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ORIGINAL ARTICLE

The Role of Integrated F-18-FDG-PET Scanning in the Detection of M1 Disease in Oesophageal Adenocarcinoma and Impact on Clinical Management

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Abstract
Introduction The aim of this study was to evaluate the efficacy of F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning in the staging of oesophageal adenocarcinoma.
Methods One hundred four patients with biopsy-proven adenocarcinoma underwent ^{18}F-FDG-PET scan. FDG avid lesions were further investigated to their diagnostic conclusion.
Results Nineteen patients (18.26%) were found to have *non-loco-regional* FDG uptake. Of the patients, 3.84% were found to have M1 disease and 7.69% were found to have a second primary tumour. The sensitivity and specificity of FDG-PET scanning to detect metastatic disease in our series was 57.14% and 84.53%, respectively. The overall diagnostic accuracy was 82.69%.
Conclusions PET scanning improves staging and prevents unnecessary surgery in patients with M1 disease. It represents a good adjunct to computed tomography scanning and endoscopic ultrasound in the staging of oesophageal adenocarcinoma. The detection of asymptomatic coexisting synchronous cancers is an added benefit provided by PET scanning over similar diagnostic modalities.

Keywords Oeosphageal cancer · FDG-PET scans · Synchronous malignancies

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Introduction

In the Western World, oesophageal adenocarcinoma has replaced squamous cell carcinoma as the most common oesophageal malignancy.[1–4] Tumour–node–metastasis (TNM) staging is the major determinant of prognosis and provides the basis for selecting optimum treatment.[5] Among the currently available staging modalities, endoscopic ultrasound (EUS) is ideal for the loco-regional assessment of disease,[6–8], whereas for the detection of distant nodal and metastatic spread, computed tomography (CT) scanning is preferred.[8] Apart from being increasingly useful in initial staging of oesophageal cancer, F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning also helps in radiotherapy planning, assessing the therapeutic response after neoadjuvant therapy and detection of recurrent malignancy.[9–14] Furthermore, routine FDG-PET may reveal incidental hypermetabolic lesions that are possibly unrelated to the neoplasms for which these patients are initially scanned. Besides, lesions on FDG-

PET/CT that are interpreted as metastatic disease of the primary tumour, an FDG avid lesion may represent a second synchronous tumour.[15] Previous reports have suggested that due to the additional information provided by PET/CT it should be included in the routine staging of oesophageal cancer.[16] The aim of this study was to determine the impact of FDG-PET scanning and to identify its influence upon further decision making, investigations and treatment planning in patients with loco-regionally confined and potentially operable oesophageal adenocarcinoma. We specifically assessed the ability of PET scanning to detect metastatic disease (M1) and incidental occult synchronous neoplasms in patients with adenocarcinoma of oesophagus and gastroesophageal junction.

Methods

Over a 3-year period, 142 patients with biopsy-proven oesophageal cancer were referred to this specialist surgical oesophagogastric unit. Among the 142 patients, 21 were found to have distant metastasis on the initial staging CT scans and hence they were referred for palliative treatment. Of the remaining 121 patients who had localised disease, 17 patients had localised squamous cell carcinoma (SCC) of the oesophagus and were referred for definitive chemotherapy and radiation with curative intent. One hundred four patients had biopsy-proven adenocarcinoma of the oesophagus, and they were treated with intent to cure. These included 91 males (87.5%) and 12 females (12.5%) with a mean age of 63.7± 9 years (range, 26.7–85.2 years) (Table 1). All these tumours were classified according to the current American Joint Committee on Cancer TNM staging system[17] (Table 1). All patients underwent a EUS for more accurate loco-regional staging and also a FDG-PET (CT-PET) scan to detect further metastases not previously identified on CT scanning. Further to absence of distant metastases on PET scanning, all patients underwent a staging laparoscopy prior to commencement of definitive treatment. Patients were discussed in a dedicated multidisciplinary team meeting before treatment plans for each individual patient were authorised. All patients with N1 disease received neoadjuvant chemotherapy irrespective of T stage of the disease. Patients with T3/T4N0 disease also received neoadjuvant chemotherapy. For loco-regional disease staging, EUS criteria were followed to decide treatment plan. Two to three cycles of neoadjuvant chemotherapy using cisplatin/5-fluorouracil were given followed by an oesophagectomy through one of the operative approaches described depending upon the location of the primary tumour. All patients wherein FDG avid hot spots were detected, underwent further investigations to clarify the nature of these lesions. All these lesions were presumed to be metastatic unless proven otherwise and were investigated to their diagnostic conclusion. FDG-PET findings in these patients were compared with either histology, fine-needle aspiration (FNA) or a radiological finding in the relevant organ within 6 months of follow-up.

Table 1 Demographics and patient cohort data

Sex	Males	91 (87.5%)
	Females	13 (12.5%)
Age	Mean	63.7±9 years
Localization	Upper oesophagus	6 (5.8%)
	Mid-oesophagus	18(17.3%)
	Lower oesophagus including GEJ	80 (76.9%)
TNM staging-AJCC[17]	Stage 1	2 (2%)
	Stage 2	35 (33.6%)
	Stage 3	67 (64.4%)

TNM tumour–node–metastasis, *AJCC* American Joint Committee on Cancer

PET Scan and Image Interpretation

All imaging and data acquisition were performed with a combined PET-CT in-line system (Discovery DST 16, GE Healthcare), which was able to acquire CT images and PET data for the same patient in one session. Patients were fasted for a minimum of 6 h, and excessive muscle activity was avoided before the PET/CT study. CT data were acquired first. Patients were positioned on the table in a headfirst supine position, and patient's arms were placed in an elevated position above the abdomen to reduce beam-hardening artefacts at the level of the liver. PET images were acquired during shallow breathing in the two-dimensional mode for 3 min per bed position at 60–90 min after intravenous administration of 555–740 MBq of FDG. Emission images were corrected for signal attenuation using a gallium 68 transmission scan acquired immediately before or after the emission scan. PET images were then reconstructed with CT-derived attenuation correction using ordered-subset expectation maximization software. The attenuation-corrected PET images, CT images, and fused PET/CT images were available for review in axial, coronal, and sagittal planes, as was a cine display of maximum intensity projections of the PET data, using the manufacturer's review station (Xeleris; GE Healthcare). PET scans were interpreted by two experienced PET/CT specialists with full knowledge of conventional imaging results. Any focus of FDG activity that was greater than surrounding background and not attributable to normal FDG bio-distribution was evaluated as a lesion and a list of potential distant lesions was recorded. FDG avid lesions in regions not likely to be sites of metastatic deposit

from oesophageal cancer were reported as suggestive of synchronous tumour, depending mainly on intensity and pattern of distribution (focal or diffuse). When the cell type between the primary and suspected second primary cancers was identical, a determination of a metastasis or second primary cancer was made based on findings from a tumour board, which considered the comparative histological findings, the biological behaviour of the primary tumour, and the radiological appearance.[18]

Statistical Analysis

The results of the imaging modalities were compared with a reference standard provided by pathologic examination of each resection specimen. PET/CT-positive results were defined as true positive when confirmed by histopathologic examination. A site characterized as a negative area was defined as true negative when histopathologic examination of the resected nodal group or organ lesion revealed no metastatic disease. Furthermore, a negative area was classified as false negative when there was subsequent histopathologic proof of metastasis, not previously demonstrated on radiological staging. Changes in clinical staging and the therapeutic procedure as a result of the PET findings were recorded. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of PET/CT for the detection of metastatic (M1) disease were calculated. Statistical software (SPSS, version 12.0; SPSS Inc.) was used for the analysis.

Results

A total of 121 FDG-PET scans were performed. Seventeen patients with SCC were referred for radical chemotherapy and radiation. In this cohort of 17 patients, PET scans demonstrated correctly and accurately the loco-regional disease consistent with the findings of endoscopy and CT scans (100%). In three of these 17 patients, the FDG-PET scans detected metastatic disease involving high mediastinal and cervical lymph nodes not seen on CT scans, upstaging the nodal involvement in three of the 17 (17.64%) patients. The remaining 104 patients with oesophageal adenocarcinoma who underwent FDG-PET scanning were evaluated as a separate group. FDG-PET scanning confirmed the primary loco-regional disease consistent with CT and EUS findings in all patients (100%). Of these 104 FDG-PET scans performed, 19 patients (18.26%) were found to have a *non-loco-regional* FDG uptake in non-loco-regional sites (not previously seen on CT scanning), which merited further investigations (Table 2). All these patients underwent further investigations to clarify the precise nature of the non-loco-regional FDG uptake (Table 3). Eighty-five patients (85/104= 81.73%) did not have any FDG activity elsewhere. One patient was found to have FDG avid activity in the lung, liver, sternum and peritoneum, respectively (n=4, 3.84%). This patient had an FDG uptake in the liver and was recommended for further MRI and ultrasound of the liver with a liver biopsy and referred for palliative chemotherapy after histological confirmation of metastasis. The second patient with the pulmonary nodule was also referred for palliative chemotherapy after thoracoscopy, and lung biopsy confirmed metastatic disease. The third patient had high uptake in the sternum, and MRI confirmed metastatic disease. The fourth patient had a peritoneal nodule which was FDG positive, and CT-guided FNA of the nodule confirmed metastatic disease. Our incidence of upstaging disease to M1 not detected on CT scanning, in the current series was 3.84%. In two patients (1.92%) with mid-oesophageal cancer, FDG avid hot spots not visualised on CT scan were seen along the lesser curve of the stomach. Both these patients had neoadjuvant chemotherapy based on CT and EUS staging (T3/N1). Hence, PET scanning apart from more accurate depiction of lymph nodal involvement did not affect the treatment plan in these patients. In one patient (one of 104, 0.96%), PET scans

Table 2 Breakdown of 104 ^{18}F-FDG-PET scans

Total no. of FDG-PET scans	104
Total no. of FDG avid lesions apart from FDG uptake in the primary loco-regional territory	19 (18.26%)
PETs compatible with CT and no evidence of distant FDG avid lesions (PET negative)	85 (81.73%)

Table 3 Break down of 19 patients with FDG uptake in sites apart from primary loco-regional oesophageal territory, n=19 (percentages calculated on the basis of n=104)

Metastatic hot spot	
Liver	01 (0.96%)
Lung, confirmed on biopsy	01 (0.96%)
Peritoneum, confirmed on biopsy	01 (0.96%)
Sternum, confirmed on MRI/bone scan	01 (0.96%)
Non-specific	
Lung lesions, confirmed on interval imaging	01 (0.96%)
Musculoskeletal lesions (rib, spine), confirmed on MRI/bone scan and interval imaging	02 (1.92%)
Colonic uptake, confirmed on colonoscopy	01 (0.96%)
Metastatic nodes	
Left gastric territory in mid-oesophageal tumours	02 (1.92%)
Mediastinum, with primary in the CO junction	01 (0.96%)
2nd primary neoplasms	08 (7.69%)
Total	19 (18.26%)

documented FDG avid mediastinal nodes located around the carina in a patient with a T2N0 junction tumour. Based on the FDG-PET findings, this patient went on to have neoadjuvant chemotherapy and an Ivor Lewis oesophagectomy later. Thus, PET scanning in 0.96% of the patients achieved more accurate loco-regional staging thereby changing treatment plan. In two patients (1.92%), FDG avid musculoskeletal lesions were identified in the rib and spine, respectively. The patients were asymptomatic, and no abnormalities were detected on interval CT/MRI scans across 3 weeks, and these were therefore treated as insignificant. These patients went on to receive their definitive treatment with intent to cure. One patient (0.96%) similarly had non-specific FDG uptake in the lung which was investigated through further imaging including CT-guided biopsy and was found to be inflammatory only. In view of equivocal findings on clinico-radiological correlation, they went on to receive definitive treatment with intent to cure. These patients on serial imaging at 6-month interval did not demonstrate any evidence of metastatic disease, and hence these musculoskeletal and lung lesions were classified as non-malignant. Hence, we conclude that non-specific FDG uptake in three of 104 patients (2.88%) was non-specific leading to increasing investigations and delaying definitive treatment. Further investigations were carried out in nine patients (8.65%) based on the abnormal FDG uptake. While one patient (0.96%) with a FDG hot spot in the colon did not have any detectable abnormality on colonoscopy, eight (7.69%) patients were confirmed to have additional primary neoplasms (Table 4). Colonic incidentalomas were the commonest in this group, and five (4.81%) patients were found to have FDG avid lesions in the colon identified on PET scanning. All of them went on to have further colonoscopic examinations. Two patients had colonoscopic excision of adenomatous polyps while three (2.88%) patients had coexisting asymptomatic colorectal primaries that were treated alongside their esophageal cancer. All the three colorectal primaries were resected at the same time as the patients who underwent esophagectomy, and all three patients had an uncomplicated surgical recovery. One patient had FDG avid synchronous primary cancers in the pancreas, lung and prostate, respectively, discovered during appropriate investigations, and they were treated with curative intent. The patient with lung cancer had a lobectomy about 3 weeks prior to the esophagectomy while the patient with the pancreatic primary had a synchronous esophagectomy with pancreaticoduodenectomy. The patient with prostate cancer was found to have locally advanced disease with extensive iliac lymphadenopathy, proven on biopsy. This in addition to significant medical co-morbidities made him ineligible for radical treatment with curative intent. Hence, he was treated with palliative intent for his prostate cancer in addition to his oesophageal cancer. All patients wherein synchronous asymptomatic primary cancers were detected as a part of staging investigations for their oesophageal primary had histological confirmation of their synchronous cancers confirmed prior to treatment of the oesophageal cancer. The distribution of these patients was colon × 3, lung × 1 pancreas × 1, prostate × 1 and adenomatous colonic polyp with mild dysplasia excised at colonoscopy × 2. These were appropriately staged independent of the oesophageal cancer. All patients except one with the prostate cancer had early disease amenable for treatment with intent to cure. Thus, of this cohort of 19 patients, 14 patients proceeded on to have definitive treatment with curative intent for their oesophageal adenocarcinomas.

Thus, 99 patients underwent a staging laparoscopy prior to commencement of their definitive treatment. Of these 99

Table 4 Breakdown of eight patients proven to have coexisting second primary neoplasms

No.	Location of FDG hot spot	Investigations	Diagnosis	Treatment
1	Transverse colon	Colonoscopic polypectomy for polyp	Tubulovillous polyp with low-grade dysplasia	Excised at colonoscopy
2	Caecum	Colonoscopic polypectomy for polyp	Tubulovillous polyp with low-grade dysplasia	Excised at colonoscopy
3	Transverse colon	Colonoscopy	T2N0 adenocarcinoma	Synchronous resection with Ivor Lewis oesophagectomy
4	Right colon	Colonoscopy	T2N0 adenocarcinoma	Synchronous resection with Ivor Lewis oesophagectomy
5	Transverse colon	Colonoscopy	T3N0 adenocarcinoma	Synchronous resection with Ivor Lewis oesophagectomy
6	Head of pancreas	Surgery	Adenocarcinoma pancreas	Synchronous resection with Ivor Lewis oesophagectomy
7	Lung, right upper lobe	Surgery	Broncho-alveolar carcinoma	Staged resection—lung first and oesophagogastrectomy for lower oesophageal tumour 6 weeks later (left thoracoabdominal approach)
8	Prostate	Cystoscopy/CT-guided biopsy of internal iliac node	Adenocarcinoma prostate	Palliative treatment in view of locally advanced prostate cancer

patients, two patients could not proceed on for definitive surgery (with intent to cure)—for reasons mentioned below:

1. At laparoscopy—one (1.01%) patient was identified to have sub-centimetre tumour deposits on the under surface of the diaphragm. Histology confirmed adenocarcinoma, and he was referred for palliative chemotherapy. These peritoneal metastases were not picked up on FDG-PET scanning.
2. One patient with no evidence of metastatic disease developed significant side effects following neoadjuvant chemotherapy and was unfit for further surgical treatment.

Of the 97 patients (in this cohort) intended to have resection, 92 had successful oesophageal resections (94.84%) (49 Ivor Lewis, 34 left thoracoabdominal, six transhiatal and three three-stage oesophagectomy). A standard two-field regional enbloc lymphadenectomy involving the relevant lymph nodal areas in the abdomen and the chest was carried out.

Five (5.15%) patients did not have resections following explorations for the following reasons:

- Patient 1 had disease in the form of metastatic pleural plaques confirmed on a frozen section during the thoracotomy, not seen on any of the previous imaging including PET scan, thus curative surgery was not attempted.
- Patient 2 had peritoneal metastasis on the abdominal wall discovered at laparotomy. This patient had a PET scan about 3 weeks prior to his exploration, and the nodule was not detected.
- Patients 3, 4 and 5 had locally advanced disease involving the trachea, aorta and the diaphragm, respectively, that the CT scan had underestimated and hence on account of locally advanced disease the tumours were deemed unresectable. Hence at exploration, two patients (2.06%) had truly metastatic disease, not picked up on any form of preoperative imaging, while three patients (3.09%) had locally advanced T4 disease.

Discussion

Curative surgery alone or in combination with chemotherapy is the only definitive treatment for oesophageal cancer. Selection of patients eligible for oesophagectomy relies on accurate oesophageal cancer staging.[17] Historically, CT scanning has been the conventional imaging modality for detection of distant metastatic disease with a diagnostic sensitivity varying between 37–66%.[19,20] A combination of CT scan, EUS and MRI provides a combined accuracy of 70–90% for the detection of metastatic disease.[21–25] In approximately 25% of patients with oesophageal cancer, "skip" metastasis present in distant lymph nodes may occur in the absence of "more local" lymph nodes involvement.[11] Metastatic disease is present in 20–30% of patients with oesophageal cancer at initial evaluation;[11] 10–20% of patients have metastatic disease discovered during exploration for resectional surgery, rendering them inoperable at the time of surgery.[14,26] More recently, FDG-PET scanning has evolved as an accepted technique in the staging of malignancies including oesophageal cancer.[11,22,27–29] ^{18}Fluorodeoxyglucose positron emission tomography scanning provides physiologic information based on the altered glucose metabolism in malignant tissues, thereby enabling the diagnosis of cancer.[28] Thus, the investigation is more precise than the purely anatomic imaging (CT scans) and PET scanning proves to be a useful complement to the traditional staging modalities.[30] Co-registration of PET and CT images using PET/CT systems is more accurate than PET alone for detecting radiographically occult distant metastatic disease.[31–33] In this study, FDG-PET scanning obtained accurate loco-regional and distant staging, thereby enable take more judicious treatment decisions and preventing inappropriate surgery. FDG-PET scanning is not a replacement CT scanning as primary staging modality in oesophageal cancer. However, PET scanning can prove to be a valuable supplementary investigation in detection of M1 disease. In 18.26% of this cohort, detection of FDG avid incidentalomas necessitated further investigations. On the background of biopsy-proven oesophageal adenocarcinoma, it was that assumed all of these lesions are metastatic unless proven otherwise. For the detection of distant metastatic disease in oesophageal cancer, PET scanning has been reported to be more sensitive than CT.[15] Thus, routine PET scanning prevents unnecessary surgery due to its ability to pick up silent and previously undetected metastatic disease;[11,13,33] 3.85% of the patients in this series had detection of distant metastatic disease with PET scanning, not seen on CT scanning and thus avoided inappropriate attempts at curative treatment. Approximately one fifth (21.05%) of all "non-loco-regional" FDG hot spots in our series were indeed metastatic disease. The incidence of upstaging the disease based on PET findings has been reported to be between 3 and 28%.[13,26,33] Among the remaining 15 patients, "independent synchronous neoplastic incidentalomas" were picked up in 7.69% patients (8/104). Metastatic regional lymphadenoapathy not influencing course of treatment was detected in two (1.92%) patients, while "truly non-significant" FDG avid areas were present in four (3.84%) patients. Thus in 5.76% of patients, although PET findings did not change or alter the treatment strategies, significant resources and time were spent on further investigation of these patients and thus delaying definitive therapy. However, in one (0.96%)

patient with a T2 gastroesophageal junctional tumour, FDG avid nodes were picked up in the sub-carinal region and this changed the tumour stage to N1 from N0. Although biopsy confirmation of the nodes was not performed, this patient received two cycles neoadjuvant cisplatin/5 FU chemotherapy prior to Ivor Lewis oesophagectomy. Thus, FDG-PET scanning influenced administration of neoadjuvant chemotherapy in 0.96% of our patient cohort. Regarding regional lymph nodal staging, Siewert stated that the initial staging of regional lymph nodes is less important because at the moment there is no pre-therapeutic therapy stratification based on lymph node category.[34] Detection, staging and appropriate treatment of the eight synchronous primary neoplasms (Table 4) was an additional benefit obtained during the staging process of these oesophageal adenocarcinomas. In the final analysis in 3.8% of patients the FDG-PET findings were truly insignificant leading to increasing investigations and delaying treatment. The incidence of false-negative metastatic disease in this patient series was 2.88%. Therefore, the benefit of 3.84% (4/104) gained due to identification of distant metastasis was partly reduced in significance by its failure (2.88%) to prevent unnecessary procedures in three patients. Failure of esophageal resection in three patients due to unresectable local disease cannot be attributed to a failure of FDG-PET scanning with regards to optimum staging. There were no compelling criteria on CT scan or PET scans in these patients that could have avoided an attempt at curative resection. Thus in this study PET scanning demonstrated a true positive rate (four of 104) of 3.84% while the false negative (three of 104) was 2.88%, understaging the disease and failing to prevent an unnecessary surgical procedures. 18-F-fluorodeoxyglucose positron emission tomography (FDG-PET) has a high sensitivity (70–90%) and specificity (90–100%) in detecting distant and distant metastasis (M1);[16,35,36] 7.69% (eight of 104) of patients had the benefit of their second primary cancers being treated alongside their oesophageal cancer. While the patient with prostatic cancer was treated with chemotherapy and radiation only, the remainder of the patients had either synchronous resection of their extraoesophageal primary carried out along with the oesophagectomy. One patient with lung cancer her a left upper lobectomy, followed by an oesophagectomy 4 weeks later while patients with colonic polyps had colonoscopic polypectomies. Van Westreenen reported that FDG avid lesions that are interpreted as metastases of the primary tumour may, in fact, reflect a ^{18}F-FDG avid lesion in an incidental synchronous tumour.[15] Apart from providing improvising upon distant staging, PET scanning by the virtue of obtaining whole body images helps detect incidental asymptomatic synchronous neoplasms.[11] The incidence of these synchronous neoplasms has been reported at 1.5–5.5%.[11,37–39] In their study, Agress et al. found 71% of the detected abnormalities on FDG-PET scanning were premalignant or malignant lesions and they recommended aggressive follow-up in all such lesions.[40] In our present study, the incidence of premalignant or malignant lesions among the detected abnormalities was 42.10% (8/19). Recommendations are that all such non-loco-regional foci of FDG uptake should be optimally and unhesitatingly investigated.[11,37–39] In our cohort, colonic incidentalomas were the commonest with 31.5% of FDG abnormalities being due to FDG avid colonic lesions. 62.5% (5/8) of the incidental premalignant or synchronous malignant lesions picked up in this cohort, was due to either colonic polyps with low-grade dysplasia or invasive adenocarcinoma of the colon. The incidence of colonic cancer in our study was 2.88%. This is comparable to a similar incidence detected by Zhuang et al. in their study at 2.5%.[41] Zhuang et al. detected FDG uptake in the colon in 28.93% of their patients, when they performed FDG-PET scanning as part of the investigation of pulmonary nodules.[41] In another publication on the subject 79% of FDG avid colonic abnormalities were found to have histological abnormalities on investigation.[42] Both these publications have advocated aggressive investigation of incidentalomas detected on FDG-PET scanning.[41,42] In a series of publications, the incidence of colonic incidentalomas detected on FDG-PET scanning has been variously reported between 1.5% and 5.5%.[38,39,43] In a series of 1,479 patients with esophageal cancers, undergoing FDG-PET scanning the incidence of a second primary cancer was 10.5%.[43] In another similar study with 366 patients of oesophageal cancer, the incidence of synchronous neoplasms was 5.5% with 3.0% of the lesions being colonic premalignant or malignant lesions.[38] It was demonstrated that the incidence of colonic polyps in individuals with adenocarcinoma of the oesophagus was higher than in patients with SCC of the oesophagus or even normal age matched controls.[44] In our study, no patient was denied potentially curative treatment based purely on positive PET findings. Each lesion was pursued to its diagnostic end and histopathologic confirmation was obtained wherever possible. Based on these results, FDG-PET scanning had a sensitivity of 57.14%, specificity of 84.53%, a positive predictive value of 21.05%, a negative predictive value of

Table 5 Sensitivity, specificity, positive predictive value and negative predictive value in PET scanning

	M1 disease present	M1 disease absent	
^{18}F-FDG-PET positive	4 (true positive)	15 (false positive)	19
^{18}F-FDG-PET negative	3 (false negative)	82 (true negative)	85
	7	97	104

Sensitivity=57.14%; specificity=84.53%; positive predictive value=21.05%; negative predictive value=96.47%; accuracy=82.69%

96.47% and an accuracy of 82.69%, in the detection of distant metastasis in patients with oesophageal adenocarcinoma (Table 5). In their study similar to ours, Gillies et al. found additional PET/CT findings in 18.5% of patients.[16] We found an increased incidence of false positives in our study (78.94%). However out of these 15 patients, eight were ultimately found to be second primary neoplasms, which were appropriately treated. Of the remaining seven patients, only four patients had non-specific FDG positivity while three had lymph nodal disease (Table 2). In a landmark prospective multi-institutional trial, the American College of Surgeons Oncology Group Trial (Z0060), showed an increased FDG positivity rate of 14.3%, leading to detection of metastatic disease, thereby altering the management algorithm.[45] Van Westreenen in his study demonstrated distant metastasis in 4.0% of patients while the incidence of synchronous neoplasms was 3.5%.[26] They had a false-positive rate (7.5%) with a false-negative rate of 4.5%.[26] Based on these findings, they advocated that FDG-PET scans should be more selectively used in patients with advanced oesophageal cancer only. The likelihood of detecting distant metastasis in early oesophageal cancer was small and hence routine use of FDG-PET scans therefore did not seem to be justified.[26] A similar approach was also advocated in two other publications on the subject.[33,46] However, in another study Walker et al. showed PET/CT to be an ideal supplementary investigation to EUS for complete staging.[47] While the study confirmed that EUS was a superior modality to PET/CT for loco-regional staging, PET/CT was mandatory for M staging.[47] Another recent study confirmed the unquestionable benefit of PET-CT in the primary staging of oesophageal cancer.[48]

The present study has inbuilt limitations of any retrospective study. A sample size of 104 may not be an adequate sample to draw any firm objective conclusions. Furthermore, almost all patients had an adenocarcinoma involving the distal oesophagus and gastroesophageal junction and therefore there was not much variability in the disease pattern. Since we were quite aggressive in giving neoadjuvant chemotherapy to any patient with N1and/or T3 disease, we specifically did not rely upon PET scanning to make treatment decisions in our patients since EUS and CT scan are very reliable in helping us make these decisions. Only 37 of the 97 patients who underwent exploration did not receive neoadjuvant chemotherapy. Hence, 61.3% of patients received chemotherapy based on staging information obtained from the CT and EUS. The number of patients in this study is small to draw any firm conclusions on the role of PET scanning in the loco-regional staging of oesophageal cancer and given the fact that majority of patients were down-staged with neo-adjuvant chemotherapy.

Conclusions

In this analysis, we specifically evaluated the role of the FDG-PET scanning in the detection of distant metastatic disease. From the results of this study, we believe that PET scanning can be an invaluable supplementary investigation, which can prove to be very cost-effective. More studies involving larger number of patients would be required to carefully examine the precise role of PET scanning in the distant staging of oesophageal cancer while combined CT-PET has great potential in accurately defining extent of loco-regional nodal involvement.

Conflicts of Interest The authors have no conflict of interest.

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Ethical Approval Not applicable.

References

1. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst 2005; 97:142–6.
2. Devesa SS, Blot WJ, Fraumeni JF. Changing patterns in the incidence of oesophageal and gastric carcinoma in the United States. Cancer 1998; 83:2049–53.
3. Bollschweiler E, Wolfgarten E, Gutschow C, Holscher AH. Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. Cancer 2001; 92: 549–55.
4. El-Serag HB. The epidemic of oesophageal adenocarcinoma. Gastroenterol Clin North Am 2002; 31:421–40.
5. Stein HJ, Brücher BL, Sendler A, Siewert JR. Esophageal cancer: patient evaluation and pre-treatment staging. Surg Oncol. 2001 Nov;10(3):103–11. Review.
6. Pfau PR, Perlman SB, Stanko P, Frick TJ, Gopal DV, Said A, Zhang Z, Weigel T. The role and clinical value of EUS in a multimodality esophageal carcinoma staging program with CT and positron emission tomography. Gastrointest Endosc.2007 Mar;65(3):377–84.
7. Omloo JM, Sloof GW, Boellaard R, Hoekstra OS, Jager PL, van Dullemen HM, Fockens P, Plukker JT, van Lanschot JJ. Importance of fluorodeoxyglucose-positron emission tomography (FDG-PET) and endoscopic ultrasonography parameters in predicting survival following surgery for esophageal cancer. Endoscopy. 2008 Jun;40(6):464–71
8. van Vliet EP, Heijenbrok-Kal MH, Hunink MG, Kuipers EJ, Siersema PD. Staging investigations for esophageal cancer: a meta-analysis. Br J Cancer. 2008 Feb 12;98(3):547–57. Epub 2008 Jan 22.
9. MacManus M, Nestle U, Rosenzweig KE, Carrio I, Messa C, Belohlavek O, et al. Use of PET and PET/CT for radiation therapy planning: IAEA expert report 2006–2007. Radiother Oncol 2009;91(1):85–94
10. Bruzzi JF, Munden RF, Truong MT, Marom EM, Sabloff BS, Gladish GW, Iyer RB, Pan TS, Macapinlac HA, Erasmus JJ.PET/CT of esophageal Cancer: its role in clinical management. Radiographics. 2007 Nov-Dec; 27(6):1635–52. Review.
11. Liberale G, Van Laethem JL, Gay F, Goldman S, Nagy N, Coppens E, Gelin M, El Nakadi I. The role of PET scan in the

preoperative management of oesophageal cancer. Eur J Surg Oncol. 2004 Nov;30(9):942–7.
12. Flamen P, Lerut A, Van Cutsem E, De Wever W, Peeters M, Stroobants S, Dupont P, Bormans G, Hiele M, De Leyn P, Van Raemdonck D, Coosemans W, Ectors N, Haustermans K, Mortelmans L. Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. J Clin Oncol. 2000 Sep 15;18(18):3202–10.
13. van Westreenen HL, Heeren PA, van Dullemen HM, van der Jagt EJ, Jager PL, Groen H, Plukker JT. Positron emission tomography with F-18-fluorodeoxyglucose in a combined staging strategy of esophageal cancer prevents unnecessary surgical explorations. J Gastrointest Surg. 2005 Jan;9(1):54–61.
14. Westerterp M, van Westreenen HL, Reitsma JB, Hoekstra OS, Stoker J, Fockens P, Jager PL, Van Eck-Smit BL, Plukker JT, van Lanschot JJ, Sloof GW. Esophageal cancer: CT, endoscopic US, and FDG PET for assessment of response to neoadjuvant therapy—systematic review. Radiology. 2005 Sep;236(3):841–51. Review.
15. van Westreenen HL, Heeren PA, Jager PL, van Dullemen HM, Groen H, Plukker JT. Pitfalls of positive findings in staging esophageal cancer with F-18-fluorodeoxyglucose positron emission tomography. Ann Surg Oncol. 2003 Nov;10(9):1100–5.
16. Gillies RS, Middleton MR, Maynard ND, Bradley KM, Gleeson FV. Additional benefit of ^{18}F-fluorodeoxyglucose integrated positron emission tomography/computed tomography in the staging of oesophageal cancer. Eur Radiol. 2011 Feb;21(2):274–80
17. Gospodarowicz M, Wittekind C, Sobin L. Esophagus. In: Wittekind C, Sobin L (eds) UICC—TNM Classification of malignant tumours, 7th edn. Wiley, New York (2009)
18. Choi JY, Lee KS, Kwon OJ, Shim YM, Baek CH, Park K, Lee KH, Kim BT. Improved detection of second primary cancer using integrated [^{18}F]fluorodeoxyglucose positron emission tomography and computed tomography for initial tumor staging. J Clin Oncol. 2005 Oct 20;23(30):7654–9.
19. Thompson WM, Halvorsen RA Jr: Staging esophageal carcinoma II: CT and MRI. Semin Oncol 21:447–452, 1994
20. van Westreenen HL, Westerterp M, Bossuyt PM, Pruim J, Sloof GW, van Lanschot JJ, Groen H, Plukker JT. Systematic review of the staging performance of ^{18}F-fluorodeoxyglucose positron emission tomography in esophageal cancer. J Clin Oncol. 2004 Sep 15;22(18):3805–12. Review.
21. Rice TW: Clinical staging of esophageal carcinoma: CT, EUS, and PET. Chest Surg Clin N Am 10:471–485, 2000
22. Block MI, Patterson GA, Sundaresan RS, Bailey MS, Flanagan FL, Dehdashti F, Siegel BA, Cooper JD. Improvement in Staging of esophageal cancer with the addition of positron emission tomography. Ann Thorac Surg 1997;64:770 –7
23. Peters JH, Hoeft SF, Heimbucher J, Bremner RM, DeMeester TR, Bremner CG, Clark GW, Kiyabu M, Parisky Y. Selection of patients for curative or palliative resection of esophageal cancer based on preoperative endoscopic ultrasonography. Arch Surg. 1994 May;129(5):534–9.
24. Chandawarkar RY, Kakegawa R, Fujita H, Yamana H, Hayabuthi N. Comparative analysis of imaging modalities in the preoperative assessment of nodal metastasis in esophageal cancer. J Surg Oncol 1996;61:214–7.
25. Sugarbaker DJ, Jaklitsch MT, Liptay MJ. Thoracoscopic staging and surgical therapy for esophageal cancer. Chest 1995; 107:218S–23S
26. van Westreenen HL, Westerterp M, Sloof GW, Groen H, Bossuyt PM, Jager PL,Comans EF, van Dullemen HM, Fockens P, Stoker J, van der Jagt EJ, van Lanschot JJ, Plukker JT. Limited additional value of positron emission tomography in staging oesophageal cancer.Br J Surg. 2007 Dec;94(12):1515–20
27. Rigo P, Paulus P, Kaschten BJ, Hustinx R, Bury T, Jerusalem G, Benoit T, Foidart-Willems J. Oncological applications of positron emission tomography with fluorine-18 fluorodeoxyglucose. Eur J Nucl Med. 1996 Dec;23(12):1641–74. Review.
28. Conti PS, Lilien DL, Hawley K, Keppler J, Grafton ST, Bading JR. PET and [^{18}F]-FDG in oncology: a clinical update. Nucl Med Biol 1996;23:717–35.
29. Bar-Shalom R, Valdivia AY, Blaufox MD. PET imaging in oncology. Semin Nucl Med. 2000;30:150–185
30. Kato H, Miyazaki T, Nakajima M, Takita J, Kimura H, Faried A, Sohda M, Fukai Y, Masuda N, Fukuchi M, Manda R, Ojima H, Tsukada K, Kuwano H, Oriuchi N, Endo K. The incremental effect of positron emission tomography on diagnostic accuracy in the initial staging of esophageal carcinoma. Cancer. 2005 Jan 1;103(1):148–56.
31. Luketich JD, Schauer PR, Meltzer CC, Landreneau RJ, Urso GK, Townsend DW, Ferson PF, Keenan RJ, Belani CP. Role of positron emission tomography in staging esophageal cancer. Ann Thorac Surg. 1997 Sep;64(3):765–9.
32. Bar-Shalom R, Guralnik L, Tsalic M, Leiderman M, Frenkel A, Gaitini D, Ben-Nun A, Keidar Z, Israel O. The additional value of PET/CT over PET in FDG imaging of oesophageal cancer. Eur J Nucl Med Mol Imaging. 2005 Aug;32(8):918–24. Epub 2005 Apr 19.
33. Kole AC, Plukker JT, Nieweg OE, Vaalburg W. Positron emission tomography for staging of oesophageal and gastroesophageal malignancy. Br J Cancer. 1998 Aug;78(4):521–7.
34. Ott K, Weber W, Siewert JR. The importance of PET in the diagnosis and response evaluation of esophageal cancer. Dis Esophagus. 2006;19(6):433–42.
35. Wallace MB, Nietert PJ, Earle C, Krasna MJ, Hawes RH, Hoffman BJ, Reed CE. An analysis of multiple staging management strategies for carcinoma of the esophagus: computed tomography, endoscopic ultrasound, positron emission tomography, and thoracoscopy/laparoscopy. Ann Thorac Surg. 2002 Oct;74(4):1026–32.
36. Wren SM, Stijns P, Srinivas S. Positron emission tomography in the initial staging of esophageal cancer. Arch Surg 2002;137: 1001–7.
37. Bruzzi JF, Truong MT, Macapinlac H, Munden RF, Erasmus JJ. Integrated CT-PET imaging of esophageal cancer: unexpected and unusual distribution of distant organ metastases. Curr Probl Diagn Radiol 2007;36:21–29.
38. van Westreenen HL, Westerterp M, Jager PL, van Dullemen HM, Sloof GW, Comans EF, van Lanschot JJ, Wiggers T, Plukker JT. Synchronous primary neoplasms detected on ^{18}F-FDG PET in staging of patients with esophageal cancer. J Nucl Med. 2005 Aug;46(8):1321–5
39. Kumagai Y, Kawano T, Nakajima Y, et al. Multiple primary cancers associated with esophageal carcinoma. Surg Today 2001;31:872–876.
40. Agress H Jr, Cooper BZ. Detection of clinically unexpected malignant and premalignant tumors with whole-body FDG PET: histopathologic comparison. Radiology. 2004 Feb;230(2):417–22. Epub 2003 Dec 29.
41. Zhuang H, Hickeson M, Chacko TK, Duarte PS, Nakhoda KZ, Feng Q, Alavi A. Incidental detection of colon cancer by FDG positron emission tomography in patients examined for pulmonary nodules. Clin Nucl Med. 2002 Sep;27(9):628–32.
42. Tatlidil R, Jadvar H, Bading JR, Conti PS. Incidental colonic fluorodeoxyglucose uptake: correlation with colonoscopic and histopathologic findings. Radiology. 2002 Sep;224(3):783–7.
43. Kagei K, Hosokawa M, Shirato H, Kusumi T, Shimizu Y, Watanabe A, Ueda M. Efficacy of intense screening and treatment for synchronous second primary cancers in patients with esophageal cancer. Jpn J Clin Oncol. 2002 Apr;32(4):120–7.

44. Bollschweiler E, Schloesser T, Leers J, Vallböhmer D, Schäfer H, Hölscher AH. High prevalence of colonic polyps in white males with esophageal adenocarcinoma. Dis Colon Rectum. 2009 Feb;52(2):299–304.
45. Meyers BF, Downey RJ, Decker PA, Keenan RJ, Siegel BA, Cerfolio RJ, Landreneau RJ, Reed CE, Balfe DM, Dehdashti F, Ballman KV, Rusch VW, Putnam JB Jr; American College of Surgeons Oncology Group Z0060. The utility of positron emission tomography in staging of potentially operable carcinoma of the thoracic esophagus: results of the American College of Surgeons Oncology Group Z0060 trial. J Thorac Cardiovasc Surg. 2007 Mar;133(3):738–45.
46. Heeren PA, Jager PL, Bongaerts F, van Dullemen H, Sluiter W, Plukker JT. Detection of distant metastases in esophageal cancer with (18)F-FDG PET. J Nucl Med. 2004 Jun;45(6):980–7.
47. Walker AJ, Spier BJ, Perlman SB, Stangl JR, Frick TJ, Gopal DV, Lindstrom MJ, Weigel TL, Pfau PR. Integrated PET/CT fusion imaging and endoscopic ultrasound in the pre-operative staging and evaluation of esophageal cancer. Mol Imaging Biol. 2011 Feb;13(1):166–71.
48. Thurau K, Palmes D, Franzius C, Minin E, Senninger N, Juergens KU, Bruewer M. Impact of PET-CT on primary staging and response control on multimodal treatment of esophageal cancer. World J Surg. 2011 Mar;35(3):608–16

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ORIGINAL ARTICLE

Prealbumin Levels as a Useful Marker for Predicting Infectious Complications After Gastric Surgery

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Abstract
Background/Objectives Preoperative nutritional status is associated with postoperative complications. Prealbumin, a visceral protein, is sensitive to protein malnutrition. The objective of this study is to evaluate the role of preoperative prealbumin levels as a marker for predicting complications after gastric surgery.
Methods An observational study was performed on 183 patients who underwent gastric surgery due to benign or malignant gastric disease at Seoul National University Hospital (SNUH) between August 2009 and October 2010. Preoperative prealbumin levels were also measured. Nutritional variables such as prealbumin (cutoff value, 18 mg/dL), albumin, body mass index (BMI), and clinicopathologic data were collected. Postoperative hospital stay, 30-day complications and mortality rate were obtained to investigate outcomes.
Results The complication rate was 52% in the abnormal prealbumin group (n=23) and 24% in the normal prealbumin group (n=160; p=0.005). The complication rate was higher in patients with low preoperative albumin levels (<3.5 g/dL) and abnormal BMI (<18.5 kg/m^2), but the differences were not statistically significant. Comorbidity of diabetes mellitus (DM), resection extent, combined resection, TNM stage and prealbumin levels were associated with complications. In multivariate analysis, DM and combined resection were significantly correlated with complications (p=0.001 for each). In subgroup analysis, resection extent, approach, combined resection, TNM stage, and prealbumin levels were significantly associated with infectious complications. Multivariate analysis identified combined resection (p=0.001) and prealbumin levels (p=0.032) as independent variables.
Conclusions Preoperative prealbumin levels could be a useful marker for predicting complications, especially infectious complications, after gastric surgery.

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Keywords Prealbumin · Gastrectomy · Postoperative complications

Abbreviations

SNUH	Seoul National University Hospital
BMI	Body mass index
DM	Diabetes mellitus
VA	Veterans Affairs
SGA	Subjective global assessment
DNA	Detailed nutrition assessment
NRS	Nutrition risk screening
UICC/AJCC	Union for International Cancer Control/ American Joint Cancer Committee
STG	Subtotal gastrectomy
TG	Total gastrectomy

LADG	Laparoscopy-assisted distal gastrectomy
CT	Computed tomography
PCD	Percutaneous drainage
UGIS	Upper gastrointestinal series

Introduction

The effects of preoperative nutritional status on clinical outcomes have been well described. In the USA, 44 Veterans Affairs (VA) medical centers performed the National VA Surgical Risk Study in order to develop a risk-adjusted model to predict postoperative outcomes in major non-cardiac operations between October 1991 and December 1993.[1,2] In this study, the effects of various preoperative, operative, and postoperative parameters on postoperative outcomes were analyzed, and preoperative albumin levels were identified to be the best predictor of postoperative morbidity and mortality. The Centers for Disease Control and Prevention guidelines suggest that malnutrition and obesity (weight≥20% of ideal body weight) could be risk factors for surgical site infection, a major postoperative complication.[3]

Various nutritional parameters, including visceral proteins, as well as anthropometric parameters and immunocompetence have been clinically used to evaluate the degree of risk of malnutrition.[4] In addition, various nutritional assessment and screening tools, such as subjective global assessment (SGA), detailed nutrition assessment (DNA), and nutrition risk screening (NRS) 2002, have been introduced.[5,6] Many studies have been performed to determine nutritional parameters that highly correlate with clinical outcomes. Nutritional assessment parameters—such as albumin[7,8] and weight loss[9]—and tools, such as NRS 2002[10] and Seoul National University Hospital-Nutrition Screening Index,[11] have been identified to significantly correlate with clinical outcomes.

Visceral proteins frequently used in clinical practice include albumin, prealbumin, and transferrin. Unlike subjective nutritional assessment performed by nutrition experts, visceral protein test results can be quickly and easily evaluated. According to the criteria of the American Dietetic Association for establishing a diagnosis of malnutrition, body weight is associated with energy malnutrition, whereas serum albumin levels are associated with protein malnutrition.[12] It has been reported that serum albumin correlates with clinical outcomes in medical and surgical patients.[7,8,13] However, the sensitivity of albumin can be reduced in acute protein malnutrition because of a large body pool and a long half-life (20 days).[14]

Prealbumin is a rapid-turnover protein, and has a much shorter half-life (2 days) than albumin. Prealbumin is assumed to be a better indicator of protein nutrition than albumin because it contains a high percentage of essential amino acids such as tryptophan. In addition, prealbumin levels rapidly decrease in patients with pre-kwashiorkor or early marasmus.[14] Devoto et al.[15] have demonstrated that prealbumin has a high sensitivity and specificity compared to nutritional assessment tools such as DNA, SGA and Prognostic Inflammatory and Nutritional Index score. It has been suggested that prealbumin, as a single parameter, is useful for evaluating protein energy malnutrition.

Preoperative nutritional support is known to be effective for moderate-to-severe malnutrition.[16,17] Postoperative complications are significantly decreased by nutritional support after gastrointestinal surgery.[18] Discovering nutritional markers associated with postoperative complications would allow us to improve clinical outcomes by nutritional support of selected patients with nutritional risk.[16]

The objectives of this study are to investigate the usefulness of prealbumin levels as a predictor of postoperative complications and to compare it with other nutritional parameters such as serum albumin and body mass index (BMI) frequently used in clinical practice and to assess clinicopathologic factors that can affect postoperative complications.

Material and Methods

The study subjects were patients who underwent gastric surgery due to benign or malignant gastric disease at Seoul National University Hospital (SNUH) between August 2009 and October 2010 and whose preoperative prealbumin levels were measured. We prospectively collected the clinical data of 183 such patients. The following patients having factors that could be affected preoperative prealbumin levels were excluded from the study: (1) those with acute or chronic inflammation; laboratory abnormalities (C-reactive protein elevation, abnormal numbers of leukocyte) and/or clinical symptoms or signs suggestive of inflammation; (2) those with severe liver disease, Child-Pugh class B or C, and (3) those who received corticosteroid therapy.

Baseline characteristics, operation, and disease-related factors were collected. Gastric cancer patients were classified based on the seventh edition of the Union for International Cancer Control/American Joint Cancer Committee (UICC/AJCC) TNM staging system.[19] We investigated comorbidities, such as hypertension, heart disease, pulmonary disease, renal disease, liver disease, diabetes mellitus (DM), cerebrovascular disease, and other cancers. DM is reported to correlate well with surgical site infec-

Table 1 Definitions of postoperative complications

	Complications	Definitions
Infectious complications	Wound complications	Seroma, hematoma, dehiscence, evisceration of surgical wound, wound infection requiring wound repair
	Intra-abdominal fluid collection/abscess	Confirmed by abdominal ultrasonography or computed tomography (CT)
		Requiring percutaneous drainage (PCD) or antibiotic therapy
	Anastomosis leakage, fistula	Drainage of intestinal content or leakage in upper gastrointestinal series (UGIS)
		Fistula confirmed by fistulogram
	Pancreatitis	Confirmed by serum amylase and CT
	Cholangitis	Confirmed by liver function test and CT
	Pulmonary infection	Pneumonia, bronchiolitis, etc.
	Urinary tract infection	Confirmed by urine culture
	Bacteremia, sepsis	Confirmed by blood culture
Non-infectious complications	Bleeding	Requiring transfusion or intervention (angiography, reoperation)
	Intestinal obstruction	No gas passage or other symptoms suspected intestinal obstruction, the findings of suspected mechanical obstruction on abdominal radiograph
	Ileus	Vomiting during meals after surgery or difficulty with diet progression, the findings of suspected paralytic obstruction on abdominal radiograph
	Anastomosis stenosis	Anastomotic stenosis confirmed by gastrofibroscopy or UGIS, requiring intervention
	Pulmonary complications	Atelectasis, pneumothorax, pleural effusion, respiratory failure requiring PCD or mechanical ventilator support
	Renal complications	Acute renal failure
	Hepatic complications	Hepatic dysfunction
	Cardiac complications	Myocardial infarction, heart failure, arrhythmia, cardiac arrest
	Endocrine complications	Diabetes inspidus, diabetic ketoacidosis, syndrome of inappropriate secretion of anti-diuretic hormone
	Neurovascular disorders	Cerebrovascular accident, deep vein thrombosis, pulmonary embolism

tion,[20] and thus DM patients were classified into subgroups. DM was defined according to the 2011 standards of medical care in diabetes recommended by the American Diabetes Association.[21]

We collected information on weight changes before surgery, and nutritional parameters including BMI at admission, the most recent albumin level before surgery (up to 30 days), the most recent prealbumin level before surgery (from 2 days before surgery to the day of surgery) and prealbumin levels within 7 days of surgery (early [2–4 days after surgery] and late [5–7 days after surgery]).

The 30-day mortality rate, 30-day postoperative complications, and postoperative hospitalization duration were included as outcome variables. The definitions of postoperative complications are shown in Table 1. Overall complications were analyzed, and subgroup analysis was also performed on infectious complications.

The chi-square test and Fisher's exact test were used to determine the correlation between postoperative complications and variables. In multivariate analysis, a logistic regression model (stepwise) was used. A p value of <0.05 was considered to be statistically significant. Variables with a p value of <0.05 in the univariate analyses were assigned in the multivariate analysis. The ROC curve was used to obtain the cutoff value of prealbumin levels with a high sensitivity and specificity capable of predicting overall complications. The t test was used to compare the mean of prealbumin levels. Statistical analyses were performed using SPSS version 17.0.

This study was passed through the deliberations of the SNUH Institutional Review Board (IRB no. H-1007-027-322). All of authors have no actual or potential conflict of interest.

Results

Baseline Characteristics

This study included 1,029 patients who underwent gastric surgery due to benign or malignant gastric disease at SNUH between August 2009 and October 2010. Of these patients, 183 underwent measurement of preoperative prealbumin levels. The mean age of the patients was 59.3±12.3 years, and the number of patients was greater in males. The

Table 2 Baseline characteristics (n=183)

Variables		Number (%)
Age (mean±S.D.)	59.3±12.3 years (range 25–85 years)	
Gender (male/female)	131:52	
Diagnosis	Gastric cancer	168 (91.8%)
	Gastrointestinal stromal tumor	13 (7.1%)
	Others[a]	2 (1.1%)
Comorbidity	≥1[b]	81 (44.3%)
	DM	20 (10.9%)
BMI	≥18.5 kg/m^2	171 (93.4%)
	<18.5 kg/m^2	12 (6.6%)
Operation name	STG	151 (82.5%)
	TG	18 (9.8%)
	Wedge resection	12 (6.6%)
	Gastrojejunostomy	2 (1.1%)
Approach	Open surgery	103 (56.3%)
	Laparoscopic surgery	80 (43.7%)
Combined resection	No	162 (88.5%)
	Yes[c]	21 (11.5%)
Radicality (n=182)	R0	173 (95.1%)
	R1 and R2	9 (4.9%)
Gastric cancer	I	110 (65.5%)
TNM stage[d] (n=168)	II	19 (11.3%)
	III	33 (19.6%)
	IV	6 (3.6%)

[a] One carcinoid tumor and one duodenal ulcer

[b] Hypertension, heart disease, pulmonary disease, renal disease, liver disease, DM, cerebrovascular disease, and other cancers

[c] Eight gallbladder, four spleen, four spleen and pancreas, and five others

[d] Seventh UICC/AJCC TNM staging system

number of patients with gastric cancer was 168 (91.8%). Patients who had at least one underlying disease accounted for 44.3% of all patients. Of these patients, 10.9% had DM. The majority (82.5%) of patients underwent subtotal gastrectomy (STG), whereas 9.8% underwent total gastrectomy (TG), and the remaining patients underwent wedge resection or gastrojejunostomy. Patients with gastric cancer underwent D1+β or D2 lymph node dissection, and those with other diseases underwent limited lymph node dissection. Of the patients with gastric cancer, 76.8% had TNM stage I–II tumors, and 23.2% had stage III–IV tumors. Other information about the baseline characteristics of subjects is shown in Table 2.

Distribution of Nutritional Markers

We investigated BMI as an anthropometric parameter as well as visceral proteins, including albumin and prealbumin, as a nutritional marker. The distribution of each nutritional marker is shown in Fig. 1. BMI less than 18.5 kg/m^2 was found in 6.6% (12/183) of patients, and BMI 30 kg/m^2 or more (obesity) was found in 5.5% (10/183). The number of patients with albumin test results within 30 days before surgery was 145, and hypoalbuminemia (less than 3.5 g/dL) was found in 7.6% (11/145) of patients. Prealbumin levels less than 18 mg/dL were observed in 12.6% (23/183) of patients.

The mean±S.D. of BMI was 23.56±3.551 kg/m^2. The mean±S.D. of prealbumin level was 26.97±8.330 mg/dL and the mean±S.D. of albumin level was 4.09±0.446 g/dL (median, 4.2 g/dL).

Surgical Outcomes

The 30-day postoperative mortality rate was 0% (0/183). The postoperative complications during the last 30 days are shown in Table 3. The overall complication rate was 27.9% (51/183). Among postoperative complications, wound complications were most common, followed by intra-abdominal fluid collection/abscess, anastomosis stenosis, and pulmonary complications. Infectious complications, which occurred, included intra-abdominal infection, pneumonia, bronchiolitis, pancreatitis, and cholangitis, in addition to two cases before sepsis.

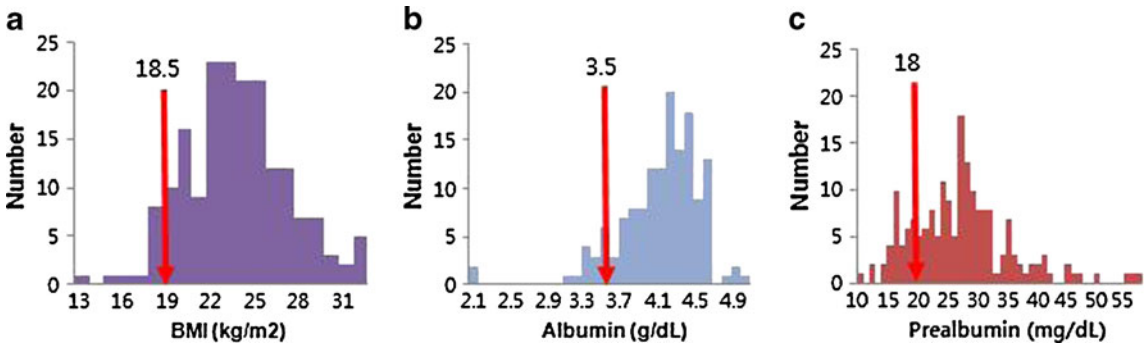

Fig. 1 Distribution of nutritional markers. **a** BMI, **b** albumin, **c** prealbumin

Table 3 Surgical outcomes: 30-day postoperative complications

	Complications	Number	Percent, %
Infectious complications	Wound complications	18	9.8
	Intra-abdominal fluid collection/abscess	11	6.0
	Pulmonary infection	6	3.3
	Sepsis	2	1.1
	Pancreatitis	1	0.5
	Cholangitis	1	0.5
	Other infection (thrombophlebitis)	1	0.5
Non-infectious complications	Anastomosis stenosis	9	4.9
	Bleeding (intra-abdominal, intraluminal)	5	2.7
	Ileus	4	2.2
	Anastomosis leakage	4	2.2
	Pulmonary complications (atelectasis, pleural effusion)	3	1.6
	Obstruction	2	1.1
	Hepatic complication (hepatic artery thromboembolism and liver enzymes elevation)	1	0.5
	Cardiac complications (ST segment elevation myocardial infarction)	1	0.5
Total		69	
Overall complication rate		51/183	27.9
Infectious complication rate		36/183	19.7

Postoperative hospital stays ranged from 5 to 44 days (median, 7 days). The median of postoperative hospital stay was 7 days in patients without complications and 12 days in those with.

Factors Affecting Postoperative Complications

Cross-analyses were performed to determine the factors affecting postoperative complications, and the results are

Table 4 Factors affecting postoperative complications: overall and infectious complications (univariate)

Variables		Overall complications		Infectious complications	
		Percent, % (no./total no.)	*P* value	Percent, % (no./total no.)	*P* value
Age (years)	<65	23.5 (27/115)	0.085	17.4 (20/115)	0.313
	≥65	35.3 (24/68)		23.5 (16/68)	
Gender	Male	26.7 (35/131)	0.581	18.3 (24/131)	0.465
	Female	30.8 (16/52)		23.1 (12/52)	
Comorbidity of DM	No	23.3 (38/163)	<0.001*	17.8 (29/163)	0.078
	Yes	65.0 (13/20)		35.0 (7/20)	
Operation name (resection extent)	STG	26.5 (40/151)	0.038*	18.5 (28/151)	0.028*
	TG	50.0 (9/18)		44.4 (8/18)	
Approach	Open surgery	33.0 (34/103)	0.078	25.2 (26/103)	0.031*
	Laparoscopic surgery	21.3 (17/80)		12.5 (10/80)	
Combined resection	No	23.5 (38/162)	<0.001*	15.4 (25/162)	<0.001*
	Yes	61.9 (13/21)		52.4 (11/21)	
TNM stage	I–II	25.6 (33/129)	0.031*	17.8 (23/129)	0.039*
	III–IV	43.6 (17/39)		33.3 (13/39)	
BMI (kg/m^2)	≥18.5	26.9 (46/171)	0.320	19.9 (34/171)	1.000
	<18.5	41.7 (5/12)		16.7 (2/12)	
Preoperative albumin (g/dL)	≥3.5	23.1 (31/134)	0.141	14.9 (20/134)	0.085
	<3.5	45.5 (5/11)		36.4 (4/11)	
Preoperative prealbumin (mg/dL)	≥18	24.4 (39/160)	0.005*	16.3 (26/160)	0.005*
	<18	52.2 (12/23)		43.5 (10/23)	

*$p<0.05$

Table 5 Factors affecting postoperative complications: overall and infectious complications (multivariate)

Variables	Overall complications			Variables	Infectious complications		
	P value	OR	95% CI		*P* value	OR	95% CI
Combined resection Yes	0.001*	6.521	2.220–19.151	Combined resection Yes	0.001*	5.720	2.029–16.127
Comorbidity DM	0.001*	6.521	2.220–19.151	Preoperative prealbumin <18 mg/dL	0.032*	2.996	1.096–8.188
Preoperative prealbumin <18 mg/dL	0.192	2.007	0.705–5.715	TNM stage III–IV	0.508	1.377	0.533–3.559
TNM stage III–IV	0.412	1.460	0.591–3.609	Operation name TG	0.642	1.367	0.366–5.102
Operation name TG	0.869	0.892	0.229–3.475	Approach Open surgery	0.837	1.102	0.438–2.773

*$p<0.05$

shown in Table 4. The complication rate was 52% in the abnormal prealbumin group ($n=23$) and 24% in the normal prealbumin group ($n=160$) ($p=0.005$). The complication rate was higher in patients with low preoperative albumin levels (<3.5 g/dL) and abnormal BMI (<18.5 kg/m^2), but the differences were not statistically significant. As for complications, DM, resection extent, combined resection, TNM stage, and preoperative prealbumin level had statistically significant correlation with postoperative complications in univariate analysis. The complication rate was higher in elderly patients (≥65 years) or in patients who underwent open surgery, but the differences were not statistically significant.

Five variables significant in the univariate analysis with complications were assigned in the multivariate analysis. In logistic regression analysis, comorbidity of DM ($p=0.001$; OR, 6.521) and combined resection ($p=0.001$; OR, 6.521) were significantly correlated with complications (Table 5).

Subgroup analysis of infectious complications was performed in the same way. As for infectious complications, resection extent, approach, combined resection, TNM stage, and preoperative prealbumin levels were associated with infectious complications in univariate analysis ($p<0.05$; Table 4). The complication rate was higher in DM patients and patients with low preoperative albumin levels (<3.5 g/dL), but the differences were not statistically significant.

Five variables significant in the univariate analysis with infectious complications were assigned in the multivariate analysis. Multivariate logistic regression analysis identified combined resection ($p=0.001$; OR, 5.720) and low preoperative prealbumin level ($p=0.032$; OR, 2.996) as independent variables for the development of postoperative infectious complications (Table 5).

Prealbumin showed a higher sensitivity than albumin for predicting overall complications (0.235 vs. 0.139) and infectious complications (0.278 vs. 0.167) (Table 6). Both visceral proteins showed good specificities.

Change of Prealbumin Levels

Prealbumin levels were gradually reduced from preoperative levels to early postoperative (2–4 days after surgery) and late postoperative (5–7 days after surgery) levels. In patients with complications, the mean of preoperative prealbumin levels were lower, and the postoperative reduction rates were higher (Fig. 2).

Discussion

In the USA, the National VA Surgical Risk Study was performed to develop a risk-adjusted model for predicting postoperative outcomes, and preoperative albumin levels were the best predictor of postoperative morbidity and mortality.[1,2] Additional analysis was performed by Gibbs et al.[7] using the albumin database. Preoperative albumin levels most significantly correlate with 30-day postoperative mortality and morbidity rates. Subgroup analysis performed in terms of general surgery, thoracic surgery, and orthopedic surgery

Table 6 Comparison of prealbumin and albumin

	Overall complications		Infectious complications	
	Sensitivity	Specificity	Sensitivity	Specificity
Prealbumin	0.235 (12/51)	0.917 (121/132)	0.278 (10/36)	0.912 (134/147)
Albumin	0.139 (5/36)	0.945 (103/109)	0.167 (4/24)	0.942 (114/121)

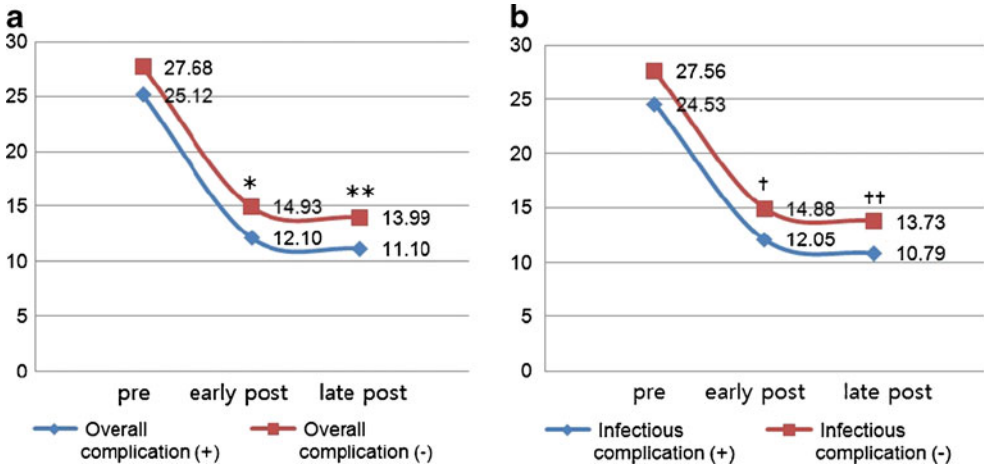

Fig. 2 Changes in prealbumin levels (mean, milligrams per deciliter). **a** overall complications, **b** infectious complications. $p^*=0.010$, $p^{**}<0.001$, $p^{\dagger}=0.011$, $p^{\dagger\dagger}=0.001$

showed that albumin-based prediction was most accurate in general surgery. Kudsk et al.[8] reported that preoperative albumin levels have inverse relationships with clinical outcomes such as postoperative complications, hospital stay, and mortality in gastrointestinal surgery patients.

In our study, among nutritional parameters, prealbumin levels were the only significant variable that correlated significantly with postoperative complications, but albumin levels had no significant correlation. These results are different from those of previous studies.[7,8] The results could be influenced by the different classifications of clinically meaningful malnutrition. Although lower cutoff values (less than 3.0 g/dL) have been used in previous studies,[22] albumin cutoff values for predicting surgical outcomes have not yet been established. In previous investigators,[4,12,14] serum albumin levels of >3.5 g/dL have been regarded as well nourished. Therefore, our study used an albumin cutoff value of 3.5 g/dL. In our study, the number of patients whose preoperative albumin levels were less than 3.0 g/dL was only 2 (1.4%) and thus it is difficult to identify significant correlations with albumin levels and postoperative complications.

The reason for the low frequency of hypoalbuminemia may be that serum albumin levels remained relatively constant because the degeneration rate is proportional to the size of the extravascular pool and that albumin levels do not fully reflect short-term malnutrition.[23] Prealbumin may be used as a marker with a higher sensitivity for screening patients at high risk of malnutrition. In our study, prealbumin showed a higher sensitivity than albumin for predicting surgical complications. Abnormal preoperative prealbumin levels (<18 mg/dL) could be regarded as a risk factor of surgical complications.

The synthesis of prealbumin is decreased in severe liver disease. Prealbumin can be decreased in patients with inflammation but increased in those with corticosteroid therapy.[14] In our study, exclusion criteria were established in order to rule out these effects and to improve the reliability of the results.

Previous studies of prealbumin were conducted mainly in patients with renal diseases or critically ill patients. These studies commonly reported mortality correlated with prealbumin.[24,25] However, studies in surgical patients have been rare. One study with Brazilian elderly patients, who underwent a major elective surgery, reported that prealbumin levels had the most significant correlation with postoperative mortality and complications in multivariate analysis which included visceral proteins, anthropometric parameters, and immunocompetence.[26] Also, it has been reported that postoperative complication rates are significantly higher in ovarian cancer patients with prealbumin levels of <18 mg/dL who underwent cytoreductive surgery.[27] However, these two studies did not eliminate the effects of surgery itself or clinicopathologic factors such as comorbidity and severity of disease.

Ryan et al.[9] have proposed that a weight loss of ≥10% before surgery is the only independent predictor of postoperative complications on multivariate analysis, considering the impact of tumor site, morphology, operation type, and comorbidity with many nutritional parameters, such as BMI, SGA, and albumin. Since most subjects in our study were asymptomatic at diagnosis, the frequency of significant weight loss before surgery was relatively low. In addition, most subjects were within normal limits of BMI and the number of patients with an abnormal BMI did not seem to be enough to identify the effect of BMI on postoperative complications.

Gibbs et al.[7] investigated 21 complications. They found that major infectious complications, such as deep wound infection, pneumonia, and systemic sepsis, significantly correlate with albumin levels. In our study, the incidence of infectious complications, such as wound infection, intra-abdominal abscess, and pneumonia, was relatively high, and there were two cases of sepsis. Our high incidence of infectious complications was similar to the results of previous studies.[7]

Besides nutritional markers, many clinicopathologic and operation-related variables could also affect postoperative outcomes. In a study by Park et al.[28], age (>50 years), combined resection, and Billroth II reconstruction are identified as independent prognostic factors of postopera-

tive complications in gastric cancer patients. In cases of Billroth II reconstruction, surgical complications, such as ileus and obstruction, occurred frequently. A previous multicenter study identified comorbidity as the most important risk factor of postoperative complications in patients who underwent laparoscopy-assisted distal gastrectomy (LADG).[29] Kim et al.[30] investigated underlying diseases in patients who underwent LADG. They found that the patients with combined pulmonary comorbidity had significantly higher postoperative complications, especially pulmonary complications. DM is correlated with surgical site infection.[20] In our study, combined resection and comorbidity of DM were significantly correlated with overall complications. The complication rate was higher in elderly patients, without any statistical significance. In analysis of infectious complications, combined resection and low preoperative prealbumin levels were identified as independent factors. As with previous studies, nutritional status was found to be related to infectious complications, and prealbumin could be used as a predictor based on our results.

In a recent study of postoperative changes in rapid-turnover proteins (prealbumin, transferrin, and retinol-binding protein) in elective gastrointestinal surgery, the serum prealbumin levels decreased 3 days after surgery, gradually increased and returned to approximately 80% of preoperative values on the 14th postoperative day.[31] In our study, early postoperative prealbumin levels decreased approximately 50% of preoperative values, and early and late postoperative prealbumin levels were significantly lower in patients with complications. Postoperative changes in prealbumin levels may be affected by preoperative nutritional status, as well as the surgical procedure, clinical course, and postoperative nutrition support.[31,32]

In our study, the total number of study patients was 183, and there were much fewer patients with abnormal prealbumin levels (n=23) than normal subjects (n=160). This may be a limitation of our study. However, the proportion of abnormal prealbumin was higher than that of albumin. When only gastric surgery patients are analyzed, the homogeneity of the sample patients could be obtained as compared to previous studies in gastrointestinal surgery patients.

Taken together, preoperative prealbumin levels showed a higher sensitivity for screening patients at risk of malnutrition than albumin and BMI. Unlike albumin and BMI, prealbumin was significantly correlated with postoperative complications. The results of this study suggest that preoperative prealbumin levels may be a useful marker for predicting surgical complications, especially infectious complications in patients undergoing gastric surgery.

Disclosure All authors have no conflict of interest.

References

1. Khuri SF, Daley J, Henderson W, Hur K, Gibbs JO, Barbour G, Demakis J, Irvin G 3rd, Stremple JF, Grover F, McDonald G, Passaro E Jr, Fabri PJ, Spencer J, Hammermeister K, Aust JB. Risk adjustment of the postoperative mortality rate for the comparative assessment of the quality of surgical care: results of the National Veterans Affairs Surgical Risk Study. J Am Coll Surg 1997;185:315–327.
2. Daley J, Khuri SF, Henderson W, Hur K, Gibbs JO, Barbour G, Demakis J, Irvin G 3rd, Stremple JF, Grover F, McDonald G, Passaro E Jr, Fabri PJ, Spencer J, Hammermeister K, Aust JB, Oprian C. Risk adjustment of the postoperative morbidity rate for the comparative assessment of the quality of surgical care: results of the National Veterans Affairs Surgical Risk Study. J Am Coll Surg 1997;185:328–340.
3. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection 1999. The Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1999;20:247–278.
4. Russell Merritt. The A.S.P.E.N. nutrition support practice manual. 2nd ed. Silver Spring, MD, USA: A.S.P.E.N., 2005, pp 3–26, 259–262.
5. Anthony PS. Nutrition screening tools for hospitalized patients. Nutr Clin Pract 2008;23:373–382.
6. Thomas DR. Nutrition assessment in long-term care. Nutr Clin Pract 2008;23:383–387.
7. Gibbs J, Cull W, Henderson W, Daley J, Hur K, Khuri SF. Preoperative serum albumin level as a predictor of operative mortality and morbidity: results from the National VA Surgical Risk Study. Arch Surg 1999;134:36–42.
8. Kudsk KA, Tolley EA, DeWitt RC, Janu PG, Blackwell AP, Yeary S, King BK. Preoperative albumin and surgical site identify surgical risk for major postoperative complications. J Parenter Enteral Nutr 2003;27:1–9.
9. Ryan AM. Healy LA, Power DG, Rowley SP, Reynolds JV. Short-term nutritional implications of total gastrectomy for malignancy, and the impact of parenteral nutritional support. Clin Nutr 2007;26:718–727.
10. Schiesser M, Müller S, Kirchhoff P, Breitenstein S, Schäfer M, Clavien PA. Assessment of a novel screening score for nutritional risk in predicting complications in gastrointestinal surgery. Clin Nutr 2008;27:565–570.
11. Kim Y, Kim WG, Lee HJ, Park MS, Lee YH, Cho JJ, Kong SH, Yang HK. Impact of malnutrition risk determined by nutrition screening index on operative morbidity after gastric cancer surgery. J Korean Surg Soc 2011;80:1–9.
12. Funk KL, Ayton CM. Improving malnutrition documentation enhances reimbursement. J Am Diet Assoc 1995;95:468–475.
13. Fuhrman MP, Charney P, Mueller CM. Hepatic proteins and nutrition assessment. J Am Diet Assoc 2004;104:1258–1264.
14. Mary L. Basic skills in interpreting laboratory data. 3rd ed. Bethesda, MD, USA: ASHP, 2004, pp 326–327.
15. Devoto G, Gallo F, Marchello C, Racchi O, Garbarini R, Bonassi S, Albalustri G, Haupt E. Prealbumin serum concentrations as a useful tool in the assessment of malnutrition in hospitalized patients. Clin Chem 2006;52:2281–2285.
16. Howard L, Ashley C. Nutrition in the perioperative patient. Annu Rev Nutr 2003;23:263–282.
17. Braga M, Ljungqvist O, Soeters P, Fearon K, Weimann A, Bozzetti F. ESPEN guidelines on parenteral nutrition: surgery. Clin Nutr 2009;28:378–386.
18. Bozzetti F, Gianotti L, Braga M, Di Carlo V, Mariani L. Postoperative complications in gastrointestinal cancer patients: the joint role of the nutritional status and the nutritional support. Clin Nutr 2007;26:698–709.

19. Leslie S, Mary G, Christian W. TNM classification of malignant tumours. 7th ed. Geneva, Switzerland: UICC International Union Against Cancer, 2009.
20. Malone DL, Genuit T, Tracy JK, Gannon C, Napolitano LM. Surgical site infections: reanalysis of risk factors. J Surg Res 2002;103:89–95.
21. American Diabetes Association. Standards of medical care in diabetes–2011. Diabetes Care 2011;34:S11-S61.
22. Rey-Ferro M, Castaño R, Orozco O, Serna A, Moreno A. Nutritional and immunologic evaluation of patients with gastric cancer before and after surgery. Nutrition 1997;13:878–881.
23. Spiekerman AM. Nutritional assessment (protein nutriture). Anal Chem 1995;67:429R-436R.
24. Devakonda A, George L, Raoof S, Esan A, Saleh A, Bernstein LH. Transthyretin as a marker to predict outcome in critically ill patients. Clin Biochem 2008;41:1126–1130.
25. Rambod M, Kovesdy CP, Bross R, Kopple JD, Kalantar-Zadeh K. Association of serum prealbumin and its changes over time with clinical outcomes and survival in patients receiving hemodialysis. Am J Clin Nutr 2008;88:1485–1494.
26. Dos Santos Junqueira JC, Cotrim Soares E, Rodrigues Corrêa Filho H, Fenalti Hoehr N, Oliveira Magro D, Ueno M. Nutritional risk factors for postoperative complications in Brazilian elderly patients undergoing major elective surgery. Nutrition 2003;19:321–326.
27. Geisler JP, Linnemeier GC, Thomas AJ, Manahan KJ. Nutritional assessment using prealbumin as an objective criterion to determine whom should not undergo primary radical cytoreductive surgery for ovarian cancer. Gynecol Oncol 2007;106:128–131.
28. Park DJ, Lee HJ, Kim HH, Yang HK, Lee KU, Choe KJ. Predictors of operative morbidity and mortality in gastric cancer surgery. Br J Surg 2005;92:1099–1102.
29. Kim MC, Kim W, Kim HH, Ryu SW, Ryu SY, Song KY, Lee HJ, Cho GS, Han SU, Hyung WJ. Korean Laparoscopic Gastrointestinal Surgery Study (KLASS) Group. Risk factors associated with complication following laparoscopy-assisted gastrectomy for gastric cancer: a large-scale Korean multicenter study. Ann Surg Oncol 2008;15:2692–2700.
30. Kim W, Song KY, Lee HJ, Han SU, Hyung WJ, Cho GS. The Impact of comorbidity on surgical outcomes in laparoscopy-assisted distal gastrectomy. A retrospective analysis of multicenter results. Ann Surg 2008;248:793–799.
31. Mizutani M, Yamamoto T, Oka R, Otsu N, Nakagawa Y, Tominaga M, Kimura W. Post operative changes of rapid turnover proteins in elective gastrointestinal surgery. Hepatogastroenterology 2009;56:167–173.
32. Nakamura K, Moriyama Y, Kariyazono H, Hamada N, Toyohira H, Taira A, Yamada K. Influence of preoperative nutritional state on inflammatory response after surgery. Nutrition 1999;15:834–841.

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ORIGINAL ARTICLE

Different Features of Complications with Billroth-I and Roux-en-Y Reconstruction After Laparoscopy-Assisted Distal Gastrectomy

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Abstract
Background This study investigated differences in the features of postoperative complications between Billroth-I (B-I) and Roux-en-Y (R-Y) reconstructions after laparoscopy-assisted distal gastrectomy (LADG) for early gastric cancer.
Material and methods The study included 424 patients who underwent LADG for cT1, cN0 gastric cancer. Patient characteristics, surgical outcomes, postoperative complications including severity assessment using the Clavien–Dindo classification, and risk factors related to postoperative complications were analyzed.
Results B-I and R-Y were performed in 329 and 95 patients, respectively. Total time in hospital was longer in R-Y (15.2± 10.5 days) than in B-I (12.8±6.4 days; P=0.034). The incidence of severe complications was higher in R-Y (13.7%) than in B-I (5.2%; P=0.009). Three cases of internal hernia and three cases of duodenal stump leakage were observed in R-Y. Univariate analysis revealed the method of reconstruction was a risk factor for severe postoperative complications after LADG (P=0.006).
Conclusions The features of postoperative complications are quite different between B-I and R-Y after LADG. Complications after R-Y were more severe than those after B-I. To avoid these severe complications in R-Y, it is necessary to understand these different features.

Keywords Laparoscopy-assisted distal gastrectomy · Postoperative complication · Billroth-I · Roux-en-Y · Reconstruction

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Introduction

In Asian countries, such as Korea and Japan, early gastric cancer (EGC) has accounted for approximately 40% to 60% of gastric cancers because of advances in diagnostic techniques and the increasing prevalence of screening programs. Distal gastrectomy is the standard treatment for EGC located in the middle or lower stomach in surgical cases.

After distal gastrectomy, three reconstruction methods are mainly used—Billroth-I (B-I), Billroth-II (B-II), and Roux-en Y (R-Y). In Japan, B-II is not often performed because of possible inflammation and carcinogenesis of the remnant stomach caused by regurgitation of duodenal juice.[1–3] Some authors have reported the merits and demerits of the different surgical procedures and the difference in the postoperative course between B-I and R-Y in conventional open distal gastrectomy.[2,4,5] The main

difference between these two reconstruction methods is that B-I has a single anastomotic site while R-Y has two anastomotic sites and an additional duodenal stump accompanied by mesenteric transection. A higher rate of anastomotic insufficiency has been reported in B-I compared with R-Y,[2] while both internal herniation through the transected mesentery and mesocolon, and duodenal stump leakage are particular complications after R-Y.[4,6,7]

In recent years, laparoscopy-assisted distal gastrectomy (LADG) has been performed in Asian countries as a treatment method for EGC.[6,8–10] Anastomosis is a difficult procedure in LADG because it is performed through a small incision by laparoscopy. In addition, the most frequent postoperative complications in LADG are considered to be anastomosis-related issues, such as anastomotic leakage, stenosis, and bleeding.[7] Although some studies have compared postoperative outcomes of B-I and R-Y after LADG, the different characteristics of these complications have not been previously discussed.[4,8–10]

In this study, we examined the differences in the features of complications of LADG between R-Y and B-I. The severity of all complications was assessed by the Clavien–Dindo classification of surgical complications,[11,12] and risk factors related to complications were analyzed.

Material and Methods

Patient Characteristics

From April 2005 to July 2009, 424 patients with EGC underwent LADG with curative intent in the Department of Gastrointestinal Surgery at The Cancer Institute Hospital, Tokyo, Japan. For each patient, surgery was either performed or supervised by one of two experts in laparoscopic surgery. In our institution, B-I is selected for cancer located in the middle or lower third of the stomach and R-Y is selected for cancer located in the middle or upper third of the stomach.

Clinical classification of tumor depth (cT) and nodal involvement (cN) was determined by preoperative evaluations, including barium radiography, upper gastrointestinal tract endoscopy, computed tomography, and endoscopic ultrasonography. All tumors were diagnosed histologically as adenocarcinomas. Preoperatively diagnosed intramucosal or submucosal carcinoma without lymph node metastasis (cT1, cN0) in the lower, middle, and part of the upper third of the stomach was suitable for LADG.

The following parameters were recorded: patient age and gender, body mass index (BMI), tumor characteristics, operation time, estimated intraoperative blood loss, postoperative complications, length of postoperative hospital stay including readmission due to complications. BMI was calculated using preoperative physical measurements. The severity of complications was graded using the Clavien–Dindo classification of surgical complications.

Surgical Procedures for Laparoscopy-Assisted Distal Gastrectomy

LADG was performed under a pneumoperitoneum that was created by injection of carbon dioxide (10–12 mmHg). A total of five ports (each 5–12 mm) were inserted, and LADG with a modified D2 (D1+8a+9+11p) or D2 lymph node dissection was conducted as reported previously.[8,13]

Procedure for Extracorporeal Billroth-I Anastomosis

After laparoscopic mobilization of the stomach and duodenum and en bloc lymph node dissection, a 4- to 5-cm midline incision was made and a hemi-double stapling technique using a circular stapler was performed for the B-I anastomosis. A purse-string suture was placed at the transecting line of the duodenum, just distal to the pylorus, using purse-string forceps and 2–0 polypropylene suture (Prolene; Ethicon Inc., Japan). After transecting the duodenum, 28 or 29 mm of the detachable anvil head of the circular stapler was inserted into the duodenal stump and the purse-string suture was tied over the anvil shaft.

The proximal stomach was transected at the appropriate line (1–2 cm proximal to the bifurcation of the gastroepiploic trunk) using a liner staple (75 mm) from the greater curvature halfway (5 cm) to the lesser curvature. The anterior gastric wall of the remnant stomach was opened partially, and the circular stapler was inserted into the stomach. The trocar was extended to penetrate the corner of the staple line at the greater curvature and then connected to the detachable anvil shaft placed in the duodenum (Fig. 1a). The instrument was gently closed so that the anastomotic line appeared on the ventral surface beyond the midline incision. After confirmation of the continuity of the anastomotic line, the circular stapler was fired to complete the end-to-end gastroduodenostomy. The instrument was opened, disengaged from the anastomosis, and gently withdrawn. The anastomosis was examined using direct vision through the opening in the anterior wall of the stomach, and hemostasis was made by direct suturing of the staple line. The remaining upper gastric segment was divided using a 75-mm linear stapler to complete the distal gastrectomy (Fig. 1b). The entry hole of the circular stapler was included in the resected specimen.

Procedure for Intracorporeal Roux-en Y Anastomosis

Resection of the Stomach

After laparoscopic en bloc lymph node dissection, the duodenum was transected intracorporeally using a 60-mm

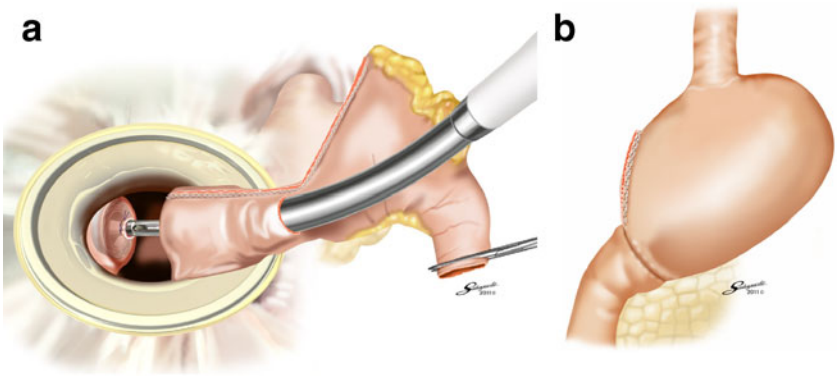

Fig. 1 Procedure for the Billroth-I reconstruction using a hemi-double stapling technique. **a** The anterior gastric wall of the remnant stomach was opened partially, and the circular stapler was inserted into the stomach. The trocar penetrating the corner of the staple line at the greater curvature was connected to the anvil shaft placed in the duodenum. **b** After gastroduodenostomy, the remaining upper gastric segment was divided using a 75-mm linear stapler to complete the distal gastrectomy

linear stapler (Fig. 2a). Before transection of the proximal stomach, an intraoperative gastroscopy was performed to confirm the location of the tumor and preoperatively placed clips, and a safe gastric transection line was determined and marked by dying or suturing in the outer gastric wall. Under direct vision through the gastroscope, the stomach was transected with two endoscopic linear staplers about 2 cm proximal to the tumor.

Gastrojejunal Anastomosis

A side-to-side gastrojejunal anastomosis was chosen if the remnant stomach was relatively large. The mesentery and jejunum were divided 20 cm distal to the ligament of Treitz. Then, the resected stomach and divided jejunum were externalized through the extended umbilical port site, and an extracorporeal anastomosis of the proximal end of the jejunum to the distal jejunum was created 45 cm distal to the jejunal division using a 60-mm linear stapler. The common entry hole was closed using a single-layer interrupted suture. After returning the jejunum to the abdominal cavity, the jejunal loop was brought up via the antecolic route and an isoperistaltic gastrojejunostomy was performed with a 60-mm linear stapler (Fig. 2b). The common entry hole was closed with a 60-mm linear stapler.

In the case of a small remnant stomach, an end-to-side gastrojejunal anastomosis was performed using a transoral anvil (OrVil™; Covidien, Mansfield, MA) with a 25-mm anvil. After gastrectomy, the OrVil™ tube was then introduced into the remnant stomach transorally. As the OrVil™ tube reached the greater curvature of the gastric stump, a small hole was created on the greater curvature of the gastric stump. The OrVil™ tube was extracted through the hole until the 25-mm anvil reached the greater curvature of gastric stump, and the tube was disconnected and pulled out from the abdomen by cutting the thread connecting the anvil to the tube. After making a side-to-side jejunojejunostomy (Y-anastomosis) extracorporeally, as mentioned above, a 25-mm circular stapler was inserted into the distal limb of the jejunum and the jejunum was tied to the stapler with a rubber band to prevent slippage of the jejunum from the circular stapler during anastomosis. The circular stapler was introduced into the abdominal cavity, and then the wound retractor which was attached to the extended umbilical port site and the circular stapler were sealed off using a surgical glove so that a pneumoperitoneum could be

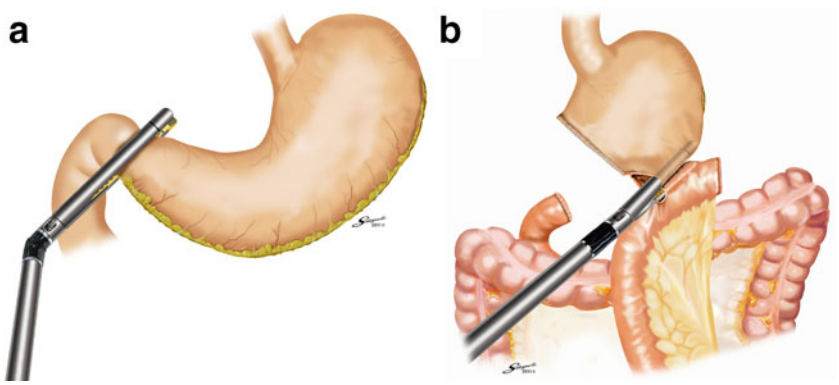

Fig. 2 Procedure for the Roux-en-Y reconstruction. **a** The duodenum was transected intracorporeally using a 60-mm linear stapler. **b** The jejunal loop was brought up via the antecolic route and an isoperistaltic side-to-side gastrojejunostomy was performed with a 60-mm linear stapler. The common entry hole was closed with a 60-mm linear stapler

reestablished. The port located at the right lower side of the abdomen was used for laparoscopy. The Roux-limb then was brought up via the antecolic route to create a gastrojejunostomy. The anvil and circular stapler were connected, and the anastomosis was performed laparoscopically using a hemi-double stapling technique. The jejunal stump was closed with an endoscopic linear stapler, and the antecolic Roux-en-Y reconstruction was completed. Finally, the gastrojejunal anastomosis was checked for no bleeding, no stenosis, and no leakage under gastroscopy. Abdominal irrigation was performed using 2,000 mL of normal saline. The operation was completed by closure of all the wounds.

Statistical Analysis

All values are expressed as mean±standard deviation. An unpaired *t* test was used to test the equality of the means of the two groups for each variable. The Fisher's exact test or χ^2 test was used to test the independence between the two groups. $P<0.05$ was considered statistically significant. Factors that might affect postoperative complications were evaluated by univariate and multivariate logistic regression analyses. Statistical analyses were performed using SPSS version 11.0 (SPSS, Chicago, IL).

Results

Patient Characteristics

Age, BMI, preoperative complications, preoperative nutritional status, and both clinical and pathological staging were not significantly different between the two groups. The proportion of males was significantly higher in the R-Y group. The percentage of tumors in the upper part of the stomach was also higher in the R-Y group compared with the B-I group (Table 1).

Surgical Data

Lymphadenectomy of D1+No. 7 dissection (D1+α), the modified D2 dissection (D1+β), and the D2 dissection were evenly distributed between the two groups (Table 1).

Operative and postoperative data

The operation time for the R-Y procedure (260±51 min) was significantly longer than for the B-I procedure (225±55 min; $P<0.001$), although the estimated blood loss with R-Y (84±127 mL) was not significantly different from B-I (62±142 mL; $P=0.154$; Table 2). The average time from surgery until the first episode of flatus was significantly longer in the R-Y group (2.6±0.7 days) than in the B-I group (2.4±0.9 days; $P=0.025$). The duration of the postoperative hospital stay in the R-Y group (14.0±9.5 days) was not significantly different from that of the B-I group (12.6±6.4 days; $P=0.183$). However, the duration of total hospitalization including rehospitalization for treatment of postoperative complications was significantly longer in the R-Y group (15.2±10.5 days) than in the B-I group (12.8±6.4 days; $P=0.034$; Table 2).

Table 1 Characteristics of patients undergoing LADG with Billroth-I or Roux-en-Y reconstruction

	Billroth-I	Roux-en-Y	*P* value
Number of cases	329	95	
Age, years (range)	63.5 (29–90)	62.7 (42–81)	0.471
Sex ratio (M/F)	197:132	74:21	0.002
ASA-PS (1/2/3)	214/106/9	69/22/4	0.302
Body mass index, kg/m^2	23.2±3.5	24.0±3.3	0.062
Prealbumin, mg/dL	26.4±5.9	28.5±5.1	0.052
Location of tumor			0.001
Upper	2 (0.6)	26 (27.4)	
Middle	152 (46.2)	55 (57.9)	
Lower	175 (53.2)	14 (14.7)	
Lymph node dissection			0.471
D1+α	1 (0.3)	1 (1.0)	
D1+β	266 (80.9)	82 (86.4)	
D2	62 (18.8)	12 (12.6)	
Tumor depth pT1/≧pT2	277/52	83/12	0.549
Lymph node metastasis pN0/≧pN1	277/52	85/10	0.264

Values in parentheses are percentages unless indicated otherwise. Data are presented as mean±standard deviation. An unpaired *t* test was used to test the equality of the two group means for each variable. The Fisher's exact test or χ^2 test was used to test the independence between the two groups. $P<0.05$ was considered statistically significant

LADG laparoscopy-assisted distal gastrectomy, *ASA-PS* American Society of Anesthesiologists physical status

Postoperative Complications

Postoperative complications classified as grade III or above on the Clavien–Dindo classification of surgical complications are shown in Table 3. The incidence of complications classified as grade III or above on the Clavien–Dindo scale was significantly higher in the R-Y group (13.7%) than in the B-I group (5.2%; $P=0.009$, χ^2 test). No significant difference was observed between the two groups for the lower grades (data not shown). Overall, the most frequent complication in both the B-I (7.0%) and R-Y (4.2%) groups was abdominal fluid collection including pancreatic leak-

Table 2 Operative and postoperative data from patients undergoing LADG with Billroth-I or Roux-en-Y reconstruction

	Billroth-I n=329	Roux-en-Y n=95	P value
Operation time, min	225±55	260±51	0.001
Blood loss, mL	62±142	84±127	0.154
Time until start of flatus, days	2.4±0.9	2.6±0.7	0.025
Time until start of oral intake, days	2.1±0.4	2.1±1.1	0.439
Postoperative hospital stay, days	12.6±6.4	14.0±9.5	0.183
Total hospitalization[a], days	12.8±6.4	15.2±10.5	0.034
Number of cases requiring rehospitalization	7 (2.1)	6 (6.3)	0.081

Data are presented as mean±standard deviation. Values in parentheses are percentages unless indicated otherwise. An unpaired t test was used to test the equality of the two group means for each variable. The Fisher's exact test or χ^2 test was used to test the independence between the two groups. $P<0.05$ was considered statistically significant

[a] Total hospitalization includes duration of postoperative hospital stay plus rehospitalization required to treat complications

age. No statistical difference was observed in the frequency of anastomotic complications associated with the remnant stomach between the two groups. On the other hand, anastomotic complications associated with the jejunum or duodenum were observed more frequently in the R-Y group (P=0.002, χ^2 test). Three cases (3.2%) of postoperative bowel obstruction due to internal herniation and three cases (3.2%) of duodenal stump leakage were observed in the R-Y group. In addition, one patient (1.1%) developed stricture of the Roux-limb jejunojejunal anastomosis.

Furthermore, the incidence of complications classified as grade IIIb was significantly higher in the R-Y group (5.3%) than in the B-I group (0.3%; P=0.002, χ^2 test). Only one patient who suffered from peritonitis due to enteric injury associated with adhesiotomy was classified as grade IIIb in the B-I group.

Risk factors were examined for postoperative complications after LADG. Univariate analysis using the logistic regression test showed that sex (P=0.049), age (P=0.002), BMI (P=0.035), and preoperative comorbidity (P=0.010) were significantly associated with the overall number of complications classified as grade II or above. Multivariate analysis identified age as a risk factor for postoperative complications classified as grade II or above (odds ratio, 2.288; 95% confidence interval, 1.158–4.521). On the other hand, univariate analysis showed the reconstruction method

Table 3 Postoperative complications classified as grade III using the Clavien–Dindo grading system in patients undergoing LADG with B-I or R-Y reconstruction

	Billroth-I n=329	Roux-en-Y n=95	P value
Grade IIIa	16 (4.9)	8 (8.4)	0.288
Anastomotic complications (remnant stomach)	6 (1.8)	3 (3.2)	0.699
Bleeding	3 (1.2)	0 (0)	
Leakage	0 (0)	1 (1.1)	
Stricture	3 (0.6)	1 (1.1)	
Ulceration	0 (0)	1 (1.1)	
Anastomotic complications (jejunum or duodenum)	0 (0)	2 (2.1)	0.074
Bleeding	0 (0)	0 (0)	
Leakage	0 (0)	2 (2.1)	
Abdominal fluid collection	7 (2.1)	2 (2.1)	0.699
Intraabdominal bleeding	1 (0.3)	1 (1.1)	0.931
Superficial SSI	1 (0.3)	0 (0)	0.505
Grade IIIb	1 (0.3)	5 (5.3)	0.002
Anastomotic complications (jejunum or duodenum)	0 (0)	2 (2.1)	0.074
Leakage	0 (0)	1 (1.1)	
Stricture	0 (0)	1 (1.1)	
Enteric injury	1 (0.3)	0 (0)	0.505
Internal herniation	0 (0)	3 (3.2)[a]	0.011

Values in parentheses are percentages unless indicated otherwise. The Fisher's exact test or χ^2 test was used to test the independence between the two groups. $P<0.05$ was considered statistically significant

LADG laparoscopy-assisted distal gastrectomy, *B-I* Billroth-I, *R-Y* Roux-en-Y, *SSI* surgical site infection

[a] One of these two patients received two operations for internal herniation

was the only risk factor for severe postoperative complications classified as grade III (P=0.006; Table 4).

Discussion

In this study, we demonstrated the different features of complications between B-I and R-Y reconstruction after LADG. The selection criteria for the reconstruction method used at our institution meant that B-I was performed for cancers located in the middle or lower third of the stomach and R-Y was performed for cancers located in the middle or upper third of the stomach. Therefore, the significant difference in tumor location between the B-I and R-Y groups can be easily explained. The ratio of male patients was significantly higher in the R-Y group, and BMI tended to be higher in the R-Y group as well. To avoid excessive tension in the gastroduodenal B-I anastomosis, R-Y is preferred for larger patients with plenty of intraabdominal adipose tissues. A longer operating time for the R-Y group can be explained by the different number of anastomoses between both methods. The average time from surgery until the first episode of flatus was significantly longer in the R-Y group. Manipulation of the jejunum during the R-Y reconstruction might affect bowel movement. Several animal studies have suggested that a major causative factor of postoperative ileus is a local inflammatory reaction within the gut induced by surgical manipulation.[14–16]

In this study, the average duration of postoperative hospital stay seemed long for the modern age. Most gastric cancer patients in Japan are medically fit to leave hospital around 7 days after surgery. However,

Table 4 Univariate analysis of risk factors for grade III postoperative complications in LADG

Variables	Patients, *n*	Complications, *n* (%)	*P* value
Sex			0.064
Male	271	24 (8.9)	
Female	153	6 (3.9)	
Age			0.131
<60 years	154	7 (4.5)	
≧60 years	270	23 (8.5)	
BMI			0.210
<24 kg/m^2	258	15 (5.8)	
≧24 kg/m^2	166	15 (9.0)	
Comorbidity (ASA)			0.971
Class 1	283	20 (7.1)	
Class 2	128	9 (7.0)	
Class 3	13	1 (7.7)	
Previous abdominal surgery			0.162
No	327	20 (6.1)	
Yes	97	10 (10.3)	
Experience of surgeon			0.142
<50	105	4 (3.8)	
≧50	319	26 (8.2)	
Combined surgery			0.199
No	420	29 (6.9)	
Yes	4	1 (25.0)	
Lymph node dissection			0.906
D1+α or D1+β	350	25 (7.1)	
D2	74	5 (6.8)	
Operation time			0.485
<230 min	224	14 (6.3)	
≧230 min	200	16 (8.0)	
Blood loss			0.681
<70 mL	324	22 (6.8)	
≧70 mL	100	8 (8.0)	
Reconstruction method			0.006
Billroth-I	329	17 (5.2)	
Roux-en-Y	95	13 (13.7)	

LADG laparoscopy-assisted distal gastrectomy, *BMI* body mass index, *ASA* American Society of Anesthesiologists

patients often want to remain in hospital for 10 days or more after surgery due to the Japanese culture and health insurance system.

The incidence of complications classified grade III or above on the Clavien–Dindo grading system was significantly higher in the R-Y group than the B-I group. Consequently, total hospitalization time including rehospitalization was longer in the R-Y group compared with the B-I group. Among the listed clinical factors, only the method of reconstruction was found to be a risk factor for severe postoperative complications of grade III or above on the Clavien–Dindo scale, while patient characteristics such as sex, age, BMI, and comorbidities were risk factors for relatively mild complications classified as grade II on the Clavien–Dindo grading system. Ryu and colleagues reported that the degree of lymph node dissection and surgical inexperience are risk factors for postoperative surgical complications of LADG.[17] A retrospective analysis of multicenter results in Korea also suggested that patient comorbidities are a predictive risk factor for surgical complications after LADG.[18] However, no previous studies of LADG used a grading system to score the severity of the postoperative complications; such severity could differ greatly and thus significantly affect therapy.

In the present study, complications associated with the anastomosis of the remnant stomach were observed equally in both groups. All six patients with complications related to the remnant stomach anastomosis did not need surgical intervention (0%), while two out of four patients (50%) with anastomotic complications such as duodenal stump leakage and jejunojejunostomy stricture required surgical intervention under general anesthesia, which might be the reason for the different severity of complications between B-I and R-Y.

No intestinal obstructions due to adhesions were observed in either group, while bowel obstructions due to internal herniation were only observed in the R-Y group. Petersen's hernia is known to be a hernia of the intestine into Petersen's defect which is the gap in the mesentery between the Roux limb and the transverse colon (Fig. 3).[19] Small bowel obstruction after R-Y gastric bypass is a well-described complication in the field of bariatric surgery. Koppman et al. reviewed 9,527 laparoscopic R-Y gastric bypass operations, in which 342 postoperative small bowel obstructions were noted including 42% (144 of 342) with internal hernias.[20] These internal hernias could be prevented by closure of the mesenteric defects, and several authors have noted a decreased incidence of internal hernias after closure of these defects.[21–27]

This study demonstrated excellent results with B-I. However, patients enrolled in this study had a unique perspective in terms of having an average BMI of 23 or 24. In patients with an extremely high BMI, B-I is difficult and

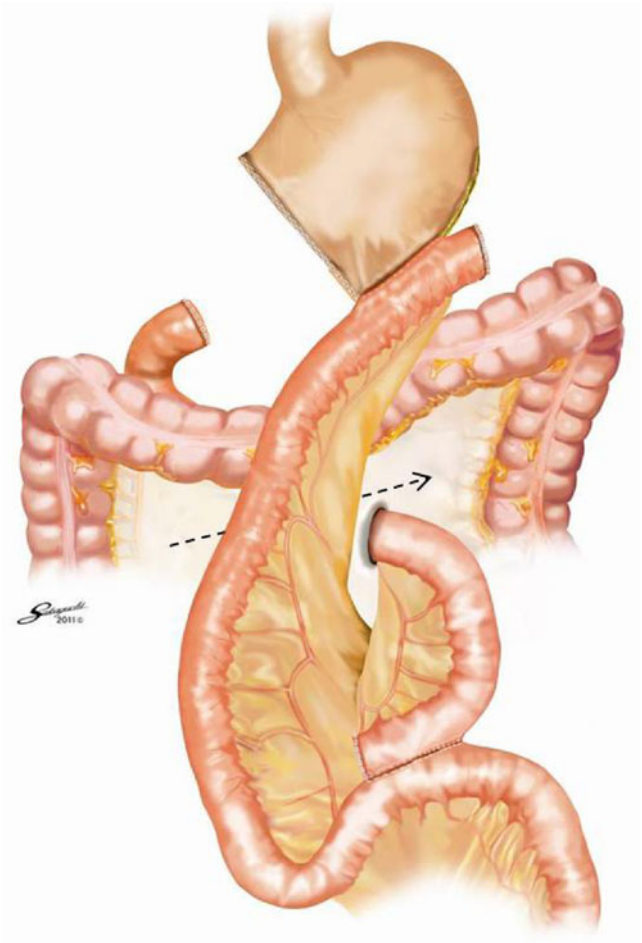

Fig. 3 Whole image of completed Roux-en-Y reconstruction. The *arrow* shows Petersen's defect which is the gap in the mesentery between the Roux limb and the transverse colon

R-Y is inevitably preferred. R-Y is also necessary when the tumor is located in the upper part of the stomach and many benefits of R-Y over B-I have been reported in terms of postoperative quality-of-life.[5,10] As a result of this study, we have employed several procedures to avoid severe postoperative complications in R-Y, as follows: (1) duodenal stump disruption; inverting the staple line of the duodenal stump with covered sutures, (2) stricture of the jejunojejunostomy; temporary intracorporeal fixation of the jejunojejunostomy with two stitches prior to extracorporeal jejunojejunal anastomosis, and (3) internal hernia; closing Petersen's defect and the mesenteric defect at the jejunojejunostomy.

In conclusion, the features of postoperative complications are quite different between B-I and R-Y after LADG. Complications seen in R-Y reconstructions are more severe than those in B-I reconstructions. These complications could be theoretically prevented by improved surgical techniques in those cases where R-Y reconstructions are still indicated. Further randomized studies are needed to

clarify the feasibility of these reconstruction methods after improved techniques have been adopted.

References

1. Lundegardh G, Adami HO, Helmick C et al. Stomach cancer after partial gastrectomy for benign ulcer disease. N Engl J Med 1988; 319:195–200.
2. Katai H, Nunobe S, Saka M et al. [Reconstruction after distal gastrectomy]. Nippon Geka Gakkai Zasshi 2008; 109:264–268.
3. Kobori O, Shimizu T, Maeda M et al. Enhancing effect of bile and bile acid on stomach tumorigenesis induced by *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine in Wistar rats. J Natl Cancer Inst 1984; 73:853–861.
4. Ishikawa M, Kitayama J, Kaizaki S et al. Prospective randomized trial comparing Billroth I and Roux-en-Y procedures after distal gastrectomy for gastric carcinoma. World J Surg 2005; 29:1415–1420.
5. Nunobe S, Okaro A, Sasako M et al. Billroth 1 versus Roux-en-Y reconstructions: a quality-of-life survey at 5 years. Int J Clin Oncol 2007; 12:433–439.
6. Kim MC, Kim W, Kim HH et al. Risk factors associated with complication following laparoscopy-assisted gastrectomy for gastric cancer: a large-scale Korean Multicenter Study. Ann Surg Oncol 2008; 15:2692–2700.
7. Kitano S, Shiraishi N, Uyama I et al. A multicenter study on oncologic outcome of laparoscopic gastrectomy for early cancer in Japan. Ann Surg 2007; 245:68–72.
8. Hiki N, Fukunaga T, Tokunaga M et al. An effective duodenum bulb mobilization for extracorporeal Billroth I anastomosis of laparoscopic gastrectomy. J Gastrointest Surg 2009; 13:230–235.
9. Katai H, Sasako M, Fukuda H et al. Safety and feasibility of laparoscopy-assisted distal gastrectomy with suprapancreatic nodal dissection for clinical stage I gastric cancer: a multicenter phase II trial (JCOG 0703). Gastric Cancer 2010; 13:238–244.
10. Kojima K, Yamada H, Inokuchi M et al. A comparison of Roux-en-Y and Billroth-I reconstruction after laparoscopy-assisted distal gastrectomy. Ann Surg 2008; 247:962–967.
11. Clavien PA, Barkun J, de Oliveira ML et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009; 250:187–196.
12. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240:205–213.
13. Hiki N, Fukunaga T, Yamaguchi T et al. Cut-and-screw insertion: a method for safe and speedy secondary trocar insertion in laparoscopic surgery. Surg Technol Int 2008; 17:121–125.
14. Kalff JC, Schraut WH, Simmons RL et al. Surgical manipulation of the gut elicits an intestinal muscularis inflammatory response resulting in postsurgical ileus. Ann Surg 1998; 228:652–663.
15. Kalff JC, Carlos TM, Schraut WH et al. Surgically induced leukocytic infiltrates within the rat intestinal muscularis mediate postoperative ileus. Gastroenterology 1999; 117:378–387.
16. Schwarz NT, Beer-Stolz D, Simmons RL et al. Pathogenesis of paralytic ileus: intestinal manipulation opens a transient pathway between the intestinal lumen and the leukocytic infiltrate of the jejunal muscularis. Ann Surg 2002; 235:31–40.
17. Ryu KW, Kim YW, Lee JH et al. Surgical complications and the risk factors of laparoscopy-assisted distal gastrectomy in early gastric cancer. Ann Surg Oncol 2008; 15:1625–1631.
18. Kim W, Song KY, Lee HJ et al. The impact of comorbidity on surgical outcomes in laparoscopy-assisted distal gastrectomy: a retrospective analysis of multicenter results. Ann Surg 2008; 248:793–799.
19. Coleman MH, Awad ZT, Pomp A et al. Laparoscopic closure of the Petersen mesenteric defect. Obes Surg 2006; 16:770–772.
20. Koppman JS, Li C, Gandsas A. Small bowel obstruction after laparoscopic Roux-en-Y gastric bypass: a review of 9,527 patients. J Am Coll Surg 2008; 206:571–584.
21. Carmody B, DeMaria EJ, Jamal M et al. Internal hernia after laparoscopic Roux-en-Y gastric bypass. Surg Obes Relat Dis 2005; 1:543–548.
22. Felsher J, Brodsky J, Brody F. Small bowel obstruction after laparoscopic Roux-en-Y gastric bypass. Surgery 2003; 134:501–505.
23. Higa KD, Ho T, Boone KB. Internal hernias after laparoscopic Roux-en-Y gastric bypass: incidence, treatment and prevention. Obes Surg 2003; 13:350–354.
24. Iannelli A, Facchiano E, Gugenheim J. Internal hernia after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Obes Surg 2006; 16:1265–1271.
25. Nguyen NT, Huerta S, Gelfand D et al. Bowel obstruction after laparoscopic Roux-en-Y gastric bypass. Obes Surg 2004; 14:190–196.
26. Podnos YD, Jimenez JC, Wilson SE et al. Complications after laparoscopic gastric bypass: a review of 3464 cases. Arch Surg 2003; 138:957–961.
27. Schauer PR, Ikramuddin S, Gourash W et al. Outcomes after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Ann Surg 2000; 232:515–529.

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ORIGINAL ARTICLE

Defining a High-Risk Subgroup of Pathological T2N0 Gastric Cancer by Prognostic Risk Stratification for Adjuvant Therapy

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Abstract
Background Adjuvant therapy is not usually recommended in AJCC T2N0M0 gastric cancer, yet sometimes is indicated for high-risk patients. The purpose of this study is to stratify the risk of pathological T2N0 gastric cancer after gastrectomy based on clinicopathological factors so as to predict prognosis and guide treatment.
Methods We analyzed our documented clinical database of 233 patients with T2N0M0 gastric cancer who underwent radical resection between 2000 and 2007. No adjuvant chemotherapy was applied.
Results For the entire study group, the overall 5-year survival rate was 88.5%. Multivariate analysis indicated there were three tumor characteristics which were independent prognostic factors: lymphatic and/or blood vessel invasion (p=0.025), tumor diameter (p=0.004), and perineural invasion (p=0.009). Three risk groups were created based on weighted variables with overall 5-year survival of 97.7%, 83%, and 50.3% as low-risk, intermediate-risk, and high-risk groups, respectively (p<0.001).
Conclusion Patients with T2N0 gastric cancer have a favorable prognosis after radical resection. A prognostic risk model of patients with pT2N0 gastric cancer undergoing radical resection is constructed based on lymphatic and/or blood vessel invasion, tumor diameter, and perineural invasion. The prognostic risk model identifies a small subgroup of patients with an increased risk of death, suggesting adjuvant therapy may be considered for these patients.

Keywords Gastric cancer · T2N0 · Prognosis · Adjuvant therapy

Introduction

The mainstream therapy for gastric cancer without distant metastases is the radical gastrectomy with lymphadenectomy.[1,2] Current guide recommendations for adjuvant treatment are based on the risk stratification according to the American Joint Committee on Cancer (AJCC) staging classification. In the lastest edition of the AJCC Cancer Staging Manual published in early 2010, T1 is further divided so that mucosal and submucosal depth of invasion could be delineated. T2a and T2b were separated into T2 (muscularis propria) and T3 (subserosa).[3] In the National Comprehensive Cancer Network guidelines, adjuvant therapy is recommended for T3, T4, and/or node-positive gastric cancer. To date, almost all data on adjuvant therapy are derived from randomized controlled trails that include a large proportion of stage II and III patients[4–6] and, very likely, too few stages I patients who definitely benefit from adjuvant therapy in these stage groups. The value of adjuvant therapy in treating patients with T2N0 gastric carcinoma is still controversial due to lack of data from randomized studies and low relapse rate. It is believed that not all T2N0 patients should be treated, but those with high risk. Identifying high-risk factors based on

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current classification will help select patients who may benefit from adjuvant therapy. To date, no study clearly identifies the high-risk factors of T2N0 gastric cancer. The purpose of this study is to stratify risk of pathological T2N0 gastric cancer after gastrectomy based on clinicopathological factors to predict prognosis and to define a high-risk subgroup that might be considered for adjuvant therapy and potentially benefit from it.

Materials and Methods

In our gastric cancer database, we documented all patients who underwent surgical resection for gastric cancer in our department. From January 2000 to December 2007, 1,745 patients with histological gastric cancer underwent curative resection of the stomach at the Department of Gastric Cancer and Soft Tissue Surgery, Fudan University Shanghai Cancer Center. For this analysis, the patients were selected according to the following criteria: (1) without any preoperative therapy, (2) had undergone radical resection of gastric cancer, (3) pathologically confirmed T2N0 gastric cancer, (4) no evidence of distant metastases, (5) no adjuvant therapy applied, and (6) available to provide follow-up information at least once. Patients who died from other diseases were excluded from the study. After careful review, 233 patients with T2N0M0 gastric cancer were identified for our retrospective analysis.

Clinicopathologic features such as age, gender, tumor location, tumor diameter, type of resection, histological type, lymphatic and/or blood vessel invasion (LBVI), perineural invasion (PNI), the total number of lymph nodes examined, and the extent of lymph node dissection were reviewed. In this study, the histology was divided into the differentiated type (papillary and tubular adenocarcinoma) and the undifferentiated type (poorly differentiated adenocarcinoma, signet-ring cell carcinoma, mucinous carcinoma, and miscellaneous). Gastric resection with an extensive (D2) lymph node dissection was recommended. This procedure entails the resection of all perigastric lymph nodes and some celiac, splenic or splenic hilar, hepatic artery, and cardial lymph nodes, depending on where the tumor was located in the stomach.

Statistical analyses were performed with SPSS statistical software, version 13.0 for Windows. Descriptive statistics was reported for relevant variables. Univariable analysis of tumor-specific survival was performed on the following prognostic factors: age (<50 vs. ≥50 years), gender (female vs. male), tumor location (upper vs. middle versus lower third), tumor diameter (≤3 cm vs. >3 cm), histological type (differentiated vs. undifferentiated), LBVI (absence vs. presence), PNI (absence vs. presence), resection type (subtotal vs. total), the total number of lymph nodes examined (<15 vs. ≥15), and extent of lymph node dissection (D1 plus vs. D2). And survival curves were constructed using the Kaplan–Meier method, and survival differences were compared using log-rank test. To investigate multivariable relationships of covariates with survival, Cox proportional hazard models with variable selection procedures were performed. A risk model was constructed to stratify pT2N0 patients into different risk groups based on factors that remained significant on multivariable analysis. And a weighting method was applied to each variable which had been employed in previous studies by other investigators.[7] The β-regression coefficients from final model applied to the original sample were used to develop prognostic scores (with low scores indicating a greater probability of overall survival (OS)) for each variable in the model. The score was calculated by dividing the regression coefficients by 1.128 (the smallest β coefficient), multiplying by 2.0, and rounding to the nearest whole number. P values less than 0.05 were taken to indicate statistically significant differences.

Results

Clinicopathologic Characteristics

A total of 233 patients with pT2N0 gastric cancer were eligible for analysis. The clinical and pathological characteristics of this cohort are shown in Table 1. The mean patient age was 57 years (SD, 13.0 years), and 68.6% were male. Most patients (n=133, 59.6%) had tumors in the lower third of the stomach as opposed to in the middle third (n=36, 16.1%) or in the upper third (n=54, 24.2%) of the stomach. One hundred twenty patients (53.8%) had undifferentiated disease as opposed to differentiated disease (n=103, 46.2%). LBVI was present in 22 patients (9.9%), and PNI was present in 17 patients (7.6%). Most patients (n=203, 91%) underwent subtotal gastrectomy. One hundred patients (44.8%) received D2 lymph node dissection, and 123 patients (55.2%) received D1 plus lymph node dissection. The median follow-up interval was 53 months. The overall 5-year survival rate was 88.5%.

Potential Risk Factors and Prognostic Significance

All potential clinicopathologic risk factors were evaluated by using the Kaplan–Meier method (compared with log-rank test). Univariate analysis shows that for overall 5-year survival, patients with tumors in the lower third of the stomach live longer than those with tumor in other sites. So are patients with tumors ≤3 cm compared to those with larger tumors, in patients without LBVI compared to

Table 1 Characteristics of 233 patients with T2N0 consensus stage gastric cancer

Variables	*N* (%)	5-year survival rate (%)	*p* value
Age (years)			0.591
<50	60 (26.9)	85.7	
≥50	163 (73.1)	89.7	
Gender			0.333
Female	70 (31.4)	84.7	
Male	153 (68.6)	90.4	
Tumor location			0.025
Upper1/3	54 (24.2)	80.9	
Middle1/3	36 (16.1)	86.2	
Lower1/3	133 (59.6)	93.6	
Tumor diameter			0.003
≤3 cm	130 (58.3)	94.5	
>3 cm	93 (41.7)	80.7	
Histological type			0.195
Differentiated	103 (46.2)	90.6	
Undifferentiated	120 (53.8)	86.4	
LBVI			0.003
Negative	201 (90.1)	90.7	
Positive	22 (9.9)	78.0	
PNI			0.001
Negative	206 (92.4)	90.6	
Positive	17 (7.6)	74.9	
Resection type			0.409
Subtotal	203 (91.0)	88.5	
Total	20 (9.0)	88.5	
Lymph node dissection			0.893
D1 plus	123 (55.2)	87.7	
D2	100 (44.8)	89.8	
Total number of lymph nodes examined			0.770
<15	111 (49.8%)	88.5	
≥15	112 (50.2%)	86.5	

patients with LBVI, and in patients without PNI compared to patients with PNI (Table 1). On multivariate analysis with the Cox regression model, tumor size, LBVI, and PNI were statistically independent poor prognostic factors (Table 2).

A prognostic risk model is constructed to predict prognosis based on tumor size, LBVI, and PNI. The range of weighted score is 0–3 for each variable with a maximum of 7 when combining the variables. Each variable has a total score to give a total risk stratification score of 0–7. Three risk groups were constructed based on the presence of 0 (low risk), 2–3 (intermediate risk), and 4–7 (high risk). The number of patients in the low-, intermediate-, and high-risk group was 109 (48.9%), 98 (43.9%), and 16 (7.2%), respectively. The overall 5-year survival of the low-, intermediate-, and high-risk group was 97.7%, 83%, and 50.3%, respectively ($p<0.001$; Tables 2 and 3, Fig. 1).

Table 2 Multivariable Cox regression analysis to evaluate potential prognostic factors for 5-year overall survival

Variable	Hazard ratio	95% CI	*p* value	β-coefficient	Prognostic score point
Tumor diameter					
≤3 cm	1				0
>3 cm	4.050	0.484–8.368	0.004	1.399	2
LBVI					
Negative	1				0
Positive	3.090	0.504–5.012	0.025	1.128	2
PNI					
Negative	1				0
Positive	4.829	0.600–6.877	0.009	1.575	3

Assignment of points to risk factors was based on a linear transformation of the corresponding β regression coefficient. The coefficient of each variable was divided by 1.128 (the lowest β value, corresponding to male sex), multiplied by a constant (2), and rounded to the nearest integer

Discussion

Our analysis of potential predictors of outcome after curative surgery for T2N0 gastric cancer revealed that the following three factors were associated with a higher risk of death: the tumor size >3 cm, the presence of LBVI, and the presence of PNI. Patients with no risk factor had a relatively higher overall 5-year survival rate (97.7%). In contrast, the same survival rate declines when risk factors are present in the intermediate- and high-risk group patients (83% and 50.3%, respectively), in which case adjuvant therapy should be considered for patients with high risk according to our scoring system, but 48.9% of those with low-risk disease may benefit from sparing of treatment-induced toxicity with adjuvant therapy.

Table 3 Prognostic model for outcomes in T2N0 consensus stage gastric cancer

Total number of points	Risk group	*N* (%)	5-year overall survival (%)
0	Low	109 (48.9)	97.7
2–3	Intermediate	98 (43.9)	83.0
4–7	High	16 (7.2)	50.3

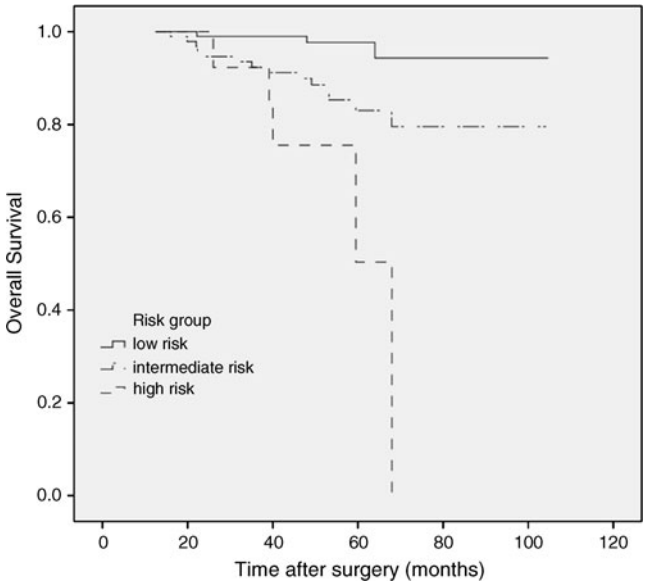

Fig. 1 Five-year overall survival based on risk groups

A meta-analysis conducted by GASTRIC Group published in *JAMA* in 2010 demonstrated that compared with surgery alone, postoperative adjuvant chemotherapy based on fluorouracil regimens was associated with reduced risk of death in gastric cancer.[8] Another meta-analysis shows a statistically significant 5-year survival benefit with the addition of radiotherapy in patients with resectable gastric cancer.[9] However, almost all data on adjuvant therapy are derived from randomized controlled trails that included a large proportion of stage II and III patients and, very likely, too few stages I patients to determine the benefit of adjuvant therapy in these stage groups. To date, the value of adjuvant therapy in treating patients with stage I gastric carcinoma is controversial due to lack of data from randomized studies and low relapse rate. The results of the INT-0116 trial have shown improvement of disease-free and overall survival by chemoradiation with a significant impact on the management of gastric cancer. INT-0116 is a phase-III trial on 556 patients with histologically proven stage Ib–IVM0 adenocarcinoma of the stomach or gastro-esophageal junction randomized to surgery versus surgery plus postoperative adjuvant chemoradiation (4,500 cGy, 5FU, Leucovorin). Thirty-six patients with stage Ib gastric cancer were included.[4] Recently, a 10-year follow-up of INT-0116 was presented. Exploratory subset analysis showed that adjuvant chemoradiation benefited stage Ib tumors; however, some groups have questioned the applicability of INT-0116 to stage Ib tumors because of small patient size in the trial (n=36) and relatively good prognosis of this early lesion with surgery alone.[10] Kunisaki et al. studied 1,880 patients with histologically proven stage I gastric cancer and identified lymphovascular invasion as a poor prognostic factor in stage Ib gastric cancer patients. In their study, patients with T2N0 gastric cancer with lymphovascular invasion or stage II gastric cancer had similar survival period. They suggested that T2N0 gastric cancer patients with moderate to severe lymphovascular invasion may be suitable for adjuvant chemotherapy.[11] For stage I gastric cancer, adjuvant therapy is recommended in AJCC T1N1 gastric cancer and may be considered for high-risk T2N0 patients, but not for T1N0 patients. However, no concurrent randomized trial data are available to support efficacy of adjuvant therapy for T2N0 gastric cancer. Our scoring system will be helpful in deciding treatment for T2N0 patients.

According to the new stage system, carcinoma that has invaded muscularis propria is categorized as T2 cancer. The possibility of gastric cancer invading the muscularis propria accounts for 9–15% of all gastric cancer patients who undergo surgical resection.[12,13] Current guidelines from NCCN recommended that not all T2N0 patients should be treated, but those with high-risk patients. The high-risk features include poorly differentiated or higher grade cancer, LBVI, PNI, or <50 years of age. Although many prognostic factors for early gastric cancer and advanced gastric cancer have been identified, there are few reports concerning prognostic factors for gastric cancer invading the muscularis propria.[14–18] Imamura et al.[14] reported that the depth of tumor invasion in the muscularis propria has an effect on lymph node metastasis and prognosis. Yokota et al.[15] conducted a multivariate analysis which also revealed that the prognosis of muscularis propria gastric cancer patients was affected most by vascular permeation, followed by tumor diameter. Son et al.[18] reported that tumors macroscopically resembling early gastric cancers, younger patient, and Lauren's diffuse type were significantly associated with a better prognosis of muscularis propria gastric cancer through multivariate analysis. The focus of this study is to evaluate commonly reported clinicopathologic features. These parameters can easily be validated in other cohorts in addition to the AJCC stages and might be helpful for designing future trials on adjuvant therapy to achieve manageable sample sizes and reasonable follow-up periods. Our study shows that tumor diameters, LBVI, and PNI were independent prognostic factors by multivariate analysis.

Based on our data, we find three clinical risk factors to predict the outcome, and the scoring system generated may help provide more tailored therapy for T2N0 patients. Based on the scoring system that we used, the 5-year OS was 97.7%, 83%, and 50.3% according to risk grouping. In our study group, 7.2% of the patients in high-risk group had two or three identified risk factors and showed significantly decreased overall 5-year survival. Patients in high risk of relapse and poor prognosis may be good candidates for

adjuvant therapy. In contrast, T2N0 patients without risk factors in low-risk group had a favorable outcome, and adjuvant therapy maybe unnecessary for these patients. As the survival curve for patients in intermediate-risk group lay in the middle between those of low- and high-risk groups, it is unclear whether adjuvant therapy will benefit those patients, which requires further study Hence, the decision to offer adjuvant therapy for T2N0 patients should be discussed in light of evidence abovementioned and must be individualized to the circumstances of each patient, and should be balanced against the possible risks of treatment-related toxicity.

There are several limitations inherent in this retrospective investigation. First is the heterogeneity in clinical decision making, surgical intervention, and pathological evaluation. The radical gastric cancer resections were performed by multiple surgeons, and the specimens were evaluated by multiple pathologists. These doctors were trained in academic centers with experience in gastrectomy, and the data are probably valid. The second limitation is the choice of overall survival as the end point. In some way, this can be regarded as a powerful end point, given that overall survival is a concrete end point that we were able to ascertain reliably for our patients using the resources described in our "Materials and Methods" Section. Although time to recurrence would be an interesting end point to analyze, patients were not on a predefined follow-up schedule and were observed at the discretion of the treating physician. Therefore, we have tried to collect recurrence data on these patients, yet there are limitations to the validity of investigating this end point due to lack of predefined surveillance plan and schedule. The third limitation is that the data remain hypothesis-generating, and further external validation in modern datasets is warranted. Validation of the prognostic risk model is expected in another patient cohort. Other limitations include the fact that we did not incorporate biomarkers, such as HER2 status, in risk stratification. Although the model includes readily available pathological data, further refinement may be possible by combining biomarkers. In our center, a study is ongoing to apply molecular-based testing using CISH/FISH analyses in addition to IHC for gastric cancer.

In this study, we categorize relatively homogeneous patients with pT2N0 stage into three prognostically different risk groups with substantial accuracy. This simple and user-friendly risk stratification based on readily available pathological features may aid in clinical decision making in respect of eligibility of pT2N0 gastric cancer patients. Based on our results, it is suggested that adjuvant radiotherapy is required for high-risk patients, and that a more aggressive chemotherapy regimen should be recommended for patients with increased risk scores. In the future, further prospective randomized trials will be focused on investigating the optimal treatment strategy in high-risk T2N0 gastric cancer. Our scoring system will serve as reference basis for future study in this group of patients.

References

1. Miyahara R, Miwa Y, Matsuura T, MaedaO, Ando T, OhmiyaN, et al. Prevalence and prognosis of gastric cancer detected by screening in a large Japanesepopulation: data froma single institute over 30 years. J Gastroenterol Hepatol. 2007;22:1435–42.
2. Desai AM, Pareek M, Nightingale PG, Fielding JW. Improving outcomes in gastric cancer over 20 years. Gastric Cancer. 2004;7:196–201.
3. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. (2010) AJCC Cancer Staging Handbook, 7th ed. American Joint Committee on Cancer, Chicago.
4. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN,et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345:725–730.
5. Kim S, Lim DH, Lee J, Kang WK, MacDonald JS, Park CH, et al. An observational study suggesting clinical benefit for adjuvant postoperative chemoradiation in a population of over 500 cases after gastric resection with D2 nodal dissection for adenocarcinoma of the stomach. Int J Radiat Oncol Biol Phys. 2005;63:1279–1285.
6. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med. 2007;357:1810–1820.
7. Rassi A Jr, Rassi A, Little WC, Xavier SS, Rassi SG, Rassi AG, et al. Development and validation of a risk score for predicting death in Chagas' heart disease. N Engl J Med. 2006; 355:799–808
8. GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group, Paoletti X, Oba K, Burzykowski T, Michiels S, Ohashi Y, et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. JAMA. 2010;303:1729–1737.
9. Valentini V, Cellini F, Minsky BD, Mattiucci GC, Balducci M, D'Agostino G, et al. Survival after radiotherapy in gastric cancer: systematic review and meta-analysis. Radiother Oncol. 2009;92:176–183.
10. Macdonald JS, Benedetti J, Smalley SR, Haller DG, Hundahl SA, Jessup JM, et al. Chemoradiation of resected gastric cancer: A 10-year follow-up of the phase III trial INT0116 (SWOG 9008). J Clin Oncol.27:15s, 2009 (suppl; abstr 4515)
11. Kunisaki C, Makino H, Kimura J, et al. Impact of lymphovascular invasion in patients with stage I gastric cancer. Surgery. 2010;147:204–211.
12. Yoshikawa K, Maruyama K. Characteristics of gastric cancer invading to the proper muscle layer with special reference to mortality and cause of death. Jpn J Clin Oncol. 1985; 15; 499–503.
13. Harrison JC, Dean PJ, Vander Zwaag R, el-Zeky F, Wruble LD. Adenocarcinoma of the stomach with invasion limited to the muscularis propria. Hum Pathol. 1991; 22; 111–117.
14. Imamura Y, Baba Y, Ishikawa S, Hiyoshi Y, Nagai Y, Nakamura T, et al. Heterogeneous prognoses of patients with tumors invaded

within muscularis propria according to tumor depth in the layers of the muscularis propria. Gastric Cancer. 2008;11:219–25.
15. Komatsu S, Ichikawa D, Kurioka H, Kan K, Shioaki Y, Ueshima Y, et al. Prognostic and clinical evaluation of patients with T2 gastric cancer. Hepatogastroenterology. 2005;52:965–968.
16. Ishigami S, Natsugoe S, Miyazono F, Hata Y, Uenosono Y, Sumikura S,et al. Clinical merit of subdividing gastric cancer according to invasion of the muscularis propria. Hepatogastroenterology. 2004;51:869–71.
17. Yokota T, Kunii Y, Teshima S, Yamada Y, Saito T, Kikuchi S, Yamauchi H. Gastric cancer with invasion limited to the muscularis propria. Int Surg. 1999;84:7–12.
18. Son HJ, Myung W, Yoo HS, Park SH, Song SY, Kwon YD, Rhee JC. Prognostic indicators of gastric carcinoma confined to the muscularis propria. Histopathology. 2007;51:105–110.

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ORIGINAL ARTICLE

Intraoperative Real-Time Cholangiography and C-tube Drainage in Donor Hepatectomy Reduce Biliary Tract Complications

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Abstract
Background In living-donor liver transplantation, biliary tract complications are a serious problem for recipients and donors.
Methods We applied intraoperative real-time cholangiography using a C-arm and/or C-tube drainage to reduce biliary tract complications in donor hepatectomy. From 2003 to 2010, intraoperative real-time cholangiography and C-tube drainage was applied to 39 and 19 donor cases, respectively. Fifteen donor cases had both procedures.
Results We confirmed the division line of the hepatic duct by visualizing a stricture on the monitor of the C-arm by pulling a thread and dissecting the proper site of the bile duct. The number of hepatic ducts of the graft to be anastomosed was 1 in 11 cases and 2 or 3 in 8 of the 19 cases without intraoperative real-time cholangiography, and it was 1 in 32 cases and 2 in 7 of the 39 cases with intraoperative real-time cholangiography. Bile leakage from the resection occurred in seven donors without, and in none of those with, C-tube drainage.
Conclusion In living-donor liver transplantation, intraoperative real-time cholangiography enables effective determination of the precise division line of the hepatic duct. Moreover, C-tube drainage is effective for reducing bile leakage from the resected surface of the liver of donors.

Keywords Living-donor liver transplantation · Cholangiography · Donor · Biliary tract complication · C-tube

Abbreviations

LDLT	Living-donor liver transplantation
IORTC	Intraoperative real-time cholangiography
CBD	Common bile duct

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Introduction

A biliary tract complication remains a serious problem in living-donor liver transplantation (LDLT), to be resolved not only for the recipients but also for the donors. A high biliary complication rate of recipients has been reported in right lobe LDLT.[1,2] The anatomic variation of the biliary tract is the main reason why complications occur. Therefore, the anatomy of the biliary tract should be evaluated in detail before the operation for both the recipients and donors. However, the preoperative radiological diagnostic examination, i.e., endoscopic retrograde cholangiography or percutaneous transhepatic cholangiography, for a healthy donor should be limited because of donor safety. Moreover, biliary complications depend on the procedure and the site of bile duct division. To reduce biliary tract complications, we applied intraoperative real-time cholangiography (IORTC) using a C-arm to aid in the division of the bile

ducts and postoperative bile drainage using a C-tube in donor hepatectomy. In this retrospective study, we evaluated their efficacy for reducing biliary tract complications in our donors of LDLT.

Patients and Methods

Sixty-five LDLTs were performed at the Department of Surgery, Kyoto Prefectural University of Medicine, between September 2003 and September 2010. Among them, 58 adult-to-adult LDLT cases were studied. These cases included 38 male patients and 20 female patients, ranging from 19 to 65 years of age (mean, 40.6 years). Other clinicopathological characteristics and surgical data are shown in Table 1. For donor hepatectomy, we changed the procedures of bile duct cutting and prevention of bile fistula. We applied IORTC using a C-arm and/or bile drainage using a C-tube, respectively, in donor hepatectomy to reduce biliary tract complications. As a result, all 58 donors consisted of four groups: 15 donors without IORTC and C-tube drainage, 24 donors with IORTC only, 4 donors with C-tube drainage only, and 15 donors with both IORTC and C-tube drainage. We compared the operative courses of 39 donors with IORTC and 19 donors without IORTC; subsequently, there were 19 donors with C-tube drainage and 38 donors without drainage. Finally, we compared the number of hepatic ducts of the graft to be anastomosed and biliary tract complications among the four groups.

Table 1 Clinico-pathologic features of 58 donors in adult-to-adult LDLT

Gender	Male	38
	Female	20
Age (years)		40.6±13.2 (19–65)
Body weight (kg)		62.0±10.0 (44.7–86.0)
Body mass index		22.3±2.5 (18.0–29.0)
Graft type	Right: right lobe	27
	Right lobe with MHV	2
	Left: left lobe with MHV	15
	Left and Spiegel lobe	14
Two interventions preventing biliary tract complications		
Neither IORTC nor C-tube drainage		15
IORTC only		24
C-tube drainage only		4
Both IORTC and C-tube drainage		15
Graft weight (g)		555.1±150.1 (298.0–890.0)
Residual liver (%)		49.9±14.4 (30.0–73.5)
Liver/spleen ratio		1.28±0.13 (1.00–1.57)
Blood loss (g)		554.9±394.4 (117–1,596)
Postoperative hospital stay (days)		19.8±11.3 (9–73)

In donor hepatectomy, we evaluated the whole liver and the graft volume, steatosis of the liver, and the anatomy of the hepatic artery and vein, and portal vein in detail by multi-detector computed tomography before the operation. With regard to the biliary tract, after the hepatic duct on the graft side was identified, a small hemostatic clamp was applied to a predetermined division line on the bile duct intraoperatively. We performed intraoperative cholangiography through a tube inserted into the cystic duct routinely after cholecystectomy. In the previous procedure of the division of the hepatic duct, we separated the hepatoduodenal ligament and identified the hepatic duct on the graft after intraoperative cholangiography. To divide the hepatic duct at an adequate division line, we dissected the Glissonian sheath around it and exposed the branch origin of the duct with scissors 2–3 mm away from the common hepatic duct to prevent its stenosis. The cut end of the hepatic duct of the donor was closed with an absorbable suture.

We began to perform IORTC in addition to routine intraoperative cholangiography when we divided the bile duct from the 23rd case onwards. With regard to the procedure for dividing the bile duct, the hepatic duct wall was not exposed, the duct was ligated twice with the Glissonian sheath around it, and the duct was divided. In this procedure, we can precisely confirm the division line using IORTC on the monitor of the C-arm. A proper division line can prevent bile duct stenosis of the donors or multi-anastomosis of the hepatic duct of the recipients. Therefore, to divide the hepatic duct, it was not necessary to expose the branch origin of the bile duct or to use sutures.

Reduction of the intra-bile ductal pressure is thought to be effective for preventing bile leakage. Therefore, we performed postoperative bile drainage using a C-tube from the cystic duct, but this was not carried out routinely. We inserted a C-tube into the cystic duct and turned the tip of the C-tube toward the hepatic hilus using the curve of a clamp pinching the proximal side of the common bile duct (CBD). The tube was removed 3 weeks after LDLT at our outpatient clinic.

IORTC

IORTC using a C-arm can easily acquire three-dimensional images during a 190° orbital rotation. The bile duct, as displayed three-dimensionally, assists in understanding the architecture of the biliary tree. In our donor hepatectomy, we performed IORTC through a tube inserted into the cystic duct routinely after cholecystectomy, or via a 24-G puncture needle with a trocar inserted into the CBD during dissection of the hepatic duct. In our new donor hepatec-

tomy surgical procedure, the hepatic duct was divided from the hepatoduodenal ligaments while attached to the Glissonian sheath at the hepatic hilus to preserve the blood supply. We used a thread to determine the proper division line of the hepatic duct while performing the IORTC. We confirmed it by visualizing a stricture on the monitor of the C-arm, and this occurs by pulling the thread (Fig. 1a and b).

We describe one case of a right lobe graft donor, who has a right hepatic duct, which separates into both anterior and posterior branches at a point approximately 5 mm from the CBD as follows. First, we evaluated the anatomy of the biliary tract by routine intraoperative cholangiography. We then performed IORTC to divide the right hepatic duct. Pulling the thread, which encircled the right hepatic duct, we recognized that the stricture induced by the thread was near the separation point of the anterior and posterior branches. If we were to divide the hepatic duct at this site, two anastomoses would have been necessary in the recipient operation. Therefore, we adjusted the thread to the CBD side (Fig. 1c). After a double ligation, we divided the right hepatic duct and thus obtained a single lumen, making it easier to perform anastomosis.

Definitions of Bile Leakage

Postoperative bile leakage was defined as discharge from the drain with macroscopic bile staining or a bilirubin level of 5 mg/dL or more in the discharge from the drain or an intra-abdominal fluid collection associated with a feverish episode (>38°C).

Statistical Methods

Continuous data are expressed as median values with ranges and were compared using the Mann–Whitney *U* test. Categorical data were compared using the Fisher exact test or chi-square test.

Statistical significance was defined as $p<0.05$. All statistical analyses were performed using statistical software (StatView 5.0; SAS Institute, Cary, NC, USA).

Results

We found that the number of hepatic ducts of the graft to be anastomosed was 1 in 11 cases, 2 in 7 cases (36.8%), and 3 in 1 (5.2%) of the 19 cases without IORTC (mean, 1.47). The number of hepatic ducts of the graft to be anastomosed was 1 in 32 cases and 2 in 7 (17.9%) of the 39 cases with IORTC (mean, 1.21). There was a significant difference in the rate of multi-ducts between cases with and those without IORTC ($p=0.043$) (Table 2).

With regard to biliary tract complications, we experienced one major biliary fistula originating from the suture site in patients without IORTC and C-tube drainage. Surface bile leakage from resection occurred in seven

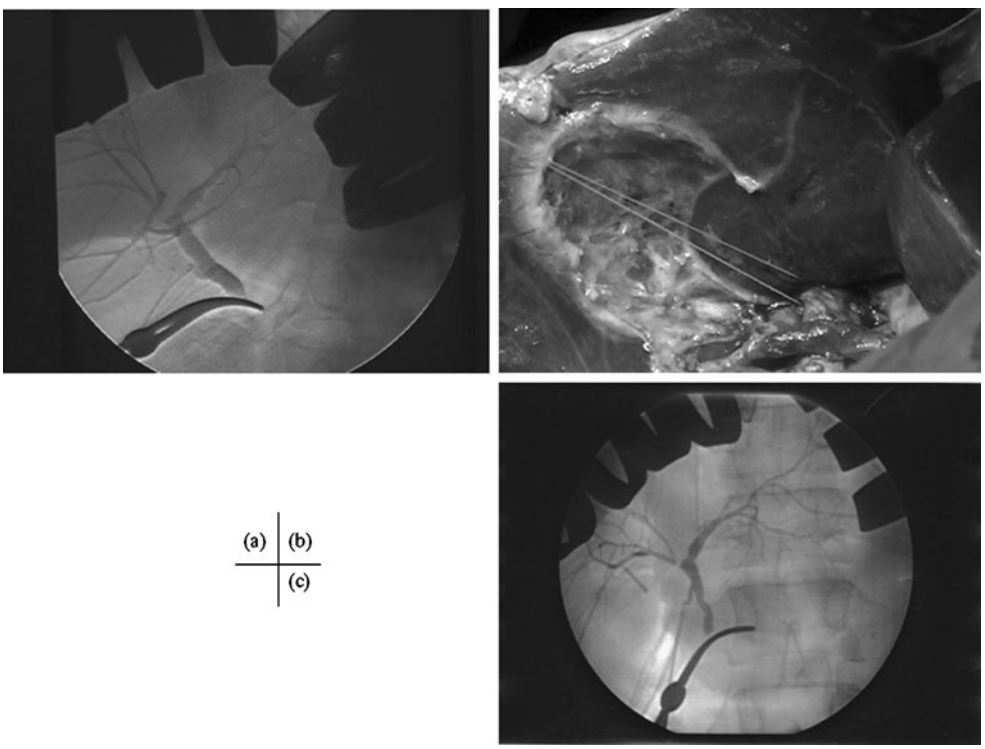

Fig. 1 Determination of the hepatic duct division line. We confirmed the hepatic duct division line by visualizing a stricture on the monitor of the C-arm, and this occurs by pulling a thread (**a**, **b**). By pulling the thread encircling the right hepatic duct, we recognized that the stricture by the thread was near the separation point of the anterior and posterior branches. IORTC showed that the thread moved to the CBD side. After double ligation, we divided the right hepatic duct and obtained a single lumen, which made anastomosis easier (**c**)

Table 2 Postoperative biliary complications of donors with and without IORTC in adult-to-adult LDLT

	IORTC(−) (n=19)	IORTC(+) (n=39)	p value
Gender			
Male	13	25	
Female	6	14	0.745
Age (years)	39.4±13.2	41.2±13.3	0.590
Graft type			
rt	14	15	
lt	5	24	0.012*
No. of hepatic ducts	1.47±0.61	1.18±0.39	0.043*
Complications of biliary tract	2 (10.5%)	5 (12.8%)	0.801
(rt hepatectomy)[a]	(2) (14.3%)[a]	(3) (20.0%)[a]	0.684
Postoperative hospital stay (days)	22.3±15.0	18.1±8.8	0.502

*p<0.05, statistically significant
[a]Subgroup

donors who did not have C-tube drainage and in none of the donors who had C-tube drainage (p=0.049) (Table 3).

The profiles of our two interventions to prevent biliary tract complications, IORTC and C-tube drainage, are shown in Table 4. The number of hepatic ducts of the graft to be anastomosed of donors with IORTC and C-tube drainage was lower than that of donors without them (p=0.033). Moreover, the occurrence rate of biliary fistula of donors with IORTC and C-tube drainage was lower than donors with IORTC (p=0.058). The combined application of IORTC and C-tube drainage reduced the rate of bile duct anastomoses and bile leakage.

Discussion

Biliary stenosis and leakage are the main complications of biliary reconstruction, which is one of the most difficult aspects of right lobe LDLT. Fan et al.[2] described that the causes of biliary complications are hepatic duct ischemia, double or triple hepaticojejunostomies, the presence of an unrecognized branch of the right hepatic duct, a jejunal opening smaller than the size of the right hepatic duct, and ductal plasty without division of a newly created septum. In a recipient operation, the rate of biliary complications, including bile duct anastomosis or a resection surface, has been reported as 2.5–64%.[2–4] In donor hepatectomy, biliary complications are also the most common and serious problems.[5,6] With regard to the biliary tract of a donor, direct fluorography is the best method to estimate any anatomic variations, but preoperative endoscopic retrograde cholangiography or percutaneous transhepatic cholangiography is much too invasive an examination for healthy donors, with the associated complication risks of hemorrhage, cholangitis, and pancreatitis. Magnetic resonance cholangio-pancreaticography is thought to be insufficient to estimate a small bile duct. Therefore, we have not performed any precise examinations preoperatively. Even if we can determine the exact biliary anatomy preoperatively, biliary complications will generally occur because of the procedure or the site of bile duct division. It has been reported that the morbidity rate for a donor is 9.3% in the lateral segment or left lobe graft procurement and 19.7% for right lobe graft procurement.[7] However, the precise rate of

Table 3 Postoperative biliary complications of donors with and without C-tube drainage in adult-to-adult LDLT

	C-tube (−) (n=39)	C-tube (+) (n=19)	p value
Gender			
Male	12	8	
Female	27	11	0.394
Age (years)	39.4±13.5	37.0±13.4	0.954
Graft type			
rt	20	9	
lt	19	10	0.780
No. of hepatic ducts	1.16±0.60	1.33±0.50	0.214
Complications of biliary tract	7 (17.9%)	0 (0.0%)	0.049*
(rt hepatectomy)[a]	(5) (25.0%)[a]	(0) (0.0%)[a]	0.083
Postoperative hospital stay (days)	20.7±16.3	27.1±4.8	0.914

*p<0.05, statistically significant
[a]Subgroup

Table 4 Our two interventions to reduce biliary tract complications of donors in adult-to-adult LDLT

	No. of hepatic ducts of the graft to be anastomosed	The incidence of biliary tract complications
Neither IORTC nor C-tube drainage (n=15)	1.47±0.64*	2/15 (13.3%)
IORTC only (n=24)	1.25±0.44	5/24 (20.8%)**
C-tube drainage only (n=4)	1.50±0.58	0/4 (0.0%)
Both IORTC and C-tube drainage (n=15)	1.07±0.26*	0/15 (0.0%)**

*p=0.033, statistically significant

**p=0.058, marginally significant

biliary complications of a donor has not yet been determined.

Various methods have been attempted to decrease the biliary complication rate. A modified technique to preserve the blood supply to the bile duct, or attention and surgical refinement, can lead to a significant reduction of these problems. Lee et al.[8] reported that the Glissonian dissection technique at the high hilar level is useful for reducing the rate of biliary complications. Suehiro et al.[3] reported that an in situ dye injection leakage test of the resection surface can minimize the incidence of bile leakage of a resected surface. Moreover, Takatsuki et al. introduced the new technique of division of the hepatic duct to reduce the number of bile duct anastomoses and biliary complications in 2006.[9] This technique using a C-arm is similar to our procedure.

In our series, we experienced one case of severe bile leakage in a right lobe LDLT donor case. In this case, the anterior and posterior branches arose from the CBD separately. Therefore, the closure site of the CBD was large. The bile leakage was successfully treated by endoscopic retrograde biliary drainage. However, the closure site developed stenosis. It was necessary to maintain an endoscopic retrograde bile drainage tube in the CBD. After that experience, we initiated our procedure of division of the biliary duct including IORTC. Since initiating this procedure, there have been no severe biliary tract complications arising at the division site of the biliary tract in the donor. In the recipient, biliary duct complications have also tended to decrease (data not shown). The use of double ligation, while including the tissue around the bile duct, was thought to preserve blood flow to the anastomotic site. We found that the number of bile duct anastomoses decreased because of a double ligation and IORTC, which is similar to a previous report.[9] However, IORTC cases had more left graft types than cases without IORTC. This may affect the number of bile duct anastomoses because the distance between the first and second branches of the left hepatic duct is longer than that of the right hepatic duct. IORTC is thought to be effective for preventing severe bile leakage from the division site of the first branch of the bile duct.

IORTC did not effectively reduce bile leakage of the resected surface in the donor. If we could recognize the small bile duct around the hepatic cut surface by IORTC, the occurrence rate of biliary complications may decrease. We must also be extremely careful not to damage any small bile ducts from the caudate lobe. However, it is nearly impossible to predict bile leakage from a resected surface that occurs more than 1 week after hepatectomy. All cases of bile leakage from a resected surface were successfully treated with percutaneous transhepatic abscess drainage and endoscopic nasal bile duct drainage. Therefore, we performed C-tube drainage, especially for hemi-lobe graft donors. We did not experience any bile leakage in patients who had C-tube drainage. Hotta et al.[10] also reported that transcystic duct tube drainage after hepatectomy is useful for decreasing postoperative bile leakage. They observed bile leakage in 3.6% of patients with transcystic duct tube drainage and in 26.3% of patients without drainage. On the other hand, retrograde transhepatic biliary drainage via a tube inserted through a choledochostomy is reported to be ineffective in preventing postoperative bile leakage.[11] In our donor series, the backgrounds of the patients and operative methods were similar, which is different from other previous studies. Furthermore, all bile leakage in donor hemi-hepatectomy originating from the biliary duct communicates with the main biliary tree. Therefore, C-tube drainage is thought to be effective in preventing bile leakage in donor hepatectomy.

The C-arm has been applied for three-dimensional imaging during liver resection, cholecystectomy, and percutaneous transhepatic biliary drainage.[12,13] This procedure creates an excellent visualization of the anatomy of the extrahepatic biliary tree and can be used to find bile duct stones, strictures, and tumors, as well as for defining the function and anatomy of Oddi's sphincter.[14] For performing hepatectomy for hepatic malignancy, this procedure could be an important prerequisite for defining the landmarks of the liver, which are necessary for a curative resection in a three-dimensional space.[15] In comparison with using a mobile X-ray machine and static films, C-arm fluorography has been found to be superior in terms of a reduced time to carry out the procedure and the total abolition of unsatisfactory radiological exposure of the biliary tract.[16] The introduction of a new device to obtain superior imagery is expected to improve the biliary complication rate, while also improving the overall results of LDLT.

Conclusion

In conclusion, the safety of the donor is one of the most important aspects in LDLT. From this point of view, a

combined application of IORTC and C-tube drainage is a useful technique to determine the precise division line of the hepatic duct and to avoid severe bile leakage or stenosis at the division site or the resected surface of the donor in adult-to-adult LDLT.

References

1. Ramacciato G, Varotti G, Quintini C, Masetti M, Di Benedetto F, Grazi GL, Ercolani G, Cescon M, Ravaioli M, Lauro A, Pinna A. Impact of biliary complications in right lobe living donor liver transplantation. Transpl Int. 2006;19:122–127.
2. Fan ST, Lo CM, Liu CL, Tso WK, Wong J. Biliary reconstruction and complications of right lobe live donor liver transplantation. Ann Surg. 2002; 236:676–683.
3. Suehiro T, Shimada M, Kishikawa K, Shimura T, Soejima Y, Yoshizumi T, Hashimoto K, Mochida Y, Maehara Y, Kuwano H. In situ dye injection bile leakage test of the graft in living donor liver transplantation. Transplantation. 2005; 80:1398–1401.
4. Giacomoni A, Lauterio A, Slim AO, Vanzulli A, Calcagno A, Mangoni I, Belli LS, De Gasperi A, De Carlis L. Biliary complications after living donor adult liver transplantation. Transpl Int. 2006; 19:466–473.
5. Fujita S, Kim ID, Uryuhara K, Asonuma K, Egawa H, Kiuchi T, Hayashi M, Uemeto S, Inomata Y, Tanaka K. Hepatic grafts from live donors: donor morbidity for 470 cases of live donation. Transpl Int. 2000; 13:333–339.
6. Mlddleton PF, Duffleld M, Lynch SV, Padbury RT, House T, Stanton P, Verran D, Maddern G.Living donor liver transplantation-adult donor outcome: a systematic review. Liver Transpl. 2006; 12:24–30.
7. Tanaka K, Inomata Y, Kaihara S. Living-donor liver transplantation. Prous Science, Barcelona, 2003; 113.
8. Lee KW, Joh JW, Kim SJ, Choi SH, Heo JS, Lee HH, Park JW, Lee SK.High hilar dissection: new technique to reduce biliary complication in living donor liver transplantation. Liver Transpl. 2004; 10:1158–1162.
9. Takatsuki M, Eguchi S, Takai H, Hidaka M, Soyama A, Tajima Y, Kanematsu T. A secured technique for bile duct division during living donor right hepatectomy. Liver Transpl.2006; 12:1435–1436.
10. Hotta T, Kobayashi Y, Taniguchi K, Johata K, Sahara M, Naka T, Maeda T, Tanimura H. Postoperative evaluation of C-tube drainage after hepatectomy. Hepatogastroenterology 2003; 50: 485–490.
11. Nakai T, Kawabe T, Shiraishi O, Shiozaki H. Prevention of bile leak after major hepatectomy. Hepatogastroenterology 2004; 51: 1286–1288.
12. Cuschieri A, Shimi S, Banting S, Nathanson LK, Pietrabissa A. Intraoperative cholangiography during laparoscopic cholecystectomy. Routine vs selective policy. Surg Endosc. 1994; 8:302–305.
13. Laufer U, Kirchner J, Kickuth R, Adams S, Jendreck M, Liermann D. A comparative study of CT fluoroscopy combined with fluoroscopy versus fluoroscopy alone for percutaneous transhepatic biliary drainage. Cardiovasc Intervent Radiol. 2001; 24:240–244.
14. MacFadyen BV. Intraoperative cholangiography: past, present, and future. Surg Endosc. 2006; 20 suppl 2:S436-440.
15. Beldi G, Styner M, Schindera S, Inderbitzin D, Candinas D. Intraoperative three-dimensional fluoroscopic cholangiography. Hepatogastroenterology. 2006; 53:157–159.
16. Mofti AB, Ahmed I, Tandon RC, Al-Tameem MM, Al-Khudairy NN. Routine or selective preoperative cholangiography. Br J Surg. 1986; 73:548–550.

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ORIGINAL ARTICLE

Long-Term Outcome of Percutaneous Ablation in Very Early-Stage Hepatocellular Carcinoma

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Abstract
Purpose The aim of this study was to investigate the long-term outcomes of percutaneous ablation (PA) of very early-stage hepatocellulcar carcinoma (HCC) with a multimodal strategy.
Methods Written informed consent was obtained from all patients before treatment. Percutaneous ethanol injection (PEI) was performed for tumors in unfavorable locations; microwave ablation (MWA) was performed for tumors in favorable positions without a capsule; and radiofrequency ablation (RFA) was carried out in favorable tumors with a capsule. Since 2003, these advanced PA techniques have been used.
Results Eighty-three patients with very early HCC were treated with PA, including 33 with PEI, 19 with MWA, and 31 with RFA. Initial complete response (CR) was achieved in 79 patients (95%). The mean follow-up period was 45±27 months (range, 24–155 months). Late treatment failure was observed in eight patients (10%), which was significantly associated with tumor size (P=0.046) and technique advancements (P=0.009). Sustained CR was achieved in 51 patients (61%) at the end of follow-up. Major complications occurred in two patients (2%). The 1-, 3-, 5-, and 6-year disease-free survival rates were 87%, 69%, 62%, and 59%, respectively. The 1-, 3-, 5-, and 7-year overall survival rates were 94%, 88%, 78%, and 74%, respectively.
Conclusions Treatment of very early-stage HCC using a multimodal strategy tailored to tumor characteristics achieves equivalent initial CR rates and long-term survival rates compared to surgical resection.

Synopsis This study assessed different modalities of percutaneous ablation (PA) for the treatment of 83 patients with very early-stage hepatocellular carcinoma. PA produced results that were comparable to surgical resection in terms of initial response, complications, and overall survival.

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Keywords Percutaneous ablation · Hepatocellular carcinoma · Early stage

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and its incidence in developed countries is rising.[1–3] HCC is the second highest cause of malignancy-associated mortality in China.[4] Early-stage HCC can be successfully treated with the use of hepatic resection, liver transplantation, or percutaneous ablation (PA).[5–7] Transplantation achieves the best survival results but high costs and donor shortages limit its use. Therefore, surgical resection remains the treatment of choice.[8]

In the past two decades, methods of PA, such as percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), and microwave ablation (MWA), have been widely used for the treatment of small HCC in patients who

are not candidates for resection or transplantation.[5, 9, 10] Recently, several randomized clinical trials demonstrated that PA is as safe and effective as surgical resection of small HCC.[11–13] Furthermore, PA has been shown to be less invasive, simpler to perform, less costly, and requires a shorter duration of hospitalization. Therefore, some centers now use PA as the first-line treatment for HCC that are ≤3 cm,[14, 15] but the debate continues about which is the more optimal treatment for small HCC.

Although most studies have focused on comparing the efficacy of RFA and surgical resection, such comparisons are incomplete, as RFA is contraindicated in 10–25% of tumors that are located close to critical structures, unlike surgery.[16] Other forms of PA, such as PEI and MWA, are promising as the former could be used to eradicate high-risk tumors with lower complication rates, and the latter has equivalent efficacy to RFA.[17] Therefore, the combined use of multiple PA modalities might be more efficacious and safer compared to surgical resection.

In this study, we present our 11-year experience in treating single HCC ≤2 cm in size using a multimodal PA strategy. The primary endpoints were disease-free survival (DFS) and overall survival (OS) rates. Prognostic factors that influenced survival were also analyzed.

Patients and Methods

Patients

This study was performed according to the guidelines of the Helsinki Declaration. It was registered and approved by the ethics committee at The First Affiliated Hospital of Sun Yat-Sen University. All patients gave written informed consent before treatment.

Surgical resection remains the first choice for very early-stage HCC at this institution. PA is an alternative option when surgery is contraindicated. From November 1997 to October 2008, 92 patients with HCC and cirrhosis were enrolled in this study. The inclusion criteria were (a) single ≤2-cm tumor with a very early HCC stage according to the Barcelona Clinic Liver Cancer (BCLC) staging system;[5] (b) tumor detectable on ultrasound (US); (c) Child–Pugh A or B liver function; and (d) grade 0 or 1 performance status.[5] The exclusion criteria were evidence of vascular invasion or extrahepatic spread, a platelet count <50,000/mm^3, or <50% prothrombin activity.

HCC was confirmed by evaluating vascular profile or biopsy. Characteristic vascular profile was successful in confirming 57 tumors. Evaluation of vascular profile was accomplished using two dynamic imaging techniques, such as contrast-enhanced ultrasound, dynamic CT, or MRI. Biopsy was used to confirm HCC in 35 tumors, in which vascular profile on dynamic imaging was not characteristic and the AFP was less than 200 ng/mL. Liver disease was evaluated with standard US and spiral computed tomography (CT) imaging. US was used to detect vascular invasion. A tumor capsule was defined as the presence of a peritumoral hypoechoic halo as visualized by US. Unfavorable target tumors were subcapsular nodules or those located ≤5 mm from critical structures, such as the gallbladder, gastrointestinal tract, inferior vena cava, hilum, heart, or diaphragm. The general health status of each patient was evaluated using routine liver, renal, and hematological investigations. Portal hypertension (PHT) was defined as the existence of esophageal varices or splenomegaly with a platelet count <100,000/mm^3. Diagnostic and management decisions were made by consensus of the hepatobiliary surgery and interventional radiology teams.

Percutaneous Ablation Procedures

According to our protocol, PEI was performed for unfavorable tumors, MWA was used to treat favorable tumors without a capsule, and RFA was used to treat favorable tumors with a capsule. A safety margin of 0.5–1.0 cm was employed during all thermal ablations.

Percutaneous Ethanol Injection

All patients were hospitalized prior to treatment. Two needles were used: a 21-gauge needle (PEI needle, Silux, Saitama, Japan) and a multipronged 20-cm-long 18-gauge needle (Quadra-Fuse, Rex-Medical Co., USA). The latter consisted of three retractable tines that each had two evenly spaced through-holes (four fluid exits); the tines could be deployed up to 5 cm.[18] After administration of local anesthesia, the needle was inserted into the center of the tumor nodule under US guidance, and the tip of the needle was positioned at the inferior aspect of the tumor. For 21-gauge PEI, ethanol was injected until the entire tumor appeared hyperechoic upon using the pullback technique. The amount of ethanol injected per session was 2–10 mL, and a treatment cycle consisted of three or four sessions.

Multipronged PEI was used after November 2004. In this modification, the tines were deployed into the area of the target tumor with the largest diameter. We calculated the amount of ethanol necessary for injection based on the volume of a sphere: $V_1=4/3\ \pi\ [(D/2+0.5)^3]$, where V is the volume and D is the largest tumor dimension. After half of this volume of ethanol was injected, the tines were retracted into the cannula. The cannula was then rotated 60°, the tines were redeployed, and the remaining ethanol was injected. The procedure was completed with one needle insertion in a single treatment session.

Microwave Ablation

MWA was performed under local anesthesia with sedation and US guidance. Two systems were used: a 16-gauge monopolar antenna with a 2.7-cm-long active tip connected to a UMC-I MW generator (Institute 207 of Aerospace Industry Company and PLA General Hospital, Beijing, China), and a 14-gauge cooled-shaft antenna containing a 16.5-cm-long double-lumen shaft and a 1.5-cm-long active tip connected to a MTC-3MW generator (FORSEA™, Qinghai Microwave Electronic Institute, Nanjing, China). Noncooled-shaft MWA was performed at 60 W for a duration of 5 min, producing a coagulation zone of 3.7× 2.6 cm; one or two insertions were required for a single treatment session.[19]

Since August 2003, a cooled-shaft antenna was used with continuously circulating chilled saline solution (4°C) in the double-lumen shaft to maintain a shaft temperature at 10±2°C during ablation. One insertion and a single energy application of a cooled-shaft MWA was performed using 80 W for a duration of 25 min in a single session, and a radiological necrosis zone of 5.0×3.6 cm was produced.[20]

Radiofrequency Ablation

US-guided RFA was performed under local anesthesia and sedation. RFA was initially carried out with WE-7568 RF delivery system (Welfare Electronic Co., Beijing, China), which consisted of a RF generator producing a frequency of 290 kHz and a maximum power of 200 W, and a 14-gauge electrode that contained ten expandable tines. After October 2005, a Cool-tip™ RFA system (Valleylab, Boulder, CO, USA) was used instead, which consisted of a RF generator with a maximum power of 200 W and a 17-gauge internally cooled electrode. Radiofrequency energy was delivered for 10 or 12 min for expandable-tip RFA or cool-tip RFA, respectively. Treatment was completed within one or two insertions in a single treatment session.[17]

Evaluation of Treatment Response and Follow-up

One month after PA was completed, a contrast-enhanced CT was performed. The local treatment response was classified according to radiological findings.[9] A complete response (CR) was defined as no enhancement within the tumor area. If residual enhancement of the tumor was detected, another treatment cycle or session was performed. "Initial CR" depicted the status of CR after the completion of the first or second PA cycle. "Initial treatment failure" was defined as the presence of tumor enhancement after the second PA. These patients received other treatment modalities, such as resection or transarterial chemoembolization (TACE).

All patients who underwent PA were enrolled in follow-up studies. Follow-up was performed using US and evaluation of serum alpha-fetoprotein (AFP) levels every 2–3 months, and a CT scan every 6 months. "Sustained CR" referred to the tumor-free status at the end of follow-up. "Late treatment failure" was defined as the reappearance of an enhancing zone inside the tumor that was initially completely ablated or ≤2 cm of the surrounding liver parenchyma.[16, 21] Tumors with late failure were treated using the same modality as given initially. "Disease recurrence (DR)" was defined as the appearance of new intrahepatic tumors in areas other than the treated area in the absence of failure of treatment. Early DR was defined as occurrence of new intrahepatic tumors 12 months or less after the initial treatment, and those occurred more than 12 months after treatment was defined as late DR. "Total recurrence" included late failure and DR. For patients with DR, the appropriate treatment modality, including PEI, RFA, MWA, resection or TACE, were applied, depending on the individual status of each case. Any ablation-related complication or side effect was documented. In cases with suspicious image findings, a fine-needle biopsy was performed.

Statistical Analysis

SPSS (version 13.0; SPSS, Chicago, IL, USA) was used for the statistical analysis. Continuous data were expressed as mean ± SD. Differences between patient subgroups with regards to initial response, late failure, DR, and complications were analyzed using the Pearson's chi-square test or Fisher's exact probability test for categorical variables and a *t* test for continuous variables. Univariate analysis was used to identify variables that predicted survival. Twenty-one variables were assessed, and those are as follows: sex, age, etiology, cirrhosis, Child–Pugh class, PHT, alanine aminotransferase, bilirubin, albumin, platelet count level, AFP, tumor size, tumor pattern, tumor location, PA modality (thermal vs. PEI), technique advancement (multipronged PEI, cooled-shaft MWA and cool-tip RFA vs. initial modalities), initial CR, late treatment failure, DR, operability (absence of PHT, or total bilirubin <1.5 mg/dL)[5], and complication. DFS and OS curves were evaluated using Kaplan–Meier curves and compared with the log-rank test. Variables with $P<0.05$ in the univariate analysis were entered into a Cox's proportional hazard model for multivariate analysis. Two-tailed P values <0.05 were considered statistically significant.

Results

Patients and Tumor Profile

Of the 92 patients who met the inclusion criteria, 9 (10%) were excluded because of coagulopathy ($n=4$), vascular

invasion (n=2), the development of Child–Pugh C liver function before treatment (n=2), or the appearance of new tumor tissue (n=1). Finally, 83 (90%) patients (age range, 27–74 years; mean, 55 years) were treated with PA: 33 underwent treatment with PEI, 19 with MWA, and 31 with RFA. The number of treatment sessions for each modality was 1.5±1.0, 1.2±0.4, and 1.2±0.4, respectively. The average hospitalization time was 3±2 days (range, 1–17 days). Detailed patient characteristics and tumor profiles are presented in Table 1.

Local Effectiveness

Treatment effectiveness was assessed in all patients. Initial CR was achieved in 79 patients (95%), including 31 (94%) who were treated with PEI, 18 with MWA (95%), and 30 with RFA (97%; Table 2). Four patients (5%) with initial treatment failure underwent resection (n=2) or TACE (n=2). The mean follow-up period was 45±27 months (range, 24 to 155 months). Late treatment failure was observed in eight patients (10%) between 3 and 89 months (mean, 18±29 months) after initial treatment with 21-gauge PEI (n=4), multipronged PEI (n=1), expandable-tip RFA (n=2), and noncooled-shaft MWA (n=1). Late failure was significantly associated with tumor size (P=0.046) and technique advancement (P=0.009). DR was observed in 29 patients (35%), including 22 (76%) of early DR and 7 (24%) of late DR. DR was significantly associated with age >65 years (P=0.014) and technique advancement (P=0.002; Table 3). Sustained CR was achieved in 51 patients (61%) at the end of the follow-up period.

Table 1 Patient characteristics and tumor profile

Clinical	(n=83)
Sex: M/F	78 (94%)/5 (6%)
Age (year): ≤65/>65	62 (75%)/21 (25%)
Etiology: hepatitis B/hepatitis C/other	77 (93%)/2 (2%)/4 (5%)
Child–Turcotte–Pugh class: A/B	70 (84%)/13 (16%)
Portal hypertension: present/absent	21 (27%)/62 (73%)
ALT (U/L): ≤40/>40	46 (55%)/37 (45%)
Total bilirubin (mg/dL): ≤1/>1	56 (67%)/27 (33%)
Albumin (g/L): ≤35/>35	12 (14%)/71 (86%)
Platelets (1000/mm^3): <100/≥100	21 (27%)/62 (73%)
AFP (ng/mL): ≤20/21–200/>200	33 (40%)/19 (23%)/31 (37%)
Tumor	
Tumor size (cm): ≤1.5/>1.5	26 (31%)/57 (69%)
Location: unfavorable/favorable	33 (40%)/50 (60%)
Encapsulated/noncapsulated	61 (73%)/22 (27%)

M male, *F* female, *AFP* alpha-fetoprotein, *ALT* alanine aminotransferase

Complications

Twenty (24%) patients complained of grade 1 (NCI Common Toxicity Criteria Version 2.0) intraprocedural pain, which resolved immediately after the PA ceased. Ten (12%) patients had a low-grade fever that resolved within 12–72 h of treatment. In the majority of patients, serum transaminase levels increased two to six times over baseline levels during the first 3–5 days after PA. Tumor seeding did not occur in any of the patients.

Major complications occurred in two patients (2%), who both developed liver decompensation after MWA. These patients were hospitalized for 10 and 17 days, and completely recovered after medical intervention. There were no treatment-related deaths (Table 3).

Survival

No patient was lost during follow-up. Fifteen patients died at the end of follow-up, due to recurrent cancer (n=9), liver failure (n=4), and upper gastrointestinal bleeding (n=2), respectively. The 1-, 3-, 5-, and 6-year DFS were 87%, 69%, 62%, and 59%, respectively. The 1-, 3-, 5-, and 7-year OS were 94%, 88%, 78%, and 74%, respectively (Fig. 1). Univariate analysis revealed that Child–Pugh class, ALB, PHT, DR, and operability significantly affected OS. Only DR was an independent predictor of OS in the multivariate analysis (Table 4). Patients without DR after treatment completion achieved 1-, 3-, 5-, and 7-year OS rates of 98%, 98%, 94%, and 94%, respectively; those who developed DR had OS rates of 86%, 69%, 51%, and 42%, respectively (P=0.000) (Fig. 2). Patients with early DR achieved 1-, 3-, 5-, and 7-year OS rates of 82%, 64%, 46%, and 34%, respectively; those with late DR had OS rates of 100%, 86%, 69%, and 69%, respectively (P=0.253)

Sixty patients (72%) were considered to be potential candidates for resection. The 1-, 3-, 5-, and 7-year OS of these operable patients were 97%, 89%, 83%, and 83%, respectively, which was significantly better than 87%, 83%, 62%, and 47% in inoperable patients (P=0.049).

Discussion

Treatment selection for specific stages of HCC should be based on clinical data, including local tumor control and technical limitations. According to the BCLC staging system, single HCC tumors sized ≤2 cm represent the earliest stage of disease and are suitable for potentially curative therapies, such as hepatic resection, liver transplantation, and PA. In this study, we treated very early HCC with PEI, MWA, or RFA, depending on the tumor characteristics. Initial CR rates of 94% or higher were

Table 2 Treatment response according to type of percutaneous ablation

According to type of PA	All patients n=83	PEI n=33	MWA n=19	RFA n=31
Initial response				
Initial CR	79 (95%)	31 (94%)	18 (95%)	30 (97%)
Initial treatment failure	4 (5%)	2 (6%)	1 (5%)	1 (3%)
Response at the end of follow-up				
Late failure	8 (10%)	5 (15%)	1 (5%)	2 (6%)
Disease recurrence	29 (35%)	12 (36%)	7 (37%)	10 (32%)
Sustained CR	51 (61%)	17 (52%)	11 (58%)	21 (68%)
Failure/recurrence	32 (39%)	16 (48%)	8 (42%)	10 (32%)

obtained for all three modalities, and a sustained CR rate of 61% was achieved at the end of follow-up, which were both higher than previously reported.[9] We documented a major complication rate of 2%, which is similar to previous studies.[22]

Although several randomized clinical trials have shown that PA achieved similar survival rates as hepatectomy, the latter was superior in terms of local tumor control as potential satellite nodules and emboli in small portal branches <1 cm from the main tumor were more likely to be eliminated.[23] Therefore, both the American Association for the Study of Liver Disease and the European Association for the Study of the Liver recommend that PA should be used in patients who are not surgical candidates. However, recent technique advancement in PA has enabled a larger ablation zone that envelops peritumoral satellites with fewer treatments.

Multipronged PEI is capable of overcoming the shortcomings of conventional PEI by disrupting the intratumoral septa with the deployment of multiple prongs. Ethanol injected from multiple holes in various directions produces a homogeneous distribution across the whole tumor, as ethanol usually diffuses with a radius of 2–3 cm around a single-needle tip.[24]

Table 3 Variables associated with late failure and disease recurrence

Variables	Patient subgroups		P value[a]
	Late failure	No late failure	
Technique advancement: yes/no	1/7	47/28	0.009
Tumor size	1.7±0.3	1.5±0.3	0.046
	Disease recurrence	No disease recurrence	
Age (year): ≤65/>65	17/12	45/9	0.014
Technique advancement: yes/no	10/19	38/16	0.002

[a] Pearson's test was used to compare age and technique advancement in DR, and Fisher's exact test was used to compare technique advancement in cases of late failure as categorical variables. The unpaired t test was used for the size of main tumor as a continuous variable

The high-dose single-session strategy used in our treatment scheme simplified the PEI procedure. Although the late failure rate of all PEI procedures was 15%, that of multipronged PEI was only 4%. Additionally, the high-risk location of all PEI-treated tumors made it difficult to confirm a safe margin of more than 0.5 cm, which may have contributed to the high rate of late failure in PEI.

MWA is theoretically better than RFA in producing large coagulation area and is less influenced by heat-sink phenomenon, while RFA is safer and more convenient than MWA with the use of a thinner electrode. To treat tumors without clear edge, we selected MWA for production of a large coagulation area in order to confirm local efficacy. Existence of tumor capsule allows the puncture and position of electrode easier to perform, RFA was the first choice. The single application of cooled-shaft MWA achieved a 1-cm wider coagulation zone than noncooled-shaft MWA, and cool-tip RFA produced a more stable coagulation area than expandable-tip RFA, although both achieve an ablation margin of at least 0.5–1 cm. This may explain why late failure was not observed in any of the

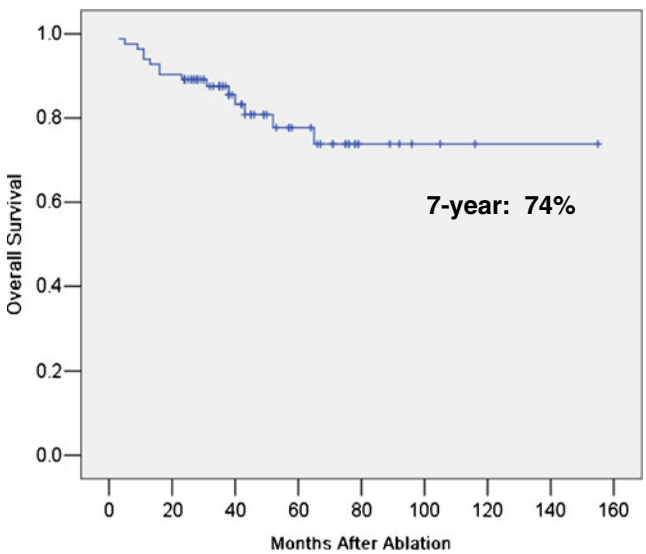

Fig. 1 Overall survival of the patients

Table 4 Predictors of overall survival: univariate and multivariate analysis

Variables	Univariate analysis	Multivariate analysis	
	P value	Odds ratio (95% CI)	*P* value
Child–Turcotte–Pugh class: A vs. B	0.003	0.984 (0.184–5.254)	0.185
Albumin (g/L): ≤35 vs. >35	0.001	6.148 (0.997–37.910)	0.050
Portal hypertension: present vs. absent	0.045	1.816 (0.547–6.029)	0.329
Disease recurrence: yes vs. no	0.000	11.565 (2.455–54.475)	0.002
Operability: yes vs. no	0.049	1.809 (0.545–6.009)	0.333

DFS disease-free survival, *OS* overall survival, *ALT* alanine aminotransferase

tumors treated by the two advanced thermal PA techniques. The total late failure rate in this study was 10%, but only 2% occurred with advanced techniques, which was much lower than the rate of 31% reported previously.[9] As these results suggest that the technique advancement has improved every PA modality, studies that compare surgery and PA in very early HCC should consider PA as a single arm of therapy, rather than individual PA modalities.

Tumors ≥1.5 cm had a significantly higher rate of late failure than those ≤1.5 cm in the present study. Histological studies have shown that HCC nodules ≤1.5 cm are uniformly well-differentiated, while 1.5–2.0 cm nodules often contain fewer differentiated cells with more proliferative activity.[23, 25] Portal microinvasion and peritumoral micrometastases are observed more frequently in larger tumors.[26, 27] Almost 70% of the tumors treated in this study were ≥1.5 cm in diameter (average, 1.7 cm). Therefore, our study may have included patients with more advanced HCC which could have resulted in increased tumor invasion prior to ablation and an altered treatment response.

It has been reported that intrahepatic recurrence observed 12 months or less after curative resection was considered as early recurrence and was a significant factor to poor prognosis.[28, 29] Our study revealed early DR-related 7-year survival was worse than those with late DR, which was similar to previous reports. Advanced PA modalities achieved improved local tumor control than initial modalities, and could therefore prevent potential tumor dissemination to the remote sites from peritumoral micrometastases and portal emboli. This may explain why the DR rate was significantly lower in patients who underwent the more advanced forms of PA. Patients older than 65 years of age had a higher rate of DR than younger patients, which may be because the longer duration of cirrhosis increased the likelihood of developing new HCC nodules.

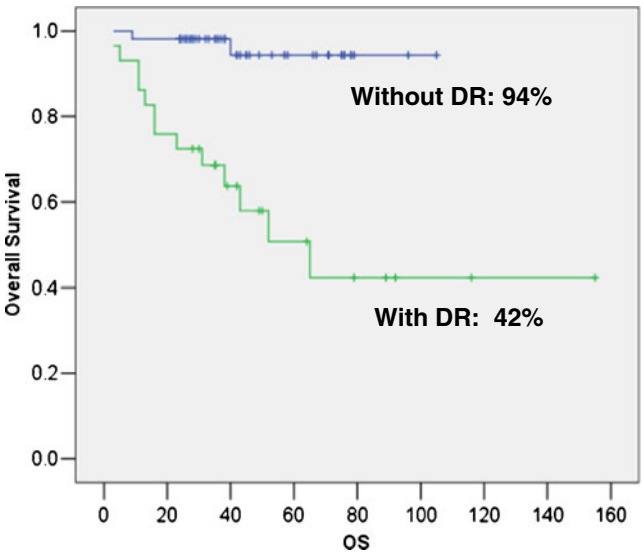

Fig. 2 Overall survival of patients with and without distant recurrence (*DR*)

The 5-year OS of 78% in this study was similar to previous reports.[9, 22] Three of the five predictors that significantly influenced OS in the univariate analysis were liver function factors, which demonstrates that pretreatment liver function status plays an important role in the survival outcomes of patients with the earliest stage of HCC. For patients with inadequate liver reserve, PA should be considered advantageous as a bridge to transplantation compared to resection because of its decreased invasiveness, lower complication rates, and sustained local CR rate. Patients with operable tumors had a 5-year survival of 83%, which was significantly better than the 47% observed in inoperable patients, and equivalent to the resection outcomes of 67–70%.[30–32] Previous guidelines that PA can only be used when surgery becomes unavailable requires further evaluation. DR was the only independent predictor of OS in the multivariate analysis, which suggests that the natural history of the disease governs the prognosis.[22]

One limitation of this study is that the results of tumor differentiation were only known in one third of the patients. Furthermore, a larger sample size and longer average follow-up may help provide more conclusive information in the future.

In conclusion, a multimodal strategy that considers both the tumor characteristics and the suitability of each PA modality for very early-stage HCC achieves equivalent initial CR and long-term survival rates to surgical resection. Technique advancement has improved the coagulation

efficacy of PA and decreased late treatment failures and disease recurrence. The advantages of PA over surgery suggest that PA should be the first-line treatment choice for very early-stage HCC in certain patients.

References

1. El-Serag HB, and Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999; 340: 745–750.
2. Peto J. Cancer epidermiology in the last century and the next decades. Nature 2001; 411: 390–395.
3. Bosch FX, Ribes J, Diaz M, Cleries R. Primary liver cancer: worldwide incidence and trends. Gastroenterology 2004; 127(5 suppl 1): S5–S16.
4. Pisani P, Parkin M, Bray F, Ferlay J. Estimates of the worldwide morality from 25 cancers in 1990. Int J Cancer 1999; 83:18–29.
5. Bruix J and Sherman M. Management of Hepatocellular Carcinoma. Hepatology 2005; 42:1208–1236.
6. Llovet JM, Fuster J, and Bruix J of the Barcelona-Clı′nic Liver Cancer Group. The Barcelona Approach: Diagnosis, Staging, and Treatment of Hepatocellular Carcinoma. Liver Transpl 2004;10: S115-S120.
7. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003; 362: 1907–1917.
8. Zhou XD, Tang ZY, Yang BH, Lin ZY, Ma ZC, Ye SL, et al. Experience of 1000 patients who underwent hepatectomy for small hepatocellular carcinoma. Cancer 2001; 91: 1479–1486.
9. Sala M, Llovet JM, Vilana R, et al. Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. Hepatology 2004; 40: 1352–1360.
10. Livraghi T, Giorgio A, Marin G, et al. Hepatocellular carcinoma and cirrhosis in 746 patients: long-term results of percutaneous ethanol injection. Radiology 1995; 197: 101–08.
11. Huang GT, Lee PH, Tsang YM, Lai MY, Yang PM, Hu RH, et al. Percutaneous ethanol injection versus surgical resection for the treatment of small hepatocellulcar carcinoma. Ann Surg 2005; 242: 36–42.
12. Lu MD, Kuang M, Liang LJ, Xie XY, Peng BG, Liu GJ, et al. Surgical resection versus percutaneous thermal ablation for early-stage hepatocellular carcinoma: a randomized clinical trial. Zhonghua Yi Xue Za Zhi 2006; 86: 801–805.
13. Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellulcar carcinoma. Ann Surg 2006; 243: 321–328.
14. Omata M, Tateishi R, Yoshida H, Shiina S. Treatment of hepatocellulcar carcinoma by percutaneous tumor ablation methods: ethanol injection therapy and radiofrequency ablation. Gastroenterology 2004; 127(Suppl): 159A–169A.
15. Choi D, Lim HK, Rhim H, Kim YS, Lee WJ, Paik SW, et al. Percutaneous radiofrequency ablation for early-stage hepatocellulcar carcinoma as a first-line treatment: long-term results and prognostic factors in a large single-institute series. Eur Radiol 2007; 17: 684–692.
16. Lencioni R, Cioni D, Crocetti L, Franchini C, Della Pina C, Lera J, et al. Early-stage hepatocellular carcinoma in cirrhosis: long term results of percutaneous image-guided radiofrequency ablation. Radiology 2005; 234: 961–967
17. Xu HX, Xie XY, Lu MD, Chen JW, YinXY, Xu ZF, et al. Ultrasound-guided percutaneous thermal ablation of hepatocellular carcinoma using microwave and radiofrequency ablation. Clin Radiol 2004; 59: 53–61.
18. Hines-Peralta A, Liu ZJ, Horkan C, Solazzo S, Goldberg SN. Chemical tumor ablation with use of a novel multiple-tine infusion system in a canine sarcoma model. J Vasc Interv Radiol 2006; 17: 351–358.
19. Lu MD, Chen JW, Xie XY, Liu L, Huang XQ, Liang LJ, et al. Hepatocellulcar carcinoma: US-guided percutaneous microwave coagulation therapy. Radiology 2001; 221: 167–172.
20. Kuang M, Lu MD, Xie XY, Xu HX, Mo LQ, Liu GJ, et al. Liver cancer: Increased microwave delivery to ablation zone with cooled-shaft antenna: Experimental and clinical studies. Radiology 2007, 242: 914–924.
21. Ebara M, Okabe S, Kita K, Sugiura N, Fukuda H, et al. Percutaneous ethanol injection for small hepatocellular carcinoma: Therapeutic efficacy based on 20-year observation. J Hepatol 2005; 43: 458–464.
22. Livraghi T, Meloni F, Stasi MD, Rolle E, Solbiati L, Tinelli G, et al. Sustained complete response and complications rate after radiofrequency ablation of very early hepatocellulcar carcinoma in cirrhosis: Is resection still the treatment of choice? Hepatology 2008; 47: 82–89.
23. Kojiro M. Focus on dysplastic nodules and early hepatocellular carcinoma: an eastern point of view. Liver Transpl 2004; 10: S3–S8.
24. Livraghi T. Role of Percutaneous ethanol injection in the treatment of hepatocellular Carcinoma. Dig Dis 2001; 19: 292–300.
25. Sasaki Y, Imaoka S, Ishiguro S, Nakano H, Kasugai H, Fujiita M, et al. Clinical features of small hepatocellular carcinoma as assessed by histologic grades. Surgery 1996; 119: 252–260.
26. Okusaka T, Okada S, Ueno H, Ikeda M, Shimada K, Yamamoto J, et al. Satellites lesions in patients with small hepatocellular carcinoma with reference to clinipathologic features. Cancer 22; 95: 1931–1937.
27. Nakashima Y, Nakashima O, Tanaka M, Okuda K, Nakashima M, Kojiro M. Portal invasion and intrahepatic micrometastasis in small hepatocellulcar carcinoma by gross type. Hepatol Res 2003; 26: 142–147.
28. Shimada M, Takenaka K, Gion T, et al. Prognosis of recurrent hepatocellular carcinoma: a 10-year surgical experience in Japan. Gastroenterology 1996; 111:720–726.
29. Choi GH, Kim DH, Kang CM, et al. Prognostic factors and optimal treatment strategy for intrahepatic nodular recurrence after curative resection of hepatocellular carcinoma. Ann Surg Oncol. 2008; 15: 618–629.
30. Yamamoto M, Takasaki K, Otsubo T, Katsugarawa H, Katagiri S, Yshitoshi K, et al. Favorable surgical outcomes in patients with early hepatocellulcar carcinoma. Ann Surg 2004; 239: 395–399.
31. Minagawa M. Ikai I, Matsuyama Y, Yamaoka Y, Makuuchi M. Staging of hepatocellulcar carcinoma assessment of the Japanese TNM and AJCC/UICC TNM system in a cohort of 13,772 patients in Japan. Ann Surg 2007; 245: 909–922.
32. Sangiovanni A, Del Ninno E, Fasani P, De Fazio C, Ronchi G, Romeo R, et al. Increased survival of cirrhotic patients with a hepatocellular carcinoma detected during surveillance. Gastroenterology 2004; 126: 1005–1014.

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ORIGINAL ARTICLE

Biliary Tract Tuberculosis—a Diagnostic Dilemma

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Abstract
Introduction Most western patients who have not had a previous operation and present with biliary obstruction are thought to have a malignant lesion. However in our country where the disease is common, we found that some of these patients had a tuberculous cause which considerably altered their management as well as their prognosis. We herein present our experience of these patients whom we had operated with a preoperative diagnosis of biliary tract malignancy and discuss, retrospectively, how they might have been detected before operation to have tuberculosis.
Methods Between August 1996 and June 2010, we operated on 209 patients with a preoperative diagnosis of carcinoma of the gallbladder and common bile duct. Seven out of these 209 patients had biliary tuberculosis. We retrospectively analyzed the clinical features of these patients from our prospectively maintained database.
Results There were four males and three females who had a mean age of 54 (32–65) years. The bile duct was involved in four and gallbladder in three patients. In contrast to those with malignancy, patients with tuberculosis had a longer history (122 vs 44 days), an abdominal mass was present less frequently (28% vs 57%), the serum bilirubin was lower (1.6 vs 6 mg/dl), and they also had evidence of tuberculosis elsewhere in the body (28.5%). There was no operative mortality in biliary tract tuberculosis in contrast to 7.5% in biliary tract malignancy.
Conclusion Though tuberculosis of the biliary tract is rare, it needs to be considered in the differential diagnosis of patients with biliary obstruction especially in countries where the disease is endemic.

Keywords Bile duct · Gallbladder · Tuberculosis · Carcinoma

Introduction

Most patients with biliary stricture or mass who have not had a previous operation are thought to have a malignant lesion because another diagnosis like isolated biliary tuberculosis (TB) is rare.[1,2] However, in contrast to biliary tract malignancy, biliary TB is almost always curable and has a better outcome. Hence it is important to be aware of the clinical profile of biliary TB, which will help to rule it out in any case of biliary tract malignancy, especially in countries where tuberculosis is endemic. Biliary symptoms can be caused by pericholedochal or portal tuberculous lymphadenitis, lymph nodes fistulating into the common bile duct or biliary stricture due to fibrosis.[3,4] The most common symptoms of biliary tuberculosis including jaundice, abdominal pain, and weight loss are usually indistinguishable from those of cholangiocarcinoma or gallbladder carcinoma.[5,6] Most cases of biliary TB require relief of obstruction and antituberculosis therapy. Surgery is most often required for relief of biliary obstruction.[7] The diagnosis is mostly based on postsurgical histopathological examination showing caseating granuloma and Langhans giant cells.[8,9]

Between 1996 and 2010, we operated on a large number of patients with a preoperative diagnosis of biliary tract

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malignancy, a few of whom turned out to have tuberculosis. In this series, we present our experience of these patients and discuss how they might have been recognized to have tuberculosis preoperatively.

Patients and Methods

Between August 1996 and June 2010, 209 patients were operated for biliary tract malignancy including both carcinoma of the gallbladder and common bile duct in the department of Surgical Gastroenterology and Liver Transplantation at Sir Ganga Ram Hospital, New Delhi (India). Seven out of these 209 patients had biliary tuberculosis. We retrospectively reviewed, from a prospectively collected database, their demographic profile, clinical presentation, routine blood investigations (hemogram, liver and renal function tests) and imaging [ultrasonography (USG), contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreaticography (ERCP)], operative procedures performed, and the outcomes. The diagnosis of biliary TB was based on the presence of at least one of the following: (1) positive acid-fast bacilli stain of the tissue biopsy or biliary tract aspirate, (2) histopathological demonstration of caseating granulomatous necrosis, or (3) positive polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* on tissue biopsy or biliary tract aspirate.[10,11]

Results

Demographic Profile

Out of seven patients, four were male and three were female, and their mean age was 54 years (range 32–65 years).

Sites Involved

Four patients had common bile duct involvement, and three had gall bladder disease. Three patients had associated duodenal involvement; one each had involvement of the liver and pancreas (Table 1).

Clinical Presentation

Jaundice (six of seven) and abdominal pain (four of seven) were the most common presenting symptoms. Constitutional symptoms like fever, weight loss, and anorexia occurred in three patients each. Other symptoms like vomiting, itching, and an abdominal mass were seen in two patients (Table 2).

Table 1 Sites involved

Site involved	No. of patients
Common bile duct	4
Gall bladder	3
Other abdominal organs	
Duodenum	3
Liver	1
Pancreas	1
Systemic	
Pulmonary	1
Generalized lymphadenopathy	1

The mean delay in presentation from the onset of symptoms was 122 days (range 16–240) and did not differ with the site of involvement. One patient with bile duct TB with associated duodenal involvement had duodenal ulcer perforation and presented in the emergency department with jaundice, fever, hematemesis, and generalized lymphadenopathy.

None of the patients had biliary TB in isolation. Other associated sites of abdominal TB were the duodenum (three), liver (one), pancreas (one), and intestine (one). Two patients had systemic involvement, one each with pulmonary TB and generalized lymphadenopathy. The patient with pulmonary TB had hemoptysis and was on antitubercular therapy. Another patient had a childhood history of pulmonary TB with repair of a tracheoesophageal fistula.

The serum bilirubin was elevated in four patients with a median of 1.6 mg/dl (range 0.4–30), and serum alkaline phosphatase was elevated in all patients with a median of 324 IU/l (range 77–2,840). One patient with bile duct TB had a high bilirubin of 30 mg/dl because of a fibrous stricture in the bile duct at the hilum.

Imaging and Diagnostic Procedures

Ultrasonography and CECT abdomen were the commonly used diagnostic modalities (five of seven). The most

Table 2 Clinical characteristics of biliary tract tuberculosis

Clinical presentation	Common bile duct	Gall bladder
Jaundice	4	2
Abdominal pain	1	3
Fever	1	2
Anorexia	1	2
Weight loss	1	2
Vomiting	1	1
Itching	2	0
Abdominal mass	1	1
Hematemesis	1	0

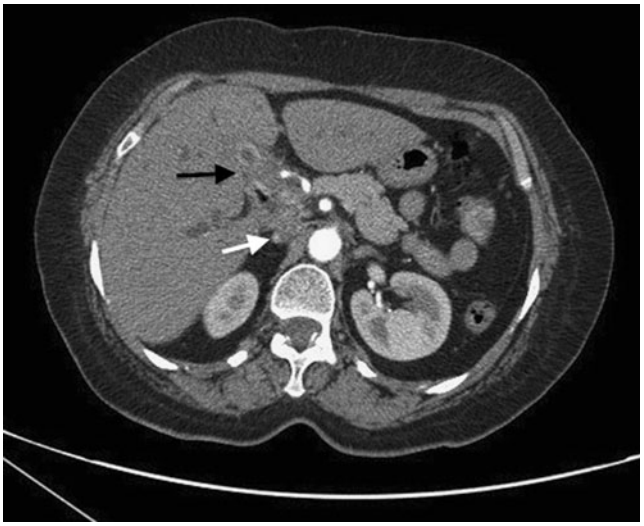

Fig. 1 Computed tomography scan—showing a mass in the gallbladder (*black arrow*) with associated lymphadenopathy (*white arrow*) in a patient with gallbladder tuberculosis

common findings were dilated intrahepatic biliary radicles (four of seven) and a mass lesion at the hilum (two), CBD (one), or gallbladder (one, Fig. 1). Three patients had cholelithiasis. MRCP was the next commonly used diagnostic modality (four of seven), and it showed either a CBD stricture (two of seven) or a mass lesion in the common bile duct (one of seven).

One patient with common bile duct TB who presented with gastric outlet obstruction underwent a barium meal follow through examination which showed duodenal obstruction. ERCP was suggestive of an ampullary ulcer and was provisionally diagnosed to have periampullary carcinoma.

None of the patients were diagnosed to have biliary tuberculosis preoperatively. The preoperative diagnoses were carcinoma of the gall bladder (two), hilar cholangiocarcinoma (two), periampullary carcinoma (one), duodenal perforation (one), or the Mirizzi syndrome (one, Tables 3 and 4). The final diagnosis was based on the postoperative histopathological examination showing caseating granulomata (Fig. 2).

Management and Outcomes

Cholecystectomy (five of seven) and hepaticojejunostomy (four of seven) were the most commonly performed procedures. T-tube drainage was done in all patients undergoing hepaticojejunostomy according to our unit protocol. Gastrojejunostomy was performed in four patients, following duodenal repair in two patients and for duodenal obstruction in two patients. Cholecystostomy was performed in one patient who was suspected to have locally advanced gallbladder carcinoma with hilar infiltration with a raised bilirubin (10 mg/dl) and cholangitis. Another

Table 3 Clinical characteristics of patients with common bile duct TB

Age	48/M	63/M	32/M	59/M
Comorbidities	Nil	DM, HT	Nil	Nil
Symptoms[a]	2, 4, 5, 9	1, 2, 3	2, 3, 6, 7, 8	2
Duration (days)	210	16	30	90
Past H/o TB	Nil	Nil	Yes	Yes
Other organs involved	Duodenum, generalized lymphadenopathy	Pancreas	Nil	Intestine
Serum total bilirubin	5.8	1.0	30	1.6
Investigations USG	Not done	Dilated IHBR	Dilated IHBR	CBD calculi
CECT	Not done	Mass distal CBD	Mass at confluence	CBD calculi
MRI	Not done	Not done	Mass at confluence	Type IV hilar cholangiocarcinoma
Preoperative diagnosis	Duodenal ulcer perforation	Periampullary carcinoma	Hilar cholangiocarcinoma	Hilar cholangiocarcinoma
Perioperative findings	D II perforation, retroperitoneal hematoma, pericholedochal and para-aortic lymphadenopathy	Mass head of pancreas, mesenteric lymphadenopathy	Firm mass at the hilum	Stricture in CHD 2 cm from confluence, stones in RHD, duodenum and colon stuck to liver
Procedure	Perforation closure, GJ, FJ	Cholecystectomy, HJ	Cholecystectomy, HJ	Cholecystectomy, HJ
Mortality	Nil	Nil	Nil	Nil
Priority	Emergency	Elective	Elective	Elective

M male, *F* female, *DM* diabetes mellitus, *HT* hypertension, *IHBR* intrahepatic biliary radicles, *CBD* common bile duct, *USG* ultrasonography, *CECT* contrast-enhanced computed tomography, *MRI* magnetic resonance imaging, *HJ* hepaticojejunostomy, *GJ* gastrojejunostomy, *FJ* feeding jejunostomy

[a] 1—abdominal pain, 2—jaundice, 3—itching, 4—fever, 5—vomiting, 6—anorexia, 7—weight loss, 8—abdominal mass, 9—hematemesis

Table 4 Clinical characteristics of patients with gall bladder tuberculosis

Age/sex	52/M	65/F	64/F
Comorbidities	Nil	DM	DM
Symptoms[a]	1, 2, 6, 7, 8	1, 4, 6, 7	1, 2, 4, 5
Duration (days)	240	210	60
Past H/o TB	Nil	Nil	Nil
Serum total bilirubin	9.9	0.8	0.4
Other organs involved	Pulmonary	Duodenum	Duodenum, liver
Investigations USG	Dilated IHBR	Hypoechoic lesion GB with calculi	Thickened GB
CECT	Dilated IHBR, Mass near porta encasing PV, HA	Irregular GB wall thickening	Not done
MRI	Stricture CHD	Not done	Calculous cholecystitis
Preoperative diagnosis	GB carcinoma	Mirrizzi type II	GB carcinoma with duodenal obstruction
Perioperative findings	Firm mass GB neck infiltrating PV with thrombosis	Contracted GB with calculi; Mirrizzi type II with cholecystoduodenal fistula	Thickened GB, dilated stomach, multiple liver nodules
Procedure	GB biopsy, cholecystostomy, GJ	Cholecystectomy, duodenal repair, GJ	Cholecystectomy, HJ, GJ, JJ
Mortality	Nil	Nil	Nil
Priority	Elective	Elective	Elective

M male, *F* female, *DM* diabetes mellitus, *HT* hypertension, *IHBR* intrahepatic biliary radicles, *GB* gall bladder, *CBD* common bile duct, *USG* ultrasonography, *CECT* contrast-enhanced computed tomography, *MRI* magnetic resonance imaging, *HJ* hepaticojejunostomy, *GJ* gastrojejunostomy, *FJ* feeding jejunostomy, *JJ* jejunojejnostomy, *PV* portal vein, *HA* hepatic artery

[a] 1—abdominal pain, 2—jaundice, 3—itching, 4—fever, 5—vomiting, 6—anorexia, 7—weight loss, 8—abdominal mass, 9—hematemesis

patient with a mass lesion in the head of pancreas and raised CA 19–9 (66 units) was suspected to have a periampullary carcinoma and underwent ERCP and biliary stenting before surgery.

The operative findings were a firm mass in and around the gall bladder (two), common bile duct (one), retroperitoneal hematoma (one), mesenteric lymphadenopathy (one), and mass in the head of the pancreas (one). One patient had a mass encasing the main portal vein with a resulting thrombosis of the vein. Three patients had pericholedochal, para-aortic, or mesenteric lymphadenopathy. Two patients had associated gallbladder calculi, and one had calculi in the right hepatic duct.

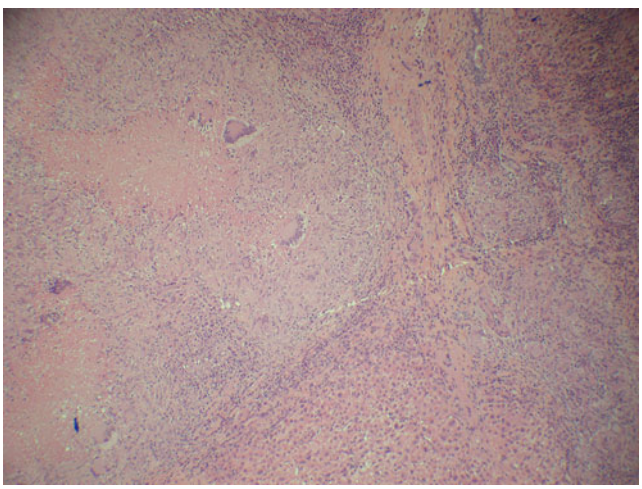

Fig. 2 Histopathological examination—showing caseating granuloma and Langhans giant cell

In the postoperative period, all the patients were started on antitubercular therapy after histopathological confirmation of biliary TB. One patient had collapse consolidation due to a mucus plug on postoperative day 2, which required bronchoscopy and removal. One patient with a cholecystostomy had prolonged peridrain leakage which gradually reduced and stopped with antitubercular therapy. One patient had a feeding jejunostomy site leak and was managed conservatively. One patient had a hepaticojejunostomy anastomotic site stricture for which percutaneous balloon dilatation was done (Fig. 3). There was no postoperative mortality.

Discussion

Abdominal TB is usually a primary gastrointestinal disease, and active pulmonary TB has been reported in only a minority (6–38%) of these cases.[12,13] Biliary involvement is extremely rare in abdominal TB. The clinical presentation of biliary TB is slow and insidious, and it is usually indistinguishable from malignancy. The most common symptoms are abdominal pain, jaundice, malaise, anorexia,

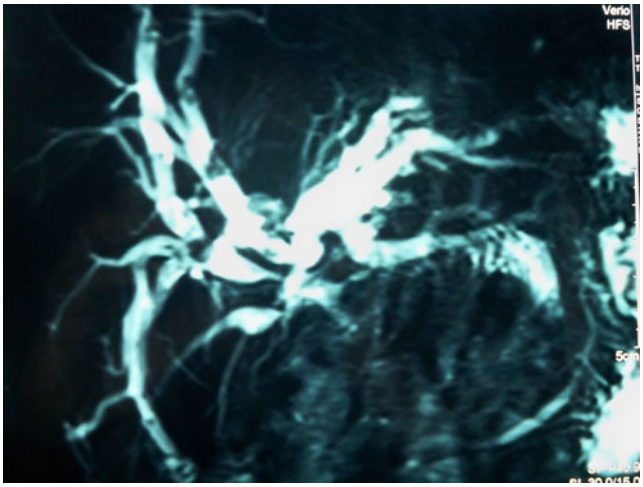

Fig. 3 MRCP scan—showing hepaticojejunostomy site stricture with dilated IHBR in a follow-up case of bile duct tuberculosis

weight loss, and fever.[14] In concordance with the study by Saluja et al. and Chong et al., we also found the most common symptoms to be jaundice (85%) and abdominal pain (57%) followed by nonspecific symptoms like fever, weight loss, and anorexia (43%).[15,16] This is in contrast to a study by Amarapurkar et al., where fever and weight loss were the commonest presenting symptoms[1] (Table 5). The mean delay in presentation was longer in biliary tract tuberculosis than malignancy (122 vs 44 days).

From a previous study in our institution on biliary tract malignancy, 57% of patients presented with an abdominal mass.[17] In the presence of abdominal mass and jaundice, almost 88% of the patients had advanced carcinoma, i.e., beyond stage III.[17] But in the present study, only 28% of patients with biliary TB had an abdominal mass and most of them presented with abdominal pain. The bilirubin levels as in other benign conditions are usually not as high as they are in those with malignant obstruction. The median serum bilirubin in biliary TB according to this study was 1.6 mg/dl compared to 6.0 mg/dl (range 0.2–29.3) and 14 mg/dl (range 3.0–31) in cases of carcinoma gallbladder and cholangiocarcinoma respectively in our previous report.[17] In this study 42.8% of the patients had bile duct obstruction due to lymphadenopathy, similar to 35% and 36.8% in studies by Alvarez and Amarapurkar et al. respectively.[1,2]

Stemmerman et al. in an autopsy series of 1,500 cases of TB reported a 3% incidence of biliary TB and Kok et al., from Brunei, in a 10-year study period described four cases of biliary TB.[18,19] Biliary TB occurs from three routes of spread: (1) descending infection from the portal tracts into the bile ducts which is the most common, (2) tuberculous periportal lymphadenitis, and (3) ascending infection through the ampulla of Vater.[2] The symptoms in biliary TB can be due to (1) primary TB involving the biliary tract causing strictures, (2) cholangitis due to rupture of caseating granulomas into the bile duct, (3) compression related to periportal, pericholedochal or peripancreatic tuberculous adenitis, (4) posttreatment stricture after antitubercular therapy, or (5) compression due to pseudotumor.[1]

The diagnostic modalities like ultrasonography, computed tomography, ERCP, and MRCP are all useful in evaluating these patients with biliary tuberculosis, but they are seldom pathognomonic of the condition.[15] Alvarez and Sollano et al. published the characteristic cholangiographic features of biliary TB like (1) pruning of the distal intrahepatic ducts, (2) tight hilar strictures with dilated IHBR, (3) long smooth stricture of the distal bile duct, and (4) sclerosing cholangitis-like changes.[2] Even with the clinical and cholangiographic features of biliary TB, it is usually difficult to differentiate it from cholangiocarcinoma or gallbladder carcinoma.

Isolated biliary TB is rare. In our study two patients had systemic disease, one with pulmonary and the other with generalized lymphadenopathy constituting about 28.5%, similar to 28.9% by Amarapurkar et al.[1] Another patient had a history of pulmonary tuberculosis in childhood. One patient also had intestinal TB and was on antitubercular therapy. Other abdominal sites like the liver and pancreas were involved in one each of the patients in this series. Hence the associated tuberculosis infection of other sites and past history of TB should provide a clue to the diagnosis of biliary TB.

Most of the reported cases of biliary TB were diagnosed after surgery with histopathological findings

Table 5 Review of literature

Author	*N*	Symptoms	Time delay in presentation (days)	Serum bilirubin (mg/dl)	Other organ involvement	Preop diagnosis of TB
Present study	7	Jaundice, abdominal pain	122 (16–240)	1.6 (0.4–30)	5 (71%)	0
Saluja et al.	9	Abdominal pain, jaundice	140 (14–720)	5.8 (0.5–25.4)	5 (55.5%)	1
Amarapurkar et al.	15	Fever and weight loss	105 (75–135)	2.4	4 (27%)	–
Kok et al.	4	Jaundice	–	–	–	–
Chong et al.	–	Jaundice, abdominal pain	–	–	–	–

of caseating granuloma and Langhans giant cells.[8,9] In this series biliary TB was diagnosed in all patients after the operation, and the common preoperative diagnosis was that of bile duct or gallbladder malignancy (5/7). In contrast with 7.5% operative mortality in biliary tract malignancy, there was no operative mortality in tuberculosis in this study.[17] In previous studies even FDG-PET scanning has not been shown to be useful in differentiating TB from malignancy.[15] Other modalities like USG or CT-guided FNAC of the enlarged lymph nodes can be useful in diagnosis. Though the yield is only 0–10%, some cases can be diagnosed by acid-fast bacilli staining or culture of the biliary fluid aspirate during ERCP.[20,21] PCR testing of the bile aspirate or ERCP brushings for *M. tuberculosis* is extremely sensitive and should probably be used more commonly.[22,23]

In most of the cases reported, the biliary stricture did not resolve with medical therapy alone and usually required biliary metallic stent placement or surgical intervention.[20,22] A fibrotic reaction during antituberculosis therapy leading to worsening of jaundice has been reported in 6–25% of patients.[24,25]

Summary

Biliary TB closely mimics malignancy. Hence even though it is a rare entity, it should be considered in the differential diagnosis of biliary tract carcinomas, especially in areas where tuberculosis is highly prevalent. The factors like (1) a past history of TB, (2) other systemic manifestations like pulmonary or generalized lymph node involvement, (3) associated involvement of other abdominal organs, (4) mild jaundice, (5) abdominal pain more than an abdominal mass, (6) image-guided FNAC or biopsy in suspected cases, and (7) the geographic area where the patient resides might help in differentiating biliary tuberculosis from biliary tract malignancy. We suggest that for the preoperative diagnosis of biliary tuberculosis, PCR testing of bile aspirate being more sensitive might be used more extensively, especially in patients who present with these clinical features.

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References

1. Amarapurkar DN, Patel ND, Amarapurkar AD. Hepatobiliary tuberculosis in western India. Indian J Pathol Microbiol 2008;51:175–181.
2. Alvarez SZ, carpio R. Hepatobiliary tuberculosis. Dig Dis Sci 1983;28:193–200.
3. Maher D, Chaulet P, Spinaci S, Harries A. Treatment of tuberculosis: Guidelines for national programs. WHO Global tuberculosis program. WHO/TB/97;220.
4. Leder RA, Low VHS. Tuberculosis of the abdomen. Radiol Clin N Am 1995;33:691–705.
5. Yeh TS, Chen NH, Jan YY, Hwang TL, Jeng LB, Chen MF. Obstructive jaundice caused by biliary tuberculosis: Spectrum of the diagnosis and management. Gastrointest Endosc 1999;50:105–108.
6. Murphy TF, Gray GF. Biliary tract obstruction due to tuberculous adenitis. Am J Med 1980; 68:452–454.
7. Miyamoto S, Furuse J, Maru Y, Tajiri H, Muto M, Yoshino M. Duodenal tuberculosis with a choledocho-duodenal fistula. J Gastroenterol Hepatol 2001; 16:235–238.
8. Behera A, Kochhar R, Dhavan S, Aggarwal S, Singh K. Isolated common bile duct tuberculosis mimicking malignant obstruction. Am J Gastroenterol 1997;92: 2122–2123.
9. Fan ST, Ng IO, Choi TK, Lai EC. Tuberculosis of the bile duct: a rare cause of biliary stricture. Am J Gastroenterol 1989;84:413–414.
10. Khosla SN, Chhabra HK, Mehrotra GC. Liver in abdominal tuberculosis. J Assoc Physicians India 1986;34:501–502.
11. Maharaj B, Leary WP, Pudifin DJ. A prospective study of hepatic tuberculosis in 41 black patients. Q J Med 1987;63:517–522.
12. Chen CH, Yang CC, Yeh YH, et al. Pancreatic tuberculosis with obstructive jaundice—a case report. Am J Gastroenterol 1999;94 (9):2534–2536.
13. Hulnick DH, Megibow AJ, Naidich DP, et al. Abdominal tuberculosis: CT evaluation. Radiology 1985;157(1):199–204.
14. Bhansali SK. Abdominal tuberculosis. Experiences with 300 cases. Am J Gastroenterol 1977; 67(4):324–337.
15. Saluja SS, Ray S, Pal S, et al. Hepatobiliary and pancreatic tuberculosis: a two decade experience. BMC Surg 2007; 7:10.
16. Chong VH, Lim KS. Hepatobiliary tuberculosis. Singapore Med J 2010;51(9):744–751.
17. Varma V, Gupta S, Soin AS, Nundy. Does the presence of jaundice and/or a lump in a patient with gall bladder cancer mean that the lesion is not resectable? Dig Surg 2009;26:306–311.
18. Stemmerman M. Bile duct tuberculosis. Q Bull Sea View Hosp 1941;6:316–24.
19. Kok KY, Yap SK. Tuberculosis of the bile duct: a rare cause of obstructive jaundice. J Clin Gastroenterol 1999;29:161–164.
20. Bearer EA, Savides TJ, McCutchan JA. Endoscopic diagnosis and management of hepatobiliary tuberculosis. Am J Gastroenterol 1996;91:2602–2604.
21. Alcantara-Payawal DE, Matsumura M, Shiratori Y, Okudaira T, Sollano JD, Omata M. Direct detection of *Mycobacterium tuberculosis* using polymerase chain reaction assay among patients with hepatic granuloma. J Hepatol 1997;27: 620–627.
22. Inal M, Aksungur E, Akgul E, Demirbas O, Oguz M, Erkocak E. Biliary tuberculosis mimicking cholangiocarcinoma: treatment with metallic biliary endoprothesis. Am J Gastroenterol 2000;95:1069–1071.
23. Mallery JS, Centeno BA, Hahn PF, Chang Y, Warshaw AL, Brugge WR. Pancreatic tissue sampling guided by EUS, CT/US, and surgery: a comparison of sensitivity and specificity. Gastrointest Endosc 2002;56:218–224.
24. Breen RA, Smith CJ, Bettinson H, et al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. Thorax 2004;59:704–707.
25. Cheng VC, Ho PL, Lee RA, et al. Clinical spectrum of paradoxical deterioration during antituberculosis therapy in non-HIV-infected patients. Eur J Clin Microbiol Infect Dis 2002;21:803–809.

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ORIGINAL ARTICLE

Zinc and Copper Serum Levels of Morbidly Obese Patients Before and After Biliopancreatic Diversion: 4 Years of Follow-up

Daniel A. de Luis · David Pacheco · Olatz Izaola · Maria Concepcion Terroba · Luis Cuellar · Tomas Martin

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Abstract
Background Zinc and copper are two essential trace elements. However, few studies have been conducted specifically to investigate these deficiencies in patients who underwent bariatric surgery. The aim of our work was to describe the influence of biliopancreatic diversion (BPD) on serum copper and zinc levels during 4 years.
Methods We have analyzed a consecutive series of 65 patients who have been followed-up for 4 years after undergoing open BPD.
Results The final (4 years) initial excess weight percent loss was 63.5%. A significant improvement of BMI, weight, waist circumference, and fat mass was detected. The preoperative average zinc (42.2±53.2 μg/dl) and copper (61.3±58.6 μg/dl) levels are under the lower limit of the normal values. These data show a deficient micronutrient status in morbidly obese patients, 73.8% of patients had low basal zinc values and 67.8% low basal copper values. Values of both micronutrients at different times (6 months, 1, 2, 3, and 4 years) were lower than basal value.
Conclusion BPD is an effective method of sustainable weight loss. Otherwise, a high prevalence of zinc and copper basal deficiencies in morbidly obese seeking bariatric surgery was detected. These deficiencies of copper and zinc increased during the 4 years of follow-up after BDP.

Keywords Biliopancreatic diversion · Copper · Morbid obesity · Zinc

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Introduction

Obesity, specifically severe obesity, markedly lessens life expectancy, especially among younger adults.[1] Bariatric surgery is the most effective long-term treatment for morbid obesity, reducing obesity-associated comorbidities. Biliopancreatic diversion (BPD)[2,3] is a mixed and complex operation that has shown good long-term results regarding weight loss. It is well-known that as complexity increases in bariatric surgery, effectiveness also increases, but risk of secondary effects and potential complications, likewise, may increase. The severity of the postoperative nutritional deficit is dependent on several factors, including the preoperative nutritional status, the type of bariatric procedure performed, the occurrence of postoperative complications, the ability to modify eating behavior, and compliance with regular follow-up and prescribed vitamin and mineral supplementation.

Zinc and copper are two essential trace elements. Zinc is a component of the catalytic site of more than 300

Table 1 Preoperative characteristics of the patients

Gender (women/men)	55/10
Age (years)	42.4±10.2
BMI (kg/m^2)	47.8±6.4
Weight (kg)	126.5±22.2

BMI body mass index

metalloenzymes, and more than 2,000 transcription factors that work to regulate gene expression require zinc to maintain their structural integrity and bind to DNA.[4] Severe zinc deficiency has been shown to increase susceptibility to infection as well as to affect different organ systems, including the gastrointestinal, skeletal, and reproductive systems.[4] Although zinc deficiency is common after bariatric surgery, it has not been shown to be clinically relevant to date.

Copper is used as a catalytic cofactor for a variety of metalloenzymes involved in many processes as pigmentation (tyrosinase), energy generation (cytochrome c oxidase), and free radical scavenging (superoxide dismutase), and in central nervous system functioning.[5] Copper deficiency has been shown to cause hematological and neurological disorders, and many of these cases have been described in the setting of derivative bariatric surgery.[6] However, few studies have been conducted specifically to investigate these deficiencies in patients who underwent bariatric surgery. Comminetti et al.[7] evaluated zinc deficiency in patients after Roux-en-Y gastric bypass, Madan et al.[8] studied zinc deficiency in patients after laparoscopic bypass, and Balsa et al.[9] evaluated zinc and copper deficiencies after gastric bypass and BPD.

According to these previous data of the association of copper and zinc deficiency with bariatric surgery and the limited long-term data on their incidence,[7–10] we realized the present study with the aim of evaluating the influence of BPD on serum copper and zinc levels during 4 years.

Subjects and Methods

Patients and Surgical Technique

We analyzed restrospectively 65 consecutive morbidly obese patients (BMI >40) who were operated upon from December 2002 to December 2008. These patients were followed-up for 4 years after undergoing open BPD by the Scopinaro technique. At our institution, the main characteristics of BPD were a 200- to 250-ml gastric pounch, a 200-cm alimentary limb, and a 70-cm common limb. Intestinal limbs were measured during the surgery with a sterile tape measure.

Follow-up visits were carried out at set intervals (6 months, 1, 2, 3, and 4 years). The following variables were specifically recorded: age, weight, body mass index (BMI), waist circumference, and fat mass. Copper and zinc blood levels were measured at basal visit and at each visit.

All enrolled patients received instruction to reach a daily dietary intake of 70 g of protein per day and 30 kcal/kg of ideal weight. All patients received two tablets of a multivitamin supplement containing 15 mg of elemental zinc and 2 mg of elemental copper each tablet, total daily amount (30 mg of elemental zinc and 4 mg of elemental copper).

Biochemical Assays and Anthropometric Measurements

Copper (reference, 80–155 μg/dL) and zinc (60–150 μg/dL) were measured by spectophometry (Varian, Inc. Corporate Headquaters, NY, USA).

Body weight was measured to an accuracy of 0.1 kg and BMI computed as body weight/(height^2). Waist circumference was measured at narrowest diameter between xiphoid process and iliac crest. Tetrapolar body electrical bioimpedance was used to determine fat mass (Biodynamics Model 310e, Seattle, WA, USA).

Table 2 Anthropometric parameters along the follow-up

Characteristics	Basal time	6 months	1 year	2 years	3 years	4 years
BMI(kg/m^2)	47.8±6.4	43.9±18.4*	36.7±6.1*	34.8±7.2*	32.9±6.5*	32.5±7.4*
Weight (kg)	126.5±22.2	108.9±20*	93.6±14.1*	87.4±17.4*	85.2±18.8*	81.1±17.2*
WC(cm)	132.9±20.3	113.5±17.3*	104.6±11.5*	99.2±11.8*	97.9±12.6*	97.2±13.4*
Fat mass (kg)	51.1±11.6	49.0±10.2*	38.2±13.8*	34.5±13.7*	34.4±12*	34.6±5.2*
IEWL%	–	25.24	43.4	60.1	61.2	63.5

WC waist circumference, *IEWL%* initial excess weight percent loss

*$p<0.05$ to basal data

Table 3 Serum zinc and copper levels along the follow-up

Characteristics	Basal time	6 months	1 year	2 years	3 years	4 years
Zinc(μg/dL)	42.2±53.2	25.3±36.2*	19.8±25.9*	18.7±28.4*	18.8±33.2*	9.8±4.9*
Copper (μg/dL)	61.3±58.6	45.8±55.3*	30.6±37.8*	33.5±42.4*	26.3±35.4*	17.3±4.6*

*$p<0.05$ to basal data

Statistical Analysis

SPSS software program (SPSS 15.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Quantitative variables are expressed as mean±standard deviation. The distribution of continuous variables was analyzed with Kolmogorov–Smirnov statistics. Quantitative variables with normal distribution were analyzed with a two-tailed, paired Student's *t* test. Non-parametric variables were analyzed with the Mann–Whitney *U* test. Differences in serum zinc and copper levels along the follow-up were analyzed using repeat measures analysis of variance. Qualitative variables were analyzed with the chi-square test, with Yates correction as necessary, and Fisher's test. Pearson's test was used to correlation analysis. A *p* value under 0.05 was considered statistically significant.

Results

The preoperative characteristics of the patients are shown in Table 1. Initial perceptual excess weight loss (IEW%L) is shown in Table 2, with a significant BMI, weight, waist circumference, and fat mass improvement. All parameters were significantly different from basal values. The final initial excess weight percent loss was 63.5%.

Table 3 shows modifications of zinc and copper levels. The preoperative average zinc (42.2±53.2 μg/dl) and copper (61.3±58.6 μg/dl) levels are under the lower limit of the normal values. These data show a deficient micronutrient status in morbidly obese patients; 73.8% of patients had low basal zinc values and 67.8% low basal copper values.

Although the adherence of mineral supplementation was 100%, levels of zinc and copper decrease during follow-up. Values of both micronutrients at different times (6 months, 1, 2, 3, and 4 years) were lower than basal value.

Table 4 shows the percentage of patients with low serum status of zinc and copper. Prevalence of zinc and copper deficiency increased during the follow-up.

Correlation analysis between basal micronutrient levels or decrease of micronutrient levels and BMI or decrease of BMI did not show statistical association.

Discussion

Our results show a significant loss of body weight, fat mass, and waist circumference in patients having undergone BPD. However, blood levels of zinc and copper decreased during the follow-up, and our results indicate a high prevalence of basal zinc and copper deficiencies.

Loss of weight in our patients was important amounting to 25.4% at 6 months and 63.5% at 4 years of follow-up. IEW%L after 4 years was 70% in other studies[11] and 77% in the 12th year in Scopinaro's patients.[2]

Serum basal deficiencies of copper and zinc could be explained with the fact if the accumulation of adipose tissue increases the production of cortisol and adipocytokines, which produces chronic inflammatory process, the inflammation induces the expression of metallothionein and zinc–copper transporter in hepatocytes, and these proteins promote the metal accumulation in the liver and in adipocites, which may have contributed to low zinc and copper concentrations.[12,13] However, serum zinc concentrations varied in different studies of morbid obese patients and in some of them serum concentrations did not correlate with weight before surgery.[14–16]

Ours results agree with previous studies showing a decrease in serum zinc and copper concentrations post-surgery. Deficiencies of zinc and copper are common after BPD.[7–9,17,18] Our study showed an increased incidence of both deficiencies, although patients were taking 30 mg/day of zinc and 4 mg/day of copper with a multivitamin–mineral supplement. Copper absorption seemed to be predominant in the proximal small bowel[19] and zinc is also absorbed in the small intestine, primarily in the jejunum.[20] Our findings are in agreement with these data as the prevalence of copper and zinc deficiency was larger in our patients treated with BPD. This procedure excludes the duodenum and all jejunum from the alimentary limb.

Our patients had no clinical problems secondary to neurological deficits or hematological problems, although the copper and zinc deficiencies remained along the 4 years of follow-up. Perhaps, this follow-up of 4 years is short to detect these clinical problems and deficits above 11 years

Table 4 Percentage of patients with low serum zinc and copper levels

Characteristics	Basal time	6 months	1 year	2 years	3 years	4 years
Zinc (<60 μg/dL)	73.8%	73.8%*	86.1%*	86.1%*	90.7%*	90.7%*
Copper (<80 μg/dL)	67.8%	76.9%*	76.9%*	87.7%*	87.7%*	90.7%*

*$p<0.05$ to basal data

are needed to develop neurological and hematological deficits.[21]

Current zinc and copper dietary reference intakes are 11 and 0.9 mg/day, respectively. A limitation of our study is the lack of dietary control, although these requirements are achieved when a multivitamin tablet is taken on a daily regimen after bariatric surgery. This recommendation is realized by AACE guidelines.[22] These guidelines do not indicate a specific mineral supplementation and also indicate that minerals should be tested annually after malabsorptive surgery. An empirical zinc supplementation of an additional 200% dietary recommendation has been suggested after malabsorptive bariatric techniques.[23] However, an additional 400% of zinc and copper was given in our study and normal serum levels were not achieved during the follow-up. Perhaps, higher doses are necessary to restore normal serum mineral levels in BPD patients.

Limitations of our study are the retrospective design with potential bias the technique to measure zinc and copper, which could be influenced by hypoalbuminemia.[24]

In conclusion, BPD is an effective method of sustainable weight loss. Otherwise, a high prevalence of zinc and copper basal deficiencies in morbidly obese seeking bariatric surgery was detected. Although, a standard multivitamin supplementation approach was realized in all patients, the deficiencies of copper and zinc increased during the 4 years of follow-up. Proper monitoring of mineral status and other additional supplementation must be investigated.

References

1. Fontaine KR, Redden DT, Wang C, Westfal AO, ALlison DB. Years of life lost due to obesity. JAMA 2003;289:187–193
2. Scopinaro N, Adami GF, Marinari GM: Biliopancreatic diversión. World J Surg 1998;22:936–946
3. Scopinaro N, Giannetta E, Adami GF. Biliopancreatic diversion for obesity at eighteen years. Surgery 1996;119:261–268.
4. Tuerk MJ, Fazel N. Zinc deficiency. Curr Opin Gastroenterol. 2009;25:136–43.
5. Arredondo M, Nunez MT. Iron and copper metabolism. Mol Aspects Med. 2005;26:313–27
6. Jaiser SR, Winston GP. Copper deficiency myelopathy. J Neurol. 2010;257:869–81
7. Cominetti C, Garrido A, Franciscato Zozzolino MF. Zinc nutritional status of morbidly obese patients before and after Roux-en-Y Gastric Byapss: A preliminary report. Obes Surg 2006;16:448–453
8. Madan A, Orth W, Tichansky DS, Ternovits CA. Vitamina d Trace mineral levels after laparoscopic gastric bypass. Obes Sur 2006;16:603–606.
9. Balsa J, Botella J, Gomez Martin J, Peromingo R, Arrieta F, Santiuste C, Zamarron I, Vazquez C. Copper and zinc serum levels after derivate bariatric surgery: differences beteen roux en Y castric bypass and biliopancreatic diversion. Obes Surg 2011;21:744–750.
10. Klevay LM. Bariatric surgery and the assessment of copper and zinc nutriture. Obes Surg. 2010;20:672–3.
11. Elia M, Arribas D, Gracia JA, Artigas C, Jimenez A, Bielsa MA. Results of biliopancreatic diversion after five years. Obesity Surgery 2004;766–772
12. Liuzzi JP, Lichten LA, Rivera S, Blanchard RK, Aydemir TB, Knutson MD et al. Interleukin-6 regulates the zinc transporter Zip-14 in liver and contributes to the hypozincemia in the acute-phase response. Proc Natl Acad Sci 2005; 102: 6843–48.
13. Kim JR, Ryu HH, Chung HJ, Lee JH, Kim SW, Kwun WH et al. Association of anti-obesity activity of N-acetylcysteine with metallothionein-II down-regulation. Exp Mol Med 2006; 38: 162–72.
14. Schroeder JJ, Cousins RJ. Interleukin 6 regulates metallothionein gene expression and zinc metabolism in hepatocyte monolayer cultures. Proc Natl Acad Sci 1990; 87: 3137–41.
15. Hashim Z, Woodhouse L, King JC. Interindividual variation in circulating zinc concentrations among healthy adult men and women. Int J Food Sci Nutr. 1996;47:383–90.
16. Hyun TH, Barrett-Connor E, Milne DB. Zinc intakes and plasma concentrations in men with osteoporosis: the Rancho Bernardo Study. Am J Clin Nutr. 2004;80:715–21
17. Newbury L, Dolan K, Hatzifotis M. Calcium and vitamin D depletion and elevated parathyroid hormone following biliopancreatic diversion. Obs Surg 2003;13:893–895
18. Hatizifotis M, Dolan K, newbury L. Symptomatic vitamin A deficiency following biliopancreatic diversion. Obes Surg 2003:13:655–657
19. Sternlieb I, Janowitz HD. Absorption of copper in malabsorption syndrome. J Clin Invest. 1964;43:1049–55.
20. Lee HH, Prasad AS, Brewer GJ, et al. Zinc absorption in human small intestine. Am J Physiol. 1989;256:G87–91.
21. Prasad AS. Zinc deficiency. BMJ. 2003;326:409–10
22. Mechanick JI, Kushner RF, Sugerman HJ, et al. American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic and Bariatric Surgery Medical Guidelines for Clinical Practice for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient. Endocr Pract. 2008;14:1–83
23. Pournaras DJ, Le Roux CW. After bariatric surgery, what vitamins should be measured and what supplements should be given? Clin Endocrinol. 2009;71:322–5.
24. Hess SY, Peerson JM, King JC. Use of serum zinc concentration as an indicator of population zinc status. Food Nutr Bull 2007;28: S403–S29

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Robotic Single-Port Cholecystectomy Using a New Platform: Initial Clinical Experience

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Abstract
Background The technique of single-port laparoscopy was developed over the past years in an attempt to reduce the invasiveness of surgery. A reduction of incisions and their overall size might result in enhanced postoperative cosmesis and potentially reduce pain when compared to conventional techniques. While manual single-port laparoscopy is technically challenging, a newly approved robotic platform used with the da Vinci Si System (Intuitive Surgical, Sunnyvale, CA, USA) might overcome some of the difficulties of this technique.
Methods Patients with cholelithiasis were scheduled for robotic single-port cholecystectomy in an initial clinical trial. Demographic data, intra- and short-term postoperative results were assessed prospectively.
Results Twenty-eight patients (22 females/6 males; median age, 48 years) underwent robotic single-port cholecystectomy in our first week of clinical cases. Median OR time was 80 min with a median docking time of 8 min and median robotic console time of 53 min. Two patients underwent intraoperative cholangiography. Eight cases presented with adhesions, tissue alterations, or anatomical abnormalities. No conversions, intra- or postoperative complications occurred.
Conclusion Robotic single-port cholecystectomy appears feasible and safe in our early experience. The robotic approach to single-port surgery seems to overcome some of the technical difficulties of manual single-port surgery. This robotic platform may facilitate completion of more complex cases.

Keywords Robotic surgery · Single incision · Laparoendoscopic single site · SILS · Laparoscopy

Introduction

Recently, minimally invasive cholecystectomy underwent a strong development towards less invasive methods such as natural orifice transluminal endoscopic surgery, reduced port, and single-incision surgery.[1–7] Reports of these new methods indicate theoretic improvements in some clinical parameters such as pain, wound-related complications, and cosmetic outcomes.[8–10] Additionally, such less invasive methods seem to find great patient acceptance.[11–13] Among the above-mentioned methods, single-port cholecystectomy appears to be gaining clinical significance with numerous reports in the recent literature.[14–18]

Besides this enthusiasm, single-port cholecystectomy is associated with technical limitations due to the enhanced complexity of the approach and limited number of specialized instruments or platforms.[19] Using conventional laparoscopic instruments for a single-port or single-incision approach leads to collisions and reduction of triangulation. Specific curved or articulated instruments on the other hand add complexity in handling especially when used crossing at the abdominal wall (right hand controls left instrument and vice versa). While instrumentation for manual single-incision surgery continuously improves and standard cases of cholecystectomy seem to be successfully performed, more complex cases, for example high body mass index (BMI) or male patients, are more likely to result in conversions to standard laparoscopy.[20]

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In an attempt to overcome the above-mentioned limitations, a few experimental reports about robotic single-incision laparoscopy can be found in the literature.[21,22] In a couple of studies, authors have used robotic instruments crossing at the level of the abdominal wall and switching robotic arm control to regain dexterity[23,24]. While these reports on the experimental setup were very promising, clinical adoption has been limited.

In the meantime, specific robotic instruments using the same principle have been developed and recently received approval in the European market. These new *da Vinci Single-Site*™ Instruments and Accessories are designed to be used with the da Vinci Si Surgical System (Intuitive Surgical International, Sunnyvale, CA, USA) to perform single-incision laparoscopic surgery. This setup re-creates intuitive control at the surgical console and should therefore facilitate single-incision surgery. We present our early clinical experience that was gathered during a limited product launch after the device received CE mark approval.

Methods

After approval of the new robotic instruments for the European market, initial patients with confirmed cholelithiasis were consented and scheduled for robotic single-incision cholecystectomy under an IRB-approved protocol. The inclusion criteria were patients between 18 and 80 years old with symptomatic cholelithiasis. The exclusion criteria included acute cholecystitis, suspicion of common bile duct stones, pregnant patients, severe lack of cooperation due to psychological or severe systemic illness, or the presence of medical conditions contraindicating general anesthesia or standard surgical approaches. All patients underwent surgery by two different surgeons already experienced in standard single-site surgery (>50 cases) and robotic surgery (>100 cases).

Demographic, intra- and postoperative data were prospectively collected. Case difficulty based solely on underlying disease and anatomy was estimated by the operating surgeon upon completion of cases based on a scale of 1 (very easy) to 10 (most difficult). All the patients were followed up at postoperative day 14 for a clinical visit and at postoperative week 6 with a phone call.

To enable single-incision surgery, curved cannulae (Fig. 1) are placed through a special silicone port, with the curves of the cannulae crossing over each other at the level of the abdominal wall. This allows alignment of the remote center and effectively re-creates triangulation of the instruments. The da Vinci Surgical System automatically switches arm control for ease of instrument control. Available instruments include non-articulating needle driver, atraumatic grasper, right-angle dissector, curved scissors, hook, clip applier, and a suction/irrigator device. The single-site instruments are flexible but not endowristed, and this is their main difference with the standard robotic instruments.

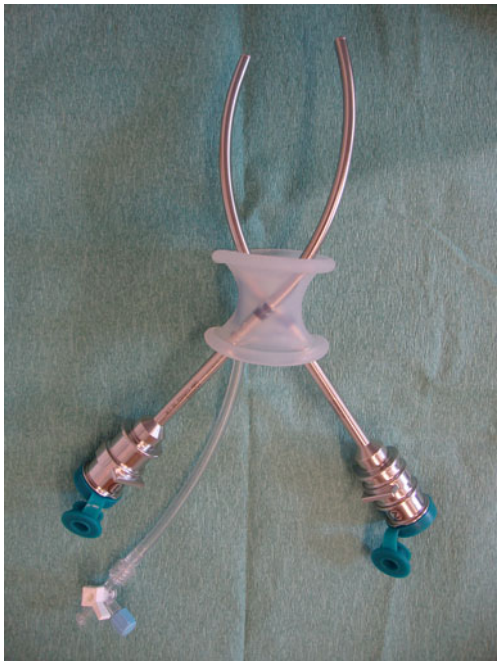

Fig. 1 Curved cannulae

Surgical Procedure

The patients were placed in supine position with the legs apart. A periumbilical skin incision of 2.0–3.5 cm was formed followed by blunt dissection to the abdominal fascia. The abdomen was entered under direct vision and a finger sweep performed to check for adhesions. Using an atraumatic clamp, a specific silicon port was grasped (Fig. 2) and inserted through the previously formed incision (Fig. 3). Insufflation to about 12 mm Hg was installed through the port using a

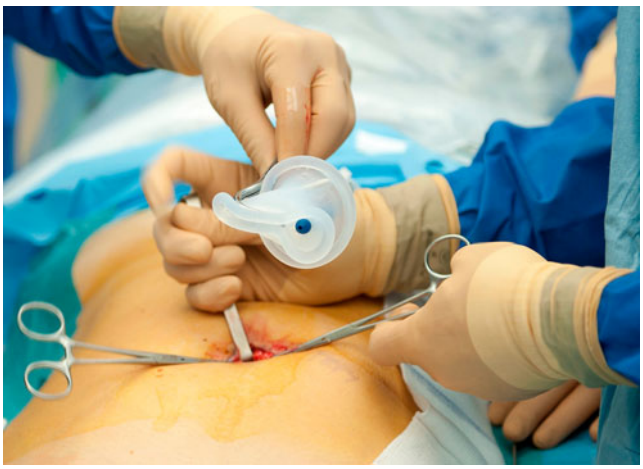

Fig. 2 Intuitive single-incision port before insertion

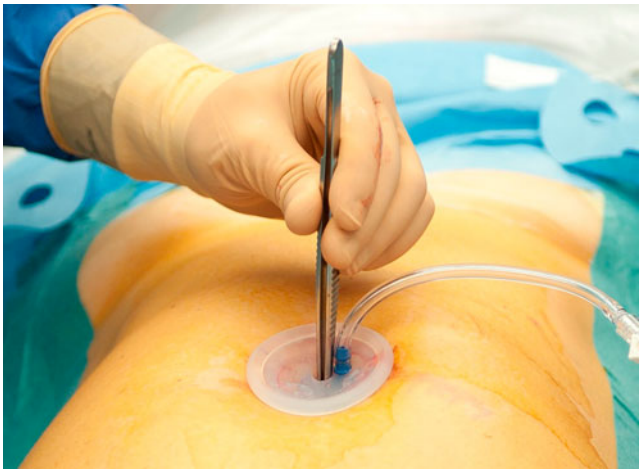

Fig. 3 Intuitive single-incision port placed in a periumbilical incision

conventional laparoscopic insufflator. A straight 8.5-mm trocar for the camera and a 5-mm laparoscopic port were introduced to confirm the operability. The 5-mm port was then removed. The patients were then placed in an 8 to 10° reversed Trendelenburg position with a slight roll to the left. The camera arm was docked to the corresponding trocar and the robotic camera was inserted. Next, curved robotic cannulae were inserted under direct vision. Two arms of the da Vinci surgical system were docked to the cannulae, and flexible robotic instruments were mounted (Fig. 4). The 5-mm assistant's trocar was reinserted. A laparoscopic grasper was used to retract the gallbladder at its fundus in a cephalad direction (Fig. 5). The triangle of Calot was exposed by lateral retraction from the robotic surgeon's left hand. The anatomy was dissected using a robotic cautery hook, and if needed, a robotic Maryland forceps. After clear identification of cystic duct and artery, both structures were clipped with robotic Hem-o-lock clips (Teleflex Medical, Ireland) and transected using robotic scissors. The gallbladder was then

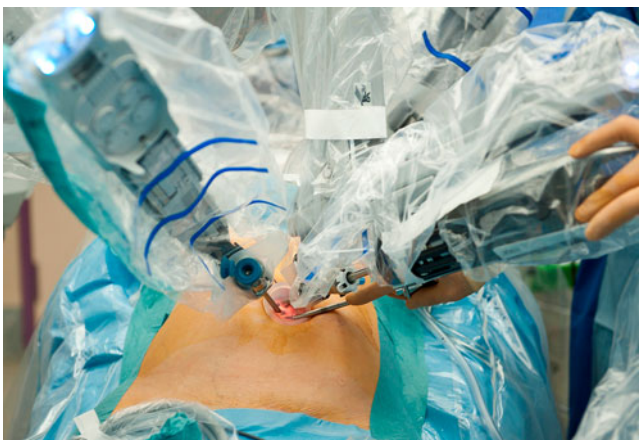

Fig. 4 Insertion of second robotic cannulae

Fig. 5 The da Vinci SP Surgical System during surgery

dissected off the liver bed using the robotic cautery hook and retraction from the robotic as well as the laparoscopic grasper. After completing the dissection, the liver bed was controlled for hemostasis and the surgical field flushed using robotic suction and irrigation. The laparoscopic grasper was removed together with its trocar, and a MemoBag (Teleflex Medical, Ireland) was placed intra-abdominally through the port. The gallbladder was placed inside the bag using the robotic instruments and laparoscopic assistance. The bag was held using a laparoscopic grasper. The robotic instruments and camera were removed and the robot undocked. The robotic trocars were removed, and the port was exteriorized. Lastly, the gallbladder was removed, and the incision was closed in layers.

In the case where cholangiography was needed, this step was performed before complete dissection of the cystic duct. After proximal clipping of the cystic duct, the laparoscopic grasper was removed, and a laparoscopic balloon cholangiocatheter was inserted intra-abdominally. The catheter was placed into the cystic duct, and the balloon was insufflated to secure the correct location. The robotic instruments and camera were removed and the robot re-docked. The robotic arms were moved out of the surgical field. The C-arm was brought to the patient's left side, and cholangiography was performed in the usual fashion. After completion, the C-arm was removed. The balloon of the cholangiocatheter was desufflated to remove the catheter. The da Vinci Surgical System was re-docked and the procedure completed in its standard fashion.

Results

Twenty-eight patients underwent robotic single-incision cholecystectomy as part of this initial case series. Twenty-two patients were female and six were male. The median age was 48 years (range, 28–77). The median body mass

index was 26 kg/m² (range, 18–36). The median ASA score was 2 (range, 1–3).

The median OR time was 80 min (range, 45–195), with a median port placement time of 3 min (range, 1–8), a median docking time of 8 min (range, 1–18), and a median console time of 53 min (range, 23–134). The median estimated blood loss was 5 ml (range, 0–50). The median length of skin incision was 3 cm (range, 2–3.5). The estimated case difficulty was five cases (range, two to eight): eight cases were rated with a difficulty of five or above.

The learning curve of the procedure, with respect to operative time, is summarized in Figs. 6 and 7. Of note, the operative time decreased during the study period as the robot docking time.

Two patients underwent intraoperative cholangiography. No complications associated with this additional step were observed. The cholangiography added an additional 19 min to the operating time including additional robotic docking time. The robotic setup did not interfere with the technique of intraoperative cholangiography.

Concerning the outcomes, no intraoperative complications occurred, and no conversions or additional ports were required. Moreover, no postoperative complications, readmissions, or reoperations were reported.

Discussion

Single-incision and single-port surgery underwent a massive movement over the past years with growing numbers of procedures performed and scientific articles published. It appears that this surgical approach might become a valid method for certain procedures such as cholecystectomy under specific circumstances. While many specific instruments became available on the market to support this new surgical access with camera and multiple instruments through one incision, a recent review of single-incision laparoscopic

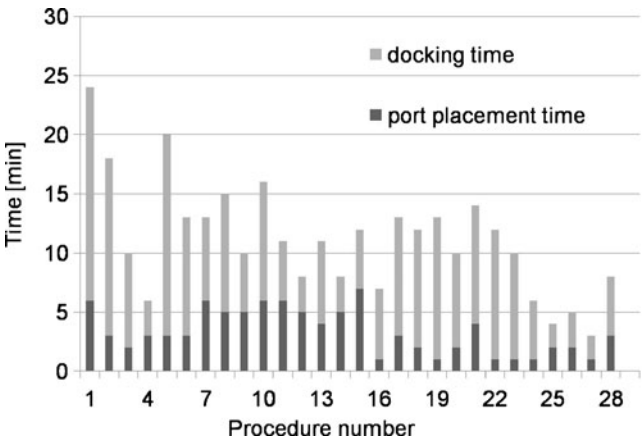

Fig. 6 Learning curve for port placement and robot docking time

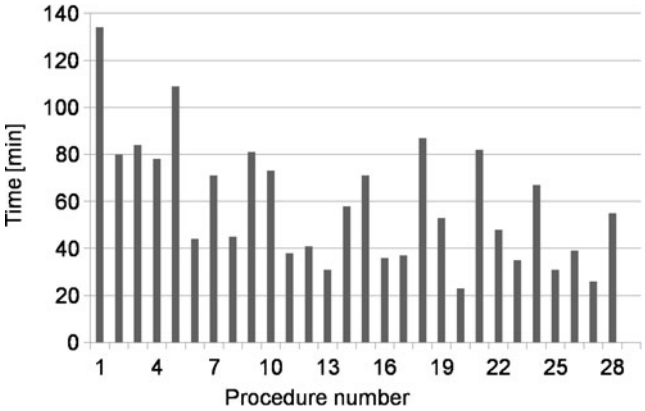

Fig. 7 Learning curve for da Vinci console time

cholecystectomy concluded that instruments still need further improvement.[20] A potential solution to such an improvement might be the robotic technology. The above described new single-site instruments by Intuitive Surgical (Sunnyvale, CA, USA) were only recently approved for the European market. The main difference between the standard robotic approach and the new single-site platform remains the semiflexible instruments with however the loss of endowristed technology. These instruments can be inserted in curved cannulae, allowing for improved triangulation that was not possible to achieve with the rigid straight cannulae.

We present a first series of clinical cases. Our very early experience suggests that robotic single-incision cholecystectomy is feasible and safe using this new platform. Previous literature suggests that conventional single-incision cholecystectomy can lead to a higher conversion rate and longer operative times.[20] Our overall operating times fall well within the available data,[20] but are longer than previously published case series of single-incision cholecystectomy from our institution.[25] We noted that a significant number of relatively difficult cases were encountered in this series (extensive adhesions, post-infectious tissue alterations, atypical anatomy, acute cholecystitis, and higher BMI) and were completed without conversions or complications. We believe that the relative complexity of cases and a certain learning curve regarding system installation and handling are responsible for the longer operative times. Docking times of the system were overall within reason, but still contribute to the length of the cases. Since the docking time already significantly decreased during these initial 28 cases, we are confident that the system can be installed in acceptable times after a few initial cases. In that sense, the last five docking took a median of 4 min. Our console times showed that these complex cases were completed successfully with reasonable surgical times comparable to the literature. Work at the console was very comfortable for the surgeon and surgical dexterity felt restored, especially when compared to manual single-port surgery. We suspect that a number of these complex cases would have been

extremely difficult to be performed with manual single-port laparoscopy, and we would have expected a higher conversion rate. Therefore, we assume after this initial clinical assessment of the da Vinci Single-Site Instruments that it might be an excellent option for complicated cases such as those with acute or chronic cholecystitis, higher BMI, or more advanced single-port procedures. Further clinical trials will have to confirm these potential advantages over manual single-port cholecystectomy, as well as the suitability of the system for other indications and cost-related issues.

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References

1. Swain P, Bagga HS, Su LM. Status of endoscopes and instruments used during NOTES. J Endourol 2009;23:773–780.
2. Swanström LL. Natural orifice transluminal endoscopic surgery. Endoscopy 2009;41:82–85.
3. Bucher P, Pugin F, Morel P, Hagen M. Scarless surgery: Myth or reality through NOTES? Chirurgie sans cicatrice: Mythe ou réalité grâce à la chirurgie par les orifices naturels? Rev Med Suisse 2008;4:1550–1552.
4. Besarani D, Umranikar S, Patil K. Single-port 'scarless' laparoscopic nephrectomies: The United Kingdom experience. BJU Int 2009;104:1795–1796.
5. Allemann P, Schafer M, Demartines N. Critical appraisal of single port access cholecystectomy. Br J Surg 2010;97:1476–1480.
6. Hernandez JM, Morton CA, Ross S, Albrink M, Rosemurgy AS. Laparoendoscopic single site cholecystectomy: The first 100 patients. Am Surg 2009;75:681–685.
7. Rivas H, Varela E, Scott D. Single-incision laparoscopic cholecystectomy: Initial evaluation of a large series of patients. Surg Endosc 2010;24:1403–1412.
8. Curcillo Ii PG, Wu AS, Podolsky ER, Graybeal C, Katkhouda N, Saenz A, Dunham R, Fendley S, Neff M, Copper C, Bessler M, Gumbs AA, Norton M, Iannelli A, Mason R, Moazzez A, Cohen L, Mouhlas A (2010) Poor A. Single-port-access (SPA™) cholecystectomy: A multi-institutional report of the first 297 cases. Surg Endosc 24:1854–1860.
9. Dominguez G, Durand L, De Rosa J, Danguise E, Arozamena C, Ferraina PA. Retraction and triangulation with neodymium magnetic forceps for single-port laparoscopic cholecystectomy. Surg Endosc 2009;23:1660–1666.
10. Kirschniak A, Bollmann S, Pointner R, Granderath FA. Transumbilical single-incision laparoscopic cholecystectomy: Preliminary experiences. Surg Laparosc Endosc Percutan Techn 2009;19:436–438.
11. Hagen ME, Wagner OJ, Christen D, Morel P. Cosmetic issues of abdominal surgery: Results of an enquiry into possible grounds for a natural orifice transluminal endoscopic surgery (NOTES) approach. Endoscopy 2008;40:581–583.
12. Peterson CY, Ramamoorthy S, Andrews B, Horgan S, Talamini M, Chock A. Women's positive perception of transvaginal NOTES surgery. Surg Endosc 2009;23:1770–1774.
13. Swanstrom LL, Volckmann E, Hungness E, Soper NJ. Patient attitudes and expectations regarding natural orifice translumenal endoscopic surgery. Surg Endosc 2009;23:1519–1525.
14. Chouillard E, Dache A, Torcivia A, Helmy N, Ruseykin I, Gumbs A. Single-incision laparoscopic appendectomy for acute appendicitis: A preliminary experience. Surg Endosc 2010;24:1861–1865.
15. Takemasa I, Sekimoto M, Ikeda M, Mizushima T, Yamamoto H, Doki Y, Mori M. Transumbilical single-incision laparoscopic surgery for sigmoid colon cancer. Surg Endosc 2010;24:2321.
16. Castellucci SA, Curcillo PG, Ginsberg PC, Saba SC, Jaffe JS, Harmon JD. Single port access adrenalectomy. J Endourol 2008;22:1573–1576.
17. Targarona EM, Pallares JL, Balague C, Luppi CR, Marinello F, Hernández P, Martínez C, Trias M. Single incision approach for splenic diseases: A preliminary report on a series of 8 cases. Surg Endosc 2010;24:2236–2240.
18. Saber AA, El-Ghazaly TH, Minnick DB. Single port access transumbilical laparoscopic roux-en-y gastric bypass using the SILS port: First reported case. Surg Innov 2009;16:343–347.
19. Canes D, Desai MM, Aron M, Haber GP, Goel RK, Stein RJ, Kaouk JH, Gill IS. Transumbilical Single-Port Surgery: Evolution and Current Status. Eur Urol 2008;54:1020–1030.
20. Antoniou SA, Pointner R, Granderath FA. Single-incision laparoscopic cholecystectomy: a systematic review. Surg Endosc 2011;25:367–377.
21. Escobar PF, Fader AN, Paraiso MF, Kaouk JH, Falcone T. Robotic-Assisted Laparoendoscopic Single-Site Surgery in Gynecology: Initial Report and Technique. J Minim Invasive Gynecol 2009;16:589–591.
22. Kaouk. Robotic single-port transumbilical surgery in humans: Initial report. BJU Int 2009;103:366–369.
23. Hagen ME, Wagner OJ, Inan I, Morel P, Fasel J, Jacobsen G, Spivack A, Thompson K, Wong B, Fischer L, Talamini M, Horgan S. Robotic single-incision transabdominal and transvaginal surgery: Initial experience with intersecting robotic arms. Int J Med Robot 2010;6:251–255.
24. Joseph RA, Goh AC, Cuevas SP, Donovan MA, Kauffman MG, Salas NA, Miles B, Bass BL, Dunkin BJ. "Chopstick" surgery: A novel technique improves surgeon performance and eliminates arm collision in robotic single-incision laparoscopic surgery. Surg Endosc 2010;24:1331–1335.
25. Bucher P, Pugin F, Buchs N, Ostermann S, Charara F, Morel P. Single port access laparoscopic cholecystectomy (with video). World J Surg 2009;33:1015–1019.

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ORIGINAL ARTICLE

Clinical Validation of the ISGPF Classification and the Risk Factors of Pancreatic Fistula Formation Following Duct-to-Mucosa Pancreaticojejunostomy by One Surgeon at a Single Center

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Abstract
Background Postoperative pancreatic fistula remains a troublesome complication after pancreatoduodenectomy (PD), and many authors have suggested factors that affect pancreatic leakage after PD. The International Study Group on Pancreatic Fistula (ISGPF) published a classification, but the new criteria adopted have not been substantially validated. The aims of this study were to validate the ISGPF classification and to analyze the risk factors of pancreatic leakage after duct-to-mucosa pancreatojejunostomy by a single surgeon.
Methods All patient data were entered prospectively into a database. The risk factors for pancreatic fistula were analyzed retrospectively for 247 consecutive patients who underwent conventional pancreatoduodenectomy or pylorus-preserving pancreatoduodenectomy between June 2005 and March 2009 at the Samsung Medical Center by a single surgeon. Duct-to-mucosa pancreatojejunostomy was performed on all patients. The ISGPF criteria were used to define postoperative pancreatic fistula.
Results Conventional pancreatoduodenectomy was performed in 84 patients and pylorus-preserving pancreatoduodenectomy in 163. Postoperative complications occurred in 144 (58.3%) patients, but there was no postoperative in-hospital mortality. Pancreatic fistula occurred in 105 (42.5%) [grade A, 82 (33.2%); grade B, 9 (3.6%); grade C, 14 (5.7%)]. However, no difference was evident between the no fistula group and the grade A fistula group in terms of clinical findings, including postoperative hospital stays (11 versus 12 days, respectively, $p=0.332$). Mean durations of hospital stay in the grade B and C fistula groups were significantly longer than in the no fistula group (21 and 28.5 days, respectively; $p<0.001$). Multivariate analysis revealed that a soft pancreas and a long operation time (>300 min) were individually associated with pancreatic fistula formation of grades B and C.
Conclusions Although the new ISGPF classification appears to be sound in terms of postoperative pancreatic leakage, grade A fistulas lack clinical implications; thus, we are of the opinion that only grade B and C fistulas should be considered in practice. A soft pancreatic texture and an operation time exceeding 300 min were found to be risk factors of grade B and C pancreatic fistulas.

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Keywords Pancreatic fistula · ISGPF validation · Risk factor of pancreatic fistula

Introduction

Pancreatoduodenectomy is the treatment of choice for some benign lesions in the pancreatic head and for periampullary cancer. At high-volume centers, mortality after pancreatoduodenectomy is currently around 3–5%, but postoperative morbidity rates are considerable at around 30–50%.[1, 2] Furthermore, despite recent advances in surgical procedures and postoperative management techniques, pancreatic fistula remains the most common postoperative complication after pancreatoduodenectomy even at high-volume centers.[3] The development of a pancreatic fistula increases hospital stay and the cost of treatment, necessitates the use of additional investigations and interventional procedures, and can cause life-threatening complications. One of the problems encountered by those studying postoperative pancreatic fistula is the heterogeneity of the definitions applied. In order to overcome this problem, the International Study Group on Pancreatic Fistula (ISGPF) defined grades of pancreatic fistula severity in terms of their clinical impacts on hospital course. However, the ISGPF classification has not been rigorously tested or validated.

The aims of this study were to validate the ISGPF classification and to identify the risk factors of pancreatic leakage after duct-to-mucosa pancreatojejunostomy by a single surgeon specializing in pancreatobiliary surgery at a high-volume center.

Materials and Methods

Between June 2005 and May 2009, 247 consecutive patients underwent pancreatoduodenectomy by an experienced surgeon at the Samsung Medical Center. All patients underwent elective surgery after a full workup. All preoperative, intraoperative, and postoperative data were prospectively collected and maintained on a secure database. Preoperative parameters included patient age, gender, and laboratory findings; intraoperative parameters included operative time, pancreas texture, and the use of stents. Postoperative parameters and events were recorded and included the use of antibiotics, nutritional support, laboratory and imaging studies, postoperative hospital duration, hospital readmissions, reoperations, and mortality.

All operations were performed by an experienced single surgeon. Patients received single-shot intravenous antibiotic prophylaxis on induction of anesthesia, and all 247 underwent pancreatojejunal anastomosis, which was performed using a double-layer duct-to-mucosa technique where the jejunal mucosa (full layer) was stitched to the pancreatic duct with 5–0 absorbable coated Vicryl interrupt sutures and the edge of the parenchymal resection surface was stitched to the serosa of the jejunum using 5–0 Prolene single continuous sutures. Ductal short stents were often used in small pancreatic ducts, and no external pancreatic duct stent was used. Two Jackson-Pratt drainages were placed around the pancreatojejunal anastomosis and hepatojejunal anastomosis and then exteriorized through the lateral abdominal wall. Adjacent organ resection (colon, portal vein) was performed in accord with malignant extension. Prophylactic octreotide was given subcutaneously (100 μg every 8 h for 5 days). Computed tomography (CT) was performed routinely at postoperative day 7. Drained fluid volumes were measured daily, and serum and drain fluid amylase levels were determined on postoperative days 1, 2, 3, 4, 5, and 7 and daily thereafter if there was evidence of persistent leakage. For the no fistula group and the grade A group, drains were removed routinely on the eighth postoperative day, except for extraordinary large drainage amount if there was no evidence of elevated drain amylase activity and no abnormal CT finding on the seventh postoperative day. For the grade B and C groups, drains were kept longer until the amylase concentration of the drainage fluid was below the normal serum range (<100 IU/L) or the 24-h drainage fluid volume was <10 mL in case of higher amylase concentration level of the drainage fluid with or without interventional procedure.

Pancreatic fistula grades were defined as described by the ISGPF.[4] Mortality and morbidity were defined as death or complications occurring within 30 days of surgery. Detailed analysis of collated data and clinical course was performed for each of the 247 consecutive patients. To identify possible risk factors of a grade B and C pancreatic fistula, we reviewed the records of 23 (9.3%) patients with

Table 1 Pathologic indication for 247 consecutive patients undergoing pancreatoduodenectomy

Disease	Conventional PD (n=84)	PPPD (n=163)	N=247
Pancreas cancer	42	38	80
CBD cancer	18	55	73
AoV cancer	7	35	42
Duodenal cancer	8	4	12
Pancreas benign tumor	5	23	28
Pancreatitis	1	4	5
AoV benign tumor	2	2	4
Duodenal benign tumor	1	1	2
CBD benign tumor	0	1	1

PD pancreatoduodenectomy, *PPPD* pylorus-preserving pancreatoduodenectomy, *CBD* common bile duct, *AoV* ampulla of Vater

Table 2 Comparison of postoperative course between non-pancreatic fistula group and grade a pancreatic fistula group

Postoperative parameters	Non-fistula	Grade A	*P*
N (%)	142 (57.5)	82 (33.2)	
Gender (male)	86(60.6)	45(54.9)	0.405
Age (>60 years)	78(54.9)	36(43.9)	0.112
Operation time (>300 min)	65(45.8)	35(42.7)	0.654
Postop. hospital stay (days)	11	12	0.332
Drain removal (postoperative day)	9	10	0.789
Complications[a] (%)	40 (28.2)	28(34.1)	0.368
CT positive finding (%)	0 (0.0)	0 (0.0)	–
Supplemental nutrition (%)	5 (3.5)	0 (0.0)	1.000
Antibiotics use (%)	4 (2.8)	0(0.0)	0.709
Positive drainage culture (%)	2 (1.4)	3 (3.7)	0.358
Percutaneous drainage (%)	0 (0.0)	0 (0.0)	–
Persistent drainage[b] (%)	0 (0.0)	0 (0.0)	–
Readmission (%)	1 (0.7)	2 (2.4) [c]	0.556

[a] Complications except pancreatic fistula

[b] Persistent drainage after 3 weeks

[c] Two patients was excluded because they were reclassified as grade C after readmission.

a postoperative pancreatic fistula and compared these with those of non-pancreatic fistula cases. Categorical variables were compared using the chi-square test, and *P* values <0.05 were considered statistically significant.

Results

Of the 247 patients treated during the 4-year study period, 152 were males; the median patient age was 62 years (range, 26–85 years). Pylorus-preserving pancreatoduodenectomy was performed in 163 and conventional pancreatoduodenectomy in 84, although conventional pancreatoduodenectomy was performed more frequently in patients with pancreatic head carcinoma or duodenal carcinoma (Table 1). The most common indication for pancreatoduodenectomy was peri-ampullary cancer (n=207, 83.8%). Pathologic examinations revealed pancreatic carcinoma in 80 patients (32.4%), distal common bile duct carcinoma in 73 (29.6%), ampullary carcinoma in 42 (17.0%), duodenal cancer in 12 (4.9%), and a benign disease of the pancreatic head in 40 (16.2%).

Median operation time was 300 min (range, 200–540 min) and median operative blood loss was 400 mL (range, 50–2,500 mL). Twenty (8.1%) patients required operative blood transfusion [mean, 2.5 U (range, 1–5 U) of packed red blood cells] due to bleeding. Median postoperative length of hospital stay was 12 days (range, 8–48 days).

Of the 247 study subjects, 105 (42.5%) developed a pancreatic fistula postoperatively. Pancreatic fistula grades A, B, and C occurred in 33.2%, 3.6%, and 5.7% of the study subjects, respectively. In the 105 patients with a pancreatic fistula, 82 (78.1%) had a grade A fistula, 9 (8.6%) had a grade B fistula, and 14 (13.3%) had a grade C fistula. Grade C fistula was developed after discharge in two patients who were initially classified as grade A when they were discharged. Anyway, they were classified as grade C fistula group finally. Reoperation was not required in any patient, and no in-hospital mortality occurred. Duration of hospital stay progressively increased with fistula severity (grade A, 12 days; grade B, 21 days; grade C, 28.5 days, p<0.001). In addition, other parameters also progressively increased.

The median maximal drain amylase level for fistula grade A was 548 IU/L. Although two patients maintained a

Table 3 Comparison of post-operative course between the non-pancreatic fistula group and the grade B and C pancreatic fistula group

Postoperative parameters	Non-fistula	Grade B and C	*P*
N (%)	142 (57.5)	23 (9.3)	
Gender (male)	86(60.6)	14(60.9)	0.978
Age (>60 years)	78(54.9)	14(60.9)	0.595
Operation time (>300 min)	65(45.8)	17(73.9)	0.012
Postop. hospital stay (days)	11	23	<0.001
Drain removal (postoperative day)	9	18	<0.001
Complications[a] (%)	40 (28.2)	21 (91.3)	<0.001
CT positive finding (%)	0 (0.0)	20 (87.0)	<0.001
Supplemental nutrition (%)	5 (3.5)	5 (21.5)	0.005
Antibiotics use (%)	4 (2.8)	22 (95.7)	<0.001
Positive drainage culture (%)	2 (1.4)	16 (69.9)	<0.001
Percutaneous drainage (%)	0 (0.0)	14 (60.9)	<0.001
Persistent drainage[b] (%)	0 (0.0)	17 (73.9)	<0.001
Readmission (%)	1 (0.7)	2 (8.7)	0.051

[a]Complications except pancreatic fistula

[b]Persistent drainage after 3 weeks

Table 4 Risk factors for grade B and C pancreatic fistulas by univariate analysis

Parameters	Non-fistula (*N*=142)	Grade B and C (N=23)	*P*
Age (>60 years)	78 (54.9)	14 (60.9)	0.595
Gender (Male)	86(60.6)	14(60.9)	0.978
Operation time (>300 min)	65(45.8)	17(73.9)	0.012
Preop. T-bilirubin (>1.6 mg/dL)	80 (56.3)	12 (52.2)	0.709
Preop. biliary drainage (yes)	80 (56.3)	13 (56.5)	0.987
Preop. CA19-9 (>35 U/mL)	78 (56.1)	12 (54.5)	0.890
Preop. amlyase (>100 U/L)	42 (31.1)	3 (15.8)	0.169
Preop. lipase (>60 U/L)	59 (43.7)	4 (21.1)	0.060
Pancreatic duct size (>3 mm)	66 (46.5)	8 (34.8)	0.295
Location of the lesion (pancreas)	80 (56.3)	8 (34.8)	0.055
Operation type (PPPD)	81 (57.0)	15 (65.2)	0.461
PJ stent insertion (no)	97 (68.3)	17 (73.9)	0.590
Pancreas texture (soft)	64 (45.1)	16 (69.6)	0.029
Pathology (malignant)	124 (87.3)	17 (73.9)	0.110

drain at hospital discharge, no patient experienced drainage for more than 3 weeks. This variability in drain removal reflects the surgeon's clinical judgment because customary drain removal was delayed in some cases due to a higher than expected volume at the scheduled time of discharge. Readmission via emergency room was required in four patients who were initially classified as grade A when they were discharged. Readmission rate of grade A was not different from that of the no fistula group (p=0.065). Among them, two patients with intraabdominal amylase-rich fluid collection by CT scan were reclassified as grade C pancreatic fistula and treated with percutaneous drainage on admission.

For grade B fistulas, the median maximal drain amylase level was 49,800 IU/L. Drains were removed at a median 17 days postoperatively. The majority of patients (six of the nine) were suspected to have fluid collection by CT, and three of these patients were accessible to percutaneous drainage. All patients with a grade B pancreatic fistula had other complications.

For grade C fistulas, the median drain amylase was significantly elevated (117,181 IU/L); drains were removed late at a median 25.5 days postoperatively. All 14 grade C patients had other complications that required specific treatments such as antibiotics (100%) or minimally invasive drainage (78.6%). In addition, three of these patients (21.4%) developed pseudoaneurysmal bleeding and were managed by embolization. However, despite the severity of these fistulas and the pseudoaneurysmal ruptures, no mortality occurred.

In terms of clinical course, grade A pancreatic fistula patients were no different from no fistula patients (Table 2). In grade A pancreatic fistula, drain fluid amylase levels were tender to highest at postoperative day 2 or 3, but progressively decreased. Patients with no pancreatic fistula and patients with a grade B or C fistula were compared with respect to ten clinical parameters related to postoperative course (Table 3). No significant differences were observed between these two groups (p<0.05), although the readmission rates were approaching significance (p=0.051).

Patients with a grade B or C pancreatic fistula were compared with patients without a pancreatic fistula with respect to 14 risk factors of pancreatic fistula development (Table 4). Multivariate analysis showed that a soft pancreatic texture and a long operation time (>300 min) were independently associated with pancreatic fistula development (Table 5).

Discussion

The guidelines issued by the International Study Group on Pancreatic Fistula (ISGPF) enable pancreatic fistula to be defined and graded more precisely based on considerations of clinical procedures and outcomes, and allow realistic comparisons of surgical experiences to be made between different hepatopancreatobiliary centers. Thus, the new guidelines will undoubtedly simplify evaluations of new surgical techniques and pharmacological interventions.

Some studies that have used this new ISGPF classification have confirmed its usefulness. Pratt et al.[3] reported that

Table 5 Multivariate analysis for predictive factors influencing grade B and C pancreatic fistulas, performed based on the result of the univariate analysis

Variable	OR	95% CI	*P* value
Operation time (>300 min)	3.774	1.375–10.355	0.010
Pancreas texture (soft)	3.175	1.199–8.409	0.020

increasing fistula severity has negative clinical and economic impacts on patients and their healthcare resources. Frymerman et al.[5] suggested that a soft pancreatic consistency and a high drain lipase activity on postoperative day 3 are early predictors of the development of a postoperative pancreatic fistula, and C. Fuks et al.[6] reported that the risk factors of a grade C pancreatic fistula are soft pancreatic parenchyma, preoperative transfusion, and postoperative bleeding.

In the present study, the ISGPF classification scheme was examined in a high-volume pancreatobiliary surgical specialty setting using patients treated by a single surgeon. Furthermore, all patients were treated using the same operative procedure.

In the present study, grade A pancreatic fistula was most commonly encountered, but no significant difference was evident between these patients and those that did not develop a pancreatic fistula. Accordingly, it seems that grade A pancreatic fistulas are biochemically apparent only. On the other hand, patients with a clinically relevant (grade B or C) pancreatic fistula followed a more severe clinical course than those without a fistula. The present study indicates that grade A fistulas scarcely merit consideration as complications because they lack clinical consequences, whereas grades B and C are valuable for categorizing and delineating the impact of fistula severity.

The pancreatic anastomosis technique has been considered to the most important factor of fistula development by several authors.[7–9] Various anastomotic methods have been developed to reduce pancreatic fistula rates, such as end-to-end dunking PJ, the duct-to-mucosa technique, external drainage of the pancreatic duct, internal stenting of the pancreatic duct, and modifications of these techniques.[10–15] Poon et al.[16] reported that the use of an external stent to drain the pancreatic duct significantly reduced the pancreatic fistula rate. In the present study, no external stent to drain was used; thus, we are not in a position to compare the external and internal pancreatic drain methods with respect to pancreatic fistula development rates. However, internal short stent insertion was not found to affect the pancreatic fistula rates significantly (p=0.590).

The nature of the pancreatic parenchyma has already been described to be a risk factor of fistula development. Mathur et al.[17] recently reported that fatty pancreatic parenchyma is significantly associated with fistula development after pancreatoduodenectomy, and Frymerman et al.[5] reported that a soft pancreatic consistency and a high drain lipase activity on postoperative day 3 are early predictors of the development of a grade C fistula. Our multivariate analysis also showed that soft pancreatic parenchyma is a risk factor for grade B and C pancreatic fistulas and that an operation time of more than 300 min is also an independent risk factor.

In conclusion, it appears that the new ISGPF classification is satisfactory in terms of comparing outcomes between surgeons or centers, but we are concerned that grade A fistulas lacked any clinical manifestations. Accordingly, we recommend that only grade B and C fistulas be considered practical criteria. We found that a soft pancreatic texture and a protracted operation time (>300 min) were risk factors for grade B and C pancreatic fistulas; thus, we suggest that more attention be paid to pancreatic texture during pancreaticojejunostomy and that patients with a soft pancreatic texture or a long operation time be monitored closely for fistula development.

References

1. Shrikhande SV, Barreto G, Shukla PJ. Pancreatic fistula after pancreaticoduodenectomy: the impact of a standardized technique of pancreaticojejunostomy. Langenbecks Arch Surg 2008;393:87–91.
2. Schmidt CM, Powell ES, Yiannoutsos CT, Howard TJ, Wiebke EA, Wiesenauer CA, Baumgardner JA, Cummings OW, Jacobson LE, Broadie TA, Canal DF, Goulet RJ, Jr., Curie EA, Cardenes H, Watkins JM, Loehrer PJ, Lillemoe KD, Madura JA. Pancreaticoduodenectomy: a 20-year experience in 516 patients. Arch Surg 2004;139:718–725; discussion 725–727.
3. Pratt WB, Maithel SK, Vanounou T, Huang ZS, Callery MP, Vollmer CM, Jr. Clinical and economic validation of the International Study Group of Pancreatic Fistula (ISGPF) classification scheme. Ann Surg 2007;245:443–451.
4. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138:8–13.
5. Frymerman AS, Schuld J, Ziehen P, Kollmar O, Justinger C, Merai M, Richter S, Schilling MK, Moussavian MR. Impact of postoperative pancreatic fistula on surgical outcome–the need for a classification-driven risk management. J Gastrointest Surg 2010;14:711–718.
6. Fuks D, Piessen G, Huet E, Tavernier M, Zerbib P, Michot F, Scotte M, Triboulet JP, Mariette C, Chiche L, Salame E, Segol P, Pruvot FR, Mauvais F, Roman H, Verhaeghe P, Regimbeau JM. Life-threatening postoperative pancreatic fistula (grade C) after pancreaticoduodenectomy: incidence, prognosis, and risk factors. Am J Surg 2009;197:702–709.
7. Buchler MW, Friess H, Wagner M, Kulli C, Wagener V, Z'Graggen K. Pancreatic fistula after pancreatic head resection. Br J Surg 2000;87:883–889.
8. Marcus SG, Cohen H, Ranson JH. Optimal management of the pancreatic remnant after pancreaticoduodenectomy. Ann Surg 1995;221:635–645; discussion 645–648.
9. Suc B, Msika S, Fingerhut A, Fourtanier G, Hay JM, Holmieres F, Sastre B, Fagniez PL. Temporary fibrin glue occlusion of the main pancreatic duct in the prevention of intra-abdominal complications after pancreatic resection: prospective randomized trial. Ann Surg 2003;237:57–65.
10. Khan AW, Agarwal AK, Davidson BR. Isolated Roux Loop duct-to-mucosa pancreaticojejunostomy avoids pancreatic leaks in pancreaticoduodenectomy. Dig Surg 2002;19:199–204.
11. Batignani G, Fratini G, Zuckermann M, Bianchini E, Tonelli F. Comparison of Wirsung-jejunal duct-to-mucosa and dunking

technique for pancreatojejunostomy after pancreatoduodenectomy. Hepatobiliary Pancreat Dis Int 2005;4:450–455.
12. Ohwada S, Tanahashi Y, Ogawa T, Kawate S, Hamada K, Tago KI, Yamada T, Morishita Y. In situ vs ex situ pancreatic duct stents of duct-to-mucosa pancreaticojejunostomy after pancreaticoduodenectomy with billroth I-type reconstruction. Arch Surg 2002;137:1289–1293.
13. Asopa HS, Garg M, Singhal GG, Singh L, Asopa J. Pancreaticojejunostomy with invagination of spatulated pancreatic stump into a jejunal pouch. Am J Surg 2002;183:138–141.
14. Okamoto A, Tsuruta K. Fistulation method: simple and safe pancreaticojejunostomy after pancreatoduodenectomy. Surgery 2000;127:433–438.
15. Tsuji M, Kimura H, Konishi K, Yabushita K, Maeda K, Kuroda Y. Management of continuous anastomosis of pancreatic duct and jejunal mucosa after pancreaticoduodenectomy: historical study of 300 patients. Surgery 1998;123:617–621.
16. Poon RT, Fan ST, Lo CM, Ng KK, Yuen WK, Yeung C, Wong J. External drainage of pancreatic duct with a stent to reduce leakage rate of pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized trial. Ann Surg 2007;246:425–433; discussion 433–435.
17. Mathur A, Pitt HA, Marine M, Saxena R, Schmidt CM, Howard TJ, Nakeeb A, Zyromski NJ, Lillemoe KD. Fatty pancreas: a factor in postoperative pancreatic fistula. Ann Surg 2007;246:1058–1064.

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ORIGINAL ARTICLE

Dual-Phase Computed Tomography for Assessment of Pancreatic Fibrosis and Anastomotic Failure Risk Following Pancreatoduodenectomy

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Abstract
Introduction Delayed or decreased computed tomography (CT) enhancement characteristics in pancreatic fibrosis have been described.
Methods A review of 157 consecutive patients with preoperative dual-phase CT between 2004 and 2009 was performed. Pancreatic CT attenuation upstream from the tumor was measured in the pancreatic and hepatic imaging phases. The ratio of the mean CT attenuation value [hepatic to pancreatic phase; late/early (L/E) ratio] and histological grade of pancreatic fibrosis was correlated with the development of a clinically relevant pancreatic anastomotic failure (PAF) and other clinical parameters.
Results A clinically relevant PAF was observed in 21 patients (13.4%) with morbidity and mortality of 39.5% and 0%, respectively. The PAF group showed maximum enhancement in the pancreatic and washout in the hepatic CT phase, while the no PAF group showed a delayed enhancement pattern. Degree of pancreatic fibrosis and L/E ratio were significantly lower for the PAF group than the no PAF group (0.86±0.14 vs. 1.09±0.24; $P<0.0001$ and 21.0±17.9 vs. 40.4±29.8; $P<0.0001$); fewer PAF patients showed an atrophic histological pattern (14% vs. 39%; $P=0.046$). The L/E ratio was positively correlated with pancreatic fibrosis. Pancreatic fibrosis and L/E ratio increased with larger duct size ($P<0.001$), the presence of diabetes ($P<0.05$), and the surgeon's assessment of pancreas firmness ($P<0.001$). In multivariate analyses, L/E ratio and body mass index were significant predictors for the development of a clinically relevant PAF; a 0.1-U increase of L/E ratio decreased the odds of a PAF by 54%.
Conclusion Pancreatic CT enhancement pattern can accurately assess pancreatic fibrosis and is a powerful tool to predict the risk of developing a clinically relevant PAF following PD.

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Introduction

The safety of pancreatic resections has substantially improved over the last decades. However, pancreatic anastomotic failure (PAF) following pancreatoduodenectomy (PD) remains a significant problem without further decrease in most recent years. A clinically relevant PAF occurs in 5–30% of cases,[1–13] contributes significantly to the 30–50% morbidity rate observed after PD,[3,7,9,10] and results in longer hospital stay, increased health care costs, or even death. Identifying patients with a high risk for PAF is critical to further decrease morbidity and mortality after PD and to improve clinical outcomes.

A soft pancreas is the most widely accepted risk factor for developing a PAF following PD.[3,13,14] Pancreatic fibrosis with decreased softness of the gland is thought to be associated with a decreased risk of PAF. Previous studies have reported low rates of PAF in the presence of firm pancreatic parenchyma.[14–17] Assessment of the degree of pancreatic fibrosis may be helpful in preoperative patient counseling, risk stratification for development of PAF, and in postoperative patient management. The degree of pancreatic fibrosis may also be associated with pancreatic duct size and endocrine and exocrine gland function[3,4,13,15,16] which are additional factors potentially contributing to the risk of developing a PAF.

So far only few radiological studies have addressed if the degree of pancreatic fibrosis can be reliably detected and quantified.[18–22] In a recent study, we reported that patients with autoimmune pancreatitis show enhancement characteristics distinct from patients with adenocarcinoma on dual-phase computed tomography (CT).[22] A delayed enhancement with a slow increase followed by a slow decline or a plateau was characteristic for a fibrotic pancreas in patients with autoimmune pancreatitis; a rapid increase followed by a rapid decrease indicated a "normal" pancreas with lower degrees of fibrosis.[18–22] The aim of this study was to investigate the ability of dual-phase CT to assess the histological degree of pancreatic fibrosis and to predict the risk of developing a clinically relevant PAF after PD in a large single surgeon cohort of patients undergoing PD.

Methods

Patients and Clinical Data Collection

The study was approved by the institutional review board. Using a prospectively maintained database, we identified 289 consecutive patients undergoing PD performed by a single surgeon (MBF) between January 2004 and August 2009. One hundred fifty-seven (54%) of these patients underwent a preoperative dual-phase pancreas protocol CT at Mayo Clinic and were included in the study. Demographic data, preoperative American Society of Anesthesiology (ASA) grade, medical comorbidities, operative procedure, pathology, perioperative data, and clinical follow-up were reviewed.

Definitions of Pancreatic Anastomotic Failure

PAF, pancreatic anastomotic "leak," or pancreatic "fistula" were considered synonyms for the purpose of this study. PAF was defined and classified in accordance with the International Study Group of Pancreatic Surgery (ISGPS) classification.[3,23] The ISGPS definition of PAF provides three levels of severity. Whereas grades B and C are clinically relevant as they require changes in the postoperative management and further diagnostic and therapeutic interventions, grade A is not. For the purpose of this study, we combined grades B and C in the clinically relevant "PAF group," while grade A and no PAF were combined in the no PAF group.

Surgical Technique

A pylorus-preserving or standard PD with a two-layer end-to-side, duct-to-mucosa pancreaticojejunostomy was performed. Pancreatojejunostomy was stented with an indwelling silastic catheter until May 2008; thereafter, the stent was removed intraoperatively before completing the anterior part of the anastomosis. An end-to-side hepaticojejunostomy was performed with running (bile duct>5 mm) or interrupted (bile duct≤5 mm) sutures approximately 10 cm distally. Approximately 40 cm distal to the biliary anastomosis, an antecolic, end-to-side duodenojejunostomy or gastrojejunostomy was performed. One closed-suction drain was routinely placed in proximity to the pancreatic and biliary anastomosis. Intraoperatively, the texture of the pancreatic gland was subjectively assessed by the surgeon using a 1–10 scale and classified into three grades as "soft" (scale 1–3), "firm" (4–7), or "very firm" (8–10).

Perioperative Care

Patients went from the recovery room to the regular surgical floor unless significant medical comorbidities or intraoperative events warranted prolonged continuous monitoring. The nasogastric tube was removed on the first postoperative day. A clear liquid diet was started on the second postoperative day and advanced to a regular diet as tolerated. The amylase concentration in the drain fluid was

measured once the patient was tolerating unlimited oral intake. The operative drain was discontinued if the amylase concentration was normal (<3× upper limit of normal serum amylase level), and there were no clinical concerns for PAF. All patients with symptoms concerning for PAF underwent a contrast-enhanced CT. Patients were dismissed from the hospital when tolerating a solid diet, postoperative pain was controlled with oral analgesics, and clinically stable.

Histological Analysis

Sections from the surgical pancreatic cut margin were used for immunohistochemistry. Masson's trichrome staining was used to identify collagen tissue and was reviewed by a single pathologist (TCS) blinded to the clinical information. The degree of fibrosis was calculated as ratio of the stained collagen tissue area to total area measured in the entire section. Further, the pattern of pancreatic fibrosis was recorded as acinar (intralobular), lobular (interlobular), or atrophic.

CT Protocol

The dual-phase pancreatic CT protocol included an unenhanced scan followed by dual-phase contrast-enhanced scans through the abdomen as described before.[22] Briefly, scanning delay after administration of contrast material depended on the contrast injection rate: 45- and 70-s delays at 3 mL/s injection, 40- and 65-s delays at 4 mL/s injection, and 35- and 60-s delays at 5 mL/s injection. A total of 150 mL of IV contrast material (Iohexol, Omnipaque 300, GE Healthcare) was used. The median slice thickness for contrast-enhanced images was 3 mm (2–4 mm).

CT Evaluation

CT attenuation values were independently measured by two of the authors (YH and YK) on the electronically stored CT images without knowledge of the clinical information. CT images taken for diagnostic purposes within 30 days before PD were included in this analysis. CT attenuation values were measured on both unenhanced images and images obtained in the pancreatic (early) and hepatic (late) phases after contrast administration. CT attenuation values of the pancreatic parenchyma were quantified by use of Hounsfield unit thresholds placing a region of interest (ROI) in six points in two segments of the pancreas (body and tail). The mean value for the two segments was computed for each patient. ROIs in the body were placed over the superior mesenteric artery in an area unaffected by the tumor and in the tail about two thirds distal from the body–tail transition. The largest possible spherical ROI was placed making every effort to avoid the pancreatic duct and extrapancreatic structures. The smallest ROI measured was approximately 3 mm in diameter in a case with an atrophic pancreas. The CT attenuation values of the abdominal aorta, main portal vein, liver, and spleen were similarly measured on unenhanced images and on images obtained in the pancreatic and hepatic phases. The enhancement ratio expressed as late phase/early phase ratio (L/E ratio) was calculated as (hepatic phase − unenhanced phase)/(pancreatic phase − unenhanced phase) to indicate delayed-phase enhancement. The pancreatic duct size was measured in millimeter at the presumed surgical pancreatic neck margin at the right border of the superior mesenteric artery.

Statistical Analyses

Patients with a clinically relevant PAF (grade B/C PAF) and those with no and grade A PAF were compared using two-sided *t* tests for continuous variables with 95% confidence intervals (CIs) and chi-square tests for categorical variables. Logistic regression models were used to evaluate risk factors for a clinically relevant PAF for univariate analysis. For multivariate analysis, the area under the curve (AUC) was calculated to aid in model selection. An AUC of 0.5 is a random prediction while a perfect model has an AUC of 1. A model is considered reliable with an AUC>0.8. Odds ratios (ORs) and 95% CIs for the ORs were computed. To identify a threshold value for L/E ratios that would best discriminate patients with and without a clinically relevant PAF, a sequence from 0.05 to 1.4 in steps of 0.05 was chosen for the L/E ratios. To estimate robustness of the threshold, 1,000 bootstrap samples were selected,[24] and univariate logistic regression models were applied to random samples with replacements of the patients. Each model's accuracy was measured by the AUC to evaluate how well the model distinguished patients with and without a clinically relevant PAF. Contour lines for the multivariate logistic regression model with two predictors were computed. All statistical tests were two-sided, and a $P<0.05$ was considered significant. Data analyses were performed using R version 2.10.1.[25] and SPSS 18.0 for Windows (SPSS, Chicago, IL, USA).

Results

Patient Population and Outcomes

There were 94 men (60%) and 63 women (40%) among the 157 study patients with a mean age of 62.5 years (median, 63 years; range, 26–86 years). No postoperative mortality was observed. Postoperative complications occurred in 62 of 157 patients (39.5%). Based on the ISGPS classification, 21 patients (13.4%) developed a clinically relevant PAF (15

grade B and 6 grade C) and constituted the PAF group for this study; all were managed without reoperation. The no PAF group consisted of the remaining 136 patients (no PAF or grade A). The overall mean postoperative length of hospital stay (LOS) was 12 days (median, 10 days; range, 5–74 days); for the PAF group, it was 20 days (median, 16 days; range, 9–74 days) and significantly longer than for the no PAF group with a mean LOS of 11 days (median, 10 days; range 5–30 days, $P<0.001$).

Patient Characteristics, Operative, and Histological Factors

Patient characteristics are presented in Table 1. The PAF group showed a significantly higher body mass index (BMI) compared to the no PAF group ($P=0.002$). No differences were observed for age, sex, ASA classification, medical history, preoperative symptoms/interventions, or neoadjuvant therapy. Table 2 details the operative and histological features. No differences were observed for pathological diagnosis, type of procedure, portal vein resection, estimated blood loss, perioperative blood transfusion, or operative time. However, more patients in the PAF group had a smaller pancreatic duct size and a soft pancreatic gland compared to the no PAF group ($P=0.024$ and 0.047, respectively).

CT Assessment

To assure the reproducibility of the method, we first validated the inter-observers variability. The calculated L/E ratio was highly correlated ($r=0.92$) between two observers indicating that CT assessment can be reliably reproduced among various observers. The observed CT enhancement characteristics are presented in Fig. 1 and Table 3.

In the PAF group, the pancreatic parenchyma showed maximum enhancement in the pancreatic and washout in the hepatic phase, whereas in the no PAF group, the pancreas showed decreased enhancement in the pancreatic phase and maintained higher attenuation values in hepatic phase, findings consistent with a delayed enhancement pattern. Therefore, the mean value of the L/E ratio was significantly lower in the PAF group compared to the no PAF group (0.86±0.14, 95% CI 0.80–0.93 vs. 1.09±0.24, 95% CI 1.05–1.13; $P<0.0001$).

Table 1 Patient demographics

Variables	No PAF group ($n=136$)		PAF group ($n=21$)		P value
Age (years)	62.4 (62.5)	[31–86]	63.3 (67.0)	[26–78]	0.741
Male, sex	78	(57%)	16	(76%)	0.101
Body mass index (kg/m^2)	26.4 (25.9)	[14.8–41.9]	30.1 (29.3)	[24.6–39.9]	0.002
≥30 kg/m^2	24	(18%)	7	(33%)	0.087
ASA					
I	2	(1%)	0	(0%)	0.920
II	61	(45%)	10	(48%)	
III	72	(53%)	11	(52%)	
IV	1	(1%)	0	(0%)	
Medical history					
Diabetes mellitus	34	(25%)	5	(24%)	0.906
Pancreatitis	34	(25%)	5	(24%)	0.906
Hypertension	56	(41%)	9	(43%)	0.884
Chronic cardiovascular disease[a]	37	(27%)	8	(38%)	0.310
Alcohol use	27	(20%)	3	(14%)	0.397
Smoking	65	(48%)	7	(33%)	0.216
Abdominal surgery	51	(38%)	9	(43%)	0.638
Preoperative symptom and intervention					
Clinical jaundice	84	62%	10	48%	0.218
Endoscopic biliary stenting	88	65%	10	48%	0.132
Endoscopic pancreatic duct stenting	15	11%	1	5%	0.334
FNA biopsy	67	49%	9	43%	0.584
Neoadjuvant chemoradiation therapy	8	(6%)	0	(0%)	0.308

Values are mean (median) with range or number (in percent) of patients

ASA the American Society of Anesthesiologists classification of comorbidities, *FNA* fine needle aspiration

[a] Except hypertension

Table 2 Operative and histological factors

Variables	No PAF group (n=136)		PAF group (n=21)		P value
Disease status					
Malignant disease	116	85%	16	76%	0.222
Pathological diagnosis					
Pancreatic tumors	105	77%	13	62%	0.172
Ductal adenocarcinoma	66	49%	6	29%	0.103
Cystic neoplasms[a]	33	24%	6	29%	0.786
Neuroendocrine tumor	6	4%	1	5%	0.999
Chronic pancreatitis	6	4%	1	5%	0.999
Periampullary tumor[b]	21	15%	7	33%	0.064
Others[c]	4	3%	1	5%	
Type of procedure					
Pylorus-preserving PD	122	90%	19	90%	0.637
Standard PD	14	10%	2	10%	
PV/SMV resection	17	13%	1	5%	0.267
Pancreatic duct size (mm)	4.6 (4.5)	0–15 (not identified, n=2)	3.5 (3)	1.5–6	0.024
≤3 mm	35	26%	11	52%	0.013
>3 mm	101	74%	10	48%	
Pancreatic texture[d]					
Soft (1–3)	16	12%	5	24%	0.047
Firm (4–7)	57	42%	12	57%	
Very firm (8–10)	63	46%	4	19%	
Estimated blood loss (mL)	731 (550)	50–2,800	690 (650)	250–1,400	0.744
Operative time (min)	371 (366)	229–700	357 (363)	267–459	0.374
Blood transfusion, perioperative	59	43%	11	52%	0.440

Values are mean (median) with range or number (%) of patients

PD pancreatoduodenectomy, *PV/SMV* portal vein/superior mesenteric vein

[a] Including intraductal papillary mucinous neoplasm, serous cystic tumor, and mucinous cystic neoplasm

[b] Including ampullary adenocarcinoma, bile duct adenocarcinoma, and duodenal adenocarcinoma

[c] Including metastatic pancreatic tumor (n=2), epithelioid sarcoma (n=1), IgG4-associated cholangitis (n=1), and lymphoma (n=1)

[d] Subjectively assessed by surgeons during operation using 1–10 scale and classified as "soft" (scale 1–3), "firm" (4–7), or "very firm" (8–10)

The threshold for the L/E ratio in discriminating patients developing PAF from those without PAF was determined to be 1.0 on the basis of the AUC criteria. Hence, in the models below, the variable L/E ratio was dichotomized as L/E ratio≤1.0 or >1.0 and accordingly defined as "normal" (L/E ratio≤1.0) or "delayed" (L/E ratio>1.0) enhancement. Only two of 21 (10%) patients in the PAF group showed delayed enhancement (L/E ratio>1.0) compared with 88 of 136 (65%) patients in the no PAF group (P<0.0001). These two patients in the PAF group had multiple other risk factors for developing a PAF: morbid obesity with BMI of 38 and 39 kg/m^2, soft pancreatic texture on surgeon's assessment, small pancreatic duct, and lower degrees of pancreatic fibrosis (10% and 30%). Both patients also underwent endoscopic procedures preoperatively: One with a neuroendocrine tumor had a common bile duct stent placed; the other one with an intraductal papillary mucinous neoplasm required repetitive, endoscopic retrograde cholangiography for recurrent mucinous obstruction of the pancreatic duct.

Pancreatic Fibrosis

Results of immunohistochemical analysis of pancreatic fibrosis are shown in Table 4. In the PAF group, the mean degree of fibrosis was significantly lower than in the no PAF group (21.0±17.9 vs. 40.4±29.8; P<0.0001). In addition, fewer patients in the PAF group showed an atrophic fibrosis pattern (14% vs. 39%; P=0.046). Further, the L/E ratio based on CT enhancement characteristics correlated positively with the degree of pancreatic fibrosis found on immunohistochemical analysis with a regression coefficient of 0.75 (Fig. 2). In contrast, the mean CT attenuation values of the abdominal aorta, main portal vein,

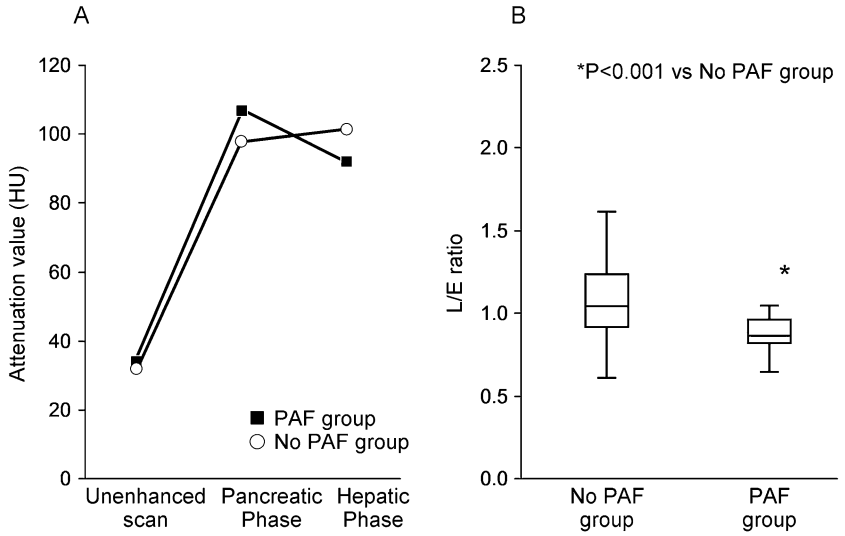

Fig. 1 CT enhancement characteristics of PAF and no PAF Group. **a** *Bar graph* shows mean CT attenuation values of pancreatic parenchyma in PAF group (*squares*) and No PAF group (*circles*) in relation to phase of contrast enhancement. **b** The CT attenuation ratio (late phase/early phase [L/E] ratio) was calculated as (hepatic phase − unenhanced phase)/(pancreatic phase − unenhanced phase) to indicate delayed-phase enhancement. The PAF group shows a significantly lower L/E ratio compared with no PAF group ($P<0.001$). *Box* lower and upper boundaries=25th and 75th percentiles. *Center line* = median. *Error bars*=10th and 90th percentiles

spleen, and liver were not significantly different for the two groups in the unenhanced, pancreatic, and hepatic CT phases.

Correlation of Pancreatic Fibrosis and CT Enhancement Pattern with Pancreatic Texture, Pancreatic Duct Size, and Diabetes Mellitus

The association of pancreatic fibrosis and L/E ratio with pancreatic texture, pancreatic duct size, and diabetes mellitus is presented in Figs. 3, 4, and 5. Figure 3 shows the correlation with surgeon's assessment of pancreatic texture; the degree of pancreatic fibrosis was 16.6±14.0% in soft pancreas, 31.5±27.2% in firm pancreas, and 52.0±28.5% in very firm pancreas ($P<0.05$ resp. <0.001). The same observation was made for the CT enhancement pattern; the L/E ratio was significantly higher in patients with very firm pancreas than those with soft or firm pancreas ($P<0.05$ resp. <0.001). Figure 4 shows the findings for pancreatic duct size. Patients with a dilated duct, i.e., >3 mm, had a higher percentage of fibrosis than those with a small duct (42.1±25.3% vs. 27.3±21.5%; $P<0.001$). Also L/E ratio was significantly higher in patients with a dilated duct compared to those with a small duct ($P<0.001$). Figure 5 shows the findings looking at diabetes mellitus. Pancreatic fibrosis was increased in patients with diabetes compared with non-diabetic patients (48.0±28.5% vs. 34.3±28.7%; $P=0.01$). The median L/E ratio for diabetic patients was significantly higher compared to non-diabetic patients (1.09 vs. 1.01; $P=0.005$).

Risk Factors for a Clinically Relevant PAF

Factors for developing a clinically relevant PAF were subsequently included into a multivariate regression model, and a stepwise selection procedure was applied (Table 5). To properly measure the effects of variables on prediction accuracy for development of a PAF, an important score was computed using the random forest algorithm. Multivariate analyses identified that L/E ratio and BMI were the most significant predictors of a clinically relevant PAF. The stepwise increase of L/E ratio by 0.1 U decreased the odds

Table 3 CT enhancement characteristics

Variables	No PAF group (n=136)		PAF group (n=21)		P value
L/E ratio	1.09±0.24	1.05–1.13	0.86±0.14	0.80–0.93	<0.0001
<1.0	48	35%	19	90%	<0.0001
≥1.0	88	65%	2	10%	
Unenhanced scan (HU)	31.5±14.5	28.0–35.1	33.7±8.9	28.5–38.9	0.634
Pancreatic phase (HU)	98.3±29.5	93.4–103.3	107.4±23.0	97.6–117.2	0.179
Hepatic phase (HU)	101.7±21.2	98.1–105.2	92.2±20.3	83.5–100.9	0.057

Values are mean±SD with 95% confidence interval or number (in percent) of patients

L/E ratio late/early phase ratio, *HU* Hounsfield unit

Table 4 Pancreatic fibrosis by immunohistochemistry

Variables	No PAF group (n=136)		PAF group (n=21)		P value
Pancreatic fibrosis (%)	40.4±29.8	35.4–45.4	21.0±17.9	13.3–28.6	<0.0001
Fibrosis pattern					
Atrophic	53	39%	3	14%	0.046
Acinar (intralobular)	18	13%	2	10%	
Lobular (interlobular)	65	48%	16	76%	

Values are mean±SD with 95% confidence interval or number (in percent) of patients

of developing a clinically relevant PAF by 54%. The model with the dichotomized L/E ratio as a single factor had an AUC of 0.81 while the AUC for the model with both L/E ratio and BMI was 0.89. Figure 6 shows the logistic regression model for predicting a PAF with L/E ratio and BMI. The contour lines show regions of a constant 5%, 30%, 70%, and 90% predictive probability for developing a clinically relevant PAF. This indicates a clear separation of PAF cases from non-PAF cases for various L/E ratio and BMI combinations.

Discussion

With advances in perioperative care and surgical technique, PD-associated mortality has decreased to less than 5% in high volume centers.[1–6,8,11–13] Morbidity remains fairly high with a rate of 30–50% and is often seen in conjunction with the occurrence of a PAF.[7,9,10] A clinically relevant PAF still occurs in 5–30% of cases despite all efforts and remains the major cause of postoperative morbidity resulting in an extended hospital stay, increased health care costs, and perioperative mortality.[1–13] To achieve acceptable outcomes, patient selection is crucial; however, a simple quantitative method to estimate preoperatively the risk of developing a PAF after PD has been lacking.

This study to our knowledge is the first to describe the quantitative assessment of enhancement characteristics on preoperative dual-phase pancreatic CT as a method to estimate the risk of developing a clinically relevant PAF (ISGPS grade B/C) after PD. The assessment can be easily performed on a standard pancreas protocol CT and is therefore readily available in the preoperative setting; moreover, it can be reliably reproduced among various observers as shown in this study.

Although with this method no absolute prediction of a postoperative clinically relevant pancreatic anastomotic failure can be made, we believe that this method is of clinical relevance due to its simplicity, noninvasive characteristics, and ready availability in the preoperative setting based upon a routine preoperative evaluation. We also believe that this method is a highly valuable tool in preoperative patient counseling. This is crucial in this special patient cohort with expected high postoperative morbidity, which may impact greatly upon the postoperative quality of life and limited prognosis inherent to the underlying disease. In addition, the preoperative quantitative assessment of pancreatic fibrosis may be useful in stratifying patients for enrollment in clinical trials evaluating as yet to be determined techniques for decreasing the risk of clinically relevant postoperative pancreatic fistula.

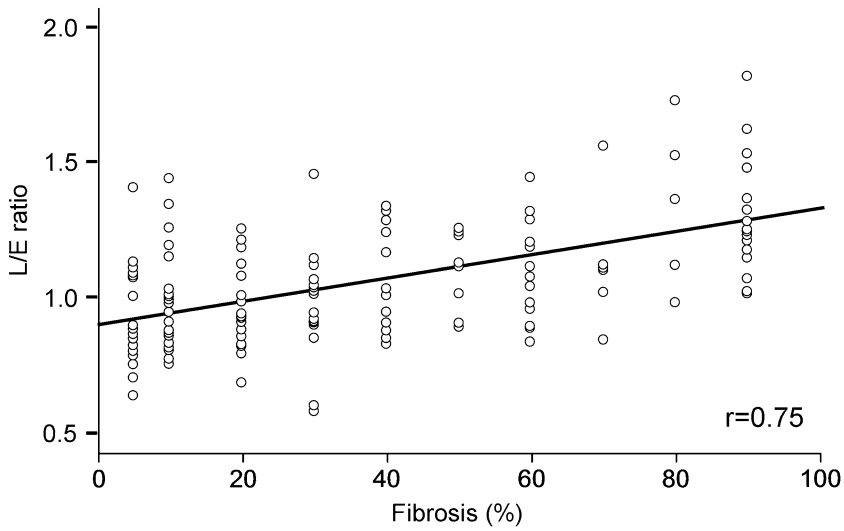

Fig. 2 Correlation between CT enhancement ratio (L/E ratio) and pancreatic fibrosis by histology (r=0.75; P< 0.001)

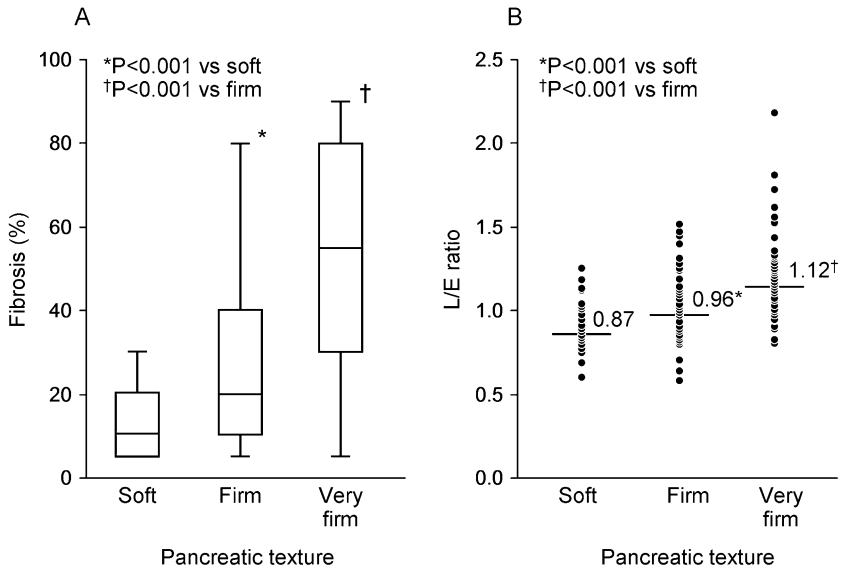

Fig. 3 Correlation between pancreatic texture and histological pancreatic fibrosis (**a**) and CT enhancement ratio (L/E ratio) (**b**)

Factors underlying the development of a PAF have been extensively studied.[2,3,5,7–15,26] Soft pancreatic parenchyma is the most widely recognized risk factor for development of a PAF.[3,4,10,13] On the other hand, pancreatic fibrosis is thought to decrease the softness of the gland.[18–22,27] Recently, it has been shown that CT or magnetic resonance (MR) perfusion imaging can detect microcirculatory changes caused by collagen deposits in the liver and pancreas.[18–20,22,28,29] Romero-Gomez et al.[28] studied liver fibrosis in patients with chronic hepatitis C and concluded that optical digital analysis of conventional CT images is effective in determining the stage and distribution of liver fibrosis. Ronot et al.[29] examined 52 patients with chronic hepatitis C who underwent perfusion CT and liver biopsy at the same time. They report that CT perfusion changes occurred early during liver fibrosis and may help differentiate minimal from intermediate fibrosis. Tajima et al.[21] used dynamic contrast-enhanced MR to assess fibrosis in the remnant pancreas after PD. They describe that time–signal intensity curve (TIC) in normal pancreas showed a rapid rise followed by a rapid decline while TIC in fibrotic pancreas showed a slow rise to a peak followed by a slow decline or plateau. They conclude that the time–signal intensity curve obtained from dynamic MR is a reliable indicator for fibrosis in the remnant pancreas. We recently reported similar findings with dual-phase CT; enhancement characteristics of pancreatic parenchyma and pancreatic masses in patients with autoimmune pancreatitis were distinct from those of pancreatic carcinoma and normal pancreas.[22] As in the MR study of Tajima et al., pancreatic fibrosis was characterized by a delayed CT enhancement with a slow rise to a peak followed by a slow decline or plateau. Normal pancreas showed a rapid rise to a peak followed by a rapid decline. In the present study, we

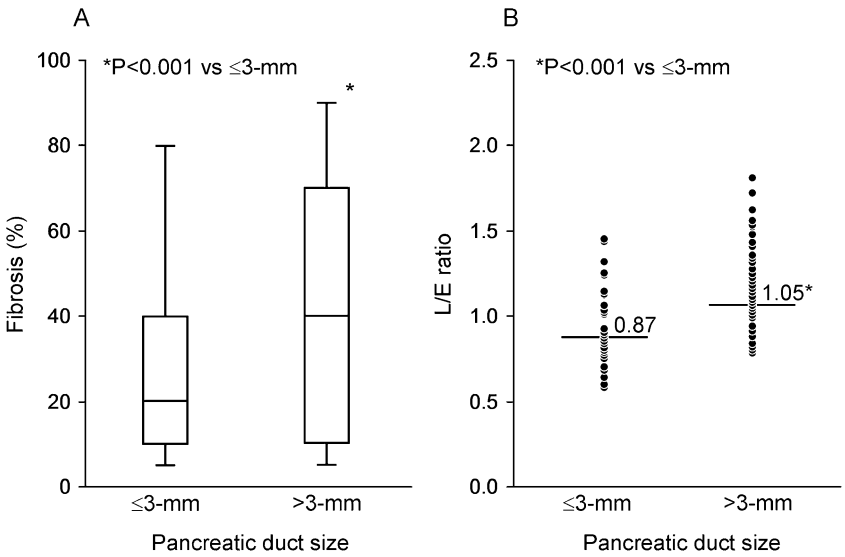

Fig. 4 Correlation between pancreatic duct size and histological pancreatic fibrosis (**a**) and CT enhancement ratio (L/E ratio) (**b**)

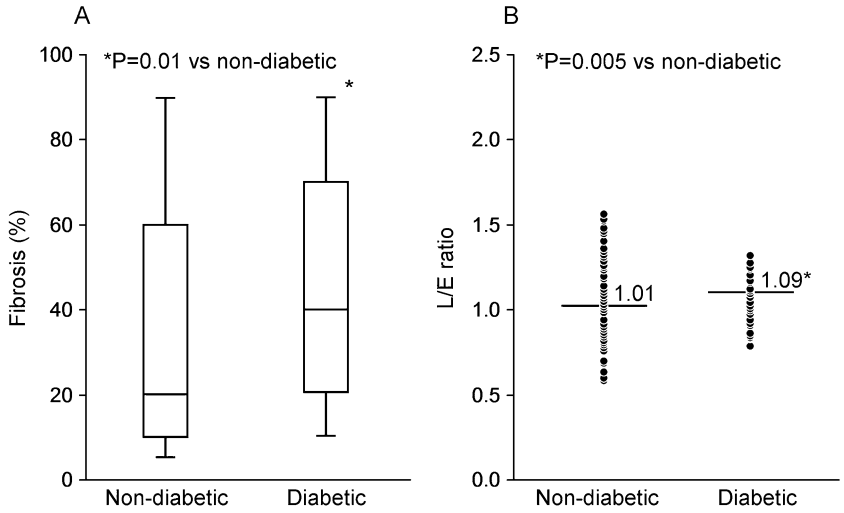

Fig. 5 Correlation between diabetes mellitus and histological pancreatic fibrosis (**a**) and CT enhancement ratio (L/E ratio) (**b**)

observed a normal pancreatic enhancement pattern in the PAF group while the no PAF group showed a delayed enhancement pattern consistent with fibrosis. To quantify the histological degree of pancreatic fibrosis based on CT enhancement characteristics, we used the pancreatic enhancement ratio or L/E ratio, which is the ratio of pancreatic enhancement in the liver (late) phase of CT to the enhancement during the pancreatic (early) phase. The histologic degree of pancreatic fibrosis showed good correlation with the L/E ratio (r=0.75). Further, a L/E ratio≤1.0 was the optimal cutoff associated with a clinically relevant PAF and maybe consistent with normal non-fibrotic pancreatic parenchyma. L/E ratio also showed good interobserver reproducibility (r=0.92). Taken together, these data suggest that calculating the L/E ratio is an excellent method to noninvasively assess pancreatic fibrosis preoperatively and risk stratify patients for development of a clinically relevant PAF. Noninvasive assessment of the degree of pancreatic fibrosis may have an impact on preoperative patient management. Neoadjuvant radiation and chemotherapy may be considered in patients with a very soft pancreas and confirmed cancer diagnosis in order to make the pancreas more fibrotic and less likely to leak.

So far no data were available that compared the surgeon's subjective assessment of pancreatic firmness with the histological degree of fibrosis. Our data showed that degree of fibrosis as well as L/E ratio correlated with the surgeon's assessment of firmness. Consistent with the previous findings, more patients with a surgeon's assessment of soft pancreas were found in the PAF group (24% vs. 12%; P=0.047). This is consistent with other studies that observed significantly higher rates of PAF in patients with soft than firm glands.[3,14,17] For example, Yeo et al.[17] reported no PAF in patients with a firm pancreas compared to a 25% PAF rate in patients with a soft pancreas (P<0.0001).

The subjective impression of pancreatic firmness maybe also influenced by pancreatic fat infiltration, a relatively common condition most frequently found in the elderly and obese.[20,30] Mathur et al.[30] compared 40 patients who developed a PAF after PD to matched controls and found that the PAF group had significantly more pancreatic fat on histological exam at the pancreatic neck margin than the control group. They concluded that fatty pancreas was a risk factor for PAF. Only few radiographic studies looked at the possibility of predicting PAF after PD based on the pancreatic fat content.[18,20] Using dual-gradient-echo MR imaging, Lee et al. found that relative signal intensity decrease correlated with pancreatic fat content and were predictive of developing a PAF after PD.[20] Similar to Marthur's study, pancreatic fat content was a risk factor for developing a PAF, and measurement of pancreatic fat content by MRI allowed them to predict occurrence of a PAF with a 72.7% sensitivity and 75.9% specificity. Using dynamic contrast-enhanced MR imaging, Dinter et al. calculated a muscle-normalized signal intensity (SI) curve with SI ratio in 72 patients who underwent PD with duct-to-mucosa pancreatojejunostomy.[18] Rapid increase in signal intensity was found in soft pancreas with a SI ratio≥1.1 (early arterial value>portal venous value), while a SI ratio< 1.1 was seen in firm pancreas. Patients with a SI ratio≥1.1 more frequently developed a PAF than patients with a SI ratio<1.1 (32% vs. 6%, P=0.006), and in multivariate

Table 5 Results of multivariable logistic regression modeling risk of clinically relevant pancreatic anastomotic failure (ISGPS grade B/C)

Variables	Odds ratio	95% confidence interval	*P* value
Body mass index	1.17	1.05–1.31	0.005
L/E ratio	0.46[a]	0.29–0.66	0.0002

ISGPS International Study Group of Pancreatic Surgery

[a] Represents each 0.1-U increase in L/E ratio

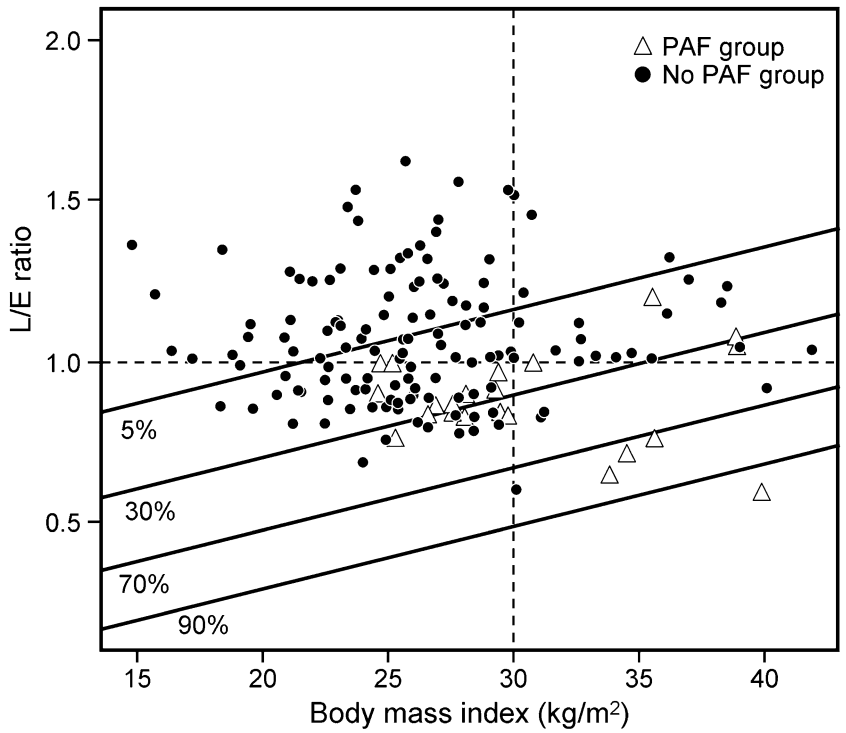

Fig. 6 Logistic regression model for predicting a PAF with L/E ratio and BMI. The *contour lines* show regions of constant 5%, 30%, 70%, and 90% predictive probability for developing a clinically relevant PAF. This indicates a clear separation of PAF cases from non-PAF cases for various L/E ratio and BMI combinations

analysis, SI ratio≥1.1 was the only preoperative parameter predicting leakage (odds ratio=7.9). Therefore, the SI ratio may be used for identifying patients at risk for developing a PAF. Their SI ratio≥1.1 corresponds to our L/E ratio≤1.0 as cutoff between soft and firm pancreas and as an independent predictor of leakage in multivariate analysis. The advantage of the LE ratio, however, is that it can quantify the risk of developing a clinically significant PAF; a 0.1-U increase in L/E ratio decreased the odds of developing a PAF by 54%. Also, pancreas protocol CT seems more readily available than dynamic pancreas protocol MRI and can be read and the LE ratio calculated by the surgeon after basic training. Interpretation and evaluation of MRI requires the availability of a radiologist experienced in that field.

Pancreatic firmness maybe also affected by underlying pancreatic pathology like chronic pancreatitis.[31–33] Further, pancreatic head neoplasms, especially ductal adenocarcinoma, can cause upstream fibrotic changes due to obstructive pancreatitis. In 1992, Buchler et al.[31] were among the first to describe that patients with chronic pancreatitis had considerably lower rates of postoperative morbidity, including PAF, than patients with pancreatic or periampullary tumors. Similarly, PAF was more frequently observed in patients with periampullary neoplasms than other pathologies. Although further studies are needed to assess the relevance of these findings, these data suggest that patients with a low degree of pancreatic fibrosis and a high pancreatic fat content are at highest risk for developing a PAF after PD.

Pancreatic duct size is another recognized risk factor for PAF.[3,7,9,10,14,15,17] In our study, patients with a dilated duct, i.e., >3 mm, had a higher degree of fibrosis than those with a small duct. Duct size also correlated with an increased L/E ratio on dual-phase CT. Consistent with these findings, more patients in the no PAF than the PAF group had a dilated pancreatic duct. A fibrotic pancreas together with a dilated duct may make the performance of the anastomosis technically easier as sutures have better purchase in the firm pancreas and the duct-to-mucosa stitches can be placed easier. Moreover, the presence of a fibrotic gland maybe associated with a decreased production of pancreatic juice reducing the risk of perioperative pancreatitis. Those factors associated with pancreatic fibrosis, while protective against postoperative PAF, might also be associated with endocrine insufficiency. Patients with diabetes mellitus had a higher degree of fibrosis and a higher L/E ratio than non-diabetic patients in our study. Friess et al.[26] demonstrated that increased pancreatic fibrosis is associated with decreased exocrine activity. Replacement of acini and islet cells by fibrotic tissue may lead to exocrine and endocrine pancreatic insufficiency.[26,27] Assessment of perfusion changes over time may also be used to monitor for fibrotic changes in the remnant pancreas for early detection of exocrine and endocrine pancreatic insufficiency.

Obesity is another factor thought to increase the risk for developing a PAF.[3,10,15] Multivariate analysis in our study identified two factors independently associated with the development of a clinically relevant PAF: L/E ratio and

BMI: Each 0.1-U increase in the L/E ratio decreased the odds of developing a clinically relevant PAF by 54%, while each 1.0-U increase in BMI increased the odds by 17%. Further, we observed a clear separation of PAF cases from non-PAF cases for various L/E ratio and BMI combinations. In the PAF group, only two patients (10%) showed a delayed enhancement pattern compared to 88 (65%) in the no PAF group. Interestingly, both of these two patients had several other risk factors for developing a PAF: high BMI, soft pancreatic texture on surgeon's assessment, small duct, lower degrees of pancreatic fibrosis, and potential for infectious complications from preoperative endoscopic manipulation.

Despite these interesting and useful findings, this analysis has inherent limitations. First, our study included a variation of imaging protocols. For our protocol, a fixed scan delay at a specific contrast injection rate is required because bolus tracking was not used. The effect of timing differences between performance of scan and arrival of contrast in the structures was not taken into account. Further, the iodine concentration of the contrast used could affect the magnitude of enhancement. However, these two factors are more important when used in conjunction with an absolute than a relative measure. Because enhancement ratio is a relative measure, it should not be affected by the amount or concentration of the utilized contrast. Also, the enhancement of the splenic vein and aorta can be used as internal control to monitor for errors in contrast injection rate or timing of the scan. Second, other circumstances that affect pancreatic perfusion have to be taken into consideration, e.g., occlusion of the SMA, celiac trunk, or portal vein. Pancreatic perfusion could also be affected by previous surgical interventions like splenectomy or partial pancreatectomy. Patients with these conditions are not suitable for analysis with the described method. None of our study patients fell into these categories. Other variables which affect the contrast transit time include idiosyncratic factors such as age, body weight, and ejection fraction. Lastly, atrophic parenchyma and fatty replacement could interfere with the correct assessment of enhancement characteristics due to limitations in the current CT technique.

Conclusion

This study showed that dual-phase CT scan can be used as a powerful tool in the noninvasive assessment of pancreatic fibrosis with an accuracy similar to that achieved by immunohistochemical staining of histopathology specimens. CT enhancement characteristics can be quantified with help of the pancreatic enhancement ratio (L/E ratio). An L/E ratio$\leq$1.0 correlated with a soft pancreas, a small pancreatic duct, and an increased risk of developing a clinically relevant PAF. L/E ratio and BMI were independent predictors for development of a clinically relevant PAF in multivariate analysis; a 0.1-U increase in L/E ratio decreased the odds of developing a PAF by 54%. Therefore, CT enhancement characteristics of the pancreas may be useful in preoperative risk stratification, patient counseling, and to help direct the pre- and postoperative patient management. Ultimately, this may help to further improve clinical outcomes after PD.

References

1. Cameron JL, Pitt HA, Yeo CJ, Lillemoe KD, Kaufman HS, Coleman J. One hundred and forty-five consecutive pancreaticoduodenectomies without mortality. Ann Surg 1993; 217:430–435; discussion 435–438.
2. Farnell MB, Pearson RK, Sarr MG, DiMagno EP, Burgart LJ, Dahl TR, Foster N, Sargent DJ. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery 2005; 138:618–628; discussion 628–630.
3. Hashimoto Y, Traverso LW. Incidence of pancreatic anastomotic failure and delayed gastric emptying after pancreatoduodenectomy in 507 consecutive patients: use of a web-based calculator to improve homogeneity of definition. Surgery 2010;147:503–515.
4. Lillemoe KD, Cameron JL, Kim MP, Campbell KA, Sauter PK, Coleman JA, Yeo CJ. Does fibrin glue sealant decrease the rate of pancreatic fistula after pancreaticoduodenectomy? Results of a prospective randomized trial. J Gastrointest Surg 2004; 8:766–772; discussion 772–764.
5. Lowy AM, Lee JE, Pisters PW, Davidson BS, Fenoglio CJ, Stanford P, Jinnah R, Evans DB. Prospective, randomized trial of octreotide to prevent pancreatic fistula after pancreaticoduodenectomy for malignant disease. Ann Surg 1997; 226:632–641.
6. Marcus SG, Cohen H, Ranson JH. Optimal management of the pancreatic remnant after pancreaticoduodenectomy. Ann Surg 1995; 221:635–645; discussion 645–638.
7. Murakami Y, Uemura K, Hayashidani Y, Sudo T, Hashimoto Y, Nakagawa N, Ohge H, Sueda T. No mortality after 150 consecutive pancreatoduodenectomies with duct-to-mucosa pancreaticogastrostomy. J Surg Oncol 2008; 97:205–209.
8. Pedrazzoli S, Liessi G, Pasquali C, Ragazzi R, Berselli M, Sperti C. Postoperative pancreatic fistulas: preventing severe complications and reducing reoperation and mortality rate. Ann Surg 2009; 249:97–104.
9. Poon RT, Fan ST, Lo CM, Ng KK, Yuen WK, Yeung C, Wong J. External drainage of pancreatic duct with a stent to reduce leakage rate of pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized trial. Ann Surg 2007; 246:425–433; discussion 433–425.
10. Pratt WB, Maithel SK, Vanounou T, Huang ZS, Callery MP, Vollmer CM, Jr. Clinical and economic validation of the International Study Group of Pancreatic Fistula (ISGPF) classification scheme. Ann Surg 2007; 245:443–451.
11. Roder JD, Stein HJ, Bottcher KA, Busch R, Heidecke CD, Siewert JR. Stented versus nonstented pancreaticojejunostomy after pancreatoduodenectomy: a prospective study. Ann Surg 1999; 229:41–48.

12. Sarr MG. The potent somatostatin analogue vapreotide does not decrease pancreas-specific complications after elective pancreatectomy: a prospective, multicenter, double-blinded, randomized, placebo-controlled trial. J Am Coll Surg 2003; 196:556–564; discussion 564–555; author reply 565.
13. Yeo CJ, Cameron JL, Maher MM, Sauter PK, Zahurak ML, Talamini MA, Lillemoe KD, Pitt HA. A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. Ann Surg 1995; 222:580–588; discussion 588–592.
14. Lin JW, Cameron JL, Yeo CJ, Riall TS, Lillemoe KD. Risk factors and outcomes in postpancreaticoduodenectomy pancreaticocutaneous fistula. J Gastrointest Surg 2004; 8:951–959.
15. Hashimoto Y, Traverso LW. Pancreatic anastomotic failure rate after pancreaticoduodenectomy decreases with microsurgery. J Am Coll Surg 2010; 211:510–521.
16. Nakamura H, Murakami Y, Uemura K, Hayashidani Y, Sudo T, Ohge H, Sueda T. Predictive factors for exocrine pancreatic insufficiency after pancreatoduodenectomy with pancreaticogastrostomy. J Gastrointest Surg 2009; 13:1321–1327.
17. Yeo CJ, Cameron JL, Lillemoe KD, Sauter PK, Coleman J, Sohn TA, Campbell KA, Choti MA. Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial. Ann Surg 2000; 232:419–429.
18. Dinter DJ, Aramin N, Weiss C, Singer C, Weisser G, Schoenberg SO, Post S, Niedergethmann M. Prediction of anastomotic leakage after pancreatic head resections by dynamic magnetic resonance imaging (dMRI). J Gastrointest Surg 2009; 13:735–744.
19. Kim T, Murakami T, Takamura M, Hori M, Takahashi S, Nakamori S, Sakon M, Tanji Y, Wakasa K, Nakamura H. Pancreatic mass due to chronic pancreatitis: correlation of CT and MR imaging features with pathologic findings. AJR Am J Roentgenol 2001; 177:367–371.
20. Lee SE, Jang JY, Lim CS, Kang MJ, Kim SH, Kim MA, Kim SW. Measurement of pancreatic fat by magnetic resonance imaging: predicting the occurrence of pancreatic fistula after pancreatoduodenectomy. Ann Surg 2010; 251:932–936.
21. Tajima Y, Matsuzaki S, Furui J, Isomoto I, Hayashi K, Kanematsu T. Use of the time-signal intensity curve from dynamic magnetic resonance imaging to evaluate remnant pancreatic fibrosis after pancreaticojejunostomy in patients undergoing pancreaticoduodenectomy. Br J Surg 2004; 91:595–600.
22. 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.
23. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005; 138:8–13.
24. Harrell F. Regression modeling strategies. New York: Springer, 2001.
25. R: A Language and Environment for Statistical Computing. Version 2.10.1. Available from: R Foundation for Statistical Computing, Vienna, Austria. Available at: http://www.R-project.org.
26. Friess H, Malfertheiner P, Isenmann R, Kuhne H, Beger HG, Buchler MW. The risk of pancreaticointestinal anastomosis can be predicted preoperatively. Pancreas 1996; 13:202–208.
27. Hamanaka Y, Nishihara K, Hamasaki T, Kawabata A, Yamamoto S, Tsurumi M, Ueno T, Suzuki T. Pancreatic juice output after pancreatoduodenectomy in relation to pancreatic consistency, duct size, and leakage. Surgery 1996; 119:281–287.
28. Romero-Gomez M, Gomez-Gonzalez E, Madrazo A, Vera-Valencia M, Rodrigo L, Perez-Alvarez R, Perez-Lopez R, Castellano-Megias VM, Nevado-Santos M, Alcon JC, Sola R, Perez-Moreno JM, Navarro JM, Andrade RJ, Salmeron J, Fernandez-Lopez M, Aznar R, Diago M. Optical analysis of computed tomography images of the liver predicts fibrosis stage and distribution in chronic hepatitis C. Hepatology 2008; 47:810–816.
29. Ronot M, Asselah T, Paradis V, Michoux N, Dorvillius M, Baron G, Marcellin P, Van Beers BE, Vilgrain V. Liver fibrosis in chronic hepatitis C virus infection: differentiating minimal from intermediate fibrosis with perfusion CT. Radiology 2010; 256:135–142.
30. Mathur A, Pitt HA, Marine M, Saxena R, Schmidt CM, Howard TJ, Nakeeb A, Zyromski NJ, Lillemoe KD. Fatty pancreas: a factor in postoperative pancreatic fistula. Ann Surg 2007; 246:1058–1064.
31. Buchler M, Friess H, Klempa I, Hermanek P, Sulkowski U, Becker H, Schafmayer A, Baca I, Lorenz D, Meister R, et al. Role of octreotide in the prevention of postoperative complications following pancreatic resection. Am J Surg 1992; 163:125–130; discussion 130–121.
32. Traverso LW, Kozarek RA. Pancreatoduodenectomy for chronic pancreatitis: anatomic selection criteria and subsequent long-term outcome analysis. Ann Surg 1997; 226:429–435; discussion 435–428.
33. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, Hruban RH, Ord SE, Sauter PK, Coleman J, Zahurak ML, Grochow LB, Abrams RA. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg 1997; 226:248–257; discussion 257–260.

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ORIGINAL ARTICLE

ERCP and Endoscopic Sphincterotomy (ES): A Safe and Definitive Management of Gallstone Pancreatitis with the Gallbladder Left In Situ

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Abstract
Background and Aims UK guidelines recommend that patients with gallstone pancreatitis have cholecystectomy within 2 weeks of their pancreatitis. A proportion of these are elderly with significant comorbidities rendering them high risk for general anaesthesia and surgery. Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (ES) may offer a safe alternative to cholecystectomy as definitive treatment in these patients.
Patients and Methods A retrospective review of all cases of gallstone pancreatitis presenting between 1999 and 2009 was undertaken.
Results One hundred one patients underwent ERCP and ES as a definitive treatment for gallstone pancreatitis with a median age of 78 years (range, 43–96 years) and a median American Society of Anesthesiologists grade of 2. Three patients died from pancreatitis despite successful ERCP. Eighty-nine patients were successfully treated with an ERCP alone, and 84 patients (94%) had no recurrence of pancreatitis with a mean follow-up of 41 months (±32 months, range 4–118 months). The total patient follow-up was 3,260 months. Twenty-seven patients (33%) died within the follow-up period of unrelated causes, explaining the lower than expected median follow-up. Five patients had a recurrence of pancreatitis during follow-up (6%).
Conclusion ERCP with ES is a safe alternative to laparoscopic cholecystectomy to prevent further attacks of gallstone pancreatitis in high-risk surgical patients and the elderly.

Keywords Cholecystectomy · Pancreatitis · Gallstones · ERCP and ES

Introduction

The incidence of pancreatitis is increasing and approximately 50% of these cases are related to gallstone disease.[1] The role of gallstones in the aetiology of pancreatitis was first described by Opie in 1901.[2] The passage of gallstones through the ampulla of Vater may precipitate an attack of pancreatitis[3–6] with the length of time that the calculus is impacted at the sphincter of Oddi relating to the severity of the episode.[7] The benefits of early endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (ES) in acute severe pancreatitis compared with no treatment[8,9] and the role of ERCP and ES in preventing recurrence of pancreatitis prior to interval cholecystectomy have been well documented.[10,11] Despite the benefit of ERCP in acute cases, cholecystectomy is still recommended in the UK within 2 weeks of their pancreatitis.[12] In an ageing population with increased comorbidities however, this treatment is not always appropriate. ERCP and sphincterotomy alone has been shown to be effective in the prevention of gallstone pancreatitis, and this has increasingly been used in the elderly and frail,[13–15] but these studies are often limited by small patient numbers or short duration of follow-up. Only the study by Vazquez-

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Iglesias et al.[13] which followed up 88 patients over a median follow-up period of 51 months supports the long-term effectiveness of this strategy. We therefore present the follow-up of patients treated in this way over a 10-year period.

Materials and Methods

A retrospective analysis of all patients admitted with pancreatitis to the Norfolk and Norwich hospital between May 1999 and 2009 was performed. Using computerised records, a diagnosis of pancreatitis was made when the serum amylase was three times greater than normal or if there was radiological evidence of pancreatitis. Gallstones as the aetiological factor was then confirmed after demonstration on ultrasound scan, CT scan or ERCP of gallstones in the gallbladder or biliary tree. All patients with proven gallstones on admission who underwent ERCP were further analysed by retrieval of their full clinical notes. The full clinical notes were also retrieved in any patient where the aetiology of the pancreatitis or their subsequent management was unclear. The full clinical notes were reviewed, and data regarding demographics, inpatient management, and any evidence of recurrence of pancreatitis or biliary-related admissions after discharge were then extracted. Recurrent pancreatitis was diagnosed if there was a consistent history with biochemical or radiological evidence of pancreatitis on repeat admission. Statistical analysis was undertaken using Fisher's exact test.

During the study period, there were 1,132 admissions for pancreatitis with an equal sex distribution. The median age was 62. Twenty-two patients whose notes had been routinely destroyed were excluded; they had died in 1999 or 2000 and in line with Department of Health policy had their notes destroyed 10 years after death. The documented cause for each episode of pancreatitis is listed in Table 1. Thirty-seven patients (3%) died as a result of acute pancreatitis.

Results

There were 536 cases (48%) of gallstone pancreatitis. The mean age at presentation was 62±18.4 years, with a female to male ratio of 2:1. Full hospital follow-up was available on 524 of 536 admissions (98%). Twelve patients lived elsewhere in the UK, and follow-up was performed in their local hospital and was not available for this review. Seventeen patients died during their acute admission before any intervention by ERCP or surgery and were excluded from further analysis, leaving 507 cases of gallstone pancreatitis in our review.

Table 1 Table to show the aetiology of pancreatitis of patients admitted to the NNUH between 1999 and 2009

Aetiology	Number of cases
Gallstones	536
Alcohol	116
Idiopathic	285
Autoimmune	3
Drugs	6
Hypercholestrolaemia	8
Hypercalcaemia	3
Trauma	2
Tumour (benign or malignant)	16
Post-ERCP	16
Recurrent pancreatitis, aetiology unknown	43
Pancreatitis post-cholecystectomy	69
Congenital	3
Other	4

Three hundred ten (61%) patients underwent cholecystectomy alone, and 62 patients underwent ERCP and planned cholecystectomy (12%). These will be considered together. One hundred one patients (20%) were managed with ERCP and ES alone with the remaining 34 (7%) being deemed unfit for intervention (Fig. 1).

Cholecystectomy

The mean age of the patients undergoing cholecystectomy alone or ERCP and cholecystectomy was 56± 17.7 years. In total, 371 underwent a cholecystectomy (±ERCP) as definitive management of gallstone pancreatitis. Twenty-three patients had a further episode of pancreatitis following cholecystectomy during the 10-year follow-up period giving a recurrence rate of pancreatitis following cholecystectomy of 6%.

ERCP and ES Alone

The 101 patients who underwent ERCP and ES as a definitive treatment for gallstone pancreatitis had a mean age of 76±9.5 years and a median American Society of Anesthesiologists (ASA) grade of 2 (range, 1–4; IQR, 2–3). The median Imrie score was 2 (0–5; Fig. 2). There were three deaths following ERCP (3%). Two patients died during the same admission following their ERCP and ES, one the following day and the other 8 days later. These patients both had severe pancreatitis (Imrie scores of 3), were aged 84 and 88 years and were being cared for on the High Dependency Unit. The cause of death in both cases was attributed to their pancreatitis. The third patient underwent successful ERCP and ES but died within

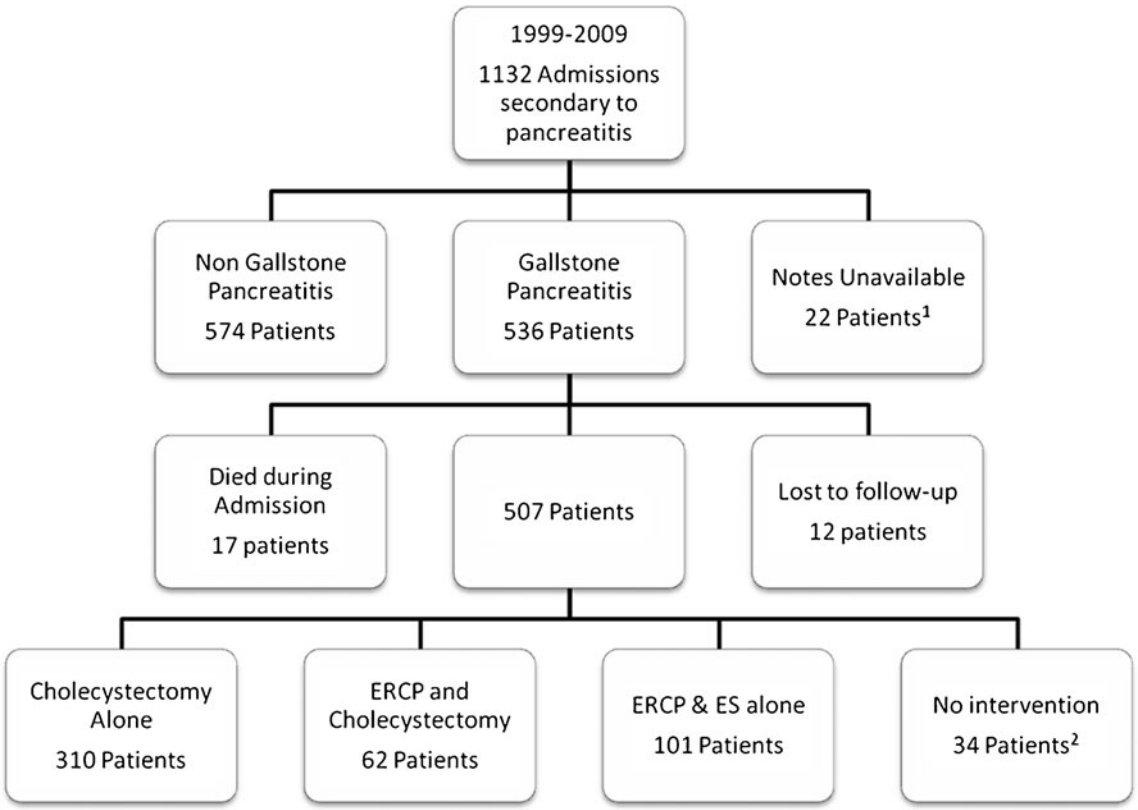

Fig. 1 A diagram to show management of gallstone pancreatitis between 1999 and 2009 at NNUH. *1* Twenty-two patients had been dead for over 10 years at the time of our review, and in line with UK Department of Health policy, their medical records had been destroyed. *2* A small cohort of 34 patients were deemed unfit for intervention by the surgeon in charge of their care, and these patients were managed expectantly

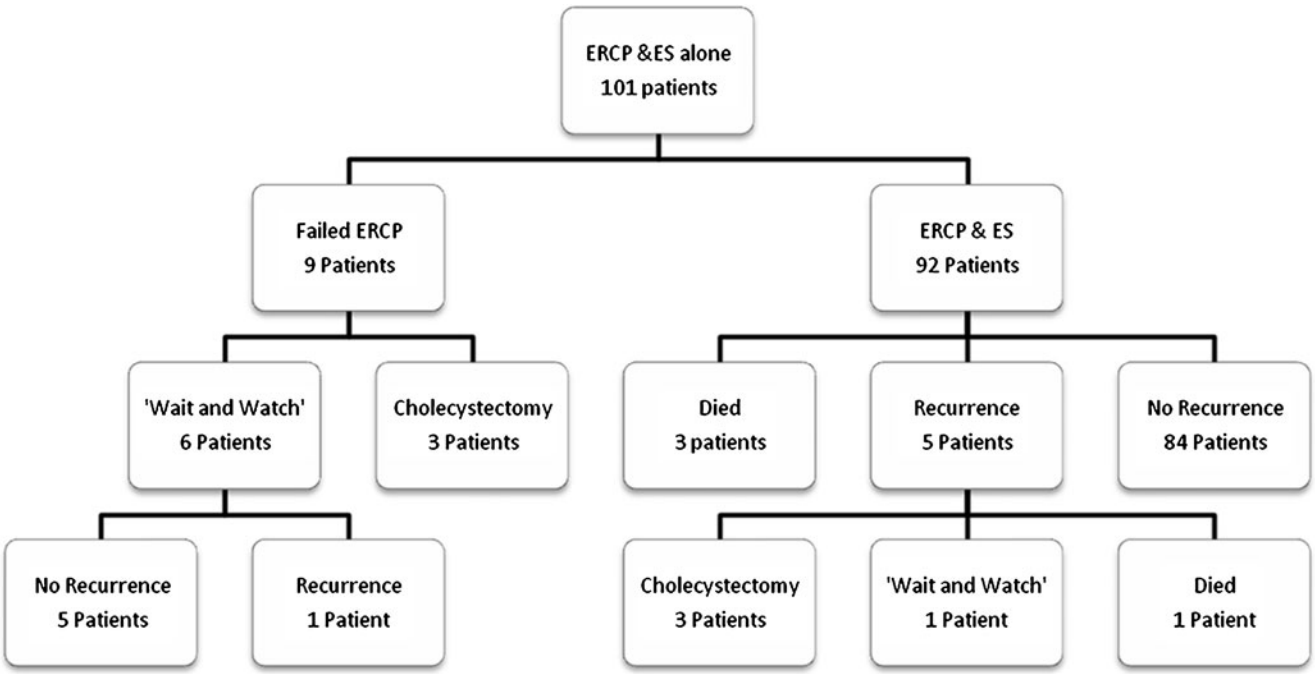

Fig. 2 A diagram to show outcome of those patients with gallstone pancreatitis who were managed with ERCP and ES alone

1 month of ERCP as a result of continued pancreatitis having been discharged to a rehabilitation ward.

Nine of the 101 (8%) patients had a failed ERCP and ES for technical reasons. Three patients were managed with a laparoscopic cholecystectomy, five, who were deemed unfit for surgery, were managed expectantly with no recurrence of pancreatitis and the final patient was successfully managed with a further ERCP and ES after failed conservative management. One patient who was managed conservatively was admitted on two separate occasions for acute cholecystitis and cholangitis which were managed conservatively.

Eighty-nine patients underwent a successful ERCP and ES, eight of which required at least two attempts to cannulate the ducts. The reasons given for failure were: oedema surrounding the ampulla at the initial ERCP (six patients), restlessness (one patient) and bleeding (one patient). One patient required a second ERCP as his liver function tests failed to improve after initial ERCP and ES. A stent was inserted with good effect. The ERCP findings for these patients are shown in Table 2.

Eighty-four patients (94%) had no recurrence of pancreatitis with a median follow-up of 29 months (range, 4–118; IQR, 12–60). The total patient follow-up was 3,260 months. Five patients had a recurrence of pancreatitis during follow-up (6%). The length of their follow-up ranged from 3 to 89 months with a median of 5 months (IQR, 4–65). Three patients were treated with cholecystectomy after normal (two patients) or failed (one patient) ERCP. One patient with an acute gastrointestinal bleeding and recurrent pancreatitis died and the final patient was managed expectantly after a failed ERCP as they were a high anaesthetic risk. Twenty-eight patients (30%) died within the follow-up period of unrelated causes, explaining the lower than expected median follow-up in both groups.

There was no significant difference in the recurrence rate between those managed with ERCP and ES and cholecystectomy (P=0.8132). The median length of stay of patients following ERCP was 2 days (range, 1–49; IQR, 1–7) with a median total length of stay of 11.5 days (range, 4–85; IQR, 8–20). One ERCP and ES was complicated by pancreatitis post-procedure which extended the hospital stay by 30 days. Although the patient was discharged, he subsequently suffered from two episodes of acute upper gastrointestinal bleeding secondary to a duodenal ulcer, the second of which necessitated a laparotomy where pancreatitis was noted. There were no episodes of bleeding as a result of ERCP and ES. The failed ERCP and ES described above was abandoned due to bleeding at a friable ampulla in the presence of a coagulopathy, and no sphincterotomy had been performed. One patient contracted *Clostridium difficile* infection following ERCP and ES.

Table 2 Table to show the ERC findings in those who successfully underwent an ERCP and ES

Findings	Number of cases
Dilated bile ducts	7
Common bile duct stones	29
Normal	49
Stricture	1
Filling defect—no calculus	2
Fistula	1

During the follow-up period, 10% of patients (9/89) were readmitted for biliary complications: one empyema, two episodes of cholangitis, two episodes of cholecystitis and four episodes of right upper quadrant pain attributed to biliary colic in the presence of a normal amylase. The empyema was managed with a laparoscopic cholecystectomy, and both episodes of cholangitis were managed with a further ERCP and sphincterotomy despite no evidence of a stricture or common duct stone. One case of biliary colic was recurrent and was managed with a laparoscopic cholecystectomy. The other cases were managed conservatively.

Wait and Watch

Thirty four patients were managed expectantly with a mean age of 77±12.5 years, a median ASA of 2 (range, 1–4; IQR, 1–3) and a median Imrie of 3 (range, 1–4; IQR, 2–3) during a median follow-up of 34 months (range, 1–120; IQR, 13–60). Four patients had a further episode of pancreatitis (12%).

Discussion

The British Society of Gastroenterologists recommends that cholecystectomy is the definitive treatment of choice following gallstone pancreatitis. The results of this study demonstrate ERCP and ES to be an effective treatment to prevent recurrence of pancreatitis secondary to gallstones with a low complication rate. The recurrence rate of pancreatitis of 6% is higher than the results published by Vazquez-Iglesias,[13] Welbourn,[14] and Lee[15] who quote figures of 2%, 0% and 0%, respectively. The discrepancy between the published data is most likely due to the small numbers and short follow-up by Welbourn and Lee since two of our recurrences occurred at 24 and 60 months. The presence of fibrosis following ES is named as a cause of recurrence of pancreatitis,[13,14] but in those cases in this study where a further ERCP was undertaken, there was no evidence of fibrosis to explain the recurrence. All patients in this study had documented evidence of gallstones, either

radiologically or at ERCP, but at recurrence, there were no common bile duct (CBD) stones on repeat ERCP which revealed a dilated CBD in only one patient. It can therefore be implied that the gallstone had passed as suggested by Johnson[16] prior to the second ERCP. The cause of recurrence in this series can therefore not be explained by incomplete sphincterotomy or fibrosis.

The mortality rate from this series of ERCP and ES alone is 3% with a complication rate of 2%. Although three patients died within 30 days of their ERCP and ES, it was not felt in any of these cases that the ERCP and ES had contributed to their death giving a mortality rate of 0% which is consistent with the published data[17,18] as is the major complication rate of 1%. It is possible that the overall complication rate of 2% is an underestimation given the retrospective nature of the study, although it is the minor complications that are likely to have been underreported. The failure rate of 9% is similar to that reported by Salminen et al.[17] and in 50% of cases was due to oedema at the ampulla where a repeat ERCP and ES may have been successful if it had been attempted once the patient was well and the oedema had subsided.

This is a large retrospective study with a long follow-up (up to10 years) in the use of ERCP and ES as a definitive management for gallstone pancreatitis. As with all retrospective studies, errors can exist in the follow-up, and it is possible that the recurrence rate quoted may be an underestimation. It has been assumed that if there is no documented evidence of pancreatitis in the medical notes, then recurrence did not occur. This study involves patients under the care of 30 consultant surgeons and physicians over a 10-year period. The patients who underwent an ERCP and ES are heterogenous with varying ages and ASAs. Despite this, the ERCP and ES group had a mean age that was 20 years greater than the laparoscopic cholecystectomy group, and the heterogeneity of this group has no impact on the primary outcome of incidence of pancreatitis recurrence in the follow-up period. The net flow of the population of Norfolk over 75 years of age is one of immigration year on year over the study period.[19] This, combined with the extensive medical records, corroborates our good follow-up, but the possibility exists that patients may have moved elsewhere towards the end of the follow-up period. There is more likely to be an error in the reporting of biliary complications as these do not always require hospital admission as patients can be managed at home or by their family doctor. The biliary complication rate after ERCP and ES for common ductal stones followed by a wait and see policy ranges from 20% to 40%,[20,21] with 70% requiring cholecystectomy. These studies however had a limited follow-up, and there was an eagerness to manage recurrence with a cholecystectomy rather than a continued wait and watch policy combined with a low-fat diet which resulted in a cholecystectomy rate of 20% in our series.

Laparoscopic cholecystectomy (LC) and preoperative cholangiogram remain the gold standard in the BSG guidelines[12] but is not without risk. Elective mortality rates are low (0.5%) with conversion and complication rates of up to 5%[22–24] with no real difference for LC performed after pancreatitis except a slightly prolonged hospital stay.[25] However, the risk of LC increases with age, with conversion rates increasing to 16% and complication rates increasing to 10% in patients over 80 years of age.[26,27] This, combined with a pancreatitis recurrence rate of 6% in our study and 13% in the study by Gloor et al.,[28] makes LC a less attractive treatment option in the elderly.

Conclusion

The results of this study demonstrate that ERCP and ES combined with a low-fat diet should be used as an alternative to cholecystectomy in the treatment of gallstone pancreatitis in high-risk surgical patients and those over 75 years of age. It is not clear from this study if this approach should be adopted in those under 75 years of age due to the high risk of biliary complications, and randomised controlled trials will be needed to determine this.

Conflicts of interest None of the authors have any conflict of interests or disclosures to make.

References

1. Yadav D and Lowenfels A. Trends in the epidemiology of the first attack of pancreatitis: A systematic review. Pancreas. 2006; 33 (4):323–330.
2. Opie EL. The aetiology of acute haemorrhagic pancreatitis. Bulletin of John Hopkins Hospital. 1901; 12:182–8.
3. Acosta J, and Ledesma C. Gallstone migration as a cause of acute pancreatitis. New England Journal of medicine. 1974; 290:484–7.
4. Kelly TR. Gallstone pancreatitis: pathophysiology. Surgery. 1976; 80:488–92.
5. Kelly TR. Gallstone pancreatitis: The timing of surgery. Surgery. 1980; 88:345–9.
6. Armstrong C, Taylor T, Jeacock J, and Lucas S. The biliary tract in patients with acute gallstone pancreatitis. British Journal of Surgery. 1985; 72:551–555.
7. Acosta J, Rubio Galli O, Rossi R, Chinellato A, and Pellegrini C. Effect of duration of ampullary gallstone obstruction on severity of lesion of acute pancreatitis. Journal of the American College of Surgeons. 1997; 184:499–504
8. Neoptolemos JP, Carr-Locke DL, London NJ et al. Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis secondary to gallstones. Lancet. 1988; 2:979–83

9. Fan ST, Lai EC, Mok FP et al. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. New England Journal of Medicine. 1993; 328:228–232.
10. Sanjay P, Yeeting S, Whigham C et al. Endoscopic sphincterotomy and interval cholecystectomy are reasonable alternatives to index cholecystectomy in severe acute gallstone pancreatitis. Surgical Endoscopy. 2008; 22:1832–1837.
11. Hammarstrom LE, Stridbeck H and Ihse I. Effect of endoscopic sphincterotomy and interval cholecystectomy on late outcome after gallstone pancreatitis. British Journal of Surgery. 1998; 85:333–336.
12. UK guideline for the management of acute pancreatitis. UK working party on acute pancreatitis. Gut. 2005; 54(suppl III): iii1–iii9
13. Vazquez-Lglesias J, Gonzalez-Conde B, Lopez-Roses L et al. Endoscopic sphincterotomy for prevention of the recurrence of acute biliary pancreatitis in patients with gallbladder in situ. Long-term follow-up of 88 patients. Surgical Endoscopy. 2004; 18:1442–1446
14. Welbourn C, Beckly D and Eyre-Brook I. Endoscopic sphincterotomy without cholecystectomy for gallstone pancreatitis. Gut. 1995; 37:119–120
15. Lee J, Ryu J, Park J, et al. Roles of endoscopic sphincterotomy and cholecystectomy in acute biliary pancreatitis. Hepatogastroenterology. 2008; 55:1981–1985
16. Johnson A and Hosking S. Appraisal of the management of bile duct stones. British Journal of Surgery. 1987; 74:555–560.
17. Andriulli A, Loperfido S, Napolitano G et al. Incidence rates of post-ERCP complications: A systematic survey of prospective studies. American journal of Gastroenterology. 2007; 102:1781–1788.
18. Salminen P, Laine S and Gullichsen R. Severe and fatal complications after ERCP: Analysis of 2555 procedures in a single experienced center. Surgical Endoscopy. 2008; 22:1965–1970.
19. Data from Norfolk County Council. http://www.norfolkinsight.org.uk/population.asp. Accessed Jan 2011
20. Targarona E, Ayuso R, Bordas J et al. Randomised trial of endoscopic sphincterotomy with gallbladder left in situ verus open surgery for common bile duct calculi in high-risk patients. The Lancet. 1996; 347:926–29
21. Boerma D, Rauws E, Keulemans C et al. Wait-and-see policy or laparoscopic cholecystectomy after endoscopic sphincterotomy for bile-duct stones: a randomised trial. The Lancet. 2002; 360:761–65
22. Zacks S, Sandler R, Rutledge R et al. A population-based cohort study comparing laparoscopic cholecystectomy and open cholecystectomy. American Journal of Gastroenterology. 2002; 97:334–40
23. McMahon A, Fischbacher C, Frame S, et al. Impact of laparoscopic cholecystectomy: A population-based study. Lancet 2000; 356:1632–37
24. A prospective analysis of 1518 laparoscopic cholecystectomies. The Southern Surgeons Club. New England Journal of Medicine. 1991; 324:1073–1078
25. Sandzen B, Haapamaki M, Nilsson E et al. Cholecystectomy and sphincterotomy in patients with mild acute biliary pancreatitis in Sweden 1988 – 2003: a nationwide register study. BMC Gastroenterology. 2009; 9:80–86.
26. Brunt L, Quasebarth D, Dunnegan et al. Outcome analysis of laparoscopic cholecystectomy in the extremely elderly. Surgical Endoscopy. 2001; 15:700–705
27. Hazzan D, Geron N, Golijanin D et al. Laparoscopic cholecystectomy in octogenarians. Surgical Endoscopy. 2003; 17:773–776
28. Gloor B, Stahel P, Muller et al. Incidence and management of biliary pancreatitis in cholecystectomized patients. Results of a 7-year study. Journal of Gastrointestinal Surgery. 2003; 7:372–7.

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ORIGINAL ARTICLE

A Tailored Approach to the Management of Perforations Following Endoscopic Retrograde Cholangiopancreatography and Sphincterotomy

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Abstract
Background The management of endoscopic retrograde cholangiopancreatography (ERCP)-related perforations remains controversial. The aim of the study was to determine the incidence of perforations following ERCP, their characteristics, operative and non-operative management options and clinical outcome.
Methods A retrospective review of ERCP-related perforations, during a 21-year period, was performed. Each perforation was categorized into types I to IV according to the location, mechanism and radiographic evaluation of the injury. Comparisons were made between patients treated operatively and non-operatively.
Results Forty-four perforations (0.4%) occurred in 9,880 procedures. They were mainly caused by the passage of the endoscope (type I) in 7 (16%) and sphincterotomy (type II) in 30 (68%) patients. The management was non-operative in 32 (72%) and operative in 12 patients. In multivariate analysis, only the type of perforation (type I: endoscope-related) was found significant for predicting operative treatment. The hospital stay was longer for patients requiring an operation (median, 24 vs 9 days). The overall mortality was 2/44 (4.5%). There was no death in the non-operative group.
Conclusions The need for immediate operative intervention should be based on the type of injury and clinical findings. Patients with type I perforations should be treated surgically and primary repair should be tried. Patients with type II injuries may be treated initially non-operatively. Delayed operative intervention will be required in a minority of these patients.

Keywords ERCP · Endoscopic sphincterotomy · Complications · Perforation · Management

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) has evolved from a diagnostic tool to an interventional therapy for biliary and pancreatic diseases. The increase in volume and complexity of these procedures has led to an increase in number and spectrum of complications.[1]

The incidence of complications varies widely and appears to be related primarily to the indication for the procedure and the technical skill of the endoscopist.[2] ERCP and endoscopic sphincterotomy carry the risk of perforation of the bile duct, pancreatic duct, and duodenum. Duodenal injury is reported to have an incidence of 0.3% to 1.3%, with a reported mortality of up to 25%.[3–6] Duodenal perforations may be retroperitoneal (usually due to sphincterotomy) and much less commonly intraperitoneal (due to endoscope passage).

The management of ERCP-related perforations remains controversial. The traditional approach entails immediate surgical intervention. However, over the last decade, reports of successful conservative treatment, in selected patients, are increasing.[3,7,8] The aim of this study was to determine the incidence of duodenal and biliary perforations following ERCP, their characteristics, operative and non-operative management options, and clinical outcome.

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Patients and Methods

A retrospective review of ERCP-related perforations was conducted during a 21-year period (June 1989–August 2010) in an attempt to identify their incidence, indications and ERCP findings, management, time to intervention, and clinical outcome. All procedures, including ERCP and surgery, were performed by the same two operators (AP and AV) in tertiary referral centers.

The perforations were categorized according to the Stapfer et al. classification[3] with a modification in types III and IV (Table 1).

Primarily, clinical and radiologic criteria were used to determine conservative or surgical management. Stable patients without signs of peritonitis were observed, whereas patients with clinical signs of sepsis were operated upon. Conservative treatment consisted of the administration of parenteral fluids, broad-spectrum antibiotics, and nasogastric drainage. Total parenteral nutrition was started in malnourished patients or in patients expected to restrict oral diet for a long period. Prior to reinstituting oral intake, a contrast study or cross-sectional imaging (CT) was performed to document no retroperitoneal leakage.

Data were organized and reported as mean ± SEM or median and range. Categorical variables were compared by means of the chi-square test or Fisher's exact test. Continuous variables were analyzed using Student's *t* test or Mann–Whitney test depending on the distribution of the data. A multivariate logistic regression analysis was performed to adjust for confounding variables between operative and non-operative management. Statistical analysis was performed by using the Minitab 16 Statistical Software.

Results

During the 21-year period, 9,880 ERCPs were performed. Forty-four of these procedures (0.4%) resulted in biliary and duodenal perforations. The characteristics of the patients and type of injuries are shown in Table 2.

The most common indications for performing an ERCP were management of known or suspected choledocholithiasis in 30 patients (68%) and malignant obstructive jaundice in 9 patients (20%). Other less common indications included pancreatic duct stones, postoperative bile leak, benign biliary stricture, hepatojejunal stenosis, and ampullectomy. The mechanisms of injury are shown in Table 3. The pre-intervention plan was executed endoscopically with success in 35 patients (79%); however, nine procedures were abandoned prematurely because of the perforation. After recognition of the perforation, 32 patients (74%) were managed non-operatively, and 12 (26%) underwent an operation (Table 4). The mean hospital stay for the entire group was 18±3 days (range, 4–95) with two deaths (4.5%).

In seven patients with type I perforation, the injury resulted from passage of the endoscope. Three of them had a history of gastrectomy and Billroth II reconstruction. The perforation was immediately recognized in six patients, and the endoscopic procedure was completed in two of them. One had an endoscopic sphincterotomy and stone extraction and the other placement of a plastic stent for drainage of malignant obstructive jaundice, so that only repair of the perforation was needed at the time of surgery. All six patients had an immediate operation (Table 4). Primary repair was tried in four and tube-duodenostomy in one patient, with simultaneous treatment of any retained common bile duct (CBD) stones. In a patient with pancreatic cancer, during the exploratory laparotomy, the tumor was found to be resectable, and a Whipple's procedure was performed. Two patients, aged 85 and 93, died from respiratory insufficiency and aspiration pneumonia 5 and 60 days postoperatively, respectively. In one patient, the perforation was identified the next day. She was apyrexial, with no signs of sepsis, with mild abdominal pain, and she was treated conservatively with success. Re-operation was required in patient 2 (Table 4) after a primary repair, and a tube-duodenostomy was performed because of leaking from the closure site.

There were 30 patients with type II injury. The perforation was caused by the sphincterotomy, and in eight of them (26%), a needle-knife precut was performed. The injury was identified during the procedure in all but one patient. In that patient, the perforation was identified 24 h later by using CT scan. The pre-intervention plan was completed in 25 cases (83%). Six patients (20%) required operative intervention. That included drainage of the retroperitoneal space and common bile duct exploration (CBDE) with T-tube placement for patients with retained CBD stones and intraoperative stent placement for patients with malignancy (Table 4). One patient with type II injury

Table 1 Modified classification of ERCP-related perforations

Type	Definition
I	Lateral or medial duodenal wall perforations (endoscope related)
II	Periampullary perforations (sphincterotomy related)
III	Ductal or duodenal perforations due to endoscopic instruments (not guidewires)
IV	Guidewire perforation with presence of retroperitoneal air at X-ray

Table 2 Characteristics of the patients and injuries

Number of pts	44
M/F	11/33
Median age (years, range)	62 (36–93)
Periampullary diverticula	5 (11%)
Billroth II gastrectomy	3 (7%)
Type of injury	
I	7 (16%)
II	30 (68%)
III	5 (11%)
IV	2 (4%)

was operated the same day. The remaining patients failed to respond to the conservative treatment and were operated after 4 to 15 days. A covered self-expandable metallic biliary stent (SEMBS) was placed endoscopically in order to cover the laceration (Fig. 1) in three patients (two during the initial ERCP and one at repeat ERCP after the operation). In two patients without malignancy, the stents were removed a month later. A CT-guided percutaneous drainage of a retroperitoneal abscess was required in one patient. All patients with type II injury had a complete recovery.

Type III perforations were related to basket entrapment (2/5), balloon dilatation of strictures (2/5), and lithotripsy techniques (1/5). Balloon dilatation of a malignant stricture resulted in bile duct tearing and was treated with placement of a plastic stent. One patient with stenosis of a hepatojejunal anastomosis, performed for CBD injury during laparoscopic cholecystectomy, had tearing of the anastomosis during dilatation. The endoscopic procedure in that patient was performed through a subcutaneous access loop. She was treated non-operatively but with percutaneous drainage of a collection 5 days later. All patients with type III injuries were treated non-operatively, but two patients required percutaneous drainage.

The two patients with type IV injury were treated conservatively with success.

Thirty-two patients were treated non-operatively. A CT scan (Fig. 2) was performed in most of these patients for the exclusion of contrast leaking from the duodenum and the existence of intraperitoneal or retroperitoneal fluid collections. CT-or US-guided percutaneous drainage of retroperitoneal abscesses or fluid collections was required in three patients.

Table 3 Mechanisms of endoscopic perforations

Mechanism	
Sphincterotomy	30[a]
Endoscope-related	7
Guidewire	2
Dilatation of stricture	2
Difficult stone extraction (basket)	2
Lithotripsy	1

[a] Needle-knife preceded in eight patients

Operative intervention was required in 12 patients. The operations performed are shown in Table 4. Complications after operative treatment included duodenal leakage in four (33%) patients (patients 2, 6, 8, and 11) and retroperitoneal abscess in one patient (patient 12). The leakage was treated conservatively in two patients, reoperation was required in one, and repeat ERCP with placement of metallic covered stent in one. The abscess was treated with percutaneous drainage.

A univariate analysis was performed to identify the association of variables such as age, sex, ASA grade, indication for ERCP, type of perforation, and duration of hospital stay between operative and non-operative management (Table 5). An association was found between higher ASA grade (≥3) and the need for operative treatment. Patients with type I perforations were more likely to require an operation. In multivariate analysis using logistic regression, only the type of perforation remained significant for predicting operative treatment. The hospital stay was longer for patients requiring an operation (24 vs. 9 days). The overall mortality due to perforations was 4.5% (2/44). There was no death in the non-operative group, in contrast with two deaths (16%) in the operative group.

Discussion

Generally, ERCP is regarded as a safe procedure in the hands of experienced endoscopists. However, the rate of complications including bleeding, pancreatitis, cholangitis, and perforation approaches 10%.[5,9] ERCP-related perforation is a major complication, with great mortality if overlooked and left untreated.

This retrospective review of 9,880 ERCPs during a long time period identified 44 perforations, which could be one of the largest series taking into consideration that most guidewire perforations were not included in the study. All the procedures regarding endoscopic and operative interventions were performed by the same two surgeon endoscopists, who were dedicated to the treatment of biliary and pancreatic diseases. There was a tendency for more perforations during the last years of the study. The most possible explanation for this is that by growing experience, we undertake more difficult cases and cases with failed attempts at other centers.

The presence of periampullary diverticula, abnormal anatomy (Billroth II gastrectomy), and precut techniques are considered to be risk factors for perforation.[1,2] In our

Table 4 Details of patients who required operation

	Sex	Age	Perf type	Indication	Days after perf	Operation type	Hospital stay (post-ERCP)	Outcome
1	F	70	I	Malignant stricture	0	Whipple's	7	Complete recovery
2	M	56	I	CBD stones	0	Primary repair, CBDE, T-tube[a]	78	Complete recovery
3	M	85	I	CBD stones	0	Primary repair, CBDE, T-tube	5	Death
4	F	74	I	Malignant stricture	0	Primary repair, pyloric exclusion	19	Complete recovery
5	F	75	I	CBD stones	0	Primary repair	8	Complete recovery
6	F	93	I	CBD stones	0	CBDE, T-tube, tube-duodenostomy	60	Death
7	F	68	II	CBD stones	8	CBDE, T-tube, drainage	22	Complete recovery
8	F	75	II	CBD stones	4	CBDE, T-tube, drainage	95	Complete recovery
9	M	52	II	Malignant stricture	0	Drainage, stent	26	Complete recovery
10	M	49	II	Malignant stricture	13	Drainage, stent	18	Complete recovery
11	F	58	II	Dilated ducts	14	Debridement, drainage, gastrojejunostomy	70	Complete recovery
12	F	69	II	CBD stones	15	Debridement, drainage	40	Complete recovery

CBD common bile duct, *CBDE* common bile duct exploration

[a] Reoperation required (tube-duodenostomy)

series, duodenal diverticula were present in five patients (11%), which is lower than our previous published experience (20%) for patients who undergo ERCP.[10] There were no data regarding the presence of a diverticulum in all our ERCPs, and we cannot compare the association of a perforation in the entire experience. In three out of seven (43%) type I duodenal perforations, the patients had a Billroth II gastrectomy. In all of them, the perforation occurred in the third part of the duodenum during maneuvers to access the papilla through the afferent loop. The manipulations of the endoscope in association with insufflation, when the procedure takes long, are responsible for these perforations. There is controversy whether precut papillotomy increases the risk of perforation compared with sphincterotomy alone.[11] In our series, 8 out of 30 (26%) patients with type II perforation had a needle-knife precut performed. In our technique, we use needle-knife precut quite often (27%),[10] when we have difficulties at cannulation, but we do not have complete data to make true comparisons. The needle-knife technique is associated mainly with guide wire perforations, most of which are not included in our study.

There are mainly two classifications for ERCP-related perforations. Howard et al.[7] classified perforations into three types according to the mechanism of injury. Type I refers to guidewire perforations, type II to periampullary, and type III to duodenal perforations. Guidewire perforation is considered as the entrance of the guidewire into the retroperitoneal space during attempts for cannulation or attempts to pass a stricture. It may be associated with injection of contrast into the retroperitoneal space. The

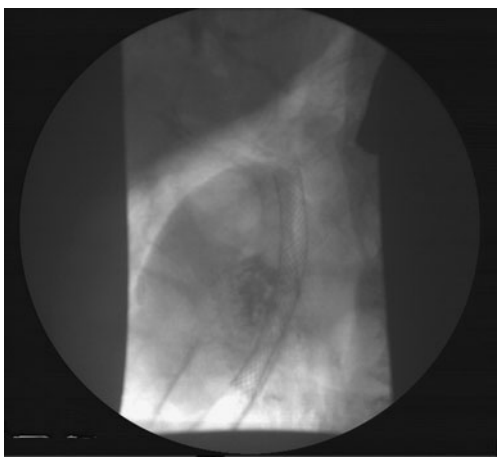

Fig. 1 A metallic biliary stent placed in a patient with type II perforation. The presence of retroperitoneal air is also obvious outlining the kidney margins

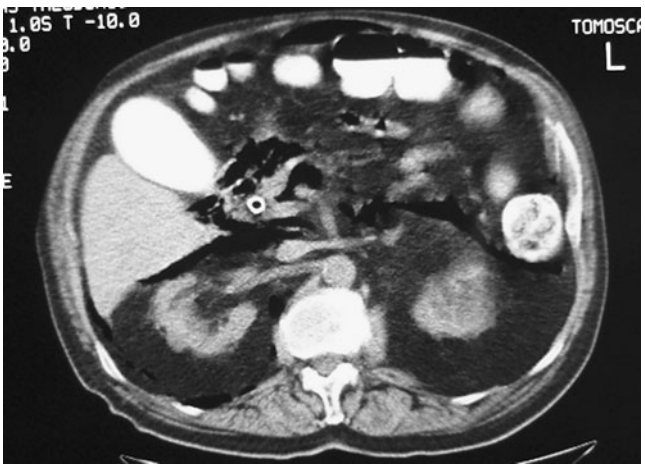

Fig. 2 A CT scan showing the presence of retroperitoneal air and a metallic stent in the common bile duct

Table 5 Univariate and multivariate analysis between operative and non-operative group

	Non-operative group	Operative group	Univariate p value	Multivariate p value[d]	Odds ratio
Median age (years)	60 (31–93)	69.50 (49/93)	0.15[a]	0.704	
Sex (M/F)	7/25	4/8	0.434[b]		
ASA (I, II/≥III)	28/4	7/5	0.033[b]	0.731	1.49 (0.15–14.6)
Type (I/II, III, IV)	1/31	6/6	0.000[b]	0.017	0.09 (0.01–0.65)
Indication (stones/malignancy)	22/5	7/4	0.241[b]		
Median hospital stay (days)	9 (4–36)	24 (7–95)	0.003[a]		
Deaths	0	2	0.069[c]		

[a] Mann–Whitney U test

[b] Chi-squared test

[c] Fisher's exact test

[d] Binary logistic regression

duodenal or bile duct tearing in such cases is quite small and closes spontaneously. In the first years of our study, we referred these events as perforations, but soon we realized that there were no clinical consequences, and we stopped noting them in our database. Only in cases where retroperitoneal air was seen at the X-ray during the ERCP, we considered them as true perforations. Stapfer et al.[3] classified perforations into four types, based on severity and anatomical location. Stapfer's classification includes the following:

1. Type I: lateral or medial duodenal wall perforation
2. Type II: perivaterian injury
3. Type III: bile or pancreatic duct injury
4. Type IV: presence of retroperitoneal air alone.

The majority of type III injuries are caused by guidewires. In our modified classification (Table 1), type III includes injuries caused by instruments such as baskets, lithotriptors, dilators, but no guidewires. The presence of retroperitoneal air alone should not be considered a true perforation since the presence of retroperitoneal air on CT scan occurs in up to 29% of asymptomatic patients after an ERCP and sphincterotomy.[12,13] When retroperitoneal air was seen at X-ray at the end of the procedure and a sphincterotomy had preceded, without any other obvious cause of perforation, we considered that as a sphincterotomy-related perforation. According to our classification, type IV includes guidewire perforations with the presence of retroperitoneal air at X-ray.

A high clinical suspicion is essential for diagnosing ERCP-related perforations. Early diagnosis and prompt treatment during the endoscopic procedure are essential for a better outcome. At the end of every endoscopic procedure, thorough evaluation for any possible perforation should be performed. The endoscopist should inspect the circumference of the duodenum carefully and check the X-ray for the presence of retroperitoneal air. This is especially true when the procedure is technically difficult; needle-knife precut has been performed; there are variations in the usual anatomy due to previous operative interventions; strictures are dilated. If there is high suspicion, contrast medium can be infused through the endoscope to facilitate identification of the injury. CT scan should be reserved for selected patients according to their clinical condition.

The clinical presentation of patients with ERCP-related perforation is non-specific. The initial symptoms, and clinical and laboratory findings are shown in Table 6.[14]

Treatment of patients with ERCP-related perforations depends on the type of injury and clinical symptomatology. A clinical index score, including fever, tachycardia, guarding, and leukocytosis, has been devised[15] to predict the need for operative intervention. Although it has not been validated prospectively, it emphasizes the importance of clinical findings to guide therapy. The presence of retroperitoneal or even free air is not reliable in determining the need for operative intervention (Fig. 3). The extent of retroperitoneal air correlates more closely with the manipulations and amount of insufflation after the injury occurs, than with the type or size of perforation.[4,16]

Table 6 Clinical and laboratory findings in patients with ERCP-related perforations[15]

Abdominal or flank discomfort	100%
Tachycardia	74%
Mild to moderate abdominal tenderness	64%
Low-grade fever	47%
Hyperamylasaimia	37%
Mild leukocytosis	32%
Peritoneal signs	18%
Subcutaneous emphysema	16%

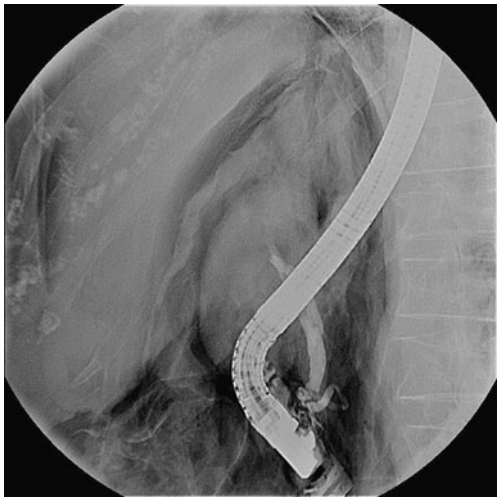

Fig. 3 Despite the presence of extensive amount of air in the retroperitoneal space, that patient was treated conservatively with success

In our series, patients with endoscope-related perforations (type I) were much more likely to require an operation (83%) in comparison with other types of perforations (17%). Type I perforations are usually large, and immediate surgical repair is required (Fig. 4). The type of surgery depends on the extent and site of the perforation and ranges from single closure to oversewing with omental patch, pyloric exclusion, gastrojejunostomy, and tube-duodenostomy. The endoscopic completion of the pre-intervention plan permits the simple repair of the perforation, which happened in two patients (patients 4 and 5; Table 3). The addition of pyloric exclusion to simple closure in patient 4 was performed because the patient had undergone gastrojejunostomy in a previous operation. In the rest type I cases (patients 1, 2, 3, and 6; Table 4), the primary disease had to be treated during the same operation. A Whipple operation was performed in one patient, and a CBDE was done in three patients. The simultaneous treatment of bile duct stones seems inevitable, but the performance of a Whipple procedure is controversial. It depends from the clinical status of the patient, patient's consent, and availability of an experienced surgeon. All the previous requirements were achieved, and the patient underwent the procedure with success. In one patient with type I injury, the diagnosis was delayed. It was a technically easy procedure, and the existence of retroperitoneal air was overlooked. Because of mild symptoms, the perforation was clinically realized next morning from the subcutaneous emphysema. The ERCP X-ray images were reviewed, and it was found that retroperitoneal air existed before the first attempt for cholangiography, so the perforation was classified as endoscope related, probably due to the rupture of a small duodenal diverticulum. CT failed to identify contrast leakage; the patient remained clinically well and was successfully treated conservatively.

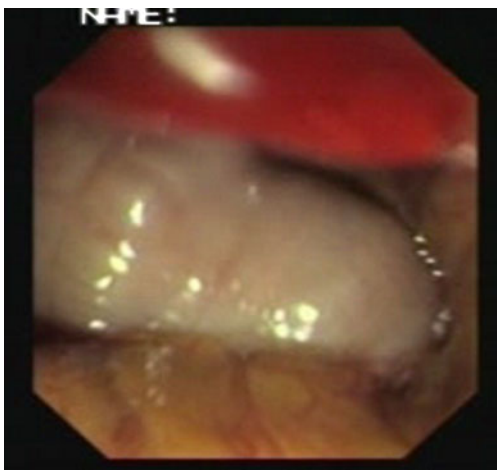

Fig. 4 During manipulations of the endoscope to access the afferent loop, in a patient with Billroth II gastrectomy, the duodenum was perforated and the endoscope passed into the peritoneal cavity. This is the endoscopic view obtained, showing the presence of a small bowel loop

Type III and IV perforations usually close spontaneously and can be managed conservatively or with placement of a biliary stent. Additional procedures like percutaneous drainage of an abscess may be required later.

The approach to patients with type II injury is controversial. Endoscopic findings like a large hole in the periampullary area or radiographic findings like large contrast extravasation during the ERCP could suggest an immediate laparotomy. The use of covered SEMBS was attempted with success, in two patients without malignancy, during the initial ERCP. Covered SEMBS cover the laceration, divert the bile away from the site of perforation, and can be easily removed after healing of the perforation. The placement of stents (either plastic or metallic) should be tried in all patients with malignancy after recognition of the periampullary perforation. Closure of ERCP-related perforations using endoclipping devices or other endoscopic modalities has also been described and seems promising.[17,18] If the periampullary laceration is not considered large, patients with type II injuries can be managed initially conservatively, provided that they are stable without clinical signs of sepsis. Five from 29 patients (17%) treated that way finally required operative treatment. CT scan is essential in these patients, since it demonstrates the presence of peritoneal or retroperitoneal fluid, which suggests continuous leak from the perforation site. The decision for surgery in these patients depends on clinical evaluation and CT findings. Operative exploration should be considered if the patient becomes septic, despite conservative treatment, especially in elderly and frail patients with no reserves to withstand the physiological stress. The type of surgery depends on local conditions. Since most of these patients have a delayed operation, primary repair is not advised, and

drainage with debridement of necrotic retroperitoneal tissue is applied. Simultaneous treatment of retained bile duct stones is advisory with CBDE and T-tube placement. In patients with malignancy (which was considered previously unresectable in our patients), the placement of a plastic stent intraoperatively was possible, and the jaundice was palliated during the same procedure. Using the above-described methodology, there was no mortality in patients with type II injury, even with delayed surgery.

Conclusions

Guidewire perforations with no presence of retroperitoneal air should not be considered as true perforations. The need for immediate operative intervention should be based on the type of injury and clinical findings. Type I perforations should be treated surgically. Primary repair should be tried in these patients, although sometimes it will leak. If the pre-intervention plan was not completed during endoscopy, simultaneous treatment of the underlying disease (stones and malignant jaundice) should be undertaken. Advances in technology, such as endoscopic suturing devices, may permit non-operative treatment in the near future. Type II injuries may be treated initially non-operatively, unless there is a large hole. The placement of covered SEMBS for a short period facilitates healing. Delayed operative intervention will be required in a minority of patients and should depend on clinical findings, laboratory tests, and CT imaging. Primary repair should be avoided in these patients. Debridement with drainage of the retroperitoneal space is essential, with biliary decompression and gastrojejunostomy when required. Non-operative treatment is usually sufficient for type III and IV injuries. Elderly patients with comorbidities need special care.

Disclosures Drs. Andreas Polydorou, Antonios Vezakis, Georgios Fraguludis, Demetrios Katsarelias, Constantinos Vagianos, and Georgios Polymeneas have no conflicts of interest or financial ties to disclose.

References

1. Fatima J, Baron TH, Topazian MD, Houghton SG, Iqbal CW, Ott BJ, Farley DR, Farnell MB, Sarr MG. Pancreatobiliary and duodenal perforations after periampullary endoscopic procedures: diagnosis and management. Arch Surg 2007; 142:448–54; discussion 454–5.
2. Freeman ML. Complications of endoscopic biliary sphincterotomy: a review. Endoscopy 1997; 29:288–97.
3. Stapfer M, Selby RR, Stain SC, Katkhouda N, Parekh D, Jabbour N, Garry D. Management of duodenal perforation after endoscopic retrograde cholangiopancreatography and sphincterotomy. Ann Surg 2000; 232:191–198.
4. Enns R, Eloubeidi MA, Mergener K, Jowell PS, Branch MS, Pappas TM, Baillie J. ERCP-related perforations: risk factors and management. Endoscopy 2002; 34:293–98.
5. Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, Fennerty MB, Ryan ME, Shaw MJ, Lande JD, Pheley AM. Complications of endoscopic sphincterotomy. N Engl J Med 1996; 335:909–18.
6. Avgerinos DV, Llaguna OH, Lo AY, Voli J, Leitman IM. Management of endoscopic retrograde cholangiopancreatography: related duodenal perforations. Surg Endosc 2009; 23:833–38.
7. Howard TJ, Tan T, Lehman GA, Sherman S, Madura JA, Fogel E, Swack ML, Kopecky KK. Classification and management of perforations complicating endoscopic sphincterotomy. Surgery 1999; 126:658–63.
8. Preetha M, Chung YF, Chan WH, Ong HS, Chow PK, Wong WK, OOi LL, Soo KC. Surgical management of endoscopic retrograde cholangiopancreatography-related perforations. ANZ J Surg 2003; 73(12):1011–14.
9. Cotton PB, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nickl N. Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest Endosc 1991; 37:383–93.
10. Panteris V, Vezakis A, Filippou G, Filippou D, Karamanolis D, Rizos S. Influence of juxtapapillary diverticula on the success or difficulty of cannulation and complication rate. Gastrointest Endosc 2008; 68(5):903–10.
11. Lai CHE, Lau WY. Management of endoscopic retrograde cholangiopancreatography related perforation. Surgeon 2008; 6 (1):45–48.
12. De Vries JH, Duijm LE, Dekker W, Guit GL, Ferwerda J, Scholten ET. CT before and after ERCP: detection of pancreatic pseudotumor, asymptomatic retroperitoneal perforation, and duodenal diverticulum. Gastrointest Endosc 1997; 45:231–35.
13. Genzlinger JL, McPhee MS, Fisher JK, Jacob KM, Helzberg JH. Significance of retroperitoneal air after endoscopic retrograde cholangiopancreatography with sphincterotomy. Am J Gastroenterol 1999; 94:1267–70.
14. Assalia A, Suissa A, Ilivitzki A, Mahajna A, Yassin K, Hashmonai M, Krausz MM. Validity of clinical criteria in the management of endoscopic retrograde cholangiopancreatography-related duodenal perforations. Arch Surg 2007; 142(11):1059–64.
15. Knudson K, Raeburn CD, McIntyre RC, Shah RJ, Chen YK, Brown WR, Stiegmann G. Management of duodenal and pancreatobiliary perforations associated with periampullary endoscopic procedures. Am J Surg 2008; 196:975–82.
16. Ferrara F, Luigiano C, Billi P, Jovine E, Cinquantini F, D' Imperio N. Pneumothorax, pneumomediastinum, pneumoperitoneum, pneumoretroperitoneum and subcutaneous emphysema after ERCP. Gastrointest Endosc 2009; 69(7):1398–401.
17. Baron TH, Gostout CJ, Herman L. Hemoclip repair of a sphincterotomy-induced duodenal perforation. Gastrointest Endosc 2000; 52(4):566–568.
18. Multignani M, Iacopinin F, Dokas S, Larghi A, Familiari P, Tringali A, Costamagna G. Successful endoscopic closure of a lateral duodenal perforation at ERCP with fibrin glue. Gastrointest Endosc 2006; 63:725–27.

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ORIGINAL ARTICLE

Clinical Presentations and Surgical Approach of Acute Intussusception Caused by Peutz–Jeghers Syndrome in Adults

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Abstract
Introduction Peutz–Jeghers syndrome is a rare autosomal dominantly inherited disease characterized by mucocutaneous pigmentations and gastrointestinal polyps. The polyps are located predominantly in the small intestine and usually cause intussusceptions. Adult intussusception caused by Peutz–Jeghers syndrome occurs very rarely. The purpose of this study was to analyze the clinical characteristics, preoperative diagnosis, and surgical management of Peutz–Jeghers syndrome associated with acute intussusception in adult patients.
Discussion Consecutive patients with the postoperative diagnosis of acute intussusception caused by Peutz–Jeghers syndrome from 1995 to 2010 were reviewed retrospectively for this study. Data concerning clinical considerations, morphological examinations, and surgical procedure were analyzed. Different clinical manifestations were presented in patients with intussusception due to Peutz–Jeghers syndrome. Computed tomography associated or not with ultrasonography may be the most accurate examination for acute intussusceptions caused by Peutz–Jeghers syndrome. Surgical intervention is the first choice regimen in acute intussusceptions caused by Peutz–Jeghers syndrome. Prophylaxis and polypectomy of the entire small bowel is a worthy way in Peutz–Jeghers syndrome patients to reduce the frequency of laparotomies.

Keywords Peutz–Jeghers syndrome · Intussusception · Intestinal polyposis · Acute abdomen

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Introduction

Intussusception is the most common cause of intestinal obstruction in children between ages 3 months and 6 years and is the second most common cause of acute abdomen in this age group. However, adult intussusception is relatively rare, and only 5% to 16% of cases have been previously reported [1]. Although the clinical, pathologic, and radiologic features of the complications of intussusception are well known, a variety of clinical manifestations makes the preoperative diagnosis difficult. Diagnosis even can be delayed because of its longstanding, intermittent, and nonspecific symptoms, and most cases are diagnosed at emergency laparotomy subsequently requiring bowel resection and anastomosis of the intussusception in most adult cases.

Peutz–Jeghers syndrome (PJS) is an autosomal dominant rare syndrome characterized by pigmented mucocutaneous spots and intestinal and extraintestinal polyposis. Polyps are most common in the small intestine, but can also occur in the stomach, large bowel, and nasal passages. Gastrointestinal polyps can result in chronic bleeding and anemia and cause recurrent obstruction and intussusception requiring repeated laparotomy and bowel resection. Furthermore, intussusception is the most frequent abdominal complication of PJS. Children with PJS have a high risk of suffering from intussusception, but it occurs very rarely in adults. The association between adult intussusception and PJS is a very predictable but unusual complication. Adult intussusception is elusive and difficult to diagnose due to its vague presentation. Most patients have a characteristic clinical course of recurrent episodes of polyp-induced intussusception. Although surgical resection is recommended, repeated abdominal surgery for intussusception may cause short bowel syndrome.

The purposes of the present study are to review and update the data of 11 adult patients during the last 152 months and to improve the preoperative diagnosis and eventually determine and discuss the value of surgical management and prevention.

Methods

Patients were followed prospectively between January 1995 and May 2010, and clinical data from the period before 1995 were collected retrospectively. We included patients diagnosed with PJS on the basis of the diagnostic criteria as defined by the World Health Organization [2]. Selection criteria included family history of PJS, intestinal polyposis, and pigmented macules of buccal mucosa, lips, fingers, and toes [2, 3]. The following data were collected: sex, date of birth, family history of PJS, diagnosis of PJS, diagnosis and characteristics of intussusception, and follow-up. Information was collected on the family history of each of the affected patients. Clinical findings of 11 patients were collected from patients' charts, operative notes, and pathology reports. Presentation of intussusception was defined as an acute abdomen in case of acute abdominal pain in combination with nausea and vomiting. Intussusception characteristics that were recorded included date of diagnosis as well as data on confirmation, presentation, localization, therapy, and size of the polyp causing the intussusception. Localization of the intussusception was classified as small intestinal or colonic based on the site of the leading point. The small intestinal intussusceptions were further subdivided according to the most proximal small intestinal segment involved.

Surgical procedures are performed in all cases. We only used the size of en bloc resected polyps, as measured by the pathologist, in order to get an objective measurement. Finally, all diagnoses were surgically proven by laparotomy and routine pathological examination. The study protocol was approved by the West China Hospital Ethics Committee and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Results

A total of 11 PJS patients from 11 families were included for analysis. The patients ranged in age from 19 to 67 years old, with a mean age of 31.7 years. Female predominated in a ratio of 2.7:1 (Table 1). Ten patients had family history with PJS. Eleven families with PJS, altogether containing 25 affected and 40 unaffected individuals, were identified through probands (Fig. 1). In 25 PJS patients from 11 families, 11 adult patients (44%) had suffered from acute intussusception, and 2 patients (8%) had experienced at least one intussusception. Case 7 had a prior laparotomy. No polyps had been detected in ten patients in the past, and one had a history of gastric polypectomy (Table 1). All of the patients from PJS families did not have screening before surgery.

The different clinical manifestations were summed up in Table 1. In 11 patients, 10 had differently hyperchromatic spots in the buccal mucosa, finger, and lips with more than 3 spots, but 1 patient had none. The spot diameter oscillated between 2 and 5 mm. All patients presented with an acute abdomen. Pain was the most common presenting complaint, associated or not with an intestinal obstructive syndrome. Palpable abdominal mass was found out in 72.7% of the patients. Six patients had abdominal pain along with constipation, and diarrhea developed in three patients. Hematochezia was found in three patients. Peritonitis occurred in two patients, one of which was caused by jejunal perforation (Fig. 5c). Fifty percent of the

Table 1 General characteristics of the patients

Age (years)	
19–35	n=7
35.1–39.9	n=2
>40	n=2
Gender	
Male	n=2
Female	n=9
Family history	n=10
Pigmentation	
Lips	9
Buccal	6
Finger	3
Toenails	1
Symptoms	
Abdominal pain	11
Obstruction	7
Constipation	6
Diarrhea	3
Abdominal mass	8
Hematochezia	3
Peritonitis	2

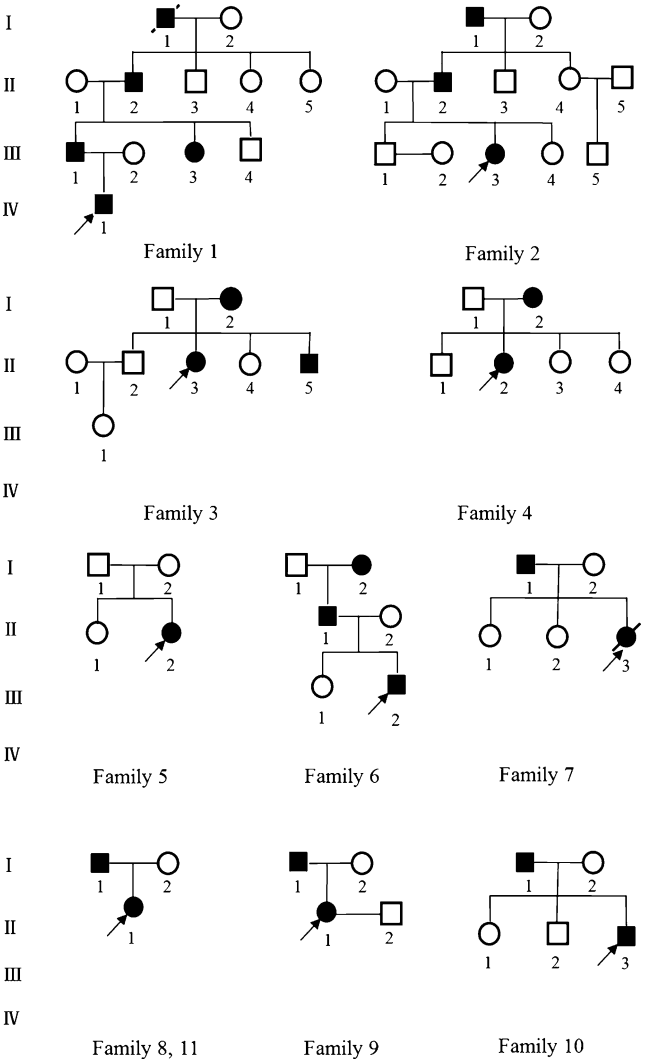

Fig. 1 Pedigrees of 11 families with Peutz–Jeghers syndrome (*arrows* represent proband)

patients had symptoms for more than 2 weeks before presentation to the hospital.

Intussusception was a preoperative diagnosis in 91% of patients (Tables 2 and 3). In 11 cases, the examinations had already been done by abdominal ultrasounds (9 times), barium enema (twice), plain abdominal radiographs (11 times), and abdominal computed tomography (CT) (8 times). When plain abdominal radiographs (nine times), abdominal ultrasonography (three times), and barium enema (one time) were not able to demonstrate intussusception, a CT scan was performed (eight times) but provided the diagnosis of intussusception eight times (Table 3). CT scan was also performed to try to precise the nature of the causative pathology (Figs. 2 and 3). Finally, preoperative diagnosis of our patients was confirmed by surgical intervention.

There were 11 patients with intussusception confirmed at operation. Polyps vary in type, shape, size, location, and number (Table 2). On the basis of 11 intussusceptions, localization of polyps was classified as small intestine in 8 events and colonic in only 2 events. These intussusceptions had been caused by polyps with a median size of 23 mm (range 10–50 mm) (Figs. 4 and 5). Different types of intussusceptions were analyzed in Table 2. The choice of procedure was determined by location, size, cause, and viability of the bowel. Overall, 11 patients underwent primary resections. Three reductions were attempted before a resection and anastomosis, but this manipulation was unsuccessful. All patients had a laparotomy and eight patients underwent enteric resection and anastomosis, and two patients underwent tumorectomy. One patient underwent enteric resection and ileostomy. Intraoperative enteroscopy (IOE) through the incision point was performed in order to examine the small intestine segment without the need for additional enterotomies in two patients (Fig. 4). Histological study reported the presence of an acute inflammatory infiltrate and hamartomatous polyps. Microscopically, typical Peutz–Jeghers polyp shows branched proliferation of non-atypical glandular cells with a core of smooth muscle (Fig. 6).

This manipulation was successful in 11 patients. No patient suffered postoperative complications. In this study, no anastomotic leak was noticed. Of these 11 patients, all underwent successful surgeries, and 1 patient died 5 months after surgery because of metastatic melanomas (Table 2). A resection of the lesion by tumorectomy has been performed once with an adenoma of ileum.

Table 2 Clinical characteristics of adult intussusception caused by Peutz–Jeghers syndrome

Case	Preoperative diagnosis	Previous surgery	Intraoperative manifestation	Location of polyps	Size (mm)	Surgical treatment	Cancer	Follow-up
1	No/BE	No	Jejunoileal intussusception	Jejunoileum	50	Resection/ anastomosis		?
2	Yes/BE, US	No	Ileocolic intussusception	Ileum	17	Resection and ileostomy		?
3	Yes/US	No	Jejunojejunal intussusception	Jejunum	20	Resection/ anastomosis		Alive at 152 months
4	Yes/CT	No	Ileocolic intussusception	Colon	31	Tumorectomy	Colonic adenocarcinoma	?
5	Yes/US, CT	No	Jejunojejunal intussusception	Jejunum	22	Resection/ anastomosis		Alive at 89 months
6	Yes/US, CT	No	Ileoileal intussusception	Ileum	10	Resection/ anastomosis		Alive at 65 months
7	Yes/US, CT	Yes/ laparotomy	Ileocolic intussusception	Colon	23	Tumorectomy	Colonic leiomyosarcoma /Metastatic melanoma	Dead at 5 months
8	Yes/US, CT	No	Jejunoileal intussusception	Jejunoileum	20	Resection/ anastomosis	Ileal adenocarcinoma	Alive at 36 months
9	Yes/US, CT	No	Jejunoileal intussusception	Jejunoileum	25	Resection/ anastomosis		Alive at 12 months
10	Yes/US, CT	No	Ileoileal intussusception	Ileum	14	Resection/ anastomosis/IOE		Alive at 4 months
11	Yes/US, CT	Yes/gastric polypectomy	Jejunojejunal intussusception	Jejunum	21	Resection/ anastomosis/IOE		Alive at 2 months

CT computed tomography, *US* ultrasounds, *BE* barium enema, *IOE* intraoperative enteroscopy

Discussion

Early diagnosis of PJS associated with acute intussusception is crucial because many of these adult patients need usually an emergency surgical treatment [4–6]. A diagnosis of intussusception caused by PJS will be based on family medical history and physical examination. Including symptoms of intussusception, there are at least two of the following clinical criteria that need to be present: a family history of the syndrome, melanin deposits, and bowel polyposis [3, 7]. Studies have shown that intussusception was observed in 47–69% in adult patients with PJS [3, 6]. Because PJS patients carry a high incidence of intussusception, a careful and detailed review of a person's medical family history is important in diagnosing PJS. Moreover, the family history can provide effective information to the patient and families about likely disease outcomes and following surveillance. At the same time, physical examination is an important element to this diagnosis [8]. The diagnosis of the syndrome is easy because the hyperpigmented spots are in general evident. The mucocutaneous pigmentations caused by melanin aggregation can be seen in 93% of patients even in infancy [9]. They are generally located around the lips, buccal, hand, foot, and sometimes perianal and genital areas (Table 1) [10]. The clinical presentation of adult intussusception varies considerably depending on the site of intussusception and the possibility of self reduction. The symptoms can range from mild abdominal pain to more acute signs of intestinal obstruction. The classic triad of abdominal pain, mass, and jam-like stools is not found and mentioned in our study [3, 5, 6, 11, 12]. In addition, it is noteworthy that some patients with a solitary Peutz–Jeghers-type polyp have none of the other clinical features associated with PJS, and it is difficult to identify before surgery [13–15]. In short, complete family medical history and physical examination by mucocutaneous pigmentation are most important in diagnosing acute intussusception caused by PJS because there is no obvious difference between PJS associated with intussusception and ordinary intussusception in other clinical manifestations.

Table 3 Preoperative examination

Procedure	No. of patients (n)	Accuracy (%)
Plain radiographs of the abdomen	11	18.2
Barium enema	2	50.0
Abdominal ultrasound	9	66.7
Abdominal CT scan	8	100.0

Conventional barium studies have nowadays been replaced by cross-sectional techniques, such as ultrasonography, CT and magnetic resonance imaging (MRI), and enteroclysis, which not only improve visualization of the

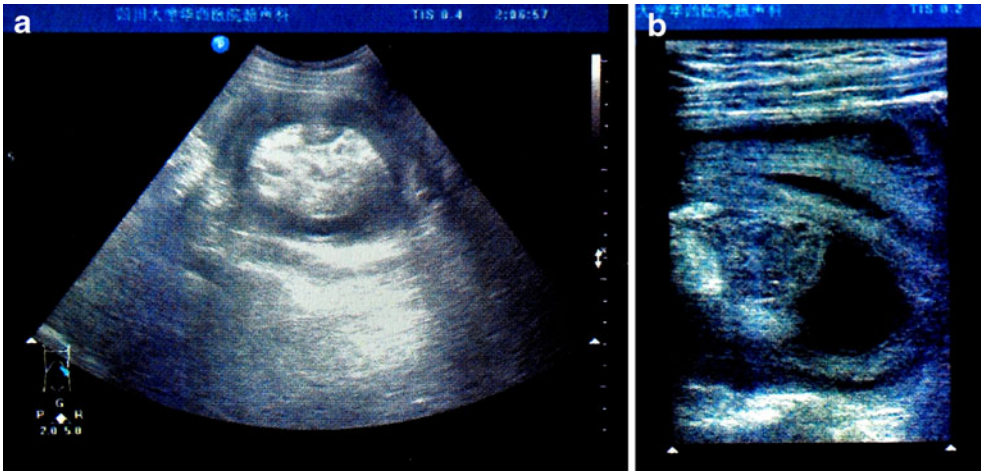

Fig. 2 Examples of emergency medicine bedside ultrasound showing adult intussusception in a PJS patient. **a** A transverse sonographic image of the left lower quadrant demonstrates a "doughnut" or "target" sign created by multiple. **b** A longitudinal image also shows the concentric layers of bowel in a separate area of intussusceptions with a nodular soft tissue mass in the center thought to be a polyp

intestinal lumen, but also detect intestinal wall and extraluminal diseases. As a noninvasive, inexpensive, and readily available method, ultrasonography may demonstrate small bowel polyps in patient with Peutz–Jeghers [8, 16]. Ultrasonography may typical show a "doughnut" or "target" sign with a nodular soft tissue mass in the center thought to be a polyp in the abdomen (Fig. 2) [8, 17]. In addition, the presence of blood flow by color Doppler between the layers of bowel is typically seen and can be helpful in making the diagnosis, though whether or not this absolutely excludes bowel wall ischemia is not known. Abdominal CT scan has been reported to be the most useful imaging modality [18]. CT is most available for making the diagnosis of adult intussusception and is helpful in revealing the underlying lesion, although a barium enema can help to diagnose colonic intussusceptions. A multicentric study shows that CT associated or not with barium enema may be the most accurate modality for diagnosis of adult intussusceptions [19]. In our study, CT scan was used eight times and made the preoperative diagnosis in eight cases. Intussusception may represent a "target mass" on both CT and ultrasound (Figs. 2 and 3). More importantly, CT scans may help to delineate the precise location of polyps because differentiating between lead point and non-lead point intussusception is important in determining the appropriate treatment and has the potential to reduce the prevalence of unnecessary surgery [20]. CT associated or not with ultrasonography is cheap, quite easy to carry out, and timely and, therefore, may be the most accurate examination for acute intussusceptions caused by PJS. It is emphasized that there is no single generally accepted approach for evaluating patients with suspected intussusception. The diagnostic approach also depends on the clinical presentation.

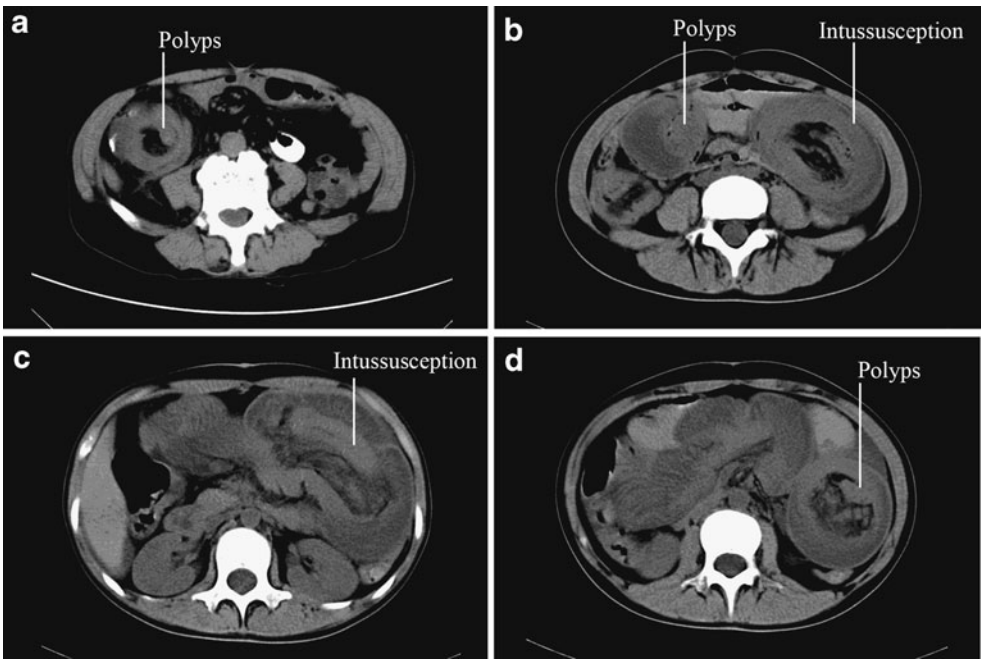

Fig. 3 **a** Abdominal computed tomography scan shows bowel wall thickening and polyps within the bowel. **b** Abdominal computed tomography scan reveals the obstructing intussusception and small intestinal polyps. **c** Computed tomography of the abdomen reveals the obstructing intussusception. **d** In the same patient as shown in **c**, polyps in the center of bowel and a doughnut-shaped mass consisting of different densities are seen in the left mid-abdomen

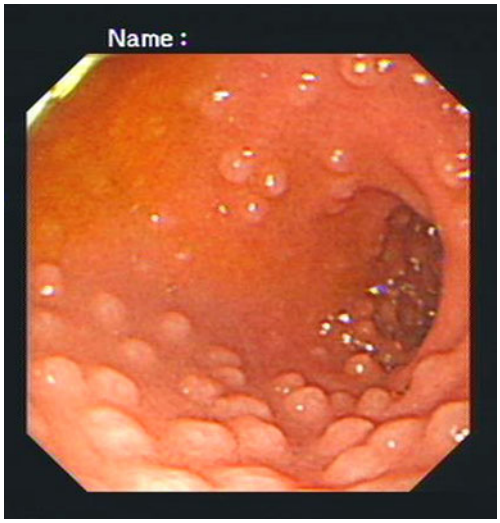

Fig. 4 Intraoperative enteroscopy view of polyps in jejunum

Although surgical resection is recommended, there is still no consensus regarding optimal management of adult intussusception [3, 19, 21]. Definitive surgical resection remains the recommended treatment in most cases of PJS associated with intussusception because of the large proportion of structural causes and the relatively high incidence of malignancy [19, 22–25]. Previous studies have also shown that the majority of the patients suffer from recurrent episodes of intussusception induced by polyps who require laparotomy [5, 26]. Few options exist for the therapeutic management of PJS. During the surgical procedure, this reduction can lead to a more limited bowel resection [27]. Based on our experience, all patients with obstructive symptoms, hematochezia, and palpable polyps associated with intussusception should undergo primary surgical resection without prior reduction to avoid unnecessary manipulation of a potential neoplasm. Surgical strategies are common with dealing with the sequelae of PJS such as small bowel intussusception due to hamartomatous polyps or resection of neoplastic lesions. The choice of procedure was determined by the location, size, cause, and viability of the bowel. Abdominal exploration with conventional resection and anastomosis of the involved section of bowel is usually recommended. Based on intraoperative biopsy, it seems logical to recommend a radical excision intestinal tumor to malignant tumor. Occasionally, ostomy is performed due to the poor general condition of the patient and insufficient preoperative preparation in emergency surgery.

In emergency surgical procedures, combined endoscopic and surgical treatment generally is advocated, including IOE with endoscopic and/or surgical resection of polyps, with or without resection of short segments of intestine [21, 28–30]. IOE is a combination of laparotomy with endoscopy, which was accepted as the ultimate diagnostic and/or therapeutic procedure for complete investigation of the small intestine.

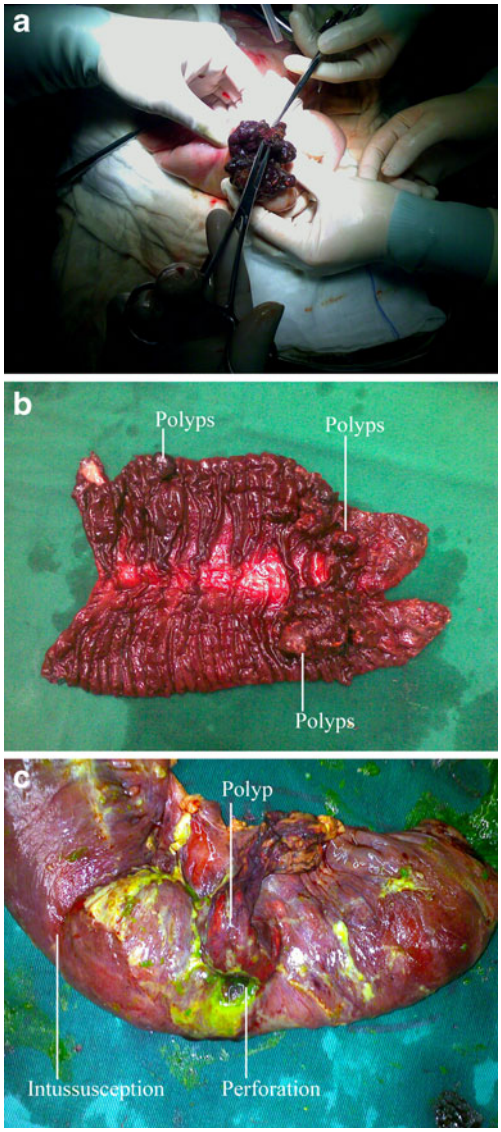

Fig. 5 **a** An intraoperative photograph showing the lobulated Peutz–Jeghers polyp that caused the intussusception. **b** Postoperative photograph demonstrating the jejunal intraintestinal polyps, responsible for intussusception. **c** Postoperative photograph revealed the intussusception segment with a leading polyp, and a perforation was found in polyp root

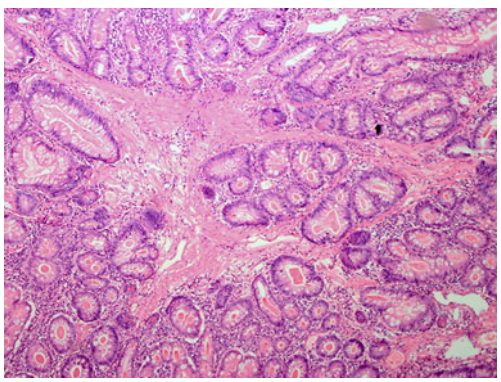

Fig. 6 Typical histological features of a Peutz–Jeghers polyp (H&E, ×100)

It allows manipulation to ensure the entire small bowel is visualized and nearly all polyps are removed in an endoscopic or surgical manner. A systematic review suggests that an attempt to clear the small intestine of polyps should be made during laparotomy in PJS patients [21]. Oncel et al [30]. have compared two groups of PJS patients. The group of PJS Patients who were operated upon using IOE to remove all small intestinal polyps did not require any further surgery within 21 patient follow-up years. But control group patients required 23 further operations within 87 patient follow-up years (2.64 operations per year). IOE for PJS improves polyp clearance without the need for additional enterotomies and may help to reduce the frequency of laparotomies. In addition, polyp size probably is the most important risk factor for intussusception, as the cause of the polypectomy is prevention of intussusception [6]. The intussusceptions are generally caused by polyps ≥15 mm in diameter in PJS patients [6]. In the light of our limited experience, when polyps ≥10 mm in diameter are discovered in non-intussusception segment, we recommend removing polyps and complete detection of the small intestine by IOE. To ensure patient safety and optimal surgical conditions, timely clearance of all small intestinal polyps and careful screening are beneficial for PJS patients [30]. Although this study has some limitations, including a limited number of patients, IOE is still a useful method for small bowel investigation and a solution for some pathological findings.

With the development of endoscopic techniques, there are other ways to prevent obstruction/intussusception in PJS patients. Combined endoscopic and surgical treatment for PJS together with gastroduodenoscopy and colonoscopy remains the best method for controlling polyposis. Endoscopic treatment has been performed with successful reduction of an ileoileal intussusception followed by endoscopic resection of the responsible polyp by using double-balloon endoscopy (DBE) in a PJS patient [31]. Endoscopic management of small bowel polyps by using DBE is safe and effective and avoids urgent laparotomy [32]. Furthermore, the use of this combined approach can lead to a healthier life and to a longer life expectancy for the patient to avoid short bowel syndrome in multiple intussusception. This combined procedure may obviate the need for emergency laparotomies for an intestinal resection and also limit the risk of the development of short bowel syndrome. Prophylaxis and polypectomy of the entire small bowel is a good procedure in PJS patients to avoid intussusception. Noteworthy, patients with PJS should be in medical care and periodic follow-up examinations should be performed such as blood cell count determination, gastrointestinal passage, colonoscopy, and esophagogastroduodenoscopy in order to avoid complications of the disease [30]. Finally, the optimal surveillance strategy remains to be established in prospective trials.

Conclusions

PJS is characterized by the association of gastrointestinal polyposis and mucocutaneous pigmentation. Gastrointestinal polyps can result in chronic bleeding and anemia and cause recurrent obstruction and intussusception requiring repeated laparotomy and bowel resection. A careful and detailed review of a patient's family medical history and physical examination are important in diagnosing PJS associated with intussusception. CT associated or not with ultrasonography may be the most accurate examination for acute intussusceptions caused by PJS. Surgical management of PJS associated with intussusception is the recommended treatment, and combined endoscopic and surgical treatment generally is advocated for controlling polyposis. Recent advances in genetic testing, magnetic resonance enterography, DBE, IOE, and capsule endoscopy should result in improved timely diagnosis and management of patients with PJS. Patients with PJS should be followed up/monitored throughout their lives because of the increased risk of malignant change and to reduce the number of laparotomies.

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References

1. Tabrizian P, Nguyen SQ, Greenstein A, Rajhbeharrysingh U, Argiriadi P, Barlow M, Chao TE, and Divino CM. Significant parameters for surgery in adult intussusception. Surgery 2010;147:227–32.
2. Hamilton SR, Aaltonen LA. (Eds.): World Health Organization Classification of Tumours. Pathology and Genetics of Tumours Edsof the Digestive System. IARC: Lyon 2000.
3. Giardiello FM, and Trimbath JD. Peutz–Jeghers syndrome and management recommendations. Clin Gastroenterol Hepatol 2006;4:408–15.
4. Haas EM, Etter EL, Ellis S, and Taylor TV. Adult intussusception. Am J Surg 2003;186:75–76.
5. Baeza-Herrera C, Garcia-Cabello LM, Najera-Garduno HM, Sanchez-Fernandez LA, Mora-Hernandez F, and Ortiz-Zuniga AI. Surgical aspects of intussusception secondary to Peutz–Jeghers syndrome. Cir Cir 2005;73:91–95.
6. van Lier MG, Mathus-Vliegen EM, Wagner A, van Leerdam ME, and Kuipers EJ. High cumulative risk of intussusception in patients with Peutz–Jeghers syndrome: time to update surveillance guidelines? Am J Gastroenterol 2011;106:940–45.
7. Giardiello FM, Welsh SB, Hamilton SR, Offerhaus GJ, Gittelsohn AM, Booker SV, Krush AJ, Yardley JH, and Luk GD. Increased risk of cancer in the Peutz–Jeghers syndrome. N Engl J Med 1987;316:1511–14.
8. Dean AJ, Lafferty K, and Villanueva TC. Emergency medicine bedside ultrasound diagnosis of intussusception in a patient with chronic abdominal pain and unrecognized Peutz–Jeghers syndrome. J Emerg Med 2003;24:203–10.

9. Choi HS, Park YJ, Youk EG, Yoon KA, Ku JL, Kim NK, Kim SM, Kim YJ, Moon DJ, Min JS, Park CJ, Bae OS, Yang DH, Jun SH, Chung ES, Jung PM, Whang Y, and Park JG. Clinical characteristics of Peutz–Jeghers syndrome in Korean polyposis patients. Int J Colorectal Dis 2000;15:35–38.
10. Higham P, Alawi F, and Stoopler ET. Medical management update: Peutz Jeghers syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:5–11.
11. Kopacova M, Tacheci I, Rejchrt S, and Bures J. Peutz–Jeghers syndrome: diagnostic and therapeutic approach. World J Gastroenterol 2009;15:5397–408.
12. Rufener SL, Koujok K, McKenna BJ, and Walsh M. Small bowel intussusception secondary to Peutz–Jeghers polyp. Radiographics 2008;28:284–88.
13. Oncel M, Remzi FH, Church JM, Goldblum JR, Zutshi M, and Fazio VW. Course and follow-up of solitary Peutz–Jeghers polyps: a case series. Int J Colorectal Dis 2003;18:33–35.
14. Lantz H, Doos WG, and Affi A. Peutz–Jeghers-type hamartomatous polyp in a patient without Peutz–Jeghers syndrome. Gastrointest Endosc 2004;60:316–17.
15. Sone Y, Nakano S, Takeda I, Kumada T, Kiriyama S, and Hisanaga Y. Solitary hamartomatous polyp of Peutz–Jeghers type in the jejunum resected endoscopically. Gastrointest Endosc 2000;51:620–22.
16. Izzidien AY, Davies RA, Masoud AG, Kibru S, Abuhamed A, Lodhi JS, Abid G, and Jouanroyee A. The use of ultrasound to demonstrate small bowel polyps in a patient with Peutz–Jeghers syndrome. Surg Endosc 2002;16:715.
17. Naganuma H, Ishida H, Konno K, Komatsuda T, Sato M, Funaoka M, and Fujimori S. Intussusception in Peutz–Jeghers syndrome: sonographic findings. Abdom Imaging 1999;24:333–35.
18. Bruel JM, Gallix B, Achard C, Pierredon MA, and Molina E. [Multidetector CT and MRI in diseases of the gastrointestinal tract]. J Radiol 2003;84:499–513, 514–15.
19. Barussaud M, Regenet N, Briennon X, de Kerviler B, Pessaux P, Kohneh-Sharhi N, Lehur PA, Hamy A, Leborgne J, le NJ, and Mirallie E. Clinical spectrum and surgical approach of adult intussusceptions: a multicentric study. Int J Colorectal Dis 2006;21:834–39.
20. Kim YH, Blake MA, Harisinghani MG, Archer-Arroyo K, Hahn PF, Pitman MB, and Mueller PR. Adult intestinal intussusception: CT appearances and identification of a causative lead point. Radiographics 2006;26:733–44.
21. Beggs AD, Latchford AR, Vasen HF, Moslein G, Alonso A, Aretz S, Bertario L, Blanco I, Bulow S, Burn J, Capella G, Colas C, Friedl W, Moller P, Hes FJ, Jarvinen H, Mecklin JP, Nagengast FM, Parc Y, Phillips RK, Hyer W, Ponz DLM, Renkonen-Sinisalo L, Sampson JR, Stormorken A, Tejpar S, Thomas HJ, Wijnen JT, Clark SK, and Hodgson SV. Peutz–Jeghers syndrome: a systematic review and recommendations for management. Gut 2010;59:975–86.
22. Fraser JD, Briggs SE, St PS, De Petris G, and Heppell J. Intussusception in the adult: an unsuspected case of Peutz–Jeghers syndrome with review of the literature. Fam Cancer 2008;95–101.
23. Gonzalez AM, and Clapp B. Laparoscopic management of small bowel intussusception in a 16-year-old with Peutz–Jeghers syndrome. JSLS 2008;12:332–34.
24. Akimaru K, Katoh S, Ishiguro S, Miyake K, Shimanuki K, and Tajiri T. Resection of over 290 polyps during emergency surgery for four intussusceptions with Peutz–Jeghers syndrome: Report of a case. Surg Today 2006;36:997–1002.
25. van Lier MG, Westerman AM, Wagner A, Looman CW, Wilson JH, de Rooij FW, Lemmens VE, Kuipers EJ, Mathus-Vliegen EM, and van Leerdam ME. High cancer risk and increased mortality in patients with Peutz–Jeghers syndrome. Gut 2011;60:141–47.
26. Rathore MA, Andrabi SI, and Mansha M. Adult intussusception—a surgical dilemma. J Ayub Med Coll Abbottabad 2006;18:3–06.
27. Barussaud M, Regenet N, Briennon X, de Kerviler B, Pessaux P, Kohneh-Sharhi N, Lehur PA, Hamy A, Leborgne J, le Neel JC, and Mirallie E. Clinical spectrum and surgical approach of adult intussusceptions: a multicentric study. Int J Colorectal Dis 2006;21:834–39.
28. Pennazio M, and Rossini FP. Small bowel polyps in Peutz–Jeghers syndrome: management by combined push enteroscopy and intraoperative enteroscopy. Gastrointest Endosc 2000;51:304–08.
29. Edwards DP, Khosraviani K, Stafferton R, and Phillips RK. Long-term results of polyp clearance by intraoperative enteroscopy in the Peutz–Jeghers syndrome. Dis Colon Rectum 2003;46:48–50.
30. Oncel M, Remzi FH, Church JM, Connor JT, and Fazio VW. Benefits of 'clean sweep' in Peutz–Jeghers patients. Colorectal Dis 2004;6:332–35.
31. Miura Y, Yamamoto H, Sunada K, Yano T, Arashiro M, Miyata T, and Sugano K. Reduction of ileoileal intussusception by using double-balloon endoscopy in Peutz–Jeghers syndrome (with video). Gastrointest Endosc 2010;72:658–59.
32. Sakamoto H, Yamamoto H, Hayashi Y, Yano T, Miyata T, Nishimura N, Shinhata H, Sato H, Sunada K, and Sugano K. Nonsurgical management of small-bowel polyps in Peutz–Jeghers syndrome with extensive polypectomy by using double-balloon endoscopy. Gastrointest Endosc 2011;74(2):328–33.

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ORIGINAL ARTICLE

Comparison of Outcomes of Laparoscopic Versus Open Appendectomy in Adults: Data from the Nationwide Inpatient Sample (NIS), 2006–2008

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Abstract
Introduction Although laparoscopic appendectomy (LA) is being performed with increased frequency, the utilization of laparoscopy in the management of acute appendicitis remains controversial, and it continues to be used selectively.
Objectives This study aims to evaluate outcomes of LA vs. open appendectomy (OA) in perforated and non-perforated appendicitis in adults.
Methods Using the Nationwide Inpatient Sample database, clinical data of adults who underwent LA and OA for suspected acute appendicitis were evaluated from 2006 to 2008. Incidental and elective appendectomies were excluded.
Results A total of 573,244 adults underwent urgent appendectomy during these 3 years. Overall, 65.2% of all appendectomies were performed laparoscopically. Utilization of LA increased 23.7% from 58.2% in 2006 to 72.0% in 2008. In acute non-perforated appendicitis, LA had a lower overall complication rate (4.13% vs. 6.39%, $p<0.01$), lower in-hospital mortality (0.03% vs. 0.05%, $p<0.01$), and shorter mean length of hospital stay (LOS; 1.7 vs. 2.4 days, $p<0.01$) compared with OA; however, hospital charges were higher in the LA group ($22,948 vs. $20,944, $p<0.01$). Similarly, in perforated appendicitis, LA was associated with a lower overall complication rate (18.75% vs. 26.76%, $p<0.01$), lower in-hospital mortality (0.06% vs. 0.31%, $p<0.01$), lower mean hospital charges ($32,487 vs. $38,503, $p<0.01$), and shorter mean LOS (4.0 vs. 6.0 days, $p<0.01$) compared with OA.
Conclusion LA is safe and associated with lower morbidity, lower mortality, and shorter hospital stay with acute perforated and non-perforated appendicitis. Also, in perforated cases, LA had an advantage over OA in hospital charges. LA should be considered the procedure of choice for perforated and non-perforated appendicitis in adults.

Keywords Laparoscopic appendectomy · Open appendectomy · Acute appendicitis · Adults

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Introduction

Appendicitis is the most common emergency surgical disease in the USA, with a lifetime risk of 8.6% in males and 6.7% in females; the lifetime risk of appendectomy is 12% for males and 23% for females.[1] For the past century, the conventional management of appendicitis has been open appendectomy (OA) due to its efficient, dependable, and almost infallible outcomes. In 1983, Semm[2] introduced laparoscopic appendectomy (LA) several years before laparoscopic cholecystectomy; however, LA was not broadly performed until the success of laparoscopic cholecystectomy was demonstrated.[3] LA has shown advantages over OA such as shorter length of hospital stay (LOS), better cosmetic

appearance, faster recovery and return to normal activities, and less postoperative pain.[3–7] However, LA has been disfavored due to longer operating times, greater hospital costs, and concern of increased postoperative abscess formation.[7,8] LA has been recommended for select patients with suspected appendicitis, especially young female, obese patients, and employed patients unless laparoscopy itself is contraindicated or not feasible.[7]

Even after LA's widespread use, there has been much controversy over the utilization of LA over OA, mainly because OA already involves a minimal incision.[9] Despite LA's advantages, a consensus has not been reached as to whether LA is more favorable over OA, or if LA will replace the time validated OA. Many randomized control trials,[10–13] retrospective studies,[14,15] and meta-analyses[7,16–19] have been conducted to compare the outcomes of LA and OA for acute appendicitis in adults; all of these studies have produced conflicting findings; some studies claim the superiority of LA over OA, some reported no difference between the two, and some found OA still produced better outcomes than LA.

We hypothesized that LA is safe and effective and has superior outcomes compared with OA in the management of acute perforated and non-perforated appendicitis in adults. To investigate this hypothesis, we evaluated appendicitis in adults, from 2006 to 2008 in the USA: (1) to examine the utilization rate of LA in adults in the USA and (2) to evaluate the outcomes of LA vs. OA in perforated and non-perforated appendicitis in adults.

Materials and Methods

Database

Data were obtained from the Nationwide Inpatient Sample (NIS) database. The NIS is the largest inpatient care database in the USA consisting of a nationally representative sample of approximately 20% of US community hospitals, providing a sampling frame that comprises approximately 90% of all hospital discharges in the USA. Affiliates with the NIS include approximately 1,000 hospitals across the nation, and the NIS includes annual data on about eight million hospital stays. NIS data were collected from hospital discharge abstracts that allow determination of all procedures performed during a given hospital admission. Additionally, the NIS has a collection of discharge information on inpatient hospital stay, including patient characteristics, length of hospital stay, specific postoperative morbidity, and in-hospital mortality. However, the NIS database has no information on complications arising after discharge. Approval usage for the NIS patient-level data in this study was acquired from the Institutional Review Board of the University of California, Irvine School of Medicine and the NIS.

Data Analysis

We analyzed discharge data of adult patients (18–65 years) who underwent appendectomy for suspected acute appendicitis from 2006 to 2008, which are the most recent years included in this database. Adult patients, hospitalized with a diagnosis of appendicitis who underwent appendectomy, were selected by identifying discharges with International Classification of Disease ninth revision (ICD-9) appendectomy codes (laparoscopic 47.01 and open 47.09)—these patients were admitted emergently with a diagnosis of appendicitis. Based on ICD-9 diagnosis codes, these patients were divided into the perforated (540.0, 540.1) or non-perforated (540.09, 541, and 542) groups. Omitted from this study were cases of incidental appendectomies, elective appendectomies, and patients who were treated non-operatively for acute appendicitis. We separately compared the outcomes of LA with OA in perforated and non-perforated appendicitis. Patient characteristics of interest included age, gender, race, and comorbidities. Other data of interest included postoperative complications, LOS, total hospital charges, and in-hospital mortality.

Statistical Analysis

The frequencies of categorical variables are expressed as a percentage of the group of origin. Continuous variable are reported as means for patient age, LOS, and total hospital charges. All statistical analyses were conducted using SAS version 9.2 (SAS institute, Cary, NC, USA). Since the NIS database is a 20% sample of the USA yearly inpatient admissions, weighted samples (NIS variable DISCWT) were used to produce national estimates for all analyses. Appropriate statistical tests were used for both categorical variables (chi-square analysis) and continuous variables (the Student *t* test) in the univariate analysis comparing demographic and outcomes variables for patients undergoing LA or OA. Multivariable analysis was determined to analyze the risk-adjusted influence of the type of procedure (LA vs. OA) on postoperative complications, in-hospital mortality, and hospital stay. Statistical significance was set at p value <0.05 and odds ratios and 95% confidence intervals that excluded 1.

Results

From 2006 to 2008, a total of 573,244 adults underwent appendectomy for suspected appendicitis, accounting for 67.3% of all appendectomies. The mean age was 37 years old; the majority of the patients were male (54.1%) and Caucasian (69.5%). Overall, 65.2% of the appendectomies

were performed laparoscopically. However, LA was performed more frequently on females than males (67.6% vs. 63.1%, $p<0.01$), and the rate of perforated appendicitis was lower for females than males (22.0% vs. 26.1%, $p<0.01$). Between 2006 and 2008, the utilization rate of LA increased 21.8% for non-perforated appendicitis and 27% for perforated appendicitis (Table 1).

Laparoscopic vs. Open Appendectomy in Acute Non-perforated Appendicitis

Table 2 lists patients' characteristics and postoperative outcomes for non-perforated appendicitis. For non-perforated appendicitis, out of a total of 435,060 patients, 303,888 patients underwent LA (69.9%) and 131,172 patients underwent OA (30.1%). In both OA and LA, most of the patients were males (LA 51.5% vs. OA 55.7%, $p<0.1$) and Caucasian (LA 65.7% vs. OA 63.1%, $p<0.1$). The average age in both groups was 35 years. The overall postoperative complication rate was significantly lower for LA than OA (LA 4.13% vs. OA 6.39%, $p<0.01$). Most of the postoperative complications (acute renal failure, pneumonia, respiratory failure, deep vein thrombosis, ileus, abdominal abscess, wound infection, and bowel obstruction) were significantly lower for LA than OA except for urinary tract infection and pulmonary emboli which were comparable between the two groups. In-hospital mortality was lower for LA than OA (LA 0.03 vs. OA 0.05; $p<0.01$). Mean LOS was shorter for LA than OA (LA 1.7 days vs. OA 2.4 days, $p<0.01$). However, the total hospital charges were higher for LA than OA (LA $22,948 vs. OA $20,944, $p<0.01$).

Laparoscopic vs. Open Appendectomy in Acute Perforated Appendicitis

Table 3 lists patients' characteristics and postoperative outcomes for perforated appendicitis. For perforated appendicitis, out of a total of 138,184 patients, 69,840 (50.5%) underwent LA and 68,344 (49.5%) underwent OA. The average age was higher in the OA group (LA 42 years old vs. OA 41 years old, $p<0.01$). Overall, the majority of patients were males (LA 56.4% vs. OA 60.3%, $p<0.01$) and Caucasian (LA 69.5% vs. OA 64.9%, $p<0.01$). The overall postoperative complications were significantly lower for LA than OA (LA 18.75% vs. OA 26.76%, $p<0.01$). Most of the postoperative complications (urinary tract infection, pneumonia, acute renal failure, respiratory

Table 1 Trends of utilization of laparoscopic appendectomy in the adults in the USA, 2006–2008

	Non-perforated (%)	Perforated (%)	Total (%)
2006	62.8	45.0	58.2
2007	69.7	50.5	65.1
2008	76.5	57.1	72.0
2006–2008	69.9	50.5	65.2
2008 vs. 2006 (% increase)	21.8%	27.0%	23.7%

Table 2 Acute non-perforated appendicitis in adult patients: LA vs. OA, 2006–2008

Characteristics and perioperative outcomes	LA N=303,888	OA N=131,172	p value
Demographics			
Mean age (year)	35.3	35.8	<0.01
Male (%)	51.5	55.7	<0.01
Race (%)			
Caucasian	65.7	63.1	<0.01
African-American	6.7	7.8	
Hispanic	19.3	20.8	
Asian-Pacific Islander	3.3	3.6	
Native American	0.6	0.6	
Other	4.4	4.1	
Comorbidities (%)			
Diabetes mellitus	3.7	4.1	<0.01
Hypertension	11.6	12.5	<0.01
Congestive heart failure	0.3	0.5	<0.01
Chronic pulmonary disease	5.8	5.7	0.42
Liver disease	0.6	0.6	0.67
Renal failure	0.4	0.6	<0.01
Alcohol abuse	0.8	0.4	<0.01
Peripheral vascular disease	0.2	0.4	<0.01
Postoperative complications (%)			
Urinary tract infection	1.05	1.01	0.24
Pneumonia	0.31	0.49	<0.01
Acute renal failure	0.25	0.36	<0.01
Respiratory failure	0.34	0.51	<0.01
Myocardial infarction/angina	0.05	0.08	<0.01
Deep vein thrombosis	0.02	0.04	<0.01
Pulmonary emboli	0.02	0.01	0.08
Ileus	1.92	3.11	<0.01
Abdominal abscess	0.26	0.76	<0.01
Wound infection	0.15	0.42	<0.01
Bowell obstruction	0.23	0.80	<0.01
Incidental puncture	0.24	0.56	<0.01
Overall complication rate	4.13	6.39	<0.01
Length of hospital stay (days)			
Mean	1.7	2.4	<0.01
Median	1	2	
In-hospital mortality (%)	0.03	0.05	<0.01
Mean total hospital charge ($)	22,948	20,944	<0.01

Table 3 Acute perforated appendicitis in adult patients: LA vs. OA

Characteristics and perioperative outcomes	LA N=69,840	OA N=68,344	p value
Demographics			
Mean age (years)	41.1	42.0	<0.01
Male (%)	56.4	60.3	<0.01
Race			
Caucasian	69.5	64.9	<0.01
African-American	5.9	8.3	
Hispanic	17.2	19.3	
Asian-Pacific Islander	3.4	3.1	
Native American	0.5	0.8	
Other	3.5	3.6	
Comorbidities (%)			
Diabetes mellitus	6.0	7.8	<0.01
Hypertension	19.4	21.3	<0.01
Congestive heart failure	0.8	1.3	<0.01
Chronic pulmonary disease	5.9	7.1	<0.01
Liver disease	0.8	1.0	<0.01
Chronic renal failure	0.9	1.4	<0.01
Alcohol abuse	1.4	2.1	<0.01
Peripheral vascular disease	0.4	0.9	<0.01
Postoperative complications (%)			
Urinary tract infection	1.33	1.62	<0.01
Pneumonia	1.48	2.34	<0.01
Acute renal failure	1.08	2.77	<0.01
Respiratory failure	1.33	3.06	<0.01
Myocardial infarction/angina	0.11	0.10	0.51
Deep vein thrombosis	0.08	0.18	<0.01
Pulmonary emboli	0.08	0.12	0.04
Ileus	13.34	16.64	<0.01
Abdominal abscess	1.65	3.57	<0.01
Wound infection	0.58	2.09	<0.01
Bowel obstruction	1.24	2.84	<0.01
Overall complication rate	18.75	26.76	<0.1
Length of hospital stay (days)			
Mean	4.0	6.0	<0.01
Median	3	5	
In-hospital mortality (%)	0.06	0.31	<0.01
Mean total hospital charge (%)	32,487	38,503	<0.01

failure, deep vein thrombosis, ileus, abdominal abscess, wound infection, and bowel obstruction) were significantly lower for LA compared with OA; only myocardial infarction/angina was similar between two groups. The average LOS was shorter for LA than OA (LA 4.0 days vs. OA 6.0 days, p<0.01). Mortality rate was lower for LA than OA (LA 0.06% vs. OA 0.31%, p<0.01). Unlike in the non-perforated appendicitis group, total hospital charges were lower for LA than OA (LA $32,487 vs. OA $38,503, p<0.01).

Risk-Adjusted Outcomes

Table 4 indicates the multivariate regression analysis for the outcome of LA vs. OA in adults. After adjusting for variables (patient characteristics (age, sex, and race), comorbidities, and type of appendicitis), LA was still associated with a lower mortality rate (odd ratio (OR) 0.41; 95% confidence interval (CI) 0.32–0.51; p<0.01), lower complication rate (OR 0.65; 95% CI 0.64–0.67; p<0.01), and shorter LOS (OR 0.37; 95% CI 0.36–0.0.38; p<0.01). Additionally, all of the complications were lower for LA except for pulmonary embolism and myocardial infarction which there was no effect of type of procedure in these complications.

Discussion

This study is the most recent retrospective analysis based on a large administrative database that compares the outcomes of LA to OA in adults. Interestingly, the utilization rate of LA increased from 58.2% in 2006 to 72% in 2008—a 23.7% difference. Additionally, LA was used at a greater rate for non-perforated appendicitis (69.9%) while for perforated appendicitis LA was utilized for just over half (50.5%) of all appendectomies. Previous studies have also shown an increase in the utilization rate of LA,[20,21] yet our findings show rates exceeding OA. Using a nationwide administrative database (NIS) from 1997 to 2003, Van Hove et al. reported that LA was performed 19.1% of the time in 1997 to 39.7% in 2003, while 11.8% of the complicated cases were treated laparoscopically in 1997 and 23.5% in 2003.[20] Our study shows that more than

Table 4 Multivariate regression analyses for outcome after LA vs. OA

Outcomes	OR (95% CI)	p value
In-hospital mortality	0.41 (0.32–0.51)	<0.01
Complication rate	0.65 (0.64–0.67)	<0.01
Urinary tract infection	0.93 (0.88–0.99)	0.02
Pneumonia	0.69 (0.64–0.74)	<0.01
Acute respiratory failure	0.56 (0.53–0.60)	<0.01
Acute renal failure	0.53 (0.49–0.57)	<0.01
Deep vein thrombosis	0.56 (0.43–0.73)	0.04
Pulmonary embolism	1.11 (0.80–1.54)	0.51
Myocardial infarction	0.88 (0.70–1.11)	0.28
Ileus	0.73 (0.71–0.75)	<0.01
Abdominal abscess	0.45 (0.42–0.48)	<0.01
Wound infection	0.33 (0.30–0.37)	<0.01
Bowel obstruction	0.37 (0.35–0.40)	<0.01
Length of hospital stay	0.37 (0.36–0.38)	<0.01

OR odds ratio, *CI* confidence interval

two third (72%) of all appendectomies were performed laparoscopically in 2008 in the USA and LA is rapidly replacing OA.

According to our findings, the overall rate of LA performed on females was higher than males; however, the rate of perforated appendicitis was actually higher for males than females. The high utilization rate of LA for females could have contributed to the lower perforation rate in females, or more likely these differences might be due to the fact that laparoscopy is used as a convenient diagnostic tool for exploration of right lower quadrant pain in females more often than males. This might have led to earlier appendectomies thus fewer perforations in females.[10,22,23]

Early studies on LA often reported higher complication rates for LA than OA[16–19]; recent studies have noticeably found LA to have lower complication rates than OA for appendicitis or found no difference between the two procedures, yet none of these studies distinguishes between perforated and non-perforated appendicitis.[12,21,24,25] Surprisingly, Sporn et al. examined LA vs. OA using the NIS from 2000 to 2005 and found that LA was associated with higher complications than OA; when conducting risk-adjusted analysis, Sporn and colleagues reported significantly higher complications in the LA group for uncomplicated appendicitis (OR 1.07; 95% CI 1.00–1.14; $p=0.05$) and no difference in overall complication rate between procedures for complicated appendicitis (OR 1.01; 95% CI 0.96–1.06; $p=0.74$).[26] However, we found that the overall frequency of postoperative complications was significantly lower for LA than OA in both perforated and non-perforated appendicitis. Furthermore, risk-adjusted analysis indicated that LA had an advantage over the OA group for complication rate (OR 0.65). Common concerns over postoperative complications for LA include abdominal abscess formation.[7] Our study shows that the abdominal abscess rates were significantly lower for LA than OA in both perforated and non-perforated appendicitis.

For non-perforated appendicitis, the LOS was shorter for LA than OA by 0.7 of a day. For perforated, the difference in LOS was much more pronounced where LA was shorter than OA by 2 days. Furthermore, risk-adjusted analysis for LOS showed that the LA group had shorter LOS than the OA group (OR 0.37). Previous studies have also reported shorter LOS for LA, but many of these studies have averaged a day or less difference with no distinction between perforated and non-perforated appendicitis.[15–19,21] When examining costs, many of the early studies found that LA's total hospital charges were more expensive than OA,[23,27–29] but these studies did not distinguish between perforated and non-perforated appendicitis. We found that the total hospital charges for non-perforated appendicitis were substantial with lower costs for OA than LA by about $2,000. However, in perforated appendicitis, the difference between procedures more pronounced, with OA being more expensive than LA by about $6,000. LA's reduced hospitalization might have contributed to the lower hospital charges associated with perforated appendicitis. Likewise, Kurtz et al. found that while laparoscopic operating costs were greater than open, the difference between costs were offset by shorter LOS.[30]

The in-hospital mortality rate was lower for LA than OA for both non-perforated and perforated appendicitis. The small mortality rate in all four groups and the small differences in percentage between the two procedures can be due to the fact that appendicitis is not commonly a fatal disease for adults. However, when using risk-adjusted analysis for in-hospital mortality, we found that mortality was independently lower in the LA group (OR 0.41). Only a few studies had cases of mortality and those that did either experienced a low mortality for OA[17,31,32] or found no significant difference between LA and OA.[14,21] In a 1997 nationwide administrative database, Guller et al. reported a lower mortality rate for LA in appendicitis, but did not distinguish between perforated and non-perforated appendicitis (LA 0.05% vs. OA 0.30%, $p=0.002$).[14]

The limitations of this study are similar to other retrospective studies utilizing administrative databases. For example, many of the differences between groups are statistically significant; however, they may not be clinically significant. Also, the NIS does not provide the conversion rate of laparoscopic to open procedures, or final pathology. Breakdown of operating costs relative to hospital stay was unknown. Case selection bias is also a factor which cannot be discerned, and it is certainly possible or even likely that choice of LA vs. OA was influenced by patient presentation. Additionally, we did not have severity of illness in this patient population which could be an important factor in selection of type of appendectomy. Although patients in the OA groups had higher comorbidities compared with patients in the LA groups, risk-adjusted analyses showed that LA is still associated with superior outcomes in terms of morbidity, mortality, and length of hospital stay. Lastly, data of patients after discharge are unknown such as post-discharge readmission, complications, morbidity, and mortality. Despite these limitations, the data presented in this study are based on a large sample population supported by multivariate statistical analysis from which consistent conclusions can be drawn.

Data from this study show that LA has become an established procedure for adults with perforated and non-perforated appendicitis with rates exceeding OA. For non-perforated appendicitis, LA was associated with shorter hospital stay, lower mortality, lower postoperative complications but with modest differences in total hospital charges. The benefits of LA are much more pronounced in perforated appendicitis, where LA had much shorter hospital stay, much lower mortality rate, significantly lower postoperative complications, and much lower total hospital charges. Based on the findings of this study,

LA is safe and effective in the management of perforated and non-perforated appendicitis and should be considered the procedure of choice in acute appendicitis.

Conflicts of Interest In this study, all authors have no conflicts of interest or financial ties to disclose.

References

1. Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol 1990;132:910–925.
2. Semm K. Endoscopic appendectomy. Endoscopy 1983;15:59–64.
3. Ortega AE, Hunter JG, Peters JH, Swanstrom LL, Schirmer B. A prospective, randomized comparison of laparoscopic appendectomy with open appendectomy. Laparoscopic Appendectomy Study Group. Am J Surg 1995;169:208–12.
4. Fingerhut A, Millat B, Borrie F: Laparoscopic versus open appendectomy: time to decide. World J Surg 1999;23(8):835–45.
5. McCall JL, Sharples K, Jadallah F: Systematic review of randomized controlled trials comparing laparoscopic with open appendicectomy. Br J Surg 1997;84(4):1045–50.
6. Pedersen AG, Petersen OB, Wara P, Rønning H, Qvist N, Laurberg S. Randomized clinical trial of laparoscopic versus open appendicectomy. Br J Surg 2001;88(2):200–5.
7. Sauerland S, Lefering R, Neugebauer EA. Laparoscopic versus open surgery for suspected appendicitis. Cochrane Database Syst Rev Issue 2010 Oct 6;(10):CD001546.
8. Hunter JG: Clinical trials and the development of laparoscopic surgery. Surg Endosc 2001;15(1):1–3.
9. Jaffe BM, Berger DH. The Appendix. In: Brunicardi FC, Anderson DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE. Schwartz's principles of surgery. 8th ed. New York: McGraw-Hill, 2005, pp 1119–1139.
10. Laine S, Rantala A, Gullichsen R, Ovaska J. Laparoscopic appendectomy—is it worthwhile? A prospective, randomized study in young women. Surg Endosc 1997;11:95–7.
11. Slim K, Pezet D, Chipponi. Analysis of randomized controlled trials in laparoscopic surgery. Br J Surg 1997;84:610–4.
12. Katkhouda N, Mason RJ, Towfigh S, Gevorgyan A, Essani R. Laparoscopic versus open appendectomy a prospective randomized double-blind study. Ann Surg 2005;242:439–450.
13. Long KH, Bannon MP, Zietlow SP, Helgeson ER, Harmsen WS, Smith CD, MD, Ilstrup DM, Baerga-Varela Y, Sarr MG, Laparoscopic Appendectomy Interest Group. A prospective randomized comparison of laparoscopic appendectomy with open appendectomy: clinical and economic analyses. Surgery 2001;129:390–400.
14. Guller U, Hervey S, Purves H, Muhlbaier LH, Peterson ED, Eubanks S, Pietrobon R. Laparoscopic versus open appendectomy outcomes comparison based on a large administrative database. Ann Surg 2004;239:43–52.
15. Merhoff AM, Merhoff GC, Franklin ME. Laparoscopic versus open appendectomy. Am J Surg 2000; 179:375–378.
16. Chung RS, Rowland DY, Li P, Diaz J. A meta-analysis of randomized controlled trials of laparoscopic versus conventional appendectomy. Am J Surg 1999;177:250–256.
17. Markides G, Subar D, Riyad K. Laparoscopic versus open appendectomy in adults with complicated appendicitis: systematic review and meta-analysis. World J Surg 2010; 34:2026–2040.
18. Sauerland S, Lefering R, Holthausen U, Neugebauer EA. Laparoscopic vs conventional appendectomy—a meta-analysis of randomised controlled trials. Langenbeck's Arch Surg 1998;383:289–295.
19. Golub R, Siddiqui F, Pohl D. Laparoscopic versus open appendectomy: a metaanalysis. J Am Coll Surg 1998;186:545–553.
20. Van Hove C, Hardiman K, Diggs B, Deveney C, Sheppard B, Demographic and socioeconomic trends in the use of laparoscopic appendectomy from 1997 to 2003. Am J Surg 2008;195:580–584.
21. Nguyen NT, Zainabadi K, Mavandadi S, Paya M, Stevens CM, Root J, Wilson SE. Trends in utilization and outcomes of laparoscopic versus open appendectomy. Am J Surg 2004;188:813–820.
22. Larsson PG, Henriksson G, Olsson M, Boris J, Ströberg P, Tronstad SE, Skullman S. Laparoscopy reduces unnecessary appendicectomies and improves diagnosis in fertile women. A randomized study. Surg Endosc 2001;15:200–2.
23. Mutter D, Vix M, Bui A, Evrard S, Tassetti V, Breton JF, Marescaux J. Laparoscopy not recommended for routine appendectomy in men: results of a prospective randomized study. Surgery 1996;120:71–4.
24. Brugger L, Rosella L, Candinas D, Guller U. Improving outcomes after laparoscopic appendectomy a population-based, 12-year trend analysis of 7446 patients. Ann Surg 2011; 253:309–313.
25. Moberg AC, Berndsen F, Palmquist I, Petersson U, Resch T Montgomery A. Randomized clinical trial of laparoscopic versus open appendicectomy for confirmed appendicitis. B J Surg 2005; 92:298–304.
26. Sporn E, Petroski GF, Mancini GJ, Astudillo JA, Miedema BW, Thaler K. Laparoscopic appendectomy—is it worth the cost? Trend analysis in the US from 2000 to 2005. J Am Coll Surg 2009;208:179–185.
27. Martin LC, Puente I, Sosa JL, Bassin A, Breslaw R, McKenney MG, Ginzburg E, Sleeman D. Open versus laparoscopic appendectomy: a prospective randomized comparison. Ann Surg 1995;222:256–262.
28. Minné L, Varner D, Burnell A, Ratzer E, Clark J, Haun W. Laparoscopic vs open appendectomy. Arch Surg 1997;132:708–712.
29. Williams MD, Collins JN, Wright TF, Fenoglio ME. Laparoscopic versus open appendectomy. South Med J 1996;89:668–674.
30. Kurtz RJ, Heimann TM. Comparison of open and laparoscopic treatment of acute appendicitis. Am J Surg 2001; 182: 211–214.
31. Stoltzing H, Thon K. Perforated appendicitis: is laparoscopic operation advisable? Digest Surg 2000;17:610–616.
32. Pokala N, Sadhasivam S, Kiran RP, Parithivel V. Complicated appendicitis—is the laparoscopic approach appropriate? A comparative study with the open approach: outcome in a community hospital setting. Am Surg 2007;73:737–741.

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ORIGINAL ARTICLE

Emergency Management of Perforated Colon Cancers: How Aggressive Should We Be?

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Abstract
Background Emergency treatment of perforated colon cancer has traditionally been linked with dismal outcomes due to the double jeopardy of a septic insult combined with a malignant disease, leaving unclear how aggressive emergency surgical procedures should be. We aimed to define short- and long-term outcomes in the current era of critical care support and oncologic advances, to provide updated data for decision making.
Study Design Patients with perforations associated with a primary colon cancer were identified. Peri-operative and long-term survival were compared among free (FP; n=41) and contained perforations (CP; n=45) and to age-, stage-, and resection status case-matched, non-perforated (NP; n=85), controls.
Results Tumors were completely resected in 67% of FP but fewer lymph nodes were harvested (median, 11 vs. 11 and 16 in CP and NP; p=0.21 and p<0.001). Peri-operative mortality was highest in FP: 19% vs. 0% and 5% in CP and NP (p=0.038), respectively. After adjusting for peri-operative mortality, 5-year overall survival was comparable: 55%, 59%, and 54% for FP, CP, and NP, respectively. Advanced age, higher ASA class, presence of residual disease, and advanced stage, but not perforation, were independent predictors of poorer long-term overall survival.
Conclusions Patients with malignant colonic perforation face high risk of peri-operative death, making septic source control the priority in the acute setting. Pursuit of an oncologically oriented resection and long-term cancer-directed treatments, however, may lead to improved long-term outcomes.

Keywords Complicated colon cancer · Peforated viscous · Long-term outcomes · Septic shock · Intensive care

Introduction

Colon cancer is the third most common and the second most lethal malignancy in the USA.[1] Despite established guidelines for cancer screening, compliance rates remain low. Fewer than half of the adults age 50 or older undergo recommended screening for colorectal cancer.[2] Consequently, up to 30% of colon cancers can present in a complicated fashion, with obstruction or perforation.[3–7] The management and outcomes of obstructing colon cancers have been well investigated, with the surgical literature replete with levels I and II evidence.[8–11] Substantiation, however, does not exist regarding perforated colon cancers.

Patients with free perforations in the setting of colon cancer represent a unique challenge in management. In contrast to locally perforated, fistulous, and non-perforated colon cancers, patients with free perforation generally require emergent surgical intervention. The surgeon must contend with a multitude of unfavorable factors including septic shock, poorly defined tissue planes, and the technical demands of an oncologic resection without the leisure of time or adequate oncologic work-up. Previous literature has

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reported dismal outcomes in patients with acutely perforated colon cancers, leaving unclear how aggressive the treating surgeon should be in these unstable patients.[7,12] In addition, advances in critical care and adjuvant therapy have improved outcomes in septic shock and metastatic colon cancer.[13,14] This study aimed to define the short- and long-term outcomes of patients with perforated colon cancers with particular attention to peri-operative factors that affect long-term overall survival (OS), information which is critical for surgeons and the patients/families who are challenged to make complex decisions in the acute care setting.

Methods

After approval by the Institutional Review Board, the institutional prospective tumor registry was queried. Eighty-five patients underwent operative intervention for a primary colon cancer complicated by perforation between 1993 and 2008. Iatrogenic perforations during the operation and rectal malignancies (within 15 cm from the anal verge) were excluded. Within the study cohort, subgroups of patients with free perforation (FP; n=41) and contained perforation (CP; n=44) were identified based on review of medical records. FP was defined by intra-operative finding of feculent or purulent peritonitis (modified Hinchey 3 or 4). CP was defined by abscess formation or fistulous connection into an adjacent organ or structure (modified Hinchey 1/2). The tumor registry was further queried to identify a matched control cohort of patients with non-perforated colon cancers (n=85) treated over the same time period. Patients were matched for age within 5 years, AJCC stage[14] and residual disease status (R0 vs. non-R0) after resection.

Remaining data points of interest were obtained by review of the medical record. Post-operative mortality was considered as 30-day or in-hospital mortality. Long-term follow-up was conducted at the discretion of the treating surgeon but consisted of a minimum of annual clinical examination, carcinoembryonic antigen, and chest and abdominal imaging through 5 years. Colonoscopy was

Table 1 Patient and tumor characteristics

	Free perforation (n=41) No. (% or IQR)	Contained perforation (n=44) No. (% or IQR)	No perforation (n=85) No. (% or IQR)	P value FP vs. CP	P value perforation vs. NP
Patient characteristics					
Age (years (median, IQR))	70 (57, 80)	72 (61, 78)	71 (58, 81)	0.54	0.55
Female sex	54 (63)	30 (69)	32 (33)	0.76	<0.001
Co-morbidities					
Cardiac disease	14 (34)	15 (35)	24 (32)	0.88	0.73
Diabetes mellitus	6 (15)	7 (16)	16 (21)	0.92	0.34
Peripheral vascular disease	7 (17)	6 (14)	12 (16)	0.70	0.93
Pulmonary disease	7 (17)	5 (11)	6 (8)	0.32	0.21
Chronic renal failure	6 (15)	4 (9)	9 (12)	0.45	0.99
Pre-operative labs					
WBC ($\times 10^9$/L, median, IQR)	13.1 (10.4, 16.1)	13.5 (8.1, 16.5)	10.9 (8.1, 15.5)	0.73	0.20
Lactate (mmol/L, median, IQR)	1.9 (1.1, 2.1)	2.2 (1.5, 8.3)	1.6 (1.0, 4.3)	0.27	0.60
ASA class					
1–2	25 (62)	27 (64)	35 (51)		0.021
3	14 (33)	11 (26)	28 (41)	0.35	
4	2 (5)	4 (10)	5 (7)		
Pathologic AJCC stage					
II	12 (29)	22 (51)	40 (47)		
III	14 (34)	16 (35)	29 (34)	0.11	0.08
IV	15 (37)	6 (14)	17 (20)		
Tumor size (mm)	52 (36–74)	70 (60–102)	67 (48–80)	0.002	0.89
Histologic grade					
1–2	2 (5)	10 (23)	17 (20)	0.048	0.054
3–4	39 (95)	34 (77)	67 (80)		

Column total may be less than 100% due to missing data

IQR interquartile range, *WBC* white blood cell, *ASA* American Society of Anesthesiologists, *AJCC* American Joint Commission on Cancer

performed at years 1 and 4 or 5. Patients were followed up for vital status and disease recurrence. Recurrent disease was categorized as local if occurred at the anastomosis, previous tumor site, or mesentery nodal basin of the previous tumor; and as distant if elsewhere.

Statistical Analysis

The primary endpoints were OS and adjusted OS; the latter endpoint excluded patients who experienced post-operative mortality. The secondary endpoints were disease-free survival (DFS) and tumor recurrence. All continuous variables are described as median and interquartile range (IQR) while categorical variables are described as number and percent. Comparisons between the FP vs. CP groups as well as between the P vs. NP groups were conducted using Wilcoxon rank-sum test for continuous variables, and the Chi-square (or Fisher's exact) tests for categorical variables. Survival analyses were conducted according to the Kaplan–Meier method, and comparisons between cohorts were conducted using the log-rank test. Significant predictors of OS were identified through a Cox proportional hazards regression model. All tests were two sided with significance determined by p value of <0.05.

Results

Patients and Tumors

No significant differences were found in age and pathologic stage of the patients (Table 1). Fewer females were present in the NP group when compared with either the FP or CP groups (Table 1). Nineteen patients (22%) had known colon cancer pre-operatively in the perforation groups (nine FP and ten CP). Similarly, there was a trend, albeit not statistically significant, toward lower pre-operative leukocyte count and lactate levels in the non-perforated patients, when compared with those with free or contained perforation (Table 1). Significantly, vasopressor support was required pre-operatively in 14 (35%) and two (4%) of the free and contained perforation patients, respectively. The worst pre-operative base deficits were 3.5 (median—IQR, 1.78–7) and 0.5 (median—IQR, 0–3.8), for the FP and CP patients, respectively.

While the median tumor size did not differ between the free perforation and NP groups, the tumors that presented with CP were larger (Table 1). Slightly more tumors in the FP group were of high histologic grade, but this difference again did not reach statistical significance (Table 1).

Treatments

All patients with FP and 2 in the CP group underwent emergency surgical intervention; 37 perforated tumors were right sided, 41 were left, and seven were transverse. Nine perforations were remote from the tumor, five as a result of distal obstruction, and four were secondary to colonoscopic perforations. Forty-six patients received stomas; one ascending colostomy, 23 descending colostomies, 18 end ileostomies, and four diverting loop ileostomies. The median total number of lymph nodes harvested was significantly higher in the NP group (Table 2). While the

Table 2 Treatments and short-term outcomes in patients with perforated and non-perforated colon cancer

	Free perforation (n=41) No. (%)	Contained perforation (n=44) No. (%)	No perforation (n=85) No. (%)	P value FP vs. CP	P value perforation vs. NP
Stoma rate	29 (71)	17 (39)	25 (29)	0.008	<0.001
Stomas reversed	3 (7)	1 (2)	5 (6)		
Total number of nodes examined (median, IQR)	11 (5.5, 14.8)	11 (6.5, 17.5)	16 (10, 25)	0.21	<0.001
Positive nodes (median, IQR)	1 (0, 3)	0 (0, 2)	1 (0, 4)	0.30	0.23
Resection of malignant disease				0.062	0.80
R0 resection of primary tumor	25 (62)	30 (68)	52 (61)		
R1 resection of primary tumor	2 (5)	7 (16)	11 (13)		
R2 resection of primary tumor	14 (33)	7 (16)	23 (27)		
Post-operative mortality	7 (19)	0 (0)	4 (5)		0.038
Post-operative complication	27 (66)	20 (46)	24 (28)	0.095	<0.001
Adjuvant therapy received	16 (38)	27 (56)	43 (50)	0.066	0.31
Days to adjuvant therapy (days (median, range))	47 (27–159)	58 (17–718)	44 (15, 371)	0.13	0.72

Column total may be less than 100% due to missing data

IQR interquartile range, *R2* residual gross disease, *R1* residual microscopic disease, *R0* no residual disease

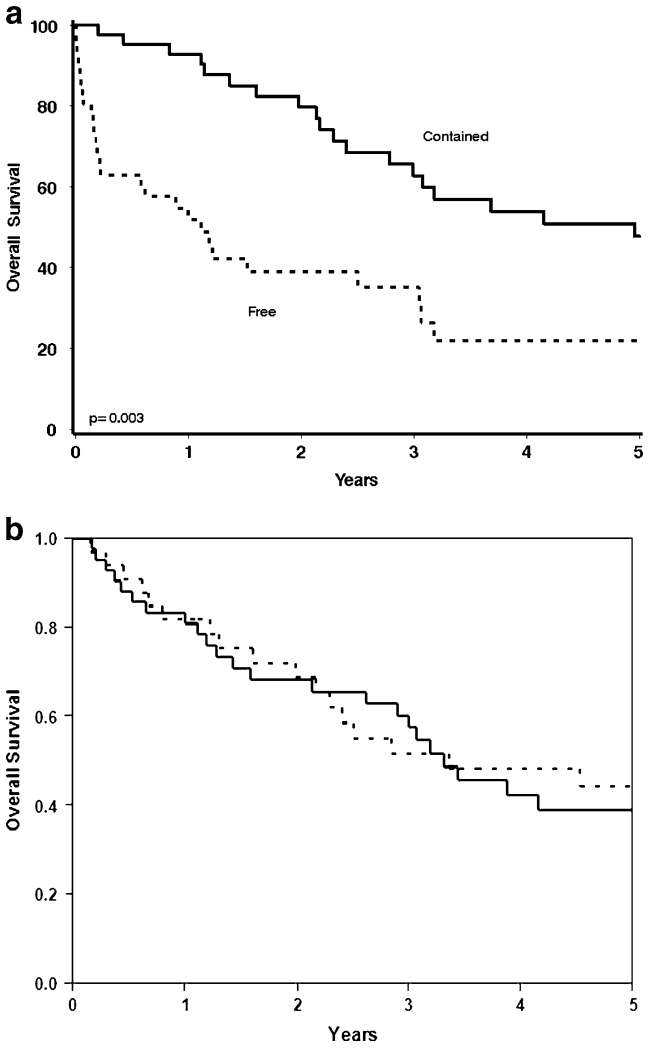

Fig. 1 **a** Overall survival for patients with FP vs. CP (24% vs. 62%; p=0.003). *Dashed line*, free perforation (FP). *Solid line*, contained perforation (CP). **b** Adjusted overall survival for patients with FP vs. CP (44% vs. 38%; p=0.924). *Dashed line*, FP. *Solid line*, CP

proportion of node-positive tumors did not differ, a substantial proportion of patients presenting with perforation (21 patients, 24.4%) were discovered to have stage IV disease at the time of their emergent surgical intervention. Complete resection of gross tumor (R0 or R1 resection) could be achieved in a majority of the patients with free perforation (67%; Table 2), where distant metastatic disease constituted the majority of the unresected gross residual disease (Table 2). Patients with CP were often managed by en bloc resection of adjacent organ(s) and a trend toward higher rate of complete gross tumor resection (84%; Table 2) was observed. By design, we selected a similar proportion of patients with unresected distant metastatic disease in the NP control group.

Post-operative mortality was significantly higher for the FP patients (19% vs. 0% in CP group and 5% in NP group; Table 2). Postoperatively, similar proportions of patients received adjuvant therapy, and there was no statistically significant delay in the initiation of chemotherapy (Table 2). A significantly higher proportion of patients with FP received a stoma compared with the CP and NP patients, and few were reversed. (Table 2)

Oncologic Outcomes

Patients with perforated (free or contained) and NP colon cancers were followed up for a median of 26.5 and 35.4 months, respectively. The median follow-up among living patients was 55.8 months (range, 0.3–205).

Comparing patients with FP and CP, the OS was significantly worse in the FP group, with 5-year estimated OS at 24% vs. 62%, p=0.003 (Fig. 1a). After excluding

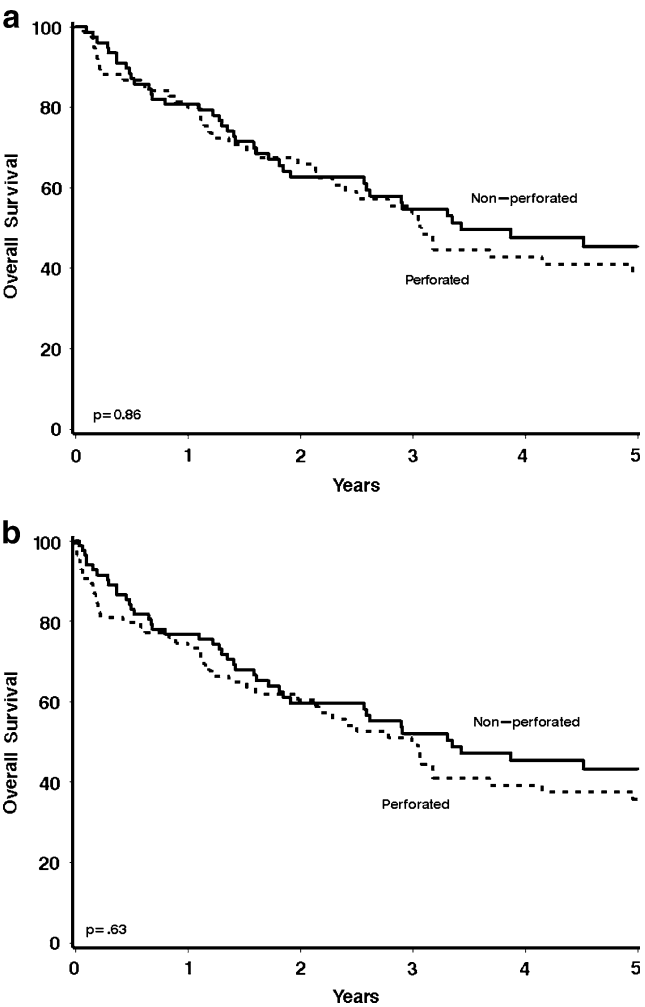

Fig. 2 **a** Overall survival for patients with perforated and non-perforated colon cancer (41% vs. 48%; p=0.860). *Dashed line*, all perforated patients. *Solid line*, non-perforated patients. **b** Adjusted overall survival for patients with perforated and non-perforated colon cancer (38% vs. 44%; p=0.180). *Dashed line*, all perforated patients. *Solid line*, non-perforated patients

Table 3 Multivariate analysis of independent predictors of poor adjusted overall survival

Feature	Hazard ratio (95% CI)	*P* value
Age (10-year increase)	1.55 (1.28–1.87)	<0.001
ASA class		
1–3	1.0	
4	4.26 (1.60–11.34)	0.004
Pathologic AJCC stage		
1–2	1.0	
3	2.61 (1.50–4.52)	<0.001
4	6.50 (3.09–13.67)	<0.001
Resection status		
R0–R1	1.0	
R2	1.94 (1.09–3.46)	0.024
Perforation		
No	1.0	
Yes	0.85 (0.52–1.38)	0.51

ASA American Society of Anesthesiologists, *AJCC* American joint commission on cancer, *R2* residual gross disease, *R1* residual microscopic disease, *R0* no residual disease

peri-operative mortality, however, no difference was observed in 5-year adjusted OS: 44% vs. 38% (FP vs. CP, $p=0.924$; Fig. 1b). The 5-year OS and the 5-year adjusted OS of all patients with perforated tumors was equivalent to their case-matched, non-perforated controls (41% vs. 48%, $p=0.860$ and 38% vs. 44%, $p=0.180$ respectively; Fig. 2a, b). Multivariate analysis revealed that older age, ASA class IV, advanced AJCC-stage, and unresected gross residual tumor, but not the presence of perforation, were independent predictors of poor adjusted OS (Table 3).

Recurrent or persistent disease was similar among all groups (Table 4). The 5-year DFS of patients with FP was 15%, compared with 53% for those with contained perforation ($p<0.001$) and 50% for stage-matched and resection status-matched non-perforated cohort ($p=0.16$). Metastectomy for recurrence was performed in 13 patients, five from each perforation group, and three in the NP controls.

Discussion

In 2010, the 7th edition of the AJCC staging system defined two subgroups of T4 tumors[15]: (1) T4a including non-perforated cancers invading the visceral peritoneum and (2) T4b including colon cancers complicated by direct invasion into adjacent organs or malignant fistulae. Colon cancers complicated by free perforation, however, were not explicitly defined in either substage. Opinion has been divergent in the literature as to whether the previously reported dismal oncologic outcomes in the setting of perforated colorectal cancer is due to the dissemination of tumor within the peritoneal cavity or other, peri-operative, factors. An early study found that intra-operative perforation of colorectal cancer led to a high local recurrence rate of 65% and a low 5-year OS of 14% suggesting that perforation leads to carcinomatosis and subsequent death.[16] This theory was supported by Chen at al who reported a 5-year survival of 33% in perforated malignancies, significantly inferior to the 50% in non-perforated cases.[17] Interpretation of these results, however, is complicated as patients presenting with perforation or other complications of colon cancer tend to have higher incidence of metastatic disease, higher disease stage and greater residual tumor burden.[6,18–29]

In the current study, we found that, while patients with FP generally present in extremis, those with CP tend to present in a more elective fashion, albeit with signs of infection (fever and leukocytosis). The peri-operative mortality in FP patients is substantial, but, once the septic insult has been conquered, age, co-morbidities, disease stage and resection status are key determinants of long-term OS, not perforation status. The implication, therefore, is that peritoneal seeding of cancer cells does not occur to a degree that allows for tumor implantation. A plausible, but unproven, reason for this is likely due to the very alterations in homeostasis that is responsible for the high peri-operative mortality; Lehnert et al. theorized that the intense inflammatory reaction of the peritoneum and other structures combined with poor oxygen delivery creates an environment that inhibits tumor growth during the septic episode.[30]

Table 4 Patterns of disease recurrence

	Free perforation ($n=41$) No. (%)	Contained perforation ($n=44$) No. (%)	No perforation ($n=85$) No. (%)	*P* value free vs. contained perforation	*P* value perforation vs. no perforation
Never disease					
Free	6 (15)	4 (9)	6 (7)	0.75	0.11
Disease					
Recurrence	10 (24)	11(25)	16 (19)		
Local recurrence	3 (7)	6 (14)	4 (5)		

While previous studies had not controlled for confounding factors, we conducted a comparison with a control cohort of NP colon cancer patients matched in age, disease stage and residual tumor burden. We found no difference in long-term OS after adjusting for peri-operative mortality.

Contrary to an elective resection, the surgeon facing a perforated colon cancer, unfortunately, has more limited options. The presence of intra-operative hemodynamic instability, gross contamination of the field, obscuring of tissue planes, and hyperemia of the mesentery may preclude the surgeon from performing an often more time-consuming, and technically difficult, operation following oncologic principles. We believe these conditions are responsible for the lower lymph node harvest seen in both perforation populations when compared to NP controls. In addition, a proper work-up for metastatic disease is not feasible. "Prima non nocere"; source control and aggressive supportive care for sepsis physiology must be the primary goal. This approach is supported by the substantial risk of peri-operative mortality faced by these patients. Peri-operative mortality is the main reason for inferior OS in the unadjusted analysis when compared to NP controls. Although others reported lower rates of successful resection in complicated colorectal cancer, we found that R0 resection could be achieved in 62–68% of patients with perforated colon cancer, with gross residual disease being mostly distant metastases.[19,22,24,25] Taken together, early and aggressive source control to minimize the risk of peri-operative death is the primary treatment goal. In patients whose hemodynamic status allows for consideration of an oncologic resection, it is often feasible and can be pursued if the patient's condition allows. If the patient has easily resectable extra-colonic, but exclusively intra-abdominal, disease, an expeditious attempt at resection could be considered provided that appropriate physiologic parameters have been achieved. More likely, after the patient recovers, adjuvant therapy and/or secondary surgical procedures for recurrence or persistence should be undertaken. Combined with recent, substantial, advances in adjuvant systemic therapy, cancer specific follow-up and treatment may allow patients with perforated colon cancer to achieve comparable outcomes to patients with non-perforated colon cancer in the long term.

As a retrospective review, there are inherent drawbacks to our analysis. Although we herein report the largest series of perforated colon cancers, our subgroup comparison between patients with free and contained perforations may lack adequate sample size and power to detect significant differences. Our findings therefore warrant further validation in adequately powered, larger data sets. Secondly, patients with FP might be under-staged since some might have not undergone the extensive metastatic work-up pre-operatively. This may lead to under staging at the time of resection due to missed disease outside the abdominal cavity that may become detected in follow-up. This supports the notion that patients who are initially managed in an emergent fashion and who survive the acute phase of care should be followed as other oncologic patients who present in the elective setting. Thirdly, the advances in colon cancer adjuvant therapy have led to longer survival, biasing the results of this study which includes patients receiving chemotherapy prior to the widespread use of leucovorin, oxaliplatin, and bevacizumab.[13]

Conclusions

Patients with freely perforated colon cancer face what has been termed "the double jeopardy": first from the diagnosis of malignancy, and secondly from the septic complications that result from perforation.[31] Our study confirms that these patients have significant peri-operative and long-term mortality risks; they present with severe physiologic disturbances requiring emergency intervention and critical care support. Fortunately, gross total resection is feasible in nearly all patients without distant metastatic disease as oncologic surgical principles can be followed even in the acute surgery setting. If the peri-operative disturbances inherently present in freely perforated colon cancer can be overcome, then continued oncologic treatments for persistent/recurrent disease are warranted and may lead to similar long-term survival compared with non-perforated controls.

References

1. Edwards, BK, Ward, E, Kohler, BA, et al. Annual report to the nation on the status of cancer, 1975–2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer. 116:544–573,2010.
2. The United States Center for Disease Control.
3. Gunnarsson H, Holm T, Ekholm A, et al. Emergency presentation of colon cancer is most frequent during summer. Colorectal Dis. 13:663–668,2010
4. Bass G, Fleming C, Conneely J, et al. Emergency first presentation of colorectal cancer predicts significantly poorer outcomes: a review of 356 consecutive Irish patients. Dis Colon Rectum. 52:678–684,2009.
5. Smothers L, Hynan L, Fleming J, et al. Emergency surgery for colon carcinoma. Dis Colon Rectum. 46:24–30,2003.
6. Runkel NS, Hinz U, Lehnert T, et al. Improved outcome after emergency surgery for cancer of the large intestine. Br J Surg. 85:1260–1265,1998.
7. Kelley WE Jr., Brown PW, Lawrence W, Jr., et al. Penetrating, obstructing, and perforating carcinomas of the colon and rectum. Arch Surg. 116:381–384,1981.
8. Cheung HY, Chung CC, Tsang WW, et al. Endolaparoscopic approach vs conventional open surgery in the treatment of obstructing left-sided colon cancer: a randomized controlled trial. Arch Surg. 144:1127–1132,2009.
9. Lim JF, Tang CL, Seow-Choen F, et al. Prospective, randomized trial comparing intraoperative colonic irrigation with manual

decompression only for obstructed left-sided colorectal cancer. Dis Colon Rectum. 48:205–209,2005.
10. Breitenstein S, Rickenbacher A, Berdajs D, et al. Systematic evaluation of surgical strategies for acute malignant left-sided colonic obstruction. Br J Surg. 94:1451–1460,2007.
11. Tilney HS, Lovegrove RE, Purkayastha S, et al. Comparison of colonic stenting and open surgery for malignant large bowel obstruction. Surg Endosc. 21:225–233,2007.
12. Welch JP, Donaldson GA. Perforative carcinoma of colon and rectum. Ann Surg. 180:734–740,1974.
13. Murphy JE, Ryan DP. American Society of Clinical Oncology 2010 colorectal update. Expert Rev Anticancer Ther. 2010 Sep;10 (9):1371–3.
14. Dellinger RP, Levy MM for the International Surviving Sepsis Campaign Guidelines Committee. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med (2008) 34:17–60.
15. Gunderson LL, Jessup JM, Sargent DJ, et al. Revised TN categorization for colon cancer based on national survival outcomes data. J Clin Oncol. 28:264–271,2010.
16. Badia JM, Sitges-Serra A, Pla J, et al. Perforation of colonic neoplasms. A review of 36 cases. Int J Colorectal Dis. 2:187–189,1987
17. Chen HS, Sheen-Chen SM. Obstruction and perforation in colorectal adenocarcinoma: an analysis of prognosis and current trends. Surgery. 127:370–376,2000.
18. Biondo S, Kreisler E, Millan M, et al. Differences in patient postoperative and long-term outcomes between obstructive and perforated colonic cancer. Am J Surg. 195:427–432,2008.
19. Abdelrazeq AS, Scott N, Thorn C, et al. The impact of spontaneous tumour perforation on outcome following colon cancer surgery. Colorectal Dis. 10:775–780,2008.
20. Anwar MA, D'Souza F, Coulter R, et al. Outcome of acutely perforated colorectal cancers: experience of a single district general hospital. Surg Oncol. 15:91–96,2006.
21. Khan S, Pawlak SE, Eggenberger JC, et al. Acute colonic perforation associated with colorectal cancer. Am Surg. 67:261–264,2001.
22. Mandava N, Kumar S, Pizzi WF, et al. Perforated colorectal carcinomas. Am J Surg. 172:236–238,1996.
23. Kriwanek S, Armbruster C, Dittrich K, et al. Perforated colorectal cancer. Dis Colon Rectum. 39:1409–1414,1996.
24. Lee IK, Sung NY, Lee YS, et al. The survival rate and prognostic factors in 26 perforated colorectal cancer patients. Int J Colorectal Dis. 22:467–473,2007.
25. Wong SK, Jalaludin BB, Morgan MJ, et al. Tumor pathology and long-term survival in emergency colorectal cancer. Dis Colon Rectum. 51:223–230,2008.
26. Tan KK, Hong CC, Zhang J, et al. Surgery for perforated colorectal malignancy in an Asian population: an institution's experience over 5 years. Int J Colorectal Dis. 25:989–995,2010.
27. Cuffy M, Abir F, Audisio RA, et al. Colorectal cancer presenting as surgical emergencies. Surg Oncol. 13:149–157,2004.
28. Carraro PG, Segala M, Orlotti C, et al. Outcome of large-bowel perforation in patients with colorectal cancer. Dis Colon Rectum. 41:1421–1426,1998.
29. Jestin P, Nilsson J, Heurgren M, Påhlman L, Glimelius B, Gunnarsson U. Emergency surgery for colonic cancer in a defined population. Br J Surg. 2005 Jan;92(1):94–100.
30. Lehnert T, Buhl K, Dueck M, Hinz U, Herfarth C. Two-stage radical gastrectomy for perforated gastric cancer. Eur J Surgical Oncology 2000; 26: 780–784
31. Crowder VH, Cohn I. Perforation in cancer of the colon and rectum. Dis Colon Rectum. 10:415–420,1967.

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ORIGINAL ARTICLE

Long-Term Survival Results of Surgery Alone Versus Surgery plus UFT (Uracil and Tegafur)-Based Adjuvant Therapy in Patients with Stage II Colon Cancer

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Abstract
Background It is well established that adjuvant chemotherapy with 5-fluouracil and leucovorin (5-FU/LV) improves survival for patients with resected colon cancer; however, the benefits of oral uracil and tegafur (UFT) chemotherapy in these patients are still uncertain.
Methods All patients enrolled in this retrospective study with stage II disease who were treated with surgery or surgery plus UFT were examined to determine the overall survival and disease-free interval. Time-to-event by treatment group was examined using Kaplan–Meier estimates and multivariable Cox regression analysis.
Results There were 456 eligible patients—217 (47.5%) patients had surgery and 239 (52.5%) patients had surgery plus UFT. In patients aged ≧65 years, deeper tumor depth and fewer nodes observed were associated with lower survival. The 5-year survival rate was 84.2% in the surgery group and 89.1% in the surgery plus UFT group (P=0.006). Treatment with UFT after surgery was associated with improved outcome compared with surgery alone: overall survival (HR=0.611, P=0.018) and disease-free survival (HR=0.590, P=0.032).
Conclusions Oral fluoropyrimidines improve the disease-free rate and the overall survival of patients after resection of stage II colon cancer. These observations support the use of these agents following surgery as it provides a benefit over surgery alone.

Keywords Colon cancer · UFT · Adjuvant chemotherapy

Introduction

Colorectal cancer is the fourth leading cause of cancer-related death in the world and the third leading cause in the USA.[1] In Taiwan, colon cancer is the most prevalent gastrointestinal malignancy with 10,600 new cases diagnosed in 2009.[2] Of these patients, around 40% of the patients presented with localized node negative (TNM stage II) disease and 36% with regional node positive (TMN stage III) disease. It is critically important to differentiate between stage II and III disease because this has a direct effect on prognosis and treatment. Patients with metastatic lymph nodes have a 5-year survival of approximately 44–70%.[1, 3] Therefore, postoperative adjuvant chemotherapy has been widely recommended as the standard treatment for stage III colon cancer since the early 1990s.[4] In contrast, stage II colon cancers are highly heterogeneous, with 5-year survival rates ranging from 87.5% to 58.4%.[5] Most patients with stage II colon cancer can be cured with surgery alone; the use of chemotherapy in patients with stage II colon cancer has been controversial.[6] The main question concerns the selection of stage II patients. For example, how to select patients most likely to benefit from chemotherapy? How to identify the patients who do not need chemotherapy?

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Different studies had defined high-risk stage II patients as those who need adjuvant chemotherapy, including those with T4 tumors, poor differentiation, occlusion/perforation, and a low number of lymph nodes examined.[7]

The primary drug used for chemotherapy in colorectal cancer is 5-flurouracil (5-FU), and therapeutic regimens containing 5-FU or its derivatives, such as UFT, composed of uracil and tegafur, are recommended not only for patients with metastatic disease but also for patients after complete resection.[8] Two phase III trials comparing oral UFT + LV with FU + LV administered intravenously to patients with previously untreated stage IV colorectal cancer showed no significant differences in tumor response rates, time to progression, or survival.[9, 10] Recently, the results of an NSABP C-06 trial[11] revealed that an oral UFT + LV regimen and a weekly bolus FU + LV regimen had similar effects with respect to disease-free and overall survival; these were equally toxic and were generally tolerated in patients with stage II and III colon cancer. A meta-analysis of 5,233 patients with stage I to III colorectal cancer in Japan found that 1 year of fluorinated pyrimidine regimens reduced the risk of death by 21% and the risk of tumor recurrence by 22% in subgroups of stage II patients.[12] However, the results of this study were obtained from heterogeneous populations and different treatment remedies, and there is also a lack of consensus on the utility of adjuvant chemotherapy for stage II colon cancer.

Therefore, the aim of this study is to examine the survival benefit of UFT-based adjuvant chemotherapy for stage II colon cancer under clearly defined entry, treatment, and follow-up criteria. We also sought to examine whether the tumor recurrence was influenced by UFT-based adjuvant chemotherapy following surgical resection of the primary tumor.

Methods

Patients who underwent elective surgical intervention alone or surgery plus UFT were enrolled. Only cases of resections with curative intent which could include the removal of adjacent organs but not the metastatic disease were enrolled. Emergent operations for colon obstruction or perforation were excluded in the trial. There were 512 patients without lymph node metastasis treated and followed in our hospital. Two patients with T1 lesions, 17 with T2 lesions, five cases with perioperative (<30 days post-operation) mortality, and 32 with incomplete oral adjuvant therapy (<6 months) were all excluded. Thus, there were 456 patients with stage II colon cancer enrolled in this study, and their postoperative performance status was less than two for all patients.

Patients included retrospectively in this analysis were not randomized between surgery alone and surgery plus UFT. The surgery-alone patients were treated from 1999 to 2002, and the surgery plus UFT patients were treated from 2003 to 2004 because the National Health Insurance Act in Taiwan offers coverage for UFT as adjuvant chemotherapy of stage II colon cancer after 2003. All the patients in this study agreed to receive UFT-based chemotherapy after discussion on potential morbidity and benefits after treatment. Although the treatment comparison is not randomized, we controlled for the important prognostic factors of age, gender, and lymph nodes examined in all treatment comparisons. No significant difference in clinicopathological prognostic factors (including patients' performance) was found between the group treated with

Table 1 Clinicopathological distribution of patients included in analyses by characteristics and treatment group

Characteristics	Surgery	Surgery + UFT	*P* value
Patient number	217	239	
Median follow time (months)	72	63	
Age			0.109
<65	87	114	
≧65	130	125	
Gender			0.411
Male	123	139	
Female	94	100	
Performance status[a]			0.347
0	200	226	
1	17	13	
Location[b]			0.869
Right	87	101	
Left	35	39	
Sigmoid	95	99	
Differentiation			0.392
Well	13	17	
Moderate	190	199	
Poor	14	23	
Tumor depth			0.354
T3	192	218	
T4	25	21	
Invasion[c]			0.120
Present	43	63	
Absent	174	176	
LN number			0.091
≧12	105	135	
<12	112	104	

[a] Performance status: according to the definition of ECOG–WHO

[b] Location: right—cecum to middle transverse colon, left—middle transverse to descending colon

[c] Invasion (present): if the pathological report revealed venous, lympho-vessel, or perineural invasion

chemotherapy and without chemotherapy (Table 1). However, a shorter follow-up period following UFT treatment could be problematic since it does not allow sufficient time for some adverse "events" to set in and would be mistakenly accounted as "benefit" of UFT. Patients were subscribed UFT (300 mg tegafur/m^2/day) and leucovorin (LV) 90 mg/day for 28 days, followed by 7 days of rest. The daily doses of both UFT and LV were divided into three doses administered 8 h apart. Patients were instructed to avoid food consumption 1 h before and 1 h after each dose. This cycle was repeated every 35 days for at least 6 months. The compliance with an oral UFT regimen in this study was around 88%. The most common drug toxicities included severe nausea and diarrhea (4–8%), and the risks of severe stomatitis, neutropenia, or hand–foot syndrome were less than 2%.

All patients had regular follow-up consisting of periodic examinations including blood chemistry panels (such as complete blood cell count and liver function tests), carcinoembryonic antigen (CEA) level, endoscopy, abdominal ultrasonography, and radiographs of the thorax. Computed tomography (CT) or magnetic resonance imaging (MRI) was also performed in cases where there was a suspected tumor recurrence.

The overall survival time was calculated from the date of surgery to the time of the last visit or death. Follow-up was updated in January 2011 for the current study. Each variable factor of survival rate was estimated using the Kaplan–Meier method. The significance of differences between subgroups was calculated using the log-rank test. Multivariate Cox regression analysis with stepwise selection was used to search for independent prognostic factors associated with survival. A probability value of less than 0.05 was considered as significant.

Results

During the study period, a total of 410 eligible patients with T3N0 and 46 patients with T4N0 colon cancer were all treated with complete tumor resection. There were 262 males and 194 females. The mean age was 65.4 years (range 25 to 97 years). The median follow-up was

Table 2 Univariate analysis for 5-year overall and disease-free survival in 456 patients who underwent curative surgery for stage II colon cancer

Characteristics	Number	5-year survival rate	*P* value	5-year disease-free rate	*P* value
Age			<0.001		0.021
<65	201	89.6%		88.2%	
≧65	255	84.6%		84.4%	
Gender			0.100		0.237
Male	262	86.5%		85.7%	
Female	194	85.8%		86.2%	
Location[a]			0.861		0.251
Right	188	84.7%		87.4%	
Left	74	73.5%		76.8%	
Sigmoid	194	83.2%		83.3%	
Differentiation			0.728		0.241
Well	30	75.6%		89.5%	
Moderate	389	90.6%		83.1%	
Poor	37	62.7%		78.2%	
Tumor depth			<0.001		<0.001
T3	410	92.1%		90.4%	
T4	46	42.6%		62.7%	
Invasion[b]			0.569		0.028
Present	106	76.8%		77.1%	
Absent	350	89.3%		89.7%	
LN number			0.005		0.007
≧12	240	87.9%		88.3%	
<12	216	81.6%		80.5%	
Treatment			0.006		0.001
Surgery + UFT	239	89.1%		88.7%	
Surgery	217	84.2%		82.8%	

[a]Location: right—cecum to middle transverse colon, left—middle transverse to descending colon

[b]Invasion (present): if pathological report revealed one of venous, lympho-vessel, or perineural invasion

60 months. Of the 456 patients, 217 (47.5%) received surgery alone and 239 (52.5%) received surgery followed by UFT-based chemotherapy. The distribution of patients by demographic characteristics is shown in Table 1. The two treatment groups were similar with respect to age, gender, performance status, tumor differentiation, and the number of lymph nodes examined.

Poor 5-year survival rates in the "high risk" subgroups was the trend observed in this study. For example, the 5-year survival rate in patients with poor tumor differentiation was 62.7%, as compared with 75.6% to 90.6% in patients with moderate or well differentiation, respectively. Patients with lymphovascular or perineurial invasion had a lower 5-year survival rate (76.8%) compared to that of 89.3% in patients with absence of these intra-tumor invasions. However, there was no significant difference in survival based on tumor grading (P=0.728) or the presence of intra-tumor invasion (P=0.569) after univariate analysis. Table 2 shows that survival and recurrence-free rates were significantly dependent on patients with age ≧65 years, deeper invasion of tumor depth (T4), or fewer nodes examined. There is a statistically significant effect of treatment with UFT evident for both outcomes. Patients who received UFT had a significantly better survival rate and disease-free advantage than those who did not receive chemotherapy (89.1% vs. 84.2%, P=0.006 and 88.7% vs. 82.8%, P=0.001, respectively). In addition, the presence of intra-tumor invasion was also associated with significantly frequent recurrence. Kaplan–Meier estimates of overall survival and disease-free rate by treatment are presented in Fig. 1.

In Table 3 and Fig. 2, the Cox regression analysis showed that in the stage II group, patients' age, depth of tumor invasion, extent of nodal examination, and treatment with UFT were significant contributors to the overall survival. Treatment with UFT was associated with improved overall survival compared with surgery only (HR=0.61, P=0.018). The examination of less than 12 lymph nodes was associated with increasing hazard ratios (HR), when the number of lymph nodes was analyzed as a categorized variable (95% CI=1.17–2.58, P=0.006). For recurrence-free survival, similar patterns of effects were found for these variables except for patients' age. The presence of intra-tumor invasion was also statistically associated with increasing recurrence (HR=1.67, 95% CI=1.01–2.78, P=0.049).

To better understand the progression of stage II colon cancer, we analyzed the timing of recurrent disease following surgical resection year by year as shown in Table 4. It shows that the risk for recurrence for the first 5 years was 16.2% in the surgery alone cohort and 10.9% in the UFT cohort. These results confirm that adjuvant chemotherapy with UFT provides a meaningful survival advantage to patients with stage II colon cancer.

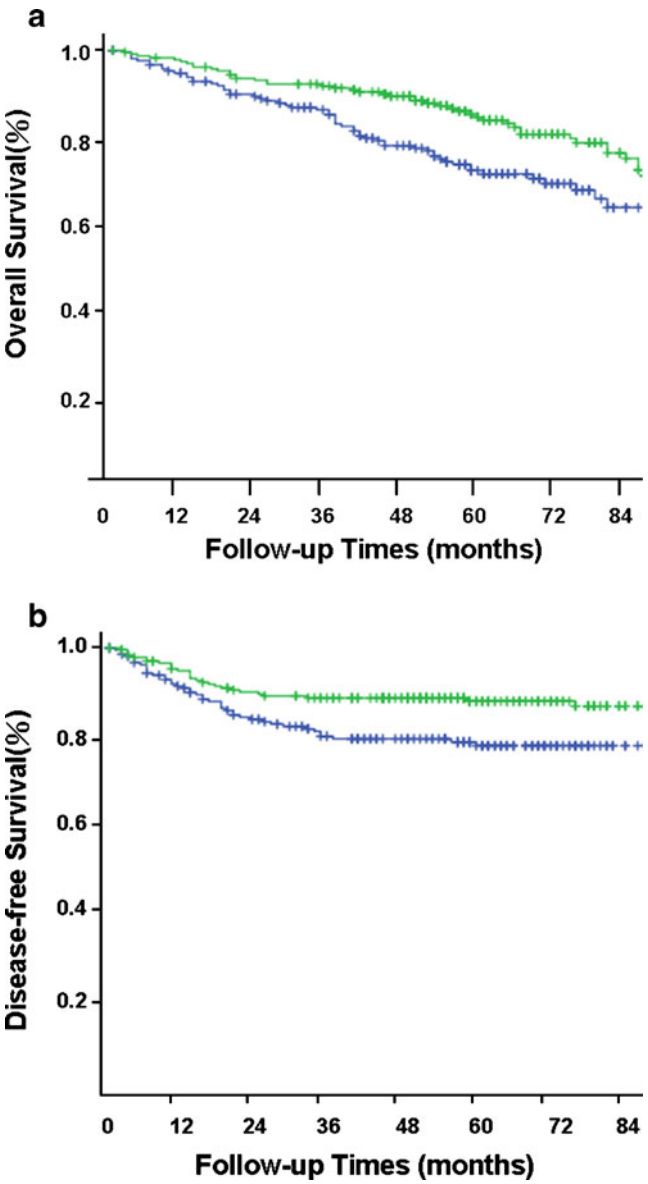

Fig. 1 Analysis of survival (Kaplan–Meier) in 456 patients with colon cancer: (**a**) overall survival and (**b**) disease-free survival according to treatment (surgery alone with blue line vs. surgery plus UFT with green line)

Discussion

In this study, some important concepts for the management of stage II colon cancer are illustrated as follows: adjuvant UFT-based treatment actually eradicates colon cancer cells; thereby the reduced recurrence could translate into its effect on prolonging survival; late relapse can occur after 5 years and most relapses occur in the first 4 years. Our findings also emphasize the importance of accurate determination of the lymph node status for patients with early-stage colon cancers. These concepts are pertinent to our understanding of tumor biology, clinical practice, and future clinical trial design.

Table 3 Results of multivariate Cox regression modeling of overall survival and recurrence-free rate in stage II colon cancer

Characteristics		Overall survival			Disease-free rate		
		Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age	<65	1.00		0.001	1.00		0.117
	≧65	2.38	1.54–3.70		1.59	0.068–3.75	
Gender	Male	1.00		0.384	1.00		0.099
	Female	0.92	0.89–1.12		0.95	0.62–1.54	
Location	Right	1.00		0.597	1.00		0.516
	Left	1.14	0.95–1.43		1.39	0.72–2.87	
	Sigmoid	0.95	0.84–1.09		0.99	0.84–1.17	
Differentiation	Well	1.00		0.659	1.00		0.156
	Moderate	0.92	0.83–1.11		0.95	0.83–1.21	
	Poor	1.23	0.91–1.21		1.87	0.85–3.52	
Tumor depth	T3	1.00		0.001	1.00		0.001
	T4	3.65	2.25–5.93		2.85	1.58–5.15	
Invasion	Absent	1.00		0.238	1.00		0.049
	Present	1.14	0.96–1.34		1.67	1.01–2.78	
Treatment	Op	1.00		0.018	1.00		0.032
	Op + UFT	0.61	0.40–0.92		0.59	0.36–0.95	
Lymph node examination	≧12	1.00		0.006	1.00		0.005
	<12	1.76	1.17–2.58		2.02	1.24–3.28	

In general, patients with stage II colon cancer are considered to have a good prognosis after surgery alone. Nevertheless, the outcome for these patients remains highly variable, with the 5-year survival ranging from 87.5% to 58.4%.[5] A 30% difference in 5-year survival for the same stage suggests that there are certain subgroups of the population with frequent recurrence resulting in a decreased survival. Based on this scenario, several high-risk features including T4 lesions, tumor perforation or obstruction, poor or high-grade differentiation, lymphovascular invasion, and inadequate lymph node examination are likely associated with poor prognosis. An American Society of Clinical Oncology Panel, in collaboration with the Cancer Care Ontario Practice Guideline Initiative, reviewed literatures from before May 2003, and this meta-analysis found that direct evidence does not support the routine use of chemotherapy for stage II patients. Meanwhile, the study did reveal that there are populations of patients with high-risk features that may benefit from adjuvant chemotherapy.[6] Later, study of a pooled analysis of infusional FU-based adjuvant chemotherapy revealed that the improvement with adjuvant chemotherapy reached statistical significance for 5-year disease-free survival (76% vs. 72%, $P=0.049$) but not for 5-year overall survival (81% vs. 80%, $P=0.1127$) in patients with stage II colon cancer.[13] Similarly, in high-risk stage II patients (22.4% of all patients) of the MOSAIC study (T4, obstruction/perforation, poorly differentiated tumor, venous invasion, and <10 lymph nodes examined), the risk of relapse was reduced by 26% with FOLFOX4 relative to LV5-FU2. However, no benefit in survival after the 6-year follow-up was observed.[14] This discrepancy between disease-free survival and overall survival may be partially explained by the overall good prognosis, the confounding deaths from causes other than colon cancer, and, more importantly, due to less intensive therapy or more advanced disease progression for patients who relapsed. In contrast, the report of Wilkinson et al.[15] and Sargent et al.[16] showed the 5FU-based chemotherapy was associated with significantly improved overall survival compared with surgery alone in patients with stage II colon cancer. However, different control and treatment arms in the trials may create bias in the results. Fortunately, we now have randomized data from a large single clinical trial. QUASAR study of 3,239 patients, in which 91.5% had stage II colorectal cancer, showed that adjuvant therapy with FU resulted in a reduced risk of tumor recurrence ($P=0.01$) and a reduced risk of dying from colorectal cancer ($P=0.008$).[17] Therefore, our results, in concert with those aforementioned results,[15–17] demonstrate that patients with stage II colon cancer will probably benefit from 5FU-based adjuvant chemotherapy.

Our results also provide invaluable data to clinical practice regarding the long-term risk of recurrence in patients with colon cancer who undergo curative resection. The risk of recurrence in patients treated with adjuvant

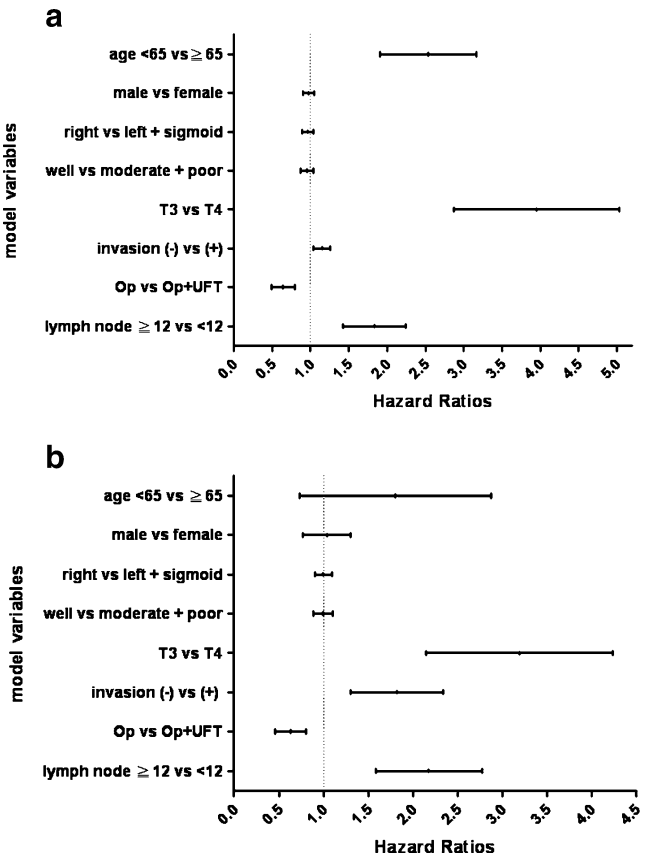

Fig. 2 Forest plot of multivariate model hazard ratio for (**a**) overall and (**b**) disease-free survival by clinicopathological characteristic and treatment options

chemotherapy never exceeds that of the control patients, and chemotherapy reduced the risk of recurrence for the first 5 years of stage II patients from 16.2% to 10.9%. After 5 years, recurrence rates were less than 2% per year. Based on the pattern of recurrence seen in this analysis, it is clear that all surveillance efforts should be directed toward the critical first 5 years. Once a patient had been recurrence free for 5 years after surgery plus UFT-based adjuvant chemotherapy, continued medical care can be focused on other issues beyond the patient's prior colon cancer. These conclusions support those by Wilkinson et al.[15] in a recent pooled analysis of NSABP C-01 through C-05.

Table 4 Probability of recurrence in the interval given the patient is alive and recurrence free at the beginning of the interval

	Surgery alone (%)	Surgery + 5FU/LV
1 year	2.7	2.5
2 years	3.9	3.1
3 years	3.6	3.2
4 years	4.9	1.5
5 years	2.9	0.5
6 years	1.9	0
Years 1–6	16.2	10.9

Finally, these analyses clearly demonstrate that the current prognostic factor with proven worth and greatest importance is pathological staging. The depth of tumor invasion is the most important characteristic in stage II colon cancer. The greatest difference in overall survival and recurrence-free rates between T3N0 and T4N0 means that these patients with T4 lesion should be offered postoperative chemotherapy. In addition, there has been evidence supporting the pivotal role of lymph node evaluation in predicting the prognosis of patients with stage II colon cancer.[18–24] These reports suggest that due to "understaging or inadequate resection", patients are often falsely identified as having negative nodes. These incorrectly staged patients are less likely to receive chemotherapy and have a survival risk similar to their true node-positive status. However, there is still controversy regarding the number of nodes by which a colonic tumor can be deemed as "accurately staged." Recently, the American College of Surgeons, the American Society of Clinical Oncology, the National Comprehensive Cancer Network as well as other groups agreed on the cutoff value of 12 as the required number of lymph nodes for the assurance of an adequate resection and precise pathological staging examination of colon cancer.[25, 26] Our results also support the findings that the prognosis of stage II colon cancer is dependent on the number of lymph nodes examined. For stage II colon cancer, all gross disease and regional lymph nodes at risk for metastasis must be resected surgically. The incremental benefits of UFT-based chemotherapy will not replace adequate lymphadenectomy.

Although there are some limitations in this non-randomized study, including different follow-up duration, the retrospective nature of the data analysis, and the inadequate number of patients, our study still provides the observed survival outcome for stage II colon cancer patients after UFT-based chemotherapy. The tolerability of oral fluoropyrimidines may make them an attractive treatment option; however, the incremental benefits in survival should be balanced against the possibility of treatment-related toxicities and costs. Importantly, the decision to offer adjuvant therapy for stage II colon cancer needs to be individualized with respect to the presence of risk factors in each patient. Given the potential poor prognosis of stage II colon cancer, our future task is crucial to identify patients likely to develop metastasis and/or benefit from adjuvant chemotherapy.

Author disclosures We certify that the authors of this article do not have commercial associations that might pose a conflict of interest in connection with the submitted article.

References

1. Jemal A, Siegel R, Ward E, et al.: Cancer statistics, 2009. CA Cancer J Clin 2009;59:225-249.
2. Annual Cancer report from Taiwan Cancer Registration system; Department of Health, ROC. 2009.
3. O'Connell JB, Maggard MA, Ko CY: Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. J Natl Cancer Inst 2004;96:1420-1425.
4. NIH Consensus Conference: Adjuvant cancer therapy. JAMA 1990;264:1444-1450.
5. Edge SB, Byrd DR, Compton CC, et al.: *AJCC Cancer Staging Manual*. 7th ed. Philadelphia: Springer; 2010. pp. 143-164.
6. Benson AB 3 rd, Schrag D, Somerfield MR, et al.: American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 2004;22: 3408-3419.
7. Rousseau B, Chibaudel B, Bachet JB, et al.: Stage II and stage III colon cancer: treatment advances and future directions. Cancer J. 2010;16: 202-209
8. Tanaka F: UFT (tegafur and uracil) as postoperative adjuvant chemotherapy for solid tumors (carcinoma of the lung, stomach, colon/rectum, and breast): clinical evidence, mechanism of action, and future direction. Surg Today 2007;37:923-943.
9. Carmichael J, Popiela T, Radstone D, et al.: Randomized comparative study of tegafur/uracil and oral leucovorin versus parenteral fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2002;20:3617-3627.
10. Douillard JY, Hoff PM, Skillings JR, et al.: Multicenter phase III study of uracil/tegafur and oral leucovorin versus fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2002;20:3605-3616.
11. Lembersky BC, Wieand HS, Petrelli NJ, et al.: Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project Protocol C-06. J Clin Oncol 2006;24:2059-2064.
12. Sakamoto J, Ohashi Y, Hamada C, et al.: Efficacy of oral adjuvant therapy after resection of colorectal cancer: 5-year results from three randomized trials. J Clin Oncol 2004;22:484-492.
13. Gill S, Loprinzi CL, Sargent DJ, et al.: Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? J Clin Oncol 2004;22: 1797-1806.
14. André T, Boni C, Navarro M, et al.: Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol. 2009;27:3109–3116.
15. Wilkinson NW, Yothers G, Lopa S, et al.: Long-term survival results of surgery alone versus surgery plus 5-fluorouracil and leucovorin for stage II and stage III colon cancer: pooled analysis of NSABP C-01 through C-05. A baseline from which to compare modern adjuvant trials. Ann Surg Oncol. 2010;17: 959-66.
16. Sargent D, Sobrero A, Grothey A, et al.: Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol. 2009;27: 872-877
17. Quasar Collaborative Group, Gray R, Barnwell J, et al.: Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet 2007;370: 2020-2029.
18. Swanson RS, Compton CC, Stewart AK, et al.: The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. Ann Surg Oncol 2003;10:65–71.
19. Prandi M, Lionetto R, Bini A, et al.: Prognostic evaluation of stage B colon cancer patients is improved by an adequate lymphadenectomy: results of a secondary analysis of a large scale adjuvant trial. Ann Surg 2002;235:458–463.
20. Le Voyer TE, Sigurdson ER, Hanlon AL, et al.: Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of Intergroup trial INT-0089. J Clin Oncol 2003;21:2912–2919.
21. Joseph NE, Sigurdson ER, Hanlon AL, et al.: Accuracy of determining nodal negativity in colorectal cancer on the basis of the number of nodes retrieved on resection. Ann Surg Oncol 2003;10:213–218.
22. Vather R, Sammour T, Kahokehr A, et al.: Lymph node evaluation and long-term survival in stage II and stage III colon cancer: a national study. Ann Surg Oncol 2009;16:585-593.
23. Chang GJ, Rodriguez-Bigas MA, Skibber JM, et al.: Lymph node evaluation and survival after curative resection of colon cancer: systematic review. J Natl Cancer Inst 2007;99:433-441.
24. Earle CC, Weiser MR, Ter Veer A, et al.: Effect of lymph node retrieval rates on the utilization of adjuvant chemotherapy in stage II colon cancer. J Surg Oncol 2009;100:525-528
25. Wong SL, Ji H, Hollenbeck BK, et al.: Hospital lymph node examination rates and survival after resection for colon cancer. JAMA 2007;298:2149-2154.
26. Bilimoria KY, Bentrem DJ, Stewart AK, et al.: Lymph node evaluation as a colon cancer quality measure: a national hospital report card. J Natl Cancer Inst 2008;100:1310-1317.

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ORIGINAL ARTICLE

One-Stage Transanal Endorectal Pull-through for Treatment of Hirschsprung's Disease in Adolescents and Adults

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Abstract
Background One-stage pull-through operation has become increasingly popular for treatment of Hirschsprung's disease. The one-stage transanal pull-through was introduced in the late 1990s and has rapidly replaced traditional procedures in infants and young children in many surgical centers.
Objective The aim of this study is to determine feasibility and safety of transanal primary repair in adolescent and adults.
Methods Fifteen patients who underwent transanal endorectal pull-through were prospectively studied. All patients presented by chronic refractory constipation with the age ranged from 11 to 22 years. The patients were followed up for a mean of 18 months. Anal continence and postoperative complication were evaluated.
Results Incomplete continence in the form of soiling occurred in four patients (26.6%) and improved gradually with conservative management. No patients suffered from complete incontinence. Anastomotic strictures occurred in two patients and were successfully treated with regular dilatations. One patient had continued outlet obstruction and revision was considered for him. One patient complicated with low perianal fistula which needed fistulectomy. There was no impotence in adults.
Conclusion These findings indicate that one-stage transanal endorectal pull-through operation in adolescent and adults is feasible and safe.

Keywords Hirschsprung's disease · Constipation · Megacolon · Adult · Transanal pull-through

Introduction

Hirschsprung's disease (HD) is a congenital aganglionosis of the submucosal and myenteric neural plexuses principally affecting the rectosigmoid or rectal segments of varying length. Most cases manifest during the neonatal period,[1] but in rare instances, the disease is initially diagnosed in older children and adult patients.[2,3]

Swenson first described definitive surgical management of infants and children with HD in the late 1940s.[4] Because these children often presented with severe malnutrition or enterocolitis, a preliminary colostomy was usually done, followed by a pull-through procedure many months later. Earlier recognition and diagnosis of the disease led a number of surgeons in the 1980s to report series of single-stage pull-through procedures in small infants, using each of the three common operations (Swenson, Duhamel, and Soave). Since then, one-stage operations have become increasingly popular because of its safety and cost-effectiveness.[5] The one-stage transanal endorectal pull-through operation (TEPT) was introduced in the late 1990s and has rapidly replaced traditional procedures in infants and young children in many surgical centers around the world.[6–10] However, no studies address TEPT for treatment of HD in adolescent and adults.

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The purpose of this study is to evaluate feasibility and safety of TEPT for treatment of HD in adolescent and adults.

Materials and Methods

The study protocol was approved by the ethics committee of our institution and all patients or their parents gave written informed consent. Data were prospectively collected on 15 consecutive patients (11 males and 4 females), all of whom underwent TEPT for HD in the Surgery Department, Assiut University Hospital between January 2004 and May 2010. TEPT was the standard operative technique for HD at Assiut University Hospital during the period of performance of this study. Patients with HD above 10 years old were included in the study. Patients having enterocolitis, acute obstruction not responding to conservative measures, and patients with bad general condition were excluded from this study. For the excluded patients, the initial surgical intervention consisted of formation of a leveling stoma in the ganglionic bowel and the definitive transabdominal pull-through procedure was performed electively at a later stage.

All the diagnoses were made based on clinical symptoms and barium enema showing the classic rectosigmoid transition zone. All patients reported long-standing refractory constipation as the predominant symptom. The diagnoses were confirmed by rectal biopsy showing absence of ganglion cells.

Preoperative chemical preparation was done using a third generation cephalosporin and metronidazole started 12 h before surgery. Mechanical preparation starts 2 days preoperatively using rectal wash two to three times daily. The results were expressed as the mean±SD or percentage.

Surgical Technique

The patient was anesthetized and placed in the supine lithotomy position. Caudal block was given to all patients. Complete relaxation using neuromuscular blocking agents excludes any interference due to reflex contraction of striated pelvic floor muscles and permits the level of the force necessary for the dilatation to be reduced. Complete relaxation and gradual dilatation prevent injury of the striated muscles. Anal retraction was performed using four traction sutures placed at the four corners of the anus (Fig. 1). The mucosa was incised circumferentially 1.5 cm above the dentate line, and a submucosal dissection was carried out proximally (Fig. 2) until above the peritoneal reflection. The submucosal dissection was carried out using combination of sharp and blunt dissection. To promote hemostasis and facilitate dissection 1:200,000 epinephrine was injected into the submucosa above the dentate line. The muscle of rectum was then incised circumferentially

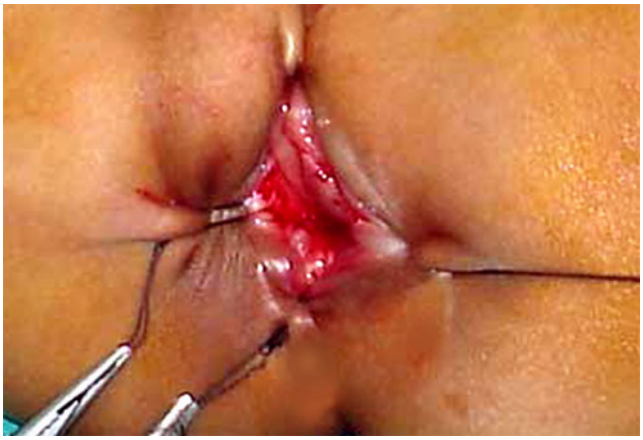

Fig. 1 Operative view showing four traction sutures placed at the four corners of the anus

allowing exposure of the full thickness of the colon, and the dissection was carried proximally along the outer wall of the rectal muscle. The vessels were ligated and divided just as they enter the bowel wall to avoid injury of the pelvic nerves and vessels and to avoid injuries of nearby structures such as vagina or prostate. The proximal mobilization and dissection of the colon were continued until the caliber was nearly normal. The bowel was then transected and the posterior wall of the muscular cuff was split. Coloanal anastomosis (Fig. 3) was done using braided absorbable suture material. A good bite of the colon was anastomosed to the underlying muscles of the rectum including a small bite of the distal mucosa. The anastomosis should be done above the dentate line so that the transitional epithelium is not damaged. This is important to prevent loss of

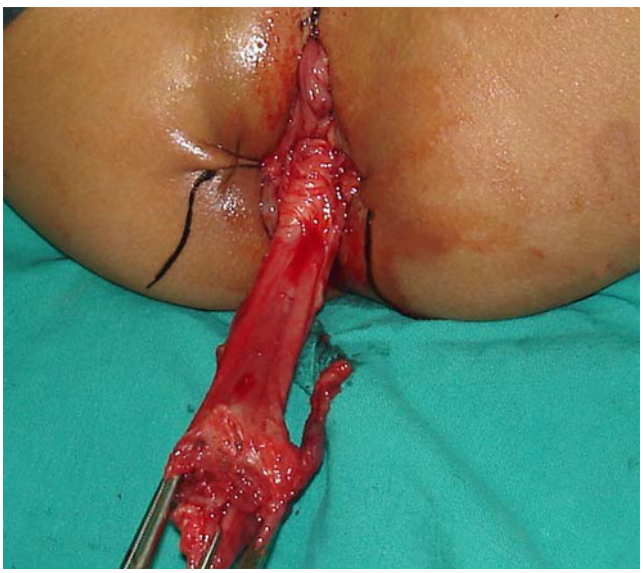

Fig. 2 Operative view showing submucosal dissection of the rectum

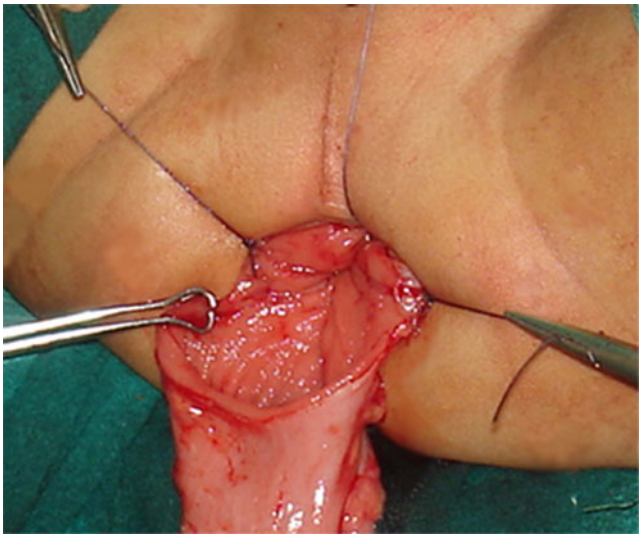

Fig. 3 Operative view of coloanal anastomosis

sensation, which may predispose to long-term problems with anal continence. A drain was placed paracolic and extracted after 24 h. Antibiotics were discontinued after 48 h, and feeding was begun when bowel function returned. The first per rectal examination of the patients was done 15 days postoperatively and followed by dilatation on regular basis in any patients with suspicion of anastomotic narrowing.

Results

Age at operation was 12.6±1.9 years (range 11–22). Operating time was 121±19.9 min (range 90–150). Bowel movements returned to normal within 24 h in all patients. Progression of oral feeding was uneventful. Postoperative hospital stay was 2.7±0.95 days (range 2–5). Two patients had postoperative bleeding (350–400 cc) and both of them were treated conservatively with blood transfusion without the need for re-exploration. The mean follow-up time was 18 months (range 6 months to 4 years). There was no urinary complication and no impotence in adults. None of the patients suffered from postoperative enterocolitis. The most frequent early complications after TEPT were frequent defecation (up to ten times per day), perineal dermatitis, and skin rash in four patients (26.6%). The rash was probably caused by frequent bowel movements. Frequent defecation and skin rash usually lasted for 6–10 weeks and improved gradually with conservative management. Anastomotic strictures occurred in two patients (13.3%) and were successfully treated with regular dilatations. One patient complicated with low perianal fistula which needed fistulectomy. There was no exposure of anal mucosa in any of the patients.

Functional Outcome

Continence was considered complete when the patient spontaneously evacuated soft stools, and there were no diurnal or nocturnal fecal soiling. When the patient had voluntary evacuations and few episodes of fecal soiling, he was considered partially continent. Data on fecal continence and bowel control of the patients were based on short-term follow-up. The frequency of stool in all patients 4 months after surgery was one to three bowel movements per day. None of the patients suffered from complete fecal incontinence. Partial incontinence in the form of soiling occurred in four patients (26.6%) and improved gradually within 10–16 weeks. One patient had continued outlet obstruction with failure of conservative management and revision was considered for him

Discussion

HD in adolescents and adults is a rare and frequently misdiagnosed cause of long-standing refractory constipation. All patients in this study reported long-standing refractory constipation as the predominant symptom. In these cases, the disease goes undiagnosed early because the proximal innervated colon can be hypertrophied and, thus, compensates for the distal obstructed, aganglionic rectum. In addition, these patients often try to relieve the constipation by taking cathartics and using enemas. Eventually, the dilated colon is no longer able to propel the feces distally. The term adult HD has been arbitrarily applied by some investigators to cases in which the patient is older than 10 years when the diagnosis is established,[11–13] whereas others have defined adult HD as cases in which the diagnosis was made after the age of 18 or 19 years.[14]

One-stage operation is safe, cost-effective, and avoids the morbidity of stomas. Specific stoma complications, including prolapse, stenosis, and wound infection, are prone to occur.[5,15] The requirement for multiple admissions and operations places a significant burden on both the family and the health-care system. Thus, the desire to avoid stoma creation and to reduce the duration of treatment prompted surgeons to adopt a strategy of primary one-stage repair once a definitive diagnosis of HD was established.[5,15] A preliminary colostomy is still needed in some conditions as presentation by complication as enterocolitis, acute on top of chronic intestinal obstruction not respond to conservative methods of treatment, and patients in bad general condition who cannot withstand major surgery.

In the early 1990s, Georgeson et al.[16] described a minimal access approach consisting of a laparoscopic biopsy to identify the transition zone, laparoscopic mobilization of the rectum below the peritoneal reflection, and a short endorectal

mucosal dissection from below. The anastomosis was done from below after prolapsing and excising the rectum. Subsequently, laparoscopic approaches have been described for the Duhamel and Swenson operations with good short-term results reported.[17,18]

In adults, transanal technique has been used successfully in the treatment of rectal malignancies, ulcerative colitis, familial polyposis coli, and colorectal vascular malformation.[19–23] The one-stage TEPT for the treatment of HD in infants and children was introduced in the late 1990s[6] and presents several advantages compared to classical pull-through techniques; it is a one-stage approach that can be conducted even during the neonatal period, previous colostomy is unnecessary, it is technically simple, no intraperitoneal adherence or scarring is observed, and it is associated with good fecal continence.[6–10]

Most of older children with congenital megacolon have short aganglionic segment.[24] All patients in the present study had short aganglionic segment and no patients required laparotomy. This is in contrast to congenital megacolon in infants and children by Tannuri et al.[25] who reported that three cases (8.5%) in TEPT group, age ranged from 10 days to 6 years, required laparotomies because the normoganglionic colon could not be reached or clearly identified.

All studies involving patients who underwent TEPT report the occurrence of coloanal anastomosis stricture although the incidence rate varies. The reported incidence of stricture ranged from 4.8% by Elhalaby et al.[8] to 43% by Stensrud et al.[26] Anastomotic stricture may be the result of ischemia of the lowest part of the mobilized colon and can be successfully managed by anal dilatations.[8,25,26] The incidence of anastomotic stricture in the present study was 13.3%. The strictures were easily treated and completely resolved with serial anal dilatations. There was no routine prophylactic dilatation because of the trauma, anxiety, and pain caused to the patient and to the parents.

During TEPT procedure, the use of four traction sutures and not using retractors is to avoid injury to the internal sphincter.[25] A general anesthesia in addition to regional sacral anesthesia induces satisfactory relaxation of both the internal and external sphincters. This makes it possible to perform free dissection of the rectal mucosa without using retractors. Attention to these fine details is important so as to avoid long-term continence issues from sphincter injury during the operation.[24,25] None of the patients in this study suffered from complete fecal incontinence.

Partial incontinence in the form of soiling occurred in four patients (26.6%). Patients with partial incontinence showed a steady improvement in their continence status. One multicenter study with a median follow-up of 12 months revealed that complete anorectal continence was achieved in 83.3% of patients who underwent TEPT older than 3 years.[8] In another study done by Tannuri et al.[25] complete continence was achieved in 70.8% of patients who underwent TEPT pull-through.

Conclusion

Hirschsprung's disease should be suspected in the context of refractory chronic constipation. One-stage TEPT in older children and adults is feasible and safe.

References

1. Roy CC, A. Silverman A, Alagille D. Congenital aganglionic megacolon (Hirschsprung's disease). In: Roy CC, Silverman A and Alagille D, ed, Pediatric clinical gastroenterology, 4th ed, Mosby, St. Louis, 1995 pp. 503–515.
2. Miyamoto M, Egami K, Maeda S, Ohkawa K; Tanaka N; Uchida E; Tajiri T. Hirschsprung's disease in adults: report of a case and review of the literature, J Nippon Med Sch. 2005; 72:113–120
3. Chen F, Winston III J, Jain S, Frankel W. Hirschsprung's disease in a young adult: report of a case and review of the literature. Ann Diagn Pathol 2006; 10: 347–351
4. Swenson O, How the cause and cure of Hirschsprung's disease were discovered. J Pediatr Surg. 1999; 34:1580–1581.
5. Somme S, Langer JC. Primary vs staged pull-through for the treatment of Hirschsprung disease. Semin Pediatr Surg. 2004;13:249–255
6. De la Torre-Mondragon L, Ortega-Salgado JA. Transanal endorectal pull-through for Hirschsprung's disease. J Pediatr Surg. 1998;33:1283–1286.
7. Langer JC, Minkes RK, Mazziotti MV Skinner MA, Winthrop A L. Transanal one-stage Soave procedure for infants with Hirschsprung's disease. J Pediatr Surg. 1999;34:148–151
8. Elhalaby EA, Hashish A, Elbarbary MM, Soliman HA, Wishahy MK, Elkholy A, Abdelhay S, Elbehery M, Halawa N, Gobran T, Shehata S, Elkhouly N, Hamza AF. Transanal one-stage endorectal pull-through for Hirschsprung's disease: a multicenterstudy. J Pediatr Surg. 2004;39:345–51.
9. Wester T, Rintala RJ. Early outcome of transanal endorectal pullthrough with a short muscle cuff during the neonatal period. J Pediatr Surg 2004;39:157–60.
10. Zhang SC, Bai YZ, Wang W, Wang WL. Clinical outcome in children after transanal 1-stage endorectal pull-through operation for Hirschsprung disease. J Pediatr Surg. 2005;40:1307–11.
11. Fairgrieve J. Hirschsprung's disease in the adult. Br J Surg. 1963;50: 506–514.
12. Barnes PR, Lennard-Jones JE, Hawley PR Todd IP. Hirschsprung's disease and idiopathic megacolon in adults and adolescents. Gut. 1986;27:534–541.
13. Kim CY, Park JG, Park KW, Park KJ, Cho MH, KIM WK. Adult Hirschsprung's disease. Int J Colorectal Dis. 1995; 10:156–160
14. Anuras S, Hade JE, Soffer E. Natural history of adult Hirschsprung's disease. J Clin Gastroenterol. 1984; 6: 205–210
15. Langer JC, Fitzgerald PG, Winthrop AL, Srinathan SK, Foglia RP, Skinner MA, Ternberg JL, Lau GY. One stage versus two stage soave pullthrough for Hirschspmng's disease m the first year of life. J Pediatr Surg 1996;31:333–36.
16. Georgeson KE, Cohen RD, Hebra A et al., Primary laparoscopic-assisted endorectal colon pull-through for Hirschsprung's disease: a new gold standard. Ann Surg. 1999; 229: 678–683

17. Travassos DV, Bax NM, Van der Zee DC. Duhamel procedure: a comparative retrospective study between an open and a laparoscopic technique. Surg Endosc. 2007; 21: 2163–2165.
18. Curran TJ, Raffensperger JG. Laparoscopic Swenson pull-through: a comparison with the open procedure. J Pediatr Surg. 1996; 31: 1155–1156
19. Maeda K, Maruta M, Sato H. Hanai T, Masumori K, Matumoto M, Koide Y, Matuoka H, Katuno H. Outcomes of novel transanal operation for selected tumors in the rectum. J Am Coll Surg. 2004; 199: 353–360
20. Zacharakis E, Freilich S, Rekhraj S, Athanasiou T, Paraskeva P, Ziprin P, Darzi A . Transanal endoscopic microsurgery for rectal tumors: the St. Mary's experience. Am J Surg. 2007; 194: 694-69
21. Fishman S J, Shamberger RC, Fox V L, Burrows P E. Endorectal pull-through abates gastrointestinal hemorrhage from colorectal venous malformations. J Pediatr Surg. 2000; 35: 982–984
22. Dolgin SE, Shlasko E, Gorfine S, Benkov K, Leleiko N. Restorative proctocolectomy in children with ulcerative colitis utilizing rectal mucosectomy with or without diverting ileostomy. J Pediatr Surg. 1999; 34: 837–840
23. Kartheuser AH, Parc R, Penna CP, Tiret E, Frileux P, Hannoun L, Nordlinger B, Loygue J. Ileal pouch-anal anastomosis as the first choice operation in patients with familial adenomatous polyposis: A ten-year experience. Surg. 1996; 119: 615–623
24. De La Torre L, Langer JC. Transanal endorectal pull-through for Hirschsprung disease: technique, controversies, pearls, pitfalls, and an organized approach to the management of postoperative obstructive symptoms. Semin Pediatr Surg. 2010; 19: 96–106
25. Tannuri A, Tannuri U, Romão R. Transanal endorectal pull-through in children with Hirschsprung's disease—technical refinements and comparison of results with the Duhamel procedure. J Pediatr Surg. 2009; 44: 767–772
26. Stensrud KJ, Emblem R, Bjørnland K. Functional outcome after operation for Hirschsprung disease-transanal vs transabdominal approach. J Pediatr Surg. 2010; 45(8):1640–4

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ORIGINAL ARTICLE

The Influence of Fecal Diversion and Anastomotic Leakage on Survival after Resection of Rectal Cancer

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Abstract
Background We analyzed factors associated with the occurrence of anastomotic leakage (AL) and its impact on long-term survival in patients who have undergone resection for rectal cancer. We also investigated the effect of fecal diversion on survival.
Method Clinical data of patients who received surgery for rectal cancer were reviewed. The difference in AL incidence among different groups was compared and survival rates were calculated. Cox's proportional hazards model was used to compare survival in patients who developed AL or received diversion stoma with those who did not.
Results Of 999 patients who received resection and anastomosis, 53 patients experienced AL. Multivariate analysis revealed advanced age ($P=0.009$) and operative method ($P=0.002$) were independent risk factors for AL. Anastomotic leakage was an independent risk factor for overall recurrence (HR 2.30; 95% CI 1.12–4.73). Anastomotic leakage and fecal diversion were independent prognostic factors of overall survival ($P=0.002$ and $P<0.001$, respectively), cancer-specific survival ($P=0.002$ and $P<0.001$, respectively), and disease-free survival ($P<0.001$, respectively).
Conclusions Patients who are older and have anastomosis at the anorectal junction or dentate line have an increased risk of AL. A diversion stoma does not appear to decrease the incidence of anastomotic leakage, but may decrease the need of reoperation when leakage occurred. Anastomotic leakage and fecal diversion are independent prognostic factors of overall, cancer-specific, and disease-free survival.

Keywords Rectum · Cancer · Anastomotic leakage · Diversion stoma · Recurrence · Survival

Jen-Kou Lin and Te-Cheng Yueh contributed equally to this article.

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Introduction

Symptomatic anastomotic leakage is the most significant surgical complication following rectal resection with anastomosis, especially after resection of middle and lower rectal cancers. Anastomotic leakage is also a major cause of postoperative morbidity and mortality in patients with rectal cancer undergoing sphincter preservation surgery.[1,2] Leakage rates from 2.8% to more than 15% have been reported.[1–12] Many factors may influence the risk and the outcome of anastomotic leakage, including the patient's condition, tumor characteristics, and surgical technique. Identification of risk factors for leakage may lead to preventive measures. Intraoperative tests for determining the integrity of anastomosis, fecal diversion, and pelvic

drainage have been reported by several authors to decrease the occurrence and effects of anastomotic leakage.[12–17]

The impact of anastomotic leakage on the long-term oncological outcome is not clear. Some authors suggest that anastomotic leakage is an independent prognostic factor for local recurrence; however, others take the opposite view.[3,18–21] The aim of this study is to analyze factors that may influence the incidence of anastomotic leakage and examine the long-term oncological impact of anastomotic leakage. In addition, we investigate the effect of fecal diversion with respect to prognosis after resection of rectal cancer with anastomosis.

Methods

Patient Demography

Prospective data collection of consecutive patients with colorectal cancer was begun at the inception of the Colorectal Surgery Service at our hospital in 1959. The database includes patient age; sex; family history of colorectal cancer; major medical conditions and previous major surgeries; the location, size, and histological characteristics of the tumor; surgical procedure for colorectal cancer and complications; and recurrence and survival. All patients have been followed up regularly.

From January 1993 to June 2003, a total of 999 patients with rectal cancer located at or distal to 16 cm from the anal verge received resection and anastomosis at a tertiary care referral hospital. Patients who did not have an anastomosis or who received preoperative radiotherapy (RT) or chemoradiotherapy (CRT) were excluded from the study. Tumor location was measured from the lower border of the tumor to the anal verge with a rigid sigmoidoscope and was classified as low when the distance was <6 cm from the anal verge, middle when between 6 and 12 cm from the anal verge, and upper when it was more than 12 cm from the anal verge.

The operation was defined as an anterior resection (AR) when the anastomosis was performed above the peritoneal reflection, a low anterior resection (LAR) when the anastomosis was constructed below the peritoneal reflection, and an ultra-low anterior resection (ultra-LAR) when the anastomosis was located at the level of the anorectal junction, near the pelvic outlet or at the dentate line.

Surgical Techniques

Standard procedures for resection of rectal cancers were followed. High ligation of the inferior mesenteric vessels proximal to the left colic vessels was routine procedure. The mobilization of the rectum was achieved by sharp dissection and autonomic nerve preservation under direct visual inspection so that the rectal fascia propriae, which enclosed the mesorectum, was kept intact. Adequate mesorectal excision with at least 4 cm distal clear margin was the rule for resection of upper and most middle rectal cancers. For low and some middle lesions, total mesorectal excision (TME) with an ultra-low anastomosis was adopted as the standard surgical technique. In TME resection and ultra-low anastomosis, a clear distal margin of 2 cm was considered adequate. Only resections with pathologically confirmed clear lateral margins and both cut ends clear were considered radically curative.

End-to-end colorectal or colo-anal anastomosis (straight or J pouch) was performed using circular staplers or hand-suture technique. A diversion colostomy or ileostomy was performed when the anastomosis was difficult to accomplish as judged by the surgeon, when the anastomosis was ultra-low, or when there was an incomplete doughnut or leakage on the air-tight test. Pelvic drains placed behind the anastomosis in the presacral space were usually used. Of the 999 patients, 155 received defunctional fecal diversion, either colostomy or ileostomy.

According to the selection of the individual surgeon, 41 patients received postoperative radiotherapy or chemoradiotherapy. In these, 35 patients were in curative resection group.

Definition of Anastomotic Leakage and Tumor Recurrence

The definition of anastomotic leakage in the present study was based on the clinical findings of pus or fecal discharge from the drain, pelvic abscess, peritonitis, discharge of pus per rectum, or the development of a colo-cutaneous or rectovaginal fistula. Subclinical leakage was considered when there was leakage of water-soluble contrast media during enema examination performed before considering reversal of the diversion.

Local recurrence was defined as recurrence at or near the anastomotic site, limited to the pelvic cavity. Distant metastasis was defined as recurrence at various distant organs or tissues, including intraperitoneal dissemination. Recurrence was confirmed by histological examination of tissue or progressive or new radiological findings, with or without elevation of tumor makers. The time to recurrence was defined as the duration between the time of surgical resection and identification of the recurrence. Only patients who underwent curative resection were included in the analysis of survival and recurrence. One hundred and forty-nine patients had stage IV disease with distant metastasis, and in 22 patients the lateral cut margin was not described or was not clear. These 171 patients and seven patients with postoperative mortality in curative resection group were not included in the analysis of survival and recurrence. The

remaining 821 cases were included in survival and recurrence analysis.

Statistical Analysis

To investigate the factors that might influence the occurrence of anastomotic leakage, 13 variables were analyzed: age, gender, systemic disease (none or presence of any major systemic disease, such as diabetes mellitus, hypertension, heart, liver, or kidney disease), tumor location, tumor invasion depth (T1–3 versus T4), TNM staging (stage I and II versus III and IV), lymphovascular or perineural invasion, quality of resection (curative versus palliative), operation methods (LAR versus ultra-LAR versus AR), type of anastomosis (hand-sutured or stapled), fecal diversion, associated organ resection, and related surgical complications (such as stroke, arrhythmia, atelectasis of lungs, or pneumonia). Continuous variables, such as age, were dichotomized using the mean value as a cut-off point. Logistic regression analysis was used for univariate analysis of the prognostic value of these variables. Recurrence pattern and interval related to anastomotic leakage were examined using chi-squared test, Fisher's exact test, or *t* test, as appropriate. All variables with a value of $P < 0.1$ were included in the multivariate model. A P value<0.05 was considered statistically significant. The odds ratios (OR) and 95% confidence interval (CI) were quoted.

Five-year survival rates were calculated using the Kaplan–Meier method and compared by using log-rank test. Cox's proportional hazards model was used to compare survival in patients who developed an anastomotic leakage or received a diversion stoma to those who did not. Statistical analyses were performed using the SPSS package (version 16.0 for Windows; SPSS, Chicago, IL, USA).

Results

Of the 999 patients, 53 patients experienced anastomotic leakage with an incidence of 5.3% (53 of 999 patients). The leakage rate between patients with diversion (6.5%, 10 of 155) compared to those without diversion (5.1%, 43 of 844) showed no significant difference ($P=0.49$). Fourteen patients died within 30 days after surgery or during hospitalization, resulting in a surgical mortality of 1.4% (14 of 999 patients). Only one patient who died was in the leakage group.

Risk Factors for Anastomotic Leakage

The patients were divided into two groups according to the presence of clinical anastomotic leakage. Patient and tumor characteristics and treatment-related variables of both groups are shown in Table 1. Univariate analysis revealed that the patient age ($P=0.008$ for age >70 years), tumor location ($P=0.026$ for location 6–12 cm from the anal verge), and operative method ($P=0.002$ for ultra-LAR) were associated with an increased anastomotic leakage rate. Multivariable analysis revealed that only older age and operative method were independent risk factors for the occurrence of anastomotic leakage. The risk of leakage was 2.2 times higher for patients >70 years of age compared to those <70 years of age ($P=0.009$; 95% CI 1.21–3.88). The risk of leakage was 3.1 times higher in anastomoses at the level of the anorectal junction or dentate line than in anastomoses below the peritoneal reflection but above anorectal junction ($P=0.002$; 95% CI 1.53–6.22). Tumor in the middle rectum (6–12 cm) also showed a borderline significant increased risk of anastomotic leakage ($P=0.078$). Results of the multivariable analysis are shown in Table 2.

Recurrence

The overall recurrence rate was 18.6% (186 of 999) and the local recurrence rate was 4.7% (47 of 999). In 22 patients with lateral margin not mentioned or not clear, the local recurrence rate was 13.6% (3/22) and the 5-year overall survival rate was 44.3%. In the curative resection patients, the comparison of the incidence and pattern of recurrence between patients with and without anastomotic leakage is shown in Table 3. It showed no difference between the two groups in terms of the incidence of local, distant, and overall recurrence. There was also no difference of time to recurrence and time to local recurrence between the two groups. Univariable analysis showed that local recurrence and overall recurrence were more common in the presence of deeper tumor invasion, lymph node metastasis, and poor cell differentiation ($P<0.05$). The relationship between recurrence and anastomotic leakage showed borderline significance ($P=0.095$ for local recurrence; $P=0.093$ for overall recurrence). Multivariable analysis identified lymph node metastasis (HR 3.56; 95% CI 1.76–7.17) and poor cell differentiation (HR 2.75; 95% CI 0.99–7.61) as independent risk factors for local recurrence. However, tumor invasion depth (HR 2.63; 95% CI 1.54–4.49), lymph node metastasis (HR 4.62; 95% CI 3.17–6.74), and anastomotic leakage (HR 2.30; 95% CI 1.12–4.73) were identified as independent risk factors for overall recurrence. There was no influence of anastomotic leakage on local recurrence. Postoperative radiotherapy had no influence on either local or overall recurrence (Table 4).

Table 1 Univariate analysis of predictive factors for anastomotic leakage in 999 patients undergoing resection of rectal cancer

Variables	Anastomotic leakage (%)		*P* value[a]	OR	95% CI
	Yes (*n*=53)	No (*n*=946)			
Age (years)					
≦70	21 (3.7)	553 (96.3)			
>70	32 (7.5)	393 (92.5)	0.008	2.14	1.22–3.77
Gender (M/F)					
Female	10 (3.4)	287 (96.6)			
Male	43 (6.1)	659 (93.9)	0.08	1.87	0.93–3.78
Systemic disease					
Absence	23 (4.5)	492 (95.5)			
Presence	30 (6.2)	454 (93.8)	0.224	0.71	0.41–1.24
Tumor location					
>12 cm	3 (1.7)	172 (98.3)			
6–12 cm	46 (6.3)	689 (93.7)	0.026	3.83	1.18–12.45
<6 cm	4 (4.5)	85 (95.5)	0.200	2.70	0.59–12.33
Tumor invasion depth					
T1, T2, T3	50 (5.6)	843 (94.4)			
T4	3 (2.8)	103 (97.2)	0.239	0.49	0.15–1.60
TNM staging					
I and II	34 (6.4)	495 (93.6)			
III and IV	19 (4.0)	451 (96.0)	0.096	0.61	0.35–1.09
Lymphovascular or perineural invasion					
No	45 (5.1)	841 (94.9)			
Yes	8 (7.1)	105 (92.9)	0.374	1.42	0.65–3.10
Quality of resection					
Curative	46 (5.4)	813 (94.6)			
Palliative	7 (5.0)	133 (95.0)	0.862	0.93	0.41–2.10
Operative method					
LAR	39 (4.7)	789 (95.3)			
Ultra-LAR	14 (12)	103 (88)	0.002	2.75	1.44–5.27
AR	0 (0)	54 (100)	0.997	0.00	0.00
Anastomosis type					
Hand suture	3 (2.1)	143 (97.9)			
Staple	50 (5.9)	803 (94.1)	0.070	2.97	0.91–9.65
Fecal diversion					
No	43 (5.1)	801 (94.9)			
Yes	10 (6.5)	145 (93.5)	0.490	1.285	0.63–2.61
Associated organ resection					
No	38 (5.2)	698 (94.8)			
Yes	15 (5.7)	248 (94.3)	0.737	1.111	0.60–2.06
Surgical complication					
Absence	51 (5.2)	926 (94.8)			
Presence	2 (9.1)	20 (90.9)	0.430	1.82	0.41–7.98

CI confidence interval, *OR* odds ratio, *LAR* low anterior resection, *AR* anterior resection

[a] As determined by logistic regression

Table 2 Multivariate analysis of risk factors for anastomotic leakage

	Odds ratio	95% confidence interval	*P* values[a]
Age (years)			
≦70			
>70	2.17	1.21–3.88	0.009
Gender			
Female			
Male	1.37	0.63–2.98	0.431
Tumor location			
>12 cm			
6–12 cm	2.93	0.89–9.71	0.078
<6 cm	1.26	0.25–6.35	0.782
Operative method			
LAR			
Ultra-LAR	3.08	1.53–6.22	0.002
AR	0.00	0.00	0.997
Anastomosis type			
Hand suture			
Staple	2.34	0.65–8.37	0.192

LAR low anterior resection, *AR* anterior resection

[a] As determined by logistic regression

Diversion Stoma

We analyzed the influence of the timing of the diversion stoma on the recurrence of the tumor and the survival of the patients. The selection of whether diversion stoma should be done after rectal resection was judged by the surgeons. As shown in Table 5, male gender, low cancer (<6 cm from anal verge), low anastomosis, and associated organ resection were factors related to performance of diversion stoma. Associated medical disease was not an independent factor for selection of diversion stoma (Table 5). In the 43 patients with anastomotic leakage, there was no significant difference in local, distant, and overall recurrence rates, recurrence-free periods, or 5-year survival rates between patients who received a diversion stoma before the leakage occurred compared to those who received a diversion stoma after leakage occurred (Table 6). However, only 25% (two of eight) of the leakage patients who had diversion stoma before leakage occurrence needed reoperation to treat the abdominal sepsis caused by the leakage. In contrast, 100% (35 of 35) of the patients who did not have a diversion stoma before leakage occurrence required reoperation to treat abdominal sepsis caused by leakage ($P<0.001$).

Survival

The 5-year overall survival rates were 74.2% in the non-leakage group and 52.9% in the leakage group ($P=0.001$; Fig. 1). The cancer-specific survival rates were 82.5% in the

Table 3 Site of tumor recurrence and survival

Recurrence and survival	Anastomotic leakage		*P* values
	Yes (*n*=43)	No (*n*=778)	
Local recurrence, *n* (%)	3 (7.0)	41 (5.3)	0.497[a]
Distant recurrence, *n* (%)	11 (25.6)	142 (18.3)	0.230[a]
Total recurrence, *n* (%)	13 (30.2)	163 (21.0)	0.179[a]
Time to recurrence (months)	22.1±12.2	24.1±19.5	0.590[b]
Time to local recurrence (months)	23.7±16.3	25.7±24.8	0.859[b]
5-year overall survival	57.4%	74.8%	0.005[c]
5-year CSS	69.6%	83.2%	0.020[c]
5-year disease-free survival	54.9%	76.7%	0.002[c]

n number of cases, *CSS* cancer-specific survival

[a]As determined by chi-squared or Fisher's exact tests

[b]As determined by *t* test

[c]As determined by Kaplan–Meier method

Table 4 Multivariate analysis of factors affecting local recurrence and overall recurrence after curative resection for rectal cancer

	Odds ratio	95% confidence interval	*P* values[a]
Local recurrence			
Tumor invasion depth			
T1, T2, T3			
T4	2.17	0.98–4.81	0.057
TNM staging			
I and II			
III	3.56	1.76–7.17	<0.001
Cell differentiation			
Well and moderate			
Poor	2.75	0.99–7.61	0.052
Post-op chemoradiation			
No			
Yes	1.32	0.42–4.14	0.636
Anastomotic leakage			
No			
Yes	1.65	0.47–5.83	0.436
Overall recurrence			
Tumor invasion depth			
T1, T2, T3			
T4	2.63	1.54–4.49	<0.001
TNM staging			
I and II			
III	4.62	3.17–6.74	<0.001
Cell differentiation			
Well and moderate			
Poor	1.05	0.45–2.43	0.915
Post-op radiation			
No			
Yes	1.27	0.60–2.72	0.532
Anastomotic leakage			
No			
Yes	2.30	1.12–4.73	0.024

non-leakage group and 65.5% in the leakage group (P=0.005; Fig. 2). The disease-free survival rates were 76.2% in the non-leakage group and 52.2% in the leakage group (P<0.001; Fig. 3). All differences were statistically significant.

Cox's regression model, including all known prognostic factors, was performed to determine whether anastomotic leakage and diversion stoma were prognostic factors in overall 5-year survival, cancer-specific survival, and disease-free survival. In the multivariable model, lymph node metastasis (P<0.001), lymphovascular or perineural invasion (P=0.007), systemic disease (P=0.001), anastomotic leakage (P=0.002), and diversion stoma (P<0.001) were independent variables of 5-year overall survival (Table 7). In the analysis of cancer-specific survival, deeper tumor invasion (P=0.005), lymph node metastasis (P<0.001), anastomotic leakage (P=0.002), and diversion stoma (P<0.001) were independent variables (Table 8). In the analysis of disease-free survival, deeper tumor invasion (P<0.001), lymph node metastasis (P<0.001), systemic disease (P=0.014), anastomotic leakage (P<0.001), and diversion stoma (P<0.001) were independent variables (Table 9). Anastomotic leakage and diversion stoma are consistent independent prognostic factors for overall, cancer-specific, and disease-free survival, with power comparable to lymph node metastasis.

Discussion

Clinical anastomotic leakage is one of the most serious complications of rectal cancer surgery. Although better survival and reduced local recurrence have been achieved in rectal cancer surgery patients,[22] treatment with low colorectal anastomosis is still associated with a high risk of leakage at the anastomosis. Reports in the literature indicate that anastomotic leakage following resection of rectal cancer is associated with high morbidity and mortality rates.[18,23,24] The present study found a clinical leakage rate

Table 5 Univariate analysis of pathological and medical co-morbidity difference between patients with or without diversion stoma after curative resection of rectal cancer

Variables	Defunctional stoma (%)		*P* value[a]	OR	95% CI
	Yes (*n*=145)	No (*n*=676)			
Age (years)					
≦70	79 (16.9)	388(83.1)			
>70	66(18.6)	288(81.4)	0.52	1.13	0.79–1.61
Gender (MF)					
Female	1 (0.4)	255 (99.6)			
Male	144(25.5)	421(74.5)	<0.001	87.22	12.1–627.2
Systemic disease					
Absence	78(18.2)	350(81.8)			
Presence	67(17.0)	326(83.0)	0.659	0.93	0.65–1.32
Tunior location					
>12 cm	19(13.4)	123(86.6)			
6–12 cm	103(17.1)	499(82.9)	0.282	1.34	0.79–2.26
<6 cm	23 (29.9)	54(70.1)	0.004	1.66	1.18–2.34
Tumor invasion depth					
Ti. Ti T3	135 (18.0)	615 (82.0)			
T4	10(14.1)	61(85.9)	0.41	0.75	0.37–1.50
TNM staging					
I and II	98 (18.9)	421 (81.1)			
III	47(15.6)	255(84.4)	0.23	0.79	0.54–1.16
Lymphovascular orperineural invasion					
No	133 (17.7)	618(82.3)			
Yes	12(17.1)	58(82.9)	0.905	0.96	0.50–1.84
Histological differentiation					
W&M	141 (17.8)	652(82.2)			
Poor	4(14.3)	24(85.7)	0.635	0.77	0.26–2.26
Operative method					
AR	2(4.1)	47(95.9)			
LAR	111 (16.5)	562 (83.5)	0.035	4.64	1.11–19.39
Ultra-LAR	32(32.3)	67(67.79)	0.001	3.35	1.60–7.01
Anastomosis type					
Handsuture	0(0)	122(100)			
Staple	145(20.7)	554(79.3)	0.996	0.00	0.00
Associated organ resection					
No	8(1.4)	564(98.6)			
Yes	137(55.0)	112(45.0)	<0.001	86.2	41.1–181.0
Surgical complication					
Absence	142(17.6)	667(82.4)			
Presence	3(25.0)	9(75.0)	0.505	1.57	0.42–5.86

CI confidence interval, *OR* odds ratio, *LAR* low anterior resection, *AR* anterior resection, *W & M* well and moderate

[a] As determined by logistic regression

of 5.3%, and there was no leakage occurrence if the anastomosis was done above the peritoneal reflection. Only one death occurred in the leakage group. The rate is at the lower end of the rates reported by several investigators, which range from 2.8% to more than 15%.[1–12] The definition of leakage varies, and clinical leakage differs from subclinical leakage. In this study, the diagnosis of anastomotic leakage was dependent on clinical presentation, and subclinical leakage was not considered because routine contrast enema was not performed after surgery. We also excluded patients who received preoperative radiotherapy (RT) treatment to simplify the analysis because some literature has indicated that preoperative RT is a risk factor for anastomotic leakage. This may partially explain our relatively low leakage rate as compared to other reports.

Several factors, such as age, gender, tumor characteristics, and surgical method, may be related to the incidence of leakage. Other possible factors, such as body mass index, tumor diameter, gross appearance of an advanced tumor, and American Society of Anesthesiologists (ASA) score, were not analyzed using our limited database.

In patient-related factors, male gender is generally accepted as a risk factor for anastomotic leakage.[1,8,25] In the present study, male gender showed borderline significance in univariable analysis but no significance in multivariable analysis. Proportions of the two groups were unequal (F/M=297:702) because of the special condition of our hospital. Older age and ultra-LAR remained independent risk factors associated with anastomotic leakage in multivariable analysis, and this has also been found in other studies.[1,8,12,25] Poor general condition and potentially compromised microcirculation may explain the higher incidence of anastomotic leakage in older patients. Tumor located at 6 to 12 cm from the anal verge had a significantly higher rate of anastomotic leakage in the univariable analysis, but in multivariable analysis the significance was borderline. Ultra-LAR anastomosis had a significant higher incidence of anastomotic leakage than LAR anastomosis. Usually, a diverting stoma was added after an ultra-LAR anastomosis. However, the leakage rate of ultra-LAR anastomosis in this series was still high (12%). Tumor in the middle or lower third, with subsequent lower anastomosis, is generally accepted as a risk factor for anastomotic leakage.[23,26] For lower locations of tumor and lower anastomosis, tissue tension, poor circulation at anastomotic ends, and technical difficulty may explain the higher incidence of leakage.

Many factors are known to be associated with local recurrence, including tumor stage, histological differentiation, obstruction, perforation, type of operation, distal margin of clearance, venous invasion, adjuvant therapy, and the experience of the surgeon.[18] Multivariable analysis showed that anastomotic leakage was not associated with local recurrence, while it was an independent factor

Table 6 Influence of timing of diversion stoma on tumor recurrence and survival of patients

Recurrence and survival	Time of diversion performed		*P* values
	Before AL (*n*=8)	AfterAL (*n*=35)	
Local recurrence, *n* (%)	2 (25.0)	1 (2.9)	0.084[a]
Distant recurrence, *n* (%)	1 (12.5)	10 (28.6)	0.656[a]
Overall recurrence, *n* (%)	2 (25.0)	11 (31.4)	1.000[a]
Time to recurrence (months)	26.7±21.8	21.2±11.2	0.581[b]
Time to local recurrence (months)	26.7±21.8	17.7±0	0.792[b]
5 year overall survival	65.6%	55.8%	0.626[c]
5 year CSS	87.5%	66.0%	0.395[c]
5 year disease-free survival	60.0%	53.9%	0.764[c]

AL anastomotic leakage, *n* number of cases, *CSS* cancer-specific survival

[a]As determined by chi-squared or Fisher's exact tests

[b]As determined by *t* test

[c]As determined by Kaplan–Meier method

associated with overall recurrence. However, the interval from operation to recurrence in both the leakage and non-leakage groups showed no difference. Typically, 55–80% of recurrences present in the first 2 years after surgery.[18] We had similar findings in that the average interval from surgery to recurrence was 22 to 24 months and the average interval from surgery to local recurrence was 23 to 26 months. The present study confirmed that lymph node metastasis and poor cell differentiation were independent risk factors for local recurrence, and the independent factors for overall recurrence were deeper tumor invasion, lymph node metastasis, and anastomotic leakage. Some studies have reported a significant association between anastomotic leakage and local recurrence.[19,27–30]

The influence of long-term prognosis after anastomotic leakage is still controversial.[18,20,24,28–32] The proportion of patients with anastomotic leakage is usually small, thus it is difficult to determine if it is a factor in long-term survival. In the present analysis, the negative prognostic impact of anastomotic leakage on long-term overall survival, disease-free survival, and cancer-specific survival was confirmed by both univariable and multivariable analyses. The pathological mechanism responsible for the adverse oncological influence of anastomotic leakage is presumably related to the release of exfoliated cancer cells that remain in the bowel lumen of patients with colorectal cancer at the time of operation,[33,34] which have been reportedly detected on the suture or staple lines of the anastomosis.[35,36] In addition, the inflammatory response to anastomotic leakage may enhance tumor spread and metastasis.[37,38]

Anastomotic leakage results in delayed mucosal healing and provides a way for the exfoliated tumor cells to implant on a highly vascular surface, which allows for tumor

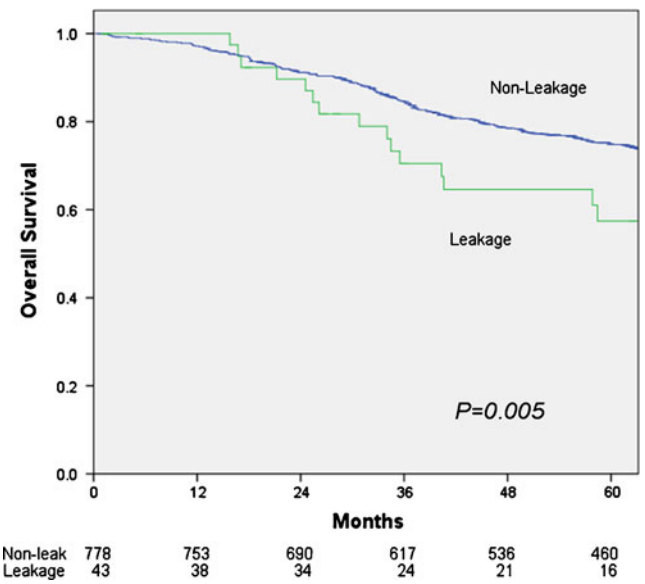

Fig. 1 Analysis of overall survival in patients with and without anastomotic leakage after curative resection of their rectal cancer

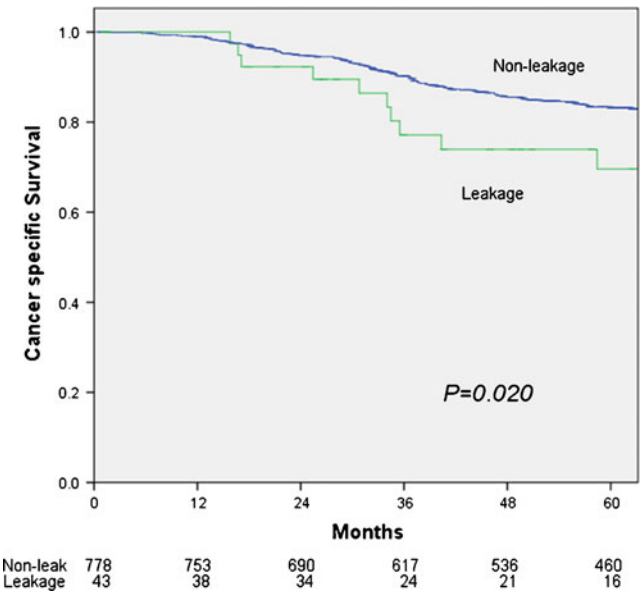

Fig. 2 Analysis of cancer-specific survival in patients with and without anastomotic leakage after curative resection of their rectal cancer

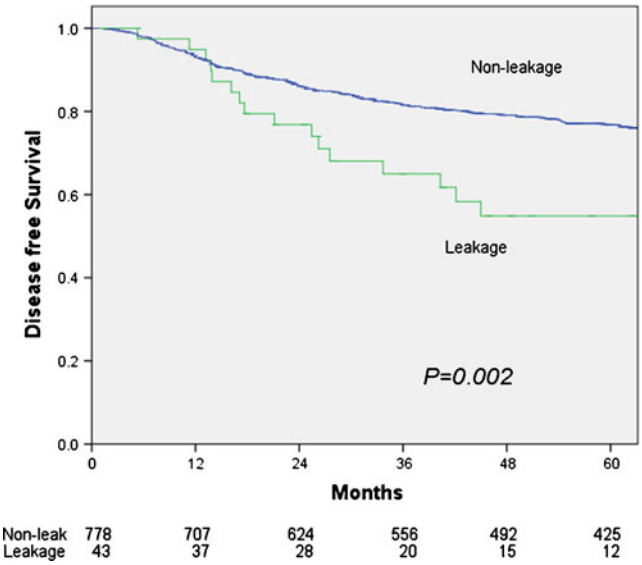

Fig. 3 Analysis of disease-free survival in patients with and without anastomotic leakage after curative resection of their rectal cancer

growth or distant spread. These mechanisms may account for the association of poor survival and anastomotic leakage.[19,27,30] In a recent multicenter pooled data analysis, authors reported that anastomotic leakage had no significant impact on the oncological outcome (local recurrence, distant metastasis, cancer-specific survival, or disease-free survival) after rectal cancer surgery, except for reducing overall survival.[39] However, in that study, a large number of the patients received preoperative CRT or RT. Preoperative CRT or RT may have some positive influence of the tumor control, especially in local control and even in prolonging the survival. The negative impact of anastomotic leakage on oncological control may be balanced by the beneficial effect of CRT or RT. Clinically, many patients with colorectal anastomotic leakage after CRT or RT had unhealed anastomosis or fistula, but no local or distant recurrence in long-term follow-up.

The role of a temporary diverting stoma in patients undergoing LAR remains controversial.[40–42] Some reports showed that proximal diversion is unable to protect the patient from anastomotic dehiscence.[2,4] Other reports showed a significant decrease in the incidence of clinically relevant leakage and the risks of reoperation.[43,44] A diversion stoma is the best strategy to minimize the occurrence of severe pelvic sepsis caused by anastomotic leakage.[10] In the present study, the reoperation rate in patients with a diversion stoma was significantly decreased, although the leakage rate of patients with and without diversion stoma revealed no significant difference.

Interestingly, in the 43 clinical leakage patients after curative resection, preventive fecal diversion did not have a beneficial influence on recurrence or survival. On the contrary, fecal diversion was an independent beneficial prognostic factor for overall recurrence, overall survival, cancer-specific survival, and disease-free survival, and a borderline good prognostic factor for local recurrence. It is possible that some minor or subclinical leakage may occur without local or systemic inflammatory reaction in the presence of preventive fecal diversion. In the clinical leakage patient, the protective effect of fecal diversion is overcome by the pollution of a large

Table 7 Prognostic factors influencing overall survival rate after curative resection of rectal cancer

Univariate analysis	5-year survival rate (%)		*P* value[a]
Tumor invasion depth			<0.001
T1, T2, T3	74.8		
T4	55.3		
TNM staging			<0.001
I and II	81.3		
III	60.0		
Lymphovascular or perineural invasion			<0.001
No	75.0		
Yes	53.3		
Histological differentiation			0.386
Well and moderate	73.7		
Poor	60.5		
Systemic disease			0.003
Absence	77.5		
Presence	68.4		
Post-opradiation			0.288
No	44		
Yes	64.9		
Anastomotic leakage			0.001
No	74.2		
Yes	52.9		
Diversion			<0.001
No	68.5		
Yes	95.8		
Multivariate analysis	Hazard ratio	95% confidence interval	*P* values[b]
Tumor invasion depth	1.42	0.96–2.10	0.077
TNM staging	1.98	1.50–2.60	<0.001
Lymphovascular or perineural invasion	1.69	1.15–2.48	0.007
Systemic disease	1.54	1.19–2.00	0.001
Anastomotic leakage	2.14	1.32–3.48	0.002
Diversion	0.16	0.08–0.31	<0.001

Post-op postoperative

[a] As determined by log-rank test

[b] As determined by Cox's proportional hazard model

Table 8 Prognostic factors influencing cancer-specific survival rate after curative resection of rectal cancer

Univariate analysis	5-year survival rate (%)		*P* value[a]
Tumor invasion depth			<0.001
T1, T2, T3	83.7		
T4	60.6		
TNM staging			<0.001
I and II	91.6		
III	65.8		
Lymphovascular or perineural invasion			<0.001
No	83.5		
Yes	62.3		
Histological differentiation			0.0 74
Well and moderate	82.3		
Poor	65.0		
Systemic disease			0.243
Absence	83.2		
Presence	79.8		
Post-op radiation			0.021
No	83.4		
Yes	64.9		
Anastomotic leakage			0.005
No	82.5		
Yes	65.5		
Diversion			<0.001
No	77.9		
Yes	95.8		
Multivariate analysis	Hazard ratio	95% confidence interval	*P* values[b]
Tumor invasion depth	1.89	1.21–2.96	0.005
TNM staging	3.76	2.54–5.57	<0.001
Lymphovascular or perineural invasion	1.58	0.99–2.51	0.055
Histological differentiation	0.81	0.39–1.70	0.581
Post-op radiation	1.40	0.74–2.63	0.303
Anastomotic leakage	2.67	1.42–5.03	0.002
Diversion	0.10	0.03–0.30	<0.001

Post-op postoperative

[a] As determined by log-rank test

[b] As determined by Cox's proportional hazard model

Table 9 Prognostic factors influencing disease-free survival rate after curative resection of rectal cancer

Univariate analysis	5-year survival rate (%)		*P* value[a]
Tumor invasion depth			<0.001
T1, T2, T3	77.8		
T4	46.0		
TNM staging			<0.001
I and II	86.2		
III	57.0		
Lymphovascular or perineural invasion			<0.001
No	76.7		
Yes	56.8		
Histological differentiation			0.047
Well and moderate	75.7		
Poor	56.3		
Systemic disease			0.076
Absence	77.7		
Presence	72.0		
Post-op radiation			0.007
No	76.7		
Yes	55.0		
Anastomotic leakage			<0.001
No	76.2		
Yes	52.2		
Muhivariate analysis	Hazard ratio	95% confidence interval	*P* values[b]
Tumor invasion depth	2.07	1.42–3.02	<0.001
TNM staging	3.40	2.48–4.67	<0.001
Lymphovascular or perineural invasion	1.41	0.94–2.11	0.099
Histological differentiation	0.87	0.46–1.63	0.661
Systemic disease	1.42	1.08–1.89	0.014
Post-op radiation	1.38	0.80–2.39	0.246
Anastomoticleakage	2.85	1.71–4.76	<0.001
Diversion	0.39	0.24–0.65	<0.001

Post-op postoperative

[a] As determined by log-rank test

[b] As determined by Cox's proportional hazard model

volume of leakage material. Once clinical leakage occurs, a local and systemic septic reaction cannot be avoided regardless of the presence or absence of a diverting stoma. The adverse consequences of a leakage and poor prognosis can be expected. Therefore, it is critical to identify high-risk patients and to perform a diversion stoma in high-risk anastomoses.

Conclusion

According to our results, older age and anastomosis at the anorectal junction or dentate line are associated with an increased risk of anastomotic leakage in rectal cancer patients undergoing surgical resection. Anastomotic leakage is independently associated with overall recurrence and is an independent adverse prognostic factor of overall survival, disease-free survival, and cancer-specific survival. A diversion stoma does not appear to decrease the incidence of anastomotic leakage. However, a diversion stoma may

decrease the severity of intra-abdominal sepsis and subsequent necessity of reoperation in most leakage patients, and possibly provide a better oncological impact if leakage occurs.

References

1. Rullier E, Laurent C, Garrelon JL, Michel P, Saric J, Parneix M. Risk factors for anastomotic leakage after resection of rectal cancer. Br J Surg 1998; 85: 355–358.
2. Pakkasite TE, Luukkonen PE, Jarvien HJ. Anastomotic leakage after anterior resection of the rectum. Eur J Surg 1994; 160: 293–297; discussion 299–300.
3. Peeters KC, Tollenaar RA, Marijnen CA, Klein Kranenbarg E, Steup WH, Wiggers T, Rutten HJ, van de Velde CJ; Dutch Colorectal Cancer Group. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg 2005; 92: 211–216.
4. Vignali A, Fazio VW, Lavery IC, Milsom JW, Church JM, Hull TL et al. Factors associated with the occurrence of leaks in stapled rectal anastomoses: a review of 1,014 patients. J Am Coll Surg 1997; 185: 105–113.
5. Alves A, Panis Y, Trancart D, Regimbeau JM, Pocard M, Valleur P. Factors associated with clinically significant anastomotic leakage after large bowel resection: multivariate analysis of 707 patients. World J Surg 2002; 26: 499–502.
6. Vignali A, Gianotti L, Braga M, Radaelli G, Malvezzi L, Di Carlo V. Altered microperfusion at the rectal stump is predictive for rectal anastomotic leak. Dis Colon Rectum 2000; 43: 76–82.
7. Luna-Pérez P, Rodríguez-Ramírez SE, Gutiérrez de la Barrera M, Labastida S. [Multivariate analysis of risk factors associated with dehiscence of colorectal anastomosis after anterior or lower anterior resection for sigmoid or rectal cancer.] Rev Invest Clin 2002; 54: 501–508. [Article in Spanish]
8. Matthiessen P, Hallböök O, Andersson M, Rutegård J, Sjödahl R. Risk factors for anastomotic leakage after anterior resection of the rectum. Colorectal Dis 2004; 6: 462–469.
9. Konishi T, Watanabe T, Kishimoto J, Nagawa H. Risk factors for anastomotic leakage after surgery for colorectal cancer: results of prospective surveillance. J Am Coll Surg 2006; 202: 439–444.
10. Alberts JC, Parvaiz A, Moran BJ. Predicting risk and diminishing the consequences of anastomotic dehiscence following rectal resection. Colorectal Dis 2003; 5: 478–482.
11. Mäkelä JT, Kiviniemi H, Laitinen S. Risk factors for anastomotic leakage after left-sided colorectal resection with rectal anastomosis. Dis Colon Rectum 2003; 46: 653–660.
12. Law WI, Chu KW, Ho JW, Chan CW. Risk factors for anastomotic leakage after low anterior resection with total mesorectal excision. Am J Surg 2000; 179: 92–96.
13. Pakkastie TE, Ovaska JT, Pekkala ES, Luukkonen PE, Jarvinen HJ. A randomised study of colostomies in low colorectal anastomoses. Eur J Surg 1997; 163: 929–933.
14. Allen-Mersh TG, Sprague DB, Mann CV, Turner MJ. Pelvic drainage after anterior resection of the rectum. Dis Colon Rectum 1989; 32: 223–226.
15. Beard JD, Nicholson ML, Sayers RD, Lloyd D, Everson NW. Intraoperative air testing of colorectal anastomoses: a prospective, randomized trial. Br J Surg 1990; 77: 1095–1097.
16. Schmidt O, Merkel S, Hohenberger W. Anastomotic leakage after low rectal stapler anastomosis: significance of intraoperative anastomotic testing. Eur J Surg Oncol 2003; 29: 239–243.
17. Yalin R, Aktan AO, Yegen C, Dosluoglu H, Okboy N. Importance of testing stapled rectal anastomoses with air. Eur J Surg 1993; 159: 49–51.
18. Abulafi AM, Williams NS. Local recurrence of colorectal cancer: the problem, mechanisms, management and adjuvant therapy. Br J Surg 1994; 81: 7–19.
19. 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.
20. 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.
21. Petersen 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.
22. Jatzko GR, Jagoditsch M, Lisborg PH. Long-term results of radical surgery for rectal cancer: multivariate analysis of prognostic factors influence survival and local recurrence. Eur J Surg Oncol 1999; 25: 284–291.
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. Branagan G, Finnes D; Wessex Colorectal Cancer Audit Working Group. Prognosis after anastomotic leakage in colorectal surgery. Dis Colon Rectum 2005; 48: 1021–1026.
25. 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.
26. Lee MR, Hong CW, Yoon SN, Lim SB, Park KJ, Park JG. Risk factors for anastomotic leakage after resection for rectal cancer. Hepatogastroenterology 2006; 53: 682–686.
27. Akyol AM, McGregor JR, Galloway DJ, Murray G, George WD. Anastomotic leaks after colorectal cancer surgery: a risk factor for recurrence? Int J Colorectal Dis 1991; 6: 179–183.
28. Graffner H, Fredlund P, Olsson SA, Oscarson J, Petersson BG. Protective colostomy in low anterior resection of the rectum using EEA stapling instrument. A randomized study. Dis Colon Rectum 1983; 26: 87–90.
29. Phillips RK, Hittinger R, Blesovsky L, Fry JS, Fielding LP. Local recurrence following 'curative' surgery for large bowel cancer: II. The rectum and rectosigmoid. Br J Surg 1984; 71: 17–20.
30. 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.
31. 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.
32. 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.
33. Umpleby HC, Fermor B, Symes MO, Williamson RC. Viability of exfoliated colorectal carcinoma cells. Br J Surg 1984; 71: 659–663.
34. Skipper D, Cooper AJ, Marston JE, Taylor I. Exfoliated cells and in vitro growth in colorectal cancer. Br J Surg 1987; 74: 1049–1052.
35. Jenner DC, de Boer WB, Clarke G, Levitt MD. Rectal washout eliminates exfoliated malignant cells. Dis Colon Rectum 1998; 41: 1432–1434.
36. Gertsch P, Baer HU, Kraft R, Maddern GJ, Altermatt HJ. Malignant cells are collected on circular staples. Dis Colon Rectum 1992; 35: 238–241.

37. DerHagopian RP, Sugarbaker EV, Ketcham A. Inflammatory oncotaxis. JAMA 1978; 240: 374–375.
38. Shine T, Wallack MK. Inflammatory oncotaxis after testing the skin of the cancer patient. Cancer 1981; 47: 1325–1328.
39. 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.
40. Karanjia ND, Corder AP, Holdsworth PJ, Heald RJ. Risk of peritonitis and fatal septicaemia and the need to defunction the low anastomosis. Br J Surg 1991; 78: 196–198.
41. Mealy K, Burke P, Hyland J. Anterior resection without a defunctioning colostomy: questions of safety. Br J Surg 1992; 79: 305–307.
42. Meleagros L, Varty PP, Delrio P, Boulos PB. Influence of temporary faecal diversion on long-term survival after curative surgery for colorectal cancer. Br J Surg 1995; 82: 21–25.
43. Karanjia ND, Corder AP, Bearn P, Heald RJ. Leakage from stapled low anastomosis after total mesorectal excision for carcinoma of the rectum. Br J Surg 1994; 81: 1224–1226.
44. Fielding LP, Stewart-Brown S, Hittinger R, Blesovsky L. Covering stoma for elective anterior resection of the rectum: an outmoded operation? Am J Surg 1984; 147: 524–530.

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CASE REPORT

"Surgical" Abdomen in a Patient with Chronic Lymphocytic Leukemia: A Case of Acquired Angioedema

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Abstract
Introduction Acquired angioedema (AAE), an acquired deficiency of C1esterase inhibitor, is a medically treatable condition which can cause severe abdominal pain mimicking an acute surgical abdomen. This disorder is strongly associated with chronic lymphocytic leukemia (CLL) and other indolent lymphoplasmacytic disorders.
Discussion We describe a patient with known CLL who developed incapacitating, recurrent severe abdominal pains, culminating in partial bowel resection. Signs, symptoms, laboratory and pathologic findings demonstrated AAE.
Conclusion Wider appreciation of the possibility of AAE, particularly in patients with lymphoproliferative disorders, could lead to preventive therapy and spare unnecessary surgery. This is more important now that more effective medical therapies are available.

Keywords Acquired angioedema · Chronic lymphocytic leukemia · Autoimmunity · C1 inhibitor deficiency

Introduction

Acquired angioedema (AAE) is due to acquired deficiency of C1 inhibitor (C1Inh), resulting in excessive complement and bradykinin activities. Blood vessel permeability is increased; thus, angioedema occurs. Just as with hereditary angioedema (hereditary C1Inh deficiency; HAE), common clinical manifestations are skin swelling, laryngeal edema, and/or abdominal pain.[1,2]

AAE often occurs in the context of lymphoplasmacytic disorders, such as monoclonal gammopathy of unknown significance (MGUS), non-Hodgkin's lymphoma, or chronic lymphocytic leukemia (CLL).[1,3] Among 32 patients with AAE, Castelli found that 13 (40%) had MGUS and 9 (28%) had lymphoproliferative disease.[3] Therefore, all cases of AAE should be evaluated for the possibility of underlying lymphoplasmacytic disorder. Conversely, when patients with known lymphoproliferative disease manifest compatible symptoms, AAE should be expeditiously considered. This is important because AAE can be effectively treated medically, but delayed diagnosis can lead to unnecessary diagnostic procedures, therapeutic interventions, or life-threatening complications, well-illustrated by our case.

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Case Presentation

A 78-year-old woman with atherosclerotic vascular disease was transferred to our hospital with abdominal pain and underwent emergent laparotomy. One year earlier, she had been diagnosed with Rai Stage I CLL which had been observed without treatment. Two months earlier, she presented with severe abdominal pain, nausea, and vomiting. Over the next 8 weeks, she had six emergency room and/or hospital admissions for identical symptoms. The episodes left the patient weak and incapacitated. Pains would begin at rest in the lower abdomen, spread to the upper abdomen, described as "gas-like", non-radiating, constant. There was no

association with meals, exertion, or bowel movements. Subsequent vomiting was nonbloody, nonbilious, and did not relieve the pain. Episodes resolved spontaneously within 2–3 days with intravenous hydration and pain control. Extensive evaluation included colonoscopy, endoscopic retrograde cholangiopancreatography, magnetic resonance angiography, and abdominal aortography. Benign colon polyps and small gallstones were removed, mesenteric stenoses ruled out, yet pains recurred unabated. She had lost 12 lbs. There was no dysphagia, change in bowel habits, GI bleeding, fever, or sweats. Medications included baby aspirin, clopidogrel, benazepril, hydrochlorothiazide, and glipizide.

Physical examination on transfer revealed blood pressure 130/88 mmHg, pulse 88 beats per minute, respiratory rate 20 cycles per minute, pulse oximetry of 95% on ambient air, and temperature 97.0°F. The patient was in acute distress due to abdominal pain. Left cervical and axillary lymph nodes were enlarged to 1.5 cm in diameter. Cardiopulmonary examination was unremarkable. Abdomen was slightly distended, diffusely exquisitely tender with guarding and rebound. Bowel sounds were hypoactive. Rectal examination showed guaiac-negative brown stool.

Hemoglobin was 18.1 g/dL, hematocrit 55%, platelets 146×10^9/L, and leukocytes elevated to 34,500 cells/μL with 47% neutrophils and 48% lymphocytes. Chemistries and liver function tests were normal. Abdominal X-ray showed no free air, nor air-fluid levels. CT scan of abdomen and pelvis with IV contrast showed multiple abnormal loops of small bowel with contrast-enhanced bowel wall edema (Fig. 1a).

At laparotomy, massively swollen small bowel was encountered and resected. Pathologic examination revealed massive submucosal edema (Fig. 1b). There was no leukemic infiltration visible.

A hematology consultant, called postoperatively, suspected AAE. C4 was 3 mg/dL (normal 17–46), C3 66 mg/dL (85–200), and C1Inh activity reportedly 83% (68–200%). Serum protein electrophoresis revealed two faint bands immunofixing as monoclonal IgM kappa and IgG kappa. Chlorambucil was started for CLL and danazol to raise C1Inh. Lymphocytosis and lymphadenopathy improved and C1Inh activity increased to 110%. Over 3 years of follow-up, abdominal symptoms never recurred.

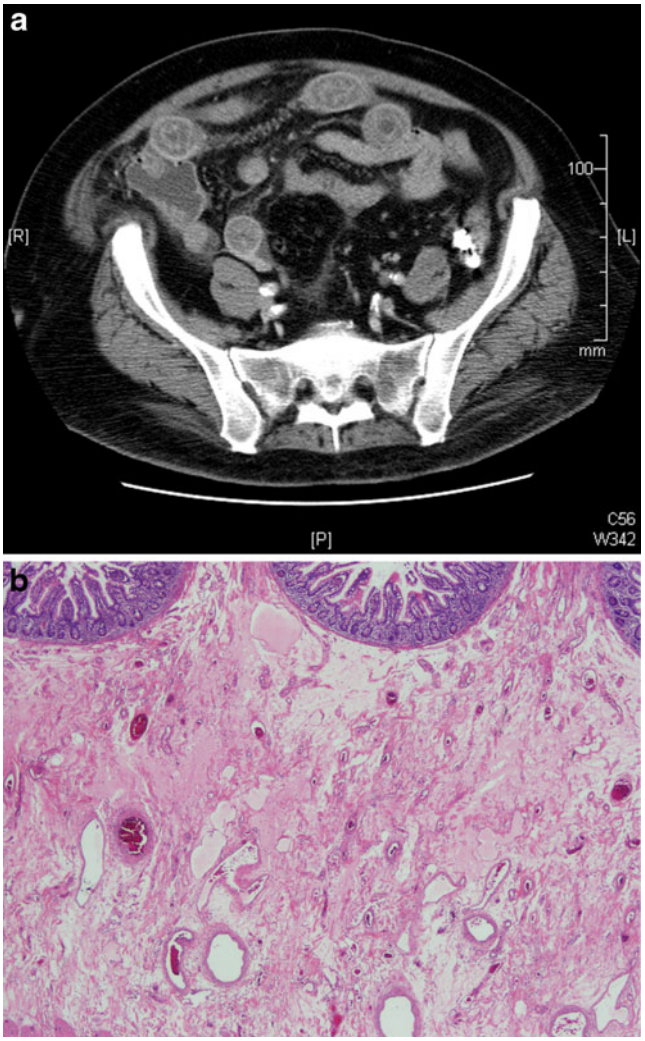

Fig. 1 **a** CT scan of abdomen and pelvis with intravenous contrast shows several abnormal loops of small bowel with a target appearance indicating bowel wall edema. **b** A section of small bowel shows massive submucosal edema. There is no infiltration of the wall by lymphocytes

Discussion

Approximately 145 cases have been reported of AAE,[3] and this is one of four cases that we have diagnosed in the last decade with abdominal pains from AAE with associated CLL. Table 1 shows characteristics of patients with CLL and AAE we have seen (some briefly mentioned in a prior report).[4] This is our only case to undergo surgery, allowing unique and dramatic demonstration of massive bowel edema visible radiographically, on surgical inspection and on histopathology. An initial C1Inh activity was reported low normal, but there can be no doubt about the diagnosis based on radiologic/surgical/histologic findings, further laboratory results, and the clinical course. Characteristic are very low C4 level and low C3; diagnostic recommendations currently add C1q and anti-C1Inh antibody levels. Autoantibody is demonstrable in up to 70% with AAE.[1] Our patient had monoclonal gammopathy, which frequently corresponds to the C1Inh autoantibody. Patients with the hereditary form (HAE)

Table 1 Characteristics of patients with AAE

Patient	Underlying diagnosis	Manifestations of acquired angioedema	Months before diagnosis	Laboratory values		Interventions prior to diagnosis	Treatment	Angioeedema episodes post-treatment (years of follow-up)
				Pretreatment	Post-treatment			
78 years old/F	CLL	Recurrent abdominal pain	2	C1 inh activity: 83% (68–200) C4: 3 mg/dL (17–46) C3: 66 mg/dL (85–200) small monoclonal gammopathy	C1 inh activity: 110% (68–200)	Exploratory laparotomy with small bowel resection CT scan Colonoscopy ERCP MRA Abdominal aortography	Chemotherapy Danazol	None (3 years)
74 years old/F	SLL/CLL	Recurrent abdominal pain Episodic oropharyngeal swelling	24	C1 inh activity: 1% (68–200%) C1 inh quantitative: 6.7 mg/dL (>11 mg/dL) C4: 13 mg/dL (16–47) C3: 70 mg/dL (75–161) small monoclonal gammopathy	C1 inh activity: 117% (68–200%) C1 inh quantitative: 21 mg/dL (10–25)	CT scan Colonoscopy	Chemotherapy Danazol	None (6 years)
61 years old/M	CLL	Recurrent abdominal pain	5	C1 inh activity: 4% (68–200%) small monoclonal gammopathy	Not available	CT scan Colonoscopy	Chemotherapy Danazol	None (10 years)
67 years old/M	CLL	Recurrent abdominal pain Oropharyngeal swelling	3	C1 inh activity: 6% (68–200) C1 inh quantitative: 3 mg/dL (21–39) C1q: 3.6 mg/dL (5–8.6) C4: <2 mg/dL (17–46) small monoclonal gammopathy	C1 inh quantitative: 38 mg/dL (21–39)	Colonoscopy Laryngoscopy	Chemotherapy Danazol	None (3 months)

usually manifest before age 20 and give a family history of symptoms. In all our patients with CLL and AAE, chemotherapy and androgens increased C1Inh and produced durable remission.

Angioedema should be borne in mind among "medical" illnesses that can mimic acute surgical abdomen, along with such other disorders as porphyria, Familial Mediterranean fever and sickle cell disease (Fig. 2). One may need to discern whether a true surgical emergency might supervene even when one of these disorders is present. Our patient had typical symptoms of acute bowel edema, including diffuse abdominal pain, occasionally rebound tenderness and vomiting, with spontaneous resolution within 1–5 days.[1,2] Some patients with AAE have cutaneous or upper respiratory edema in addition, or instead of, bowel symptoms. Because of cardiovascular comorbidities, there was a high suspicion for ischemic bowel in our patient, but radiography and endoscopy did not support this. In the differential diagnosis, angiotensin-converting enzyme inhibitors rarely precipitate angioedema, but our patient had taken benazepril many years and continued it without incident after AAE therapy.

In 2009, the US FDA approved the C1Inh concentrate Berinert P® and the kallikrein inhibitor ecallantide (Kalbitor®) for treatment of acute attacks, and the C1Inh concentrate Cinryze® for prophylaxis in severely affected patients.[5] Fresh frozen plasma can be given when these are unavailable. C1Inh concentrates are highly safe and effective; the standard of care for decades in other countries, but US approval was delayed by concerns of virus transmissibility.[1,5–9] Doses used in the clinical HAE trials may need to be higher for AAE because of increased enzyme clearance. Ecallantide is subcutaneous, facilitating patient self-administration out of hospital. A bradykinin B2 receptor antagonist icatibant (Firazyr®) is under investigation. For long-term control, the underlying cause should be addressed, CLL in our case. Commonly used for prophylaxis are anti-fibrinolytic drugs or the attenuated androgen danazol, which increases C1Inh synthesis at low cost.[10]

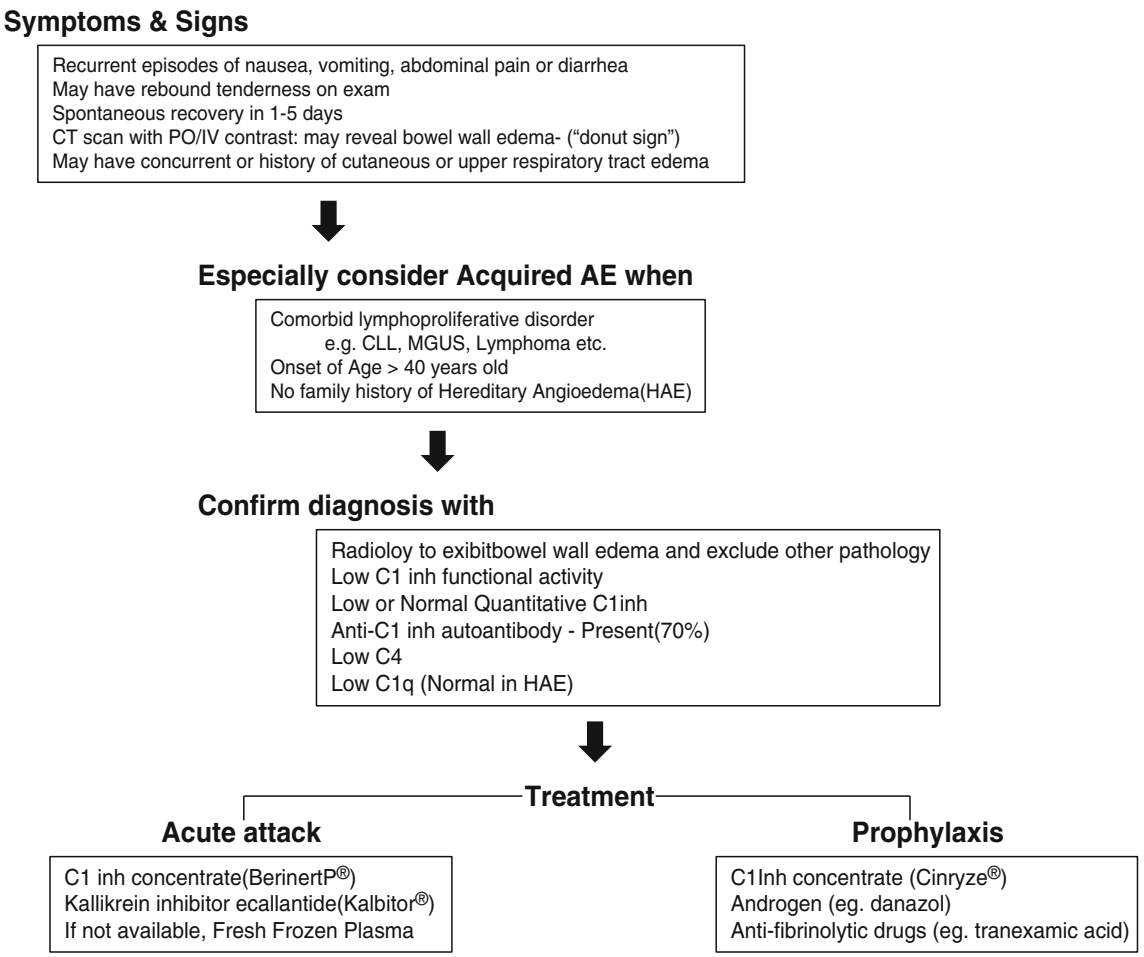

Fig. 2 Algorithm for diagnosis and treatment for suspected AAE

In conclusion, earlier suspicion for AAE in our known CLL patient could have spared her the morbidities of recurrent abdominal pains, hospitalizations, morbid interventions, and bowel resection. Wider appreciation of this disorder takes on added importance as our ability to effectively treat the problem has grown.

References

1. Cicardi M, Zanichelli A. Angioedema due to C1 inhibitor deficiency in 2010. Intern Emerg Med. 2010; doi:10.1007/s11739-010-0408-3.
2. Eck SL, Morse JH, et al. Angioedema presenting as chronic gastrointestinal symptoms. Am J Gastroenterol. 1993;88(3):436–9.
3. Castelli R, Deliliers DL, et al. Lymphoproliferative disease and acquired C1 inhibitor deficiency. Hematologica/the hematology journal. 2007;92:5:716–718.
4. Jung M, Rice L. Unusual autoimmune non-hematologic complications in chronic lymphocytic leukemia. Clin Lymphoma Myeloma Leuk. 2011 (In press).
5. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angiodedma. N Engl J Med. 2010;262:513–22.
6. Gadek JE, Hosea SW, Gelfand JA et al. Replacement therapy in hereditary angioedema: successful treatment of acute episodes of angioedema with partly purified C1 inhibitor. N Engl J Med. 1980;302:542–546.
7. Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. N Engl J Med. 1996;334:1630–4.
8. Kunschak M. Engl W, Maritsch, et l. A randomized, controlled trial to study the efficacy and safety of C1 ihibitor concentrate in treating hereditary angioedema. Transfusion. 1998;38:540–9.
9. Morgan BP. Hereditary angioedema—Therapies old and new. N Engl J Med. 2010;363:581–583.
10. Bork K, Bygum A, Hardt J Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients. Ann Allergy Asthma Immunol. 2008;100:153–161.

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CASE REPORT

Gastric Volvulus Associated with a Wandering Liver: A Case Report and Review of the Literature

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Introduction

Wandering liver has been described in the literature as a rare entity.[1–6] Described clinical features include complete dislocation of the liver into the left upper quadrant and congenital absence of the falciform and triangular ligaments. The condition is believed to be associated with a persistent ventral mesentery, and most reported cases are diagnosed during investigation of intestinal obstruction.[3]

Case Report

A 39-year-old male patient was admitted to our hospital with feeding intolerance and repeated gastric obstruction. He had developed neurological impairment associated with infantile spasms and had been a resident in a facility specifically caring for the severely handicapped. At 24 years of age, the patient suddenly developed abdominal distension most marked at the epigastrium and subsequently food intolerance. Upper gastrointestinal series examination was suspicious for gastric volvulus. At this time, he had developed gastric obstruction and developed a state of poor nutrition. At 30 years of age, he underwent gastropexy by percutaneous endoscopic gastrostomy. Three years later, the patient developed a recurrence of gastric obstruction. Prior to admission to our hospital, the patient was able to tolerate a liquid food diet by mouth (approximately 1,000 kcal/day), but during the period of mechanical gastric obstruction, oral feeding had often been stopped. At the time of surgical consultation, the patient had developed severe nutritional disturbance, weighing only 30 kg in body weight and 160 cm in height. Body mass index [body weight (kilograms)/height (meter)^2] was 11.7 (normal range, 18.5~25; emaciation, <18.5; obesity, >25). Before transfer to our institution, abdominal radiographs suggested a pattern of oral intolerance. The gastric gas pattern was very prominent indicating significant gastric distention; however, due to intermittent oral tolerance, there was marked distension of the colon (Fig. 1a, b). Abdominal computed tomography (CT) demonstrated displacement of the right lobe of the liver into the left upper abdominal quadrant and displacement of the spleen (Fig. 2a–d). Based on these CT findings, a mobile liver (wandering liver) and a wandering spleen were surmised to carry a significant risk of mesenteroaxial gastric volvulus. At this time, the patient was transferred to our institution to undergo redo-gastropexy to prevent gastric volvulus. On admission, the patient was noted to be suffering from air swallowing (aerophagia) due to bruxism (teeth grinding). Left lateral decubitus, supine, and right lateral decubitus abdominal radiographs demonstrated displacement of the right lobe of the liver (Fig. 3a–c). The patient underwent laparoscopic surgery after closure of the prior gastrostomy site. Intraoperatively, the spleen was partially fixed to the retroperitoneum, but located at a different anatomic site than usual, and the lienorenal and lienophrenic ligaments exhibited abnormal laxity (Fig. 4a, b). Laparoscopic splenic fixation was initially attempted; however, splenic injury was sustained during this maneuver necessitating conversion to an open laparotomy to remove the spleen. The cecum was normally situated. A portion of the small intestine was remarkably dilated. There was no abnormal colonic fixation appreciated. Due to the fact that the Angle of His was redundant, an anterior fundoplication

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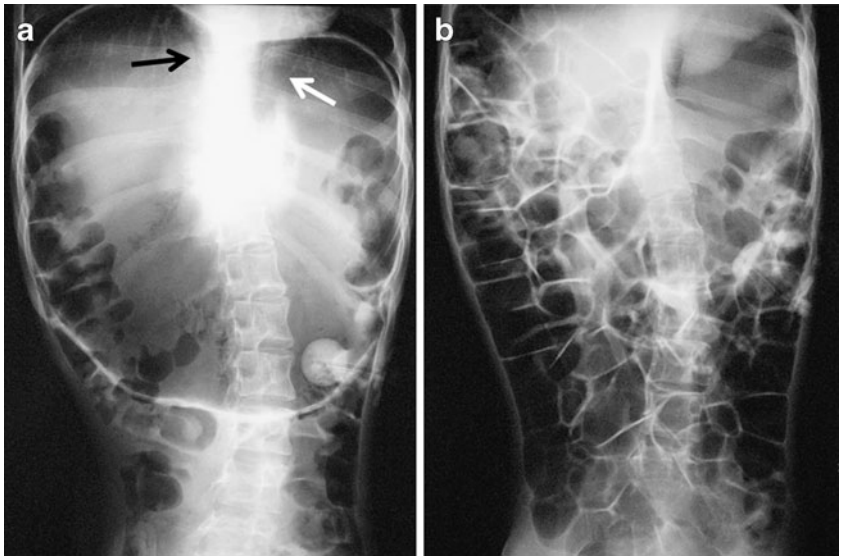

Fig. 1 Abdominal radiographs during states of oral intolerance and tolerance. **a** Abdominal radiographs at 5 months prior to admission were taken during a state of oral intolerance and demonstrate a remarkably dilated gastric gas pattern due to mechanical obstruction (mesenteroaxial gastric volvulus) in the presence of an otherwise gasless abdomen (*black arrow* esophago-cardiac junction, *white arrow* pyloric junction). **b** Abdominal radiograph at 3 months prior to admission taken during a state of oral tolerance and demonstrates a marked colonic gas pattern

(Thal fundoplication) was performed to prevent gastroesophageal reflux. A redo-gastropexy was then performed at the greater curvature of the stomach after confirmation of the shape of the stomach by intraoperative contrast radiography. Diaphragmatic attachments such as the falciform and triangular ligaments on the bilateral sides were congenitally absent. The liver was suspended by an elongated midline falciform ligament (Fig. 4c, d). Therefore, hepatopexy was performed by suturing the round ligament to the right-sided abdominal wall to prevent further mobility of the liver. As a final procedure, a gastrostomy tube was placed at the

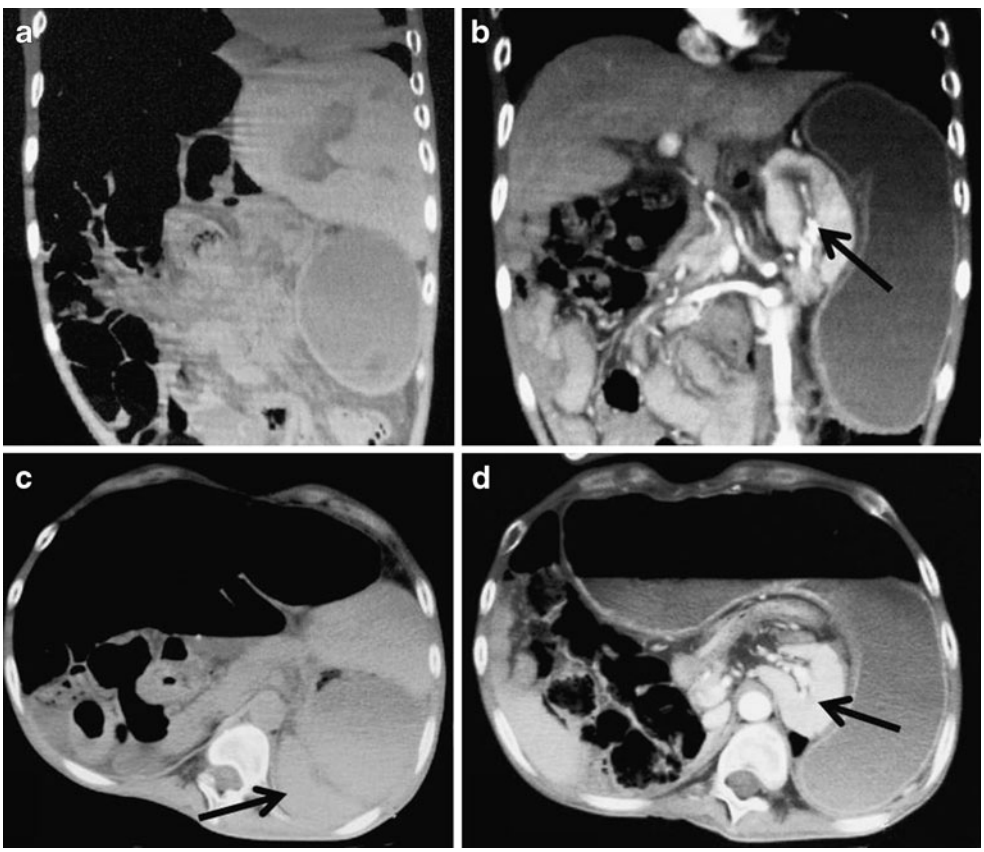

Fig. 2 Abdominal computed tomography (CT) before admission. **a**, **c** A plain CT at 2 months prior to admission demonstrating displacement of the right lobe of the liver into the left upper abdominal quadrant (*black arrow* spleen). **b**, **d** An enhanced CT at 1 month prior to admission demonstrating the right lobe of the liver was located at a normal anatomic site (*black arrow* spleen)

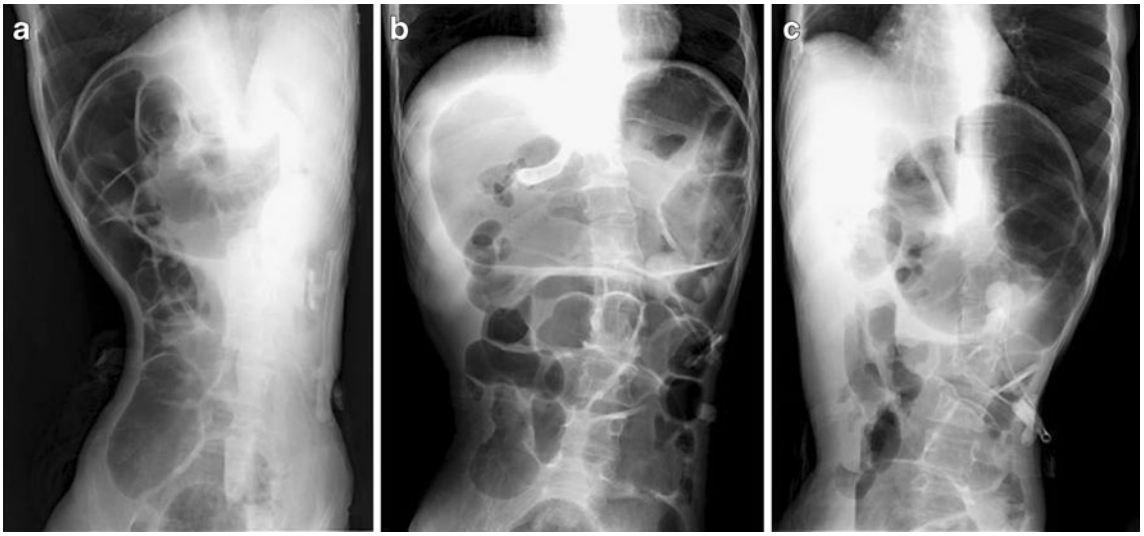

Fig. 3 Abdominal radiographs on admission. **a** Radiograph in the left lateral decubitus position demonstrating the liver located in the left hypochondrium. **b** Radiograph in the supine position demonstrating the liver in the normal position and a dilated gastric gas pattern. **c** Radiograph in the right lateral decubitus position demonstrating the liver was located in the right hypochondrium

gastric antrum. Postoperatively, the patient's abdominal distension did not improve, and the patient was medicated with Daikenchuto (TU-100), a traditional Japanese (Kampo) medicine. Furthermore, as the treatment of air swallowing due to bruxism, occlusal splint (mouthpiece) was fitted. The patient underwent decompression of intestinal gas by an anal tube. The gastrostomy tube was used as a desufflator mechanism when the patient experienced gastric bloating. During the postoperative period, the symptoms of abdominal distension and signs of intestine gas distension gradually resolved.

Conclusions

The term wandering liver is synonymous with hepatic hypermobility resulting in displacement of the liver from its normal position within the right upper quadrant of the

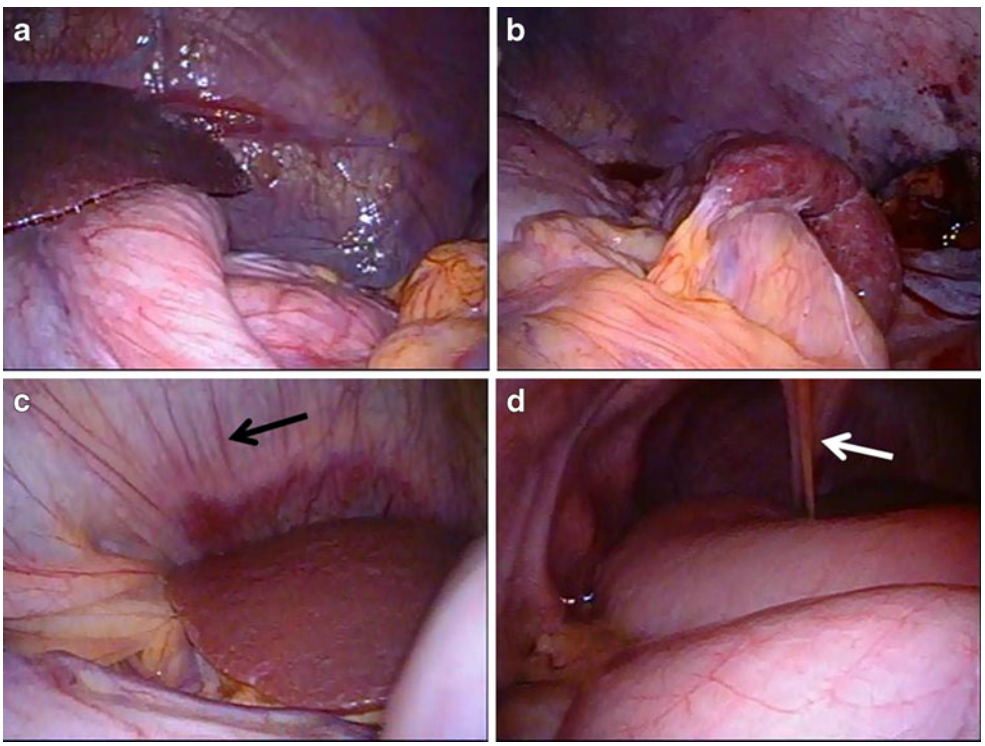

Fig. 4 Intraoperative findings at laparoscopic surgery**. a**, **b** The spleen was partially fixed to the retroperitoneum, but located at a different anatomic site. The lienorenal and lienophrenic ligaments exhibited abnormal laxity. **c**, **d** The diaphragmatic attachments such as the falciform and triangular ligaments on the bilateral sides were congenitally absent. The liver was suspended by an elongated midline falciform ligament (*black arrow* persistent ventral mesentery)

abdomen.[1–6] Described clinical features include a congenital absence of the falciform and triangular ligaments. The condition is usually associated with bowel obstruction. However, it is still unclear whether hepatic displacement is the mechanism of action that results in bowel obstruction. Thompson et al. describe a freely mobile right lobe of the liver that was intermittently displaced into the left upper abdomen leading to volvulus of both the stomach and transverse colon.[1] In cases of wandering liver, volvulus of segments of mobile colon often coexists and presents as a surgical emergency. In the diagnosis of a wandering liver, right and left lateral decubitus abdominal radiographic films confirm that the liver tends to be located in the most dependent quadrant of the abdomen. Furthermore, repeated CT scan demonstrates displacement of the right lobe of the liver into the left upper abdominal quadrant.[3–6]

In this particular case, it was considered that a wandering liver could lead to gastric volvulus. When the right lobe of the liver shifts to the left side of the abdomen by rotating counterclockwise under the round ligament, mesenteroaxial gastric volvulus can theoretically occur. During embryonic development of the liver, a ventral mesentery persists as the falciform ligament, while the dorsal mesentery gives rise to the gastrohepatic and duodenohepatic (lesser) omenta. Initially, the dorsal and ventral mesenteries are continuous via a simple median subphrenic peritoneal reflection. Expansion of the hepatic parenchyma subsequently separates left and right peritoneal leaves, forming a bare area, bounded by the coronary and triangular ligaments.[3] Upon review of the literature pertaining to wandering liver, persistence of the undifferentiated ventral mesentery (persisting ventral mesogastrium) results in the liver retaining a midline peritoneal attachment. Resultantly, the liver is suspended by an elongated midline falciform ligament.[3–6] Because of this process, many authors believe that due to the association of a persistent ventral mesentery, a wandering liver can precipitate volvulus of both the stomach and colon.

Bruxism is characterized by the grinding of the teeth and allows increase in the large amount of air swallowed unconsciously, which is one of factors to the occurrence of aerophagia. As treatments of aerophagia in mentally retarded patients, affected patients are able to reduce the number of biting events and are able to express saliva due to the fact that patients can observe the effect of unconscious biting when wearing a Sprint.

Routine decompression of intestinal gas by an anal tube and gastrostomy tube used as a desufflator mechanism can prove to be useful in the management of these patients.[7] Furthermore, the addition of a traditional Japanese medicine, Daikenchuto (TU-100), may reduce bloating and abdominal pain in patients with chronic constipation, possibly by decreasing bowel gas volume.[8] As mechanism, TU-100 dose dependently increases gastrointestinal motility by modulating cholinergic and serotonergic mechanisms in animal studies.[9]

References

1. Miller T, Thompson NW. Intermittent dislocation of the liver. A syndrome associated with volvulus of the transverse colon and stomach and obstructive jaundice. Arch Surg. 1977; 112: 658–662.
2. Tate PS. Hepatic torsion and dislocation with hypotension and colonic obstruction. Am Surg. 1993; 59: 455–458.
3. Siddins MT, Cade RJ. Hepatocolonic vagrancy: wandering liver with colonic abnormalities. Aust N Z J Surg. 1990; 60: 400–403.
4. Howenstein M, Yaghmai V, Grant T. Wandering liver: multidetector CT features and the importance of multiplanar reformations. Emerg Radiol. 2009; 16:155–157.
5. Nichols BW, Figarola MS, Standley TB. A wandering liver. Pediatr Radiol. 2010; 40:1443–1445.
6. Svensson JF, Schlinzig T, Kaiser S. "Wandering liver" in a neonate: case report and review of the literature. J Pediatr Surg. 2010; 45 :635–638.
7. van der Kolk MB, Bender MH, Goris Rj. Acute abdomen in mentally retarded patients: role of aerophagia. Report of nine cases. Eur J Surg. 1999; 165: 507–511.
8. Horiuchi A, Nakayama Y, Tanaka N. Effect of Traditional Japanese Medicine, Daikenchuto (TJ-100) in Patients With Chronic Constipation. Gastroenterology Research. 2010;3:151–155.
9. Satoh K, Hayakawa T, Kase Y. Mechanisms for contractile effect of Dai-kenchu-to in isolated guinea pig ileum. Dig Dis Sci. 2001;46:250–256.

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HOW I DO IT

Segmental Internal Sphincterotomy—A New Technique for Treatment of Chronic Anal Fissure

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Abstract
Objective Lateral internal sphincterotomy is an effective treatment for fissure in ano but carries a definite risk of incontinence. In trial to avoid this complication, segmental lateral internal sphincterotomy was used to treat chronic anal fissures.
Design The lateral internal sphincterotomy was done in two parts and at different planes.
Setting This study was conducted in the General Surgery Department, Zagazig University Hospital, Egypt.
Patients This study was undertaken on 50 patients (43 men and seven women, with mean age of 37.3 years) with chronic fissure in ano from January 2009 to December 2010.
Interventions Under general or local anesthesia, lateral internal sphincterotomy was done in two segments under direct vision. Preoperative and postoperative anal manometry study was recorded.
Main Outcome Measures Postoperative course with early and long-term results were recorded. Mean follow-up was 18.5 months (ranging from 6 to 24 months).
Results In 31 patients, the technique was done under general anesthesia and the remainder under local anesthesia. The fissures and anal wounds were healed within 4 weeks. Pain was significantly reduced in all patients at day 1 postoperative. Early complications included mild hematoma and urine retention in one male patient (2%). No transient or any persistent degree of incontinence occurred in these patients group.
Conclusion Segmental lateral internal sphincterotomy is a safe, easy, and effective procedure and not associated with risk of incontinence for the treatment of chronic anal fissure.

Keywords Segmental · Internal sphincterotomy · Anal fissure

Introduction

Anal fissure (AF) is a common disorder which affects all age groups with an equal incidence in both sexes; 90% are situated posteriorly and 10% anteriorly.[1] The exact etiology of AF is unknown but trauma caused by fecal mass, diarrhea, constant saddle vibration in bikers, water steam from bidet toilets, and hypertonicity of the internal sphincter are thought to be initiating factors.[2–5] Lateral internal sphincterotomy is considered the gold standard therapy of chronic anal fissure. It relieves symptoms with high rate of healing and less long-term recurrence.[6] This optimal therapy has, however, been associated with the development of period of transient postoperative impairment of anal continence in 30% of patients which can become permanent.[7,8] To avoid these side effects, segmental lateral internal sphincterotomy was used for treatment of chronic anal fissure in this study.

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Patients and Methods

During a period of 2 years between January 2009 and December 2010, 50 patients (43 males and seven females, with median age of 37.3 years; range, 17–57 years) with

chronic anal fissure have been enrolled in this study. A chronic anal fissure was defined by duration of symptoms longer than 3 months, presence of induration at fissure edges, sentinel pile, hypertrophied anal papillae, and circular muscle fibers at the base of the cutaneous defect. The fissure was found posterior in 44 patients, anterior in five patients, and both in one patient. The most common symptoms encountered in this series were: pain and discomfort with bowel movements in all cases (100%) and bright rectal bleeding in 80%. Also, an occasional undue expulsive force from a hard fecal mass was found in 60% of our patients, and constipation in 53%. No history of anal incontinence was found in this patient group. Anal manometry was performed for all patients preoperatively and 3 months postoperatively, using the waterfilled 10 F balloon rectal catheter of the Ellipse 4 Andromeda water cystometry system (Andromeda, Medizinishe Systeme GambH Wallbergstr, 5 D-82024 Taufkinhen) and recorded in centimeters H_2O for each case. All patients have received medical therapy as the first line of treatment but presented with recurrent or persistent fissures. The medical treatment was in the form of a stool softener, analgesics, and 0.2% glyceryl trinitate for at least 6 weeks. Informed consent was obtained from all patients after the nature of the procedure was explained. In the lithotomy position, segmental lateral sphincterotomy was performed under general anesthesia in 31 cases and under local anesthesia in 19 cases, using an Eisenhammer speculum in the anal canal. The internal sphincter is divided in two segments from anoderm up to dentate line but not in the same line. First segment starts from anoderm line to a point midway between it and the dentate line, where the internal sphincter is divided under direct vision. Second segment starts from a part midway point between the anoderm line and dentate line to dentate line, where the internal sphincter is divided under direct vision. The two segments are equal in length and parallel with about 1 cm between them. Good haemostasis is achieved by using diathermy. The wounds were left open to heal with secondary intention (Fig. 1). Third generation cephalosporin antibiotics were given perioperatively, in all patients. The mean follow-up period was 18.5 months (6–24 months) for early and late complications.

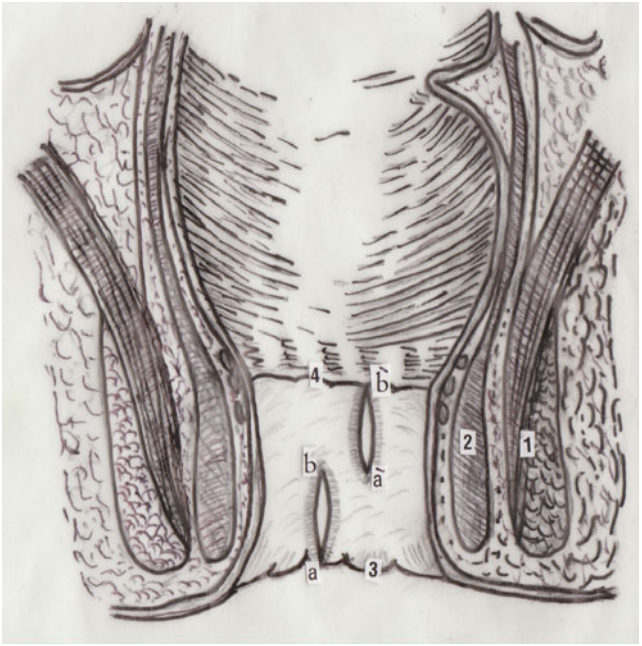

Fig. 1 *1* External anal sphincter. *2* Internal anal sphincter. *3* Anal verge. *4* Dentate line. Segmental lateral internal sphincterotomy procedure. In this procedure, internal sphincterotomy is done in two incisions: first incision (*a–b*) extends from the anal verge points *a′* to *b* midway between the anal verge and dentate line and divided the internal anal sphincter in this area. Second incision (*a′–b′*) extends from the midway point between the anal verge to dentate line *a′* and to dentate line point *b′* and divided the internal anal sphincter in this area. The two incisions *a–b* and *a′–b′* are equal in length and are parallel with about 1 cm between them

Results

The main presenting symptom in this group of patients was pain, which occurred during defecation and hours afterwards. Pain was significantly reduced in all patients in the first postoperative hours while symptoms such as bleeding and irritation were reduced in most patients in the next day. No patient reported incontinence on direct questioning preoperative. The operation time ranged from 15 to 25 min (mean, 17 min). The main hospital stay was 1 day. During follow-up, one patient complained of minor bleeding during the first 3 days (2%) and one patient (2%) developed perianal abscess at 2 weeks postoperative, which was incised and drained under general anesthesia. No fissure relapse was observed during follow-up period. Anal fissures and sphincterotomy wounds show complete healing within 4 weeks (ranging from 2 to 5 weeks). An increased basal tone of the internal sphincter and an elevated resting pressure were the preoperative manometric findings in all of our patients. After 3 months postoperatively, basal tone of the internal sphincter and resting anal pressure retuned to normal levels in all patients. The mean maximal resting pressure value was found to be 108.19± 15.18 cm H_2O preoperatively and 70.27±9.33 cm H_2O at 3 months postoperatively. No anal incontinence was reported in this patients group after segmental lateral sphincterotomy during the period of follow-up.

Discussion

In our study, 100% patients were presented with painful defecation and 80% with bleeding, corresponding to 98.8% and 71.4% in other study. High percentage of male to

female (6.1:1) in our study was due to the fact that most of the female patients avoid presenting to male surgeons for treatment due to shyness or modesty. This study favored the reports that anal fissure is common in middle age and at posterior midline of anus.[9] The most recent theories on etiopathogenesis of anal fissures have focused on increased tonicity of the internal anal sphincter, which contains smooth muscle fibers whose contraction is controlled by neural influences and myogenic mechanism.[10] Factors causing internal sphincter hypertonia are not well understood, but a significant role in perpetrating the muscle spasm is played by the trauma caused by passage of hard stools on the mucosa.[4,5] Spasm of the sphincter not only promotes constipation (thus setting up a vicious cycle) but also leads to compression of the terminal arterioles supplying the mucosa of the anal canal. Impaired blood flow in this already poorly perfused area prevents fissure healing.[10] Since the introduction of the posterior internal sphincterotomy by Eisenhammer[11] in 1951, chronic anal fissure has been managed with surgery once conservative measures failed. The more safe lateral sphincterotomy, popularized by Notaras[12] in 1969, has until now been the mainstay of treatment to reduce the pathologically raised pressure profile within the anal canal. Despite the surgery is highly efficacious and succeeds in curing chronic anal fissure in more than 90% of patients (often exceeds 95% with high satisfaction), postoperative impairment of continence is not uncommon. The incidence is not well documented and varies between 0% and 35% for flatus incontinence, 0% and 21% for liquid incontinence, and 0% and 5% for solid stool incontinence.[13] To minimize this risk, several authors have tried a more limited division of internal sphincter, a tailored or controlled sphincterotomy [14] and recently, injection of botulinum toxin.[15] No incontinence or failure of fissure healing were reported in this patients group which treated by segmental lateral internal sphincterotomy. From the data of previous studies, we believed that the incontinence follow lateral internal sphincterotomy due to gutter formation at the site of sphincter division. This gutter allowed to rectal contents (flatus or stool) to pass through it in spite of internal anal sphincter contraction. The prove for this theory that, the risk of incontinence more with total (up to dentate line) than limited (up to fissure apex only) lateral internal sphincterotomy,[16] because total technique produces groove extends from the anal verge to the dentate line in same continuity. Also, open lateral sphincterotomy is associated with more risk of incontinence than the closed one because the groove after the open one is deeper. Also, incontinence after lateral internal sphincterotomy is usually in a form of flatus incontinence,[9] because flatus are easy to pass through this groove. One study reported that perianal injection of autologous fat treated the anal incontinence well.[17] We think this is due to obliteration of anal gutters by the injected fat. The extended gutter formation from the anal verge to the dentate line is responsible for incontinence complication after total lateral internal sphincterotomy. With our technique, total internal sphincterotomy was done in two short incisions and not in the same continuity, producing good relief of sphincter hypertonia leading to good fissure healing, and secondly, two short incisions healed rapidly by second intension and without gutter formation avoiding anal incontinence. This manuscript represents preliminary data, which need more evaluation studies on long run about its efficacy and complications.

Conclusion

Segmental lateral internal sphincterotomy is a novel, safe, and effective way of treating chronic anal fissure, and it is not associated with any risk of anal incontinence.

References

1. Dykes SL, Madoff RD. Benign anorectal: anal fissure. In: Wolff BG, Fleshman JW, Beck DE, Pemberton JH, Wexner SD, eds. The ASCRS textbook of colon and rectal surgery. New York: Springer, 2007: 178–191
2. Brisinda G, Cadeddu F, Brandara F, Brisinda D, Maria G. Treating chronic anal fissure with botulinum neurotoxin. Nat Clin Pract Gastroenterol Hepatol 2004; 1:82–89
3. Elia Guedea M, Gracia Solanas JA, Royo Dachary P, Ramirez Rodriguez JM, Aguilella Diago V, Martinez Diez M. Prevalence of anal diseases after Scopinaro's biliopancreatic bypass for super-obese patients. Cir Esp 2008; 84:132–137
4. Sauper T, Lanthaler M, Biebl M, Weiss H, Nehoda H. Impaired anal sphincter function in professional cyclists. Wien Klin Wochenschr 2007; 119: 170–173
5. Garg P. Water stream in a bidet-toilet as a cause of anterior fissure-in-ano: a preliminary report. Colorectal Dis 2010; 12:601–602
6. Aivaz O, Rayhanabad J, Nguyen V, Haigh PI, Abbas M. Botulinum toxin A with Fissurectomy is a viable alternative to lateral internal sphincterotomy for chronic anal fissure. Am Surg 2009; 75: 925–928
7. Hyman N. Incontinence after lateral internal sphincterotomy: a prospective study and quality of life assessment. Dis Colon Rectum 2004; 47:35–38
8. Brown CJ, Dubreuil D, Santoro L, Liu M, O'Connor BI, McLeod RS. Lateral internal sphincterotomy is superior to topical nitroglycerin for healing chronic anal fissure and does not compromise long-term fecal continence: six-years follow up of multicenter, randomized, controlled trail. Dis Colon Rectum 2007; 50:442–448.
9. García-Granero E, Sanahuja A, García-Botello SA, Faiz O, Esclápez P, Espí A, Flor B, Minguez M, Lledó S. The ideal lateral internal sphincterotomy: clinical and endosonographic evaluation following open and closed internal anal sphincterotomy. Colorectal Dis. 2009; 11:502–7
10. Ayantunde AA, Debrah SA. Current concepts in anal fissures. World J Surg 2006; 30:2246–60.
11. Eisenhammer S. The evaluation of the internal anal sphincterotomy operation with special reference to anal fissure. Surg Gynecol Obstet 1959; 109:583–90.

12. Notaras MJ. Lateral subcutaneous sphincterotomy for anal fissure-a new technique. J R Soc Med 1969; 62:713.
13. Nelson R. Non surgical therapy for anal fissure. Cochrane Database Syst Rev 2006; 4:CD003431.
14. Menteş BB, Güner MK, Leventoglu S, Akyürek N. Fine-tuning of the extent of the lateral internal sphincterotomy: spasm-controlled vs. up to the fissure apex. Dis Colon Rectum 2008; 51:128–33.
15. Wollina U. Pharmacological sphincterotomy for chronic anal fissures by botulinum toxin a. J Cutan Aesthet Surg. 2008 Jul;1 (2):58–63.
16. Menteş BB, Ege B, Leventoglu S, Oguz M, Karadag A Extent of lateral internal sphincterotomy: up to the dentate line or up to the fissure apex? Dis Colon Rectum. 2005; 48:365–70.
17. Shafik A. Perianal injection of autologous fat for treatment of sphincteric incontinence. Dis Colon Rectum 1995; 38:583–7.

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REVIEW ARTICLE

Focal Nodular Hyperplasia—A Review of Myths and Truths

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Abstract
Background Focal nodular hyperplasia (FNH) is a benign hyperplastic lesion of the liver with no known malignant potential. It has generated much interest due to the frequency with which it presents with atypical features on radiological imaging. Often resulting in misdiagnosis. Moreover, the understanding of particular subtypes of this lesion at a molecular level has changed in recent years. This may have implications on how certain subtypes should be managed.
Purpose This review aims to analyse current literature pertaining to FNH and to provide clinically relevant advice regarding diagnosis and management.

Keywords Diagnosis · Focal nodular hyperplasia · Liver · Neoplasms · Treatment

Introduction

Focal nodular hyperplasia (FNH) is a benign tumour of the liver with an indolent course, no known potential for malignant transformation, and an extremely low rate of rupture or haemorrhage. It is thought to arise as a hyperplastic lesion in response to a preexisting arterial malformation. The widespread use of imaging has resulted in FNH being found occasionally as an incidental finding. Although this lesion has a well-documented natural history, management decisions may be difficult because of atypical radiological features and because there is still uncertainty as to whether growth is influenced by the hormonal milieu. Moreover, with recent developments in the understanding of certain FNH subtypes at a molecular level, management options are still evolving. The aim of this review is to analyse the current literature regarding FNH in order to provide clinically relevant advice about the diagnosis and management of these lesions.

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Epidemiology

FNH is the second most common benign liver tumour after liver haemangiomas.[1] In a large autopsy study of 2,270 cadaveric specimens there was an incidence of 0.31%[1] which fits with our clinical experience and confirms that this diagnosis is far less common than liver haemangioma. Although FNH may affect both women and men of all ages,[1,2] it is most often found in females between the ages of 30 and 50[1,3] with a reported female-to-male ratio of between 8:1 and 12:1.[2,3] This diagnosis is rarely made in the paediatric population. In fact, one case series claiming to describe 21 paediatric cases of FNH should be interpreted with caution as the microscopic findings of a fibrous tumour in many of the lesions in this study do not match with the currently accepted histopathological descriptions of FNH.[4]

Accordingly, the diagnosis of FNH in a child should be questioned. Equally puzzling is the fact that this lesion is almost never seen in elderly patients, suggesting that focal nodular hyperplastic lesions may involute as women pass through menopause.

Clinical Manifestations

From the literature, it is difficult to determine what proportion of patients with FNH suffers from symptoms directly attributable to the lesion itself. Most cases are discovered incidentally on abdominal imaging.[3] Some authors have suggested that large subcapsular lesions may cause stretching of Glisson's capsule or displacement of adjacent organs and that this might lead to vague abdominal pain.[5] Many reports attributing abdominal pain to the presence of an FNH do not describe rigorous attempts to exclude alternative causes for the patients' symptoms.[6,7]

Clinicians should be cautious when attributing symptoms to FNH as the physiological mechanisms of pain in the context of this lesion have not been specifically identified. Nevertheless, FNH may grow extremely large, up to 190 mm,[2] and occasionally present with an abdominal mass or hepatomegaly.[2,3] Liver function test abnormalities are uncommon unless the FNH is large enough to cause extrinsic intrahepatic biliary duct compression, which usually manifests as a mildly elevated serum gamma-glutamyl transferase level.

There are several case reports describing a first presentation of FNH in patients with acute abdominal pain due to intratumoral haemorrhage and a subsequent haemoperitoneum.[8,9] However, this is rare and is most often in patients with large exophytic tumours or in those with multiple FNH lesions.[10] In this latter case report, the histopathological description of the culprit lesion describes the presence of "portal triads" which many experts believe do not occur in true FNH. This is a typical example of how the literature has become confused on this topic and why there needs to be a consensus regarding diagnostic criteria for FNH.

Histopathology and Pathogenesis

The classic histopathological description of FNH is that of a non-encapsulated nodule with a central fibrous body from which there are radiating septa dividing nodules of hyperplastic hepatocytes sometimes forming plates that are two cells thick. The central fibrous regions usually contain abnormal vessels of different sizes, as well as proliferating bile ductules. However, FNH is typically void of any formal portal triads.[1] In addition to this classical FNH description, Nguyen et al., in a study of 305 FNH lesions, defined three "nonclassical" histological subtypes. These accounted for 20% of their series, and there was no central fibrous scar in any of these cases.[2] The subtypes described include the telangiectatic FNH (tFNH), the mixed hyperplastic and adenomatous forms, and FNH with cytologic atypia. tFNH is characterised by dilated sinusoids and a gross resemblance to hepatic adenoma. Mixed hyperplastic and adenomatous forms essentially contain separate regions resembling tFNH and hepatic adenoma but with some lesions showing transitional morphological features between the two. This transitional appearance is an interesting observation consistent with recent molecular studies of FNH discussed below. Only eight of 305 lesions in this series were categorised as FNH with cytologic atypia. This group of lesions was characterised by the presence of atypical hepatocytes with enlarged hyperchromatic nuclei with irregular contours frequently demonstrating cytoplasmic–nuclear inclusions. Five of these lesions demonstrated classical FNH morphology, two lesions demonstrated tFNH, and one lesion was of mixed type.

FNH nodules are usually solitary but may be multiple in approximately 20% of cases.[1,2] Reports of up to 30 lesions in one patient have been documented.[2] The size of the lesion can vary between 1 and 190 mm in diameter, but most are in the range of 40–50 mm at the time of presentation.[11,12]

The exact aetiology of FNH is not known, but the most accepted theory describes a vascular malformation as the trigger event. It is thought to arise as a result of preexisting spider-like arterial structures larger than expected in the liver cellular architecture, leading to heterogeneous blood flow causing a hyperplastic hepatocytic response.[1] Sato et al. conclude from their immunohistochemical analyses on sections of FNH that the central scar forms as a result of hepatic stellate cell activation secondary to hyperoxic conditions due to arterial hyperperfusion (Fig. 1). In addition, they propose that vascular endothelial growth factor, also activated by increased oxygen tension, may play a role in the proliferation of abnormal vessels.[13]

Of great clinical interest is the debate about the exact role of the oestrogen or progesterone milieu in the development or growth of FNH. The clinical dilemma about whether pregnancy or the oral contraceptive pill has any impact on incidental or suspiciously symptomatic lesions is ongoing. However, a review of the relevant literature does allow some sensible conclusions. Importantly, there has been a lack of prospective comparative series of decent sample size to make any firm statement regarding the impact of the hormonal milieu on FNH. There are numerous series and reports suggesting that oral contraceptives are a contributing factor in the development of FNH, especially with long-term use.[14,15] Some of these

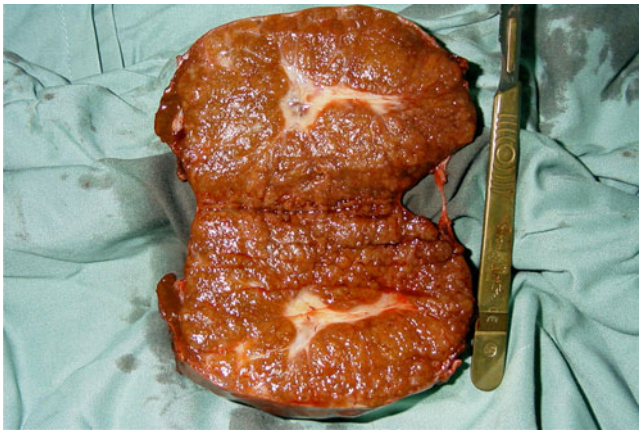

Fig. 1 Resected FNH specimen demonstrating the characteristic fibrous central scar. The figure was kindly provided by Professor Jonathan Fawcett, Princess Alexandra Hospital, Brisbane, Australia

reports, although small in sample size and lacking rigorous study design, attained histological confirmation for the majority of the lesions that were diagnosed as FNH.[14,16] However, much of the supportive literature describes patients presenting in the 1960s and 1970s when oral contraceptive formulations contained much higher doses of oestrogen (>50 mcg) than at present. Also, radiological and even histological diagnosis was not as accurate as it is today. More recent literature, albeit the majority only with a radiological diagnosis of FNH, seems to refute the argument for an association.[7,17,18] However, it is also possible that modern low-dose oestrogen formulations of oral contraceptives have averted the risk of patients developing FNH. Regardless, and to be definitive, more prospective studies of larger sample sizes and with histopathological confirmation of the diagnosis of FNH would need to be undertaken.

The effect of pregnancy on the behaviour of FNH has only been observed in a few small case series and individual case reports, most of which describe stable appearances of the lesion and uncomplicated deliveries.[7,19]

More recent developments in the study of FNH pathogenesis have been at a molecular level, focussing on clonal analysis. Most of the literature dealing with this subject supports a polyclonal origin of FNH,[20–22] which is consistent with the most accepted theory that it is a hyperplastic lesion. Only one series of ten lesions in nine patients has proposed that most FNH lesions are monoclonal.[23] This last series describes the histopathology of each studied FNH lesion as demonstrating a thin fibrous capsule demarcating it from the surrounding liver parenchyma, which is not in keeping with the current understanding of FNH. It is possible that the lesions studied in this paper were not true FNH. Others have demonstrated a lack of somatic gene mutations, especially of those involved in liver tumorigenesis, further supporting the theory that FNH is truly a nonneoplastic lesion.[21,22,24] However, several small but recent pathological series found parts of the FNH nodules were monoclonal, suggesting, at least, partial neoplastic transformation.[25,26] These intriguing findings raise further questions about malignant potential but may be specific only for certain subtypes of FNH. In this regard, Bioulac-Sage et al., in a series that compares 13 telangiectatic FNH (tFNH) with 28 classical FNH and 17 hepatic adenomas, showed that 100% of tFNH are monoclonal in origin and more closely resemble hepatic adenomas than classical FNH.[21] Paradis et al. made similar conclusions in a series studying the patterns of X-chromosome inactivation in ten tFNH, six typical FNH, and six hepatocellular adenoma lesions. Seventy-five percent of tFNH lesions in this series were monoclonal in nature, whereas 100% of typical FNH lesions were polyclonal and 100% of hepatocellular adenoma lesions were monoclonal.[27] This confirms that tFNH should be considered as a separate subtype when classifying FNH.

The Natural History of FNH

Apart from scattered case reports of the synchronous discovery of FNH and hepatocellular carcinoma,[28,29] there has never been a documented case of transformation of a histologically proven FNH into a malignant lesion. In support of this lack of risk, numerous series describe long-term follow-up imaging of histologically proven FNH where no malignant transformation occurred.[30–32]

Changes in the size of FNH lesions are common and may simply reflect dynamic growth fluctuations known to occur in normal liver tissue. In an ultrasound study of 16 cases of FNH in which 14 cases were histologically proven, size reduction was noted over a mean follow-up of 33 months in seven cases, with complete disappearance of the lesion in one patient. A larger study following 53 patients with conservatively managed FNH over a mean of 32 months demonstrated that a minority of lesions may increase in size.[32] Another imaging study using ultrasound that followed 30 patients with 34 FNH nodules followed for a mean period of 42 months showed 71% were stable in size, 3% increased in diameter by more than 30%, and 27% even regressed in size over the follow-up period.[33] It has been postulated that lesion regression occurs as a result of thrombosis of the feeding artery, a pathological finding that was confirmed in one large autopsy study.[1] The stability of most FNH lesions along with the likelihood of regression with age, the lack of potential for malignant transformation, and the extremely low risk of rupture and haemorrhage supports a conservative approach to the management of most patients with radiologically convincing or histologically proven FNH.

Imaging of FNH

The similarity on imaging between FNH and other hepatic lesions may cause diagnostic dilemmas. FNH, on multiple imaging modalities, may mimic a liver cell adenoma[34] and even a hepatocellular carcinoma (particularly the fibrolamellar subtype).[35] Obviously, it is important to differentiate FNH from both of these diagnoses which usually mandate resection. The typical appearance of FNH as seen with different imaging modalities has been described. When these findings are atypical more invasive diagnostic measures may be required to confirm or exclude the diagnosis.

Transabdominal Ultrasound

Although ultrasound is highly sensitive for diagnosing FNH, frequently FNH cannot be characterised well, and therefore, further imaging may be required to make a confident diagnosis. The typical ultrasound (US) appearance is a well-demarcated homogeneous hypo- or isoechoic lesion, although confusingly FNH can sometimes be hyperechoic. A hyper- or hypoechoic central scar is particularly helpful for a diagnosis, but is seen in less than 20% of cases.[36,37] Usually, there is absence of a peripheral hypoechoic rim, compatible with the absence of a true capsule.

Colour Doppler US may assist by identifying a central arterial structure, with a "spoke-wheel" pattern of peripherally radiating smaller aberrant vessels, or even a basket pattern of vessels in some cases.[37,38] However, similar vascular patterns can also be seen in hepatic malignancy and therefore these findings should be interpreted with caution.[38]

Overall, US is attractive because it avoids the radiation risks of computed tomography (CT) scanning, and is more accessible than magnetic resonance imaging. However, US is operator-dependent, and image quality may be limited by large body habitus or overlying bowel gas.

Computed Tomography (CT) Scanning

Early reports of CT scanning in the detection of FNH showed that it has a sensitivity and specificity of 75% and 92%, respectively.[39,40] Despite the advent of more sophisticated scanning protocols and hardware, there have been no recent studies measuring the sensitivity and specificity of CT for the diagnosis of focal nodular hyperplasia. The typical findings on CT scan are that of a well-circumscribed lesion appearing iso- or hypodense on the non-contrast studies,[41] with a hypodense scar visible in a minority of cases (Fig. 2). The rich arterial supply of the feeding arteries, as well as the uniform cellular architecture, is responsible for rapid homogeneous intense enhancement throughout the lesion in the arterial phase. The feeding arteries are seen in approximately 6% of cases. The

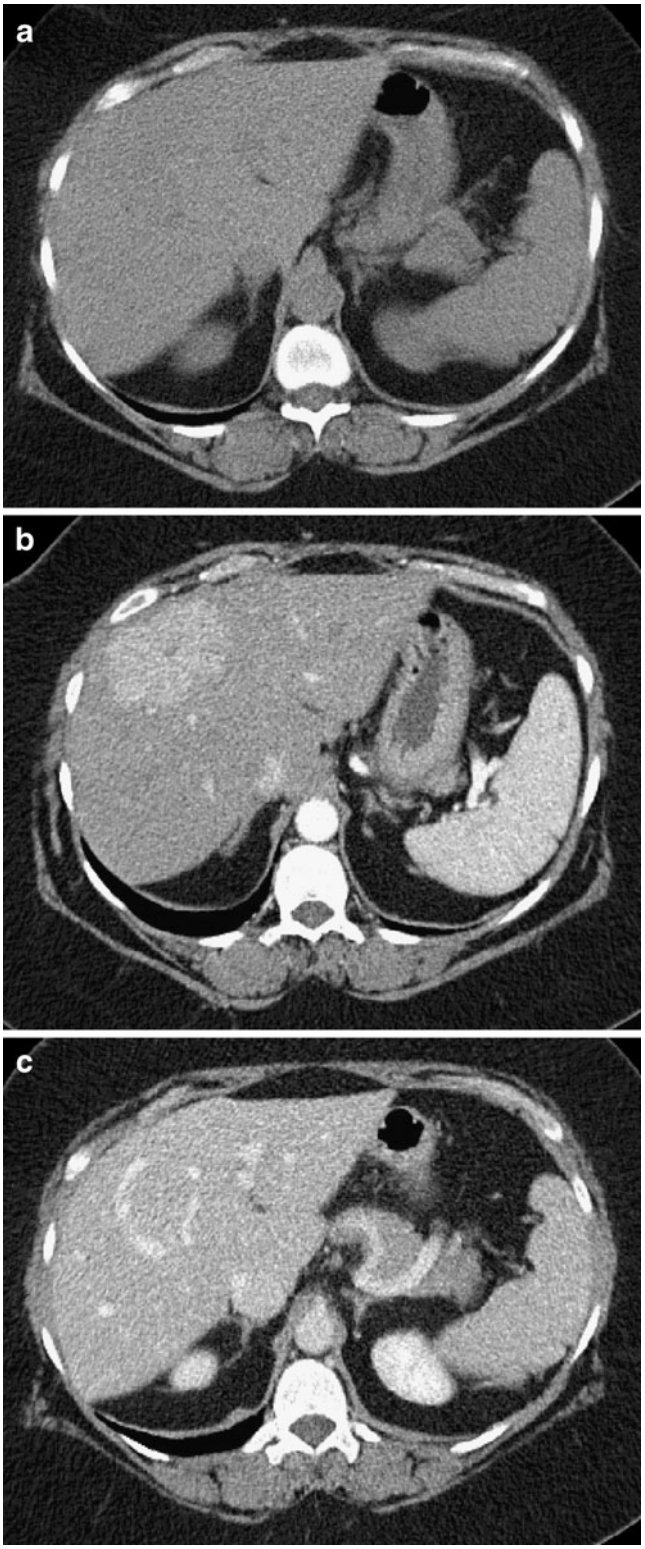

Fig. 2 CT images of FNH during the **a** non-contrast phase, **b** arterial phase, and **c** portal venous phase. Note the hypodense central scar demonstrated on arterial phase and the discontinuous peripheral vascular rim on portal venous phase

presence of large sinusoids and draining veins cause the lesion to become iso- or hypodense in the portal venous phase, followed by gradual enhancement of the central scar on delayed scans as the contrast diffuses slowly into the fibrous tissue. This latter feature is most apparent in large lesions. A discontinuous peripheral vascular rim is seen in this phase in approximately 40% of cases.[36,42] This rim may be confused with a true fibrous capsule that is completely continuous in hepatocellular carcinoma (HCC)[43] or hepatic adenomas.[42] Critically a multiphase scan should be performed if FNH is to be diagnosed accurately.

A radiological examination of 13 patients with histologically proven tFNH found features on CT that distinctly differed from those of classical FNH. Comparatively, tFNH lesions were more likely to be multiple in number (62%), heterogeneous (43%), without a central scar (92%), and persistently enhancing on delayed phase imaging.[44] Lesions with this appearance on CT should be approached with suspicion, especially in light of new molecular evidence that supports the classification of tFNH as a variant of hepatic adenoma rather than of FNH, as previously discussed.

There are some features on multiphase CT which can assist in the differentiation between FNH and hepatocellular adenoma. On non-contrast scans, hepatocellular adenomas may exhibit hyperdensity if there has been prior haemorrhage and may contain low attenuating focal fat deposits. This contrasts with FNH which tends to be relatively homogenously iso- or hypodense. In the arterial phase, hepatocellular adenomas also exhibit hyperdense enhancement, but in a more heterogeneous pattern and usually to a lesser degree than FNH. Adenomas then gradually lose their heterogeneity and hyperdensity, eventually becoming homogenously hypodense during the delayed phase due to arteriovenous shunting. The presence of a central hypodense area in FNH, representing a fibrous central scar, is rare in hepatocellular adenoma.[45]

Differentiation of FNH from the fibrolamellar subtype of hepatocellular carcinoma (FLHCC) may be difficult on CT, particularly if FNH exhibits atypical findings such as the presence of intralesional calcification.[46] In a retrospective analysis of FNH in 295 patients, calcification was demonstrated in only 1.4% of cases, and this prompted resection. This pathological feature may also be seen in cholangiocarcinoma, hepatocellular carcinoma, as well as in some hepatic metastases.[47,48] Obviously, the presence of a very large lesion (such as greater than 100 mm) or any associated vascular or biliary tract invasion or locoregional lymphadenopathy would go against a diagnosis of FNH. Nonetheless, the fact that FNH and FLHCC occur in the same age groups and in those patients with no underlying liver disease may lead to confusion if the lesions have an atypical appearance.[35]

Magnetic Resonance Imaging

As a modality with no radiation risk and excellent tumour characterisation capabilities, magnetic resonance (MR) imaging is a valuable tool in the diagnosis of FNH and other liver lesions that occur in women of child-bearing age. The typical findings on MR are that of a homogeneous lesion that is isointense or slightly hypointense on T1-weighted images, and isointense or slightly hyperintense on T2-weighted images. The central scar is typically hypointense on T1 and hyperintense on T2. During arterial phase enhancement, a typical FNH appears homogenously hyperintense apart from a hypointense central scar. During the portal phase, the lesion returns to isointensity or occasionally remains slightly hyperintense. On delayed phase images, the FNH is either isointense or slightly hyperintense, with the central scar often exhibiting avid enhancement due to slow diffusion of contrast through the myxomatous stroma.[49,50] In one series of 41 patients with FNH reported by Cherqui et al., a central scar was visualised on MR imaging in 78% of cases.[51]

Although MR may be very helpful for diagnosing FNH, unusual or atypical features are frequently found. In one series of 37 patients with 48 histologically proven FNH lesions, the typical appearance of isointensity on T1- and T2-weighted images and a central hyperintense scar on T2 was seen only in 43% of cases. However, this particular series may represent surgical bias as these cases were resected presumably because of unusual radiological features.[34]

Unusual or atypical features of FNH on MR, including the absence of a central scar, a strong hyperintense signal on T1 (which may occur due to steatosis), a hypointense central scar on T2, the presence of a complete or incomplete pseudocapsule (which may occur due to dilated vessels and sinusoids around the lesion), or a strong hyperintense lesion on T2 make diagnosis difficult and, from a clinical viewpoint, suggest either biopsy, resection, or a period of observation. In particular, a T2 hypointense central scar is often suggestive of fibrolamellar HCC.

As in CT imaging, telangiectatic FNH demonstrates different imaging features on MR as compared with classical FNH. tFNH, as detected by MR, is more likely to be heterogeneous (43% of lesions), hyperintense on T1 (53%), strongly hyperintense on T2 (44%), without a central scar (92%), and to demonstrate persistent enhancement in delayed phase imaging.[44]

One study using delayed phase contrast-enhanced MR imaging showed that FNH could be successfully differentiated from other benign or malignant liver lesions with an overall accuracy of 98%.[52] Unfortunately, as with many studies related to FNH imaging, only 58 of 100 patients in this series had a histopathological diagnosis, and therefore, the results are difficult to interpret.

Nuclear Medicine

Nuclear medicine imaging has an important role in differentiating FNH from other liver lesions. Uptake of radiolabelled colloids (technetium Tc 99 m sulphur colloid) occurs because of Kupffer cell activity within many FNH.[53] Although this is considered highly diagnostic, unfortunately only 7–30% of cases show increased uptake.[54] While frustrating, this test is still important because uptake demonstrated as a "hot spot" excludes a malignant lesion or a liver cell adenoma.[55]

Biopsy

There are conflicting reports regarding the benefits of needle biopsy in the diagnostic work-up of FNH. Due to the high specificity of CT and MRI in diagnosing most FNH, there is usually no indication for biopsy in the presence of typical radiological features. However, needle biopsy may be appropriate in selected cases if imaging is indeterminate.[56] In these situations, the risks of a biopsy have to be balanced with the potential benefits. These risks include the small but real chance of bleeding or seeding of malignant cells if the lesion is not benign.

In a series of 155 patients with benign liver tumours (including 42 FNH), 30 patients underwent percutaneous needle biopsy, 19 of which were incorrect or indeterminate when compared with histopathology of the resected specimen. It is not stated whether the specimens were fine needle aspirates or core biopsies. This likely relates to sampling error, and the authors concluded that percutaneous needle biopsy rarely influences management of benign liver tumours.[57] In another study retrospectively analysing patients with FNH with atypical imaging, only 14 of 24 patients (58.3%) who underwent ultrasound-guided needle core biopsy had a correct diagnosis of FNH.[56] A large collated series of 100 archival cases of needle biopsy specimens of FNH from a number of different hospitals confirmed that a confident diagnosis of FNH was made by the initial pathologist in only 24 of 100 cases. Overall, these data suggest that there is still a need for consensus about diagnostic criteria regarding needle biopsy features of FNH, and that this investigation has a limited role to play. An alternative approach for managing patients with atypical imaging features is to "observe" the lesions over a defined time period (usually 3–4 months) and then to repeat the imaging to exclude a change in the size or characteristics of the lesion.

Management

Considering the indolent natural history of focal nodular hyperplasia, the rare chance of acute complications, and the fact that there is no potential for malignant change, patients with asymptomatic FNH should be treated conservatively. If there is a typical radiological appearance of FNH, then patients should be reassured that no further imaging is required. Importantly, they should also be strongly encouraged to keep the films safe for future reference in the event that this liver lesion is identified again.

Even with multiple imaging modalities (ultrasound, multiphase CT, multiphase MR, and nuclear scintigraphy), some patients have lesions that are likely to be benign but have atypical features of FNH. This typically occurs in patients over 40 years of age and may reflect fluctuations in the hormonal milieu as women reach menopause. It is interesting that FNH is almost never seen in elderly women despite the widespread use of imaging in this age group. Presumably, this is because many focal nodular hyperplastic lesions involute following menopause. In patients with atypical but likely benign imaging features, and when there are no other worrying features to the presentation, then a period of observation is reasonable with repeat imaging approximately 3 to 4 months later. This is long enough to detect any change but not too long to cause undue anxiety for the patient or for the clinician. The choice of the most appropriate imaging modality depends on the location of the lesion as well as the available local resources. A simple transabdominal ultrasound or a contrast-enhanced MR scan will avoid the need for further radiation dosage. If the lesion changes in imaging characteristics or enlarges significantly or becomes symptomatic over that observation period, then surgical intervention should be considered for both therapeutic and diagnostic purposes.[58]

Although the majority of patients with FNH are completely asymptomatic, there is a subgroup who do develop symptoms that may require resection. This is usually in patients with large and subcapsular lesions. It is

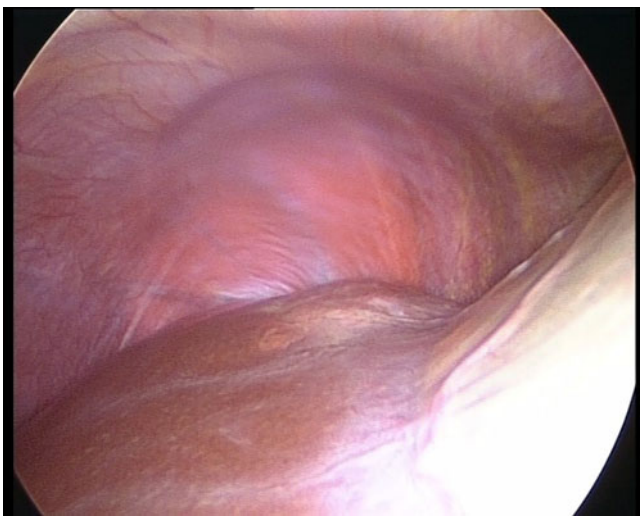

Fig. 3 Laparoscopic view of FNH in segment 4A of the liver

appropriate to consider resection in these patients but only after other causes for these patients' symptoms are ruled out. In our practice, we perform a biliary ultrasound to exclude gallstones, a HIDA scan to exclude chronic acalculous cholecystitis, and an upper endoscopy to rule out oesophageal or gastroduodenal pathology. The indications for resection include patients with persistent symptoms, those with atypical lesions that have increased in size or changed their imaging characteristics, or when symptoms develop after a period of observation. Also, patients should be offered immediate resection when there are such atypical radiological features that it is not possible to confidently rule out a malignant process. In those patients who are offered a period of observation, the oral contraceptive pill should be stopped in the first instance even though there is only limited data supporting an association between the low-dose oral contraceptive pill and FNH. In women who are pregnant or in those who wish to become pregnant, there is no need to resect these lesions, and most patients can be observed carefully with serial ultrasounds throughout the pregnancy.

Notwithstanding the above recommendations, evidence supporting the role of surgery in the management of focal nodular hyperplasia is at best, level 3 or 4. There are no randomised controlled trials studying the benefit of elective surgery for any benign liver tumour versus conservative management.[59] In one retrospective series comparing 15 patients with resections specifically for FNH versus 37 patients who underwent conservative management with observation only, there was a 20% perioperative complication rate (including chest infection, subhepatic abscess, and wound infection), a median hospital stay of 9 days but no postoperative mortality. Two out of 15 of the resected cases had a recurrence of their FNH at 29 and 48 months, respectively. In the conservatively managed group, of the 13 patients who had pain, five continued to have pain after a median follow-up of 23 months. Unfortunately, there was no follow-up information about persistent pain postoperatively in the 13 patients who underwent resection when the preoperative indication for surgery was pain.[60] In a retrospective series analysing eight patients with symptomatic FNH who underwent resection, symptoms were relieved in all of these patients at a median of 24 months follow-up.[61] Laparoscopic liver resection may provide additional benefits over open resection in terms of postoperative hospital stay and early return to normal activities (Fig. 3). A multicentre retrospective study of laparoscopic liver resections for benign liver tumours in 87 patients (48 of whom had resections for FNH) showed that the mean postoperative hospital stay was 5 days. There was a 10% open conversion rate and no postoperative mortality.[62] There are sporadic reports of shrinkage and disappearance of FNH following angiographic embolisation in cases where resection was contraindicated because of comorbidity or difficult anatomical locations of the lesion.[30,63] However, there are no controlled studies closely analysing the benefit of this procedure compared with observation alone or resection. Importantly, the indications for resection should not change just because laparoscopic surgery is possible.

In conclusion, our understanding of FNH has evolved over the past 30 years. The rapid advances in imaging have allowed more accurate diagnoses without the need for biopsy or resection. The natural history of FNH is still not fully understood, although multiple different pathological subtypes have now been described, and this may explain the heterogeneous clinical behaviour. The fact that the diagnosis of focal nodular hyperplasia is almost never made in postmenopausal women strongly supports the role of the hormonal milieu in influencing the development and growth of these benign lesions. Longitudinal studies are required to better understand the natural history of this condition.

References

1. Wanless IR, Mawdsley C, Adams R. On the pathogenesis of focal nodular hyperplasia of the liver. Hepatology 1985;5:1194–1200.
2. Nguyen BN, Flejou JF, Terris B, Belghiti J, Degott C. Focal nodular hyperplasia of the liver: a comprehensive pathologic study of 305 lesions and recognition of new histologic forms. Am J Surg Pathol 1999;23:1441–1454.
3. Luciani A, Kobeiter H, Maison P, Cherqui D, Zafrani ES, Dhumeaux D, Mathieu D. Focal nodular hyperplasia of the liver in men: is presentation the same in men and women? Gut 2002;50:877–880.
4. Stocker JT, Ishak KG. Focal nodular hyperplasia of the liver: a study of 21 pediatric cases. Cancer 1981;48:336–345.
5. Buetow PC, Pantongrag-Brown L, Buck JL, Ros PR, Goodman ZD. Focal nodular hyperplasia of the liver: radiologic–pathologic correlation. Radiographics 1996;16:369–388.
6. Shen YH, Fan J, Wu ZQ, Ma ZC, Zhou XD, Zhou J, Qiu SJ, Qin LX, Ye QH, Sun HC, Huang XW, Tang ZY. Focal nodular hyperplasia of the liver in 86 patients. Hepatobiliary Pancreat Dis Int 2007;6:52–57.
7. Mathieu D, Kobeiter H, Maison P, Rahmouni A, Cherqui D, Zafrani ES, Dhumeaux D. Oral contraceptive use and focal nodular hyperplasia of the liver. Gastroenterology 2000;118:560–564.
8. Becker YT, Raiford DS, Webb L, Wright JK, Chapman WC, Pinson CW. Rupture and hemorrhage of hepatic focal nodular hyperplasia. Am Surg 1995;61:210–214.
9. Hardwigsen J, Pons J, Veit V, Garcia S, Le Treut YP. A life-threatening complication of focal nodular hyperplasia. J Hepatol 2001;35:310–312.
10. Demarco MP, Shen P, Bradley RF, Levine EA. Intraperitoneal hemorrhage in a patient with hepatic focal nodular hyperplasia. Am Surg 2006;72:555–559.
11. Uggowitzer M, Kugler C, Groll R, Mischinger HJ, Stacher R, Fickert P, Weiglein A. Sonographic evaluation of focal nodular hyperplasias (FNH) of the liver with a transpulmonary galactose-based contrast agent (Levovist). Br J Radiol 1998;71:1026–1032.

12. Ishak KG, Rabin L. Benign tumors of the liver. Med Clin North Am 1975;59:995–1013.
13. Sato Y, Harada K, Ikeda H, Fijii T, Sasaki M, Zen Y, Nakanuma Y. Hepatic stellate cells are activated around central scars of focal nodular hyperplasia of the liver—a potential mechanism of central scar formation. Hum Pathol 2009;40:181–188.
14. Scalori A, Tavani A, Gallus S, La Vecchia C, Colombo M. Oral contraceptives and the risk of focal nodular hyperplasia of the liver: a case-control study. Am J Obstet Gynecol 2002;186:195–197.
15. Klatskin G. Hepatic tumors: possible relationship to use of oral contraceptives. Gastroenterology 1977;73:386–394.
16. Heinemann LA, Weimann A, Gerken G, Thiel C, Schlaud M, DoMinh T. Modern oral contraceptive use and benign liver tumors: the German Benign Liver Tumor Case-Control Study. Eur J Contracept Reprod Health Care 1998;3:194–200.
17. Mathieu D, Kobeiter H, Cherqui D, Rahmouni A, Dhumeaux D. Oral contraceptive intake in women with focal nodular hyperplasia of the liver. Lancet 1998;352:1679–1680.
18. Kapp N, Curtis KM. Hormonal contraceptive use among women with liver tumors: a systematic review. Contraception 2009;80:387–390.
19. Weimann A, Mossinger M, Fronhoff K, Nadalin S, Raab R. Pregnancy in women with observed focal nodular hyperplasia of the liver. Lancet 1998;351:1251–1252.
20. Paradis V, Laurent A, Flejou JF, Vidaud M, Bedossa P. Evidence for the polyclonal nature of focal nodular hyperplasia of the liver by the study of X-chromosome inactivation. Hepatology 1997;26:891–895.
21. Bioulac-Sage P, Rebouissou S, Sa Cunha A, Jeannot E, Lepreux S, Blanc JF, Blanche H, Le Bail B, Saric J, Laurent-Puig P, Balabaud C, Zucman-Rossi J. Clinical, morphologic, and molecular features defining so-called telangiectatic focal nodular hyperplasias of the liver. Gastroenterology 2005;128:1211–1218.
22. Chen YW, Jeng YM, Yeh SH, Chen PJ. P53 gene and Wnt signaling in benign neoplasms: beta-catenin mutations in hepatic adenoma but not in focal nodular hyperplasia. Hepatology 2002;36:927–935.
23. Gaffey MJ, Iezzoni JC, Weiss LM. Clonal analysis of focal nodular hyperplasia of the liver. Am J Pathol 1996;148:1089–1096.
24. Chen YJ, Chen PJ, Lee MC, Yeh SH, Hsu MT, Lin CH. Chromosomal analysis of hepatic adenoma and focal nodular hyperplasia by comparative genomic hybridization. Genes Chromosomes Cancer 2002;35:138–143.
25. Cai YR, Gong L, Teng XY, Zhang HT, Wang CF, Wei GL, Guo L, Ding F, Liu ZH, Pan QJ, Su Q. Clonality and allelotype analyses of focal nodular hyperplasia compared with hepatocellular adenoma and carcinoma. World J Gastroenterol 2009;15:4695–4708.
26. Gong L, Li YH, Su Q, Li G, Zhang WD, Zhang W. Use of X-chromosome inactivation pattern and laser microdissection to determine the clonal origin of focal nodular hyperplasia of the liver. Pathology 2009;41:348–355.
27. Paradis V, Benzekri A, Dargere D, Bieche I, Laurendeau I, Vilgrain V, Belghiti J, Vidaud M, Degott C, Bedossa P. Telangiectatic focal nodular hyperplasia: a variant of hepatocellular adenoma. Gastroenterology 2004;126:1323–1329.
28. Saul SH, Titelbaum DS, Gansler TS, Varello M, Burke DR, Atkinson BF, Rosato EF. The fibrolamellar variant of hepatocellular carcinoma. Its association with focal nodular hyperplasia. Cancer 1987;60:3049–3055.
29. Petsas T, Tsamandas A, Tsota I, Karavias D, Karatza C, Vassiliou V, Kardamakis D. A case of hepatocellular carcinoma arising within large focal nodular hyperplasia with review of the literature. World J Gastroenterol 2006;12:6567–6571.
30. Pain JA, Gimson AE, Williams R, Howard ER. Focal nodular hyperplasia of the liver: results of treatment and options in management. Gut 1991;32:524–527.
31. Kerlin P, Davis GL, McGill DB, Weiland LH, Adson MA, Sheedy PF, 2nd. Hepatic adenoma and focal nodular hyperplasia: clinical, pathologic, and radiologic features. Gastroenterology 1983;84:994–1002.
32. Weimann A, Ringe B, Klempnauer J, Lamesch P, Gratz KF, Prokop M, Maschek H, Tusch G, Pichlmayr R. Benign liver tumors: differential diagnosis and indications for surgery. World J Surg 1997;21:983–990; discussion 990–981.
33. Kuo YH, Wang JH, Lu SN, Hung CH, Wei YC, Hu TH, Chen CH, Yen YH, Lee CM, Eng HL. Natural course of hepatic focal nodular hyperplasia: a long-term follow-up study with sonography. J Clin Ultrasound 2009;37:132–137.
34. Vilgrain V, Flejou JF, Arrive L, Belghiti J, Najmark D, Menu Y, Zins M, Vullierme MP, Nahum H. Focal nodular hyperplasia of the liver: MR imaging and pathologic correlation in 37 patients. Radiology 1992;184:699–703.
35. Caseiro-Alves F, Zins M, Mahfouz AE, Rahmouni A, Vilgrain V, Menu Y, Mathieu D. Calcification in focal nodular hyperplasia: a new problem for differentiation from fibrolamellar hepatocellular carcinoma. Radiology 1996;198:889–892.
36. Shamsi K, De Schepper A, Degryse H, Deckers F. Focal nodular hyperplasia of the liver: radiologic findings. Abdom Imaging 1993;18:32–38.
37. Golli M, Mathieu D, Anglade MC, Cherqui D, Vasile N, Rahmouni A. Focal nodular hyperplasia of the liver: value of color Doppler US in association with MR imaging. Radiology 1993;187:113–117.
38. Wang LY, Wang JH, Lin ZY, Yu ML, Lu SN, Chuang WL, Chen SC, Hseih MY, Tsai JF, Chang WY. Hepatic focal nodular hyperplasia: findings on color Doppler ultrasound. Abdom Imaging 1997;22:178–181.
39. Rogers JV, Mack LA, Freeny PC, Johnson ML, Sones PJ. Hepatic focal nodular hyperplasia: angiography, CT, sonography, and scintigraphy. AJR Am J Roentgenol 1981;137:983–990.
40. Procacci C, Fugazzola C, Cinquino M, Mangiante G, Zonta L, Andreis IA, Nicoli N, Pistolesi GF. Contribution of CT to characterization of focal nodular hyperplasia of the liver. Gastrointest Radiol 1992;17:63–73.
41. Shirkhoda A, Farah MC, Bernacki E, Madrazo B, Roberts J. Hepatic focal nodular hyperplasia: CT and sonographic spectrum. Abdom Imaging 1994;19:34–38.
42. Carlson SK, Johnson CD, Bender CE, Welch TJ. CT of focal nodular hyperplasia of the liver. AJR Am J Roentgenol 2000;174:705–712.
43. Choi CS, Freeny PC. Triphasic helical CT of hepatic focal nodular hyperplasia: incidence of atypical findings. AJR Am J Roentgenol 1998;170:391–395.
44. Attal P, Vilgrain V, Brancatelli G, Paradis V, Terris B, Belghiti J, Taouli B, Menu Y. Telangiectatic focal nodular hyperplasia: US, CT, and MR imaging findings with histopathologic correlation in 13 cases. Radiology 2003;228:465–472.
45. Ruppert-Kohlmayr AJ, Uggowitzer MM, Kugler C, Zebedin D, Schaffler G, Ruppert GS. Focal nodular hyperplasia and hepatocellular adenoma of the liver: differentiation with multiphasic helical CT. AJR Am J Roentgenol 2001;176:1493–1498.
46. Friedman AC, Lichtenstein JE, Goodman Z, Fishman EK, Siegelman SS, Dachman AH. Fibrolamellar hepatocellular carcinoma. Radiology 1985;157:583–587.
47. Teefey SA, Stephens DH, Weiland LH. Calcification in hepatocellular carcinoma: not always an indication of fibrolamellar histology. AJR Am J Roentgenol 1987;149:1173–1174.

48. Scatarige JC, Fishman EK, Saksouk FA, Siegelman SS. Computed tomography of calcified liver masses. J Comput Assist Tomogr 1983;7:83–89.
49. Mathieu D, Vilgrain V, Mahfouz AE, Anglade MC, Vullierme MP, Denys A. Benign liver tumors. Magn Reson Imaging Clin N Am 1997;5:255–288.
50. Lee MJ, Saini S, Hamm B, Taupitz M, Hahn PF, Seneterre E, Ferrucci JT. Focal nodular hyperplasia of the liver: MR findings in 35 proved cases. AJR Am J Roentgenol 1991;156:317–320.
51. Cherqui D, Rahmouni A, Charlotte F, Boulahdour H, Metreau JM, Meignan M, Fagniez PL, Zafrani ES, Mathieu D, Dhumeaux D. Management of focal nodular hyperplasia and hepatocellular adenoma in young women: a series of 41 patients with clinical, radiological, and pathological correlations. Hepatology 1995;22:1674–1681.
52. Grazioli L, Morana G, Kirchin MA, Schneider G. Accurate differentiation of focal nodular hyperplasia from hepatic adenoma at gadobenate dimeglumine-enhanced MR imaging: prospective study. Radiology 2005;236:166–177.
53. Boulahdour H, Cherqui D, Charlotte F, Rahmouni A, Dhumeaux D, Zafrani ES, Meignan M. The hot spot hepatobiliary scan in focal nodular hyperplasia. J Nucl Med 1993;34:2105–2110.
54. Davis LP, McCarroll K. Correlative imaging of the liver and hepatobiliary system. Semin Nucl Med 1994;24:208–218.
55. Kurtaran A, Muller C, Novacek G, Kaserer K, Mentes M, Raderer M, Pidlich J, Eibenberger K, Angelberger P, Virgolini I. Distinction between hepatic focal nodular hyperplasia and malignant liver lesions using technetium-99m-galactosyl-neoglycoalbumin. J Nucl Med 1997;38:1912–1915.
56. Fabre A, Audet P, Vilgrain V, Nguyen BN, Valla D, Belghiti J, Degott C. Histologic scoring of liver biopsy in focal nodular hyperplasia with atypical presentation. Hepatology 2002;35:414–420.
57. Charny CK, Jarnagin WR, Schwartz LH, Frommeyer HS, DeMatteo RP, Fong Y, Blumgart LH. Management of 155 patients with benign liver tumours. Br J Surg 2001;88:808–813.
58. Reddy KR, Kligerman S, Levi J, Livingstone A, Molina E, Franceschi D, Badalamenti S, Jeffers L, Tzakis A, Schiff ER. Benign and solid tumors of the liver: relationship to sex, age, size of tumors, and outcome. Am Surg 2001;67:173–178.
59. Colli A, Fraquelli M, Massironi S, Colucci A, Paggi S, Conte D. Elective surgery for benign liver tumours. Cochrane Database Syst Rev 2007:CD005164.
60. Bonney GK, Gomez D, Al-Mukhtar A, Toogood GJ, Lodge JP, Prasad R. Indication for treatment and long-term outcome of focal nodular hyperplasia. HPB (Oxford) 2007;9:368–372.
61. Hsee LC, McCall JL, Koea JB. Focal nodular hyperplasia: what are the indications for resection? HPB (Oxford) 2005;7:298–302.
62. Descottes B, Glineur D, Lachachi F, Valleix D, Paineau J, Hamy A, Morino M, Bismuth H, Castaing D, Savier E, Honore P, Detry O, Legrand M, Azagra JS, Goergen M, Ceuterick M, Marescaux J, Mutter D, de Hemptinne B, Troisi R, Weerts J, Dallemagne B, Jehaes C, Gelin M, Donckier V, Aerts R, Topal B, Bertrand C, Mansvelt B, Van Krunckelsven L, Herman D, Kint M, Totte E, Schockmel R, Gigot JF. Laparoscopic liver resection of benign liver tumors. Surg Endosc 2003;17:23–30.
63. Amesur N, Hammond JS, Zajko AB, Geller DA, Gamblin TC. Management of unresectable symptomatic focal nodular hyperplasia with arterial embolization. J Vasc Interv Radiol 2009;20:543–547.

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REVIEW ARTICLE

Subject Review: Pancreatic Ductal Adenocarcinoma in the Setting of Mutations in the Cystic Fibrosis Transmembrane Conductance Regulator Gene: Case Report and Review of the Literature

David W. Rittenhouse · Vanessa A. Talbott · Zafia Anklesaria · Jonathan R. Brody · Agneszkia K. Witkiewicz · Charles J. Yeo

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Abstract
Background Cystic fibrosis (CF) is the most commonly inherited lethal autosomal recessive genetic disease amongst Caucasians. CF results from mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Patients with homozygous or compound heterozygous CFTR mutations have a risk of pancreatitis, but typically do not live long enough to develop pancreatic ductal adenocarcinoma (PDA), a disease that has an average age at diagnosis of 65 years. Little is known about the risk of the development of PDA in people who are heterozygous for mutations in the CFTR gene.
Patients and Methods We report a case of a patient with PDA who underwent resection, who is a carrier for the W1282X nonsense mutation in the CFTR gene. The patient is of Ashkenazi Jewish ethnicity and has a family history of CF, but no family history of PDA. We reviewed the English language literature for the prevalence of PDA in CF patients (and CFTR mutations in the setting of PDA) and their significance in terms of screening, and the use of this mutation as a biomarker for an increased risk of the development of PDA.
Conclusion We conclude that patients with CFTR mutations, who also have other risks for the development of PDA such as a family history of the disease, should undergo screening and be educated about their risks.

Keywords Cystic fibrosis · Pancreatic ductal adenocarcinoma · W1282X mutation

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Introduction

Cystic fibrosis (CF) is the most common lethal autosomal recessive inherited disease amongst Caucasians.[1] The gene responsible for CF is on chromosome 7 and encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which functions as a chloride channel regulated by cyclic AMP.[2] Much work has been accomplished over the past 20 years identifying over 1,300 different mutations in the CFTR gene. A genotype to phenotype profile classification system has been developed for mutations in the CFTR gene.[3] Classifications of mutations include missense, nonsense, and splice-site alterations which typically lead to reduction in CFTR gene expression. Homozygous and compound heterozygous mutations of the most severe classes produce the most severe phenotypes.[4] In regards to pancreatic exocrine physiology, these genetic alterations affect CFTR protein

expression. Under normal circumstances, the CFTR protein is highly expressed on the apical side of pancreatic ductal epithelial cells. The protein serves as an ion channel for the secretion of chloride and bicarbonate into the epithelial lumen to solubilize digestive enzymes and alkalinize pancreatic secretions. However, with certain CFTR mutations, the protein function is impaired or absent. Dysregulation in the CFTR protein leads to an acidic milieu, with inspissated pancreatic secretions and ductal obstruction.[3]

Approximately 80% to 90% of CF patients have pancreatic insufficiency.[5] Cohn et al. found an increased association of CFTR mutations in patients with idiopathic chronic pancreatitis.[6] It has been controversial if patients with chronic pancreatitis have an increased risk of developing pancreatic ductal adenocarcinoma (PDA). In some settings, CF has also been shown to lead to an increased risk of the development of PDA.[7] For instance, Neglia et al. showed that there was an increased risk of many gastrointestinal cancers in CF with an odds ratio of 9.5 (95% confidence interval, 3.5–11.1), and McWilliams et al. showed that there was a modest increased risk of the development of PDA in CF patients.[1,8]

The most common (up to 70%) disease causing mutation in the CFTR gene is the ΔF508 mutation, which results from a base pair deletion in exon 10 that leads to a loss of a phenylalanine at position 508.[3,9] This has been the most commonly occuring CFTR mutation associated with idiopathic pancreatitis and PDA; however, less common mutations have also been associated with other disease phenotypes. A less common mutation in the CFTR gene is the W1282X, where a G to A base pair substitution at nucleotide 3978 leads to a substitution of a tryptophan amino acid residue with generation of a premature stop codon. Albeit far less common than the ΔF508 mutation, the W1282X mutation has been shown to occur with a tenfold higher frequency in patients with PDA when compared to controls.[8] We recently operated on a patient with PDA who had a family history of CF. The patient underwent genetic testing and was found to harbor a heterozygous W1282X mutation in the CFTR gene. We sought to review the English literature for PDA in cystic fibrosis patients as well as patients harboring CFTR gene mutations.

Methods

We reviewed the patient demographics, preoperative studies, operative details, hospital course, and family history of a patient with a family history of CF that underwent a pancreaticoduodenectomy for PDA at the Thomas Jefferson University Hospital. Appropriate operative and tumor banking consents were obtained, and the review was IRB exempt. Mutational analysis of the CFTR gene was detected from the patient's DNA extracted from peripheral blood cells. The genomic DNA underwent polymerase chain reaction amplification of specific CF gene regions testing for 32 common mutations recommended by the American College of Medical Genetics and American College of Obstetricians and Gynecologists for CF carrier screening (Quest Diagnostics Nichols Institute, Chantilly, VA, USA). A literature review was conducted searching the English language literature for all cases of PDA-associated CF and CFTR mutations, using the search terms PDA, CF, and CFTR mutation.

Patient Details

A 77-year-old male of Ashkenazi Jewish ethnicity, with a past medical history significant for duodenal adenomatous polyps under yearly endoscopic surveillance, and a history of cigarette smoking, presented to his gastroenterologist with complaints of dark urine, pale stools, and fatigue. Laboratory analysis revealed an elevated total bilirubin of 2.5 mg/dL, alkaline phosphatase of 381 IU/L, SGOT of 113 IU/L, and SGPT of 224 IU/L. He underwent a magnetic resonance imaging/magnetic resonance cholangiopancreatography which revealed a 1.5-cm occlusive stricture in the distal common bile duct with dilation of the common bile duct proximal to the stricture and a thick, irregular duodenal wall (Fig. 1). The patient then underwent an endoscopic retrograde cholangiopancreatography with bile duct and duodenal brushings, and placement of a metallic endoprosthesis to relieve the symptoms of obstructive jaundice. Cytology from these brush biopsies revealed adenomatous changes with no evidence of dysplasia. An abdominal computed tomography (CT) scan with intravenous contrast showed mild dilation of the pancreatic duct

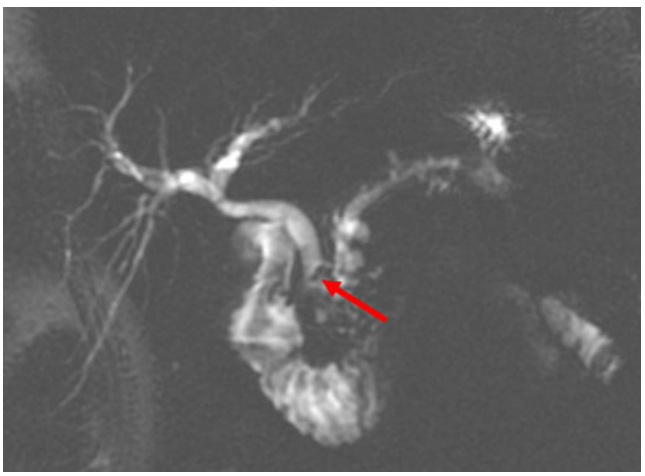

Fig. 1 An MRCP revealed a 1.5-cm occlusive stricture in the distal common bile duct (*arrow*) with dilation of the common bile duct proximal to the stricture and a thick, irregular duodenal wall

and evidence of pancreatitis. The combination of the patient's symptoms and radiological findings were suggestive of a malignant process in the periampullary region. The patient was offered exploration and was scheduled for a pancreaticoduodenectomy. Preoperative tumor markers revealed a normal CEA of 2.1 ng/mL and an elevated CA 19–9 of 159 U/mL.

At operation, there was no evidence of malignant ascites or distant metastases. A pylorus-preserving pancreaticoduodenectomy was performed, and the resulting specimen was sent for pathological evaluation. Pathology revealed a 1.5×1.5×1.3 cm moderately differentiated ductal adenocarcinoma originating in the head of the pancreas and extending into the duodenal wall and peripancreatic fat, with negative surgical resection margins (Fig. 2a). Nine of 26 peripancreatic lymph nodes were positive for metastatic disease leading to an American Joint Commission on Cancer pathologic stage of IIb (T3N1M0). In addition to the PDA, the specimen contained a dilated main pancreatic duct (diameter of a 1.5 cm) containing an intraductal papillary mucinous neoplasm (IPMN) with mild to moderate dysplasia (Fig. 2b), and an incidental 0.2-cm endocrine microadenoma in the uncinate process. The patient had an uneventful postoperative course and was discharged home on postoperative day 7.

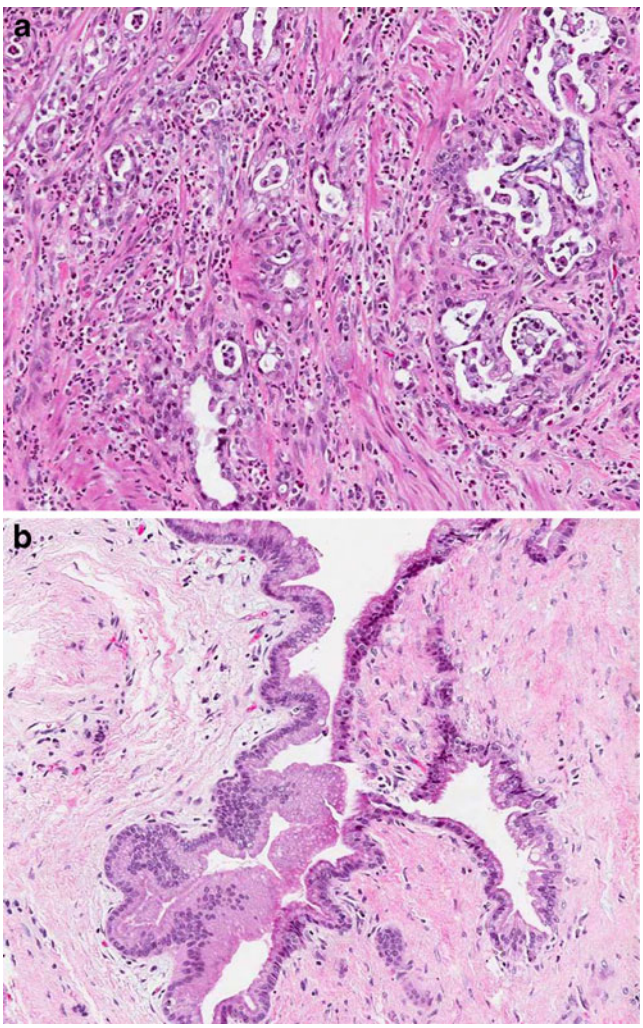

Fig. 2 **a** Moderately differentiated pancreatic ductal adenocarcinoma composed of malignant glands and desmoplastic stroma. **b** Intraductal papillary mucinous neoplasm with mild dysplasia in the mucinous cells lining cyst wall (hematoxylin and eosin stain, ×200 original magnification)

The patient revealed to us that he had a family history of CF, but no family history of PDA (Fig. 3). We ordered genetic tests to determine his CFTR carrier status. Genetic analysis revealed the patient to harbor a heterozygous W1282X mutation in the CFTR gene. The patient is now alive 8 months post-resection and undergoing gemcitabine-based chemoradiation therapy. In addition, he is enrolled in a phase III pancreatic hyperimmune vaccine therapy trial. Recent surveillance abdominal CT scan showed no evidence of recurrent disease.

Literature Review

We reviewed the English language literature for two topics: all CF patients who have developed a pancreatic tumor (Table 1), as well as all patients who have been diagnosed with a pancreatic neoplasm and subsequently have been found to harbor CFTR gene mutations on genetic testing (Table 2).

In CF patients with pancreatic tumors, there have been six reports describing PDA and one report of a mucinous cystadenoma (Table 1).[10–16] The average age of CF patients with PDA is 29.6 and 19 years in the patient with mucinous cystadenoma. Of the CF patients with pancreatic tumors and reported comorbidities, five of the six cases had pancreatic insufficiency. The most common presentation of pancreatic tumors in the patients was abdominal pain occurring in four of the six reported cases. The most prevalent genotype was that of the homozygous ΔF508 mutation occurring in every reported case.

In patients with PDA or precursor lesions for PDA who have been screened for CFTR mutations, there have been 107 reported cases (Table 2).[8,17–21] There were 106 cases of PDA and 1 case of IPMN with PanIN-2 on pathologic analysis. The average age of patients with PDA who had CFTR mutations was 66.6 years. The four most prevalent genotypes were the ΔF508 mutation (n=47), 5T allele (n=44), W1282X mutation (n=6), and R117H mutation (n=5).

The present case is the sixth W1282X mutation in the setting of PDA to have been reported in the English literature, and only the second publication to note this association. Our study describes a proband of Ashkenazi Jewish ethnicity with a family history of CF who underwent resection for PDA. The

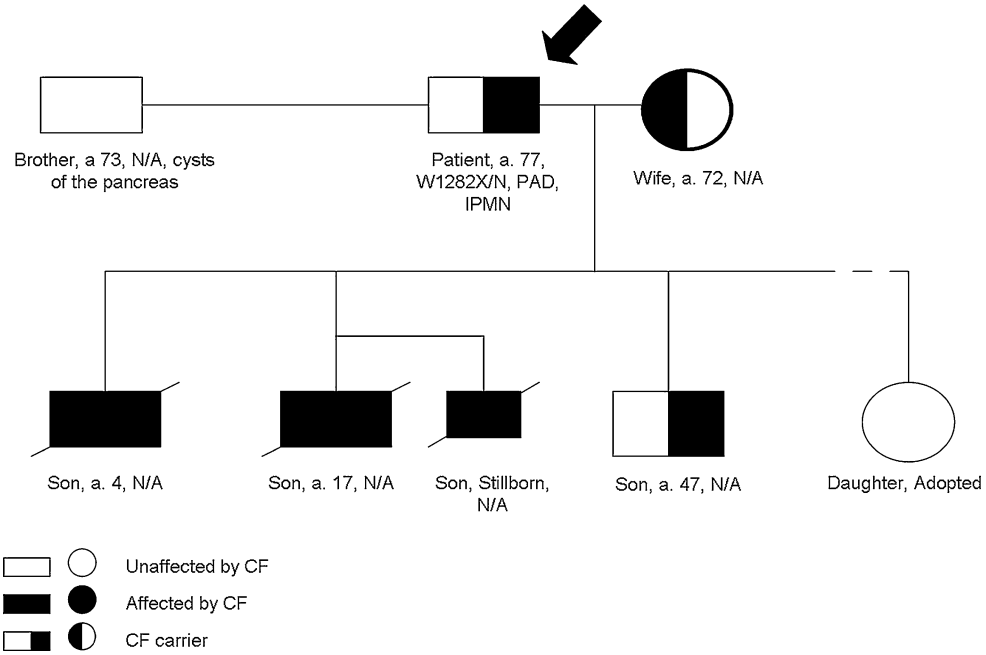

Fig. 3 Pedigree analysis: The index patient (proband) (*arrow*) had a brother that had a history of cysts of the pancreas, and an eldest son who died of CF at 4 years of age. The proband had twins affected with CF. One was dead at birth and the other died at 17 years of age from complications from CF. The proband also had a youngest son who was a known CF carrier, and one adopted daughter

patient underwent genetic testing and was found to be heterozygous for the W1282X CFTR gene mutation. The W1282X mutation is a class I CFTR gene nonsense mutation that occurs with a frequency of 1% in the population and has only been reported in one publication with five other patients with PDA.[8] Below, we discuss the significance of CFTR gene mutation carrier status in the risk of developing PDA and what this means in terms of cancer screening and surveillance.

Discussion

In CF patients, there is a known increased risk of gastrointestinal tract tumors as documented in large retrospective and prospective studies. Neglia et al. showed an increased risk of digestive tract tumors in patients with CF after retrospectively examining cohorts of patients from CF centers in North America and Europe.[1] Most of these affected patients were in their third decade of life, and the tumors originated in the large bowel (n=9), liver/biliary system (n=5), small bowel (n=3), pancreas (n=3), stomach (n=1), and esophagus (n=1).[1] Maisonneuve et al., in a 10-year prospective study, reported a significant increased risk of digestive tract tumors in adults with cystic fibrosis, with a standardized incidence ratio of 5.1, (95% CI=3.2–7.6).[14] The most common digestive tract tumors originated in the large bowel (n=11), liver/biliary tract (n=5), small bowel (n=4), and pancreas (n=1).[14] While it has been observed

Table 1 Cystic fibrosis patients with pancreatic tumors

Year	Author	Number of patients	Age	Comorbidities	Presentation	Pathology	Genotype
1985	Davis	1	23	Pancreatic insufficiency	Abdominal pain	PDA	Unknown
1986	Tedesco	1	42	Pancreatic insufficiency, pulmonary disease	Abdominal pain, anorexia	PDA	Unknown
1987	McIntosh	1	26	Insulin dependent diabetes, pulmonary disease	Abdominal pain	PDA	Unknown
1994	Tsongalis	1	39	Pancreatic insufficiency, diabetes, pulmonary disease	Gastric outlet obstruction	PDA	ΔF508/ΔF508
2000	Maisoneuve	1	Not reported	Not reported	Not reported	PDA	ΔF508/ΔF508
2004	Oermann	1	19	Pancreatic insufficiency, pulmonary disease, sinusitis, gastroesophageal reflux	Incidental finding on imaging for esophageal reflux	Mucinous cystadenoma	ΔF508/ΔF508
2005	Petrowsky	1	18	Pancreatic insufficiency, pulmonary disease	Abdominal pain, cholestasis	PDA	Unknown

PDA pancreatic ductal adenocarcinoma, Δ*F508* Delta F508

Table 2 Patients with pancreatic tumors and heterozygous mutations in the CFTR gene

Year	Author	Number of patients	Average age (years)	Pathology	Genotype
2001	Malats	9	66.5	PDA	3 ΔF508
					6 5T Allele
2003	Pezzilli	1	73.8	PDA	5T Allele
2003	Matsubayashi	42	Not reported	PDA	6 ΔF508
					36 5T Allele
2006	Piepoli	3	63	PDA	3 ΔF508
2010	Rebours	1	52	IPMN with PanIN-2	2789+G>A/5T Allele
2010	McWilliams	50	67	PDA	35 ΔF508
					5 R117H
					5 W1282X
					G551D
					N1303K
					R347 P
					S549R
					Δ1507
2011	Present Study	1	77	PDA	W1282X

CFTR cystic fibrosis transmembrane regulator, *PDA* pancreatic ductal adenocarcinoma, Δ*F508* Delta F508, *IPMN* intraductal papillary mucinous neoplasm, *PanIN-2* pancreatic intraepithelial neoplasia-2

that there is an increase in gastrointestinal tract tumors in patients with CF, the number of patients with pancreatic tumors is quite small in relation to the incidence of CF per year. This is partially attributable to the fact that most patients with CF typically do not live long enough to develop PDA, which has an average age of onset of 65 years.

Less is known about the risk for the development of PDA in people who harbor heterozygous mutations in the CFTR gene. It is interesting to postulate that heterozygous carriers may silence the other copy of the gene (e.g., through loss of heterozygosity) during the clonal development of PDA. McWilliams et al. in 2005 showed a positive association with the development of pancreatic cancer and CFTR carrier status.[22] The presence of a heterozygous CFTR gene mutation conferred a two-fold risk for the development of PDA in patients younger than 60 years. None of the patients tested in the McWilliams study had the W1282X mutation. Interestingly enough, only one of the CFTR carriers in the McWilliams study that developed PDA had a clinical history of pancreatitis. This suggests that these patients may have had a subclinical pancreatitis that predisposed them to the development of PDA, or there was another direct molecular mechanism at play. Later, McWilliams et al. in 2010 examined a larger cohort of patients and found that the relative risk for being a carrier of a heterozygous CFTR gene mutation was 1.40 (95% confidence interval 1.04–1.89; p=0.027) for the development of PDA, which increased to 1.82 in patients younger than 60 years old.[8]

These data suggest that being a heterozygous carrier for a CFTR allele does lead to an increased risk for the development of PDA. This risk may be secondary to the development of a subclinical chronic pancreatitis or some other unknown mechanism. Cohn et al. showed that being a carrier of a CFTR mutation did lead to an increased risk for the development of idiopathic chronic pancreatitis. Our patient displayed evidence of pancreatitis on gross pathology as well as a dilated pancreatic duct on histologic examination. The heterozygous mutation in the CFTR mutation likely predisposed our patient to pancreatitis and subsequently may have set the stage for genetic instability or other molecular events that could contribute to or facilitate pancreatic tumorigenesis.

Molecular data exist to suggest that loss of CFTR expression, as occurs in heterozygous CFTR mutations, contributes to the development of PDA.[23] Singh et al. showed that in PDA cell lines, CFTR expression negatively regulated the expression of *MUC4*, a transmembrane glycoprotein that plays an important role in PDA tumorigenesis.[23] The authors also showed that CFTR was expressed in normal pancreatic cells and was downregulated in 81% of PDA cell lines. This correlated with *MUC4* expression, which was not detectable in normal pancreatic cells but overexpressed in 81% of PDA cell lines.[23] These data provide an exciting molecular mechanism by which loss of CFTR expression may lead to PDA tumorigenesis.

Our patient had a known family history of CF as well as a history of smoking, and was discovered to be a CF carrier upon genetic testing. Approximately 10% of PDA cases have a familial component. It would be beneficial to establish a screening protocol for those patients that are known to be at the highest risk for the development of PDA. Klapman et al. suggested screening those patients that have two or more first degree relatives with PDA as

well as those with a family history of any of the known hereditary pancreatic cancer syndromes such as familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer syndrome, hereditary pancreatitis, hereditary breast/ovarian cancer syndrome, Peutz–Jeghers syndrome, and familial atypical multiple mole and melanoma syndrome.[24] It might be worthwhile for those patients with a family history of CF and who have other risk factors such as smoking and obesity, who are known carriers of any of the more disease-associated mutations (i.e., ΔF508, W1282X) to be screened for PDA. The W1282X mutation, found in our proband, is approximately 66 times less common than the ΔF508 mutation in the general population. However, it comprises 52% of the CFTR gene mutations in the Ashkenazi Jewish population.[25] Multiple studies have also shown an increased life-time risk of pancreatic cancer in patients of Ashkenazi Jewish ethnicity who harbor a germline BRCA2 mutation.[26–29] Identifying patients who have a specific ethnicity that conveys a greater likelihood of harboring mutations in cancer-causing genes, in addition to recognizing patients with known environmental risk factors such as smoking and obesity, could lower the threshold for screening.

In conclusion, we have described a case of PDA in a patient of Ashkenazi Jewish ethnicity with a family history of CF. The patient was found to harbor a rare nonsense mutation in the CFTR gene (W1282X) that has an increased prevalence in the Ashkenazi Jewish population. Carrier status of this gene, as well as other genetic alterations in hereditary pancreatic cancer susceptibility genes (i.e., BRCA2, p16), may convey a risk for the development of PDA over time and therefore may serve as a panel of biomarkers for both detection and therapeutic intervention options. Patients who have a family history of CF and harbor this gene may be considered for early screening for PDA, especially if other risk factors exist such as ethnicity, a history of smoking and obesity. Future large, epidemiologic studies will likely further unravel the contribution of CFTR mutations in the development of sporadic and familial forms of pancreatic cancer.

References

1. Neglia JP, FitzSimmons SC, Maisonneuve P, et al. The risk of cancer among patients with cystic fibrosis. Cystic Fibrosis and Cancer Study Group. N Engl J Med 1995; 332(8):494–9.
2. Riordan JR, Rommens JM, Kerem B, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science 1989; 245(4922):1066–73.
3. Wilschanski M, Durie PR. Patterns of GI disease in adulthood associated with mutations in the CFTR gene. Gut 2007; 56 (8):1153–63.
4. Ahmed N, Corey M, Forstner G, et al. Molecular consequences of cystic fibrosis transmembrane regulator (CFTR) gene mutations in the exocrine pancreas. Gut 2003; 52(8):1159–64.
5. Augarten A, Ben Tov A, Madgar I, et al. The changing face of the exocrine pancreas in cystic fibrosis: the correlation between pancreatic status, pancreatitis and cystic fibrosis genotype. Eur J Gastroenterol Hepatol 2008; 20(3):164–8.
6. Cohn JA, Friedman KJ, Noone PG, et al. Relation between mutations of the cystic fibrosis gene and idiopathic pancreatitis. N Engl J Med 1998; 339(10):653–8.
7. Sheldon CD, Hodson ME, Carpenter LM, Swerdlow AJ. A cohort study of cystic fibrosis and malignancy. Br J Cancer 1993; 68 (5):1025–8.
8. McWilliams RR, Petersen GM, Rabe KG, et al. Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations and risk for pancreatic adenocarcinoma. Cancer 2010; 116 (1):203–9.
9. Durno C, Corey M, Zielenski J, et al. Genotype and phenotype correlations in patients with cystic fibrosis and pancreatitis. Gastroenterology 2002; 123(6):1857–64.
10. Davis TM, Sawicka EH. Adenocarcinoma in cystic fibrosis. Thorax 1985; 40(3):199–200.
11. Tedesco FJ, Brown R, Schuman BM. Pancreatic carcinoma in a patient with cystic fibrosis. Gastrointest Endosc 1986; 32 (1):25–6.
12. McIntosh JC, Schoumacher RA, Tiller RE. Pancreatic adenocarcinoma in a patient with cystic fibrosis. Am J Med 1988; 85 (4):592.
13. Tsongalis GJ, Faber G, Dalldorf FG, et al. Association of pancreatic adenocarcinoma, mild lung disease, and delta F508 mutation in a cystic fibrosis patient. Clin Chem 1994; 40 (10):1972–4.
14. Maisonneuve P, FitzSimmons SC, Neglia JP, et al. Cancer risk in nontransplanted and transplanted cystic fibrosis patients: a 10-year study. J Natl Cancer Inst 2003; 95(5):381–7.
15. Oermann CM, Al-Salmi Q, Seilheimer DK, et al. Mucinous cystadenocarcinoma of the pancreas in an adolescent with cystic fibrosis. Pediatr Dev Pathol 2005; 8(3):391–6.
16. Petrowsky H, Schuster H, Irani S, et al. Pancreatic cancer in cystic fibrosis after bilateral lung transplantation. Pancreas 2006; 33 (4):430–2.
17. Malats N, Casals T, Porta M, et al. Cystic fibrosis transmembrane regulator (CFTR) DeltaF508 mutation and 5 T allele in patients with chronic pancreatitis and exocrine pancreatic cancer. PANKRAS II Study Group. Gut 2001; 48(1):70–4.
18. Pezzilli R, Morselli-Labate AM, Mantovani V, et al. Mutations of the CFTR gene in pancreatic disease. Pancreas 2003; 27(4):332–6.
19. Matsubayashi H, Fukushima N, Sato N, et al. Polymorphisms of SPINK1 N34S and CFTR in patients with sporadic and familial pancreatic cancer. Cancer Biol Ther 2003; 2(6):652–5.
20. Piepoli A, Gentile A, Valvano MR, et al. Lack of association between UGT1A7, UGT1A9, ARP, SPINK1 and CFTR gene polymorphisms and pancreatic cancer in Italian patients. World J Gastroenterol 2006; 12(39):6343–8.
21. Rebours V, Couvelard A, Sauvanet A, et al. Pancreatic intraepithelial neoplasia is associated with chronic pancreatitis due to serine protease inhibitor kazal type 1 and cystic fibrosis transmembrane conductance regulator mutations. Pancreas 2010; 39(6):947–8.
22. McWilliams R, Highsmith WE, Rabe KG, et al. Cystic fibrosis transmembrane regulator gene carrier status is a risk factor for young onset pancreatic adenocarcinoma. Gut 2005; 54 (11):1661–2.
23. Singh AP, Chauhan SC, Andrianifahanana M, et al. MUC4 expression is regulated by cystic fibrosis transmembrane conductance regulator in pancreatic adenocarcinoma cells via

transcriptional and post-translational mechanisms. Oncogene 2007; 26(1):30–41.
24. Klapman J, Malafa MP. Early detection of pancreatic cancer: why, who, and how to screen. Cancer Control 2008; 15 (4):280–7.
25. Shoshani T, Augarten A, Gazit E, et al. Association of a nonsense mutation (W1282X), the most common mutation in the Ashkenazi Jewish cystic fibrosis patients in Israel, with presentation of severe disease. Am J Hum Genet 1992; 50 (1):222–8.
26. Lynch HT, Deters CA, Lynch JF, Brand RE. Familial pancreatic carcinoma in Jews. Fam Cancer 2004; 3(3–4):233–40.
27. Goggins M, Schutte M, Lu J, et al. Germline BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas. Cancer Res 1996; 56(23):5360–4.
28. Naderi A, Couch FJ. BRCA2 and pancreatic cancer. Int J Gastrointest Cancer 2002; 31(1–3):99–106.
29. Hahn SA, Greenhalf B, Ellis I, et al. BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst 2003; 95 (3):214–21.

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GI IMAGE

Jejunal Subserosal Hematoma in an 11-Year-Old Boy

Hui Chen · Yu Zuo Bai · Wei Lin Wang

Published online: 25 June 2011

Abstract
Introduction Intramural hematoma may be subserosal, intramuscular, or submucosal or may involve the entire thickness of the bowel wall. Subserosal hematoma of the jejunum in children is uncommon.
Discussion We report a case of an 11-year-old boy with a jejunal subserosal hematoma presenting with duodenojejunal obstruction. Emergency laparotomy was performed and subserous hematoma involving the 7-cm long bowel was found. Serosal incision was done for evacuation of blood and clots. The patient had an uneventful postoperative course. The clinical picture and radiological findings were presented and discussed.

Keywords Hematoma · Small bowel · Child

An 11-year-old boy admitted to our hospital with bilious vomiting and severe abdominal pain of 3-h duration. Two days prior to admission, he was struck by a moving car which bruised his abdomen. At the time of admission, his temperature was 37.4°C, pulse rate was 90, and his blood pressure was 110/70 mmHg. Exquisite tenderness and muscle guarding were present in the left upper abdominal quadrant; rebound tenderness was positive. The bowel sounds were decreased. Hemoglobin was 126 g/l. Upper GI contrast study showed duodenojejunal obstruction and an extramural round-shaped compression of the jejunum (Fig. 1). Oral contrast CT scan revealed a large mass measuring 6.5×3.5 cm occupying the majority of the jejunal lumen with luminal narrowing and causing bowel obstruction (Fig. 2). Emergency laparotomy was performed. On opening the peritoneal cavity, a very large subserous hematoma involving 7-cm long bowel was found close up to the duodenojejunal flexure (Fig. 3). Serosal incision was done releasing about 100 ml of blood and clots. No bleeding vessel was found. After closure of the serosal incision, the abdomen was closed without drainage. The postoperative recovery was uneventful and upper GI contrast study on the 14th day revealed a free flow through the duodenum and jejunum. He was discharged on that day and continues to be symptom-free during 2 years of follow-up.

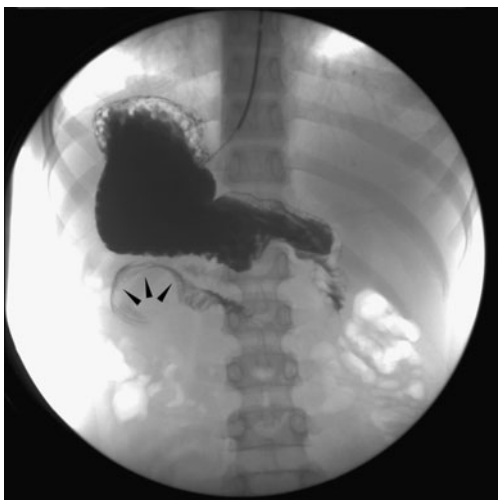

Fig. 1 Upper GI contrast study showed duodenojejunal obstruction and an extramural round-shaped compression of the jejunum (*arrow*)

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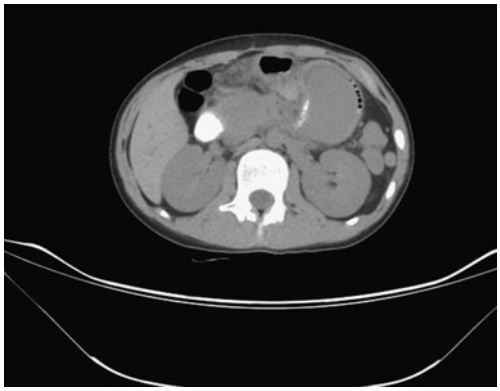

Fig. 2 Oral contrast CT scan revealed a large mass occupying the majority of the jejunal lumen with luminal narrowing

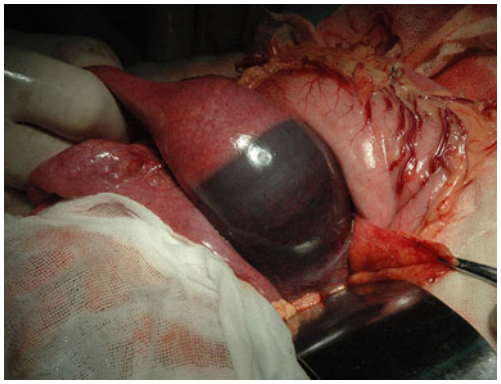

Fig. 3 At surgery, a red-black subserous haematoma was seen near the duodenojejunal flexure

Intramural hematoma may be subserosal, intramuscular, or submucosal, or may involve the entire thickness of the bowel wall. Subserosal hematoma of the jejunum is uncommon. Abdominal CT scan plays a critical role in the evaluation of intramural hematoma, bowel perforation, and mesenteric injuries in children. [1, 2]

In our patient, the clinical picture was typical of subserosal hematoma, with signs of jejunal obstruction, extramural compression of the jejunum of GI contrast study, an intramural mass on CT scan, and a delay of 48 h between injury and onset of symptoms.

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References

1. Hom J. The risk of intra-abdominal injuries in pediatric patients with stable blunt abdominal trauma and negative abdominal Computed tomography. Acad Emerg Med 2010;17 (5):469–475
2. Strouse PJ, Close BJ, Marshall KW, et al. CT of bowel and mesenteric trauma in children. Radiographics. 1999;19 (5):1237–1250.

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GI IMAGE

Phytobezoar as a Cause of Intestinal Obstruction

Brian M. Hall · Marc J. Shapiro · James A. Vosswinkel · Scott Meisel · Nicole Curci

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Abstract
Introduction A small bowel phytobezoar is a rare cause of intestinal obstruction, whose most common cause is adhesion.
Case Report This is a case report in which the etiology of small bowel obstruction was identified due to intussusception via computed tomography scan, and upon exploration, was found to be due to a small bowel phytobezoar.

Keywords Bezoar · Phytobezoar · Obstruction

Introduction

A bezoar is an accumulation of partially digested or undigested material. A mass made up of fruit or vegetable matter is termed a phytobezoar. Consisting of non-digestible material such as cellulose, lignin, hemicellulose, and tannium, persimmon fruit is a common cause of phytobezoar formation reported in the literature.[1] Other types of bezoars include lactobezoars (undigested milk products), phycobezoars (medications—pills), and trichobezoars (hair). A gastric operation for peptic ulcer disease is a common predisposing factor and bezoars may manifest as post-gastrectomy syndrome.

Case Report

A 75-year-old woman presented to our emergency department with a 2-day history of diffuse abdominal pain. She had been unable to pass flatus or have a bowel movement during this time. She denied nausea, vomiting, blood in her stool in the past, weight loss, or previous change in bowel habits. Her past medical history was significant for a subtotal gastrectomy with vagotomy over 30 years ago for treatment of peptic ulcer disease.

On admission, her vital signs were acceptable with BP of 146/66 and HR of 84. Her abdomen was slightly distended and tender, with the pain most pronounced in the left lower quadrant. Bowel sounds were hypoactive, and there was no stool on rectal l exam. The physical exam was otherwise unremarkable with normal basic metabolic panel, complete blood count, and lactic acid results. Medically, she was being treated for hypertension and coronary artery disease and she had an unremarkable cardiac catherization 2 days prior.

An obstruction series film of the abdomen revealed multiple air–fluid levels. There was no free air in the abdomen or air in bowel wall. The CT scan revealed dilated loops of jejunum and there was a small amount of intra-abdominal free fluid with a transition point in the left abdomen, suggestive of an intussusception (Figs. 1 and 2). No evidence of strangulation was evident.

At exploratory laparotomy, she had a complete obstruction at the level of the distal jejunum with collapse of the ileum distally. On palpation, a firm immobile mass was palpated measuring approximately 10 cm. Intussusception could not be identified within the small bowel. The mass was resected with its mesentery and a primary small bowel anastamosis was made. The specimen was opened at the end of the case and a large soft mass that resembled a fruit was found (Fig. 3). The specimen was

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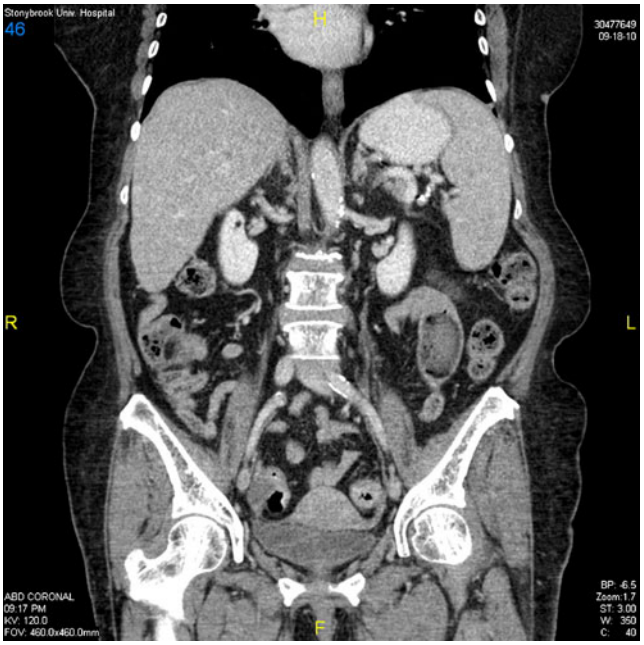

Fig. 1 The CT scan revealed dilated loops of jejunum

sent to the surgical pathology lab which confirmed the bezoar to be a fruit. The patient had an unremarkable postoperative course.

Discussion

A small bowel obstruction is not an uncommon cause for surgical admission, with adhesions being the most common

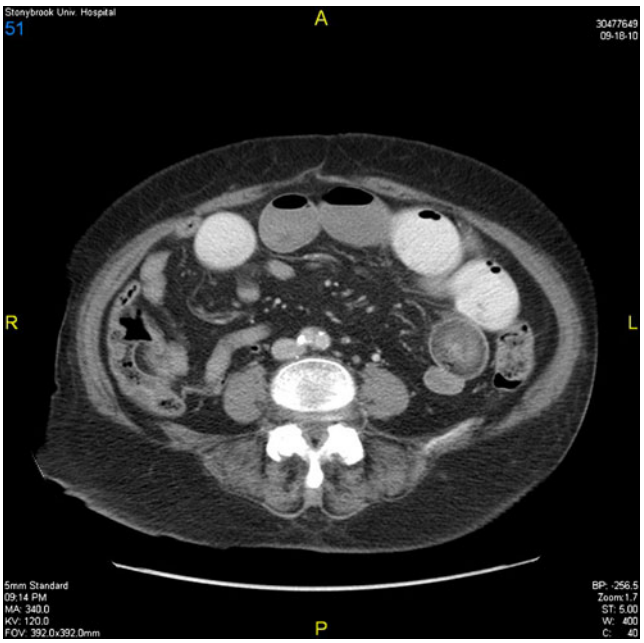

Fig. 2 Intra-abdominal free fluid with a transition point in the left abdomen, suggestive of an intussusception

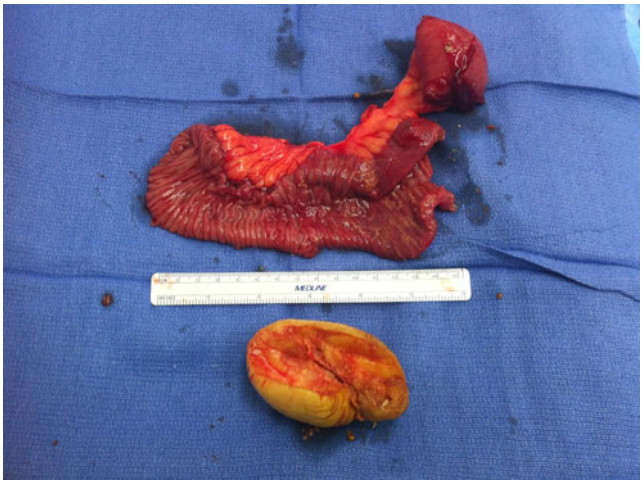

Fig. 3 Large soft mass

culprit. Hernias and cancer are the second and third most common causes, respectively. The incidence of bezoars causing a small bowel obstruction is approximately 4%.[2]

Risk factors associated with bowel obstructions secondary to bezoars are edentulous patients and previous gastric resection. Furthermore, the formation of a bezoar may develop in a patient with diabetic gastroparesis or those on a strict vegan diet.[3]

Digestion is both a chemical and a mechanical process. Lack of either may result in an obstructive process. With patients that are unable to masticate, the likelihood of an obstruction is directly related to the size of the food bolus. Under normal conditions, a food bolus undergoes a chemical breakdown within the stomach. This allows an easier transit through the gastrointestinal tract. Following gastric surgery, both gastric motility and acidity are decreased.[4] In addition, the lack of an intact pylorus sphincter, allows the food bolus to travel down the gastrointestinal tract in an unaltered form. All of these factors play a role in the formation of a bezoar. Although the incidence of post-gastrectomy bezoar formation is unknown, it can range between 5% and 12%.[5]

There are a variety of surgical and medical options in regards to the management of bezoars. They include, but are not limited, to endoscopy with retrieval or break up, enterotomy and/or entrectomy. These treatment modalities need to be individualized, such as in this patient where an intussusception was felt to be present. Although not evident, an intussusception can occur with the bezoar forming the leading edge of the intussuscipiens. Similarly, pain would be colicky in nature. In conclusion, bezoars are a rare cause of bowel obstruction. A thorough history and physical exam is always warranted. Once diagnosed, observation versus endoscopy and/or surgery should be considered. Finally, upon discussion with this patient, the phytobezoar was confirmed to be a half of a peach.

References

1. Nadeem-ul-Nazeer, et al. Phytobezoar: A Rare Cause Of Intestinal Obstruction And Perforation . *The Internet Journal of Surgery.* 2009; Volume 18 Number 1
2. Ho TW, Koh CK. Small-Bowel Obstruction Secondary to Bezoar Impaction: A Diagnostic Dilemma. *World Journal of Surgery.* 2007; 31:1072–1078
3. Filipi CJ, et al. An intraluminal surgical approach to the management of gastric bezoars. *Surgical Endoscopy.* 1995; 9:831–833
4. Teng HC, Nawawi O, Ng KL, Yik YI, Phytobezoar: an unusual cause of intestinal obstruction , Biomed Imaging Interv J 2005; 1(1):e4
5. Acar T, Tuncal S, Aydin R. An unusual cause of gastrointestinal obstruction: bezoar. *The New Zealand Medical Journal.* 2003; 116:1173.

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GI IMAGE

A Focal Mass-Forming Autoimmune Pancreatitis Mimicking Pancreatic Cancer with Obstruction of the Main Pancreatic Duct

Ippei Matsumoto · Makoto Shinzeki · Hirochika Toyama · Sadaki Asari · Tadahiro Goto · Isamu Yamada · Tetsuo Ajiki · Takumi Fukumoto · Yonson Ku

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Abstract
Introduction and background Autoimmune pancreatitis (AIP) is a rare disease that closely mimics pancreatic cancer (PC) in its presentation. It is very important for clinicians to distinguish one from the other because their treatment and prognosis are vastly different. Typical radiological imaging findings, in particular observation of diffusely or segmentally narrowed main pancreatic duct (MPD) with an irregular wall by endoscopic retrograde cholangiopancreatography (ERCP), are essential for making the diagnosis of AIP. On the other hand, MPD obstruction is one of the most frequent features on ERCP.
Case report We report a rare case of a patient with focal mass-forming AIP strongly suspected of being PC because of MPD obstruction on ERCP.
Conclusion It was difficult to distinguish PC from AIP with current diagnostic modalities. We will continue to make an effort to distinguish between the two disorders to prevent unnecessary surgery.

Keywords Autoimmune pancreatitis · Pancreatic cancer · Endoscopic retrograde cholangiopancreatography · Main pancreatic duct · Diagnosis

Autoimmune pancreatitis (AIP) is a rare disease that closely mimics pancreatic cancer (PC) in its presentation. It is very important for clinicians to distinguish one from the other because their treatment and prognosis are vastly different. In 2006, the Japanese Pancreas Society proposed clinical diagnostic criteria for AIP based on a combination of clinical, laboratory, imaging, and histological findings.[1] According to these criteria, typical radiological imaging findings, in particular observation of diffusely or segmentally narrowed main pancreatic duct (MPD) with an irregular wall by endoscopic retrograde cholangiopancreatography (ERCP), are essential for making the diagnosis of AIP. On the other hand, MPD obstruction is one of the most frequent features on ERCP.

Here, we report a rare case of a patient with focal mass-forming (FMF) AIP strongly suspected of being PC because of MPD obstruction on ERCP.

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Case Report

A previously healthy 79-year-old man with epigastric pain was admitted to another hospital. After examination, he was diagnosed as having acute pancreatitis due to a tumor of the pancreatic tail. After treatment for pancreatitis, he was referred to our hospital for further examination and treatment of the tumor. The patient's blood chemistry data were within normal limits except for slightly elevated serum pancreatic amylase (264 IU/l) and lipase levels (430 IU/l). Serum levels of CA19-9 and CEA were both normal. Serum gamma globulin and total IgG were normal, but IgG4 was elevated (256 mg/dl). Serum autoantibodies and rheumatoid factor were negative. Dynamic CT imaging revealed an irregular mass measuring 40×23 mm in the tail of the pancreas. The tumor was not enhanced on the arterial phase and slightly enhanced on the portal phase (Fig. 1a).

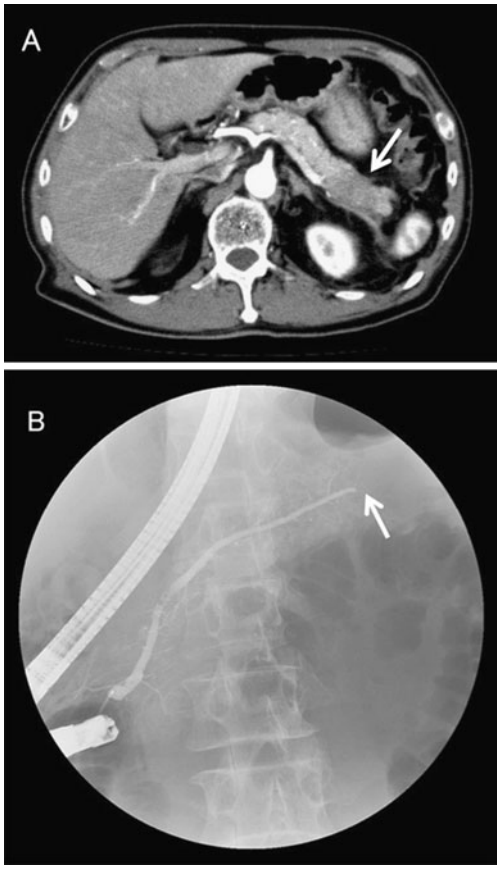

Fig. 1 Dynamic abdominal CT scans in arterial phase showed a low-density mass (*arrow*) measuring 40×23 mm in the tail of the pancreas (**a**). ERCP showed an obstruction of the MPD (*arrow*) at the site of the pancreatic mass (**b**)

The splenic vein was obstructed by the tumor. MRI imaging showed that the intensity decreased in the T1-weighted images of the pancreas and increased in the T2-weighted images. Endoscopic ultrasonography (EUS) revealed a hypoechoic lesion detected in the tail of the pancreas. EUS-guided fine needle aspiration (EUS-FNA), however, did not reveal any cancer cells. 18-Fluorodeoxyglucose positron emission tomography (FDG-PET) showed hot spots of FDG uptake at the site of the pancreatic mass. No extrapancreatic lesions were detected. ERCP revealed an obstruction of the MPD at the site of the tumor (Fig. 1b). Insertion of a guidewire to the distal MPD was impossible. Brush cytology was negative for cancer cells. We suspected PC concomitant with AIP or rather than AIP. The patient underwent a distal pancreatectomy with an uneventful postoperative course.

Gross inspection of the resected specimen revealed a diffusely enlarged and firm pancreas. Histologically, it was remarkable for an intense mixed inflammatory cell infiltrate predominantly composed of lymphocytes and plasma cells, and centered on the pancreatic ducts. The inflammation was associated with significant acinar dropout and parenchymal fibrosis. An obliterative venulitis was noted at the leading edges of the inflammatory cell infiltrate. Immunohistochemical labeling with an antibody to IgG4 revealed large numbers of IgG4-expressing plasma cells.

Discussion

Although diagnosis of AIP has improved thanks to a growing awareness of the condition and proposed diagnostic criteria,[1] there remains no practical strategy to differentiate PC from AIP. One must distinguish between the two disorders to prevent unnecessary surgery or delayed initiation of corticosteroid therapy. However, about 3–5% of patients undergoing pancreatic resection for presumed PC in fact has AIP.[2] Kamisawa et al.[3] reported that 7 of 37 (18.9%) AIP patients had surgery because they were misdiagnosed as having PC or bile duct cancer. In particular, it is very difficult to differentiate between FMF AIP and PC. Chang et al.[4] reported that 8 of 26 (31.8%) AIP patients were FMF AIP who were frequently surgically treated because differentiating FMF AIP from PC was so difficult. Kamisawa et al.[3] also reported that 6 of 17 (35.3%) FMF AIP patients were surgically treated (resection; 3, bypass operation; 3) because PC was suspected.

To obtain images of the pancreatic duct, it is necessary to use ERCP, and additionally direct images taken during the operation or of specimens. Kamisawa et al.[3] reported that the three ERCP features required for AIP diagnosis were (1) a >3-cm-long narrowed main pancreatic duct; (2) skip lesion of the MPD; and (3) maximal upstream MPD diameter of <5 mm. On the other hand, features highly suggestive of PC were a pancreatic low density mass, MPD obstruction, distal pancreatic atrophy, and metastases. There have been four reports of retrospective evaluation of ERCP imaging in AIP patient.[3,5–7] The frequency of MPD obstruction on ERCP in AIP patients was 0–5.9%, whereas in PC patients, it was 35–60%, but only three patients with MPD obstruction have been reported. Although the measurement of serum IgG4 level is useful for differentiating between the two diseases, 10% of PC patients also has elevated IgG4.[8] Moreover, there are a few reports of AIP patients with concomitant PC.[9,10] EUS-FNA is frequently used to rule out PC. However, its accuracy for PC is not perfect (about 70–90%) because some cases of PC are accompanied by chronic inflammation and fibrosis around the mass, so a negative biopsy does not rule out cancer. Diagnosis of AIP by EUS-FNA is difficult because the specimen is too small. Taken together, we cannot exclude the presence of PC in many cases. Further improvement of diagnostic strategies, such as core biopsy techniques, or development of new immunohistological diagnostic criteria from results of cytologic and tissue specimen analyses are needed to avoid unnecessary surgery.

In conclusion, we report an extremely rare case of FMF AIP mimicking PC with MPD obstruction. It was difficult to distinguish PC from AIP with current diagnostic modalities.

References

1. Okazaki K, Kawa S, Kamisawa T et al. Clinical diagnostic criteria of autoimmune pancreatitis: revised proposal. J Gastroenterol 2006; 41: 626–631.
2. Wolfson D, Barkin JS, Chari ST et al. Management of pancreatic masses. Pancreas 2005; 31: 203–217.
3. Kamisawa T, Imai M, Yui Chen P et al. Strategy for differentiating autoimmune pancreatitis from pancreatic cancer. Pancreas 2008; 37: e62–67
4. Chang WI, Kim BJ, Lee JK et al. The clinical and radiological characteristics of focal mass-forming autoimmune pancreatitis: comparison with chronic pancreatitis and pancreatic cancer. Pancreas 2009; 38: 401–408.
5. Horiuchi A, Kawa S, Hamano H et al. ERCP features in 27 patients with autoimmune pancreatitis. Gastrointest Endosc 2002; 55: 494–499.
6. Wakabayashi T, Kawaura Y, Satomura Y et al. Clinical and imaging features of autoimmune pancreatitis with focal pancreatic swelling or mass formation: comparison with so-called tumor-forming pancreatitis and pancreatic carcinoma. Am J Gastroenterol 2003; 98: 2679–2687.
7. Nishino T, Oyama H, Toki F, Shiratori K. Differentiation between autoimmune pancreatitis and pancreatic carcinoma based on endoscopic retrograde cholangiopancreatography findings. J Gastroenterol 2010; 45: 988–996.
8. Ghazale A, Chari ST, Smyrk TC et al. Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. The American journal of gastroenterology 2007; 102: 1646–1653.
9. Inoue H, Miyatani H, Sawada Y, Yoshida Y. A case of pancreas cancer with autoimmune pancreatitis. Pancreas 2006; 33: 208–209.
10. Witkiewicz AK, Kennedy EP, Kennyon L et al. Synchronous autoimmune pancreatitis and infiltrating pancreatic ductal adenocarcinoma: case report and review of the literature. Hum Pathol 2008; 39: 1548–1551.

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MULTIMEDIA ARTICLE

Monoquadrant Robotic Roux-en-Y Gastric Bypass

Subhashini M. Ayloo · Nicolas Christian Buchs · Pietro Addeo · Francesco M. Bianco · Pier C. Giulianotti

Received: 23 February 2011 / Accepted: 10 August 2011 / Published online: 14 September 2011

Abstract
Background While laparoscopic Roux-en-Y gastric bypass is one of the most commonly performed procedures for morbid obesity in the USA, robotic application has been viewed as a valid option. However, the technique is not firmly established with single robotic docking. The objective of this video is to demonstrate the technical details of performing a standardized monoquadrant robotic Roux-en-Y gastric bypass (RRYGB).
Methods Between April 2008 and May 2009, 15 patients meeting the NIH consensus criteria for bariatric surgery underwent a monoquadrant RRYGB. The data were prospectively collected in a dedicated bariatric database and reviewed retrospectively. The patient was positioned supine. Subsequent to creating a 30-ml gastric pouch using a series of endostaplers, the da Vinci robotic system (Intuitive, Sunnyvale, CA) was docked cranially. The robotic arms were attached in the double cannulation fashion. The gastrojejunostomy (GJ) was performed by a robot-assisted hand-sewn double-layered technique, followed by the creation of a jejunojejunostomy (JJ) with an endostapler. The common enterotomy of the JJ was closed with robot-assisted hand-sewn double-layered fashion. The bridge of jejunum between the GJ and JJ was transected separating both anastomoses. The mesenteric defect was not routinely closed at the end of the procedure.
Results There were 13 women and 2 men with a median age of 36 years included in this study. The procedure was successfully accomplished by a monoquadrant robotic technique in 14 cases (93.3%). One case was converted to open procedure because of an intra-operative enterotomy by an endostapler. The mean operative time was 202 min (range 158–353 min). There was no postoperative complication, notably no GI leak or anastomotic bleeding. The median hospital stay was 2.4 days (range 1.7–4 days). The mean weight loss after 1 year was 38.5 kg.
Conclusions This video highlights the feasibility of performing a standardized monoquadrant RRYGB in its entirety with single docking of the da Vinci robotic system.

Keywords Video · Monoquadrant · Single docking · Robotic · Gastric bypass · Obesity

Disclosure Drs. Ayloo, Buchs, Addeo, Bianco, and Giulianotti have no conflict of interest or financial ties to disclose.

Electronic supplementary material The online version of this article (doi:10.1007/s11605-011-1672-x) contains supplementary material, which is available to authorized users.

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LETTER TO THE EDITOR

Intra-Abdominal Pressure and Abdominal Perfusion Pressure Early in Severe Acute Pancreatitis Misses the Forest for the Trees

Charles Joseph Miranda

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I read with interest the results of Ke et al.'s[1] recent study comparing intra-abdominal pressure (IAP) to abdominal perfusion pressure (APP) as a marker of severity in severe acute pancreatitis (SAP) published in this journal in April 2011. The rise in intra-abdominal pressure sometimes observed in severe acute pancreatitis continues to pose a clinical conundrum. Although the presence of abdominal compartment syndrome is usually treated with a decompressive laparotomy,[2] advocating the same in acute pancreatitis would run contrary to the dogma that operations early in acute pancreatitis are associated with an increase in morbidity and mortality.[3,4]

The study purports to judge the efficacy of IAP and APP early in the onset of the disease as predictors of outcome. The authors agree that infection is a significant contributor to mortality after the early phase of the disease,[5,6] but there is no evidence to indicate that this can be adequately detected 72 h after admission.

While I laud Ke et al.'s[1] efforts to clarify the role of raised IAP in SAP, their conclusion that an intra-abdominal pressure >15 mmHg in SAP, within 72 h of admission, which is a valuable predictor of the outcome in SAP, should be approached with caution. In the absence of the consort data, we do not have information on patients who met the entry criteria but declined or were unable to participate in the study. Furthermore the definition of what constituted an infection was not stated (for example, Systemic Inflammatory Response Syndrome, positive blood cultures, fine needle aspiration and culture, or computed tomography evidence of free gas in the presence of pancreatic necrosis).

Even with the limitations described, demonstrating causality between the presence of raised IAP/reduced APP and the onset of infection requires the results from prospective controlled trial (i.e. incidence of infection in SAP patients with an IAP>15 is greater than the incidence of infection in SAP patients with an IAP<15). As it stands, it could be argued that a raised IAP in SAP is an epiphenomenon of the underlying disease process.

References

1. Ke L, Ni HB, Tong ZH, Li WQ, Li N, Li JS (2011) Intra-abdominal Pressure and Abdominal Perfusion Pressure: Which is a Better Marker of Severity in Patients with Severe Acute Pancreatitis. J Gastrointest Surg 15(8):1426-32
2. Chiara O, Cimbanassi S, Boati S, Bassi G (2011) Surgical management of abdominal compartment syndrome. Minerva Anestesiol 77 (4):457–62.
3. Tsiotos G, Luque-de Leon E, Sarr M. Long-term outcome of necrotizing pancreatitis treated by necrosectomy. Br J Surg. 1998;85(12):1650–3.
4. Will U, Wegener C, Graf K, Wanzar I, Manger T, Meyer F. Differential treatment and early outcome in the interventional endoscopic management of pancreatic pseudocysts in 27 patients. World J Gastroenterol. 2006;12(26):4175–8.
5. Büchler MW, Gloor B, Müller CA, Friess H, Seiler CA, Uhl W. Acute necrotizing pancreatitis: treatment strategy according to the status of infection. Ann Surg. 2000;232(5):619–26.
6. Lytras D, Manes K, Triantopoulou C, Paraskeva C, Delis S, Avgerinos C, et al. Persistent early organ failure: defining the high-risk group of patients with severe acute pancreatitis? Pancreas. 2008;36 (3):249–54.

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LETTER TO THE EDITOR

Response to Letter to the Editor: Intra-abdominal Pressure and Abdominal Perfusion Pressure Early in Severe Acute Pancreatitis Miss the Forest for the Trees

Lu Ke · Zhi-hui Tong · Hai-bin Ni · Wei-qin Li · Ning Li · Jie-shou Li

Received: 15 August 2011 / Accepted: 14 September 2011 / Published online: 29 September 2011

To the Editor:

Thanks to Dr. Miranda's recent letter and thoughtful comments regarding our article. We really appreciate and agree with his suggestion that the cutoff level of intra-abdominal pressure (IAP, 15 mmHg for the maximal value and 12 mmHg for the mean value) demonstrated from the ROC curves[1] should be cautiously used; however, there are several important issues that need to be clarified.

We agree with Dr. Miranda's statement that pancreatic infection could not be adequately detected 72 h after admission. In fact, secondary pancreatic infections we mentioned in this study were mostly diagnosed 2 weeks after the onset of severe acute pancreatitis (SAP), which is in accordance with previous studies and the natural course of SAP.[2] Moreover, we have stated our standards for the diagnosis of pancreatic infection in the Methods section, which is "positive findings in bacterial culture of abdominal fluid and temperature increased consistently." The samples were obtained through imaging-guided aspiration or drainage, and/or imaging-guided fine needle aspiration, and/or surgical drainage. Consistently increased temperature was confirmed in patients whose body temperatures were greater than 38°C for three consecutive days. In the article, we did not describe the criteria in detail for concision.

It is really true that a prospective controlled trial with a large sample size will make great sense. Actually, there were several studies regarding the different outcomes between SAP patients with or without raised IAP like what Dr. Miranda suggested in the letter had been published, some of which used the reference level (15 mmHg) we demonstrated in our article.[3,4] However, these studies including ours were all single-center ones with limited sample size. We do agree that causality between increased IAP and the onset of infection or other important complications need to be further confirmed by a large, multi-center, prospective study.

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References

1. Ke L, Ni HB, Tong ZH, Li WQ, Li N, Li JS. Intra-abdominal Pressure and Abdominal Perfusion Pressure: Which is a Better Marker of Severity in Patients with Severe Acute Pancreatitis. *J Gastrointest Surg* 2011;15(8): 1426–1432.
2. Uhl W, Warshaw A, Imrie C, Bassi C, McKay CJ, Lankisch PG, Carter R, Di Magno E, Banks PA, Whitcomb DC, Dervenis C, Ulrich CD, Satake K, Ghaneh P, Hartwig W, Werner J, McEntee G, Neoptolemos JP, Buchler MW. IAP Guidelines for the Surgical Management of Acute Pancreatitis. *Pancreatology* 2002;2(6): 565–573.
3. Al-Bahrani AZ, Abid GH, Holt A, McCloy RF, Benson J, Eddleston J, Ammori BJ. Clinical relevance of intra-abdominal hypertension in patients with severe acute pancreatitis. *Pancreas* 2008;36(1): 39–43.
4. De Waele JJ, Hoste E, Blot SI, Decruyenaere J, Colardyn F. Intra-abdominal hypertension in patients with severe acute pancreatitis. *Crit Care* 2005;9(4): R452-457.

J Gastrointest Surg (2011) 15:2302
DOI 10.1007/s11605-011-1676-6

RETRACTION NOTE

Retraction Note to: Conservative Management of Acute Appendicitis

A. A. Malik · S.-u. Bari

Published online: 26 October 2011

Retraction to: J Gastrointest Surg
DOI 10.1007/s11605-009-0835-5

The editors of the *Journal of Gastrointestinal Surgery* as well as the SSAT Board of Directors have retracted the article Malik, A.A. & Bari, S.U. Conservative management of acute appendicitis. *J Gastrointest. Surg* **13**, 966–970 (2009) since significant portions of the article were published earlier in the following articles:

Eriksson,S. & Granstrom,L. Randomized controlled trial of appendectomy versus antibiotic therapy for acute appendicitis. *Br J Surg* **82**, 166–169 (1995).

Horton,M.D., Counter,S.F., Florence,M.G. & Hart,M.J. A prospective trial of computed tomography and ultrasonography for diagnosing appendicitis in the atypical patient. *Am J Surg* **179**, 379–381 (2000).

The online version of the original article can be found at http://dx.doi.org/10.1007/s11605-009-0835-5.

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