cysts can be allowed as medical therapy is able to complete the treatment in order to decrease or stabilize cyst's grow.[30]

Recurrence's risk is two-fold when patient has history of LHC (p=0.018). Most of the authors disregard to take into consideration this factor or even exclude patients with history of LHC.[11] Our patients had history of LHC in 30.3%. In other studies, it may range from 27% to 29.5% of all patients.[12,17]

Each cyst represents a new and particular surgical situation. Careful preoperative evaluation of the extent of the disease and meticulous surgical technique will lead to a satisfactory outcomes.[8] Some surgeons may fail to insure a meticulous strategy in order to avoid missing residual vesicles in place.[26] Surgeon's skills and experiences can be another determinant factor of recurrences.[14,22] Peritoneal soiling during emptying

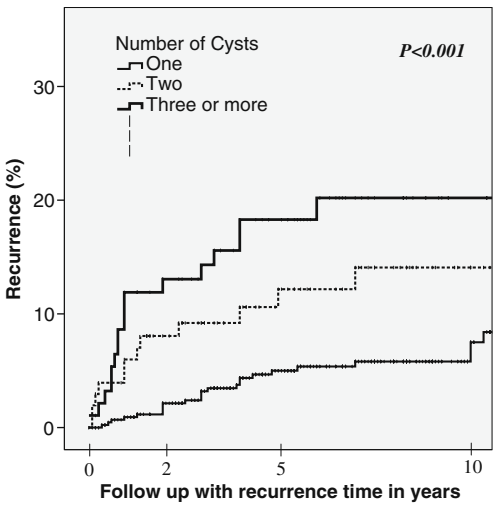

Fig. 2 Comparison of recurrence rates of LHC after surgery in patients considering cyst's number after univariate analysis using Kaplan–Meier estimation and log-rank test.

of the cysts could explain some recurrences and seems to be a more complex problem.[26] In another study, we are willing to determine the special role of spillage in the occurrence of recurrence. Reinfestation can explain some cases of recurrence. More improvements in agriculture, educational, social, and economic factors should be done. Identification of a vaccine can change epidemiologic and clinic data.[20,31]

Albendazole may play an interesting role after surgery to prevent recurrences using 800 mg/d taking in two times during at least 6 to 12 months.[30,32] According to a recommendation of the WHO Informal Working Group on Echinococcosis and others studies, antiparasitic chemotherapy is considered as important indication to prevent secondary echinococcosis and reduce the risk of recurrence.[33–36] It has been demonstrated that in patients who did not receive any albendazole therapy, recurrence rate was 18.75%, whereas recurrence was 4.16% in patients who received albendazole therapy.[37]

Recurrence rate rises by the delay of follow-up. It ranges from 2.3% the first year after surgery to 9.1% at the tenth year. Longer follow-up is strongly recommended. Recurrence usually symptomatic 3–4 years after surgery.[6,11,19,24] In the current study, median duration recurrence was diagnosed at 24 months after surgery (IQR: 10–48 months). Thus, we suggest a follow-up of 5 years using US twice yearly and a CT scan per year. Patients should take chemotherapy with benzimidazole compounds as possible as they can, according to their laboratory findings. Patients with any suspicion of recurrence on US should perform an abdominal CT scan to confirm it. In equivocal cases, FNAC may be done. However, we insist on the fact that anthelmintic chemotherapy should be prescribe before performing a FNAC.

In our opinion, surgeon's degree of practice and experience are one of the most important secrets to a successful LHC surgical treatment. It prevents complications and recurrences. When patients have multiple cysts in liver or history of LHC surgery, they should be referred to reference center with high experience in LHC surgery. Follow-up should be continued for 5 years. More effort in educational strategy can help to decrease this public health problem in endemic areas.

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Conflicts of interest No financial disclosure and conflicts of interest exist

References

1. Service des maladies parasitaires et service de lutte antivectorielle. Rapport annuel d'activités: Etat d'avancement des programmes de lutte contre les maladies parasitaires. Royaume du Maroc Ministère de la santé Direction de l'épidémiologie et de lutte contre les maladies. 2004
2. El Malki HO, El Mejdoubi Y, Souadka Am, Mohsine R, Ifrine L, Abouqal R, Belkouchi A. Predictive factors of deep abdominal complications after operation for hydatid cyst of the liver: 15 years of experience with 672 patients. J Am Coll Surg 2008;206:629–637.
3. Smego RA Jr, Bhatti S, Khaliq AA, Beg MA. Percutaneous aspiration-injection-reaspiration drainage plus albendazole or mebendazole for hepatic cystic echinococcosis: a meta-analysis. Clin Infect Dis 2003;37:1073–1083.
4. Ustunsoz B, Akhan O, Kamiloglu MA, Somuncu I, Ugurel MS, Cetiner S. Percutaneous treatment of hydatid cysts of the liver: long-term results. AJR Am J Roentgenol 1999;172:91–96.
5. Klutman NE, Delcore R, Hinthorn DR. Combined albendazole and surgical therapy for echinococcal liver cysts. Infect Dis Clin Pract 1997;6:159–165.
6. Safioleas MC, Misiakos EP, Kouvaraki M, Stamatakos MK, Manti CP, Felekouras ES. Hydatid disease of the liver: a continuing surgical problem. Arch Surg 2006;141:1101–1108.
7. Karavias DD, Vagianos CE, Bouboulis N, Rathosis S, Androulakis J. Improved techniques in the surgical treatment of hepatic hydatidosis. Surg Gynecol Obstet 1992;174:176–180.
8. Vagianos CE, Karavias DD, Kakkos SK, Vagenas CA, Androulakis JA. Conservative surgery in the treatment of hepatic hydatidosis. Eur J Surg 1995;161:415–420.
9. Akgun Y, Yilmaz G. Efficiency of obliteration procedures in the surgical treatment of hydatid cyst of the liver. ANZ J Surg 2004;74:968–973.
10. Chautems R, Bühler LH, Gold B, Giostra E, Poletti P, Chilcott M, Morel P, Mentha G. Surgical management and long-term outcome of complicated liver hydatid cysts caused by *Echinococcus granulosus*. Surgery 2005;137:312–316.
11. Kapan M, Kapan S, Goksoy E, Perek S, Kol E. Postoperative recurrence in hepatic hydatid disease. J Gastrointest Surg 2006;10:734–739.
12. Atmatzidis KS, Pavlidis TE, Papaziogas BT, Mirelis C, Papaziogas TB. Recurrence and long-term outcome after open cystectomy with omentoplasty for hepatic hydatid disease in an endemic area. Acta Chir Belg 2005;105:198–202.
13. Gollackner B, Längle F, Auer H, Maier A, Mittlböck M, Agstner I, Karner J, Langer F, Aspöck H, Loidolt H, Rockenschaub S, Steininger R. Radical surgical therapy of abdominal cystic hydatid disease: factors of recurrence. World J Surg 2000;24:717–721.
14. Cirenei A, Bertoldi I. Evolution of surgery for liver hydatidosis from 1950 to today: analysis of a personal experience. World J Surg 2001;25:87–92.
15. Little JM, Hollands MJ, Ekberg H. Recurrence of hydatid disease. World J Surg 1988;12:700–704.
16. Sielaff TD, Taylor B, Langer B. Recurrence of hydatid disease. World J Surg 2001;25:83–86.
17. Yorganci K, Sayek I. Surgical treatment of hydatid cysts of the liver in the era of percutaneous treatment. Am J Surg 2002;184:63–69.
18. Turkçapar AG, Ersoz S, Gungor C, Aydinuraz K, Yerdel MA, Aras N. Surgical treatment of hepatic hydatidosis combined with perioperative treatment with albendazole. Eur J Surg 1997;163:923–928.
19. Agaoglu N, Turkyilmaz S, Arslan MK. Surgical treatment of hydatid cysts of the liver. Br J Surg 2003;90:1536–1541.
20. Dervenis C, Delis S, Avgerinos C, Madariaga J, Milicevic M. Changing concepts in the management of liver hydatid disease. J Gastrointest Surg 2005;9:869–877.
21. Demirci S, Eraslan S, Anadol E, Bozatli L. Comparison of the results of different surgical techniques in the management of hydatid cysts of the liver. World J Surg 1989;13:88–91.
22. Safioleas M, Misiakos E, Manti C, Katsikas D, Skalkeas G. Diagnostic evaluation and surgical management of hydatid disease of the liver. World J Surg 1994;18:859–865.
23. Yagci G, Ustunsoz B, Kaymakcioglu N, Bozlar U, Gorgulu S, Simsek A, Akdeniz A, Cetiner S, Tufan T. Results of surgical,

laparoscopic, and percutaneous treatment for hydatid disease of the liver: 10 years experience with 355 patients. World J Surg 2005;29:1670–1679.
24. Bulbuller N, Ilhan YS, Kirkil C, Yeniçerioglu A, Ayten R, Cetinkaya Z. The results of surgical treatment for hepatic hydatid cysts in an endemic area. Turk J Gastroenterol 2006;17:273–278.
25. El Malki HO, Dziri C, El Mejdoubi Y, Souadka A, Zakri B, Mohsine R, Ifrine L, Belkouchi A. Why fine-needle aspiration cytology is not an adequate diagnostic method for liver hydatid cyst. Arch Surg 2007;142:690.
26. Mottaghian H, Saidi F. Postoperative recurrence of hydatid disease. Br J Surg 1978;65:237–242.
27. El Malki HO, El Mejdoubi Y, Souadka Am, Mohsine R, Ifrine L, Abouqal R, Belkouchi A. Predictive model of biliocystic communication in liver hydatid cysts using classification and regression tree analysis. BMC Surg 2010;10:16.
28. Maaouni A, Elalaoui M, Hamiani O, Benmansour A, Belkouchi A, Ahyoud F, Jalil A, Faik M. Chirurgie des kystes hydatiques du foie 581 patients. 952 kystes. Chirurgie 1989;115 Suppl 1:61–69.
29. Chautems R, Buhler L, Gold B, Chilcott M, Morel P, Mentha G. Long term results after complete or incomplete surgical resection of liver hydatid disease. Swiss Med Wkly 2003;133:258–262.
30. El Malki HO, El Mejdoubi Y, Mohsine R, Ifrine L, Belkouchi A. La rupture intraperitoneale du kyste hydatique du foie. Gastroenterol Clin Biol 2006;30:1214–1216.
31. Dziri C. Hydatid disease-continuing serious public health problem: introduction. World J Surg 2001;25:1–3.
32. Michail OP, Georgiou C, Michail PO, Felekouras E, Karavokyros I, Marinos G, Giannopoulos A, Griniatsos J. Disappearance of recurrent intra-abdominal extrahepatic hydatid cyst following oral albendazole administration. West Indian Med J 2007;56:372–375.
33. WHO Informal Working Group on Echinococcosis. Guidelines for treatment of cystic and alveolar echinococcosis in humans. Bull World Health Organ 1996;74:231–242.
34. Dziri C, Haouet K, Zaouche A, et al. Comment traiter un kyste hydatique du foie non compliqué? Ann Chir 2005;130:249–251.
35. Menezes da Silva A. Hydatid cyst of the liver-criteria for the selection of appropriate treatment. Acta Trop 2003;85:237–242.
36. Wani RA, Malik AA, Chowdri NA, Wani KA, Naqash SH. Primary extrahepatic abdominal hydatidosis. Int J Surg 2005;3:125–127.
37. Arif SH, Shams-Ul-Bari, Wani NA, Zargar SA, Wani MA, Tabassum R, Hussain Z, Baba AA, Lone RA. Albendazole as an adjuvant to the standard surgical management of hydatid cyst liver. Int J Surg 2008;6:448–451.

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ORIGINAL ARTICLE

Clinicopathologic and Treatment-Related Factors Influencing Recurrence and Survival after Hepatic Resection of Intrahepatic Cholangiocarcinoma: A 19-Year Experience from an Established Australian Hepatobiliary Unit

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Abstract
Background Intrahepatic cholangiocarcinoma is rare, but its incidence is rapidly increasing in developed countries. Early detection and surgical extirpation offer the only hope for cure. Given the rarity of intrahepatic cholangiocarcinoma, there is limited knowledge regarding its natural history, clinicopathological characteristics, or outcomes following surgery. The primary aim of the current study is to report overall survival and recurrence-free survival outcomes following resection of intrahepatic cholangiocarcinoma. The secondary aim is to evaluate the impact of prognostic variables on outcomes.
Methods Between November 1990 and November 2009, 88 patients were evaluated for their suitability for potentially curative surgery; of these, 40 patients underwent potentially curative surgery. These patients are the principal subjects of the current analysis. Patients were assessed at monthly intervals for the first 3 months and then at six monthly intervals after treatment. Recurrence-free survival and overall survival were determined; 17 clinicopathological and treatment-related factors associated with recurrence-free survival and overall survival were evaluated through univariate and multivariate analyses.
Results No patient was lost to follow-up. The median follow-up was 31 months (range=0–142 months). The median recurrence-free survival and overall survival after resection were 21 and 33 months, respectively. The 5-year survival rate was 28%. Four factors were associated with overall survival: carbohydrate antigen 19.9 (p=0.020), clinical stage (p=0.018), histological grade (p=0.020), and lymph node metastases (p=0.003). Two factors were associated with recurrence-free survival: carbohydrate antigen 19.9 (p=0.002) and margin status (p=0.002).
Conclusion Hepatic resection is an efficacious treatment for intrahepatic cholangiocarcinoma. Clincopathological factors can predict outcome and should be used in the preoperative assessment of operability.

Keywords Intrahepatic · Cholangiocarcinoma · Hepatectomy · Survival · Recurrence

Introduction

Intrahepatic cholangiocarcinoma (IHC), a tumor that arises from the epithelium of the biliary ducts within the liver, was first reported by Durand-Fardel in 1840.[1] This disease is characterised by delayed presentation where symptoms do not manifest until disease is extensive. The increased incidence and mortality of this disease, especially in Western countries, have renewed interest in its management. Thailand records the highest number of cases with an estimated prevalence of 96 per 100,000 men,[2] which far exceeds the prevalence in the USA, which stands at about 1 per 100,000.[3] From the SEER database, the incidence of IHC diangosed between 1976 and 2000 increased by

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121.9%.[3] Although primary sclerosing cholangitis is a known risk factor of IHC, the stable incidence of primary sclerosing cholangitis makes this association an unlikely explanation for the rising trend of IHC.[2] Other known risk factors including viral hepatitis, parasitic liver infections, and exposure to chemical carcinogens may possibly explain this phenomenon.

This disease is highly morbid and mortal. Patients with unresectable disease die within 12 months from cancer cachexia, liver failure, and biliary sepsis. Common nonsurgical therapeutic modalities employed include liver-targeted radiotherapy via yttrium-90 microspheres[4] or stereotactic body radiotherapy,[5] gemcitabine and oxaliplatin chemotherapy,[6] and locoregional chemotherapy using transarterial chemoembolization.[7] These therapeutic modalities achieve an overall median survival and 5-year survival of 12 months and 10%, respectively.[4–7] Progression-free survival ranges between 4 and 7 months, and 5-year progression free survival rarely exceeds 5%.[5,6] These outcomes represent a marginal improvement on the survival outcomes of patients with untreated disease.[8–10] Hepatic resection where possible confers the only chance of long-term survival with 5-year survival rates ranging between 21% and 35%.[8,10–12]

In such a rare disease, optimizing and possibly individualizing therapy will improve outcome. Despite the increased interest within the oncological community regarding management of IHC, the rarity of this disease in the Western world has limited efforts to identify the relevant prognostic factors. The purpose of this study is to review our institution's experience with management of 88 patients with IHC, specifically analyzing the outcomes of patients who were treated by hepatic resection, with an emphasis on the clinicopathologic factors associated with recurrence-free and overall survival.

Patients and Methods

Patient Selection

Following approval by an institutional review board, we reviewed the records of 88 patients with IHC who were referred as potential candidates for surgery at the St George Hospital, Sydney, between November 1990 and December 2009. IHC is a malignancy arising from the intrahepatic bile ducts; peri-hilar (klatskin) tumors were excluded. Patients were evaluated with a baseline medical history, clinical examination, full blood count, liver function tests, serum carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19.9 assays, and chest radiography. Tumor stage was evaluated with liver ultrasonography (US), abdominal computed tomography (CT), abdominal magnetic resonance imaging (MRI) with cholangiopancreatography (MRCP), endocscopic retrograde cholangiography (ERCP), and/or percutaneous transhepatic cholangiography (PTC), as appropriate. Tumor markers (CEA and CA19.9) were routinely measured preoperatively because they may help confirm a diagnosis of IHC in the setting of a good clinical history and imaging. On their own, these tumors are not specific or sensitive enough to allow a diagnosis of IHC to be made.

Preoperative evaluation of vascular involvement was performed with CT, and angiography in select cases. A primary aim of preoperative evaluation was to assess the suitability of patients for potentially curative surgery. Patients with evidence of extrahepatic metastases, peritoneal dissemination, and para-aortic lymph node metastases were not considered as operative candidates. Patients of advanced age (>85 years), very extensive disease involvement, or occlusion of the major vascular structures predisposing to high risk of treatment failure and mortality (in particular the inferior vena cava) or a combination of these factors were also not considered to be operative candidates. After preoperative evaluation, 31 patients were deemed nonoperative candidates because of the abovementioned factors.

Surgical Technique

Once submitted for surgery, patients were explored through a bilateral subcostal incision with vertical midline upward extension (i.e., Mercedes incision). Intraoperative ultrasound was then performed to evaluate the presence of intrahepatic metastases, to detect any tumor invasion of portal vein or hepatic veins, and to define the relationship between the tumor and major intrahepatic structures. Systematic examination of the hepatoduodenal ligament and celiac axis was performed to evaluate for lymph node metastasis. Suspicious lymph nodes were sent for frozen section analysis; tumor presence on a lymph node influenced the decision to proceed with surgery. Following an intraoperative exploration, a decision to proceed with a potentially “curative” operation was made by the attending surgeon. A potentially “curative” resection is one where there was complete macroscopic excision of disease. Patients were precluded from undergoing a curative procedure using the same selection criteria as described above. In the current study, 40 patients underwent a potentially curative procedure and are the principal focus of the study; the remaining 17 underwent a palliative procedure.

Parenchymal transection was performed using an ultrasonic dissection device (Cavitron ultrasonic surgical aspirator, CUSA®; Valleylab, Boulder, CO, USA). Pringle maneuver was applied as required. Enlarged lymph nodes were submitted for frozen section analysis, and if positive,

systematic lymphadenectomy was performed. Extrahepatic bile duct resection was performed if there was suspicion that the tumor had invaded the bile duct or metastasized to lymph nodes within the hepatoduodenal ligament. Resection and reconstruction of major vascular structures (inferior vena cava, portal vein, and hepatic artery) were performed when tumor had invaded these vessels. Intra-abdominal drains were placed in situ prior to laparotomy closure.

Histopathological Examination

Pathological examination was performed on all resected specimens. A negative margin was microscopically tumor-free (R0) and a microscopically positive margin was defined as R1. R2 resections resulted in grossly positive margins. Gross appearance of the cut surface of IHCs was categorized into the following types according to the classification proposed by the Liver Study Group of Japan: mass forming (MF), periductal infiltrating (PI), intraductal growth (IG), and other.[13] When more than one type was found, all of the types involved were recorded, in order of the degree of involvement; the first recorded type was the predominant type, for example, "MF+PI" type. Tumor stage was defined according to the pathologic tumor node metastases (pTNM) classification proposed by the Union Internacional Contra la Cancrum, UICC).[14]

Postoperative Follow-Up

All patients were followed up prospectively by the consultant surgeon at monthly intervals for the first 3 months and at six monthly intervals thereafter with examinations of full blood count, liver function tests, tumor markers (CA 19.9 and CEA), US, and abdominal CT. Tumor recurrence was detected by means of imaging, tumor markers, and/or histopathological examination. Chest CT or bone scanning was performed on clinical suspicion of distant metastases or diagnosis of recurrence. Upon diagnosis of recurrence, an appropriate management strategy for the patient was devised by a multidisciplinary team, which included the operating surgeon, medical oncologist, radiologist, and radiation oncologist. This was based on, among other factors, the patient's performance status, liver function, extent of hepatic disease, and concurrent extrahepatic disease. The management strategy was personalized on an individual basis, and the suitability of possible treatment options was discussed for each case. There was a particular focus on incorporating the results from the most recent studies into decision making. For isolated liver recurrence, repeat resection was considered the ideal treatment. In patients with unresectable liver disease or disseminated disease, systemic chemotherapy (in particular gemcitabine) was used. More recently, we have used yttrium-90 radioembolization for the treatment of unresectable liver disease unresponsive to systemic chemotherapy. The treatment of recurrence was thus individualized and based on the latest published data.

Data Collection and Statistical Analysis

Patient demographic data, disease-related factors, pathologic factors, and treatment-related factors were collected and analyzed. The primary endpoints were the time from hepatic resection to the time of disease recurrence (recurrence-free survival) and cancer-related death (overall survival). Data analyses were performed using SPSS® for Windows version 15.0 (SPSS, Munich, Germany). The Kaplan–Meier method was used to analyze recurrence-free survival and overall survival. Univariate analysis (log rank) was performed to examine the relationship of clinicopathological and treatment-related factors with recurrence-free survival and overall survival. Multivariate analysis was performed on all factors $p<0.10$ using the Cox proportional hazards regression model. The median time to death was defined as the time where 50% of patients have died. Follow-up was calculated from the date of surgery to the date of death or last follow-up. $p<0.05$ was considered statistically significant.

Results

Between November 1990 and December 2009, a total of 88 patients were referred to our institution as potential surgical candidates. After preoperative evaluation, 57 (65%) patients underwent surgical exploration; of these, 17(30%) patients did not undergo a potentially curative procedure. Of the 17 patients, 8(47%) were found to have peritoneal dissemination. The remaining 40(70%) patients underwent a potentially curative surgical procedure with complete macroscopic excision of disease. These patients are the principal subjects of the current analysis, and their descriptive characteristics are summarized in Table 1. There were 21(53%) male patients. The mean age of patients at the time of resection was 61 years (SD=11, median=60, range=38–83). Twenty-nine (73%) patients presented with symptomatic manifestation of their disease. Biliary stones, viral hepatitis, inflammatory bowel disease, and primary sclerosing cholangitis were the concomitant diagnoses in 5 (13%), 3 (8%), 2 (5%), and 2 (5%) patients, respectively. Preoperative laboratory data showed that the mean levels of bilirubin (mg/dl), alkaline phosphatase (IU/L), aspartate aminotransferase (IU/L), alanine aminotransferase (IU/L), and albumin (g/dL) were 35 (SD=88), 211 (SD=189), 47 (SD=40), 56 (SD=49), and 40 (SD=5), respectively. The CEA level was elevated

Table 1 Descriptive Characteristics of Patients who Underwent Hepatic Resection of IHC

Descriptive characteristics	*n* (%)
Sex	
Male	21 (53)
Female	19 (47)
Age at time of resection	
Mean (SD)	61 (11)
<61 years	21 (53)
≥61 years	19 (47)
Co-existing medical conditions	
Biliary stones	5 (20)
Viral hepatitis	3 (8)
Inflammatory bowel disease	2 (5)
Primary sclerosing cholangitis	2 (5)
Preoperative laboratory data (mean/SD)	
Bilirubin (mg/dl)	35 (88)
Alkaline phosphatase (IU/L)	211 (189)
Aspartate aminotransferase (IU/L)	47 (40)
Alanine aminotransferase (IU/L)	56 (49)
Albumin (g/dL)	40 (5)
Symptom presentation	
Yes	29 (73)
No	11 (28)
Size of largest hepatic tumor	
Mean (SD)	74 (38)
Median	65
≥65 mm	22 (55)
<65 mm	18 (45)
CA 19.9	
≥37 U/mL	22 (58)
<37 U/mL	16 (42)
CEA	
≥5 μg/mL	7 (17)
<5 μg/mL	30 (83)
Portal vein resection and reconstruction	
Yes	5 (13)
No	35 (87)
Operative procedure	
Trisegmentectomy	15 (38)
Lobectomy	14 (35)
Sublobar resection	11 (28)
Number of liver segments resected	
Mean (SD)	3 (3.5)
≥4 segments	19 (47)
<4 segments	21 (53)
Bile duct resection	
Yes	12 (30)
No	28 (70)
Satellite tumors	
Present	14 (35)
Absent	26 (65)
Pathologic margin evaluation	
R0	28 (70)
R1	12 (30)
Histopathological grade	
Moderate differentiation	29 (73)
Poor differentiation	11 (28)
Lymph node metastases	
Yes	11 (28)
No	29 (73)
Perineural invasion	
Yes	10 (25)
No	30 (75)
Morphological tumor type	
MF	22 (55)
MF and PI	12 (30)
PI	5 (13)
ID	1 (3)
Tumor stage	
I	5 (13)
II	4 (10)
IIIa	15 (38)
IIIb	10 (40)
IIIc	5 (13)
TNM classification	
1	5 (13)
2	8 (20)
3	22 (55)
4	4 (10)
ECOG performance status	
0	16 (40)
1	18 (45)
2	6 (15)

in 7 patients (of 37 patients, 17%) (mean=5; range=0–48; normal value<5 μg/mL), and the CA 19.9 level was elevated in 22 patients (of 38 patients, 58%) (mean=1,070; range=2–15,634; normal value<37 U/mL). The median interval from the diagnosis of IHC to liver resection was 2 months (range=0–12).

Operative procedures included trisegmentectomy in 15 (38%) patients, lobectomy in 14 (35%) patients, and sublobar resections in 11 (28%) patients. The median number of segments resected was 3 (mean=3.5, SD=1.5, range=1–6). Twenty-nine (73%) patients underwent a major liver resection. Extrahepatic bile duct resection was performed in 11 (28%) patients in whom the tumor was

judged to have invaded the biliary confluence. Portal vein resection and reconstruction were necessary in 5 (13%) patients. Macroscopic satellite lesions were noted in 14 (35%) patients.

Pathological analysis of the resected specimen identified 29 (73%) patients with moderately differentiated tumor and 11 (27%) had poorly differentiated tumor. Resected tumor was classified as mass-forming in 22 (55%) patients, mass-forming and periductal infiltrating in 12 (30%) patients, periductal-infiltrating in 5 (13%) patients, and intraductal in 1 (2%) patient. The median size of the largest resected hepatic tumor was 65 mm (mean=74, SD=38, range=11–200). Twenty-eight (70%) specimens had microscopically negative margins (R0 resection), and the remaining 12 (30%) specimens harboured microscopically positive margins (R1 resection). Lymph node metastases and perineural invasion were noted in 11 (28%) and 10 (25%) patients, respectively. TNM classification of tumors was T1 in 5 (13%) patients, T2 in 8 (20%) patients, T3 in 22 (55%), and T4 in 5 (13%). Clinical staging of the tumors according to the Liver Cancer Study Group of Japan classification was I in 5 (13%) patients, II in 4 (10%) patients, IIIa in 15 (38%) patients, IIIb in 10 (40%) patients, and IIIc in 5 (13%) patients.

Morbidity and Mortality

One patient (2%) died during hospital stay. This patient had tumor around the IVC and extending to the right hepatic vein. Nevertheless, this patient was adjudged intraoperatively to have resectable disease given the absence of significant comorbidities and extrahepatic disease. Unfortunately, during mobilisation behind the IVC, the right hepatic vein tore, causing massive bleeding. A salvage liver and IVC resection was performed. Unfortunately, this patient developed persistent hypotension and died intraoperatively from massive haemorrhage. Postoperative complications developed in 15 patients, resulting in an overall morbidity rate of 38%. The major complications included bile leakage in 7 (18%) patients, subphrenic abscess in 4 (10%) patients, liver dysfunction in 3 (8%) patients, wound infection in 2 (5%) patients, and atelectasis in 2 (5%) patients. Pneumonia, intestinal obstruction, and ascites developed in one patient (2%), respectively.

Overall Survival Analysis

No patient was lost to follow-up. Twenty-six (65%) patients died at the time of last follow-up. The median follow-up of period for all patients was 31 months (range=0 to 142 months). The median survival after hepatic resection was 33 months with 1-, 3-, and 5-year survival of 79%, 48%, and 28%, respectively. The median survival of patients who were deemed unresectable following surgical exploration was 6 months with 1-, 2-, 3-, and 5-year survival of 14%, 7%, 7%, and 0%, respectively. Compared to patients who underwent a macroscopically complete hepatic resection, this difference was statistically significant ($p<0.001$) (Fig. 1).

Recurrence-Free Survival Analysis

Recurrence-free survival was assessed in the 38 patients (95%) who survived beyond 2 months of surgery. Of these 38 patients, 26 (68%) developed disease recurrence during follow-up. The median time to disease recurrence was 21 months. Recurrence-free survival after 1, 2, 3, and 5 years was 69%, 44%, 34%, and 14%, respectively (Fig. 2). The site of initial recurrence was the liver in 22 (58%) patients, lymph nodes in 4 (11%) patients, lung in 2 (5%) patients, bone in 2 (5%) patients, and peritoneum in 1 (3%) patient. Five (13%) patients demonstrated disease progression in multiple organ sites simultaneously. Of the 26 patients who developed recurrent disease, 19 (73%) received some additional form of oncological therapy for recurrent disease; the remaining 7 (27%) patients were managed with best supportive care. Best supportive care represented no attempt at active treatment of disease with a primary focus on symptomatic management and comfort care. Additional forms of treatment post-recurrence included cytotoxic chemotherapy in 14 patients (including gemcitabine in 11 patients), yttrium-90 radioembolization in 2 patients, repeat resection in 2 patients, cryoablation in 1 patient, and radiofrequency ablation in 1 patient.

Prognostic Factors for Overall Survival and Recurrence-Free Survival

Of 17 clinicopathological and treatment-related variables, 8 variables were shown to influence overall survival following resection of IHC on univariate analysis (Table 2). These included the histological grade (moderate vs. poor differentiation; 44 vs. 15 months; $p=0.036$), CA 19.9 (>37 U/ml vs. ≤37 U/ml; 16 vs. 44 months; $p=0.016$), CEA (>5 μg/L vs. ≤5 μg/L; 5 vs. 38 months; $p=0.009$), pathologic margin status (R0 vs. R1; 44 vs. 15 months; $p<0.001$), lymph node metastases (yes vs. no; 38 vs. 15 months; $p=0.001$), presence of satellite tumors (yes vs. no; 20 vs. 48 months; $p=0.007$), clinical stage (I and II vs. III; 67 months vs. 23 months; $p=0.004$) and TNM classification (1 and 2 vs. 3 and 4; 44 vs. 23; $p=0.023$).

Six variables were shown to influence recurrence-free survival following resection of IHC. These included a CA 19.9 (>37 U/ml vs. ≤37 U/ml; 10 vs. 31 months; $p=0.008$), CEA (>5 μg/L vs. ≤5 μg/L; 7 vs. 23 months; $p=0.018$),

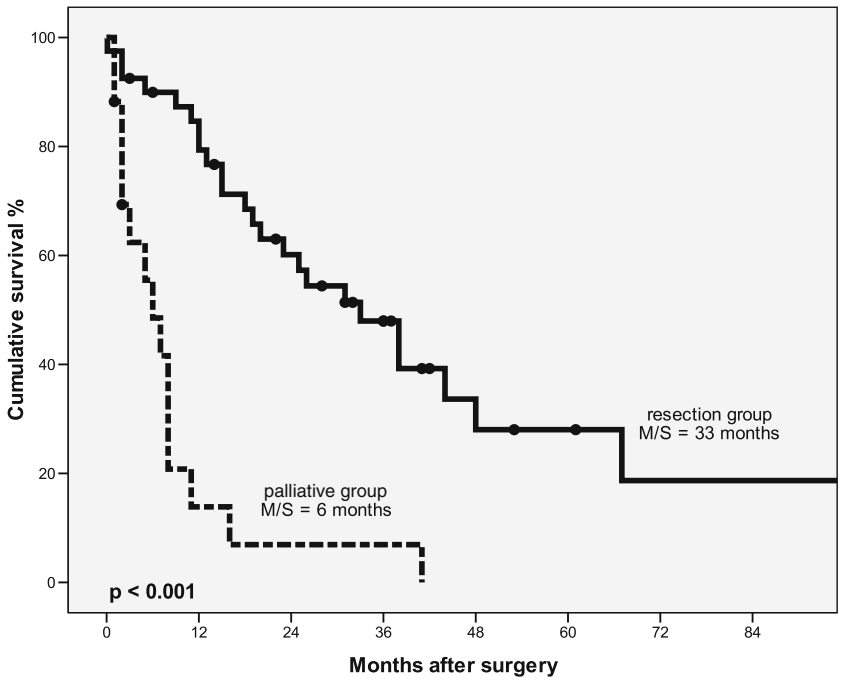

Figure 1 Overall survival after hepatic resection or palliative surgery for IHC (n=57).

pathologic margin status (R0 vs. R1; 31 vs. 10 months; $p<$ 0.001), lymph node metastases (yes vs. no; 14 vs. 30 months; p=0.024), presence of satellite tumors (yes vs. no; 14 vs. 21 months; p=0.027), and clinical stage (I and II vs. III; 31 months vs. 15 months; p=0.049).

Variables $p<0.10$ in the univariate analysis were subjected to a Cox proportional hazards regression model for a multivariate analysis. Independent predictors for overall survival included CA 19.9 [hazard ratio (95% CI); 4.14 (1.25 to 13.70), p=0.020] (Fig. 3), clinical stage [hazard ratio (95% CI); 6.08 (1.36 to 27.28), p=0.018], histological grade [hazard ratio (95% CI); 4.14 (1.25 to 13.70), p= 0.020], and lymph node metastases [hazard ratio (95% CI); 5.60 (1.80 to 17.42), p=0.003] (Fig. 4). Independent predictors of recurrence-free survival included CA 19.9 [hazard ratio (95% CI); 3.96 (1.63 to 9.60), p=0.002] and pathologic margin status [hazard ratio (95% CI); 4.99 (1.83 to 13.63), p=0.002] (Fig. 5).

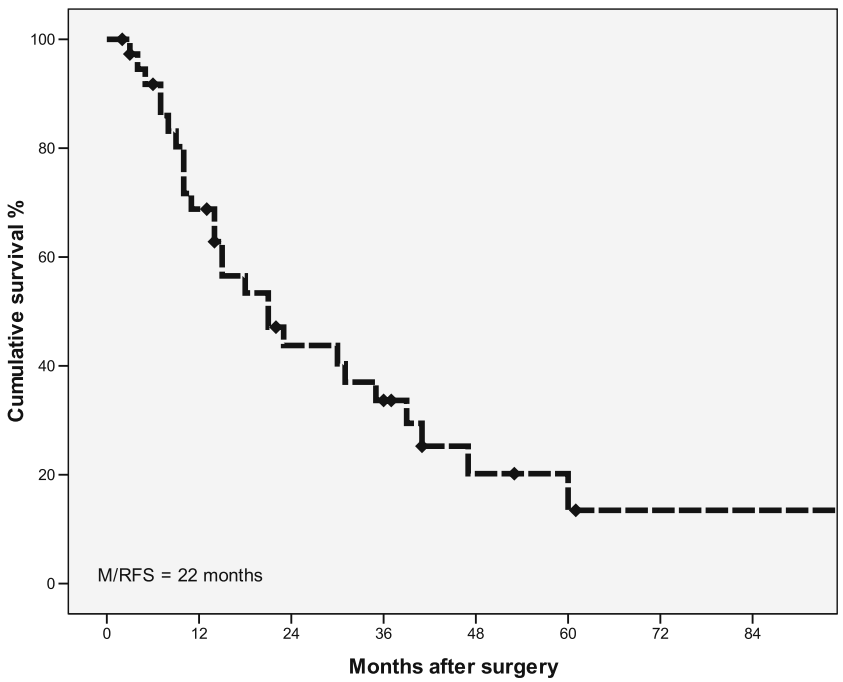

Figure 2 Recurrence-free survival after hepatic resection of IHC (n=38).

Table 2 Univariate Analysis of Clinicopathologic and Treatment-Related Factors for Overall Survival and Recurrence-Free Survival After Hepatic Resection of IHC

Clinicopathological and treatment-related factors	Analysis of overall survival			Analysis of recurrence-free survival[a]		
	Patients (n=40)	Median overall survival (months)	Univariate analysis p value	Patients (n=38)	Median recurrence-free survival (months)	Univariate analysis p value
Sex	–	–	0.989	–	–	0.449
Male	21	38	–	21	18	–
Female	19	31	–	17	23	–
Age at time of resection	–	–	0.912	–	–	0.752
<61 years	21	25	–	19	21	–
≥61 years	19	38	–	19	18	–
Symptom presentation	–	–	0.373	–	–	0.766
Yes	29	31	–	27	23	–
No	11	38	–	11	14	–
Size of largest hepatic tumor	–	–	0.060	–	–	0.775
≥65 mm	22	44	–	20	18	–
<65 mm	18	25	–	18	21	–
CA 19.9	–	–	0.016[a]	–	–	0.008[a]
≥37 U/mL	22	19	–	20	31	–
<37 U/mL	16	44	–	16	10	–
CEA	–	–	0.009[a]	–	–	0.018[a]
≥5 μg/mL	7	15	–	7	7	–
<5 μg/mL	30	38	–	29	23	–
Number of liver segments resected	–	–	0.907	–	–	0.853
≥4 segments	19	33	–	17	31	–
<4 segments	21	44	–	21	21	–
Bile duct resection	–	–	0.706	–	–	0.531
Yes	12	33	–	12	15	–
No	28	38	–	26	31	–
Satellite tumors	–	–	0.007[a]	–	–	0.027[a]
Present	14	20	–	12	14	–
Absent	26	48	–	26	31	–
Pathologic margin evaluation	–	–	<0.001[a]	–	–	<0.001[a]
R0	28	44	–	28	31	–
R1	12	15	–	10	10	–
Histopathological grade	–	–	0.036[a]	–	–	0.583
Moderate differentiation	29	44	–	28	21	–
Poor differentiation	11	15	–	10	21	–
Lymph node metastases	–	–	0.001[a]	–	–	0.024[a]
Yes	11	15	–	10	14	–
No	29	38	–	28	30	–
Perineural invasion	–	–	0.727	–	–	0.139
Yes	10	33	–	10	15	–
No	30	38	–	28	23	–
Morphological tumor type	–	–	0.510	–	–	0.132
MF	22	44	–	22	39	–
MF and PI	12	26	–	10	21	–
PI	5	23	–	5	14	–
ID	1	NR	–	1	NR	–

Table 2 (continued)

Clinicopathological and treatment-related factors	Analysis of overall survival			Analysis of recurrence-free survival[a]		
	Patients (n=40)	Median overall survival (months)	Univariate analysis p value	Patients (n=38)	Median recurrence-free survival (months)	Univariate analysis p value
Tumor stage	–	–	0.004[a]	–	–	0.049[a]
I and II	10	67	–	10	31	–
IIIa and IIIb and IIIc	30	23	–	28	15	–
TNM classification	–	–	0.023[a]	–	–	0.157
1 and 2	13	44	–	13	31	–
3 and 4	27	23	–	25	15	–
ECOG performance status	–	–	0.259	–	–	0.993
0	16	38	–	16	30	–
1	18	25	–	17	21	–
2	6	19	–	5	21	–

[a] Analysis of recurrence-free survival was performed in 38 patients

Discussion

Although IHC is regarded as a disease with a poor prognosis, selected patients with resectable disease may benefit from hepatic resection. Hepatic surgery in the current era is regarded as a safe procedure, and its role in primary and secondary liver cancers is well established.[15] To our knowledge, this is the first and largest contemporary hepatic resection series from Australia.

We report a median survival of 33 months and a 5-year survival of 28%. Our survival results are comparable to other published series.[8,10,11,16,17] Patients who underwent exploration but whose disease was unresectable survived a median of 6 months. Following resection, majority of patients (68%) developed recurrence with a median recurrence-free survival time of 21 months. Common sites of recurrence were in the liver and abdominal lymph nodes. Systemic dissemination was less common, but 5 patients (13%) did present with recurrent disease at multiple disease sites. In light of this, a thorough preoperative exploration for metastatic disease using positron emission tomography (PET) imaging or other forms of metastatic workup may be worthwhile. This has not

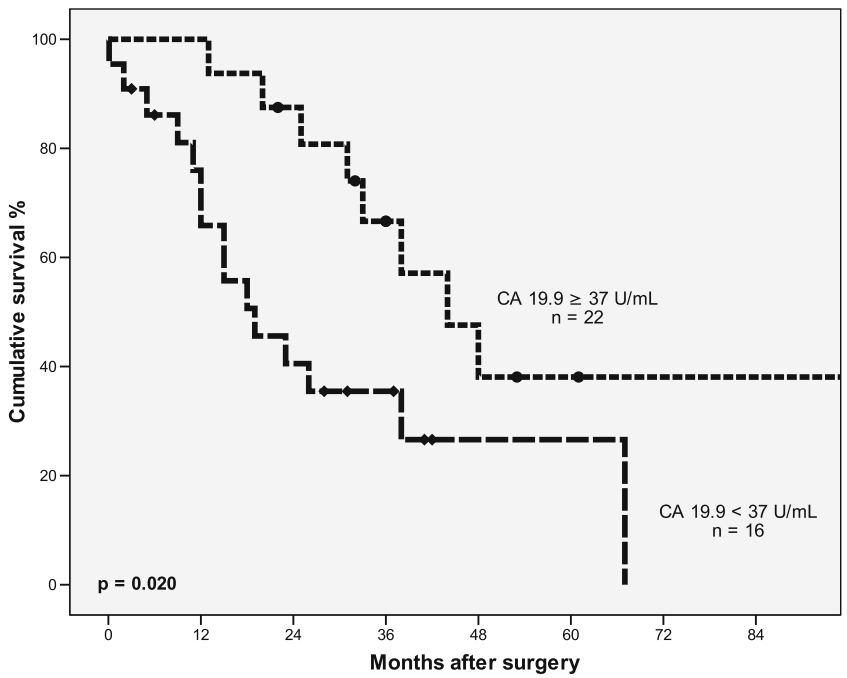

Figure 3 Overall survival after hepatic resection of IHC, stratified by CA 19.9 (p=0.002).

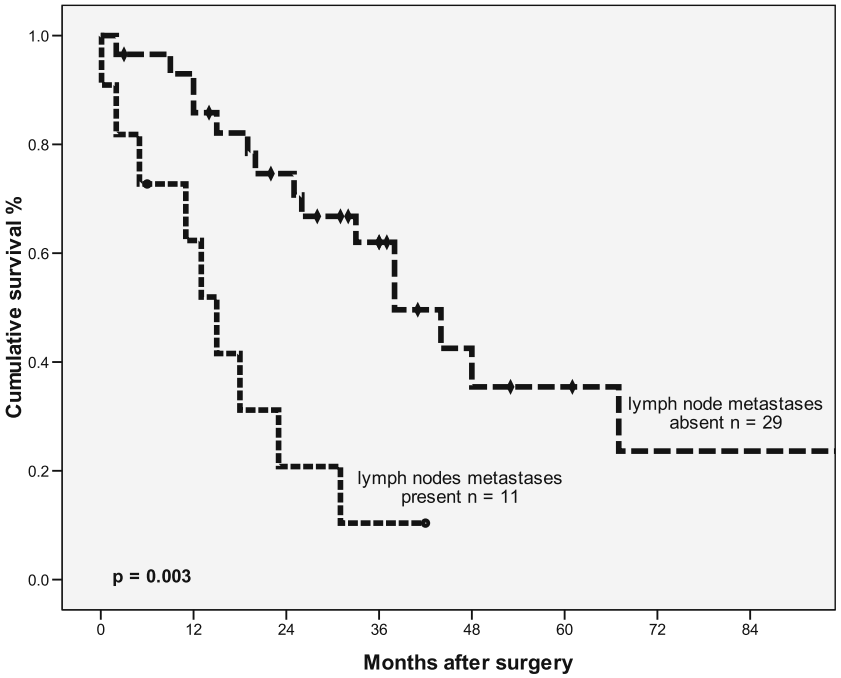

Figure 4 Overall survival after hepatic resection of IHC, stratified by lymph node metastases (p=0.003).

been routinely performed at our institution and the majority of other high-volume institutions but may represent a potential avenue to improve selection and outcomes in the future. Owing to the propensity for an intra-abdominal pattern of recurrence, repeat resection may be a feasible option in highly selected patients to prolong survival. Two of our patients in this current series were subjected to repeat resections. Saiura et al. reported in their institutional experience of five cases of repeat resections of the liver in four cases and lung in one case, achieving a median survival ranging from 33 to 137 months. This demonstrates that repeat resection may improve overall survival.[17] Other oncological therapies employed in treatment of recurrence include chemotherapy and radioembolization, both of which are largely considered palliative therapies.

In the analysis of prognostic factors, a CA 19.9>37 U/ml and CEA>5 μg/L and poorly differentiated tumors, which are surrogate markers of tumor aggressiveness, were identified to

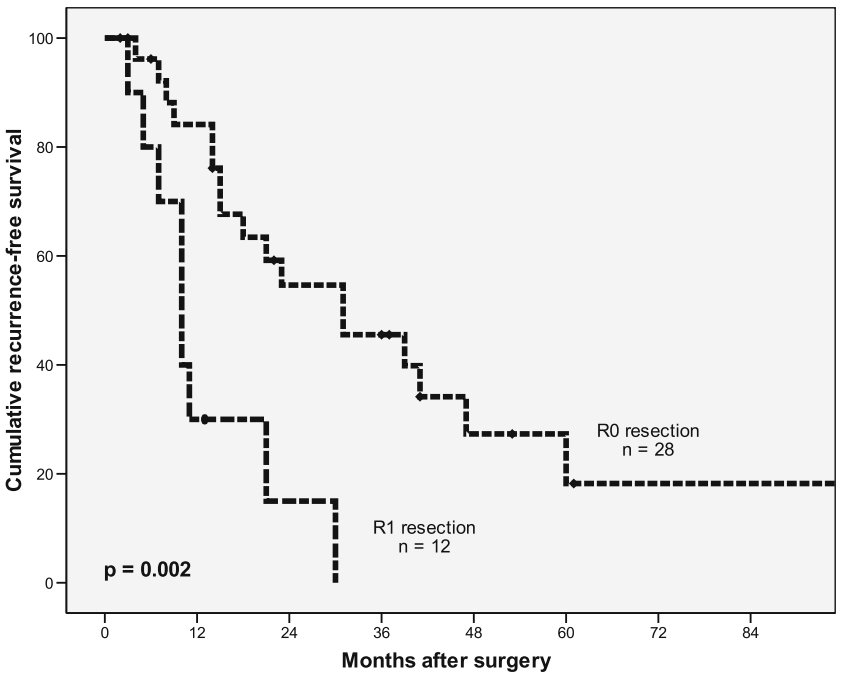

Figure 5 Recurrence-free survival after hepatic resection of IHC, stratified by pathologic margin status (p=0.002).

be associated with a poorer overall survival. Further, CA 19.9> 37 U/ml and CEA>5 μg/L were associated with early disease recurrence. Clinical stage III, presence of satellite tumors and lymph node metastases, and TNM classification (predicts for overall survival only), as indicators of extent of disease, all predicted for an early recurrence and overall survival. In this aggressive disease, unlike colorectal liver metastases, where R0 and R1 resections have not been shown to result in increased recurrence rates but similar overall survival outcome,[18] R1 resections in IHC were associated with early recurrence and resulted in a poorer overall survival. When these factors were subjected to a multivariate analysis to control for interdependent factors, CA 19.9 was associated with both recurrence and overall survival. Resection margin status predicted for recurrence; clinical stage, lymph node metastases, and histological grade predicted for overall survival.

IHC has a propensity to spread via the lymphatic system.[19] Lymph node metastasis drain first to lymph nodes along the hepatic pedicle before disseminating distally to the central abdominal lymph node primarily along the celiac axis. The association of lymph node metastases with a poor outcome even after lymphadenectomy has been extensively reported. Uenishi et al. reviewed their experience of 133 patients who underwent hepatic resection for IHC, reported 13 patients with lymph node metastases present within the hepatoduodenal ligament, and compared their outcomes to 34 patients with positive nodes present along the common hepatic artery, celiac artery, left gastric artery, or posterior surface of the pancreatic head, and paraaortic lymph nodes showed a 5-year survival of 14% and 12%, respectively (p=0.404), demonstrating no significant impact of distant lymph node metastasis.[20] Choi et al. found that lymph node metastases were associated with various histopathological features including poor or undifferentiated tumors, vascular invasion, and perineural invasion, indicating that lymph node metastases tend to be found in tumors that are biologically more aggressive.[21] Tamandl et al. corroborated the association of lymph node ratio with tumors with aggressive features of lymphatic vessel invasion and satellite metastases.[22] The authors also showed that the number of lymph node retrieved from lymphadenectomy specimen did not improve overall or recurrence-free survival, demonstrating an association between the number of positive lymph nodes with poor survival and early recurrence.[22] In these series, patients with positive lymph node who underwent lymphadenectomy had a median survival ranging between 15 and 26 months.[21–23] This parallels the survival figure in our study where patients with lymph node metastases survived a median of 15 months. The dismal outcomes in this subgroup of patients have been a subject of controversy on whether resection is truly beneficial.[24] Unfortunately, an effective comparison of published series and, therefore, the impact of various prognostic factors are also limited by the retrospective nature of most studies. This is likely to introduce bias, which limits the applicability of the findings in a true clinical setting. In light of this, the retrospective nature of the current analyses may limit its utility in a true clinical setting.

To date, there has been little emphasis on the role of adjuvant therapy after resection of IHC. In view of the high rates of R1 resections, negative impact of lymph node metastases, the inherently aggressive nature of this tumor, and the high likelihood of recurrence, adjuvant therapy in patients with resected tumors may potentially improve survival outcome. In the analysis of the SEER database, Shinohara et al. analyzed subgroups of patients who underwent surgery alone or surgery with adjuvant radiation therapy and median survival of 6 and 11 months, respectively (p=0.014), hence suggesting that adjuvant radiotherapy prolongs survival.[25] The current progress and availability of liver-specific regional therapy, for example, transarterial chemoembolization, yttrium-90 microspheres, isolated hepatic perfusion, and hepatic artery infusion, may all be modalities that are potentially useful in the adjuvant setting after resection.

In summary, IHC is a disease characterised by a poor prognosis even after treatment. Evaluation and undertaking of hepatic resection, even in the context of microscopically positive margins, should be pursued given that nonsurgical therapies have not proven effective in providing a sustainable disease control. Continuous research must ensue so as to improve our knowledge of this disease such that when faced with this disease during the current time of its rising incidence, an appropriate and patient-tailored management strategy may be employed.

References

1. Olnes MJ, Erlich R. A review and update on cholangiocarcinoma. Oncology 2004;66:167–179.
2. Shaib Y, El-Serag HB. The epidemiology of cholangiocarcinoma. Semin Liver Dis 2004;24(2):115–125.
3. McGlynn KA, Tarone RE, El-Serag HB. A comparison of trends in the incidence of hepatocellular carcinoma and intrahepatic cholangiocarcinoma in the United States. Cancer Epidemiol Biomarkers Prev 2006;15(6):1198–1203.
4. Saxena A, Bester L, Chua TC, et al. Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: a preliminary assessment of this novel treatment option. Ann Surg Oncol 2010; Epub.
5. Kopek N, Holt MI, Hansen AT, Hoyer M. Stereotactic body radiotherapy for unresectable cholangiocarcinoma. Radiother Oncol 2010;Epub.
6. Jang JS, Lim HY, Hwang IG, et al. Gemcitabine and oxaliplatin in patients with unresectable biliary cancer including gall bladder

cancer: a Korean Cancer Study Group phase II trial. Cancer Chemother Pharmacol 2010;65(4):641–647.
7. Jin Hyoung K, Hyun-Ki Y, Kyu-Bo S, et al. Transcatheter arterial chemoembolization or chemoinfusion for unresectable intrahepatic cholangiocarcinoma. Cancer 2008;113(7):1614–1622.
8. Lang H, Sotiropoulos GC, Sgourakis G, et al. Operations for intrahepatic cholangiocarcinoma: single-institution experience of 158 patients. J Am Coll Surg 2009;208(2):218–228.
9. Lang H, Sotiropoulos GC, Fruhauf Nr, et al. Extended hepatectomy for intrahepatic cholangiocellular carcinoma (ICC) When is it worthwhile? Single center experience with 27 resections in 50 patients over a 5-year period. Ann Surg 2005;241:134–143.
10. Shen WF, Zhong W, Xu F, et al. Clinicopathological and prognostic analysis of 429 patients with intrahepatic cholangiocarcinoma. World J Gastroenterol 2009;15(47):5976–5982.
11. Zhou XD, Tang ZY, Fan J, et al. Intrahepatic cholangiocarcinoma: report of 272 patients compared with 5,829 patients with hepatocellular carcinoma. J Cancer Res Clin Oncol 2009;135:1073–1080.
12. Yedibela S, Demir R, Zhang W, et al. Surgical treatment of mass-forming intrahepatic cholangiocarcinoma: an 11-year Western single-center experience in 107 patients. Ann Surg Oncol 2009;16(2):404–412.
13. Japan LCSGo. 2003.
14. Sobin LH, Wittekind CH. TNM classification of malignant tumours, 6th ed. West Sussex: John Wiley & Sons, 2002.
15. Kavolius J, Fong Y, Blumgart LH. Surgical resection of metastatic liver tumors. Surg Oncol Clin N Am 1996;5 (2):337–352.
16. Nakagohri T, Kinoshita T, Konishi M, et al. Surgical outcome and prognostic factors in intrahepatic cholangiocarcinoma. World J Surg 2008;32:2675–2680.
17. Saiura A, Yamamoto J, Kokudo N, et al. Intrahepatic cholangiocarcinoma: analysis of 44 consecutive resected cases including 5 cases with repeat resections. Am J Surg 2010;Epub.
18. de Haas RJ, Wicherts DA, Flores E, et al. R1 resection by necessity for colorectal liver metastases: is it still a contraindication to surgery? Ann Surg 2008;248(4):626–637.
19. Yoshihiro N, Masayuki Y, Iwao I, et al. Reconsideration of the lymph node metastasis pattern (N factor) from intrahepatic cholangiocarcinoma using the International Union Against Cancer TNM staging system for primary liver carcinoma. Cancer 1998;83 (9):1923–1929.
20. Uenishi T, Kubo S, Yamazaki O, et al. Indications for surgical treatment of intrahepatic cholangiocarcinoma with lymph node metastases. J Hepatobiliary Pancreat Surg 2008;15(4):417–422.
21. Choi SB, Kim KS, Choi JY, et al. The prognosis and survival outcome of intrahepatic cholangiocarcinoma following surgical resection: association of lymph node metastasis and lymph node dissection with survival. Ann Surg Oncol 2009;16:3048–3056.
22. Tamandl D, Kaczirek K, Gruenberger B, et al. Lymph node ratio after curative surgery for intrahepatic cholangiocarcinoma. Br J Surg 2009;96:919–925.
23. Uenishi T, Kubo S, Yamazaki O, et al. Indications for surgical treatment of intrahepatic cholangiocarcinoma with lymph node metastases. J Hepatobiliary Pancreat Surg 2008;15:417–422.
24. Manousos MK, Sasan R, Ilias PG, et al. Fifteen-year, single-center experience with the surgical management of intrahepatic cholangiocarcinoma: operative results and long-term outcome. Surgery 2008;143(3):366–374.
25. Eric TS, Nandita M, Mengye G, James MM. Radiation therapy is associated with improved survival in the adjuvant and definitive treatment of intrahepatic cholangiocarcinoma. Int J Radiat Oncol Biol Phys 2008;72(5):1495–1501.

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ORIGINAL ARTICLE

Incidence of Benign Disease in Patients that Underwent Resection for Presumed Pancreatic Cancer Diagnosed by Endoscopic Ultrasonography (EUS) and Fine-Needle Aspiration (FNA)

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Abstract
Introduction The lack of accurate markers makes preoperative differentiation between pancreatic cancer and non-malignant head lesions clinically challenging. In this study, we investigated the incidence of benign disease in patients that underwent resection for presumed pancreatic cancer diagnosed by EUS and EUS-guided FNA.
Methods Medical records of consecutive patients who underwent pancreaticoduodenectomy at Duke University were reviewed. Demographics, clinicopathologic characteristics, preoperative imaging, EUS, EUS-guided FNA, and postoperative outcomes were analyzed.
Results Seven percent of the total 494 patients studied were found to have benign disease on postoperative pathology. Fifty-nine percent of these patients with benign disease underwent preoperative EUS. EUS was positive for a head mass in 70%, demonstrated enlarged lymph nodes in 27%, and showed signs concerning for vascular invasion in 13%. FNA was suspicious or indeterminate for cancer in 63% of patients. Postoperative complications occurred in 47% and one patient died after surgery. The overall pancreatic leak rate was 15%.
Conclusions Even with aggressive use of preoperative evaluation, there is still a small subset of patients where malignancy cannot be excluded without pancreaticoduodenectomy.

Keywords Pancreas · Cancer · Endoscopic ultrasonography · Pancreaticoduodenectomy

Surgical resection provides the best chances for survival in patients diagnosed with pancreatic malignancies. The American Cancer Society estimates that 37,680 patients were diagnosed with cancer of the pancreas during 2008 in the USA[1] and pancreatic cancer is the eighth cause of cancer-related death worldwide. Unfortunately, most patients are deemed unresectable at the time of presentation, and even in those patients that undergo margin-negative resection, the prognosis continuous to be grim.

Over the last several years, data have shown that pancreaticoduodenectomies can be performed safely in large-volume institutions.[2] Imaging testing has improved enormously the accuracy of the preoperative diagnosis but most diagnostic methods are useful once the tumor is large enough to cause symptoms, which in many instances is indicative of advanced stage and unresectability. In addition, the lack of reliable tumor markers makes the diagnosis of pancreatic cancer challenging. In patients presenting with a head mass and with superimposed chronic pancreatitis, recent episode of acute pancreatitis, or anatomic pancreatic variances, the diagnosis of cancer is even more difficult.[3] For these reasons, in those patients in which a pancreatic head mass is identified and the diagnosis of cancer is uncertain, resection is often recommended.

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The purpose of this study was to evaluate the incidence of benign disease in patients that underwent pancreaticoduodenectomy at a high-volume institution for presumed pancreatic cancer. All patients included in this analysis underwent standard preoperative evaluation including tumor markers, CT scanning, endoscopic ultrasonography (EUS), and EUS-guided fine-needle aspiration (FNA). Patients included in this analysis had findings on preoperative testing worrisome for malignancy, such as a pancreatic head mass on imaging or EUS, elevated biomarkers, or cytology indeterminate or worrisome for cancer. Patients previously diagnosed with lymphoplasmocytic sclerosing pancreatitis were excluded from the study.

Methods

The Institutional Review Board at Duke University Medical Center approved all aspects of this research. Electronic medical records of patients that underwent pancreaticoduodenectomy at Duke University Medical Center from 1992 to 2007 were reviewed in a retrospective fashion. Basic demographics such as age, gender, and race were recorded. The most common presenting symptom was also documented. Patients presenting with signs and symptoms concerning for pancreatic malignancy at our institution routinely undergo a complete preoperative work-up including basic laboratory tests, CA19-9, CEA, a CT dual-phase pancreatic protocol scan, ERCP with brushing, EUS, and EUS-guided FNA.

All specimens including cytology, brushing and final operative specimen pathology were analyzed by the Pathology Department using standard techniques. The FNA report was divided in four categories for analysis purposes: (1) benign, (2) indeterminate, (3) suspicious for malignancy, or (4) malignant. Postoperative pathology report included: diagnosis, type and grade of cancer if present, total number and positive lymph nodes if present, and margin status.

All EUS and EUS-guided FNAs were performed by the Gastroenterology Service. Postoperative 30-day mortality was recorded. Postoperative complications were defined as all complications noted during the patient's hospitalization as well as late complications on routine clinic visits. Pancreatic leak rate refers to increased drain amylase levels (i.e., drain amylase levels threefold above the serum levels as previously published by our group).[4] Amylase levels were measured based on clinical suspicion for leak (e.g., increased in volume output, changes in consistency, color, etc.) or when the patient was started on regular diet. Follow-up refers to the period in months between the operation and the last time the patient was seen at our clinics. All surgeries were performed and supervised by the senior authors of this paper (B.M.C, D.S.T, and T.N.P). Analysis of the data was done using Microsoft Excel 2007 Descriptive Analysis tool when indicated. Age and follow-up are indicated as means.

Results

A total of 494 patients underwent a pancreaticoduodenectomy during the study period. All of these patients were presumed to have a malignant process in the head of the pancreas by preoperative testing. Patients with no suspicious of cancer and known history of chronic pancreatitis were excluded from the analysis. As mentioned above, patients with known history of lymphoplasmocytic sclerosing pancreatitis were excluded from the study as these patients commonly present with pancreatic head masses that mimic cancer.

Of the total number of patients that underwent resection, 37 (7.4%) subjects were found to have benign disease with no evidence of cancer on the final pathology examination. All of the pathology specimens showed various degrees of pancreatitis with no evidence of malignancy. One patient was found to have a benign cystoadenoma with superimposed pancreatitis.

The majority of the patients in the group of benign postoperative pathology were white males with a mean age of 53 years. No patient had a preoperative diagnosis of chronic pancreatitis. The most common presenting symptom in this population was obstructive jaundice, but 35% of them had multiple other symptoms such as abdominal pain, weight loss, decreased appetite, etc. (Fig. 1). Forty-four percent of these patients admitted use of tobacco and alcohol, and only one patient acknowledged drug abuse.

Fifty-nine percent of the patients with benign disease (n= 22) underwent preoperative EUS. EUS results are illustrated in Table 1. When preoperative cytology was analyzed, FNA

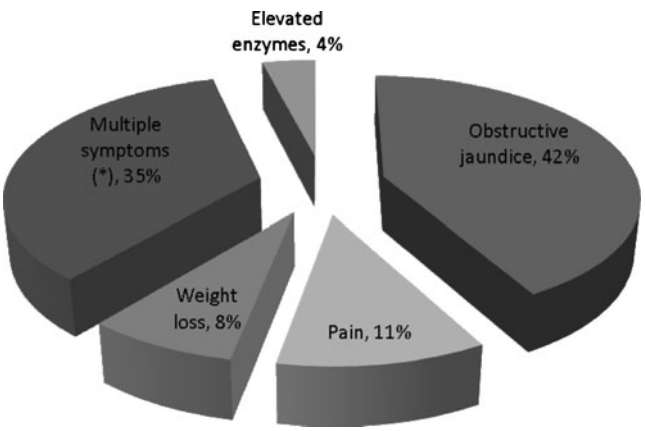

Figure 1 Presenting symptoms in patients with benign disease. (*) multiple symptoms included nausea, vomiting, abdominal pain, intolerance to oral intake, weight loss, decreased appetite, etc.

Table 1 EUS Findings in Patients with Postoperative Benign Disease

	Positive findings	Negative findings	Percentage
Head mass	16	6	70[a]
Enlarged lymph nodes	6	16	27
Vascular involvement	3	19	13

Vascular compromise refers to loss of acoustic plane between the mass and superior mesenteric vein, portal vein, or irregularities of the venous walls

[a] Of note, some patients with a head mass were also found to have enlarged lymph nodes

was suspicious or indeterminate for cancer in 63% of patients (benign [n=8], malignant [n=0], suspicious [n=12], indeterminate [n=2]).

The median follow-up was 10 months (range 3−240 months). Early and delayed (i.e., beyond 30 days) postoperative complications occurred in 47% of these patients. These included nausea and vomiting, tachycardia, postoperative bleeding, ileus, wound infections, hernias, etc. The overall pancreatic leak was 15%. One patient died postoperatively from gastrointestinal bleeding from the gastrojejunostomy stapled line.

Discussion

This study shows that despite the use of aggressive preoperative work-up for pancreatic cancer, up to 7% of patients that undergo resection will have benign disease on postoperative pathologic examination. All of these patients had findings concerning for malignancy on both CT scanning and endosonography preoperatively. Despite the increasing use of these diagnostic tools in patients with pancreatic conditions, there is still a small subset of patients where malignancy cannot be excluded without pancreaticoduodenectomy.

The introduction of endoscopic procedures such as endosonography and EUS-guided FNA has improved the overall sensitivity and specificity of the diagnosis and staging of pancreatic cancer. The benefits of EUS became apparent soon after its introduction in the mid 1980s.[5,6] EUS allows staging of patients with an accuracy that ranges between 80% and 85%.[7–10] Even though there is evidence that this degree of accuracy depends greatly on the experience of the endosonographer,[7] lesions that are difficult to be diagnosed with traditional cross-imaging techniques such as CT and MRI are easily seen on EUS.[11] EUS also expands the ability of diagnosing vascular invasion. Well-defined criteria such as irregular venous wall, loss of acoustic interface, and proximity of the mass to the portal vein, has been established to evaluate for vascular involvement. In a prospective study comparing EUS to angiography to evaluate for vascular invasion of the portal system, Brugge and colleagues showed that EUS allowed determination of surgical resection in 78% of patients compared to 60% accuracy when angiography was used alone.[12]

These widely recognized benefits of EUS and EUS-guided FNA are less evident in patients with malignancy and underlying chronic pancreatitis. The presence of chronic pancreatitis has been associated with increased rates of missed diagnoses and need for additional diagnostic modalities.[13–17] Sensitivity and accuracy of EUS-FNA for the diagnosis of cancer in chronic pancreatitis patients drops to approximately 50% and 73%, respectively.[18,19] One approach to this problem is the use of endoscopic elastography to measure tissue stiffness.[20] This technique used in many other organs, has proven to be innacurate in patients with chronic pancreatitis and cancer.[21] The introduction of digital analysis of EUS-obtained images may allow in the future better characterization of patients presenting with the diagnosis dilemma of chronic pancreatitis or cancer.[22]

The presence of lymphoplasmocytic sclerosing pancreatitis makes the diagnosis of cancer even more challenging since this form of pancreatitis frequently presents as a defined mass. Lymphoplasmocytic sclerosing pancreatitis is the pancreatic manifestation of a systemic condition (IgG4-related disease with increased antibodies such as rheumatoid factor, lactoferrin antibodies, carbonic anhydrase II, etc.) in which affected organs demonstrate dense lymphoplasmacytic infiltration with abundant IgG4-positive cells.[23] Certain enhancing patterns have been shown on dual-phase CT scanning to be dissimilar between autoimmune pancreatitis and pancreatic cancer.[24,25] The role of EUS in diagnosing lymphoplasmocytic sclerosing pancreatitis continues to be defined. [26]

Although atypical cytology may support the clinical suspicion of malignancy, it is usually not sufficient to subject patients to resection. Isolated case reports and small case series have been reported of patients undergoing pancreaticoduodenectomy for presumed pancreatic cancer who were found postopearatively to have benign disease.[27–30] Two larger series report an incidence of 5–11% of benign disease in patients operated on for presumed pancreatic cancer. In 1994, Smith and colleagues reported 603 consecutive patients who underwent pancreaticoduodenectomy at the Mayo Clinic during a 35-year period; approximately 5% of these patients were found to have a benign condition of postoperative pathologic examination.[31] In an attempt to identify hystopathologic variables that would allow recognition of benign disease preoperatively, Abraham et al. published a series of 47 patients with benign disease that underwent resection.[32] In this study, the most common benign condition found was lymphoplasmacytic sclerosing

pancreatitis followed by alcohol-associated chronic pancreatitis, and gallstone-associated pancreatitis. It is unclear from these studies how many of these patients first presented with a pancreatic head mass or radiologic findings consistent only with chronic pancreatitis. None of the patients in our study had pre- or postoperative findings consistent with lymphoplasmocytic sclerosing pancreatitis. Our study is unique in that the majority of our patients had a preoperative EUS and EUS-guided FNA as part of their preoperative work-up.

To conclude, extensive data supports that margin-negative resection offers the best chance for survival in patients with pancreatic cancer. Pancreaticoduodenectomy can be offered to patients with low mortality rates and acceptable morbidity in high-volume institutions. For these reasons, patients presenting with clinical and radiologic findings concerning for cancer should undergo resection until more reliable diagnostic techniques become available.

References

1. American Cancer Society. Cancer Facts and Figures 2008. Atlanta: American Cancer Society, 2008.
2. Sohn TA, Yeo CJ, Cameron JL, Koniaris L, Kaushal S, Abrams RA, Sauter PK, Coleman J, Hruban RH, Lillemoe KD. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. J Gastrointest Surg 2000;4:567–579.
3. Bhutani MS. Endoscopic ultrasonography. Endoscopy 2000;32: 853–862.
4. Cheng TY, Sheth K, White RR, Ueno T, Hung CF, Clary BM, Pappas TN, Tyler DS. Effect of neoadjuvant chemoradiation on operative mortality and morbidity for pancreaticoduodenectomy. Ann Surg Oncol 2006;13: 66–74.
5. Yasuda K, Mukai H, Fujimoto S, Nakajima M, Kawai K. The diagnosis of pancreatic cancer by endoscopic ultrasonography. Gastrointest Endosc 1988;34:1–8.
6. Rösch T, Lorenz R, Braig C, Feuerbach S, Siewert JR, Schusdziarra V, Classen M. Endoscopic ultrasound in pancreatic tumor diagnosis. Gastrointest Endosc 1991;37:347–352.
7. Gress FG, Hawes RH, Savides TJ, Ikenberry SO, Cummings O, Kopecky K, Sherman S, Wiersema M, Lehman GA. Role of EUS in the preoperative staging of pancreatic cancer: a large single-center experience. Gastrointest Endosc 1999;50:786–791.
8. Harewood GC, Wiersema LM, Halling AC, Keeney GL, Salamao DR, Wiersema MJ. Influence of EUS training and pathology interpretation on accuracy of EUS-guided fine needle aspiration of pancreatic masses. Gastrointest Endosc 2002;55:669–673.
9. Rösch T. Staging of pancreatic cancer. Analysis of literature results. Gastrointest Endosc Clin N Am 1995;5:735–739.
10. Tio TL, Sie LH, Kallimanis G, Luiken GJ, Kimmings AN, Huibregtse K, Tytgat GN. Staging of ampullary and pancreatic carcinoma: comparison between endosonography and surgery. Gastrointest Endosc 1996;44:706–713.
11. Dewitt J, Devereaux BM, Lehman GA, Sherman S, Imperiale TF. Comparison of endoscopic ultrasound and computed tomography for the preoperative evaluation of pancreatic cancer: a systematic review. Clin Gastroenterol Hepatol 2006;4:717–725.
12. Brugge WR, Lee MJ, Kelsey PB, Schapiro RH, Warshaw AL. The use of EUS to diagnose malignant portal venous system invasion by pancreatic cancer. Gastrointest Endosc 1996;43:561–567.
13. Vilmann P, Jacobsen GK, Henriksen FW, Hancke S. Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreatic disease. Gastrointest Endosc 1992;38:172–173.
14. Müller MF, Meyenberger C, Bertschinger P, Schaer R, Marincek B. Pancreatic tumors: evaluation with endoscopic US, CT, and MR imaging. Radiology 1994;190(3):745–751.
15. Bhutani MS. Endoscopic ultrasonography in pancreatic disease. Semin Gastrointest Dis 1998;9:51–60.
16. Bhutani MS, Hawes RH, Baron PL, Sanders-Cliette A, van Velse A, Osborne JF, Hoffman BJ. Endoscopic ultrasound guided fine needle aspiration of malignant pancreatic lesions. Endoscopy 1997;29:854–858
17. Erickson RA, Sayage-Rabie L, Beissner RS. Factors predicting the number of EUS-guided fine-needle passes for diagnosis of pancreatic malignancies. Gastrointest Endosc 2000;51:184–190
18. Iordache S, Saftoiu A, Cazacu S, Gheonea DI, Dumitrescu D, Popescu C, Ciurea T. Endoscopic ultrasound approach of pancreatic cancer in chronic pancreatitis patients in a tertiary referral centre. Clin Gastroenterol Hepatol 2006;4:717–725.
19. Varadarajulu S, Tamhane A, Eloubeidi MA. Yield of EUS-guided FNA of pancreatic masses in the presence or the absence of chronic pancreatitis, Gastrointest Endosc 2005;62:728–736.
20. Micames CG, Gress FG. EUS elastography: a step ahead? Gastrointest Endosc 2007;65:979–981.
21. Janssen J, Schlörer E, Greiner L. EUS elastography of the pancreas: feasibility and pattern description of the normal pancreas, chronic pancreatitis, and focal pancreatic lesions. Gastrointest Endosc 2007;65:971–978.
22. Bhutani MS. Digital analysis of EUS images: "promising" method, but is it ready for "prime time"? Gastrointest Endosc 2008;67:868–870.
23. Zandieh I, Byrne MF. Autoimmune pancreatitis: a review. World J Gastroenterol 2007;21(47):6327–6332.
24. Takahashi N, Fletcher JG, Hough DM, Fidler JL, Kawashima A, Mandrekar JN, Chari ST. Autoimmune pancreatitis: differentiation from pancreatic carcinoma and normal pancreas on the basis of enhancement characteristics at dual-phase CT. AJR Am J Roentgenol 2009;193:479–484.
25. Chang WI, Kim BJ, Lee JK, Kang P, Lee KH, Lee KT, Rhee JC, Jang KT, Choi SH, Choi DW, Choi DI, Lim JH. The clinical and radiological characteristics of focal mass-forming autoimmune pancreatitis: comparison with chronic pancreatitis and pancreatic cancer. Pancreas 2009;38:401–408.
26. Hoki N, Mizuno N, Sawaki A, Tajika M, Takayama R, Shimizu Y, Bhatia V, Yamao K. Diagnosis of autoimmune pancreatitis using endoscopic ultrasonography. J Gastroenterol 2009;44:154–159.
27. Barthet M, Hastier P, Buckley MJ, Bernard JP, Sastre B, Baroni JL, Salducci J, Delmont J. Eosinophilic pancreatitis mimicking pancreatic neoplasia: EUS and ERCP findings—is nonsurgical diagnosis possible? Pancreas 1998;17:419–422.
28. Bastid C, Sahel J, Choux R, Payan MJ, Sarles H. Eosinophilic pancreatitis: report of a case. Pancreas 1990;5:104–107.
29. Kawaguchi K, Koike M, Tsuruta K. Okamoto A, Tabata I, Fujita N.. Lymphoplasmacyticsclerosing pancreatitis with cholangitis: a variant of primary sclerosing cholangitis extensively involving pancreas. Hum Pathol 1991;22:387–395
30. Scully KA, Li SC, Hebert JC, Trainer TD. The characteristic appearance of nonalcoholic duct destructive chronic pancreatitis: a report of 2 cases. Arch Pathol Lab Med 2000;124:1535–1538.
31. Smith CD, Behrns KE, van Heerden JA, Sarr MG. Radical pancreatoduodenectomy for misdiagnosed pancreatic mass. Br J Surg 1994;81:585–589.
32. Abraham SC, Wilentz RE, Yeo CJ, Sohn TA, Cameron JL, Boitnott JK, Hruban RH. Pancreaticoduodenectomy (Whipple resections) in patients without malignancy: are they all 'chronic pancreatitis'? Am J Surg Pathol 2003;27:110–120.

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ORIGINAL ARTICLE

Impact of Obesity on Perioperative Outcomes and Survival Following Pancreaticoduodenectomy for Pancreatic Cancer: A Large Single-Institution Study

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Abstract
Background To examine the effect of body mass index (BMI) on clinicopathologic factors and long-term survival in patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma.
Methods Data on BMI, weight loss, operative details, surgical pathology, and long-term survival were collected on 795 patients who underwent pancreaticoduodenectomy. Patients were categorized as obese (BMI>30 kg/m^2), overweight (BMI 25 to <30 kg/m^2), or normal weight (BMI<25 kg/m^2) and compared using univariate and multivariate analyses.
Results At the time of surgery, 14% of patients were obese, 33% overweight, and 53% normal weight. Overall, 32% of patients had preoperative weight loss of >10%. There were no differences in operative times among the groups; however, higher BMI was associated with increased risk of blood loss (P<0.001) and pancreatic fistula (P=0.01). On pathologic analysis, BMI was not associated with tumor stage or number of lymph nodes harvested (both P>0.05). Higher BMI patients had a lower incidence of a positive retroperitoneal/uncinate margin versus normal weight patients (P=0.03). Perioperative morbidity and mortality were similar among the groups. Obese and overweight patients had better 5-year survival (22% and 22%, respectively) versus normal weight patients (15%; P=0.02). After adjusting for other prognostic factors, as well as preoperative weight loss, higher BMI remained independently associated with improved cancer-specific survival (overweight: hazard ratio, 0.68; obese: hazard ratio, 0.72; both P<0.05).
Conclusion Obese patients had similar tumor-specific characteristics, as well as perioperative outcomes, compared with normal weight patients. However, obese patients undergoing pancreaticoduodenectomy for pancreatic cancer had an improved long-term survival independent of known clinicopathologic factors.

Keywords Pancreaticoduodenectomy · Obesity · Pancreatic adenocarcinoma · Outcomes

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Introduction

The prevalence of obesity in the United States has increased over the last quarter century in all age groups.[1] In 2005, over 72 million adults in the United States were obese, accounting for up to one third of the adult population. As a greater portion of the population struggles with obesity, the management of associated comorbidities places a strain on the health care system and has been considered a national health care crisis.[2] Obesity increases the risk for many diseases including coronary artery disease and diabetes. In fact, obese individuals have a reduced overall life expectancy, with a twofold to threefold increased risk of death from all causes.[3] Obesity has also been linked to a higher risk of death from esophageal, colorectal, liver, gallbladder,

and pancreas cancer.[4] The association with obesity and pancreatic cancer has been reported in multiple epidemiologic studies.[4–8] In one cohort study of over 150,000 adults, a body mass index (BMI) of 30 kg/m^2 or higher was associated with a 72% increased risk of pancreatic cancer.[7] Given that the incidence of obesity is increasing, and that obese patients appear to have a higher risk of pancreatic cancer, data on perioperative outcomes of obese patients undergoing pancreatic surgery are important.

Obese cancer patients have often been perceived to be at high risk for surgical complications. Several studies have noted that obesity is strongly associated with increased risk of postoperative wound infection.[9–11] There are minimal data, however, that have supported an overall increased risk in morbidity or mortality for obese patients undergoing major intra-abdominal surgery.[9–11] Data from the National Surgical Quality Improvement Program (NSQIP) demonstrated a modest increase in 30-day morbidity rates following intra-abdominal surgery with increasing BMI; however, this finding was not statistically significant.[11] Data from the same study revealed no increased risk of perioperative mortality associated with increasing BMI.[11] The effect of obesity on oncologic surgical procedures has been examined to a more limited extent. While some authors have reported a lower lymph node yield in obese patients undergoing surgery for gastric or rectal cancer,[12,13] other studies have failed to corroborate these findings.[14,15] Currently, there has been only one report examining the association between obesity and cancer-related outcomes following pancreatectomy.[16] In this study, the authors reported no association between obesity and the rate of R1 (microscopically positive) resections or number of lymph nodes harvested. The authors did note an increased risk of lymph node metastasis and subsequent disease-specific death in obese patients.[16] This study, however, had several limitations including a small sample size of obese patients (e.g. BMI>30 kg/m^2, n=61). Given the limited existing data, as well as the importance of understanding perioperative outcomes of pancreatic surgery in obese patients, the objective of the current study was to examine the impact of obesity on cancer-related outcomes, including survival, in patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma. In addition, we sought to examine more rigorously the association of BMI with tumor-specific clinicopathologic factors, as well as perioperative outcomes in a large single-institution cohort of patients.

Methods

Between December 1995 and December 2005, 795 out of 1,116 patients who underwent a pancreaticoduodenectomy for a diagnosis of pancreatic adenocarcinoma and who had available information on BMI were identified from the Johns Hopkins Pancreatic Cancer Database. The study was approved by the institutional review board. Only patients who underwent a pancreaticoduodenectomy for a pathologically confirmed adenocarcinoma and who had data available on BMI at the time of surgery were included in the study. BMI was calculated as the weight in kilograms (kg) divided by the height in meters squared (m^2). For the purpose of analyses, patients were divided into three categories based on BMI: normal weight (BMI<25 kg/m^2), overweight (BMI≥25 kg/m^2 and <30 kg/m^2), or obese (≥30 kg/m^2). This BMI classification system is endorsed by the World Health Organization and the National Institutes of Health and is the most widely accepted means of stratifying individuals based on weight.[17] In order to assess the relative contribution of weight loss on outcomes, self-reported preoperative weight loss was also recorded.

In addition to data on weight, the following data were collected: demographics, tumor location, and size; total number of lymph nodes harvested and total number of metastatic lymph nodes; pathologic margin status; presence of lymphovascular invasion and perineural invasion; and tumor-node-metastasis (TMN) staging according to the American Joint Committee on Cancer staging system.[18] Operative details including operative time and blood loss, as well as perioperative complications/morbidity and 30-day perioperative mortality were also collected. Data on the incidence of postoperative fistula, as previously defined,[19] were collected. Date and status at last follow-up and, when applicable, date of death were also recorded. Long-term survival status (alive vs. dead) was determined by review of the medical records as well as through use of the US social security death index.

Summary statistics were reported using mean or median values where appropriate. Student's t test was used for mean comparison of continuous variables, while Fisher's exact tests were used to compare frequencies of categorical variables between groups. Long-term survival was estimated using the nonparametric product limit method (Kaplan and Meier). Differences in survival were examined using the log-rank test. Cox proportional hazard models were used to estimate long-term risk of death while accounting for other competing risk factors.[14] All statistical analyses were performed using SPSS version 11.5 (SPSS inc, Chicago, IL).

Results

Clinical Characteristics

Table 1 shows the clinical characteristics of the 795 patients in the study. Most patients had a normal weight (n=428;

Table 1 Comparison of Clinicopathologic Features of Patients Undergoing Pancreaticoduodenectomy for Pancreatic Adenocarcinoma Based on Weight

	No. (%)			*P*-value
	Normal (n=428)	Overweight (n=261)	Obese (106)	
Baseline Characteristics				
Age (median, y)	66.9	65.5	64.5	0.008
Female	199 (46.5)	110 (42.1)	57 (53.8)	0.10
White	374 (87.4)	235 (90.0)	92 (86.6)	0.05
Any weight loss (n=744)	236 (58.9)	126 (51.2)	47 (48.5)	0.03
Pathologic Characteristics				
Tumor Size (median, cm)	3 (2.3–3.5)	3 (2.0–3.5)	3 (2.5–4.0)	0.05
Stage				0.34
I	15 (4.6)	12 (5.7)	1 (1.1)	
II	300 (92.0)	191 (91.4)	90 (98.9)	
III–IV	11(3.3)	6 (2.9)	0 (0)	
Tumor Differentiation				0.43
Well	16 (3.9)	4 (1.6)	3 (2.9)	
Moderate	218 (53.4)	133 (51.8)	53 (50.5)	
Poor	174 (42.6)	84 (40.4)	49 (46.7)	
Microvascular Invasion	170 (50.3)	84 (40.4)	48 (52.2)	0.06
Perineural Invasion	326 (89.6)	211 (93.0)	90 (92.8)	0.31
Positive Margin	196 (45.8)	115(44.1)	37 (34.9)	0.10
Retroperitoneal	144 (34.7)	81 (31.0)	23(21.7)	0.03
Total LN Harvested	17 (12–23)	18 (13–22)	19 (14–27)	0.08
Lymph Node Metastasis	347 (81.1)	208 (79.7)	85 (80.2)	0.91
Surgical Details				
Type of operation				0.07
Classic Whipple	132 (31.8)	71 (27.3)	22 (22.0)	
Pylorus Preserving	283 (68.2)	189 (72.7)	83 (79.0)	
Estimated Blood Loss (EBL) (median, L)	0.7 (0.5–1.0)	0.8 (0.6–1.2)	1.0 (0.6–1.5)	<0.001
Operative Time (median, min)	364	375	380	0.07
Pancreas Texture (n=258)				0.23
Soft	68 (50.0)	43(46.7)	18 (60.0)	
Moderate	44 (32.4)	23 (25.0)	6 (20.0)	
Hard	24 (17.6)	26 (28.3)	6 (20.0)	
Length of Stay (range, days)	11 (9–15)	10 (9–14)	10 (8–16)	0.67

53.8%), while other patients were categorized as overweight (n=261; 32.8%) or obese (n=106; 13.3%). Normal weight patients were slightly older (67 years) compared with patients who were overweight (66 years) or obese (65 years; P=0.008). Obese patients tended more likely to be black (12.3%) compared with normal (5.1%) or overweight (6.9%) patients (P=0.05).

Of the 795 patients, 744 (93.6%) patients had information regarding preoperative weight loss. Overall, those patients reporting "any" weight loss were higher among those patients with a normal preoperative BMI (normal, 58.9% vs. overweight, 51.2% vs. obese, 48.5%; P=0.03). In the 607 (76.3%) patients who had information regarding the amount of weight loss prior to surgery, those patients reporting >10% preoperative weight loss within 6 months of surgery were similar (normal, 58.9% vs. overweight, 51.2% vs. obese, 48.5%; P=0.83).

Operative and Pathology Details

At the time of surgery, 555 (69.8%) patients underwent a pylorus preserving pancreaticoduodenectomy, while 225 (28.3%) patients underwent a classic pancreaticoduodenectomy. Patient weight was not associated with the use of pylorus preserving versus classic pancreaticoduodenectomy (Table 1). In 258 (32.5%) patients, information was available regarding the texture of the pancreatic gland. Obese patients (60.1%) were not more likely to have a "soft" pancreatic gland compared with overweight (46.7%) or normal weight (50.0%) patients (P=0.23).

Overall, the median operative time was 378 min and the median operative blood loss was 900 ml. Operative pancreaticoduodenectomy time was similar among patients, regardless of their weight (normal, 364 min vs. overweight, 375 min vs. obese, 380 min; $P=0.07$). In contrast, obese patients (median estimated blood loss, 1,000 ml) were more likely to have increased operative blood loss compared with both overweight (median estimated blood loss, 800 ml) and normal weight (median estimated blood loss, 700 ml) patients ($P<0.01$).

On final pathologic analysis, the median size of the primary tumor was 3.5 cm (range, 2.3–4.0 cm). Overall, 97.3% of patients had American Joint Committee on Cancer stage I or II pancreatic cancer. The distribution of patients with T1 tumors was similar among obese (1.1%), overweight (5.7%), and normal weight (4.6%) patients ($P=0.34$). Specifically, obese patients had a comparable primary tumors size (median: 3 cm, range 2.5–4 cm) versus overweight (median: 3 cm, range 2.0–3.5 cm) or normal weight (median: 3 cm, range 2.3–3.5 cm) patients ($P=0.05$). The median number of nodes evaluated was 18 (range, 12–27), and there was no difference in the median number of lymph nodes harvested stratified by BMI (obese, 19 vs. overweight, 18 vs. normal weight, 17; $P=0.08$). Of the 795 patients who underwent pancreaticoduodenectomy, 155 (19.5%) had no lymph node metastasis (N0), while 640 (80.5%) had lymph nodes metastasis (N1). BMI was not associated with a higher incidence of lymph node metastasis. Specifically, the percent of patients with lymph node metastasis was similar in each BMI category (obese, 80.2% vs. overweight, 79.7% vs. normal weight, 81.1%; $P=0.91$). BMI was also not associated with a greater number of positive lymph nodes in each surgical specimen, as the mean number of lymph nodes with metastatic disease was 3 for each BMI category.

Overall, the pathologic margin status was microscopically positive (R1) in 356 (45.2%) patients and microscopically negative (R0) in 436 (54.8%) patients. BMI was not associated with the overall risk of an R1 resection (obese, 65.7% vs. overweight, 55.8% vs. normal weight, 54.1%; $P=0.10$). However, interestingly, the location of microscopic carcinoma at the surgical margin was different based on BMI. Specifically, the risk of uncinate/retroperitoneal margin was lowest in obese patients (obese, 21.7% vs. overweight, 31.1% vs. normal weight, 34.7%; $P=0.03$).

Perioperative Morbidity and Mortality

The median length of stay following pancreaticoduodenectomy was 10 days (range, 9–16). Obese patients had a similar median length of stay (10 days, range 9–14 days) as overweight (10 days, range 8–16 days) and normal weight (11 days, range 9–15 days) patients. The overall 30-day perioperative mortality rate was 1.7%. BMI was not associated with perioperative mortality (obese, 1.9% vs. overweight, 1.5% vs. normal weight, 1.3%; $P=0.34$).

Overall operative morbidity was similar following pancreaticoduodenectomy in obese patients (44.3%) compared with overweight (39.3%) or normal weight (37.2%) patients ($P=0.40$). The rate of surgical site wound infections was slightly higher in obese (11.3%) and overweight (8.9%) patients compared with normal weight (6.6%) patients, but this was not statistically significant ($P=0.23$). Similarly, there were no differences in the rate of other postoperative complications, including delayed gastric emptying (Table 2). BMI was, however, associated with an increased risk of pancreatic fistula (obese, 9.4% vs. overweight, 5.8% vs. normal weight, 2.9%; $P=0.01$).

Long-Term Survival

With regard to long-term outcome, 1-, 3-, and 5-year overall survival following pancreaticoduodenectomy were 65.4%, 26.9%, and 18.3%, respectively, with a median survival of 17.3 months. On univariate analysis, a number of clinicopathologic factors were associated with survival. Specifically, tumor size (hazard ratio [HR], 1.13), poor tumor differentiation (HR, 2.32), presence of perineural invasion (HR, 1.41), R1 margin status (HR, 1.38) and lymph node metastasis (HR, 1.49) were all indicative of worse survival following pancreaticoduodenectomy (Table 3). Of note, BMI was also strongly associated with risk of disease-specific death on univariate analysis (Fig. 1). Whereas patients with a normal weight had a median survival of 14.6 months, those who were overweight or obese had a median survival of 20.1 and 20.3 months, respectively ($P<0.01$). Patients with a normal BMI also had a worse 5-year survival (15.4%) versus both overweight (22.2%) and obese (22.1%) patients ($P<0.01$). On multivariate analysis, after adjusting for competing risk factors, BMI remained a strong predictor of long-term outcome. High BMI was associated with a decreased risk of disease-specific death versus normal weight patients (overweight, HR 0.74; obese, HR 0.73; both $P<0.01$;

Table 2 Number of Patients Undergoing Pancreatectomy for Pancreatic Adenocarcinoma Who Had Complications

Complication	No. (%)			*P* value
	Normal	Overweight	Obese	
Any	152 (37.2)	101 (39.3)	47 (44.3)	0.40
Pancreatic Fistula	12 (2.9)	15 (5.8)	10 (9.4)	0.01
Surgical Site Infection	27 (6.6)	23 (8.9)	12 (11.3)	0.23

Complications are stratified weight

Table 3 Univariate and Multivariate Analysis of Factors Associated With Long-Term Outcome Among Patients Undergoing Pancreatectomy for Pancreatic Adenocarcinoma

Variable	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	95% CI	*P*-value	Hazard Ratio	95% CI	*P*-value
Tumor Size (continuous)	1.13	1.08–1.18	<0.001	1.16	1.16–1.24	<0.001
Positive Retroperitoneal Margin	1.17	1.00–1.37	0.05	1.08	0.90–1.69	0.44
Other Positive Margin	1.38	1.24–1.67	<0.001	1.36	1.10–1.68	0.005
Lymph Node Metastases	1.49	1.28–1.76	<0.001	1.33	1.06–1.68	0.015
Tumor Differentiation						
Well	1.00			1.00		
Moderate	1.53	1.02–2.28	0.04	1.28	0.74–2.21	0.37
Poor	2.32	1.55–3.48	<0.001	2.17	1.25–3.74	0.006
Weight						
Normal	1.00			1.00		
Overweight	0.73	0.60–0.88	<0.001	0.74	0.61–0.89	0.002
Obese	0.75	0.58–0.98	0.03	0.73	0.56–0.95	0.02

CI confidence interval

Fig. 2a). Using data from the 607 (76.3%) patients who had information regarding the amount of weight loss prior to surgery, weight loss was entered into the multivariate model to assess whether weight loss—rather than absolute BMI—was associated with survival. Even after accounting for the amount of preoperative weight loss, BMI at the time of surgery remained associated with risk of disease-specific death (normal weight, referent vs. overweight, HR 0.68; obese, HR 0.72; both $P<0.05$; Fig. 2b).

To assess whether the inferior long-term survival noted for normal weight patients was actually due to the presence of underweight patients within the normal weight referent cohort, we performed additional analyses. Among the 428 patients with a normal BMI, 32 (7.5%) had a BMI<18 kg/m^2 and could be classified as underweight. Repeat univariate and multivariate analyses comparing obese, overweight, and normal weight patients (excluding underweight patients) revealed overall similar results (normal weight, referent vs. overweight, HR 0.87; obese, HR 0.77; both $P<0.01$).

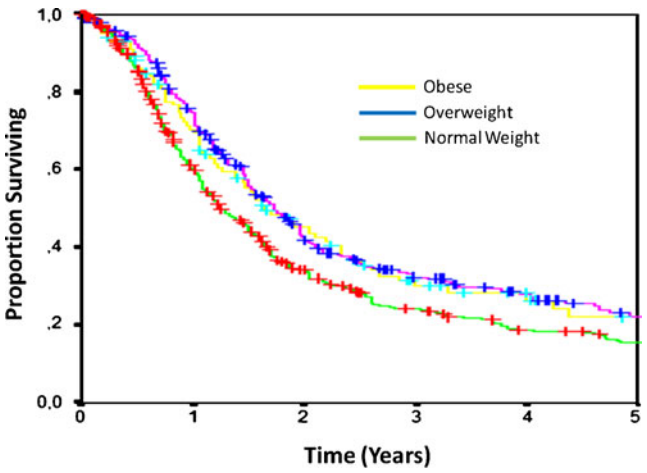

Figure 1 BMI was also strongly associated with risk of disease-specific death with normal weight patients having a worse 5-year survival (15.4%) compared with both overweight (22.2%) and obese (22.1%) patients ($P<0.01$).

Discussion

Obesity is a public health care crisis, as nearly one in three American adults is obese.[20] In turn, as more and more patients are obese, accurate data on the impact of obesity on cancer-related outcomes are critical. While some data have implicated obesity as an adverse factor impairing the oncologic adequacy of surgical resection of gastric and rectal cancers,[12,13] other studies have not noted similar results.[14,15] The data on obesity and its association with resection of pancreatic cancer are even more limited. Specifically, there are limited data examining the association between obesity and cancer-related outcomes following pancreatectomy.[16] This study, however, included a heterogeneous cohort of patients who had undergone pancreaticoduodenectomy, distal pancreatectomy, or total pancreatectomy. The study by Fleming et al.[16] also included only a limited number of patients who were obese (BMI>30 kg/m^2, $n=61$). The current study is important because it reports the largest single-institution experience analyzing the association of obesity with outcomes following pancreaticoduodenectomy for adenocarcinoma. In the current study, over one hundred obese patients were included, thereby allowing for a more rigorous analysis of

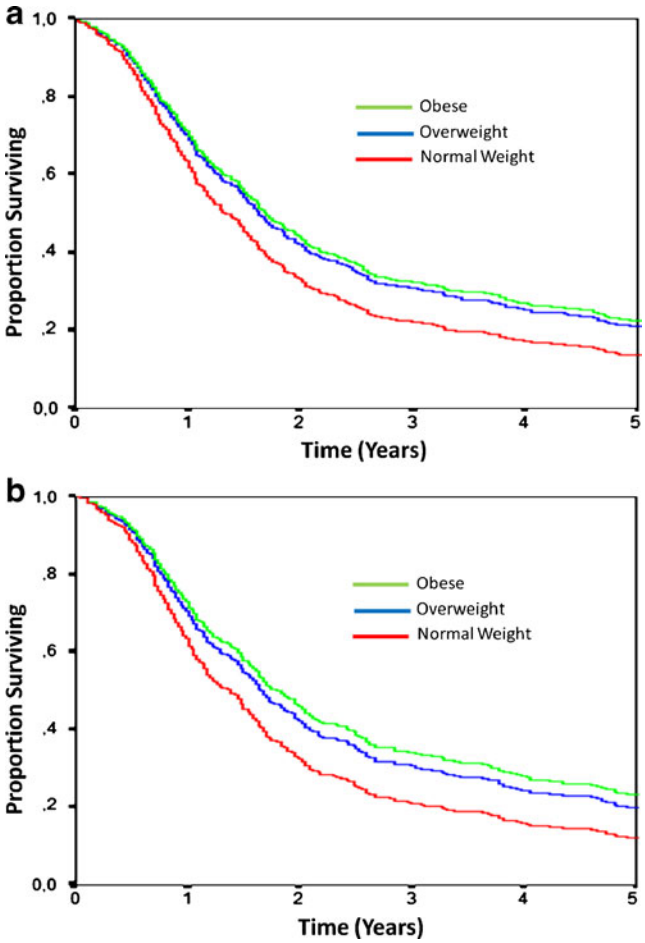

Figure 2 **a** After adjusting for competing risk factors, BMI remained a strong predictor of long-term outcome with high BMI patients having about a 25% risk reduction in disease-specific death versus normal weight patients. **b** Even after accounting for the amount of preoperative weight loss, BMI at the time of surgery remained associated with risk of disease-specific death.

the impact of BMI on clinicopathologic tumor characteristics as well as long-term outcome. Unlike previous data, our study also included a homogeneous group of patients who underwent only pancreaticoduodenectomy. The data demonstrate that obese patients had similar tumor-specific characteristics, as well as perioperative outcomes, compared with normal weight patients. We also report that obese patients undergoing pancreaticoduodenectomy for pancreatic cancer had an improved long-term survival independent of known clinicopathologic factors. In aggregate, these data strongly suggest that pancreaticoduodenectomy is both safe and efficacious for obese patients.

A major concern in performing pancreaticoduodenectomy in obese patients has been the associated morbidity. As pancreaticoduodenectomy entails a large operation with potential morbidity even in nonobese patients, there has been a fear that perioperative morbidity would be increased in patients who are obese. Our data indicate that surrogate measures of surgical complexity were similar in obese patients compared with overweight or normal weight patients. While operative blood loss was slightly higher in obese patients, the median operative time was similar among the patient cohorts. Perhaps more importantly, data from the current study also demonstrated that perioperative morbidity was similar in obese patients compared with overweight or normal weight patients (Table 2). While morbidity was in the 35% to 40% range, the majority of perioperative complications following pancreaticoduodenectomy were minor and did not require either any therapy or a simple routine intervention. Of note, perioperative mortality was also low with less than a 2% mortality rate in all weight classifications. Data from other institutions [21,22] had similarly noted that BMI was not an independent predictor of postoperative complications. In a report from the Memorial Sloan Kettering Cancer Center, while the incidence of wound infections was higher in obese patients, overall postoperative complication rates were similar among patients with varying BMI.[21] In a separate study from Thomas Jefferson University, which included pancreatic resections for both benign and malignant indications, obese patients had a slightly higher rate of intra-abdominal collections (7% vs. 14%), but this did not reach statistical significance (P=0.05).[22] Taken together with previous data, the present study provides strong evidence that the perioperative risk of pancreaticoduodenectomy in the obese population is low.

Pancreatic fistula is one of the most common, and potentially morbid, complications following pancreaticoduodenectomy. Among surgeons, there has been a perception that obese patients may be more susceptible to having a "fatty," soft pancreas and therefore be at higher risk of pancreatic fistula. In fact, data from animal models have shown that pancreata from obese mice have increased total fat content compared with lean controls.[23] In the current study, we did not directly assess the quantity of fat in the pancreatic gland, as had been done in one previous study.[24] However, in 258 (32.5%) patients, data on the texture of the pancreatic gland were available. Of these patients, obese patients were noted to have a slightly higher incidence of a "soft" pancreatic gland compared with normal weight patients, but this did not reach statistical significance. We did note, however, that BMI was associated with risk of pancreatic fistula. Specifically, the rate of pancreatic fistula was over three times higher in obese patients (9.4%) compared with normal weight (2.9%) patients (P=0.01). In a series of 92 patients who underwent pancreaticoduodenectomy for benign and malignant indications, Noun et al.[25] similarly reported a higher pancreatic fistula rate in obese compared with nonobese patients. Williams et al.[22] also reported a higher rate of pancreatic fistula in obese patients and, interestingly, noted that retrorenal visceral fat thickness correlated with risk of pancreatic fistula.

Some investigators have proposed BMI-associated differences in tumor specific clinicopathologic factors. Specifically, Fleming et al.[16] reported that obese patients were more likely to have node-positive pancreatic cancer compared with normal weight patients. In contrast, we noted that obesity was not associated with an increased risk of lymph node metastasis. In fact, the percent of patients with lymph node metastasis was similar in each BMI category (obese, 80.2% vs. overweight, 79.7% vs. normal weight, 81.1%; $P=0.91$). The reasons for these disparate findings are undoubtedly multifactorial, but probably largely relate to the differential use of preoperative therapy. In the report by Fleming et al.[16] while most patients received preoperative therapy, patients with a BMI>35 kg/m^2 were significantly less likely to receive neoadjuvant treatment. The decreased use of preoperative therapy in the high BMI group could help explain the increased risk of lymph node metastasis in this group of patients.[26] Although the authors did appropriately adjust for neoadjuvant therapy in their analyses, the issue of selection bias in the cohort population may be difficult to resolve through purely statistical methods.[27] In the current study, as a matter of institutional policy, neoadjuvant therapy was not routinely employed. Data from the current study therefore represent a more homogeneous cohort of patients who were not pretreated. As such, our analyses may have been less susceptible to treatment selection bias and provide strong evidence that obese patients are not necessarily at higher risk of node-positive pancreatic adenocarcinoma.

Another interesting finding of the current study related to surgical margin status. Fleming et al.[16] reported no difference in the incidence of an R1 surgical resection margin among obese versus nonobese patients. In the current study, we similarly noted that BMI was not associated with overall risk of R1 resection (obese, 65.7% vs. overweight, 55.8% vs. normal weight, 54.1%; $P=0.10$). However, unlike other studies that reported R1 margin status as a categorical variable defined as "any" positive margin, we specifically examined the location of microscopic carcinoma at the surgical margin stratified by BMI category. Interestingly, while obese patients had the highest risk of microscopic residual disease at the pancreatic neck margin, obese patients had the lowest risk of microscopic carcinoma at the uncinate/retroperitoneal margin. While the reason for the decreased risk of a positive uncinate/retroperitoneal margin among obese patients remains unknown, one possible reason may be the increase in retrorenal/retroperitoneal fat thickness present in obese patients.[22]

We noted that obese patients also had an improved long-term survival compared with normal weight patients. This again was in contrast to the findings of Fleming et al.[16] who reported that obese patients had a decreased survival after surgical resection. Obese patients in the study by Fleming et al.[16] did, however, have more aggressive tumor characteristics compared with normal weight patients—unlike in the current study. The difference in survival among obese versus normal weight patients in the study by Fleming et al. was therefore difficult to interpret. Not only was the finding of worse survival isolated to only "super-obese" patients with BMI>35 kg/m^2, it was potentially biased by the fact that these patients were significantly less likely to receive preoperative therapy than patients in other BMI groups. Analysis of data to assess the treatment effect of surgery that is based on patients who have been nonrandomly assigned a specific treatment can be difficult. Data from the current study may represent a much more homogeneous pool of patients who were not pretreated. For this reason, our survival analyses based on BMI can be interpreted in a more straightforward fashion with less concern for overt treatment selection bias. Our finding that obese patients have an improved long-term survival following resection of pancreatic adenocarcinoma is not unique. Other studies have similarly reported that obese patients may have a more favorable prognosis than normal weight patients following resection of other malignancies such as renal cell carcinoma.[28,29]

Several limitations should be considered in interpreting our study. Despite having the largest pancreaticobiliary surgical experience in the country, the total number of obese patients in the current study was still only 13.8% of the patients treated. As such, the current study has limited statistical power; due to this constraint, some statistical analyses and inferences may be limited. The conclusion that obese patients did better than normal weight patients may also have been confounded by the inclusion of underweight (BMI<18 kg/m^2) patients in the referent "normal" weight cohort. This is particularly important because underweight patients are known to have a decreased overall survival following major oncologic intra-abdominal surgery.[11] However, we specifically undertook additional analyses that excluded underweight patients from the normal weight referent cohort and found similar results with regard to overall survival.

In conclusion, our data demonstrate that obese patients have similar tumor-specific characteristics, as well as perioperative outcomes, compared with normal weight patients. Specifically, obesity was not associated with an increase in perioperative morbidity or mortality, although obese patients did have a higher risk of postoperative pancreatic fistula. Obese patients who underwent pancreaticoduodenectomy for pancreatic cancer had an improved long-term survival compared with normal weight patients independent of known clinicopathologic factors. Obese patients, therefore, should not be denied pancreaticoduodenectomy based solely on their BMI. Rather, our data emphasize that obese patients should be considered for pancreaticoduodenectomy when oncologically appropriate.

References

1. CDC. State-specific prevalence of obesity among adults: United States, 2005. Center of Disease Control and Prevention 2006.
2. CDC. Overweight and obesity: health consequences. In Prevention. CfDCa, ed., Vol. 2007, 2007. eb Site. www.cdc.gov/obesity/causes/health.html.
3. Adams KF, Schatzkin A, Harris TB, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med 2006;355(8):763–778.
4. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348(17):1625–1638.
5. Larsson SC, Permert J, Hakansson N, et al. Overall obesity, abdominal adiposity, diabetes and cigarette smoking in relation to the risk of pancreatic cancer in two Swedish population-based cohorts. Br J Cancer 2005;93(11):1310–1315.
6. Hanley AJ, Johnson KC, Villeneuve PJ, Mao Y. Physical activity, anthropometric factors and risk of pancreatic cancer: results from the Canadian enhanced cancer surveillance system. Int J Cancer 2001;94(1):140–147.
7. Michaud DS, Giovannucci E, Willett WC, et al. Physical activity, obesity, height, and the risk of pancreatic cancer. Jama 2001;286(8):921–929.
8. Li D, Morris JS, Liu J, et al. Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. Jama 2009;301(24):2553–2562.
9. Klasen J, Junger A, Hartmann B, et al. Increased body mass index and peri-operative risk in patients undergoing non-cardiac surgery. Obes Surg 2004;14(2):275–281.
10. Dindo D, Muller MK, Weber M, Clavien PA. Obesity in general elective surgery. Lancet 2003;361(9374):2032–2035.
11. Mullen JT, Davenport DL, Hutter MM, et al. Impact of body mass index on perioperative outcomes in patients undergoing major intra-abdominal cancer surgery. Ann Surg Oncol 2008;15(8):2164–2172.
12. Dhar DK, Kubota H, Tachibana M, et al. Body mass index determines the success of lymph node dissection and predicts the outcome of gastric carcinoma patients. Oncology 2000;59(1):18–23.
13. Gorog D, Nagy P, Peter A, Perner F. Influence of obesity on lymph node recovery from rectal resection specimens. Pathol Oncol Res 2003;9(3):180–183.
14. Gretschel S, Christoph F, Bembenek A, et al. Body mass index does not affect systematic D2 lymph node dissection and postoperative morbidity in gastric cancer patients. Ann Surg Oncol 2003;10(4):363–368.
15. Damadi AA, Julien L, Arrangoiz R, et al. Does obesity influence lymph node harvest among patients undergoing colectomy for colon cancer? Am Surg 2008;74(11):1073–1077.
16. Fleming JB, Gonzalez RJ, Petzel MQ, et al. Influence of obesity on cancer-related outcomes after pancreatectomy to treat pancreatic adenocarcinoma. Arch Surg 2009;144(3):216–221.
17. Physical Status: The Use and Interpretation of Anthropometry: Report of a WHO Expert Committee, 1995.
18. Greene FL, Page DL, Fleming ID (eds). AJCC Staging manual and handbook. 6th ed. Philadelphia: Lippincott Raven Publishers, 2002.
19. Winter JM, Cameron JL, Campbell KA, et al. Does pancreatic duct stenting decrease the rate of pancreatic fistula following pancreaticoduodenectomy? Results of a prospective randomized trial. J Gastrointest Surg 2006;10(9):1280–1290. discussion 90.
20. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999–2004. Jama 2006;295(13):1549–1555.
21. House MG, Fong Y, Arnaoutakis DJ, et al. Preoperative predictors for complications after pancreaticoduodenectomy: impact of BMI and body fat distribution. J Gastrointest Surg 2008;12(2):270–278.
22. Williams TK, Rosato EL, Kennedy EP, et al. Impact of obesity on perioperative morbidity and mortality after pancreaticoduodenectomy. J Am Coll Surg 2009;208(2):210–217.
23. Mathur A, Marine M, Lu D, et al. Nonalcoholic fatty pancreas disease. HPB (Oxford) 2007;9(4):312–318.
24. Mathur A, Zyromski NJ, Pitt HA, et al. Pancreatic steatosis promotes dissemination and lethality of pancreatic cancer. J Am Coll Surg 2009;208(5):989–994. discussion 94-6.
25. Noun R, Riachy E, Ghorra C, et al. The impact of obesity on surgical outcome after pancreaticoduodenectomy. Jop 2008;9(4):468–476.
26. White RR, Xie HB, Gottfried MR, et al. Significance of histological response to preoperative chemoradiotherapy for pancreatic cancer. Ann Surg Oncol 2005;12(3):214–221.
27. Gleisner AL, Choti MA, Assumpcao L, et al. Colorectal liver metastases: recurrence and survival following hepatic resection, radiofrequency ablation, and combined resection-radiofrequency ablation. Arch Surg 2008;143(12):1204–1212.
28. Kamat AM, Shock RP, Naya Y, et al. Prognostic value of body mass index in patients undergoing nephrectomy for localized renal tumors. Urology 2004;63(1):46–50.
29. Yu ML, Asal NR, Geyer JR. Later recurrence and longer survival among obese patients with renal cell carcinoma. Cancer 1991;68(7):1648–1655.

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ORIGINAL ARTICLE

Impact of 18-Fluorodeoxyglucose Positron Emission Tomography on the Management of Pancreatic Cancer

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Abstract
Background We compared the usefulness of positron emission tomography with the glucose analogue 2-deoxy-2-[18*F*]-fluoro-D-glucose (FDG-PET) and multidetector-row computed tomography (MD-CT) in diagnosing pancreatic cancer and in determining the patients' suitability for surgery.
Methods We reviewed the clinical FDG-PET data of 103 consecutive pancreatic cancer patients between July 2004 and March 2009.
Results The detection rates of pancreatic cancer by MD-CT (89%) and FDG-PET (91%) were similar. From the MD-CT findings, 38 patients were judged as operable, and 65, inoperable. Among the inoperable patients, noncurative factors (metastasis to the liver, peritoneum, remote lymph nodes, bones, and other organs and major arterial invasion) were detected by MD-CT and/or FDG-PET. Detection rates of liver metastasis and arterial invasion by FDG-PET were significantly inferior to those of MD-CT (neither was detected by FDG-PET alone). Remote lymph nodes and bone metastasis were detected in 20 lesions by FDG-PET alone; however, MD-CT indicated other noncurative factors in these patients. All 65 patients could be diagnosed as inoperable without FDG-PET.
Conclusions FDG-PET is not a suitable imaging modality for either diagnosis or preoperative treatment in pancreatic cancer patients. Since it is expensive, FDG-PET as a routine diagnostic tool in pancreatic cancer patients must be used with caution.

Keywords 18-Fluorodeoxyglucose · Positron emission tomography · Pancreatic cancer · Multidetector-row computed tomography

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Introduction

Pancreatic cancer has been globally responsible for a significant number of cancer-related deaths. The prognosis is very dismal, with a 5-year survival rate of less than 5%.[1] At the time of initial diagnosis, 80% of patients present with a metastatic disease or a locally advanced tumor, and only 20% of patients are diagnosed with a resectable tumor.[2] Recent data indicate that the 5-year survival rate is very poor (22.5%) even if the patients undergo surgery and adjuvant chemotherapy.[3] In addition, many patients have been reported to suffer from complications such as fistulae, leakage, and abscesses after undergoing pancreatectomy. Even in experienced hospitals, the morbidity and mortality rates remain at 30%–50% and 2%–4%, respectively.[4] Therefore, unnecessary surgery must be avoided in incurable patients. Accurate staging, including diagnosis of distant metastases and locally advanced tumors, is very important.

Positron emission tomography (PET) with the glucose analogue 2-deoxy-2-[18*F*]-fluoro-D-glucose (FDG) is a noninvasive modality; several excellent results have been reported of its use in the diagnosis or preoperative staging of various cancers.[5–8] This also applies to whole body examinations with respect to pancreatic cancer. Many studies have reported the usefulness of FDG-PET in the detection or diagnosis of pancreatic cancer.[9–11] However, these results may contain publication bias; since negative data are not published, the majority of these reports reflect only a few cases, representing less than 100 patients. When we compared computed tomography (CT) scans to those of the FDG-PET, it was not clear as to how FDG-PET contributes to the findings of the CT scans. In other words, it must be determined whether FDG-PET contributes new information to the findings of CT or the FDG-PET information is already included in the findings of CT. However, the FDG-PET scan would not justify its high operational costs if it did not contribute to the findings of the CT scans. Recently, the combination scanning of FDG-PET and CT has been developed with the aim to coregister functional (PET) and anatomic information (CT) using the same scanner (PET/CT) [12]. This highly technological modality should provide better images by supplying more information than either the CT or FDG-PET alone. However, current studies suggest that the diagnostic accuracy of this modality is similar to that of CT (contrast-enhanced) alone [9], and further, if the findings of FDG-PET include those of the CT as well, then the PET/CT examination becomes redundant. Therefore, to reduce the costs of using FDG-PET scans, it is important to obtain a detailed analysis of the information from the FDG-PET and CT scans, including the detection of pancreatic cancer or metastatic sites.

In this report, to examine the usefulness of FDG-PET examination, we focused on several important points regarding the diagnostic impact of this modality pancreatic cancer, namely, (1) the detection rate of pancreatic cancer, (2) the detection of pancreatic cancer undetected by CT examination, and (3) the detection of cancer metastasis for decisions regarding therapeutic procedures, operations, or chemotherapy.

Materials and Methods

Patients and Analysis

We reviewed the clinical database of FDG-PET scans of 103 consecutive patients (50 male and 53 female; mean ± SD age, 67.9±11.7 years) diagnosed with histologic or clinical pancreatic cancer in our hospital from July 2004 to March 2009. PET imaging was performed on all patients within a 1-month interval for the multidetector-row CT (MD-CT) scan. The final diagnosis was decided by histology in 50 patients and by cytology brushings obtained during endoscopic retrograde cholangiopancreatography in 17 patients. The other 36 patients were diagnosed by clinical and radiology follow-up. None of the patients were diagnosed as inoperable using only endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography, or magnetic resonance imaging.

In order to evaluate and compare the impact of FDG-PET and MD-CT on the diagnosis and decision for resection in pancreatic cancer, we examined the detection rates of MD-CT and FDG-PET and the relationship between the detection rates and tumor size and/or standardized uptake value (SUV) on the basis of therapeutic decisions (operable or inoperable) or MD-CT findings (visible or invisible). We measured the tumor size using MD-CT and then by abdominal echo or EUS, when the tumor was deemed invisible by MD-CT (11 cases). Further, we also examined the feature of noncurative factors that were diagnosed as inoperable by MD-CT and/or FDG-PET.

Computed Tomography

All patients underwent MD-CT in 64-, 16-, or 4-row scanners (Aquilion 64, Aquilion 16, Aquilion 4; Toshiba, Tokyo, Japan) with contrast enhancement. The axial images of the abdomen were routinely obtained and reconstructed with a 5-mm thickness. Coronal and sagittal multiplanar reconstruction images were acquired on a workstation using raw data. The multiplanar reconstruction images were obtained at 2.5-mm intervals with a slice thickness of 2.5 mm. The CT images were interpreted independently and consecutively by two radiologists with extensive experience in CT examination. The findings of the CT scans were considered positive when both the radiologists strongly suspected malignant disease due to a discrete low-attenuation mass within the pancreas and/or involving the adjacent vessels and/or swelling of the regional lymph nodes.

PET with the Glucose Analogue FDG

The FDG-PET images were acquired with a PET scanner (ECAT EXACT HR+; Siemens/CTI, Knoxville, TN, USA). The patients were required to fast for at least 5 h before FDG was injected. The PET images were acquired 1 h after the intravenous administration of FDG (3.5 MBq/kg). The transmission images were acquired to correct for attenuation. The FDG-PET images were interpreted independently and consecutively by two radiologists with extensive experience in FDG-PET imaging. The findings were considered to be positive when both the radiologists

strongly suspected malignant disease. In addition, the images were analyzed semiquantitatively using the standardized uptake value (SUV); the regions of interest were drawn over the area of the primary lesion including the largest amount of radioactivity. The maximum SUV was calculated by using the following formula: $SUV = c_{dc}/(d_i/w)$, where c_{dc} is the decay-corrected tracer tissue concentration (in Bq/g); d_i, the injected dose (in Bq); and w, the patient's body weight (in g).

Statistical Analysis

The chi-square test was employed for statistical comparison of the detection rates of FDG-PET and CT, or CA19-9 (the tumor marker for pancreatic cancer). The Student's *t*-test was used to compare the values of the SUV, tumor size, and serum level of CA19-9 between the two groups. Correlations between the SUV and the maximum diameter of the primary lesion determined on the CT scan were examined by the Pearson's correlation test. All statistical analyses were performed using the SPSS software program (version 9.0; SPSS Chicago, IL). A P value of <0.05 was considered to be statistically significant.

Results

Therapeutic Decision in All Pancreatic Cancer Patients

Figure 1 shows the clinical profiles and the therapeutic decisions for all the 103 consecutive patients. The patients were diagnosed as follows. A total of 65 patients had unresectable pancreatic cancer, and 38 had resectable cancer. Among the 38 patients with resectable cancer, 35 underwent surgery and 3 did not because of poor performance status. However, 34.2% (12/35 cases) of the patients underwent laparotomy only because of unexpected metastasis (small peritoneal dissemination $n=1$; peritoneal washing cytology positive $n=3$; liver metastasis $n=4$; paraaortic lymph node metastasis $n=2$; massive retroperitoneal invasion $n=2$.) Finally, only 23 patients (22.3%; 23/103 cases) underwent pancreatectomy.

Comparison of Detection Rates of Pancreatic Cancer by MD-CT and FDG-PET

We examined the contributions of MD-CT and FDG-PET in the detection of pancreatic cancer (Table 1). The detection rates of MD-CT (89.3%) were similar to those of FDG-PET (91.3%). The detection rates of MD-CT and FDG-PET for operable pancreatic cancers were 76.3% and 96.9%, respectively, but these rates were not statistically significant ($P=0.056$).

Contribution of FDG-PET to the Decision of Operative Indication

The advanced stages of various cancers have been reported to be indicated by a high SUV, which reflects biologically malignant behavior.[13,14] It might be possible to distinguish between operable and inoperable tumors by the SUV in the primary tumor. Therefore, we examined the relationship between the maximum tumor diameter and SUV of the FDG-PET. There was a possible correlation between the SUV and the maximum tumor diameter (Fig. 2; Pearson's correlation coefficient $r=0.347$; $P<0.001$). On comparing the tumor size in operable and inoperable patients diagnosed by MD-CT and/or FGD-PET, we found that the tumor size was significantly smaller in operable patients than in inoperable patients ($P=0.0004$; Fig. 3a). Therefore, the above two results suggested the possibility that operable and inoperable tumors can be distinguished by SUV analysis. However, as shown in Fig. 3b-1, the SUV in the main tumor did not indicate the ability to undergo resection ($P=0.064$). We obtained the same result by comparing the FDG uptake positive and negative tumors in operable or inoperable patients by the chi-square test (Fig. 3b-2).

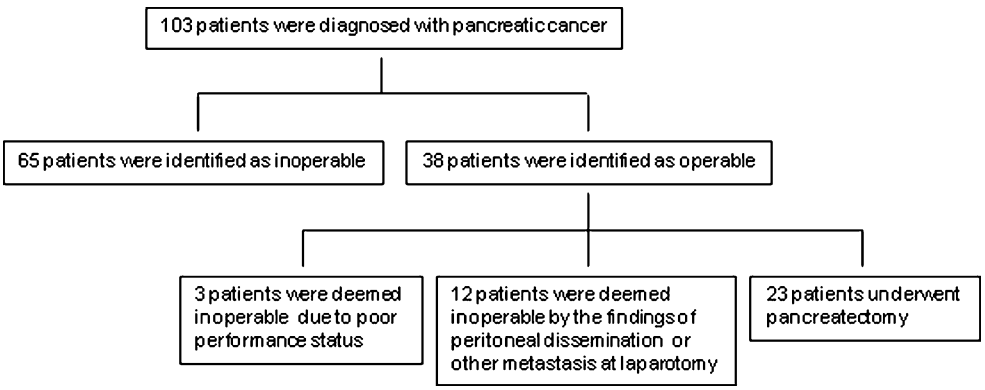

Figure 1 Clinical profile and therapeutic decision in this study. Therapeutic decision based on the radiologic examination and surgical findings of laparotomy is indicated; this determined whether the patients were operable or inoperable in a consecutive series of patients with pancreatic cancer. Two patients who were diagnosed as operable did not undergo surgery due to poor physical status.

Table 1 Detection Rates of Pancreatic Cancer by MD-CT and FDG-PET

	All patients (103)	Patients with operable pancreatic cancer (38)	Patients with inoperable pancreatic cancer (65)
MD-CT	89.3% (92)	76.3% (29)	96.9% (63)
FDG-PET	91.3% (94)	92.1% (35)	89.2% (58)

The detection ratio was listed in all the operable and inoperable patients. There was no statistical difference in their detection rates between the operable and inoperable groups. The numbers in parentheses indicate the number of patients

Usefulness of FDG-PET in the Detection of Pancreatic Cancer Not Detected by MD-CT

Another potential benefit of FDG-PET is as a diagnostic modality in the detection of pancreatic cancer that goes undetected on MD-CT examination. In our study, 92 patients had visible cancer by MD-CT, and 11 had invisible cancer. The size of the invisible tumors (2.4±0.7 cm) in MD-CT was measured by abdominal echo or EUS. These were significantly smaller than the visible tumors 3.9±1.8. cm (P=0.004). The SUV in the invisible tumors was lower than that in the visible tumors, (3.5±1.3 and 7.0±3.7, respectively; P=0.004; Fig. 4b-1). As shown in Fig. 4b-2, seven tumors were detected by FDG-PET in 11 patients with invisible tumors, whereas five tumors were not detected by FDG-PET in 92 patients with visible tumors. Interestingly, when examining CA19-9 (the tumor marker for pancreatic cancer), the mean value was not different among these groups due to a large standard difference (Fig. 4c-1). However, as shown in Fig. 4c-2, on dividing the mean values into two groups, namely, abnormal and normal, abnormal values for CA19-9 were found in 7 of the 11 patients with invisible tumors. Therefore, the contribution of FDG-PET to the diagnosis of invisible tumors by MD-CT may be equal to the significance of CA19-9 examination.

Impact of FDG-PET on the Detection of Cancer Metastasis for Decisions Regarding Therapeutic Procedures, Operations, or Chemotherapy

To clarify the diagnostic potential of MD-CT and FDG-PET for noncurative factors, we examined the detection rates of MD-CT and/or FDG-PET. Table 2 lists the noncurative factors such as liver metastasis, arterial invasion, paraaortic lymph node metastasis, peritoneal dissemination, lung metastasis, remote lymph node metastasis (mediastinal or supraclavicular LN, etc.), bone metastasis, and their detection modality, either MD-CT or FDG-PET. In the 65 inoperable patients, 61.5% (40 patients) had liver metastasis (Fig. 5 shows the typical images of pancreatic cancer and liver metastasis of MD-CT and FDG-PET), 53.8% (35 patients) showed arterial invasion, and 33.8% (22 patients) had paraaortic lymph node metastasis. These lesions were all diagnosed by MD-CT scan only, and the FDG-PET examination provided no further diagnostic usefulness. There were two patients with peritoneal metastasis which was detected in the pelvic cavity by FDG-PET only; the medical practitioners did not perform unnecessary CT examination of the lower abdomen due to arterial invasion and many liver metastases were detected in the upper abdominal CT scans. Because, if the lesions were detected by the MD-CT scan, the tumor stage and therapeutic decision were never changed.

The advantages of FDG-PET indicated the detection of remote lymph node metastasis and bone metastasis only. In the 26 total lesions with remote lymph node metastasis and/or bone metastasis, the majority of lesions, 76.9% (20/26), were detected by FDG-PET only; nevertheless, six lesions were indicated by both MD-CT and FDG-PET. However, all 26 patients had other noncurative factors such as liver metastasis or arterial invasion. Patients with remote metastasis demonstrated an advanced stage in the upper abdomen (local), and therefore, we believe a whole body examination was unnecessary.

Usually, inoperable patients with pancreatic cancer have two or three noncurative factors. Therefore, misdiagnosis of 1 noncurative factor would not cause a missed indication for surgery. However, in the patients who had only a single noncurative factor, the overlooked cause was a significant missed indication for surgery. Therefore, we examined the

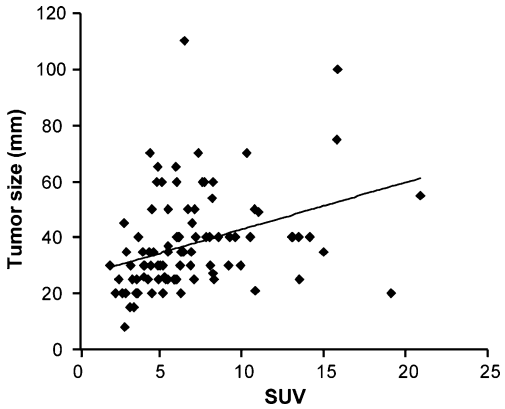

Figure 2 Relationship between tumor size and standardized uptake value (SUV). Correlation between maximum tumor diameter and SUV by Pearson's correlation test was found statistically (r=0.36, P<0.001).

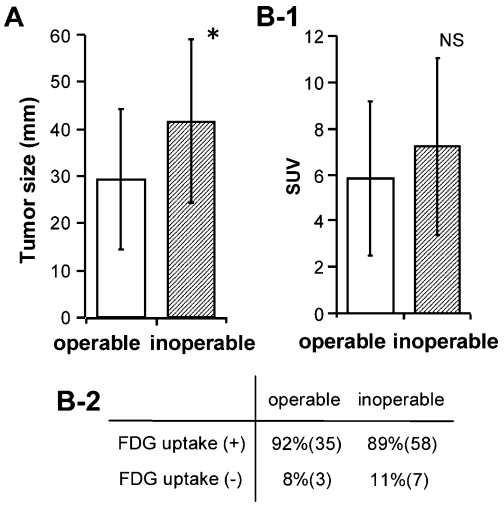

Figure 3 Tumor size and standardized uptake value (SUV) in operable and inoperable patients (**a**). The tumor size in the operable patients was significantly larger than that in the inoperable patients ($P<0.001$; **b-1**). The SUV in the tumor did not indicate the need for operation or therapeutic intervention ($P=0.064$; **b-2**). On comparing visible and invisible tumors by FDG-PET, we did not find any statistical difference in either the operable or inoperable patients, as determined by the $\chi 2$ test.

number of single noncurative factors diagnosed by MD-CT or FDG-PET (Table 3). Single noncurative factors were found in 26 of the 65 inoperable patients. Liver metastasis or arterial invasion was experienced by 92.3% (24/26) of the patients. MD-CT scans diagnosed all single noncurative factors, but no single noncurative factor was pointed out by FDG-PET scans only.

Discussion

FDG-PET has been described in several literature reviews as a modality with high-sensitivity rates in whole body inspection, with respect to malignancies in various organs.[5–8,13] This is a significant advantage in the examination of the whole body distribution of malignant cells, such as malignant lymphoma. In their large metaanalysis of FDG-PET involving 20 studies, Isasi et al.[15] reported a high median sensitivity of 90.3% and a median specificity of 91.1%. Owing to this high level of accuracy, FDG-PET has been recommended to the routine staging workup of patients with lymphoma. Conversely, the diagnostic accuracy of this test in lung malignancy is also well established as an appropriate application of FDG-PET imaging. Gould et al.[16] reported the meta-analysis of 1,474 nodules in 40 studies and revealed a high sensitivity of 96.8% and high specificity of 77.8%. From the viewpoint of preoperative staging, Fisher et al.[5] conducted a randomization study and reported the addition of PET/CT to conventional radiologic staging for preoperative staging of non-small-cell lung cancer and reduced the number of futile thoracotomies without affecting the overall mortality, compared with the use of conventional radiologic staging alone.

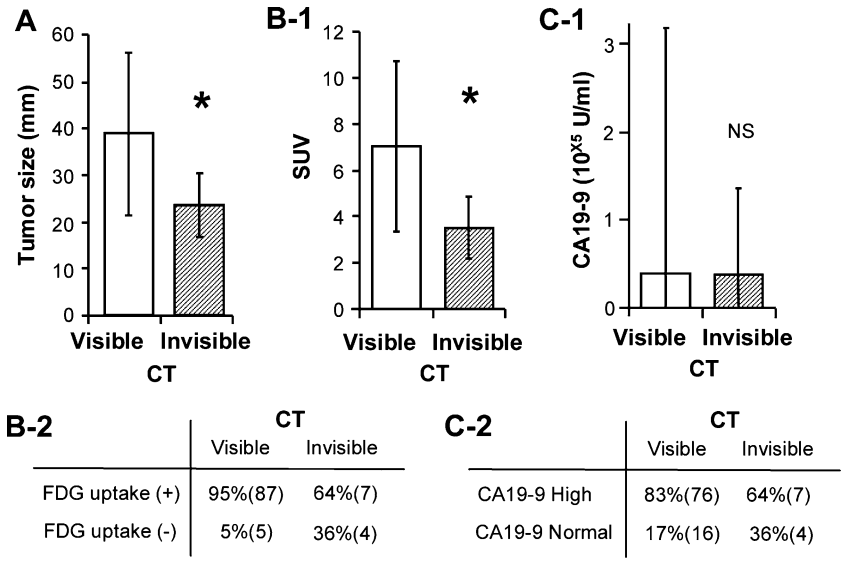

Figure 4 Detection rates of FDG-PET for pancreatic cancer not detected by MD-CT. In our study, 92 patients had visible cancer and 11 had invisible cancer, as observed by MD-CT (**a**). The invisible tumor sizes were significantly smaller than the visible tumors ($P=0.004$; **b-1**). The SUV in the invisible tumors was smaller than that in the visible tumors ($P=0.004$; **b-2**). However, when we divided the patients into the two groups, FDG-positive and FDG-negative tumors, we detected seven tumors in the 11 patients with invisible tumors by FDG-PET (**c-1**). Interestingly, the level of CA19-9 was not different in these groups due to a large value variation (**c-2**); however, in the 11 patients with invisible tumors, an abnormally high value of CA19-9 was seen in 7 patients. CA19-9 levels also contributed to the diagnosis of invisible pancreatic cancer, and the rate of diagnosis was equal to that of FDG-PET.

Table 2 Number of Noncurative Factors Diagnosed by MD-CT and FDG-PET: Comparison of MD-CT and FDG-PET

	Total number of patients	MD-CT and FDG-PET	MD-CT	FDG-PET
Liver metastasis	40	27	13	0
Arterial invasion	35	0	35	0
Paraaortic lymph node metastasis	22	11	11	0
Peritoneal dissemination	11	7	4	2
Lung metastasis	9	5	4	0
Other organ metastasis	2	1	1	0
Remote lymph node metastasis	13	4	0	9
Bone metastasis	13	2	0	11

The modalities of detection are listed according to both MD-CT and FDG-PET, MD-CT, and FDG-PET. The total number of patients is listed. When the patient had multiple metastatic sites, we considered them as being overlapped. The patients were divided by diagnosed modality, with both MD-CT and FDG-PET, only MD-CT, and only FDG-PET. In the 65 inoperable patients, 61.5% (40 patients) had liver metastasis, 53.8% (35 patients) showed arterial invasion, and 33.8% (22 patients) indicated paraaortic lymph node metastasis

However, unlike lung fields, which have a low background of FGD uptake, the validity of routine FDG-PET use remains to be assessed for the diagnosis of tumors in the abdominal cavity. Many reports have published successful results for the detection of abdominal malignancies. However, there are some challenges in obtaining good images of tumors in other organs using FDG-PET. For example, the diagnosis of liver metastasis indicated a high sensitivity of more than 85%.[17] However, the liver itself shows a high background due to upregulated physiological uptake of FDG; therefore, faint accumulation is not distinguishable in the liver. In addition, the majority of hepatocellular carcinomas are known to be FDG-PET-negative cancers. Prostate cancer is also essentially difficult to detect using FDG-PET.[18] On the other hand, advanced cancer of the stomach or colon shows strong accumulation of FDG, but in cases of small-sized tumors, the relatively strong physiological accumulation of FDG in the stomach or intestine hinders accurate diagnosis.[19] Of course, FDG clearance through the urine prevents the visualization of kidney and bladder tumors.

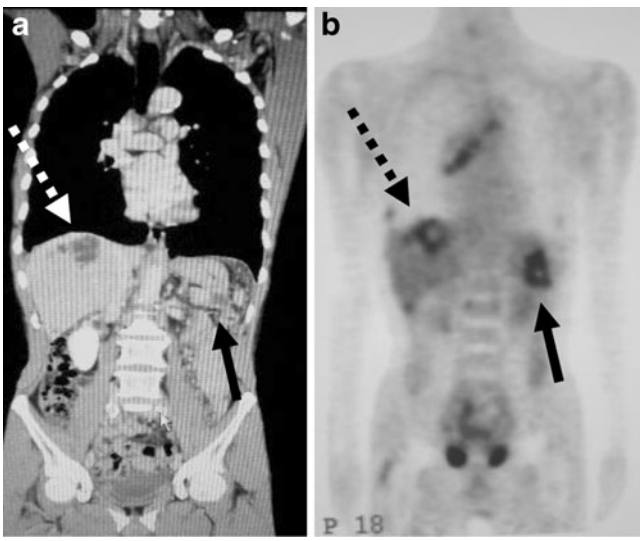

Figure 5 Images of pancreatic cancer and liver metastasis depicted by MD-CT and FDG-PET. The development of recent CT technology such as FDG-PET facilitated whole body examination. **a** The CT image and **b** shows the FDG-PET image of the patient with pancreatic cancer. The *solid arrows* indicate primary pancreatic cancer, and the *dotted arrows* indicate liver metastasis.

The usefulness of FDG-PET scans in the diagnosis of pancreatic cancer has been published in many journals, which report a high sensitivity of over 90%, which is equal to or greater than the sensitivity of the CT scan.[9–11] Heinrich et al.[9] reported that the sensitivity and specificity in PET/CT scanning for pancreatic cancer in 51 patients were 91% and 64%, respectively. In addition, PET/CT changed the management routine in 16% of patients by the detection of five cases of additional distant metastases and two cases of synchronous rectal cancer. They concluded that PET/CT represents an important staging procedure prior to pancreatic resection for cancer, since it improves patient selection and is cost-effective. Zafra et al.[7] reported that FDG-PET results modified therapeutic management in 34% of patients. The most frequent type of treatment change (18% of cases) was the decision to administer chemotherapy. This indicates that more extensive tumor metastasis was detected in 6% of patients; surgical resection was avoided in them. In our study, FDG-PET scanning detected rectal cancer in 1 patient. The patient presented with tarry stool, and therefore, the diagnosis of rectal cancer was an expected result, given the patient's chief complaint. FDG-PET examination can be used to screen for other unsuspected forms of colorectal cancer; however, stool examination is more convenient and cost-effective for determining more frequent forms of cancer.

Our results clearly indicated the situation in cancer diagnosis using FDG-PET. First, the detection rates of

Table 3 Number of Single Noncurative Factors Diagnosed by MD-CT or FDG-PET

	Total number of patients	MD-CT and FDG-PET	MD-CT	FDG-PET
Liver metastasis	11	5	6	0
Arterial invasion	13	0	13	0
Paraaortic lymph node metastasis	1	0	1	0
Peritoneal dissemination	0	0	0	0
Lung metastasis	1	1	0	0
Other organ metastasis	0	0	0	0
Remote lymph node metastasis	0	0	0	0
Bone metastasis	0	0	0	0

The number of single noncurative factors is listed in this table. A single noncurative factor was found in 26 of the 65 inoperable patients. It is noted that 92.3% (24/26) of single noncurative factors involved liver metastasis or arterial invasion. MD-CT diagnosed all single noncurative factors; however, no single noncurative factor was detected by FDG-PET only

FDG-PET were equal to that of MD-CT examination. However, since the SUV is related to tumor size, it was difficult to detect small tumors. On the other hand, for the diagnosis of tumors that were not detected by MD-CT examination, FDG-PET revealed accumulation in 60% of tumors that were invisible during the MD-CT examination. However, these detection rates were similar to those of the tumor marker CA19-9. From the viewpoint of cost effectiveness, the tumor markers are more economical than FDG-PET. In addition, FDG-PET was not particularly good as a decision-making modality prior to surgery in patients with pancreatic cancer. The most important preoperative variable for resectability was vascular infiltration of the superior mesenteric artery (SMA) and celiac axis, a diagnosis that was very difficult to determine using FDG-PET. The diagnosis of small liver metastasis also proved difficult by FDG-PET. It is well known that FDG-PET has difficulty imaging a tumor of less than 1 cm due to the low spatial resolution of the PET scanner.[20] In addition, physiological FDG accumulation or faintly heterogeneous FDG uptake in normal liver parenchyma also makes the detection of liver metastasis difficult.[13] On the other hand, FDG-PET had an advantage in detecting remote metastases such as supraclavicular lymph nodes or bone metastases. However, all of our patients with remote metastases already had indicated localized advanced cancer. Our results showed that precise intra-abdominal tumor staging by MD-CT was more important than the diagnosis of the remote metastatic lesions made by FDG-PET.

In general, the application of FDG-PET may not be suitable for the diagnosis of pancreatic cancer. Malignant lymphoma shows a high accumulation of FDG, occasionally with an SUV of over 40.[21] However, pancreatic cancer does not have a high accumulation of FDG, as the mean SUV in our patients was only 6.7±3.7, which is half the mean value observed in patients with colon cancer at our institution (data not shown). This poor accumulation makes tumor identification difficult. In addition, in the report suggesting a high sensitivity, the cutoff value for SUV was 2.5.[7] Other reports also suggested that the optimal cutoff value of FDG uptake in differentiating benign from malignant pancreatic lesions was 2.0.[10] On examining the SUV of the normal pancreas, we found that the mean SUV value was 2.0 (n=10). Therefore, these small differences (6.7–2.0) might be an important contributing factor in the overestimation or misdiagnosis of pancreatic cancer. In addition, FDG accumulation is not specific to malignant tumors. It is well known that inflammatory cells show glucose accumulation due to up-regulated glucose uptake in macrophages and other cell lines.[22] Even in tumor tissues, it has been estimated that 24% of the FDG uptake is related to tumor-associated inflammatory cells.[13] This can be problematic, particularly in papers reporting on the usefulness of FDG-PET in evaluating tumor response to chemoradiation therapy where the contribution from changing inflammatory cell response can be misinterpreted as actual tumor cell response. Given these issues, assessing the therapeutic effect of pancreatic cancer, especially in weak SUV lesions of the pancreas, appears problematic using FDG-PET.

This study has several limitations. First, our analysis is retrospective to data collection. However, our data were collected in a consecutive manner and from a corrected database. This differs from previous studies reported in a small number of patients. In our study, we evaluated over 100 patients and determined the relative value of pancreatic cancer. Second, in our analysis of the detection rates of metastatic lesions using either MD-CT or FDG-PET, we lack pathological confirmation of cancer tissues from the tumor invading arteries or distant metastases (bone or remote lymph nodes), which limits the precision of our findings, although clinical decisions are made quite frequently based on solid imaging findings without corresponding pathologic confirmation. There have been no studies that analyze the detection rates of metastatic sites

of cancer using FDG-PET, but there are many studies that examine the sensitivity and specificity of detecting the main tumors. Therefore, in this paper, we focused on the impact of therapeutic decision making for therapy.

The revolution in technological advances in diagnostic imaging is prominent. MD-CT scanning speeds have markedly improved. Faster scanners make it possible to get a large volume of data from the whole body and high spatial resolution images during different phases (arterial and venous) after intravenous contrast administration in a single breath-hold.[24] Now, it is possible to obtain whole body imaging by MD-CT scanning (Fig. 5). Therefore, the value of FDG-PET as a whole body examination becomes less interesting. However, our study is not meant to discourage the use of FDG-PET. Indeed, FDG-PET scanning makes a significant contribution in the search for unknown tumor spread and recurrence. FDG-PET scanning may be useful in conducting an approximate screening for tumor spread and recurrence. Therefore, while our data show that FDG-PET is not useful as a routine diagnostic tool in patients with pancreatic cancer, it may be useful on a selective basis in conducting screening for distant metastatic disease.

Conflict of interest The authors declare no conflict of interest and no financial arrangement with any company.

References

1. Brennan DD, Zamboni GA, Raptopoulos VD et al. Comprehensive preoperative assessment of pancreatic adenocarcinoma with 64-section volumetric CT. Radiographics 2007;27:1653–1666
2. Huguet F, Girard N, Guerche CS, et al. Chemoradiotherapy in the management of locally advanced pancreatic carcinoma: a qualitative systematic review. J Clin Oncol 2009;27:2269–2277
3. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA 2007;297:267–277
4. Vin Y, Sima CS, Getrajdman GI, et al. Management and outcomes of postpancreatectomy fistula, leak, and abscess: results of 908 patients resected at a single institution between 2000 and 2005. J Am Coll Surg 2008;207:490–498
5. Fischer B, Lassen U, Mortensen J, et al. Preoperative staging of lung cancer with combined PET-CT. N Engl J Med 2009;361:32–39
6. Seam P, Juweid ME, Cheson BD. The role of FDG-PET scans in patients with lymphoma. Blood 2007;110:3507–3516
7. Zafra M, Ayala F, Gonzalez-Billalabeitia E, et al. Impact of whole-body 18F-FDG PET on diagnostic and therapeutic management of Medical Oncology patients. Eur J Cancer 2008;4:1678–1683
8. Annovazzi A, Peeters M, Maenhout A, et al. 18-fluorodeoxyglucose positron emission tomography in nonendocrine neoplastic disorders of the gastrointestinal tract. Gastroenterology 2003;125:1235–1245
9. Heinrich S, Goerres GW, Schäfer M et al. Positron emission tomography/computed tomography influences on the management of resectable pancreatic cancer and its cost-effectiveness. Ann Surg 2005;242:235–243
10. Delbeke D, Rose DM, Chapman WC, et al. Optimal interpretation of FDG PET in the diagnosis, staging and management of pancreatic carcinoma. J Nucl Med 1999;40:1784–1791
11. Saif MW, Cornfeld D, Modarresifar H, et al. 18F-FDG positron emission tomography CT (FDG PET-CT) in the management of pancreatic cancer: initial experience in 12 patients. J Gastrointestin Liver Dis 2008;17:173–178
12. Beyer T, Townsend DW, Brun T, et al. A combined PET/CT scanner for clinical oncology. J Nucl Med 2000;41:1369–1379
13. Higashi T, Saga T, Nakamoto Y, et al. Diagnosis of pancreatic cancer using fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET)—usefulness and limitations in "clinical reality." Ann Nucl Med 2003;17:261–279
14. Fortner JG, Klimstra DS, Senie RT, et al. Tumor size is the primary prognosticator for pancreatic cancer after regional pancreatectomy. Ann Surg 1996;223:147–153
15. Isasi CR, Lu P, Blaufox MD. A metaanalysis of 18*F*-2-deoxy-2-fluoro-D-glucose positron emission tomography in the staging and restaging of patients with lymphoma. Cancer 2005;104:1066–1074
16. Gould MK, Maclean CC, Kuschner WG, et al. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. JAMA 2001;285:914–924
17. Frohlich A, Diederichs CG, Staib L. Detection of liver metastases from pancreatic cancer using FDG PET. J Nucl Med 1999;40:250–255
18. Terauchi T, Murano T, Daisaki H, et al. Evaluation of whole-body cancer screening using 18*F*-2-deoxy-2-fluoro-D-glucose positron emission tomography: a preliminary report. Ann Nucl Med 2008;22:379–385
19. Yamamoto F, Nakada K, Zhao S, et al. Gastrointestinal uptake of FDG after *N*-butylscopolamine or omeprazole treatment in the rat. Ann Nucl Med 2004:18:637–640
20. Gambhir SS, Shepherd JE, Shah BD, et al. Analytical decision model for the cost-effectiveness management of solitary pulmonary nodules. J Clin Oncol 1998;16:2113–2125
21. Ngeow JY, Quek RH, Ng DC, et al. High SUV uptake on FDG-PET/CT predicts for an aggressive B-cell lymphoma in a prospective study of primary FDG-PET/CT staging in lymphoma. Ann Oncol 2009;20:1543–1547
22. Miele E, Spinelli GP, Tomao F, et al. Positron emission tomography (PET) radiotracers in oncology—utility of 18*F*-fluoro-deoxy-glucose (FDG)-PET in the management of patients with non-small-cell lung cancer (NSCLC). J Exp Clin Cancer Res 2008;27:52
23. Bang S, Chung HW, Park SW, et al. The clinical usefulness of 18-fluorodeoxyglucose positron emission tomography in the differential diagnosis, staging, and response evaluation after concurrent chemoradiotherapy for pancreatic cancer. J Clin Gastroenterol. 2006;40:923–929.
24. Parsons CM, Sutcliffe JL, Bold RJ. Preoperative evaluation of pancreatic adenocarcinoma. J Hepatobiliary Pancreat Surg 2008;15:429–435

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ORIGINAL ARTICLE

A Single Institution Review of Adjuvant Therapy Outcomes for Resectable Pancreatic Adenocarcinoma: Outcome and Prognostic Indicators

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Abstract
Introduction A large single-institution series of patients who recently underwent pancreaticoduodenectomy for resectable pancreatic cancer was analyzed to determine prognostic factors for overall survival, including the impact of adjuvant radiation and chemotherapy.
Methods Medical records were reviewed for 179 consecutive patients treated at The Cleveland Clinic with pancreaticoduodenectomy for resectable pancreatic adenocarcinoma from 1999 to 2006. Clinical data were collected, and Kaplan–Meier method was used to estimate overall survival. Univariate and multivariate analysis was performed.
Results One hundred seventy-nine patients with pT1-3N0-1M0 pancreatic cancer met the above criteria. But analysis was available for 158 patients. Median age at diagnosis was 67 (range 35–93). Peri-operative mortality rate was 0.6%. On univariate analysis, poor prognostic factors for overall survival were poorly differentiated histology, lymph node positive disease, elevated alkaline phosphatase, elevated total bilirubin, elevated AST, age at diagnosis >70, and high T stage. On multivariate analysis, poorly differentiated histology (p=.001), age >70 (p=.007), lymph node involvement (≥3 positive vs <3, p=.03), and elevated LFTs (alkaline phosphatase and/or bilirubin and/or AST; p=.002) were independent predictors of survival. Median survival for patients treated with adjuvant chemo-XRT was 28.4 months (vs. 11.8 months for patients receiving no adjuvant therapy (p<.001) in both univariate analysis and in multivariate analysis after adjusting for the independent prognostic factors described above). Median survival for patients treated with adjuvant chemotherapy alone had not yet been reached (p<.001 compared to no adjuvant therapy, in both univariate and multivariate analysis).
Conclusion In the twenty-first century, curative-intent surgery for pancreatic cancer at large academic institutions can have very low mortality rates. Pathology findings are valuable prognostic markers in resected pancreatic cancer. Few studies have examined the prognostic value of preoperative LFTs or lymph node ratio, and our analysis indicates they may have prognostic value—this should be confirmed in other series. Pts who receive adjuvant therapy (chemo-XRT or chemotherapy) appear to live longer than patients who receive no adjuvant therapy in this retrospective analysis.

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Introduction

In the USA, approximately 37,000 people are diagnosed each year with pancreatic cancer.[1] Approximately 20% of these cases are resectable, and surgical resection remains the only curative treatment modality for this disease.

Table 1 Patient Characteristics

	All patients n=158	Observation n=26	Chemotherapy n=25	Chemo-radiation n=107	p Value[a]
Gender—no (%)					
Male	88 (56)	14 (54)	16 (64)	58 (54)	
Female	70 (44)	12 (46)	9 (36)	49 (46)	.66
Age					
≤70	108 (68)	15 (58)	10 (40)	83 (78)	
>70	50 (32)	11 (42)	15 (60)	24 (22)	<.001
Age, median (range)	66 (35–93)	68 (41–81)	75 (53–93)	65 (35–82)	<.001[j]
T stage—no. (%)[b]					
T1	16 (10)	3 (12)	7 (29)	6 (6)	
T2	41 (26)	7 (28)	6 (25)	28 (26)	
T3	98 (63)	15 (60)	11 (46)	73 (68)	.02
No. nodes sampled[c]					
Median (range)	10 (0–56)	8 (0–26)	12 (6–36)	10 (0–56)	.05[j]
No. positive nodes—no. (%)[c]					
≤3	118 (77%)	20 (80%)	17 (71%)	81 (77%)	
>3	36 (23%)	5 (20%)	7 (29%)	24 (23%)	.73
Median (range)	1 (0–13)	2 (0–6)	1 (0–13)	1 (0–13)	.48[j]
% Positive nodes—no. (%)[c,d]					
≤15%	84 (55%)	12 (50%)	15 (63%)	57 (55%)	
>15%	68 (45%)	12 (50%)	9 (37%)	47 (45%)	.68
Median (range)	13 (0–100)	15 (0–100)	12 (0–67)	12 (0–100)	.75[j]
N stage—no. (%)[c]					
N0	47 (31)	7 (28)	4 (17)	36 (34)	
N+	107 (69)	18 (72)	20 (83)	69 (66)	.23
Resection margin—no. (%)					
R0	120 (76)	16 (62)	20 (80)	84 (78)	
R1	38 (24)	10 (38)	5 (20)	23 (22)	.17
Grade—no. (%)[c]					
Well-differentiated	17 (11)	3 (12)	4 (16)	10 (10)	
Moderate	83 (54)	13 (52)	15 (60)	55 (53)	
Poor	54 (35)	9 (36)	6 (24)	39 (37)	.73
Alkaline phosphatase—no. (%)[e,i]					
Normal	61 (39)	12 (46)	11 (44)	38 (36)	
Elevated	95 (61)	14 (54)	14 (56)	67 (64)	.56
Median (range)	203 (4–2,349)	178 (34–999)	173 (4–2,349)	242 (33–1,938)	.07[j]
Total bilirubin—no. (%)[e,i]					
Normal	74 (47)	16 (62)	14 (56)	44 (42)	
Elevated	82 (53)	10 (38)	11 (44)	61 (58)	.13
Median (range)	1.8 (0.2–88.0)	0.9 (0.2–18.0)	1.0 (0.3–28.0)	2.0 (0.3–88.0)	.06[j]
AST (SGOT)—no. (%)[e,i]					
Normal	56 (36)	12 (46)	10 (40)	34 (32)	
Elevated	100 (64)	14 (54)	15 (60)	71 (68)	.38
Median (range)	56 (8–795)	44 (14–271)	47 (15–795)	61 (8–523)	.27[j]
ALT (SGPT)—no. (%)[f,i]					
Normal	57 (38)	11 (46)	11 (44)	35 (34)	
Elevated	94 (62)	13 (54)	13 (56)	67 (66)	.45
Median (range)	66 (2–758)	62 (12–443)	50 (4–758)	67 (2–722)	.21[j]
Albumin—no. (%)[f,i]					
Normal	84 (55)	9 (35)	12 (50)	63 (62)	

Table 1 (continued)

	All patients $n=158$	Observation $n=26$	Chemotherapy $n=25$	Chemo-radiation $n=107$	p Value[a]
Decreased	68 (45)	17 (65)	12 (50)	39 (38)	.04
Median (range)	3.6 (1.7–152.0)	3.1 (1.8–4.7)	3.4 (1.7–4.8)	3.7 (1.8–152.0)	.02[j]
Anemia—no. (%)[h,i]					
No	78 (50)	13 (50)	9 (36)	56 (53)	
Yes	79 (50)	13 (50)	16 (64)	50 (47)	.32
Median (range)	13.0 (5.0–112.0)	13.0 (5.0–15.0)	12.0 (8.9–15.0)	13.0(6.0–112.0)	.54[j]

[a] Overall p values for the comparing distributions between patients who received no adjuvant therapy, adjuvant chemotherapy only, and adjuvant chemoradiation; p values are from chi-square tests unless otherwise specified

[b] Missing for three patients

[c] Missing for four patients

[d] Number of positive nodes as a percentage of the number sampled; patients with no sampling were assigned a value of 0

[e] Missing for two patients

[f] Missing for seven patients

[g] Missing for six patients

[h] Missing for one patient

[i] Upper limit of laboratory's reference range: alkaline phosphatase, 120 U/L; total bilirubin, 1.5 mg/dL; AST, 40 U/L; ALT males 50 U/L, females 45 U/L; lower limit of laboratory's reference range: albumin, 3.5 g/dL; hemoglobin males 13.5 g/dL, females 12.0 g/dL

[j] Kruskal–Wallis test

Even in patients with resected pancreatic cancer, 5-year survival rates remain low at 10–30%.[2–4]Median survival is only 10–20 months secondary to local as well as systemic re-occurrence.[2,5,6] Therefore, adjuvant therapy (chemotherapy or chemo-XRT) has been widely used in an attempt to improve outcomes. However, clinical trials investigating adjuvant therapy have resulted in conflicting results.

Two retrospective analysis of statistics from the SEER registry concluded that there was improved survival with the use of adjuvant XRT compared to surgery alone[7,8]while EORTC trial did not find a statistically significant benefit for adjuvant chemo-XRT, and the ESPAC-1 trial found that outcome was worse with use of chemo-XRT [5,9]

Therefore, in Europe, chemotherapy is generally used without radiation in adjuvant treatment of pancreatic cancer. In advanced pancreatic cancer, gemcitabine is considered standard chemotherapy based on phase III trial by Burris et al. showing clinical benefit as well as overall survival compared to 5-FU.[10] Based on this promising result, CONKO-001 (Charité Onkologie) trial was initiated using gemcitabine as an adjuvant treatment. This trial showed that adjuvant chemotherapy gemcitabine was associated with not only significant increase in median disease free survival but also overall survival.[11]

Because of these conflicting trial results, the continued reporting of patient outcomes based on type of adjuvant therapy in pancreatic cancer remains worthwhile. The goal of this study was to examine modern outcomes of resected pancreatic cancer at a large single institution. This included an analyses of prognostic factors and impact of adjuvant therapy.

Methods

This study was approved by the Cleveland Clinic Institutional Review Board. A single institution surgical archive was searched for patients who underwent pancreaticoduodenectomy for resectable pancreatic adenocarcinoma from 1999 and 2006. Patients were required to be pT1-3N0-1M0. Exclusion criteria included metastatic or unresectable disease at time of surgery, indolent tumor types (e.g., islet cell, mucinous cystadenoma/cystadenocarcinoma), R2 resection, and ampullary carcinoma. One hundred seventy-nine consecutive patients were identified, and institutional review board approval was obtained to conduct this study.

Patient Clinical Data

Clinical, perioperative, and pathology data were collected retrospectively using medical records to extract clinical information (see Table 1). Clinical factors analyzed were age at cancer diagnosis, gender, preoperative labs values (CA19-9, AST/SGOT, ALT/SGPT, alkaline phosphatase, total bilirubin, albumin, white blood count, hemoglobin, platelet count), length of hospital stay, postoperative complications, adjuvant therapy (chemo-XRT, chemothera-

Table 2 Characteristics of Patients Who Did Not Receive Adjuvant Therapy Due to Medical Reasons (n=13)

Factor	Parameter (%)
Gender	
Male	10 (77%)
Female	3 (23%)
Age	
≤70	8 (62%)
>70	5 (38%)
Median (range)	71 (54–80)
T Stage	
T1	0
T2	5 (38%)
T3	8 (62%)
No. nodes sampled	
Median (range)	8 (4–24)
No. positive nodes	
≤3	9 (75%)
>3	3 (25%)
Median (range)	1 (0–6)
% Positive nodes	
≤15%	7 (58%)
>15%	5 (42%)
Median (range)	13% (0–50%)
N Stage	
N0	4 (33%)
N+	8 (67%)
Resection margin	
R0	11 (85%)
R1	2 (15%)
Grade	
Well-differentiated	0
Moderate	5 (42%)
Poor	7 (58%)
Alkaline phosphatase	
Normal	3 (23%)
Elevated	10 (77%)
Median (range)	351 (66–1,918)
Total bilirubin	
Normal	2 (15%)
Elevated	11 (85%)
Median (range)	4.0 (0.2–20.0)
AST	
Normal	3 (23%)
Elevated	10 (77%)
Median (range)	58 (15–329)
ALT	
Normal	3 (23%)
Elevated	10 (77%)
Median (range)	91 (6–313)
Albumin	
Normal	7 (58%)
Decreased	5 (42%)
Median (range)	3.6 (2.0–4.0)
Anemia	
No	7 (54%)
Yes	6 (46%)
Median (range)	12.0 (9.5–15.4)
Survival	
No. deaths	12 (92%)
Median (months)	5.6

py, no adjuvant therapy), length of survival after diagnosis, and cause of death. Pathological data included: tumor location, histologic grade (well, moderate, poorly differentiated), presence of perineural invasion or angiolymphatic invasion, tumor size, T stage, N stage, number of lymph nodes (LNs) dissected, and surgical margin status.

Statistical Analysis

Data were summarized as frequency counts and medians and ranges. For convenience, laboratory data were categorized as being within the normal limits of our laboratory's reference range or above (below) the upper (lower) limit of the range (see Table 3). Overall survival (OS) was defined as time from initial cancer diagnosis until death or until the end of follow-up. Survival distributions were estimated using the method of Kaplan–Meier. The relationships between OS and individual factors were analyzed using the logrank test and Cox proportional hazards model depending on whether the factors were nominal (e.g., resection margin), ordinal (e.g., histologic grade), or measured on a continuum (e.g., age). The Cox proportional hazards model with stepwise variable selection was used to simultaneously assess multiple factors. Significance levels of .10 and .05 were used as the criteria for determining variable entry and retention in models, respectively. Once a final model was determined, internal validation was performed using a bootstrap procedure in which samples of 179 patients were generated randomly (with replacement) from the original study population (also of size n= 179) and analyzed using the stepwise procedure described above. One thousand such samples were generated and analyzed, and the frequency of each factor's inclusion in the resulting models was calculated. Factors that were present in >50% of the models were considered significant and

Table 3 Univariable Survival

Factor	Parameter	Parameter (%) Deaths	Median survival (months)	Hazard ratio (95% CI)[a]	*p* Value[b]
Adj. treatment					
None	26	20 (77%)	11.8		
Chemotherapy	25	7 (28%)	NR[c]	0.22 (0.09–0.53)	<.001
Chemoradiation	107	59 (55%)	28.4	0.34 (0.20–0.57)	<.001
Gender					
Male	88	46 (53%)	27.1		
Female	70	40 (57%)	27.4	0.85 (0.56–1.30)	.45
Age					
≤70	108	59 (55%)	28.1		
>70	50	27 (54%)	17.3	1.26 (0.80–2.00)	.33
Continuous version				1.01 (0.99–1.03)	.61
T Stage					
T1	16	5 (31%)	90.5		
T2	41	18 (44%)	28.4		
T3	98	61 (62%)	19.6	1.55 (1.06–2.25)	.02
No. nodes sampled					
Continuous version				1.00 (0.97–1.03)	.82
No. positive nodes					
≤3	118	59 (50%)	28.5		
>3	36	24 (67%)	17.2	1.82 (1.12–2.94)	.02
Continuous version				1.09 (1.01–1.17)	.03
% Positive nodes					
≤15%	84	34 (40%)	40.9		
>15%	68	47 (69%)	17.3	1.99 (1.28–3.11)	.002
Continuous version				2.42 (1.12–5.24)	.03
N Stage					
N0	47	20 (43%)	46.3		
N+	107	63 (59%)	20.2	1.68 (1.01–2.79)	.04
Resection margin					
R0	120	68 (57%)	27.1		
R1	38	18 (47%)	19.1	0.92 (0.55–1.56)	.77
Grade					
Well-differentiated	17	5 (29%)	NR[c]		
Moderate	83	40 (48%)	29.3		
Poorly	54	38 (70%)	15.1	1.67 (1.17–2.40)	.005
Alkaline phosphatase					
Normal	61	27 (44%)	46.3		
Elevated	95	58 (61%)	19.6	1.69 (1.06–2.67)	.03
Continuous version				1.00 (1.00–1.01)	.02
Total bilirubin					
Normal	74	35 (47%)	36.6		
Elevated	82	50 (61%)	19.6	1.33 (0.86–2.05)	.20
Continuous version				1.02 (0.99–1.05)	.24
AST					
Normal	56	26 (46%)	36.6		
Elevated	100	59 (59%)	19.6	1.49 (0.94–2.37)	.09
Continuous version				1.00 (0.99–1.01)	.17

Table 3 (continued)

Factor	Parameter	Parameter (%) Deaths	Median survival (months)	Hazard ratio (95% CI)[a]	*p* Value[b]
ALT					
Normal	57	31 (54%)	27.1		
Elevated	94	50 (53%)	27.4	1.10 (0.70–1.73)	.67
Continuous version				1.00 (0.99–1.01)	.42
Albumin					
Normal	84	44 (52%)	28.4		
Decreased	68	38 (56%)	23.3	1.29 (0.83–1.99)	.26
Continuous version				1.01 (0.99–1.03)	.14
Anemia					
No	78	43 (55%)	28.1		
Yes	79	43 (54%)	23.3	1.06 (0.70–1.63)	.77
Continuous version				1.00 (0.98–1.03)	.85
No. abnormal labs[d]					
None	38	15 (39%)	90.4		
At least one	118	70 (59%)	19.6	1.99 (1.13–3.48)	.02

[a] For nominal categorical variables, the first group listed is the reference group. For categorical variables that are ordinal and continuous variables, the hazard ratio is the risk associated with an increase of one "unit"—e.g., for each 1 mg/dL increase in bilirubin or T1 vs T2 vs T3

[b] Wald test from proportional hazards model

[c] Not reached

[d] Based on alkaline phosphatase and AST

were used to build a final "bootstrap-based" model. All statistical tests were two-sided, and all analyses were performed using SAS (version 8; SAS Institute Inc, Cary, NC).

Results

Patient Characteristics

One hundred seventy-nine patients with pT1-3N0-1Mo pancreatic adenocarcinoma who underwent pancreaticoduodenectomy were included in this analysis. However, after review of the data, 13 of 40 patients who did not receive adjuvant therapy were not treated for medical reasons such as the presence of metastatic disease, postoperative complications, and poor health; three patients received adjuvant radiation only, two patients received adjuvant therapy but the type was unknown, one patient was a postoperative mortality, and postoperative therapy was unknown for two patients. The present analysis excludes these 21 patients in order to have a homogenous set of patients who were not treated adjuvantly for reasons not specifically (though possibly) linked to the patient's medical condition (e.g., patient choice, lost to follow-up, no reason given), or who received adjuvant chemotherapy or chemoradiation.

Median age at diagnosis was 67 (range 35–93). Median length of postoperative hospital stay was 10 days with in-hospital mortality rate of .6% and a 30-day mortality rate of 2.2%. Out of 158 patients, 86 patients have died (54%) at a median of 27.1 months. Median follow-up for the 72 patients coded as still alive is 24.1 months (range 7.5–92.8 months).

Patient characteristics and pathology characteristics are listed in Table 1. Patients who did not receive adjuvant therapy were generally similar to those who received adjuvant chemotherapy or chemo-XRT. However, patients treated with chemo-XRT tended to be younger ($p<.001$) and to have larger tumors ($p=.003$) than either of the other two treatment groups.

For completeness, Table 2 summarizes characteristics of the patients who did not receive adjuvant therapy for medical reasons. The number of such patients is small; therefore, it is difficult to formally compare them to each of the other patient groups. However, as can be seen by comparing the data in Table 2 to Table 1, patients who did not receive adjuvant therapy for medical reasons tended to be older ($p=.11$), have higher grade tumors ($p=.07$), and higher bilirubin levels ($p=.05$) than the other patients. In addition, they tended to have higher alkaline phosphatase levels than patients who did not receive adjuvant therapy for nonmedical reasons ($p=.03$) and those who received

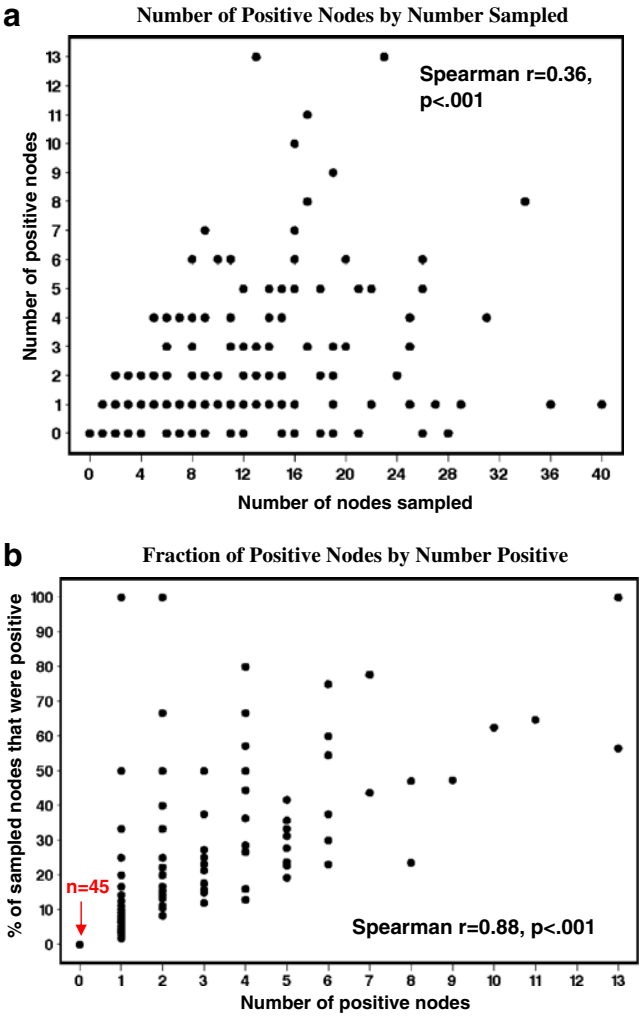

Fig. 1 Positive lymph node fraction by number of positive nodes. **a** Number of positive nodes by number sampled; **b** fraction of positive nodes by number positive.

adjuvant chemotherapy (p=.10). These patients also had a significantly worse prognosis than the other groups—all but one patient have died at a median 5.6 months compared to median survivals of 11.8 months (p=.12) for other untreated patients, 28.4 months for patients treated with chemoradiation (p<.001), and 1-year survival of 88% (median cannot be estimated) for patients treated with chemotherapy alone (p<.001).

Prognostic Factors

Table 3 summarizes univariable analyses of survival. Both categorical and continuous versions of the laboratory data, age, and involved lymph nodes were considered. Groupings of age, number of positive lymph nodes, and proportion of positive lymph nodes where determined using a recursive partioning algorithm.

As shown in Table 3, no adjuvant treatment (p<.001), higher T stage (p=.02), positive lymph nodes (p≤.04 regardless of how it is measured), higher nuclear grade (p=.005), elevated alkaline phosphatase (p≤.03), and elevated AST (p=.09) were all associated with decreased survival. In multivariable analysis, which employed a stepwise selection algorithm with p=.10 and .05 as the criteria for entry and retention in the model, treatment (p<.001), nuclear grade (p=.003), number of elevated labs (based on alkaline phosphatase, and AST (p=.005)), stage (p=.01), and lymph node involvement (≥3 positive vs <3, p=.03) were identified as independent predictors of outcome. Note that the other versions of lymph node status were considered, but this was the only one found to be of prognostic value. It should also be noted that the number of positive nodes was modestly correlated with the number of nodes sampled (Spearman r=0.36, p<.001) but strongly correlated with the proportion of nodes sampled that were positive (Spearman r=0.88, p<.001—Fig. 1). The results of this analysis are summarized in Table 4. Figs. 2 and 3 give Kaplan–Meier plots for each of the factors.

Survival Data Based on Type of Adjuvant Therapy

One hundred seven patients (67%) received chemo-XRT consisting of infusional 5-fluorouracil (225 mg/m^2) concurrent with 50.4 Gy in 1.8 daily fractions. Beginning in 2004, chemo-XRT included 4 months of adjuvant gemcitabine 1,000 mg/m^2 (based on RTOG 9704).[12] Twenty-nine

Table 4 Multivariable Results

Factor	Hazard ratio (95% CI)[a]	p Value[b]
Adjuvant treatment		
None vs chemotherapy	5.00 (1.98–12.66)	<.001
None vs chemoradiation	3.70 (2.13–6.45)	<.001
Grade		
Well vs moderate vs poor	1.75 (1.20–2.56)	.003
Number of elevated labs[c]		
1 or 2 vs 0	2.31 (1.28–4.15)	.005
T stage		
T1 vs T2 vs T3	1.65 (1.13–2.40)	.01
No. (+) lymph nodes		
>3 vs ≤3	1.73 (1.06–2.82)	.03

[a] For treatment, chemotherapy and chemoradiation are each compared to no adjuvant therapy; for number of elevated labs and number of positive lymph nodes, the first group listed is the reference group; for grade and stage the hazard ratio corresponds to the effect of increasing from one group to the next "higher" group, e.g., T1 to T2 and T2 to T3

[b] Wald test from proportional hazards model

[c] Based on alkaline phosphatase and AST

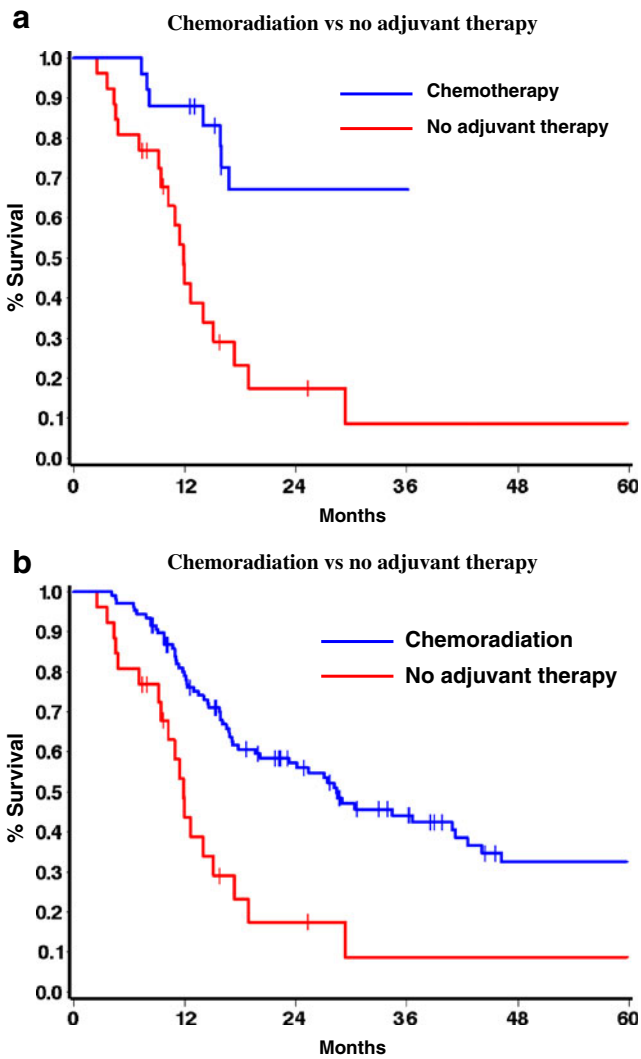

Fig. 2 Overall survival based on type of adjuvant therapy. **a** Chemotherapy vs no adjuvant therapy; **b** chemoradiation vs no adjuvant therapy.

of 107 (27%) chemo-XRT patients received gemcitabine in this manner.

Twenty-three patients (13%) received adjuvant chemotherapy, consisting of gemcitabine 1,000 mg/m^2 (3 out of 4 weeks for 6 months). Twenty-six patients (16%) received no adjuvant therapy after surgical resection.

Median OS for all patients is estimated to be 19.6 months (Table 3). Median survival for the chemo-XRT group was 28.4 months, compared to 11.8 months in the no-adjuvant-therapy group ($p<.001$). Median survival for the chemotherapy group has not yet been reached; however, it also is significantly better than in the no-adjuvant-therapy group ($p<.001$). These differences were still statistically significant ($p<.001$ in both cases) even after adjusting for patient age, histology, and number of elevated liver function tests in multivariate analysis. Fig. 2 shows survival curves based on type of adjuvant therapy.

Discussion

At our institution, 30-day mortality associated with pancreatic surgery was very low at 2.2%. Over time, published series on surgical outcomes for pancreaticoduodenectomy at major academic centers have shown declining in-hospital mortality rates. In the 1960s–1970s, mortality rates of approximately 8–24% were reported but then declined to <5% in the 1980s.[13,14] A Johns Hopkins series from the 1990s reported a further decline to <2% in-hospital mortality,[15] and our modern series of patients (from 1999–2006) continues this clear trend.

In the literature, there definitely appears to be a role for adjuvant therapy for pancreatic cancer with respect to prolonging disease-free survival and also in moderately improving overall survival.[12] But the role of XRT remains undefined. Our findings, from a modern series of Cleveland Clinic patients, clearly demonstrate the benefit from adjuvant treatment after resection of pancreatic cancer but do not answer the question of role of XRT. Overall survival of 28.4 months in patients who received adjuvant chemo-XRT is better than most reported studies.

Our retrospective study suggests either adjuvant chemotherapy or adjuvant chemo-XRT is superior to observation. Our adjuvant chemotherapy cohort typically had lymph node involvement (82%), and usually moderately–poorly differentiated tumors (87%), suggesting that even patients with adverse prognostic features may benefit from chemotherapy. Also notable is the advanced age of the chemotherapy group (median age 75, range 54–93), suggesting that even elderly patients should be considered for adjuvant therapy. For comparison, the median age of patients treated with gemcitabine in the CONKO-001 trial was 62 (range 34–82) with 71% of patients N1 positive and 92% of patients with grade 2–3 tumors. Review of the characteristics of our chemo-XRT cohort (in comparison to our chemotherapy patients) shows a similar rate of poor prognostic features: 65% with lymph node involvement and 90% with high-grade tumors. Our chemo-XRT patients, however, had a higher rate of T3 tumors (68% vs 46%) and were younger (median age 65 vs 75). These differences between the chemo-XRT and chemotherapy groups in our series can be expected since: (1) it is an uncontrolled series and (2) chemo-XRT is a more aggressive approach than chemotherapy and usually associated with more toxicity.

A recent meta-analysis from Europe of 875 patients, including data from three of the major randomized trials, suggested a benefit for chemo-XRT in selected patients but

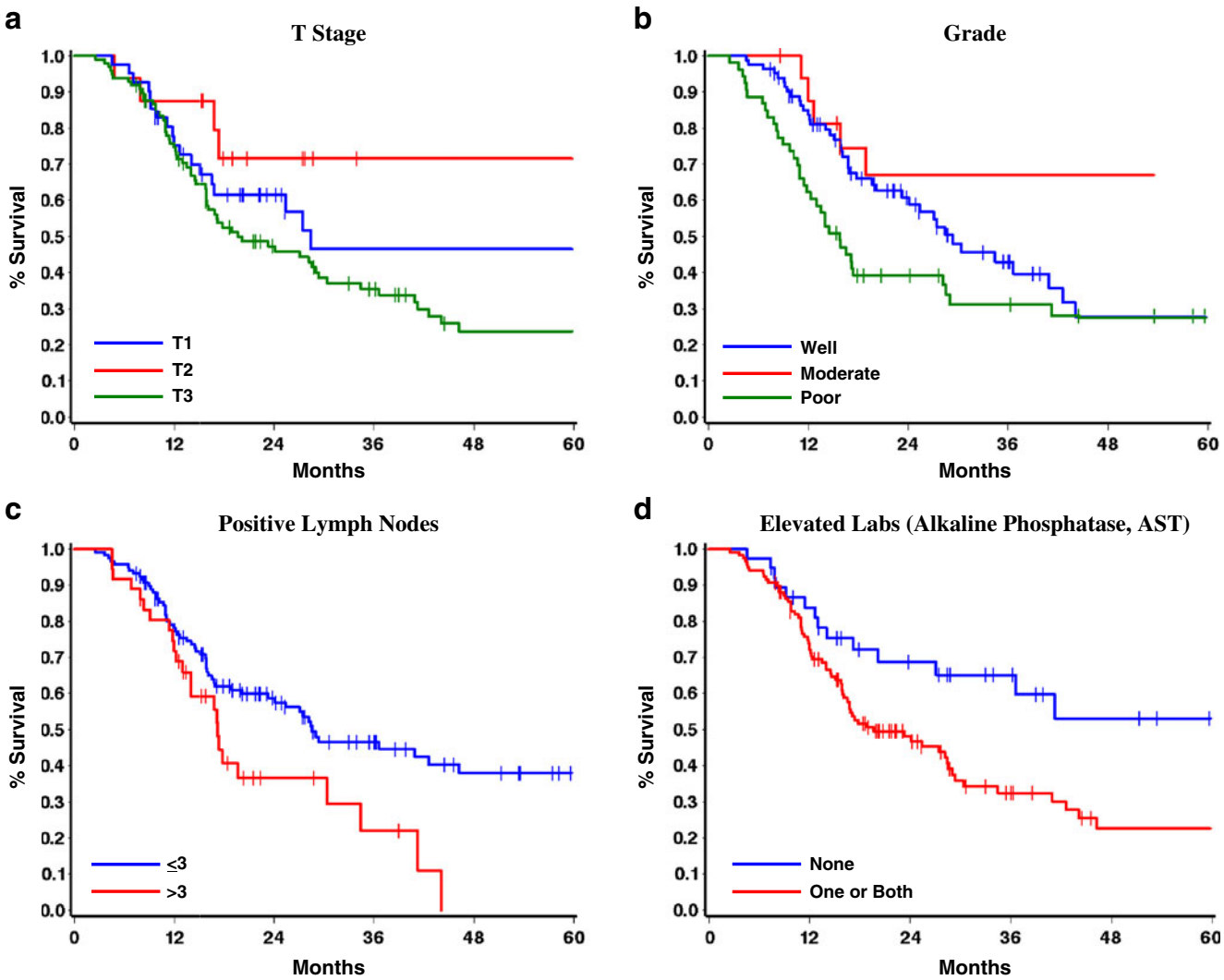

Fig. 3 Clinical factors and survival. **a** T stage; **b** grade; **c** positive lymph nodes; **d** elevated labs (alkaline phosphatase *AST*).

also concluded that chemotherapy alone could be a standard of care.[16]

Our results, showing benefit of chemo-XRT, are supported by data from Johns Hopkins.[17,18] In an early retrospective series of 174 patients,[17] of which 120 patients received adjuvant 5-FU-based chemo-XRT, postoperative chemo-XRT was associated with a significantly better median survival compared to no postoperative treatment. Their findings were later confirmed in another series at the same institution.[18]

It is tempting to postulate that a combination of chemotherapy and chemo-XRT aimed at controlling both local and distant relapses would be of potential benefit in the adjuvant setting. However, RTOG 9704[19] was disappointing as patients who were randomized to gemcitabine followed by 5-FU-based chemo-XRT did not show overall survival benefit.

The poor prognostic factors identified in this study (high-grade tumor, high T stage, positive lymph node involvement, advanced age) are consistent with prior reports on resected pancreatic cancer. A larger retrospective study from Mayo Clinic came to a similar conclusion.[20] In their investigation, the most significant negative prognostic factors for patient survival after an R0 resection were: LN involvement and histologically proven high-grade tumor. A 2003 review of prognostic features in elderly Medicare patients identified important histopathologic factors to be high grade, tumor size, and positive lymph node involvement.[21] In our cohort, patients with R0 resection margin had a trend to living longer (27 vs 19 months), but the finding was not statistically significant. Prior reports have found resection margin to be a valuable prognostic marker, and the reason for a lack of significance in our analysis is unclear.[22,23]

To our knowledge, few studies have examined the prognostic value of preoperative lab values in pancreatic cancer. Previous large series on pancreaticoduodenectomy outcomes did find that surgical morbidity and mortality could be predicted by preoperative liver function tests.[24,25]Our study finds that preoperative liver function tests are of prognostic value in pancreatic cancer. The patients with >1 liver lab abnormalities the median OS was only 19.6 months compared to patients with no lab abnormality in which median OS exceeded 90 months (see Table 3).

In this analysis, we also looked at the prognostic significance of LN status, number of disease-positive nodes, and node ratio. Similar to other studies, patients with nodal involvement did worse in our study (20.2 vs 46.3 months). But prognostic influence of the LN ratio is unclear. In our univariate analysis, number of nodes sampled was not a prognostic factor, but LN ratio and number of positive lymph nodes were independent prognostic factors (Fig. 1). However, in our multivariate analysis, number of positive nodes (>3 nodes) was much stronger predictor of overall outcome (Table 4).

Using preoperative liver function test or LN ratio can become useful tool not only for the individual prediction of prognosis but also for the indication of adjuvant therapy. Ideally, it would be useful if these negative prognostic factors can help us to decide who would benefit from 5-FU-based chemo-XRT versus chemotherapy alone. Future trial should consider stratifying patients based on poor prognostic features to determine which subsets of patients may benefit from XRT.

However, there are several limitations of the current study. This is a retrospective study, which can lead to potential selection bias, as patients who receive no adjuvant therapy are more likely to be older and to have medical comorbidities. Also, because of the low number of patients getting chemotherapy alone, we were not able to interpret whether chemo-XRT was superior to chemotherapy alone in the adjuvant setting.

In conclusion, based on multiple prospective and retrospective data including our own, patients definitely do benefit from adjuvant treatment after pancreatic surgery. Current National Comprehensive Cancer network guidelines suggest either 5-FU-based chemo-XRT (with or without additional gemcitabine) or chemotherapy alone (5-FU or gemcitabine) as reasonable treatment options.

The question remains what is the most optimal adjuvant treatment? Is it chemotherapy or is it chemo-XRT? In Europe, adjuvant chemotherapy is considered standard therapy, while in USA, there is strong feeling towards using concurrent chemo-XRT with or without maintenance chemotherapy. The proponents of XRT believe trials such as ESPAC-1 trial was flawed and misleading because of inferior radiation therapy technique and doses and high rate of positive retroperitoneal margins. The ongoing EORTC phase III trial comparing gemcitabine-based chemo-XRT versus single agent gemcitabine will hopefully provide more insight.[26] Future studies will include the use of novel systemic therapies to reduce the risk of systemic relapses, the use of molecular targeted therapies, and better radiation techniques to reduce the risk of local recurrence. Stratification based on prognostic markers such as extent of resection, lymph node involvement, and margin status before randomization will be crucial to the success of such studies. Continued analysis and trials are needed to establish which type of adjuvant therapy would offer the most benefit to each individual patient. For example, use of XRT in patients with R1 resection or positive lymph nodes should be looked at prospectively to better define the role of XRT. A definitive answer on the optimal adjuvant treatment in pancreatic cancer is unlikely to come in the near future; thus, the debate continues.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. Cancer statistics. CA Cancer J Clin. 2008;58(2):71–96.
2. Yeo CJ, Cameron JL, Lillemoe KD, Sitzmann JV, Hruban RH, Goodman SN, et al. Pancreaticoduodenectomy for cancer of the head of the pancreas. 201 patients. Ann Surg. 1995;221(6):721–31; discussion 731-733.
3. Trede M, Schwall G, Saeger HD. Survival after pancreatoduodenectomy. 118 consecutive resections without an operative mortality. Ann Surg. 1990;211(4):447–458.
4. Tsao JI, Rossi RL, Lowell JA. Pylorus-preserving pancreatoduodenectomy. Is it an adequate cancer operation. Arch Surg. 1994;129(4):405–412.
5. Neoptolemos JP, Dunn JA, Stocken DD, Almond J, Link K, Beger H, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: A randomised controlled trial. Lancet. 2001;358(9293):1576–1585.
6. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: A randomized controlled trial. JAMA. 2007;297(3):267–277.
7. Hazard L, Tward JD, Szabo A, Shrieve DC. Radiation therapy is associated with improved survival in patients with pancreatic adenocarcinoma: Results of a study from the surveillance, epidemiology, and end results (SEER) registry data. Cancer. 2007;110(10):2191–2201.
8. Artinyan A, Hellan M, Mojica-Manosa P, Chen YJ, Pezner R, Ellenhorn JD, et al. Improved survival with adjuvant external-beam radiation therapy in lymph node-negative pancreatic cancer: A united states population-based assessment. Cancer. 2008;112(1):34–42.
9. Klinkenbijl JH, Jeekel J, Sahmoud T, van Pel R, Couvreur ML, Veenhof CH, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: Phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg. 1999;230(6):776,82; discussion 782-4.
10. Burris HA 3 rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical

benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. J Clin Oncol. 1997;15(6):2403–2413.
11. Neuhaus P, Riess H, Post S. CONKO-001: Final results of the randomized, prospective, multicenter phase III trial of adjuvant chemotherapy with gemcitabine versus observation in patients with resected pancreatic cancer (PC). J Clin Oncol. 2008;26. May 20 suppl; abstr LBA4504
12. Boeck S, Ankerst DP, Heinemann V. The role of adjuvant chemotherapy for patients with resected pancreatic cancer: Systematic review of randomized controlled trials and meta-analysis. Oncology. 2007;72(5-6):314–321.
13. Shapiro TM. Adenocarcinoma of the pancreas: A statistical analysis of biliary bypass vs whipple resection in good risk patients. Ann Surg. 1975;182(6):715–721.
14. Crist DW, Sitzmann JV, Cameron JL. Improved hospital morbidity, mortality, and survival after the whipple procedure. Ann Surg. 1987;206(3):358–365.
15. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990 s: Pathology, complications, and outcomes. Ann Surg. 1997;226(3):248–257; discussion 257-60.
16. Butturini G, Stocken DD, Wente MN, Jeekel H, Klinkenbijl JH, Bakkevold KE, et al. Influence of resection margins and treatment on survival in patients with pancreatic cancer: Meta-analysis of randomized controlled trials. Arch Surg. 2008;143(1):75–83; discussion 83.
17. Yeo CJ, Abrams RA, Grochow LB, Sohn TA, Ord SE, Hruban RH, et al. Pancreaticoduodenectomy for pancreatic adenocarcinoma: Postoperative adjuvant chemoradiation improves survival. A prospective, single-institution experience. Ann Surg. 1997;225(5):621–633; discussion 633-6.
18. Herman JM, Swartz MJ, Hsu CC, Winter J, Pawlik TM, Sugar E, et al. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: Results of a large, prospectively collected database at the johns hopkins hospital. J Clin Oncol. 2008;26(21):3503–3510.
19. Regine WF, Winter KA, Abrams RA, Safran H, Hoffman JP, Konski A, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: A randomized controlled trial. JAMA. 2008;299(9):1019–1026.
20. Corsini MM, Miller RC, Haddock MG, Donohue JH, Farnell MB, Nagorney DM, et al. Adjuvant radiotherapy and chemotherapy for pancreatic carcinoma: The mayo clinic experience (1975-2005). J Clin Oncol. 2008;26(21):3511–3516.
21. Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: A population-based, linked database analysis of 396 patients. Ann Surg. 2003;237(1):74–85.
22. Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. Ann Surg. 2006;244(1):10–15.
23. Millikan KW, Deziel DJ, Silverstein JC, Kanjo TM, Christein JD, Doolas A, et al. Prognostic factors associated with resectable adenocarcinoma of the head of the pancreas. Am Surg. 1999;65(7):618–623; discussion 623-4.
24. Winter JM, Cameron JL, Yeo CJ, Alao B, Lillemoe KD, Campbell KA, et al. Biochemical markers predict morbidity and mortality after pancreaticoduodenectomy. J Am Coll Surg. 2007;204(5):1029,36; discussion 1037-8.
25. Schmidt CM, Powell ES, Yiannoutsos CT, Howard TJ, Wiebke EA, Wiesenauer CA, et al. Pancreaticoduodenectomy: A 20-year experience in 516 patients. Arch Surg. 2004;139(7):718–725; discussion 725-7.
26. ClinicalTrials.gov. gemcitabine and radiation therapy compared with gemcitabine alone in treating patients who have undergone surgery for pancreatic cancer. available from URL: http://www.clinicaltrials.gov/ct/show/NCT00064207

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ORIGINAL ARTICLE

Altered Expression of MiR-148a and MiR-152 in Gastrointestinal Cancers and Its Clinical Significance

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Abstract
Background MicroRNAs are endogenous small noncoding RNAs that aberrantly expressed in various carcinomas. MiR-148a and miR-152, which have the same "seed region", have not been comprehensively investigated in gastrointestinal cancers.
Methods Total RNA was extracted from the tissues of 101 patients with gastric cancer and 101 patients with colorectal cancer as well as their matched nontumor adjacent tissues. After polyadenylation and reverse transcription, the expression of miR-148a and miR-152 was determined using quantitative real-time polymerase chain reaction. The protein level of cholecystokinin B receptor, which might be the target gene of miR-148a and miR-152, was analyzed by Western blot in 40 patients with gastric cancer.
Results Expression levels of miR-148a and miR-152 in human gastric ($p<0.001$ and $p=0.038$, respectively, *t*-test) and colorectal (all $p<0.001$) cancers were significantly lower than that in their matched nontumor adjacent tissues. Moreover, their low expression was also found in several gastrointestinal cancer cell lines compared with normal gastric epithelial cell line and normal colorectal tissue, respectively. A strong correlation was found between the expression of miR-148a and miR-152 (all $p<0.001$, Pearson's correlation). Furthermore, low expression of miR-152 was correlated with increased tumor size ($p=0.023$ and 0.004, respectively, Mann–Whitney *U* test) and advanced pT stage ($p=0.018$ and 0.002, respectively) in gastrointestinal cancers. Low expression of miR-148a was also correlated with increased tumor size ($p=0.045$ and 0.018, respectively) in gastrointestinal cancers, but only correlated with advanced pT stage ($p=0.023$) in colorectal cancer. We also found the expression of miR-148a ($p<0.001$, chi-square test) and miR-152 ($p=0.002$) inversely correlated with cholecystokinin B receptor protein in gastric cancer.
Conclusion MiR-148a and miR-152 may be involved in the carcinogenesis of gastrointestinal cancers and might be potential biomarkers in these cancers.

Keywords MicroRNA · Gastrointestinal cancers · miR-148a · miR-152 · Clinicopathologic characteristics

Introduction

MicroRNAs (miRNAs) are endogenously expressed non-coding RNAs that regulate expression of their target genes.[1] In 2002 and 2005, Calin et al.[2,3] studied the expression of miR-15a and miR-16-1 in human B-cell chronic lymphocytic leukemia (CLL) and found that both were absent or down-regulated in patients. Their results provided the first evidence of the involvement of miRNAs in human cancers. Since then, increasing numbers of studies have shown aberrant expression of miRNAs presented in different types of cancers and have shown that miRNAs were involved in the regulation of the proliferation, differentiation, and

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apoptosis.[4] Therefore, miRNAs were deemed to play a crucial role in the initiation and progression of human cancers, which could regulate many oncogenes and tumor suppressor genes.[5]

Several miRNAs have been found to be associated with gastrointestinal cancers. In 2003, Micheal et al.[6] studied the expression of miRNAs in colon cancer and identified miR-143 and miR-145 as potential factors in colon tumorigenesis. Transfection of miR-143 and miR-145 precursors into colon cancer cell lines led to inhibition of cell growth. A member of the let-7 family, let-7a-1, was also found to be down-regulated in colon cancer. Transfection with let-7a-1 precursor decreased expression of RAS and *c*-myc and reduced cell growth.[7] Volinia et al.[8] analyzed the miRNA profiles in 540 samples from six solid tumors, including gastric and colorectal cancer. They identified 22 overexpressed and six down-regulated miRNAs in gastric cancer and 21 overexpressed and one down-regulated miRNAs in colon cancer. MiR-21 was found to be overexpressed in 92% of gastric cancer samples and served as an efficient diagnostic marker in gastric cancer.[9] Xiao B et al.[10] reported overexpression of miR-106a in human gastric cancer and found that it was significantly associated with tumor stage, size, differentiation, metastasis, and invasion. Katada et al.[11] studied the expression of miR-148a in 42 undifferentiated gastric cancer and found that it was down-regulated compared with their matched nontumor adjacent tissues (NATs). Many miRNAs are implicated in gastrointestinal cancers, but studies of a large number of cases about the roles of miR-148a and miR-152 in such cancers are lacking.

Here, for the first time, we examined the expression of miR-148a and miR-152 in a large number of gastrointestinal cancer tissues and several cell lines. We found that miR-148a and miR-152 were down-regulated in cancer tissues compared with their pair-matched NATs. We also discussed the associations between the low expression of these two miRNAs and their clinicopathologic characteristics.

Materials and Methods

Ethical Approval of the Study Protocol

The present study was approved by the Research Ethics Committee of China Medical University (Shenyang, China). Written informed consent was obtained from all patients.

Tissue Samples

Samples of human gastric and colorectal cancer tissues and their corresponding NATs were obtained from 202 patients who underwent radical resection in the First Hospital of China Medical University. Fresh samples were snap-frozen in liquid nitrogen immediately after resection and stored at –80°C. Matching nontumor mucosa specimens were obtained from a part of the resected specimen that was the farthest from the cancer. One section of each sample was stained with hematoxylin–eosin (H&E) for histopathologic evaluation.

One hundred one patients (76 males and 25 females) suffered gastric cancer; the median age was 61 years (range, 26–84 years). The other 101 patients (60 males and 41 females) suffered colorectal cancer; the median age was 63 years (range, 17–82 years). The histologic grade of cancers was assessed according to criteria set by the World Health Organization. The pT classification representing the depth of wall invasion and the pN classification representing the extent of regional lymph node metastasis were performed using standard criteria of 6th TNM staging system.

Cell Lines and Culture Conditions

Human gastric cancer cell lines (AGS, SGC-7901, MGC-803, BGC-823) and one normal gastric epithelial cell line, GES-1 (as control), were obtained from the Institute of Biochemistry and Cell Biology at the Chinese Academy of Sciences (Shanghai, China), as well as colorectal cancer cell lines (HCT-116, SW-620). SGC-7901, MGC-803, and BGC-823 were cultured in RPMI 1640 medium (Invitrogen, Carlsbad, CA) AGS in F-12 K Medium (Invitrogen); GES-1 in Dulbecco's modified Eagle medium (Invitrogen); HCT-116 in McCoy's 5a medium (Invitrogen); and SW-620 in Leibovitz's L-15 medium (Invitrogen). Media were supplied with 10% fetal bovine serum (FBS). Cell lines were cultured at 37°C in a humidified atmosphere of 5% CO_2.

Extraction of Total RNA

Isolation of total RNA and enrichment of small RNA were carried out with the mirVana miRNA Isolation Kit (Ambion, Austin, TX) according to manufacturer's instruction. The concentration and purity of RNA were controlled by UV spectrophotometry (A260/A280 >1.9) using an NanoPhotometer UV/Vis spectrophotometer (Implen, Schatzbogen, München, Germany).

Polyadenylation and Reverse Transcriptase Reaction

Total RNA was polyadenylated with ATP by *Escherichia coli* poly (A) polymerase (E-PAP) at 37°C for 30 min following the manufacturer's instructions for a Poly (A) Tailing Kit (Ambion).[12] After extraction with phenol–chloroform and precipitation with ethanol, RNA was

dissolved in diethyl pyrocarbonate-treated water and reverse transcribed with a superscript III First-Strand Synthesis System for a reverse transcriptase (RT) polymerase chain reaction (PCR) kit (Invitrogen). First, a 10-μL reverse transcriptase reaction mixture containing 1 μg RNA samples, 1 μL RT primer (Table 1), 1 μL 10 mM deoxyribonucleotide triphosphate (dNTP) mix and diethyl pyrocarbonate-treated water at 65°C was incubated for 5 min. Then, a 10-μL mixture containing 2 μL 10× RT buffer, 4 μL 25 mM $MgCl_2$, 2 μL 0.1 M DTT, 1 μL RNaseOUT (40 U/μL), and 1 μL SuperScript III RT (200 U/μL) was added. The total reaction mixture was incubated in an GeneAmp PCR 9700 Thermocycler (Applied Biosystems, Hayward, CA) in a 96-well plate for 50 min at 50°C, 5 min at 85°C, and 20 min at 37°C after adding 1 μL RNase H to the mixture. The mixture was subsequently held at 4°C.

Real-Time PCR

Real-time PCR was done using an Express SYBR greener qPCR supermix Universal Kit (Invitrogen) on a Rotor-gene 6000 system (QIAGEN, Valencia, CA).[12] The 25-μL PCR mixture contained 2 μL reverse-transcribed product, 12.5 μL SYBR Green supermix, 8.5 μL RNase-free water, 1 μL forward, and 1 μL reverse primers (Table 1). The reaction was incubated in a 36-well optical plate by 45 amplification cycles of 94°C for 5 s, 58°C for 20 s, and 72°C for 30 s. We also used U6 RNA as an endogenous reference for normalizing the expression levels of miR-148a and miR-152. Threshold cycle data were determined using default threshold settings. The relative expression levels of miRNAs in cancer compared with their nontumorous controls were calculated using the method of $2^{-\Delta\Delta CT}$.[13] The relative expression ratio of miR-148a and miR-152 was presented as the fold change normalized to an endogenous reference (U6 RNA) and relative to the nontumorous control (normal tissue and normal cell line). Therefore, the value of the relative expression ratio <1.0 was considered as low expression in cancer relative to the nontumorous control.[14] Initially, the amplification efficiencies of miRNAs and U6 RNA were adjusted to be approximately equal. Each sample was analyzed in triplicate and repeated three times. The products of real-time PCR were confirmed by TA cloning and sequencing assay.

Bioinformatics Method

The miRNA targets predicted by computational algorithms[15] were obtained from TargetScan,[16] PicTar,[17] and miRBase targets.[18] The most important criterium for target recognition is base pairing between the "seed region" of miRNA and its target. Seed region, which is the core sequence that encompasses the first two to seven nucleotides at the 5′ portion of miRNA, is essential for the specific suppression of target genes.[19]

Protein Extraction and Western Blot

We randomly selected 40 patients from 101 patients with gastric cancer for Western blot. Total protein was extracted using Total Protein Extraction Kit (KeyGen, Nanjing, JiangSu, China) according to the manufacturer's instruction. Proteins were separated by sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) and electrophoretically transferred to polyvinylidene difluoride membranes (Millipore, Billerica, MA). The membranes were blocked with 5% nonfat dry milk at room temperature for 1 h and incubated at 4°C overnight with antibodies directed against CCKBR (1:200; Abcam, Cambridge, MA) and β-actin (1:5,000; Sigma, St. Louis, MO). The proteins were visualized with ECL Kit (Rockford, IL) and MF-Chemi BIS 3.2 Pro (Micro Photonics, Allentown, PA). The intensity of protein fragments was quantified by FluorChem 2.01 (Alpha Innotech, Santa Clara, CA). CCKBR protein level in

Table 1 RT-PCR Primers for Amplification of Expression of MiR-148a and MiR-152

Primer	Primer Sequence (5′-3′)
RT-primer-1	GCTGTCAACGATACGCTACGTAACGGCATGACAGTGTTTTTTTTTTTTTTTTTTTTTTTA
RT-primer-2	GCTGTCAACGATACGCTACGTAACGGCATGACAGTGTTTTTTTTTTTTTTTTTTTTTTTG
RT-primer-3	GCTGTCAACGATACGCTACGTAACGGCATGACAGTGTTTTTTTTTTTTTTTTTTTTTTTC
miR-148a-F[a]	TCAGTGCACTACAGAACTTTGT
miR-148a-R[b]	GCTGTCAACGATACGCTACGT
miR-152-F[a]	TCAGTGCATGACAGAACTTGGAA
miR-152-R[b]	GCTGTCAACGATACGCTACGT
U6 RNA-F[a]	CGCTTCGGCAGCACATATAC
U6 RNA-R[b]	TTCACGAATTTGCGTGTCAT

[a] Forward primer

[b] Reverse primer

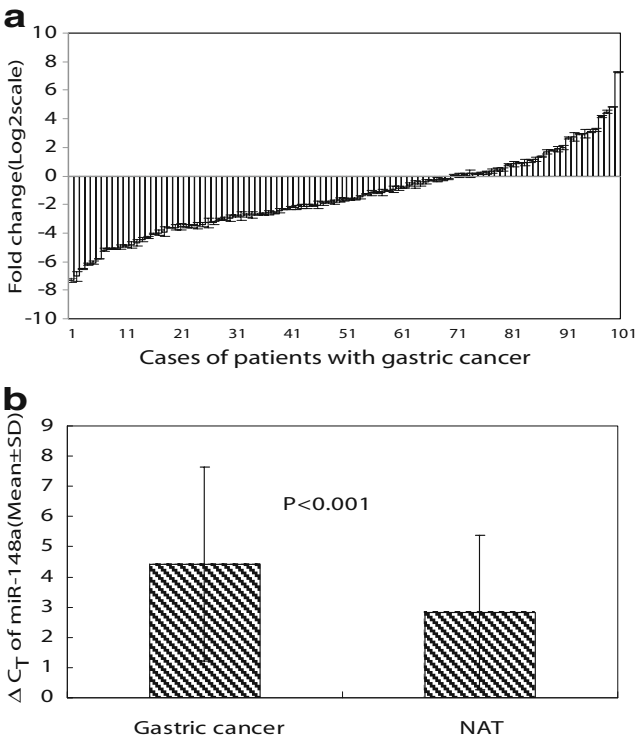

Figure 1 Expression of miR-148a in 101 patients with gastric cancer. **a** Quantification of miR-148a was measured by SYBR Green real-time PCR. Each sample was analyzed in triplicate and repeated three times. Data are presented as log2 of fold-change of gastric cancer relative to its NAT. Boxes represent mean. Error bars represent SD. **b** MiR-148a was differently expressed between gastric cancer and NAT. MiR-148a was normalized by U6RNA. $\Delta C_T = C_{T\ miR\text{-}148a} - C_{T\ U6RNA}$. The ΔC_T of miR-148a in gastric cancer was significantly higher than NAT ($p<0.001$, *t*-test). Boxes represent mean. Error bars represent SD.

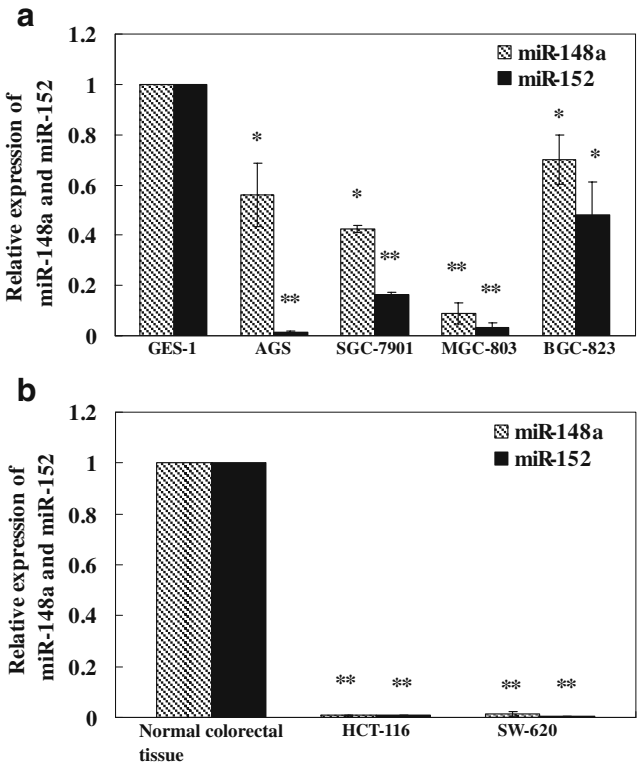

Figure 2 Expression of miR-148a and miR-152 in four gastric cancer cell lines (AGS, SGC-7901, MGC-803, BGC-823) and two colorectal cancer cell lines (HCT-116, SW-620). Quantification of miRNAs was measured by SYBR Green real-time PCR. Data are presented in gastric cancer cell lines relative to GES-1 (which is a normal gastric epithelial cell line and was chosen as control). There is no normal colorectal cell line, so we randomly chose three normal colorectal tissues as control. **a** MiR-148a and miR-152 expression in four gastric cancer cell lines. *$p<0.05$, **$p<0.01$. **b** MiR-148a and miR-152 expression in two colorectal cancer cell lines. **$p<0.01$.

cancer was presented as fold change normalized to an endogenous reference (β-actin protein) and relative to NAT. Therefore, the fold change of CCKBR protein <1.0 was considered as low expression, whereas the fold change of CCKBR protein >1.0 was regarded as high expression.

Statistical Analysis

The expression level in cancer relative to its nontumorous control was calculated using the formula: $2^{-\Delta\Delta CT}$, where $\Delta\Delta C_T$ is the difference of ΔC_T value between the target and the nontumorous control ($\Delta\Delta C_T = \Delta C_{T\ tumor\ miRNA} - \Delta C_T$ nontumor $_{miRNA}$), and ΔC_T is the difference of C_T value between the target and endogenous reference (U6 RNA) ($\Delta C_T = C_{T\ miRNA} - C_{T\ U6\ RNA}$). If expression level of the target and the nontumorous control is equal, $\Delta\Delta C_T$ equals zero and 2^0 equals one.[13] Therefore, by comparing the value of $\Delta C_{T\ tumor\ miRNA}$ and ΔC_T nontumor $_{miRNA}$, we could compare the expression level of miRNA in cancer with its nontumorous control. Statistical differences in the expression of miRNAs in cancer tissues and cell lines relative to the nontumorous control were analyzed by

Table 2 Comparison of ΔCT of Cancer and NAT in Gastrointestinal Cancers

	Gastric Cancer		Colorectal Cancer	
	miR-148a	miR-152	miR-148a	miR-152
ΔCT of cancer (mean±SD)	4.43±3.22	8.57±3.28	6.75±2.17	11.37±2.48
ΔCT of NAT (mean±SD)	2.82±2.56	7.70±2.73	5.49±1.89	8.64±2.34
p	<0.001	0.038	<0.001	<0.001

Table 3 Associations Between the Expression of MiR-148a and MiR-152 With Clinicopathologic Features in Patients With Gastric Cancer

	n	MiR-148a[a]	MiR-152[a]
Sex			
Male	76	0.23 (0.09–1.13)	0.40 (0.15–1.87)
Female	25	0.45 (0.13–1.03)	0.86 (0.25–1.59)
p		0.494	0.532
Age (y)			
≤65	62	0.36 (0.09–1.08)	0.63 (0.19–2.46)
>65	39	0.23 (0.08–1.18)	0.40 (0.14–1.30)
p		0.532	0.299
Tumor size (cm)			
<6	70	0.40 (0.10–1.47)	0.83 (0.28–1.81)
≥6	31	0.16 (0.08–0.57)	0.24 (0.08–1.30)
p		0.045*	0.023*
Tumor location			
Upper stomach	5	0.18 (0.09–0.80)	0.41 (0.15–1.91)
Middle stomach	29	0.49 (0.08–1.15)	0.43 (0.21–2.32)
Lower stomach	65	0.31 (0.09–1.12)	0.53 (0.19–1.53)
Entire stomach	2	14.33 (0.03–28.64)	34.43 (0.10–68.75)
p		0.915	0.971
Macroscopic type			
Early stage	3	1.35 (1.11–1.75)	2.53 (2.23–5.48)
Borrmann I+II	9	0.55 (0.09–0.85)	0.97 (0.24–3.30)
Borrmann III+IV	89	0.25 (0.09–1.09)	0.42 (0.15–1.30)
p		0.212	0.091
Histologic grade			
Good	19	0.21 (0.10–0.75)	0.55 (0.19–1.28)
Poor	82	0.32 (0.09–1.12)	0.47 (0.18–1.89)
p		0.705	0.845
Lauren grade			
Intestinal type	34	0.16 (0.06–1.19)	0.36 (0.13–1.27)
Diffuse type	67	0.35 (0.12–1.11)	0.53 (0.20–2.38)
p		0.200	0.181
pT stage			
T1 + T2	43	0.66 (0.10–1.28)	1.07 (0.28–2.50)
T3+T4	58	0.20 (0.08–0.71)	0.35 (0.11–1.20)
p		0.060	0.018*
pN stage			
N0	24	0.21 (0.07–1.04)	0.47 (0.19–1.97)
N1	38	0.34 (0.12–1.04)	1.04 (0.22–2.30)
N2	22	0.33 (0.08–2.03)	0.36 (0.18–1.39)
N3	17	0.28 (0.09–1.92)	0.35 (0.07–2.77)
p		0.788	0.642
pTNM stage			
I	21	0.31 (0.09–1.12)	0.53 (0.26–2.31)
II	18	0.40 (0.09–1.02)	1.02 (0.20–1.91)
III	38	0.23 (0.08–1.13)	0.38 (0.14–1.20)
IV	24	0.39 (0.15–3.29)	0.61 (0.10–7.47)
p		0.709	0.612
Invasion into lymphatic vessels			
Negative	72	0.33 (0.10–1.12)	0.56 (0.23–2.12)
Positive	29	0.22 (0.06–1.12)	0.40 (0.11–1.39)
p		0.358	0.398

[a] Median of relative expression, with 25th–75th percentile in parenthesis

*Indicated statistical significance ($p<0.05$)

Student's *t*-test, and correlations between miRNA expression and clinicopathologic parameters were analyzed by nonparametric test: Mann–Whitney *U* test between two groups and Kruskal–Wallis test for three or more groups. Correlations between expression levels of miR-148a and miR-152 in gastric and colorectal tissues were evaluated by Pearson's correlation. Statistical significance of correlations between the expression of the two miRNAs and CCKBR protein were calculated by chi-square test (2×2 table Pearson's analysis). Statistical analysis was preformed using SPSS 16.0 computer software (SPSS Inc., Chicago, IL). $p<0.05$ was considered significant.

Results

Expression of miR-148a and miR-152 were down-regulated in gastrointestinal cancer tissues and cancer cell lines compared with nontumorous control Among 101 patients with gastric cancer, 72 (70%) cases showed low expression of miR-148a ($p<0.001$; Fig. 1), and 60 (58%) cases showed low expression of miR-152 ($p=0.038$) in cancer tissues compared with their NATs; The median fold change was 0.28 and 0.50, respectively. Among 101 patients with colorectal cancer, 69 (68%) cases showed low expression of miR-148a ($p<0.001$), and 80 (79%) cases showed low expression of miR-152 ($p<0.001$) in cancer tissues compared with their NATs. The median fold change was 0.36 and 0.11, respectively (Table 2). We also found the low expression of miR-148a and miR-152 with different expression levels among gastric cancer cell lines (AGS [$p=0.026$ and 0.006, respectively], SGC-7901 [$p=0.011$ and 0.004, respectively], MGC-803 [all $p<0.001$], BGC-823 [$p=0.034$ and 0.022, respectively]) relative to normal gastric epithelial cell line (GES-1), and colorectal cancer cell lines (HCT-116, SW-620; all $p<0.001$) relative to three normal colorectal tissues (Fig. 2).

Low expression of miR-148a and miR-152 were associated with increased tumor size and advanced pT stage Patients with lower expression of miR-148a tended to have larger tumor size ($p=0.045$) and patients with lower expression of

miR-152 tended to have larger tumor size (p=0.023) and more advanced pT stage (p=0.018) in gastric cancer (Table 3). In patients with colorectal cancer, lower expression of miR-148a and miR-152 tended to have larger tumor size (p=0.018 and 0.004, respectively) and more advanced pT stage (p=0.023 and 0.002, respectively; Table 4). There were no significant differences between expression of miR-148a and miR-152 with other clinico-

Table 4 Associations Between the Expressions of MiR-148a and MiR-152 with Clinicopathologic Features in Patients with Colorectal Cancer

	n	MiR-148a[a]	MiR-152[a]
Sex			
Male	60	0.30 (0.08–1.09)	0.10 (0.02–0.59)
Female	41	0.64 (0.23–1.25)	0.12 (0.06–1.02)
p		0.096	0.211
Age (y)			
≤65	60	0.40 (0.18–1.23)	0.11 (0.04–0.91)
>65	41	0.32 (0.08–1.14)	0.10 (0.02–0.44)
p		0.367	0.236
Tumor size (cm)			
<6	75	0.54 (0.14–1.72)	0.12 (0.06–1.40)
≥6	26	0.24 (0.07–0.51)	0.05 (0.01–0.19)
p		0.018*	0.004*
Tumor location[b]			
Proximal colon	24	0.46 (0.16–1.40)	0.09 (0.02–0.54)
Distal colon and rectum	77	0.33 (0.11–1.19)	0.11 (0.04–0.90)
p		0.574	0.453
Histologic grade			
Good	80	0.37 (0.15–1.23)	0.11 (0.03–0.97)
Poor	21	0.33 (0.09–1.16)	0.10 (0.03–0.28)
p		0.630	0.555
Dukes stage			
A	15	0.70 (0.06–2.76)	0.11 (0.03–0.47)
B	41	0.37 (0.13–1.02)	0.11 (0.03–0.72)
C	35	0.23 (0.10–1.72)	0.10 (0.03–0.98)
D	10	0.79 (0.30–1.21)	0.17 (0.06–0.93)
p		0.594	0.918
pT stage			
T2 + T3	72	0.57 (0.15–1.58)	0.18 (0.06–0.97)
T4	29	0.21 (0.10–0.47)	0.05 (0.02–0.13)
p		0.023*	0.002*
pN stage			
N0	68	0.37 (0.11–1.17)	0.11 (0.03–0.61)
N1	18	0.21 (0.10–1.14)	0.07 (0.02–0.48)
N2	15	0.41 (0.20–3.23)	0.18 (0.06–2.66)
p		0.535	0.273
pTNM stage			
I	18	0.36 (0.09–1.67)	0.11 (0.05–0.33)
II	50	0.39 (0.15–1.12)	0.11 (0.02–0.73)
III	33	0.33 (0.14–1.45)	0.10 (0.04–1.34)
p		0.892	0.856
Invasion into lymphatic vessels			
Negative	91	0.34 (0.13–1.19)	0.11 (0.03–0.61)
positive	10	0.39 (0.18–3.33)	0.08 (0.04–3.38)
p		0.539	0.838

[a] Median of relative expression, with 25th–75th percentile in parenthesis

[b] Anatomic localization according to splenic flexure

*Indicated statistical significance (p<0.05)

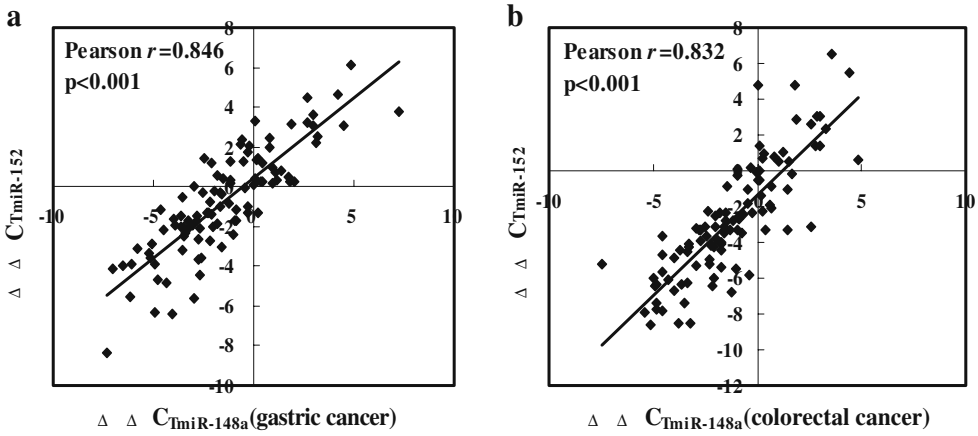

Figure 3 Correlations of expression of miR-148a and miR-152 in patients with gastric and colorectal cancers. $\Delta\Delta C_{TmiRNA} = (C_{TTumormiRNA} - C_{TTumorU6RNA}) - (C_TNontumor_{miRNA} - C_TNontumor_{U6RNA})$. **a** Correlation of the expression of miR-148a and miR-152 in patients with gastric cancer (Pearson r=0.846, p<0.001). **b** Correlation of the expression of miR-148a and miR-152 in patients with colorectal cancer (Pearson r=0.832, p<0.001).

pathologic characteristics including sex, age, tumor location, histologic grade, pN stage, clinical stage, or lymphatic vessel invasion in gastrointestinal cancers.

A strong correlation between the expression miR-148a and miR-152 A strong correlation between the expression levels of miR-148a and miR-152 in gastric and colorectal cancer tissues evaluated by Pearson's regression (p<0.001) was noted in Fig. 3. The correlation coefficients were 0.846 and 0.832, respectively.

The expression of miR-148a and miR-152 inversely correlated with CCKBR Based on computational algorithms obtained from TargetScan, PicTar, and miRBase targets, we predicted six target genes, including CCKBR (Table 5). Western blot from 40 patients in gastric cancer showed an inverse correlation between the protein level of CCKBR and the expression of miR-148a (p<0.001) and miR-152 (p=0.002; Fig. 4 and Table 6).

Discussion

Studies have revealed that miRNAs constitute a robust regulatory network with posttranscription regulation for almost one third of human coding genes. Altered expression of miRNAs has been reported in several tumors and may play a critical role in carcinogenesis.[20] The physiological and pathological roles of miRNAs have been demonstrated in many cancers.[3,10,21] MiRNAs could be quantified by many approaches, including microarray,[22] bead-based flow cytometric assay,[23] and real-time PCR.[12] The main advantage of real-time PCR is more quantitative and sensitive than other assays. In the present study, we used real-time PCR to detect the expression of miR-148a and miR-152 in gastrointestinal cancers.

Real-time PCR results showed the low expression of miR-148a and miR-152 in gastric cancer tissues and cancer cell lines relative to the nontumorous control. Katada et al.[11] studied the expression of miR-148a in 42 undifferentiated gastric cancers and found that it was down-regulated compared with their NATs. Duursma et al.[24] studied the target of miR-148 and found that human miR-148 represses the expression of DNA methyltransferase 3b (Dnmt3b) gene which is frequently disrupted in cancer and contribute directly to carcinogenesis.[25] Taken together, these two miRNAs might play important roles in carcinogenesis of gastric cancer.

Despite some evidence suggesting that miR-148a and miR-152 might be tumor suppressor genes in gastric cancer, the roles of these two miRNAs in cancer progression, such as proliferation and invasion, remain unclear. In the present study, the low expression of miR-148a was found to be associated with increased tumor size and the low expression of miR-152 was associated with increased tumor size and more advanced pT stage in gastric cancer. It is known that tumor size and depth of invasion were significant prognos-

Table 5 Putative Target Genes of MiR-148a and MiR-152

GenBank No.	Official Symbol	Official Full Name
NM_176875	CCKBR	Cholecystokinin B receptor
NM_001130823	DNMT1	DNA (cytosine-5-)-methyltransferase 1
NM_001924	GADD45A	Growth arrest and DNA-damage-inducible, alpha
NM_005450	NOG	Noggin
NM_002941	ROBO1	Roundabout, axon guidance receptor, homolog 1 (Drosophila)
NM_003394	WNT10B	Wingless-type MMTV integration site family, member 10B

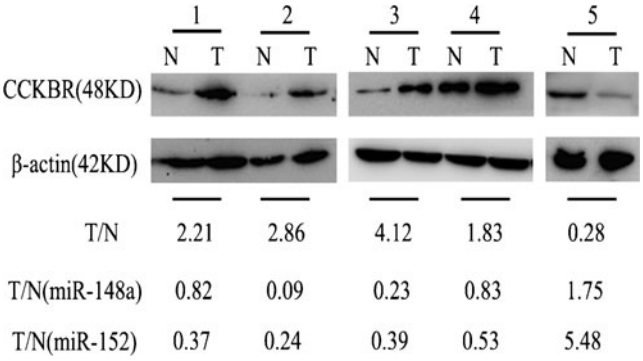

Figure 4 Analysis of CCKBR protein in five gastric cancers and their NATs by Western blot. β-Actin protein was used as an endogenous reference. The intensity of each band was densitometrically quantified. The value of T/N under each paired tissue sample indicated the fold change of level of CCKBR protein in cancer tissues relative to NATs. *T* tumor tissue, *N* NAT, *T/N (miR-148a)* the expression of miR-148a in cancer tissues relative to NATs, *T/N (miR-152)* the expression of miR-152 in cancer tissues relative to NATs.

tic factors for gastric cancer patients.[26,27] Hence, we speculated that low expression of miR-148a and miR-152 might contribute to proliferation and invasion of gastric cancer.

We have similar result concerning colorectal cancer. The low expression of miR-148a and miR-152 was associated with increased tumor size and more advanced pT stage. Takagi et al.[28] found differential expression of miR-148a in two colon cancer cell lines (Caco-2 and differentiated Caco-2) and speculated that miR-148a was increased with differentiation. However, our data from colorectal tissues showed no significant correlation between miR-148a expression and the grade of differentiation.

MiRNAs exert their function by binding to their target genes and constitute a network with posttranscription regulation. In the present study, we found that the low expression of miR-148a was associated with pT stage in colorectal cancer tissues, but was not in gastric cancer tissues. It is known that a single miRNA has multiple targets, and different miRNAs might target the same gene. Hence, miR-148a might have different targets and act differently in gastric and colorectal cancers.

Based on three well-known computational algorithms, we predicted six target genes. CCKBR, one of the predicted target genes, is widely distributed throughout the human gastrointestinal tract tissues. It has proliferative effect on various malignancies including gastric and colorectal cancers.[29,30] Our result revealed an inverse correlation between the protein level of CCKBR and expression of miR-148a and miR-152. Therefore, CCKBR might be one of the target genes of miR-148a and miR-152.

In the present study, we found a strong correlation between miR-148a and miR-152 in gastrointestinal cancer tissues. As shown on the miRbase Website, miR-148a and miR-152 have the same "seed region". Therefore, these two miRNAs might play the similar roles in gastrointestinal cancers.

Many factors reduce the expression of miRNAs. Calin et al.[2] found that loss of miR-15a and miR-16-1 genes was detected in most CLL cases. Three years later, the same research team also identified mutations in the precursor of mir-15a and mir-16-1 in the CLL cases.[3] Epigenetic silencing of miR-124a gene shown by CpG island hypermethylation was found in acute lymphoblastic leukemia.[31] Transcription factors also regulated the expression of miRNAs. MiR-10b, which was highly expressed in metastatic breast cancer, was directly regulated by the transcription factor Twist.[32] These indicated that miRNAs could be regulated by many factors, including deletions, mutations, transcription factors, and methylation. Lehmann et al.[33] demonstrated the aberrant hypermethylation of miR-148 and miR-152 genes in the most of primary human breast cancer tissues. We speculated that methylation of miR-148a and miR-152 might be one of mechanisms of the down-regulation of these two miRNAs in human gastrointestinal cancers. To confirm, it needs further investigation.

Conclusion

This is the first study to show the down-regulation of miR-148a and miR-152 in a large number of gastrointestinal

Table 6 Correlation Between the Expression Of MiR-148a and MiR-152 and CCKBR Protein in Gastric Cancer

	MiR-148a[a]				MiR-152[a]			
	Low	High	*n*	*p*	Low	High	*n*	*p*
CCKBR[b]								
Low	4	7	40	<0.001	3	8	40	0.002
High	28	1			23	6		

[a] Number of cancers with reduced or increased levels of miRNA relative to NATs

[b] Number of cancers with reduced or increased levels of CCKBR protein relative to NATs

cancer tissues, and we also found that their low expression was correlated with increased tumor size and more advanced pT stage. CCKBR might be one of the target genes of miR-148a and miR-152 in gastrointestinal cancers.

Furthermore, large-scale and long-term follow-up studies focusing on the prognostic significance as well as molecular biologic studies that clarify the roles of miR-148a and miR-152 are proceeding in our research group.

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References

1. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 2004;116:281-297.
2. Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, Aldler H, Rattan S, Keating M, Rai K, Rassenti L, Kipps T, Negrini M, Bullrich F, Croce CM. Frequent deletions and down-regulation of micro- RNA genes mir15 and mir16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci USA 2002;99:15524-15529.
3. Calin GA, Ferracin M, Cimmino A, Di Leva G, Shimizu M, Wojcik SE, Iorio MV, Visone R, Sever NI, Fabbri M, Iuliano R, Palumbo T, Pichiorri F, Roldo C, Garzon R, Sevignani C, Rassenti L, Alder H, Volinia S, Liu CG, Kipps TJ, Negrini M, Croce CM. A microRNA signature associated with prognosis and progression in chronic lymphocytic leukemia. N Engl J Med 2005;353:1793-1801.
4. Krützfeldt J, Poy MN, Stoffel M. Strategies to determine the biological function of microRNAs. Nat Genet 2006;38(Suppl): S14-S19.
5. Cho WC. Oncomirs: the discovery and progress of microRNAs in cancers. Mol Cancer 2007;6:60.
6. Michael MZ, O' Connor SM, van Holst Pellekaan NG, Young GP, James RJ. Reduced accumulation of specific microRNAs in colorectal neoplasia. Mol Cancer Res 2003;1:882-891.
7. Akao Y, Nakagawa Y, Naoe T. Let-7 microRNA functions as a potential growth suppressor in human colon cancer cells. Biol Pharm Bull 2006;29:903-906.
8. Volinia S, Calin GA, Liu CG, Ambs S, Cimmino A, Petrocca F, Visone R, Iorio M, Roldo C, Ferracin M, Prueitt RL, Yanaihara N, Lanza G, Scarpa A, Vecchione A, Negrini M, Harris CC, Croce CM. A microRNA expression signature of human solid tumors defines cancer gene targets. Proc Natl Acad Sci USA 2006; 103:2257-2261.
9. Chan SH, Wu CW, Li AF, et al. Mir-21 microRNA expression in human gastric carcinomas and its clinical association. Anticancer Res 2008;28:907-911.
10. Xiao B, Guo J, Miao Y, Jiang Z, Huan R, Zhang Y, Li D, Zhong J. Detection of miR-106a in gastric carcinoma and its clinical significance. Clin Chim Acta 2009;400:97-102.
11. Katada T, Ishiguro H, Kuwabara Y, Kimura M, Mitui A, Mori Y, Ogawa R, Harata K, Fujii Y. MicroRNA expression profile in undifferentiated gastric cancer. Int J Oncol 2009;34:537-542.
12. Shi R, Chiang VL. Facile means for quantifying microRNA expression by real-time PCR. Biotechniques 2005;39:519-525.
13. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2 (delta delta c (T)) method. Methods 2001;25:402-408.
14. Wang CJ, Zhou ZG, Wang L, Yang L, Zhou B, Gu J, Chen HY, Sun XF. Clinicopathological significance of microRNA-31, -143 and -145 expression in colorectal cancer. Dis Markers 2009;26:27-34.
15. Sethupathy P, Megraw M, Hatzigeorgiou AG. A guide through present computational approaches for the identification of mammalian microRNA targets. Nat Methods 2006;3:881-886.
16. Lewis BP, Shih IH, Jones-Rhoades MW, Bartel DP, Burge CB. Prediction of mammalian microRNA targets. Cell 2003;115:787-798.
17. Krek A, Grün D, Poy MN, Wolf R, Rosenberg L, Epstein EJ, MacMenamin P, da Piedade I, Gunsalus KC, Stoffel M, Rajewsky N. Combinatorial microRNA target predictions. Nat Genet 2005;37: 495-500.
18. Griffiths-Jones S, Grocock RJ, van Dongen S, Bateman A, Enright AJ. miRBase: microRNA sequences, targets and gene nomenclature. Nucleic Acids Res 2006;34(Database issue):D140-D144.
19. Lewis BP, Burge CB, Bartel DP. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell 2005;120:15-20.
20. Esquela-Kerscher A, Slack FJ. Oncomirs - microRNAs with a role in cancer. Nat Rev Cancer 2006;6:259-269.
21. Slaby O, Svoboda M, Fabian P, Smerdova T, Knoflickova D, Bednarikova M, Nenutil R, Vyzula R. Altered expression of miR-21, miR-31, miR-143 and miR-145 is related to clinicopathologic features of colorectal cancer. Oncology 2007;72:397-402.
22. Liang RQ, Li W, Li Y, Tan CY, Li JX, Jin YX, Ruan KC. An oligonucleotide microarray for microRNA expression analysis based on labeling RNA with quantum dot and nanogold probe. Nucleic Acids Res 2005;33:e17.
23. Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, Sweet-Cordero A, Ebert BL, Mak RH, Ferrando AA, Downing JR, Jacks T, Horvitz HR, Golub TR. MicroRNA expression profiles classify human cancers. Nature 2005;435:834-838.
24. Duursma AM, Kedde M, Schrier M, le Sage C, Agami R. Mir-148 targets human DNMT3b protein coding region. RNA 2008;14: 872-877.
25. Jin B, Yao B, Li JL, Fields CR, Delmas AL, Liu C, Robertson KD. DNMT1 and DNMT3B modulate distinct polycomb-mediated histone modifications in colon cancer. Cancer Res 2009; 69:7412-7421.
26. Kim DY, Joo JK, Park YK, Ryu SY, Kim YJ, Kim SK. Predictors of long-term survival in node-positive gastric carcinoma patients with curative resection. Langenbecks Arch Surg 2007;392:131-134.
27. Kim JP, Kim YW, Yang HK, Noh DY. Significant prognostic factors by multivariate analysis of 3926 gastric cancer patients. World J Surg 1994;18:872-877; discussion 877-878.
28. Takagi S, Nakajima M, Mohri T, Yokoi T. Post-transcriptional regulation of human pregnane X receptor by Micro-RNA affects the expression of cytochrome P450 3A4. J Biol Chem 2008;283: 9674-9680.
29. Pagliocca A, Wroblewski LE, Ashcroft FJ, Noble PJ, Dockray GJ, Varro A. Stimulation of the gastrin-cholecystokinin(B) receptor promotes branching morphogenesis in gastric AGS cells. Am J Physiol Gastrointest Liver Physiol 2002;283:G292-G299.
30. Colucci R, Blandizzi C, Tanini M, Vassalle C, Breschi MC, Del Tacca M. Gastrin promotes human colon cancer cell growth via CCK-2 receptor-mediated cyclooxygenase-2 induction and prostaglandin E2 production. Br J Pharmacol 2005;144:338-348.
31. Agirre X, Vilas-Zornoza A, Jiménez-Velasco A, Martin-Subero JI, Cordeu L, Gárate L, San José-Eneriz E, Abizanda G, Rodríguez-

Otero P, Fortes P, Rifón J, Bandrés E, Calasanz MJ, Martín V, Heiniger A, Torres A, Siebert R, Román-Gomez J, Prósper F. Epigenetic silencing of the tumor suppressor microRNA Hsa-miR-124a regulates CDK6 expression and confers a poor prognosis in acute lymphoblastic leukemia. Cancer Res 2009;69: 4443-4453.

32. Ma L, Teruya-Feldstein J, Weinberg RA. Tumour invasion and metastasis initiated by microRNA-10b in breast cancer. Nature 2007;449:682-688.
33. Lehmann U, Hasemeier B, Christgen M, Müller M, Römermann D, Länger F, Kreipe H. Epigenetic inactivation of microRNA gene hsa-mir-9-1 in human breast cancer. 2008;214:17-24.

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ORIGINAL ARTICLE

Regulatory Effect of Histamine on the Barrier Function of Intestinal Mucosal

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Abstract
Objectives To investigate the regulatory effect of histamine on the barrier function of intestinal mucosal.
Methods The monolayer Caco-2 cell system in vitro and the model of hemorrhage infection in rats in vivo were established as experimental models. The amount of bacterial translocation was taken as an index of the effect of histamine and its receptor antagon, cimetidine on the intestinal mucosal barrier function.
Results (1) The in vitro experiment showed that after treatment with histamine, the CFU of *Escherichia coli* 075 invading into Caco-2 cells were much lower than that in the control group ($P<0.05$). (2) The animal experiment showed that in the histamine group (hemorrhage infection rats treated with histamine), the average numbers of bacteria in the liver and lymph nodes were much lower than that in control group ($P<0.05$). The mean bacterial number in the cimetidine group (hemorrhage infection rats treated both with histamine and cimetidine) was more than that in the histamine group, but without statistical signification ($P>0.05$). But the rate of translocation to the liver between histamine group (37.5%) and cimetidine group (100%) was statistically different ($P<0.05$)
Conclusion Small concentration of histamine can inhibit bacteria from entering epithelial cells and inhibit intestinal bacterial translocation.

Keywords Histamine · Cimetidine · Intestinal mucosal barrier · Bacterial translocation

Introduction

Recently, the connection between nosocomial pneumonia (NP) and treatment with H2 blockers in critically ill patients has been of concern. The morbidity of NP has been increasing recently, from 0.5% to 11% in all hospitalized patients, even as high as 7% to 49% in patients in intensive care unit (ICU). Nosocomial pneumonia is the second cause of all hospital-acquired infection in America. In some individual studies, morbidity of NP approached 80% of cases in ICU. The mortality of NP varies from 50% to 70%; about 15% of all hospital-associated deaths are directly related to NP.[1–6] H2 blockers are commonly used in ICU to prevent the occurrence of stress ulceration. Clinical studies showed that in critical ill patients, the incidence of NP is 39% in cases treated with cimetidine and ranitidine, while it was 18% in cases treated with antacids and only 8% in cases who had never used such prophylaxis.[7] More and more evidences suggest that the incidence of NP is associated with bacteria coming from the upper intestinal tract in patients treated with H2 blockers.[8–16] Kappstein[17] investigated 104 mechanically ventilated patients in the ICU who were receiving sucralfate ($n=49$) or cimetidine ($n=55$) for stress ulcer prophylaxis. The incidence of pneumonia was 45.5% in the cimetidine group and 26.5% in the sucralfate group (95% confidence interval, 0.98–6.97; odds ratio, 2.61). Mortality rates were 18.4% in the sucralfate group versus 25.5% in the cimetidine

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group ($P>0.05$). The mean pH value of gastric juice was significantly lower in patients treated with sucralfate than in patients with cimetidine, but the number of colony-forming units of Enterobacteriaceae in gastric aspirates was significantly lower in the sucralfate group.[17] In some studies, conventional treatment with H2 blockers did not decrease the incidence of gastrointestinal (GI) bleeding due to stress ulceration but increase the mortality in critically ill patients.[18–21] Conversely, Simms and his colleagues[22] studied 89 critically ill trauma patients in a prospective, randomized trial, and their result suggested that the incidence of pneumonia was not increased by using of stress ulcer prophylaxis agents that elevated gastric pH in trauma patients. They thought that in previous studies there were several apparent flaws in designs. Their opinion was supported by other studies.[23–26] Although there have been numerous clinical and animal experimental studies about cimetidine, there has been no direct evidence about effect of histamine on intestinal microbial translocation. Here, we use the established monolayer Caco-2 cell system[27] and hemorrhage infection animal model to investigate the effect of histamine and cimetidine on intestinal mucosal barrier function in order to provide experimental evidence concerning the relationship between intestinal microbial translocation and H2 blockers.

Materials and Methods

Materials

Caco-2 cell line (HTB38, human colorectal cancer cell line) was purchased from American Type Culture Collection, USA; Dulbecco's modified Eagle medium (DMEM), selected for cell culture medium, was purchased from GIBCO Company, USA. *Escherichia coli* 075 was provided by the Shriners Burn Institute, OH, USA; histamine was obtained from Sigma Company, USA; and SD rats were purchased from the Experimental Animal Center, West China University of Medical Sciences, Chengdu, China.

Methods

Part 1: Experiment In vitro

Monolayer Caco-2 Cell System Caco-2 cells, prepared in a concentration of 1×10^6 cells/ml in Dulbecco's modified eagle's medium (DMEM) with gentamicin, were plated to a 24-well plate, gassed with 5% CO_2, and cultivated for 2 weeks. Fresh medium was replaced every 3 days, and growth status of the cells was evaluated with a microscope. By the second week, the cells spread uniformly at the bottom of the wells, forming a white membrane layer and suitable for the experiments.

Effect of Histamine on the Monolayer Caco-2 Cell System The cultured cells were washed thrice with DMEM to eliminate gentamicin in the culture solution. Then we dispersed 2 mL of DMEM with different concentrations of histamine (1×10^{-6}, 1×10^{-7}, and 1×10^{-8} mol/L) to different well (each concentration of histamine, $n=8$ wells). DMEM without histamine was used as control ($n=8$ wells). After incubating for 2 h, a standard bacterial suspension (3×10^8 CFU/ml) was added into the each well, which was preincubated with histamine-treated or -untreated DMEM (100 μL per well), centrifuged at 3,000 rpm for 5 min in order to make bacteria contact with Caco-2 cells fully, and then incubated for 2 h. After incubation, the medium was removed by aspiration. Gentamicin (5 mg/mL, 20 μL per well) was added to kill extracellular bacteria, and the Caco-2 cells were incubated again for 1 h. The medium was then removed and the wells were washed twice with PBS, and 1% Triton × 100 (oetylphenoxy polythoxyethanol, Sigma), 0.4 ml per well was added. Plates were held at room temperature for 5 to 30 min and then rinsed with pipette repeatedly. The 0.1-ml suspension in each well was taken and diluted six times to do standard bacterial culture. The colon count was observed and recorded for each treatment groups to evaluate bacterial penetration.

Part 2: Animal Experiment

Animal Model Hemorrhage model: Under phenobarbital peritoneal cavity anesthesia, jugular vein catheterization was established and 20% of total blood volume was drawn according rat's body weight. The infection model was created by instilling of 0.3-ml standard bacterial suspension of *E. coli* 075 (3×10^8 CFU/ml) into rats' duodenum by cannulation during laparotomy under anesthesia. Forty-six SD rats were randomly allocated into six groups: Group 1, Sham operation group ($n=7$), these rats were cannulated into duodenum but not inoculated with bacterial mixture. Group 2, hemorrhage group ($n=8$). Group 3, infection group ($n=8$). Group 4, hemorrhage infection group; rats were treated as both method of the groups 2 and 3 ($n=8$). Group 5, histamine treatment group ($n=8$); after the hemorrhage infection models were established as in group 4, then histamine solution (1×10^{-6} mol/L) was infused into the intestinal lumen at a rate of 1.2 ml/h by cannulation. Before the infusion, the peritoneal cavity was closed while a terminal of the canal was left outside. Animals were under anesthesia throughout the process until they were executed 3 h later. Group 6, cimetidine-histamine group ($n=7$); in this group, the cimetidine solution was infused at a dose of 100 mg/kg•d for 2 days before operation and infused with 0.6 mL of histamine solution (1×10^{-6} mol/L) 1 h before. Hemorrhage infection model was established as group 4.

After 3 h, these rats were killed. Mesenteric lymph nodes and liver were removed under strictly aseptic condition and were homogenized with natural saline in ten times of the weight of tissue (1 g/10 mL); then, 0.2 mL of homogenate was inoculated for bacteria quantification.

Statistical Methods

The results of the experiments were expressed as the mean ± standard deviation, and ANOVA test or q test was used for comparing experimental data. The incidence of infected liver and lymph node was tested by Fisher's Confirmed Probability test. The level of significance was taken at a P value of<0.05.

Results

Cell and Bacteria Culture

In this study, after treatment with different concentrations of histamine (1×10^{-6}, 1×10^{-7}, and 1×10^{-8} mmol/L), the CFU of *E. coli* 075 invading into Caco-2 cells were 52.5×10^6, 30.3×10^6, and 91.3×10^6 CFU/mL, respectively, compared to 536.2×10^6 CFU/ml in control group ($P<0.05$). This showed that histamine could remarkably inhibit *E. coli* 075 from invading intestinal epithelial cells ($P<0.05$). There was no statistical significance among each histamine groups with different concentrations ($P>0.05$) (Fig. 1).

Animal Experiment

There was no bacterial translocation in the control group and small amount of bacterial translocation in hemorrhage group and infection group. Bacterial translocation occurred to the liver and lymph nodes in all of the rats in hemorrhage infection group. The average counts of bacteria in lymph nodes and liver were 48.46×10^6 and 82.62×10^6 CFU/g, respectively. There was bacterial translocation found in 62.5% of lymph nodes and 37.5% of liver in rats in histamine group, and the average count of bacteria in lymph nodes and liver in animals of the histamine group was 1.69×10^6 and 0.88×10^6 CFU/g, respectively, which was significantly lower than that in hemorrhage infection group ($P<0.05$).

In cimetidine–histamine group, the incidence of bacterial translocation occurred in 100% of liver and 100% lymph nodes. The average count of bacteria in lymph nodes and liver was 14.69×10^6 and 11.31×10^6 CFU/g, respectively, which was ten times higher than that of the histamine group, but not statistically significant. However, the rate of translocation to the liver between two groups is remarkably different ($P<0.05$) (Tables 1 and 2).

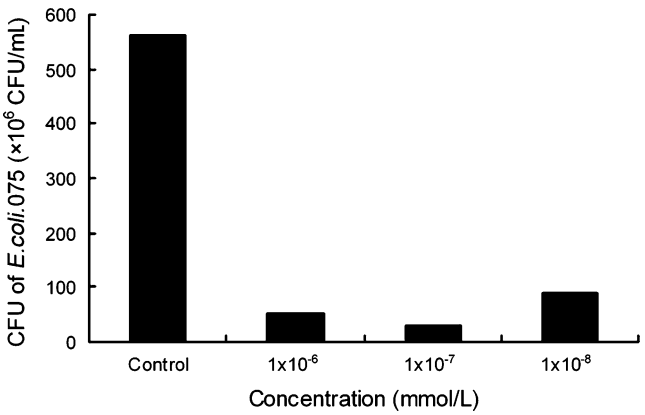

Figure 1 Effect of histamine on bacterial translocation (unit: 1×10^6CFU/mL). *Compared with control group, $P<0.05$.

Discussion

It is well known that the intestinal mucosal barrier is the center of the intestinal defense mechanism. In normal condition, intestinal mucosa can prevent bacteria and endotoxin in the GI tract from entering lymph nodes and the bloodstream. It has been argued that microbial translocation resulting from intestinal barrier dysfunction is the main cause leading to systemic inflammatory reaction syndrome, sepsis, and multiple organs dysfunction.[28–30] Searching for the modulatory factors for intestinal barrier function will help identify effective prevention and treatment for bacterial translocation. Intestinal barrier is a complicated defensive system. It has demonstrated that the important physiological defensive system of intestine consists of the normal intestinal bacterial ecology, expellant movement of intestine, chemical protection of peptic juice, mucosal barrier, and distinctive immune system. It had been found that some members in the growth factor family, such as epithelial growth factor and fibroblast growth factor, can promote growth and maturation of intestinal mucosal epithelium,[31,32] and some proinflammatory cytokines can also modulate the barrier function.[33,34] Ingredients of food, such as glutamine and some special fibers, are important for sustaining the integrity of mucosa.[35–37] But these cannot adequately maintain the modulatory mechanism of mucosal barrier on physiological and pathological conditions.

Histamine is an important mediator, which is abundant in the gastroenteric tract, and it has been proven to be a crucial modulatory factor for the intestinal mucosal barrier.[38,39] Utgaard and other doctors[40] found that after treatment of cultured human microvascular endothelial cells from the intestine (HIMEC) with histamine, a dramatic increase in supernatant IL-8 concentration was observed within 3 min. This indicated that histamine treatment could cause IL-8-containing granules to rapidly release from HIMEC, promote

Table 1 Translocation to Liver and Lymph Nodes (1×10^6CFU/g)

	SG	HG	IG	HIG	HTG1 (1×10^{-4}M)	HTG2 (1×10^{-6}M)	HTG3 (1×10^{-8}M)	CHG
Liver	0	1.38	0.25	82.62	1.214*	1.69*	0.67*	14.69
Lymph *N*	0	0.66	0.59	48.46	1.893*	1.88*	0.25*	11.31

SG sham operation group, *HG* hemorrhage group, *IG* infection group, *HIG* hemorrhage infection group, *HTG1,2,3* histamine treatment group with different concentration, *CHG* cimetidine–histamine group

* HTG compared with the HIG ($P<0.05$)

chemoattractive and adherence of the leukocytes, and alter the local defensive function of intestine.[41] It has been confirmed that enterobacteria can induce mastocyte to proliferate and release histamine and inflammatory cytokines continually to maintain the growth of mucosal epithelial cells and intestinal barrier function.[42] Histamine can facilitate peristalsis of GI tract and reduce the time bacteria stagnate in it, induce secretion of stomach acid, suppress bacterial growth, enhance mucus exudation, improve microcirculation of mucosa, and promote epithelial development and trauma restoration, as well as regulate the amount and function of lymphocyte. All the effects of histamine referred to above can directly or indirectly reinforce the mucosal barrier function, then inhibit bacterial translocation and decrease the morbidity of infection originating in intestine of critical ill patients. In the research of Huneau et al.[43], histamine contents of jejunum, ilenum and colon of rat are 11.9, 11.7, and 7.3 ng/mg w/w, respectively. The histamine content of whole intestinal tract is over 1×10^4 ng by conservative estimation. In our preliminary experiment, histamine was diluted to several concentrations to test the effectiveness and safety on rats. Based on preliminary experiment, we chose a few low but effective concentrations. In the in vivo experiments, the dosing of histamine (399.6 ng [3.6×10^{-6} mmol]) was shown effective, despite the fact that it is much lower than the normal histamine content of intestinal tract of rat. None of the adverse reactions such as flushing of skin or dyspnea were found during the infusion of histamine. However, histamine has been considered to be of no therapeutic value and has not been applied in clinic practice for a long time; the effective and safe dosing for rats or even humans still needs more research.

H_2 receptor antagonists are the main means of treatment and prevention for stress ulceration in many critical conditions. The rationale for this approach is based on reports of reduction in bleeding rates among patients receiving prophylaxis with histamine-2-receptor antagonists.[12–14] However, recent reports found that it had not decreased the mortality of critical diseases. Instead, the incidence of infection in critical patients treated with H_2 receptor antagonists increased significantly.[14,15] Hence, it was felt that H_2 receptor antagonists resulted in bacterial translocation, a major risk factors for systemic infection and MODS. In this experiment, the rates of translocation to lymph node and liver in rats of the cimetidine–histamine group was much higher than those in histamine group ($P<0.05$), and counts of *E. coli* 075 invading intestinal epithelium in cimetidine-histamine group were higher than those of in the histamine group but did not reach statistical significance. The mechanism of histamine inhibiting bacterial translocation is unclear. According to complicated function of histamine, multiplicity of its receptors and receptor antagonists, discordance of the effect, and the advantages and disadvantages in application of H2 blockers to critically ill patients need to be further evaluated.

Table 2 Translocation Rate to Liver and Lymph Nodes

	SG	HG	IG	HIG	HTG1 (1×10^{-4}M)	HTG2 (1×10^{-6}M)	HTG3 (1×10^{-8}M)	CHG
Liver	0%	50%	50%	100%	87%	38%*,#	42%*,#	100%
	(0/7)	(4/8)	(4/8)	(8/8)	(7/8)	(3/8)	(3/7)	(7/7)
Lymph *N*	0%	62%	62%	100%	14%*,#	62%	68%	100%
	(0/7)	(5/8)	(5/8)	(8/8)	(1/7)	(5/8)	(5/7)	(7/7)

SG sham operation group; *HG* hemorrhage group; *IG* infection group, *HIG* hemorrhage infection group; *HTG1,2,3* histamine treatment group with different concentration; *CHG* cimetidine–histamine group

*HTG1,2,3 compare to HIG, $P<0.05$

HTG1,2,3 compare to CHG, $P<0.05$

Competing Interests The authors declare that they have no competing interests.

References

1. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, Wolff M, Spencer RC, Hemmer M. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. JAMA 1995;274:639–644.
2. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement, American Thoracic Society, November 1995. Am J Respir Crit Care Med 1996;153:1711–1725.
3. Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. Am J Med 1993;94:281–288.
4. Leu HS, Kaiser DL, Mori M, Woolson RF, Wenzel RP. Hospital-acquired pneumonia. Attributable mortality and morbidity. Am J Epidemiol 1989;129:1258–1267.
5. Craven DE, Kunches LM, Lichtenberg DA, Kollisch NR, Barry MA, Heeren TC, McCabe WR. Nosocomial infection and fatality in medical and surgical intensive care unit patients. Arch Intern Med 1988;148:1161–1168.
6. Wenzel RP. The mortality of hospital-acquired bloodstream infections: need for a new vital statistic? Int J Epidemiol 1988;17:225–227.
7. Driks MR, Craven DE, Celli BR, Manning M, Burke RA, Garvin GM, Kunches LM, Farber HW, Wedel SA, McCabe WR. Nosocomial pneumonia in intubated patients given sucralfate as compared with antacids or histamine type 2 blockers. The role of gastric colonization. N Engl J Med 1987;317:1376–1382.
8. du Moulin GC, Paterson DG, Hedley-Whyte J, Lisbon A. Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of postoperative colonisation of the airway. Lancet 1982;1:242–245.
9. Daschner F, Kappstein I, Engels I, Reuschenbach K, Pfisterer J, Krieg N, Vogel W. Stress ulcer prophylaxis and ventilation pneumonia: prevention by antibacterial cytoprotective agents? Infect Control Hosp Epidemiol 1988;9:59–65.
10. Tryba M. Prophylaxis of stress ulcer bleeding. A meta-analysis. J Clin Gastroenterol 1991;13 Suppl 2:S44–55.
11. Laggner AN, Lenz K, Gentey LO. The influence of pH elevation on the incidence of nosocomial pneumonia. J Intensive Care Med 1990;5:S17–S21.
12. Garvey BM, McCambley JA, Tuxen DV. Effects of gastric alkalization on bacterial colonization in critically ill patients. Crit Care Med 1989;17:211–216.
13. Tran DD, Cuesta MA, van Leeuwen PA, Nauta JJ, Wesdorp RI. Risk factors for multiple organ system failure and death in critically injured patients. Surgery 1993;114:21–30.
14. Avanoglu A, Herek O, Ulman I, Ergun O, Tunger A, Alkanat M, Erdener A. Effects of H2 receptor blocking agents on bacterial translocation in burn injury. Eur J Pediatr Surg 1997;7:278–281.
15. O'Keefe GE, Gentilello LM, Maier RV. Incidence of infectious complications associated with the use of histamine2-receptor antagonists in critically ill trauma patients. Ann Surg 1998;227:120–125.
16. Basaran UN, Celayir S, Eray N, Ozturk R, Senyuz OF. The effect of an H2-receptor antagonist on small-bowel colonization and bacterial translocation in newborn rats. Pediatr Surg Int 1998;13:118–120.
17. Kappstein I, Schulgen G, Friedrich T, Hellinger P, Benzing A, Geiger K, Daschner FD. Incidence of pneumonia in mechanically ventilated patients treated with sucralfate or cimetidine as prophylaxis for stress bleeding: bacterial colonization of the stomach. Am J Med 1991;91:125S–131S.
18. Ben-Menachem T, Fogel R, Patel RV, Touchette M, Zarowitz BJ, Hadzijahic N, Divine G, Verter J, Bresalier RS. Prophylaxis for stress-related gastric hemorrhage in the medical intensive care unit. A randomized, controlled, single-blind study. Ann Intern Med 1994;121:568–575.
19. Eddleston JM, Vohra A, Scott P, Tooth JA, Pearson RC, McCloy RF, Morton AK, Doran BH. A comparison of the frequency of stress ulceration and secondary pneumonia in sucralfate- or ranitidine-treated intensive care unit patients. Crit Care Med 1991;19:1491–1496.
20. Reusser P, Gyr K, Scheidegger D, Buchmann B, Buser M, Zimmerli W. Prospective endoscopic study of stress erosions and ulcers in critically ill neurosurgical patients: current incidence and effect of acid-reducing prophylaxis. Crit Care Med 1990;18:270–274.
21. Laggner AN, Lenz K, Base W, Druml W, Schneeweiss B, Grimm G. Prevention of upper gastrointestinal bleeding in long-term ventilated patients. Sucralfate versus ranitidine. Am J Med 1989;86:81–84.
22. Simms HH, DeMaria E, McDonald L, Peterson D, Robinson A, Burchard KW. Role of gastric colonization in the development of pneumonia in critically ill trauma patients: results of a prospective randomized trial. J Trauma 1991;31:531–536; discussion 536–537.
23. Ryan P, Dawson J, Teres D, Celoria G, Navab F. Nosocomial pneumonia during stress ulcer prophylaxis with cimetidine and sucralfate. Arch Surg 1993;128:1353–1357.
24. Martin LF, Booth FV, Karlstadt RG, Silverstein JH, Jacobs DM, Hampsey J, Bowman SC, D'Ambrosio CA, Rockhold FW. Continuous intravenous cimetidine decreases stress-related upper gastrointestinal hemorrhage without promoting pneumonia. Crit Care Med 1993;21:19–30.
25. Fiddian-Green RG, Baker S. Nosocomial pneumonia in the critically ill: product of aspiration or translocation? Crit Care Med 1991;19:763–769.
26. Hanisch EW, Encke A, Naujoks F, Windolf J. A randomized, double-blind trial for stress ulcer prophylaxis shows no evidence of increased pneumonia. Am J Surg 1998;176:453–457.
27. Cruz N, Qi L, Alvarez X, Berg RD, Deitch EA. The Caco-2 cell monolayer system as an in vitro model for studying bacterial–enterocyte interactions and bacterial translocation. J Burn Care Rehabil 1994;15:207–212.
28. Nieuwenhuijzen GA, Goris RJ. The gut: the "motor" of multiple organ dysfunction syndrome? Curr Opin Clin Nutr Metab Care 1999;2:399–404.
29. Yao Y, Yu Y, Wu Y, Shi Z, Sheng Z. The role of gut as a cytokine-generating organ in remote organ dysfunction after intestinal ischemia and reperfusion. Chin Med J (Engl) 1998;111:514–518.
30. Ammori BJ. Role of the gut in the course of severe acute pancreatitis. Pancreas 2003;26:122–129.
31. Stern LE, Erwin CR, O'Brien DP, Huang F, Warner BW. Epidermal growth factor is critical for intestinal adaptation following small bowel resection. Microsc Res Tech 2000;51:138–148.
32. Chen W, Fu XB, Ge SL, Sun TZ, Li WJ, Sheng ZY. Acid fibroblast growth factor reduces rat intestinal mucosal damage caused by ischemia-reperfusion insult. World J Gastroenterol 2005;11:6477–6482.
33. McAlindon ME, Mahida YR. Pro-inflammatory cytokines in inflammatory bowel disease. Aliment Pharmacol Ther 1996;10 Suppl 2:72–74.
34. Wong SC, Macrae VE, McGrogan P, Ahmed SF. The role of pro-inflammatory cytokines in inflammatory bowel disease growth retardation. J Pediatr Gastroenterol Nutr 2006;43:144–155.

35. Chen K, Okuma T, Okamura K, Torigoe Y, Miyauchi Y. Glutamine-supplemented parenteral nutrition improves gut mucosa integrity and function in endotoxemic rats. JPEN J Parenter Enteral Nutr 1994;18:167–171.
36. Rao XP, Zhu LQ, Lian HH. Protective effects of glutamine on the intestinal mucosal barrier in young rabbits under hemorrhagic shock. Zhongguo Dang Dai Er Ke Za Zhi 2006;8:66–70.
37. Spaeth G, Specian RD, Berg RD, Deitch EA. Bulk prevents bacterial translocation induced by the oral administration of total parenteral nutrition solution. JPEN J Parenter Enteral Nutr 1990;14:442–447.
38. Chen D, Aihara T, Zhao CM, Hakanson R, Okabe S. Differentiation of the gastric mucosa. I. Role of histamine in control of function and integrity of oxyntic mucosa: understanding gastric physiology through disruption of targeted genes. Am J Physiol Gastrointest Liver Physiol 2006;291:G539–544.
39. Schubert ML. Gastric secretion. Curr Opin Gastroenterol 2005;21:636–643.
40. Utgaard JO, Jahnsen FL, Bakka A, Brandtzaeg P, Haraldsen G. Rapid secretion of prestored interleukin 8 from Weibel–Palade bodies of microvascular endothelial cells. J Exp Med 1998;188:1751–1756.
41. Miyata R, Iwabuchi K, Watanabe S, Sato N, Nagaoka I. Short exposure of intestinal epithelial cells to TNF-alpha and histamine induces Mac-1-mediated neutrophil adhesion independent of protein synthesis. J Leukoc Biol 1999;66:437–446.
42. Meslin JC, Wal JM, Rochet V. Histamine and mast cell distribution in the intestinal wall of the germ free and conventional rats. Influence of the mode of sterilization of the diet. Agents Actions 1990;29:131–137.
43. Huneau JF, Tome D, Wal JM. Histamine content, diamine oxydase and histidine decarboxylase activities along the intestinal tract of the rat. Agents Actions 1989;28:231–234.

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HOW I DO IT

Retrograde Endoscopic-Assisted Esophageal Dilation

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Abstract
Background Esophageal stricture is a well-known complication of chemoradiotherapy for head and neck malignancies. These strictures almost exclusively occur in the cervical esophagus within the field of radiation. For some patients, identification of the esophageal lumen for antegrade dilation of these strictures can be a challenge, and creation of a false lumen can occur during attempts at dilation.
Methods We report a method of identifying the esophageal lumen using retrograde esophagoscopy through an existing gastrostomy, thereby allowing confident dilation of an esophageal stricture.
Results and discussion The esophagoscope is used to pass a guide wire from below the stricture, and this guide wire is used for bougie dilation of the stricture. Following retrograde dilation, we often place a modified feeding tube to preserve the lumen for future dilation attempts.
Conclusion This method can be used to safely place a guide wire for dilation in patients who have a difficult cervical esophageal stricture and an established gastrostomy.

Keywords Esophageal dilation · Esophageal stricture · Retrograde dilation · Head and neck cancer · Chemoradiation

Introduction

Stricture of the esophagus occurs in approximately 20% of patients who undergo chemoradiotherapy for head and neck malignancies.[1,2] These strictures almost exclusively occur in the cervical esophagus within the field of radiation and can be as high as the level of the pyriform sinuses.[3] The resulting fibrosis and tissue fragility, combined with the altered anatomy from previous tumor and postradiation changes, can make safe identification of the esophageal lumen a challenge. "Blind" passage of guide wires or dilators risks the creation of a false lumen or frank perforation and resultant severe infection.

In response to the challenges of safely dilating a completely obstructing cervical esophageal stricture, various authors have described methods of approaching esophageal strictures in a retrograde fashion for dilation with a bougie over guide wire [4,5] or a balloon.[6] We present our method and experience with retrograde placement of a guide wire for dilation of chemoradiotherapy-associated strictures in head and neck cancer patients. This method takes advantage of an existing gastrostomy that is created in all of our advanced head and neck cancer patients who have limited esophageal transit and allows confident passage of a guide wire, enabling restoration of the esophageal lumen.

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Methods

After induction of anesthesia, the patient is turned 90° with respect to the anesthesiologist. We first attempt antegrade rigid or flexible esophagoscopy. In those patients in whom we are unable to safely identify a lumen, either because of an inability to advance the esophagoscope to a place where we can observe distal passage of a guide wire or because of complete stricture, we convert to our retrograde approach.

The patient's gastrostomy tube is removed, and the gastrostomy is dilated with Hegar dilators (Codman, Raynham, MA) to 14 mm, allowing the gastrostomy to accommodate a flexible diagnostic esophagoscope (GIF Q180; Olympus, Center Valley, PA). Care is taken during dilation to prevent separating the gastrostomy opening from the abdominal wall. The esophagoscope is introduced through the gastrostomy and the stomach insufflated with air. The gastroesophageal junction is identified by tracking from the antrum retrograde along the lesser curvature until the dimple that represents this region is evident. Use of fluoroscopy is helpful in accomplishing this. The esophagus is entered and the endoscope advanced to the distal end of the stricture. Sometimes a small lumen is identified in this manner, and a guide wire is passed through the stricture and into the patient's mouth.

At other times, the stricture is confirmed to be complete (Fig. 1). Transillumination with the flexible esophagoscope through the stricture allows a second operator performing antegrade rigid esophagoscopy with a Jesberg rigid esophagoscope to judge the thickness of the stricture (Fig. 2a). Fluoroscopy can also aid in this assessment. If the ends of the esophagoscopes are in close approximation, a 16-Ga needle is passed through the rigid esophagoscope across the stricture and into the distal esophagus, and a guide wire is threaded from the flexible esophagoscope through it in a

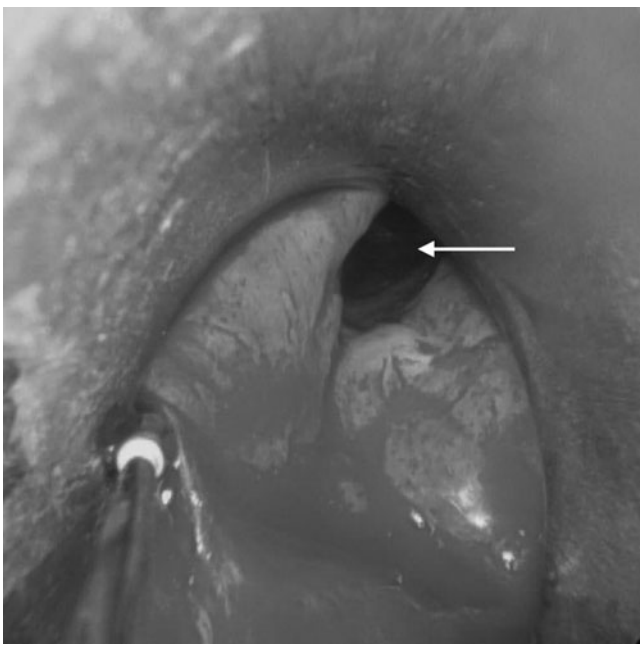

Figure 1 Complete hypopharyngeal/upper esophageal stricture as seen through a Jesberg esophagoscope. The laryngeal inlet is seen superiorly (*arrow*) and blood pools in the postcricoid area.

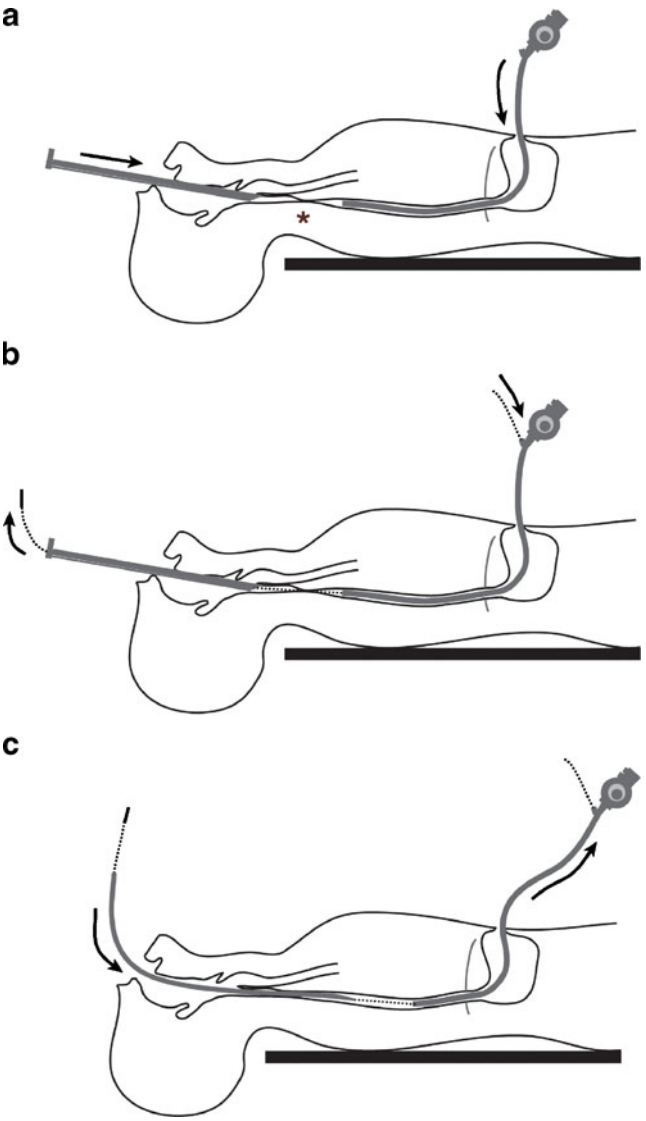

Figure 2 Retrograde esophagoscopy-assisted esophageal dilation. **a** The esophagoscope is passed in a retrograde fashion through a gastrostomy into the esophagus to the level of the stricture (*asterisk*). **b** A guide wire is passed through the working part of the esophagoscope through the stricture and retrieved by an operator performing antegrade rigid esophagoscopy. **c** The rigid esophagoscope is removed and the flexible esophagoscope withdrawn slightly to allow antegrade dilation of the esophagus with a dilator. At the conclusion of the dilation, a nasogastric tube is fed over the guide wire and secured to the gastrostomy to serve as a placeholder for future dilations (not shown).

cephalad direction (Fig. 2b). If a complete stricture is deemed too thick to safely traverse and dilate, the procedure is aborted.

The flexible, blunt tip of the guide wire is clipped off with wire cutters because this tip will not permit passage of a dilator. With the tip removed, Savary-Gilliard (Cook Medical, Bloomberg, IN) or American (CR Bard, Tewksberg, MA) dilators of increasing diameter are serially passed over the wire under fluoroscopic guidance, taking care to gain proximal control of the wire prior to dilation. The transgastric esophagoscope is withdrawn slightly to observe passage of the dilators (Fig. 2c). Typically, we dilate to the largest diameter achievable without tearing the mucosa (Fig. 3). If a linear rent in the mucosa occurs, the procedure is terminated at that point. When the dilation is finished, we use 2 mL of topical Mitomycin C (2 mg/mL) on a cottonoid pledget in three consecutive 2-min applications to retard stricture recurrence; the use of mitomycin C for treatment of esophageal stricture is still under investigation.[7] Alternatively, injection with 80 mg of Kenalog divided in four quadrants may retard stricture recurrence.[8]

At the conclusion of the procedure, prior to replacement of the gastrostomy tube, we pass a Dobbhoff nasogastric feeding tube (Covidien, Dublin, Ireland) through the nose, cut off the weighted end, and then feed the tube over the wire down the esophagus and out of the gastrostomy. The wire is then removed, and the feeding tube is sewn to the gastrostomy site and the anterior nasal septum. This tube serves as a guide to find the lumen in future dilations and to allow easy antegrade passage of a guide wire.

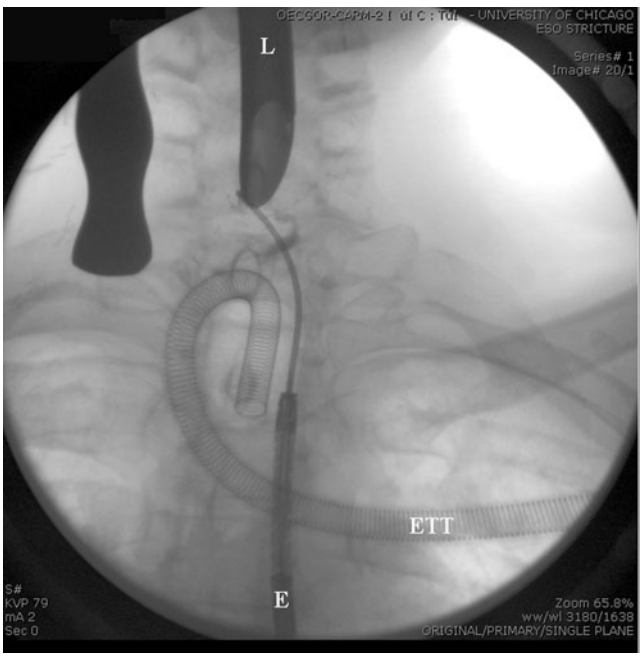

Figure 3 Intraoperative fluoroscopy demonstrates retrograde passage of a guide wire from the esophagoscope (E) in the distal esophagus to the laryngoscope (L) in the hypopharynx. A reinforced endotracheal tube (ETT) placed in the patient's stoma is also seen.

Results

We began using this procedure in 2005. From 2005 to 2008, we employed it on 7 patients, approximately 1.9% of the 361 patients who underwent at least one esophageal dilation by our service during this period for a chemoradiotherapy-associated stricture. One additional patient underwent retrograde esophagoscopy to confirm intraluminal placement of a dilator that demonstrated unusual resistance during passage. Of the seven patients who underwent retrograde placement of guide wire, five were for complete stricture, one was for fibrosis and altered anatomy that made assessment of the cervical esophagus difficult, and one was to ensure esophageal placement in a patient with a history of laryngectomy who had a near-complete stricture that occurred in proximity to the previous pharyngotomy suture line.

Early in our experience, two patients required a repeat retrograde approach on subsequent dilations until we began placing nasogastric feeding tubes as placeholders in the esophagus. The remaining five patients only required one retrograde placement of guide wire, after which time the feeding tube served as a guide. Ultimately, four patients have been able to be sufficiently dilated to no longer need a feeding tube placeholder, two patients continue to have persistent stricture recurrence, and one patient is currently recovering from salvage resection of a postchemoradiation cancer recurrence and is unevaluable with regard to the stricture.

One patient experienced a complication—separation of the stomach from the abdominal wall during dilation of the gastrostomy for passage of the esophagoscope. This was recognized immediately, and an intraoperative repair was performed through a small laparotomy. The patient subsequently underwent retrograde esophagoscopy on another occasion without complication.

Conclusion

In patients with difficult anatomy associated with esophageal stricture, retrograde esophagoscopy can be employed to help safely place a guide wire for esophageal dilation. Care must be taken when dilating the gastrostomy for passage of the esophagoscope. With use of a modified

feeding tube as a placeholder, subsequent dilations can be performed in a standard antegrade manner.

References

1. Lee WT, Akst LM, Adelstein DJ, et al. Risk factors for hypopharyngeal/upper esophageal stricture formation after concurrent chemoradiation. Head Neck 2006;28:808-812.
2. Caudell JJ, Schaner PE, Meredeth RF, et al. Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. Int J Radiation Oncol Biol Phys 2008;73:410–415.
3. Franzmann EJ, Lundy DS, Abitbol AA, Goodwin WJ. Complete hypopharyngeal obstruction by mucosal adhesions: a complication of intensive chemoradiation for advanced head and neck cancer. Head Neck 2006;28:663–670.
4. Garcia A, Flores RM, Schattner M, et al. Endoscopic retrograde dilation of completely occlusive esophageal strictures. Ann Thorac Surg 2006;82:1240–1244.
5. Valentino J, Freeman S, Nickl N. Retrograde esophageal dilation using savary dilators. Laryngoscope 2006;116:2227–2228.
6. Steel NP, Tokayer A, Smith RV. Retrograde endoscopic balloon dilation of chemotherapy- and radiation-induced esophageal stenosis under direct visualization. Am J Otolaryngol 2007;28:98–102.
7. Gillespie MB, Day TA, Sharma AK, Brodsky MB, Martin-Harris B. Role of mitomycin in upper digestive tract strictures. Head Neck 2007;29:12–17.
8. Ramage JI Jr, Rumalla A, Baron TH, et al. A prospective, randomized, double-blind, placebo-controlled trial of endoscopic steroid injection therapy for recalcitrant esophageal peptic strictures. Am J Gastroenterol 2005;100:2419–2425.

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REVIEW ARTICLE

Influence of Anastomotic Leakage on Oncological Outcome in Patients with Rectal Cancer

In Ja Park

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Abstract
Introduction Anastomotic leakages are one of the most serious complications of postoperative recovery among patients that undergo rectal cancer resection. Some investigators have suggested that anastomotic leakages have an impact on the oncological outcome; however, this is currently controversial.
Procedure Considering the increase of sphincter-preserving procedures for rectal cancer, anastomotic leakage, and its impact on oncological outcomes has become an important issue.
Outcome The rates of anastomotic leakage are reported to range between 0.6% and 17.4%, depending on the definitions used. Here, we review the available information on anastomotic leakage and its association with oncological outcome.

Keywords Anastomotic leakage · Rectal cancer · Local recurrence · Survival

Introduction

An anastomotic leakage is one of the most serious complications of rectal cancer resection.

Recently, with an increasing number of sphincter-preserving procedures, there are more patients at risk for possible anastomotic leakage. Despite improvements over the past decade regarding surgical techniques and peri-operative management, anastomotic leakage remains a major problem. Long-term survival has been reported to be affected in patients that develop postoperative complications after major surgery.[1] However, the impact of postoperative complications on the survival and oncological outcomes of patients with colorectal cancer have not been well studied.

Several factors have been shown to be independent prognostic significance for survival following potentially curative resection of colorectal cancer.[2–5] When viable tumor cells in the bowel lumen of patients with colorectal cancer are present at the time of surgery, the risk for micro-metastasis is increased and the presence of anastomotic leakage would be an additional prognostic risk factor. However, there are only a few reports on the association between anastomotic leakage and long-term survival.[6–9] The impact of anastomotic leakage on the immediate postoperative morbidity and mortality is well known. However, it is controversial whether the anastomotic leakage itself is a prognostic factor for local recurrence and/or survival of patients with colorectal cancer.[10] Although some investigators report that anastomotic leakage is an independent prognostic factor associated with local recurrence or survival, others do not support this point of view. Thus, it remains unclear whether anastomotic leakage is an independent prognostic factor for survival and/or recurrence after sphincter-saving resection for rectal cancer.

Therefore, considering the increase of sphincter-preserving procedures for rectal cancer, it is important to determine the impact of anastomotic leakage on oncological outcomes. Such information will help guide improvements in patient management. I performed a systematic literature search of National Library of Medicine (PubMed; January 1980 to October 2009). The following medical subject headings were used: rectal cancer, leakage, anastomotic leakage, leak, stoma, defunctioning stoma, protective stoma, surgery, recurrence,

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and survival. Literatures written in English were included. The bibliographies and all potentially relevant articles were then retrieved.

Definition of Anastomotic Leakage and Incidence

There is no universally accepted definition of anastomotic leakage. In a recent review, Bruce et al.[11] identified 29 separate definitions among 49 studies of anastomotic leakage in patients with lower gastrointestinal surgery. The lack of precise definitions, as well as the variation in anastomotic levels reported, makes the comparison of data on anastomotic leakage confusing and inaccurate. In addition, advances in surgical techniques as well as preoperative chemoradiotherapy have added to the variable treatment categories of patients including shorter distal resection margins and an increased sphincter preservation rate.

The increase in sphincter-preserving resection and the subsequently higher proportion of patients with a distal anastomosis may contribute to an increased risk of anastomotic leakage.[12–15] The rate of anastomotic leakage has been reported to be between 0.6% and 17%, depending on the inclusion criteria, definition of a leakage, tumor location, and operative technique (Table 1).[9,11,13,16–35]

The complications associated with anastomotic leakages range from sepsis to subclinical radiological evidence of fecal spillage. Indeed, some cases with late leakage, such as rectovaginal fistula or abscess, have very different clinical implications compared to early leaks occurring soon after surgery.

Many studies have defined anastomotic leakage as clinical leakage. Clinical anastomotic leakages have been considered to be present if any of the following features were observed: the presence of peritonitis caused by anastomotic dehiscence and/or the presence of feculent substances or gas from a drain. Radiological studies such as the abdominopelvic computed tomography and water-soluble contrast enema or endoscopy have been performed for the purpose of confirming the diagnosis. However, only 50% of radiological leaks were classified as clinical leaks in a study where routine contrast enemas were performed.[6] Therefore, the leakage rate reported in the literature has included both cases with sepsis and those with subclinical leakage. Such differences could have a significant impact on the association of anastomotic leakage with disease recurrence and/or patient survival.

Influence of Anastomotic Leakage on Oncological Outcomes

Many studies, especially earlier investigations, did not demonstrate any association between anastomotic leakage and long-term outcomes (Table 2).[13,23,25,36] With the improvement in peri-operative care, more patients have survived the septic consequences of anastomotic leakage, and long-term outcome can be analyzed including a larger number of patients. Whether anastomotic leakage itself is a prognostic factor for local recurrence and/or survival of patients with colorectal cancer continues to be debated.[10] Some authors have found a significantly higher incidence of local recurrence and increased cancer-related mortality in patients with anastomotic leakage;[6,8] while others have failed to confirm such an association.[17] The decreased survival reported in patients with an anastomotic leakage is clearly affected by higher hospital mortality due to direct acute consequences of the leakage. However, apart from the early post surgical consequences of a leakage, such as sepsis-related death, anastomotic failure has been reported to be associated with decreased local disease control[9,26–29] and patient survival.[30,31]

In two studies with a relatively limited number of patients,[32,36] a trend towards increased local recurrence rates in patients with anastomotic leakage was reported. This was confirmed in a study reported by Bertelsen et al.[34] (1,495 patients); however, neither study reports a statistical analysis of the differences observed. Akyol et al.[6] published the results of a 2-year follow-up of 167 patients that underwent potentially curative resection for rectal cancer. Anastomotic leakage was associated with higher overall and local recurrence rates and a higher cancer-specific mortality rate. Fujita et al.[8] reported similar results in a study of 980 patients that had surgery over a 20-year period with a 5-year follow-up period. The local recurrence rate was higher in patients with an anastomotic leakage. However, their study had some important limitations. The groups were poorly matched and there were a higher proportion of patients with advanced stage disease in the group with anastomotic leakage. Docherty et al.[7] studied the effects of stapled versus sutured anastomoses on the leakage rates in 171 patients. The prevalence of local recurrence after a 4-year follow-up period was found to be higher in the patients that had anastomotic leakage. Petersen et al.[9] noted a higher local recurrence rate among patients with anastomotic leakage and also a trend towards a shorter time to local recurrence in a retrospective study of 331 patients that underwent potentially curative resection of left colon and rectal cancers. Among 331 patients, 29 had an anastomotic leakage. Five of the 29 patients developed a local recurrence in the leakage group (17.2%) and only 26 out of 302 patients developed a local recurrence in the group without leakage (8.6%). For local recurrence, the multivariate analysis revealed that the tumor stage and anastomotic leakage were independent significant factors. In addition, disease-related survival has been reported to be considerably decreased in patients with leakage. However, anastomotic leakage was not

Table 1 Anastomotic Leakage Rate after Resection for Rectal Cancer

Author	Year	Patients (*n*)	Leakage rate, %	Definition of leakage	Approach
Karanjia ND[13]	1994	219	17	Clinical	Open
Averbach AM[19]	1996	165	6	Clinical, need surgery	Open
Mann B[21]	1996	320	3.4	Clinical	Open
Merkel S[35]	2001	940	10.9	Clinical	Open
Scheidbach H[22]	2002	308	13.9	Clinical	Laparoscopic
Bell SW[27]	2003	403	12.7	Clinical	Open
Anthubar M[16]	2003	101	9	Clinical	Laparoscopic
Chang SC[25]	2003	372	6.2	Clinical	Open
Law WL[32]	2004	100	3	Clinical	Laparoscopic
Eckmann C[18]	2004	306	9.8	Clinical	Open
Law WL[14]	2004	396	8.1	Clinical	Open
Walker KG[31]	2004	609	10.2	Clinical and radiological	Open
Eriksen MT[23]	2005	1,958	11.6	Clinical	Open
McArdle CS[30]	2005	746	6.4	Clinical	Open
Branagan G[34]	2005	633	6.3	Clinical	Open
Lim M[12]	2006	138	17	Clinical (9%) and radiological (8%)	Open
Law WL[26]	2007	647	6.3	Clinical	Open
Kim JC[24]	2007	309	0.6	Clinical	Open
Ptok H[29]	2007	2,044	14.3	Clinical	Open
Lee WS[10]	2008	1,130	4	Clinical	Open
Jung SH[28]	2008	1,391	2.5	Clinical	Open
Kim NK[15]	2009	723	3.6	Clinical	Open
Bertelsen CA[33]	2009	1,495	10.9	Clinical and radiological	-
Ng NH[20]	2009	579	3.5	Clinical	Laparoscopic

shown in this study to be an independent prognostic factor for overall survival due to the absence of statistical significance.

Subsequent studies on rectal cancer also demonstrated a higher local recurrence rate in patients with anastomotic leakage.[27,34,35] Branagan et al.[34] studied 633 patients that underwent curative resection involving a rectal anastomosis for colorectal cancer. The anastomotic leakage rate was 6.3%. The cumulative 5-year local recurrence rate was significantly higher in the group with leakage: 25.1% in the group with leakage and 10.4% in the group without leakage. The 5-year overall survival was lower in the group with leakage (52.8% in the group with leakage vs. 63.9% in the group without leakage); however, the differences were not statistically significant.

The association between anastomotic leakage and local control has not been confirmed in any study reported to date. Law and Chu.[14,37] were unable to confirm an association of anastomotic leakage with either local recurrence or cancer-specific survival. In addition, a larger analysis of 1,958 patients failed to detect any influence of anastomotic leakage on the local recurrence rate; however, no data on the disease-free survival were provided.[23] In their study, the overall rate of anastomotic leakage was 11.6%. The 30-day mortality was significantly higher for the patients with anastomotic leakage (7.0%) compared to patients without anastomotic leakage (2.4%). The results of the logrank test showed that anastomotic leakage had no significant effects on the local recurrence rate. In 2002, Kressner et al.[38] reported a retrospective study of 228 patients that had a curative resection for rectal cancer, including 90 abdominoperineal resections. He analyzed the prognostic importance of postoperative intra-abdominal or perineal infections. An association was found between perineal wound infections and local recurrence; however, the study did not show an association between anastomotic leakage and local recurrence.

The effect of anastomotic leakage on long-term oncological outcomes is more controversial. The negative effect of anastomotic leakage on survival and recurrence has recently been demonstrated. In an Australian study on 1,722 patients that underwent curative resection with a colorectal anastomosis at a single institution over more than 20 years, Walker et al.[31] speculated that the adverse impact of anastomotic leakage on long-term survival may be attributed not only to the high postoperative morbidity

Table 2 Impact of Anastomotic Leakage on Oncological Outcomes

Author	Year	Patients (*n*)	FU duration, months	Leakage rate, %	Local recurrence rate, %			Overall survival rate, %			Cancer-specific survival rate, %		
					Leak	No leak	*p*	Leak	No leak	*p*	Leak	No leak	*p*
Fujita S[8]	1993	980			30.4	4.9	<0.01	-	-	-	46	58	-
Peterson S[9]	1998	142		22.5	17.2	8.6	0.035	46.3	49.5	0.57	75.9	87.1	0.045
Eriksen MT[23]	2005	1,958	-	11.6	11.6	10.5	0.608	59.0	67.4	0.021			
Law WL[26]	2007	647	46.2	6.3	12.9	5.7	0.009	-	-	-	56.9	75.9	0.012
Jung SH[28]	2008	1,391	40.1	2.5	9.6	2.2	0.14	55.1	74.1	<0.05	63.0	78.3	<0.005
Ptok H[29]	2007	2,044	40	14.3	12.1	10.1	0.062	-	-	-	72.3	75.4	-
Walker KG[31]	2004	609	-	10.2				44.3	64.0	0.0002			
Branagan G[34]	2005	633	60	6.3	25.1	10.4	0.007	52.8	63.9	0.19	-	-	-
Merkel S[35]	2001	940	90	10.9	22.0	12.5	0.0178	-	-	-	69.6	77.8	0.0035
Bell SW[27]	2003	403		12.7	25.5	10.0	<0.001	-	-	-	-	-	-
Chang SC[25]	2003	372	-	6.2	20.0	8.4	0.031	-	-	-	32.5	71.0	0.001
Lee WS[10]	2008	1,278	44.6	4.0	-	-	0.08	64.9	80.2	0.17	65.9	78.1	0.166
Eberhardt JM[26]	2009	291	7.5 years	-	11.0	5.0	0.04	53.2	71.1	<0.01	71.3	82	0.03
Bertelsen CA[33]	2009				11.0	6.4	NS	-	-	-	-	-	-
Jorgen F[17]	2009	250	-	9.1	8	9	0.97	63	66	0.38	79	77	0.50

associated with the development of intra-abdominal sepsis, but also to some unknown inflammation-related immunological process that might enhance cancer recurrence. The findings from this study demonstrated that anastomotic leakage was associated with a poor overall survival and cancer-specific survival.[31] The total leakage rate was 5.1%. In patients with a leak, the 5-year overall survival rate was 44.3% compared to 64.0% in those without a leak. The proportional hazards regression, after adjustment for age, gender, urgent resection, site, size, stage, grade, venous invasion, apical node metastasis, and serosal surface involvement, showed that anastomotic leakage had an independent negative association with the overall survival (hazard ratio [HR] 1.6) as well as the cancer-specific survival (HR 1.8). In addition, McArdle et al.[30] reported similar results in a multicenter study of 2,235 patients in the United Kingdom. The 5-year cancer-specific survival rate, including postoperative death, was 42% in patients with an anastomotic leakage compared to 66.9% in patients without a leakage. Excluding the postoperative deaths, the respective values were 50% and 68.0%. The adjusted relative hazard ratios, for patients with an anastomotic leakage compared to those without a leakage, and excluding the 30-day mortality, were 1.61 (P=0.002) for overall survival and 1.99 for cancer-specific survival. However, in the present study, the increased risk of cancer-specific death in patients with an anastomotic leak was most apparent between 2 and 4 years. These results are consistent with the suggestion that a systemic inflammatory response plays a significant role in stimulating the growth of micrometastases. Furthermore, Law WL et al.[26] reported a worse oncological outcome in patients with an anastomotic leakage. They reviewed prospectively collected data among 1,580 patients (rectal cancer; 647) that underwent potentially curative resection for colorectal cancer. The 5-year cancer-specific survivals were 56.9% in those with leakage and 75.9% in the patients without leakage. The 5-year systemic recurrence rates were 48.4% and 22.6% in patients with and without anastomotic leakage, respectively; whereas the 5-year local recurrence rates were 12.9% and 5.7%, respectively. For rectal cancer, anastomotic leakage was an independent risk factor associated with a higher local recurrence rate (HR 2.55). Recent reports as well as these prior studies continue to provide contradictory findings with regard to the long-term prognosis of anastomotic leakage.[2,10,26,27,30,34]

Mechanism of AL on Survival

The mechanisms associated with a high recurrence rate, and thus a poor survival outcome after anastomotic leakage, have not been elucidated. The presence of viable tumor cells in the bowel lumen of patients with colorectal cancer,

at the time of surgery, has been demonstrated.[29–41] In the event of an anastomotic leakage, this may lead to extraluminal implantation of cancer cells, and this might account for disease recurrence. Similar to cases where cancer cell involvement of a free serosal surface has been shown or cancer cells in a resection line. Patients with perforated tumors have been reported to have a poor survival.[42] Moreover, occult distant metastasis and circulating tumor cells in patients after a curative resection for colorectal cancer are not uncommon.[43–45] The mechanism whereby residual viable tumor cells cause disease progression is unclear. The progression and growth of these viable tumor cells might be associated with an interaction with some host response. Recent studies have shown that the presence of a systemic inflammatory response, as evidenced by increased circulating concentrations of C-reactive protein, is associated with poor survival in patients undergoing potentially curative resection for colorectal cancer.[46,47] The systemic inflammatory response has been shown to be associated with a poor outcome in patients after curative treatment of colorectal cancer.[46–48] The release of pro-inflammatory cytokines may alter the host defense and promote the growth of the residual or implanted tumor cells.[48–50] In patients that develop sepsis associated with anastomotic leakage, the systemic inflammatory response is exaggerated. Indeed, it is well established that there is a profound, but self-limiting, systemic inflammatory response after surgery in patients with an uncomplicated postoperative course. However, patients that develop an anastomotic leakage suffer a double burden of inflammatory response, the first as a result of surgery and the second as a result of sepsis. It is possible that the duration and magnitude of the systemic inflammatory response is an important factor associated with the long-term outcome of patients that develop an anastomotic leakage.

The demonstration of adverse effects of postoperative complications on long-term outcome supports the importance of good peri-operative care and meticulous surgical technique to avoid morbidity. In rectal cancer patients that underwent sphincter-preserving surgery, some investigators have studied the influence of a diverting stoma for reducing the rate of anastomotic leakage and the serious consequences of sepsis associated with anastomotic leakage (Table 3).[51–60] Low-level anastomoses are consistently shown to give rise to higher rates of leakage.[12,15,32,51,52] Despite some reports showing low rates of leakage without a diverting stoma,[53] the most widely held opinion seems to be defunctioning of anastomoses 6 cm and below.[22] Some investigators[13,23,51,54,55] have found that a diverting stoma both protected against the occurrence as well as the consequences of an anastomotic leakage. Patients without a protective stoma who developed a leakage suffered significantly higher peri-operative mortality than patients without leakage. Marusch F et al.[56] reported that defunctioning stoma reduce the consequences but not the rate of leakage itself. Graffner et al.[57] advocated that fecal diversion did not prevent anastomotic leakage per se but did appear to mitigate the clinical symptoms and signs that were the consequences of such leakage. The influence of a defunctioning stoma on the oncological outcome has not been well studied. In the opinion of Law WL et al.,[26] the presence of diversion stoma did not have any impact on the local or systemic recurrence rates in those patients with a total mesorectal excision for mid- and distal rectal cancer. A larger analysis of 1,958 patients reported by Eriksen MT et al.[23] failed to detect any influence of anastomotic leakage on the local recurrence rate, but no data on disease-free survival were provided. However, they reported that the presence of a diverting stoma was associated with a 60% reduction in the risk of anastomotic leakage (odds ratio 0.4) for anastomoses 6 cm and below.[29]

Table 3 Impact of Stoma on Anastomotic Leakage

Author	Year	Patients (*n*)	Stoma (*n*)	Anastomotic leakage rate		
				Stoma, %	No stoma, %	*p*
Graffner H[58]	1983	50	25	4	12	-
Karanjia ND[13]	1994	219	157	8.3	17.7	0.03
Marusch F[56]	2002	482	148	10.8	10.5	NS[a]
Law WL[14]	2004	622	310	5.5	5.8	NS[a]
Eriksen MT[23]	2005	1,958	622	10.3	12.3	0.202
Gastinger I[58]	2005	2,729	881	14.5	14.2	NS[a]
				3.6[b]	10.1[b]	<0.001[b]
Peeters KC[59]	2005	924	523	8.2	16.0	<0.001
Wong NY[60]	2005	1,066	742	3.8	4.0	NS[a]
Matthiessen P[55]	2007	234	116	10.3	28.0	<0.001
den Dulk M[54]	2009	2,726	1,226	7.8	11.6	0.02

[a] Non-specific

[b] Anasomotic leakage requiring reoperation

Conclusion

Anastomotic leakage is a feared complication of surgery for rectal cancer due to its association with postoperative mortality. In addition, there are questions about its association with local recurrence and oncological outcomes. Sphincter-preserving surgery has increased and so has the frequency of anastomotic leakage; attempts to avoid this complication by techniques such as a diverting stoma has not been successful to date. The long-term consequences of anastomatic leakage continue to be debated. Host inflammation associated with leakage perhaps in response to viable exfoliated cancer cells may play an important role in patient outcome. However, evidence is needed to support this suggestion. MacArdle et al.[31] reported that recurrence in patients with anastomotic leakage was apparent between 2 and 4 years. Therefore, in future studies, the timing of recurrence in cases with anastomotic leakage should be taken into consideration. In addition, the classification and definitions used to describe patients must be unified to avoid the confusion and inaccuracies of the data that have been present in the medical literature to date. One problem with this type of analysis is that usually the proportion of patients with anastomotic leakage is so small that it is difficult to identify it as a factor in long-term survival. Actually, recently, anastomotic leakage after surgery for rectal cancer has been reported less than 10% in most studies. Therefore, impact of anastomotic leakage on recurrence and/or survival could not be evaluated properly. Although we consider these limitations, anastomotic leakage has potent possibility as a risk factor for oncologic outcomes especially for survival. But, for the mechanism how it affects on survival, we need more evidences.

References

1. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg 2005;242:326–341.
2. Chapuis PH, Dent OF, Fisher R, Newland RC, Phelis MT, Smyth E, et al. A multivariate analysis of clinical and pathological variables in prognosis after resection of large bowel cancer. Br J Surg. 1985;72:698–702.
3. Newland RC, Dent OF, Chapuis PH, Bokey EL. Clinicopathologically diagnosed residual tumour after resection for colorectal cancer. A 20-year prospective study. Cancer. 1993;72:1536–1542.
4. Newland RC, Dent OF, Lyttle MN, Chapuis PH, Bokey EL. Pathologic determinants of survival associated with colorectal cancer with lymph node metastases. Cancer 1994;73:2076–2082.
5. Fielding LP, Arsenault PA, Chapuis PH, Dent O, Gathright B, Hardcastle JD, et al. Clinicopathological staging for colorectal cancer: an international documentation system (IDS) and an international comprehensive anatomical terminology (ICAT). J Gastroenterol Hepatol 1991;6:325–344.
6. Akyol AM, McGregor JR, Galloway DJ, Murray GD, George WD. Anastomotic leaks in colorectal cancer surgery: a risk factor for recurrence? Int J Colorect Dis 1991;6:179–183.
7. Docherty JG, McGregor JR, Akyol AM, Murray GD, Galloway DJ. Comparison of manually constructed and stapled anastomoses in colorectal surgery. West of Scotland and Highland Anastomosis Study Group. Ann Surg 1995;221:176–184.
8. Fujita S, Teramoto T, Watanabe M, Kodaira S, Kitajima M. Anastomotic leakage after colorectal cancer surgery: a risk factor for recurrence and poor prognosis. Jpn J Clin Oncol 1993;23:299–302.
9. Peterson S, Freitag M, Hellmich G, Ludwig K. Anastomotic leakage: impact on local recurrence and survival in surgery of colorectal cancer. Int J Colorectal Dis 1998;13:160–163.
10. Lee WS, Yun SH, Roh YN, Yun HR, Lee WY, Cho YB, et al. Risk factors and clinical outcome for anastomotic leakage after total mesorectal excision for rectal cancer. World J Surg 2008;32:1124–1129.
11. Bruce J, Krukowski ZH, Al-Khairy G, Russell EM, Park KG. Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery. Br J Surg 2001;88:1157–1168.
12. Lim M, Akhtar S, Sasapu K, Harris K, Burke D, Sagar P, et al. Clinical and subclinical leaks after low colorectal anastomosis; a clinical and radiologic study. Dis Colon Rectum 2006;49:1611–1619.
13. Karanjia ND, Corder AP, Bearn P, Heald RJ. Leakage from stapled anastomosis after total mesorectal excision for carcinoma of the rectum. Br J Surg 1994; 81: 1224–1226.
14. Law WL, Chu KW. Anterior resection for rectal cancer with mesorectal excision: a prospective evaluation of 622 patients. Ann Surg 2004;240:260–268.
15. Kim NK, Kim YW, Min BS, Lee KY, Shon SK, Cho CH. Operative safety and oncologic outcomes of anal sphincter-preserving surgery with mesorectal excision for rectal cancer: 931 consecutive patients treated at a single institution. Ann Surg Oncol 2009;16:900–909.
16. Anthuber M, Fuerst A, Elser F, Berger R, Jauch KW. Outcome of laparoscopic surgery for rectal cancer in 101 patients. Dis Colon Rectum 2003;46:1047–1053.
17. Jörgren F, Johansson R, Damber L, Lindmark G. Anastomotic leakage after surgery for rectal cancer: a risk factor of local recurrence, distant metastasis and reduced cancer-specific survival? Colorect Dis 2009. doi:10.1111/j.1463-1318.2009.02136.x
18. Eckmann C, Kujath P, Schiedeck TH, Shekarriz H, Bruch HP. Anastomotic leakage following low anterior resection: results of a standardized diagnostic and therapeutic approach. Int J Colorect Dis 2004; 19:128–133.
19. Averbach AM, Chang D, Koslowe P, Sugarbaker PH. Anastomotic leak after double-stapled low colorectal resection. Dis Colon Rectum 1996; 39:780–787.
20. Ng NH, Ng DC, Cheung HY, Wong JC, Yau KK, Chung CC, et al. Laparoscopic resection for rectal cancers: lessons learned from 579 cases. Ann Surg 2009;249:82–86.
21. Mann B, Kleinschmidt S, Stremmel W. Prospective study of hand-sutured anastomosis after colorectal resection. Br J Surg 1996;83:29–31
22. Scheidbach H, Schneider C, Konradt J, Bärlehner E, Köhler L, Wittekind Ch, et al. Laparoscopic abdominoperineal resection and anterior resection with curative intent for carcinoma of the rectum. Surg Endosc 2002;16:7–13.
23. Eriksen MT, Wibe A, Norstein J, Haffner J, Wiig JN, Norwegian Rectal Cancer Group. Anastomotic leakage following routine mesorectal excision for rectal cancer in a national cohort of patients. Colorectal Dis 2005;7:51–57.
24. Kim JC, Takahashi K, Yu CS, Kim HC, Kim TW, Ryu MH, et al. Comparative outcomes between chemoradiotherapy and lateral

pelvic lymph node dissection following total mesorectal excision in rectal cancer. Ann Surg 2007;246:754–762.
25. Chang SC, Lin JK, Yang SH, Jiang JK, Chen WC, Lin TC. Long-term outcome of anastomosis leakage after curative resection for mid and low rectal cancer. Hepatogastroenterology 2003;50:1898–1902.
26. Law WL, Choi HK, Lee YM, Ho JW, Seto CL. Anastomotic leakage is associated with poor long-term outcome in patients after curative colorectal resection for malignancy. J Gastrointest Surg 2007;11:8–15.
27. Bell SW, Walker KG, Rickard MJ, Sinclair G, Dent OF, Chapuis PH, et al. Anastomotic leakage after curative anterior resection results in a higher prevalence of local recurrence. Br J Surg 2003;90:1261–1266.
28. Jung SH, Yu CS, Choi PW, Kim DD, Park IJ, Kim HC, et al. Risk factors and oncologic impact of anastomotic leakage after rectal cancer surgery. Dis Colon Rectum 2008;51:902–908.
29. Ptok H, Marusch F, Meyer F, Schubert D, Gastinger I, Lippert H. Impact of anastomotic leakage on oncological outcome after rectal cancer resection. Br J Surg 2007;94:1548–1554.
30. McArdle CS, McMillan DC, Hole DJ. Impact of anastomotic leakage on long-term survival of patients undergoing curative resection for colorectal cancer. Br J Surg 2005;92:1150–1154.
31. Walker KG, Bell SW, Rickard MJ, Mehanna D, Dent OF, Chapuis PH et al. Anastomotic leakage is predictive of diminished survival after potentially curative resection for colorectal cancer. Ann Surg 2004;240: 255–259.
32. Law WL, Chu KW, Tung HM. Early outcomes of 100 patients with laparoscopic resection for rectal neoplasm. Surg Endosc 2004;18:1592–1596.
33. Bertelsen CA, Andreasen AH, Jørgensen T, Harling H; on behalf of the Danish Colorectal Cancer Group. Anastomotic leakage after curative anterior resection for rectal cancer. Colorect Dis 2009 (in press)
34. Branagan G, Finnis D, Wessex Colorectal Cancer Audit Working Group. Prognosis after anastomotic leakage in colorectal surgery. Dis Colon Rectum 2005;48:1021–1026.
35. Merkel S, Wang WY, Schmidt O, Dworak O, Wittekind C, Hohenberger W, Hermanek P. Locoregional recurrence in patients with anastomotic leakage after anterior resection for rectal carcinoma. Colorectal Dis 2001;3:154–160.
36. Eberhardt JM, Kiran RP, Lavery IC. The impact of anastomotic leak and intra-abdominal abscess on cancer-related outcomes after resection for colorectal cancer: a case control study. Dis Colon Rectum 2009;52:380–386.
37. Law WL, Chu KW. Local recurrence following total mesorectal excision with double-stapling anastomosis for rectal cancers: analysis of risk factors. World J Surg 2002;26:1272–1276.
38. Kressner U, Graf W, Mahteme H, Pahlman L, Glimelius B. Septic complications and prognosis after surgery for rectal cancer. Dis Colon Rectum 2002;45:316–321.
39. Fermor B, Umpleby HC, Lever JV, Symes MO, Williamson RC. Proliferative and metastatic potential of exfoliated colorectal cancer cells. J Natl Cancer Inst 1986;76:347–349.
40. van den Tol PM, van Rossen EE, van Eijck CH, Bonthuis F, Marquet RL, Jeekel H. Reduction of peritoneal trauma by using nonsurgical gauze leads to less implantation metastasis of spilled tumor cells. Ann Surg 1998;227:242–248.
41. Umpleby HC, Fermor B, Symes MO, Williamson RC. Viability of exfoliated colorectal carcinoma cells. Br J Surg 1984;71:659–663.
42. Slanetz CA Jr. The effect of inadvertent intraoperative perforation on survival and recurrence in colorectal cancer. Dis Colon Rectum 1984;27:792–797
43. Finlay IG, McArdle CS. Occult hepatic metastases in colorectal carcinoma. Br J Surg 1986;73:732–735.
44. Denis MG, Lipart C, Leborgne J, LeHur PA, Galmiche JP, Denis M, et al. Detection of disseminated tumor cells in peripheral blood of colorectal cancer patients. Int J Cancer 1997;74:540–544.
45. Molnar B, Ladanyi A, Tanko L, Sreter L, Tulassay Z. Circulating tumor cell clusters in the peripheral blood of colorectal cancer patients. Clin Cancer Res 2001;7:4080–4085.
46. Nielsen HJ, Christensen IJ, Sorensen S, Moesgaard F, Brunner N. Preoperative plasma plasminogen activator inhibitor type-1 and serum C-reactive protein levels in patients with colorectal cancer. The RANX05 Colorectal Cancer Study Group. Ann Surg Oncol 2000;7:617–623.
47. McMillan DC, Canna K, McArdle CS. Systemic inflammatory response predicts survival following curative resection of colorectal cancer. Br J Surg 2003;90:215–219.
48. Balkwill F, Mantovani A. Inflammation and cancer: Back to Virchow? Lancet 2001;357:539–545.
49. Abramovitch R, Marikovsky M, Meir G, Neeman M. Stimulation of tumour growth by wound-derived growth factors. Br J Cancer 1999;79:1392–1398.
50. Mynster T, Christensen IJ, Moesgaard F, Nielsen HJ. Effects of the combination of blood transfusion and postoperative infectious complications on prognosis after surgery for colorectal cancer. Danish RANX05 Colorectal Cancer Study Group. Br J Surg 2000;87:1553–1562.
51. Marusch F, Koch A, Schmidt U, Wenisch H, Ernst M, Manger T, et al. Early postoperative results of surgery for rectal carcinoma as a function of the distance of the tumor from the anal verge: results of a multicenter prospective evaluation. Langenbecks Arch Surg 2002; 387: 94–100.
52. Heald RJ, Leicester RJ. The low stapled anastomosis. Br J Surg 1981;68:333–337.
53. Kanellos I, Zacharakis E, Christoforidis E, Demetriades H, Betsis D. Low anterior resection without defunctioning stoma. Tech Coloproctol 2002;6:153–157.
54. den Dulk M, Marijnen CA, Collette L, Putter H, Påhlman L, Folkesson J, et al. Multicentre analysis of oncological and survival outcomes following anastomotic leakage after rectal cancer surgery. Br J Surg 2009;96:1066–1075.
55. Matthiessen P, Hallbö-ök O, Rutegård J, Simert G, Sjöndahl R. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg 2007;246:207–214.
56. Marusch F, Koch A, Schmidt U, Geibetaler S, Dralle H, Saeger HD, et al. Value of a protective stoma in low anterior resections for rectal cancer. Dis Colon Rectum 2002; 45: 1164–71.
57. Graffner H, Fredlund P, Olsson SA, Oscarson J, Petersson BG. Protective colostomy in low anterior resection of the rectum using the EEA stapling instrument. A randomized study. Dis Colon Rectum 1983;26:87–90.
58. Gastinger I, Marusch F, Steinert R, Wolff S, Koeckerling F, Lippert H, Working Group Colon/Rectum Carcinoma. Protective defunctioning stoma in low anterior resection for rectal carcinoma. Br J Surg. 2005;92:1137–1142.
59. Peeters KC, Tollenaar RA, Marijnen CA, Klein Krnenbarg E, Steup WH, Wiggers T, et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg. 2005;92:211–216.
60. Wong NY, Eu KW. A defunctioning ileostomy does not prevent clinical anastomotic leak after a low anterior resection: a prospective, comparative study. Dis Colon Rectum. 2005; 48:2076 –2079.

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GI IMAGE

Giant Mucinous Cystic Neoplasm of the Pancreas

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History

A 32-year-old woman was referred to our hospital for evaluation of an abdominal tumor that had been detected during investigation of mild abdominal pain. The tumor was diagnosed as a mucinous cystic neoplasm (MCN) of the pancreas. We performed en bloc distal pancreatectomy and splenectomy. The patient could begin oral feeding 2 days after the operation. No complications occurred either during or after surgery. The patient had an uneventful recovery.

Imaging Findings

The contrast-enhanced multidetector abdominal CT showed a solitary, hypodense cyst with 16 cm in diameter with internal septations localized in the tail of the pancreas with no dilatation of the main ductal system. No evidence of radiological concerns as calcifications of the cystic wall, irregularity or thickening, solid components, or mural nodularity was noted (Figs. 1 and 2).

Pathologic Evaluation

Macroscopic description was consistent with MCN by evidence of a large, septated, thick-walled cyst, filled with mucoid material in the body and tail of the pancreas specimen with the cyst extending to the topography of the splenic hilum (Figs. 3 and 4). Microscopic description

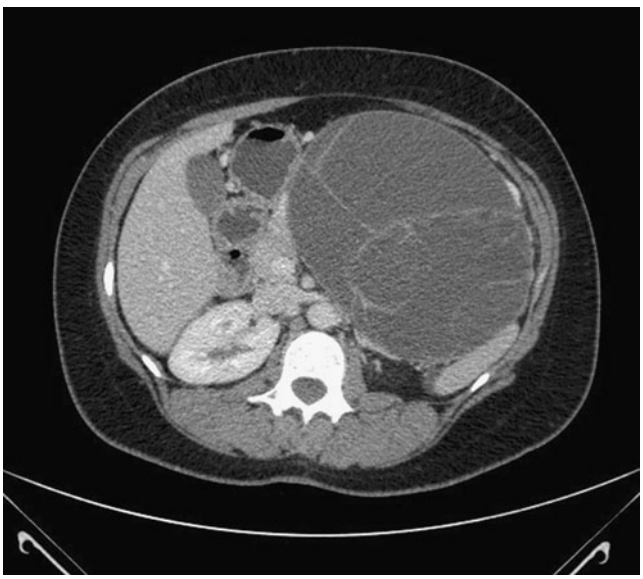

Figure 1 CT scan showing a giant pancreatic cyst compressing adjacent structures.

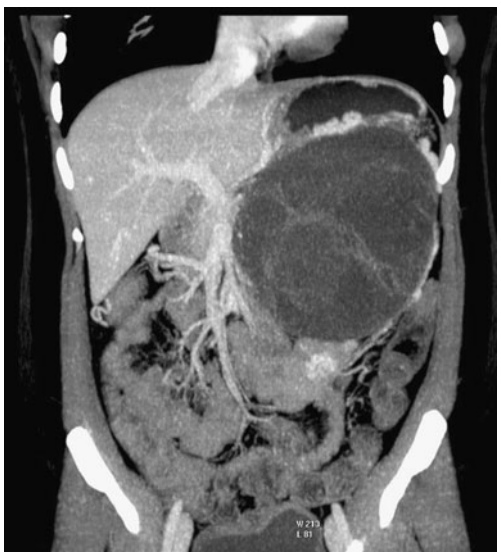

Figure 2 CT scan showing close relation of the cyst with superior mesenteric and portal veins.

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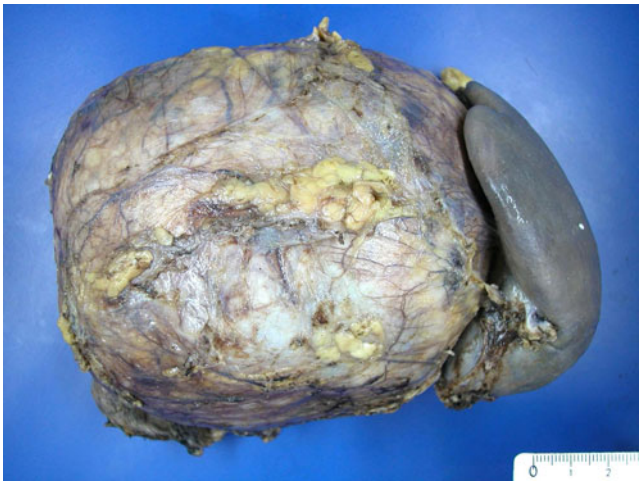

Figure 3 Large thick-walled cyst extending to the splenic hilum.

identified an epithelium composed by mucin-secreting cells without severe atypia. In the outer layer could be noted the presence of a dense cellular ovarian-type stroma. No evidence of carcinoma in situ or invasive cancer was observed in the specimen confirming the final diagnosis of mucynous cystadenoma.

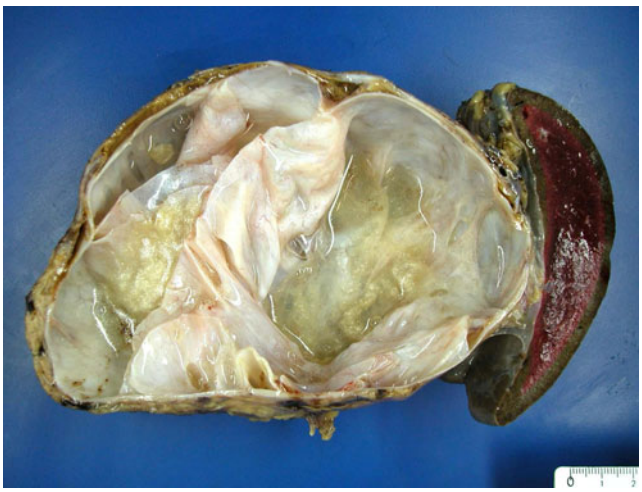

Figure 4 Coronal section of the cyst. Multiple internal septations.

Discussion

Mucinous cystic neoplasms of the pancreas are uncommon tumors that occur almost exclusively in the pancreatic body and tail of young or middle-aged women. A MCN should be suspected whenever a single cyst is seen by CT or MRI in the body or tail of the pancreas of a young or middle-age woman[1]. Endoscopic ultrasound with aspiration of the cyst contents and biopsy of the wall is indicated when radiologic imaging is equivocal[2].

Surgery is the treatment of choice for all MCNs and is supported by the current thinking that these tumors will evolve into cancer if left untreated. Also invasive cancer is observed in older patients with larger tumors[1–3]. Although laparoscopic resection is an alternative approach for small MCNs, the risk of tumor rupture and spillage of cyst contents should be considered in the surgical resection of giant MCNs making open en bloc distal pancreatectomy with splenectomy the option of choice[4]. Regional lymphadenectomy is not advised even if there is a high suspicion of malignancy. In the absence of invasive carcinoma present within the specimen, the cure rate is 100%[5]. Because multifocality is not present in MCNs, there is no need of long-term surveillance if negative margins of resection were obtained in noninvasive tumors[6].

References

1. Khalid A, Brugge W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. Am J Gastroenterol 2007;102:2339–2349.
2. Allen PJ, Brennan MF. The management of cystic lesions of the pancreas. Adv in Surg 2007;41:211–228.
3. Garcea G, Ong Sl, Rajesh A et al. Cystic lesions of the pancreas. Pancreatology 2008;8:236–251.
4. Edirimanne S, Connor S. Incidental pancreatic cystic lesions. World J Surg 2008;32(9):2028–37.
5. Fernández-del Castillo C. Mucynous cystic neoplasms. J Gastrointestinal Surg 2008;12:411–413.
6. Gourgiotis S, Germanos S, Ridolfini MP. Presentation and management of pancreatic cystic neoplasms. J Clin Gastroenterol 2007;6:599–608.

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GI IMAGE

Acute Giant Gastric Volvulus Causing Cardiac Tamponade

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Abstract
Introduction Acute gastric volvulus is an uncommon condition which is rarely associated with cardiac impairment.
Discussion We report a patient with an acute giant gastric volvulus causing cardiac tamponade. Prompt decompression was unsuccessful and the patient died prior to definitive treatment.

Keywords Gastric volvulus · Cardiac tamponade

An 86-year-old woman presented with a 3-day history of vomiting and epigastric discomfort. Immediately prior to admission, she felt her abdomen had become increasingly distended. Past medical history included a benign esophageal stricture with hiatus hernia and atrial fibrillation. Examination detected signs of shock and a grossly distended tympanic abdomen. The patient was resuscitated and a nasogastric tube was inserted; while this produced aspirate, it did not decompress the abdomen. Urgent computed tomography (CT) showed a large gastric volvulus extending from the left ventricle (with associated compression) to the pelvis (Figs. 1 and 2). The patient died prior to definitive treatment.

Acute gastric volvulus (torsion of the stomach causing complete luminal obstruction that accompanies intrathoracic herniation) is an uncommon condition, and complications include ischemia and infarction, perforation, peritonitis, shock, and death.[1–3] Seventy percent of patients may have Brochart's triad: epigastric pain, retching without vomitus, and inability to pass a nasogastric tube. Examination may detect little except for signs of shock (hypovolemic or cardiac) and abdominal distension.[1–5] Plain radiographs, barium studies, endoscopy, and CT are used as diagnostic adjuncts.[1,2]

Gastric volvulus should be managed by prompt reduction. Both operative (open or laparoscopic) and endoscopic techniques have been used to treat acute volvulus.[1–3] Operative intervention can identify and repair any of the secondary predisposing factors for volvulus formation while also managing any associated perforation and subsequent peritonitis.[1,2] Endoscopy can be successfully utilized to reduce gastric volvulus and has the added advantage that the procedure can be undertaken without a

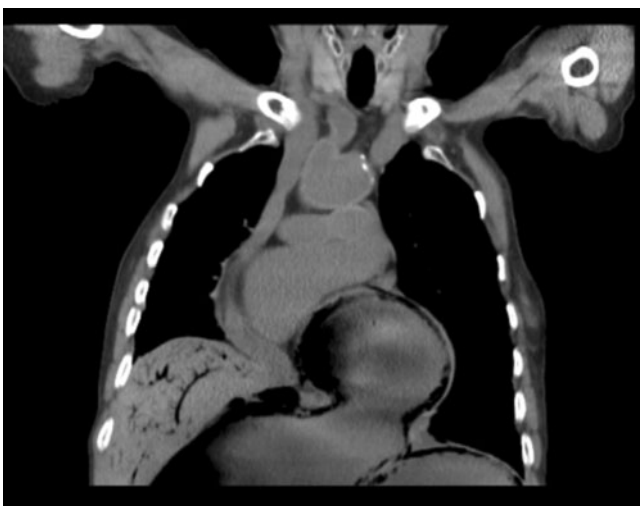

Figure 1 Thoracic CT showing the gastric volvulus causing cardiac compression (especially left ventricular tamponade).

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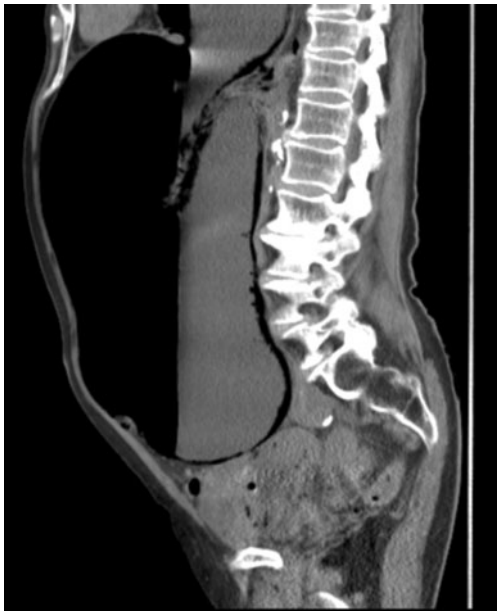

Figure 2 Abdominal CT showing the extent of gastric volvulus extending from above the diaphragm to the pelvis, with associated displacement of abdominal contents. Gas is seen within the gastric wall, suggesting infarction.

general anesthetic—this is a significant in patients with cardiac compromise that may not survive the cardiac insult of anesthesia.[3] When gastric volvulus causes cardiac compromise, it is likely that that volvulus itself causes direct compression on the mediastinal structures.

References

1. Palanivelu C, Rangarajan M, Shetty AR, Senthilkumar R. Laparoscopic suture gastroexy for gastric volvulus: a repost of 14 cases. Surgical Endoscopy 2007;21:893–866.
2. Shivanand G, Seema S, Srivastava DN, Pande GK, Sahni P, Prasad R, Ramachandra N. Gastric volvulus acute and chronic presentation. Journal of Clinical Imaging 2003;27:265–268.
3. Wolfgang R, Lee JG. Endoscopic treatment of acute gastric vovulus causing cardiac tamponade. J Clin Gastroenterol 2001;32:336–339.
4. Shriki JE, Nguyen K, Rozo JC, Reul GJ, Mortazavi A. Rare chronic gastric volvulus associated with left atrial and mediastinal compression. Texas Heart Institute 2002;29:234–328.
5. Karla PR, Frymann R, Allen DR. Images in cardiology: strangulated gastric volvulus: an unusual cause of cardiac compression resulting in electromechanical dissociation. Heart 2000;83:550.