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Cystic Neoplasia of the Pancreas: Pathology and Biology

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Abstract In contrast with solid tumors, most of which are invasive ductal adenocarcinoma with dismal prognosis, cystic lesions of the pancreas are often either benign or low-grade indolent neoplasia. Those that are mucinous, namely, intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs), constitute the most important category, not only because they are the most common, but more importantly because they have well-established malignant potential, representing an adenomacarcinoma sequence. While many are innocuous adenomas — in particular, those that are small and less complex, and in the case of IPMN, those that are branch-duct type are more commonly benign, some harbor or progress into in situ or invasive carcinomas. For this reason, pancreatic cysts with mucinous differentiation ought to be evaluated carefully, preferably by experts familiar with subtle evidences of malignancy in these tumors. In the past few years, the definition of IPMNs and MCNs has become more refined. The presence of ovarian-type stroma has now almost become a requirement for the diagnosis of MCN, and when defined as such, MCN is seen almost exclusively in women of perimenopausal age group as thick-walled multilocular cystic mass in the tail of the pancreas in contrast with IPMN which afflicts an elder population, both genders in almost equal numbers, and occur predominantly in the head of the organ. While mucinous lesions have well-established pre-malignant properties, most of the entities that fall into the nonmucinous true cyst category such as serous tumors, lymphoepithelial cysts, congenital cysts, and squamoid cyst of ducts have virtually no malignant potential. In contrast, the rare cystic tumors that occur as a result of degenerative/necrotic changes in otherwise solid neoplasia such as the rare cystic ductal adenocarcinomas, cystic endocrine neoplasia, and most importantly, solid-pseudopapillary tumor (SPT) in which cystic change is so common that it used to be incorporated into its name ("solid-cystic," "papillary-cystic") are malignant neoplasia, albeit variable degrees of aggressiveness. SPT holds a distinctive place among pancreatic neoplasia because of its highly peculiar characteristics, undetermined cell lineage, occurrence almost exclusively in young females, association with β-catenin pathway, and also by being a very low-grade curable malignancy. In conclusion, cystic lesions in the pancreas constitute a biologically and pathologically diverse category most (but not all) of which are either benign or treatable diseases; however, a substantial subset, especially mucinous ones, has malignant potential that requires careful analysis.

This paper was originally presented as part of the SSAT/AGA/ASGE State-of-the-Art Conference on Management of Cystic Lesions of the Pancreas at the SSAT 48th Annual Meeting, May 2007 in Washington, DC. The other articles presented in the conference were Scheiman JM, Management of Cystic Lesions of the Pancreas: Diagnosis: Radiographic Imaging, EUS and Fluid Analysis; Tseng JF, Management of Serous Cystadenoma of the Pancreas; Fernández-del Castillo C, Mucinous Cystic Neoplasms; and Farnell MB, Surgical Management of Intraductal Papillary Mucinous Neoplasm (IPMN) of the Pancreas.

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Cystic lesions of the pancreas are relatively rare but constitute an important category in this organ because, interestingly but perhaps not too surprisingly, most of these are either benign or indolent neoplasms with a prognosis significantly better than the dismal outcome of ductal adenocarcinoma.[1]

The relative frequencies of cystic lesions in the pancreas vary substantially from institution to institution, from primary versus tertiary care centers, and presumably even from region to region.[1,12] The lesions below are discussed in an order that reflects both the frequency and clinical significance of different cystic lesions in this author's experience based upon a large surgical and autopsy

database from an institution that serves both as a primary and tertiary care center, as well as a consultation database. The estimated relative frequency of cystic lesions is accordingly shown in Table 1.

True Cysts

Cystic Neoplasia of "Mucinous" Type

Intraductal papillary mucinous neoplasms (IPMNs) are characterized by cystic dilatation of pancreatic ducts in which an intraductal proliferation of neoplastic mucin-producing cells is usually arranged in papillary pattern.[4,10,13–17] The papillae may range from microscopic to large nodular masses. Mucin production by the neoplastic cells is usually associated with intraluminal mucin secretion, which leads to cystic dilatation of the ducts, and at times, to mucin extrusion from the ampulla of Vater, a finding that is virtually diagnostic of an intraductal papillary mucinous neoplasm. Clinically, patients with an intraductal papillary mucinous neoplasm usually present in the seventh to eighth decade of life with nonspecific abdominal symptoms, although in some, a history of pancreatitis is noted.

In some cases, the intraductal papillary mucinous neoplasm primarily involves the main pancreatic duct, and in others, the branch ducts; the latter is predominant particularly in those that arise in the uncinate process. The *branch-duct type* is usually smaller and typically proves to be adenoma on microscopic examination, thus more amenable to conservative therapy than the main-duct type.[17,16]

Microscopically, the cystically dilated ducts of intraductal papillary mucinous neoplasms contain mucin-producing cells with various degrees of atypia.[4] Papillae with three distinct morphologic patterns have been discerned: (1) intestinal, morphologically similar to that of colonic villous adenomas of the colon and express CDX2 and MUC2; (2) pancreatobiliary, more complex and are lined by cuboidal cells with prominent nucleoli and express MUC1; and (3) gastric with gastric foveolar appearance. Intraductal oncocytic papillary neoplasm, characterized by exuberant, complex, delicate papillae lined by oncocytic cells, and intraepithelial lumina, is considered a subset of IPMN by some authors, but a distinct variant by others.

Intraductal papillary mucinous neoplasms need to be distinguished both conceptually and practically from the smaller (microscopic) lesions of the pancreatic ducts known as pancreatic intraepithelial neoplasia (PanIN),[10] and from nonneoplastic localized duct-ectasia (Kimura lesions and retention cysts). The separation of intraductal papillary mucinous neoplasms and PanIN is based primarily on size. Intraductal papillary mucinous neoplasms are larger (>1 cm) and usually form a macroscopic and/or radiologic detectable mass.[10]

As advocated by the World Health Organization, noninvasive intraductal papillary mucinous neoplasms are graded as adenoma (no or low-grade dysplasia), borderline-tumor (moderate dysplasia), and in situ carcinoma. Invasive adenocarcinoma, which is seen in approximately 30% of resected cases is usually either of the colloid or tubular (ordinary ductal) types.[5] The former has been found to have indolent behavior, whether it is associated with IPMN or not.[5]

The overall 5-year survival for patients with a resected intraductal papillary mucinous neoplasm is >70%. This is not surprising, considering that most intraductal papillary mucinous neoplasms are noninvasive. It is interesting to note that some patients with surgically resected noninvasive intraductal papillary mucinous neoplasms later develop recurrence and some even develop metastases. These cases most likely represent multifocal disease or undersampling (by either the surgeons or pathologists).

Another problematic area in the management of intraductal papillary mucinous neoplasms is the status of surgical resection margins. In general, it is felt that the presence of carcinoma at the surgical margins bears too high a risk for the patient, and further therapy is probably warranted for these patients, if clinically feasible. On the other hand, the presence of "adenomatous" epithelium at the pancreatic parenchymal margin is probably negligible (based on what we extrapolate from the branch-duct literature);[16] however, the relative risk of later developing an invasive carcinoma in these patients is also rather difficult to determine.

Mucinous cystic neoplasms share various features with IPMNs.[18,19] In contrast with IPMNs, which are cystic

Table 1 Estimated Relative Frequency of the Cystic Lesions in the Pancreas

Frequency of cystic lesions in the pancreas		
No lining	"Pseudocyst": pancreatitis-associated	30
True lining	Mucinous	
	Intraductal papillary mucinous neoplasm	20
	Mucinous cystic neoplasm	10
	Serous	20
	Others (squamous, acinar, endothelial…)	<5
Degenerative/necrotic change in a neoplasm	Solid-pseudopapillary neoplasm	5
	Cystic ductal adenocarcinoma	<5
	Others (endocrine, mets., etc.)	<5

Numbers reflect approximate percentages.[1,12]

dilatations of preexisting ducts, MCNs presumably form de novo cystic tumors, and they are characterized by an underlying ovarian type of stroma. Mucinous cystic neoplasms have distinctive clinicopathologic characteristics: they are seen almost exclusively in perimenopausal females (mean age, 48 years; male to female ratio, <1/20; only rare male patients with ovarian stroma are on record) and the neoplasm is most often located in the tail of the pancreas. Macroscopically, MCNs are composed of large multilocular cysts. The cysts have thick fibrotic walls. Unless there is fistula formation, the cysts do not visibly communicate with the pancreatic ductal system. MCNs are now defined by the presence of a distinctive stroma (referred as ovarian-like) around the cysts. This stroma is similar not only morphologically to ovarian cortex, but it is also hormone-sensitive, often admixed with luteal-type cells and it regularly expresses progesterone receptors.

As in IPMNs, there is a wide range of cytologic and architectural atypia in mucinous cystic neoplasms.[16,18,19] Carcinomatous foci may be patchy and difficult to discern macroscopically. This may explain why the studies from the Armed Forces Institute of Pathology (AFIP), a referral center where the diagnosis is generally based on a few selected slides submitted for consultation, have failed to demonstrate that dysplasia and even the presence of an invasive cancer are prognostically relevant. For that reason, the authors from the AFIP regard all MCNs,[19] regardless of their grade, as "low-grade malignant neoplasms", i.e., cystadenocarcinoma. However, more recently,[19] a number of studies from other authors who performed more complete examination and extensive sampling of the neoplasms concluded that grade does accurately predict the outcome. It is also our experience that patients with completely resected mucinous cystic neoplasms without atypia (mucinous cystadenomas) are almost always cured. These tend to be small as well (<3 cm). MCNs with in situ carcinoma or invasion that is limited to the cyst wall often behave benign. Those with more extensive invasive carcinoma, however, in our experience, behave fairly aggressively.

Serous Cystic Neoplasms

Serous cystadenoma is a benign neoplasm composed of uniform cuboidal glycogen-rich epithelial cells presumably originating from centroacinar cell/intercalated duct system and typically forms innumerable small cysts containing serous fluid.[6–9] The sponge-like gross appearance that brings this tumor the name microcystic is diagnostic of the entity. Rare oligocystic and solid variants have also been described. Serous cystadenomas usually present as relatively large masses measuring up to 25 cm, mostly in the body or tail of the pancreas, and are seen predominantly in females (female to male ratio, 3:1). The mean age of the patients is 61 years.

Of interest, serous cystadenomas are often reported to coexist or "collide" with other pancreatic neoplasms and congenital pathologic conditions.

The overwhelming majority of serous cystic neoplasms of the pancreas are benign serous cystadenomas; however, a handful of malignant serous cystic neoplasms, serous cystadenocarcinomas, have been reported. Many of these are morphologically identical to adenomas, raising the question of whether they may have been multifocal tumors rather than metastasis.

Other Rare True Cysts

Squamous-lined cysts,[2] namely lympoepithelial cysts, epidermoid cysts within the intrapancreatic accessory spleen, dermoid cysts, and squamoid cyst of pancreatic ducts are being encountered increasingly with the advances in radiology, mostly as incidental findings.

Other true cystic lesions (lined by epithelial cells) are acinar cell cystadenoma, acinar cell cystadenocarcinoma, congenital cysts, duplication cysts, deverticulae, and others.[1,12]

Degenerative or Necrotic Changes in Solid Tumors

Degenerative necrotic changes with cavity formation have been described virtually in all otherwise typically solid pancreatic tumors.[2] Altogether, this group constitutes an estimated 10% of the pancreatic cysts (Table 1). It is important to recognize this group because, unlike the true cysts, these are often either low-grade malignancies as in the case of *solid-pseudopapillary tumor* or even true carcinomas as in the case of *cystic change in ductal adenocarcinoma*.

Solid-pseudopapillary tumor (SPT) is the most recent name advocated by the WHO for a distinctive tumor type in the pancreas that often presents as a cystic mass,[11] and for this reason was previously referred to as "solid and cystic", "papillary-cystic", and others. The plethora of names used previously for solid-pseudopapillary tumor reflects the enigmatic nature of this neoplasm. It is now known that the cavities that form in solid-pseudopapillary tumors are not "true" cysts (there is no epithelial lining) but rather represent a necrotic/degenerative process containing blood and debris. In the cavity wall, characteristic morphologic features of these neoplasms include round to ovoid cytologically bland uniform cells (mimicking endocrine neoplasia) in pseudopapillary architecture, and showing hyaline globules, grooved nuclei, and zones of macrophages.

Solid-pseudopapillary tumor is one of very few neoplasms in which the direction of differentiation of the neoplastic cells has yet to be established. It is practically unique to the pancreas with no close kindred in any other

organ. Meanwhile, it does not show clear-cut evidence for ductal, acinar, or frank endocrine differentiation. Even the epithelial differentiation is incomplete and dubious; keratins are often focal or weak. Immunohistochemically, the most specific markers are beta-catenin (nuclear) and loss of e-cadherin whereas chromogranin, the most specific endocrine marker, is typically negative.

Another puzzling aspect of solid-pseudopapillary tumors is that they almost exclusively occur in young females (mean age, 25 years; male to female ratio, 1:20). Moreover, the neoplastic cells consistently express progesterone receptors and also the beta form of estrogen receptors, suggesting a role for hormones in the evolution of these neoplasms.

Yet another peculiar aspect of the solid-pseudopapillary tumor is its clinical behavior. More than 80% of solid-pseudopapillary tumors are cured by surgical resection. Metastases (either to the liver or peritoneum, but only seldom to the lymph nodes) may be seen in a small percentage of patients, but even some patients with metastases are typically cured. Seldom has death been attributed to solid-pseudopapillary neoplasm. There do not appear to be any reliable histopathologic criteria to distinguish solid-pseudopapillary tumors that can metastasize from those that do not. Recently, rare cases with anaplastic transformation and aggressive clinical course were reported.

Degenerative cystic change may also occur in other otherwise typically solid tumors of conventional type.[1,3] Rarely, *ductal adenocarcinoma* of the pancreas may undergo cystic change. In our experience, this occurs in less than 1% of the cases, mostly as a necrotic change in the tail carcinomas. *Cystic pancreatic endocrine neoplasms* are rare, constituting 5–10% of pancreatic endocrine neoplasms. The cyst is typically filled with a clear serosanguineous fluid instead of necrotic debris.

In conclusion, cystic tumors constitute an increasingly important category in the pancreas. It is imperative to appreciate the indolent and benign subsets of the entities that belong to this category and to recognize the tumor types that fall into the differential diagnosis of these neoplasms.

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Management of Cystic Lesions of the Pancreas

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Abstract Pancreatic cystic lesions are being increasingly identified. Clinical decision making is driven by the differential diagnosis of the cyst and, for the asymptomatic patient, its likelihood of causing harm. The fundamental issue is whether the cyst is neoplastic, and, if so, what is its risk for malignant degeneration. High-resolution computed tomography provides detailed information about cyst structure and may facilitate differentiation from mucin-secreting tumors of the pancreas. Magnetic resonance imaging has the potential added advantage of determining communication between the cyst and pancreatic duct. Endoscopic ultrasound (EUS) imaging provides additional characterization of the lesion. While EUS morphology alone has limitations regarding definitive diagnosis, aspiration, and characterization of cyst, fluid contents may provide incremental information. Aspiration is well tolerated and safe, with a complication rate of less than 1%. In the absence of a history of pancreatitis, pseudocyst is quite unlikely, and the concern of a cystic neoplasm is paramount. In general, all symptomatic lesions should proceed to appropriate surgical resection. If preoperative characterization of the lesion will change management, EUS + FNA for cytology and fluid analysis (CEA) may characterize the lesion as mucinous, although cytology alone is rarely definitive. For those patients with benign-appearing lesions, such as classic appearance of a serous cystadenoma, observation alone seems appropriate. In some circumstances, EUS + FNA confirmation of a negative cytology and low fluid CEA can further provide evidence to support a monitoring approach and deferral of surgical intervention.

Keywords Radiographic imaging · EUS · Fluid analysis

This paper was originally presented as part of the SSAT/AGA/ASGE State-of-the-Art Conference on Management of Cystic Lesions of the Pancreas at the SSAT 48th Annual Meeting, May 2007, in Washington, DC. The other articles presented in the conference were Adsay NV, Cystic Neoplasia of the Pancreas: Pathology and Biology; Tseng JF, Management of Serous Cystadenoma of the Pancreas; Fernández-del Castillo C, Mucinous Cystic Neoplasms; and Farnell MB, Surgical Management of Intraductal Papillary Mucinous Neoplasm (IPMN) of the Pancreas.

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Background

Cystic lesions in the pancreas are being identified with increasing frequency related to the increased utilization of cross-sectional imaging for the evaluation of unrelated abdominal complaints.

The approach to the patient begins with a detailed history looking for symptoms related to the lesion itself or a related condition such as pancreatitis. Most asymptomatic patients have lesions too small to cause symptoms. Typical symptoms of malignancy are usually absent. Clinical decision making is driven by an understanding of the differential diagnosis of the cyst and, in the case of the asymptomatic patient, its likelihood of causing harm with

intervention. The fundamental issue to be addressed is whether the cyst is neoplastic or not, and if so, what is its risk for malignant degeneration?

Differential Diagnosis

Inflammatory pancreatic cysts (i.e., pseudocysts) are by far the most common cystic lesions. In the past, these non-neoplastic cysts were thought to represent up to 90% of all cysts, but this estimate includes autopsy and radiology series whose data may not be currently relevant.[1] When a cyst arises in a patient with known chronic pancreatitis, the clinical concern of a neoplasm is minimal. When patients present with unexplained pancreatitis for the first time with a cyst, or have only subtle changes of chronic pancreatitis by a sensitive imaging modality such as endoscopic ultrasound (EUS), the clinician should consider whether the cyst may be a neoplasm and the lesion is the cause of the pancreatitis instead of assuming that the cyst is the consequence of the pancreatitis.

Cystic neoplasms of the pancreas represent a diverse collection of tumors with varied malignant potential and clinical presentation. They can be predominantly cystic or can result from cystic degeneration of a solid tumor. Cystic metastatic tumors in the pancreas are rare.[2] Solitary true cysts of the pancreas are felt to be extremely rare, but may need to be considered in the asymptomatic patient with an incidentally found cyst.[3]

Potential Management Strategies

Radiographic Imaging Studies

High-resolution computed tomography (CT) using thin sections with both enhanced and unenhanced technique provides detailed information about cyst structure and may facilitate differentiation from mucin-secreting tumors of the pancreas.[4] Magnetic resonance imaging (MRI) has the potential added advantage of determining communication between the cyst and pancreatic duct. The presence of a central scar is a highly diagnostic feature of serous lesions, but is seen in only one in five of such patients. The role of PET-CT remains under investigation, showing some value for the diagnosis of malignant lesions.

Despite the high quality of contemporary CT and MRI, their ability to distinguish neoplastic from non-neoplastic cystic pancreatic lesions remains imperfect. Because of this, EUS imaging has emerged as a useful tool. Enthusiastic publications on the endosonographic architecture of pancreatic lesions have suggested an accuracy of more than 90% in differentiating benign neoplasms from malignant ones and from non-neoplastic cysts. However, other reports emphasize that the technique is not sufficiently accurate to differentiate benign from malignant lesions, unless there is evidence of a solid mass or invasive tumor.[5,6] The presence of septations and solid components can be observed in both benign and malignant lesions as well as in non-neoplastic cysts. Further, while EUS is quite sensitive in terms of the detection and evaluation of cyst morphology, it is highly operator-dependent.

Typically, EUS of serous cystadenomas demonstrates numerous small cysts with thin-walled septae and possibly calcification in the central septae.[7] Mucinous tumors may be uni- or multilocular and may have macrocystic septations and/or an adjacent mass. IPMN findings at EUS may include mural ductal nodules that demonstrate invasive features used to target fine-needle aspiration (FNA); however, inflammatory changes may compromise staging accuracy. A patulous papilla at ERCP with extruding mucous, along with a pancreatogram showing profound ductal dilation is essentially pathagnomonic for main duct disease. In the side branch variant, ductal communication with multiple cystic lesions is present.

Nonfunctioning islet cell tumors of the pancreas are typically quite large by the time of clinical presentation and may be reliably detected with conventional imaging modalities including transabdominal ultrasound and CT. Useful CT findings include the presence of a hypervascular rim or images of cysts within cysts.[8]

Characterize the Cyst Fluid

While EUS morphology alone has limitations regarding definitive diagnosis, aspiration and characterization of cyst fluid contents has demonstrated somewhat greater utility. EUS aspiration is well tolerated and safe in the hands of an experienced operator, with a complication rate of less than 1% of bleeding, perforation or infection. Most experts use peri-procedural antibiotics to reduce the risk of infection, limit the

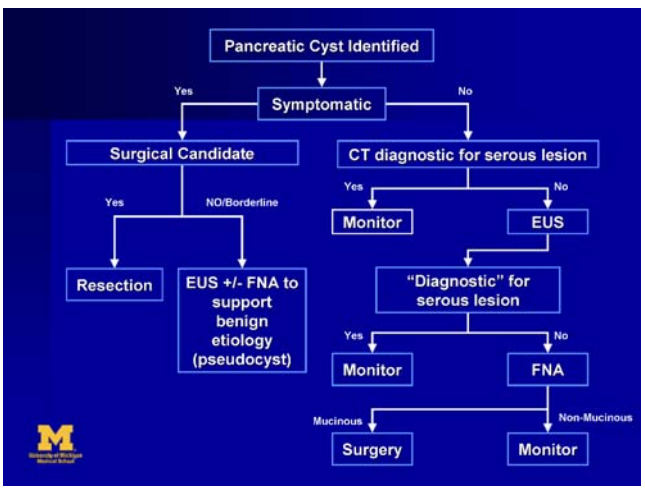

Figure 1 Strategy for pancreatic cystic lesions.

number of needle passes, and remove as much fluid as possible to reduce the risk of bacterial inoculation of the fluid.[9]

Aspirated fluid has been evaluated by cytology and chemical measurements of amylase and tumor markers. Characterization of cyst fluid is best used to differentiate those with malignant potential-mucinous cysts, from serous and non-neoplastic pseudocysts. A large prospective study, the Cooperative Pancreatic Cyst Study, assessed a large number of cyst fluid tumor markers and concluded that CEA was the most useful. Using receiver operator curve analysis, the optimal cyst fluid CEA cutoff of 192 ng/ml was 79% sensitive for differentiating mucinous from non-mucinous lesions. The accuracy of cytology was poor (59%). No combination of tests, including EUS appearance, was more accurate than CEA alone in that study.[10] While CEA levels are most useful at the extremes, fluid amylase is of limited value, and many experts do not even measure it. Recent interest in analysis of the fluid for DNA quality and a panel of mutations has shown promise in differentiation of benign versus malignant lesions; the value of the test to predict the risk of progression requires confirmation in prospective trials.[11]

Characteristic findings on FNA for serous cystadenomas include low tumor CEA and low amylase. Cyst fluid cytology and even operative frozen section have a diagnostic accuracy as low as 50%, unless the characteristic cuboidal cells are seen.[5] In a patient with characteristic morphology on EUS, the incremental value of FNA to confirm clinical impression may have potential value, but should be individualized for each patient given the small but measurable risk of needle aspiration. Consideration should be given to the size of the lesion, as aspirates may be very limited for small lesions. An estimate of the cyst fluid volume can by made from cyst size by the formula $4r^3$, r being the radius of the cyst.[9]

A Suggested Strategy

The approach to the patient with a pancreatic cystic lesion begins with a detailed history[12]—prior pancreatitis or abdominal trauma should be defined (Fig. 1). A review for symptoms of a hormone excess state should be sought. In the absence of a history of pancreatitis, pseudocyst is quite unlikely (but not impossible), and the concern of a cystic neoplasm is paramount. In general, all symptomatic lesions should proceed to appropriate surgical resection. If preoperative characterization of the lesion will change management, EUS ± FNA for cytology and fluid analysis may provide information of diagnostic and prognostic value. For those patients with benign appearing lesions, such as those with a classic appearance of a serous cystadenoma, a decision regarding the patient's willingness to observe the lesion should be developed in collaboration with a pancreatic surgeon. In many circumstances, selected use of EUS ± FNA with cytology and fluid measurement can further provide evidence to support the approach of watchful waiting. Patients can then be carefully monitored with serial examinations to exclude change in size. Watchful waiting clearly represents a trade-off between delayed surgery for unresectable disease and unnecessary surgical morbidity and mortality.

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Management of Serous Cystadenoma of the Pancreas

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Abstract Serous cystadenoma of the pancreas is a diagnosis being entertained with increasing frequency. The histopathologic findings, diagnostic strategy, differential diagnosis, and treatment strategy of these generally benign but sometimes symptomatic lesions are discussed. Based on the available case series, surgical resection should be considered in good-risk patients with symptomatic tumors, with tumors at least 4 cm in maximum diameter, or in whom a more worrisome diagnosis cannot be excluded.

Keywords Serous cystadenoma · Pancreas · Cystic neoplasms

In 1978, Compagno and Oertel[1] first described 34 cases of serous cystadenoma of the pancreas. In the current era, cystic neoplasms of the pancreas, including serous cystadenoma, mucinous cystic neoplasms, intraductal papillary mucinous neoplasms, etc., are increasingly diagnosed. The increased use of radiography and advances in imaging techniques have led to larger numbers of cystic lesions being identified.[2–5] For many years, correctly differentiating between a cystic neoplasm and a pseudocyst has been essential in determining correct treatment of these lesions.[6] More recently, as the divergent natural histories and malignant potentials of the various cystic neoplasms have been elucidated, differentiating between mucinous cystic neoplasms (MCNs), intraductal papillary mucinous neoplasms (IPMNs), serous cystadenomas, and other less common tumors has become crucial.[1,7–9]

This high rate of incidental detection of serous cystadenomas and other cystic lesions of the pancreas makes management challenging. First, accurate diagnosis is crucial to rule out mucin-producing cystic lesions and other pancreatic cystic neoplasms that have malignant potential. Second, even when the diagnosis of serous cystadenoma is certain, until recently, there have been no data that allow one to predict if an asymptomatic tumor will grow sufficiently to cause symptoms during the life span of a given patient. This is an important issue because although the mortality of pancreatic resection has decreased markedly in experienced hands, the morbidity remains high and the consequences of loss of pancreatic tissue are not trivial.

Radiographic imaging is a potent tool with which to diagnose serous cystadenoma of the pancreas, but limitations exist. The most widely applicable radiographic test at the current time is helical computed tomography (CT) scanning with thin cuts through the pancreas, which often can provide assistance in the differentiation between serous and mucinous neoplasms. Classic CT findings suggestive of serous cystadenoma include a central scar with the "honeycomb" appearance of microcysts found in the more common microcystic variant of serous cystadenoma. However, the rarer oligocystic or macrocystic variants may be more difficult to differentiate from mucinous tumors based

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on CT findings.[10–14] Other modalities such as magnetic resonance image and magnetic resonance cholangiopancreatography may be more useful in differentiating mucinous tumors such as IPMT from serous cystadenoma.[3] In blinded studies, the ability of radiologists to accurately distinguish serous neoplasms has ranged from 23 to 82%, although component cysts smaller than 2 cm have been found to be significantly associated with serous tumors, and peripheral tumor calcification has been found to be significantly associated with mucinous tumors.[15–18] In the near future, additional techniques including F-18-fluorodeoxyglucose positron emission tomography may help distinguish benign and malignant pancreatic cystic lesions.[19,20]

Endoscopic ultrasound has been proposed as an ideal imaging technique for pancreatic cystic lesions.[21–23] Ultrasound can readily characterize cysts, and high resolution imaging of the pancreas can be achieved through endoscopic means. Needle aspiration of pancreatic cystic lesions can be used to obtain fluid for cytology, and cyst fluid tumor markers can be used for diagnostic purposes. Cyst fluid carcinoembryonic antigen values are universally low in serous cystadenomas, trend higher in mucinous lesions, and are generally even more elevated in mucinous cystadenocarcinomas.[23,24] Although cytologic samples diagnostic of serous cystadenoma are obtained in less than 50% of cases, when such samples are positive, the specificity is high. Clinical acumen and radiologic testing can often be used to differentiate cystic neoplasms from pseudocysts. However, when the operative or non-operative plan hinges upon differentiating a serous from a mucinous cystic neoplasm, cyst fluid analysis via endoscopic ultrasound or CT-guided aspiration and biopsy is particularly useful.[25]

As opposed to pancreatic pseudocysts, serous and mucinous cystic tumors have an epithelial lining. The epithelium of IPMNs and MCNs is made up of columnar mucin-producing epithelium. However, MCNs, which occur almost exclusively in women, are devoid of communication with the ductal system and supported by ovarian-type stroma, whereas IPMNs arise in the main pancreatic duct or its major branches. In contrast, serous cystic tumors are lined by an inconspicuous single layer of either cuboidal or flattened cells. The cytoplasm of the cells is either clear or eosinophilic, and the nuclei are usually centrally located, small, and hyperchromatic. Mitoses are conspicuously absent in serous cystic tumors.

Most serous cystadenomas are microcystic, forming a honeycomb-like appearance, but macrocystic variants have been described frequently in the literature.[11,12,14] The vast majority of these tumors are benign, with only a handful of case reports of serous cystadenocarcinomas.[26–31] Operative resection is generally carried out for symptoms, large size, or the inability to distinguish a serous cystic neoplasm from a mucinous lesion, which has greater malignant potential. Some authors have recommended resection for all cystic neoplasms of the pancreas,[27,28,32] whereas others advocate a more selective approach.[5,10]

In 2005, we reviewed 106 patients at the Massachusetts General Hospital presenting with serous cystadenoma of the pancreas from 1976 to 2004.[33] Mean age at presentation was 61.5 years. Seventy-five percent of patients were female. Interestingly, the mean age of males was >7 years greater than that of females, and males had larger tumors at presentation, suggesting a delay in diagnosis in men. No cystadenocarcinomas were identified in the MGH series. Forty-seven percent of patients were asymptomatic. The most common symptoms were abdominal pain (25%), fullness/mass (10%), and jaundice (7%). Mean tumor diameter was 4.9±3.1 cm, which did not vary by location. Tumors <4 cm were less commonly symptomatic than tumors ≥4 cm (22 vs 72%, $p<0.001$). Twenty-four patients had serial radiography, and tumor growth curves were calculated. The median growth rate in the patients who had serial radiography was 0.60 cm/year. For tumors <4 cm at presentation ($n=15$), the rate was 0.12 cm/year, whereas for tumors ≥4 cm ($n=9$), the rate was 1.98 cm/year ($p=0.0002$).

The reasons why larger tumors appear to have a faster rate of growth than smaller tumors remain unclear. Whether serous cystadenomas that present at and grow to larger dimensions differ biologically, and perhaps bear a greater propensity for malignant degeneration[27] compared to their smaller counterparts, remains an open question.

The following guidelines may be useful to the clinician with a suspected serous cystadenoma of the pancreas. Patients should be diagnosed with serous cystadenoma based upon a compatible clinical presentation and characteristic radiographic evidence. When this concordance is not present, endoscopic ultrasound should be utilized.

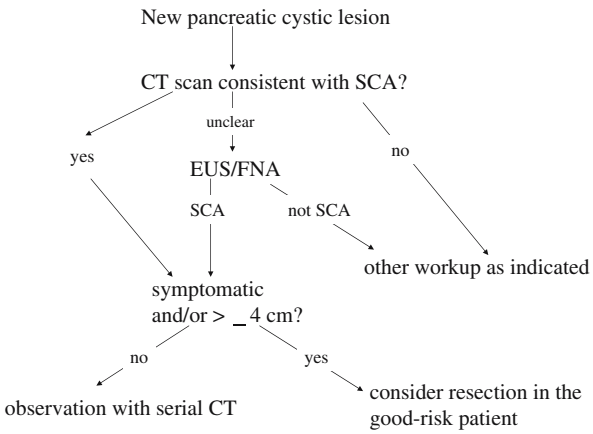

Figure 1 Diagnostic and management algorithm for suspected serous cystadenoma of the pancreas (after Tseng et al.[33]) sCA (serous cystadenoma).

Patients with the above criteria who are asymptomatic and have tumors less than 4 cm in maximal diameter are candidates for non-operative management, with clinical follow-up and serial imaging (Fig. 1). The interval between serial imaging is subject to debate, but 2 years may be reasonable. Patients with symptoms attributable to their tumors, patients in whom a mucinous or other potentially malignant tumor cannot be comfortably excluded, and patients with serous cystadenomas measuring 4 cm or more in maximal diameter who are reasonable surgical candidates should be offered resection. This recommendation to proceed with surgery in asymptomatic patients with larger tumors is based both on their more rapid growth rate as well as in a more than threefold increase in the likelihood of developing symptoms.

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Mucinous Cystic Neoplasms

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Abstract Mucinous cystic neoplasms of the pancreas are uncommon tumors of the pancreas that occur predominantly in middle-aged women and almost exclusively in the body and tail of the pancreas. They are lined by a mucinous epithelium that can exhibit varying grades of dysplasia and are surrounded by a characteristic ovarian-like stroma. Surgery is the treatment of choice, and prognosis is excellent in the absence of invasive carcinoma.

Keywords Mucinous cystic neoplasm · Ovarian stroma · Intraductal papillary mucinous neoplasm

Introduction

The initial description of mucinous cystic neoplasms (MCN) as a distinct entity affecting the pancreas was made by Compagno and Oertel in 1978.[1] They described them as large, septated, thick-walled cysts, filled with mucoid and occasionally hemorrhagic material, and occurring almost exclusively in the pancreatic body and tail of middle-aged women. The cysts were lined by an epithelium composed of tall mucin-secreting cells with various degrees of atypia. They also noted the presence of a dense cellular ovarian-type stroma in the outer layer, and contrasted MCNs with microcystic or serous cystadenomas,[2] describing the former as lesions with overt or latent malignancy and the latter as benign tumors. This was an important observation because, prior to that, pancreatic neoplastic cysts were simply referred to as cystadenomas and cystadenocarcinomas.

However, the presence of ovarian stroma was not considered a specific diagnostic criterion for MCNs, and as a consequence, for many years, MCNs and intraductal papillary mucinous neoplasms (IPMNs) were frequently confused.[3–6] Although the World Health Organization (WHO) defined and distinguished between IPMNs and MCNs as early as 1996 and emphasized the presence of ovarian stroma in MCNs,[7] it was not until recently, at a consensus conference held in Sendai, Japan, that the International Association of Pancreatology put forward guidelines requiring the presence of ovarian stroma to establish the diagnosis of MCNs.[8]

Using this criterion, we recently put together the surgical experiences of the Massachusetts General Hospital and the University of Verona.[9] Surgical specimens of all mucin-producing cystic lesions of the pancreas were carefully reviewed, and 163 patients who were identified with only lesions that had both an ovarian-like stromal layer and no communication with the pancreatic ductal system were included. These were mostly women (95%) and the MCNs were almost exclusively located in the body or tail of the pancreas (97%). None of the tumors were multifocal. The median age at the time of diagnosis was 45 years, with a range of 16 to 82. Twenty-five percent of tumors were incidentally discovered, 9% presented with acute pancreatitis (presumably from compression of the pancreatic duct) and

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the remaining with vague symptoms including mild abdominal pain. One hundred and eighteen of the tumors (72%) were classified as adenomas, 17 (10.5%) as borderline neoplasms, 9 (5.5%) as having carcinoma in-situ, and 19 (12%) as invasive carcinomas. This age and gender distribution, as well as the tumor location, is strikingly similar to those described in other published large series of MCNs where ovarian stroma has been a requirement for diagnosis[10–12]; the frequency of invasive cancer within these series has ranged from 7 to 36%.

By contrast, series of MCNs where ovarian-like stroma is not a requirement for diagnosis involve older patients, a higher proportion of males, and an even distribution throughout the pancreas,[3–6] which likely indicates inclusion of patients with branch duct IPMNs that appear to have a different biological behavior.[13]

In our study we found that malignant MCNs (both in-situ and invasive carcinoma) were significantly larger than benign ones (80 vs. 45 mm) and were 16 times more likely to harbor nodules (64 vs. 4%).[9] All MCNs with cancer were either greater than 40 mm in size or had nodules.

Management of Mucinous Cystic Neoplasms

A MCN should be suspected whenever a single cyst is seen by CT or MRI in the body or tail of the pancreas of a young or middle-aged woman. The wall of the cyst may appear thick, and an MRCP should show no communication with the pancreatic ductal system. If the demographics of the patient do not fit this pattern, or if the radiologic imaging is equivocal, then an endoscopic ultrasound (EUS) with aspiration of the cyst contents and biopsy of the wall is warranted. For an MCN, the EUS may show septations or nodules within the cyst, and the aspirate is characteristically thick and mucoid, with an elevated CEA level and a normal amylase. Cytology of the centrifuged cyst fluid or of the cyst wall may demonstrate mucinous epithelial cells. The main differential diagnosis is with unilocular serous cystadenomas (which have a low CEA in the fluid), solid pseudopapillary neoplasms (which often show necrotic debris within the cyst cavity), and branch duct IPMNs, which communicate with the ductal pancreatic system and therefore generally have an elevated cyst fluid amylase.

Surgical excison is indicated for all MCNs because extensive histological sampling (and, thus, certainty of benignancy) cannot be achieved until the tumor is excised. Whereas the risk of malignancy in tumors less than 4 cm and without nodules is low, the current thinking is that the majority, if not all of these tumors, will evolve into cancer if left untreated. This concept is based on epidemiological data showing that patients with invasive cancer within a MCN are older and have larger tumors.[3,6,10] This was also the case in our series, where patients with invasive mucinous cystadenocarcinoma had an average age of 55 years, compared to 44 years in the patients with noninvasive MCNs (adenoma, borderline tumors, and carcinoma in-situ).[9] Further evidence to this progression is derived from studies on the molecular pathology of these lesions indicating a stepwise increase in the frequency of K-ras and p53 mutations in a manner similar to that seen in the adenoma–carcinoma sequence of colon cancer.[14] If an expectant approach were to be followed, frequent surveillance with either CT or MRI would be required. Given the mean age of presentation of 45 years, this would not be cost-effective or practical.

Because most MCNs will be located in the body and tail of the pancreas, the appropriate operation is a distal pancreatectomy. A laparoscopic approach is a very good alternative for small or even medium-sized MCNs located in the tail of the pancreas,[15] but it is very important not to rupture the cyst during the procedure because spillage of contents could potentially lead to tumor spread. In addition, the cyst should be removed intact (i.e., not morselized) so the pathologist can do an appropriate examination. It may be reasonable to preserve the spleen in small or medium-sized lesions. There is no evidence to indicate that excision of lymph nodes beyond those immediately adjacent to the pancreas is necessary or beneficial even if there is a high suspicion of malignancy. In our series, none of the 19 cases with invasive carcinoma in our series had positive lymph nodes,[9] and a review of the literature failed to identify a single case with lymph node metastases. A similar biology is seen in ovarian MCNs, were the frequency of nodal metastases is less than 10%.[16,17] For MCNs that are located in the proximal body of the pancreas, close to the neck, a middle pancreatectomy is an option,[18] whereas some are amenable to enucleation.

Results of surgical treatment are excellent. Four recent large series, including ours, show that as long as there is no invasive carcinoma present within the specimen, the cure rate is 100%.[3,6,9,10] Because MCNs are never multifocal, there is no need for long-term surveillance after complete resection of noninvasive tumors. For patients with invasive mucinous cystadenocarcinoma, the 5-year survival in our series was 57%[9]; in other series, it has ranged from 30 to 63%.[3–6,10–12] There are no data on adjuvant treatment for these lesions.

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Surgical Management of Intraductal Papillary Mucinous Neoplasm (IPMN) of the Pancreas

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Abstract Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is characterized by papillary growths within the pancreatic ductal system that are at risk for undergoing malignant transformation. Main duct IPMN carries a significant risk of malignancy, and operation is recommended regardless of the presence of symptoms. The risk of malignancy is much lower for side branch IPMN, and current evidence suggests that, in the absence of symptoms, mural nodules, positive cytology, or cyst size less than 3 cm, observation is warranted. When operation is indicated, targeted pancreatic resection with frozen-section analysis of margins is recommended. Pancreatoduodenectomy or distal pacreatectomy is appropriate for the majority. Only in about 10% of patients is the disease so diffuse at presentation that total pancreatectomy is necessary. Survival following pancreatic resection for noninvasive IPMN is excellent. The risk of recurrence following pancreatic resection for invasive IPMN is significant. Surveillance is warranted both for patients subjected to pancreatic resection and for those under observation with side branch IPMN. Much is yet to be learned regarding this neoplasm, and surgical management remains in evolution.

Keywords Intraductal papillary mucinous neoplasm · Surgical treatment · Malignant transformation

The appropriate surgical treatment for intraductal papillary mucinous neoplasm (IPMN) remains unclear because both natural history and long-term postoperative follow-up are not as yet available. That said, current evidence suggests that if untreated, IPMN will follow the dysplasia–carcinoma sequence undergoing malignant transformation, invasion, and ultimately distant spread, albeit at a rate of progression which is unknown. The operative strategy, therefore, is designed to eradicate premalignant neoplasia, ameliorate symptoms caused by ductal obstruction, and to perform potentially curative resection in those with malignant transformation.

The World Health Organization has classified IPMN into four categories based upon the degree of epithelial dysplasia: adenoma, borderline, carcinoma in situ, or invasive carcinoma.[1] From a morphologic point of view, IPMN may involve the main pancreatic duct, a side branch, or both. The latter is termed "mixed" type.

A consensus conference was convened by the International Association of Pancreatology, and its recommendations were published in 2006.[2] The consensus panel reviewed collected series of patients with IPMN involving the main pancreatic duct (IPMN-M) and found that the majority either had carcinoma in situ or invasive cancer, while for collected series of patients with side branch disease (IPMN-BR), the risk of malignancy was much lower. The implications of their observations regarding the prevalence of malignancy in IPMN-M and IPMN-BR will be addressed subsequently.

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The preoperative diagnosis and classification of IPMN is based upon imaging and cyst fluid analysis obtained preoperatively. Diagnostic investigations that are useful include abdominal computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance imaging (MRI), and magnetic resonance cholangiopancreatography. Endoscopic ultrasound (EUS) is also very useful and has the added benefit of enabling fine needle aspirate of the cyst fluid to analyze for cytology, amylase, and tumor markers. The diagnosis of IPMN hinges upon the demonstration of papillary growths in the branch ducts, the main duct, or both. Duct size >1 cm is highly suggestive of main duct disease. Cyst communication with the pancreatic ductal system strongly supports the diagnosis of IPMN. Communication can be delineated with ERP; however, viscid mucin may result in nonopacification of a cyst when communication is present. EUS is very useful in demonstrating communication but, of course, is operator dependent. EUS with cyst fluid analysis for cytology, extracellular mucin, and carcinoembryonic antigen (CEA) level may be helpful in decision-making. We have found cytology and mucin staining to be only occasionally useful (only when positive) and rely on CEA cyst fluid levels. With the threshold of 192 ng/mL, serum CEA is 79% accurate in the diagnosis of mucin-producing cystic neoplasm.[3,4]

Histopathologic classification of IPMN into two subtypes has been recently reported: gastric type and intestinal type.[5] The former was mostly branch duct IPMN, the latter main duct IPMN. Distinct histopathologic features and mucin immunohistochemical profiles of these two subtypes suggest differing biologic pathways. Also, telomerase activity in pancreatic juice may be an indicator of malignancy.[6] Mucin and telomerase assessment are of great interest but are not widely available. At this time, morphologic classification based upon imaging and cyst fluid analysis using standard techniques dictate management strategy.

Which patients with IPMN should undergo surgery? Based upon current thinking, patients with IPMN-M or mixed-duct-type IPMN have a risk of malignancy of approximately 70%, and fit candidates should be offered resection regardless of the presence of symptoms.[7–15] On the other hand, the risk of malignancy in patients with IPMN-BR is much lower.[7–14] The factors that correlate with malignancy in side branch IPMN include the presence of symptoms, mural nodules, and cyst size >3 cm. In the absence of these three criteria, observation may well be indicated.

In an effort to determine if the consensus indications for resection (CIR) predict malignancy, we analyzed 147 patients with IPMN-BR.[16] Sixty-six underwent surgical resection at diagnosis, and initially 81 were followed conservatively, of whom 11 ultimately underwent operation. Malignancy was present in 9/61 (15%) with CIR and 0/16 without CIR ($p=0.1$). We concluded that the suggested CIR identify all patients with malignancy, but with low specificity. In the short term, it is reasonable to follow IPMN-BR without CIR. However, because only 15% who had an indication for surgery had cancer, there is a need for a continued search for better predictors of malignancy in IPMN-BR.

The morphologic pattern of duct dilation is dependent upon both tumor location and mucus production. Four patterns have been recognized: (1) diffuse main duct ectasia, (2) segmental main duct ectasia, (3) side branch ectasia, and (4) multifocal cysts with pancreatic duct communication.[17,18] Each pattern has implications with regard to the extent of resection.

Diffuse main duct ectasia may be due to obstruction by neoplasm growth, mucus production by a tumor in the head of the gland, or a neoplasm diffusely involving the pancreatic duct. While the initial approach would be to perform a pancreatoduodenectomy, frozen section analysis of the resection margin may dictate iterative resection of additional pancreas or even total pancreatectomy.

Segmental main duct ectasia usually involves the body and tail. Distal pancreatectomy with frozen section analysis of the resection margin is preferred. In our experience, only about 25% of patients had disease localized to the body and tail.[19]

Side branch ectasia usually is recognized in the head or uncinate process and is the pattern that causes the most diagnostic uncertainty. This pattern is often seen in asymptomatic patients and precise preoperative diagnosis is generally recommended before embarking upon pancreatic head resection. Pseudocysts, simple cysts, and serous cystadenomas may appear similar on imaging. It is in this setting that EUS for presence of mural nodules and with cyst fluid analysis for cytology, extracellular mucin, and CEA level may be helpful in decision-making. With IPMN-BR, the absence of CIR warrants observation.

The fourth pattern represents diffuse disease and warrants total pancreatectomy. Usually, it is obvious based on preoperative imaging which patients will require total pancreatectomy as, in addition to ectasia of the main pancreatic duct, there exist multifocal cysts throughout the entire pancreas. The survival following pancreatic resection for noninvasive IPMN is excellent. While the risk of recurrence following pancreatic resection for invasive IPMN is significant, the overall survival in reported series is generally better than that for ordinary ductal adenocarcinoma of the pancreas.[19,10–23]

What is the role of frozen section for intraoperative decision making? Ideally, one would hope to perform a targeted pancreatic resection with negative margins; how-

ever, if adenoma or borderline tumor is present at a margin, current evidence suggests that no further resection is warranted.[2] On the other hand, the presence of carcinoma in situ or invasive cancer at the resection margins warrants aggressive resection to completion pancreatectomy.

In the Mayo series,[19] for invasive IPMN, recurrence after partial pancreatectomy (18/27; 67%) was similar to that observed after total pancreatectomy (8/13; 62%), suggesting no oncologic advantage to total pancreatectomy. For benign IPMN, the recurrence rate following partial pancreatectomy was low (5/60; 8%) with a median follow-up of 37 months. While recurrence was not observed after total pancreatectomy for benign IPMN in 13 patients followed a median of 32 months, more recent analysis of quality of life in our patients undergoing total pancreatectomy suggests that the long-term effects of total pancreatectomy are appreciable.[24] Based upon the aforementioned considerations, it is our preference to limit total pancreatectomy to those patients with obvious diffuse disease or to those in whom the finding of carcinoma in situ or invasive neoplasm on frozen section analysis dictates completion pancreatectomy.

How should patients be followed following resection? For noninvasive IPMN, the consensus panel recommended yearly follow-up with abdominal CT or MRI.[2] For resected invasive IPMN, as for other oncologic surveillance programs, evaluation every 6 months is recommended. For patients with side branch IPMN who are asymptomatic without mural nodules in whom the main duct is less than <6 mm, and the cyst size is <3 cm, observation may well be indicated. The frequency of follow-up is based upon the size of the side branch cyst: 0–1 cm, yearly; 1–2 cm, every 6 to 12 months; 2–3 cm, every 3 to 6 months. Abdominal CT, ERCP, and EUS are utilized for assessing cyst size and the presence of mural nodules. The interval of follow-up may be lengthened if, with 2 years of follow-up, no change is observed.

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Sclerosing Cholangitis Epidemiology and Etiology

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Abstract Sclerosing cholangitis represents a spectrum of chronic biliary diseases that either has an unknown etiology (i.e., primary) or is caused by identifiable insults to the biliary tree (i.e., secondary). To date, the epidemiology of primary sclerosing cholangitis has been appraised; however, its etiology continues to be unclear. In contrast, the etiology of secondary sclerosing cholangitis is always known, but the epidemiology of this clinical entity is difficult to study.

Keywords Cholestasis · Epidemiology · Pathogenesis

Introduction—Definitions

Sclerosing cholangitis is a chronic cholestatic liver disease characterized by induration (sclerosing) caused by obliterative fibrosis and inflammation of bile ducts (cholangitis) resulting in strictures and destruction of the biliary tree. Sclerosing cholangitis can be either primary or secondary. Primary Sclerosing Cholangitis (PSC) is idiopathic. Secondary Sclerosing Cholangitis (SSC) is caused by known insults to the biliary tree (Table 1). This review will focus on the epidemiology and etiology of both PSC and SSC. When sclerosing cholangitis occurs in association with inflammatory bowel disease (IBD), some experts have been reluctant to use the designation "primary" because they regard the hepatobiliary disease as secondary to the intestinal illness. Although likely a complex relationship exists between PSC and IBD, there is no evidence that the former is directly caused by the latter.

PSC is an acquired disease that is characterized by chronic cholestasis caused by diffuse inflammation and fibrosis of the intra- and extrahepatic bile ducts. PSC is often a progressive and at times fatal disease. The classic form of PSC involves both intrahepatic and extrahepatic bile ducts and displays typical findings on liver biopsy. Large-duct PSC involves mainly the extrahepatic biliary tree as seen by cholangiography. Small-duct PSC affects only the small intrahepatic ducts; thus, it is characterized by positive findings on liver biopsy, although cholangiography shows normal bile ducts. Small-duct PSC accounts for ~5% of patients with PSC. SSC is also an acquired cholestatic liver disease, however, in contrast to PSC is caused by identifiable injuries to bile ducts (Table 1).

Epidemiology

In the late 1970s, fewer than 100 PSC cases were reported in the English literature. After the introduction of endoscopic retrograde cholangiopancreatography in clinical practice, the diagnosis of PSC became more often. This increase in the incidence of PSC likely reflects higher awareness of the disease among physicians, although long-term epidemiological studies to address this issue are lacking.

In the United States (year 2000), the age-adjusted estimated incidence of PSC was 0.9 per 100,000 persons (1.25 for men and 0.54 for women), whereas the calculated prevalence was 13.6 per 100,000 individuals (20.9 and 6.3

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Table 1 Causes of Secondary Sclerosing Cholangitis

Causes
Intraductal stone disease (in the absence of PSC)
Biliary or blunt abdominal trauma
Bile duct neoplasms (in the absence of PSC)
Congenital bile duct abnormalities (i.e., Caroli's disease)
Biliary ischemia
Intrahepatic artery chemotherapy (i.e., 5-fluoracil)
Recurrent pancreatitis
Autoimmune pancreatitis
Eosinophilic or mast cell cholangitis/cholangiopathy
Hepatic inflammatory pseudotumor
Primary immune deficiency
AIDS-related cholangiopathy
Recurrent pyogenic cholangitis

for men and women, respectively).[1] It is calculated that approximately 29,000 individuals suffer from PSC across the United States.[1] PSC is mainly a disease that affects young men, and the average age at the time of diagnosis is 40 years.[1] The reason for this sex and age distribution is unknown. However, there appear to be no major differences between male and female PSC patients with regard to the frequency of associated IBD or the complications of biliary cirrhosis. Despite available data about the basic epidemiological parameters of PSC, more epidemiological studies are needed to assess the environmental risks and exposures that contribute to PSC development.

The epidemiology of SSC is largely unknown because of the diverse causes of this clinical entity and the lack of relevant studies. A retrospective study from Mayo Clinic identified 31 patients with SSC over a decade (1992–2002).[2] The mean age at diagnosis was 57 years (range 28–79). Fifty eight percent of the patients were males. The most common causes of SSC in this series were surgical trauma during cholecystectomy (13 out of 31, 42%) and intraductal stones (12 out of 31, 39%).[2] Nearly 20% of patients develop SSC as a result of recurrent pancreatitis and abdominal injury.[2]

The authors of the above study reported that the life expectancy of patients with SSC is shortened compared to a group of matched PSC controls.[2] Indeed, in the SSC group, the median time of transplant-free survival was 72 months (95% confidence interval 40, 102) compared with 89 months (95% confidence interval 74, 117) in the PSC group ($P< 0.03$).[2] Although this finding suggests that patients with SSC may have poorer prognosis than those with PSC, additional studies are required to further evaluate this observation.

Etiology

The cause of PSC remains obscure. A consensus hypothesis proposes that environmental exposures (whether microbial or not) interact with certain inherited factors to result in PSC. At the core of the PSC pathogenesis, there is an initial damage of the cholangiocyte, the epithelial cell that lines the bile ducts. Additional genetic factors in combination with other unknown mechanisms lead to persistent inflammation of the bile ducts in susceptible individuals, resulting in progressive biliary destruction and the complications of PSC.[3] Several observations are consistent with the contribution of genetic factors in PSC. First, familial PSC cases have been reported.[4] Second, a recent study demonstrated increased prevalence of PSC in first-degree relatives of affected patients.[5] These authors calculated an almost 100-fold increased risk of developing PSC in families with an affected member.

A number of case-control studies have described genetic variants associated with PSC. For instance, the HLA genes have been studied in PSC and two susceptibility haplotypes have been identified: HLA A1-B8-DRB1*0301-DQA1*0501-DQB1*0201 and DRB1*1301-DQA1*0103-DQB1*0603.[6,7,8] However, it is uncertain whether these haplotype associations are specific to PSC or to the IBD background of PSC patients. In addition, genetic polymorphisms in non-HLA genes have been associated with susceptibility to or protection from PSC. Those include the tumor necrosis factor-α (TNF-α),[9] the matrix metallopeptidase 3 (MMP3),[10] the MHC class I polypeptide-related sequence A (MICA),[11] the chemokine C-C motif receptor 5 (CCR5),[12] and the intracellular adhesion molecule-1, CD54 (ICAM-1).[13]

Beyond inherited factors, potential acquired exposures including toxins, infectious agents, and xenobiotics have been postulated to contribute to PSC pathogenesis. Nonetheless, no specific environmental exposures or other non-genetic risk factors have been yet linked to PSC. Although increased hepatic copper levels were thought to be potentially important in the development of PSC, accumulation of copper in liver is a nearly universal finding of chronic cholestasis. Furthermore, negative results from a controlled trial with D-penicillamine (i.e., a copper chelating agent) made it unlikely that increased hepatic copper levels are pathogenetically important in PSC.[14] Viruses such as cytomegalovirus and reovirus type 3 have been proposed to cause PSC, but the data were not conclusive. Another hypothesis postulated portal bacteremia to cause PSC in the context of IBD.[15] This scenario seems unlikely for several reasons. Approximately 20% of patients have PSC without evidence of IBD. There are no striking differences in liver biopsy specimens from patients with PSC with and without IBD. Finally, portal phlebitis is mild and uncommon in liver biopsy specimens from patients with PSC.[16]

Immune-mediated damage of cholangiocytes is a credible mechanism leading to PSC. Indeed, abnormalities of the humoral and cellular immune system in PSC have been

described including the presence of hypergammaglobulinemia, particularly elevated immunoglobulin M levels, circulating immune complexes, activated complement, decrease in the total number of circulating T-cells caused by a decline in CD8 (suppressor/cytotoxic cells) and an increase in circulating B-cells.[17] Moreover, PSC patients have serum positivity for several auto-antibodies including anti-neutrophil cytoplasmic antibodies (ANCA), anti-cardiolipin antibodies, anti-nuclear antibodies, and anti-*Saccharomyces cerevisiae* antibodies.[18,19] However, these abnormalities of the immune system in PSC patients likely represent an epiphenomenon of the disease rather than a direct link to its pathogenesis.

By definition, the etiology of SSC is always identified (Table 1). However, given the spectrum of diseases that the classification of SSC embraces a detailed review of these clinical entities is not possible in this review. To this end, we will briefly discuss on an emerging cause of SSC, namely, autoimmune pancreatitis (AIP) with biliary involvement. In fact, many case series of patients with biliary strictures associated with autoimmune pancreatitis have been reported.[20] AIP is believed to be a primary pancreatic disorder, which at times can affect the bile ducts and gallbladder. The pathogenesis of AIP remains unknown, but is characterized by high IgG_4 in serum and infiltration of the involved tissues with IgG_4-bearing plasma cells. Of interest, in a group of 127 patients with established diagnosis of PSC elevated serum IgG_4 was found in 12 (9%).[21] Therefore, patients who present with biliary strictures of unknown etiology should be tested first for IgG_4 before a diagnosis of PSC is made.

Summary

Sclerosing cholangitis is a chronic cholestatic liver disease that continues to affect the quality of life and the survival of patients. Despite progress on the epidemiology of PSC, more translational studies are needed to shed light on the pathogenesis of this mysterious liver disease.

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Primary Sclerosing Cholangitis Detection of Cancer in Strictures

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Abstract Primary sclerosing cholangitis (PSC) is a significant risk factor for developing cholangiocarcinoma. Tests currently used to screen patients with PSC include serum tumor markers, invasive biliary imaging and sampling techniques, and noninvasive biliary imaging. The most commonly used serum markers are carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA). Invasive biliary imaging includes endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC). In addition to standard cytology, the bile can be tested for CA 19-9 levels, as well as other novel tumor markers. In addition, the brushed cells can be analyzed for chromosomal abnormalities using digital image analysis (DIA) or fluorescence in situ hybridization (FISH). Nonivasive imaging techniques include computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), and positron emission tomography (PET).

Keywords Sclerosing cholangitis · Detection · Cancer

Longstanding cholangitis such as in primary sclerosing cholangitis (PSC) greatly increases the incidence of the development of cholangiocarcinoma by those affected. The risk of developing cholangiocarcinoma is increased approximately 30-fold over background. The development of cholangiocarcinoma will complicate the clinical course of 10–30% of patients with PSC.[1] Autopsy series of patients with PSC have demonstrated that 33–42% of affected individuals also have histological evidence of cholangiocarcinoma.[2] A difficult problem with cholangiocarcinoma complicating PSC is that it is often discovered too late and at an advanced stage precluding a curative resection. It is clear that to increase the survival of patients with PSC who develop cholangiocarcinoma, early detection of malignant transformation is necessary so that they may undergo liver transplantation or appropriate surgical resection in a timely fashion allowing for a potential cure.

Tests currently used to screen PSC patients for cholangiocarcinoma include the use of serum tumor markers, invasive biliary imaging and sampling techniques, and noninvasive biliary imaging. The most commonly used serum markers are Carbohydrate Antigen 19-9 (CA 19-9) and Carcinoembryonic Antigen (CEA). Some groups have also attempted to measure potential tumor markers within collected bile samples. Invasive biliary imaging includes endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), and direct cholangioscopy. Noninvasive biliary imaging includes computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), and positron emission tomography (PET). The noninvasive modalities have the advantage of being better tolerated by the patients, and having fewer complications. Their main disadvantage is the inability to acquire cytologic specimens or to perform adjunctive therapeutic maneuvers.

This paper was originally presented as part of the SSAT/AHPBA Joint Symposium on Sclerosing Cholangitis at the SSAT 48th Annual Meeting, May 2007, in Washington, DC. The other articles presented in the symposium were Lazaridis KN, Sclerosing Cholangitis: Epidemiology and Etiology; Ahrendt SA, Surgical Approaches to Strictures in Primary Sclerosing Cholangitis; and Chapman WC, Primary Sclerosing Cholangitis: Role of Liver Transplantation.

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Tumor Markers

The most common tumor marker used to screen for the development of cholangiocarcinoma in PSC patients is serum CA 19-9. One of the classic studies that established CA 19-9 as a tool to screen this patient population was performed at the Mayo Clinic.[3] In this study, nine out of 37 patients with PSC also had cholangiocarcinoma. When a threshold level of 100 U/ml serum CA 19-9 was used, the sensitivity and specificity for detecting cholangiocarcinoma was 89 and 86%, respectively. In another classic study from King's College Hospital, 15 of 74 patients with PSC also had cholangiocarcinoma. They employed the sum of the serum CA 19-9 (U/ml) and 40×serum CEA (ng/ml). When a threshold level of 400 units from this equation was used, the sensitivity and specificity for detecting cholangiocarcinoma was 67 and 100%, respectively. These two strategies were also validated in a multiinstitutional study also using retrospective data with similar results.[4] When serum CA 19-9 levels were used prospectively to try to identify PSC patients with cholangiocarcinoma, only one in four patients who developed cancer out of 75 with PSC followed over 8 years could be identified using this tumor marker.[5]

Standard Cholangiography

Standard cholangiography including ERCP and PTC are helpful in making the diagnosis of PSC and for defining the location of strictures within the biliary tree. These tests, however, are relatively insensitive and nonspecific at determining which strictures are malignant.[6] Performing cytologic brushings and or biopsies does increase the diagnostic accuracy of these cholangiographic tests, but they still have significant false negative and false positive rates. In a study from the University of Washington, 51 patients with PSC underwent 107 invasive cholangiographic examinations over a 9-year period with cytologic examination.[7] Using a threshold of cytology that was suspicious for carcinoma, the sensitivity was 88% and the specificity was 82% in determining the presence of cholangiocarcinoma. In another study from Johns Hopkins, 47 patients with PSC underwent 101 invasive cholangiographic examinations over a 3-year period with cytologic examination.[8] Using a threshold of cytology with marked atypia, the sensitivity was only 50% and specificity was 86% in determining the presence of cholangiocarcinoma. Some groups have incorporated direct cholangioscopy to guide the brushings and biopsies, but this is currently experimental. The early experience has demonstrated difficulties in detecting cholangiocarcinoma located in the more peripheral biliary tree. The use of collected biliary specimens and analysis for potential tumor markers has also been attempted. Measurement of biliary CA 19-9 and other novel tumor markers such as Mac-2-binding protein (Mac-2-BP) have resulted in sensitivities and specificities that are similar to measuring serum CA 19-9 and CEA.[9] The use of advanced cytologic techniques that detect chromosomal instability may hold promise. Specifically, detection of chromosomal abnormalities has the potential to increase sensitivity and specificity of diagnosis of cholangiocarcinoma in cytology specimens, as 80% of biliary cancers exhibit aneuploidy. Two such techniques include Digital Image Analysis (DIA) (uses microscope and camera to quantify the amount of cellular DNA using a dye) and Fluorescence in situ Hybridization (FISH) (uses fluorescently labeled DNA probes to detect chromosomal abnormalities). These techniques have been demonstrated to increase the sensitivity and specificity of the diagnosis of cholangiocarcinoma over conventional cytology alone.[10]

Noninvasive Imaging

As noninvasive imaging techniques improve, their clinical utility also increases. CT has been relatively insensitive and nonspecific at detecting malignant strictures, but in the past decade, their resolution has increased tremendously. MRCP has also been more frequently utilized to follow patients with PSC. There are limited data to date that rigorously evaluate the abilities of MRCP in detecting malignant strictures. MRCP has the advantages of being easier to tolerate and avoidance of a significant false positive rate experienced with cytologic techniques. However, all of the noninvasive techniques do not allow therapeutic intervention or directed cytologic examination of discovered dominant strictures.

Several groups are studying the clinical utility of PET scans in determining the presence of cholangiocarcinoma in patients with PSC. In a report on 24 consecutive patients with PSC within 2 weeks after listing for liver transplant and with no evidence of malignancy on CT, MRI, or US, the sensitivity and specificity for detecting cholangiocarcinoma were 75 and 95%, respectively.[11]

Summary

Patients with primary sclerosing cholangitis are at high risk for developing cholangiocarcinoma. Cholangiocarcinoma complicating primary sclerosing cholangitis is usually discovered at an advanced stage precluding curative therapy.

Early detection of malignant transformation is necessary to increase survival from this malignancy. No test currently used is both highly sensitive and specific for detecting cholangiocarcinoma in this population. Advanced cytologic

techniques such as flourescence in-situ hybridization (FISH) and dynamic PET need further study.

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Surgical Approaches to Strictures in Primary Sclerosing Cholangitis

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Abstract Primary sclerosing cholangitis (PSC) is an idiopathic inflammatory disease resulting in multifocal intra- and extrahepatic biliary strictures. Dominant strictures occur commonly in PSC and may contribute to the progressive hepatic fibrosis in this disease. Extrahepatic bile duct resection should be considered for selected noncirrhotic patients with symptomatic biliary obstruction and dominant strictures, particularly in those who fail in endoscopic therapy. In addition, patients with dominant strictures and equivocal results on cancer screening tests should be managed with resection rather than prolonged efforts at cancer diagnosis.

Keywords Primary Sclerosing Cholangitis · Strictures · Cholangiocarcinoma

Introduction

Primary sclerosing cholangitis (PSC) is a progressive chronic inflammatory disease of the intra- and extrahepatic biliary tree resulting in multifocal biliary strictures, chronic cholestasis, and eventual cirrhosis. Patients are at increased risk for developing cholangiocarcinoma, with a reported lifetime prevalence of 10–30%.[1] These cholangiocarcinomas are usually diagnosed at an advanced stage, and the likelihood that they will be resectable is quite low. Most patients with PSC will develop symptoms of fatigue, itching, and jaundice within several years of diagnosis. Progression to portal hypertension and cirrhosis ensues, and once liver failure develops, liver transplantation is the only therapeutic option. For patients early in the course of their disease, however, the most effective management remains controversial.

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Medical Management

Although numerous randomized trials examining a variety of medical therapies for PSC have been reported, no drug has demonstrated that it can slow the progression of the disease to cirrhosis or produce clinically meaningful symptomatic improvement. Ursodeoxycholic acid has been the most extensively studied and has been shown to improve serum liver function tests and the histological stage of disease on liver biopsy. However, no difference in clinical outcome has been observed. Multiple other agents have also been evaluated including methotrexate, tacrolimus, cladibrine, budesonide, and colchicine. None of these agents have demonstrated any significant improvement in symptoms or outcome.

Management of Dominant Strictures

Dominant strictures occur commonly in PSC and may impede bile flow contributing to the progressive hepatic fibrosis and cirrhosis in this disease. Dominant strictures have been defined cholangiographically as strictures of the common bile duct or common hepatic duct with a diameter ≤1.5 mm and/or strictures of a hepatic duct with diameter ≤1 mm within 2 cm of the hepatic duct bifurcation.[2] The incidence of dominant strictures ranges from 10 to 50% in patients with PSC. Stiehl et al. identified dominant strictures in approximately 50% of patients with stage II or stage III PSC undergoing surveillance ERCP.[2]

Endoscopic balloon dilation or stenting is being increasingly utilized to relieve biliary obstruction in patients with PSC. Endoscopic procedures include a small papillotomy followed by balloon dilation of extrahepatic and perihilar strictures with 18 to 24 French balloon catheters. Endoscopically placed stents have not been beneficial and are associated with an increased risk of bacterial cholangitis. Repeat procedures are often needed and most patients will need annual dilations to address new or recurrent strictures.

Stiehl et al. prospectively studied 106 patients treated with ursodeoxycholic acid.[2] Over a 5-year period, 52 patients developed dominant stenoses and were managed endoscopically. The technical failure rate in hepatic duct strictures was 12.5%. The actuarial survival free of liver transplantation at 5 years was significantly better than predicted with the Mayo multicenter survival model (94% vs. 77%). Other centers have produced comparable results. An NIH-convened expert panel concluded that endoscopic balloon dilation of high-grade strictures is beneficial.[3]

Surgical Management

Before the widespread use of liver transplantation and endoscopic balloon dilation to manage primary sclerosing cholangitis, surgical resection was used as the predominant method of treatment. Operative management of primary sclerosing cholangitis entails resection of the extrahepatic biliary tree including the hepatic duct bifurcation and postoperative transhepatic stenting. The operative approach for patients with PSC is based on the observation that the hepatic duct bifurcation is frequently involved with a dominant stricture. The extrahepatic biliary tree and the hepatic duct bifurcation are then resected, and bilateral hepaticojejunostomies are constructed over Silastic stents. The transhepatic stents are removed at 1 year if there is free flow across the biliary enteric anastomosis.

The largest published nontransplant surgical experience in the management of patients with primary sclerosing cholangitis is from the Johns Hopkins Hospital.[4] Between 1980 and 1994, 146 patients with primary sclerosing cholangitis were treated at Johns Hopkins. Fifty patients underwent resection of the extrahepatic biliary tract. Forty of these patients were noncirrhotic. All patients had symptomatic biliary obstruction, and the primary indications for treatment were persistent jaundice and cholangitis. Operative mortality in patients with and without cirrhosis was 20 and 2.5%, respectively. The overall 1-, 3-, and 5-year survival rates after bile duct resection were 86, 84, and 76%, respectively. Patients without cirrhosis had 1-, 3-, and 5-year survival rates of 95, 92, and 85%. Biliary resection also significantly reduced serum bilirubin levels at 1, 2, and 3 years after resection when compared to preoperative levels. None of the resected patients developed cholangiocarcinoma during a mean follow-up of 62 months.

This analysis is the only study comparing the long-term results of extrahepatic bile duct resection with endoscopic therapy in the same clinical setting. Endoscopic balloon dilation was performed in 35 patients with PSC and symptomatic biliary obstruction between 1990 and 1994. The overall complication rate was lower than in the resected patients (14%), the most common being mild pancreatitis. The overall 5-year survival rate in noncirrhotic patients managed with endoscopic dilation was 58%, significantly lower than the 5-year survival after resection (85%). Similarly, transplant-free survival was also longer for managed patients treated operatively when compared to patients treated nonoperatively. Three (8%) of 35 patients treated endoscopically developed cholangiocarcinoma.

Currently, endoscopic biliary dilation should be used as the initial approach to dominant strictures in PSC. This technique carries acceptable procedure-related morbidity. Surgical approaches should be reserved to endoscopic treatment failures, who continue to experience significant symptoms.

Surgical resection also plays a critical role in the management of patients with a confirmed diagnosis of or suspected cholangiocarcinoma. Cholangiocarcinoma is the most feared complication of primary sclerosing cholangitis and is a major cause of death in patients with PSC. Because the early diagnosis of cholangiocarcinoma remains elusive, extrahepatic bile duct resection should be considered in patients with PSC in whom the diagnosis of cholangiocarcinoma is suspected but not proven. In many patients, cholangiocarcinoma is identified soon after the initial diagnosis of PSC, and clinical suspicion must be high at this time.[1] Dominant strictures that recur or persist after endoscopic dilation should be resected to exclude the possibility of cholangiocarcinoma. Patients may also be diagnosed with PSC after the pathological evaluation of a resected isolated biliary stricture is benign and has the characteristics of sclerosing cholangitis. A variety of benign conditions

including PSC can present with an isolated biliary stricture mimicking cholangiocarcinoma.[5]

Summary

Primary sclerosing cholangitis is a progressive disease that eventually leads to cirrhosis, portal hypertension, and liver failure. Management of the patient with primary sclerosing cholangitis is based on a careful assessment of the cholangiographic appearance of the biliary tract, histological stage of the disease on liver biopsy, and the presence of symptoms. Resection of the hepatic duct bifurcation with long-term transhepatic stenting should be considered for selected noncirrhotic patients who have symptomatic biliary obstruction and dominant extrahepatic strictures—particularly in those who fail endoscopic therapy. Patients with dominant strictures and equivocal results on cancer screening tests should be managed with resection rather than prolonged efforts at cancer diagnosis. Liver transplantation is clearly the best treatment option once cirrhosis has developed.

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Primary Sclerosing Cholangitis: Role of Liver Transplantation

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Keywords Liver disease · Fibrosing · Biliary tree · Cholangiocarcinoma

Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by fibrosing inflammation of the intrahepatic and extrahepatic biliary tree. PSC typically presents in men younger than 50 years of age and is associated with coexisting inflammatory bowel disease (IBD, usually ulcerative colitis) in greater than 70% of patients. This association can present special problems, sometimes making decisions regarding timing of surgical treatment of the intestinal and liver disease challenging.

Currently, there are no effective medical treatments to reverse the course of PSC, and medical measures are directed at ameliorating symptoms associated with progressive biliary obstruction including bacterial cholangitis and pruritus. Liver transplantation is the only curative therapy, which effectively reverses the disease. Once performed, liver transplantation usually provides lifelong curative treatment, although graft recurrence can sometimes occur, with studies suggesting a 5–15% incidence in long-term follow-up.

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Prognostic Models and Timing of Liver Transplantation

As PSC is a chronic and slowly progressive disease, timing of liver transplantation is frequently a consideration of patients and their physicians. Prognostic models have been developed to predict the natural history and mortality risk in individual patients, including the revised Mayo model and others (http://www.mayoclinic.org/gi-rst/mayomodel3.html). The Mayo model is based on patient age, serum bilirubin, history of variceal bleeding, and serum albumin. Since the introduction of the Model for End Stage Liver Disease (MELD) for organ allocation by the United Network for Organ Sharing (UNOS) in the US in 2002, organ allocation priority is now stratified based on serum bilirubin, creatinine, and International Normalized Ratio (INR). In some respects, prognostic natural history modeling is less important today than before 2002, as liver transplant organ allocation is no longer based on waiting time on a transplant center list. Today, patients should be referred for consideration of orthotopic liver transplantation (OLT) when they suffer a significant complication of their liver disease, or with significant life-limiting symptoms of PSC.

Results of Liver Transplantation

Patients with PCS usually represent 5–10% of the indications for patients undergoing OLT. OLT provides both a rescue therapy from liver failure and also reverses the symptoms of

PSC including recurrent infections associated with bacterial cholangitis, pruritus, and bone demineralization (hepatic osteodystrophy). The long-term outcomes of liver transplantation in patients with PSC have been excellent, with most reports demonstrating upward of 80% patient- and graft-survival at 10 years and beyond.[1] In reports comparing all indications for OLT, the best results appear to be in patients with PSC.

Decisions regarding timing of liver transplantation can be challenging, especially in patients with significant symptoms from the PSC (cholangitis, pruritus), but with well-compensated liver disease. Currently, standard cadaveric organ allocation is essentially restricted for patients with MELD scores ≥15. In this regard, some have felt that patients with PSC are disadvantaged by MELD allocation as cholangitis and pruritus are not taken into account by MELD modeling. For such affected patients, exception point requests and use of living donor transplantation are options that may allow earlier transplantation.

A complicating feature of PSC management is the frequent association of ulcerative colitis, known to occur in a significant percentage of PSC patients in long-term follow-up. For this reason, all patients with PSC should undergo screening colonoscopy as part of their evaluation, with surveillance biopsies performed randomly in representative regions of the colon and rectum and of any suspicious-appearing areas. Whereas the risk of patients with known ulcerative cholitis (UC) developing PSC is much less, such patients should also have interval assessment of liver tests with appropriate follow-up studies for possible PSC if abnormal LFTs are encountered.

Management of Inflammatory Bowel Disease in the Setting of Primary Sclerosing Cholangitis

The association between IBD and PSC has long been recognized, especially between UC and PSC. Approximately 70–75% of PSC patients will be found to have UC, either known or found at the time of PSC diagnosis, or subsequently discovered. The contrary is not true, as only a small percentage of UC patients will be likely to develop PSC in long-term follow-up—approximately 5% overall. In patients with known co-existing PSC and UC, the status of the liver disease should be taken into consideration when making decisions about UC management.

For patients with well-compensated or early-stage PSC or in those who have previously undergone successful liver transplantation, these patients can be managed like patients with UC alone. In general, such individuals can undergo a 1-, 2-, or 3-stage ileal pouch anal anastomosis (IPAA) depending on surgeon preference. Patients with advanced-stage liver disease and quiescent UC should be considered for liver transplantation and follow-up of their UC. Finally, patients with evidence of hepatic decompensation from PSC and active UC can undergo simultaneous OLT and colectomy, but this should only be done on a highly selective basis, as the concurrent performance of these operations significantly increases the risks associated with performance individually.[2] Conflicting reports exist regarding the effect of liver transplantation on coexisting UC, with some authors proposing that the immunosuppression required to prevent liver transplant rejection has a favorable effect on the inflammatory component of UC, whereas others suggest that OLT can result in a worsening UC course.[3]

Cholangiocarcinoma

The chronic fibrosing inflammation associated with PSC is a known risk factor for development of cholangiocarcinoma, reported to occur in 10–20% of PSC patients.[4] The potential development of cholangiocarcinoma is particularly challenging, as it can be very difficult to distinguish a typical PSC stricture from an early stricture of cholangiocarcinoma. Elevation of CA19-9 to >100 can increase the diagnostic sensitivity; however, this marker may not be elevated with small tumors. Whereas computed tomography (CT) and magnetic resonance imaging (MRI) may be suggestive of the diagnosis of cholangiocarcinoma, unless there is a mass effect, the wall thickening sometimes observed is a nonspecific finding. In addition to cytologic assessment of brush samples obtained at endoscopic retrograde cholangiopancreatography (ERCP), fluorescent in situ hybridization (FISH) can be performed to look for aneuploidy. FISH is also performed on fresh brush specimens obtained at ERCP and should be considered in difficult cases, especially when a positive diagnosis will alter patient management.

Historically, results for liver transplantation for cholangiocarcinoma have been poor, and most centers have considered known cholangiocarcinoma a contraindication for OLT. Recent reports from the Mayo clinic have demonstrated satisfactory results when the indication for OLT is cholangiocarcinoma, as long as OLT is performed as part of a neoadjuvant chemoradiation protocol and when pretransplant staging laparotomy demonstrates no evidence of metastatic disease in regional lymph nodes or elsewhere.[5] Among patients who have unresectable cholangiocarcinoma, patients with PSC-associated cholangiocarcinoma may represent the “best” candidates for OLT, as

these patients are frequently "unresectable" because of the liver disease associated with their PSC, not because of advanced-stage tumors. In the most recent Mayo series reports, survival after OLT for cholangiocarcinoma is essentially the same as for liver transplantation for all other indications (i.e., approximately 70–75% at 5 years). An important consideration of the neoadjuvant therapy is the approximately 50% dropout rate for enrolled patients, occurring either from failure to complete the chemo-radiation therapy and/or from development of metastatic disease. In addition, this protocol is used only for patients with localized hilar tumors (<3 cm) in whom there have been no prior attempts at resection and no evidence of metastatic disease, including intrahepatic metastases. Transplantation for cholangiocarcinoma is now being utilized at other US centers under similar highly selective protocols; however, there are no reports yet demonstrating a duplication of the favorable Mayo clinic results.

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Interdisciplinary Management of Pediatric Intestinal Failure: A 10-Year Review of Rehabilitation and Transplantation

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Abstract Management of children with intestinal failure is optimized by interdisciplinary coordination of parenteral and enteral nutrition support, medical management of associated complications, surgical lengthening procedures, and intestinal transplantation. Three hundred eighty-nine pediatric patients have been referred to our center for interdisciplinary assessment of intestinal failure since 1996 (median age=1 year; range 1 day–28.8 years). Factors predictive of weaning from parenteral nutrition without transplantation included increased mean bowel length for patients with gastroschisis (44 vs. 23 cm, $p<0.05$) and atresia (35 vs. 20 cm, $p<0.01$) and lower mean total bilirubin for patients with NEC (6.1 vs. 12.7 mg/dL, $p<0.05$). Others were also more likely to survive if referred with a lower mean total bilirubin (NEC, 7.9 vs. 12.7 mg/dL, $p<0.05$; pseudo-obstruction, 2.3 vs. 16.3 mg/dL, $p<0.01$). Patients weaned from parenteral nutrition by 2.5 years after referral achieved 95% survival at 5 years vs. 52% for those not weaned. Bowel lengthening procedures were performed on 25 patients. Eight subsequently weaned from parenteral nutrition without transplantation. Aggressive medical and nutritional intervention along with early referral, intestinal lengthening procedures, and intestinal transplantation in children with intestinal failure dependent on parenteral nutrition can result in the achievement of enteral autonomy and improved survival.

Keywords Short bowel syndrome · Intestinal transplantation

Introduction

Intestinal failure (IF) in the pediatric population is a clinical condition characterized by malabsorption, malnutrition, and growth retardation secondary to extensive loss of intestinal

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length or function.[1,2] Short bowel syndrome (SBS) occurs after massive resection of the small bowel because of many reasons including necrotizing enterocolitis (NEC), intestinal atresia, midgut volvulus or gastroschisis, and resection is the most common cause of IF in children.[3] Alternatively, patients with IF caused by microvillus atrophy or intestinal pseudo-obstruction may have diminished intestinal function secondary to impaired absorption or altered motility.

Many children with IF caused by SBS undergo progressive intestinal adaptation of their remaining bowel over a period of a few months with subsequent independence from parenteral nutrition (PN). During this time, medical and surgical management includes maintenance of fluid and electrolyte balance as well as enteral and parenteral nutrition support.[4] Adaptation is characterized by enhanced absorptive capacity of residual small bowel through increases in cellular proliferation, villus height, and crypt depth as well as dilation of the intestinal remnant. Clinically, the children are characterized by tolerance of enteral feeding, satisfactory growth, development, and weight gain that continues beyond discontinuation of PN. However, a number of children initially diagnosed with SBS require many months to years to adapt, and still others are never able to be weaned from PN. These children may benefit from other established medical and surgical interventions intended to improve the function of the remnant small intestine and facilitate weaning of PN and eventual enteral autonomy.[5]

Estimates of the incidence and prevalence of SBS and IF are difficult to determine in children as they are based on the number of patients receiving home PN, which is most often indicated for SBS. However, these numbers inherently exclude SBS patients who weaned from PN before hospital discharge.[3] One population-based estimate of neonatal SBS incidence and mortality rates was conducted retrospectively in Canada on data collected from 1997 to 1999.[6] The overall incidence of SBS was determined to be 22.1 per 1,000 neonatal intensive care unit admissions and 24.5 per 100,000 live births, with a case fatality rate of 37.5% (9.2 per 100,000 live births) most often caused by hepatic failure over 4 years of follow-up. Hepatobiliary disease is a chronic complication of long-term use of PN and along with a shortened length of remaining small bowel, multiple episodes of sepsis, and loss of the ileocecal valve (ICV), is thought to be a major contributor to the high morbidity and mortality of children with SBS.[7,8] The objective of this review is to identify factors predictive of successful outcomes, including survival and successful weaning from PN in a large population of children with IF.

Material and Methods

The Intestinal Care Clinic (ICC) at the Children's Hospital of Pittsburgh was established in December 1996, and serves as a regional, national, and international referral center for patients with SBS. Patient outcomes reported in this review include those from children seen initially and evaluated in the ICC from its inception through and including December 2006. Patients include those managed primarily by physicians in the ICC and those referred for intestinal transplantation (ITx), but were managed primarily by their local care team, with the physicians in the ICC providing a consultative role.

The ICC center is staffed by an interdisciplinary team of pediatric specialists including a gastroenterologist, pediatric surgeon, transplant surgeons, clinical dietitians, and a clinical nurse specialist. Each patient is evaluated with a history and physical examination, review of pertinent laboratory data, and nutritional assessment. Subsequently, a coordinated treatment plan and goals are constructed and implemented for our local patients or communicated to local physicians.

After informed consent was obtained at the time of their initial evaluation, database registry information was recorded for each patient from patient or parental reports, medical records as well as operative and pathology reports (approved by the Institutional Review Board of the University of Pittsburgh, no. 0405214). Registry data include demographic information, a baseline physical assessment by systems, intestinal characteristics (including small bowel length, the percent of small bowel remaining after initial surgery, bowel lengthening procedures and the presence/absence of an ICV and large intestine), anthropometric data, mode of nutrition therapy, and transplant status. The percent of small bowel remaining after initial surgery was estimated using normal values for intestinal length identified by Touloukian.[9] Follow-up anthropometric and nutrition therapy data were also collected biannually. Disease associated complications including death, graft failure, or the development of micronutrient deficiencies and food allergies, among others, were monitored and recorded.

Weight (kilograms) and height (centimeters) indices were measured with a standard medical balance scale with a rigid vertical height rod. Infants and young toddlers (newborn to 18 months) were weighed and measured using an infant scale and recumbent length board. Nutritional outcomes for children evaluated since the inception of the ICC were assessed by cessation of PN, transition from enteral to oral feeding, and maintenance of linear growth. The identification of factors associated with the cessation of PN was performed using the *t* test for quantitative variables. To obtain an overall assessment of linear growth in a population of patients of varying age and gender, the *z*-score statistic was used to standardize values of relative position on a percentile growth curve. Positive or negative trends in *z*-scores between baseline measurements and those

taken 1, 2, and 3 years (± 2 months) postreferral was assessed using the paired *t* test. Survival function estimates were calculated using the Kaplan–Meier method. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 14.0.1, SPSS Inc., Chicago, IL).

Results

Clinical Characteristics

The demographic and clinical characteristics of the ICC population are shown in Table 1. Since the inception of the ICC center, a total of 389 patients (61% male, 70% Caucasian) have been evaluated with a median age of 1 year at referral (range 1 day to 28.8 years). Median small bowel length was 25 cm. Forty percent had a functional ICV and approximately half (43%) had all of their large intestine. One hundred twenty-two patients had a small bowel ostomy at the time of referral (62 were ileostomies).

The primary diagnosis distribution of the population is shown in Fig. 1. The majority of cases (47%) included children with developmental defects that include abdominal wall defects (gastroschisis), volvulus, and intestinal atresia. Children with pseudo-obstruction and microvillus atrophy comprised only 12% of the cases. Seventy-three percent of patients had evidence of hepatic disease upon referral with total bilirubin levels exceeding 2.0 mg/dL.

Table 1 Demographic and Clinical Characteristics of the Intestinal Care Center Population from December 1996 to December 2006 (n=389)

Characteristics	Number (n)	Percent
Gender (%)		
Male	239	(61)
Female	150	(39)
Race (%)		
Caucasian	272	(70)
African American	59	(15)
Hispanic	20	(5)
Other	25	(7)
Unknown	13	(3)
Median Age (years)	1.0	(Range newborn–28.8 years)
Median Gestational Age (weeks)[a]	36	(Range 23–41 weeks)
Median Small Bowel Length (cm)[b]	25	
Median % Small Bowel Remaining after Initial Surgery[c]	15	(Range 0–100%)
Presence/Absence of ICV (%)		
Present (including 1 artificial)	156	(40)
Absent/Non-functioning	203	(52)
Unknown	30	(8)
Area of Large Intestine (%)		
All	169	(43)
Partial	182	(47)
None/Non-functioning	26	(7)
Unknown	12	(3)

[a] n=361
[b] n=264
[c] n=339

Management Outcomes

For the majority of our patients, the mode of nutritional therapy upon initial consultation was PN with enteral supplementation (n=338, 87%), followed by oral intake alone (9%) and enteral feedings with or without oral intake (4%). Outcomes for patients on PN are shown in Table 2. Medical management of the patients who were PN-dependent resulted in 42 (12%) subsequently being weaned from PN to oral and/or enteral feeds without further surgical intervention (median time to wean=1.5 years). Active patients on PN who continue to be managed medically (n=23) have advanced from a mean of 88% caloric intake from PN at referral (range 50–100%) to 56% currently (range 0–100%) with a median follow-up time of 2 years. Twenty-five patients received a bowel lengthening procedure (15 Bianchi, six tapering, four serial transverse enteroplasty [STEP]). Of these, 8 (32%) successfully weaned from PN without transplantation and 11 proceeded to transplant with the majority (82%) subsequently weaning from PN. The remaining six patients failed to wean from PN without transplantation (three were followed for <1 year and three

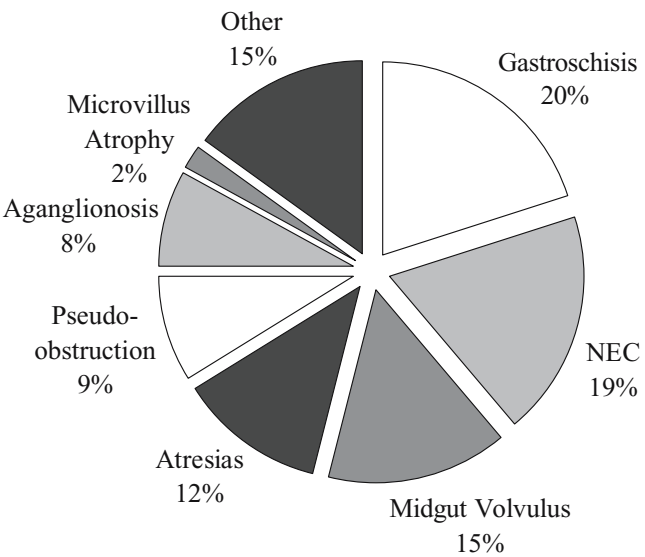

Figure 1 Primary diagnosis distribution in the intestinal care and rehabilitation center population (n=389).

Table 2 Distribution of Management Outcomes for Patients on Parenteral Nutrition (n=338)

Outcome	Number (n)
Successful medical management	42
Continued medical management	23
Surgical lengthening procedures	25
Weaned from PN	8
Transplanted	11
Failed to wean from PN (alive)	3
Failed to wean from PN (died)	3
Intestinal Transplantation	119
Died	109
Inactive/Lost to follow-up	20
Total	338

died within 1.5 years). Approximately one third of patients referred on PN (n=119, 35%) received an intestinal transplant. Survival rates at 1, 5, and 10 years posttransplant were 94%, 73%, and 69%, respectively. Ninety-five percent of patients who received an intestinal transplant and survived were weaned from PN. Within 2 years of referral, 109 patients died, and many while waiting for transplantation. The primary causes of death included sepsis, liver failure, or multiple system organ failure. The remaining 20 patients were lost to follow-up.

Successful weaning of PN was not associated with the estimated percent of small bowel remaining at diagnosis, the presence or absence of an ICV, or age at referral. Factors predictive of weaning from PN without transplantation included increased mean bowel length (50 vs. 32 cm, $p<0.05$) and mean total bilirubin level at referral (6.9 vs. 10.1 mg/dL, $p<0.05$). When subdivided by diagnosis, intestinal length was predictive specifically for patients with gastroschisis (44 vs. 23 cm, $p<0.05$) and atresia (35 vs. 20 cm, $p<0.01$) and lower mean total bilirubin for patients with NEC (6.1 vs. 12.7 mg/dL, $p<0.05$). Others were also more likely to survive if referred with a lower mean total bilirubin (NEC, 7.9 vs. 12.7 mg/dL, $p<0.05$; pseudo-obstruction, 2.3 vs. 16.3 mg/dL, $p<0.01$). A summary of the number of patients who weaned from PN and survived by intestinal transplant status and diagnosis is shown in Table 3. Patients weaned from PN with or without transplantation achieved 95% survival at 5 years versus 52% for those not weaned.

Anthropometrics and Nutrition

No statistically significant relationship was found between the mode of nutrition therapy and growth failure status. However, 7% of patients who were receiving enteral and/or oral feedings without PN supplementation at the time of referral had a z-score for weight and height >-1.65 (equivalent to the fifth percentile or less on the National Center for Health Statistics percentile growth curves[8]) versus 38% and 46% for weight and height, respectively, in those dependent on PN.

Sixty-five percent of patients have been followed in the ICC for at least 1 year (median follow-up time = 2 years). Whereas positive trends in z-scores for weight and height were observed in patients who were medically managed and weaned from PN, statistical significance was achieved only for linear growth between baseline and 2 years postreferral (-3.1 versus -1.7, $p<0.01$) in these children. Linear growth velocity within 2 years after intestinal transplantation was maintained or slightly improved (mean height z-score at transplant, 1 year and 2 years posttransplant was -2.4, -2.2, and -2.2, respectively).

Discussion

The medical and nutritional care of children with chronic intestinal disease remains a challenge for many pediatric specialists. Interdisciplinary management of these children is essential to improve the outcome of the disease process. Moreover, an interdisciplinary center serves to enhance

Table 3 Parenteral Nutrition Wean and Transplant Status by Diagnosis

Diagnosis	Number (n)	PN Weaned n (% survival)		PN Not Weaned n (% survival)		Wean Status Unknown
		ITx	No ITx	ITx	No ITx	
Gastroschisis	72	26 (92)	6 (67)	3 (0)	25 (28)	12
NEC	63	8 (75)	13 (92)	3 (0)	23 (26)	16
Midgut volvulus	53	26 (92)	3 (100)	6 (100)	14 (14)	4
Atresias	49	10 (90)	8 (100)	–	20 (25)	11
Aganglionosis	27	9 (89)	2 (100)	4 (0)	7 (29)	5
Pseudo-obstruction	26	9 (100)	3 (100)	3 (100)	7 (29)	4
Microvillus atrophy	9	4 (25)	–	3 (0)	2 (0)	0
Other	39	7 (71)	7 (100)	5 (60)	15 (80)	5
TOTAL	338	99 (87)	42 (93)	27 (44)	113 (26)	57

communication of the individualized treatment plan to the patient/family as well as maintain the continuity of care throughout the entire treatment process. The development of a database registry for our ICC has not only allowed us to assess clinical outcomes, but also expand on the treatment strategies and standards of medical practice or nutritional care for our patients.

Although the provision of PN has resulted in a reduction in the mortality rate for infants and children with intestinal failure, the complications associated with its long-term use may still be life-threatening. Multiple years of nutrition support therapy can result in catheter sepsis, loss of venous access, and the development of PN-induced liver dysfunction.[10,11] The high mortality rate of patients in our population who were neither weaned from PN nor transplanted emphasizes the critical importance of a concentrated effort toward our goal of eliminating PN support. We continue to practice conventional and systematic nutritional strategies to reverse the development or slow the progression of PN-induced liver disease in our patients with SBS while simultaneously supporting intestinal adaptation and maintaining adequate nutrition.[12] The nutritional support of patients with SBS is complex and must be individualized based on the acute and chronic medical issues and conditions of each patient. After patients are stabilized postoperatively, we begin to gradually cycle PN hours downward over a period of several weeks. The next phase of care focuses on continued cycling of PN while concurrently maximizing enteral feedings. We generally begin with a semielemental product and progress in both the volume and complexity of the formula and/or diet. It is in the final maintenance phase of care that the majority of intestinal adaptation occurs and opportunities for consideration of intestinal lengthening procedures arise. During this phase, it is important to monitor growth, development, and cognitive function.

Luminal nutrients such as glutamine and fiber as well as short- and long-chain fat have been examined for their role in intestinal adaptation. Although glutamine is believed to be the primary fuel of enterocytes, it is not used routinely in our center as the results from studies investigating its benefit on absorption are inconsistent.[7] Studies that have examined the effect of dietary fiber on nutrient absorption have also yielded mixed results. However, soluble fiber does slow gut transit and may reduce stool output. Soluble fiber supplements are used in our population on a regular basis when stool output exceeds 40 mL kg^{-1} day^{-1}. Enteral formulas containing medium-chain triglycerides (MCT) are often selected for children with SBS, particularly those with cholestasis, as MCTs do not require micelle formation to be absorbed. Long-chain fats have been shown to slow gut transit and reduce the number and volume of stools.[13] Majority of our patients receive enteral formulas that contain both medium- and long-chain fatty acids.

Gut hormones such as glucagon-like peptide 2 (GLP-2) and growth hormone (GH) have been investigated to determine their role in intestinal adaptation after surgical bowel resection. In an effort to enhance growth and development, we have used GH or growth releasing factor in several children with short bowel syndrome and growth failure. These children showed the greatest acceleration in linear growth velocity while they were receiving growth factors in addition to parenteral and/or enteral nutrition support.[14] Another case study that included two children with SBS off of PN reported improvement in growth after GH therapy.[15] Some studies in adults have shown increases in water, electrolyte, and carbohydrate absorption and a decrease in stool output with the use of growth hormone and glutamine in addition to a diet high in complex carbohydrate and low in fat.[16,17] Whereas subsequent studies could not confirm these results a recent randomized clinical trial demonstrated that PN volume and calories could be reduced with this therapy.[18–20] A small trial investigated the effects of GLP-2 in SBS patients without a colon.[21] Positive outcomes including an increase in energy absorption and a slowing of gastric emptying were observed. Although there may be promise in the use of these and other potentially proadaptive hormones, we believe current data do not support their use outside a well-designed clinical trial.

We were able to identify some clinical characteristics that might predict who would be more likely to transition from parenteral to enteral nutrition without transplantation, such as increased bowel length for patients with gastroschisis or atresia and lower total bilirubin levels at referral for patients with NEC and pseudo-obstruction. Spencer and colleagues[22] found cholestasis (conjugated bilirubin ≥2.5 mg/dL) and percentage of small bowel length (<10% of expected length) to be predictive of mortality in a large population of children with SBS, whereas the presence of an ileocecal valve and a small bowel length ≥10% of expected length were predictors of weaning from PN. Despite the use of PN and standard medical management, we and others continue to observe growth failure by anthropometry in a high percentage of our patients. The conservative use of PN to avoid overfeeding and the unknown variation in enteral nutrient absorption may result in inadequate nutritional support of children with SBS. However, a significantly positive trend for mean linear growth in children previously dependent on PN was observed after children in the ICC were followed up for at least 2 years.

Nutritional management of postintestinal transplant recipients includes the continuation of PN until enteral nutrition is established. The progression of enteral and/or oral feeds depends on whether or not postoperative complications develop. In our practice, patients initially receive an isotonic peptide-based formula containing medium-chain triglycerides and are subsequently transi-

tioned over a period of weeks and months to a formula product or oral diet with intact macronutrients. Ostomy output is monitored and enteral/oral advancements continued when output is maintained at ≤40 mL kg^{-1} day^{-1}. We have previously observed the development of food allergies after transplant and as a result milk, eggs, and wheat are initially avoided to minimize the allergic response. Immunosuppressant treatment for children after intestinal transplant recently changed at our institution to the use of a lymphocyte-depleting agent pretransplant with tacrolimus monotherapy posttransplant. As steroids are now used for rejection episodes only, we have observed improved growth in children posttransplant.

Conclusion

The survival rate for children with intestinal failure who are weaned from PN with or without transplantation is considerably superior to those who fail to wean from PN with or without transplant. Interdisciplinary team management and early referral of children dependent on PN can result in positive outcomes, including cessation of PN support, accelerated growth, and improved survival. Moreover, intestinal transplantation has become a feasible and life-saving therapeutic option for children who fail to respond to measures aimed at reducing PN-associated complications and who are unable to achieve adequate growth/development on an enteral diet without PN support. For the subpopulation of patients who cannot be weaned from PN, either by intensive medical management and/or following surgical bowel lengthening procedures, new and innovative strategies need to be developed to reduce the morbidity and mortality associated with its long-term use. A national consortium of pediatric practitioners who specialize in the care of children with intestinal failure has recently been established and plans to begin reviewing current practices of medical, nutritional, and surgical care for children with intestinal failure. It is anticipated that a multicenter, prospective study will be required to fully evaluate treatment strategies to enhance the quality of life for children with intestinal failure.

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Discussion

Brad W. Warner, M.D. (Cincinnati, OH): This was a very nice presentation and I enjoyed it very much. Your hypothesis is that a multidisciplinary program results in better outcomes and this is the best way to manage these children. However, a little more than 10% actually wean from TPN in your series. I guess that may be viewed as not such a great outcome. The best outcome parameter would seem to be a high percentage of patients that completely wean from TPN.

In addition, one of the things that I noticed is that you had a rather small number of patients that were subjected to lengthening procedures. I think only 14 or so patients underwent Bianchi and STEP procedures combined. In contrast with Deb Sudan's series that was recently presented from the University of Nebraska at the American Surgical a few weeks ago, about 80 patients underwent STEP and lengthening procedures combined. So, assuming you have a similar patient population, why are they doing much more lengthening procedures and you are doing more transplantation?

My other question is what are your specific criteria for going right to transplantation before attempting a lengthening procedure? Is it intestinal length, is it the presence or absence of cirrhosis, or is it a specific bilirubin level? When do you pull the trigger and go right to transplant versus allowing a patient to either continue to adapt or subject them to a lengthening procedure?

I very much enjoyed your presentation. Thank you for the opportunity to comment.

Anita Nucci, Ph.D. (Pittsburgh, PA): We were surprised at the numbers as well. Our program has evolved over the last year. We have now a number of surgeons and gastroenterologists on our team as well as representatives from radiology that attend our weekly clinical meetings. I think our population is pretty sick; about a third of the children who come to us have bili's over 12. So sometimes it is not an option. We have actually changed the name of our center from the intestinal care center to the intestinal care and rehabilitation center. We are certainly looking to do more rehabilitation, and part of the reason that I am here is to spread the word that we believe getting the children to us sooner will have better results in terms of weaning from TPN and adaptation. I hope that answers the first question.

The second one, the criteria, many of the children that come to us have had multiple hospitalizations for sepsis line infections, and we have the whole team there and we talk about, okay, when is enough enough? We have tried too advance feedings; it has been unsuccessful. I can't say that there is a specific time period at which we say, okay, that's it, it is time to stop. But if we have multiple hospitalizations, are unable to advance feedings, the liver function tests are increasing, then the transplant team is right there and we move forward. If there are any of my colleagues here in the audience who would like to expand on that, I don't have specific numbers.

Christopher Duggan, M.D. (Boston, MA): I had a question about the mortality rate. The 93% figure wasn't clear to me, because it looked like the total number of deaths was 109 and the denominator would be 389. So I didn't quite figure the 93%. The 93% was the survival rate of the people who came off of PN?

Dr. Nucci: That survived? Yes, that is correct.

Dr. Duggan: The overall mortality rate would obviously be much higher, correct?

Dr. Nucci: Yes.

Dr. Duggan: And the causes of death of children weaned from parenteral nutrition?

Dr. Nucci: That is a very good question. I apologize, I don't know it off the top of my head.

Alan L. Buchman, M.D., M.S.P.H. (Chicago, IL): The title of your talk was a multidisciplinary approach, but the only thing that I heard anything about were the surgeons, intestinal lengthening procedures, and intestinal transplantation, the latter of which I wonder if you were quick to jump to. What exactly did the gastroenterologists, the nurses, the pharmacists and everybody else do? Do you use algorithms in the management of your patients? Why are you an intestinal rehabilitation center? What is it that you do? And what is your approach to your patients other than transplantation?

Dr. Nucci: Well, that is a great question. I think Pittsburgh is well known for transplantation, and quite honestly, a huge number of the population I just presented were really referred for intestinal transplantation. We have a wonderful gastroenterology team, and we have recently added a physician assistant; we will be getting a second.

We have focused our attention on medical management in the last year, and that is really where we would like to take this program. So the gastroenterologists are working very closely with the patients. We now have an inpatient intestinal care rehabilitation service where the gastroenterologists round with the physician assistant and the dietitian and the nurse on a daily basis.

Dr. Buchman: They round, but my question was, do you have an algorithm approach? What do you do? What is your intestinal rehabilitation?

Dr. Nucci: We are in the process of creating policies. We are very individualized. I can't say that we have a certain criteria: okay, we start at 10 ml/hr and we go to 20 and then we go to 30 and we use X formula and then go to Y formula. We don't have it that specific. Many of the children who come to us are on different products, different phases of their disease, and so it is very much individualized. However, we are in the process of trying to get at least some standards for our institution.

Dr. Buchman: We will look forward to that next year.

Dr. Nucci: Thank you very much.

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Morbidity of Ostomy Takedown

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Abstract
Purpose Creation of a temporary ostomy is a surgical tool to divert stool from a more distal area of concern (anastomosis, inflammation, etc). To provide a true benefit, the morbidity/mortality from the ostomy takedown itself should be minimal. The aim of our study was therefore to evaluate our own experience and determine the complications and mortality of stoma closure in relation to the type and location of the respective ostomy.
Methods Patients undergoing an elective takedown of a temporary ostomy at our teaching institution between January 1999 and July 2005 were included in our analysis, and the medical records were retrospectively reviewed. Excluded were only patients with relevant chart deficiencies and nonelective stoma revisions/takedowns. Data collected included general demographics; the type and location of the stoma; the operative technique; and the type, timing, and impact of complications. Perioperative morbidity was defined as complications occurring within 30 days from the operation.
Results 156 patients (median age 45 years, range 18–85) were included in the analysis: 31 loop and 59 end colostomy reversals and 56 loop and 10 end ileostomy takedowns. Mean follow-up was 6 months. The overall mortality rate was low (0.65%, 1/156 patients). However, the morbidity rate was 36.5% (57 patients), with 6 (3.8%) systemic complications and 51 (32.7%) local complications. Minor would infection (34 patients, 21.8%) and postoperative ileus (9 patients, 5.7%) were the most common surgery-related complications, but they generally resolved with conservative management. Anastomotic leak and formation/persistence of an enterocutaneous fistula (6 patients, 3.8%) were the most serious local complications and required reintervention in all of the patients. Closure of a loop colostomy accounted for half and Hartmann reversals for one third of these complications, as opposed to ileostomy takedowns, which accounted for only one sixth (1.8% absolute risk).
Conclusion Takedown of a temporary ostomy has a low mortality but a nonnegligible morbidity. The stoma location (large vs. small bowel) has a higher impact than the type of stoma construction (end vs. loop) on the incidence and severity of complications.

Keywords Stoma · Ostomy · Ileostomy · Colostomy · Reversal · Takedown · Morbidity

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Introduction

Creation of a temporary ostomy is a common surgical tool to avoid an anastomosis or to divert stool from a more distal area of concern. The purpose and the type of construction may vary according to the individual circumstances and the surgeon's preference. From a technical point of view, an ileostomy is to be distinguished from a colostomy; an end from a loop ostomy. The indications for performing a diverting ostomy generally belong to one of three categories: (1) therapeutic intent, (2) symptom relief, or (3) prophylaxis. Therapeutic indications include discontinuous resections, often performed under emergency conditions

(e.g., perforated viscus, obstructing tumor, fulminant colitis) to completely eliminate the risk of an anastomosis under unfavorable conditions. Symptom relief and prophylaxis aim at reducing the negative impact of stool in these distal segments. While it has become clear that an anastomotic leak cannot be prevented by a proximal diversion,[1] the negative impacts thereof can.[2,3] Hence, the ostomy reduces the septic sequelae and allows a critical distal anastomosis to heal or an area of inflammation, for example diverticulitis or an anastomotic leak, to resolve.[4,5] Furthermore, symptomatic relief may be achieved in a patient who experiences a relevant distal problem, e.g., lack of fecal control, large rectovaginal fistula, pelvic sepsis, etc.

Nonetheless, creation of an ostomy remains a mixed blessing. While there are some obvious advantages in defined situations, the disadvantages should not be overlooked. These range from the general negative impact of an ostomy on the patient's quality of life to the fact that 20–40% of "temporary" ostomies are never reversed. Furthermore, with a reported 5–15% leak rate for a total mesorectal excision,[2,6–8] the majority of prophylactic ostomies in the end are not needed. Most importantly, however, an ostomy will only provide a true benefit if the morbidity and mortality from the ostomy takedown/reversal itself remains minimal and is taken into the overall risk/benefit calculation. The aim of our study was therefore to evaluate our own experience and determine the complications and mortality of elective stoma closure in relation to the type and location of the respective ostomy.

Methods

Patients who underwent an elective takedown of an ostomy between January 1999 and July 2005 at our teaching institution were identified from the operating room case logs and scheduling records. The medical records were retrieved and retrospectively reviewed. Excluded were patients with relevant chart deficiencies and patients with emergency indications for ostomy revisions or takedowns. Data collection included general demographics; the type and location of the stoma; the operative technique; and the type, timing, and impact of complications. Perioperative morbidity was defined as complications occurring within 30 days from the operation.

Descriptive statistics were used for data analysis and presentation. Differences between groups were assessed for statistical significance ($p<0.05$) using either χ^2 test (comparison of proportions), unpaired Student's t test (comparison of two groups), or one-way analysis of variance (ANOVA) and the Student's–Newman–Keuls test as a post hoc test (comparison of more than two groups). This study was approved by the Institutional Review Board of the University of Southern California and is in compliance with current Health Insurance Portability and Accountability Act regulations.

Results

One hundred fifty six patients (108 males, 48 females) with a mean patient age of 44.8±15 years (median 45.5, range 18–85 years) fulfilled the study criteria and were included in the analysis. Mean follow-up after discharge was 24±15 months (range 13–96 months), excluding one patient after an ileostomy takedown who left against medical advice on postoperative day 4 and was lost to follow up.

The patient characteristics are shown in Table 1. Thirty one loop and 59 Hartmann-type end colostomy reversals and 56 loop and 10 end ileostomy takedowns were included in the analysis. Mean follow-up was 6.3±1 months (median 3, range 1–72 months). The underlying conditions for which the ostomies were created differed considerably for the various types of ostomy (see Fig. 1, Table 1). Loop colostomies were overwhelmingly done for trauma (61%), end ileostomies for fulminant colitis (100%). Both of these categories are therefore characterized by relatively young average ages at 37.3±12.9 and 38.2±12.8 years, respectively. In contrast, end colostomies or loop ileostomies were more frequently performed in the context of malignancy or diverticulitis, and the average ages in these groups are evidently higher at 44.3±13.7 and 50.8±16.8 years ($p<0.05$). We did not perform statistical comparisons between the groups for the parameters "duration since the creation of the ostomy" or for the "causative nature" because these parameters were outside our direct realm of influence and were largely the result of other surgeons' practice patterns or of logistic factors related to the indigent patient population.

Operative time overall was 132±73 min (range 25–360 min), but a difference could be observed between the shorter time needed for takedown of loop ostomies (116±52 and 77±33 min, see Table 1) as compared to the often more complex and, hence, time-consuming reversal of end ostomies (ileostomy 133±90 and colostomy 171±59 min, respectively, $p<0.05$ when compared to loops). No statistical difference between the groups was noted for the length of stay.

The overall mortality rate was low, as only 1 out of 156 patients died (0.65%) due to a bleeding complication after he was started on warfarin for a pulmonary embolism. The overall perioperative morbidity rate (≤30 days) was 36.5% (57/156 patients). Systemic complications occurred in 6 patients (3.8%) and included pulmonary complications (pneumonia, pulmonary embolism, adult respiratory distress syndrome, $n=3$), temporary hyperbilirubinemia of unknown

Table 1 Baseline Characteristics

	Loop colostomy n=31 (%)	End colostomy n=59 (%)	Loop ileostomy n=56 (%)	End ileostomy n=10 (%)	Total n=156 (%)
Age (years)[a]	37±13	44±14	51±17	38±13	45±15
Creation of stoma for[b]					
Trauma	19 (61.3)	17 (28.8)	3 (5.4)	–	39 (25.0)
Cancer	2 (6.5)	10 (16.9)	30 (53.6)	–	42 (26.9)
Benign	9 (29.0)	30 (50.8)	22 39.3)	10 (100)	71 (45.5)
Iatrogenic	1 (3.2)	2 (3.4)	1 (1.8)	–	4 (2.6)
Interval since creation of ostomy (months)[b]	17±33	15±25	13±24	11±9	15±29
Duration of surgery (min)[c]	116±52	171±59	77±33	133±90	132±73
Median length of stay (days)[d]	5	6	6	8	6

[a] Groupwise comparison of age by ANOVA found differences significant between loop ileostomy vs. loop colostomy (p<0.001), loop ileostomy vs. end ileostomy (p=0.033), and loop ileostomy vs. end colostomy (p=0.017). Other differences between groups were not significant
[b] Not tested for significance (see text)
[c] Groupwise comparison of duration of surgery by ANOVA found differences significant between end colostomy vs. loop ileostomy (p<0.001), end colostomy vs. loop colostomy (p<0.001), end colostomy vs. end ileostomy (p=0.041), and end ileostomy vs. loop ileostomy (p=0.004). Other differences between groups were not significant
[d] Not significant differences

cause (n=1), acute gastric dilatation (n=1), and mental confusion (n=1) (Table 2). These numbers were too small to reveal any trend with regards to the type of stoma being reversed.

Local complications were more common and involved 51 patients (32.7%). All wounds were primarily closed with mass closure of the fascia and muscle layer, irrigation of the wound with diluted povidone-iodine, loose approximation of the fat layer, and skin closure with either staples or subcuticular sutures (according to surgeon's preference). No abdominal wall drain was left. Antibiotic prophylaxis was given for 24 h. Minor wound infections developed in 34 individuals (21.8%). All of these infections could be managed conservatively (open wound care) and did not require any surgical intervention. Prolonged postoperative ileus or small bowel obstruction was present in 9 patients (5.7%, 5 end colostomies, 4 loop ileostomies), but these resolved with conservative measures in all patients.

Anastomotic leak and formation/persistence of an enterocutaneous fistula were the most serious local complications (6 patients, 3.8%) and required reintervention in all of the patients. Closure of a loop colostomy was responsible for half and reversal of an end colostomy for one third of these complications and, hence, set the absolute risk for

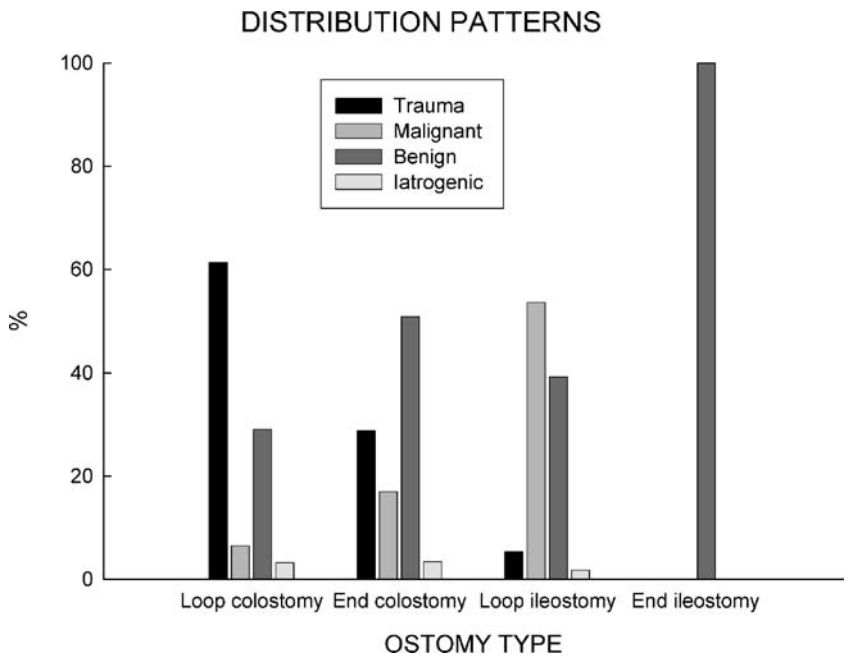

Figure 1 Distribution pattern of the various types of ostomies in relation to the reasons requiring creation of an ostomy: trauma, malignancy, benign diseases (e.g., diverticulitis, inflammatory bowel disease), iatrogenic (e.g., instrument perforation, anastomotic leak).

Table 2 Complications Separated per Type of Ostomy

	Loop colostomy		End colostomy		End ileostomy		Loop ileostomy		Total		$p<0.05$
	$n=31$	(%)	$n=59$	(%)	$n=10$	(%)	$n=56$	(%)	156	(%)	
Systemic complication	0	–	3	(5.1)	1	(10.0)	2	(3.6)	6	(3.8)	
Bleeding	0	–	0	–	0	–	0	–	0	–	
Wound infection	8[a]	(25.8)	20[b]	(33.9)	2	(20.0)	4[a,b]	(7.1)	34	(21.8)	0.04[a,b]
Anastomotic leak	1	(3.2)	1	(1.7)	0	–	0	–	2	(1.3)	ns
Enterocutaneous fistula	2	(6.5)	1	(1.7)	0	–	1	(1.8)	4	(2.6)	
Abscess	0	–	0	–	0	–	0	–	0	–	
Ileus	0	–	4	(6.8)	0	–	2	(3.6)	6	(3.8)	
Obstruction	0	–	1	(1.7)	0	–	2	(3.6)	3	(1.9)	
Fascial dehiscence	1	(3.2)	0	–	1	(10.0)	0	–	2	(1.3)	
Stricture	0	–	0	–	0	–	0	–	0	–	
Late obstruction	0	–	0	–	0	–	0	–	0	–	
Incisional hernia	1	(3.2)	5	(8.5)	0	–	0	–	6	(3.8)	

[a] Significant difference between loop ileostomy and loop colostomy.
[b] Significant difference between loop ileostomy and end colostomy.

those two ostomy reversals at 9.7 and 3.7%, respectively. In contrast, only one ileostomy takedown (loop) resulted in formation of an enterocutaneous fistula (1.8% absolute risk, 16.7% relative risk).

Information about long-term risks beyond the 30 perioperative days is limited because of the relatively short follow-up: none of the patients developed a stricture or a bowel obstruction. However, 6 patients developed an incisional hernia (3.8%).

Discussion

Ostomies are considered as both friend and enemy. Creation of a temporary ostomy is commonly used to avoid an anastomosis or to divert stool from a more distal area of concern. While an anastomotic leak cannot be prevented by a proximal diversion, the septic sequelae thereof can be reduced and give an area sufficient time to heal.[2,3] In addition, some patients just symptomatically benefit if they are very symptomatic from a distal problem that cannot immediately be fixed.

In the trauma literature, the traditional paradigm of avoiding an anastomosis in severe multiorgan injury[9,10] is shifted to the opposite. In fact, an increasing trend is observed to avoid any ostomy but to perform a primary repair of even severe colonic injuries.[11] One of the arguments for this strategy comes from the fear of complications related to the ostomies.[12] The data, however, are too confusing to support such a counterintuitive statement. Nonetheless, it is obvious that an ostomy will only provide a true benefit if the presence of the ostomy as such does not interfere with the patient's ability to recover and if the morbidity and mortality from the ostomy takedown/reversal itself remains minimal. Treatment algorithms should be developed that take these additional parameters into the overall risk/benefit calculation. The aim of our study was therefore to determine the incidence and impact of complications and mortality after various types of elective stoma closure.

Our data show that the overall risk of serious complications is low, particularly if local wound complications are not taken into consideration. The justification for doing that has to be seen from a different angle and in the context that many surgeons leave an ostomy site primarily open, hence treating 100% of these wounds with open wound care. We, however, closed all sites for the benefit of the 78% of patients who heal just fine in much shorter time and accept the 22% wound infection rate because only that minority has to deal with the prolonged hassle of open wound care. Although there was also a relevant morbidity in our series, it was a magnitude lower than that reported in the trauma literature.[12]

The risk of serious local complications is low, and overall, it is too low to establish a direct comparison and analysis of the causative factors. Nonetheless, the trend to a higher and relevant leak rate in colostomy takedowns as opposed to ileostomy takedowns is concerning. While the creation of a temporary ileostomy is truly associated with minimal risks and, thus, fulfills the criteria for a beneficial prophylaxis, this cannot be stated for temporary colostomies that carry a relevant risk of intraoperative difficulties at the time of the takedown and of postoperative complications.[13]

Our data are in line with published data from the literature,[14–19] although there are also some controversial reports.[3] In terms of establishing algorithms, a diverting colostomy or discontinuous resection should therefore be avoided if possible.[8] There are a number of recent

publications and reviews in the literature that question the value of a discontinuous Hartmann-type resection, as no striking benefit compared to a primary anastomosis could be documented.[20,21] In case a diversion is felt to be needed, an ileostomy appears to be preferable and simplifies the later takedown.[22] Trauma surgeons appear somewhat more reluctant to consider an ileostomy, but when a primary anastomosis appears delicate, creation of an ileostomy should be contemplated.

Preference to create an ileostomy has essentially become the common practice in the colorectal subspecialty at our institution. Low anterior resections are not routinely diverted, unless specific risk constellations (neoadjuvant chemoradiation, malnutrition) are present. Hartmann-type discontinuous resections are avoided if possible. Where tissue quality and the patients' overall condition permit, a primary anastomosis is fashioned, which – if necessary – is protected with an ileostomy.

The retrospective nature of our study has obvious limitations, and the differences noted therefore have to be interpreted with caution. Nonetheless, the trend is obvious and should be further assessed in a prospective fashion.

Conclusion

Takedown of a temporary ostomy is safe and has a low mortality. There is a nonnegligible overall morbidity, but the risk of serious complications that would require another surgery is low. The stoma location (large vs. small bowel) has a higher impact than the type of stoma construction (end vs. loop) on the incidence and severity of complications. The reported risks have to be taken into the overall benefit/risk analysis before deciding on a discontinuous colonic resection or a prophylactic fecal diversion.

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Frequency With Which Surgeons Undertake Pancreaticoduodenectomy Continues to Determine Length of Stay, Hospital Charges, and In-Hospital Mortality

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Abstract
Introduction This study was undertaken to determine changes in the frequency of, volume of, and outcomes after pancreaticoduodenectomy 6 years after a study denoted that, in Florida, the frequency and volume of pancreaticoduodenectomy impacted outcome.
Methods Using the State of Florida Agency for Health Care Administration database, the frequency and volume of pancreaticoduodenectomy was correlated with average length of hospital stay (ALOS), in-hospital mortality, and hospital charges for identical periods in 1995–1997 and 2003–2005.
Results Compared to 1995–1997, 88% more pancreaticoduodenectomy was performed in 2003–2005 by 6% fewer surgeons; the majority of pancreaticoduodenectomies were conducted by surgeons doing <1 pancreaticoduodenectomy every 2 months. In-hospital mortality rate did not decrease from 1995–1997 to 2003–2005 (5.1 to 5.9%); in-hospital mortality rate increased for surgeons undertaking <1 pancreaticoduodenectomy every 2 months (5.5 to 12.3%, $p<0.01$). For 2003–2005, frequency with which pancreaticoduodenectomy is conducted inversely correlates with ALOS ($p=0.001$), hospital charges ($p=0.001$), and in-hospital mortality ($p=0.001$).
Conclusions In Florida, more pancreaticoduodenectomies are carried out by fewer surgeons. Mortality has not decreased because of surgeons infrequently performing pancreaticoduodenectomy. Most pancreaticoduodenectomies are still undertaken by surgeons who conduct pancreaticoduodenectomy infrequently with greater lengths of stay, hospital costs, and in-hospital mortality rates. To an even greater extent than previously documented, patients are best served by surgeons frequently performing pancreaticoduodenectomy.

Keywords Pancreaticoduodenectomy · Pancreatic cancer · High-volume

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Introduction

Numerous studies purport that complex operations are best carried out by "high-volume" surgeons and/or at "high-volume" centers.[1–4] With the initial realization that "volume" might impact outcome and best results might be obtained at "high-volume" centers and/or by "high-volume" practitioners, numerous disorders, diseases, and procedures were studied to determine if the implications of "volume" applied specifically to them. Among many disorders, diseases, and procedures, pancreatic cancer and pancreaticoduodenectomy were studied.[1–15] In 2001, we documented that the frequency with which surgeons in Florida conduct pancreaticoduodenectomy impacted length of hospital stay, hospital charges, and in-hospital mortality.[16]

That study documented a direct parallel between the frequency with which pancreaticoduodenectomy is undertaken by surgeons and outcome and documented that this parallel is independent of hospital volume.

Times change, and progress inexorably moves forward. Presumably, given the body of work that promotes the relationship between "volume" and outcome, practice patterns of care-providers and medical centers would change promoting preferential utilization of "high-volume" surgeons and "high-volume" centers for complex procedures. Notably, this has not been documented. Although great enthusiasm and notice were given to reports documenting the relationship between "volume" or "frequency" and outcome, little effort has been expended to measure the impact of these reports on changing the practice patterns of care-providers and medical centers.

Given that 6 years has passed as publication of our report documenting the relationship between frequency of pancreaticoduodenectomy in Florida and outcome, we thought it fitting to determine the impact of the report and the collective body of supportive work. Specifically, we sought to determine changes in the number of pancreaticoduodenectomies conducted in Florida and to again determine outcomes after pancreaticoduodenectomy in Florida. We also sought to assess if the frequency with which surgeons perform pancreaticoduodenectomy in Florida has changed and to reassess the impact of the frequency of pancreaticoduodenectomy on outcome. Finally, we again sought to determine the impact of hospital volume on the relationship between the frequency with which surgeons undertake pancreaticoduodenectomy and outcome.

Our hypotheses in undertaking this study were that, as our last study was performed, pancreaticoduodenectomy would be more often conducted in Florida and outcome after pancreaticoduodenectomy in Florida would be improved. As well, we hypothesized that pancreaticoduodenectomy in Florida would now be relatively concentrated, with more resections being carried out by relatively fewer surgeons. We also hypothesized that the frequency with which surgeons perform pancreaticoduodenectomy would impact length of hospital stay, hospital charges, and in-hospital mortality.

Methods

The database for the State of Florida Agency for Health Care Administration was queried to identify all pancreaticoduodenectomies undertaken over a 33-month period from January 1, 2003 through September 30, 2005. Previously, the database for the State of Florida Agency for Health Care Administration had been queried to identify all pancreaticoduodenectomies conducted over a 33-month period from January 1, 1995 through September 30, 1997.[16] Surgeons conducting pancreaticoduodenectomy were identified, as were the medical centers (e.g., hospitals) at which the resections were undertaken. The number of pancreaticoduodenectomies per surgeon was calculated. For illustrative purposes, surgeons were grouped by the number of pancreaticoduodenectomies they performed over the 33-month periods, ranging from 1–3 pancreaticoduodenectomies (i.e., 1 or fewer per year), 4–9 pancreaticoduodenectomies (i.e., 1–3 per year), 10–16 pancreaticoduodenectomies (i.e., 4–6 per year), or 17 or more pancreaticoduodenectomies (i.e., more than one every other month). Rather arbitrarily, the frequency with which surgeons carry out pancreaticoduodenectomy was designated as "high-volume" when surgeons undertook, on average, more than one pancreaticoduodenectomy every other month over the 33 months of the study periods. The number of surgeons conducting pancreaticoduodenectomies at each hospital was determined, as was the comorbidities of the patients they operated upon and the nature of their results.

In the state database, comorbidities of patients operated upon were stratified by coders at the time of discharge, as none, minor, moderate, major, or extreme. Average length of hospital stay (ALOS), average hospital charges, and in-hospital mortality after pancreaticoduodenectomy, stratified by patient comorbidities, were calculated for each surgeon.

Data from three medical schools in Florida, which included the University of South Florida, the University of Florida, and the University of Miami, were analyzed to investigate the interplay between "high-volume" centers and the frequency with which surgeons perform pancreaticoduodenectomy on outcome.

Data Management

Data were entered and stored in Microsoft Excel (Microsoft Corp., Redmond, WA, USA). Statistical analyses were undertaken utilizing Graphpad Instat version 3.06 (Graphpad Software Inc., San Diego, CA, USA). Because the Agency for Health Care Administration groups data by year of pancreaticoduodenectomy and by perioperative comorbidities, some data were summary (i.e., pooled) data and, thereby, not amenable to some statistical analyses.

Results

The number of pancreaticoduodenectomies undertaken in the State of Florida increased from 698 over 33 months in 1995–1997 to 1,314 over an identical 33-month period in 2003–2005. This represents an increase of 88% in the number of pancreaticoduodenectomies. These pancreaticoduodenectomies were conducted by 6% fewer surgeons in 2003–2005 (266 surgeons versus 282 surgeons; Table 1).

Table 1 Pancreaticoduodenectomies (PD) Undertaken in Florida in 1995–1997 and 2003–2005, Stratified by the Frequency with which Surgeons Undertook Pancreaticoduodenectomy

# PD per surgeon over 33 months	Period	# surgeons	# PD over 33 months
1 to 3 (≤1 PD every year)	1995–1997	251	365
	2003–2005	192	284
4 to 9 (≤1 PD every 4 months)	1995–1997	21	111
	2003–2005	50	287
10 to 16 (≤1 PD every 2 months)	1995–1997	4	52
	2003–2005	9	113
≥17 (>1 PD every 2 months)	1995–1997	6	170
	2003–2005	15	630
TOTAL	1995–1997	282	698
	2003–2005	266	1,314

In 1995–1997, surgeons undertaking one or fewer pancreaticoduodenectomies per year (i.e., three or fewer pancreaticoduodenectomies over 33 months) undertook 365 pancreaticoduodenectomies, which accounts for 52% of all pancreaticoduodenectomies performed. In 2003–2005, surgeons conducting one or fewer pancreaticoduodenectomies per year conducted 284 pancreaticoduodenectomies, which accounts for 22% of all pancreaticoduodenectomies carried out in 2003–2005. This is a decrease of 22% from 1995–1997 to 2003–2005 (Table 1). In 1995–1997, surgeons performing less than one pancreaticoduodenectomy every other month (i.e., 16 or fewer pancreaticoduodenectomies over 33 months) undertook 528 pancreaticoduodenectomies. This accounts for 76% of all pancreaticoduodenectomies undertaken in the 33 months of 1995–1997. In 2003–2005, surgeons conducting less than one pancreaticoduodenectomy every other month carried out 684 pancreaticoduodenectomies, which is an increase of 30% from 1995–1997 and accounts for 52% of all pancreaticoduodenectomies conducted in 2003–2005 (Table 1). In 2003–2005, surgeons conducted more than one pancreaticoduodenectomy every other month performed 630 pancreaticoduodenectomies, which accounts for 48% of all pancreaticoduodenectomies undertaken. This volume of pancreaticoduodenectomies by "high-volume" surgeons represents an increase of 271% over 1995–1997 (Table 1).

In 1995–1997, the ALOS after pancreaticoduodenectomy was 21 days versus 16 days in 2003–2005, representing a 24% decrease in length of stay (Table 2). Average length of in-hospital stay was inversely related to the frequency with which surgeons undertook pancreaticoduodenectomy in 1995–1997 (p=0.03) and in 2003–2005 (p=0.001, Spearman regression; Table 2).

From 1995–1997 to 2003–2005, in-hospital mortality did not change (5.1 versus 5.9%; p=0.45, chi-square test; Table 2). However, from 1995–1997 to 2003–2005, in-hospital mortality significantly increased for surgeons performing one or fewer pancreaticoduodenectomy per year (5.5 to 12.3%; p=0.003, Fisher exact test; Table 2). Primarily, as a consequence of this increased mortality rate in 2003–2005, in-hospital mortality significantly increased for surgeons conducting less than one pancreaticoduodenectomy every 2 months (i.e., <16 pancreaticoduodenectomies over 33 months; p=0.03, chi-square test). In both 1995–1997 and 2003–2005, in-hospital mortality inversely related to frequency with which surgeons carried out pancreaticoduodenectomy (p=0.001, Spearman regression; Table 2).

Unadjusted cost of care increased from 1995–1997 to 2003–2005 by 63% (Table 3). Per patient, cost of care increased by *<45,455. In-hospital cost of care inversely related to the frequency with which surgeons performed pancreaticoduodenectomy in 1995–1997 and 2003–2005 (p=0.001, chi-square test for trend; Table 3).

Of patients undergoing pancreaticoduodenectomy in 2003–2005, 80% had major or extreme comorbidities (Table 4). The percentage of patients having major or extreme comorbidities was inversely related to the frequency with which surgeons undertook pancreaticoduodenectomy (p<0.0001, Spearman regression; Table 4).

Of six surgeons conducting more than one pancreaticoduodenectomy every other month in 1995–1997, five (83%) were at a medical school (Table 5). These five surgeons conducted 150 pancreaticoduodenectomies, which accounts for 21% of the pancreaticoduodenectomies performed in 1995–1997. By 2003–2005, the number of "high-volume" surgeons increased by 9 to 15, equating to

Table 2 Average Length of Stay (ALOS) and In-Hospital Mortality After Pancreaticoduodenectomy (PD) in Florida during 1995–1997 and 2003–2005 Stratified by the Frequency with which Surgeons Undertook Pancreaticoduodenectomy

# PD per surgeon over 33 months	Period	ALOS[a] (days)	In-hospital mortality[a] (%)
1 to 3 (≤1 PD every year)	1995–1997	23	5.5
	2003–2005	18	12.3[b]
4 to 9 (≤1 PD every 4 months)	1995–1997	20	9.9
	2003–2005	16	7.3
10 to 16 (≤1 PD every 2 months)	1995–1997	18	0
	2003–2005	15	7.1
≥17 (>1 PD every 2 months)	1995–1997	17	2.6
	2003–2005	15	2.2
TOTAL	1995–1997	21	5.1
	2003–2005	16	5.9

[a] Significantly inversely related to the frequency with which surgeons undertook pancreaticoduodenectomy in 1995–1997 and in 2003–2005 (p<0.05; Spearman regression)

[b] Significantly greater than in 1995–1997, p<0.03, chi-square test

Table 3 Percentage of Hospital Charges for Pancreaticoduodenectomy in 1995–1997 and 2003–2005 Stratified by the Frequency with which Surgeons Undertook Pancreaticoduodenectomy Relative to the "High Frequency" Surgeon Group and Total Hospital Charges during both Time Periods

# PD per surgeon over 33 months	Period	Hospital charges[a]	Percentage of hospital charges relative to the "high frequency" surgeons (≥17 PD over 33 months or > 1 PD every 2 months)	Percentage of hospital charges relative to total hospital charges during time period (%)
1 to 3 (≤1 PD every year)	1995–1997	$83,352	172.10%	30.93
	2003–2005	$145,115	137.90%	30.33
4 to 9 (≤1 PD every 4 months)	1995–1997	$70,479	145.60%	26.15
	2003–2005	$122,509	116.50%	25.61
10 to 16 (≤1 PD every 2 months)	1995–1997	$67,193	138.80%	24.94
	2003–2005	$105,589	100.40%	22.07
≥17 (>1 PD every 2 months)	1995–1997	$48,419	N/A	17.97
	2003–2005	$105,168	N/A	21.98
Total	1995–1997	$269,443		
	2003–2005	$478,381		

[a] In-hospital cost of care inversely related to the frequency with which surgeons performed pancreaticoduodenectomy in 1995–1997 and in 2003–2005 ($p=0.001$, chi-square test for trend)

a 150% increase. In 2003–2005, of 15 "high-volume" surgeons, 10 (67%) were at medical schools (Table 5). These ten surgeons carried out 452 pancreaticoduodenectomies, which accounts for 34% of the pancreaticoduodenectomies undertaken in 2003–2005. This represents significantly more and relatively more pancreaticoduodenectomies performed by "high-volume" surgeons at medical schools ($p<0.0001$, chi-square test).

The number of pancreaticoduodenectomies at Florida's medical schools increased from 204 in 1995–1997 to 582 in 2003–2005, an increase of 185% (Table 6). Of the increase in pancreaticoduodenectomies, 48% were patients with major comorbidities. Medical school A had the relatively largest number of patients with extreme comorbidities, 29%. In 2003–2005, the percentage of patients with major or extreme comorbidities undergoing pancreaticoduodenectomy in the State of Florida or at medical school A, B, or C was 80, 76, 75, or 62%, respectively. The degree of comorbidities impacted length of stay, with significantly greater average in-hospital length of stay for patients with increased severity of comorbidities ($p<0.01$, Spearman regression; Table 7).

Medical school A had six surgeons undertaking pancreaticoduodenectomies in 1995–1997 and 18 surgeons undertaking pancreaticoduodenectomies in 2003–2005 (Table 8). In 1995–1997, the highest volume surgeon undertook 46 pancreaticoduodenectomies, whereas in 2003–2005, the highest volume surgeon undertook 106 pancreaticoduodenectomies, an increase of 130%. The frequency with which surgeons undertook pancreaticoduodenectomy was inversely related to the severity of comorbidities in 2003–2005 ($p=0.056$) but not in 1995–1997 ($p=0.71$, Spearman regression). ALOS significantly correlated inversely with frequency with which surgeons undertook pancreaticoduodenectomy in 1995–1997 ($p=0.035$) but not in 2003–2005 ($p=0.10$, Spearman regres-

Table 4 The Percentage of Patients with Major or Extreme Comorbidities Undergoing Pancreaticoduodenectomy in 2003–2005 Stratified by the Frequency with which Surgeons Undertook Pancreaticoduodenectomy

# PD per surgeon over 33 months	Major/extreme comorbidities[a] (%)
1 to 3 (≤1 PD every year)	90
4 to 9 (≤1 PD every 4 months)	87
10 to 16 (≤1 PD every 2 months)	78
≥17 (>1 PD every 2 months)	73
Total	80

[a] The percentage of patients having major or extreme comorbidities was inversely related to the frequency with which surgeons undertook pancreaticoduodenectomy ($p<0.0001$, Spearman regression)

Table 5 Number of Pancreaticoduodenectomies (PD) Undertaken by High-Volume Surgeons at Three Medical Schools in Florida in 1995–1997 and 2003–2005 with Associated Average Length of Stay (ALOS), Preoperative Comorbidities, and In-Hospital Mortality

Medical school		# high-volume surgeons	# PD	ALOS (days)	% major/extreme comorbidities	In-hospital mortality (%)
A	1995–1997	3	86	20	84	3.5
	2003–2005	5	225	15	76	2.2
B	1995–1997	2	64	13	61	0.0
	2003–2005	3	61	16	73	1.6
C	1995–1997	0	0	–	–	–
	2003–2005	2	166	15	62	0.0

Table 6 Severity of Perioperative Comorbidities in Patients Undergoing Pancreaticoduodenectomy (PD) at Each of the Three Medical Schools in Florida

Medical school	Age (years)	Minor (%)	Moderate (%)	Major (%)	Extreme (%)	Total # PD
A 1995–1997	65	7	9	57	27[a]	97
2003–2005	62	15[b]	8	47[b]	29[c]	295
B 1995–1997	60	20	18	49	12[b]	88
2003–2005	60	13	12	57	18[b]	83
C 1995–1997	64	–	16	32	53	19
2003–2005	60	20	17	48	14[b]	204

All but one death occurred in patients with major or extreme comorbidities.
[a] Three deaths
[b] One death
[c] Five deaths

sion; Table 8). In-hospital mortality did significantly correlate inversely with frequency with which surgeons conducted pancreaticoduodenectomy in 1995–1997 (p= 0.033) and in 2003–2005 (p=0.027, Spearman regression; Table 8).

Discussion

The medical literature has documented that major medical illnesses and operative conditions are typically cared for at less cost, with shorter hospitalizations, and with lower in-hospital mortality at centers where the illnesses and operations are relatively more often treated or undertaken.[1–15] Six years ago, we documented that, in Florida in 1995–1997, the frequency with which surgeons conduct pancreaticoduodenectomy determined length of hospital stay, cost of hospital care, and in-hospital mortality.[16] Other reports have documented similar findings.[17,18] As well, we documented that, independent of hospital volume, surgeons who perform pancreaticoduodenectomy more frequently have shorter hospital stays, lower costs of hospital care, and lower in-hospital mortality rates, detracting from the concept of "center effect."[16] It is attractive to presume that, rather than just documenting "what is," this body of medical literature would direct medical professionals and systems to support the undertaking of complex care and operations by "high-volume" providers. This report documents that, in general, "high-volume" providers are more frequently conducting pancreaticoduodenectomies and doing so with results more disparate from "low-volume" providers, even in "high-volume" centers. Nonetheless, most pancreaticoduodenectomies in Florida are still undertaken by surgeons infrequently performing the operation with consequentially greater lengths of stay, hospital costs, and in-hospital mortality rates. Given increased in-hospital mortality from 1995–1997 to 2003–2005 for surgeons infrequently undertaking pancreaticoduodenectomy, patients needing pancrea-

Table 7 Average Length of Hospital Stay After Pancreaticoduodenectomy at Medical Schools A, B, and C in Florida in 1995–1997 and 2003–2005 Stratified by Preoperative Comorbidity

Medical School	Minor (days)	Moderate (days)	Major (days)	Extreme (days)	ALOS[a] (days)
A 1995–1997	17	18	18	27	20
2003–2005	14	12	14	20	16
B 1995–1997	11	11	14	30	15
2003–2005	11	14	15	24	16
C 1995–1997	–	21	18	27	24
2003–2005	13	10	15	21	15

[a] Degree of comorbidities significantly impacted length of stay (p< 0.01, Spearman regression)

Table 8 Summary Outcomes After Pancreaticoduodenectomy (PD) at Medical School A in Florida for 1995–1997 and 2003–2005 Stratified by Surgeons Undertaking the Procedures

Surgeon	Number of PD	% major or extreme comorbidity *	ALOS[a] (days)	In-hospital Mortality (%)[a, b]
1995–1997				
1	46	78	14	2.2
2	23	91	17	4.3
3	17	83	16	5.9
4	5	80	22	0.0
5	4	67	21	0.0
6	3	100	25	0.0
2003–2005				
1	106	74	14	3.7
2	37	70	15	0.0
3	33	85	18	0.0
4	31	81	13	0.0
5	18	78	18	5.6
6	15	67	15	6.7
7	15	80	18	13.3
8	15	87	29	6.7
9	6	67	20	0.0
10	5	80	15	0.0
11	5	80	18	0.0
12	4	75	14	0.0
13	1	100	7	0.0
14	1	0	1	0.0
15	1	100	10	0.0
16	1	100	39	0.0
17	1	100	5	0.0
18	1	100	7	0.0

[a] Significantly inversely related to frequency with which surgeons undertook pancreaticoduodenectomy in 1995–1997 ($p \leq 0.05$, Spearman regression)
[b] Significantly inversely related to frequency with which surgeons undertook pancreaticoduodenectomy in 2003–2005 (p=0.027, Spearman regression)

ticoduodenectomy are to an even greater extent than previously documented best served by surgeons frequently performing pancreaticoduodenectomy.

From 1995–1997 to 2003–2005, pancreaticoduodenectomy was nearly twice as often undertaken by nearly 10% fewer surgeons. This increase in the number of pancreaticoduodenectomies far exceeds the increase in population in the State of Florida. Furthermore, the reduction in the number of surgeons carrying out pancreaticoduodenectomy is incongruous with the growth in the number of surgeons in Florida. Surgeons conducting one or fewer pancreaticoduodenectomies per year have decreased, both in absolute number and in relative number. Surgeons performing six or fewer pancreaticoduodenectomies per year undertook nearly 30% more pancreaticoduodenectomies in 2003–2005, but that number of pancreaticoduodenectomies decreased as a portion of all the pancreaticoduodenectomies conducted from nearly three-quarters to nearly one-half. Thereby, more care is concentrated into the hands of fewer surgeons.

ALOS decreased from 1995–1997 to 2003–2005. As well, this report documents that the more frequently surgeons undertook pancreaticoduodenectomy, the shorter the ALOS. Although in-hospital mortality did not change between 1995–1997 and 2003–2005, it did increase for surgeons infrequently conducting pancreaticoduodenectomy. In-hospital mortality most notably increased for surgeons most infrequently performing pancreaticoduodenectomy. As in 1995–1997, in 2003–2005, mortality correlated inversely with the frequency with which surgeons undertook pancreaticoduodenectomy. Furthermore, cost of care correlated inversely with the frequency that surgeons carried out pancreaticoduodenectomy. Although cost of care increased dramatically, the cost data are unadjusted for inflation and changes in healthcare. Notably, with this dramatic rise in cost of care, surgeon remuneration has been without significant increase from 1995 through 2005 (Medicare reimbursement has increased by $767.88 from $1,779.42 in 1995 to $2,547.30 in 2007).

It is notable and not intuitive that surgeons most frequently undertaking pancreaticoduodenectomy, in general, operated upon patients with the least severe comorbidities. This implies that, in general, patients of highest medical risk were not preferentially sent to "high-volume" providers or "high-volume" centers. It also suggests that surgeons infrequently conducting pancreaticoduodenectomy may due so in suboptimal circumstances, at least relatively frequently operating on patients with higher medical comorbidities. The possibility of this surprising relationship between preoperative medical comorbidities and frequency of pancreaticoduodenectomy has been thoughtfully considered by others.[11] However, patients with lesser medical comorbidities are not always the "best" operative candidates. There are "tumor specific" issues that can impact outcome such as tumor size or tumor invasion into the portal vein.

The number of "high-volume" surgeons more than doubled from 1995–1997 to 2003–2005. Although that is notable, our definition of "high-volume" is certainly not rigorous. In 1995–1997, considerably more than three-quarters of the "high-volume" surgeons were on medical school faculties, whereas by 2003–2005, that number had decreased to two-thirds. Although the medical schools and their medical centers saw growth in their number of "high-volume" surgeons, growth in the number of "high-volume" surgeons outside the medical schools was relatively greater. Nonetheless, although most pancreaticoduodenectomies are performed outside the medical schools, the schools saw their faculty increase by more than 200% in the number of pancreaticoduodenectomies they undertook, which represents a larger proportion of pancreaticoduodenectomies undertaken in Florida (i.e., 21% in 1995–1997 to 34% in 2003–2005).

Most of the increase in pancreaticoduodenectomies by "high-volume" surgeons at the medical schools occurred with patients with major comorbidities. This may reflect that referring physicians recognize that pancreaticoduodenectomy now carries less major morbidity than in years past and they, thereby, refer patients of "marginal" health. This might also reflect increased patient awareness of the grave nature of pancreatic cancer and the critical role of resection. The impact of preoperative medical comorbidity on in-hospital mortality is impressive, as shown in Table 6. Notably, the general age of patients undergoing pancreaticoduodenectomies did not change from 1995–1997 to 2003–2005, unlike in New Jersey and New York.[18]

Each medical school had an increased number of "high-volume" providers. In general, each "high-volume" provider conducted more pancreaticoduodenectomies in 2003–2005 than in 1995–1997. At medical school A, five surgeons qualified as "high-volume" providers, and three more nearly did. Surgeons at medical school A doing the most pancreaticoduodenectomies operated upon "healthier" patients than surgeons infrequently undertaking pancreaticoduodenectomy, i.e., patients less likely to have major or extreme comorbidities. Consistent with state-wide data, the frequency with which surgeons at medical schools in Florida, including medical school A, performed pancreaticoduodenectomy correlated inversely with in-hospital mortality. Therefore, this report supports that the impact of "surgeon volume" on outcome seems more important than "hospital volume" or a hospital's designation as a "teaching hospital."[3]

The impact of the frequency with which surgeons conduct pancreaticoduodenectomy on ALOS seen in 1995–1997 was less apparent in 2003–2005. ALOS may

be and probably is impacted by general trends in medicine and surgery to shorten hospital confinement. As well, specific action has been undertaken to establish care pathways for patients undergoing pancreaticoduodenectomy, and these data have been disseminated. More pronounced than ALOS, in 2003–2005 as in 1995–1997, pronounced differences in in-hospital mortality rates were noted between surgeons frequently as opposed to infrequently conducting pancreaticoduodenectomy.

This study documents that, although results differ among surgeons performing pancreaticoduodenectomy and results vary among medical centers where pancreaticoduodenectomies are conducted, differences are also noted among surgeons within a single "high-volume" center. Although there undoubtedly is a "center effect," there is also a significant "surgeon effect." This has been noted by others.[17,18] As well, a "high-volume" surgeon at a "low-volume" center can produce outcomes consistent with national "benchmarks."[19] "High-volume" centers and "high-volume" surgeons are intuitively inextricably related, but the impact of each on objective outcome measures, such as in-hospital mortality, can be estimated.[17,18] However, it is important to note that not all "low-volume" surgeons work in "low-volume" hospitals. "Surgeon effect" is undoubtedly multifactorial and includes issues such as operative blood loss, duration of operation, and occurrence of complications.[20,21] However, "surgeon effect" extends beyond technical prowess. Although technical skills are a critical issue, so are other skills essential to becoming a master surgeon, such as patient selection, preoperative preparation, and postoperative care. These latter skills help explain why the inverse relationship between "high-volume" and "risk of death" is not necessarily specific to the volume of the procedure studied.[4,22] "Surgeon effect can also be negatively impacted by patient selection, as busiest surgeons are most likely to operate on patients with more advanced tumor-specific issues, such as patients with larger tumors or those with tumors invading into the portal vein. In sum, in 2003–2005, the frequency with which pancreaticoduodenectomy is undertaken inversely correlates with ALOS, hospital charges, and in-hospital mortality. Given the data herein, the busiest surgeons appear to be the best surgeons, and surgeons more frequently conducting pancreaticoduodenectomy may also have better 5-year survival rates; although this has been stated, further study is necessary.[8]

Conclusions

In Florida, more pancreaticoduodenectomies are now performed by fewer surgeons. Overall mortality has not decreased because of the very high mortality in patients operated upon by surgeons infrequently conducting pancreaticoduodenectomy. Best results with length of stay, hospital charges, and in-hospital mortality after pancreaticoduodenectomy are seen with surgeons most frequently undertaking pancreaticoduodenectomy, even in "high-volume" centers. Although specialization in surgery may be occurring, most pancreaticoduodenectomies are still carried out by surgeons infrequently undertaking pancreaticoduodenectomy with ensuing greater lengths of stay, hospital costs, and in-hospital mortality rates. To an even greater extent than previously demonstrated, patients needing pancreaticoduodenectomy are best served by surgeons frequently conducting the procedure. The medical literature, with the addition of this report, promotes referral by healthcare professionals and healthcare systems for patients needing pancreaticoduodenectomy to "high-volume" providers to optimize outcomes.

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Pancreatic Cystic Neuroendocrine Tumors: Preoperative Diagnosis with Endoscopic Ultrasound and Fine-Needle Immunocytology

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Abstract
Background Pancreatic cystic neuroendocrine tumors (CNETs) are rare premalignant conditions. Computed tomography (CT) occasionally demonstrates the hypervascular border characteristic of NETs. Endoscopic ultrasound (EUS) with fine-needle aspiration and immunocytology may be a more consistent means to establish the diagnosis, but no data on the role of EUS are available. This report represents the largest series of CNETs treated to date, documents the role of EUS in preoperative diagnosis, and describes current management.
Methods Retrospective review of our experience with CNETs treated at an academic center between 1999 and 2006.
Results Thirteen patients with CNETs were identified. One had symptoms consistent with a functional tumor; the others were nonfunctional. Twelve were detected by CT; only three had peripheral hypervascularity. Nine were studied with preoperative EUS/immunocytology; each of these demonstrated strong staining for chromogranin and synaptophysin. All were resected: four by pancreaticoduodenectomy, one by total pancreatectomy, and one by enucleation. Perioperative morbidity occurred in 39%. Perioperative mortality was 0%. Average follow-up was 3.3+0.5 years. One patient had late hepatic recurrence and ultimately died of disease. Two developed recurrent NET in the context of MEN I and required additional surgery. Twelve are alive with no evidence of disease.
Conclusions EUS-guided immunocytology with staining for neuroendocrine markers is an accurate method to establish the diagnosis of CNET preoperatively. Short- and long-term outcomes after resection are excellent.

Keywords Pancreatic cyst · Neuroendocrine tumors · Synaptophysin · Chromogranin

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Introduction

Advances in axial imaging for evaluation of patients with nonspecific abdominal symptoms have led to an increase in the detection of intraabdominal neoplasia including incidentally discovered adrenal, liver, and pancreatic tumors.[1–3] An incidental pancreatic mass may represent a number of different pathologies with a substantial range of malignant potential from benign cysts, which may be managed with observation to pancreatic adenocarcinomas that ideally require aggressive surgical intervention.[3,4] Cystic neuroendocrine tumors (CNETs) of the pancreas are rare premalignant lesions with fewer than 60 cases reported in the medical literature.[5] These tumors are most often nonfunctional and are almost always detected as incidental findings. They have a definite malignant potential but only infrequently demonstrate features on axial imaging that allow

reliable preoperative diagnosis. CNETs are consequently, commonly mistaken for simple cysts, pseudocysts, or serous cystadenomas and may, therefore, be mismanaged.[6]

Methods for further clarification of the diagnosis of incidentally identified pancreatic pathology before intervention continue to be refined. Endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) for tumor cytology or for tumor marker immunoassay has emerged as one method for effectively identifying carcinoma and/or distinguishing mucinous from serous cystic lesions.[6–10] FNA with immunostaining of isolated cells for neuroendocrine makers including synaptophysin and chromogranin-A has also increasingly been used to evaluate incidentally detected solid masses for potential neuroendocrine origin.[11,12] There has been, however, no report to date on the use of endoscopic FNA with neuroendocrine immunocytochemistry for the preoperative evaluation of cystic pancreatic tumors. It has been our practice in recent years to routinely evaluate most cystic lesions with EUS and FNA cytology and to pursue immunostaining for neuroendocrine markers when FNA cytology demonstrates cellular morphology suggesting neuroendocrine pathology. In effort to more clearly define a role for FNA and immunocytochemistry in the preoperative diagnosis of CNETs of the pancreas and to further clarify the presentation, malignant potential, and proper management of these rare tumors, we reviewed our experience with CNETs managed over an 8-year period.

Materials and Methods

Study population A retrospective review of the medical records of all patients undergoing major pancreatic resection at the Indiana University Hospital between January 1999 and December 2006 was conducted. Patients were initially selected by search through a comprehensive operative database maintained by the hospital. Any patient listed as undergoing pancreaticoduodenectomy, distal pancreatectomy (laparoscopic or open), pancreatic enucleation (laparoscopic or open), or duodenal preserving pancreatic head resection regardless of preoperative clinical diagnosis was selected for initial review. All procedures listed as either pancreatic debridement or necrosectomy were excluded from the analysis. We identified a total of 1,030 major resections. We then searched the electronic medical record for each patient. Preoperative imaging, operative reports, and pathology were evaluated for each. Those patients having preoperative imaging [EUS, computed tomography (CT), or magnetic resonance imaging] suggesting a pancreatic cystic neoplasm or a pancreatic NET and/or those with a pathologic diagnosis of cystic neoplasm or solid NET or CNET were selected for a more detailed review.

Diagnostic criteria Solid tumors were classified as solid NETs if the final pathology report made the diagnosis of a solid NET. Cystic tumors were classified as CNETs if the final pathology report (a) made a definitive diagnosis of CNET (cyst on gross pathology and final microscopic pathology specimen stained positive for neuroendocrine markers) or (b) described a cystic tumor with features of NET and prior aspiration of that lesion had stained positive for neuroendocrine markers. Patients presenting with appropriate symptoms and biochemical evidence of hormone excess were classified as having a functional NET. Patients without symptoms consistent with a specific clinical syndrome were classified as nonfunctional tumors regardless of the results for immunohistochemical staining. Nonneuroendocrine cystic tumors were classified as previously described[13] and included any tumor with the following diagnoses on final pathology: simple cysts, serous cystadenomas, solid pseudopapillary neoplasm, lymphoepithelial cysts, mucinous neoplasm, mucinous cystadenocarcinoma, intraductal papillary mucinous neoplasms.

Tumor characteristics Information on tumor characteristics including tumor size, immunohistochemical staining on FNA, and evidence of malignancy was obtained from the final cytology and pathology reports. Solid NETs and CNETs were classified as malignant only if the final pathology report identified tumor in the lymph nodes taken with the specimen or if distant metastases were identified on preoperative or postoperative surveillance and confirmed by biopsy. Tumors that demonstrated microscopic evidence of lymphvascular invasion but had no positive lymph nodes and no evidence of distant metastasis were not classified as malignant lesions.

Patient characteristics Pre- and postoperative clinical and demographic characteristics were collected from the medical record of each patient identified as having a CNET. This information included: age, sex, presenting symptoms, preoperative imaging including EUS reports, preoperative cytology, exact nature of surgical intervention, perioperative morbidities, final pathologic diagnosis, long-term follow-up, and additional intervention for recurrent disease. Patients who had been discharged from follow-up in the years before the review were contacted by phone to confirm their health and insure that no further disease had been detected.

Patient anonymity Formal approval for the review was obtained from the institutional review board of Indiana University School of Medicine before beginning the review. The study was conducted in accordance with all IU Medical Center policies protecting patient anonymity.

Table 1 Pancreatic CNETs: Clinical, Radiologic, and Pathologic Characteristics

Case	Age (year)	Gender	Presentation	CT appearance	FNA markers[a]	Size (cm)	Functional status	Malignant[b]
1	57	M	Pancreatitis	Bland cyst	NSE, PPP	1.0	Nonfunctional	No
2	39	M	Peptic ulcer	No CT scan	No EUS	2.5	Nonfunctional	No
3	69	M	Pancreatitis	Bland cyst	Chrom-A, SYN	2.0	Nonfunctional	No
4	58	M	Chest pain	Bland cyst	Chrom- A, SYN	1.4	Nonfunctional	No
5	43	M	MEN 1 *hypoglycemia*	Hypervascular	Chrom-A, SYN, Glucagon	2.5	Insulinoma	No
6	59	F	Reflux	Bland cyst	Chrom-A, SYN	2.5	Nonfunctional	No
7	71	M	Hematemesis	Bland cyst	Chrom-A, SYN	1.5	Nonfunctional	No
8	61	M	Hematuria	Bland cyst	Chrom-A, SYN	4.0	Nonfunctional	No
9	48	M	MEN 1 *asymptomatic*	Bland cyst	No EUS	1.8	Nonfunctional	No
10	41	M	Abdominal pain	Bland cyst	SYN	5.0	Nonfunctional	Yes
11	45	M	MEN 1 *asymptomatic*	Bland cyst	Chrom-A, SYN, NSE	1.3	Nonfunctional	Yes
12	80	F	Abdominal pain *hypoglycemia*	Hypervascular	No EUS	2.0	Insulinoma	No
13	62	M	Gastritis	Hypervascular	No EUS	2.4	Nonfunctional	No
Sum	56.4± 3.5	85% M		3/12 hypervascular	9/9 positive immunostain	2.3± 0.3	2/13 functional	2/13 malignant

[a] Immunomarkers are abbreviated as follows: *NSE* neuron specific enolase, *PPP* pancreatic polypeptide, *Chrom-A* chromogranin A, *SYN* synaptophysin.
[b] Only tumors demonstrating clear evidence of nodal involvement or distant metastasis were given the designation malignant.

Statistical analysis Data are presented as mean±standard error of the mean. Comparisons among groups were performed using Student's *t* test or χ^2 analysis where appropriate.

Results

Prevalence Of the 1,030 total cases initially identified, 217 (21.1%) were resectional procedures done for cystic pancreatic disease. Of those, 15 resections in 13 patients or 1.5% of the total cases and only 6.9% of the cases done for cystic disease were performed for pathology ultimately identified as a CNET. In addition, 53 resections in 49 patients or 5.1% of the total number of resections were performed for solid neuroendocrine pathology. Thus, 13 of 62 (21%) patients with resectable NETs had CNET.

Clinical and pathologic characteristics The clinical characteristics for each of the 13 patients identified are presented in Table 1. The mean age at time of diagnosis was 56.4 years with a range from 39 to 80 years. Eleven of the 13 patients (85%) were men.

In the majority of patients, the CNETs presented as an incidental finding through workup done to evaluate symptoms that would not otherwise be associated with a pancreatic neoplasm. Of the 13 patients, 5 (38%) had either symptoms or clinical history clearly concerning pancreatic disease. Two (15%) had functional lesions with clinical evidence of excess hormone production by the endocrine pancreas. Both had cystic insulinomas. Two patients presented with pain and biochemical evidence of pancreatitis. One other patient was asymptomatic but presented with a family history of MEN I and was diagnosed with a

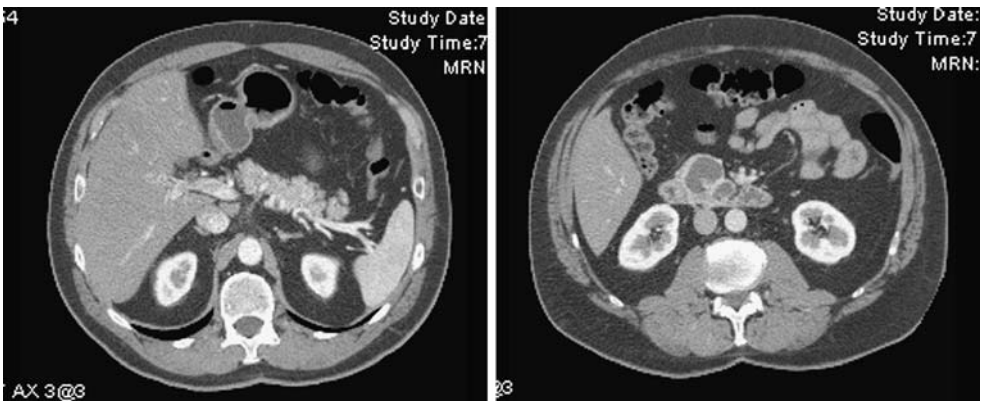

Figure 1 CT images from case 8. The image at the *left* demonstrates the normal appearing pancreatic body and tail. The image at the *right* demonstrates a 4-cm cystic lesion at the base of the uncinate process with slight enhancement in the arterial phase of the scan.

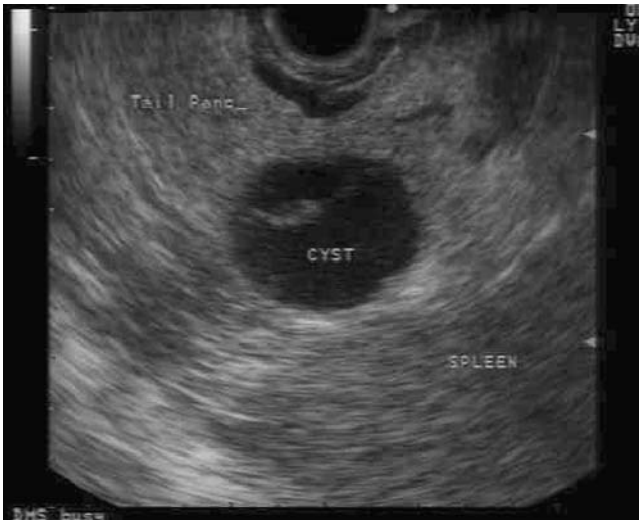

Figure 2 EUS image from case 7. The image demonstrates a cystic lesion in the tail of the pancreas with the spleen at the *right* of the image.

pancreatic lesion in the process of being evaluated for that syndrome. The remaining 8 patients (62%) presented with nonspecific symptoms. Consistent with this nondescript pattern of presentation, only 3 of 12 (25%) patients evaluated by CT demonstrated findings on CT imaging that was suggestive of a NET (Fig. 1). In these three patients, a hypervascular (enhancing) rim in the arterial phase of the CT was observed. The remaining patients had bland, homogenous, uniformly hypoenhancing lesions.

The final pathologic size of the 13 CNETs was 2.3+ 0.3 cm with a range from 1.0 to 5.0 cm (Table 1). Only 2 of the 13 (15%) lesions were either clearly malignant at the time of resection or developed late evidence of metastasis.

Endoscopic ultrasound The majority (nine) of the patients identified in our series were evaluated by preoperative EUS, FNA, and immunocytology (Table 1; Fig. 2). All nine lesions yielded cells that stained strongly positive for the neuroendocrine markers synaptophysin and chromogranin-A (Fig. 3). These nine lesions were then subsequently identified as CNETs on final pathologic evaluation. Although the number is small, the positive predictive value of the EUS/FNA with immunocytology for synaptophysin and chromogranin is 100%.

Management and outcomes The operative management and clinical outcomes are presented in Table 2. The tumors occurred throughout the parenchyma of the gland with 4 of 13 tumors in the pancreatic head, 7 of 13 in the neck, body, or tail of the pancreas. In two patients, tumors were present in the head and the tail simultaneously at the time of diagnosis. Of the lesions found in the head of the gland, four were treated with pancreaticoduodenectomy; one was enucleated. Of the remaining patients, seven were treated with distal pancreatectomy, and one was treated with total pancreatectomy. The overall morbidity rate was 39%. Two patients (15%) developed intraabdominal abscess and required drainage by interventional

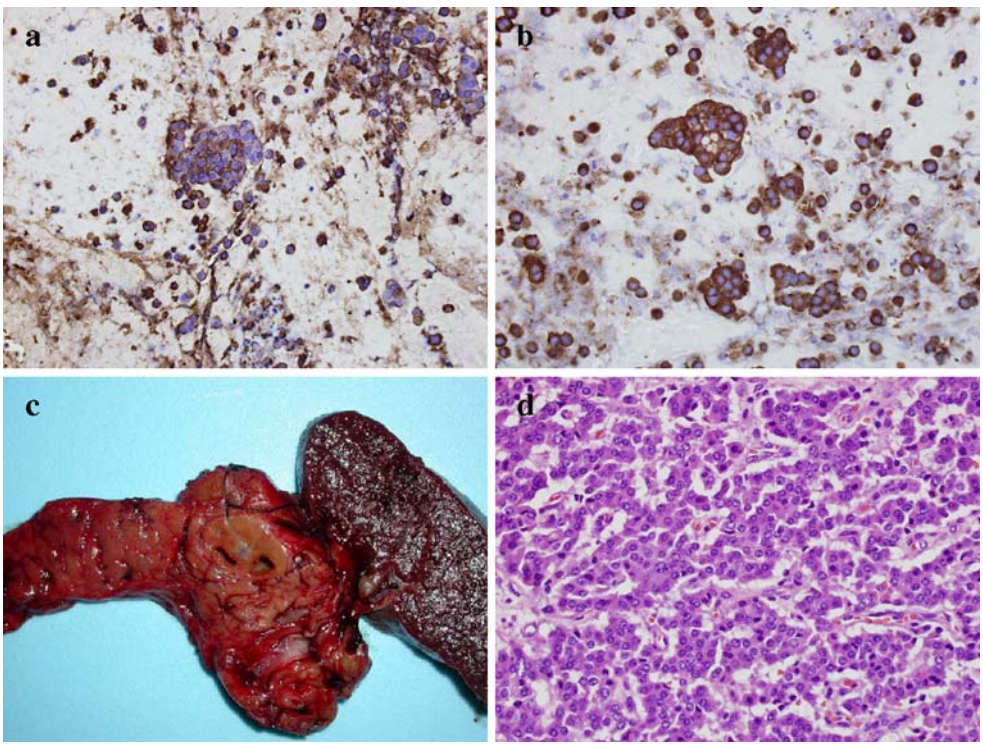

Figure 3 Preoperative immunocytology and pathology from case 7. The figure shows representative photomicrographs of cells obtained from the preoperative EUS-guided FNA and stained for tumor markers chromogranin-A (**a**) and synaptophysin (**b**); a cross-section of the gross pathology (**c**); a photomicrograph of a section of the cyst wall stained with hematoxylin and eosin demonstrating nests of pancreatic islet cells (**d**).

Table 2 Pancreatic CNETs: Management and Clinical Outcomes

Case	Site	Procedure[a]	Morbidity	Recurrence	Further intervention	Follow-up
1	Head	PPPD	None	NED	None	Alive 5 years
2	Head	PPPD	None	NED	None	Alive 5 years
3	Body	DP	None	NED	None	Alive 44 months
4	Tail	DP	Abscess	NED	None	Alive 40 months
5	Multiple	Enucleation	Fistula	NED	None	Alive 41 months
6	Multiple	TP	Abscess	NED	None	Alive 2 years
7	Tail	DP	None	NED	None	Alive 8 months
8	Head	PPPD	None	NED	None	Alive 8 months
9	Body	DP	None	Recurrent head lesions *(3 years post-procedure)*	Completion pancreatectomy	Alive 58 months
10	Tail	DP	None	Liver metastasis *(8 months post-procedure)*	Adjuvant chemotherapy	Died 59 months
11	Head	PPPD	Fistula	Recurrent tail lesions *(1.5 years post-procedure)*	Additional enucleation	Alive 5 years
12	Tail	DP	None	NED	None	Alive 2 years
13	Body	DP	Ileus	NED	None	Alive 2 years
Aggregate			39%	23%	23%	39.2± 5.5 months

[a] Procedures performed are abbreviated as follows: *PPPD* pancreaticoduodenectomy, *DP* distal pancreatectomy, *TP* total pancreatectomy.

radiology. Two patients (15%) developed pancreatic fistulae as evidenced by persistent drainage of amylase-rich effluent from their operative drains. Both responded to conservative management and healed their fistulas within weeks of the operation. One patient suffered a postoperative ileus and required prolonged nasogastric decompression but eventually resolved this without further operative intervention. There were no perioperative mortalities.

Long-term follow-up of most of the patients in the series demonstrated encouraging results with 10 of 13 patients (77%) having no further evidence of disease. Only two patients (15%) were noted to have definite evidence of malignancy. One patient (case 10) had a functional insulinoma and presented with recurrent hypoglycemia several months after initial resection. Axial imaging at that time demonstrated multiple bilobar liver lesions, which were subsequently proven by core biopsy to be metastatic neuroendocrine disease. This individual received systemic chemotherapy but eventually succumbed to the disease almost 5 years after the initial resection. One (case 11) had tumor in lymph nodes resected with the specimen. That patient was ultimately diagnosed with MEN I and subsequently developed additional foci of disease in the pancreatic tail that required further enucleation. This patient is currently alive and without evidence of disease. Only one other patient (Case 9) demonstrated evidence of postresection recurrence. This individual also presented in the context of MEN I and developed additional cystic neuroendocrine disease in the residual pancreas. This was treated completion pancreaticoduodenectomy and the patient is now alive without evidence of further recurrence.

Cystic vs solid NETs A comparison of the clinical characteristics for the cystic and solid NETs identified in this series is presented in Table 3. Patients with cystic tumors were more likely to be male ($p<0.05$) and were slightly, but not significantly, older than patients with solid tumors. Cystic tumors were on average smaller than solid tumors, although this difference was also not statistically significant. Cystic and solid tumors had a similar topologic distribution in the pancreas and an equally small propensity to present with a functional syndrome. Solid NETs were statistically more likely to demonstrate malignant behavior. Almost 50% of the solid tumors demonstrated either evidence of lymph node involvement at the time of resection or distant metastasis at some time during follow-

Table 3 Cystic vs Solid NETs: A Comparison of Clinical Characteristics

Group	No. of patients	Age (years)	% Male	Tumor size (cm)	% Body/tail	% Functional	% Malignant
Cystic NET	13	56.4±3.5	85*	2.3±0.3	69	15	15
Solid NET	49	53.0±1.9	47	3.5±0.4	47	18	49*

NET Neuroendocrine tumor
*$p<0.05$ cystic vs solid NET

up, whereas only 15% of cystic lesions showed evidence of such aggressive behavior ($p<0.05$).

Discussion

We reviewed the experience at Indiana University Hospital with CNETs to further clarify their incidence, clinical characteristics, preoperative evaluation, and proper management. We identified 1,030 pancreatic resections performed between January 1999 and December 2006. Of that total, 217 resections (21%) were for cystic tumors of any type, and of those, 15 (in 13 patients) were for CNETs. Nine patients evaluated with preoperative EUS and FNA with immunocytology for NET markers were diagnosed preoperatively. Thus, these lesions can be identified preoperatively, and management can be planned appropriately. Two patients (15%) had evidence of either lymph node involvement at the time of resection or distant metastasis during follow-up. During the same time period, 53 of the 1,030 resections (5.1%) were for solid NETs. In comparing cystic to solid NETs, patients with CNETs were statistically ($p<0.05$) more likely to be male, and the cystic tumors are less likely to be malignant than solid NETs.

The current series represents the largest series of CNETs reported to date. In general, our results are comparable to prior reports with regard to absolute incidence of CNET, presentation, and malignant potential. One recent review of the world literature on CNETs was summarized for publication by the senior author (HAP) 5 years ago along with a report of his experience with solid and cystic NETs at another academic institution.[5] At that time, the largest single institutional series of patients with the diagnosis of CNET was the senior author's series of 4 patients, and the total number of patients reported in the medical literature was 42. In the senior author's description of his series, CNETs tended to be nonfunctional and benign in one of the four patients having an insulinoma and none of the tumors being malignant. By comparison, solid NETs in his series were more likely to be functional (38%) and more likely to be malignant (32%). His review of the world literature at the time revealed a somewhat greater functional (60%) and malignant (21%) propensity among all reported cystic NETs.

Since that series report and review, one additional paper dedicated specifically to the clinical characteristics of CNETs has been published.[7] This paper details ten patients treated at a single institution over a 15-year period. Those 10 patients required 13 procedures. The findings in that series are similar to prior results reported in the literature and to our results in general. CNETs in that series had a measurable propensity to be both functional and malignant but again tended to be both nonfunctional and benign. One patient demonstrated symptoms of hyperinsulinemia, and three patients demonstrated symptoms of hypergastinemia. Only three of ten patients demonstrated lymph node involvement at the time of resection, and none demonstrated distant metastasis in follow-up. In contrast to our results, the authors found the CNETs to be hypervascular with a fair level of consistency with seven of ten patients demonstrating peripheral enhancement on preoperative CT imaging. The authors did not use preoperative immunocytochemistry to further evaluate the cysts before resection but did note that on final pathologic evaluation, all resected tumors demonstrated strong staining for the NET marker synaptophysin.

Our outcomes after treatment of CNETs are also generally comparable to these prior reports. With no perioperative deaths, a pancreatic fistula rate of 15%, and a general morbidity rate of 39%, our rates of morbidity and perioperative mortality are also comparable to prior large series on major pancreatic resection and are acceptable.[13–15] In our series, only three patients developed recurrent disease requiring additional intervention. Twelve were alive at end follow-up with no evidence of disease, and one died of distant metastases. In the major prior series on CNETs, there has been one other reported disease-related mortality, and the rate of recurrence is generally less than 10%.[5,7]

The current series is the first series in the literature to clearly demonstrate a role for preoperative immunohistochemistry in the evaluation of CNETs of the pancreas. Several prior reports by other groups have employed EUS-guided FNA with standard cytology to characterize cystic tumors in general and CNETs in specific before surgical intervention. These studies used light microscopy and nonspecific stains to examine cells from aspirates for cellular atypia and for the neuroendocrine granules seen in the cytoplasm of epithelial cells in neuroendocrine tumors. They also looked for evidence of mucin in the aspirate. None used preoperative immunocytochemical staining for NET markers. The findings in these prior studies demonstrate that EUS and FNA with evaluation for mucin and cellular atypia are reasonably effective in identifying mucinous cysts with malignant potential and intraductal papillary mucinous neoplasm (IPMN) but are less accurate in clearly providing a diagnosis of CNET. In each of these series, the number of CNETs was small (two to six cases), and the CNETs were frequently mischaracterized by the preresection FNA. In contrast, nine of our patients were accurately identified preoperatively as having CNETs.

Our series clearly suggests, as do others, that CNETs have a malignant potential. As mentioned above, our findings also indicate that current conventional methods of axial imaging may be unreliable in providing diagnostic information for these rare tumors. Given the malignant potential of these tumors, a clear need for accurate preoperative diagnosis exists. Further, given that axial

imaging by CT has a relatively poor ability to diagnose the pathology, this study suggests that endoscopically guided FNA is a *more* effective means for identifying the pathologic nature of the CNETs before surgical intervention. This contention is further supported by the results of what is currently the largest series in the literature in which the postoperative pathologic analysis demonstrated that 100% of the specimens stained positively for synaptophysin.[7] Thus, we recommend the use of EUS, FNA with immunocytology, and staining for synaptophysin and chromogranin in evaluating all lesions with the potential to be CNETs.

The major limitations of the current study are the relatively small population size and the fact that it is a retrospective review. Given the rare nature of these entities, prospective study would be impractical. Further, the consistent nature of the results with regard to FNA immunocytology strongly suggests that the conclusions made are reasonable and very likely reliable.

Conclusions

We present the largest known series on CNETs of the pancreas. This series indicates that these lesions have a real/demonstrable malignant potential, that conventional axial imagining is poor in distinguishing CNETs from other cystic pancreatic lesions, and that EUS/FNA with immunocytologic staining for neuroendocrine markers is an effective modality for preoperative identification of these tumors. Finally, we again demonstrate that surgical intervention is an effective therapy and can be accomplished with acceptable levels of morbidity even in the face of relatively normal pancreatic parenchyma.

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A Prospective Evaluation of Laparoscopic Versus Open Left Lateral Hepatic Sectionectomy

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Abstract
Background Left lateral sectionectomy is one of the most commonly performed laparoscopic liver resections, but limited clinical data are actually available to support the advantage of laparoscopic versus open-liver surgery. The present study compared the short-term outcomes of laparoscopic versus open surgery in a case-matched analysis.
Materials and Methods Surgical outcome of 20 patients who underwent left lateral sectionectomy by laparoscopic approach (LHR group) from September 2005 to January 2007 were compared in a case-control analysis with those of 20 patients who underwent open left lateral sectionectomy (OHR group). Both groups were similar for: tumor size, preoperative laboratory data, presence of cirrhosis, and histology of the lesion. Surgical procedures were performed in both groups combining the ultrasonic dissector and the ultrasonic coagulating cutter without portal clamping.
Results Compared with OHR, the LHR group had a decreased blood loss (165 mL versus 214 mL, P=0.001), and earlier postoperative recovery (4.5 versus 5.8 days, P=0.003). There were no significant differences in terms of surgical margin and operative time. Morbidity was comparable between the two groups, but two cases of postoperative ascites were recorded in two cirrhotic patients in the OHR. Major complications were not observed in either groups.
Conclusions Laparoscopic resection results in reduced operative blood loss and earlier recovery with oncologic clearance and operative time comparable with open surgery. Laparoscopic liver surgery may be considered the approach of choice for tumors located in the left hepatic lobe.

Keywords Liver surgery · Laparoscopic liver resection · Ultrasonic dissector · Ultrasonic coagulating cutter

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Introduction

Laparoscopic liver surgery is gaining progressive interest for the treatment of benign or malignant neoplasms.[1–3] Despite the recent advances in laparoscopic liver surgery, it remains a subject of controversy among liver surgeons.[4] Previous studies have demonstrated the feasibility and safety of laparoscopic liver resections, but all included heterogeneous groups of patients, with only a few studies comparing short-term outcomes of laparoscopic versus conventional liver resection.[5–10] Although some authors have reported major liver resections, limited resections for peripheral lesion represent actually the main indication for laparoscopic liver surgery. Left lateral sectionectomy (resection of segments 2–3 according to Coinaud) is one of the most commonly performed laparoscopic liver resections, but limited clinical data are available to support the advantage of laparoscopic over open-liver surgery.

The aim of this study was to perform a case-control study to evaluate the outcome of laparoscopic left lateral sectionectomy compared to the same operation performed by open surgery.

Materials and Methods

Beginning in January 2004, hepatic resections were performed at the Department of Surgery—Liver Unit at Scientific Institute San Raffaele, Milan, Italy, combining the ultrasonic dissector and the ultrasonic coagulating cutter. Having experienced the usefulness and the safety of this technique for liver transection in open hepatectomy,[11,12] we decided to extend its application in laparoscopic liver surgery, supposing that this could improve the quality of laparoscopic liver resection.

In September 2005, we started a prospective evaluation of laparoscopic liver resection. Patients who were potential candidates for liver resection were systematically evaluated for laparoscopic liver resection at weekly multidisciplinary meetings. Indications included benign lesions, hepatocellular carcinomas (HCC) in cirrhotic patients, and metastases. Laparoscopic approach was indicated for tumor smaller than 12 cm, and if there were no doubts about adequate margins. Liver lesions larger than 12 cm may make the laparoscopic approach more difficult because of increased difficulty in mobilizing the liver and higher risk of positive surgical margin.

We searched from a prospectively collected hepatobiliary surgical database for patients who underwent laparoscopic left lateral sectionectomy. Twenty patients from September 2005 to January 2007 underwent left lateral sectionectomy with a laparoscopic approach (LHR group). In a matched-pair analysis, data from the LHR group were compared with outcomes of patients who underwent left lateral sectionectomy by open-liver resection from January 2004 to August 2005. The following criteria were matched for each patient in the LHR: tumor size, preoperative laboratory data, the presence of cirrhosis, and the histology of the lesion. Twenty patients fulfilled all selection criteria and formed the open hepatic resection (OHR) group.

The following data were collected: operating time, blood loss, blood transfusion, and hystologic tumor exposure at the transection surface. Abnormal liver function tests including total bilirubin, alanine aminotransferase, aspartate aminotransferase, and prothrombin time through patient discharge were recorded. Morbidity and hospital stay were also compared according to a new classification of complications by severity,[13] with an additional emphasis on bile leaks, underlying liver disease and hospital stay.

Patients were monitored for the development of postoperative fluid collections and/or biliary fistulas. For the purpose of this study, we defined biliary fistula as bilious drainage lasting more than 7 postoperative days. Bile leakage was suspected by evaluating drainage fluid color and confirmed assaying total bilirubin level in the drainage. Packed red blood cells were administered according to internal standardized guidelines. Anesthetic technique and postoperative management were not modified during the study period.

Surgical Techniques

The detailed technique used for laparotomic resection was described elsewhere.[11,12] Briefly, laparotomy was performed through a right subcostal incision extended to the midline, and liver resection was performed combining the ultrasonic dissector for liver transection and the ultrasonic coagulating cutter for hemostasis. No other hemostatic agents or devices were used and a closed suction drain was routinely placed along the transection surface in all patients. The intermittent Pringle maneuver was not applied during liver transection.

For laparoscopic liver resection, the patient is placed in the "French" position, with the first surgeon standing between the patient's legs, with one assistant on each side. With an open laparoscopy technique, continuous CO_2 pneumoperitoneum is induced at a pressure of 12 mmHg. Usually a four-trocar configuration is used. A 15-mm port above the umbilicus houses the 30° laparoscope. Other three 12-mm trocars are located as shown in Fig. 1.

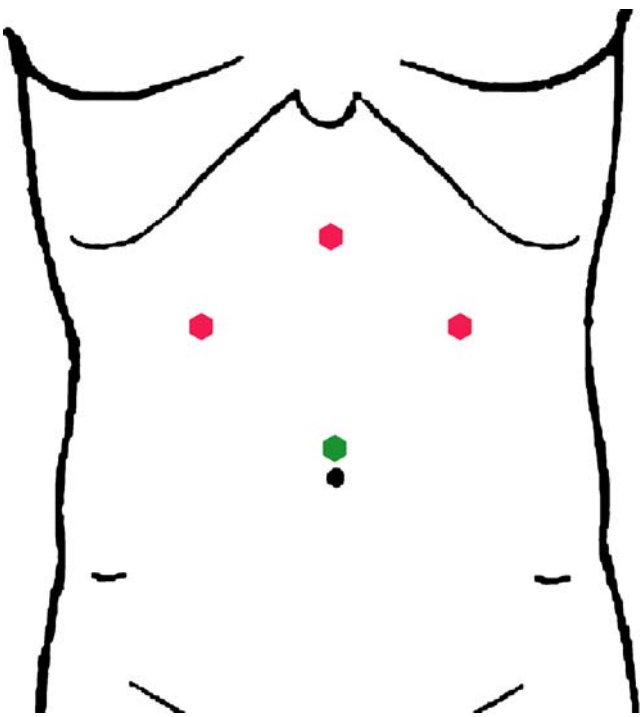

Figure 1 Trocar location.

Table 1 Preoperative Features

Groups Comparison	LHR Group	OHR Group	*P*
Gender ratio, F/M	8/12	7/13	NS
Age mean (year) ±SD	63±13	66±11	NS
Underlying liver disease (normal/cirrhosis)	12/8	12/8	NS
ALT < or >60 U/L	14/6	14/6	NS
Total bilirubin < or >1.2 mg <7 dL	12/8	12/8	NS
PT-INR < or >1.2	13/7	13/7	NS
Tumor size (mm) ±SD	52±28	59±25	NS

Intraoperative ultrasonography is used to plan the parenchymal transection plane, and the extent of the resection is outlined with electrocautery marks. Liver resection is performed using the SonoSurg system (Olympus, Tokyo, Japan) that integrates two major surgical instruments, the ultrasonic coagulating cutter and the conventional ultrasonic dissector. Both tools are activated by ultrasonic energy produced by a single generator. However, the two hand pieces are independent, and cannot be used at the same time.

The superficial liver tissue is divided using the ultrasonic coagulating cutter; with the absence of large vessels and bile ducts, nearly all of the peripheral liver parenchyma can easily be divided without causing bleeding or bile leakage. The ultrasonic dissector is used to fracture hepatocytes along the proposed line of division. This leaves intact arteries, veins, and bile ducts crossing the line of division and the uncovered bridging structures are sealed and divided using the ultrasonic coagulating cutter. Repeated, alternating use of the ultrasonic dissector and the ultrasonic coagulating cutter is continued until resection is complete.

The intraparenchymal vascular anatomy is easily defined using the ultrasonic dissector so that a decision on hemostatic technique could be made based on vessel size. Blood vessels up to 4 mm in diameter are easily coagulated in 4–5 sec using the ultrasonic coagulating cutter and larger vessels up to 15 mm and biliary branches are sealed with titanium clip. The few larger vessels and portal triads that are encountered are ultrasonically dissected and divided using linear stapler. The triangular and coronary ligament are divided, using the ultrasonic coagulating cutter, leaving the left lobe attached only by the hepatic vein. At this point, the limited liver tissue surrounding the hepatic vein is divided using the ultrasonic dissector and the hepatic vein can be easily sectioned using a linear stapler. Argon beam coagulator is not used for hemostasis. The specimen was removed using a retrieval bag through the umbilical port by extending the incision. The hepatic pedicle is never encircled for Pringle maneuver. A single, flat Jackson–Pratt drain is then placed in the posterior aspect of the resection bed through a port site.

Statistical Analysis

Demographic, pathologic, operative details, and surgical outcomes between the two groups were compared using the χ^2 test or Fisher's exact test for categorical data and the Mann–Whitney *U* test for ordinal data. All data were expressed as mean plus the standard deviation or range. Significance was defined as $P<0.05$. All analyses were performed using the statistical package SPSS 14.0 (SPSS, Chicago, IL, USA).

Results

The two groups were well matched for all baseline characteristics (Table 1).

Table 2 Operative Variables

Surgical Outcome	LHR Group	OHR Group	*P*
Blood loss (mL), median ±SD	165±43	214±47	0.001
Operative time (min), median ±SD	260±50	220±30	NS
Mean peak ALT (U/L) ±SD	340±160	367±149	NS
Mean peak AST (U/L) ±SD	378±144	390±172	NS
Mean peak total bilirubin (mg/dL) ±SD	1.8±0.6	1.9±0.4	NS
Mean peak prothrombin time INR ±SD	1.23±0.4	1.26±0.5	NS
Histologic tumor exposure (*n*)	0	0	NS
Minimal surgical margin	1.1±0.3	1.3±0.5	NS

Table 3 Complications

Complications	LHR Group	OHR Group	*P*
Grade I			
Wound Infection	0	1	
Grade II			
Cardiac Arrhythmia	1	1	
Urine Infection	1	1	
Ascites (>500 mL/day on POD5)	0	2	
Total minor complications (grades 1+2)	2	5	NS
Grade III	0	0	
Grade IV	0	0	
Grade V (Death)	0	0	
Hospital stay (days) median (range)	4.5 (4–5)	6 (5–9)	0.003

Fourteen patients were operated for liver metastases, mainly from colorectal cancer, and 16 patients for HCC. In 10 patients, liver resection was performed for benign diseases, such as focal nodular hyperplasia, adenoma, and hemangioma.

Patients in the LHR group had a mean blood loss of 165±43 mL (range 110–280) versus 214±47 mL (range 150–310) in the OHR group (P=0.001). No patients in either group received blood transfusion.

Operative time was comparable between the LHR group and the OHR group, (260±50 min versus 220±30 min, P=NS). No conversion to open surgery was necessary. Postoperative peak values of alanine aminotransferase, aspartate aminotransferase, total bilirubin, and prothrombin time were comparable between the two groups with no statistical difference. Final pathologic analysis identified no case of hystologic tumor exposure at the transection surface in either groups. The mean operative margin obtained during all benign and malignant lesions in LHR group was 1.1 cm (range, 0.9–3.2 cm). In contrast, resections performed for a malignant diagnosis resulted in a mean margin of 1.9 cm (range, 1.5–3.2 cm). Operative results are summarized in Table 2.

There were no postoperative deaths. Postoperative complications occurred in two patients (10%) in the LHR group, and in five patients (25%) in the OHR group with no significant difference (Table 3). Postoperative complications included two urine infection, two cardiac arrhythmia, one wound infection, and two cases of transitory postoperative ascites. Mean hospital stay was 4.5±0.6 days (range 4–6) in the LHR group and 5.8±1.6 (5–11) in the OHR group (P=0.003).

Discussion

In recent years, progress in preoperative patient selection and the continuous technological improvements in surgical instruments have greatly enhanced the interest about laparoscopic liver resection. Although the feasibility of minor laparoscopic liver resections has been demonstrated, limited clinical data are available comparing the open vs the laparoscopic approach to liver resection.[5,7,14,15] Randomized trials should be the ideal method to compare laparoscopic liver surgery and open surgery, but no such studies have been reported so far.

Retrospective comparative studies have been based on small retrospective series and various types of liver resection were included, therefore, the precise role of laparoscopy in resection of liver neoplasms remains controversial. For this reason, we have decided to limit the analysis to a homogeneous group of patients who underwent the same type of procedure.

As this is not a randomized study, some bias may be present. However, the same technique of liver transection was adopted for laparoscopic and open-liver resection and portal clamping was not used.

In addition, postoperative management was not modified by the type of operative technique used.

Left lateral sectionectomy (resection of segments 2–3 according to Coinaud) is among the first liver resections to be performed laparoscopically and one of the most commonly performed laparoscopic liver resections. Only one study compared laparoscopic and open left lateral sectionectomy.[15] That study found that, although blood loss was significantly lower in the laparoscopic group, longer operative (202 vs 145 min) and portal clamping times (39 vs 23 min) were required. In addition, no significant difference in hospital stay was recorded.

Our data showed that, in two well-matched patient groups undergoing liver resection, the laparoscopic approach for left lateral sectionectomy resulted in significantly less operative blood loss when compared with classic open technique. This improvement in bleeding control cannot be explained by the use of portal clamping as previously reported by other authors.[3,15] In fact, as our series of laparoscopic liver resection were performed without the need of portal clamping, other factors such as the hemostatic effect of the pneumoperitoneum and the advantage of magnification may have been contributing factors. However, these differences did not result in a different incidence of blood transfusion between the two groups; blood loss were low in both groups and no patient received blood transfusion in either group.

Whereas other series of laparoscopic left lateral sectionectomy required the use of Pringle maneuver to reduce blood losses,[1,15] in the present series the Pringle maneuver was never necessary. We suppose that the combined use of ultrasonic dissector and ultrasonic coagulating cutter offers several advantages in laparoscopic and open-liver surgery. The ultrasonic dissector allows clear visualization of tissues

especially when exposure of the major vascular is required for delineation of the transection plane and allow the identification of key vascular structures, which can then be divided or preserved in a precise fashion. The occlusion of arteries and veins crossing the line of transection by the ultrasonic coagulating cutter is therefore made easier and safer by the use of ultrasonic dissector, reducing the bleeding from the transected liver parenchyma.

One of the main concerns of laparoscopic liver resection remains the risk of major bleeding from hepatic vein injuries[4]. In the present series, no such event occurred. One advantage of our technique is that hepatic veins are clearly exposed so that the use of endovascular stapler is not done blindly through the parenchyma as with some stapling technique. This approach helps to avoid to damage the hepatic vein reducing the risk of large blood losses and air embolism.

With our technique of laparoscopic left lateral sectionectomy the round ligament is never divided and the left triangular and coronary ligaments are divided only at the end of transection, so that the liver remains attached to the abdominal wall. This allows the possibility of opening widely the liver parenchyma, so that the laparoscope is located just in front of the transection line, reproducing a visual surgical field very similar to laparoscopic cholecystectomy. In addition, the use of a fifth port just for the placement of a forcep to hold up the liver[1] is avoided, and a four-trocar approach is adequate to perform the procedure.

Because of the position of the patient, visual surgical field, number and placement of ports, our approach to laparoscopic left lateral sectionectomy resembles for many aspects of laparoscopic cholecystectomy with “French”-like technique. This may facilitate the further diffusion of this approach among less expert surgeons in laparoscopic liver surgery.

Increased surgical times have been reported for other laparoscopic procedures when compared with open surgery.[8,14,15] However, in our study the operating time was comparable between LHR and OHR, with a progressive reduction of operating time during the most recent laparoscopic cases.

Adequate surgical margin still remains a significant concern of laparoscopic liver surgery[16] In the present series, no case of surgical margin involvement was recorded, and a tumor-free surgical margin of >1 cm was achieved for all malignant lesions in the laparoscopic group. Consequently, laparoscopic liver surgery does not seem to increase the risk of positive surgical margin as reported by some authors.

Our study shows that laparoscopic left lateral sectionectomy is safe. Complications following laparoscopic liver resection were comparable to that of open resection. In particular, surgical complications such as biliary fistula of any grade or bleeding did not occur in either group. However, two cases of postoperative ascites, treated successfully with diuretics, were recorded in two cirrhotic patients in the OHR.

According to several reports, the laparoscopic approach might reduce postoperative complications in patients with chronic underlying liver disease because the abdominal wall is preserved and collateral venous drainage is conserved, resulting in less postoperative ascites.[9,10]

By decreasing surgical stress, laparoscopic surgery has been shown to result in reduced postoperative pain, cosmetic benefits, and shorter hospital stay. While a previous comparative study on laparoscopic versus open left lateral sectionectomy reported no significant difference in terms of hospital stay,[15] the present series showed a obvious advantage for laparoscopic liver resection compared to open liver resection in terms of hospital stay. These benefits may in turn improve tolerance for reoperations, in case of repeat liver resection for recurrent colorectal liver metastases or subsequent liver transplantation. However, as it is not a randomized blinded study the supposed benefits of laparoscopic technique may have led to earlier discharge.

In conclusion, the present study has shown that laparoscopic left lateral sectionectomy was associated with reduced operative blood loss, earlier postoperative recovery, and a resected specimen that was oncologically comparable with open surgery. Laparoscopic liver surgery may be considered the approach of choice for tumors located in the left hepatic lobe.

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Guidelines for Power and Time Variables for Microwave Ablation in a Porcine Liver

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Abstract
The purpose of our study was to provide guidelines for the use of a novel microwave ablation system. Microwave ablations using a 915-MHz system were evaluated in a porcine liver. The independent variables were power and time, with the outcome variable being diameter of ablation. After ablations, livers were procured for measurement and histologic evaluation. Our study consisted of 420 ablations. The outcome variable, ablation diameter, was affected significantly by time, power, and time/power interaction ($p<0.0001$). For each time point, a one-way analysis of variance (ANOVA) showed an overall significant difference in ablation size X wattage ($p<0.0001$). Tukey tests at each time point showed ablation sizes at 45, 50, and 60 W were not significantly different. After it was determined that 45 W was optimal, a one-way ANOVA showed an overall significant difference in ablation sizes for time points at 45 W ($p<0.0001$). Tukey tests revealed that at 45 W, ablation sizes at 10, 15, and 20 min were not statistically different. We propose guidelines for diameters based on different time and power variables and recommend 45 W for 10 min to achieve optimal diameters at the shortest time and lowest wattage.

Keywords Microwave ablation · Guidelines · Liver cancer

Introduction

Malignant hepatic tumors, whether primary or secondary, are a challenging problem for all clinicians. The American Cancer Society estimates that 18,510 new cases of primary liver and intrahepatic bile duct tumors and 148,610 cases of colorectal cancer were diagnosed in the United States in 2006.[1] Of the patients presenting with colorectal cancer, 25% have metastatic disease.[1] Few cases of liver cancer are diagnosed in the early stages of the disease because of the lack of signs and symptoms. Therefore, few patients are candidates for surgical removal. Less than 30% of patients undergoing exploratory surgery for liver cancer are able to undergo surgical resection.[1] In addition, only 10% to 20% of patients, with colorectal carcinoma metastasized to the liver, are candidates for resection.[1]

As many malignant liver tumors are unresectable at the time of presentation, there is much interest and research in local ablative techniques for treatment of these patients. Radiofrequency ablation (RFA), which uses the flow of current through conducting electrodes within body tissue, has become the most universally adopted technique for ablation and has shown good safety and efficacy.[2,3] Microwave ablation is the most recent development in the field of tumor ablation and allows flexible approaches to treatment, including percutaneous, laparoscopic, and open surgical access. Microwave antennae are placed directly into tumors, and a microwave generator emits an electro-

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magnetic wave through the exposed, noninsulated portion of the antenna.

Recently, a new microwave ablation system using a 915-MHz generator has become clinically available. Guidelines about ideal time and power settings to yield a maximum diameter ablation using this technology have not been published. The purpose of our study was to devise guidelines for the use of this novel microwave ablation technology and to determine the ideal power and time variables to achieve the largest ablation diameters.

Material and Methods

All experiments were performed in accordance with experimental protocols approved by the Carolinas Medical Center Institutional Animal Care and Use Committee. Female Yorkshire pigs (Baux Mountain Farm, Germanton, NC, USA) weighing 40–50 kg were used in the experiments. Midline laparotomies were performed under general anesthesia induced with telazol (4.4 mg/kg), atropine (0.4 mg/kg), and xylazine (1.5 mg/kg). A retractor was placed, and the liver attachments were taken down. Microwave ablations followed using a 3.7-cm active tip antenna (VivaTip™ Surgical Microwave Energy Applicator, Valleylab™, Boulder, CO, USA) (Fig. 1) and a 915-MHz microwave generator (VivaWave™ System, Valleylab™, Boulder, CO, USA). The independent variables were power and time. Power variables included 20, 30, 40, 45, 50, and 60 W, and time variables included 2, 4, 6, 8, 10, 15, and 20 min. The outcome variable was diameter of ablation measured in millimeters. Ten ablations were performed for each power and time period. After ablations, the animals were euthanized and the livers procured for measurement of ablation diameter and sectioning for histologic analysis. Representative samples were sectioned and underwent nicotinamide adenine dinucleotide (NADH) and hematoxylin–eosin (H&E) staining. NADH staining was used to prove or disprove tissue viability caused by its unambiguous binary staining characteristic of positive staining indicating tissue viability and nonstaining indicating cellular death.[4] Based on NADH staining, inner ablation diameter was reported showing the minimum ablation diameter correlating with uniform cell death by coagulation necrosis. Ablation diameters are reported as mean ± standard deviation (SD). For comparison of means, analysis of variance (ANOVA) was used followed by Tukey tests when appropriate. A p value of <0.05 was considered statistically significant.

Figure 1 Microwave antenna (VivaTip™ Surgical Microwave Energy Applicator, Valleylab™, Boulder, CO, USA).

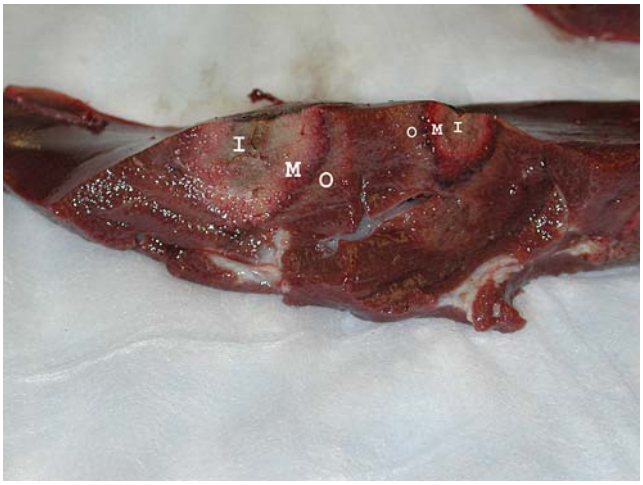

Figure 2 Gross pathologic appearance of microwave ablation in porcine liver demonstrating the three zones of ablation obtained. The inner zone (*I*) is pale and necrotic appearing with a middle zone (*M*) that appears hyperemic and is *pink* with a border of *dark purple*. The outer zone (*O*) is faint with a *white* appearance.

Results

Our study consisted of 420 ablations. On gross inspection of the ablated liver, three zones of ablation were noted (Fig. 2). The inner zone was pale and necrotic appearing, the middle zone appeared hyperemic and was pink with a border of dark purple, and the outer zone appeared white. Ablation zones were also noted to be affected by penetration of the microwave antenna. When the active tip of the microwave antenna pierced the whole portion of the liver parenchyma, a cylindrical ablation zone was obtained (Fig. 3). When the active tip of the microwave antenna did not penetrate the entire hepatic parenchyma, a more spherical zone was obtained (Fig. 2).

Hematoxylin–eosin staining showed a central area of coagulation necrosis in which the hepatocytes had amor-

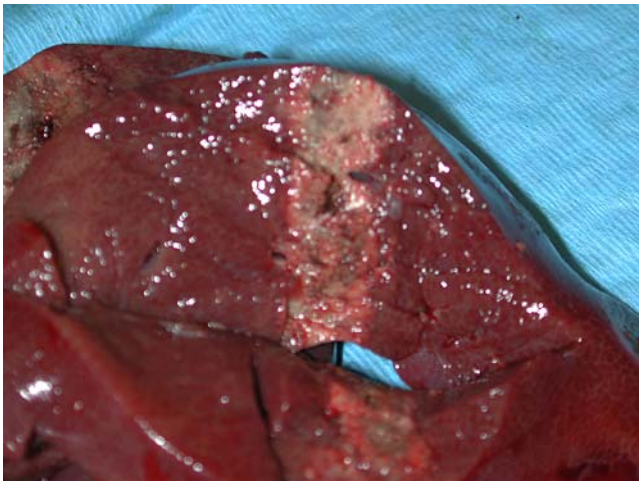

Figure 3 Gross pathologic appearance of microwave ablation in a porcine liver showing cylindrical ablation shape when antenna penetrated entire liver parenchyma.

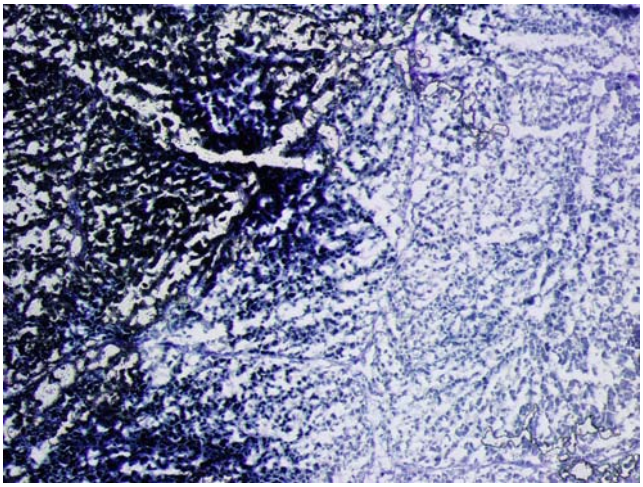

Figure 5 Histologic section obtained at coagulation margin showing sharp demarcation of viable and nonviable tissue (nicotinamide adenine dinucleotide staining, original magnification, ×4).

phous cytoplasm and loss of cellular structure with no discernable cell membranes (Fig. 4). Whereas cells in this central area retained the appearance of cellular nuclei, further histologic review with NADH staining of the three zones of ablation showed uniform cell death in the inner necrotic zone (Fig. 5).

The average inner ablation diameters (with standard deviations) are listed in Table 1 and displayed in Fig. 6. The outcome variable, ablation diameter, was affected significantly by time, power, and the time/power interaction ($p<0.0001$). For each time point, a one-way ANOVA showed an overall significant difference in ablation size × wattage ($p<0.0001$). Tukey tests revealed that at each time point, ablation sizes at 45, 50, and 60 W were not significantly different. When it was determined that 45 W was optimal, a one-way ANOVA was used and showed an overall significant difference in ablation sizes for time points at 45 W ($p<0.0001$). Tukey tests showed that at 45 W, ablation sizes at 10, 15, and 20 min were not statistically different.

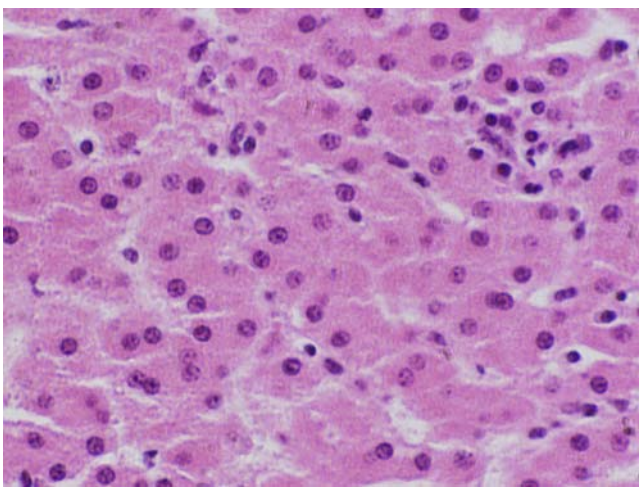

Figure 4 Histologic section obtained at inner ablation zone showing coagulation necrosis (amorphous cytoplasm and loss of cellular structure with no discernible cell membranes; hematoxylin-eosin stain; original magnification, ×40).

Discussion

Currently, radiofrequency is the most used and studied local ablative technique. The challenges associated with radiofrequency ablation are the inability to consistently destroy adequate volumes of tumor,[5] the difficulty in treating large tumors (greater than 3 cm in diameter),[6] and the survival of tumor cells within radiofrequency ablated lesions.[7] Other thermal ablative energy sources have been used to try and overcome these problems and include laser,[8] high-intensity focused ultrasound,[9] and microwave ablation.[10–15]

Microwave technology is an emerging thermal ablative technique that generates an electromagnetic wave around insulated, electrically independent antennae.[16] The wave causes the agitation of polar water molecules within the surrounding tissue, which raises the temperature in the adjacent tissue. This frictional heating induces cell death by coagulation necrosis.

We report guidelines for use of a novel 915-MHz microwave system, reporting expected diameters of ablations for every power setting at various times. Although several time points and power settings are not clinically appropriate, we evaluated the new system at both extremes (short time periods at low wattage and long time periods at high wattage) to evaluate the full range of ablations that can be obtained. One limitation of our study is that we only

Table 1 Average Inner Ablation Diameters[a]

	20 W (mm)	30 W (mm)	40 W (mm)	45 W (mm)	50 W (mm)	60 W (mm)
2 min	3.3±0.7	7.1±2.3	6.9±1.6	6.6±1.8	10.4±3.5	10.2±1.4
4 min	4.3±0.7	10.7±3.1	7.6±2.3	9.0±1.3	13.8±2.7	13.5±1.9
6 min	5.2±2.1	10.5±2.0	11.9±3.2	10.4±1.9	13.7±2.2	13.4±2.2
8 min	7.6±2.4	13.0±1.5	10.5±2.3	11.9±6.5	12.6±2.4	14.1±1.8
10 min	5.1±1.5	12.6±1.2	13.7±6.2	15.9±3.5	11.6±2.4	15.6±2.7
15 min	5.9±1.9	12.2±1.8	11.7±1.6	16.5±1.9	12.6±1.5	14.4±1.8
20 min	12.7±2.8	12.1±2.0	13.1±3.1	20.9±5.5	16.2±4.1	22.9±4.2

[a] Mean ± SD

report the diameter of ablations and not ablation surface area or volume. Part of the difficulty in determining surface area or volume relates to differences in the shapes of ablations. Based on the position and depth of the microwave antenna, cylindrical and spherical ablation shapes were obtained. We attempted to place all antennae entering at a 90-degree angle to the surface of the liver and at the same depth. However, because of the physical constraints of the porcine liver, this was not possible in all cases. Also, ablations at the higher power settings and longer time periods often went beyond the confines of the liver in one direction, making measurement of diameter the only feasible option. Another limitation of our study relates to the possibility that the proximity of ablations to major vascular structures may have affected our outcomes. Whereas the study was not designed to evaluate the "heat sink" phenomenon as ablations were randomly performed in the liver, we did not observe large differences in ablation sizes based on proximity to vascular structures. The observation that microwave may be less susceptible to "heat sink" than RFA has been reported previously from Wright et al.,[13] who evaluated these two technologies in a porcine model.

For 915-MHz microwave ablations, we recommend a power of 45 W for 10 min, which gives the largest diameter ablation for the shortest time period and the lowest wattage. These recommendations correlate with the settings that most clinicians are using with this system. Reports of U.S. clinical trials are now appearing in the medical literature. Simon et al.[17] evaluated microwave ablation in an ablate and resect trial for primary and secondary hepatic malignancies. They used a 915-MHz microwave ablation system with three single microwave antennae arranged in a three-probe triangular cluster-like configuration at a setting of 45 W for 10 min. This resulted in a mean maximal ablation diameter of 5.5 cm with an average ablation zone volume of 50.8 cm^3.[17] Recently, a phase II trial was reported by Iannitti and colleagues[18] in which 87 patients underwent 94 ablations procedures for 224 unresectable primary or metastatic hepatic tumors. In this protocol, they used a 915-MHz generator at a setting of 45 W for 10 min and reported single-antenna ablation volumes of 10.0 cc (range 7.8–14.0 cc), and clustered antennae ablation volumes of 50.5 cc (range 21.1–146.5 cc) with a local recurrence rate of 2.7% and regional recurrence of 43% at a mean follow-up of 19 months.[18]

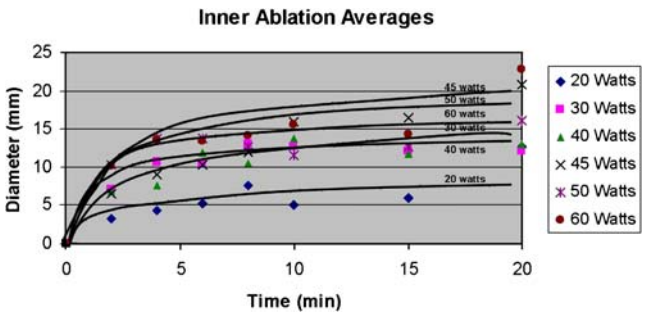

Figure 6 The average inner ablation diameters (mm) measured at 2, 4, 6, 8, 10, 15, and 20 min with power variables 20 to 60 W.

On initial evaluation, the ablation diameters obtained in our study appear small; however, the diameter we report is the inner ablation diameter. This inner ablation diameter is the smallest diameter that correlates with uniform cell death by NADH staining. Another important point is that in clinical use, microwave antennae are often clustered to create larger ablation volumes. As a result of its mechanism of action being different from radiofrequency ablation, microwave use is postulated to be more amenable to synchronous ablations using multiple applicators creating larger tumor coagulation zones in short time periods.

Wright et al.[14] showed that simultaneous three-probe microwave ablation lesions were significantly higher than single-probe ablations and resulted in qualitatively better lesions, with more uniform ablation coagulation and better performance near blood vessels. Yu et al.[19] evaluated how different configurations of the microwave antennae can affect the ablation shape and coagulation volumes. In patients treated with microwave ablation for hepatocellular carcinoma, they reported that a triple-loop configuration yielded the most uniformly round ablation shape compared

with single straight and triangular triple straight configurations.[19] They also reported that simultaneous activation of multiple antennae produced higher coagulation volumes than single straight antennae and postulated that this may be a potentially promising technique for rapid and effective treatment of large hepatocellular carcinomas.[19] Whereas our study is limited by only evaluating coagulation diameters for single antennae, making it less clinically applicable, we believe that the information gained by this study is important before moving on to more complex clustering or configurations of antennae.

Other studies, using different microwave systems, have also evaluated ablation diameters. Hines-Peralta et al.[20] evaluated microwave ablation in *ex vivo* bovine livers and *in vivo* porcine livers using a 5.7-mm diameter 2.45-GHz microwave applicator. In the *in vivo* study, they found a relative plateau in coagulation size achieved within 8 min at all power levels, and the diameter at this ablation was statistically larger ($p<0.05$) than the diameter obtained in the *ex vivo* experiment at the same wattage and time.[20] Our study had similar findings regarding a plateau in ablation diameters at a certain time; however, our plateau time tended to be higher and was usually around 10 min. One important point in the study by Hines-Peralta[20] is that the ablation coagulation zones for short durations were higher for the *in vivo* porcine livers compared with the *ex vivo* bovine livers. This observation shows promise that microwave ablation can potentially overcome some of the negative effects that perfusion has on ablation, and *in vivo* tissue composition can improve the outcome of microwave ablation, a finding that has not been previously observed with radiofrequency.

Conclusions

Microwave ablation is a promising thermal ablative technique. Our study offers guidelines for use of a novel 915-MHz microwave ablation system and shows that ablation diameter is significantly dependent on time, power, and a time/power interaction. We recommend using power settings of 45 W for 10 min for maximum ablation diameters at the shortest time period and lowest wattage.

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Differences in Long-term Outcome and Prognostic Factors According to Viral Status in Patients with Hepatocellular Carcinoma Treated by Surgery

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Abstract Long-term postoperative survival and prognostic factors were examined retrospectively in patients with hepatocellular carcinoma (HCC) with serum hepatitis B surface antigen (HBsAg) or hepatitis C antibody (HCVAb) and in those without virus infection. Subjects were 265 consecutive HCC patients treated surgically at one institution during the period 1990 to 2006. Postoperative survival was analyzed and compared between HBsAg-positive (B-HCC), HCVAb-positive (C-HCC), and hepatitis B- and C-negative (NBNC-HCC) patients. Prognostic factors for overall and recurrence-free survival were also analyzed. Overall and recurrence-free survival rates were significantly higher in the NBNC-HCC group than in the C-HCC group. Significant prognostic factors for overall survival identified by univariate and multivariate analyses were age, serum alkaline phosphatase (ALP) level, tumor multiplicity, portal vein invasion (Vp), hepatic vein invasion (Vv), and operative blood loss in the B-HCC group; serum albumin level, ALP level, tumor size, and Vv in the C-HCC group; and tumor multiplicity in the NBNC-HCC group. Significant factors for recurrence-free survival were age, ALP level, tumor multiplicity, Vp, and operation time in the B-HCC group; ALP level, prothrombin time, tumor size, Vv, and width of the surgical margin in the C-HCC group; and age, tumor size, tumor multiplicity, and Vp in the NBNC-HCC group. Thus, postoperative survival and prognostic factors in cases of HCC differ according to the presence of serologic viral markers.

Keywords Hepatocellular carcinoma · Viral status · Surgery · Prognostic factors

Introduction

Hepatocellular carcinoma (HCC) is a major cause of cancer deaths worldwide. Despite multiple treatment options, including surgical resection, percutaneous ablation, transcatheter arterial chemoembolization (TACE), and liver transplantation, survival rates remain unsatisfactory.[1]

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HCC tends to occur in patients with chronic liver disorder because of hepatitis B (HB) or hepatitis C (HC) infection. Therefore, all patients with HCC are tested for hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCVAb) before surgery. Does the presence or absence of these markers change the factors influencing postoperative prognosis for HCC patients? Both HB virus (HBV) and HC virus (HCV) cause chronic hepatocellular injury and hepatic regeneration in patients with either virus results in cumulative genetic alterations that may lead to malignant transformation. Differences in carcinogenetic mechanisms between these viruses have been reported. HBV DNA is integrated into the hepatocyte DNA, resulting in genomic instability, and the gene product HBx promotes HCC carcinogenesis.[2] Specific gene products of HCV are also reported to be involved in malignant transformation.[3] Therefore, characteristics of HCC-related viruses may affect HCC characteristics. In addition, there is a substantial population of patients in whom HCC is not related to viral hepatitis.[4] Although there are many reports of differences between HCC associated with HBV

and HCC associated with HCV,[5–8] differences in prognostic factors in relation to the viral status of HCC patients are unclear and have been seldom investigated.[9]

Surgical resection is one of the most effective treatment options for HCC.[1] Prognostic factors are very important in determining whether surgery is indicated. If factors indicate a poor prognosis, other treatments may be chosen or postoperative adjuvant therapy may be applied. To investigate the influence of viral status on prognostic factors in a surgical context, we examined the differences in prognostic factors between three groups of patients treated surgically for HCC who were exclusively HBsAg-positive, HCVAb-positive, or negative for both markers.

Patients and Methods

Two hundred eighty-three patients who underwent hepatic resection for HCC at our institute during the period January 1990 through December 2006 were considered for this study. Of these patients, three patients in whom HCVAb was not tested, nine patients in whom both HBsAg and HCVAb were positive, two patients with autoimmune hepatitis, and four patients who died within 30 postoperative days were excluded from the study. Thus, 265 patients were the subjects of this investigation. HCC was histologically confirmed in all patients. Postoperative follow-up included abdominal ultrasonography (US) or computed tomography (CT) study every 3 months and laboratory testing of serum alpha-fetoprotein (AFP) and/or protein induced by vitamin K absence or antagonist II level every 1 to 3 months at our outpatient clinic. Patients underwent US, CT, and hepatic angiography when recurrence was suspected. Bone scintigraphy or chest CT was performed when clinically indicated. If cancer recurrence was confirmed, various treatments, including repeat hepatectomy, TACE, percutaneous ablation, and radiation therapy were applied as deemed necessary. Treatments and follow-up strategies were not changed on the basis of hepatitis virus status. The median follow-up time was 780 days, and the mean follow-up time was 1,235 days. Recurrence-free survival time was defined as the interval between the day of surgery and diagnosis of recurrence. In the calculation of recurrence-free survival, patients with residual tumor in the remnant liver or other organs at the time of surgery (n=9) and patients in whom the time of recurrence was unknown (n=6) were excluded.

The 265 patients were classified into three groups: a B-HCC group in which patients were HBsAg-positive and HCVAb-negative (n=78), a C-HCC group in which patients were HBsAg-negative and HCVAb-positive (n=127), and a NBNC-HCC group in which patients were both HBsAg-negative and HCVAb-negative (n=60). In the NBNC-HCC group, 14 patients (23.3%) abused alcohol (intake of ≥86 g ethanol per day for at least 10 years, as defined by the Liver Cancer Study Group of Japan),[10] and 13 patients (21.7%) were positive for hepatitis B surface antibody (HBsAb). For all three groups, factors possibly influencing overall postoperative survival and recurrence-free survival were listed and classified into one of four categories: patient characteristics, preoperative liver function, tumor characteristics obtained by preoperative imaging (including CT during hepatic arteriography and arterioportography performed in all patients) and blood analysis (serum AFP level), and treatment (Table 1). Overall postoperative survival and recurrence-free survival were also compared between these groups. Univariate analysis was used to identify significant prognostic factors in each group. If more than two factors in each category were shown to be significant, multivariate analysis was used to detect independent prognostic factors. Obtained prognostic factors were evaluated in relation to postoperative survival curves.

Differences in variables between groups were analyzed by unpaired Student's t test (for continuous variables, expressed as the mean±SD) and chi-square test (for categorical variables). Prognostic factors for overall and recurrence-free survival rates in each group were identified by univariate and multivariate analyses with the Cox proportional hazards regression model. To evaluate the obtained prognostic factors, survival curves calculated by the Kaplan–Meier method were compared by log-rank test. Statistical significance was defined as $p<0.05$. All analyses were performed with StatView statistical software (version 5.0; SAS Institute, Cary, NC, USA).

Results

Patient Characteristics and Outcomes

Results of comparisons of various factors examined for prognostic significance in each group are shown in Table 1. Many factors differed between groups. Age was lower in the B-HCC group than in the other two groups. With respect to liver function, the serum total bilirubin (T-Bil) level was higher and the serum albumin (ALB) level was lower in the C-HCC group than in the NBNC-HCC group. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels and indocyanine green retention rate at 15 min (ICGR15) were higher in the C-HCC group than in the other two groups. The platelet count (Plt) was higher, and the proportion of patients with liver cirrhosis was lower in the NBNC-HCC group than in the other two groups. With respect to tumor characteristics, tumors were smaller in the C-HCC group, and hepatic vein invasion (Vv) was observed more frequently in the NBNC-HCC

Table 1 Possible Factors Influencing Overall Postoperative and Recurrence-free Survival and Comparison of These Factors Between the Groups

				p value		
	B-HCC	C-HCC	NBNC-HCC	(B/NBNC)[a]	(C/NBNC)[b]	(B/C)[c]
Patient characteristics						
Age (years, mean±SD)	54.7±11.6	67.2±6.7	67.9±10.3	*<0.0001*	0.6164	*<0.0001*
Sex (male/female)	58/20	94/33	43/17	0.7234	0.7348	0.9565
Liver function						
T-Bil (mean±SD, mg/dl)	0.82±0.35	0.82±0.29	0.73±0.26	0.0913	*0.0496*	0.9120
ALB (mean±SD, g/dl)	3.75±0.42	3.66±0.42	3.87±0.54	0.1619	*0.0048*	0.1304
ALP (mean±SD, IU/l)	288±165	306±178	307±148	0.4851	0.9869	0.4580
AST (mean±SD, IU/l)	47.6±46.4	59.4±28.6	42.7±29.8	0.4814	*0.0003*	*0.0253*
ALT (mean±SD, IU/l)	43.1±28.8	56.5±34.2	39.8±35.5	0.5595	*0.0026*	*0.0048*
Plt (mean±SD, /μl)	14.1±6.1	14.1±7.5	18.0±7.9	*0.0015*	*0.0014*	0.9955
PT (mean±SD, %)	85.6±15.9	87.5±15.0	88.6±16.3	0.2771	0.6323	0.4134
ICGR15 (mean±SD, %)	15.5±9.9	20.8±11.4	16.6±7.6	0.4752	*0.0129*	*0.0009*
Liver cirrhosis (+/−)	42/36	70/57	17/43	*0.0027*	*0.0006*	0.8590
Tumor characteristics						
Maximum diameter (mean±SD, cm)	6.2±4.5	4.9±3.6	6.2±3.4	0.9398	*0.0296*	*0.0271*
Tumor number (St/Mt)	57/21	85/42	48/12	0.3446	0.0656	0.3543
Portal vein invasion (Vp, +/−)	15/63	13/114	11/49	0.8937	0.1223	0.0687
Hepatic vein invasion (Vv, +/−)	3/75	5/122	8/52	*0.0414*	*0.0184*	0.9740
AFP (mean±SD, $\times 10^3$ ng/ml)	58.7±255.2	2.8±7.3	3.4±8.8	0.1048	0.4567	*0.0138*
Treatment						
Preoperative TACE (+/−)	18/60	42/85	17/43	0.4817	0.5152	0.1268
Resection (nonanatomic/anatomic)	19/59	43/84	9/51	0.1753	*0.0072*	0.1505
Operative blood loss (mean±SD, ml)	1594±1702	1216±1245	1326±1252	0.3079	0.5748	0.0690
Operation time (mean±SD, min)	387±163	331±161	375±163	0.6648	0.0898	*0.0182*
SM ≥5 mm (+/−)	41/37	75/52	32/28	0.9285	0.4604	0.3626

p values <0.05 are italicized.

T-Bil: total bilirubin, *ALB*: albumin, *ALP*: alkaline phosphatase, *AST*: aspartate aminotransferase, *ALT*: alanine aminotransferase, *Plt*: platelet count, *PT*: prothrombin time, *ICGR15*: indocyanine green retention rate at 15 min, *St*: single tumor, *Mt*: multiple tumors, *AFP*: alpha-fetoprotein, *TACE*: transcatheter arterial chemoembolization, *SM*: surgical margin

[a] B-HCC group vs NBNC-HCC group.

[b] C-HCC group vs NBNC-HCC group.

[c] B-HCC group vs C-HCC group.

group than in the other two groups. The serum AFP level was higher in the B-HCC group than in the C-HCC group. With respect to treatment, anatomic resection was performed more often in the NBNC-HCC group than in the C-HCC group. Operation time was shorter in the C-HCC group than in the B-HCC group.

Both overall survival and recurrence-free survival rates, as calculated by the Kaplan–Meier method, were higher in the NBNC-HCC group than in the C-HCC group (Fig. 1). Although there was a tendency toward higher overall and recurrence-free survival rates in the NBNC-HCC group compared to those in the B-HCC group, these differences

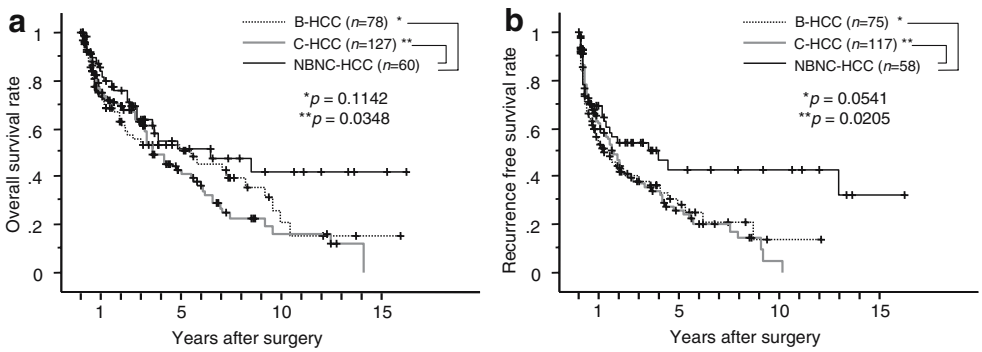

Figure 1 Overall postoperative survival rates (**a**) and recurrence-free survival rates (**b**) in the B-HCC group, C-HCC group, and NBNC-HCC group. Both survival rates were significantly higher in the NBNC-HCC group than in the C-HCC group. The same tendency was observed for the NBNC-HCC group compared to the B-HCC group, but this tendency was not statistically significant.

were not statistically significant. No difference in survival rate was found between the B-HCC and C-HCC groups.

Prognostic Factors for Overall Survival in Each Group

B-HCC group Univariate analysis by the Cox proportional hazards model showed that age in the patient characteristics category; alkaline phosphatase (ALP) level in the liver function category; and tumor size, number of tumors, portal vein invasion (Vp), Vv, and AFP level in the tumor characteristics category were significant prognostic factors (Table 2). Operative blood loss in the treatment category was also a significant factor. Stepwise multivariate Cox proportional hazards analysis of the tumor characteristics category showed that tumor number, Vp, and Vv were independent prognostic factors (Table 2).

C-HCC group Serum ALB, ALP, and AST levels and ICGR15 in the liver function category and tumor size, Vv, and AFP level in the tumor characteristics category were shown to be significant prognostic factors by univariate analysis (Table 2). Multivariate analysis showed that of the

Table 2 Univariate and Multivariate Analyses of Prognostic Factors for Overall Survival in Each Group

	p value					
	B-HCC		C-HCC		NBNC-HCC	
	Univariate (Risk ratio, 95%CI)	Multivariate	Univariate (Risk ratio, 95%CI)	Multivariate	Univariate (Risk ratio, 95%CI)	Multivariate
Patient characteristics						
Age	*0.0030* (0.958, 0.932–0.986)		0.8172		0.1381	
Sex	0.8526		0.9154		0.4201	
Liver function						
T-Bil	0.3231		0.4314		0.2426	
ALB	0.1688		*0.0007* (0.507, 0.265–0.970)	*0.0400*	0.2369	
ALP	*<0.0001* (1.003, 1.002–1.004)		*<0.0001* (1.002, 1.001–1.004)	*0.0002*	*0.0242* (1.003, 1.000–1.005)	
AST	0.9903		*0.0135*	0.3900	0.1705	
ALT	0.6180		0.2545		0.5174	
Plt	0.7628		0.2835		0.7990	
PT	0.9425		0.8816		0.0922	
ICGR15	0.2878		*0.0287*	0.5919	0.2901	
Liver cirrhosis	0.8971		0.7001		0.0584	
Tumor characteristics						
Maximum diameter	*0.0042*	0.4411	*<0.0001* (1.171, 1.096–1.251)	*<0.0001*	0.0516	
Tumor number (St/Mt)	*0.0030* (2.291, 1.160–4.523)	*0.0169*	0.1450		*0.0034* (3.586, 1.527–8.426)	
Portal vein invasion (Vp)	*0.0001* (0.339, 0.139–0.826)	*0.0174*	0.4271		0.0639	
Hepatic vein invasion (Vv)	*0.0061* (0.286, 0.084–0.974)	*0.0453*	*0.0156* (0.125, 0.028–0.567)	*0.0070*	0.5881	
AFP	*0.0064*	0.9125	*0.0182*	0.3876	0.6261	
Treatment						
Preoperative TACE	0.7942		0.6219		0.1609	
Resection (nonanatomic/anatomic)	0.0751		0.6626		–[a]	
Operative blood loss	*0.0048* (1.000, 1.000–1.000)		0.1059		0.8290	
Operation time	0.1504		0.8392		0.5598	
SM ≥5 mm	0.0711		0.0906		0.5061	

Risk ratios and 95% confidence intervals are shown under the significant independent prognostic factors in each category identified in each group by univariate or multivariate analysis. *p* values <0.05 are italicized. Abbreviations are the same as those in Table 1.
CI: confidence interval
[a] Could not be evaluated because no event was observed in patients who underwent nonanatomic resection.

liver function factors, ALB and ALP levels were independent prognostic factors, and of the tumor characteristics, tumor size and Vv were independent prognostic factors (Table 2).

NBNC-HCC group Serum ALP level in the liver function category and number of tumors in the tumor characteristics category were shown to be significant prognostic factors by univariate analysis (Table 2).

Overall postoperative survival rates (1-, 3-, 5-, 7-, and 10-year) calculated by the Kaplan–Meier method and according to the independent prognostic factors for the B-HCC, C-HCC, and NBNC-HCC groups are shown in Table 3. Significant differences in overall postoperative survival rates were observed in relation to these factors with the exception of ALP in the NBNC-HCC group. For this factor, the biggest difference in overall survival rates was obtained when the patients were classified into those with ≥350 IU/l serum ALP and those with <350 IU/l serum ALP, but this difference did not reach significance by log-rank test.

Prognostic Factors for Recurrence-free Survival in Each Group

B-HCC group Univariate analysis by the Cox proportional hazards model showed that age in the patient characteristics category; serum ALP level in the liver function category; tumor size, number of tumors, Vp, Vv, and AFP level in the tumor characteristics category; and operation time in the treatment category were significant prognostic factors (Table 4). Stepwise multivariate analysis by the Cox proportional hazards model of the tumor characteristics category showed the number of tumors and Vp to be independent prognostic factors (Table 4).

C-HCC group Serum ALP level and prothrombin time (PT) in the liver function category; tumor size and Vv in the tumor characteristics category; and distance of the surgical margin (SM ≥5 mm or not) in the treatment category were shown to be significant prognostic factors by univariate analysis (Table 4). Multivariate analysis of the liver function category and the tumor characteristics category

Table 3 Postoperative Overall Survival Rates According to the Prognostic Factors for Each Group

Prognostic factors	Survival rate					
	1-year	3-year	5-year	7-year	10-year	*p* value (log-rank test)
B-HCC						
Age ≥55 years (*n*=38)	92	69	69	62	39	
Age <55 years (*n*=40)	56	40	36	30	10	*0.0024*
ALP ≥350 IU/l (*n*=17)	41	16	0			
ALP <350 IU/l (*n*=61)	83	64	64	57	32	*<0.0001*
Tumor number, single (*n*=57)	83	71	68	57	29	
Tumor number, multiple (*n*=21)	57	17	17	17	17	*0.0021*
Portal vein invasion (Vp) + (*n*=15)	40	24	24	8	–	
Portal vein invasion (Vp) − (*n*=63)	82	64	62	57	32	*<0.0001*
Hepatic vein invasion (Vv) + (*n*=3)	32	0				
Hepatic vein invasion (Vv) − (*n*=75)	75	58	56	47	27	*0.0020*
Operative blood loss ≥1,000 ml (*n*=45)	64	41	41	34	23	
Operative blood loss <1,000 ml (*n*=33)	87	74	71	61	32	0.0307
C-HCC						
ALB ≥3.7 g/dl (*n*=61)	85	69	54	44	31	
ALB <3.7 g/dl (*n*=66)	66	56	29	8	0	*0.0003*
ALP ≥350 IU/l (*n*=33)	62	42	21	10	0	
ALP <350 IU/l (*n*=94)	81	68	48	33	20	*0.0028*
Maximum diameter ≥6 cm (*n*=34)	54	40	21	21	0	
Maximum diameter <6 cm (*n*=93)	83	71	49	27	16	*0.0009*
Hepatic vein invasion (Vv) + (*n*=5)	0					
Hepatic vein invasion (Vv) − (*n*=122)	78	64	43	27	16	*0.0055*
NBNC-HCC						
ALP ≥350 IU/l (*n*=17)	76	40	40	30	30	
ALP <350 IU/l (*n*=43)	89	74	54	54	46	0.0973
Tumor number, single (*n*=48)	91	72	61	56	48	
Tumor number, multiple (*n*=12)	61	30	15	15	15	*0.0017*

p values <0.05 are italicized. Abbreviations are the same as those in Table 1.

Table 4 Univariate and Multivariate Analyses of Prognostic Factors for Recurrence-free Survival in Each Group

	p value					
	B-HCC		C-HCC		NBNC-HCC	
	Univariate (Risk ratio, 95%CI)	Multivariate	Univariate (Risk ratio, 95%CI)	Multivariate	Univariate (Risk ratio, 95%CI)	Multivariate
Patient characteristics						
Age	*0.0171* (0.972, 0.949–0.996)		0.8975		*0.0298* (1.061, 1.008–1.116)	
Sex	0.7671		0.5601		0.7725	
Liver function						
T-Bil	0.0758		0.8747		0.3941	
ALB	0.3971		0.1195		0.2134	
ALP	*<0.0001* (1.003, 1.002–1.004)		*<0.0001* (1.002, 1.001–1.003)	*<0.0001*	0.1905	
AST	0.9265		0.0529		0.4544	
ALT	0.2501		0.5497		0.4459	
Plt	0.9100		0.2631		0.3467	
PT	0.3326		*0.0291* (0.980, 0.961–1.000)	*0.0481*	0.1085	
ICGR15	0.4278		0.2441		0.2268	
Liver cirrhosis	0.6795		0.2537		0.5203	
Tumor characteristics						
Maximum diameter	*0.0052*	0.2875	*0.0023* (1.099, 1.019–1.184)	*0.0016*	*0.0127* (1.136, 1.023–1.262)	*0.0195*
Tumor number (St/Mt)	*<0.0001* (3.413, 1.722–6.762)	*0.0016*	0.2064		*0.0196* (3.538, 1.492–8.391)	*0.0130*
Portal vein invasion (Vp)	*0.0002* (0.396, 0.177–0.885)	*0.0070*	0.1959		*0.0118* (0.318, 0.131–0.776)	*0.0327*
Hepatic vein invasion (Vv)	*0.0014*	0.0536	*<0.0001* (0.069, 0.021–0.227)	*<0.0001*	0.1204	
AFP	*0.0003*	0.2376	0.1560		0.9504	
Treatment						
Preoperative TACE	0.6040		0.2589		0.1267	
Resection (nonanatomic/anatomic)	0.0683		0.8254		0.1270	
Operative blood loss	0.0711		0.0861		*0.0227* (1.000, 1.000–1.001)	
Operation time	*0.0088* (1.002, 1.000–1.003)		0.5726		0.7846	
SM ≥5 mm	0.1791		*0.0211* (1.657, 1.058–2.596)		0.0995	

Risk ratios and 95% confidence intervals are shown under the significant independent prognostic factors in each category identified in each group by univariate or multivariate analysis. *p* values <0.05 are italicized. Abbreviations are the same as those in Table 1.
CI: confidence interval

showed ALP level, PT, tumor size, and Vv to be independent prognostic factors (Table 4).

NBNC-HCC group In the patient characteristics category, age was shown to be a significant prognostic factor by univariate analysis. No significant factor was found in the liver function category. In the tumor characteristics category, tumor size, number of tumors, and Vp were shown to be significant prognostic factors by univariate analysis. All of these factors were significant by multivariate analysis (Table 4). Operative blood loss in the treatment category was shown to be a significant prognostic factor by univariate analysis (Table 4).

Recurrence-free survival rates (1-, 3-, 5-, 7-, and 10-year) calculated by the Kaplan–Meier method and according to the independent prognostic factors for the B-HCC, C-

Table 5 Postoperative Recurrence-free Survival Rate According to the Prognostic Factors in Each Group

Prognostic factors	Survival rate					
	1-year	3-year	5-year	7-year	10-year	*p* value (log-rank test)
B-HCC						
Age ≥55 years (*n*=37)	68	48	36	29	29	
Age <55 years (*n*=38)	44	28	24	12	0	*0.0236*
ALP ≥350 IU/l (*n*=17)	32	8	–			
ALP <350 IU/l (*n*=58)	61	48	37	24	17	*<0.0001*
Tumor number, single (*n*=56)	66	50	41	27	19	
Tumor number, multiple (*n*=19)	17	0				<0.0001
Portal vein invasion (Vp) + (*n*=15)	22	11	11	–	–	
Portal vein invasion (Vp) − (*n*=60)	76	61	47	47	47	<0.0001
Operation time ≥6 h (*n*=38)	39	22	22	22	–	
Operation time <6 h (*n*=37)	68	53	41	26	12	*0.0179*
C-HCC						
ALP ≥350 IU/l (*n*=29)	39	11	–	–	–	
ALP <350 IU/l (*n*=67)	66	38	27	22	–	*0.0062*
PT ≥80% (*n*=77)	66	47	33	26	7	
PT <80% (*n*=32)	45	21	13	–	–	*0.0099*
Maximum diameter ≥6 cm (*n*=32)	41	21	–	–	–	
Maximum diameter <6 cm (*n*=85)	69	43	29	23	5	*0.0165*
Hepatic vein invasion (Vv) + (*n*=5)	0					
Hepatic vein invasion (Vv) − (*n*=112)	64	39	27	21	4	*<0.0001*
SM ≥5 mm (*n*=68)	71	44	27	27	6	
SM <5 mm (*n*=49)	48	27	23	9	–	*0.0195*
NBNC-HCC						
Age ≥65 years (*n*=44)	62	46	32	32	32	
Age <65 years (*n*=14)	92	81	81	81	81	*0.0200*
Maximum diameter ≥6 cm (*n*=28)	45	24	24	24	24	
Maximum diameter <6 cm (*n*=30)	92	84	62	62	62	*<0.0001*
Tumor number, single (*n*=47)	73	61	47	47	47	
Tumor number, multiple (*n*=11)	50	25	25	25	25	*0.0146*
Portal vein invasion (Vp) + (*n*=10)	36	17	17	17	17	
Portal vein invasion (Vp) − (*n*=48)	76	61	47	47	47	*0.0080*
Operative blood loss ≥1,000 ml (*n*=33)	58	38	38	38	38	
Operative blood loss <1,000 ml (*n*=25)	83	71	50	50	50	0.0837

p values <0.05 are italicized. Abbreviations are the same as those in Table 1.

HCC, and NBNC-HCC groups are shown in Table 5. Significant differences in postoperative recurrence-free survival rates were observed in relation to these factors with the exception of operative blood loss in the NBNC-HCC group. For this factor, the biggest difference in recurrence-free survival rate was obtained when the patients were classified into those with ≥1,000 ml blood loss and those with <1,000 ml blood loss, but this difference did not reach significance by log-rank test.

Discussion

It should be mentioned that the NBNC-HCC group and the C-HCC group may have included patients with HBV in the present study. Recent studies have shown that HBV DNA can be detected in the hepatic parenchyma of many HBsAg-negative HCC patients.[11,12] However, the determination of HBV DNA in liver tissue was not carried out in the present study and is not routinely checked during the clinical course of HCC. We believe that the investigation of prognostic factors based on generally accepted serologic virus markers, HBsAg and HCVAb, is reasonable. In addition, 21.7% of patients in the NBNC-HCC group were positive for HBsAb. In such patients, the contribution of HBV to the occurrence of HCC is unknown and the influence of HBV on the function or carcinogenesis of the remnant liver during the postoperative course is not as strong as that in HBsAg-positive patients. Therefore, HBsAb-positive patients were included in the NBNC-HCC

group. Because HB core antibody was not measured in many patients, we did not review it in the present study.

Multiple differences were observed between the three study groups. The finding that the patients in the B-HCC group were younger than those in the other groups is consistent with previously reported findings in Japan,[6,8,13] but not with findings from a study based on a multicenter international database including patients from Japan, China, France, and the United States.[5] In the liver function category, many parameters reflected that the incidence and severity of chronic hepatitis or cirrhosis were greatest in C-HCC patients, followed by B-HCC patients. Among the three groups, liver function was the best in the NBNC-HCC group. The smaller tumors and lower AFP level in the C-HCC group may be because of periodic screening for HCC in these patients. The reason for the high incidence of Vv in the NBNC-HCC group is unknown. Analysis of treatment factors suggests that in the NBNC-HCC group, the increased frequency of anatomic resection may have been related to good liver function compared to that in the C-HCC group. In the C-HCC group, short operation time may have been related to the smaller tumor size compared to that in the B-HCC group.

The question of the relation of postoperative survival rates to viral status has been quite controversial. Some reports note a higher overall or recurrence-free survival rate in HB-negative and HC-negative patients than in HB-positive patients.[4,6,14] However, previous studies showed no difference in survival with respect to viral status.[5,8] In the present study, improved overall postoperative survival and recurrence-free survival were observed in the NBNC-HCC group compared to that in the C-HCC group. This is attributed to a low incidence of multicentric carcinogenesis, which is caused by chronic viral attack. This theory is supported by the large difference in survival curves between the NBNC-HCC group and the C-HCC group that began to be observed at 2 years (recurrence-free survival) or 3 years (overall survival) after surgery. Comparison of the survival curves between the NBNC-HCC group and the B-HCC group showed the same tendency, but it was not statistically significant. A feature of the postoperative survival curve in the NBNC-HCC group is that the overall survival rate did not decrease beyond the ninth postoperative year, and the recurrence-free survival rate showed only a small decrease beyond the fifth postoperative year. Patients who survived longer than this are expected to be completely cured.

Many reports pertaining to differences in tumor characteristics and post therapeutic survival rates according to hepatitis virus status have been published, but the findings are controversial. One of the important issues is how to determine treatment strategy according to viral status, and prognostic factors are an important part of this question. In our examination of prognostic factors, we found many differences between the B-HCC, C-HCC, and NBNC-HCC groups. In the B-HCC group, patients younger than 55 years of age showed significantly lower survival rates than those 55 years of age or older. This indicates that careful follow-up and early diagnosis of HCC is important in patients less than 55 years of age with chronic HBV infection. The importance of ALP as a prognostic factor was emphasized in a previous study of liver cirrhosis.[15] ALP may also belong to the tumor characteristics category because it can reflect bile duct compression by a large or rapidly growing tumor. Patients with a high ALP level (≥350 IU/l), multiple tumors, or vascular-invading tumors have a very poor prognosis and may have to undergo challenging postoperative adjuvant therapy. Operative blood loss and operation time may affect the postoperative overall and recurrence-free survival rates, respectively, in this group.

In the C-HCC group, protein production by the liver, as represented by serum ALB level or PT, affects postoperative overall or recurrence-free survival rate. These factors representative of liver function were observed exclusively in the C-HCC group, and no liver function factor other than ALP level affected prognosis in the other two groups. ALP level was a strong prognostic factor, similar to that in the B-HCC group. The fact that large tumor size (≥6 cm) was related to poor prognosis indicates that the tumor should be detected and removed before it has grown beyond 6 cm. Patients with HCC with Vv have an extremely poor prognosis (0%, 1-year survival), and these patients may not be candidates for hepatic resection. There is a possibility that the distance of the surgical margin (≥5 mm or not) affects the postoperative recurrence-free survival rate in this group.

In the NBNC-HCC group, tumor recurrence was more frequent in elderly patients (≥65 years of age) and in patients with multiple, large tumors (≥6 cm), or Vp, and careful postoperative follow-up is required. The only significant prognostic factor for overall postoperative survival revealed by both the Cox proportional hazards model and the Kaplan–Meier method and log-rank test was tumor multiplicity. In this group, liver function, tumor characteristics of tumor size and vascular invasion, and treatment factors were not prognostic for overall survival, indicating that if the tumor is solitary, aggressive surgery can result in a good prognosis in patients with a large tumor and vascular invasion.

Conclusion

In the light of our findings, we conclude that prognostic factors obtained before surgery differ according to viral status in surgically treated HCC patients. This should be considered in the determination of the surgical treatment strategy for such patients.

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Laparoscopic Fenestration of Liver Cysts in Polycystic Liver Disease Results in a Median Volume Reduction of 12.5%

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Abstract
Introduction Patients with polycystic liver disease (PCLD) may develop symptoms due to increased liver volume. Laparoscopic fenestration is one of the options to reduce liver volume and to relieve symptoms. This study was performed to evaluate the safety and efficacy of laparoscopic liver cyst fenestration.
Patients and Methods Twelve patients (all female, median age 45 years, range 35–58) with symptomatic PCLD were included between August 2005 and April 2007. Surgical data were recorded, liver volumes were measured on pre- and postoperative computed tomography (CT) scans, and patients completed a validated symptom-based questionnaire pre- and postoperatively.
Results Median preoperative liver volume was 4,854 ml (range 1,606–8,201) and decreased to 4,153 ml postoperatively (range 1,556–8,232) resulting in median liver volume reduction of 12.5% (range +9.5 to −24.7%). Median procedural time was 123.5 min (range 50–318), and median hospitalization period was 3.5 days (range 1–8). Postoperative complications occurred in three patients including biliary leakage, obstruction of inferior vena cava and sepsis, all recovering with conservative management. Patients reported decreased symptoms of postprandial fullness and abdominal distension.
Conclusion Laparoscopic fenestration in PCLD patients results in volume reduction of 12.5% and decrease of symptoms.

Keywords Laparoscopic fenestration · Polycystic liver disease · Liver cyst

Introduction

Simple hepatic cysts can be detected in up to 5% of patients subjected to conventional abdominal imaging techniques.[1,2] Polycystic livers, characterized by a large number of liver cysts (>20) scattered throughout the liver parenchyma, are mostly seen in association with autosomal dominant polycystic kidney disease (ADPKD). Patients with ADPKD also have polycystic kidneys, a feature that is absent in patients with autosomal dominant polycystic liver disease (PCLD).[3] The genetic basis of both diseases is different; associated genes in PCLD are *PRKCSH* and *SEC63*,[4,5] while ADPKD is caused by *PKD1* or *PKD2* mutations.[6]

Symptoms in patients with a polycystic liver are mostly absent, but they may develop because of increasing cyst size. They mainly consist of abdominal pain, early satiety, dyspnea, nausea, and vomiting.[7] Complications directly related to the presence of cysts such as intracystic hemorrhage, infection, or rupture, are rare.[8]

Treatment is indicated when symptoms are thought to be severe enough to warrant intervention.[9] In general, therapy is aimed to reduce liver volume and to relieve symptoms. Several therapeutic options are presently available, which include aspiration-sclerotherapy, cyst fenestration, partial liver resection, and liver transplantation. The choice of treatment largely depends on number, size, and location of the liver cysts.[8]

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The technique of open fenestration of liver cysts was first described by Lin et al. in 1968.[10] This technique has been reported to be a safe and effective treatment for the management of symptomatic nonparasitic cysts of the liver.[11] In 1991, laparoscopic fenestration was introduced and appears to be equally effective.[12,13] The cited advantages of laparoscopic fenestration as an alternative for the open procedure concern lower morbidity and mortality rates and a reduced hospital stay.[8,14,15] In addition, it has been suggested that an open procedure may lead to the formation of adhesions, which may impede the possibility of a future liver transplantation.[16] So far, laparoscopic fenestration has mainly been evaluated in patients with either single cysts or polycystic livers due to ADPKD, while data on PCLD are conspicuously scarce.

The purpose of our study is to evaluate the efficacy of laparoscopic cyst fenestration in terms of absolute liver volume reduction and symptom relief in PCLD patients.

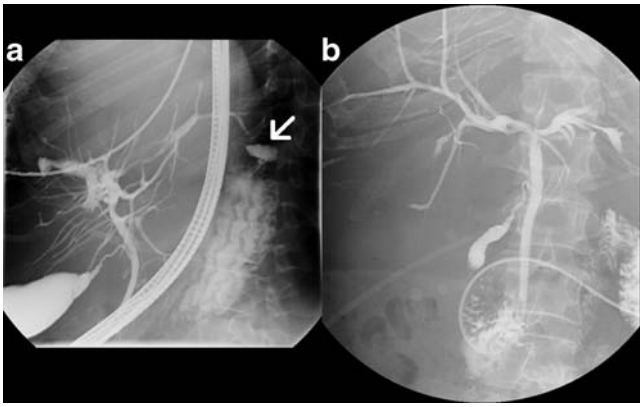

Figure 1 Biliary leakage as postoperative complication in laparoscopic fenestration. **a** Cholangiogram shows a leakage of contrast (arrow). **b** Cholangiogram, made 14 days after (**a**) shows that the leakage is closed.

Material and Methods

Subjects

Twelve patients (all female, mean age 44.9 years, range 35–58 years) with symptomatic PCLD were treated between August 2005 and April 2007 for laparoscopic fenestration of liver cysts. Five patients had *PRKCSH* gene mutations, two patients carried *SEC63* mutations, whereas the remaining five patients were wild type for both genes. Six patients had been treated initially by aspiration-sclerotherapy, one patient had been subjected to (unsuccessful) laparoscopic marsupialization of one of her liver cysts, and another patient had a history of laparoscopic cholecystectomy for symptomatic cholecystolithiasis.

Multislice computed tomography (CT) scans were performed in all patients at a median interval of 138 days before surgery (range 6–336 days). Based on this pre-procedure CT scan, patients were divided in groups according to the classification of polycystic livers as defined by Gigot et al.[11]: Type I included patients with a limited number (<10) of large cysts. Type II respresented patients with diffuse involvement of liver parenchyma by multiple medium-sized cysts with remaining large areas of non-cystic liver parenchyma. Type III was a severe form of PCLD with massive, diffuse involvement of liver parenchyma by small- and medium-sized liver cysts and only a few areas of normal liver parenchyma between cysts.

Surgical Procedure

Patients were positioned in a supine reversed Trendelenburg position. Pneumoperitoneum was established using an open introduction at the umbilicus, after which a 12-mm trocar was placed first. Based on inspection of the abdominal cavity and polycystic liver, three other trocars (5 and 12 mm) were placed at locations seeming most appropriate for fenestration.

Large and accessible cysts were punctured and aspirated with laparoscopic aspiration needle and subsequently deroofed by using ultrasonic dissection (Ultracision® harmonic scalpel, Ethicon Endo Surgery). The dissected wall and floor of all cysts were inspected for bile leakage and bleeding; if necessary, hemostasis was performed. To facilitate future liver transplantation, omentoplasty was not performed. After fenestration of all accessible cysts, trocars were removed under direct vision, and the abdomen was desufflated before closure of the skin and fascia.

3D Volumetry

Multislice CT scan was repeated at a median postoperative period of 72.5 days (range 13–587 days). The effect of the surgical procedure was evaluated by pre- and postoperative 3D total liver volume measurement of CT scan slices using Pinnacle^{3}® version 8.0d (Philips, Eindhoven, The Netherlands). CT scans had a slice thickness of 3 mm, and the liver was outlined manually every 9 mm. The software interpolated the intermediate slices and calculated the areas within the indicated circumference, and finally, the total liver volume.

Questionnaire

Finally, all patients received a 12-abdomen-symptom-based questionnaire.[17] Patients completed the questionnaire 4 weeks before and 4 weeks after the procedure. Symptoms were scored from 0 (absence of complaints) to 6 (severe complaints).

Statistical Analysis

Statistical analyses were performed using the paired *t* tests and Pearson's correlation coefficient, to study differences in severity of symptoms and compare symptoms with liver volume, respectively. A *P*-value of <0.05 was considered statistically significant.

Results

Patient Characteristics

Patient characteristics are outlined in Table 1. Four patients were classified as type II polycystic liver disease and eight as type III. The median follow-up time was 352 days (range 150–738 days).

Surgical Procedure

Laparoscopic fenestration was technically successful in all 12 patients; there was no need for conversion to laparotomy. The median duration of the procedure was 123.5 min (range 50–318 min). Minor intraoperative hemorrhage of the liver capsule occurred in four patients, which was easily controlled by surgical hemostasis. One patient had adhesions due to previous marsupialization, but adhesiolysis facilitated a good view on the polycystic liver and did not hamper the procedure. The median hospitalization time was 3.5 days (range 1–8 days).

Three postoperative complications occurred (25%). One patient developed cold chills and fever indicating bloodborne sepsis. Blood culture revealed an enterobacter cloacae. She was admitted to the intensive care unit, received inotropic support, and was treated with intravenous cefuroxime, metrodinazole in combination with tobramycine and recovered within 2 days (hospitalization was 8 days).

For the second patient, the procedure went uneventful and appeared to be effective, until 8 weeks after fenestration when she presented with nausea, fatigue, and fever. She had an increased abdominal girth because of biliary ascites. A subsequent cholangiogram was compatible with biliary leakage (Fig. 1). A nasobiliary drain was inserted and the leakage closed conservatively after 14 days. After readmission of 41 days, she was discharged in good clinical condition.

The last patient developed inferior vena cava obstruction with bilateral leg edema. She was treated with ultrasound-guided aspiration of strategically located cysts and administration of diuretics, and she recovered, but after 3 months after surgery, there was still residual ascites despite diuretic therapy. She was hospitalized for a total of 31 days.

Liver Volumetry

We measured four livers from control patients who underwent CT scanning for liver unrelated purposes. The average volume of these livers was 1,550 ml (range 1,230–1,751 ml), which corresponds to other studies.[18–20] The average variation in intraindividual observation was 1.2% (range 0.0–5.3%; seven livers), whereas the interindividual variation of the observations was 2.7% (range 2.5–2.8%; four livers).

The median liver volume before operation was 4,854 ml (range 1,606–8,201 ml) and decreased to 4,153 ml (range 1,556–8,232 ml) after the procedure. This comes down to a median reduction of liver volume of 12.5% (range +9.5 to

Table 1 Patient Characteristics

Patient number	Age (Years)	Gigot [11] 10 type	Intraoperative complication	Postoperative complication	Procedural duration (minutes)	Length of stay (days)	CT-volume before (mL)	CT-volume after (mL)	Liver volume change (%)
1[a]	54	2	None	None	91	1	2877	3151	+9.5
2	58	2	None	None	76	2	2150	1619	-24.7
3[a]	39	3	None	None	101	2	4974	5089	+2.3
4[b]	40	3	None	None	194	3	7143	6117	-14.4
5[a]	35	3	Hemorrhage	None	177	3	4484	3655	-18.5
6	45	3	Hemorrhage	Fever	195	7	5302	4310	-18.7
7[b]	37	3	Hemorrhage	Bile leakage	251	4	6344	5010	-21.0
8[a]	42	3	None	None	117	3	4735	3996	-15.6
9[a]	42	3	Hemorrhage	None	318	5	7468	6675	-10.6
10	47	2	None	None	50	4	1718	1610	-6.3
11	57	2	None	None	82	8	1606	1556	-3.2
12	43	3	None	Vena cava inferior syndrome	130	7	8201	8232	+0.4

Age reflects age at operation time.
[a] PRKCSH-mutation
[b] SEC63-mutation

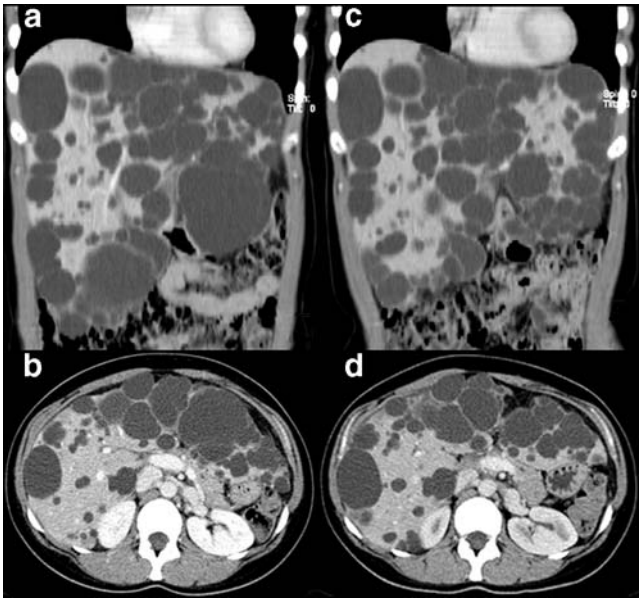

Figure 2 Sagittal and transversal CT slices of patient 8. **a** and **b** are preoperative, **c** and **d** are postoperative.

−24.7%), although not statistically significant. Figure. 2 shows a typical result of the procedure in a patient in whom we achieved a liver volume reduction of 15.6%.

Questionnaire

All patients completed the questionnaire pre- and postoperatively. The most frequent and severe symptoms recorded before surgery were abdominal distension, postprandial fullness, loss of appetite, and pain (Table 2). Before treatment, every patient reported severe abdominal distension. Eleven patients reported abdominal pain, with epigastric pain being most prominent. Postprandial fullness had been experienced by most patients (n=10) and was severe as well. On the whole, a trend to a decrease of all symptoms after laparoscopic fenestration was demonstrated, with a significant decrease of abdominal distension (p=0.01) and postprandial fullness (p=0.02). Three patients had complete remission of pain.

Pain scores decreased in patients with decreased liver volume and vice versa. Patients with liver volume increase reported an increase of pain. Figure 3 shows the correlation (r=-0.32, p=0.31) between liver volume change and decrease of symptoms. One patient (no. 4) reported more pain after laparoscopic fenestration. She was referred for liver transplantation.

Discussion

The goal of laparoscopic fenestration of liver cysts in PCLD is twofold: liver volume reduction by elimination of cysts and relief of symptoms. In this series, a median liver volume reduction of 12.5% was achieved with a concomitant decrease of the severity of symptoms. This suggests that a procedure that results in liver volume reduction has the advantage of symptom relief (Fig. 3).

Table 2 The Mean Severity of Symptoms Before and After Treatment

Symptom	Before	After
Abdominal pain:		
In common	1.8	1.2
Postprandial	2.1	1.0
Fasting	1.6	0.9
Unrelated to defecation	1.2	0.6
Epigastric pain:		
In common	2.2	1.1
During daytime	2.3	1.1
At night/asleep	1.8	0.8
Heartburn	1.7	0.8
Regurgitation	1.6	0.7
Nausea	1.7	0.7
Vomiting	0.7	0.2
Loss of appetite	2.6	0.6
Postprandial fullness	3.6	1.1[a]
Shortness of breath	1.6	0.5
Abdominal distension	4.2	1.9[a]
Involuntary weight loss	1.2	0.3
Pain	2.2	1.7

All symptoms were scored on a range of 0–6 (*0* No symptom, *6* very severe)
[a] Indicates a significant decrease

The primary endpoint of our study was volume reduction, as assessed by liver volumetry on CT scanning. We found that this technique is reliable, precise, and appears to be helpful in estimating the therapeutic efficacy. In PCLD, symptoms are more likely related to the increased

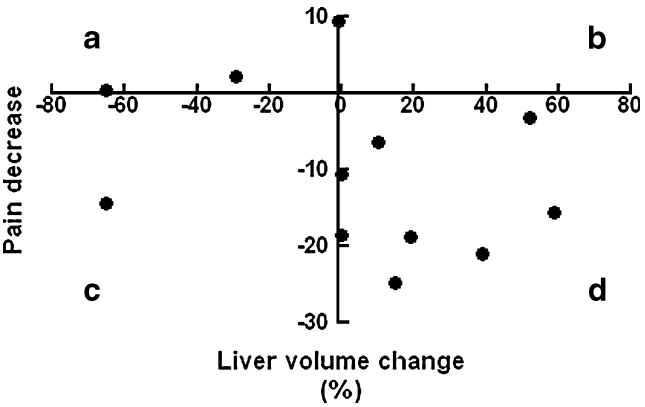

Figure 3 Correlation between total of pain decrease and liver volume change. Pain is scored on a scale of 0–100. Patients were grouped according to effect of therapy on volume and abdominal pain. **a** Patients with increase of pain and increased liver volume. **b** Patients with decrease of pain and increased liver volume. **c** Patients with increase of pain and decreased liver volume. **d** Patients with decrease of pain and decreased liver volume. Most patients had a benefit in terms of both volume reduction and decrease of abdominal pain (**d**).

liver volume than to strategically located cysts. Hence, it is reasonable to measure total liver volume instead of single cyst size. The measured liver volumes before surgery match with the classification of Gigot et al.[11]: range of liver volumes in patients with type II was 1,606–2,877 ml, and in patients with the most severe phenotype (III), range was 4,484–8,201 ml.

In 1997, Gigot et al. evaluated ten patients who had been treated by an aggressive attempt to reduce liver volume, mainly by open-liver cyst fenestration. Deep-sited cysts were also opened aided with intraoperative ultrasound. Here, the average liver volume decreased from 7,761 to 4,596 ml, a reduction of 43%. Both preoperative liver volume and volume reduction was larger than obtained in our trial. The main difference is that nine out of ten patients underwent open fenestration, and it appears that volume control can be better obtained with an open procedure under ultrasonic guidance. On the other hand, this approach is associated with a higher prevalence of intra- and postoperative complications such as intraoperative massive hemorrhage and a biliary tear, postoperative biliary leakage and ascites, and obstruction of the inferior vena cava. Intraoperative and postoperative complications are more common in patients with polycystic livers than in patients with single liver cysts. In our study, three patients (25%) had severe postoperative complications. These patients had a prolonged hospitalization or readmission with severe morbidity. The patient with the largest liver volume (8.2 l) developed inferior vena cava obstruction. We speculate that as a result of the fenestration, the liver got dislodged with subsequent compression of the inferior vena cava. Ultimately, all three patients improved on conservative management.

Our series had a median operation time of 123.5 min, which is comparable to operating times from other series.[11,14,21–30] Overall mean length of stay from our study (3.5 days) was shorter than data from the literature (1–11 days).[11,14,21–30]

One possible limitation is that the follow-up of patients in our series is not particularly long, which makes the recurrence rate difficult to judge. There was recurrence of symptoms in patient no. 1 (follow-up 18 months) which matched increased liver volume on CT. Although the natural history of PCLD dictates disease progression, its actual rate is not known. In our study, the time range between preoperative and postoperative CT scan among individual patients was considerable, which may have led to underestimation of the effect of the procedure. It is difficult to compare our recurrence rate to literature, in view of lack of an explicit definition of recurrence. Some authors defined recurrence as recurrence of cysts on imaging techniques, others as recurrence of symptoms, while some included both symptomatic and radiological recurrence. On the other hand, the majority of studies report recurrences—what makes laparoscopic fenestration not a definitive therapy for patients with polycystic livers.[11,14,21–30]

In view of the progressive nature of polycystic liver disease, we regard laparoscopic fenestration as a palliative measure. This emphasizes the need for a strict selection of patients to improve the efficacy of the operation and to decrease morbidity and mortality rate of this technique. There is a trade-off between benefit and the morbidity associated with the procedure. Our data do not allow a firm statement which patients will benefit most, but we observed a major complication in a patient with a very large liver of 8.2 l in accordance with earlier reports in the literature. Ongoing clinical evaluation of laparoscopic fenestration is needed to allow tailored patient selection. In our view, several factors affect the decision to perform laparoscopic fenestration: (1) liver volume, (2) diameter of individual cysts, (3) location of cysts, (4) complications by strategically localized cysts, (5) availability of experienced laparoscopists, (6) possible candidacy for potential liver transplantation. Although not formally supported by our study, patients with fairly large (>4 cm) well accessible located cysts who will not be an imminent candidate for liver transplantation seem fine candidates for the procedure. Cysts located in segments VI, VII, and VIII of the liver and/or located deep inside the hepatic parenchyma are difficult to reach with laparoscopic fenestration.[14] Dominant large liver cysts, are better suited for aspiration-sclerotherapy because this is less invasive than laparoscopy.[31] Other therapeutic options are partial liver resection, especially if cysts are restricted to a limited number of liver segments, but is more invasive and potentially affects the possibilities for future liver transplantation given the risk of adhesions.[8,11]

In conclusion, laparoscopic fenestration is a therapeutic option in the symptomatic treatment of PCLD. The procedure induces liver volume reduction with subsequent symptom relief.

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Efficacy of Radical Surgery in Preventing Early Local Recurrence and Cavity-Related Complications in Hydatic Liver Disease

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Abstract

Background Hydatic disease of the liver remains to be a complex worldwide problem especially in rural areas. Early local recurrence and cavity-related complications are still a matter of conflict in the management of hydatic liver disease. The aim of this study is to investigate efficacy of the type of surgical treatment in preventing early local recurrence and cavity-related complications of this disease. Here, we present the preliminary results of our study.

Methods This study was performed prospectively including 32 patients who were operated for hydatic liver disease between January 2001 and January 2005. Patients were randomized into radical and conservative surgery groups. Recurrences at the primary surgical site in the first 2 years were considered as early local recurrence and biliary leakage, biliary fistula, cavity abscess, etc. were considered as cavity-related complications.

Results Early local recurrences were observed only after conservative surgical procedures ($p=0.045$). Recurrent cysts were found to be due to satellite cysts or pericystic disease. Cavity-related complications were seen in six patients in the conservative surgery group ($p=0.011$).

Conclusions In suitable patients, radical surgical resection provides an effective surgical management option in preventing early local recurrence and cavity-related complications when compared to conservative surgical approaches.

Keywords Hydatic liver disease · Radical surgery · Conservative surgery · Early local recurrence · Cavity-related complication

Introduction

Hydatic disease is an infection caused by the larval form of *Echinococcus granulosus*. The infection is the most frequent cause of liver cysts in the world and endemic in Eastern Europe, Mediterranean Countries, South Africa, South America, the Far East, and Australia.[1,2] Early local recurrence (ELR) and cavity-related complications (CRC) still continue to be the main problems affecting the success of the surgical management of hydatic liver disease.[3,4] Therefore, the goals of the surgical treatment are to avoid ELR, minimizing morbidity via reducing the incidence of CRC while eradicating the disease.[5–12] ELR and CRC are rarely seen after radical resection of the cyst due to complete removal of the cyst wall containing germinal epithelium and daughter cyst.[4] Conservative operations are technically easier and safer but are associated with high incidence of local recurrence (LR) and CRC being more than 10 and 37%, respectively.[4,13,14] There are no randomized controlled trials investigating the efficacy of surgical procedures in the prevention of ELR and CRC.[15]

The aim of the present study is to compare radical and conservative surgical approaches in preventing ELR and

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CRC of hydatic liver disease. In this article, we present the preliminary results of an ongoing study.

Patients and Methods

Study Design and Patient Selection

This prospective randomized study was performed on patients with hydatic liver disease who admitted to our department between January 2001 and January 2005 in Gazi University School of Medicine which is an experienced unit about hepatobiliary surgery in Turkey. Preoperative evaluation of the patients included blood tests (complete blood count, liver function tests and anti-echinococcus antibody testing) and preoperative abdominal ultrasonography and computerized tomography. The cysts were classified according to WHO-IWGE,[16] and localizations were decided according to Couinaud's segmental anatomy of the liver.[17] If vascular compression was suspected, angiography was performed. Also, patients with elevated bilirubin and alkaline phosphatase levels were evaluated by endoscopic retrograde cholangiopancreatography (ERCP) to evaluate biliary communication/fistula. Patients were put on albendazole (Andazol™; Biofarma, İstanbul, Turkey) regimen 10 mg/kg/daily for at least 2 weeks before surgery and for 8 weeks after surgery.

Exclusion Criteria

According to the preoperative evaluation, the patients that were not eligible to radical surgery (RS) (cysts that are located deep parenchymally or close to vascular system) or complicated cases (communication between biliary or bronchial system) were excluded from the study. The reasons for the exclusion of the patients with deep cysts were their being unsuitable for the conservative surgery and affecting the homogeneity of the study.

Consent and Ethics Committee

All the patients eligible for the study were informed about the surgical procedures and possible outcomes. Informed consent was taken from the participants. The study was according to the Helsinki Declaration and was approved by the Local Ethics Committee of Gazi University Medical School.

Randomization

RS or conservative surgery (CS) was performed on the eligible cases. The randomization included opening sealed envelops containing the type of operation.

Surgical Procedures

Intraoperative ultrasonography was routinely done in all cases assigned to the study. In the radical surgery group (RSG), we used "closed-cyst" method (en-bloc pericystectomy or hepatectomy etc.). Ultrasonic dissector (Cavitron Ultrasonic Surgical Aspirator, CUSA) was used for parenchymal transection. Throughout the operation, afferent blood vessels and biliary ducts were ligated between the pericyst and the normal liver.[18] In the conservative surgery group (CSG), standard drainage procedure was performed, and 20% hypertonic saline was used as scolicidal solution. If the cyst fluid was bile-stained, a cysto-biliary communication was suspected. Such communications were identified by retrograde infusion technique modified from previous studies in which common bile duct were isolated, and the distal passage was impeded via using an a traumatic vascular clamp.[19] Back-flow of 50% methylene blue diluted by 0.09% saline solution was injected with 26G×10-13 mm needle to rule out the cysto-biliary communication in the cysts whose communications with biliary system were unable to be recognized in the preoperative evaluation but came across intraoperatively. Such communication, identified intraoperatively with the method described above, were classified according their orificial diameters.[19] In cases wherein dye leakage was seen in the cyst cavity, using the orifice, wherein the methylene blue was leaking, a cholangiography was performed. If orifices were smaller than 5 mm, and cholangiography was normal, the orifice was sutured primarily. However, if the orifice was greater than 5 mm, even though the cholangiography was normal, common bile duct exploration and T-tube drainage was performed after primary closure of the orifice. Following these procedures, in suitable cases, an omental flap was placed into the residual cavity. All cavities were drained to prevent bilioma and consequent biliary peritonitis.

Objectives and Follow-up Criteria

Postoperative complications were analyzed in three subsets, which were infective complications, ELR, and CRC. Infective complications are defined as high fever, elevated leukocyte count, and defined source of infection. ELR was defined as hydatic liver disease occurring near the previous operation site in the first 24 months after the primary surgery. CRC included biliary leakage, biliary fistulae, retention cyst, and cavitary abscess. Patients who had postoperative biliary drainage through the abdominal drains were accepted as having biliary leakage. Patients who continued with persistent biliary drainage more than 10 days postoperatively were accepted as having a biliary fistula. Biliary fistula with a daily drainage <100 ml were treated conservatively. Biliary fistula with a daily drainage

>100 ml were considered for ERCP and/or naso-biliary drainage. Cavitary abscess is defined as proven biliary communication together with purulent drainage. Retention cyst was defined as a cystic lesion in the cavity site, which has one border, formed by an extra hepatic structure. Postoperatively, patients were followed periodically every 6 months until the end of the study duration. The follow-up included physical examination, measurement of complete blood count, liver transaminases, serum creatinine, echinococcus serology, and ultrasonography.

Groups were compared according to the size and number of cysts, hydatic cyst hemagglutination test, viability in cyst fluid, ELR, intraoperative complications, postoperative morbidity, mortality, CRC, mean operative time, blood loss/need for transfusion, and length of hospital stay.

Statistical Analysis

Data were expressed as median (range). Quantitative data were analyzed by the Mann–Whitney *U* test. Proportions were compared using Chi-Square test. The level of significance was set at $p<0.05$.

Results

Patients Eligible for the Study and Flow Chart

A total of 65 patients were operated for hydatic liver disease in a period of four years. Between January 2001 and December 2002, 30, and between January 2003 and January 2005, 35, patients were operated for hydatic liver disease. Twenty-three patients were excluded from the study because they were not eligible. The remaining 42 patients were found to be eligible for the study. Three patients refused to participate in the study. As a result, 37 patients were included in the randomization. Patients, 16, were randomized into RSG, and 21 patients were randomized to CSG. In the follow-up period, one patient from RSG and four patients from the CSG were lost to follow-up due to immigration to another region of the country. As a result, 32 patients were instituted in the analysis (Fig. 1).

Patients' Demographics

The two groups were statistically similar in terms of patient demographics, cyst characteristics, results of the hemagglutination test, viability in cyst fluid, which is summarized in Table 1.

Interventions

The procedures performed in the RSG Pericystectomy was performed in 11 patients, nonanatomic hepatectomy in 2 patients, left lobectomy in 1 patient, and segmentectomy in 1 patient.

The procedures performed in the CSG Cholangiography was performed in four patients (24%) in the CSG because of the communication of the cyst with the biliary system. Only primary suturing of the orifice was sufficient in two patients, while the remaining two cases were treated by T-tube drainage after the primary suturing of the orifice. Median follow-up period of the patients analyzed for the study was 15 months (range, 1–36 months).

Intraoperative complications No major complication leading to enhanced morbidity was observed among the groups. There was no postoperative mortality throughout the study. The two groups were statistically similar in terms of intraoperative complications (Table 2).

Postoperative complications The median time to which infective complications developed in the RSG was 7 days (range, 2–10 days) and for the CSG was 5 days (range, 3–9 days). Antibiotics treated all the infective complications; furthermore, subhepatic abscess was treated by percutaneous drainage. The postoperative complications and operative parameters are summarized in Table 2. There was no statistical significance between the groups concerning these parameters.

During the median 15 months (range, 1–36) follow-up period, there was no ELR in the RSG, whereas four ELR (23.5%) were observed in the CSG ($p=0.045$) (Table 3). ELR was detected in a median duration of 18 months (range, 12–24 months) postoperatively. These cases were followed for 2 years with the administration of additional 8 weeks of albendazol regimen previously mentioned. At the end of follow-up period, one patient with type CE2 ELR percutaneous aspiration, injection, and reaspiration (PAIR) was instituted, but as a result of 12 months of follow-up period, patient had a recurrence, and RS was performed. The remaining three patients were directly operated at the end of 2 years due to increasing cyst size with type CE4 lesions. The recurrent cyst size, type, and treatment modality applied are summarized in Table 4. The intraoperative viability testing of ELR of all four patients was found to be positive.

There were six (35.3%) cases with CRC ($p=0.011$) in the CSG, while none of the patients in the RSG developed CRC (Table 3). Two of the patients with CRC developed biliary leakage for which conservative management was

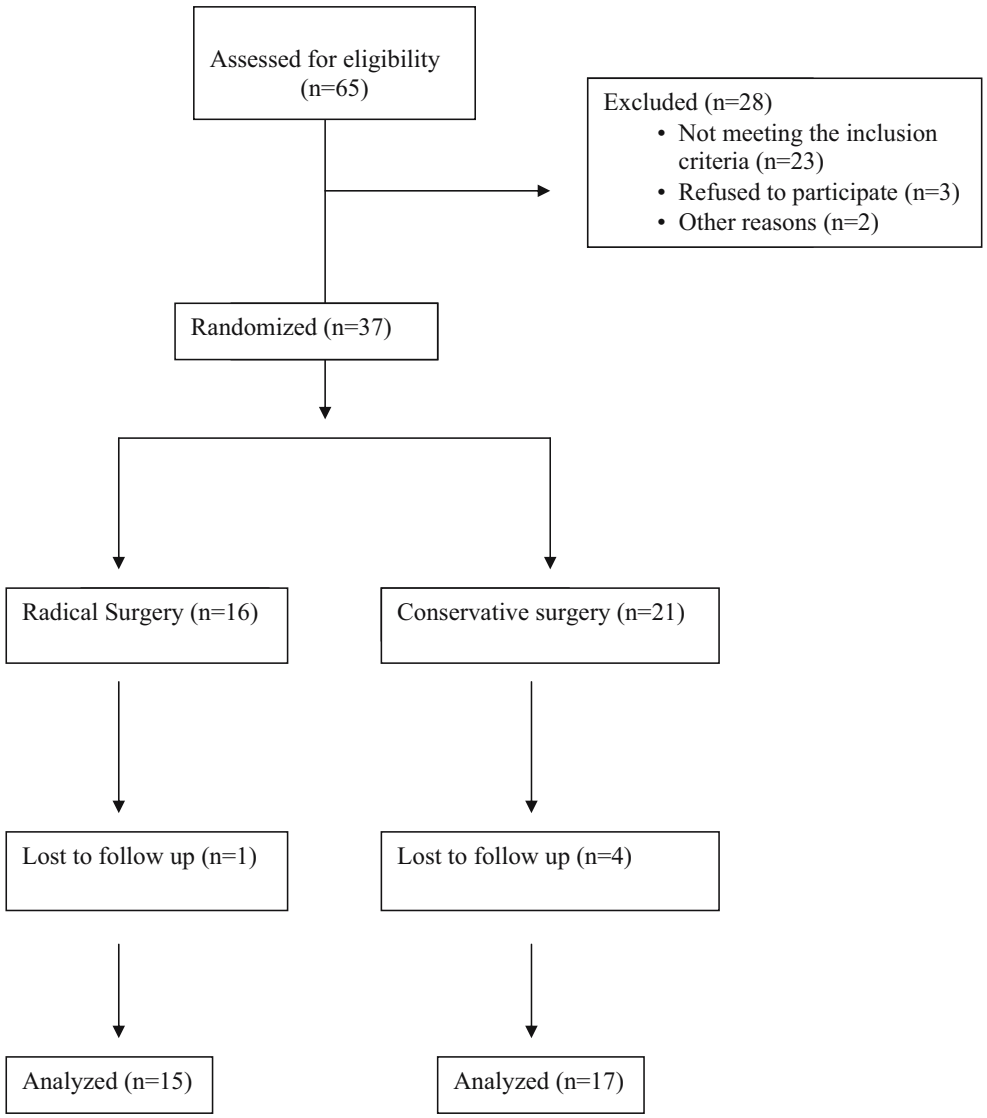

Figure 1 Flow chart of the patients assigned for the study.

applied. ERCP and naso-biliary drainage was performed in the patients with biliary fistula (n=2) in the management. Percutaneous abscess drainage was used as a first line management of the two cases with cavitary abscess, and the underlying biliary leakage was managed conservatively. In the present study, no retention cysts were observed in any case through the study.

Discussion

Patients with hydatic cysts frequently present as a therapeutic challenge to the physician. Ideal therapy of the hydatic liver disease should aim to cure the disease via eliminating the parasite with a low morbidity and zero mortality. Surgery remains the gold standard treatment for hydatic liver disease that favors rapid disappearance of the residual cavity and prevents recurrence.

LR rates after surgery is between 1.1 and 9.6% in different series.[20–22] In the present study, ELR rate is 12.5%, which is higher than other series in the literature. Although we defined ELR to develop in the first 24 months after surgery, the median follow-up period in the present study was 15 months, which differs in a wide range and may be due to several reasons. First of all, the recruitment of the patients for the study may have created the variation. Another reason may be the relative small sample size. As these represent the early results of an ongoing study with longer follow-up periods, more specific and accurate results will be obtained as the study progresses.

ELR can be interpreted as early relapse after the surgical management. Various factors are defined for this entity. A young cyst situated in the liver causes various reactions in the surrounding parenchyma so the parasitic structures ultimately become enveloped in a laminated, fibrous calcareous protective membrane or sheath. This evolution-

Table 1 Patients Demographic Data and Cyst Characteristics who Underwent RS or CS Groups

Characteristics	RS (n=15)	CS (n=17)	P
Age (years)[a]	38 (19–72)	41 (21–70)	ns[b]
Gender (M:F)	7:8	6:11	ns[c]
Cyst type (WHO-IWGE)			
CE4	10	12	ns[c]
CE2	5	5	ns[c]
Cyst localization (segment)			
II	1	1	ns[c]
III and IV	1	2	ns[c]
V and VI	9	10	ns[c]
VII	2	2	ns[c]
VIII	2	2	ns[c]
Cyst size (cm)[a]	7.8 (5–12)	8.1 (5–11)	ns[b]
Number of patients with multiple cysts (2–4)	4	7	ns[c]
Number of patients with positive hemagglutination test	12	13	ns[c]
Number of patients with positive viability in cyst fluid	10	12	ns[c]

RS Radical surgery, *CS* conservative surgery, *ns* not significant
[a] Values are median (range)
[b] Mann–Whitney U test
[c] X^2 test

ary entity is termed the pericyst. Hydatic cysts initially contains a clear watery fluid that later changes into a jelly-like magma, sometimes harboring various sizes of daughter cysts. Then, herniation appears on the outer surface of the pericyst. These outpouchings, known as exogenic vesiculations, form when hydatic material passes through pericystic fissurations or is entrapped within the layers of the pericyst itself, forming infectious foci (adventitial diverticula).[23] These changes may be responsible not only for the customary phenomena of fibrosis and calcification but also for major secondary inflammatory and parasitic complications and postoperative recurrences.[23] Especially older cysts have an increased risk of exogenic daughter cyst formation, which is an important factor for ELR.[24–26] An important factor for ELR is pre- and intraoperative undetected satellite cysts, which especially exist around the pericysts. In contrary to classical view; the true incidence of satellite cysts undetected in the pre- and perioperative stage is 29.5%.[27] In RS, whole cyst is removed that includes a small satellite cyst around the cyst wall, and therefore, ELR cannot occur. ELRs, observed in CS, were primarily mainly due to undetected satellite or exogenic vesiculations. Furthermore, satellite cysts that exist around the pericyst due to incomplete surgery can grow and became symptomatic within 12–24 months after surgery. CS or cyst evacuation with or without partial cystectomy is a safe procedure. Nevertheless in this procedure, such as evacuation and partial cystectomy, there is a possibility to leave viable material behind, especially in long-standing cysts in which there may be penetration, or budding through pericyst into the surrounding liver. Complete cystopericystectomy or liver resection has the best chance of curing hydatic liver disease completely, but also carries the highest operative risk, especially for centrally placed cysts, and should be preserved for patients in whom it can be carried out safely.[4] In the present study, it was observed that when CS and RS were compared, operative parameters, morbidity, and mortality rates were

Table 2 Intraoperative and Postoperative Complications, Operative Parameters, and Mortality of the Patients

Parameters	RS (n=15)	CS (n=17)	P
Intraoperative complications	2	1	ns[a]
Diaphragmatic injury	1	1	
Vascular injury	1	0	
Postoperative complications	3	4	ns[a]
Subhepatic abscess	1	2	
Pneumonia	1	1	
Wound infection	1	1	
Length of hospital stay (day) (±SD)	5±2.8	8±3.8	ns[a]
Mean operative time (min)	150±22.1	125±18.5	ns[a]
Blood loss (ml)	230±105.3	175±90.8	ns[a]
Need for transfusion (n)	3	1	ns[a]
Mortality	0	0	

RS Radical surgery, *CS* conservative surgery, *ns* not significant
[a] X^2 test

Table 3 Early local recurrences and cavity-related complications of the patients

Recurrence and complications	RS (n=15)	CS (n=17)	P
Early local recurrence	0	4	0.045[a]
Cavity related complications	0	6	0.011[a]
Biliary leakage	0	2	
Biliary fistula	0	2	
Cavity abscess	0	2	

RS Radical surgery, *CS* conservative surgery
[a] X^2 test

Table 4 Characteristics of cysts and treatment modality of choice in patients with early local recurrence

Characteristics and treatment	Patient 1	Patient 2	Patient 3	Patient 4
Cyst size (cm)				
Initial	2	3	2.5	3
Follow-up	5.5	6	–	6.5
Cyst type	CE4	CE4	CE2	CE4
Treatment modality	RS	RS	RS after PAIR	RS

RS Radical surgery, *PAIR* percutaneous, aspiration, injection, and reaspiration

similar, but in the CSG, there was a high rate of ELR due to residual and/or undetected satellite cysts. In our study, there were no ELR observed in the RS group. In this study, recurrent cysts were due to satellite cyst or pericystic disease; furthermore, the possibility of retention cyst was excluded for the viability test of the cyst fluid that was performed intraoperatively and was positive in all cases during the revisional surgery.

Hydatic cysts localized in the liver cause compression of biliary system up to 90% of the cases which leads to decubitic lesions resulting in biliary communication in 80% of the cases.[5] The ensuing development of biliary–cystic communications allows small amounts of hydatic fluid to enter the biliary tree. Most investigators agree that intrabiliary rupture is the commonest complication of hydatic liver disease.[7, 28, 29] In this study, the incidence of cystobiliary communication was 58.8% in CSG as a total determined both intraoperatively and postoperatively. Actually, incidence of cystobiliary communications depends largely on the criteria used for defining the communication.[14] Occasionally, communication between cyst cavity and biliary duct cannot be seen, although residual cyst cavity is fully explored during CS. In the present study, 23.5% of the communications were determined during the intraoperative insistent examination of the cavities, and this lead to the high incidence. For this reason; when a biliary communication is suspected during CS, the retrograde methylene blue infusion technique described in the present study can safely be performed. Surprisingly, in some cases, biliary leakage or fistulas may develop postoperatively, without any objective sign with manipulation described above. In concordance to this point in our study, 35.3% of the patients in CSG developed biliary leakage/fistulae postoperatively, without any evidence of intraoperative biliary communication.

CRC is a frequent problem confronting the physicians especially in cases when CS is applied. In the presence of a competent sphincter of Oddi, after cysts drainage and even in the absence of obvious bile duct pathology, there is a pressure gradient between the bile duct and the residual cavity, facilitating flow of bile through these communications toward the cavity rather than the duodenum.[30] This bile leakage represents the main source of immediate postoperative CRC. If not properly drained, it may result in abscess formation in the residual cavity or leakage to the peritoneum and eventually leading to bile peritonitis. If drained effectively, an external biliary fistula may develop, representing the commonest complication in such operations.[13] In cases with thick, calcified remnants, pericysts such as fistulas may be persistent and even requires secondary intervention. In literature, it has been reported that 12–26% of cases with biliary fistulae requires biliary drainage postoperatively.[29] In this study, postoperative endoscopic biliary drainage rate was 33.3% among the patients with CRC. This indicates that CRC rates are higher in CSG when compared with the RSG. The reason for such result is the ligation of biliary structures during dissection in radical resections. RS favors elimination of the residual cavity and prevents the development of secondary inflammatory complications and relapse due to exogenic vesiculations.

The complication rate of RS for hepatic cyst has been reported to range from 17.1 to 19.7%.[12] In this study, the overall intraoperative and postoperative complication rates were 13 and 20%, which correlate with previous studies.[12,31]

Moreover, after CS, retention cysts are one of the important cavity-related problems confronting the physicians and the patients, which may lead to a misdiagnosis of ELR and can result in unnecessary operations, which are not seen in RS. In our study, retention cysts were not observed in any case. In our opinion, may be it is due to omentoplasty performed in suitable cases.

Prospective randomized trials investigating the efficacy of surgical procedures in the prevention ELR and CRC after hydatic liver surgery, is very rare in the literature. This article gives the preliminary results of an ongoing randomized trial. Although the number of the cases in this study was low, we thought that RS is a suitable surgical treatment method for the selected hydatic liver disease with low ELR and CRC rates in experienced centers.

Conclusions

In selected cases and experienced centers, RS not only provides low ELR rate due to elimination of undetected satellite cysts but also reduced CRC by ligation of cavity-related biliary channels as well. Nevertheless, in cases of hydatic disease where both radical and conservative surgical options exist, radical surgery is to be preferred. In cases that are not eligible to RS, CS can be an effective alternative provided that remaining cavity is efficiently explored for biliary communications in which retrograde methylene blue infusion technique can be used.

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Remote Renal Injury Following Partial Hepatic Ischemia/Reperfusion Injury in Rats

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Abstract
Liver ischemia/reperfusion has been shown to result in injury of remote organs such as the heart and lungs. Whether or not acute liver injury also results in kidney injury has so far not been adequately addressed. In anesthetized Wistar rats, partial (70%) normothermic hepatic ischemia was applied for 75 min. After 24 h of reperfusion, renal injury was assessed by histology, creatinine and blood urea nitrogen (BUN) serum concentrations, renal expression of proinflammatory genes [quantitative real-time polymerase chain reaction (qRT-PCR)], caspase-3 activation (Western blot), and neutrophil accumulation (myeloperoxidase assay). Twenty-four hours after hepatic ischemia, creatinine (0.57±0.06 vs. 0.32±0.04 mg/dL) and BUN (40.7±15.3 vs. 14.3±2.0 mg/dL) were increased when compared to sham. qRT-PCR revealed higher renal intercellular adhesion molecule-1 gene expression following hepatic ischemia (166±45% when compared to sham) but no differences in renal monocyte chemoattractant protein-1, macrophage inflammatory protein-2, and inducible NO synthase expression. In both groups, kidneys showed no morphological damage and no increase in caspase-3 and myeloperoxidase activity. Severe hepatic ischemia results in a moderate impairment of renal function in rats but does not trigger an inflammatory response in the kidney and does not result in morphological damage of the kidney.

Keywords Liver · Surgery · Kidney · Inflammation · Neutrophils · Apoptosis

Introduction

Secondary renal dysfunction occurs commonly in the setting of chronic hepatic failure. This is attributed to intrarenal vasoconstriction (hepatorenal syndrome) or to the systemic inflammatory response evoked by cirrhosis and hepatic failure.[1] Acute hepatic damage as caused by hepatic ischemia/reperfusion (I/R) is also known to evoke a systemic inflammatory response that results in damage and impaired function of remote organ systems. Inflammatory lung injury after hepatic ischemia has been well documented.[2] Similarly, hepatic ischemia has been shown to induce acute myocardial dysfunction.[3,4] It is not

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established whether the inflammatory response evoked by acute hepatic I/R also results in morphological damage of the kidney, but there is evidence for resulting renal dysfunction.[5,6] Nothing is known about the potential impact of I/R injury in major hepatic surgery on renal function. Acute renal failure (ARF) is common in patients after liver transplantation,[7,8] but the origin of ARF in liver transplantation is complex. Hepatorenal syndrome already results in preexisting impairment of renal function. Prolonged hypotension, postoperative infections/sepsis, subsequent surgeries (especially retransplantation), and nephrotoxic immunosuppressive medications following transplantation further increase the risk for development of renal dysfunction. However, remote renal injury that results directly from hepatic I/R injury may contribute to renal injury and dysfunction following liver surgery and transplantation.

To investigate the effects of acute hepatic ischemia on renal morphology and function, rats underwent 75 min of partial hepatic ischemia followed by 24 h of reperfusion. We hypothesized that remote kidney injury would be associated with the induction of an inflammatory response in the kidney, resulting in upregulation of proinflammatory gene expression with subsequent neutrophil infiltration, induction of apoptosis, and cell necrosis.

Materials and Methods

Animal Model

All animal experiments were carried out with approval by the local committee on animal research. Animal care was in agreement with the National Institutes of Health (NIH) guidelines for ethical research (NIH publication no. 80-123, revised 1985). Inbred male Wistar rats (Harlan, Indianapolis, IN, USA) were used for this study. Animals' weights on arrival at our facility were 250–300 g. Animals had access to standard laboratory diet and were maintained on a light–dark cycle.

Animals were anesthetized with isoflurane. Their body temperature was continuously monitored and held constant at 37°C using a heating lamp. The liver was exposed through a midline incision. Applying a 70% liver ischemia model, the liver was mobilized and vascular structures to the left and median lobe were identified and clamped using a bulldog clamp. The rats were divided into two groups: the first group underwent 75 min of ischemia (I75, $n=7$), whereas the second group underwent a sham operation that was identical except for the absence of vascular clamping following mobilization of the liver and preparation of the hepatic vessels (sham, $n=10$). Following reperfusion, the animals received 5 ml of normal saline intraperitoneally and the incision was closed in two layers. Animals were killed and blood and tissue were harvested following a 24-h observation period. All tissue was immediately frozen in liquid nitrogen and stored at −80°C until further processing.

Biochemical Markers of Liver and Kidney Injury

Serum levels of aspartate aminotransferease and alanine aminotransferase, as well as serum levels of creatinine and blood urea nitrogen (BUN), were determined following 24 h of reperfusion (IDDEX Veterinary Services, Sacramento, CA, USA).

Assessment of Necrosis

Ischemic liver lobes and kidneys were excised immediately after animals were sacrificed. Tissues were fixed in 10% formalin and then embedded in paraffin for light microscopy. Sections were cut at 5 μm and stained with hematoxylin and eosin for histological examination. Analysis was performed on randomly selected specimens in each group by an investigator who was blinded to the experimental condition of the animals. Light microscopic examination was performed under standard conditions at 4×, 10×, and 40× magnification.

Assessment of Renal Apoptosis

Kidney tissues were homogenized in T-PER tissue protein extraction reagent (Pierce Biotechnology, Rockford, IL, USA) containing 1 mM EDTA and protease inhibitor and centrifuged at 10,000×g for 5 min at 4°C. The supernatant was aliquoted, snap frozen, and stored at −80°C. Protein concentrations of kidney homogenates were measured by the Pierce BCA protein assay (Pierce Biotechnology) with bovine serum albumin as the standard. Fifty-microgram kidney homogenates were separated on a NOVEX-NuPAGE 4–12% Bis-Tris sodium dodecyl sulfate polyacrylamide gel electrophoresis gel (Invitrogen, Carlsbad, CA, USA) and transferred to polyvinylidene difluoride membrane (Millipore, Bedford, MA, USA) using the XCell SureLock system (Invitrogen). The membrane was incubated with 1:200 dilution of primary antibody (primary rabbit anti-caspase 3 monoclonal antibody, Cell Signaling, Danvers, MA, USA) followed by incubating with 1:10,000 dilution of secondary antibody (anti-rabbit IgG, Santa Cruz Biotechnology, Santa Cruz, CA, USA). Jurkat cell (treated with cytochrome C) extracts (Cell Signaling) served as positive control. Immunoreactive proteins were developed using SuperSignal West Dura (Pierce Biotechnology) and visualized using FluorChem system from Alpha Innotech (San Leandro, CA, USA).

RNA Isolation and Quantitative Real-time Polymerase Chain Reaction

Total RNA was isolated from frozen kidneys using Rneasy Mini Kit with on-column Dnase digest according to the manufacturer's instructions (QIAGEN, Valencia, CA, USA). RNA yield and purity was determined on Smartspec 3000 (Biorad, Hercules, CA, USA), and RNA integrity was confirmed by presence of intact 28 S and 18 S bands on 1% agarose gel. One microgram of total RNA was converted to cDNA according to the manufacturer's protocol using 200 U MMLV-reverse transcriptase with 250 ng of random primers (Invitrogen).

Gene expressions for monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-2 (MIP-2), intercellular adhesion molecule-1 (ICAM-1), and inducible NO synthase (iNOS) were assessed via quantitative real-time polymerase chain reaction (PCR) (7300 Real-Time PCR System, ABI, Foster City, CA, USA). Table 1 shows primers and 5′-6-carboxyfluorescine/3′ Black Hole Quencher-labeled Taqman probes designed with ABI's Primer Express 2.0 software and synthesized by Integrated DNA Technologies (Coralville, IA, USA). Each primer–probe combination was validated to within a range of 93 to 102% efficiency. Fifty nanograms of reverse-transcribed cDNA was used as template along with 500 nM forward and reverse primers, 200 nM Taqman probe, 200 nM deoxyribonucleotide triphosphates (Allstar Scientific, Sunnyvale, CA, USA), 5.5 mM MgCl2, and TM buffer (UCSF Mt. Zion Genome Core Facility) for PCR amplification. Fluorescence was measured after each PCR cycle (initial one-time 10-min denaturation at 95°C, followed by 40 amplification cycles with 15-s denaturation at 95°C and 1 min annealing extension at 60°C). Each sample was measured in triplicate and all genes were normalized to the endogenous control B-Actin. No reverse-transcriptase negative controls were run in duplicates in parallel and found to have none to negligible genomic expression contribution. Relative quantification of target genes were standardized to sham samples by the comparative C(t) method using threshold cycle C(t) values determined on ABI's GeneAmp software.

Assessment of Renal Neutrophil Accumulation

Activity of myeloperoxidase (MPO), an enzyme stored in the azurophilic granules of neutrophils, was used to measure tissue neutrophil sequestration. We used a spectrophotometric method to assay tissue MPO activity. Frozen kidneys were thawed and extracted for MPO following homogenization and sonication. The assay is based on the oxidation of 3,3′, 5,5′-tetramethyl benzydine by MPO in the presence of H_2O_2. Units of MPO activity were calculated using a standard curve derived from a MPO standard sample (Calbiochem, EMD Bioscience, La Jolla, CA, USA). MPO data are expressed as milliunits per minute per milligram tissue. Animals that underwent sham operation (sham, $n=10$) served as controls.

Statistical Analysis

All data are presented as mean ± SD. Comparison between the two study groups was performed by unpaired t test. p values <0.05 were considered statistically significant.

Table 1 Sequences of Quantitative Real-time PCR Primers and Probes

Gene	GenBank Accession #		Sequence (5′–>3′)
β-Actin	NM_031144	Forward	CTG GCT CCT AGC ACC ATG AAG
		Reverse	GAG CCA CCA ATC CAC ACA GA
		Probe	TCA AGA TCA TTG CTC CTC CTG AGC G
MCP-1	NM_031530	Forward	CTG TCT CAG CCA GAT GCA GTT AA
		Reverse	AGC CGA CTC ATT GGG ATC AT
		Probe	CCC CAC TCA CCT GCT GCT ACT CAT TCA C
MIP-2	NM_053647	Forward	GAA GCC CCC TTG GTT CAG A
		Reverse	GCC CAT GTT CTT CCT TTC CA
		Probe	TCC AAA AGA TAC TGA ACA AAG GCA AGG CTA ACT
ICAM-1	NM_012967	Forward	CAC AAG GGC TGT CAC TGT TCA
		Reverse	CCC TAG TCG GAA GAT CGA AAG TC
		Probe	AAT GTC TCC GAG GTC AGG CAG CTC C
iNOS	NM_012967	Forward	TGG TGG TGA CAA GCA CAT TTG
		Reverse	CCC GAG TTC TTT CAT CAT GAA CA
		Probe	CCA GCA ATG GGC AGA CTC TGA AGA AAT C

Taqman probe is dual-labeled with a 5′-reporter dye (6-carboxyfluorescine) and a 3′-quencher (Black Hole Quencher). All sequences listed in 5′-to-3′ direction.

Results

Liver and Kidney Injury Seventy-five minutes of normothermic hepatic ischemia resulted in a profound increase of serum transaminase concentrations (Table 2). Morphologic examination of liver samples obtained 24 h following reperfusion revealed extensive necrosis, with more than 75% necrosis in all samples indicating the severity of hepatic I/R injury.

There was a mild, albeit significant, increase in serum creatinine and BUN following hepatic I/R injury (Table 2). Renal histology demonstrated mildly congested glomeruli, minimal interstitial lymphocytes, and focal patchy areas of tubular epithelial vacuolation and swelling, but no necrosis of the kidneys 24 h following liver I/R. However, these changes were present in the sham animals as well (Fig. 1).

Renal Caspase-3 Activity Analysis by Western blot showed no caspase-3 activity in kidneys from sham or hepatic I/R animals (Fig. 2).

Renal Gene Expression Hepatic I/R increased renal ICAM-1 gene expression to 166±45% when compared to sham animals ($p<0.001$). In contrast, renal MCP-1 expression following hepatic ischemia was identical to that of sham animals (96±22% of sham animals). Renal gene expression of MIP-2 and iNOS following either hepatic ischemia or sham procedures remained barely detectable, as indicated by high threshold cycle values above the acceptable range of quantification [C(t)>30 cycles].

Neutrophil Accumulation MPO activity in kidneys from sham-treated animals, as well as animals that underwent hepatic ischemia, was low and similar between groups: 2.27 ±1.69 (hepatic ischemia) vs. 2.10±0.60 (sham) mU min^{-1} mg^{-1} tissue, indicating the absence of relevant neutrophil migration into renal tissue.

Table 2 Liver enzyme, creatinine and BUN serum concentrations 24 h following reperfusion

	Sham	Hepatic Ischemia
AST (U/L)	133±71	15,574±6,640*
ALT (U/L)	49±18	6,807±4,163*
Creatinine	0.32±0.04	0.57±0.06*
BUN	14.3±2.0	40.7±15.3*

AST = aspartate aminotransferease; ALT = alanine aminotransferase
*$p<0.05$ vs. sham

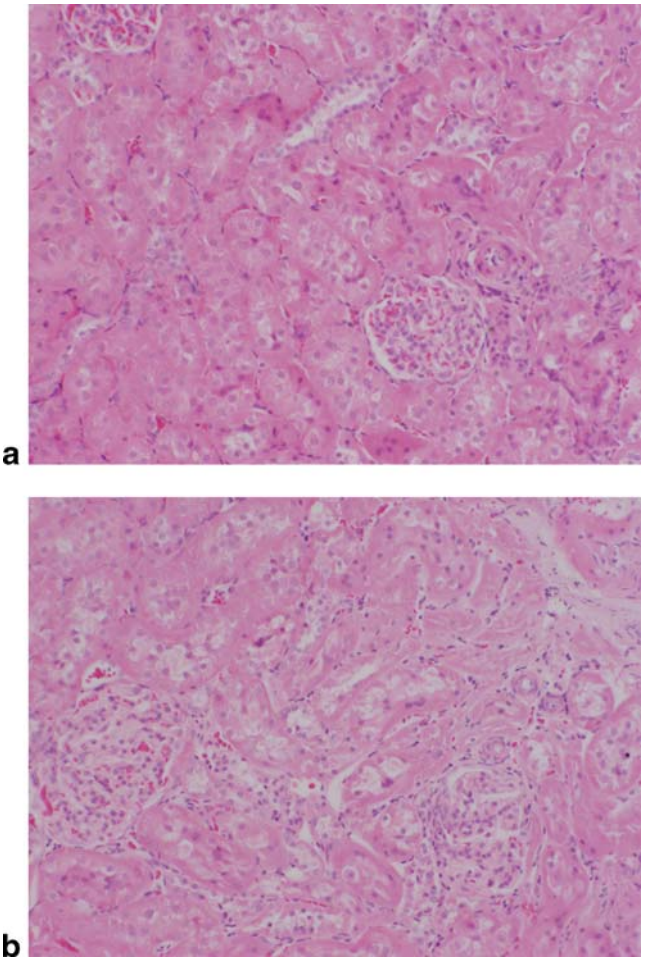

Figure 1 Histology of kidney samples 24 h following liver I/R (**a**) was similar to that seen in sham animals (**b**), including mildly congested glomeruli and focal patchy areas of tubular epithelial vacuolation.

Discussion

The present investigation demonstrates that acute hepatic injury results in – most likely only transiently impaired renal function but does not trigger an inflammatory response of the kidney itself and does not cause subsequent morphological kidney damage.

Our results seem to contradict the results of an earlier study where 20 min of global hepatic ischemia resulted in Kupffer cell-mediated cytokinemia with subsequent kidney

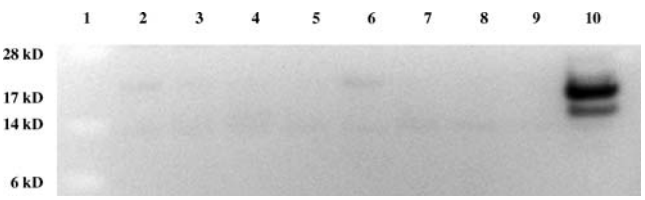

Figure 2 Western immunoblotting for caspase 3 resulted in a strong signal in treated Jurkat cells (*lane 10*, positive control) but no signal in kidney samples from sham (*lanes 6–9*) or hepatic ischemia (*lanes 2–5*) animals. *Lane 1*: protein standard.

injury in rats.[5] However, this study also shows only very moderate changes in postischemic serum urea concentrations and creatinine clearance and no change in serum creatinine concentrations. Histological changes were limited to a slight swelling of tubular epithelial cells and dilatation of capillaries. The very similar findings of Wanner et al. and our study support the hypothesis that the reduction in renal function after acute liver ischemia is only a functional defect that may be short-lived and not clinically relevant. The observed functional impairment is most likely triggered by a transient exposure to systemic cytokines, but may be attributable to postsurgical changes such as dehydration or hypotension.

In the present investigation, we attempted to clarify whether such alterations in renal function after liver ischemia are a symptom of a systemic inflammatory response that are generally mediated by a systemic release of cytokines or whether remote I/R triggers an inflammatory response in the kidney itself. We therefore assessed whether hepatic I/R triggers the renal expression of several inflammatory genes such as MCP-1, MIP-2, iNOS, and ICAM-1. We hypothesized that an inflammatory response in the kidney would result in activation of chemokines such as MCP-1 and MIP-2, which are known to amplify inflammation in the kidney. Such chemokine activation would initiate leukocyte migration into renal tissue and activate ICAM-1 to facilitate leukocyte adherence and infiltration. iNOS is known to be upregulated in epithelial and mesangial kidney cells in various models of renal inflammation and is established as a proinflammatory mediator.[9,10] However, beside a moderate increase in renal ICAM-1 expression, our results provide no evidence that hepatic injury triggers an inflammatory response in the kidney itself. These findings contrast those in intestinal I/R where transplantation of intestinal grafts results in renal ICAM-1 expression and caspase-3-like activity, which might be attributable to a more profound cytokine release following intestinal ischemia than following liver ischemia.[11]

Hepatic I/R is known to induce remote organ dysfunction in the heart and lung. Because cytokines such as tumor necrosis factor alpha (TNFα) are known to be the mediators of remote myocardial dysfunction[12] and remote lung injury,[13,14] we can only speculate that the kidney has a higher tolerance for systemic cytokines, resulting in only minimal renal effects of remote ischemia. Supporting this hypothesis, infusion of sublethal doses of TNFα results merely in forced diuresis.[15] Even the cytokine concentrations seen in septic shock, which are considerably higher than those seen after hepatic I/R, rarely result in acute tubular necrosis.[16] A possible explanation for such resistance against remote renal injury was presented in a recently published paper: Tanaka et al. demonstrated that hepatic I/R results in upregulation of renal heme oxygenase-1 (HO-1).[6] The known cytoprotective effects of HO-1 might be responsible for the only moderate effects on renal function and the lack of effects on renal morphology seen in our study.

Interestingly, 30 and 60 min of kidney ischemia results in the activation of hepatic inflammatory pathways, as demonstrated by increased hepatic TNFα concentrations and MPO activity, as well as a reduction of antioxidant enzymes.[17] Again, we can only speculate whether renal ischemia serves as a more potent trigger for remote injury or whether the liver is more sensitive to remote ischemic stress.

Our findings on the renal effects of acute hepatic ischemia have to be differentiated from findings of renal failure in end-stage liver disease and liver transplantation. The incidence of renal dysfunction following liver transplantation is high, but hepatic ischemia during transplantation is only one among several factors that impair renal function following transplantation. No data are available regarding impaired renal function following major hepatic surgery. A recently published paper associated elevated serum concentrations of cytokines, chemokines, and stress hormones following liver resection with postoperative dysfunction of remote organs including the kidneys, but kidney dysfunction was always the consequence of postoperative infection.[18] This supports our findings that hepatic ischemia alone does not result in significant renal damage. However, remote renal effects of hepatic ischemia are detectable and may contribute to renal dysfunction in concert with additional stressors such as nephrotoxic drugs or preexisting renal disease.

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Recurrent Pyogenic Cholangitis with Hepatolithiasis—The Role of Surgical Therapy in North America

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Abstract
Purpose To determine role of surgical intervention for Recurrent Pyogenic Cholangitis with hepatolithiasis at a North American hepatobiliary center.
Methods Retrospective analysis of 42 patients presenting between 1986 and 2005.
Results Mean age is 54.3 years (24–87). Twenty-seven patients (64%) underwent surgery, after unsuccessful endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous intervention in 19/27 patients. Surgical procedures were: 10 common bile duct explorations with choledochojejunostomy and a Hutson loop and 17 hepatectomies (10 with, 7 without Hutson loop). Liver resection was indicated for lobar atrophy or stones confined to single lobe. Operative mortality was zero; complication rates for hepatectomy and common bile duct exploration were comparable (35% vs. 30%). Median follow-up was 24 months (3–228). Of 21 patients with Hutson loops, only seven (33%) needed subsequent loop utilization, with three failures. At last follow-up, 4/27 (15%) surgical patients had stone-related symptoms requiring percutaneous intervention, compared to 4/11 (36%) surviving nonoperative patients. Cholangiocarcinoma was identified in 5/42 (12%) patients; four were unresectable and one was an incidental in-situ carcinoma in a resected specimen.
Conclusion Surgery is a valuable part of multidisciplinary management of recurrent pyogenic cholangitis with hepatolithiasis. Hepatectomy is a useful option for selected cases. Hutson loops are useful in some cases for managing stone recurrence. Cholangiocarcinoma risk is elevated in this disease.

Keywords Recurrent pyogenic cholangitis · Hepatolithiasis · Hepatectomy · Choledochojejunostomy · Cholangiocarcinoma

Introduction

Hepatolithiasis, the presence of stones in the intrahepatic biliary tract, is often a progressive and complicated problem. Whereas cholelithiasis and choledocholithiasis are usually effectively treated with cholecystectomy and common bile duct (CBD) exploration, the treatment of hepatolithiasis tends to be more difficult, with frequent recurrence of stones and symptoms. A multidisciplinary approach, integrating interventional radiology, interventional endoscopy, and surgery is key.

The causes of hepatolithiasis vary. In the West, the disease is most often associated with stricturing conditions of the biliary tree (e.g., primary sclerosing cholangitis [PSC], benign postoperative strictures, malignancy) or stasis (e.g., choledochal cysts). However, in other populations, particularly in East Asia, hepatolithiasis occurs in the absence of these conditions. Theirs is a progressive biliary disease characterized by diffuse biliary tract ectasia with primary biliary stone formation, limited focal stricturing, and repeated episodes of bacterial cholangitis. Hepatic segmental or lobar atrophy may result from longstanding obstruction of a major intrahepatic duct or thrombosis of a portal vein branch.

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This disease has been known by a variety of names, including "Recurrent Pyogenic Cholangitis (RPC)", "oriental cholangitis", "oriental cholangiohepatitis", and "Hong Kong Disease". In addition to affecting East Asian populations, it is also prevalent among Latin Americans, and has been associated with lower socioeconomic status and rural environments. During the 1960s, complications of primary hepatolithiasis were the third most common abdominal surgical emergency and most common hepatobiliary disease at Queen Mary Hospital in Hong Kong.[1] Since then, a decline in incidence has been observed in East Asia, which has been attributed to improved living conditions and Westernization of diet.[1] Of interest, an inverse pattern has been observed in Western countries, where RPC with hepatolithiasis was previously rare but has become increasingly more prevalent, particularly in regions receiving migrants from endemic regions.

The pathogenesis of this condition is incompletely understood. Although hepatolithiasis and recurrent cholangitis have been associated with *Clonorchis sinensis* and *Ascaris lumbricoides* infections, the evidence for these infections is absent in most patients.[1] The common finding of biliary tract ectasia, often diffuse, in the absence of distal obstruction suggests that the disease may result from a primary abnormality of the wall of the biliary tree or chemical components of bile. The pathophysiologic outcome in this disease is the formation of calcium bilirubinate stones within extra- and intrahepatic biliary ducts, although it may be that the stones are the primary event. Morbidity occurs from recurrent episodes of bacterial cholangitis and their sequelae, such as chronic biliary obstruction from stones and strictures, parenchymal atrophy, and liver abscesses. In addition, a significantly elevated risk of cholangiocarcinoma has been reported in patients with RPC.[2]

The diagnosis is based on clinical presentation in conjunction with findings on imaging, primarily ultrasound (U/S), computed tomography (CT), and magnetic resonance imaging (MRI) as well as cholangiography. Management is directed toward controlling acute episodes of biliary sepsis, extraction of stones, and correction of anatomic abnormalities or sources of chronic infections. Treatment may also require dilatation of strictures and/or resection of atrophic or lobe-dominant disease. Patient care should be multidisciplinary and may include interventional percutaneous cholangiographic (PTC) biliary drainage, ERCP, or surgery. PTC and ERCP approaches to stone extraction and stricture dilatation are often limited by the inability to access diffuse intrahepatic stones. The surgical options include CBD exploration with extraction of stones, resection of lobe- or segment-dominant disease, and the construction of a Hutson biliary access loop of jejunum (Roux-en-Y choledochojejunostomy that is fixed to the abdominal wall) to facilitate the subsequent percutaneous retrograde extraction of residual or recurrent intrahepatic stones.[2] Some surgeons have utilized indwelling transhepatic stents as an accessory to surgical procedures with a similar intention of facilitating percutaneous removal of recurrent stones.[3]

The objective of this retrospective study was to assess the role of surgical intervention in the management of patients presenting with symptomatic Recurrent Pyogenic Cholangitis caused by intrahepatic stones, at a North American center. A retrospective analysis of patients with RPC who were referred to the hepatobiliary surgeons at the Toronto General Hospital was performed to determine the outcomes of their treatment.

Methods

Patients included were referred to one of the hepatobiliary surgeons at the Toronto General Hospital between 1986 and 2005. Data were gathered from office/clinic records as well from charts identified through a search of Toronto General Hospital health records, using the ICD-9 codes 574.5, 121.1, 576.1, and the ICD-10 codes K80.30, K80.31, K80.50, K80.51 corresponding to the key words "Calculus of bile duct without mention of cholecystitis", "Clonorchiasis", "Cholangitis", "Calculus of bile duct with cholangitis", or "Calculus of bile duct without cholangitis or cholecystitis". All patients included in the study were diagnosed with "Recurrent Pyogenic Cholangitis" based on history (recurrent episodes of abdominal pain, fever, and jaundice; born in an endemic region; absent or stone-free gallbladder) and consistent radiological appearance (hepatolithiasis, intrahepatic duct dilation, lobar/segmental atrophy.) Cases were excluded if radiological appearance and/or surgical specimen was more consistent with an alternate diagnosis such as choledochal cyst or Primary Sclerosing Cholangitis. Additional information was obtained from records of the gastroenterologists who performed diagnostic and/or therapeutic ERCPs. Approval for this study was obtained from the Research Ethics Board of the Toronto General Hospital on December 2005.

Abstracted data included date of birth, gender, ethnicity, date of first presentation, date of presentation to Toronto General Hospital hepatobiliary surgeon, symptoms at presentation, anatomic distribution of disease, status of gallbladder stones, history of ERCP attempts at stone extraction, history of percutaneous attempts at stone extraction, surgical procedures performed for management of disease, prevalence of cholangiocarcinoma, and morbidity, and mortality. For each surgical procedure, data were collected on success at stone clearance, rate of stone recurrence, and subsequent management, and complications.

Therapeutic ERCP was performed by a gastroenterologist or surgeon to identify and remove biliary stones and

dilate or stent biliary strictures. If a patient had only a diagnostic ERCP, this was not considered part of therapeutic management.

Percutaneous transhepatic management by an interventional radiologist included drainage of an obstructed biliary tree and attempt at stone extraction via the PTC drain. We distinguished between stone retrieval via choledochojejunostomy (Hutson) access loop and via the percutaneous transhepatic route.

The surgical procedures performed included: CBD exploration with extraction of stones, or liver resection, with or without construction of a side-to-side choledochojejunostomy and Hutson access loop. All choledochojejunostomies performed in this series by Toronto General Hospital surgeons were done in conjunction with a Hutson access loop. All cases of liver resection included a CBD exploration. The technique used for the Hutson biliary access loop was the construction of an antecolic Roux-en-Y limb of proximal jejunum with a choledochojejunostomy to a point near the tip of the Roux. A point of the Roux limb between the biliary anastomosis and the distal enteroenterostomy was affixed to the anterior abdominal wall and marked with metal clips to facilitate subsequent localization with x-ray imaging for percutaneous access. No transhepatic stents were placed intraoperatively in this series.

Intraoperative cholangiography was used more frequently in the early part of the series, but not if either diagnostic ERCP or MRC had defined the anatomy and stones accurately within weeks of the surgical procedure. Choledochoscopy was routine when the bile duct was explored for stone extraction.

Results

A total of 42 patients with Recurrent Pyogenic Cholangitis and hepatolithiasis were identified through a search of 2,700 patient records associated with seven hepatobiliary surgeons. Twenty-seven underwent a surgical procedure and 15 did not. The two groups were similar in their presenting characteristics (Table 1). The median age was 54.3 years, with nearly equal gender distribution (55% female: 45% male). The majority of the patients were immigrants to Canada from East Asia. All patients had recurrent episodes of cholangitis. Nearly half of all patients, 20/42 (48%), had a previous cholecystectomy; among the others, the majority had no gallbladder stones on imaging (13/22, 59%). The left lobe was involved in the majority of patients, with 16 left lobe only and 19 bilobar involvement (Fig. 1). All patients demonstrated hepatolithiasis. Twenty-four patients (57%) had parenchymal atrophy: 8/24 affecting left lateral segment, 6/24 affecting entire left lobe, 5/24 affecting right lobe, and 5/24 involving segments bilaterally. The biliary tree appeared ectatic on imaging in most patients (Fig. 1). Median follow-up was 24 (3–228) months.

The number of referrals of patients with RPC and hepatolithiasis to the Toronto General Hospital hepatobiliary surgeons rose significantly over time (Fig. 2). The median time interval between patients' initial symptoms and their referral to the HBP surgeon was 108 (2–480) months.

Of the 15 nonoperative patients, 12 (80%) had undergone nonsurgical therapy before referral to surgeon, including therapeutic ERCP in nine and PTC stone removal

Table 1 Patient Characteristics at Presentation to UHN Surgeon

	All Patients (*N*=42)	Surgery (*N*=27)	No Surgery (*N*=15)
Age, years (*mean* ± *SD*)	54.3±15.2	51.2±14.4	59.8±15.6
Time from initial symptoms to referral months (median [range])	108 (2–480)	96 (7–360)	108 (2–480)
Follow-up, months (median [range])	23 (2–228)	23.5 (2–228)	12 (2–60)
Gender F:M (*n* [%])	23:19 (55:45%)	15:12 (56:44%)	8:7 (53:47%)
Ethnicity: (*n* [%])			
East Asian	28 (67%)	18 (67%)	10 (67%)
Latin American	3 (7%)	3 (11%)	0
Other/Unidentified	11 (26%)	6 (22%)	5 (33%)
Cholangitis (RUQ/epigastric abdominal pain, fever, jaundice) (*n* [%])	42 (100%)	27 (100%)	15 (100%)
Anatomic Disease Distribution: (*n* [%])			
Left lobe only	17 (40%)	10 (37%)	7 (47%)
Right lobe only	6 (14%)	5 (19%)	1 (6%)
Bilobar	19 (45%)	12 (44%)	7 (47%)
Ectatic biliary tree (*n* [%])	31 (74%)	22 (81%)	9 (60%)
Biliary tree strictures (*n* [%])	15 (36%)	12 (44%)	3 (20%)
Lobar Atrophy (*n* [%])	23 (55%)	13 (48%)	10 (67%)
Abscess (*n* [%])	6 (14%)	4 (15%)	2 (13%)
Previous cholecystectomy (*n* [%])	20 (48%)	13 (48%)	7 (47%)

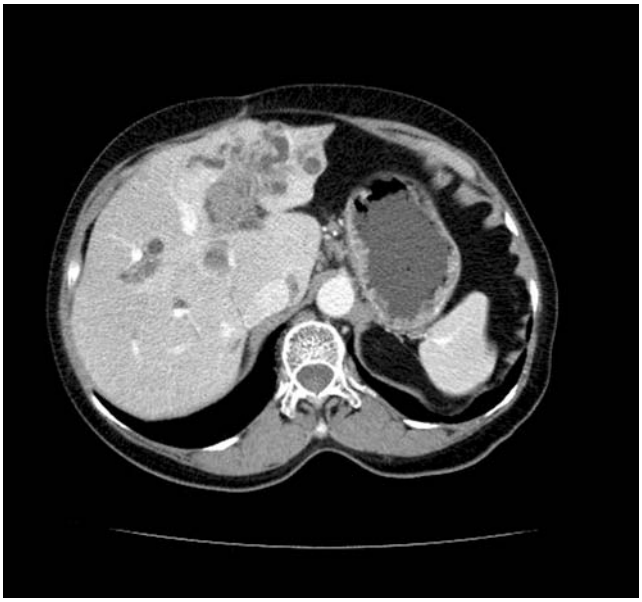

Figure 1 CT of liver affected by RPC and hepatolithiasis demonstrating atrophic left lobe, dilated intrahepatic ducts with the presence of stones, L portal vein thrombosis.

in six. A previous biliary-enteric anastomosis had been performed in two (13%) cases. Reasons for nonoperative management were: five patients declined the offer of surgery, four presented with unresectable tumors (three cholangiocarcinoma; one squamous cell carcinoma), five were considered stable at the time of presentation, and one was lost to follow-up.

In the surgical group, 19/27 (70%) had undergone prior attempts at nonoperative stone extraction: 10/27 had unsuccessful therapeutic ERCP attempts, 8/27 had unsuccessful attempts at percutaneous stone removal, and one patient had attempts at both ERCP and PTC. Four patients (15%) had a previous biliary-enteric anastomosis.

The surgical interventions performed are outlined in Fig. 3. Ten patients underwent CBD exploration with construction of side-to-side choledochojejunostomy and

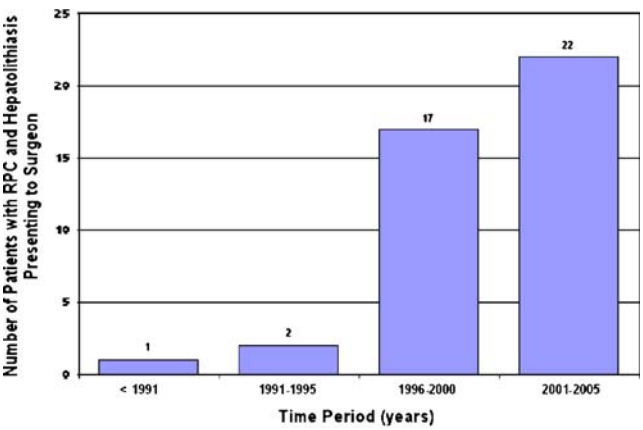

Figure 2 Number of patients with RPC and hepatolithiasis referred to Toronto General Hospital surgeons by year.

Hutson access loop. In this group, 7/10 had CBD dominant or bilobar stones, two had parenchymal atrophy but no significant intrahepatic stones, and one had right-sided stones with no atrophy and was felt to be amenable to extraction via Hutson loop.

Liver resection was performed in 17 of the 27 surgical patients, of whom 11 also had a choledochojejunostomy with Hutson access loop constructed (ten patients had loop construction at the same time as hepatectomy, and one underwent a subsequent operation to construct an access loop when symptomatic stones in the remaining lobe could not be cleared nonoperatively.) A segment 2/3 resection was performed in four patients, a left lobectomy was performed in 10 patients, and a right lobectomy was performed in three patients. The indications for a liver resection were lobar atrophy in 11/17 patients and for stones confined to one lobe in 5/17 patients. One patient underwent a segment 2/3 resection in the context of bilobar disease and required a second operation 2 years later to resect segment 6 for recurrent symptoms.

The operative morbidity and mortality for CBD exploration was similar to that of hepatic resection (Table 2). Overall, CBD exploration had a 35% complication rate compared to 30% for hepatectomy, and both procedures had zero 30-day mortality. The complication rate for liver resections in conjunction with the construction of choledochojejunostomy with Hutson access loop was no greater than the rate for liver resections alone (3/10 vs. 3/7, respectively).

A total of 21 choledochojejunostomies with Hutson access loops were constructed. At last follow-up, only 7/21 (33%) access loops had been subsequently used for percutaneous removal of stones. There were three failures to access and/or clear stones. In the four successful access procedures, two were performed for symptomatic recurrent stones and two for asymptomatic stones.

At last follow-up, four of the nonsurgical patients had died of unresectable cancer. Of the remaining eleven patients, four (36%) experienced ongoing hepatolithiasis-related symptoms. In the surgical group, only four (15%) patients had recurrent or ongoing symptoms unrelieved by the operative procedure with or without Hutson loop access; three were the patients in whom attempt to use the Hutson loop was unsuccessful, and a fourth patient developed a caudate lobe abscess requiring percutaneous drainage.

Cholangiocarcinoma was identified in five of the 42 patients (12%). Three cases were identified at the time of initial presentation and were unresectable. One was identified as in-situ carcinoma in a resected left lobe specimen, and this patient underwent a re-resection to obtain clear margins. One patient presented as a right hepatic mass 2.5 years after the CBD exploration and

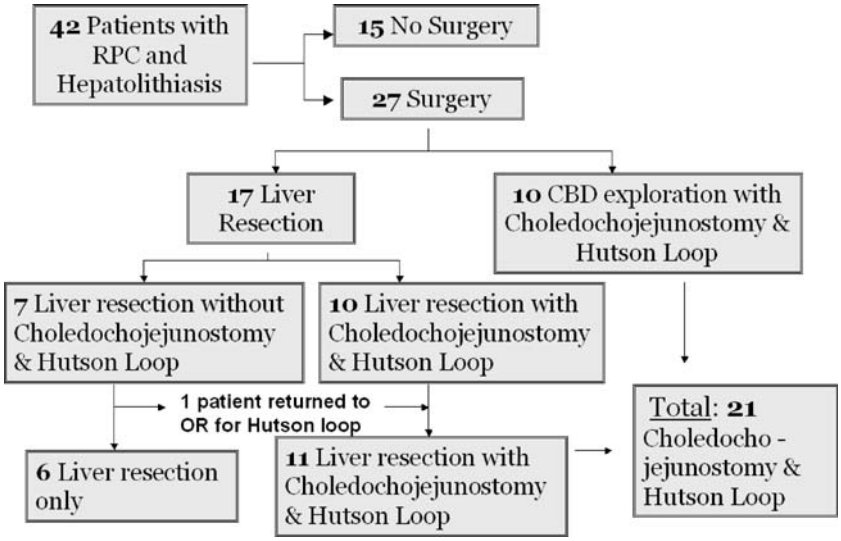

Figure 3 Surgical procedures performed on patients with RPC and hepatolithiasis by Toronto General Hospital surgeons.

choledochojejunostomy with Hutson loop construction. At last follow-up, three of the five patients (60%) had died of their malignancy.

Discussion

This study is an analysis of a 25-year experience managing patients with symptomatic RPC and hepatolithiasis at a major hepatobiliary surgery center in North America (Toronto, Canada). The North American experience with this disease is limited in comparison to East Asia, and the patient populations described in the literature are often heterogeneous. A series published by the Hopkins group in 1994 emphasized the multidisciplinary approach to hepatolithiasis in a series of 54 patients, the majority of whom were Caucasian, and most of whom had stones secondary to biliary stricturing disease (CBD injury, PSC).[3] Forty of 54 patients underwent surgery, including 36 Roux-en-Y hepatico- or choledochojejunostomies with large-bore transhepatic stents. Eighteen of 40 operated patients required subsequent percutaneous procedures for stone and/or symptom recurrence. At mean follow-up of 60 months, 94% of the population was stone-free and 87% was symptom-free. Another series published in 1998 by Harris et al. from San Francisco[4] describes 45 patients with Recurrent Pyogenic Cholangitis of whom 39 patients had surgery. All patients were born in Southeast Asia. The surgical procedures included CBD exploration, biliary-enteric anastomoses, and hepatectomies, with average follow-up of 3 years. Details on outcome after surgery were limited but included a complication rate of 6.7% and 10% incidence of postoperative hepatic failure, ultimately needing liver transplantation. In 1999, Cosenza et al.[5] published a series of 16 patients treated at the LAC/USC Medical Center, University of Southern California. Except for one, patients were either Asian or Hispanic. The majority (14/16) underwent surgery including construction of a Hutson loop, and two had partial hepatectomy for atrophied left lateral lobe. At 16-month follow-up, 4/14 cases were completely free of stones, whereas 8/14 patients had ongoing minor symptoms related to recurrent stones managed with retrieval via the Hutson loop. An earlier report by Stain et al.[6] described a series of 20 RPC patients treated surgically at a University of Southern California Medical Center between 1980 and 1994. Seventeen patients were of Asian origin and three were Hispanic. Four patients underwent hepatectomy only, eight patients had a hepati-

Table 2 Morbidity and Mortality of CBD Exploration vs. Hepatectomy

	CBD Exploration (n=10)	Hepatectomy (n=17)
Complications		
TOTAL:	3 (30%)	6 (35%)
Wound infection	1	2
DVT/PE	1	0
Perihepatic hematoma	1	0
Perihepatic abscess	0	3
Hepatic insufficiency	0	1
30-day mortality	0	0

cojejunostomy, and eight patients had a hepaticojejunostomy with temporary cutaneous stoma for subsequent access and stone retrieval. Three of the hepatectomy patients had postoperative biliary sepsis, with one mortality, and five of eight hepaticojejunostomy patients (without access loop) required reoperation for biliary sepsis. None of the access loop patients required further surgery for stone recurrence or cholangitis.

In this study, most patients were of East Asian origin. As reported previously, the left lobe was affected in the majority of cases, although nearly half of our patients had bilateral hepatic involvement. In our series, there was a long time interval between first presentation of the disease and referral to a surgeon at our institution (mean 9 years), which highlights the chronic and progressive nature of this condition.[2,7] Almost half of the patients had previous biliary surgery including cholecystectomy and/or biliary-enteric anastomoses. The relatively short median follow-up time in this study (24 months) reflects the distribution of case referrals, which increased substantially during the time period of the study. Follow-up was based on surgeons' and hospital records as Research Ethics Board permission to contact the patients for follow-up was not granted.

The changing epidemiology of RPC and hepatolithiasis has been noted previously. In the East, the prevalence is falling, whereas in the West, the incidence is increasing. The prevalence has fallen from 58% to 12% of all patients with biliary calculi at Hong Kong's Queen Mary Hospital.[1] Moreover, in China, the ratio of intrahepatic stones to gallbladder stone disease has dropped from 1:1.5 to 1:7.36 over a 10-year period.[8] In the West, this disease has become increasingly more prevalent in centers that receive immigrants from endemic regions. Harris et al.[4] describe a doubling of RPC patients presenting to their center in San Francisco during 1984–1995 relative to 1970–1983. Our own experience is similar. The number of patients seen at our center rose sharply after 1995, and has continued to increase. This trend likely reflects an actual increase in the number of patients with symptomatic hepatolithiasis resulting from the changing demographics in a multicultural city such as Toronto, but may also be caused by increasing recognition of the disease by Western radiologists, physicians, and surgeons.

In our series, patients who underwent surgery were compared to those who did not, recognizing the inherent bias that all patients had been referred to a Hepato-Pancreato-Biliary (HPB) surgeon. In most cases, there was a long duration of disease before referral to a surgeon. Nevertheless, the patient and disease characteristics for both groups were similar, and in both subgroups the majority had undergone ERCP and percutaneous attempts at stone extraction and/or biliary drainage, effectively exhausting the nonsurgical options. There is good evidence for the utility of therapeutic ERCP in managing some patients with RPC and hepatolithiasis, primarily for those with extrahepatic stones. In a series of 134 RPC patients in whom the majority had CBD-dominant disease, stone clearance was achieved by ERCP in 91.7% of cases.[9] In a report by Sperling et al.,[10] which compared 41 patients treated with ERCP, immediate surgery, or no intervention, a subgroup of 15 patients had isolated extrahepatic stones. Of these, 7/9 (71%) of patients treated with ERCP remained asymptomatic at a 2-year follow-up. The use of percutaneously placed transhepatic access catheters has also been reported to have good outcome in the Hopkins series, where this was performed as part of a combined radiologic and surgical team approach that safely allowed for complete stone clearance 51/54 (94%) of patients at 60-month follow-up.[3] In our study, the majority of patients had residual stones in the intrahepatic ducts, and the entire study population is biased toward those patients who might have exhausted nonsurgical treatment options; hence, their referral for consideration of surgery. The present series does, however, emphasize the importance of the multidisciplinary approach to the management of patients with RPC and hepatolithiasis.

In the 27 surgical patients, the decision to perform a liver resection was based predominantly on the presence of lobar atrophy (with or without portal vein thrombosis) and/or stones confined to one or more anatomical segments or one lobe. There was no additional morbidity or mortality associated with the resection compared with CBD exploration, nor was there any significant difference in disease control. Serendipitously, in one patient the liver resection identified an in-situ cholangiocarcinoma. Previous studies have described the value of liver resection in managing symptomatic hepatolithiasis. Lee et al.[11] reviewed 123 patients who underwent hepatectomy for hepatolithiasis, with median follow-up of 40.3 months. Immediate stone clearance rate was 92.7% and final stone clearance rate 96%. Complication rate was 33.3%. Similarly, Chen et al. reported a 90% immediate stone clearance rate and 98% long-term stone clearance in a series of 103 hepatolithiasis patients who underwent hepatectomy, with a 28% complication rate.[12]

Three quarters of the surgical patients received a choledochojejunostomy with Hutson access loop as part of their procedure. The purpose of this loop is to provide a more direct route for percutaneous, retrograde access to the entire biliary tree for residual, or recurrent intrahepatic stones. Interestingly, 15% of our patients had previously undergone a biliary-enteric anastomosis before their referral to our center. Creation of a Hutson loop did not appear to increase the morbidity of the operation. To date, the need to utilize the loop has arisen in only one third of patients (7/21) who had the procedure, similar to results described by others. Liu et al.[13] found that 22/70 (23%) patients who had

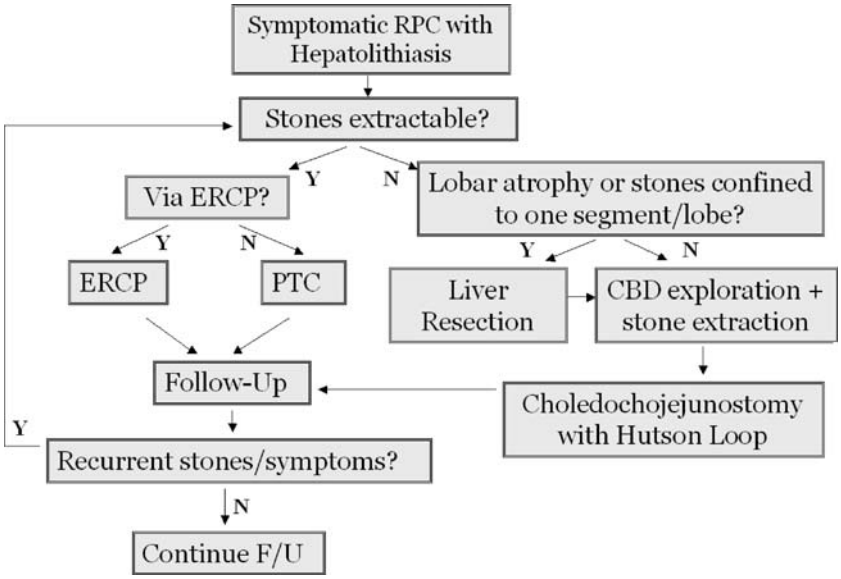

Figure 4 Suggested algorithm for approaching management of patients with RPC and hepatolithiasis.

hepaticocutaneous jejunostomy for primary biliary stones required postoperative choledochoscopic removal of residual stones. Similarly, 12/41 (29%) patients with a loop for hepatolithiasis required use of the loop at a 27-month follow-up in another report.[14]

Failure to access and clear the stones occurred in three of the seven Hutson loop attempted utilizations. Those patients, plus one other who required percutaneous drainage of a caudate lobe abscess, constitute the 15% of surgical patients whose disease was not adequately treated with the surgical procedure alone. On the other hand, in 85% of patients the surgical strategy was successful in controlling their disease. The relatively short follow-up time in this study raises the possibility of underestimating recurrence rates. Nonetheless, given the improved outcome among patients who underwent surgery within the available follow-up period, this study supports the important role for surgery in the multidisciplinary management of patients with RPC and hepatolithiasis.

The prevalence of cholangiocarcinoma (CCA) in our population was 12%, which is within the previously reported range of 5–18%;[2,15] and the mortality for patients with CCA was high at 60%. This suggests an important role for long-term screening for CCA in RPC patients, in a manner similar to those with PSC. Although the surgical options selected in this study were primarily directed toward the management of the benign, acute inflammatory, and infectious complications of RPC, the increased risk of CCA needs to be considered in the management strategy. In the context of hepatolithiasis, cholangiocarcinoma tends to be located in the atrophic hepatic lobe and/or in lobes containing significant stones.[16] The managing physician or surgeon must consider the increased risk of CCA in determining the role for liver resection in patients with RPC and hepatolithiasis. Unfortunately, most bile duct cancers in the setting of this disease are diagnosed at an advanced stage and are inoperable.[2]

Conclusion

Recurrent Pyogenic Cholangitis with hepatolithiasis is a chronic and progressive disease with significant morbidity and a high risk of cholangiocarcinoma. Surgery is an effective option and important component of multidisciplinary management of patients with this disease. Liver resection is useful in patients with stones or atrophy confined to one lobe or sector, and carries no apparent additional morbidity or mortality compared to CBD exploration and stone clearance alone. The construction of a choledochojejunostomy with Hutson access loop caries no additional morbidity and offers an additional approach to residual or recurrent stone formation.

We suggest the algorithm presented in Fig. 4 for approaching the management of patients with RPC and hepatolithiasis. Patients with extractable stones should have them removed, preferably by ERCP but otherwise by percutaneous approach. Those whose stones are not extractable by either of these methods would need surgical exploration of the CBD with extraction of stones. If they have lobar atrophy and/or stones confined to one lobe, they would likely require liver resection in addition to the CBD exploration. We recommend the choledochojejunostomy with Hutson loop construction for all patients who undergo surgery.

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Surgical Treatment of Gastroesophageal Reflux Disease and Upside-down Stomach Using the Da Vinci® Robotic System. A Prospective Study

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Abstract So far, the impact of telematic surgical approach in Gastroesophageal Reflux Disease (GERD) is still obscure. In this prospective study, we analyzed the Da Vinci® Intuitive Surgical robotic system for antireflux surgery. In April 2003, we set up a pilot study to evaluate the efficacy of laparoscopic telerobotic surgery using the three-arm Da Vinci® system. Optimal trocar positions, operating and setup times, conversion rate, intraoperative complications, and perioperative morbidity, as well as mortality rate, were analyzed. The median age was 53 years (range 25–74) in 118 patients (52 female/66 male). In 17 patients, an upside-down stomach- and in 101 GERD was surgical indication. The median operating time has been reduced from 105 min to 91 min after 40 procedures and setup time from 24.5 min to 10.4 min after 10 procedures. The system is safe and it seems to be superior to traditional laparoscopy during dissection in the esophageal hiatus region. This compensates long setup- and operating times. Disadvantages are the high costs, the time to master the setup/system and the necessity of exact trocar positioning.

Keywords GERD · Laparoscopic fundoplication · Da Vinci · Robotic system · Robotic surgery

Introduction

Gastroesophageal reflux disease (GERD) has an incidence of 10–20 % among the German population with an increasing tendency. The main cause of GERD is a hiatal hernia. At present, the treatment of choice is the administration of proton pump inhibiting drugs (PPI). Because adverse drug effects, interactions of PPI with other drugs, and the patients' wish not to be involved in a long-term treatment, antireflux surgery appears to be an interesting treatment alternative. After the introduction of laparoscopic Nissen fundoplication by Dallemagne et al. and Geagea, antireflux surgery came into an era of Renaissance.[1] Laparoscopic fundoplication has emerged as the gold standard for the surgical treatment of gastroesophageal reflux disease.[2] However, both laparoscopic and thoracoscopic techniques have been shown to have technical limits and certain disadvantages especially when advanced procedures are carried out. Most of the technically advanced operations are difficult to perform in a minimal invasive setting and involve a steep learning curve of the whole surgical team.[3] Limitations inherent to the actual minimal invasive surgery may cause certain difficulties during its performance requiring a unique set of skills, however, even after the surgeon has accumulated years of experience. Pitfalls of traditional laparoscopy include unstable video camera platform, limited motion of straight laparoscopic instruments, two-dimensional imaging, and poor ergonomics for the surgeon.[4,5] Therefore, telerobotic surgery has emerged as a promising technical innovation overcoming the present difficulties in minimal invasive surgery. In the current study, we report our experience on using the Da Vinci robotic system.

The Charité hospital Berlin Mitte has been using the Da Vinci system since October 2002. So far, approximately

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300 various laparoscopic or thoracoscopic procedures have been performed. This prospective study aimed to analyze the experiences using the 3-arm Da Vinci Intuitive Surgical® Robotic system for surgical treatment of benign gastroesophageal disease.

Materials and Methods

All surgical telematic procedures for the treatment of GERD and upside down stomach have been prospectively documented from April 2003 to April 2007. Endpoints of the study were optimal trocar positioning, operating and setup times, conversion rates, operative complications, morbidity, and mortality. Indications for surgery were hiatal hernia in the endoscopy, and/or an abnormally high ph-metry-score (DeMeester score >14.8), and/or an abnormal lower pressure of the lower esophageal sphincter with unaffected upper gastrointestinal barium swallow series in patients with symptomatic GERD.

Patients from one surgical ward were consecutively included and were operated by three surgeons with high experiences in reflux surgery using the three-arm Da Vinci system. All patients were thoroughly informed about the risks associated with the surgical procedure using the telerobotic system, as well as the potential postoperative benefit.

All patients have given their written consent before surgery. Operations were performed under an approved protocol of the local Ethics Committee of the Charité University Hospital Berlin.

Our standard surgical treatment of GERD is a partial anterior fundoplication (Dor-type) combined with a posterior hiatoplasty. In detail, we performed a partial anterior (180°) fundoplication (Dor-type) in 111 patients, a Nissen fundoplication in 16 patients as well as partial posterior fundoplication (270° Toupet-type) in one patient. Previously, we described in detail the setup of the operative room and the technical aspects of the operation.[6]

Postoperative treatment was based on a standardized protocol. A routine upper gastrointestinal series with gastrografin was performed in all patients on the first postoperative day. Patients were allowed to have liquid diet with progression to solid food already on the second postoperative day. Follow-up of the patients continued on a regular outpatient basis every 6 months after surgery. It consisted of clinical examination and endoscopy or upper GI series in case of clinical symptoms.

Results

From April 2003 until April 2007, 118 patients (52 female/66 male) were included in the study. The median age was 53 years (range 25–74 years). All patients underwent preoperative upper gastrointestinal endoscopy. The presence of a hernia was detected in more than 80% of our patients with symptomatic GERD—and therefore this is for us the major indication for operation. The preoperative median esophagitis staging (Savary/Miller) was 1.8 (range 1–4).

Manometry was performed in 80 patients (others declined diagnostic). Thirty-three patients were shown to have a decreased lower pressure of the lower esophageal sphincter. The pressure of the lower esophageal sphincter was in median 9.5 mmHg (range 4.0–11.2 mmHg). Eighty-two patients underwent a preoperative 24-h pH-metry which gave a median DeMeester-score of 46.4 (range 19.2–155.7).

All included patients had a symptomatic GERD and had been treated for more than 6 months with PPI. Most frequent symptoms were heartburn (87%) and regurgitation (60%), whereas less frequent symptoms included abdominal pain, cough, belching, and bloating. Patients presenting with radiological or endoscopic findings consistent with an "upside down" stomach were advised to undergo a prompt operative procedure to avoid severe complications such as stomach incarceration.

Initially, we analyzed the optimal trocar positioning. Trocars had to be placed in modified positions on the abdominal wall compared to traditional laparoscopy, so that the robotic arms could move freely without colliding. The exact positioning of the trocars is shown in Fig. 1. With the new approach, trocars have been placed in the shape of a flat isosceles triangle in the upper abdomen.

The overall median operating time was 105 minutes. Evaluation of operating time and set-up time showed a learning curve of approximately 10 procedures (Figs. 2 and 3). In the first six operations, the median operating time was 131 minutes. Consecutively, the median operating time decreased to 91 minutes. The median operating time was 26 minutes longer in patients with upside-down stomach (n=17 out of 118) because of demanding technical aspects.

The median set-up time could be reduced from 20 minutes (first 10 patients) to 10.4 minutes (Fig. 2). A conversion to traditional laparoscopy was necessary in six of 118 cases (5.1%) only in the first 30 procedures. No

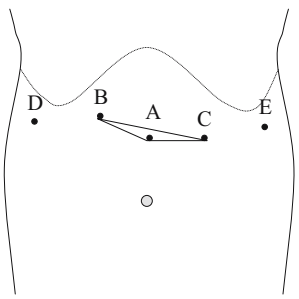

Figure 1 Position of the ports on the abdominal wall. A: endoscope port; B: port for the Cadiere grasper; C: port for electrocautery or endoscopic needle holder; D: port for the liver retractor; E: port for additional instruments (scissors, grasper) of the assistant surgeon.

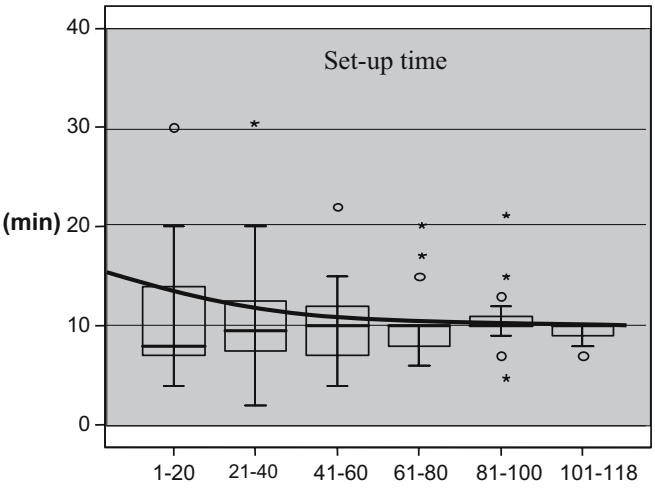

Figure 2 Reduction of setup time of robotic system to 10.4 minutes; consecutive patients (first two patients not shown 40 and 55 minutes).

laparotomy was necessary. Conversion could be attributed to a failure in trocar positioning (n=1), severe adhesions in the upper abdomen (n=4), and to a system's breakdown during the operation because of a software defect. In this case, the robotic instruments were initially taken out. The procedure continued in a traditional laparoscopic way for about 20 minutes. The system had suffered an electronical fault and the computer had to be restarted, checked, and calibrated before the operation could go on uneventfully with the robotic system. There were no perioperative surgical complications. Postoperative x-ray (gastrografin swallow) did not show any leakages, disorders, or stenosis of the region. Perioperative mortality was zero. The patients tolerated food intake without problems, and most of them were discharged on the third postoperative day. The median overall hospital stay was 4.2 days (range 2 to 10 days). All patients were examined on the postoperative day 10. Follow-up continues on an outpatient basis and is expected to last 3 years. Until now, no patient has suffered a recurrence of GERD symptoms and no one has needed a reoperation. The follow-up (6 months after surgery) showed normal findings in all cases.

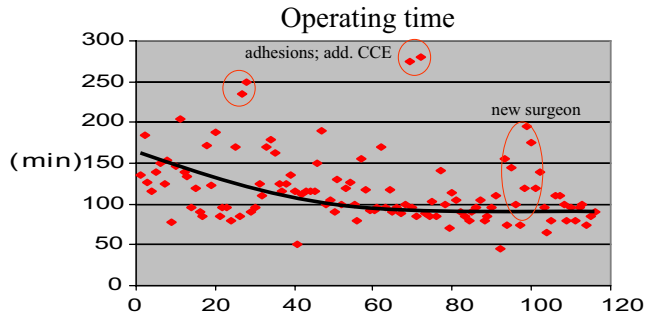

Figure 3 Reduction of median operating time from 133 to 91 minutes.

Discussion

Telerobotic surgery has inaugurated a new era in minimal invasive surgery with major potential changes concerning concept and performance of surgery itself. The Da Vinci robotic system was primarily developed for cardiac surgery and it was the first robotic system to be approved by the Food and Drug Administration (FDA) for intraabdominal surgery in the United States (July 2000). So far, more than 550 systems are in use in several institutions worldwide.

Currently, there are several reports in the literature confirming the increasing spread of the use of robotic systems in several aspects of surgery, such as colorectal surgery,[7–9] esophageal surgery,[10–13] gastric surgery,[11] bariatric surgery,[14–18] and adrenal surgery.[19,20] Moreover application of the Da Vinci system in otolaryngology has been reported in animal models and quite recently in human.[8,21,22]

Meanwhile, several studies have shown the feasibility and safety of robot-assisted antireflux surgery both in adult patients and children.[5,6,23–27]

Only three prospective randomized studies (randomized controlled trials [RCT]) have compared robot-assisted with standard laparoscopic fundoplication so far (Table 1). In their prospective randomized trial, Morino et al.[28] showed that robot-assisted laparoscopic fundoplication is comparable to the standard traditional laparoscopic procedure in terms of feasibility and outcome, but costs are higher owing to longer operating times and the use of more expensive instruments. The authors failed to show a distinct advantage for the use of the robotic system. In their randomized clinical trial of standard laparoscopic versus robot-assisted laparoscopic Nissen fundoplication for GERD, Draaisma et al.[29] detected similar subjective and objective results in both groups. The authors concluded they found no additive value of robotic systems for this procedure up to 6 months after surgery. Nakadi et al.[30] evaluated clinical results and costs of the Da Vinci Nissen Fundoplication in the settings of a RCT. Nine patients were assigned to the robot and 11 patients underwent traditional laparoscopic procedure. The authors reported significantly longer operating time and more complaints of the patients 3 months after surgery for the robotic group. Overall costs were also higher. A weak point of this study could be the limited number of patients included.

In a nonrandomized clinical trial that included 20 patients, Melvin et al.[31] reported significantly longer operating times in the robotic group (141 versus 97 minutes; P<0.001). Morbidity and postoperative hospital stay were similar. During 7 months of follow-up, a significant difference in the number of patients needing regular antisecretory medication (0% in robotic group versus 30% in the control group) was observed. Lehnert et al. compared operative time in conventional laparoscopic and robotically

Table 1 Published RCTs on Robot-Assisted Laparoscopic Fundoplication in 2006

Author	*N* (R/L)*	m/f	Age	Operating time	Setup time	Trocar time	Conversion	Alimentation	Costs (Euro)	Morbidity	Total hospital stay
Nakadi[30]	9	6 / 3	44±4	137±4	23±4	–	1	2.11±0.11	6,973	1	4.1±0.3
	11	8 / 3	48±4	96±5	–	–	–	1.81±0.18	5,167	0	4.4±0.2
Draaisma[29]	25	16 / 9	48 (20–74)	120 (80–180)	10 (3–15)	–	–	–	–	0	3 (2–6)
	25	17 / 8	52 (27–71)	95 (60–210)	–	–	2	–	–	8	3 (1–13)
Morino[28]	25	19 / 6	43±13	131±3	23±6.5	16.2±6.5	1	–	3,157	0	3.0
	25	18 / 7	46±11	91±1	–	11.6±3.5	2	–	1,527	0	2.9

Results are expressed as mean ± standard deviation or median (range)
*R/L Robotic group/traditional laparoscopic group; *N*=number of patients; m/f male/female; (−) data non available

assisted Thal-semifundoplication in children (10 patients for each group).[24] In the Da Vinci group, the setup time was significantly longer (20.8±7.5 vs 34.6±9.2 minutes, $p<0.05$). However, total operative time was similar in both groups, as the dissection of the hiatal region was accomplished 34% faster in the robotic-assisted group (30.8±8.7 vs 20.2±5.3, $p<0.05$).

Major advantages we experienced in our series were high degree of freedom of the instruments combined with few limitations of the endowrist movement, especially through the narrow hiatus. Hand-like motions of the instruments and the enhanced visualization of the operative field with a true 3-dimensional view offered us the impression of an open access. These two features of the Da Vinci robotic system made the dissection of the partial intrathoracic stomach from the surrounding tissues in the mediastinum through the hiatus quite easily compared with the traditional laparoscopic approach. Under these terms, we were able to reconstruct the sphincter mechanismus of the lower esophagus comparably if no better than traditional laparoscopic surgery. This unique feature of the Da Vinci system in this critical part of the operation has been also pointed out by other authors.[24,28] We also saw enormous improvements in suturing and tying knots, thanks to the articulated tools. The approximation of the hiatal crura and the creation of the fundic wrap were found to be easier than by traditional laparoscopy. Similar superiority of the robotic system in tissue dissection and suturing over traditional laparoscopic surgery has been reported by several authors both in animal models and humans for a variety of operative procedures.[2,10,31,32] Complete (Nissen) or partial anterior (Dor) fundoplication can be easily and safely performed with the Da Vinci robotic system. No perioperative complications were seen in our series and the learning curve was steep (approximately 10 operations). Our results confirm that robot-assisted laparoscopic fundoplication is a feasible and safe procedure, comparable to traditional laparoscopy in terms of complications, mortality, and length of hospital stay, in agreement with already published data.[5,24,26,29–31] In our Department, the median time for traditional laparoscopic antireflux surgery was 95 minutes over the last years. This is comparable to a median operating time of 105 minutes in our robotic series. Figures 1 and 2 show a clear progressive improvement in setup time and operating time in robotic-assisted fundoplication in our Department after completion of the learning curve.

Nevertheless, the Da Vinci robotic system was initially developed for heart procedures and is now used for abdominal surgery. The limited diversity of compatible instruments and equipment necessitates the presence of a table-side assistant to perform part of the operation. The three robotic arms cover a huge patient area during operation, which is uncomfortable for the assistant surgeon. In cases of demanding tissue dissection or when an intraoperative change of the operative field is needed, a fourth robotic arm would be necessary. New editions of a four-arm Da Vinci system (4S) are currently available. Therewith, the assistant surgeon is possibly not needed for several operations. This can also reduce the enormous cost of the system (e.g., service, instruments, and amortization). We have to mention that the estimated functional cost of an operation of this kind is about 800 to 1,000 Euros, depending on the number of instruments used. The approximate cost for each disposable instrument is 200 Euro. However, the huge costs could be a major impediment to the further development of the telerobotic surgery.

The setup time of the system, which includes full sterile draping, positioning of the arm cart, and attachment to the trocars is time consuming. This may be reduced through further experience of the whole team, as we actually noticed in our series (Figs. 2 and 3).[13] We also observed that pneumoperitoneum pressure during robotic procedures is higher than that used to perform the same procedures in laparoscopy. For this reason, minor misplacement of the trocars away from the ideal positions may severely hinder the performance of operations. Exact positioning of the ports is of critical

importance for the unimpeded procedure. Instruments should reach the operative field with maximum range of motion of the moving arms without them to collide or injury to the patient.[26,33] False positioning of the ports could be a reason for the conversion into traditional laparoscopy. We experienced it in one case in our series. In four cases, conversion was necessary because of extensive adhesions in patients with previous abdominal operations. In these cases, the procedure would have theoretically continued with Da Vinci, if we had intraoperatively changed the placement of the trocars, so that the laparoscopic instruments could have reached the adhesions. This would have been extremely time-consuming, so we preferred to continue with traditional laparoscopy having access to a wider operative field.

Another disadvantage of the present robotic system, extensively reported in the literature, is loss of tactile feedback (or haptics).[6,28]

A number of situations occurring during robotic cases make the lack of sensory feedback a significant drawback (inadvertent breaking of suture during knot tying, iatrogenic organ injury). High experience is necessary so that complications caused by lack of tactile feedback can be avoided.

Conclusions

Despite the above-mentioned drawbacks, our first observations from this descriptive study show that fundoplication using the Da Vinci robotic system is a feasible and safe operative procedure. We should, however, point out that the current study is a descriptive one and presents the advantages of use of the Da Vinci systems as perceived by the surgical staff of our Department. A prospective randomized trial comparing robotic and traditional laparoscopic fundoplication is currently being conducted in our Department. This study should give further information about the role of this novel approach in surgical treatment of GERD.

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Use of Antireflux Medication After Antireflux Surgery

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Abstract
Introduction It is claimed that a substantial number of patients who undergo antireflux surgery use antireflux medication postoperatively. This study was aimed to determine the prevalence and underlying reasons for antireflux medication usage in patients after surgery.
Materials and Methods A questionnaire on the usage of antireflux medication was sent to 1,008 patients identified from a prospective database of patients who had undergone a laparoscopic antireflux procedure.
Results A total of 844 patients (84%) returned the questionnaire. Mean follow-up was 5.9 years after surgery. A single or combination of medications was being taken by 312 patients (37%): 82% proton pump inhibitors, 9% H_2-blockers and 34% antacids. Fifty-two patients (17%) had never stopped taking medication, whereas 260 patients (83%) restarted medication at a mean of 2.5 years after surgery. Return of the same (31%) or different (49%) symptoms were the commonest reasons for taking medication, whereas 20% were asymptomatic or had other reasons for medication use. Postoperative 24-hour pH studies were abnormal in 16/61 patients (26%) on medication and in 5/78 patients (6%) not taking medication.
Conclusions Antireflux medication is frequently taken by many patients for various symptoms after antireflux surgery. Symptomatic patients should be properly investigated before antireflux medications are prescribed.

Keywords Medication · Gastroesophageal reflux · Fundoplication

Introduction

Laparoscopic antireflux surgery has shown to be effective in controlling gastroesophageal reflux.[1,2] However, it is also known that a substantial number of the patients after surgery still take antireflux medication.[3–5] One randomized-controlled trial that compared surgery with medical therapy for gastroesophageal reflux disease (GERD), reported regular usage of antireflux medication by 62% of patients 9 years after surgery, although most of the surgically treated patients were satisfied or very satisfied with the outcome of their operation. Other studies have reported lower rates of medication usage among patients after fundoplication, in the order of 15–20% after 4–5 years of follow up.[6–10] However, most patients who used acid suppressive medications after antireflux surgery did not have abnormal esophageal acid exposure.[11,12] Thus, the use of these medications often seems inappropriate, and it does not always indicate that surgical therapy has failed. Because it is currently not well-known why patients are taking medication, the type of medication they use and who prescribed the medication, we analyzed these aspects in a large cohort of patients who had undergone antireflux surgery.

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Materials and Methods

Patients were selected from a prospective database of individuals who underwent laparoscopic antireflux proce-

dures between March 1992 and August 1 2006 by surgeons from Flinders University Department of Surgery, Flinders Medical Centre, Bedford Park, Australia and University of Adelaide Discipline of Surgery, Royal Adelaide Hospital, Adelaide, Australia. All patients were operated in a similar fashion and according to our standard operative techniques for laparoscopic fundoplication.[13–15] In addition, the follow-up of patients was identical for both hospitals.

For the purpose of this study, a specific questionnaire on medication use was designed and added to our routine follow-up questionnaire, which is sent out to all patients at 3 months after operation, and yearly thereafter. Questionnaires were sent out to 1,008 patients who had undergone a fundoplication between March 11, 1992 and August 8, 2006. If any answers to the questionnaire were unclear, a research nurse contacted the patients by telephone to seek clarification.

The questionnaire included questions about which antireflux medications were being used: proton pump inhibitors, H_2 receptor blockers, and antacids. All generic and proprietary names of these three types of medication that are currently registered in Australia[16] were listed on the questionnaire and patients were asked to encircle the specific medications they were taking. Further questions included whether patients took these medications daily or intermittently (weekly, once per month or less than once a month), if they had ever stopped the medication after surgery and when they started taking them. In addition, we asked patients why they took the medications (symptoms same as preoperative, symptoms different from preoperative symptoms, no symptoms), who advised them to take the medications (general practitioner [GP], surgeon, other specialist, patients themselves after consultation with specialist/GP, or self medicated) and if their symptoms responded to the medication (yes, sometimes or no).

Patients were asked if they experienced symptoms of heartburn, chest pain, and regurgitation. Severity of these symptoms were assessed by a Visual Analogue Scale (VAS 0 = fully controlled, no symptoms; 10 = not controlled, severe symptoms). Overall satisfaction with the outcome of the procedure was also determined using the same VAS (0 = totally dissatisfied; 10 = totally satisfied).

Twenty-four-hour pH studies, esophageal manometry and endoscopy were not routinely scheduled during follow-up. They were only performed when clinically indicated or when patients were enrolled in a clinical trial. The prospective database was checked to see if any of the patients who returned the medication questionnaire had undergone a 24-hour pH study after the operation and these studies were analyzed for a normal or abnormal outcome (the fraction time of esophageal acidification [pH<4] being more than 4%).

The means of all continuous variables were compared using appropriate parametric or nonparametric tests. Categorical variables and proportions were compared using the Chi-square test or the Fisher Exact test. To determine which factors were independent predictive of postoperative medication use, multivariate regression using binary logistic regression analysis was performed. A $p \leq 0.05$ is considered statistically significant. Data are reported as percentage of patients or mean ± SD.

Approval for prospective follow-up of the patients in this study was obtained from the Royal Adelaide Hospital Research Ethics Committee and the Flinders Clinical Research Ethics Committee and was obtained.

Results

Patients and Operative Details

Eight hundred forty-four of the 1,008 patients (84%) returned the medication questionnaire. There were 434 males (51%) and 410 females (49%) with a mean age (±SD) 58.2±14.2 years. Mean follow-up (±SD) after fundoplication was 5.9±3.9 years.

Five hundred twenty-five patients (62%) underwent a 360° Nissen fundoplication, 176 (21%) a 180° anterior fundoplication, 124 (15%) a 90° anterior fundoplication, and 19 (2%) a 270° posterior partial fundoplication. In 768 patients (91%), the esophageal hiatus was repaired with sutures. Conversion from laparoscopy to laparotomy occurred in 37 patients (4%). Reoperations for recurrent reflux symptoms or paraesophageal herniation were undertaken in 70 patients (8%) after a median period of 14.3 months.

Use of Antireflux Medication

Three hundred twelve of the 844 patients (37%) reported that they were using a single or a combination of antireflux medications. Proton pump inhibitors are taken by 257 of the 312 patients (82%), H_2-blockers by 29 patients (9%) and antacids by 105 patients (34%). Fifty-two patients (17%) had never stopped taking medication after their operation, and 260 patients (83%) restarted 2.5±2.9 (mean ± SD) years after the operation. Figure 1 shows the cumulative percentages of patients taking medication with time after operation. The patients taking antireflux medication were more likely to be female, and their average age was higher (Table 1). These patients were more likely to have had their operation converted to an open fundoplication, and they were more likely to have had a partial fundoplication fashioned.

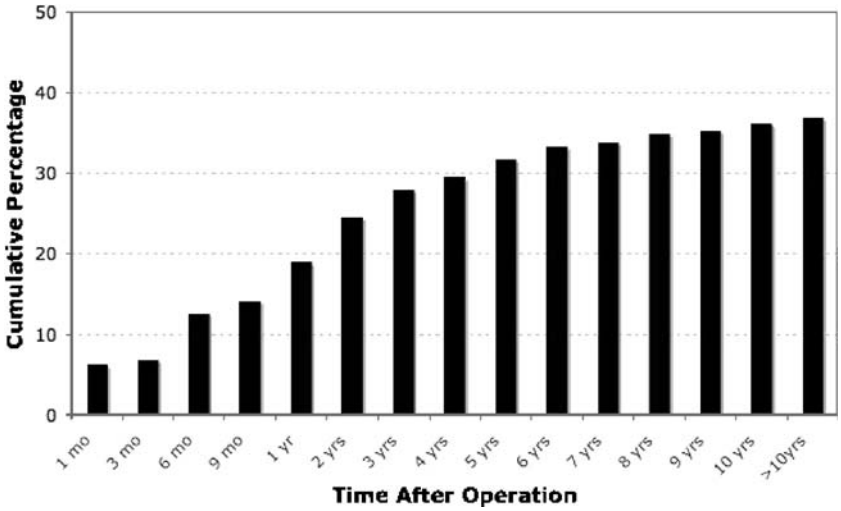

Figure 1 Percentage of patients on antireflux medication versus time after fundoplication.

Postoperative Symptoms

Postoperative symptoms (assessed by yes/no questions) of heartburn, chest pain, and regurgitation are experienced by 322 (38%), 332 (39%), and 325 (38%) of the overall group of patients, respectively. The mean (±SD) scores on a visual analogue scale (0–10) for each of these symptoms were 1.4±0.7, 1.5±0.9, and 1.7±2.6, respectively. Table 2 shows that a higher percentage of the patients who were taking medication experienced reflux symptoms, and they also had higher symptom scores compared to patients not taking medication. Patients not taking medication rated their overall satisfaction with the outcome of their operation significantly higher.

Table 1 Patient and Operative Details According to Use of Antireflux Medication

	Medication n=312	No Medication n=532	p value
Age (yrs)	62.0±13.5	56.0±14.3	<0.001
Sex (%)			<0.001
Male	130 (42)	304 (57)	
Female	182 (58)	228 (43)	
Follow-up (yrs)	5.8±3.8	5.9±4.1	0.852
Conversion Lap to Open (%)			0.011
Yes	21 (7)	16 (3)	
No	291 (93)	516 (97)	
Type of Wrap (%)			0.017
360° Nissen	172 (55)	353 (67)	
180° Anterior	74 (24)	102 (19)	
90° Anterior	59 (19)	65 (12)	
270° Posterior	7 (2)	12 (2)	
Short Gastric Vessels Ligated (%)			0.621
Yes	43 (14)	67 (13)	
No	269 (86)	465 (87)	
Hiatus Hernia present (%)			0.714
Yes	196 (63)	327 (62)	
No	116 (37)	205 (38)	
Hiatal Repair (%)			0.534
Yes	281 (90)	487 (92)	
No	31 (10)	45 (8)	
Reoperations (%)			0.018
Yes	35 (11)	35 (7)	
No	277 (89)	497 (93)	

Table 2 Postoperative Symptoms and Overall Satisfaction Score

Symptom	Medication n=312	No Medication n=532	p value
Heartburn (%)			<0.001
Yes	212 (68)	110 (21)	
No	97 (31)	421 (79)	
Not Answered	3 (1)	1 (0)	
Heartburn Score (0–10)	3.2±2.9	0.6±1.4	<0.001
Chest Pain (%)			<0.001
Yes	172 (55)	160 (30)	
No	136 (44)	365 (69)	
Not Answered	4 (1)	7 (1)	
Chest Pain Score (0–10)	2.7±3.0	1.2±2.3	<0.001
Regurgitation (%)			<0.001
Yes	179 (58)	146 (28)	
No	129 (41)	380 (71)	
Not Answered	4 (1)	6 (1)	
Regurgitation Score	2.6±2.9	0.8±1.7	<0.001
Overall Satisfaction Score (0–10)	7.1±2.8	8.9±2.8	<0.001

Values are numbers of patients with percentages in brackets. Symptom and satisfaction scores are mean values ± SD (as measured on a scale from 0 to 10).

Factors Predicting Medication Use

Table 3 shows the variables entered in the binary logistic regression analysis. Patients who underwent a 360° Nissen fundoplication were less likely to be on antireflux medication after the operation. On the contrary, higher age, conversion from laparoscopic to open and persistent symptoms of heartburn, chest pain, or regurgitation were associated with an increased risk of medication use after fundoplication.

Reasons for Taking Medication

Sixty-one percent of patients on medication took them on a daily basis, and 35% intermittently (Table 4). In 36% of cases, the patient's general practitioner advised restarting antireflux medication, and in 14% the surgeon prescribed the drugs. Thirteen percent of patients were self-medicating. Symptoms similar to the original preoperative symptoms was the indication for taking antireflux medication in 97 patients (31%; Table 4). One hundred fifty-four patients (49%) had symptoms, which were different to the preoperative symptoms, whereas 61 patients (20%) had no symptoms or had other reasons for using medication.

Symptomatic Patients

Patients who reported that their symptoms were similar to their preoperative symptoms, were more likely to have an abnormal 24-hour pH study, and a higher percentage of these patients were using medications, in particular PPIs, on a daily basis (Table 5). Moreover, these patients recorded higher symptoms scores and were less satisfied with the overall outcome of the operation compared to patients whose symptoms were different to the original preoperative symptoms (Table 5).

Objective Tests

Twenty-four-hour pH studies were performed postoperatively in 61 patients (20%) who were on medication, and in 78 patients (15%) who were not taking medication. Pathological acid exposure in the distal esophagus was

Table 3 Factors Predicting Postoperative Medication Use

Factor	OR	95% CI	p value
Age (yrs)	1.036	1.022–1.049	<0.001
Sex			
Female	1		
Male	0.918	0.650–1.294	0.626
Type of Wrap			
360° Nissen	1		
Other	1.427	1.009–2.019	0.044
Conversion Lap to Open			
No	1		
Yes	2.292	1.030–5.099	0.042
Reoperation			
No	1		
Yes	1.266	0.700–2.288	0.435
Heartburn			
No	1		
Yes	6.541	4.492–9.524	<0.001
Chest Pain			
No			
Yes	1.664	1.165–2.377	0.005
Regurgitation			
No	1		
Yes	1.666	1.156–2.400	0.006

OR=odds ratio, 95% CI=95% confidence interval

Table 4 Details of Antireflux Medication Use (n=312)

Question					
Do you use the medication intermittently or on a daily basis?	Daily 192 (61)	Intermittently 108 (35)	Not answered 12 (4)		
If using intermittently (n=108), how frequently?	Weekly 56 (52)	Once per month 19 (17)	Less than once per month 28 (26)	Not answered 5 (5)	
Who decided to restart the your medication?	General Practitioner 112 (36)	Surgeon 44 (14)	Other Specialist 42 (13)	Yourself You approached doctor n=47 (15) Without medical advice n=39 (13)	Not answered 22 (9)
Why do you use the medication?	Symptoms returned same as preoperative	Symptoms, but different to preoperative symptoms	No symptoms, just never stopped taking them	Other	
	97 (31)	154 (49)	23 (8)	Barrett's esophagus n=13 (4) Gastroprotective n=8 (3) *Helicobacter pylori* n=1 (0) Not answered n=16 (5)	
Do the symptoms respond well to the medication?	*Yes* 191 (61)	*Sometimes* 89 (28)	*No* 18 (6)	*Not answered* 14 (5)	

Values are numbers of patients with percentages in brackets.

recorded at some stage during follow-up in 16 patients (26%) who were taking medication. Four of these patients (with abnormal acid exposure) underwent surgical revision. Although no further pH monitoring was done in these four patients, all are currently still taking antireflux medication. Only 5 (6%) of the patients who were not taking antireflux medication, had an abnormal 24-hour pH study.

Discussion

Despite the success of laparoscopic antireflux surgery in controlling reflux symptoms, a substantial number of patients are still taking antireflux medication after surgery, although the reported percentages of patients taking medication vary substantially between different studies. Studies that have used pharmacy databases report use of medication to be as high as 50–72% 4 to 5 years after antireflux surgery.[17,18] However, drawbacks of these studies are that medication usage is measured indirectly by prescription dispensed to a patient, and it is not known whether the patients actually took the medication. Furthermore, medications purchased "over-the-counter" are not detected by these databases (13% patients reported self-medication in our study), and the relationship between symptom control and medication usage could not be assessed in these studies.

Our study was designed to get an accurate estimate of the percentage of patients who actually take antireflux medication. This was achieved by sending out a questionnaire to a large cohort of patients on which all antireflux medications (generic and brand names) registered in Australia were listed. Patients just had to encircle medication they were taking. In addition, the reason for taking medication was addressed in our study. This enabled us to identify patients who were taking medication for (non-) reflux related symptoms or for other reasons. Recently, a study with a similar design was published. Although the number of interviewed patients was rather smaller (94 patients), and the follow-up was shorter (mean 2.4 years), a remarkably similar percentage of patients (39%) in their study were on medication, and despite this, satisfaction with surgery was still high.[4]

A significant difference in gender and age was found between patients on and off medication. This has not been reported before. We have, however, shown in a previous study that male sex is associated with a better long-term outcome after laparoscopic antireflux surgery,[19] and the results of our current study are consistent with our previous finding. In addition, differences in operative details were

Table 5 Patients on Medication for Symptoms that Returned the Same as Preoperative Versus Patients with Symptoms Different to Preoperative Symptoms (n=251)

Factor	Same Symptoms n=97	Different Symptoms n=154	p value
24-h pH Study (%)			0.049
Normal	14 (58)	24 (83)	
Abnormal	10 (42)	5 (17)	
Type of Medication (%)*			
PPIs	87 (90)	118 (77)	0.009
H_2-Blockers	10 (10)	13 (8)	0.617
Antacids	29 (30)	63 (41)	0.078
Response to Medication (%)			0.637
No	9 (9)	8(5)	
Yes and Sometimes	86 (89)	143 (93)	
Not Answered	2 (2)	3 (2)	
Who Advised Medication (%)			0.030
GP	36 (37)	61 (40)	
Surgeon	19 (20)	10 (7)	
Other Specialist	11 (11)	25 (16)	
Yourself	27 (28)	25 (32)	
Unknown	4 (4)	8 (5)	
Use of Medication (%)			<0.001
Daily	77 (79)	72 (47)	
Intermittent	18 (19)	81 (53)	
Not Answered	2 (2)	1 (0)	
Heartburn (%)	77 (79)	113 (73)	0.443
Heartburn Score	4.3±3.1	3.2±2.8	0.007
Chest Pain (%)	57 (59)	90 (58)	0.155
Chest Pain Score	3.4±3.4	2.7±2.9	0.004
Regurgitation (%)	69 (71)	89 (58)	0.004
Regurgitation Score	3.6±3.0	2.5±2.8	0.158
Overall Satisfaction Score	5.8±3.3	7.5±2.3	<0.001

Values are numbers of patients with percentages in brackets. Symptom and satisfaction scores are mean values ± SD (as measured on a scale from 0 to 10)
*More than one answer possible, therefore percentage exceeds 100.

identified between both groups. More patients on medication had a partial fundoplication. This might reflect less control of reflux in patients after an anterior partial fundoplication, when compared to the Nissen fundoplication after long-term follow-up,[6] although this apparent advantage might also be offset by the disadvantage of side effects, which can follow the somewhat overcompetent valve produced by the Nissen fundoplication technique.

The higher rate of reoperations and conversions from laparoscopy to laparotomy in the medication group could arguably indicate a somewhat less than perfect fundoplication was performed initially, and, as a consequence, less control of gastroesophageal reflux was achieved. However, this is speculative, as others have shown that approximately 80% of patients taking medications took these for vague abdominal or chest symptoms unrelated to the original reflux symptoms.[2] Our study shows that 31% of the patients who take antireflux medication have symptoms similar to preoperative symptoms. Furthermore, these patients were more likely to be taking PPIs (and other antireflux drugs) on a daily basis. Although postsurgery 24-hour pH studies were done only in the minority of our study group, 42% of patients who claimed "reflux" symptoms had abnormal esophageal acid exposure. Therefore, this subgroup of patients is more likely to be truly refluxing and, as a consequence, these were the patients who were least satisfied with their original operation.

This underlines the role of esophageal function tests in patients with recurrent reflux symptoms after fundoplication, as it is well-known from the literature that only the minority of these patients have pathological acid exposure.[10,12,20,21] It is therefore important for physicians caring for patients with symptoms after antireflux surgery to realize this and to perform a proper diagnostic workup, rather than just commencing antireflux medications, although the majority of our patients reported that their symptoms improved with medication. To what extent a placebo effect of the medication can explain the reported response of symptoms to medication and the high satisfaction, despite the low rate of abnormal pH studies, is still an open question.[22] Alternatively, perhaps alterations in gastroesophageal physiology, which can follow the creation of a fundoplication, could be responsible for at least some of the postoperative symptoms.[23–25] We also know that patients with gastroesophageal reflux can have associated functional bowel symptoms/disorders, and that these will persist after antireflux surgery. However, these symptoms are reported to be unaffected by antireflux medication.[22,26]

It may be that these patients expected the fundoplication to cure their functional symptoms, because they believed that these symptoms were caused by gastroesophageal reflux. Lastly, one should consider other diagnoses in patients with upper gastrointestinal symptoms after fundoplication. These can include cholelithiasis, peptic ulcer disease, and even coronary artery disease.[12]

One strategy, which can be used to clarify this issue, is to advise patients to stop their antireflux medications, and to determine the effect of this action on the severity of their symptoms. In the study reported by Spechler et al., when patients who had undergone a fundoplication stopped using acid suppressants, their reflux symptom scores were usually unchanged.[27] This further supports the contention that many patients in this study were receiving these medications for unconventional reasons, after an antireflux operation, which continued to prevent gastroesophageal reflux.

Conclusion

Thirty-seven percent of patients in our study were taking antireflux medication after fundoplication. Although many of these patients reported postoperative symptoms, which were suggestive of recurrent reflux, abnormal acid exposure in the distal esophagus was only identified in 26% of these patients, and this suggests that many patients are taking these medications unnecessarily. Physicians (including general practitioners) should be aware of this, and patients who develop symptoms that are suggestive of reflux after a fundoplication should be properly investigated before antireflux medications are prescribed. Strategies need to be employed to reduce the inappropriate use of medications after surgery and to further evaluate the mechanisms underlying postoperative symptoms.

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Improved Surgical Results in Thoracic Esophageal Squamous Cell Carcinoma: A 40-year Analysis of 792 Patients

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Abstract Extensive lymphadenectomy, including upper mediastinum, for thoracic esophageal carcinoma was introduced at the beginning of 1980s. However, the efficacy has not been analyzed in large series at a single institute. We evaluated factors potentially related to improved surgical results in patients with thoracic esophageal squamous cell carcinoma (SCC). From 1959 to 1998, a total of 792 patients with thoracic esophageal SCC underwent R0 surgery. A variety of clinicopathological factors were compared among patients treated from 1990 to 1998 (recent group, $n=164$) and 1959 to 1989 (former group, $n=628$). The recent group showed significantly better survival than the former group (5-year survival rates: 51 versus 17%, $P<0.01$), partly because earlier stage disease was included in the recent group than in the former group. Multivariable analysis, using the Cox regression analysis, indicated the time period of surgery, age, tumor location, the number of positive nodes (>5), venous invasion, and tumor–node–metastasis stage. Upper mediastinum lymphadenectomy was also an independent factor to improve survival of patients with thoracic esophageal SCC.

Keywords Esophageal cancer · Upper mediastinum lymphadenectomy · Long-term survival · Number of positive lymph node

Abbreviations

SCC	squamous cell carcinoma
UMLD	upper mediastinum lymphadenectomy

Based on multivariate analysis of 792 cases during 40-years experience on thoracic esophageal cancer surgery at Chiba University Hospital, upper mediastinum lymphadenectomy was found to be one of the independent prognostic factors to improve patient's overall survival.

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Introduction

During the last 40 years, surgeons have had the primary responsibility for treating thoracic esophageal cancer. Subtotal esophagectomy with extended lymphadenectomy, such as upper mediastinum lymphadenectomy (UMLD) or three-field lymphadenectomy, were introduced to improve long-term survival after surgery.[1–3] However, there were no large series (more than 500 patients) at a single institute that investigated the impact of mode of lymphadenectomy.

Because only patients who received R0 resections according to the tumor–node–metastasis/Union International contre le Cancer (TNM/UICC) classification[4] would benefit from such aggressive surgery, the impact of lymphadenectomy should be evaluated in those patients who were treated with R0 resections. Because 97% of our series involved squamous cell carcinoma (SCC), we focused on patients with thoracic esophageal SCCs. Several reports have addressed the impact of the time period of surgery on long-term survival after surgery.[5–7] However, only a few studies have addressed the prognostic factors, including time period of surgery, in a multivariate analysis during a time period greater than 15 years.

Therefore, we designed this study to determine which factors, other than the time period of surgery, were associated with improved long-term survival. We analyzed a 40-year consecutive series of 792 patients with thoracic esophageal SCCs curatively resected at a single institute to evaluate the impact of mode of lymphadenectomy on long-term survival.

Patients and Methods

Study Population and Manner of Lymphadenectomy

From 1959 through 1998, 1,155 patients with primary thoracic esophageal carcinoma were surgically treated at the Department of Surgery, Chiba University Hospital. A total of 816 patients received an R0 operation. Among them, a total of 792 patients revealed SCC and have been followed for at least 5 years after surgery. The survival curves were compared among these patients during each decade, and then two subgroups were compared: recent group (from 1990 to 1998, $n=164$) and former group (1959 to 1989, $n=628$).

We started UMLD and/or three-filed lymphadenectomy at 1983 as a pilot study. Then, we systemically adjusted indication for three-field lymphadenectomy in the late 1980s based on surgical outcome of the pilot study. Among 792 patients, three-field lymphadenectomy (cervical, mediastinal, and abdominal lymphadenectomy)[1–3] were performed in 186 patients, and two-field lymphadenectomy (mediastinal and abdominal lymphadenectomy) were performed in 606 patients. All of the 186 patients who underwent three-field lymphadenectomy received UMLD. Among the 606 patients who underwent two-field lymphadenectomy, 53 patients underwent UMLD to remove the paratracheal lymph nodes along and around the recurrent nerve. Therefore, a total of 239 patients underwent UMLD.

After surgery, pathological TNM (pTNM)/UICC classification[4] was determined for each patient by pathological examination as follows: 57 stage I, 283 stage II, 271 stage III, and 181 stage IV. The study patients consisted of 686 men (87%) and 106 women (13%) with a mean age of 62 years (range: 33 to 88). All patients underwent clinical examination and imaging studies on a regular basis until death or for at least 60 months after surgery. A total of 604 patients died within 5 years after surgery. Preoperative adjuvant therapy was administered as follows: 321 patients received radiation therapy, 26 patients received chemotherapy, and 141 patients received chemoradiation therapy. As to which of these modalities was used depended on protocols of the Japan Esophageal Oncology Group (a group that conducted four consecutive randomized controlled trials after 1980).[8–10] Before 1980, preoperative radiation therapy was usually undertaken for clinical T2–T4 tumors.[11,12]

Surgical Techniques

The standard procedure for performing a mediastinal lymphadenectomy was described previously.[2,3,5,6] In brief, each patient underwent a right fourth or fifth intercostal thoracotomy. The arch of the azygous vein was resected, and the right bronchial artery was reserved. The tumor-bearing esophagus was resected en bloc within an envelope of adjoining tissues that included both pleural surfaces laterally, the pericardium anteriorly and all lymphovascular tissues wedged dorsally between the esophagus and the spine. The thoracic duct was included with the en bloc resection throughout its course in the posterior mediastinum in the case with T3 and T4. The brachiocephalic and right subclavian arteries were exposed to remove the bilateral recurrent nerve nodes and paratracheal nodes. The left recurrent nerve was exposed from the level of the aortic arch to the thoracic inlet. After carefully ligating the branches of the inferior thyroid artery, the esophagus was transacted proximally 2 cm below the right subclavian arteries. The middle mediastinal nodes, comprised of the infra-aortic, infracarnial, and paraesophageal nodes, were removed in conjunction with the esophagus; this resection resulted in exposure of the mail bronchus, the left pulmonary artery, branches of the vagus nerves, and the pericardium. Although the esophageal branches of the vagus nerves were resected, the pulmonary branches of the bilateral vagus nerves were reserved.

For three-field lymphadenectomy, we performed each bilateral neck lymphadenectomy through a U-shaped cervical incision. The remainder of the recurrent nerve nodes were located posterior and lateral to the carotid sheath. Thus, the cervical lymph nodes included a continuous, anatomically inseparable chain of nodes that extended from the superior mediastinum to the lower neck. The sternomastoid and strap muscle were preserved, and the cervical nodes (internal jugular nodes below the level of the cricoid cartilage, supraclavicular nodes, and cervical paraesophageal nodes) were removed bilaterally.

Preoperative Staging Techniques

Standard staging techniques from 1959 to 1979 were limited to esophagography and an esophagoscope. After 1980, standard staging techniques included endoscopic ultrasonography, computed tomography, and neck ultrasonography. After 1990, positron emission tomography was introduced for patients with advanced tumors to screen for distant metastases or to predict malignant potential.[13] We have not performed thoracoscopy nor laparoscopy.

Perioperative Care and Definition of Postoperative Complications

The anesthesia, operative procedure of esophagectomy with three-field lymphadenectomy, and postoperative care of esophageal cancer surgical patients were standardized in our department after 1980, as previously described.[14–16] The patients were postoperatively admitted to the intensive care unit of Chiba University Hospital, and initial postoperative care was provided.

Statistical Analyses

Because we systemically adjusted indication for three-field lymphadenectomy in late 1980s, 1990 was an appropriate point to divide the 40-year duration of this patient series. Thus, we divided into two periods, 1990 to 1998 and 1959 to 1989, to compare the mode of surgical treatment and several other clinicopathological variables related to long-term survival. All patients' outcomes were evaluated at the end of 2003, and survival curves were calculated based upon deaths of any causes. All patients have undergone surgery before the end of 1998 such that would have been followed at least 5 years after surgery. Survival probabilities were calculated by the product-limit method of Kaplan and Meier. Survival differences between the groups were evaluated using the log-rank test. Fisher's exact test was applied to determine the significant differences of the studied clinicopathological features between the two groups. The association of each clinicopathological variable with survival was assessed by Cox's proportional hazards model. Because tumor depth and nodal status were strongly associated with stage, these two factors were excluded from multivariate analysis.

All statistical analyses were carried out using Stat View 5.0 for Windows (SAS Institute, Cary, NC). Comparisons were considered to be statistically significant if the two-sided P values were less than 0.05.

Results

Survival According to pTNM Stage or Time Period of Surgery

Among all 792 patients, overall in-hospital mortality rate was 7.6%. A total of 604 patients died within 5 years after surgery. Follow-up evaluations revealed tumor recurrence in 498 patients, and a total of 436 patients died within 5 years after surgery because of tumor recurrence. The 5-year overall survival according to pTNM stages were 79% at stage I, 33% at stage II, 13% at stage III, and 10% at stage IV, respectively.

The survival curves (according to time period of surgery) were compared for patients treated in each decade (Fig. 1a). The 5-year overall survival rates in each decade were 51, 20, 16, and 15%, respectively. The patients treated during 1990 to 1998 showed significantly better survival than the other groups. However, there was no significant survival difference between the groups treated from 1959 to 1989. Therefore, the clinicopathological factors were compared between the recent group (1990 to 1998) and the former group (1959 to 1989) in further analysis (Fig. 1b).

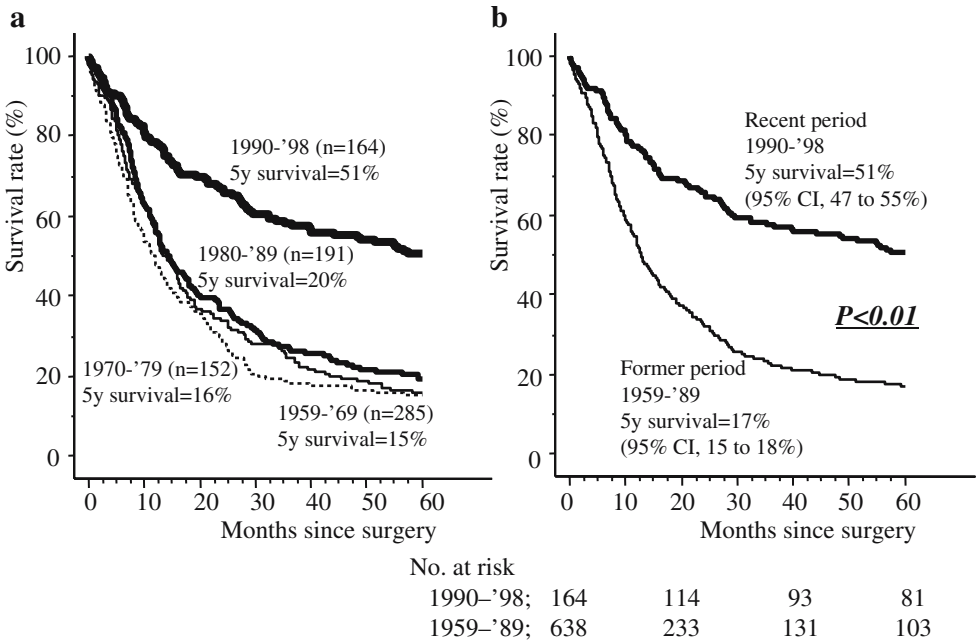

Figure 1 Over-all Kaplan–Meier survival of 792 patients with thoracic esophageal carcinoma according to time period of surgery. **a** Overall survival in each decade. Log-rank P values were $P<0.01$ (1990–1998 versus 1980–1989, 1970–1979, and 1959–1969), $P=0.39$ (1980–1989 versus 1970–1979), $P=0.28$ (1970–1979 versus 1959–1969), and $P=0.03$ (1980–1989 versus 1959–1969). **b** Overall survival in two time period. Log-rank P values were $P<0.01$.

Table 1 Comparison of Clinicopathological Features in 792 Patients with Thoracic Esophageal Squamous Cell Carcinoma According to Time Period of Surgery

Variables (Total Number of Patients)		Recent Group (1990–1998; n=164; %)	Former Group (1959–1989; n=628; %)	P Value[a]
Gender	Male (686)	141 (86)	545 (87)	0.71
	Female (106)	23 (14)	83 (13)	
Age (years)	<65 (486)	88 (54)	398 (63)	0.02
	≥65 (306)	76 (46)	230 (37)	
Tumor location	Upper (93)	24 (15)	69 (11)	0.35
	Lower (699)	140 (85)	559 (89)	
Tumor depth	T1T2 (197)	82 (50)	115 (18)	<0.01
	T3T4 (595)	82 (50)	513 (82)	
N factor	N0 (342)	68 (41)	274 (44)	0.66
	N1 (450)	96 (59)	354 (56)	
Number of node	0–4 (672)	125 (76)	547 (87)	<0.01
	≥5 (120)	39 (24)	81 (13)	
Venous invasion	(−) (403)	68 (41)	335 (53)	<0.01
	(+) (389)	96 (59)	293 (47)	
UICC/Stage Stage	I and II (340)	94 (57)	246 (39)	<0.01
	Stage III and IV (452)	70 (43)	382 (61)	
UMLD[b]	(+) (239)	133 (81)	106 (17)	<0.01
	(−) (553)	31 (19)	522 (83)	
Hospital mortality	(60)	8 (5)	52 (8)	0.18

[a] Two-tailed Fisher's exact probability
[b] Upper mediastinal lymphadenectomy

Clinicopathological Comparisons Between the Recent Group and the Former Group

Among all clinicopathological variables, more elderly patients, less invasive tumors, more positive nodes, more lymphatic invasion, and less advanced stage disease were noted in the recent group than in the former group (Table 1). UMLD was performed more frequently in the recent group than in the former group. The in-hospital mortality rates were similar in both groups.

The overall survival was significantly better in the recent group than in the former group (5-year survival rate, 51 versus 17%, P<0.01; Fig. 1b). We also compared overall survival among patients with pT1T2 tumors. The recent group showed significantly better survival than the former group (5-year survival rate, 71 versus 39%, P<0.01; Fig. 2a). Among patients with pT3T4 tumors, a similar tendency was observed (5-year survival rate, 30 versus 12%, P<0.01; Fig. 2b).

When we focus on patients with pN0 tumors, the overall survival of the recent group was significantly better than

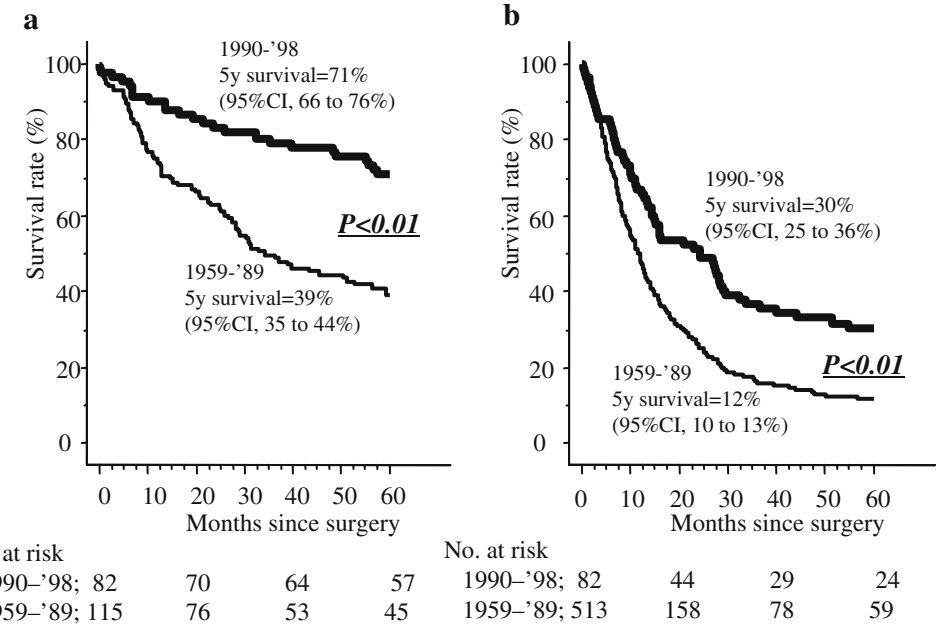

Figure 2 Over-all Kaplan–Meier survival of patients with pT1T2 tumors or pT3T4 tumors according to tumor depth. **a** *Thick lines* indicate survival curves of patients with pT1T2 tumors. **b** *Thin lines* indicate the survival curves of patients with pT3T4 tumors. P values were calculated by log-rank test.

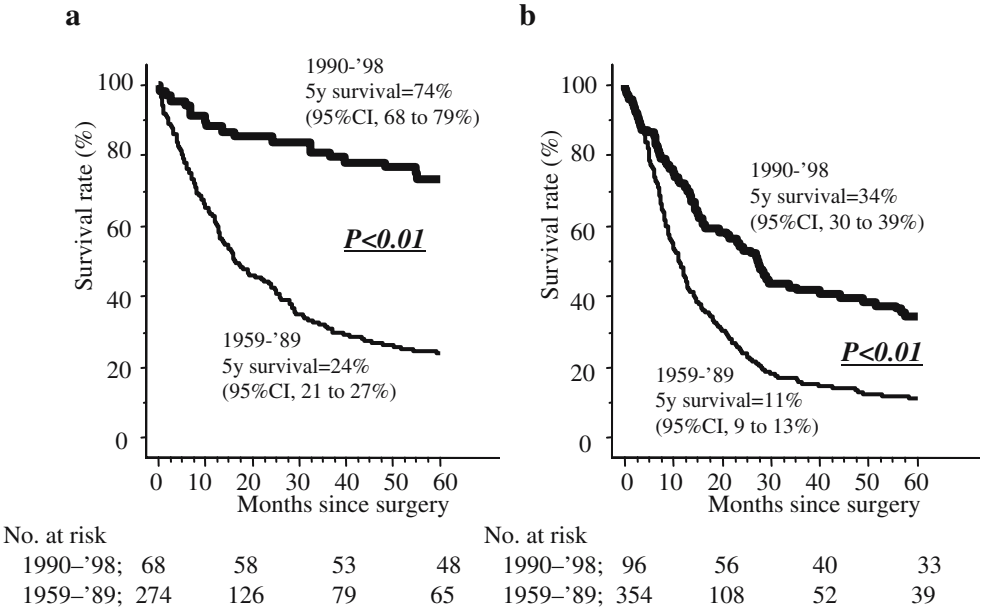

Figure 3 Overall Kaplan–Meier survival of patients with or without lymph node metastases according to time period of surgery. Survival curves of pN0 patients (**a**) and pN1 patients (**b**). *Thick lines* indicate survival curves of recent group, and *thin lines* indicate survival curves of former group. *P* values were calculated by log-rank test.

that of the former group (5-year survival rate, 74 versus 24%, $P<0.01$; Fig. 3a). Among patients with pN1 tumors, a similar tendency was observed (34 versus 11%, $P<0.01$; Fig. 3b). We also compared overall survival among patients with stage I and II tumors. The recent group showed better survival than the former group (5-year survival rate, 70 versus 30%, $P<0.01$; Fig. 4a). Among patients with stage III and IV tumors, the recent group showed better overall survival than the former group (5-year survival, 24 versus 8%, $P<0.01$; Fig. 4b).

Because the recent group received UMLD more frequently than the former group, we compared overall survival among patients with pT1T2 tumors according to the presence of UMLD. UMLD(+) showed significantly better survival than UMLD(−) (5-year survival rate, 64 versus 44%, $P=0.02$; Fig. 5a). Among patients with pT3T4 tumors, a similar tendency was observed (18 versus 13%, $P=0.03$; Fig. 5b). We also compared overall survival among patients with pN0 tumors between presence or absence of UMLD. UMLD(+) showed significantly better survival than UMLD(−) (5-year survival rate, 55 versus 28%, $P<0.01$; Fig. 6a). Among patients with pN1 tumors, a similar tendency was observed (24 versus 11%, $P<0.01$; Fig. 6b). We also compared overall survival among patients with stage I and II tumors. UMLD(+) showed better survival than UMLD(−) (5-year survival rate, 58 versus 35%, $P<0.01$; Fig. 7a). Among patients with stage III and IV tumors, UMLD(+) showed better overall survival than UMLD(−) (5-year survival, 19 versus 8%, $P<0.01$; Fig. 7b).

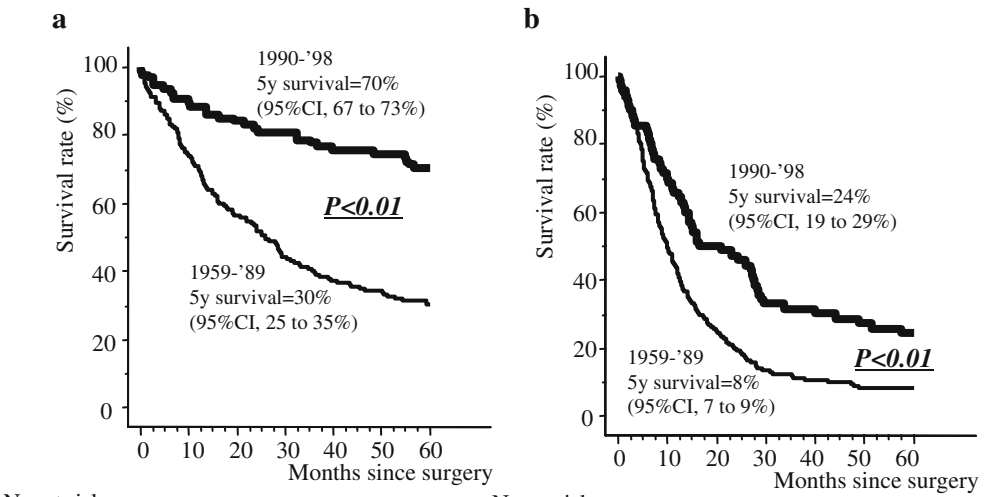

Figure 4 Overall Kaplan–Meier survival of patients with stage I and II or stage III and IV according to time period of surgery. Survival curves of stage I and II patients (**a**) and stage III and IV patients (**b**). *Thick lines* indicate survival curves of recent group, and *thin lines* indicate survival curves of former group. *P* values were calculated by log-rank test.

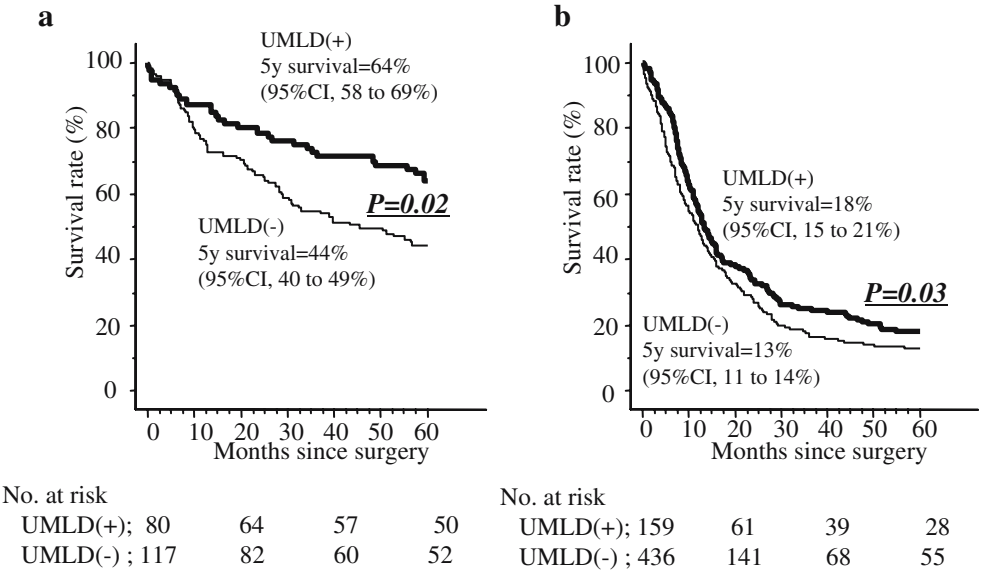

Figure 5 Overall Kaplan–Meier survival of patients with T1T2 tumors or T3T4 tumors according to presence of UMLD. Survival curves of pT1T2 patients (**a**) and pT3T4 patients (**b**). *Thick lines* indicate the survival curves of patients who underwent UMLD, and *thin lines* indicate the survival curves of patients who did not undergo UMLD. *P* values were calculated by log-rank test. *UMLD* upper mediastinal lymphadenectomy.

Univariable and Multivariable Analysis for Prognostic Variables

In univariate analysis, nine of ten variables were significantly associated with improved overall survival, including the time period of surgery and the performance of UMLD (Table 1). To further evaluate the effect of these variables upon survival, multivariate analysis using the Cox proportional hazards model was performed using all variables in univariate analysis except tumor depth and N factor (Table 2). The time period of surgery, age, tumor location, tumor depth, nodal status, number of positive node, venous invasion, stage, and performance of UMLD were identified as significant factors associated with overall survival.

Discussion

The long-term survival of patients with thoracic esophageal carcinoma remains poor because of the high incidence of lymph node metastases and early recurrences after attempted curative surgery. Although the mortality rate of radical esophagectomy is less than 5%, the 5-year survival rate is still less than 40% in Japan.[17] Although various clinicopathologic prognostic factors were examined to explore the appropriate extent of lymphadenectomy for advanced esophageal cancer, very few studies analyzed the mode of lymphadenectomy with "the time period of surgery."[18–20]

At the time of first analysis, we evaluated the patients for possible improvements in long-term survival according to

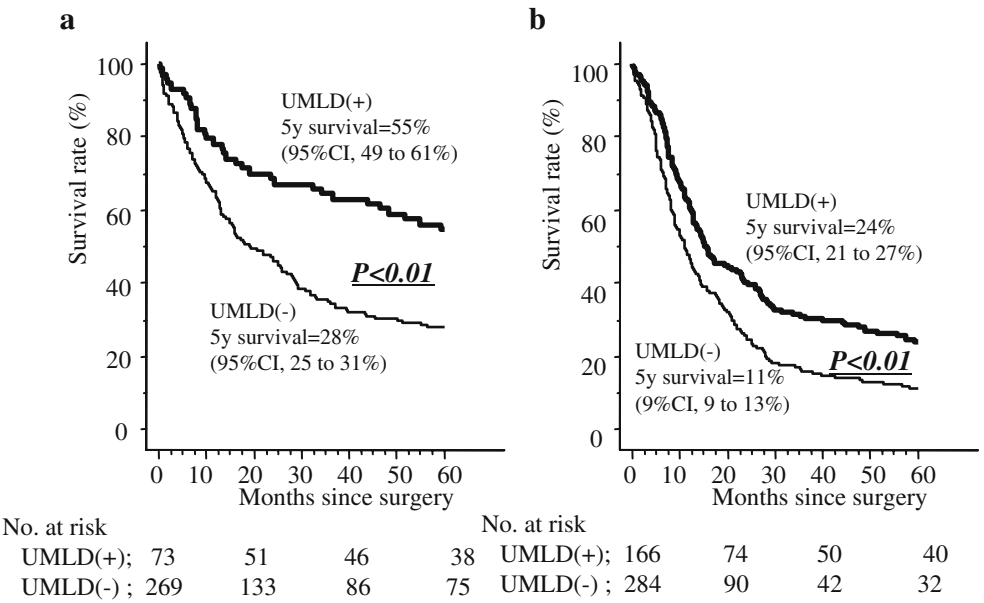

Figure 6 Overall Kaplan–Meier survival of patients with or without lymph node metastases according to the mode of lymphadenectomy. Survival curves of pN0 patients (**a**) and pN1 patients (**b**). *Thick lines* indicate the survival curves of patients who underwent upper mediastinal lymphadenectomy, and *thin lines* indicate the survival curves of patients who did not undergo upper mediastinal lymphadenectomy. *P* values were calculated by log-rank test. *UMLD* upper mediastinal lymphadenectomy.

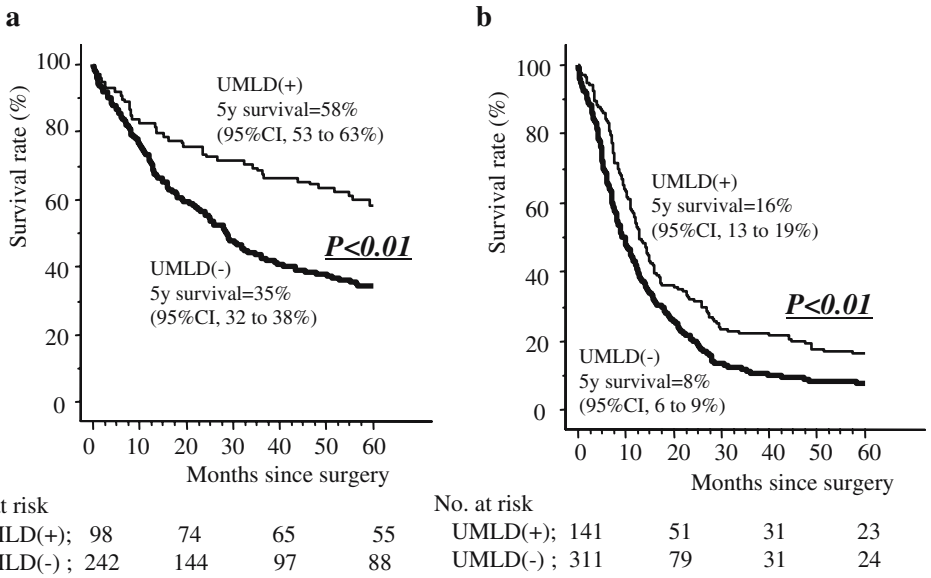

Figure 7 Overall Kaplan–Meier survival of patients with stage I&II or stage III&IV according to the mode of lymphadenectomy. Survival curves of stage I and II patients (**a**) and stage III and IV patients (**b**). *Thick lines* indicate the survival curves of patients who underwent upper mediastinal lymphadenectomy, and *thin lines* indicate the survival curves of patients who did not undergo upper mediastinal lymphadenectomy. *P* values were calculated by log-rank test. *UMLD* upper mediastinal lymphadenectomy.

the time period of surgery. The long-term survival rates were very similar during the three decades from 1959 to 1989. However, the survival rates significantly improved in the last decade of 1990 to 1998 compared to the previous decades. We started upper mediastinal lymphadenectomy and/or three-filed lymphadenectomy at 1983 as a pilot study. Then, we systemically adjusted indication for three-field lymphadenectomy in late 1980s based on surgical outcome of a pilot study. Therefore, we determined that 1990 was a good point to divide such long-term series of patients to evaluate impact of the mode of lymphadenectomy. Therefore, we divided our analysis into two time periods: recent group (1990 to 1998) and former group (1959 to 1989). We compared each of the clinicopathological factors combined with the mode of lymphadenectomy. Ando et al.[7] previously reported that improvement in the surgical treatment results of advanced esophageal carcinoma was mainly because of advanced surgical techniques and perioperative management.

UMLD was introduced in our department at the beginning of 1980s, and three-field lymphadenectomy was introduced for patients during the mid-1980s.[1] The most

Table 2 Univariate and Multivariate Analysis for Overall Survival in 792 Patients with Thoracic Esophageal Squamous Cell Carcinoma

Variables (Total Number of Patients)		Overall 5-Year Survival Rate (%)	Univariate *P* Value[a]	Multivariate *P* Value[b]	Adjusted Hazard Ratio (Adjusted 95% CI)
Time period of surgery	1959–1989	17	<0.01	<0.01	2.38 (1.78–3.17)
	1990–1998	51			
Gender	Male	23	0.01	0.08	1.33 (1.02–1.74)
	Female	32			
Age (years)	≥65	23	0.19	<0.01	1.29 (1.08–1.54)
	<65	25			
Tumor location	Upper	16	0.02	<0.01	1.69 (1.31–2.18)
	Lower	26			
Tumor depth	T3T4	13	<0.01	Not included	Not included
	T1T2	52			
N factor	N1	16	<0.01	Not included	Not included
	N0	34			
Number of node	≥5	5	<0.01	<0.01	1.66 (1.29–2.14)
	0–4	29			
Venous invasion	(+)	12	<0.01	<0.01	1.64 (1.36–1.98)
	(−)	35			
UICC/stage	Stage III and IV	10	<0.01	<0.01	2.04 (1.67–2.49)
	Stage I and II	41			
UMLD	(−)	20	<0.01	0.04	1.27 (1.02–1.59)
	(+)	34			

[a] Log-rank test
[b] Cox regression analysis

important aspect of these surgical techniques was to remove thoracic paratracheal lymph nodes along the bilateral recurrent nerve. Although pathological lymph node staging can depend on the extent of lymphadenectomy (so-called stage migration), the impact of tumor depth on long-term survival may be similar between the two time periods. Because pT4 tumors were more frequently observed in the former group than in the recent group (data not shown), the improvement in 5-year survival in patients with pT3T4 tumors could be partially explained by the distribution of pT4 tumors. Therefore, we also compared the 5-year survival rates among patients with pT1T2 tumors. An almost 30% improvement was observed in the overall 5-year survival rate among these patients, which could be explained mainly by the difference in the mode of lymphadenectomy and perioperative management. Even when divided into two group, stage I and II and stage III and IV, the recent group still showed significantly better survival than former group in each subgroup.

A total of 181 patients classified as stage IV in this present series included the patients with cervical lymph nodes or celiac lymph nodes. Although these lymph nodes were classified as distant metastases in the UICC staging system,[4] some patients with these lymph nodes survived more than 5-years in Japanese series.[21] Therefore, the Japanese guidelines for clinical studies of carcinoma of esophagus (ninth edition) did not classify these lymph nodes as distant metastases. Because quite a few patients had unresectable tumors invading into adjacent organs at the time of surgery between 1959 and 1979, these patients underwent non-curative operations and were excluded from this current study.

In terms of adjuvant therapy, neither preoperative radiation therapy nor chemotherapy demonstrated a survival benefit in this series (data not shown). However, the latest randomized trial of the Japan Esophageal Oncology Group, which included part of our series, surgery plus postoperative chemotherapy (*cis*-diamminedichloroplatinum [CDDP]+5-fluoruracil) improved disease-free survival in node-positive patients.[22] Therefore, the recent group more frequently received postoperative chemotherapy that consisted of CDDP than the former group. These differences may have partly contributed to the improvement in survival of recent group.

The cut-off point for the number of metastatic nodes affecting survival after extensive lymphadenectomy is reported to be between 5 and 8. Clark et al.[19] documented that patients with less than five metastatic nodes had a significant survival advantage after en bloc esophagectomy for carcinomas of the lower esophagus and cardia. Baba et al.[6] reported that patients with six or more metastatic nodes after a three-field approach had a poor prognosis with a 5-year survival of only 7.2%. Igaki et al.[20] also reported that the number of positive lymph nodes had the strongest impact on survival in patients with clinical T1 and T2 SCCs of the thoracic esophagus. In the present series, among 103 patients with five or more positive nodes, only eight (8%) and five (5%) were alive for more than 3- and 5-years after surgery, respectively. Such subgroups should be treated as systemic disease and be managed by multimodality therapy.

Because the present study was retrospective during four decades, several clinical factors other than analyzed factors could be associated with improvement of long-term survival. These include adjuvant treatment after recurrence, the introduction of CDDP, the quality of postoperative care, and the management of noncancer disease. However, these clinical factors might be evaluated in a multivariate that included "time period of surgery." The improvements in overall survival may be related both to advancements in the mode of lymphadenectomy and perioperative management.

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Pancreaticoduodenectomy in a Latin American Country: The Transition to a High-Volume Center

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Abstract

Objective To analyze data in a single institution series of pancreaticoduodenectomies (PD) performed in a 7-year period after the transition to a high-volume center for pancreatic surgery.

Background PD has developed dramatically in the last century. Mortality is minimal yet complications are still frequent (around 40%). There are very few reports of PD in Latin America.

Methods Data on all PDs performed by a single surgeon from March 2000 to July 2006 in our institution were collected prospectively.

Results During the study's time frame 122 PDs were performed; 84% were classical resections. Mean age was 57.9 years. Of the patients, 51% were female. Intraoperative mean values included blood loss 881 ml, operative time 5 h and 35 min, and vein resection in 14 cases. Both ampullary and pancreatic cancer accounted for 34% of cases (42 patients each), 5.7% were distal bile duct and 4% duodenal carcinomas. Benign pathology included chronic pancreatitis, neuroendocrine tumors, cystic lesions, and other miscellaneous tumors. Overall operative mortality was 6.5% in the 7-year period, 2.2% in the later 5 years. There was a total of 75 consecutive PDs without mortality. Of the patients, 41.8% had one or more complications. Mean survival for pancreatic cancer was 22.6 months and ampullary adenocarcinoma was 31.4 months.

Conclusion To our knowledge, this is the largest single surgeon series of PD performed in Latin America. It emphasizes the importance of experience and expertise at high-volume centers in developing countries.

Keywords Pancreaticoduodenectomy · Whipple · Latin America

Introduction

Although there is record of surgical treatment for periampullary cancer since 1899 in the United States [1], it is not until recently that it has become a reasonable alternative in terms of morbidity, mortality, and quality of life. The treatment of periampullary neoplasias has evolved from the early transduodenal ampullary resections performed in the late 1800s to its golden era in the present time where some referral centers perform over 200 pancreaticoduodenectomies (PD) a year with excellent results.

There are very few published reports on PD in Latin America. After extensive research in Medline, less than 30 articles regarding this subject in Latin American countries were found, most of which were reviews or case reports, some as early as 1955.[2] Only eight articles reporting hospital experience were found.

In Mexico, as in other developing countries, pancreatic resections are still performed in an isolated manner by general surgeons in the few cases where periampullary tumors are detected in time. With the introduction of hepatopancreatobiliary surgery in our country in the late 1990s and the knowledge of better outcomes in high-volume centers [3,4], the tendency to refer such patients to specialized centers for an

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adequate diagnostic approach, treatment, and follow-up are increasing.

Herein, we report the results of PD by our group after the transition to a high-volume center.

Patients and Methods

From March 2000 to July 2006, data were collected in a prospective manner on all patients on whom PD was performed by the author and his group.

The surgical technique preferred in our institution is simplified in the next ten steps. (1) A midline incision. (2) Mobilization of the duodenum and head of the pancreas (Kocher maneuver) and manual identification of the superior mesenteric artery to rule out arterial invasion. (3) Cholecystectomy and identification of the common bile duct. (4) Division of the common bile duct, gastroduodenal artery ligature, and portal vein identification. (5) Antrectomy. (6) Superior mesenteric vein identification and separation of the superior mesenteric vessels from the neck of the pancreas from bottom to top (creation of a tunnel). (7) Mobilization/division of the proximal jejunum 10 cm from the angle of Treitz, section of the mesentery, and liberation of the angle of Treitz. (8) Mobilization of the jejunum toward the right under the superior mesenteric vessels. (9) Section of the neck of the pancreas and uncinate process with ligature of tributary vessels of the superior mesenteric-portal vein and the superior mesenteric artery. (10) Pancreaticojejunal anastomosis, hepaticojejunal anastomosis, gastrojejunal anastomosis. This particular order may be altered in specific cases.

Preference biases of our institution include: (1) Classical resection over pylorus preserving resection. (2) A standard PD without extended retroperitoneal lymph node dissection is the procedure of choice. (3) The body and tail of the pancreas are resected only if there is tumor extension. (4) The pancreaticojejunostomy is the pancreatic–enteric anastomosis of choice. (5) Total parenteral nutrition and prophylactic octreotide were not used routinely. (6) Jackson–Pratt drains are routinely used.

Variables were evaluated using the following definitions. Hospital stay was defined as the length of hospitalization starting from the day of surgical intervention. Delayed gastric emptying was defined as the failure to maintain oral intake by postoperative day 7 or the need for postoperative gastric decompression for more than 7 days. Pancreatic fistula was defined as persistent drainage of ≥50 ml of amylase-rich fluid after postoperative day 7. A newer definition for pancreatic fistula, according to the IPGPF [5], was recently adopted by our institution but was not available at the beginning of this study. Mortality was defined as death during hospitalization or within the 30 days from the date of resection. Intraabdominal abscess was defined as a collection of fluid demonstrated by abdominal CT scan with purulent material drained percutaneously or surgically. Bleeding is defined as postoperative hemorrhage requiring reoperation. Bile leak is defined as drainage of fluid with elevated bilirubin levels from intraoperative placed drains or demonstrated in peripancreatic collections. Standard definitions were used for other variables such as pneumonia.

Final pathology reports were reviewed to determine the primary pathology and extent of disease. Frozen section was performed in all cases. Important definitions regarding pathology reports include: (1) Resection margins were considered positive if neoplasm was present in the pancreatic neck, uncinate, bile duct or "other" (which included duodenal and retroperitoneal soft tissue margins). (2) Margins were considered positive only when the final pathological review deemed it so, regardless of frozen section results that could have been positive before further resection was done. (3) In malignant lesions, lymph nodes were considered positive if any lymph node in the resected specimen contained tumor.

In the time frame of this study, patients with pathologic diagnosis of periampullary adenocarcinoma (e.g., pancreas, distal common bile duct [cholangiocarcinoma], ampullary or peri-Vaterian duodenal primaries) were evaluated by a multidisciplinary group (surgery, internal medicine, medical oncology, and pathology) to determine the best treatment after surgery. Despite controversy, the most common modality of treatment after surgery includes chemotherapy and radiotherapy. At present there are no specific protocols on neoadjuvant therapy for periampullary tumors up and running in our institution.

Patients' follow-up was obtained via office records or telephone contact. Patient demographics, intraoperative factors, pathologic findings, and postoperative course were recorded. For survival analysis, the Kaplan–Meier method was employed. Differences in survival between subsets were compared using log–rank test. Data are expressed as mean±standard deviation.

Results

From March 2000 to July 2006, a total of 122 pancreaticoduodenectomies were performed by a single surgeon. The distribution of surgery and main diagnosis per year are shown in Fig. 1. Table 1 shows the demographic and intraoperative characteristics. There were more women than men in the study, 51.7% and 48.3% respectively. Mean blood loss was 881 ml. The mean intraoperative transfusion rate was 1.69 U of red blood cells with a median of 1 U. In our institution, units of red blood cells do not contain a standard volume and usually contain around 250 ml. Mean operative time was 5 h and 35 min. Figure 2 shows a histogram of the distribution of age in resected patients with a

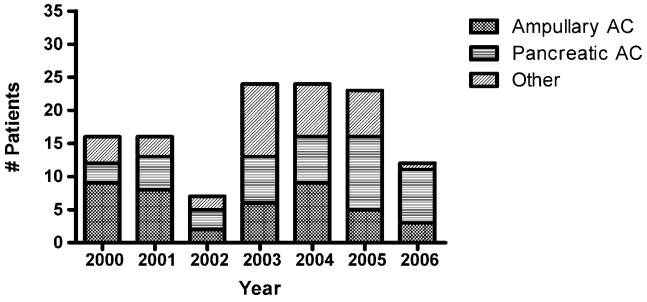

Figure 1 Pancreaticodoudenal resections.

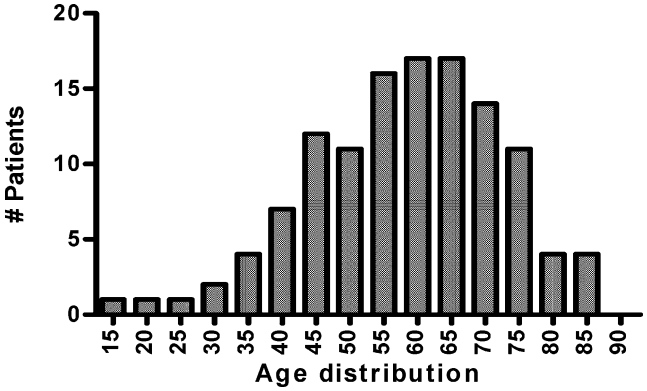

Figure 2 Pancreaticodoudenectomies.

range of 17–87 and a mean of 57.9 years. Most resections, 103 cases, were classic Whipple procedures. All pancreatic anastomosis were performed with a duct to mucosa pancreaticojejunostomy. Fourteen patients underwent vein resection because of partial invasion of the superior mesenteric or portal vein, two cases required synthetic grafting (one using Dacron and one using Gore-Tex), an autologous jugular vein graft was used in one case, and the rest were corrected with primary closure.

Table 2 shows the final pathologic diagnosis of the surgical specimens. The most common diagnosis was adenocarcinoma in over 80.3% of patients. Both pancreatic duct adenocarcinoma and ampullary adenocarcinoma accounted for 34.4%, distal bile duct 5.7%, and duodenal adenocarcinoma 4.0%. The most common benign lesion diagnosed was chronic pancreatitis (8.2%). Other diagnosis included cystic lesions and neuroendocrine tumors. Miscellaneous lesions included two metastasis from renal cell carcinoma, one from gallbladder cancer, five solid and papillary tumors, one pancreatoblastoma, and one pseudocyst.

Pathologic characteristics for the four main types of periampullary neoplasias are detailed in Table 3. Data from duodenal and distal bile duct adenocarcinoma have less statistical strength because of the small *N* value. Mean tumor size was greater for duodenal carcinoma followed by pancreatic cancer. Bile duct tumors had the smallest diameter (two of them were diagnosed in situ). The majority of tumors were moderately differentiated. Positive margin status was higher in pancreatic cancer and lower in duodenal cancer. Out of the 18 patients with pancreatic adenocarcinoma and positive margin status, 3 had a positive margin in the pancreatic neck, 4 had a positive uncinate process margin, 3 had a positive bile duct margin, and 12 were classified as "other" having a positive retroperitoneal soft tissue margin. Margin status in ampullary adenocarcinoma was high compared to other series. From a total of 12 cases with ampullary adenocarcinoma and positive margin status, 10 were classified as "other" (most being retroperitoneal soft

Table 1 Patient Characteristics and Operative Description

	Number	Percent
Number of pancreaticoduodenectomies	122	100
Demographics		
Age		
Mean (years)	57.9	
Median (years)	58.5	
Range	17–87	
Gender		
Male	59	48.3
Female	63	51.7
Intraoperative factors		
Blood loss		
Mean (ml)	881	
Median (ml)	600	
Transfusions		
Mean (U)	1.69	
Median (U)	1	
Operative time		
Mean (h:min)	5:35	
Median (h:min)	5:25	
Type of resection		
Classic	103	84.4
Pylorus-preserving	19	15.6
Vein resection		
Yes	14	11.4
No	108	88.6

Table 2 Final Pathologic Diagnosis of the Surgical Specimens

Pathology	Number (%)
Periampullary adenocarcinoma	
Pancreatic	42 (34.4)
Ampullary	42 (34.4)
Distal bile duct	7 (5.7)
Duodenal	5 (4.0)
Other	
Chronic pancreatitis	10 (8.2)
Neuroendocrine tumor	3 (2.5)
Cystic lesions	3 (2.5)
Miscellaneous	10 (8.2)

Table 3 Pathologic Characteristics for the Four Main Types of Periampullary Neoplasias

	Pancreatic	Ampullary	Distal bile duct	Duodenal
Tumor diameter (cm)				
Mean	2.87	2.27	1.85	5.0
Median	2.45	2.4	2.5	3.6
Tumor differentiation (%)				
Well	11	23	0	0
Moderate	71	54	57	40
Poor	18	23	43	60
Margin status (%)				
Negative	53	71	72	80
Positive	47	29	28	20
Node status (%)				
Negative	33	45	28	75
Positive	66	55	72	25

tissue), 5 were positive in the uncinate process, and 2 in the distal bile duct. Some cases had more than one positive margin. Positive node resections were highest in bile duct and pancreatic adenocarcinoma, and lowest in duodenal adenocarcinoma. The pathology of less common tumors was not analyzed because of the small number of specimens.

Overall operative mortality was 6.5% in the 7-year time period. In the 2002–2006 5-year period, only two patients died representing 2.2%. The last death within 30 days of operation was registered in April 2003 totaling 75 consecutive PDs without mortality in this series. Mortality was absent in patients operated for benign disease. Of the patients, 58.2% had no complications and 41.8% had one or more. The most common complications were the delay in gastric emptying and pancreatic fistula both present in 16 patients (13.1%). Other complications are depicted in Table 4. A total of 14 patients were reoperated mostly because of intraabdominal collections, abscesses or anastomotic dehiscence (9 patients) and the rest because of bleeding (5 patients). The mean postoperative length of stay was 14.1 days with a range of 5–54 days.

The mean follow-up of patients without 30-day mortality was 18 months, with a median of 14.1 months, and a range of 0.7–67 months. The mean survival for the entire series was 41.9 months (IC 35.1–48.8) with a median of 44.3. Actuarial survival at 1, 2, and 3 years in this series was 65, 59, and 46, respectively. Survival is clearly dependant on histopathology as is seen in the five major pathologic diagnoses of our series. Only cases with pancreatic and ampullary tumors are depicted in the survival curves in Fig. 3 as neither duodenal cancer, distal bile duct nor chronic pancreatitis have had mortality during follow-up. In this series, the mean survival after PD in patients with pancreatic cancer is 22.6 months. Mean survival for ampullary adenocarcinoma was 31.4 months. No patients with either cholangiocarcinoma, carcinoma of the duodenum or chronic pancreatitis have died during follow-up and so have not reached their median survival.

Discussion

Halsted was the first to perform surgery for ampullary adenocarcinoma in 1898. PD is frequently linked with Whipple [6] who popularized the procedure in the 1930s, yet the first successful pancreaticoduodenal resection is attributed to Kausch.[7] This German surgeon reported the operation almost 20 years before Whipple performed his two-stage procedure. Soon after it was performed in a one-stage procedure, PD was done sporadically in various places in the United States and Europe during the following five decades with high mortality and morbidity just like Whipple had experienced in the 1930s. After the 1980s, pancreaticoduodenal resection became increasingly popular in referral centers throughout the United States, Europe, and some countries in Asia.[8–14] There are now surgeons (Cameron and Hanyu) who are recognized for having performed 1,000 such procedures.[15] Mortality has decreased dramatically to less than 2% in recent series of the highest-volume centers, yet morbidity is still around 40% despite great efforts to reduce the incidence of delayed gastric emptying, fistula formation, wound infection, and hemorrhage that represent the most important complications directly attributed to resection.[16]

Table 4 Other Complications After PD

	Number	Percent
Mortality		
Yes	8	6.5
No	114	93.5
Mortality (2002–2006)		
Yes	2	2.2
No	88	97.8
Complications		
No	68	56.7
Yes	54	44.3
Pancreatic fistula	16	13.1
Delayed gastric emptying	16	13.1
Pneumonia	10	8.2
Bile leak	10	8.2
Wound infection	8	6.5
Bleeding	5	4.1
Reoperation	14	11.5
Postoperative length of stay (days)		
Mean	14.1	
Median	11	
Range	5–54	

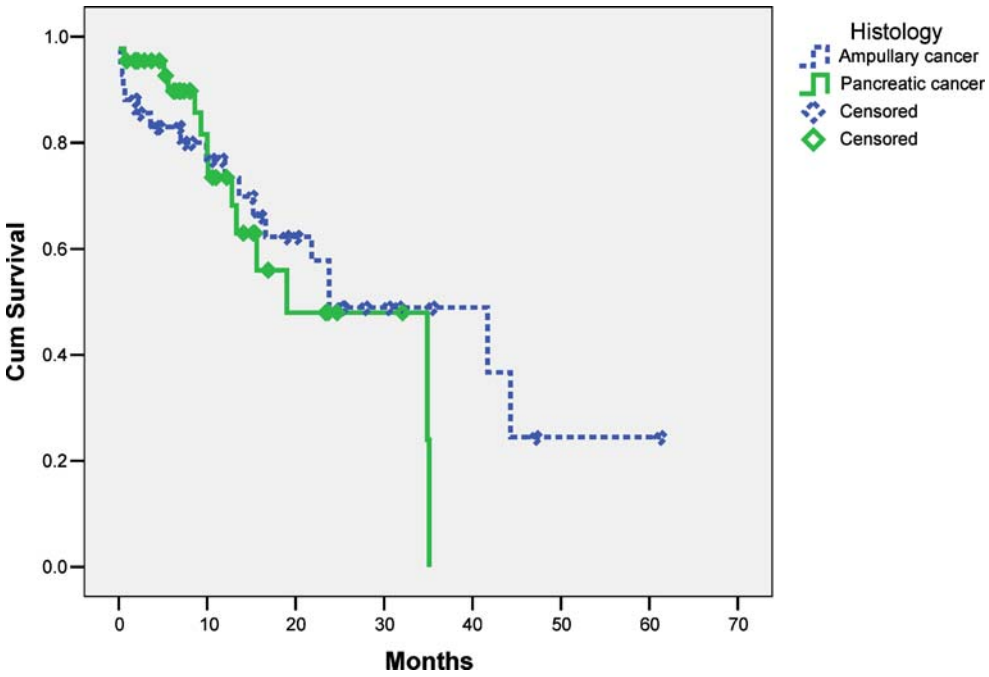

Figure 3 Survival after PD.

Important papers on this subject in Latin America include the following: Ruggieri reported a series of 19 pancreaticoduodenectomies in a 9-year period in Argentina.[17] Barboza Besada reported 61 PDs in Peru in a 20-year period.[18] Machado et al. have published extensively on topics related to PD, mostly on modified techniques regarding vein resection and chronic pancreatitis.[19–21] In México, 5 series of pancreaticoduodenal resections were found all done in our institution: a 60-patient series of resected periampullary neoplasias [22], a 7-case series of distal cholangiocarcinoma [23], a 31-case series of ampullary cancer [24], and a series of 55 Whipple procedures performed for pancreatic cancer in our institution from 1962 to 1991.[25] We recently published a similar version of the present series in the Spanish language where PD performed by surgeons other than the author were included.[26]

PD is a complex operation where many factors must be developed and conjoined to achieve good results. Although many general surgeons proudly say they are able to perform a Whipple procedure, they do so as an exception and not as a rule. When integrated to a high-volume center, surgeons develop experience in a short period of time. The pitfalls of the procedure are identified, learned, and eventually taught. Pancreatic surgeons, clinical pancreatologists, radiologists, oncologists, and endoscopists must individualize each case and decide on the best diagnostic approach and treatment for each patient as a multidisciplinary group. Thus, in referral centers, there is an accurate and prompt diagnosis and therefore an increase in the number of candidates for PD. Surgeons that develop such centers must in turn have been trained in a high-volume center. Although our hospital is considered a pioneer in hepatopancreatobiliary surgery, the concentration of all cases to a single surgeon has improved the results and increased the number of patients referred and operated. Although intended to be curative, most PD become palliative making postoperative quality of life a very important issue. Both quality of life and survival can be jeopardized if the resection is carried out by an inexperienced surgeon in a low volume center. There is an ongoing protocol on the quality of life after PD in our institution.

Indications of PD have expanded to include chronic pancreatitis, cystic neoplasias, a wider age range, superior mesenteric-portal venous involvement, and even palliation according to some authors.[27–31] Most, yet not all, resections with final histology compatible with chronic pancreatitis performed by our group were because of suspicion of cancer. Three PDs were performed because of cystic neoplasias without an evident increasing trend in the later part of the series. The oldest patient in our series was 87 years old and the youngest was 17 at the time of surgery. Fourteen vein resections were performed because of partial involvement of the superior mesenteric-portal vein. In malignant disease, all Whipple procedures were performed with an intention to cure.

In the year 2002, less pancreaticoduodenectomies were performed. The author was very active in the liver transplant program in our institution partially explaining this decline.

In contrast with other large series, the frequency of ampullary tumors was the same as pancreatic cancer whereas

most other series have the latter as the main pathological diagnosis. The reasons for this must be further studied but could be partially attributed to the fact that operable pancreatic cancer is less commonly seen because of limited diagnostic resources in our country. The positive margin status especially in ampullary tumors was much higher than other series probably because of the fact that retroperitoneal soft tissue invasion was considered a positive margin even if microscopically negative resection margins were identified. Although we are a referral center, many patients are seen with advanced disease. Two of the seven cases of cholangiocarcinoma were detected in situ partially explaining the lack of mortality in this subpopulation.

Classical Whipple resection is the technique of choice used in our institution because of surgeon preference. Most randomized trials consider both classical resection and pylorus-preserving pancreaticoduodenectomy (PPPD) equally effective for the treatment of peripancreatic carcinoma, although many experts prefer PPPD for benign disease.[32]

Despite the impressive improvement in outcome, PD remains a major gastrointestinal operation with a high morbidity rate (44% in this series). Definitions depicted in the methodology are both easy to measure at the bedside and congruent with most other large series. Delayed gastric emptying is practically absent in the last 2 years of the series. It is the author's opinion that a more ample gastrectomy reduces the rate of delayed gastric emptying and will be objectively evaluated in the near future. Pancreatic fistula was the most common complication in the latter part of this series although, overall, both gastric emptying and pancreatic fistula are present in 13% of patients. Most cases of pancreatic fistula were managed conservatively, 3 of the 16 patients were reoperated because of pancreaticojejunal dehiscence. A study group recently gathered to define postoperative pancreatic fistula in an attempt to homogenize criteria for future multicenter studies.[33] We have adopted definitions described by this group for future studies.

Although overall mortality is higher than ideal, it has decreased dramatically in the last 5 years of the series to 2.19%, making it acceptable in international standards. This phenomenon is probably due in part to the surgeon's learning curve, as well as consolidation of an organized multidisciplinary group.

Our institution is striving to follow the example of great surgeons and referral centers in other parts of the world to offer its population the best available therapy for peripancreatic disease. We are also confident that high quality pancreatic surgery is permeating other parts of Latin America. Although our statistics are approaching the gold standard set by the most important centers for pancreatic surgery, there is room for improvement.

Our institution is approaching a level of patient volume and organization necessary to perform randomized clinical trials to improve our knowledge of pancreatic disease and its treatment in our population.

Conclusion

To our knowledge, this is the largest series of PD by a single surgeon published in Latin America. The results of pancreaticoduodenectomies shown in this paper are comparable to data obtained in high-volume centers in developed countries. Thus, we conclude that good results can be obtained if a hospital evolves to a high-volume reference center regardless of geographic location.

Acknowledgments We sincerely wish to thank Dr. Manuel Campuzano, pioneer in pancreatic surgery in our institution and our country. The transition to a high-volume center couldn't have been accomplished without his lifetime effort and dedication.

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Postoperative Adjuvant Chemotherapy Improves Survival after Surgical Resection for Pancreatic Carcinoma

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Abstract Pancreatic carcinoma is one of the most aggressive types of gastrointestinal malignancy, and its prognosis remains extremely dismal. The aim of this study was to identify useful prognostic factors for patients undergoing surgical resection for pancreatic carcinoma. Medical records of 89 patients with pancreatic carcinoma who underwent surgical resection were retrospectively reviewed. Univariate and multivariate models were used to analyze the effect of various clinicopathological factors on long-term survival. There were no operative deaths. Overall 1-, 2-, and 5-year survival rates were 59, 28, and 7%, respectively (median survival time, 12.1 months). Univariate analysis revealed that postoperative adjuvant chemotherapy, portal vein invasion, lymph node metastasis, extrapancreatic nerve plexus invasion, surgical margin status, UICC pT factor, and UICC stage were significantly associated with long-term survival ($P<0.01$). Furthermore, use of postoperative adjuvant chemotherapy and absence of extrapancreatic nerve plexus invasion were found to be significant independent predictors of a favorable prognosis using a Cox proportional hazard regression model ($P<0.05$). These results suggest that postoperative adjuvant chemotherapy may improve survival after surgical resection for pancreatic carcinoma and that extrapancreatic nerve plexus invasion indicates a poor prognosis for long-term survival.

Keywords Pancreatic carcinoma · Prognostic factor · Postoperative adjuvant chemotherapy · Extrapancreatic nerve plexus invasion · Multivariate survival analysis

Introduction

Pancreatic carcinoma is a devastating disease that results in an estimated 30,000 deaths in the United States and 20,000 deaths in Japan each year.[1] The overall 5-year survival rate of this disease is less than 4% and has not significantly improved over the past decade.[2] Surgical resection, including pancreatoduodenectomy and distal pancreatectomy, has a primary role in the treatment of pancreatic carcinoma, as it provides the only chance for cure or long-term survival.[3] However, less than 20% of patients with pancreatic carcinoma are candidates for surgical resection due to locoregional spread or metastatic disease at the time of diagnosis.[4,5] Furthermore, the 5-year survival rate of patients with pancreatic carcinoma who do undergo surgical resection has been recently reported to be less than 20%.[6–21] To improve long-term survival, several surgeons have advocated the use of more extended surgical procedures including wider lymphatic and/or soft tissue clearance.[22,23] However, three randomized controlled trials that compared standard pancreatoduodenectomy with extended pancreatoduodenectomy failed to demonstrate that extended surgical resection prolonged survival.[24–26]

Recently, some investigators have reported that surgery alone is not sufficient for improving the prognosis of patients with pancreatic carcinoma.[27,28] The use of postoperative adjuvant therapy, including chemotherapy and chemoradiotherapy, may have an important impact on long-term survival.[28,29] Accurate methods for selecting patients who are eligible for resection based on reproducible prognostic factors are also urgently needed.

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The aims of this retrospective study were to identify useful prognostic factors for patients undergoing surgical resection for pancreatic carcinoma and to evaluate utility of postoperative adjuvant chemotherapy in this patient population. This was achieved by assessing cases treated at a single institution using univariate and multivariate survival analysis.

Patients and Methods

Patient Population

Medical records for 89 patients with pancreatic ductal carcinoma treated at the Department of Surgery, Hiroshima University Hospital between January 1990 and September 2006 were reviewed retrospectively. All patients underwent tumor resection with the aim of achieving cure and had a confirmed pathological diagnosis. Patients with pancreatic ductal adenocarcinoma derived from intraductal papillary–mucinous neoplasm or mucinous cystic neoplasm were excluded from this analysis.[30,31] Postoperative adjuvant chemotherapy was administered beginning in 1999 and was given to *all 41 patients who underwent pancreatic resection after 1999*. The patients who were offered postoperative adjuvant chemotherapy had three options after surgical resection: intra-arterial chemotherapy alone (n=4), intravenous chemotherapy alone (n=6), or intravenous and oral chemotherapy (n=31). Intra-arterial chemotherapy was performed by Seldinger's method. Briefly, a catheter was placed in the common hepatic artery with a reservoir in the lower abdomen. An intra-arterial bolus injection of 5-Fu 160 mg/m^2 was administered biweekly. Intravenous chemotherapy consisted of gemcitabine 700 mg/m^2 administered biweekly for 30 min by drip intravenous injection. Patients who received intravenous and oral chemotherapy were given intravenous gemcitabine 700 mg/m^2 on day 1 and orally administered S-1 50 mg/m^2 for seven consecutive days; this cycle was repeated every 14 days. No patient received radiation therapy during the study periods.

Surgical Procedures

Patients with carcinoma in the pancreatic head underwent pylorus-preserving pancreatoduodenectomy (n=48), conventional pancreatoduodenectomy (n=13), or total pancreatectomy (n=3), while all patients with carcinoma in the pancreatic body or tail underwent distal pancreatectomy with splenectomy (n=25). All 89 patients underwent reginal lymph node dissection. Additional dissection of para-aortic lymph nodes was performed in 64 patients. Intraoperative pathological assessment of the proximal or distal pancreatic margins was performed using frozen tissue sections. If the pancreatic margin was positive for cancerous cells, further resection of the pancreas was performed to the maximum extent possible.

Pathological Investigations

After tumor resection, hematoxylin and eosin staining was performed. All specimens were examined pathologically, and each tumor was classified as well-differentiated, moderately differentiated, or poorly differentiated adenocarcinoma according to the predominant pathological grading of differentiation. Anterior serosal invasion, retropancreatic tissue invasion, choledochal invasion, duodenal invasion, portal vein invasion, lymph node metastasis, and extrapancreatic nerve plexus invasion were all examined pathologically. Surgical margins were considered positive if infiltrating adenocarcinoma was present at the proximal or distal pancreatic transection line, or in dissected peripancreatic soft tissue margins. The final stage of pancreatic carcinoma was examined pathologically according to the TNM classification system of malignant tumors published by the International Union Against Cancer (UICC), 6th edition.[32]

Survival

Patients were followed regularly in outpatient clinics by undergoing computed tomography twice a year for 5 years after surgery. Information on outcome more than 5 years after surgery was collected by telephone or personal interview. For patients who died, survival time after surgery and cause of death were recorded. For surviving patients, postoperative survival time and status of recurrence were recorded. Survival analyses on 4 clinical factors (gender, age, tumor location, and use of adjuvant chemotherapy) and 12 pathological factors (tumor size, tumor differentiation, anterior serosal invasion, retropancreatic tissue invasion, choledochal invasion, duodenal invasion, portal vein invasion, lymph node metastasis, extrapancreatic nerve plexus invasion, surgical margin status, UICC pT factor, and UICC stage) were performed with univariate and multivariate methods.

Statistical Analysis

Survival curves were constructed using the Kaplan–Meier method, and differences in survival curves were compared by univariate log-rank (Mantel–Cox) test. Factors found to be significant on univariate analysis were subjected to multivariate analysis using a Cox proportional hazards model. $P<0.05$ was considered statistically significant. Statistical analysis was performed using the Macintosh version of StatView (version 5.0; SAS Institute, Cary, NC).

Results

The 89 eligible patients included 52 men and 37 women (median age, 68 years; range, 31–82 years), and 39 patients (44%) were more than 70 years old. No 30-day operative deaths occurred among the 89 patients. Tumors were located in the pancreatic head in 64 patients and in the body or tail in 25 patients.

Pathologically, tumors <2 cm in greatest diameter were found in only ten patients (11%). Anterior serosal invasion, retropancreatic tissue invasion, choledochal invasion, duodenal invasion, portal vein invasion, and extrapancreatic plexus invasion were identified in 46 patients (52%), 58 patients (65%), 38 patients (43%), 37 patients (42%), 35 patients (39%), and 38 patients (43%), respectively. There were 61 tumors (69%) with lymph node metastasis and 28 (31%) without lymph node metastasis, and 15 patients (17%) had involvement of the para-aortic lymph nodes. Fifty patients (56%) had positive surgical margins. R0, R1, and R2 resections were performed in 39 (44%), 22 (25%), and 28 (31%) patients, respectively. Tumors were identified as well-differentiated adenocarcinoma in 24 patients (27%), moderately differentiated adenocarcinoma in 52 patients (58%), and poorly differentiated adenocarcinoma in 13 patients (15%). According to the TNM system, 5 patients (6%), 5 patients (6%), 15 patients (17%), 33 patients (37%), 11 patients (12%), and 20 patients (22%) were diagnosed with stages IA, IB, IIA, IIB, III, and IV disease, respectively.

Overall survival rates for the 89 patients were 59% at 1 year, 28% at 2 years, and 7% at 5 years (median survival, 12.1 months; range, 2 to 96 months; Fig. 1).

Sixteen clinicopathological factors were investigated to determine whether they were of prognostic significance. The results of the log-rank test are shown in Table 1.

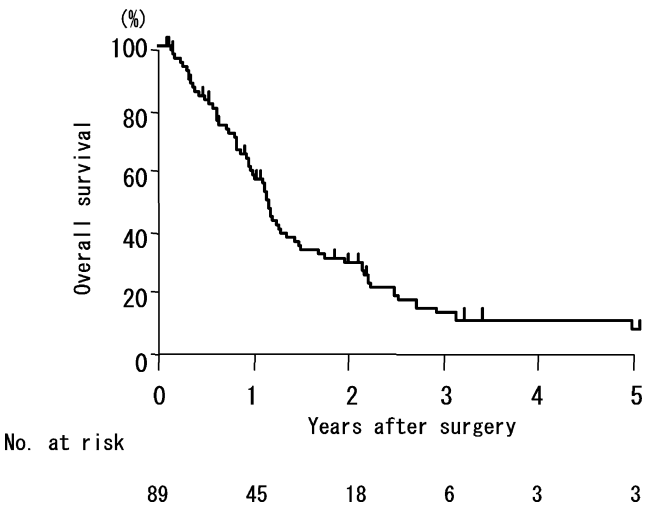

Figure 1 Overall survival in patients who underwent resection for pancreatic carcinoma.

Table 1 Univariate Survival Analysis of Prognostic Factors for Patients with Pancreatic Carcinoma

Factors	Number of patients	2-year survival rate (%)	*P* value
Clinical factors			
Gender			
Male	52	27	0.591
Female	37	30	
Age (years)			
<70	50	26	0.317
≧70	39	31	
Location of the tumor			
Head	64	31	0.698
Body or tail	25	21	
Adjuvant chemotherapy			
Yes	41	49	<0.001
No	48	15	
Pathological factors			
Tumor size			
<2 cm	10	30	0.324
≧2 cm	79	28	
Tumor differentiation			
Well–moderate	77	27	0.717
Poor	12	41	
Anterior serosal invasion			
Yes	46	19	0.062
No	43	38	
Retroperitoneal tissue invasion			
Yes	58	25	0.052
No	31	35	
Choledochal invasion			
Yes	38	31	0.766
No	51	26	
Duodenal invasion			
Yes	37	28	0.447
No	52	29	
Portal vein invasion			
Yes	35	13	<0.001
No	54	38	
Lymph node metastasis			
Yes	61	19	0.004
No	28	48	
Extrapancreatic nerve plexus invasion			
Yes	38	4	<0.001
No	51	47	
Surgical margin			
Positive	50	13	<0.001
Negative	39	49	
UICC pT factor			
Pt 1,2	15	47	0.009
Pt 3,4	74	24	
UICC stage			
IA, IB	10	67	<0.001
IIA, IIB, III, IV	79	23	

P value is the result of a log-rank (Mantel–Cox) test

Gender, age, tumor location, tumor size, tumor differentiation, anterior serosal invasion, retropancreatic tissue invasion, choledochal invasion, and duodenal invasion did not influence postoperative survival. Univariate analysis revealed that postoperative adjuvant chemotherapy ($P<0.001$), portal vein invasion ($P<0.001$), lymph node metastasis ($P=0.004$), extrapancreatic nerve plexus invasion ($P<0.001$), surgical margin status ($P<0.001$), UICC pT factor ($P=0.009$), and UICC stage ($P<0.001$) were significantly associated with increased survival (Table 1). These factors were entered into multivariate analysis with a Cox proportional hazards model, and use of postoperative adjuvant chemotherapy ($P=0.040$) and absence of extrapancreatic nerve plexus invasion ($P=0.015$) remained independently associated with longer survival (Table 2). In contrast, portal vein invasion ($P=0.121$), lymph node metastasis ($P=0.306$), and surgical margin status ($P=0.146$) were not significantly associated with survival in the final multivariate model. UICC pT factor and UICC stage were not used as dependent variables in the multivariate survival analysis to avoid compounding to nodal status and portal vein invasion. Two-year survival rates of patients who did or did not receive postoperative adjuvant chemotherapy were 49 and 15%, respectively (Fig. 2), and 2-year survival rates of patients with or without extrapancreatic nerve plexus invasion were 4 and 47%, respectively. All patients except for one who exhibited extrapancreatic nerve plexus invasion died of recurrence within 2 years after surgery (Fig. 3).

Discussion

The prognosis of patients with pancreatic carcinoma remains dismal despite the development of new imaging examinations and surgical procedures. Recent reports concerning resectional treatment of pancreatic carcinoma are listed in Table 3. In these reports,[6–21] 5-year survival ranged from 8 to 25%, with median survival being 12–22 months, although the operative mortality rates were 0–3% in most series. The unfavorable prognoses observed in these series may have been caused by lower rates of curative respectability, which were reported to range from 29 to 82% (Table 3). In our series, the 5-year survival rate and median survival time after resection were 7 and 12 months, respectively. This low 5-year survival rate can be explained by the fact that in the present study, most patients had advanced-stage pancreatic carcinoma (only 12% of patients had TNM stage IA/IB disease), and the rate of curative respectability was lower than that in previous reports.

Table 2 Multivariate Survival Analysis of Prognostic Factors for Patients with Pancreatic Carcinoma

Factors	Relative risk	95% CI	*P* value
Adjuvant chemotherapy			
Yes	1.0	1.03–3.26	0.040
No	1.83		
Extrapancreatic nerve plexus invasion			
Yes	2.15	1.16–3.99	0.015
No	1.0		

P value is the result of a Cox proportional hazards model.
CI Confidence interval

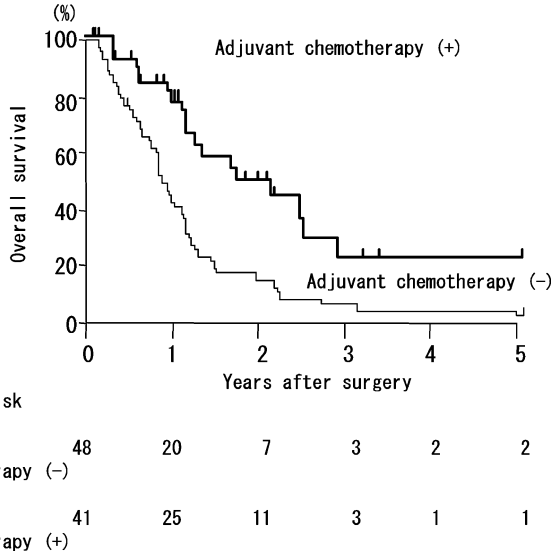

Figure 2 Comparison of postoperative survival in patients who did or did not receive postoperative adjuvant chemotherapy after resection for pancreatic carcinoma ($P<0.001$).

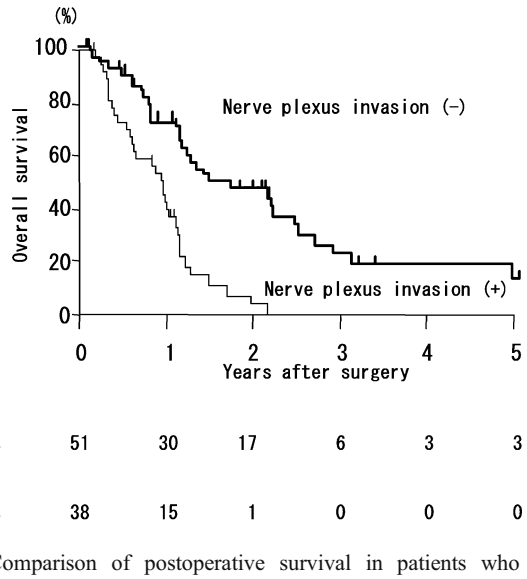

Figure 3 Comparison of postoperative survival in patients who underwent resection for pancreatic carcinoma based on the presence or absence of pathological extrapancreatic nerve plexus invasion ($P<0.001$).

Table 3 Recent Reports on Resectional Treatment of Pancreatic Carcinoma

Author	Year	Number of Patients	Location of tumor (Ph:Pbt)	Mortality (%)	Curative respectability (%)	Median survival (months)	5-year survival rate (%)	Prognostic factors by multivariate analysis
Present study	2006	89	64:25	0	44	12	7	PL, AC
Winter[6]	2006	1175	175:0	2	58	18	18	TS, SM, N, G, AC
Shimada[7]	2006	88	0:88	0	75	22	19	N, PV
Moon[8]	2006	94	71:23	2	73	12	16	SM, TS, G, AC
Tani[9]	2006	111	72:39	–	60	11	11	–
Jamieson[10]	2005	65	65:0	–	29	13	–	TS, PV, CRP
Shibata[11]	2005	69	55:14	–	48	–	21	G, PV, S
Brown[12]	2005	109	104:5	2	64	17	–	SM, N, G, PLT
Wagner[13]	2004	211	182:29	3	76	16	20	SM
Kuhlmann[14]	2004	160	160:0	0	50	17	8	SM, N, G, TS
Berger[15]	2004	129	125:4	–	45	19	11	N, CA19-9
Richter[16]	2003	194	194:0	3	63	16	5	SM
Takfsai[17]	2003	94	69:25	3	53	11	13	TS, N, SM
Gebhardt[18]	2000	113	106:7	6	82	14	11	G, TS, LY
Wenger[19]	2000	158	158:0	10	63	14	12	TS, SM
Magistrelli[20]	2000	73	63:10	0	69	12	13	pT, N
Sohn[21]	2000	616	526:52	2	70	17	17	SM, TS, BL, G, AC

Ph Pancreatic head, *Pbt* pancreatic body and tail, *PL* extrapancreatic nerve plexus invasion, *AC* adjuvant chemotherapy, *TS* tumor size, *SM* surgical margin, *N* nodal involvement, *G* pathological grading of differentiation, *PV* portal vein invasion, *S* serosal invasion, *PLT* preoperative platelet count, *CA19-9* preoperative serum carbohydrate 19-9 levels, *LY* lymph vessel invasion, *pT* pathological T factor, *BL* blood loss

Many investigators have attempted to find useful prognostic factors for pancreatic carcinoma after surgical resection using multivariate analysis. Potential factors include tumor size,[6,8,10,14,17–19,1] surgical margin status,[6,8,12–14,16,17,19,21] nodal involvement,[6,7,12,14,15,17,20]] pathological grading of differentiation,[6,8,11,12,14,18,21] portal vein invasion,[7,10,11] serosal invasion,[11] preoperative platelet count,[12] preoperative serum carbohydrate 19–9 level,[15] lymph vessel invasion,[18] pathological TNM T factor,[20] blood loss,[21] and postoperative adjuvant chemotherapy.[6, 8, 21] In this study, postoperative adjuvant chemotherapy, portal vein invasion, nodal involvement, extrapancreatic nerve plexus invasion, surgical margin status, UICC pT factor, and UICC stage were identified as significant prognostic factors by univariate analysis; similar results have been noted in previous reports. However, only extrapancreatic nerve plexus invasion and administration of postoperative adjuvant chemotherapy were found to be independent prognostic factors by multivariate analysis.

With regard to postoperative adjuvant therapy for patients with pancreatic carcinoma, a Johns Hopkins University group[6,21] and a Korean group[8] both reported that postoperative adjuvant chemoradiation was an independent prognostic factor for improved survival. To our knowledge, seven randomized controlled trials evaluating postoperative adjuvant therapy for pancreatic carcinoma have been published.[29,33–38] However, four of these studies, three of which investigated adjuvant chemotherapy[34,36,37] and one of which evaluated adjuvant chemoradiotherapy,[35] showed no significant benefit associated with postoperative adjuvant therapy. The first report to demonstrate a significant adjuvant therapy-associated survival benefit in pancreatic carcinoma patients was published by the United States Gastrointestinal Tumor Study Group (GITSG) in 1987.[33] The GITSG showed that adjuvant chemoradiation therapy consisting of 40 Gy radiation combined with 5-Fu had a significant impact on survival compared to surgery alone. However, this effect was demonstrated in only a small number of patients. Subsequently, a prospective randomized study on a larger number of patients, which was reported by the European Organization for Research and Treatment of Cancer (EORTC), showed that any survival effect of adjuvant chemoradiation therapy using 40 Gy radiation combined with 5-Fu was small.[35] With regard to postoperative adjuvant chemotherapy, a multicenter randomized trial conducted by the European Study Group for Pancreatic cancer (ESPAC) demonstrated that adjuvant chemotherapy using 5-Fu plus leucovorin had a significant survival benefit in patients with resected pancreatic carcinoma compared to surgery alone (5-year survival, 21 vs 8%).[29] Recently, in a multicenter randomized controlled phase III trial (CONKO-001), Oettle et al. [39] reported that compared with surgery alone, postoperative gemcitabine chemotherapy significantly delayed the development of recurrent disease after complete resection of pancreatic carcinoma (5-year disease-free survival, 16.5 vs 5.5%). In addition, a meta-

analysis of randomized adjuvant therapy trials for pancreatic carcinoma showed a similar result. Stocken et al. [38] concluded that chemotherapy, but not chemoradiation, was an effective adjuvant treatment for pancreatic carcinoma after reviewing the results of five randomized controlled trials. We agree that chemotherapy is preferable to chemoradiation after resection of pancreatic carcinoma.

Recently, significant effects of new anticancer drugs, including gemcitabine,[40] S-1,[41] and irinotecan[42] on patients with unresectable pancreatic carcinoma have been reported by several investigators. Prospective randomized studies evaluating these agents in postoperative adjuvant therapy regimens for pancreatic carcinoma are currently being conducted. In the present study, the majority of adjuvant chemotherapy regimens consisted of gemcitabine plus S-1, as we have used this combination as the standard adjuvant regimen at our institution in recent years. Gemcitabine plus S-1 therapy has been associated with an excellent survival benefit in patients with unresectable pancreatic carcinoma. Nakamura et al. [43] reported a phase II trial that evaluated gemcitabine plus S-1 in metastatic pancreatic carcinoma patients, which resulted in a response rate, median survival, and 1-year survival rate of 48%, 12.5 months, and 54%, respectively. We believe that this new regimen might contribute to the survival benefit associated with postoperative adjuvant chemotherapy in the current study, although this study was a small series compared with other randomized controlled studies such as the ESPAC trials.

Neural invasion is widely accepted to be a unique route for the spread of pancreatic carcinoma. However, there have been a small number of published reports concerning the relationship between extrapancreatic nerve plexus invasion and survival in pancreatic carcinoma. In these reports, the frequency of extrapancreatic nerve plexus invasion in pancreatic carcinoma patients ranged from 50 to 69%, [44–46], and the presence of extrapancreatic nerve plexus invasion was associated with lower survival after resection. Nakao et al. [44] reported that the postoperative survival rate for patients with extrapancreatic nerve plexus involvement was significantly lower than that for patients without extrapancreatic nerve plexus involvement, and most patients with extrapancreatic nerve plexus involvement died of recurrence within 2 years after surgery. In our series, almost all patients with extrapancreatic nerve plexus invasion died of tumor recurrence within 2 years, and the presence of extrapancreatic nerve plexus invasion was an independent prognostic factor for poor survival after resectional treatment of pancreatic carcinoma. We thus believe that extrapancreatic nerve plexus involvement is a powerful prognostic factor for pancreatic carcinoma patients.

To perform complete resection of the extrapancreatic nerve plexus, some surgeons emphasize the need for extended surgical procedures, including retropancreatic lymph node and nerve plexus dissection. However, according to three randomized controlled studies, this extended procedure has not contributed to longer survival of patients with pancreatic carcinoma.[24–26] Moreover, severe diarrhea frequently occurs in patients undergoing extrapancreatic nerve plexus dissection, and this complication makes it difficult to administer postoperative adjuvant therapy. Recently, it has been reported that extrapancreatic nerve plexus invasion around the common hepatic artery or superior mesenteric artery can be diagnosed preoperatively by multidetector computed tomography.[47] Based on these results, we feel that other strategies such as neoadjuvant chemotherapy or chemoradiotherapy should be evaluated to determine whether they improve survival in patients with extrapancreatic nerve plexus involvement.[48]

Conclusions

In conclusion, absence of extrapancreatic nerve plexus invasion and use of postoperative adjuvant chemotherapy are powerful prognostic factors for survival in pancreatic carcinoma patients. To improve long-term survival, postoperative adjuvant chemotherapy using new anticancer drugs is essential for patients with pancreatic carcinoma after surgical resection. Additional strategies, such as neoadjuvant chemotherapy or chemoradiotherapy, should be evaluated to assess their utility in improving survival in patients with extrapancreatic nerve plexus invasion.

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Clinical Significance of the Metastatic Lymph-Node Ratio in Early Gastric Cancer

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Abstract The metastatic lymph-node ratio has important prognostic value in gastric cancer; this study focused on its significance in early gastric cancer. In total, 1,472 patients with early gastric cancer underwent curative gastrectomy between 1992 and 2001. Of these, 166 (11.3%) had histologically proven lymph-node metastasis. Prognostic factors were identified by univariate and multivariate analyses. Metastasis was evaluated using the Japanese Classification of Gastric Carcinoma (JGC) and the Union Internationale Contre le Cancer/Tumor, Node, Metastasis (UICC/TNM) Classification. The metastatic lymph-node ratio was calculated using the hazard ratio. The cut-off values for the metastatic lymph-node ratio were set at 0, <0.15, ≥0.15 to <0.30, and ≥0.30. The numbers of dissected and metastatic lymph nodes were correlated, but the number of dissected lymph nodes and the metastatic lymph-node ratio was not related. The JGC and UICC/TNM classification demonstrated stage migration and heterogeneous stratification for disease-specific survival. The metastatic lymph-node ratio showed less stage migration and homogenous stratification. The metastatic lymph-node ratio may be a superior method of classification, which provides also accurate prognostic stratification for early gastric cancer patients.

Keywords Early gastric cancer · Lymph-node metastasis · Metastatic lymph-node ratio · Prognostic factors

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Introduction

Lymph-node metastasis is an important prognostic factor for both early and advanced gastric cancer,[1,2] and lymph-node dissection is a promising treatment for these diseases. The involvement of lymph nodes can be assessed by various classifications. For example, the Union Internationale Contre le Cancer/Tumor, Node, Metastasis (UICC/TNM) Classification [3] divides lymph-node metastasis into three categories according to the number of metastatic lymph nodes irrespective of their site. By contrast, the Japanese Classification of Gastric Carcinoma (JGC)[4] places lymph nodes into three categories according to their anatomical distribution, irrespective of their number. The metastatic lymph-node ratio (that is, the number of metastatic lymph nodes/number of dissected lymph nodes) has been reported as an additional useful method of lymph-node classification.[5–8]

Extended lymph-node dissection can cause stage migration due to the increase in the number of metastatic lymph nodes. However, classification according to metastatic lymph-node ratio can avoid the stage-migration phenomenon related to the UICC/TNM classification.[9] Several previous studies have

demonstrated the superior prognostic value of the metastatic lymph-node ratio in advanced gastric cancer,[10–12] but few have examined its use in early gastric cancer.[13] During the early stages of the disease, most lymph-node metastasis is restricted to pN1, as defined by the JGC and UICC/TNM classifications. However, it is difficult to assess whether subsets of patients with pN1 early gastric tumors have the same prognosis. In the current study, we compared the prognostic values of the JGC and UICC/TNM classifications with that of the metastatic lymph-node ratio in early gastric cancer.

Materials and Methods

The retrospective study group consisted of 1,472 patients from the Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine, Japan, and affiliated institutions. Early gastric cancer was defined as tumor invading T1 (mucosal or submucosal), and all participants had been pathologically diagnosed with early gastric cancer (T1), and had undergone potentially curative gastrectomy between April 1992 and December 2001. Data were retrieved from the operative and pathological reports. Follow-up data were obtained from the outpatient clinical database. All subjects were preoperatively confirmed to have gastric adenocarcinoma by analyses of endoscopic biopsy specimens. The mean age of the patients±standard deviation (SD) was 63.7±10.9 years, and more men than women (994 men versus 478 women) participated in the study.

The following clinicopathological variables were evaluated by experienced pathologists from each institution: gender (male or female); age (<70 or ≥70 years); location of tumor (lower third, middle third, upper third, or entire stomach); macroscopic appearance [protruded (I), elevated (IIa), flat (IIb), depressed (IIc), excavated (III), or mixed]; tumor diameter (<20, ≥20 to <40, or ≥40 mm); histological type [differentiated (well differentiated, moderately differentiated, or papillary) or undifferentiated (poorly differentiated, signet-ring cell, or mucinous)]; lymph-node metastasis; and depth of invasion (mucosa or submucosa). Lymph-node metastasis was classified by three methods: the JGC, the UICC/TNM classification, and the metastatic lymph-node ratio. The clinicopathological terminology in this article principally follows that of the JGC.

The Japanese Gastric Cancer Association has standardized lymph-node dissections for gastric cancer. In this study, D1 gastrectomy (complete dissection of the first-tier lymph nodes) plus lymph-node dissection along the left gastric artery or common hepatic artery was performed in the 827 patients diagnosed as having no metastatic lymph nodes by preoperative imaging tools, while standard D2 gastrectomy (complete dissection of the first-tier and second-tier lymph nodes) was performed in the 645 patients diagnosed with metastatic lymph nodes by preoperative imaging tools. These procedures were performed in accordance with the JGC. The number of retrieved lymph nodes were 27.3±9.0 in the D1 gastrectomy plus lymph-node dissection along the left gastric artery or common hepatic artery and 33.3±12.3 in the D2 gastrectomy. There was a significant difference in the retrieved number between the two groups ($p<0.0001$). Distal gastrectomy was performed in a total of 1,185 patients, including all those with tumors located in the lower third of the stomach, and some of those with middle third tumors according to the direction of the tumor invasion. Proximal gastrectomy was performed in the 58 patients with tumors in the upper third of the stomach. Total gastrectomy was carried out for 229 patients, including all those with tumors occupying the entire stomach, and the remaining patients with tumors in the middle third of the stomach. No additional treatment was required for any of the patients, as the therapeutic outcomes were satisfactory.

Patient follow-ups were carried out at the outpatient department according to our standard protocol (every 8–12 weeks for at least 5 years). At these appointments, a medical interview was conducted by the physician to review the progress and health of the patient. The subjects also underwent hematological examinations every 3 months, US or CT every 6 months, and chest radiography and endoscopic examinations every year. After 5 years, the follow-ups were continued on an annual basis. The median follow-up duration was 62.5±36.6 months for all registered patients. There was no significant difference in any clinicopathological factors, operative methods, and follow-up schedule between the each institution.

Statistical Analysis

Data were analyzed using the SPSS statistical software program (SPSS, Chicago, IL). Patient characteristics were compared using the two-tailed Fisher exact test or the Chi-square test with Yates correction. Quantitative variables were compared using the Student's t test and expressed as medians±SD. The Cox proportional hazards regression model was applied to identify prognostic factors using the ten variables. Step-forward regression was used to build a valid statistical model for the association of prognostic factors with disease-specific survival among patients with complete data. As the three lymph-node classifications (the JGC, UICC/TNM, and metastatic lymph-node ratio) were not added simultaneously into the multivariate analyses, ten variables were assessed in total. Disease-specific survival was calculated using the Kaplan-Meier estimation, and examined using the log-rank test. Pearson's correlation coefficient (r) was used to study the relationships between: the number of metastatic lymph nodes and the number of lymph nodes dissected; the metastatic lymph node ratio and the number of lymph nodes dissected; and the number of metastatic lymph nodes and the metastatic lymph node ratio. Prob-

ability (p) values were considered to be statistically significant at the <0.05 level.

Results

Of the 1,472 patients in the study group, 545 had tumors located in the lower third of the stomach, 720 had tumors in the middle third, 200 had tumors in the upper third, and 7 had tumors occupying the entire stomach. Flat or elevated tumors were macroscopically observed in 258 patients, depressed tumors were seen in 901 patients, and mixed-type (elevated plus depressed) tumors were seen in the remaining 313 patients. The mean (±SD) tumor diameter was 36.5±18.8 mm. Differentiated tumors were histologically observed in 967 patients, and undifferentiated tumors were found in 505 patients. Histological mucosal tumors were observed in 735 patients, and submucosal tumors were found in 737 patients. Lymph-node metastasis was observed in 166 patients (11.3%), including 1.5% of the patients with mucosal tumors and 21% of the patients with submucosal tumors. The mean (±SD) numbers of metastatic lymph nodes were 0.32±1.31 in all registered patients and 2.86±2.83 in the 166 patients with lymph-node metastasis.

Correlation Between Lymph-Node Metastasis and Retrieved Nodes

There was a significant correlation between the number of metastatic lymph nodes and retrieved nodes according to the Pearson's correlation test (r=0.057, p=0.0286; Fig. 1a), but not between the metastatic lymph-node ratio and the number of retrieved nodes (r=−0.035, p=0.1827; Fig. 1b). Therefore, no effect of stage migration was observed in the metastatic lymph-node ratio classification.

Correlation Between Number of Metastatic Lymph Nodes and Metastatic Lymph-Node Ratio

There was a significant correlation between the number of metastatic lymph nodes and the metastatic lymph-node ratio according to the Pearson's correlation test (r=0.801, p<0.0001; Fig. 1c).

Re-classification of Metastatic Lymph-Node Ratio Categories

The metastatic lymph-node ratio was classified into nine groups using 0.05 increments up to 0.40 (Table 1). The hazard ratio for each group increased with the metastatic lymph-node ratio stratifications. We then re-staged the metastatic lymph-node ratio into four subsets based on the hazard ratios (0, <0.15: ratio pN1, >0.15 to <0.30: ratio pN2, and >0.30: ratio pN3).

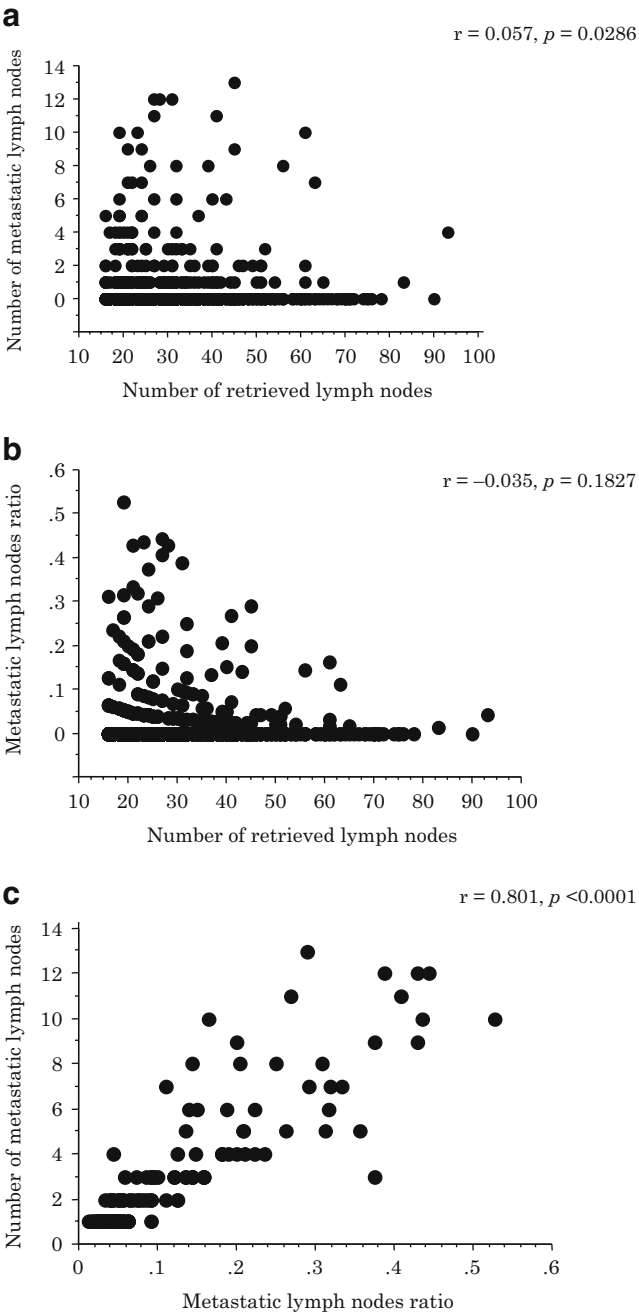

Figure 1 Pearson's correlation tests. **a** Significant correlation between the number of lymph-node metastases and retrieved lymph nodes using metastatic lymph-node ratio classification (r=0.057, p=0.0286). **b** Non-significant correlation between the metastatic lymph-node ratio and number of retrieved lymph nodes (r=−0.035, p=0.1827). **c** Significant correlation between the number of metastatic lymph nodes and the metastatic lymph-node ratio (r=0.801, p<0.0001).

Survival According to Lymph-Node Classification

Significant differences in disease-specific patient survival were observed for pN0 versus pN1, pN2, and pN3, as well as for pN1 versus pN2 and pN3, according to the JGC. However, no significant difference was observed in survival between pN2 and pN3 (Fig. 2a).

Table 1 Re-classification of Metastatic Lymph Node Ratio Categories

Stratification	Number	Coefficient	5-year Survival Rate (%)	Hazard Ratio (95% CI)	*p* Value
<0.05	68	1.096	97.1	2.992(0.368–24.343)	0.305
≥0.05 to <0.10	43	1.436	94.4	4.202 (0.517–34.167)	0.179
≥0.10 to <0.15	17	2.577	92.9	13.162 (1.618–107.1)	0.016
≥0.15 to <0.20	9	3.478	85.7	32.379 (3.971–264.03)	0.0001
≥0.20 to <0.25	9	4.315	66.7	74.789 (19.294–289.90)	<0.0001
≥0.25 to <0.30	5	3.548	75.0	34.752 (4.273–282.61)	0.0001
≥0.30 to <0.35	5	5.704	0	300.101 (72.203–1247.3)	<0.0001
≥0.35 to <0.40	4	4.684	75.0	108.170 (22.332–523.94)	<0.0001
≥0.40	6	5.632	0	279.092 (77.888–1000.1)	<0.0001

95% CI, 95% Confidence interval

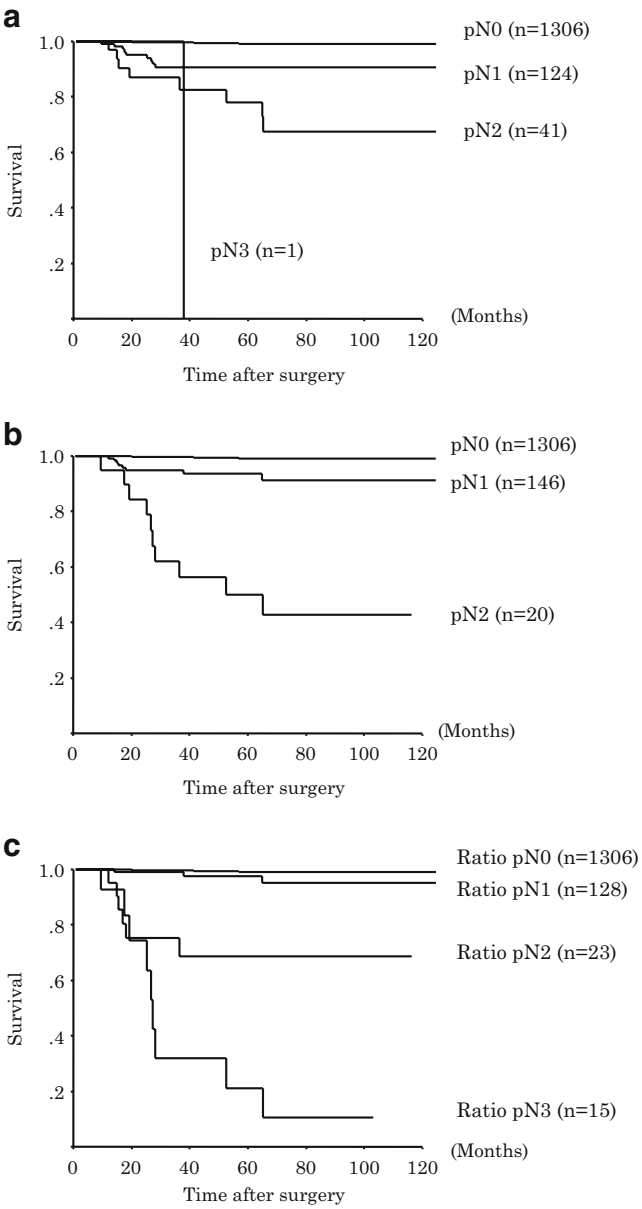

Figure 2 Survival curves of patients with early gastric cancer. **a** JGC. **b** UICC/TNM classification. **c** Metastatic lymph-node classification.

There were significant differences in disease-specific survival between each group classified by the UICC/TNM classification (Fig. 2b), as well as between those classified by the metastatic lymph-node ratio (Fig. 2c).

Prognostic Factors

The univariate analysis of 12 variables revealed that tumor location, depth of invasion, and presence of lymph-node metastasis (as assessed by JGC, UICC, or lymphatic ratio) significantly influenced disease-specific survival (Table 2). Multivariate analysis using the Cox proportional hazard regression model showed that patient age, and each lymph-node classification were independent prognostic factors for disease-specific survival (Table 3). Taking both sets of analyses into account, older age (≥70 years), tumor location in the middle/lower third of the stomach, a more extensive anatomical distribution of metastatic lymph nodes, a greater number of metastatic lymph nodes, and a greater lymphatic ratio all adversely affected patient disease-specific survival.

Comparison of Survival Between Subsets of Patients in Each Lymph-Node Classification

The patient subgroups defined by the JGC were discriminated by metastatic lymph-node ratio classification. Significant differences in survival were observed for Ratio pN1 versus pN2 ($p=0.0472$) and pN3 ($p<0.0001$), and for Ratio pN2 versus pN3 ($p=0.0008$) within JGC pN1. Significant differences in survival were observed for Ratio pN1 versus pN2 ($p=0.0364$) and pN3 ($p=0.0003$) within JGC pN2 (Fig. 3a). Similarly, significant differences in survival were observed for Ratio pN1 versus pN2 ($p<0.0001$) within UICC/TNM pN1, and for Ratio pN1 versus pN3 ($p=0.0253$), and for pN2 versus pN3 ($p=0.0007$) within UICC/TNM pN2 (Fig. 3b). By contrast, there were no significant differences in survival between each lymph-node stage classified by the JGC and UICC/TNM in the same lymph-node stage classified by the metastatic lymph-node ratio.

Table 2 Univariate Analysis of Prognostic Factors

Variables	Number	Hazard Ratio (95% CI)	*p* Value
Age (y)			0.090
<70	986	1	
≥70	486	2.004 (0.897–4.475)	
Gender			0.928
Female	478	1	
Male	994	0.962 (0.412–2.247)	
Location of tumor			0.121
Lower third	545	1	
Middle third	720	0.314 (0.122–0.810)	0.017
Upper third	200	0.607 (0.176–2.096)	0.429
Macroscopic appearance			0.220
Elevated or flat	258	1	
Depressed	901	0.568 (0.175–1.846)	0.347
Mixed	313	1.343 (0.393–4.589)	0.638
Tumor diameter (mm)			0.121
<20	404	1	
≥20 to <40	674	3.182 (0.927–10.92)	0.066
≥40	394	1.672 (0.400–6.997)	0.481
Histological type			0.812
Differentiated	967	1	
Undifferentiated	505	0.902 (1.534–11.01)	
Depth of invasion			0.005
Mucosa	735	1	
Submucosa	737	4.109 (1.493–2.556)	
Lymph node metastasis (JGC)			<0.001
pN0	1306	1	
pN1	124	13.22 (4.789–36.470	<0.001
pN2	41	42.05 (15.24–116.01)	<0.001
pN3	1	189.7 (22.97–1565.7)	<0.001
Lymph node metastasis (TNM/UICC)			<0.001
pN0	1306	1	
pN1	146	10.08 (3.533–28.74)	<0.001
pN2	20	94.38 (35.91–248.1)	<0.001
Lymph node metastasis (Lymphatic ratio)			0.001
0	1306	1	
<0.15	128	4.615 (1.193–17.849)	0.027
≥0.15 to <0.30	23	49.94 (15.830–157.5)	<0.001
≥0.30	15	201.4 (74.08–547.8)	<0.001
Extent of resection of the stomach			
Partial	1243	1	
Total	229	1.010 (0.345–2.956)	0.985
Lymph node dissection			
D1	827	1	
D2	645	2.149 (0.940–4.913)	0.070

95% CI: 95% Confidence interval; *Mixed*: Elevated plus depressed lesion; *JGC*: Japanese classification of gastric carcinoma; *D1*: D1 plus lymph nodes along the left gastric artery and the common hepatic artery

Discussion

This study showed that lymph-node metastasis (that is, the anatomical distribution of metastatic lymph nodes, number of metastatic lymph nodes, and metastatic lymph-node ratio) is an important independent prognostic factor for early gastric cancer. Of the three lymph-node classifications compared, the metastatic lymph-node ratio was superior in terms of minimizing stage migration whereas JGC and UICC/TNM classification showed stage migration according to the increase in retrieved lymph nodes. As the incidence of lymph-node metastasis is low and the number of metastatic lymph nodes is small in early gastric cancer, there is no correlation between the metastatic lymph-node ratio and the number of retrieved nodes. However, the metastatic lymph-node ratio classification system is a more rational choice for disease-specific survival due to its simplicity and reproducibility. The result that lymph-node metastasis is an important prognostic factor for early gastric cancer suggests that lymph-node dissection may be one of the treatment for early gastric cancer.

Table 3 Multivariate Analysis of Prognostic Factors

Variables	Number	Hazard Ratio (95% CI)	*p* Value
(1)			
Lymph node metastasis (JGC)			<0.001
pN0	1306	1	
pN1	124	13.62 (4.934–37.60)	<0.001
pN2	41	48.09 (17.29–133.78)	<0.001
pN3	1	289.9 (33.47–2510.7)	<0.001
Age (years)			0.017
<70	986	1	
≥70	486	2.729 (1.194–6.241)	
(2)			
Lymph node metastasis (TNM/UICC)			<0.001
pN0	1306	1	
pN1	146	10.49 (3.676–29.93)	<0.001
pN2	20	120.9 (44.9–325.8)	<0.001
Age (years)			0.007
<70	986	1	
≥70	486	3.116 (1.356–7.161)	
(3)			
Lymph node metastasis (Lymphatic ratio)			<0.001
0	1306	1	
<0.15	128	4.867 (1.258–18.84)	0.022
≥0.15 to <0.30	23	53.25 (16.83–168.47)	<0.001
≥0.30	15	248.9 (88.86–697.1)	<0.001
Age (years)			0.012
<70	986	1	
≥70	486	2.884 (1.258–6.612)	

95% CI: 95% Confidence interval; *JGC*: Japanese classification of gastric carcinoma

Patient age was revealed to be an independent prognostic factor in the present study, which supports the findings of previous investigations of early gastric cancer.[14] This might be because early gastric cancer patients have a relatively good prognosis, irrespective of other clinicopathological factors, after curative surgery.

The differences between the JGC and UICC/TNM classification systems make it difficult to compare and discuss the lymph-node staging systems used in Western and Japanese institutions. However, the metastatic lymph-node ratio can reflect both the number of metastatic lymph nodes and the total number of dissected lymph nodes, resulting in decreased stage migration. In contrast, when using the JGC or UICC/TNM classification, stage migration inevitably occurs according to extension of the dissected fields or increases in the number of dissected lymph nodes. As shown here, the metastatic lymph-node ratio provides more accurate information about lymph-node status in early gastric cancer.

The JGC demands a complex definition of the lymph-node metastasis tier, which is difficult to apply clinically, particularly for Western surgeons, who do not routinely employ this type of classification system. An ideal classification method should be simple, homogenous, reproducible, objective, and easily applicable to follow-up schedules. It should also indicate whether adjuvant chemotherapy is advisable after curative gastrectomy. Although the JGC offers reliable information about the status of lymph-node metastasis, its prognostic stratification is not homogenous in this study. Moreover, the survival time is not homogenous when classified by the metastatic lymph-node ratio in the same JGC lymph-node stage.

The UICC/TNM classification similarly fails to meet all of the criteria for an optimal method of lymph-node classification. It does not include information about the anatomical distribution of metastatic lymph nodes, the number of dissected lymph nodes, or the extension of dissected fields. Although it is a simple and reproducible technique, it has limited predictive value for patient prognosis, and its accuracy is compromised by the effects of stage migration.

Most early gastric cancer patients have a low incidence of lymph-node metastasis, and a small number of metastatic lymph nodes. Many are also categorized as JGC pN1 or UICC/TNM pN1, so it is difficult to distinguish subgroups with a diverse prognosis. The metastatic lymph-node ratio offers more precise prognostic information for such patients.

In the current study, we initially analyzed patient prognosis in metastatic lymph-node ratio increments of 0.05, which enabled us to re-group the patients into four categories according to their hazard ratios (0, < 0.15, ≥0.15 to <0.30, and ≥0.30). This modified classification reduced the stage migration phenomenon, and resulted in a homogenous and clinically available stratification for prognosis in early gastric

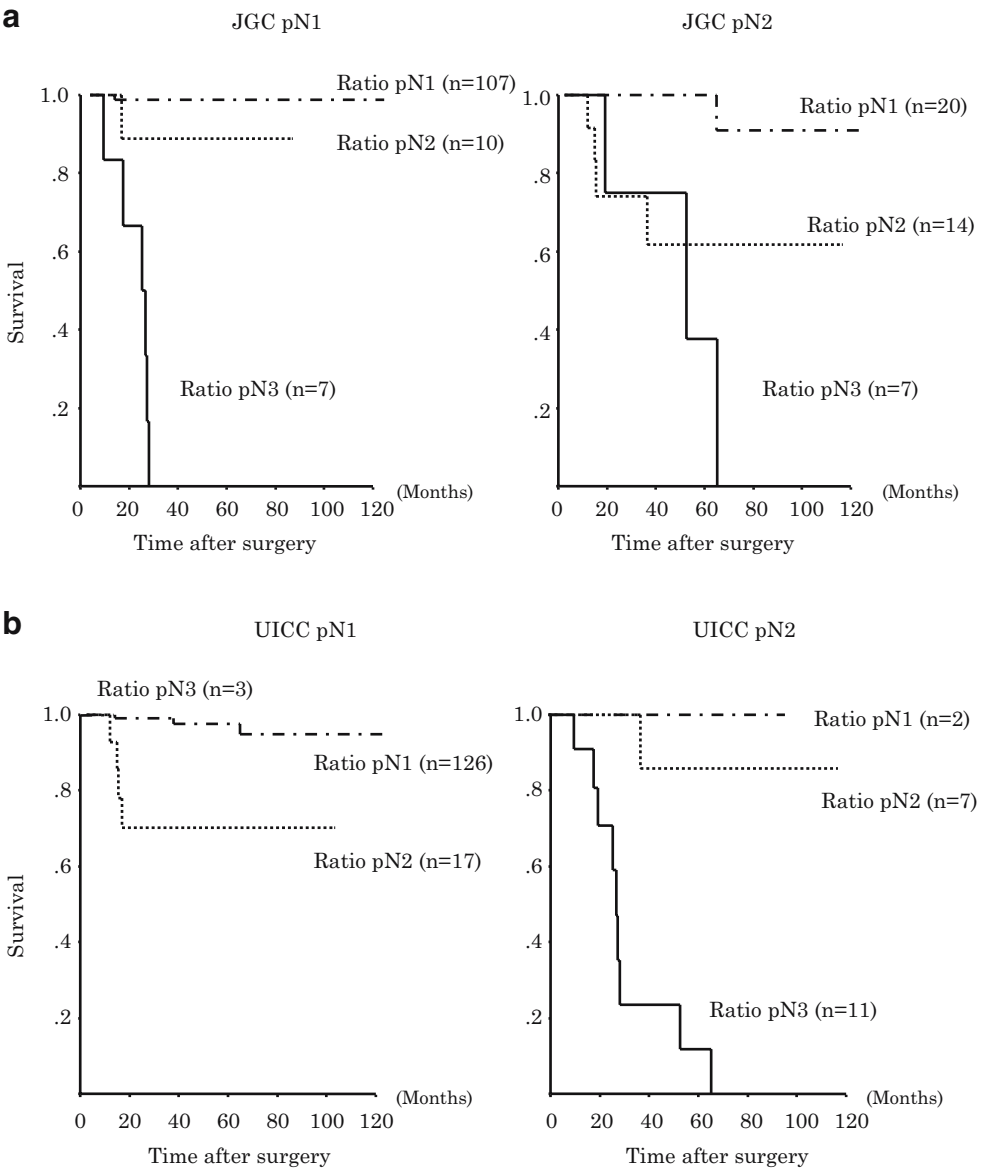

Figure 3 Comparison of survival curves of patients with early gastric cancer. **a** Classification by metastatic lymph-node ratio under the same JGC category. **b** Classification by metastatic lymph-node ratio under the same UICC/TNM classification.

cancer. The reduced incidence of stage migration might derive from low incidence of lymph node metastasis and small number of metastatic lymph nodes in patients with early gastric cancer. Moreover, the metastatic lymph-node ratio can identify a high-risk subset of patients with poor prognosis within the same degree of pN1 or pN2 category as classified by the JGC or UICC/TNM strategies. These results showed the superiority of the metastatic lymph-node classification. However, it is essential to perform further evaluation in a larger population to confirm these results. Moreover, it is useful to employ several lymph node staging systems in combination.

Surgical outcomes are usually favorable for early gastric cancer patients, so adjuvant chemotherapy is not usually administered. However, the more accurate and strict prognostic information provided by the metastatic lymph-node ratio classification enables us to plan adjuvant treatment for patients with adverse prognoses. We suggest that patients with a metastatic lymph-node ratio ≥0.30 might be considered for adjuvant chemotherapy treatment, as our system of classification demonstrated that the surgical outcome in this population was unacceptably poor. The cut-off value of the metastatic lymph-node ratio has varied in previous studies,[15–19] which might reflect differences in patient number, the proportion of different stages (early or advanced), the degree of lymph-node dissection, or the application of adjuvant chemotherapy. The current retrospective study is one of a few reports discussing the significance of the metastatic lymph-node ratio in patients with early gastric cancer [13]. As it is based on a large number of patients, it can offer reliable information, although further evaluations should be conducted in patients with early gastric cancer to clarify the advantages of the metastatic lymph-node ratio classification proposed here.

Conclusion

In conclusion, the metastatic lymph-node ratio may be a more rational and superior choice of classification than the other two classifications, and this classification provides accurate prognostic stratification after surgery for patients with early gastric cancer.

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Solitary Lymph Node Metastasis in Gastric Cancer

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Abstract The feasibility and diagnostic reliability of sentinel node (SN) biopsy for gastric cancer are still controversial. We studied the clinicopathological features and localization of solitary lymph node metastasis (SLM) in gastric cancer to provide useful information for use of the SN concept in gastric cancer. From 2000 to 2004, 3,267 patients with gastric cancer underwent D2 radical gastrectomy. The clinicopathological features of 195 patients with histologically proven SLM and the distribution of metastasized nodes were assessed. The incidence of SLM was 6.0% in all cases. Compared with the node-negative patients, significant differences were observed in age, tumor size, depth of invasion, and surgical type. The cumulative 5-year survival rate of patients with SLM was 80.5%, which was significantly lower than 90.2% for node-negative patients ($P<0.001$). Of patients with SLM, 82.6% had it in the perigastric node area (N1), and the other 17.4% patients had skip metastasis in the N2-N3 nodes. Perigastric nodes were the most common first sites of drainage from the tumor, making them the main targets of the operative SN mapping procedure. Due to the higher than expected incidence of skip metastasis in gastric cancer, D2 lymphadenectomy should be performed until the reliability of SN navigation surgery is validated in multicenter prospective clinical trials.

Keywords Solitary lymph node metastasis · Gastric cancer · Sentinel node

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Introduction

Lymph node metastasis is one of the most important prognostic factors in patients with gastric cancer.[1–3] D2 lymph node dissection can increase the long-term survival of gastric cancer patients with lymph node metastasis and therefore has become a standard surgical procedure for curative treatment in Korea and Japan. In contrast, standard D2 lymph node dissection may be unnecessary for patients without lymph node metastasis. To decrease the perioperative morbidity and mortality and to improve the quality of life, less invasive surgery has been employed on patients with node-negative gastric cancer.[4–6] However, it is difficult to precisely diagnose lymph node metastasis using preoperative examinations such as endoscopic ultrasonography and computed tomography.[7, 8]

Sentinel node (SN) biopsy, which examines the first lymph node to receive drainage from the primary tumor,

has been successfully introduced to assess tumor involvement in regional lymph nodes in patients with breast cancer[9] and malignant melanoma.[10] However, the feasibility of SN mapping of gastric cancer is still unclear and controversial because the lymphatic drainage of the stomach is considerably more complex due to its complex embryological development.[11] To explore and provide useful information about the SN concept of gastric cancer, we retrospectively analyzed the clinicopathological characteristics and location of solitary lymph node metastasis (SLM) in gastric cancer patients.

Material and Methods

From January 2000 to December 2004, 3,267 patients with gastric cancer underwent radical gastrectomy with D2 or D3 lymph node dissection at the Department of Surgery, College of Medicine, Yonsei University, Korea. Of these patients, 1,730 (56.5%) were node-negative and 1,537 (43.5%) had lymph node metastasis. Of those patients with lymph node metastasis, we enrolled 195 (6.0%) who had solitary lymph node metastasis with the following criteria: (1) the primary lesion was solitary and limited to one part of the stomach, (2) the total number of retrieved lymph nodes was more than 15, and (3) the histological examination of all resected lymph nodes revealed only one involved lymph node. According to the node metastasis system of the Japanese Classification of Gastric Carcinoma,[12] 161 patients had metastasis confined to the N1 group, and the other 34 patients had distant group lymph node metastasis (N2 or N3) without perigastric node metastasis (N1), which is defined as skip metastasis.

The resected specimens and lymph nodes were conventionally stained with hematoxylin and eosin and examined by pathologists. Clinicopathological features, such as gender, age, tumor size, tumor location, depth of tumor invasion, total number of retrieved lymph nodes, pathologic classification, surgical type, and survival rate, were compared between the patients with SLM and patients without lymph node metastasis and between the patients with and without skip metastasis.

Statistical Analysis

The statistical analysis was performed with the Statistical Package for Social Science (SPSS) version 13.0 for Windows (SPSS, Inc, Chicago, IL). Data were analyzed using the Student's *t* test, chi-square test, and Fisher's test. The survival rate was analyzed using the Kaplan–Meier method, and the difference between the curves was assessed using the log-rank test. Multivariate analysis was performed using a logistic regression model for the analysis of lymph node metastasis and a Cox proportional hazards model for survival analysis. A P value of <0.05 was considered statistically significant.

Results

The incidence of SLM was 6.0% (195 out of 3,267 patients) and 12.7% (195 out of 1,537 patients) for all cases and for node-positive cases, respectively. The clinicopathologic characteristics of the patients with SLM are compared with those of node-negative patients in Table 1. Statistically significant differences were observed for age, tumor size, depth of tumor invasion, and surgical type, but not for gender, tumor location, total number of retrieved lymph nodes, and pathologic differential classification. Logistic regression analysis revealed that the tumor size and depth of tumor invasion were independent covariates for SLM (Table 2).

The cumulative 5-year survival rate for patients with SLM was 80.5%, which was significantly lower than 90.2% for node-negative patients ($P<0.001$, Fig. 1). In multivariate analysis, only the depth of tumor invasion was an independent factor affecting the survival. The SLM itself was not an independent prognostic factor (Table 3).

Table 1 Comparison of Clinicopathologic Characteristics between Patients with Solitary Metastasized Lymph Node and Patients without Lymph Node Metastasis

Variables	Solitary LN $n=195$ (%)	Node-negative $n=1730$ (%)	P value
Age (mean, years)	58.5±11.2	56.2±11.7	0.009
Gender			0.662
Male	134(68.7)	1162(67.2)	
Female	61(31.3)	568(32.8)	
Tumor size (mean, cm)	4.2±2.5	2.8±2.0	<0.001
Tumor location			0.689
Lower	97(49.7)	890(51.4)	
Middle	78(40.0)	641(37.1)	
Upper	20(10.3)	199(11.5)	
Depth of invasion			<0.001
T1	46(23.6)	1201(69.4)	
T2	60(30.8)	263(15.3)	
T3	82(42.0)	255(14.7)	
T4	7(3.6)	11(0.6)	
Surgical type			0.005
Subtotal gastrectomy	148(75.9)	1450(83.8)	
Total gastrectomy	47(24.1)	280(16.2)	
Pathology			0.130
Differentiated	84(43.1)	844(48.8)	
Undifferentiated	111(56.9)	886(51.2)	

Table 2 Logistic Regression Analysis of the Risk for Solitary Lymph Node Metastasis

Parameter	Risk ratio	95%CI	*P* value
Age(years)			0.08
>65 vs ≤65	1.362	0.963–1.926	
Gender			0.483
Female vs male	0.888	0.638–1.237	
Tumor size			<0.001
>3cm vs ≤3 cm	2.094	1.482–2.959	
Depth of invasion			<0.001
T3-4 vs T1-2	3.230	2.276–4.585	
Histology			0.687
Undifferentiated vs differentiated	1.069	0.772–1.480	

Table 3 Multivariate Analysis of Prognostic Factors for Solitary Lymph Node Metastasis

Parameter	Risk ratio	95%CI	*P* value
Gender			0.570
Female vs male	0.843	0.468–1.520	
Age(years)			0.613
>65 vs ≤65	0.838	0.422–1.663	
Tumor size			0.793
>3cm vs ≤3 cm	1.083	0.597–1.965	
Tumor location			
Middle vs lower	0.739	0.410–1.332	0.314
Upper vs lower	1.288	0.625–2.657	0.493
Depth of invasion			0.001
T3-4 vs T1-2	2.601	1.494–4.526	
Solitary LN metastasis			0.253
With vs without	1.169	0.638–1.825	
Histology			0.076
Undifferentiated vs differentiated	0.627	0.373–1.056	

Location of the Metastasized Nodes and Skip Metastasis

Lower-third (L) tumors: Of 97 patients with lower-third tumors, 79 patients had SLM in the perigastric node (N1) close to the primary tumor. The No. 6 and No. 3 stations were involved in 31 (32.0%) and 23 (23.7%) patients, respectively, and were the most common SLM stations in the N1. In the other 18 cases, nodes metastasis was found in the N2 or N3 group without N1 involvement. Four cases were observed along the left gastric artery (No. 7 station), seven along the common hepatic artery (No. 8 station), one along the celiac trunk (No. 9 station), and five at the right cardiac (No. 1 station). The remaining one case metastasized to the No. 10 station (N3).

Middle-third (M) tumors: In 66 out of 79 patients with M tumors, the SLM was found in the N1 group. The most common metastasized lymph nodes were No. 3 station (27 cases, 34.6%) and No. 4 station (22 cases, 28.2%), and another eight, five, and three cases had SLM at the No. 1, No. 5, and No. 6 stations, respectively. Skip metastasis was found in 13 patients with M tumors. Among them, five cases metastasized to the No. 2 station and eight cases to the celiac region (Nos. 7, 8, 9).

Upper-third (U) tumors: In 20 patients with U tumors, 17 patients with SLM were found in the N1, and the most common metastasized node station was No. 3 (eight cases, 40%). Of three patients with skip metastasis, two were metastasized to the No. 7 station, and one was metastasized to the No. 9 station (N2, Table 4).

The proportion of skip metastasis was 17.4% (34 out of 195 patients) in gastric carcinoma patients with SLM. A comparison of clinicopathologic findings between the patients with and without skip metastasis is shown in Table 5. There were no differences with respect to gender,

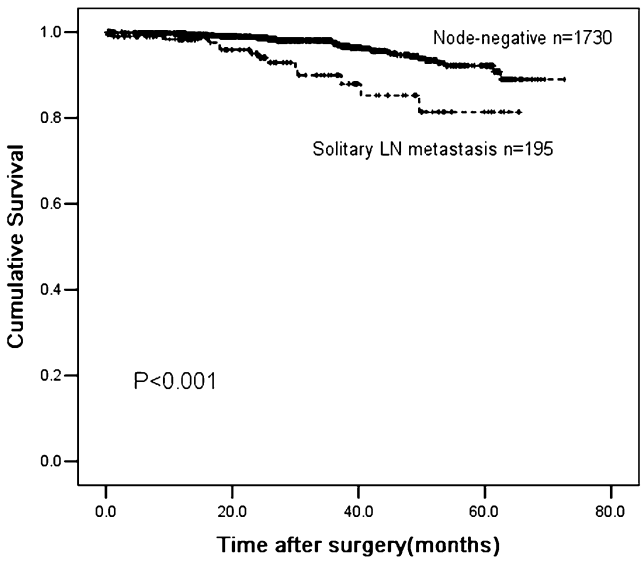

Figure 1 The comparison of survival curves between gastric carcinoma patients with solitary lymph node metastasis and without lymph node metastasis. The gastric carcinoma patients with solitary lymph node metastasis showed a significantly worse survival than patients without lymph node metastasis ($P<0.001$).

Table 4 Distribution of Solitary Lymph Node Metastasis

Station No.	Lower *n*=97 (%)	Middle *n*=78 (%)	Upper *n*=20 (%)
1	5(5.2)[a]	8(10.3)	5(25)
2	–	5(6.4)[a]	–
3	23(23.7)	27(34.6)	8(40.0)
4	12(12.4)	22(28.2)	4(20.0)
5	13(13.4)	5(6.4)	–
6	31(32.0)	3(3.8)	–
7	4(4.1)[a]	4(5.1)[a]	2(10.0)[a]
8	7(7.2)[a]	2(2.6)[a]	–
9	1(1.0)[a]	2(2.6)[a]	1(5.0)[a]
10	1(1.0)[a]	–	–

[a] Skip lymph node metastasis

Table 5 Comparison of Clinicopathologic Characteristics between the Patients with and without Skip Lymph Node Metastasis

Variables	Skip(−) n=161 (%)	Skip(+) n=34 (%)	P value
Age (mean, years)	58.8±11.1	57.2±11.6	0.447
Gender			0.796
Male	110(68.3)	24(70.6)	
Female	51(31.7)	10(29.4)	
Tumor size (cm)	4.4±2.6	3.6±1.6	0.106
Tumor location			0.905
Lower	79(49.1)	18(53.0)	
Middle	65(40.4)	13(38.2)	
Upper	17(10.5)	3(8.8)	
Depth of invasion			0.394
T1	35(21.7)	11(32.4)	
T2	50(31.1)	10(29.4)	
T3	69(42.9)	13(38.2)	
T4	7(4.3)	0(0)	
Total retrieved LN(mean)	40.3±15.4	35.4±11.8	0.077
Surgical type			0.369
Subtotal gastrectomy	121(75.2)	28(82.4)	
Total gastrectomy	40(24.8)	6(17.6)	
Pathology			0.370
Differentiated	67(41.6)	17(50.0)	
Undifferentiated	94(58.4)	17(50.0)	

age, tumor size, tumor location, depth of tumor invasion, total number of retrieved lymph nodes, surgical type, or pathological classification. The cumulative survival rate was also not statistically different between the two groups (P=0.338, Fig. 2).

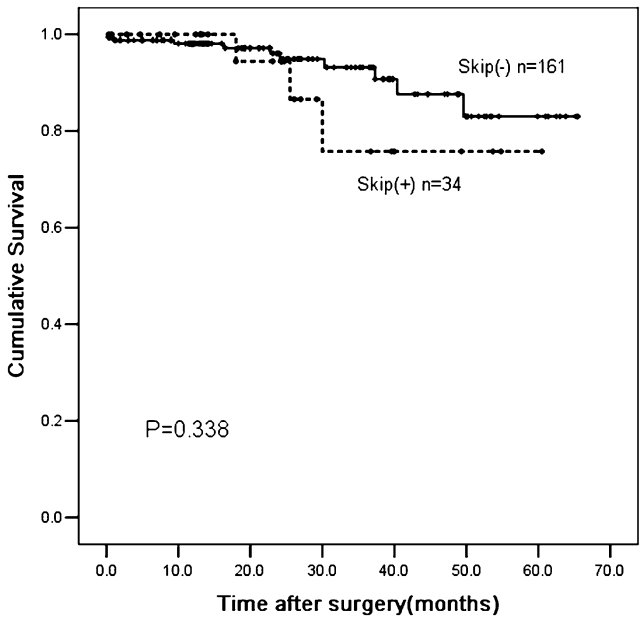

Figure 2 The cumulative survival curves for gastric carcinoma patients with or without skip lymph node metastasis. There was no significant difference between the two groups (P=0.338).

Discussion

It is well known that the status of lymph node metastasis and the depth of the tumor invasion are the most important prognostic factors in patients with gastric cancer after curative operation.[1–3, 13] Although a strong correlation has been demonstrated between survival rate and the number of positive lymph nodes in patients with gastric cancer according to the N category of the UICC, the extent of positive lymph nodes based on the Japanese Classification of Gastric Cancer is still an independent prognostic factor in multivariate survival analysis, which is considered also to reflect the anatomical pathway of lymphatic spread. In the present study, patients with SLM had a worse survival rate than did those without lymph node metastasis. T stage was not only one of the independent risk factors for SLM but also an independent prognostic factor for survival. Consequently, solitary lymph node metastasis is associated with the depth of tumor invasion and has prognostic significance for gastric cancer.

The lymphatic drainage route is patient-specific and lesion-specific in gastric cancer due to complicated lymphatic streams from the stomach. The most common channel for metastasis has been analyzed by subdividing the location of the tumor. For upper-third tumors, the left gastric artery channel (Nos. 1, 3, 7) is the most common route. For the lower- and middle-third tumors, the left gastric artery channel and right gastroepiploic artery channel (No. 4 and No. 6) are equally frequent routes.[14, 15] In this study, 82.6% of SLM cases were in the perigastric node area. The No. 1 and No. 3 stations were the most common first metastasized lymph node stations in upper-third tumors. In lower and middle tumors, Nos. 3, 4, and 6 stations were metastasized more frequently than other stations. So, the anatomical characteristics of the stomach make it relatively more suitable for SN mapping than the esophagus and rectum, and these fields are the main targets for operative SN lymphatic mapping procedures.

There have been several studies supporting the validity of the SN concept for gastric cancer in the past decade. However, the introduction of this technology into clinical practice requires considerable caution because there is a potential risk of negatively affecting long-term survival due to false negative results. Our results suggest that although most SLM is found in the perigastric node area, up to 17.4% of patients, who had the first metastasis beyond the perigastric region, demonstrate skip metastasis without N1 involvement. Some studies show that single nodal metastasis is distributed beyond the perigastric area in 12.6–29% of gastric cancer patients,[16–19] which may be caused by complicated lymphatic drainage from the stomach. In this study, we also found that there is no significant difference in survival between patients with and without skip metastasis after standard D2 lymphadenectomy, suggesting

that we would achieve the same surgical outcome if skip metastasis is found using SN mapping. The following factors could play some role in the pathogenesis of skip metastasis: (1) Occult metastasis or micrometastasis to N1 nodes may have been missed during the dissection or routine histopathologic examination; (2) There may have been some aberrant lymphatic drainage patterns in patients with gastric cancer through which metastasis bypassed the lymphatic vessels;[16,17,20] (3) Lymphatic flows to the N1 nodes may have been blocked by cancer tissue; (4) Free cancer cells may diffuse through regional nodes to distant nodes because the microenvironment in N1 nodes is unfit for the development of metastasis.[21]

Clinically, early gastric cancer seems an appropriate situation in which to use a modified therapeutic approach using the SN concept.[22,23] In this study, 46 patients with early gastric cancer had SLM, and among them, 11 patients (23.9%) had skip metastasis. Until now, the accuracy of SN mapping with a visible tracer or radio-guided approach was unsatisfactory, and surgeons have been skeptical about the application of the SN concept for gastric cancer because of the relatively high incidence of skip metastasis. Therefore, gastrectomy with D2 lymphadenectomy should be the standard procedure for gastric cancer until the reliability of SN navigation surgery is validated in multicenter prospective clinical trials.

Although the results from this study are not a realistic representation of the occurrence of SN in gastric cancer, they can provide some valuable information for the use of the SN concept in the treatment of gastric cancer.

Conclusion

Solitary lymph node metastasis is associated with the depth of tumor invasion and has prognostic significance for gastric cancer. Perigastric nodes were the most common first sites of drainage from the tumor, making them the main targets of the operative SN mapping procedure. Due to the higher than expected incidence of skip metastasis in gastric cancer, D2 lymphadenectomy should be performed until the reliability of SN navigation surgery is validated in multicenter prospective clinical trials.

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Helicobacter Genotyping and Detection in Peroperative Lavage Fluid in Patients with Perforated Peptic Ulcer

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Abstract

Introduction and Objectives Certain *Helicobacter pylori* genotypes are associated with peptic ulcer disease; however, little is known about associations between the *H. pylori* genotype and perforated peptic ulcer (PPU). The primary aim of this study was to evaluate which genotypes are present in patients with PPU and which genotype is dominant in this population. The secondary aim was to study the possibility of determining the *H. pylori* status in a way other than by biopsy.

Materials and Methods Serum samples, gastric tissue biopsies, lavage fluid, and fluid from the nasogastric tube were collected from patients operated upon for PPU. By means of PCR, DEIA, and LIPA the presence of the "cytotoxin associated gene" (*cagA*) and the genotype of the "vacuolating cytotoxin gene" were determined.

Results Fluid from the nasogastric tube was obtained from 25 patients, lavage fluid from 26 patients, serum samples from 20 patients and biopsies from 18 patients. Several genotypes were found, of which the *vacA* s1 *cagA* positive strains were predominant. Additionally, a correlation was found between the *H. pylori* presence in biopsy and its presence in lavage fluid ($p=0.015$), rendering the latter as an alternative for biopsy. Sensitivity and specificity of lavage fluid analysis were 100% and 67%, respectively.

Conclusion This study shows the *vacA* s1 *cagA* positive strain is predominant in a PPU population. The correlation found between the *H. pylori* presence in biopsy and its presence in lavage fluid suggests that analysis of the lavage fluid is sufficient to determine the *H. pylori* presence. Risks associated with biopsy taking may be avoided.

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Keywords *H. pylori* · Perforated Peptic Ulcer · Genotype · Peroperative lavage fluid · Peptic Ulcer Disease

Introduction

Over the past decades the incidence of perforated peptic ulcer (PPU) has declined in the western world. However, with an incidence varying between two and 10 per 100,000, it still is a problem in modern society.[1] Moreover, mortality rates caused by gastric and duodenal ulcer perforation vary between 10 and 40% and zero and 10% respectively, and is higher among elderly patients.[2,3] Several risk factors for PPU have been described such as smoking, alcohol abuse, and history of peptic ulcer disease (PUD).[2] However, the main pathogenic factors are considered to be the use of non-steroidal anti-inflammatory drugs (NSAID) and the presence of *H. pylori*.[2]

Helicobacter pylori are widespread bacteria, with a prevalence ranging from 25% in the industrialized world to more than 70% in developing countries.[4,5] Most infected people remain asymptomatic; however, a small group of carriers will develop PUD.

Of patients who have developed PPU, 70% will test positive for *H. pylori*,[2] suggesting the pathogenesis of perforation is associated with the presence of *H. pylori*. In addition, it is shown that different genotypes of *H. pylori* are associated with different clinical manifestations like PUD and gastric cancer.[6,7] Two well-known *H. pylori* genes that have been associated with PUD are the cytotoxin-associated gene (*cagA*) and the vacuolating cytotoxin gene (*vacA*).[6,8–10]

VacA is present in all *H. pylori* strains and is associated with gastritis, PUD, and gastric carcinoma.[10–12] It encodes for a vacuolating cytotoxin that causes epithelial cell injury and interferes with the immune system.[13,14] *VacA* contains at least two variable regions, the signal peptide (s)-region and the middle (m)-region. The s-region contains two allelic types, s1 and s2. The s1 strain has several subtypes, being s1a, s1b, and s1c.[15] Two allelic types exist for the m-region, m1 and m2. The latter has two subtypes, m2a and m2b.[16]

CagA is considered a marker for a genomic pathogenicity (cag) island that is associated with enhanced virulence.[17]

If PPU is associated with a specific *H. pylori* genotype it may be feasible to limit the patients undergoing antibiotic therapy to those who have this genotype. When this specific type is not present, another cause of PPU should be looked for and antibiotic therapy should not be started. This would mean cost reduction and, probably, a reduction in the speed of the development of antibiotic resistance.

Currently, gastric biopsy during endoscopy is a generally accepted method to diagnose *H. pylori* infection. However, patients with PPU will not undergo endoscopy but will generally be operated upon immediately. Taking a biopsy intraoperatively implicates a higher risk of bleeding and more difficult closure of the defect. Therefore, surgeons are reluctant to take a biopsy.

The primary aim of this study was to evaluate which genotypes are present in patients with PPU and if a genotype is dominant in this population. The secondary aim was to study the possibility of determining the *H. pylori* status in a manner other than by gastric tissue biopsy.

Methods

From 30 consecutive patients operated on for PPU serum samples, gastric tissue biopsies, lavage fluid, and fluid from the nasogastric tube were collected. These patients were treated in five different medical centers throughout the Netherlands. In each of these centers approval of the medical ethical committee was obtained. Immediately after collection, the materials were frozen at −20°C. One researcher performed the analysis and genotyping. For *H. pylori* genotyping, the presence of cytotoxin-associated gene (*cagA*) and the s- and m-region genotypes of the vacuolating cytotoxin gene (*vacA*) were determined.

DNA was isolated according to Boom's method as described previously.[18] A guanidine thiocyanate (GuSCN) solution was added to the collected material to induce lysis of the bacteria, releasing their DNA. After addition of the silica particles (Celite) the suspension was centrifuged. The silica particles, with the attached DNA, were washed with subsequently GuSCN-containing washing buffer, ethanol 70% and acetone. After drying, the DNA was eluted in an aqueous low salt buffer. The isolated DNA was amplified by means of polymerase chain reaction (PCR) and subsequently the presence of *cagA* and different types of *vacA* were analyzed by means of reverse hybridization on a strip (32). This assay consists of a nitrocellulose strip that contains dT-tailed oligonucleotide probes immobilized as parallel lines. For each strain, 10 μl of each PCR product (containing biotin at the 5′ end of each primer) was denatured by the addition of an equal amount of 400 mM NaOH and 10 mM EDTA in a plastic trough. After 5 min, 1 ml of prewarmed hybridization solution (2× SSC [1× SSC is 0.15 M NaCl plus 0.015 M sodium citrate], 50 mM Tris–HCl [pH 7.5], 0.1% SDS) was added, and a strip was submerged and incubated in a shaking water bath at 50°C for 1 h. The strips were washed with 2 ml of 2× SSC-0.1% SDS for 30 min at 50°C. Subsequently, the strips were rinsed three times in phosphate buffer, and conjugate (streptavidin–alkaline phosphatase) was added. After incubation at room temperature for 30 min, the strips were rinsed again and 4-nitroblue tetrazolium chloride and 5-bromo-4-chloro-3-indolylphosphate substrate was added. Hybrids are visible as purple probe lines. Interpretation of the hybridization patterns was performed visually. As a control, a β-globin PCR was performed. Patient related factors were obtained prospectively. Statistical analysis was performed with SPSS for Windows, version 11.0.

Results

A total of 30 patients were included of whom nine were women. The average age was 65 years, varying between 40 and 87. Ten patients (33.3%) were operated laparoscopically. The perforation was found prepyloric in 11 patients, at the site of the pylorus in eight patients and postpyloric in 11 patients.

A total of five (16.7%) patients had a history of PUD. Ten patients (33.3%) used NSAID's, two patients (6.7%)

Table 1 *Helicobacter pylori* Status and Genotype

Patient	Fluid from naso-gastric tube	Lavage fluid	Serum	Gastric tissue biopsy
1	s1a/m2a/cag			
2	s1a/m2a/cag	s1a/m2a/cag		s1a/m2a/cag
3	s1b	s1a/m2a/cag		
4		s1a/s2/m2a		
5		s1a		s1a/m1
6				
7	s1a/m2a			
8				
9	s1b/m1/cag	s1b/m1/cag		
10				
11				
12		s1a/m2a/cag		
13				
14	s1a/m1/cag			s1a/m1/cag
15		s1a/m1/cag		s1a
16	s1a/m1/cag	s1a/m1/cag		
17	s1a/m1/cag			
18				
19	s1a/m1/cag	s1a/m1/cag		
20	s1a/m1/cag	s1a/m1/cag		
21	s1a/m1/cag	s1a/m1/cag		
22				
23		s1a/m1/cag		
24	s1a/s1b/m1/cag	s1a/s1b/m1/cag		s1b/m1
25		s1a/m1/cag		s1b/m1/cag
26		s1a/m2a/cag		
27		s1a/m2a		s1a/m1/cag
28	s1a/s2/m2a/cag	s1a/s2/m2a/cag		s1a/s2/m2a/cag
29		s2/m2a		s2/m2a
30				
	ß-globin and *H. pylori* positive			
	ß-globin and *H. pylori* negative			
	ß-globin positive and *H. pylori* negative			
	ß-globin negative and *H. pylori* positive			
	No materials			

The colors represent the β-globin and *H. pylori* status of the patient.

used steroids, three patients (10.0%) used acid reducers, and one patient (3.3%) used a proton pump inhibitor (PPI) before admission to the hospital. The average hospital stay was 11.9 days, varying between 3 and 37 days.

Fluid from the nasogastric tube was obtained from 25 patients, lavage fluid from 26 patients, serum samples from 20 patients, and ulcer biopsies from 18 patients. The results of the genotyping are depicted in Table 1.

The β-globin determination was performed as a control. In nine samples of nasogastric tube fluid and in two samples of lavage fluid it was negative, rendering these results as unreliable. Therefore, these results were excluded from further analysis.

Table 2 represents the frequency of the individual genes and the allelic types found in the different samples by means of PCR and LiPA.

These tables show that for *vacA* the allelic type s1 is predominantly present in all three types of samples. In the s1 positive strains, subtype s1a is predominant as depicted in Table 3.

With regard to the middle region of *vacA* the incidence of m1 allelic type is slightly higher; however, the difference

Table 2 Frequencies of Individual Genes and Allelic Types

Genotype	Fluid from Naso-Gastric Tube		Lavage Fluid		Gastric Tissue Biopsy		Control Non-Ulcer
	No.	%	No.	%	No.	%	%
VacA s1	10	90.9	14	77.8	7	77.8	46.9
VacA s2	0	0	1	5.5	1	11.1	38.4
VacA multiple	1	9.1	3	16.7	1	11.1	14.7
Total	11	100	18	100	9	100	100
VacA m1	6	54.5	9	50.0	5	55.6	29.4
VacA m2	4	36.4	8	44.4	3	33.3	55.9
VacA incomplete genotype	1	9.1	1	5.6	1	11.1	0 (14.7 % incomplete)
Total	11	100	18	100	9	100	100
CagA positive	9	81.8	14	77.8	5	55.6	47.1
Total	11	100	18	100	9	100	100

"*VacA* multiple" means that more than one allelic type or subtype has been found in one sample.
In each different type of sample one incomplete genotype occurred, which is indicated as "*vacA* incomplete". The "Control non ulcer" column represents the frequencies, found by van Doorn et al., in a population without PUD and is added to allow easy comparison.

is less outspoken compared to s1. The m2a was the only subtype that was found in the samples. In three samples, the genotyping was incomplete (Tables 1 and 2), meaning that determination of the middle region was not possible. This was most likely caused by the small number of bacteria present in those samples.

With regard to the secondary aim of this study, analyzing possibilities to diagnose *H. pylori* presence in another fashion than through biopsy, the *H. pylori* status found in each type of sample was compared. A correlation was found between the *H. pylori* presence in biopsy and its presence in lavage fluid (Fisher's exact test, $p=0.015$), indicating lavage fluid is a valid alternative for determination of *H. pylori* infection.

The sensitivity and specificity of the lavage fluid analysis was calculated, considering biopsy as a golden standard. Fourteen patients, of which the lavage fluid as well as the biopsy was analyzed, were included into this calculation (patients 2, 4, 5, 6, 8, 10, 15, 23–25, 27–30, Table 1), which is shown in Table 4. Of the remaining patients, either the biopsy or the lavage fluid was missing; therefore, these data cannot be used in the sensitivity/specificity calculation.

The sensitivity was 100%, which means that in case of the presence of *H. pylori* in the biopsy specimen, the lavage fluid analysis detected it in 100% of cases. The specificity of lavage fluid analysis was 66.7%, which means the chance for false-positives is over 30%. With regard to gender, age, BMI, history of PUD, location of perforation, complications after procedure, and use of steroids, PPI, or antihistaminic medication, no statistically significant correlation was found.

Discussion

Concerning the role of *H. pylori* in the pathogenesis of PPU, some studies have been reported comparing the prevalence of *H. pylori* infection in patients with PPU to the prevalence in controls. They appear to be similar, suggesting that other factors like NSAID use play a role.[19–21] However, the substantial genetic heterogeneity

Table 3 Distribution of the *vacA* s1 Subtypes

VacA Subtype	Fluid from Naso-Gastric Tube		Lavage Fluid		Gastric Tissue Biopsy		Control Non-Ulcer
	No.	%	No.	%	No.	%	%
S1a	8	80.0	13	92.9	5	71.4	81.3
S1b	2	20.0	1	7.1	2	28.6	18.7
S1c	0	0	0	0	0	0	0
Total	10	100	14	100	7	100	100

The s1a subtype is predominant in all sample types.
The "Control non ulcer" column represents the frequencies, found by van Doorn et al., in a population without PUD and is added to allow easy comparison.

Table 4 Calculation of Sensitivity and Specificity of Lavage Fluid Analysis

	Biopsy			
Lavage fluid		+	–	Total
	+	8	2	10
	–	0	4	4
	Total	8	6	14
		Sens 8/8=1	Spec 4/6=0.67	

of *H. pylori* that has been revealed over the years leads to the hypothesis of a specific genotype causing PPU.[5] Controls might test positive for *H. pylori*, but not develop PPU because it would not be this specific genotype that is isolated. This study of a selected population of patients, all with PPU, shows a limited diversity of *H. pylori* genotypes as represented by Table 1.

VacA s1 strains are predominantly present in the three sample types of which s1a is the predominant subtype. Concerning the *vacA* m-region, the m1 strains are found in a majority of cases; however, the difference is less convincing than for *vacA* s1. Except for the biopsy samples, the *cagA* positive strains were predominantly present is this population. In the biopsy samples, the frequency of *cagA*-positive strains seemed to be low; however, this number is distorted because in two of nine positive biopsies, a decent comparison with the other samples was not possible. In patient 5, genotyping of the lavage fluid and nasogastric tube fluid was incomplete, and for patient 15, the opposite was the case. This means that the actual incidence should be 71.4 % (5/7).

Summarising, these results shows that the *vacA* s1, *cagA*-positive strains were predominant in this population of patients with PPU. This finding is in accordance with literature reporting correlations between the presence of *vacA* s1, *cagA*-positive strains and PUD.[6,10] Therefore, detection of the genotype *vacA* s1 does not specifically predict PPU; nevertheless, clinicians should be aware of this association.

In Tables 2 and 3 the genetic distribution in a Dutch population without PUD, as found by van Doorn et al., are added for comparison. The frequencies found in this study for *vacA* s1, m1, and *cagA*-positive strains are clearly higher than in the non-PUD group, confirming the aforementioned hypothesis. However, with regard to the subtypes, Table 3 shows an almost similar distribution of frequencies, suggesting that determination of the allelic subtype is of less importance.

In only 60% of patients biopsies could be analyzed. The reason for missing 40% is the restraint of the surgeon to take a biopsy when risk of bleeding and more difficult closure of the defect was estimated to be too high, which emphasizes the importance of finding an alternative. To do so, the *H. pylori* status of the patient as determined by biopsy was compared to the status as determined by analysis of nasogastric tube fluid, lavage fluid, and serum. A statistically significant correlation was found between the *H. pylori* status in biopsy and its status in lavage fluid (Fisher's exact test, $p=0.015$). This finding suggests that determination of the *H. pylori* status can be done with lavage fluid as well, obviously without any risk of bleeding and closure related difficulties. The sensitivity is 100%, but the specificity is 66.7%. This could mean the chance for false-positives is over 30%, which is not optimal and could lead to therapy overshoot. However, considering the fact that with the lavage a larger area is sampled, rendering the chance of positive test results higher than in biopsy, it is more likely to find false negative biopsy results. This could lead to a therapy undershoot, which obviates the importance having an alternative for a biopsy.

In only two samples, both nasogastric tube fluids, a *H. pylori* genotype was isolated, while β-globin tested negative. In nine samples (seven nasogastric tube fluid, two lavage fluid) both β-globin and *H. pylori* tested negative. This means that either no humane cells were present in the samples, which is unlikely, or that an error in the PCR procedure had occurred. Because this was unclear these results were considered unreliable. Therefore, it still could be possible that nasogastric tube fluid is a good alternative for determining the *H. pylori* status as well.

Overall, these results are positive, however they should be confirmed in a larger population.

Conclusion

This study shows that in a population of 30 patients with PPU, *vacA* s1, *cagA* positive strains are predominant. This finding is in accordance with literature reporting correlations between the presence of *vacA* s1, *cagA*-positive strains, and PUD. Therefore, detection of this genotype does not specifically predict PPU. Nevertheless, clinicians should be aware of this association.

This study shows as well that it is feasible to use intraoperative lavage fluid to determine the *H. pylori* status of the patient, implicating that biopsies, with a risk of bleeding and more difficult closure of the defect, are not necessary anymore. In addition, considering the fact that a larger area is sampled with lavaging, biopsies may result in more false negative results leading to insufficient therapy.

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Laparoscopic Treatment of Gastric GIST: Report of 21 Cases and Literature's Review

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Abstract
Background Although the feasibility of laparoscopic resection of gastric gastrointestinal stromal tumors (GISTs) has been established, various aspects are debated. This paper describes the problems of minimally invasive resection of gastric GISTs and compares this experience with an extensive literature review.
Study Design Between August 2001 and December 2006, 21 consecutive patients undergoing laparoscopic resection of gastric GISTs were enrolled in a prospective study. A literature review of laparoscopic treatment was performed on Pubmed using keywords GIST and surgery. A comparison with authors' experience with open wedge-segmental resection of GISTs (25 cases from November 1995 to December 2000) was also carried out. Statistical analysis was based on chi-squared test and *t* Student evaluation.
Results Twenty-one patients, mean age 50.1 years (range, 34–68 years), were submitted to laparoscopic wedge- segmental gastric resections. Mean tumor size was 4.5 cm (range, 2.0–8.5 cm). Mean operative time was 151 min (range, 52–310 min), the mean blood loss was 101 mL (range, 10–250 mL), and the mean hospital stay was 4.8 days (range 3–7 days). There were no major operative complications or mortalities. All lesions had negative resection margins. At a mean follow-up of 35 months, all patients were disease-free. Morbidity, mortality, length of stay, and oncologic outcomes were comparable to the open surgery retrospective evaluation (p=not significant).
Conclusions As found also in the literature review, the laparoscopic resection is safe and effective in treating gastric GISTs. Given these findings as well as the advantages afforded by laparoscopic surgery, a minimally invasive approach should be the preferred surgical treatment in patients with small- and medium-sized gastric GISTs.

Keywords GIST · Laparoscopy · Surgery

Abbreviations
GIST gastrointestinal stromal tumors

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Introduction

Gastrointestinal (GI) stromal tumors (GISTs) are rare tumors. Historically, most of these malignancies were classified as leiomyomas, leiomyoblastomas, and leiomyosarcomas.[1–3] However, with the advent of electron microscopy and immunohistochemistry, a pleuropotential intestinal pacemaker cell (the interstitial cell of Cajal) was identified as the origin of GISTs.[4–5] The recent identification of the CD117 antigen and CD34 in the majority of GISTs have led to further delineation of the cellular characteristics of these neoplasms.[6–8] Although GISTs are found throughout the GI tract, the stomach is the site of occurrence in more than half of patients.[2,3,9] Most

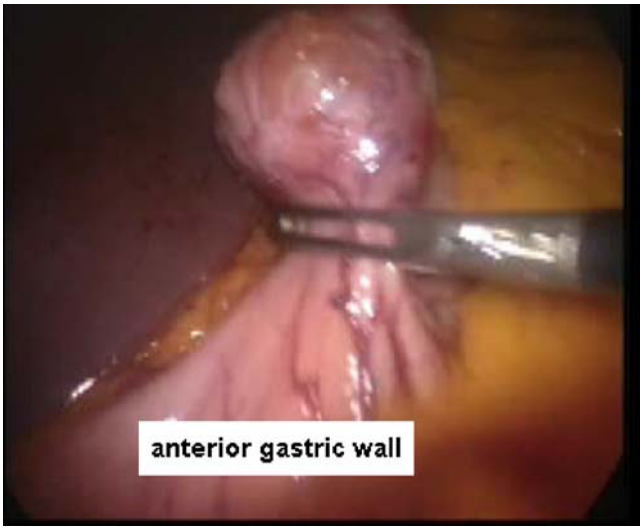

Figure 1 Gastric resection was carried out by elevating the gastric wall with a bowel clamp placed under the tumor and using a linear endoscopic GI anastomosis stapler.

patients with GIST are asymptomatic, and the lesions are discovered incidentally. Symptoms of gastric GISTs can be GI bleeding and vague abdominal pain. It is difficult to predict GIST metastatic potential: The only prognostic factors are size and grading.[9] Surgery is the standard therapy for nonmetastatic GIST: A resection with negative margin should be performed. Lymphadenectomy is not necessary because GISTs rarely give metastases to the lymph node.[10] Although the feasibility of minimally invasive resections of gastric GISTs has been established,[11–12] many aspects of this approach are debated. In this study, we present our series of 21 laparoscopically treated GISTs, and we carry out a literature review discussing problems related to invasive treatment and comparing it with the authors' experience with open wedge-segmental resection.

Material and Methods

Between August 2001 and December 2006, 21 consecutive patients undergoing laparoscopic resection of GISTs were identified in a prospective database. Patient demographic data, clinical presentation, and imaging were analyzed. Other parameters collected included operative times, blood loss, intraoperative findings, surgical technique, morbidity, and length of hospital stay. Histopathologic characteristics (size, tumor markers, and mitotic activity) were analyzed. A literature review was carried out using the terms GIST and surgery on Pubmed.[13] Laparoscopic wedge-segmental resections were utilized to treat all reported cases.

The patient was placed in a supine position with arms abducted on arm boards, and a split-leg table was used (the surgeon stood between the patient's legs). Video monitors were placed lateral to the patient's right shoulder. The first trocar was placed in the midline near the umbilicus. After insertion of other two ports in the right and left flank, the patient was placed in a reverse Trendelenburg's position. Before the resection, an abdominal exploration was carried out to exclude metastasis or peritoneal seeding. To facilitate localization of the tumor, a preoperative endoscopic marking was performed in all cases. GISTs were never directly manipulated. Gastric resection was carried out by elevating the gastric wall with a bowel clamp placed under the tumor and using a linear endoscopic GI anastomosis stapler (Figs. 1, 2). Bleeding from the stapler line was stopped with manual sutures and fibrin glue. Posterior gastric tumors were approached with the division of the gastrocolic omentum with a bipolar vessel ligation system (LigaSure; Fig. 3). For lesions nearby the curvatures, the greater omentum, lesser omentum, or gastrohepatic ligament was divided as needed with the ultrasound-coagulating shears (Ultracision). Postoperative nasogastric tubes were used in case of gastric paralysis. Patients were discharged as soon as they have a regular diet. Follow-up included physical examination, computed tomography (CT), chest radiograph, and serum chemistries every 6 months and after 2 years annually. Upper endoscopy was repeated annually. A positron emission tomography scan was performed at 1 year and after if abnormalities were found on any of the follow-up studies. All patients were visited by an Oncology Consultant for eligibility in a clinical trial for adjuvant therapy. A literature review was carried out[13] with the mesh words GIST and laparoscopy, and only single case reports were excluded. A comparison with the authors' experience with open wedge-segmental resection of GIST tumors (25 cases from November 1995 to December 2000) was also carried

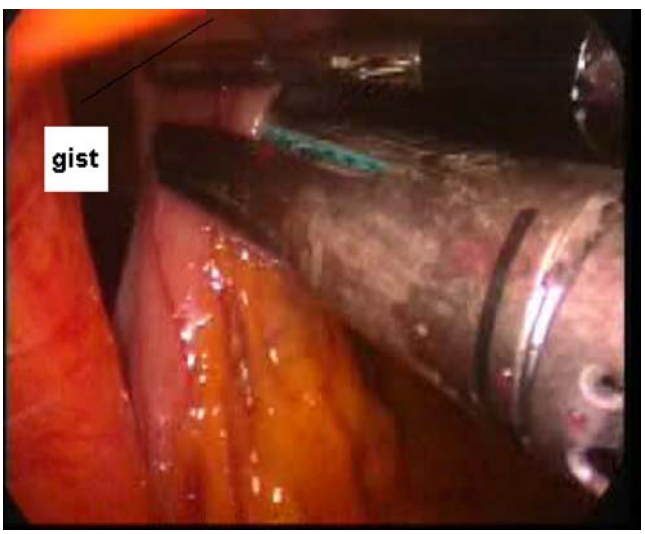

Figure 2 Gastric resection was carried out by elevating the gastric wall with a bowel clamp placed under the tumor and using a linear endoscopic GI anastomosis stapler.

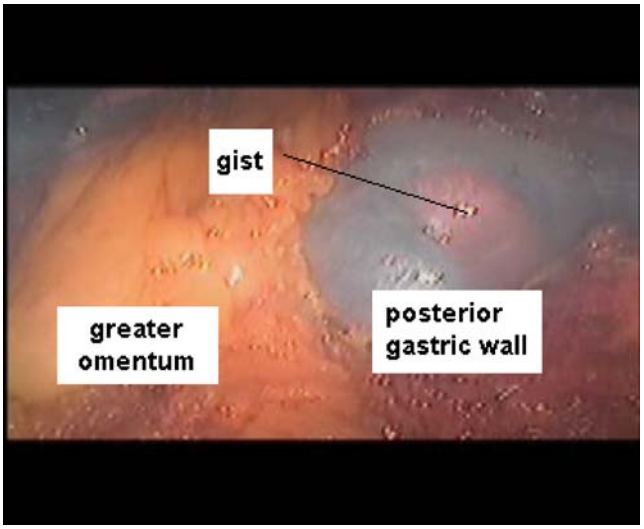

Figure 3 Posterior GIST approached with the division of the gastrocolic omentum with bipolar vessel ligation system. To facilitate localization of the tumor, a preoperative endoscopic marking was performed.

out. Statistical analysis was based on the chi-squared test and *t* Student evaluation.

Results

From August 2001 to December 2006, 21 consecutive patients undergoing laparoscopic resection of GIST were reviewed. There were 10 men and 11 women. The mean age was 50.1 years (range, 34–68 years). The presenting symptom was GI bleeding in eight subjects. Thirteen patients had lesions incidentally discovered during endoscopy for dyspepsia. All patients underwent preoperative esophagogastroduodenoscopy, endoscopic ultrasound, and abdominal CT scan.

Preoperative biopsy was carried out preoperatively in all patients with definitive diagnosis in 52.3% (11 of 21). The surgical procedures used were: laparoscopic segmental gastric resection (n=19) and laparoscopic hand-assisted segmental gastric resection (n=2; both patients had tumor size more than 5 cm). The mean operative time was 151± 56 min (range, 52–310 min), and the mean blood loss was 101±21 mL (range, 10–250 mL). There were no episodes of tumor rupture, no major intraoperative complications, and no conversions to open surgery. Postoperatively, only six (28.5%) patients needed nasogastric tubes beyond the 48-h period. We did not report either postoperative morbidity or mortality. The mean hospital stay was 4.8± 1.6 days (range, 3–7 days). The majority (16 patients 76.1%) of GIST were localized in the stomach body; four GIST were found in the antrum and one in the fundus. The mean tumor size was 4.5±2.0 cm (range, 2.0–8.5 cm). All lesions had a negative resection margins. Mucosal ulceration was found in 6 out 21 (28.5%) of the lesions, and tumor necrosis was noted in 7 out of 21 (33.3%) lesions. The mitotic index was from 0 to 50 mitotic figures (average, 4) per 10 high-power fields.

The risk classification groups are shown in Table 1. CD117 positivity was found in all patients, whereas CD34 was noted in 19 (90.4%) patients. At a mean follow-up of 35 months (range, 5–58 months), all patients are alive and disease-free without long-term morbidity related to gastric resection. Up to now, in literature, 387 gastric GISTs treated with laparoscopy are reported (all primary gastric GISTs): only single case reports were excluded from the present review (Table 1).

From November 1995 to December 2000, 25 consecutive patients undergoing open wedge-segmental resection of GIST were reviewed. There were 11 men and 14 women. The mean age was 54.6 years (range, 38–61 years). Morbidity, mortality, length of hospital stay, oncologic outcomes, and other significant parameters were comparable to the laparoscopic surgery without any statistical difference (p=not significant; Table 2).

Discussion

Mazur and Clark coined the term "gastrointestinal stromal tumor" in 1983 to identify a particular group of tumors:[14] Recently, C-kit tyrosine kinase (CD117) has been shown to be expressed by 91 to 99% of the GISTs,[15] and it can be utilized as accurate diagnostic marker.

Gastric GISTs are rare wall lesions that are becoming increasingly diagnosed because of the rising incidence of upper endoscopy and endoscopic ultrasound. Although surgical treatment is the only radical therapy for these lesions, the role of the laparoscopic approach is still discussed. This paper describes the problems of minimally invasive resection of gastric GISTs and compares this experience with an extensive literature review and with the authors' experience with open wedge-segmental resection. All patients in the present series were marked preoperatively during ultrasound endoscopy. Endoscopic ultrasound is a key component of the evaluation of submucosal lesions of the GI tract, allowing determination of the wall layer of origin of the lesion and diagnostic sampling. Endosonographic features of GIST associated with high-risk lesions include size larger than 4–5 cm, irregular or invasive border, cystic spaces, and malignant-appearing lymph nodes. Endoscopic ultrasound-guided fine-needle aspiration is generally adequate for tissue acquisition: An optimal situation is when cell blocks are made from the cytological sample. Immunohistochemical analysis is performed on the tissue to differentiate GIST from other spindle cell neo-

Table 1 Literature Review

Author	Year	Number of Patients	Method of Localization	Preoperative Biopsy	Size (Mean; Less Than)	Wedge-segmental resections (WSR)/ enucleations (E)/ Intragastric (IG) resections/ Gastrectomy (G)	Stapled (Stapl.)/ manual (Man.) sutures	Operative time (mean)	Hand assisted	Blood loss (cm^3)	Number of conversion	Surgical morbidity (Mb)/ mortality (Mt)	Postoperative stay (days, mean)	Positive margins	Risk, VL: very low, L: low, I: intermediate, H: high	Genetic markers	Mean follow-up (months), Rec: recurrence
Basso et al.[20]	2000	9	Endoscopy	n.r.	n.r.	WSR	8 Man, 1 Stapl.	97.5	No	n.r.	0	1 Mb	4	0	n.r.	n.r.	22 0 rec
Bedard et al.[21]	2006	15	Endoscopy	n.r.	4.1	14 WSR, 1 G	11 Stapl., 4 Man	174.5	No	n.r.	2	0	4.6	0	3VL; 7L; 2I; 3H	n.r.	46.5 1 rec 1 death
Berindoague et al.[22]	2007	18	n.r.	No	n.r.	10 WSR, 1IGR, 7 G	Stapl.	n.r.	No	n.r.	2	1 Mb	6	0	9L; 5I; 4H	CD 117	32 1 rec
Catena	2006	21	Marked	yes	4.5	WSR	Stapl.	151	yes	101	0	0	4.8	0	4VL; 15L; 2I	CD 117 CD 34	35
Cheng et al.[11]	1999	7	n.r.	n.r.	n.r.	WSR	n.r.	205.71	No	n.r.	0	0	6.6	0	n.r.	n.r.	n.r.
Choi et al.[23]	2000	23	Endoscopy	No	4.3	22 WSR, 1G	Stapl.	104.3	No	n.r.	0	1 Mb	5.2	0	2VL, 12 L, 7 I, 2 H	CD 117	61
Delucq et al.[24]	2007	2	Endoscopy	No	3.1	G	Stapl.	130	No	47	0	0	9.3	0	n.r.	n.r.	25
Feliu et al.[25]	2005	5	Endoscopy	n.r.	n.r.	WSR	Stapl.	49.1	No	n.r.	0	1 Mb	5.8	0	n.r.	n.r.	n.r.
Granger et al.[26]	2006	12	Endoscopy	10/12	4.1	4E, 8WSR	n.r.	138	No	n.r.	0	1Mb	2.3	0	n.r.	n.r.	19
Hepworth et al.[27]	2000	9	Gastrotomy	n.r.	n.r.	WSR	Stapl.	n.r.	No	n.r.	2	0	3	0	n.r.	n.r.	n.r.
Hindmarsh et al.[28]	2005	22	Endoscopy	3/22	4.7	WSR	Stapl.	73.8	No	196	7	n.r.	4.6	n.r.	13 L; 6 I; 3 H	n.r.	18 2 rec
Iwahashi et al.[29]	2006	22	n.r.	No	<5.0	15 WSR+ 7 IGR	n.r.	n.r.	No	n.r.	n.r.	n.r.	n.r.	0	4VL; 3 L; 7 I; 8 H	n.r.	32 4 rec death
Lai et al.[30]	2006	29	Endoscopy/ gastrotomy	No	3.4	WSR	21 Stapl. 8 Man	189.6 (Stapl. 194.3 (Man)	No	n.r.	1	0	6.7	1	n.r.	n.r.	43

Ludwig et al.[31]	2003	24	Endoscopy	Yes	3.6	E/WSR/ IGR	Stapl., Man	42.7, 69.5	No	n.r.	3	0	n.r.	0	n.r.	n.r.	23.4
Matthews et al.[12]	2002	21	Endoscopy	No	4.5	15 WSR/ 3 G/ 3 E	Stapl., Man	169	No	106	0	1Mb	3.8	1	n.r.	n.r.	20 1 rec
Mochizuki et al.[32]	2006	12	Endoscopy	yes	2.7	WSR	Stapl.	100	No	0	0	3 Mb	7	0	n.r.	10 CD34 1 S, 100 1 desmin	26
Novitsky et al.[33]	2006	46	Endoscopy	No	4.4	2G+27WSR +17 IGR	Stapl.	135	3 yes out of 46	85	0	0	3.8	0	32 LR; 4 I; 10H	39 CD117 40 CD 34	36 4 rec 2 deaths
Nguyen et al.[34]	2006	25	n.r.	n.r.	4.6	21 WSR/3 G/1 E	n.r.	143	n.r.	50	3	2 Mb 1 Mt	n.r.	n.r.	n.r.	28 CD 117	n.r.
Otani et al.[35]	2006	38	Endoscopy	Yes	4.2	37WSR+ 1 G	Stapl.	141	Yes	n.r.	0	1Mb/ 1Mt	7.2	0	n.r.	38 CD117 38 CD 34	53 1 rec
Rivera et al.[36]	2005	20	Endoscopy	n.r.	n.r.	18 WSR/ 2G	Stapl.	165	Yes	83.6	1	3 Mb	3.9	n.r.	n.r.	n.r.	16 1 rec
Rothlin and Schob[37]	2001	4	n.r.	No		WSR	Stapl.	177	No	n.r.	0	1 Mb	7.5	0	n.r.	n.r.	n.r.
Santanbrogio et al.[38]	2006	3	Endoscopic ultrasound	1/3	5.2	WSR	1 Stapl. +2 Man	n.r.	No	n.r.	0	0	6.6	0	2 L; 1H	2 CD 117; 1 S100	24
Sanchez[39]	2005	4	None	No	<1	WSR	Stapl.	n.r.	No	n.r.	0	0	n.r.	0	VL	CD 117	n.r.
Schafer et al.[40]	2006	4	Endoscopy	No	3.8	WSR	Stapl.	n.r.	No	n.r.	0	0	7	0	L	n.r.	23
Yano et al.[41]	2005	2	None	No	7.5	WSR	Stapl.	88	Yes	15	0	0	12.2	0	2 I	2 CD117 2 CD 34	11

WSR Wedge-segmental resections, *E* enucleations, *IG* intragastric resections, *G* gastrectomy, *Stapl.* stapled sutures, *Man* manual sutures, *Mb* surgical morbidity, *Mt* surgical mortality, Risk: *VL* very low, *L* low, *I* intermediate, *H* high, *Rec* recurrence

Table 2 Comparison with Open Surgery Retrospective Series

Parameter	LAP (21 cases)	Open (25 cases)	*p* value
Gender (M/F)	10:11	11: 14	N.S.
Age (years)	50.1	54.6	N.S.
Mean operative time (min)	151±56	134±33	N.S.
GIST Location (antrum/body/fundus)	4/16/1	6/17/2	N.S.
Intraoperative complications	0	0	N.S.
Morbidity	0	1 (wound infection)	N.S.
Mortality	0	0	N.S.
Mean hospital stay (days)	4.8±1.6	7.1±1.2	N.S.
Mean tumor size cm	4.5±2.0	6.2±1.9	N.S.
Negative resection margins	100%	100%	N.S.
Risk VL: very low; L: low, I: intermediate; H: high	4VL; 15L; 2I	5VL; 14L; 4I; 2H	N.S.
Follow-up (months)	35 (range 5–58)	91 (range 80–136)	N.S.
Recurrence	0	1 (with patient's death)	N.S.

N.S. Not significant, *N.A.* not applicable

plasms.[3] Preoperative biopsy was carried out in all patients with definitive diagnosis in about 50%: In the literature review, only six authors utilized a preoperative biopsy, reporting limited results. As a matter of fact, endoscopic biopsies uncommonly yield anything more than normal mucosa: A study showed that only in 35% of cases was an acceptable submucosal representation achieved with forceps biopsy during standard endoscopy, although the endoscopist intended to obtain submucosal tissue.[3]

However, an endoscopic ultrasound-directed needle biopsy frequently reveals spindle cells or can be positive for specific markers. In addition, a heterogeneous lesion larger than 4 cm and with irregular borders is reported to be highly suspicious for a malignant GIST. On the other side, the incidence of malignant seeding is relatively low, and the complication rate is about 0–2%.[16] In it is important to stress that in case of diagnostic doubts (differential diagnosis with adenocarcinoma), an intraoperative pathologic examination is mandatory.

We utilized preoperative marking and not intraoperative endoscopy only for organizational problems. In the literature review, most authors preferred an endoscopic rendezvous, and only one author utilized laparoscopic ultrasound. Otherwise, an accurate localization of the GIST is important, and only two authors used the gastrotomy to identify these tumors in case of intramural lesions. The intraoperative localization and visualization of the tumor can be difficult: We recommend the usage of intraoperative endoscopy or preoperative marking.

The mean size of laparoscopically treated GISTs in the present series was 4.5 cm, and the mean size in literature-reported cases was 4.3 cm (range 1–7.5 cm). This indicates that the laparoscopic approach has its best indications for GIST lower than 5 cm. However, in case of GISTs larger than 5 cm, the hand-assisted procedure can be utilized to facilitate gentle tumor handling, tactile feedback, and precise placement of endoscopic staplers: In the literature review, five authors reported this type of approach.

Although the National Comprehensive Cancer Network Clinical Practice Guidelines for Optimal Management of Patients with GIST suggests that laparoscopic techniques should be limited to tumors less than 2 cm[17–19]; only one author[39] reported mean tumor diameter lower than 2 cm.

Surgical resection with negative margins[2] without lymphadenectomy is the best treatment of gastric GISTs. In laparoscopic surgery, it is more difficult to define tumor borders, but we did not report infiltrated margins in our series, and in the literature review, we found only two reported cases. Wedge-segmental resection is the most performed procedure, and it is the treatment of choice. In some cases, however, tumor size and location may be an indication for a more extensive surgery, including partial or total gastrectomy[18] as occurred in a few patients in the literature-reported cases. Enucleation of the GIST, even if it still reported in literature, should be avoided to achieve oncologic safety in the resected margin. It is important to avoid direct tumor manipulation to eliminate the incidence of tumor rupture. Tumor spillage can results in dramatic consequences with disease progression, recurrence, and poor survival.[19]

The choice of manual or stapled sutures is not relevant: The majority of authors reported stapled procedures without significant differences in the leakage rate compared to manual sutured ones. All our presented patients were treated with stapled procedures without particular problems. It is important to emphasize that almost often there is a bleeding of the stapled suture line that can be easily controlled with glue and manual interrupted sutures.

In the literature review, the operative time ranged from 49 to 194.3 min, and it is obviously related to the location and size of the GIST and the surgical procedure performed. Blood loss was very low in all reported series ranging from 15 to 196 cm^3. The conversion rate ranged from 0 to 31%, and the resections were accomplished with minimal morbidity and only one perioperative death. A short in-hospital stay ranging from 2.3 to 12.2 days for complicated cases was also demonstrated.

The reported series showed the oncologic safety of the laparoscopic approach, with survival and recurrence rates similar or superior to historical open surgical controls (Table 1). Morbidity, mortality, length of stay, and oncologic outcomes were comparable also to our open surgery retrospective experience (Table 2).

In the laparoscopic treatment in the literature review enclosing the present series, only four patients died, and 15 subjects experienced a recurrence; however, patient selection bias may have contributed to the high success rate in the literature series in term of follow-up. Only patients with smaller GISTs were "preselected" for a laparoscopic resection.

Long-term follow-up is fundamental for these patients because GISTs have an unpredictable biologic behavior.

In the present series of 21 consecutive cases and in the reported literature data, laparoscopic wedge-segmental resections of gastric GISTs results in effective control of the disease with minimal perioperative morbidity and no mortality and excellent long-term survival.

GI ST are highly resistant to conventional chemotherapy and radiotherapy. Such tumors usually have activating mutations in either KIT (75–80%) or platelet-derived growth factor receptor α (PDGFRA; 5–10%), two closely related receptor tyrosine kinases. These mutations lead to ligand-independent activation and signal transduction mediated by constitutively activated KIT or PDGFRA. Targeting these activated proteins with imatinib mesylate, a small-molecule kinase inhibitor, has proven useful in the treatment of recurrent or metastatic GIST and is now being tested as an adjuvant (for medium- and high-risk patients) or neoadjuvant.

However, resistance to imatinib is a growing problem, and other targeted therapeutics such as sunitinib are available.[42]

Conclusions

As found also in the literature review, the laparoscopic resection is safe and effective in treating gastric GISTs. Given these findings as well as the advantages afforded by laparoscopic surgery, a minimally invasive approach should be the preferred surgical treatment in patients with small- and medium-sized gastric GIST.

From 2001 up to now, all patients with gastric GIST referred to our center are approached laparoscopically.

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Postoperative Complications have Little Influence on Long-term Quality of Life in Crohn's Patients

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Abstract
Purpose The purpose of the study was to determine the influence of postoperative complications on long-term quality of life in patients after abdominal operations for Crohn's disease.
Materials and Methods From 1996 to 2002, 305 Crohn's patients underwent abdominal surgery, and 66 patients developed postoperative complications. Quality of life was studied using a standardized questionnaire and four quality of life instruments. Sixty-six Crohn's patients with uneventful postoperative course matched for age, and follow-up time served as controls.
Results Forty-eight patients (81%) in the complication group (32 major and 16 minor) and 43 patients (75%) in the control group answered the questionnaire. Postoperative follow-up time was 42 (10–94) and 41 months (13–94; median (range)). Quality of life was comparable between groups, except on the subscale "physical functioning" of the Short-form 36 on which patients with minor and major complications showed impaired quality of life compared to controls (67±6, 69±4, and 84±2%; mean±standard error of the mean; both $p<0.05$ vs controls). The incidence of Crohn's disease-related symptoms at follow-up was unaffected by complications (minor 63%, major 56% vs controls 70%; both not significant).
Conclusion Postoperative complications after abdominal operations for Crohn's disease do not impair long-term quality of life in general but may affect specific dimensions of quality of life like patients' physical function.

Keywords Crohn's disease · Outcome · Postoperative complications · Quality of life · Symptoms

Introduction

Crohn's disease (CD) is considered a benign disease, which normally does not affect life expectancy.[1] Nevertheless, it has the potential to impair patients' quality of life (QOL) profoundly.[2–5] As a consequence, one of the main therapeutic goals in treatment of CD is to improve patients' QOL and maintain it on a high level. Despite dramatic advantages in medical treatment of CD, surgical interventions are still required in the majority of patients during the course of the disease, and a large part of these patients will subsequently require surgery for recurrence of CD.[6,7] Whereas the management of complications or emergencies because of failure of medical treatment of CD was the mainstay of surgical therapy in the past, nowadays, elective surgery with the aim to improve patients' symptoms

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affecting their QOL is of growing importance.[8,9] This is supported by the observation that abdominal operations for CD are normally followed by an immediate and long-lasting improvement of QOL, which appears to be mainly caused by the surgical induction of remission of CD.[2,10–13] However, this beneficial effect of surgery is not always achieved. Delaney et al.[10] showed that the improvement of QOL 30 days postoperatively is diminished, when patients develop postoperative complications.

Unfortunately, postoperative complications are observed frequently after abdominal operations for CD and occur in about 10 to 30% of patients; most of these complications are of septic nature.[14–16] A multitude of risk factors for the development of postoperative complications has been identified, such as preoperative treatment with steroids, [14,17–19] septic complications or fistulas at time of laparotomy, [16,17] as well as urgent[16] and extensive surgery.[20] However, long-term effects of these complications on patients' QOL have not been determined yet. Therefore, the aim of our study was to evaluate the effect of minor and major postoperative complications on patients' long-term QOL. For comparison, a group of Crohn's patients with an uneventful postoperative course matched for age and follow-up time served as controls. To measure effects on different dimensions of QOL, we used different instruments to evaluate general health-related as well as gastrointestinal and disease-specific QOL. Our hypothesis was that long-term postoperative QOL is impaired in patients who developed postoperative complications after abdominal operations for CD.

Materials and Methods

Patients

The computerized database of the Department of General Surgery of the University of Tuebingen, Germany, was queried for patients who underwent abdominal surgery for CD between January 1st, 1996, and December 31st, 2002, and 305 patients who had a total of 347 abdominal operations during this period were identified (reoperations for postoperative complications were excluded). Patients' charts were reviewed, and 66 patients (19% of 347 operations in 305 patients) were identified who developed postoperative complications during their hospital stay. Sixty-six patients with an uneventful postoperative course, matched for age at follow-up and follow-up time, served as controls. Because none of the patients in the two complication groups was operated laparoscopically, only patients who underwent an open operation were considered as controls. A custom-made questionnaire, evaluating the history of CD and current CD-related symptoms as well as four established QOL instruments (Short-Form General Health Survey [SF-36], Cleveland Global QOL score [CGQL], Gastrointestinal QOL Index [GIQLI], and Short Inflammatory Bowel Disease Questionnaire [SIBDQ]) were mailed to the complication and control group. When patients did not respond within 4 weeks, they were called by telephone and encouraged to answer the survey. Of 66 patients in the complication group, two had died during the follow-up period, five were not contacted because their present place of residence could not be determined, and 11 patients did not respond for unknown reasons, although they were contacted by telephone. In the control group, 3 of the 66 patients had died during the follow-up period, the place of residence was unknown in six patients, and 14 patients did not respond after the reminder. Finally, 48 patients in the complication group (81% of contacted patients) and 43 patients in the control group (75% of contacted patients) returned their questionnaires. Patients with postoperative complications were divided in patients with minor and major complications with no patient experiencing more than one complication. Urinary tract infection, paralytic ileus, wound infection, pneumonia, and conservatively treated pulmonary embolism were considered minor complications, whereas anastomotic leak, intra- abdominal abscess, postoperative hemorrhage, and mechanical bowel obstruction requiring surgical intervention were regarded as major complications. The study was approved by the Ethics Committee of the University of Tuebingen and written informed consent was obtained from each patient.

Assessment of QOL

Four well-established QOL instruments were used to determine health-related QOL. The generic SF-36 evaluates general health-related QOL and consists of eight subscales (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health), from which the physical and mental component summaries were calculated. These component summaries allow the comparison of physical and mental QOL with the general population of the USA that achieves a mean score of 50 with a standard deviation of 10 on both summaries.[21]

The CGQL also evaluates general health-related QOL and was developed by Fazio et al.[22] It is a straightforward questionnaire which asks patients to allocate 0 to 10 points (0=lowest; 10=highest quality/level) for the three subscales "current QOL," "current quality of health," and "current energy level." The total score of all subscales is divided by 30, so that the overall QOL is given as a number between 0 and 1.

The GIQLI measures gastrointestinal QOL. This questionnaire was developed primarily in German by Eypasch et al.[23,24] and was subsequently translated into English. The

Table 1 Patients' Characteristics

	Minor complications (n=32)	Major complications (n=16)	Controls (n=43)
Male/female	15:17	4:12	20:23
Follow-up time (months)	42 (10–94)	41 (12–87)	41 (13–94)
Age at follow-up (years)	42 (27–69)	46 (21–73)	46 (20–69)
Age at operation (years)	39 (21–68)	42 (18–69)	40 (19–67)
Age at initial diagnosis of CD (years)	28 (12–58)	26 (13–66)	25 (12–50)
Duration from initial diagnosis of CD to operation (years)	14 (0–29)	8 (0–24)	14 (0–44)
Segment of bowel involved (small bowel/colon/both)	25:34:41%	44:12:44%	47:16:37%
Non-perforating: perforating disease	34:66%*	19:81%*	65:35%
Elective: emergent operation	63:37%	50:50%	79:21%

CD Crohn's disease; median (range), percent of patients in each group
*Differs from controls; $p<0.05$

GIQLI comprises the five subscales "gastrointestinal symptoms," "emotional status," "physical function," "social function," and "distress by medical treatment," which are summarized in an overall score. Patients choose between 0 (worst) and 4 (best) points for each question. Between 4 and 76 points may be achieved on the five subscales with a maximum of 144 points on the overall score. Questions concerning gastrointestinal symptoms have the strongest influence on the overall score as they represent 53% of the questions.

Irvine et al.[25] developed the disease-specific Inflammatory Bowel Disease Questionnaire. The number of questions was then reduced from 32 to 10 in the SIBDQ, which was translated and validated in German.[26] The SIBDQ consists of the four subscales "bowel function," "systemic function," "emotional function," and "social function," which are summarized in an overall score. Patients can allocate between 1 (worst) and 7 points (best) for each question. To facilitate interpretation, the total count for each subscale is divided by the number of related questions, so that a score between 1 (very poor) and 7 (optimum) is finally achieved for each subscale and the overall score.[27]

Statistical Analysis

For data analysis, patients with complications were divided in patients with minor and major complications. Data concerning patients' characteristics are shown as median (range). Results from the QOL questionnaires are given as mean±standard error of the mean. To facilitate interpretation, the scores on the different subscales and overall scores are given as percentage of the maximum possible score on each scale. Differently, the two component summaries of the SF-36 are expressed as mean±standard deviation (SD) according to the published control group (US population) and are normalized in a way that the population of the USA achieves 50±10 points on each component summary.[21] Groups were compared by χ^2 test or one-way analysis of variance. A p value of less than 0.05 was considered statistically significant, and Bonferroni correction for multiple comparisons was performed whenever appropriate.

Results

Patients and Complications

Sixty-six patients were identified to have developed postoperative complications after a total of 347 abdominal operations for CD (complication rat=19%). There were no differences in patients' characteristics between the three groups, except that perforating CD was more common in the two complication groups compared to controls (Table 1). Of the 48 responders who developed postoperative complications, 32 patients (67%) experienced minor and 16 patients (33%) major complications (Table 2). No patient developed more than one postoperative complication. Urinary tract

Table 2 Minor and Major Complications

Minor complications (n=32)		Major complications (n=16)	
Urinary tract infection	n=17	Anastomotic leak	n=7
Paralytic ileus	N=9	Intra-abdominal abscess	n=7
Wound infection	n=4	Postoperative hemorrhage	n=1
Pneumonia	n=1	Mechanical bowel obstruction	n=1
Pulmonary embolism	n=1		

Table 3 Crohn's Disease-Related Medication at Time of the Operation

	Minor complications (n=32)	Major complications (n=16)	Controls (n=43)
Steroids	15 (47%)	7 (44%)	17 (40%)
Azathioprine	2 (6%)	2 (13%)	8 (19%)

Number (percent of patients in each group)

infections and pneumonia were treated with antibiotics. Absence of bowel movements until postoperative day 4 was considered as paralytic ileus and occurred in nine patients, all of which responded to conservative treatment and laxatives. Wound infections were treated with wet-to-dry dressing changes in four patients. The patient with pulmonary embolism was treated successfully conservatively with anticoagulation. No patient in the minor complication group required reoperation. In the major complication group, all seven patients with an anastomotic leak, and two of seven patients with an intra-abdominal abscess required reoperation. The five other patients with intra-abdominal abscess were treated successfully with computed tomography-guided drainage and antibiotics. Mechanical bowel obstruction and postoperative intra-abdominal hemorrhage necessitated reoperation in two other patients. Overall, 11 of 16 patients (69%) in the major complication group required reoperation. At the time of the operation, patients were under treatment with steroids or azathioprine to a similar extent in both groups, and no patient received cyclosporine, infliximab, or other immunomodulative therapy (Table 3). All patients in the two complication groups had a history of previous abdominal operations. This was less common in the controls as only 70% of these patients had a previous abdominal operation (p=0.001). Postoperative hospital stay was prolonged by minor (18 days [4–52 days]) and major complications (26 days [10–252 days]) when compared with controls (12 days [6–25 days]; both p=0.0003).

Table 4 Crohn's Disease-related Symptoms, Medication, and Fecal Diversion at Follow-Up

	Minor complications (n=32)	Major complications (n=16)	Controls (n=43)
CD-related symptoms	20 (63%)	9 (56%)	30 (70%)
Abdominal pain	7 (22%)	4 (25%)	16 (37%)
Diarrhea	12 (38%)	4 (25%)	20 (47%)
Perianal manifestation	3 (9%)	1 (6%)	1 (2%)
Extraintestinal manifestation	3 (9%)	0 (0%)	1 (2%)
CD-related medication			
Steroids	6 (19%)	1 (6%)	7 (16%)
Azathioprine	9 (28%)	5 (31%)	19 (44%)
Fecal diversion	14 (44%) *	8 (50%) *	5 (12%)

Patients could choose as many CD-related symptoms as applicable. Number (percent of patients in each group)
CD Crohn's disease
*Differs from controls; p<0.05

Table 5 Complication-related Restrictions in Everyday Life

	Minor complications (n=32)	Major complications (n=16)
Influence of complication on everyday life	12 (38%)	9 (56%)
Reduced physical energy level	10 (31%)	6 (38%)
Malnutrition	9 (28%)	6 (38%)
Recurrent abdominal pain	3 (9%)	1 (6%)
Displeasing/painful scar	12 (38%)	6 (38%)
Incisional hernia	5 (16%)	0 (0%)

Patients could choose as many complication-related restrictions as applicable. Number (percent of patients in each group)

Standardized Questionnaire

No difference was observed concerning CD-related symptoms or medication at follow-up; however, more patients in the two complication groups were diverted compared with controls (Table 4). In one of eight diverted patients in the major complication group, the stoma was created during the reoperation because of an anastomotic leak, and bowel continuity was not restored at follow-up. The other patients had their stoma as a consequence of CD and not related to the complication. Patients in the two complication groups reported restrictions in their everyday life related to the complication to a similar extent (Table 5).

QOL Instruments

Patients who developed postoperative complications showed an impaired QOL only on the subscale "physical functioning" of the SF-36 (Fig. 1a; p<0.05). There was no difference between the three groups on the other subscales and the component summaries of the SF-36 (Fig. 1b), although all groups tended to have a deteriorated QOL compared to the general population of the USA. Similarly, the CGQL did not reveal any differences in QOL between the three groups (Fig. 2a), as did not the gastrointestinal and disease-specific QOL instruments GIQLI and SIBDQ (Fig. 2b and c). The only patient with the stoma still in place at follow-up as a consequence of an anastomotic leak showed a trend toward an impaired QOL on subscales related to physical function-

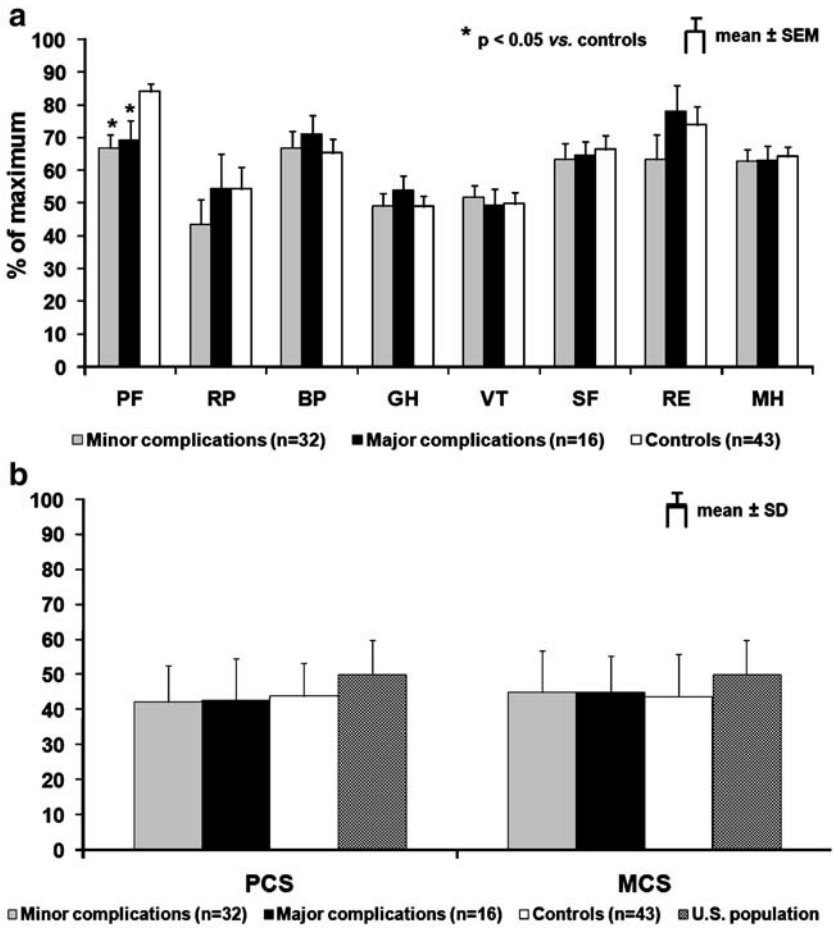

Figure 1 QOL was impaired in both complication groups compared to controls only on the subscale "physical functioning" of the SF-36 (**a**). On the SF-36 component summaries, QOL was comparable between the three patient groups and tended to be impaired compared with the population of the USA [21] (**b**). *PF* Physical functioning, *RP* role physical, *BP* bodily pain, *GH* general health, *VT* vitality, *SF* social functioning, *RE* role emotional, *MH* mental health, *SEM* standard error of the mean, *PCS* physical component summary, *MCS* mental component summary, *U.S.*: USA, *SD* standard deviation.

ing on the SF-36, GIQLI, and SIBDQ, which, however, were within 2 SD of the mean.

Discussion

The aim of this study was to determine long-term effects of postoperative complications on QOL by comparing the QOL of patients who developed postoperative complications after abdominal operations for CD with the QOL of Crohn's patients with an uneventful postoperative course. At time of follow-up, about 3 and a half years after surgery, general as well as gastrointestinal and disease-specific health-related QOL was in large part comparable between groups except on the subscale "physical functioning" of the SF-36 on which patients who experienced postoperative complications showed an impaired QOL. Incidence of CD-related symptoms and need for CD-related medication was largely comparable between groups. Patients who developed postoperative complications were more likely to have undergone abdominal surgery previously, to have a perforating CD, and to have a stoma at time of follow-up. Although the standardized assessment of QOL did not reveal a long-term impairment of QOL in general, it is of note that 38 and 56% of the patients in the minor and major complication group reported restrictions that they attributed to the complications experienced after surgery.

To delineate the influence of postoperative complications on long-term QOL, we used four well-established, validated QOL instruments, which were applied to study QOL in Crohn's patients previously.[4,5,27–29] We chose these questionnaires to differentiate between effects on general (SF-36 and CGQL) as well as on gastrointestinal and disease-specific QOL (GIQLI and SIBDQ) and hypothesized that QOL is impaired in patients who experienced postoperative complications compared to patients with an uneventful postoperative course. Surprisingly, this was generally not the case because the only difference found was an impaired QOL in patients' "physical functioning" on the SF-36 after minor or major postoperative complications. This difference was 15 and 17% between the two complication groups and controls and might therefore be of clinical relevance. However, this finding has to be interpreted with caution. A priori, it is to be expected that major complications have a more pronounced detrimental effect on QOL than minor

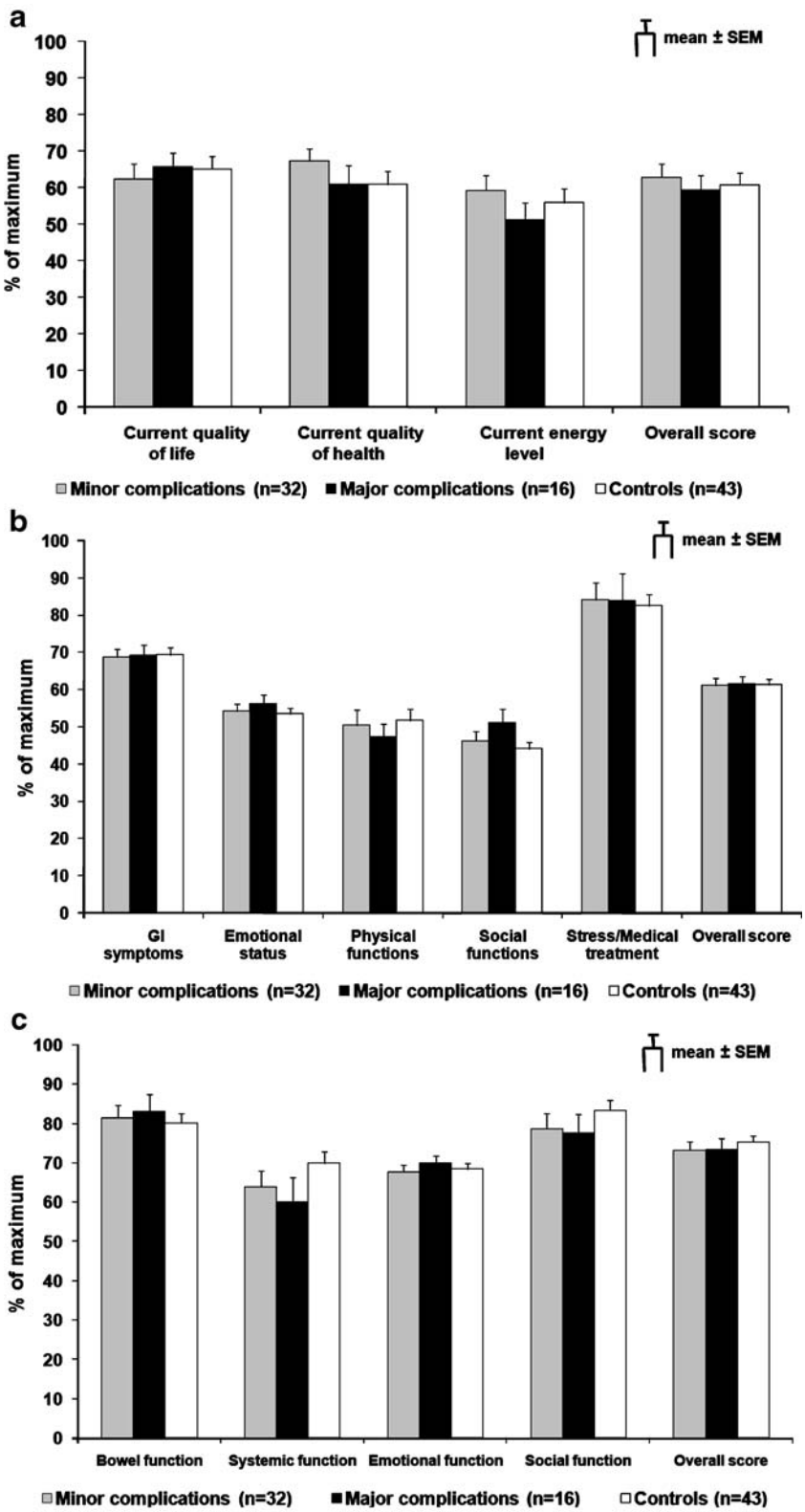

Figure 2 No difference occurred in QOL between groups on CGQL (**a**), GIQLI (**b**), and SIBDQ (**c**). *GI* Gastrointestinal, *SEM* standard error of the mean.

complications. Nevertheless, the impairment of QOL in terms of physical function was similar between the minor and major complication group. One possible explanation is that both complication groups have a more severe course of CD compared to controls what might affect their QOL. This is supported by the observation that in the two complication groups more patients had previous abdominal operations, perforating disease, and fecal diversion. In contrast, the

proportion of patients who underwent an emergent operation and the number of patients on CD-related medication were not different between patients who developed postoperative complications and those who did not, which argues against this interpretation. Even if disease severity was different at the time of the operation, it might have been altered by the operation itself or the course of the disease during the 3 and a half years of follow-up. As QOL was in large part comparable between groups in our study, a more severe course of CD in patients with postoperative complications at time of follow-up is unlikely. However, this issue cannot be settled on the basis of the data from this study. Alternatively, the difference in QOL between patients with and without complications may be secondary to a type 1 error caused by the small sample size in the patient groups. Because of the retrospective design, we are not able to comment on the postoperative development of QOL over time. Therefore, we cannot exclude that the three groups started off from a different QOL preoperatively, which may have affected our results. However, profound differences in "baseline" QOL are not very likely considering that patients' characteristics were in large part comparable between the three groups. The limited number of patients in our study cohort did not allow to match for a multitude of patients' characteristics, and we, therefore, selected age and follow-up time as the most important ones.

Surprisingly, a substantial number of patients in the two complication groups reported restrictions in everyday life, which they attributed to the postoperative complication they experienced. Possibly, the QOL instruments that were applied are not sensitive enough to identify these restrictions. Alternatively, patients are likely to have developed coping strategies over the years that enabled them to achieve a decent QOL, although the consequences and subsequent restrictions of a previous complication are still present. One example for this is that although a stoma has the potential to deteriorate QOL, [30,31] there is also evidence that under certain conditions, the effect of a stoma on QOL is different and might even improve specific aspects of gastrointestinal QOL when coping with the stoma is adequate.[32] Because the development of adequate coping strategies usually takes time, restrictions related to postoperative complications probably affect QOL more profoundly in the short term[10] when these strategies are not fully developed, while in the long term, QOL may not be different compared to patients having an uneventful postoperative course, although restrictions may persist.

The overall complication rate of 19% in this study is consistent with or even lower than complication rates reported by others.[15,16,20,33] Furthermore, the rate of patients requiring reoperation in the group of patients with major complications as well as the prolonged hospital stay in both complication groups is not surprising and is consistent with findings from other studies.[17,20] Preoperative nutritional deficiency,[16] low serum albumin levels,[17,20] preoperative septic complications or fistulas at time of laparotomy,[16,17] and urgent[16] or extensive surgery[20] are acknowledged risk factors for the development of postoperative complications in Crohn's patients. With changes in the management of patients with CD, earlier elective surgery, and the availability of more potent drugs, perioperative medical treatment as a potential contributor to postoperative complications became more relevant. It has been shown convincingly that the perioperative use of steroids is associated with an increased risk of postoperative complications after abdominal operations for inflammatory bowel disease,[14,17–19] while cyclosporine,[19,34] 6-mercaptopurine, and azathioprine,[18,19] as well as infliximab,[15,33] appear not to increase the risk of postoperative complications.[35] In our study, however, there was no difference in the number of patients on steroids or azathioprine among patients experiencing minor, major, or no complications. Most likely, the total number of complications was too small to allow their correlation with different drug regimen.

In conclusion, postoperative complications in Crohn's patients undergoing abdominal operations may entail long-term restrictions in their everyday life. However, long-term QOL is largely unaffected, which indicates that restoration of good QOL is possible despite the persistence of complication-related restrictions. We speculate, however, that adequate coping strategies are necessary to regain good QOL after a complicated postoperative course with subsequent long-term restrictions. Thus, it must be the ultimate goal to prevent surgical complications in Crohn's patients, which is usually achieved by optimal timing of the operation and adequate surgical techniques as well as state-of-the-art perioperative care. When postoperative complications occur, management should aim to achieve full restoration of body functions and rehabilitation including the development of coping strategies as this may help to regain good QOL if restrictions persist.

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Does a 48-Hour Rule Predict Outcomes in Patients with Acute Sigmoid Diverticulitis?

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Abstract
Introduction Sigmoid diverticulitis is an infection that resolves with conservative management in 70–85% of patients. Some patients require prolonged hospitalization or surgery during their admission. It has been taught that one should expect clinical improvement within 48 h. In this study, we examined whether basic clinical parameters (the maximum temperature and leukocyte count) of patients would predict improvement and discharge as expected, or prolonged hospitalization.
Materials and Methods Data was acquired from 198 patients admitted with acute sigmoid diverticulitis as confirmed by computed tomography (CT) scanning and physical exam. One hundred sixty-five patients recovered without surgery with an average hospital stay of 4 days: 120 were discharged within 4 days, whereas 45 patients required longer stays. Nineteen patients underwent surgery early during their admission (within 48 h). Fourteen patients did not improve over time and required surgery later during their hospital stay. The daily maximum temperature and leukocyte count of patients with prolonged stays was compared to the patients who were discharged within 4 days using analysis of variance analysis.
Results The average maximum temperature and leukocyte count on admission were not statistically different between the groups; therefore, maximum temperature and leukocyte count on admission alone are not predictive. After the first 24 h, however, one could see a statistically significant difference in maximum temperature ($p=0.004$). The leukocyte count responded significantly by hospital day 2 ($p=0.003$). Both trends were significant through hospital day 4.
Discussion Patients with a noticeable drop in leukocyte count and maximum temperature over the first 48 h of medical management were predictably discharged early on oral antibiotics. Patients failing to improve at 48 h required prolonged stays or surgery.
Conclusion By observing early trends in leukocyte count and maximum temperature of patients with diverticulitis, one can predict whether they will recover quickly as expected or if they will likely require prolonged IV antibiotics and/or surgery.

Keywords Acute Sigmoid Diverticulitis · Leukocyte count · Maximum temperature · Conservative management · Length of stay

Introduction

Colonic diverticulitis is a common inflammatory disease, with a significant portion of medical and surgical literature devoted to determining optimal treatment. More than 50% of the population over the age of 60 has diverticulosis and 70% of the population by age 85.[1] About 10 to 25% of these patients will eventually develop symptoms of diverticulitis.[2–8,15,16] The management of this entity is varied. Many patients have mild inflammation that can be managed in the outpatient setting. Others require hospitalization, and some require surgical resection in the setting of peritonitis, recurrence, or other complications of the disease. In fact, 15–30% of patients hospitalized for diverticulitis will eventually require operation for such complications.[9–14]

In the majority of cases (70–86%), patients who receive conservative therapy (bowel rest and IV antibiotics) recover quickly from their initial episode of diverticulitis.[9,17–20] There is a subset of patients, however, who do not seem to respond quickly to this level of care. One frequently cited

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guideline is that hospitalized patients should begin to show both subjective and objective improvement 48 h after admission.[21–23] Although this "48-h rule" is frequently quoted, it has never been given systematic scrutiny.

If one could anticipate a patient's clinical course, it is likely that patients would receive more appropriate therapy and prognostic information. For example, if a patient's clinical parameters indicated that they have not experienced significant improvement after 48 h, physicians would further investigate and may change management. This could involve procedural intervention or may lead to a continued conservative approach. In this study, our objective was to determine if simple clinical parameters (patients' leukocyte counts and fever curves) would help predict patient outcomes.

Materials and Methods

Data was collected from a retrospective chart review of 400 patients admitted to two teaching hospitals over a 2-year period with a diagnosis of diverticulitis. These charts were identified using a computer-generated search for all patients with a documented diagnosis of diverticulitis per the International Classification of Diseases. Charts were reviewed at the two institutions by three investigators.

The diagnosis of diverticulitis for the purpose of this study was defined by the clinical picture and required confirmation by CT scanning. Patients without a CT scan, with a negative CT scan, or those admitted for elective surgery because of a prior episode of diverticulitis were excluded. One hundred ninety-eight patients fulfilled all criteria and were fully analyzed. Data collected included patient age, gender, number of prior episodes of diverticulitis, timing of surgery (if surgery occurred during that admission), antimicrobial used, length of antimicrobial therapy (both intravenous and oral), admission, and daily leukocyte count, as well as admission and daily maximum temperature. During our data collection, we also attempted to obtain data regarding pain scales and physical findings; however, we found this information to be variable and incompletely documented. See Table 1 for patient characteristics.

Nineteen patients that required emergent operation within 48 h of admission were excluded. Of the remaining 179 patients, 165 (92%) recovered without surgical intervention. The average length of stay for these patients was 4 days. One hundred twenty patients (67%) had improved enough to be discharged on or before the fourth hospital day, whereas 59 (33%) required longer hospitalizations. Fourteen of these patients (8%) did not improve and required surgery during the same hospital admission.

The maximum temperature and leukocyte counts of the 59 patients with prolonged hospitalizations were compared to the patients who experienced the usual course of early recovery and were discharged within 4 days. The data were collected and subjected to analysis of variance (ANOVA) analysis. A p value of 0.05 was set as the determinant of statistical significance.

Table 1 Patient Characteristics

	Discharge on or Before HD 4 (n=120)	Discharge After HD 4 (n=59)
Age		
<50 (29%)	37 (21%)	15 (8%)
>50 (71%)	83 (46%)	44 (25%)
Gender		
Male (39%)	48 (27%)	22 (12%)
Female (61%)	72 (40%)	37 (21%)
Primary Episode?		
Yes (73%)	91 (51%)	39 (22%)
No (27%)	29 (16%)	20 (11%)

Results

On admission, the average leukocyte count of the delayed discharge cases was 12.2 compared to 12.1 for the rapidly improved cases. The average leukocyte count counts for the delayed cases were 11.2, 9.8, and 9.0 on hospital day (HD) 1, 2, and 3, respectively. The leukocyte count counts for the early discharge cases were 10.1, 8.5, and 8.2 on HD 1, 2, and 3, respectively. Application of ANOVA analysis (Table 2) reveals that there is significance in the differences in average leukocyte count counts on HD 2 (p=0.003) but not before this (p=0.08 for 24 h after admission).

On admission, the average temperature (°F) of patients in the delayed group was 99.3 compared to 99.4 for the rapid improvement group. The average maximum temperatures for the delayed cases were 100.0, 99.0, and 99.0 for HD 1, 2, and 3, respectively. For the rapidly improved cases, the average maximum temperatures were 99.1, 98.8, and 98.5 on HD 1, 2, and 3, respectively. This is demonstrated in Table 2. These values did achieve statistical significance as can be seen in the ANOVA analysis represented by Table 3. This difference is first noticed on HD 1 (p=0.004) and continues onto HD 2 (p=0.004).

Although these values did reach statistical significance as demonstrated above, we noted that numerical difference between the two groups was small (on the scale of one to 2°F). Therefore, we also calculated the average daily maximum temperature and leukocyte count by comparing the patients who had abnormal values on admission to those whose values were normal. The results are graphically represented in Tables 4 and 5. These tables demonstrate that patients with normal parameters on admission have minimal change in these parameters during their hospitalization. For example, patients admitted without

Table 2 Average Maximum Temperature and Leukocyte Count: All Patients

	Maximum Temperature (°F)			Leukocyte Count ($\times 10^9$)		
	Mean	Range	SE	Mean	Range	SE
Average LOS						
DOA	99.4	(97.0–104.4)	0.13	12.1	(3.7–25.4)	0.39
Day 1	99.1	(97.1–102.6)	0.09	10.1	(3.76–25.4)	0.41
Day 2	98.8	(96.7–101.5)	0.09	8.5	(3.1–15.0)	0.32
Day 3	98.5	(96.8–101.5)	0.10	8.2	(3.5–11.3)	0.37
Prolonged LOS						
DOA	99.3	(97.2–102.6)	0.23	12.2	(1.2–22.2)	0.71
Day 1	100.0	(97.4–102.0)	0.23	11.2	(1.4–21.5)	0.71
Day 2	99.0	(97.0–102.3)	0.42	9.8	(1.1–19.9)	0.76
Day 3	99.0	(97.2–101.5)	0.14	9.0	(1.2–20.6)	0.82

LOS Length of stay (Average LOS <4 days, Prolonged LOS ≥4 days); *DOA* day of admission; *SE* standard error

leukocytosis greater than 11,000 remain without a leukocytosis during their hospitalization regardless of the length of stay. Conversely, patients with a leukocytosis on admission will show significant reduction in this parameter if they have a normal short hospital course, whereas patients experiencing a prolonged course remain with an elevated leukocyte count. The same can be seen with maximum temperatures (fever defined as greater than or equal to 101.5°F). In general, patients that were afebrile on admission remained afebrile during the hospitalization, regardless of the length of stay, and there was no significant change in these values. However, in patients admitted with a fever and experiencing a shorter hospital stay, one sees a significant improvement in their temperature early in their course.

In our series, 14 (8%) of our patients underwent surgery after 3 days. Three went to operation because of development of a fistula, one of whom also received an interventional abscess drain. One developed a small bowel obstruction, and two had CT scans showing free air after clinical deterioration (one with the free air noted on admission CT in retrospect). Another had an interventional diverticular abscess drain placed on hospital day 1 and underwent surgery on hospital day 5 because of continued fever and inflammation despite percutaneous drainage. Three others had surgery on hospital days 7, 8, and 15, adopting a planned semi-elective approach without further imaging after the initial CT scan. The other four were documented as "failure of medical management."

These 14 patients all were hospitalized longer than 4 days. Therefore, we compared the leukocyte counts and maximum temperatures of these 14 patients with the parameters of all patients experiencing prolonged stays, as the majority of them improved with medical management alone. We wanted to evaluate for a difference in these trends that could predict if a patient was more likely to eventually require operation during their course. There were no significant differences in maximum temperature or leukocyte count between these groups within the first 4 hospital days.

Table 3 ANOVA Analysis of Early Discharge Patient vs Extended Stay Patients

	Sum of Squares	*df*	Mean Square	*F*	*p* value
Leukocyte Count 1 (24 h)					
Between Groups	56.171	1	56.171	2.950	.088
Within Groups	3,084.353	162	19.039		
Total	3,140.524	163			
Leukocyte Count 2 (48 h)					
Between Groups	132.712	1	132.712	9.048	.003
Within Groups	1,892.201	129	14.668		
Total	2,024.913	130			
Maximum Temperature 1 (24 h)					
Between Groups	11.332	1	11.332	8.491	.004
Within Groups	257.557	193	1.334		
Total	268.889	194			
Maximum Temperature 2 (48 h)					
Between Groups	17.587	1	17.587	8.486	.004
Within Groups	385.490	186	2.073		
Total	403.077	187			

Table 4 Average Leukocyte Counts

	Leukocytosis on Admission (≥11×109)			Normal Leukocyte Count on Admission (<11×109)		
	Mean	Range	SE	Mean	Range	SE
Average LOS						
DOA	14.5	(11.2-30.5)	0.37	7.8	(3.85-10.9)	0.30
Day 1	11.6	(4.8-25.4)	0.48	7.1	(3.76-15.5)	0.42
Day 2	9.1	(4.0-16.6)	0.36	6.0	(3.1-9.1)	0.35
Day 3	8.1	(4.6-11.3)	0.38	5.4	(3.5-7.8)	0.52
Prolonged LOS						
DOA	16.2	(11.3-30.2)	0.85	8.5	(1.2-10.7)	0.40
Day 1	13.4	(7.4-25.0)	0.99	8.3	(1.4-13.3)	0.61
Day 2	12.2	(5.2-25.0)	1.19	7.7	(1.1-14.1)	0.63
Day 3	10.5	(5.3-25.5)	1.12	7.7	(1.2-14.8)	0.97

LOS Length of stay (average LOS <4 days, prolonged LOS ≥4 days); *DOA* day of admission; *SE* standard error

Discussion

It is generally advised that patients with acute sigmoid diverticulitis should show signs of clinical improvement within 48 h of the onset of proper treatment. Improvement is defined as decreased pain, less tenderness, a drop in temperature toward normal, and a decrease in leukocytosis and left shift within 24 to 48 h of initiation of treatment. Stabile, in 2003, also recommended further imaging or a broadened spectrum of antibiotics if patients did not improve.[16] This adage has never been tested as a true clinical guide. In this study, we evaluated several basic clinical parameters of 179 patients presenting with acute diverticulitis who did not require urgent surgical intervention. Of our patients, 120 (67%) recovered after 4 or less days of inpatient care with antibiotics. Of those with a length of stay greater than 4 days, 45 (25%) did eventually recover with conservative management only but required admission longer than 4 days.

In evaluating the maximum temperature and leukocyte count of those who quickly recovered from their episode of diverticulitis, we noted that these clinical parameters exhibited a statistically significant difference from those who experienced prolonged hospitalization or surgery. In fact, although maximum temperature and leukocyte count were similar among both groups at admission, the early recovery group showed a rapid marked improvement that was significant. Therefore, it appears that one could use such information in predicting a patient's course during their hospitalization. This information should be used in conjunction with the entire clinical picture of the patient, as a level of statistical significance for all patients was reached in this study by using values that one may not view as clinically significant. For example, one will note that statistical significance was reached at a difference in average maximum temperature of less than 2°F in all groups.

This difference, however, is accentuated when one evaluates patients who are febrile or exhibit leukocytosis on admission; therefore, this information is even more useful for these patients. Of all admissions for diverticulitis, only approximately two thirds of patients fall exhibit these clinical abnormalities,[24–25] and the clinical application of this information is therefore not universal. On the other hand, abnormalities in these parameters can correlate with worse disease, and prognostic information in the first 48 h is

Table 5 Average Daily Maximum Temperature

	Febrile on Admission (≥101.5°F)			Afebrile on Admission (<101.5°F)		
	Mean	Range	SE	Mean	Range	SE
Average LOS						
DOA	101.3	(100.5–103.1)	0.13	98.7	(97.0–100.4)	0.10
Day 1	99.9	(97.4–102.4)	0.19	98.9	(97.3–102.6)	0.09
Day 2	99.2	(97.2–101.2)	0.17	98.6	(97.3–101.5)	0.10
Day 3	98.9	(96.8–100.8)	0.22	98.5	(97.0–100.7)	0.10
Prolonged LOS						
DOA	101.6	(100.6–102.6)	0.22	98.5	(96.8–100.4)	0.15
Day 1	100.6	(98.0–102.1)	0.29	99.0	(97.1–102.0)	0.15
Day 2	100.4	(98.0–102.4)	0.28	99.0	(97.6–101.7)	0.19
Day 3	99.7	(98.4–101.5)	0.23	98.8	(97.2–101.4)	0.17

LOS Length of stay (average LOS <4 days, prolonged LOS ≥4 days); *DOA* day of Admission; *SE* standard error

most crucial for these patients. These observations can be further substantiated by a prospective cohort study.

We also evaluated our data to see if one could predict which of our extended-stay patients would eventually require operation during their hospitalization. This, of course, had a smaller sample size, and maximum temperature and leukocyte count curves from admission through hospital day 4 did not predict who would require surgery and who would eventually improve on prolonged medical management alone. This also merits prospective evaluation with larger sample sizes, as it would be very valuable to predict early that a patient would eventually require operation. These patients could possibly undergo resection earlier in their hospital stay and return home sooner.

Fourteen patients (8%) went for surgical resection after hospital day 3 because of failure of medical management or development of complications. Of our patients, only three had a planned semi-elective approach in their management. In one series, 16% of patients underwent surgery in this delayed fashion,[26] although a recent study by Martinez et al.[22] indicated that patients did better if allowed to recover completely for several weeks prior to resection. Of the others, five developed complications during their stay. Three developed clear indicators for surgery (small bowel obstruction and free air with clinical deterioration as indicated in the medical record). The three patients with fistulas did also undergo operation, although in their situation, it is unclear from the medical record if they were or were not appropriate for conservative management with antibiotics and subsequent bowel resection in four to 6 weeks.

Four patients were documented simply as "failure of medical management." One of these patients continued to have fever of 101.4°F up to hospital day 4, at which he underwent surgery. Three patients complained of pain

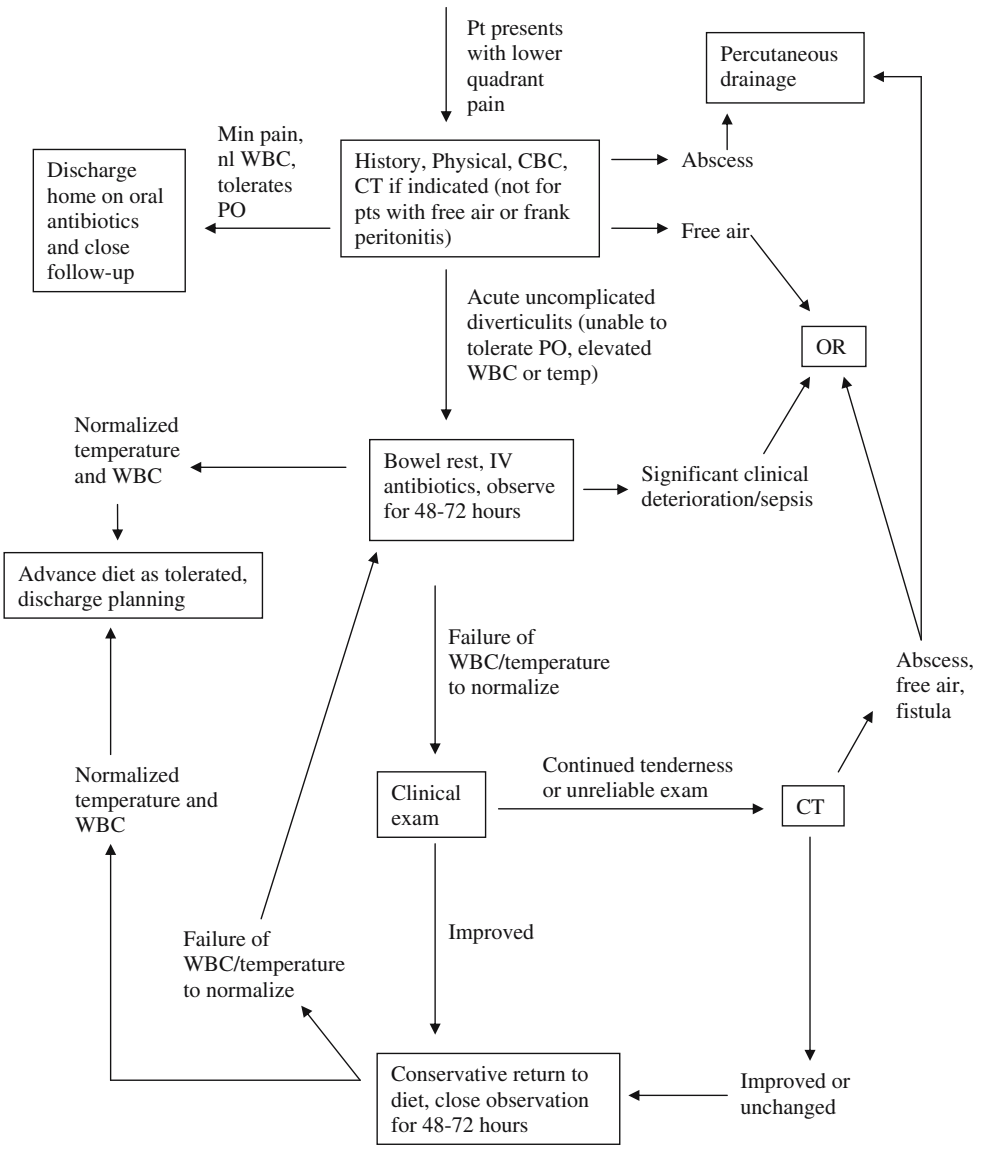

Fig. 1 Management of acute, diverticulitis flowsheet.

despite conservative management during their initial hospital stay. Of these, one was a 45-year-old patient whose symptoms and leukocytosis initially resolved, but her pain worsened after 48 h and she had a low-grade temperature of 100.1 for hospital days 2 through 5 at which time she underwent surgery. The second was a 57-year-old woman who had complained of pain for 19 days before her admission. She did not have a fever or leukocytosis, but her pain did not resolve by hospital day five and a CT scan was obtained. This still did not reveal complications of diverticulitis, but she underwent surgery hospital day 7 due to continued pain. The last patient documented as a "failure of medical management" also continued to complain of pain and underwent surgery hospital day 5, although his mild leukocytosis on admission (11.9) did resolve and his admission temperature of 101.4 did normalize. These patients represent a spectrum of clinical disease demonstrating the need to evaluate each patient's case individually and take their symptoms into account and the parameters we evaluated. An algorithm summarizing these factors is included in Fig. 1.

In summary, the clinical picture including simple parameters (temperature and leukocyte count) followed for 48 h after the commencement of proper care serves as a prognostic guide. In conjunction with physical findings, these parameters will help physicians make therapeutic decisions and will give patients a more accurate idea of what to expect during their hospital stay.

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Laparoscopic vs Open Colectomy for Colon Cancer: Results from a Large Nationwide Population-based Analysis

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Abstract

Purpose Laparoscopic colectomy has only recently become an accepted technique for the treatment of colon cancer. We sought to analyze factors that affect the type of resection performed and associated outcomes from a large nationwide database.

Methods All admissions with a primary diagnosis of colon cancer undergoing elective resection were selected from the 2003 and 2004 Nationwide Inpatient Samples. Multiple linear and logistic regression analyses were used to compare outcome measures and identify independent predictors of a laparoscopic approach.

Results We identified 98,923 admissions (mean age 69.2 years). They were predominately Caucasian (81%), had localized disease (63%), had private insurance (56%), and had surgery performed in urban hospitals (87%). Laparoscopic resection was performed in 3,296 cases (3.3%) and was associated with a lower complication rate (18% vs 22%), shorter length of stay (6 vs 7.6 days), decreased need for skilled aftercare (5% vs 11%), and lower mortality (0.6% vs 1.4%, all $P<0.01$). There was no significant difference in the total hospital charges between the groups ($34,685 vs $34,178, $P=0.19$). Independent predictors of undergoing laparoscopic resection were age<70 (odds ratio [OR]=1.2, $P<0.01$), national region (Midwest OR=1.9, West OR=2.0, $P<0.01$), and lower disease stage (OR=2.5, $P<0.01$). Ethnic category and insurance status showed no significant association with operative method ($P>0.05$).

Conclusions Laparoscopy for colon cancer is associated with improved outcomes in unadjusted analysis and similar charges compared to open resection. We found no influence of race or payer status on the utilization of a laparoscopic approach.

Keywords Laparoscopy · Colon cancer · NIS · Colectomy

Introduction

Colon cancer continues to represent a major healthcare issue in the United States with the American Cancer Society estimating 112,340 newly diagnosed cases and 52,180 deaths in 2007 alone.[1] Despite a slow decline in incidence over the past two decades, colon cancer remains the third most common malignancy and second leading cause of cancer deaths in America. Although advances in adjuvant therapy have improved survival in stage III and IV disease,[2] surgery remains the primary mode of treatment. As such, recent increasing experience and technological advances have pushed laparoscopy to the forefront of surgical approach. Originally described in 1990–1991 for both polyps[3] and cancer,[4,5] laparoscopic colectomy for colon cancer has only recently become an accepted technique after the published results of the Clinical Outcomes of Surgical Therapy Study Group (COST) trial in 2004.[6] Early concerns about loss of tactile function, inadequate margins and lymphadenectomy, worse outcomes, and malignant port site implants[7–9] have been assuaged with newer studies demonstrating equivalent oncological results,[10] improved cosmesis,[11] faster return

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of bowel function,[12] shorter hospital length of stay,[13] and even improved survival with a laparoscopic approach.[14,15]

Multiple other variables are thought to influence access and adequacy of care, treatment decisions, and overall outcomes such as survival and cancer recurrence. Factors such as geographic location, insurance, race, access to care, patient education, and socioeconomic status have been shown to influence all aspects of health care, including cancer management.[16–18] Despite many retrospective, prospective observational studies, and a few randomized trials comparing open with laparoscopic resection for cancer, there remains a paucity of information regarding what factors affect the choice of surgical approach and outcomes of each method on a larger scale. Thus, we sought to analyze patient and systemic factors that may affect the type of colon resection performed and secondarily determine the associated outcomes from a large nationwide database.

Material and Methods

After the approval by our institutional review board, data was collected from the 2003 and 2004 Nationwide Inpatient Sample (NIS) databases, a product of the Health Care Utilization Project, Association for Healthcare Research and Quality.[19] This is currently the largest all-payer inpatient care database in the United States including persons covered by Medicare, Medicaid, private insurance and the uninsured, with data from approximately 8 million hospital stays per year. The sampling frame and discharge weights provided with the NIS dataset allow for creating accurate national estimates from this approximate sample of 20% of all nationwide discharges. It includes both admission and discharge diagnoses, procedures performed, and complication and outcome data during the hospitalization. Included in the NIS database are Clinical Classifications Software (CCS), which consists of over 260 diagnosis categories based on the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Patients with a primary CCS code for cancer of the colon (CCS=14) were selected from the 2003 and 2004 NIS databases. Patients were then stratified by primary ICD-9-CM procedure codes for standard colon cancer resections including right hemicolectomy (45.73), left hemicolectomy (45.75), and sigmoid colectomy (45.76). Patients undergoing transverse colectomy (45.74), total abdominal colectomy (45.8), and all rectal cancer cases (48) were excluded as these patients may be less likely to be offered a laparoscopic approach. In addition, we excluded all patients less than 18 years old and emergent admissions (NIS variable ELECTIVE). Finally, we used the disease staging clinical criteria data included in NIS to identify and exclude urgent or emergent pathology that would usually preclude the consideration of a laparoscopic approach, such as intussusception or volvulus (2.05), fistula formation (2.06), gross perforation or peritonitis (2.07), or shock (3.03).

Definition of Variables

The primary variable in this study was the method of repair, defined by the laparoscopic designation (ICD-9-CM code 54.21) vs open colectomy. In an attempt to perform an intention to treat analysis, all patients with the 54.21 code were included in the laparoscopic group, as it was impossible to determine from this database which patients may have been converted to an open procedure. Other variables included age (years), sex, race, median household income (adjusted) for patient's ZIP code (1=$1–$24,999; 2=$25,000–$34,999; 3=$35,000–$44,999; 4=>$45,000), geographic region (Northeast, Midwest, West, South), teaching status of the hospital (teaching, nonteaching), location of the hospital (urban, rural), calendar year (2003, 2004), comorbidity, admission type (elective, nonelective), disease stage (localized, locally advanced, regional nodal disease, metastatic disease), and insurance status (Medicare, Medicaid, private insurance, other).

Race

The NIS database categorizes ethnicity as Caucasian, African-American, Hispanic, Asian, Native American, and other. Participants with Asian, Native American, and other categories (NIS variables Race 4, 5, 6; n=3397) were initially grouped together. In addition, ethnicity was also dichotomized to Caucasian and non-Caucasian for comparison in a separate analysis. Records with unknown race or incomplete operative data were analyzed for any significant deviations from the main sample and excluded from further analysis (n=26%).

Disease Stage

Patients were categorized as localized disease (AJCC Stage 1, NIS 1.01, 2.01), locally advanced disease or symptoms (AJCC Stage 2, NIS 2.02, 2.03 [bleeding], 2.04 [obstructive]), regional nodal disease (AJCC Stage 3, NIS 3.01), or metastatic disease (AJCC Stage IV, NIS 3.02).

Comorbidities

Comorbidity measures were identified using the Agency for Healthcare Research and Quality (AHRQ) comorbidity software. This includes ICD-9-CM diagnoses and the

Diagnosis Related Group (DRG) in effect on the discharge date, and is found within the NIS database.

Age

Age was analyzed as a continuous variable in univariate and multivariate analysis and was then dichotomized at age greater than 70 years (the 75th percentile for the study population) for the final multivariate model.

Insurance Status

Patients were evaluated by both primary and secondary payers (NIS variables PAY1 and PAY2, respectively). Participants were grouped into Medicare, Medicaid, and private insurance. All patients with secondary payer status private insurance were grouped and analyzed with the private insurance group. Patients with self-pay, no charge, or other (NIS PAY1/PAY2=4, 5, and 6) were grouped together as "other".

Main Outcome Measures

Hospital Charges

Total hospital charges were calculated using the NIS variable total charges cleaned (TOTCHG). In general, these are charges, not costs, and do not include professional fees and noncovered charges, but do include emergency department charges before admission to the hospital.

Length of Hospital Stay

The length of the hospital stay was measured in days and measured from the time of admission to the time of discharge.

In-Hospital Complications

In-hospital complications were based on ICD-9-CM codes and grouped into eight ifferent categories as previously described by Guller et al.: mechanical wound complications, infections, urinary, pulmonary, gastrointestinal tract, cardiovascular, systemic, and complications during the surgical procedure (Table 1).[20]

Hospital Discharge

The NIS database provides the following information about the patient's discharge status: routine discharge, short-term hospital stay, skilled nursing facility, intermediate care

Table 1 International Classification of Diseases, Ninth Revision, Clinical Modification Codes for Postoperative In-Hospital Complications

Complication	ICD-9-CM	Percent
Mechanical wound		0.7
Delayed wound healing	998.83	
Postoperative hematoma	998.12	
Postoperative seroma (noninfected)	998.13	
Disruption of operative wound	998.6	
Persistent postoperative fistula	998.3	
Infections		2.4
Postoperative infection	998.5	
Postoperative skin abscess	998.59	
Postoperative septic wound complication	998.59	
Postoperative skin infection	998.59	
Postoperative intraabdominal abscess	998.59	
Postoperative subdiaphragmatic abscess	998.59	
Postoperative infected seroma	998.51	
Urinary		1.3
Postoperative urinary retention	997.5	
Postoperative urinary tract Infection	997.5	
Pulmonary		4.5
Postoperative atelectasis	997.3	
Postoperative pneumonia	997.3	
Mendelson syndrome resulting from a procedure	997.3	
Postoperative acute respiratory insufficiency	518.5	
Postoperative acute pneumothorax	512.1	
Adult respiratory distress syndrome	518.5	
Postoperative pulmonary edema	518.4	
Gastrointestinal tract		10.9
Postoperative small bowel obstruction	997.4	
Postoperative ileus	997.4	
Postoperative ileus requiring nasogastric tube	997.4	
Postoperative nausea	997.4	
Postoperative vomiting	997.4	
Postoperative pancreatitis	997.4	
Complication of anastomosis of gastrointestinal tract	997.4	
Cardiovascular		3
Postoperative deep venous thrombosis	997.79	
Postoperative pulmonary embolism	415.11	
Postoperative stroke	997.02	
Phlebitis or thrombophlebitis from procedure	997.2	
Cardiac arrest/insufficiency during or resulting from procedure	997.1	
Systemic		1.3
Postoperative shock (septic, hypovolemic)	998.0	
Postoperative fever	998.89	
Complications during the surgical procedure		2.7
Accidental puncture or laceration, complicating surgery	998.2	
Foreign body accidentally left during procedure	998.4	
Hemorrhage/bleeding complicating procedure	998.11	

Adapted from Guller et al. [20]

Table 2 Patient Demographics

Variable (n=98,923)	Number	Percent
Type of resection		
Open	95,627	96.7
Laparoscopic	3,296	3.3
Mean age (years)	69.2±12.5	N/A
Sex		
Female	47,669	48
Male	51,095	52
Missing	158	0.2
Race		
Caucasian	58,451	81
African-American	6,799	9.4
Hispanic	3,875	5.3
Other	3,397	4.7
Missing	26,401	27
Calendar year		
2003	49,660	50.2
2004	49,262	49.8
Primary payer		
Medicare	39,186	40
Medicaid	2,041	2
Private	55,046	56
Other	2,562	2
Missing	87	0.1
Location of hospital		
Urban	85,533	87
Rural	13,384	13
Teaching status of hospital		
Teaching	42,987	44
Nonteaching	55,930	56
Disease stage		
Localized	60,858	63
Locally advanced	2,158	2
Regional nodal disease	17,712	18
Metastatic	15,465	16
Missing	2,728	3
Length of stay (days)	7.6±5.1	N/A
Any complication	21,606	22
In-hospital mortality	1,319	1.3

N/A: not applicable

facility, discharge to another type of facility, home health care, left against medical advice, and died during hospitalization. Patients who died during hospitalization (n=1,319) were excluded when evaluating this specific endpoint only. Patients who left against medical advice (n=97) were reclassified along with routine with going home (NIS variables DISPUniform 1 and 7). Patients requiring home health care (n=11,637) were similarly categorized and evaluated separately (NIS variable DISPUniform 6). Patients requiring disposition to another facility were also categorized together and evaluated separately (NIS variables DISPUniform 2, 3, 4, and 5).

In-Hospital Mortality

Because the NIS database contains information regarding in-hospital stay only, deaths after discharge from the hospital are not included in this series.

Statistical Analysis

All statistical analyses were performed using commercially available software (SPSS for Windows version 14.0; SPSS,

Table 3 Laparoscopic vs Open Colectomy: Univariate Analysis

Variable (n=98,923)	Laparoscopic	Open	P
Number	95,627 (97%)	3,296 (3%)	
Mean age (years)	67.6±12.9	69.2±12.4	<0.05
Sex			0.02
Female	50%	48%	
Male	50%	52%	
Race			0.04
Caucasian	79%	81%	
Non-Caucasian	21%	19%	
Disposition of patient			<0.001
Home	81%	76%	
Other facility	5%	11%	
Home health/hospice	14%	13%	
Primary payer			0.06
Medicare	38%	40%	
Medicaid	2%	2%	
Private	57%	55%	
Other	3%	3%	
Median household income			<0.001
$1–$24,999	17%	22%	
$25,000–$34,999	23%	27%	
$35,000–$44,999	27%	26%	
≥$45,000	33%	25%	
Region of hospital			<0.001
Northeast	20%	21%	
Midwest	27%	25%	
South	27%	36%	
West	26%	17%	
Location of hospital			<0.001
Urban	96%	86%	
Rural	4%	14%	
Teaching status of hospital			<0.001
Teaching	41%	43%	
Nonteaching	59%	57%	
Disease stage			<0.001
Localized	73%	63%	
Locally advanced	2%	2%	
Regional nodal disease	16%	19%	
Metastatic	9%	16%	
Length of stay (days)	6±6.1	7.6±5.1	0.006
Total charges	$34,685	$34,178	0.187
In-hospital complication	18%	22%	<0.001
In-hospital mortality	0.6%	1.4%	<0.001

Table 4 Independent Predictors of Undergoing Laparoscopic Resection

Variable	Odds ratio	95%CI	*P*
Age<70 years	1.2	1.1–1.3	<0.05
Female	1.1	0.99–1.17	0.06
Insurance status			
Medicare	1.0		
Medicaid	1.01	0.75–1.36	0.95
Private	1.02	0.93–1.11	0.74
Other	0.99	0.76–1.30	0.95
Non-White	1.1	0.99–1.2	0.06
Median household income			
$1–$24,999	1.0		
$25,000–$34,999	1.0	0.89–1.15	0.87
$35,000–$44,999	1.3	1.1–1.4	<0.05
≥$45,000	1.4	1.26–1.61	<0.05
Hospital region			
Northeast	1.0		
Midwest	1.89	1.67–2.13	<0.05
South	0.95	0.85–1.07	0.39
West	2.0	1.74–2.2	<0.05
Disease stage			
Metastatic	1.0		
Localized	2.5	2.2–2.9	<0.05
Locally advanced	1.5	1.1–2.1	0.02
Regional nodal	1.7	1.4–2.0	<0.05

Chicago, IL). Because the NIS database is a 20% sample of the United States yearly inpatient admissions, to produce national estimates all analyses were performed using weighted samples (NIS variable DISCWT). Patients with invalid or missing data for the primary variables of interest were analyzed for any significant variance from the study population and then excluded for evaluation of that data element. Univariate analysis was performed comparing laparoscopic vs open resection using the Student's *t* test, chi-square, or Mann–Whitney *U* test to compare patient demographics and outcome measures with significance set at $P<0.05$. Selected variables identified as significant by univariate analysis were entered into a block multivariate logistic regression model to determine independent predictors of undergoing a laparoscopic approach. Key variables of interest such as race and payer status were forced into the regression model even if they were not found to be significant on univariate analysis. Adjusted odds ratios (OR) are reported with 95% confidence intervals (95%CI) and variables with multiple categories (i.e., median income) are reported with odds ratios referenced to the first category.

Results

We identified 98,923 admissions (mean age 69.2 years), of which 95,627 (96.7%) underwent open resection and 3,296 (3.3%) underwent laparoscopic resection. The NIS population were predominately Caucasian (81%) with a slight male predominance (52%). The overall group had mostly localized disease (63%), had private insurance (56%), and had surgery performed in urban hospitals (87%) at nonteaching centers (56%) (Table 2).

When stratified by the surgical approach, laparoscopic resection was associated with a lower overall complication rate (18% vs 22%), although the complication profile by category was similar. Laparoscopy was also associated with a shorter length of stay (6 vs 7.6 days), decreased need for skilled aftercare (5% vs 11%), and lower mortality (0.6% vs 1.4%, all $P<0.01$). There was no significant difference in total hospital charges between the groups ($34,685 vs $34,178, $P=0.19$) (Table 3).

Comorbid conditions present at the time of hospital admission were analyzed for both groups. Compared with open resection, patients undergoing a laparoscopic approach had less congestive heart failure (3.3% vs 7.1%, $P<0.01$), chronic obstructive pulmonary disease (11.4% vs 14.1%, $P<0.01$), diabetes (13.5% vs 16.6%, $P<0.01$), obesity (3.1% vs 4.7%, $P<0.01$), and renal failure (0.8% vs 1.4%, $P=0.02$). Both groups had similar rates of hypertension (laparoscopic 48.9% vs open 49.3%, $P=0.65$) and peripheral vascular disease (2.8% vs 2.8%, $P=0.67$).

A missing value analysis was performed for cases that did not have a race code present. There was no significant or systematic deviation from the population means for the other study variables of interest found among this group. For the remainder of the analysis, the missing data for race was assumed to be missing at random and those cases were excluded from the multivariate analysis. After adjusting for other covariates to include age, sex, primary payer status, race, median income, region of the country, disease code, and demographics factors found on univariate analysis to be significantly different between the groups (i.e., comorbidities, teaching status of the hospital, urban vs rural), independent predictors of undergoing laparoscopic resection were age<70 (OR=1.2, $P<0.01$), national region (Midwest OR=1.9, West OR=2.0, $P<0.01$), higher median household income (OR=1.4), and lower disease stage (OR=2.5, $P<0.01$). Race and insurance status showed no significant association with the operative method ($P>0.05$) (Table 4). A separate multivariate regression model was done, which included cases with missing race data (coded as "missing"), and there remained no significant independent contribution of race or insurance status ($P>0.05$).

Discussion

Despite a plethora of randomized controlled trials currently in the literature, including a systematic review of 17

randomized trials encompassing over 4,000 patients,[21] laparoscopy for colon cancer continues to generate much controversy and discussion. To many, the COST trial marked the long-awaited arrival of justification of laparoscopy for colon cancer.[6] Yet, despite this prospective randomized trial encompassing 48 institutions and 872 patients with 3 year follow-up, this trial was done by "experts" in the field in large volume centers, each having performed a minimum of 20 cases, and do not necessarily portray what is being done on a nationwide level. The present study attempts to further clarify this, by not only evaluating the outcomes of laparoscopic vs open colectomy, but also by examining the variables that affect what approach patients undergo. Multiple factors are felt to contribute to the method of resection for various surgical diseases, including patient presentation, comorbidities, hospital capabilities, underlying disease, surgeon experience, insurance status, and ethnicity.[22–24]

Comparing the two groups by patient demographics, the laparoscopic cohort were younger, had more females, non-Caucasians, and had lower rates of comorbidities. Yet, despite these baseline differences, only age<70 years of these variables was associated in multivariate analysis with undergoing a laparoscopic resection. Multiple comorbidities, including heart and lung disease and obesity, have previously been thought to be relative contra-indications to laparoscopy.[25,26] However, laparoscopy has not only been found to be safe in patients with these comorbidities, but often associated with improved results.[27,28] In a study of 107 consecutive patients deemed complicated by either age>80 years, body mass index>30, or ASA III or IV, case-matched with those undergoing an open approach, Plocek found that the open group had higher morbidity (52% vs 26%) and were associated with prolonged length of stay and higher rate of skilled aftercare need.[27] Even in those cases in which conversion to open is required, Casillas et al. found that operative time, length of stay, in-hospital complications, and costs were similar to those undergoing scheduled open laparotomy.[29] In the present study, we chose to evaluate charges, as this is a reflection of what is actually being billed. Although charges do not reflect reimbursement or cost, which aspects that are more difficult to quantify such as healthcare system costs vs societal costs,[30] they do reflect some degree of financial equivalence as we did not find any significant differences.

In addition, concerns about laparoscopic safety in the older population do not seem to be well founded based on both previous studies and in the present series,[31,32] where the mean age in the laparoscopic group was 67 years. In a study comparing 65 patients older than 70 years (median age=75 years) undergoing a laparoscopic colorectal surgery with 89 patients less than 70 years (median age=78 years) undergoing an open resection, laparoscopy was associated with earlier return of bowel function, shorter hospital stay, and less cardiopulmonary morbidity (7.7% vs 22.4%, $P=0.03$).[33] Similarly, Stewart et al. found no complications related to laparoscopy in a cohort of 42 patients with a median age of 84 years.[34] Schwandner found that the overall complication rate and the conversion to laparotomy rate were similar between older and younger patients undergoing colorectal surgery, although older patients (age>70 years) had longer duration of surgery, postoperative ICU stay, and overall length of hospital stay.[35] In fact, the decreased complication profile and overall faster recovery demonstrated with a laparoscopic approach make it an attractive option in the elderly patient with more comorbid disease and decreased physiologic reserve.

In the current study, we were unable to find a correlation between either race or payer status as a factor for undergoing either an open or laparoscopic approach. Yet, other studies have demonstrated that each of these factors may be associated with the method of repair.[36,37] Guller et al. in a study of 145,546 patients undergoing appendectomy from 1998 to 2000 found that Caucasians were significantly more likely to undergo a laparoscopic approach than African-Americans, Hispanics, and other minorities (24.8%, 18.6%, 19.6%, and 18.8%, respectively, $P<0.001$).[38] Similarly, they found that private insurance was independently associated with the increased use of laparoscopy compared with Medicare, Medicaid, and other insurance ($P<0.001$). Hagendorf et al. found similar results for the pediatric population regarding laparoscopy and appendectomy.[39] We did find an impact of the median income for zip code on the chance of having laparoscopy with higher incomes having higher odds ratio for lap resection (median income=$35,000–44,999, OR=1.3, 95%CI=1.1–1.4; median income>$45,000, OR=1.4, 95%CI=1.26–1.61). Although it is difficult to surmise the exact reason for this finding from this type of study, this may be secondary to patients living in more affluent areas had a higher chance of having laparoscopy because of the types of hospitals available to them.

Other studies have examined the effect of race not only on the stage at presentation and outcome in patients with colorectal cancer, but also on the treatment algorithms. Some have suggested that colorectal cancer has different anatomical and physiological characteristics to account for the differences in outcomes amongst different ethnic backgrounds.[40–42] Mostafa et al. found that African-American patients were more likely to present with late stage tumor.[43] Screening may also play a role, as race has been shown to be associated with access to screening programs,[44] as well as an unawareness of the need for screening.[45] This suggests that both improved education and equal access to care may influence not only the stage at presentation but the eventual outcome. Yet, all aspects of the cancer patient's

care may account for differences in outcome. Ayanian et al. demonstrated that black patients were significantly less likely to receive chemotherapy and possibly different treatment options.[46] Regardless of the exact etiology, lower survival amongst minorities continues to be the trend nationwide, in some cases with a risk of death among black patients 20–50% higher than white patients.[47,48] In the current study, we were unable to find a correlation between either race or socioeconomic status as a factor for undergoing either an open or laparoscopic approach. Ideally, this would be interpreted as a demonstration of the equitable and equivalent delivery of cutting edge health care regardless of race for patients presenting with colon cancer. However, the overall small percentage of patients offered laparoscopic resection and the infancy of the technique for colon cancer make firm conclusions about the impact of race difficult. Further analysis of these factors as laparoscopic resection comes into widespread use outside of investigation trials and protocols will be needed.

Method of approach may also affect the outcomes besides the return of bowel function, cosmesis, pain control, perioperative morbidity, and length of stay. Originally found in a prospective randomized study of 219 patients by Lacy et al., laparoscopic colectomy was not only associated with the above outcomes, but also improved cancer-free and overall survival.[14] In their study, a laparoscopic approach was associated with a reduced risk of recurrence (hazard ratio [HR]=0.39), all cause mortality (HR=0.48), and cancer-related death (HR=0.38). It is interesting to note that the majority of improvement was noted in those patients with stage III disease. Although the authors were unable to identify the reasons for this, other authors have proposed theories. Sylla et al. have postulated that laparoscopy results not only in less trauma, but less surgery-related immune suppression leading to better outcomes.[49,50] Yet, other authors have found no differences between the two methods for overall survival.[51–53] In the present study, we were only able to focus on the perioperative outcomes and unable to examine or comment on the long-term morbidity and survival data. We should emphasize that the present study was not meant to be a primary evaluation of outcomes, as patient characteristics including comorbidities were vastly different in the groups. We simply wanted to perform an unadjusted analysis on the two cohorts to evaluate patient outcome given the selection bias of the surgeon in determining what patients underwent the identified surgical approach. Yet, should other studies continue to identify a pattern of improved survival, the push to perform laparoscopy may go beyond the short-term benefits.

We should point out several limitations to the present study. First, the latest NIS database has available data only through 2004, thus many of the laparoscopic cases in this cohort were likely done under a protocol. Although this cannot be determined from the database, this is likely the case based on the years covered in the study. This may explain the predominance in urban centers as well as influence our finding of lack of association of race and payer status on laparoscopy, although we found nonteaching centers in which protocols may be less apt to participate in to have a slight majority. Also as a consequence of this time period, there is a relative paucity of laparoscopic resections in the current population with only 3.3%. This may be reflective also of the NIS database itself, as we identified our patient population by ICD-9-CM procedure codes for the various colectomies along with the laparoscopic code. Although the use of CPT codes, which have defined laparoscopic procedures, may have avoided a selection bias or error in classification, we defined the patient categories as best as possible given the constraints and consistent with what has been used in prior published series using NIS.[20] As increasing experience with performing laparoscopic resections in general is gained and its use is broadened, it will be interesting to see how future studies may change the results found in this study. As of this writing, current recommendations by the COST study group and endorsed by the American Society of Colon and Rectal Surgeons and SAGES states that before performing laparoscopic resection for colon cancer, a minimum of 20 laparoscopic resections for benign or metastatic disease should be performed before embarking on laparoscopy for cure in colon cancer.[6,54] As the NIS and similar large-scale databases release data for the years since 2004, these results may be vastly different.

Other limitations to the present study include the mere nature of a retrospective study and the inherent biases with it. Large databases like the NIS, whereas providing a plethora of information all lack specifics that could add to the study—i.e., surgeon experience with laparoscopy, lack of long-term follow-up, etc. As this is purely a large observational study, it is not and should not be interpreted as the "gold-standard" prospectively randomized trial. Missing data is a potential confounder in analyzing the impact of race in our study, as 27% of the population did not have this data point available. This is a result of both incomplete records and the policies of several states that contribute NIS data. However, examination of the cases with missing data found no significant variations from the study population, and thus we felt they could be excluded from this aspect of the analysis. In addition, NIS provides no information on competency of the operative and perioperative outcomes including margins, recurrence, conversion rate to open, number of lymph nodes resected, readmission rates, and any data beyond the in-hospital complication or mortality data. In addition, the lower rate of true surgical complications in this series compared to that in

the literature is likely a result of the nature of this administrative database; however, the undercounting of complications is with both groups and does not add to the overall bias of the results. It also does leave open the possibility of coding errors that may not only affect the type of procedure, perioperative data, but also outcomes.[20] Yet, our goal was to identify as best as possible what was taking place on a national level. The benefits of this large sample size allow us to draw our conclusions based on all different levels of experience, skill, and institution size, and not on what are most often smaller randomized trials performed by experts in select institutions.

Conclusions

As the trend toward the expanded use of minimally invasive techniques continues, it is important to identify factors that may either inhibit or shy surgeons away from performing laparoscopy. In this large nationwide database evaluation, we found that laparoscopy for colon cancer is associated with improved outcomes in unadjusted analysis and similar charges compared to open resection. Although factors such as region of the country, urban locations, younger age, higher income, and localized disease were identified as predictors of undergoing laparoscopy, we found no influence of race or payer status on the utilization of a laparoscopic approach. Future analysis of data as laparoscopic resections for malignancy gain widespread use and acceptance will further clarify factors that influence the choice of and access to this surgical approach.

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A Prospective, Double-Blind, Multicenter, Randomized Trial Comparing Ertapenem 3 Vs ≥5 Days in Community-Acquired Intraabdominal Infection

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Abstract Severe secondary peritonitis is diagnosed in only 20–30% of all patients, but studies to date have persisted in using a standard fixed duration of antibiotic therapy. This prospective, double-blind, multicenter, randomized clinical study compared the clinical and bacteriological efficacy and tolerability of ertapenem (1 g/day) 3 days (group I) vs ≥5 days (group II) in 111 patients with localized peritonitis (appendicitis vs non-appendicitis) of mild to moderate severity, requiring surgical intervention. In evaluable patients, the clinical response as primary efficacy outcome were assessed at the test-of-cure 2 and 4 weeks after discontinuation of antibacterial therapy. Ninety patients were evaluable. In groups I and II, 92.9 and 89.6% of patients were cured, respectively; 95.3% in group I and 93.7% in group II showed eradication. These differences were not statistically significant. The most frequent bacteria recovered were *Escherichia coli* and *Bacteroides fragilis*. A wound infection developed in seven patients (7.7%) and an intraabdominal infection in one patient (1.1%). There was a low

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frequency of drug-related clinical or laboratory adverse effects in both groups. Our study demonstrated that, in patients with localized community-acquired intraabdominal infection, a 3-day course of ertapenem had the same clinical and bacteriological efficacy as a standard duration.

Keywords Peritonitis · Ertapenem · Localized intraabdominal infection · Surgical and antibiotic therapy

Introduction

Recommendations published by the Surgical Infection Society and the Infectious Disease Society of America concerning the duration of antibiotic therapy in patients with intraabdominal infection were limited and not specific enough to inform treatment. The guidelines stated only "antimicrobial therapy for established infections should be continued until resolution of clinical signs of infection occurs, including normalization of temperature and WBC count and return of gastrointestinal function" and "that definition of the appropriate duration of antimicrobial therapy is perhaps the most pressing need".[1]

This lack of specificity is mainly because of a paucity of clinical studies addressing the optimal duration of therapy.[2,3] Many trials have adopted a fixed duration, ranging from 5 up to 14 days for all patients with community-acquired intraabdominal infection, irrespective of severity of the peritonitis.[4–6] It is well known that secondary peritonitis encompasses a number of diseases and can present with a wide range of severities.[7]

It has been shown that most patients with intraabdominal infection enrolled in antibiotic treatment trials present with acute illness of mild severity, which, in 35 to 55% (and in some studies, up to 70% of evaluable patients) of cases, is represented by acute appendicitis.[7–9] Additionally, many of these patients do not have a fully developed infection but rather a local initial infection or simple contamination.[5] In a nonrandomized trial, Schein et al. demonstrated that, by tailoring the duration of the antibiotic therapy according to the operative extent of infection, the same clinical results can be obtained in all patients, thus, minimizing antibiotic administration.[5] Another recent systematic review of 28 studies examining the duration of antibiotic therapy in advanced appendicitis in children showed that limiting the duration of antibiotic use to 3 days was not associated with higher rates of intraabdominal abscess or wound infection.[10] All these studies demonstrated many patients were treated unnecessarily for several days when using a fixed standard treatment period.

There is a need for randomized studies, as has been done in patients with pneumonia,[11,12] that consider whether shorter duration therapy is as effective as a standard therapy in patients with mild to moderate peritonitis. If this was the case, the resulting reduction in antibiotic consumption could represent an important achievement not only in the treatment of these patients, but in controlling the consequences of antibiotic overuse. It is well known that overuse of antibiotics is responsible for several important consequences such as increases in the cost of therapy and adverse effects, but the main concern is emergence of resistant pathogens. The selective pressure determined by inappropriate course of antibiotics favors the emergence of resistant isolates.

In the last SIS Guidelines, it is clearly indicated that antibiotics used for empirical treatment of community-acquired intraabdominal infections should be active against enteric Gram-negative aerobic and against obligate anaerobic bacilli.[1]

Moreover, for patients with community-acquired infections of mild-to-moderate severity, agents that have a narrower spectrum of activity and that are not commonly used for nosocomial infections, such as ampicillin/sulbactam, cefazolin or cefuroxime plus metronidazole, ticarcillin/clavulanate, ertapenem, and quinolones plus metronidazole, are preferable to agents that have broader coverage against Gram-negative organisms and/or greater risk of toxicity.[1] Cost is an important factor in the selection of a specific regimen.[1]

Ertapenem, a long-acting parenteral group I carbapenem, has shown a narrowed spectrum of activity in vitro against most aerobic and anaerobic bacteria generally associated with community-acquired infections.[13–16] Ertapenem is not active against most *Pseudomonas aeruginosa* or enterococci, but as underlined in the SIS Guidelines, coverage of these organisms is not routinely required for successful treatment of community-acquired intraabdominal infections.[1,3,5,16,17] In three earlier double-blind, randomized clinical trials, a standard duration therapy with ertapenem was comparably effective and as well tolerated as a standard duration therapy with piperacillin–tazobactam and ceftriaxone plus metronidazole.[17–19]

Demonstrating that short course of ertapenem is an effective monotherapy for community acquired intraabdominal infection is particularly important in the context of resistance and of cost.

The aim of the study was to compare the efficacy and safety of ertapenem administered according to a standard treatment regimen for 5 days or more vs a shorter regimen of 3 days in patients with community-acquired intraabdominal infection of mild to moderate severity.

Materials and Methods

Study Design

This was a prospective, open-label, multicenter, randomized clinical study of adult patients diagnosed with localized

Table 1 Reasons for Exclusion of Patients from the Study

Causes	Number of Patients	Percent
No pathogens found	14	66.7
No follow-up	2	9.5
Protocol violations	5	23.8
Total	21	100

community-acquired intraabdominal infections of mild to moderate severity, who required surgical intervention within 24 h of diagnosis/admission. The institutional review board at each site approved the protocol, and written informed consent was obtained from all participants.

Localized intraabdominal infections are defined as infection from diverse sources that extends beyond the hollow viscus into the peritoneal space as a consequence of the perforation (usually with localized pus formation), but is confined near the perforated viscus and does not affect the entire peritoneal cavity. A diagnosis consistent with intraabdominal infection in the eligible patients was based on clinical syndrome (history, complete medical and physical examinations, and laboratory evaluation) and intraoperative findings. Patients were required to present with either an oral temperature≥38°C, or a WBC≥10.5×10^3/mm, with symptoms and physical findings (e.g., abdominal tenderness and pain) and radiologic, ultrasonic, or radionuclide (if performed) changes consistent with intraabdominal infection.

All patients underwent operation within 24 h of diagnosis or enrollment in the study; during the operation, the surgeon was asked to check the diffusion of the peritonitis and to take a sample of the exudates present. In addition to an evaluation of the severity of the disease with the Apache II score, all patients had an intraoperative evaluation of the severity of the secondary peritonitis based on the Mannheim peritonitis index (MPI).[20–22] After 3 days of parenteral therapy, all patients had complete medical and physical examinations and laboratory evaluation. If clinical improvement was clearly demonstrated (i.e., the patient has temperature≤100°F or 37.8°C orally for ≥24 h, a diminution or a shift of the WBC, and an improvement in abdominal signs and symptoms), the patients were randomly allocated to short-duration therapy (3 days) or standard duration therapy. Those randomized into the short duration treatment group (group I) received placebo for the remaining course (up to day 5), whereas those randomized into the standard duration treatment group (group II) continued the antibiotic for no less than 5 days, Fig. 2.

Study Population

The study was conducted in ten surgery units responsible for the emergency surgery in Italy between March 2005–September 2006.

Only patients 18 years of age or older with localized intraabdominal infections extending beyond the organ wall but confined near the hollow viscus that were mild to moderate in severity but required surgical intervention within 24 h of diagnosis were included in this trial. Excluded were patients with traumatic bowel perforation requiring surgery within 12 h, perforation of gastroduodenal ulcers requiring surgery within 24 h, or other intraabdominal processes in which the primary etiology was unlikely to be infectious.

Also excluded were patients, lactating or pregnant, with a history of allergy, hypersensitivity, or any severe reaction to the study antibiotics or to any of the components of these products; with rapidly progressive or terminal illness; with a history or presence of severe hepatic or renal disease (e.g., creatinine clearance ≤0.5 ml min^{-1} per 1.73 m^2); or with a concomitant infection that would interfere with evaluation of response to the study antibiotics.

At the enrollment, the severity of the disease was evaluated with Apache II score and MPI before the operation. Diagnosis was based on the patient's clinical syndrome and intraoperative findings, including intraoperative cultures. The study drug was started before the operation. The patients underwent operation and were treated for 3 days with ertapenem (1 g per day). Only patients with an improvement in temperature (<37.8°C), WBC (returning to the normal range), and presence of abdominal sounds at the third day were randomized into either group I, short duration therapy for 3 days plus placebo for the remaining course, or group II, standard duration (ertapenem for no less than 5 days).

Table 2 Demographic Characteristics of Randomized Patient

		3 Days		≥5 Days	
		Number of Patients (%)	Mean Age	Number of Patients (%)	Mean Age
Appendicitis	Male	17 (77.2)	25.1	15 (65.2)	39.8
	Female	5 (22.8)	36.3	8 (34.8)	57.3
	Total	22 (52.4)		23 (48.0)	
Non-Appendicitis	Male	9 (45.0)	58.3	12 (48.0)	54.5
	Female	11 (55.0)	65.0	13 (52.0)	65.7
	Total	20 (47.6)		25 (52.0)	

Table 3 Distribution of Patients in the Two Groups

	Group I (3 Days)		Group II (≥5 Days)		Total
	Number of Patients	Percent	Number of Patients	Percent	
Appendicitis	22	52.4	23	48.0	45
Non-Appendicitis	20	47.6	25	52.0	45
Total	42	100	48	100	90

To achieve balance between the treatment groups, patients were stratified according to the site of infection (complicated appendicitis vs all other diagnoses). Enrollment into each stratum was closed when nearly 50% of cases were enrolled to limit the proportion of cases with complicated appendicitis. Criteria for complicated appendicitis were appendiceal perforation or periappendiceal abscess. Adequate surgical source control is a determinant key of the outcome in the intra-abdominal infections; thus, a panel of three surgeons was asked to review the adequacy of the surgical operation under blinded conditions.

Aerobic and anaerobic cultures of intraoperative specimens were obtained at baseline and processed in the clinical microbiology laboratory of the participating hospitals. All microorganisms isolated were cultured and tested for in vitro susceptibility to the study antibiotic ertapenem by disk diffusion or microtiter dilution according to guidelines of the National Committee for Clinical Laboratory Standards (NCCLS).[23,24] Routine susceptibility testing of strict anaerobes was not required per protocol.

Clinical and Laboratory Assessments

At enrollment, all patients underwent physical examination and laboratory studies, including a CBC with WBC and differential, platelet count, serum glucose, BUN, and serum creatinine. The same procedures were performed at day 3 and at the end of the study, at the post-treatment follow-up, or more frequently, as clinically indicated. Liver function studies, serum electrolytes, and urinalysis were performed as clinically indicated and at the discontinuation of intravenous study drug therapy. When clinically indicated during antibiotic therapy, blood, urine, and specimens from other clinically relevant intraabdominal sites were obtained for culture and susceptibility testing. Cultures were also performed at the end of antibiotic therapy, unless there was no material available to culture and/or no clinical evidence of infection.

In clinically and microbiologically evaluable patients, the clinical response considered the primary efficacy outcome was assessed at the test-of-cure (TOC) visit 2 and 4 weeks after discontinuation of antibacterial therapy as in previous trials comparing ertapenem with piperacillin–tazobactam and ceftriaxone/metronidazole.[17–19]

The clinical outcome of evaluable patients was classified into three groups: cure (no signs or symptoms of infection and no further antimicrobial therapy), failure (no improvement, infection progression, or death caused by infection), or late failure (recurrence between cessation of antibiotics and follow-up).

Microbiological responses were recorded for each baseline pathogen. Favorable microbiological responses included eradication of the pathogen(s) that was either documented or presumptive (no material available for culture in clinically cured patients); unfavorable microbiologic responses included persistence of the pathogen(s), whether documented or presumed (no material available for culture in patients who had clinical failure).

Data Analysis

Treatment groups were compared using a Pearson chi-square test or Fisher's exact test. Statistical significance was

Table 4 Site of Infections

	Group I		Group II		Total	
	Number of Patients	Percent	Number of Patients	Percent	Number of Patients	Percent
Appendix	22	52.3	23	47.9	45	50
Gallbladder and biliary tree	5	11.9	3	6.2	8	8.8
Colon	8	19	10	20.8	18	20
Stomach and duodenum	4	9.5	4	8.3	8	8.8
Small intestine	1	2.3	5	10.4	6	6.6
Others	2	4.7	3	6.2	5	5
Total	42	100	48	100		

Table 5 Value of the Score Systems

Apache II Score	Number of Patients (%)	Mean Value/ Mean Score
≤10	69 (87)	5
≥10 ≤20	10 (13)	14.1
	79 (87.7)	6.2
MPI score		
≤21	68 (79)	19.4
>21	18 (21)	28.6
	86 (95.5)	21.3

declared at the 0.05 level. All tests were two-sided. Two-sided 95% confidence intervals were calculated for the difference in efficacy parameters between the two groups.

Results

Patient Characteristics

Of 111 patients enrolled in the study, 90 were evaluable. The remaining 21 (19%) patients withdrew from the study because of the absence of pathogens in the culture taken at operation (n=14), because they were lost at follow-up (n=2), and because of protocol violations (n=5; Table 1).

The most important characteristics and the distribution of the patients between groups I and II are shown in Tables 2 and 3. There was no difference between the two groups with regard to either the number of men and women or the mean age. However, an analysis showed that, in men with appendicitis, the mean age was very low (25.1 years) compared with women without appendicitis (65.7%). A slight difference was noted between non-appendicitis patients treated for 3 days compared to the group treated for 5 days (47.6 vs 52%); all the differences between the two groups were not statistically significant.

The decision to stop randomization of patients with acute appendicitis allowed us to have two identical groups with regards to the site of infection (Table 4).

The mean Apache II score for all treated patients was 6.2%, and the MPI was 21.3%, indicating that the severity of the disease was always mild to moderate, which also explains why no important differences were noted between the two scoring systems (Table 5).

The two groups were well matched for concomitant diseases, present in one third of the evaluable patients, the

Table 6 Pathogens Recovered and Their Susceptibilities to Ertapenem

	Group I (3 Days)					Group II (≥5 Days)					
	Appendicitis		Non-Appendicitis			Appendicitis		Non-Appendicitis			
	S	R	S	R		S	R	S	R		
Aerobes Gram-positive											
Staphylococcus capitis		1									
Staphylococcus coagulase-negative						1	2				
Staphylococcus haemolyticus							1				
Other staphylococci	1		1					2			
Streptococci			3			1		1			
Enterococcus faecium									2		
Enterococcus faecalis									1		
Other enterococci	1		1			2		1			
Aerobes Gram-negative											
Escherichia coli	17		7		**24**	15		16		**31**	**55, 46.20%**
Enterobacter cloacae			1								
Enterobacter faecalis				1							
Pseudomonas				1		1	4				
Klebsiella				1				1			
Other *Enterobacter* spp								2			
Proteus								1			
Serratia						1					
Citrobacter								1			
Acinetobacter baumanii		1									
Anaerobes											
Bacteroides fragilis	3		5		**8**	4		9		**13**	**21, 17.60%**
Clostridium spp	1										
Fusobacterium frigens			1								
Peptostreptococcus						2					

Table 7 Incidence of Postoperative Complication

	Group I (3 Days)		Group II (≥5 Days)		Total
Infection	Appendicitis	Non-Appendicitis	Appendicitis	Non-Appendicitis	
Wound	2	1	2	2	7
Intraabdominal		1			1

most common being heart and lung disorders and neoplasms. The mean average duration of antibiotic therapy in group II was 5.7 days with a range from 5 to 10 days. The intervention was considered inadequate to control the source of infection detected intraoperatively in only one patient.

A total of 119 isolates were obtained from the 90 evaluable patients. The most important pathogens isolated were *Escherichia coli* from 55 patients (46.2%) and *Bacteroides fragilis* from 21 patients (17.6%); both pathogens were more frequent in group II. There were 15 resistant isolates represented mainly by Gram-negative aerobes and enterococci (Table 6).

A post-operative infection was recorded in eight patients: seven had a wound infection and one an intraabdominal abscess drained without reoperation. In three patients from group I, the wound infection was drained on an outpatient basis after hospital discharge. In the other four patients from group II, the wound infection was discovered in the hospital and was treated without antibiotic therapy. The intraabdominal infection was discovered while the patient was undergoing antibiotic, and the treatment was continued after the drainage (Table 7).

Clinical and Bacteriological Outcomes

The clinical and bacteriological outcomes are shown in Fig. 1. Thirty-nine patients in group I (92.9%) and 43 patients in group II (89.6%) were cured at the test of cure. The difference between the two groups was not statistically significant (Fig. 2).

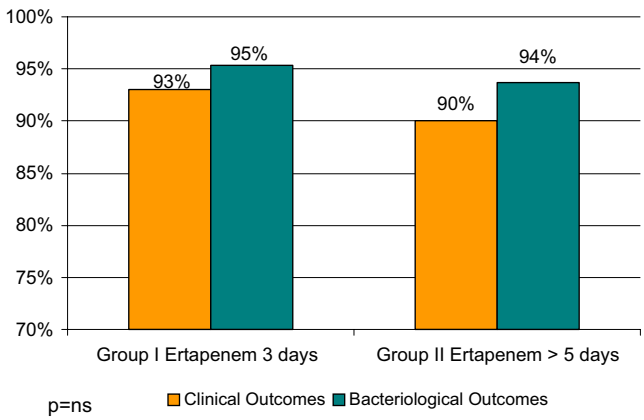


Figure 1 Clinical and bacteriological outcomes.

Complete eradication was achieved in 95.3% of patients in group I and 93.7% of patients in group II. This difference was not statistically significant. In the eight patients with a postoperative infection, cultures of the drainage material from the site of the infection were performed. The same pathogens as those present in the cultures taken at the operation were found in four patients in the cultures taken at infection site and were represented in three cases by *Staphylococcus* and in one case by *Klebsiella*, whereas in the other four patients, no germs were recovered. None of these germs were resistant to the study drug.

Safety

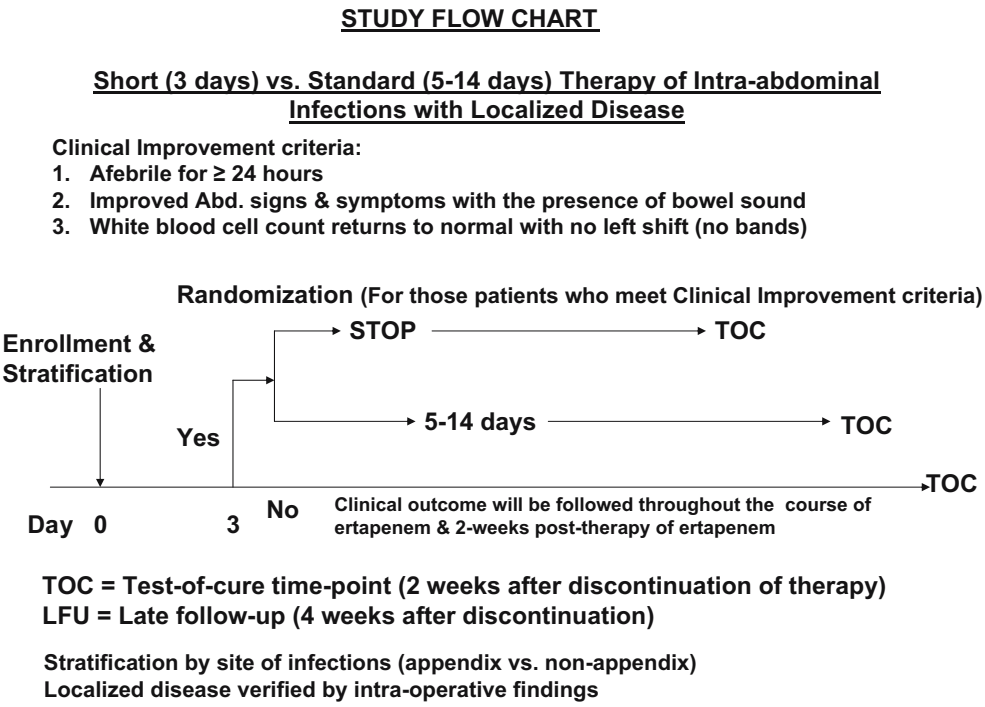
All 111 patients who received study medication were evaluated for clinical and laboratory adverse experiences. The presence of bowel movements was one of the parameters to assess the improvement of patients at day 3, and thus, specifically recorded by the investigators. None of the patients suffered from diarrhea up to day 3, whereas one case was observed in the group in a patient treated for more than 5 days. The most common drug-related adverse event was a local allergic erythema; digestive disorders were the second most common drug-related adverse event followed by mild increase of hepatic enzymes.

Discussion

The results of this study indicate that in patients with localized community-acquired intraabdominal infection (appendicitis and non-appendicitis), a short course (3 days) of ertapenem had the same clinical and bacteriological efficacy as a standard duration (≥5 days) of ertapenem. Clinical cure was achieved in 92.9% of patients in group I and in 89.6% of those in group II, whereas bacteriological eradication was achieved in 95.3% in group I and in 93.7% in group II. These differences in clinical and bacteriological outcome between the two treatments were not statistically significant. Our study demonstrated that, in patients showing clinical improvement after 3 days of treatment with ertapenem, discontinuation of antibiotic therapy was prudent and there were no differences in clinical success rates compared to patients treated with a standard duration therapy.

Our study validates for the first time the assumption that clinical parameters, such as normalization of temperature,

Figure 2 Study flow chart.



WBC count and return of gastrointestinal function, are reliable measures that can be used to monitor when to stop antibiotic therapy.[33] After discontinuation of the therapy at 3 days, none of the patients receiving placebo required another course of antibiotics. These data confirm also that the risk of subsequent treatment failure appears to be quite low for patients who have no clinical evidence of infection at the time of cessation of antimicrobial therapy.[10]

The previously reported observation that, in a certain number of patients, mainly those with acute appendicitis, there is contamination rather than an infection, as shown by the presence of negative cultures, is confirmed by our study in which sterile cultures were obtained from about 25% of patients with acute appendicitis.[4,6,9]

In these patients with non-perforated, uncomplicated appendicitis, a 24–48 h of antibiotic therapy is sufficient if a sound operative treatment has been performed.

There were no mortalities in this study, and the morbidity was represented mainly by wound infection (−n=7; 7.7%) and an intraabdominal infection (n=1; 1.1%). These figures are in line with those published in previous studies of patients with mild to moderate community-acquired intra-abdominal infections.[4,25–27]

The mild severity of the disease was also demonstrated by the low Apache II and MPI scores, although the median rates were close to those reported in published trials.[4,9]

As reported in previous studies, the bacteria recovered most frequently in this study were *E. coli* and *B. fragilis*. A number of enterococci were also present, and the majority were resistant to ertapenem.[28,29] However, we were unable to demonstrate whether they were responsible for causing postoperative wound infections. The same observation was made in other studies in which, despite the absence of coverage of bacteria present in the culture by the antibiotic regimen, the clinical success rate was similar to the other group treated with a broader-spectrum antibiotic.[30]

The bacteriological outcome was not significantly different between the two treatment groups. Eradication of the infecting organisms was observed in nearly 96% of all patients. In the four patients (4 of 90) who experienced bacteriological persistence after treatment with ertapenem, no ertapenem-resistant organisms were found. Persistence of *Staphylococcus* and *Klebsiella* spp. was recorded in those patients. None of these patients required an antibiotic course to treat the complication.

The frequency of adverse events was low in both groups and mainly represented by a local irritation and a mild elevation of hepatic enzyme. In the 3 days group was difficult to correlate this hepatic adverse event with the antibiotic treatment because of the administration of drugs concomitantly during the surgical procedure.

The conclusion of our study can be applied only to those patients with localized community-acquired intraabdominal infection who showed, after 3 days of treatment, a clinical improvement, thus, excluding patients with more severe form of peritonitis.

However, it is important to underline that the majority of patients admitted in the hospital with secondary peritonitis

present such a mild-to-moderate form of severity of the disease and that these patients are unlikely to need further parenteral antibiotic after 3 days of therapy.

Despite our study demonstrating that a 3-day course of ertapenem is as effective and safe as a standard course of ertapenem (≥5 days), additional larger prospective trials might be useful to support our results.

This reduction of antibiotic consumption may have important effects not only on the bacterial resistance[31] and but also on the cost of the health care. The possibility to discontinue the antibiotic treatment after 3 days results in a saving of the drug acquisition cost, of the cost associated with the labor (nursing time) and above all, in a shorter hospital stay (3 vs 5.6 days).

An analysis of the cost effectiveness of this trial would be worthwhile and is under evaluation.

The potential for reduced antibiotic use should be regarded as important support for the emerging concept that less antibiotic therapy to decrease antibiotic overuse may be used for less severe infections.[7,31] In such patients the fewer drugs used and the shorter the duration of treatment, the better.[7,32]

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Rectovaginal Fistula: A New Approach By Stapled Transanal Rectal Resection

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Abstract Many surgical procedures have been developed to repair rectovaginal fistulas even if no "procedure of choice" is reported. The authors report a case of relatively uncommon, complex, medium-high post-obstetric rectovaginal fistula without sphincteral lesions and treated with a novel tailored technique. Our innovative surgical management consisted of preparing the neck of the fistula inside the vagina and folding it into the rectum so as to enclose the fistula within two semicontinuous sutures (stapled transanal rectal resection); no fecal diversion was performed. Postoperative follow-up at 9 months showed no recurrence of the fistula.

Keywords Rectovaginal fistula · Obstetric trauma · STARR

Introduction

Although rectovaginal fistula (RVF) is relatively uncommon,[1,2] its prevalence is 0.1% in all vaginal deliveries,[3] and it represents what is "*probably the most distressing and demoralizing condition that a woman can experience.*"[4] Today, it is rare in developed countries, but it is still on the increase in Africa and South Asia, where it is devastating for those concerned because of the stigma attached to it and the lack of medical care resources. Indeed, currently, several international projects are targeting obstetric fistula and how to engage the issue.[5,6]

Acquired RVF can be caused by infection, inflammation, tumor or trauma, and obstetric trauma is the undoubtedly most common trauma causing the lesion.[1,2,4,7–11]

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We report a case of RVF that came to our observation and describe the patient tailored treatment adopted.

Case Presentation and Technique

The first vaginal delivery of a 29-year-old woman required episiotomy (gravida 0). Detailed information on obstetric history was not available. At bowel canalization after delivery, the patient referred transit of gas and feces into the vagina; she had no symptoms of fecal incontinence.

In the objective examination, the two-handed palpation revealed a fistula between the medial and upper third of the posterior wall of the vagina and the rectal ampulla. Vaginal exploration showed rectal mucus membrane on the posterior wall of the vagina. Rectal exploration revealed normal sphincter tone.

Proctoscopy identified RVF 6 cm from the anal orifice, and echoendoscopy showed intact internal and external anal sphincters. Anal manometry did not reveal functional changes.

The fistula was not repaired immediately to allow the fistula margins to decongest and hopefully close spontaneously. As it did not heal, surgery was performed 4 months after delivery when inflammation had reduced.

Oral cathartic bowel preparation. The presence of RVF did not allow microlax enemas preparation. The patient was placed in lithotomy or knee–chest position.

Step 1 of the surgical approach involves (vaginal site) dissection facilitated by infiltration of xylocaine 2%, with epinephrine diluted with saline. The opening in the posterior wall of the vagina was enlarged by removing all granulation tissue and left a tear about 3 cm in diameter. The vaginal wall was dissected and peeled away from the rectum wall for over 2 cm circumferentially to the fistula (Fig. 1). A cross silk suture was placed on the neck of the fistula that was then introflexed into the rectum (Fig. 2). In step 2 (rectal site), the neck of the fistula was pulled into the rectum (Fig. 3), and two semicontinuous sutures were positioned respectively 2 cm above and 1 cm below; stapled transanal rectal resection (STARR) was performed. In step 3 (vaginal site), the rectovaginal septum was advanced above the rectal staple; the vaginal wall was slipped over the rectum so as to cover the rectal staple with a flap of intact vagina. The vagina was sutured using 3/0 interrupted suture. Endovaginal drain and endorectal hemostatic gauze were put in position.

The histology describes the rectum wall as having a nonspecific chronic inflammation of the mucus layer, thickening of the submucosal layer, and tunica muscularis normal.

Follow-up at 9 months after surgery showed that no recurrence of the fistula was observed.

Discussion

RVF can be classified as low (anovaginal) or medium-high when it involves the upper two thirds of the vagina, and also as simple (low fistula under 2.5 cm in diameter) or complex (high fistula over 2.5 cm in diameter) varieties.[1] Low fistula is almost always caused by obstetric trauma,[9] is often associated with anal-sphincter disruption,[7] and is the most common type; indeed, most series only report treatment of low obstetric RVF.[1,7,9,10–13]

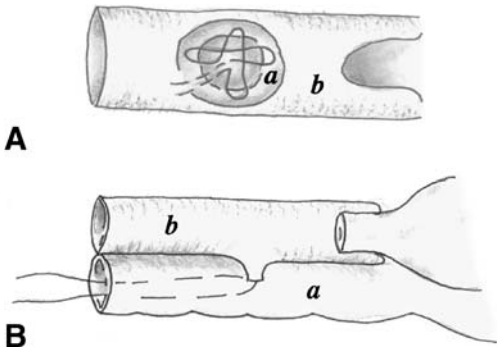

Figure 2 **A** A cross silk suture was placed on the neck of the fistula. **B** The neck of the fistula was introflexed into the rectum. *a* Rectum wall, *b* vaginal wall.

Our patient presented a relatively uncommon, complex, medium-high post obstetric RVF classified as type II by Khanduja et al.[13] Preoperative endoscopy and manometry were performed to rule out sphincteral lesions that manifest only later on in most patients with normal continence status.[14]

Spontaneous closure of RVF within 12 weeks[15] or cases of successful conservative treatment (electrocauterization, fibrin glue) are rare.[7,16] Currently, surgery repair is the most appropriate treatment.

Since the 1980s,[17] most surgeons have adopted the transanal approach where a rectal flap is advanced to close the high-pressure side.[18] Additional surgical options include the transperineal approach and direct fistula repair with or without interposition of healthy tissue[1,2] or changing the fistula into a fourth degree tear and, hence, repairing it with an overlappy sphinteroplasty.[1]

The studies reported in literature are heterogeneous or small, and thus, the incidence of postoperative recurrences

Figure 1 Rectal mucous can be observed through the posterior vaginal wall.

Figure 3 The neck of the fistula was pulled into the rectum before STARR.

varies. Moreover, there is no "procedure of choice"[16] (level I of evidence), as surgery is often not successful because surgeons have to repair traumatized, poorly vascularized tissues that are often affected by sepsis. Consequently, other surgical procedures have been developed, such as interposition of tissue (muscle or dermal graft) between vaginal and rectal suture lines.[7,12,16]

Our patient presented a relatively uncommon post-obstetric RVF, and we used a modified technique to repair the high fistula, as we felt the above-mentioned methods would not have been easy to perform. Our innovative surgical management consisted of preparing the neck of the fistula inside the vagina and folding it into the rectum so as to enclose the fistula within two semicontinuous sutures (STARR),[19] this being our standard technique to treat some defecation disorders. We performed a three-step surgical approach and feel that this prevented the vaginal and rectal sutures from overlapping and, thus, created two different levels.

Besides, we adopted a two-phase therapeutic approach. After initially allowing the inflammation to reduce, surgery was performed and the fistula repaired 4 months after it had appeared. This interval allowed us to repair the fistula directly with a good possibility of success and to avoid "painful" colostomy. It must be kept in mind that associated fecal diversion is recommended only in RVF where there is a risk of recurrence, as there are no reports in the literature showing that fecal diversion facilitates healing of non-complicated RVF.[10,20]

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Surgical Treatment of Primary Esophageal Motility Disorders

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Abstract Named primary esophageal motility disorders (PEMD) present with specific manometric patterns classified as: (1) hypertensive lower esophageal sphincter, (2) nutcracker esophagus (also hypercontratile, hypertensive, or hypercontracting esophagus), (3) diffuse esophageal spasm, and (4) achalasia. These conditions, with the exception of achalasia, are rare, poorly understood, and inadequately studied. Treatment of these conditions is based on symptoms and aimed at symptomatic improvement. The authors reviewed current literature on surgical treatment of non-achalasia PEMD. The review shows that: (a) surgical therapy may be an attractive alternative in patients with PEMD; (b) proper selection of patients based on symptoms evaluation and esophageal function tests is essential; (c) laparoscopic myotomy with proximal extent tailored to manometric findings seems to be the ideal surgical therapy; and (d) esophagectomy may be necessary as a last resource due to multiple failures of surgical conservative treatment.

Keywords Esophageal motility disorders · Hypertensive lower esophageal sphincter · Esophageal spasm · Nutcracker esophagus · Surgery · Myotomy · Esophagectomy

Introduction

Most esophageal motility abnormalities are secondary to gastroesophageal reflux disease (GERD).[1,2] Named primary esophageal motility disorders (PEMD) occur in the absence of GERD and present with specific manometric patterns classified as: (1) hypertensive lower esophageal sphincter (HLES), (2) nutcracker esophagus (NE; also hypercontratile, hypertensive, or hypercontracting esophagus), (3) diffuse esophageal spasm (DES), and (4) achalasia.[3] These conditions, with the exception of achalasia, are rare, poorly understood, and inadequately studied. Furthermore, the precise etiology for PEMD is unknown, and conflicting definitions of the diseases increase the controversies around the topic.[4]

Medical and surgical treatments are described for PEMD. This review will focus on myotomy as an operation for PEMD, its long term efficacy, and its indications. The surgical treatment of achalasia is relatively well established and will not be discussed.

Hypertensive Lower Esophageal Sphincter

HLES was first described in 1960.[5] It is defined as a resting pressure of the lower esophageal sphincter (LES) exceeding 3 standard deviations above the upper limit for normality (45 mmHg for conventional manometry in most laboratories[3] and 41 mmHg for high resolution manometry).[6] Some authors,[7,8] however, characterize HLES if LES pressure is merely above upper limit for normality. Peristalsis must be normal. Clinically, HLES is associated to chest pain and dysphagia.[9]

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Multichannel intraluminal impedance demonstrated that patients with HLES present with outflow obstruction at the LES but normal esophageal body bolus clearance.[10] Thus, treatment should be theoretically aimed solely at reducing the pressure of the LES.

Reports on myotomy and fundoplication for the treatment of HLES have been sporadic and limited to a small number of patients;[8,11–13] however, excellent results are commonly reported.[11,12] The largest series was reported by Tamhankar et al.[12] who followed four patients for 3.1 years with complete relief of symptoms (dysphagia or chest pain) and complete satisfaction with the outcome of the surgery.

Nutcracker Esophagus

NE was first described in 1979.[14] It is defined as esophageal contractions with high amplitude and normal peristalsis. The criteria most adopted are mean distal body contraction pressures exceeding 2 standard deviations above normal values (180 mmHg for conventional manometry[3] and 216 mmHg for high resolution manometry).[15] NE is the named manometric abnormality most commonly found in patients with chest pain.[3]

Similar to HLES, multichannel intraluminal impedance demonstrated that patients with NE present with normal esophageal bolus transit.[10] Furthermore, it is uncertain if high amplitudes are the cause for chest pain in these patients[11,16] leading to unpredictable results after treatment aimed at decreasing the contraction amplitudes.

Patti et al.[11] reported 12 patients submitted to esophageal myotomy for NE. Dysphagia was improved in 80% of the patients, but chest pain persisted in 50% of the patients on a long-term follow-up. The group currently performs myotomy in NE patients only when dysphagia is the leading symptom and when LES pressure is above normal, a finding in 46% of their patients. Champion et al.[17] found recurrence of symptoms (dysphagia or chest pain) in 75% of 12 patients submitted to myotomy and fundoplication. Other small published series report similar results.[18,19]

Diffuse Esophageal Spasm

DES was first described in 1889.[20] It is characterized by normal peristalsis intermittently interrupted by simultaneous contractions; that is, simultaneous contractions are present between 20 to 90% of wet swallows.[3] Chest pain and dysphagia are the main symptoms.

Multichannel intraluminal impedance studies[10,21] demonstrated that 45–65% of the patients with DES present with abnormal bolus transit. Associated to this, LES abnormalities are frequently observed. The LES is hypertensive in almost half of the patients, and abnormal relaxation is described in 70% of them.[11] Due to the functional obstructive nature of the disease, myotomy and fundoplication are the surgical options in patients with DES with good results between 70 and 95% in most reports.[11,17,22–25] Interestingly, one case of normalization of the motor function of the esophagus after myotomy have been described.[26]

The largest reported series of myotomy for DES comprised 65 patients treated with long myotomy and different types of fundoplication through thoracotomy.[27] Not surprisingly, better postoperative reflux control was obtained with partial fundoplications, whereas postoperative dysphagia was more important after total fundoplication.

All kind of symptoms seem to improve after operation. Patti et al.[11] reported their results for 34 patients with DES. Dysphagia was relieved in 80% of the patients after thoracoscopy myotomy and in 86% of patients after laparoscopic myotomy. Chest pain was relieved in 75 and 80% of the patients, respectively. Regurgitation and heartburn scores were also significantly improved after operation. Similarly, Eypasch et al.[23] and Leconte et al.[25] found significant improvement for symptoms score regarding chest pain, dysphagia, regurgitation, and heartburn after the operation.

Long-term follow-up series (over 5 years) confirm the durability of surgical repair in these patients.[22,24]

Surgical Technique

Myotomy

Esophagocardiomyotomy (Heller's operation) has been indicated in patients with spastic disorders of the esophagus refractory to medical therapy. It was described for the first time for the treatment of non-achalasia PEMD by Lortat-Jacob in 1950.[28]

The procedure may be performed through the abdomen or through the chest, via a conventional or minimally invasive approach. A fundoplication is usually associated to the myotomy based on the experience with achalasia when prohibitive rate of reflux is noticed after myotomy without fundoplication.[29,30]

Access to the esophagus can be obtained through a midline laparotomy,[25] laparoscopy,[31,32] left thoracotomy,[13,22] or thoracoscopy.[31,32] Champion et al.[31] and Patti et al.[11] compared thoracoscopic and laparoscopic approach for PEMD in retrospective series. Both authors abandoned thoracoscopic route due to technical difficulty, longer hospital stay, more difficult pain management, and poor outcome. Although the abdominal approach allows a lesser

Table 1 Indications for Surgical Treatment in Patients with Non-achalasia Primary Esophageal Motility Disorders

Disorders	Indications
Hypertensive lower esophageal sphincter	Obstructive symptoms
Nutcracker esophagus	Obstructive symptoms and elevated lower esophageal sphincter resting pressure or poor relaxation.
Diffuse esophageal spasm	Uncertain

proximal extent of the myotomy, the authors speculated that extensive dissection of the esophagus may compromise its blood supply and innervation and that exposure of the esophagogastric junction is inadequate using a thoracoscopic approach.

The myotomy is performed following the same technique employed for achalasia.[33] Most authors argue that the proximal extent of the myotomy should be guided by manometric findings and consequently spam the whole length of esophagus where abnormal contractions are noticed.[22] A short myotomy of the LES is probably an adequate operation for patients with HLES. In patients with NE, dysphagia may be caused by the high amplitude contractions and the myotomy must extent up to the level where normotensive waves are noticed. In cases of DES, long myotomy should be used due to impaired bolus clearance. In rare occasions,[22,32] the myotomy should extend above the aortic arch what makes a right thoracotomy or thoracoscopy mandatory.[32] Distally, most authors agree that the myotomy must extend for 1.5–2 cm into the stomach to include the LES, as described for achalasia.[34] Some surgeons tried to myotomyze only the esophageal body and preserved the LES in cases when the LES is functionally normal;[32,35] however, a significant number of patients developed an achalasia-like syndrome due to the effect of a long myotomy causing atony of the esophagus with an intact LES.

A partial fundoplication is usually associated to the myotomy,[13,17,25,32,34] although some cases of total (Nissen) fundoplication have been reported.[13,31] Henderson and Ryder[26] compared the outcomes of patients submitted to long myotomy and different type of fundoplications (Belsey, gastroplasty + partial wrap, gastroplasty + total wrap, and Nissen). Not surprisingly, better postoperative reflux control was obtained with partial fundoplications, whereas postoperative dysphagia was more important after total fundoplication.

Esophageal diverticula may coexist in a significant number of patients with PEMD.[13,22,36–38] Diverticula can be treated simultaneously to the myotomy with resection or upward suspension.[13] In some cases, small diverticula can vanish into the myotomy zone after herniation of the mucosa.[13]

Discussion

In patients with non-achalasia PEMD, there is no described risk for life-threatening pulmonary complications, such as aspiration, unless diverticula are present.[38] Thus, treatment is based on symptoms and aimed at symptomatic improvement. Pharmacological therapy and endoscopic dilatation for PEMD has been linked to inferior outcomes compared to surgery.[32,39] Surgical literature on the topic is, however, deficient. All series reviewed are retrospective and comprised a limited and heterogeneous group of patients.

Although surgical therapy is frequently quoted as disappointing, most series show acceptable outcomes, making surgery beneficial with appropriate selection of patients, especially after failure of medical therapy. Indications for operative approach in patients with PEMD based on the available evidence are listed on Table 1.

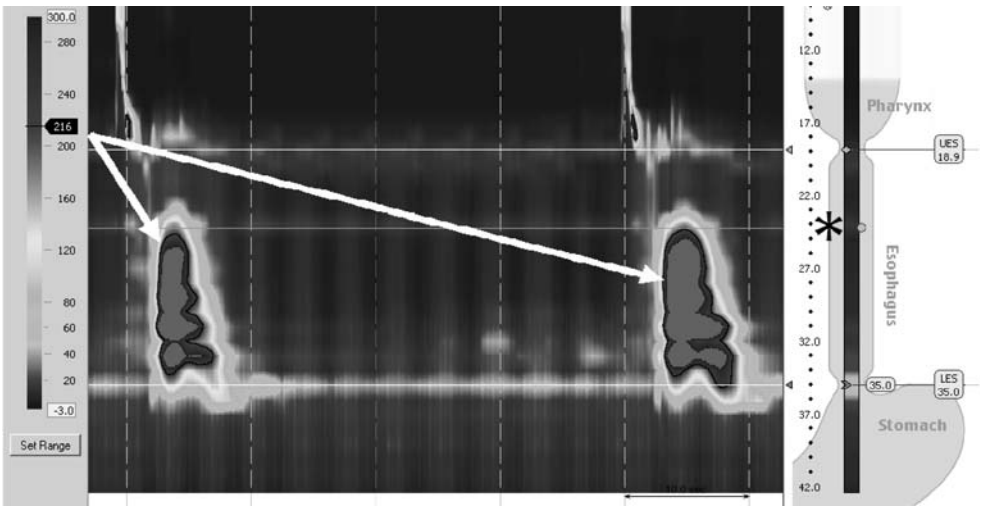

Figure 1 High resolution manometry of a patient with nutcracker esophagus. Esophageal body amplitudes above 400 mmHg are seen. Isobaric contour function shows pressures above 216 mmHg (*arrows*), correct identification of the proximal extent of the high amplitude contractions is provided (*asterisk*).

Laparoscopic myotomy seems to be the ideal surgical therapy. Myotomy PEMD series rarely reported a need for esophagectomy;[13] however, several cases of resection for non-achalasia PEMD, especially DES, are described in esophagectomy series for benign disease.[13,40–42] Esophageal resection may be necessary as a last resource due to multiple failures of surgical conservative treatment due to recurrence of symptoms or complications. Trans-hiatal approach is the technique most described in these patients;[40–42] however, some cases of trans-thoracic esophagectomy have also been reported.[40–42]

Esophageal manometry must be carefully performed in patients with PEMD, as the diagnosis of the disease, proper selection of patients for surgical therapy, and extent of the myotomy depend on this. Intraluminal multichannel impedance and manometry demonstrated that some patients with DES have abnormal bolus clearance not only outflow obstruction at the level of the LES. In these individuals, whether the myotomy must be extended to the level of abnormal clearance is still uncertain but seems intuitive. High resolution manometry is a variant of the conventional test in which multiple sensors are used allowing simultaneous acquisition of data regarding upper esophageal sphincter, esophageal body, and LES. In consequence, the whole esophageal body is profiled allowing clear diagnosis of segmental abnormalities and detailed evaluation of the extension of motor disorders. Theoretically, it would provide better guidance to the necessary extent of the myotomy, as it can precisely map the level of manometric abnormalities (Fig. 1). To date, there are no studies using high resolution manometry in patients with PEMD.

In patients with a manometric pattern of PEMD, the findings of pH monitoring study are essential, as the disease is considered a primary condition only in the absence of GERD.[11] Symptoms are unreliable to diagnosis GERD given the fact that a significant number of patients with manometric PEMD and a negative pH complain of heartburn.[8,11] Manometric PEMD is associated to GERD in approximately 70 to 75% of the patients[12,43] If GERD is present, the motility abnormality is considered secondary and treatment is directed towards reflux.[3,11,44] It has been shown that surgical or clinical reflux control provides excellent relief of symptoms in patients with manometric patterns of PEMD and GERD.[8,44,45]

We concluded that: (a) surgical therapy is an attractive alternative in patients with PEMD, although results are inferior to the ones obtained with achalasia treatment; (b) proper selection of patients based on symptoms evaluation and esophageal function tests is essential; (c) laparoscopic myotomy including the LES and with proximal extent tailored to manometric findings seems to be the ideal surgical therapy; and (d) esophagectomy may be necessary as a last resource due to multiple failures of surgical conservative treatment.

Acknowledgements Figure 1 is a courtesy of Thomas J. Watson, MD.

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A Patient with Synovial Cell Sarcoma Primary to the Gallbladder and Common Bile Duct

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Keywords Synovial cell sarcoma · Common bile duct · Obstructive jaundice

Case Report

A 51-year-old man with no significant past medical history presented with a 3-day history of nausea and vomiting and 1 month history of jaundice. He had presented to an outside hospital 1 month prior with a bilirubin of 10 mg/dL, increased liver function test values, and an increased white blood cell count. He was determined to have obstructive jaundice. He underwent an endoscopic retrograde cholangiopancreatography, which showed an irregular mass in the common bile duct, and biopsy suggested a neuroendocrine tumor but was not definitive. An endostent was placed to relieve the obstruction caused by the mass.

The patient was transferred to the University of Texas Medical Branch, where he underwent a magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRCP). The MRCP showed an intraluminal mass in the common bile duct with likely extension into the neck of the gallbladder (Fig. 1). An abdominal and pelvic computed tomography (CT) was obtained, which confirmed the presence of an obstructing mass in the common bile duct and the neck of the gallbladder. Lesions elsewhere in the abdomen and pelvis were not identified, making metastasis unlikely.

The patient was scheduled for surgical resection. After undergoing an appropriate bowel preparation, the patient underwent successful resection with pylorus-preserving pancreaticoduodenectomy.

The patient's postoperative course was complicated by a pancreatic fistula. The fistula was controlled by his operatively placed drains and was managed conservatively. He was discharged home on postoperative day 14. His pancreatic fistula drain was removed at his 2-week follow-up visit without further incident.

The tumor was extremely poorly differentiated. Immunohistochemical stains were positive for EMA, BCL2, CD99, Ck 19, and AE1/AE3 and were negative for the smooth muscle stains S-100, CD45, myogenin, TTF-1, desmin, CAM 5.2, and CK 7 (Fig. 2a–c). This pattern of staining is consistent with a high-grade, poorly differentiated monophasic synovial cell sarcoma.[1] The primary tumor was present in the common bile duct with extension into the gallbladder lumen. Three out of 10 lymph nodes were positive for the tumor. A search was performed for a different primary site of the tumor in our patient, and none was identified. He was determined to have a synovial cell sarcoma primary to the common bile duct.

Nothing is known regarding the prognosis of synovial cell sarcoma primary to the common bile duct/gallbladder. As such, there is no standardized therapy. Based on the treatment of synovial cell sarcoma at other primary sites, adjuvant radiation was recommended. He has completed his

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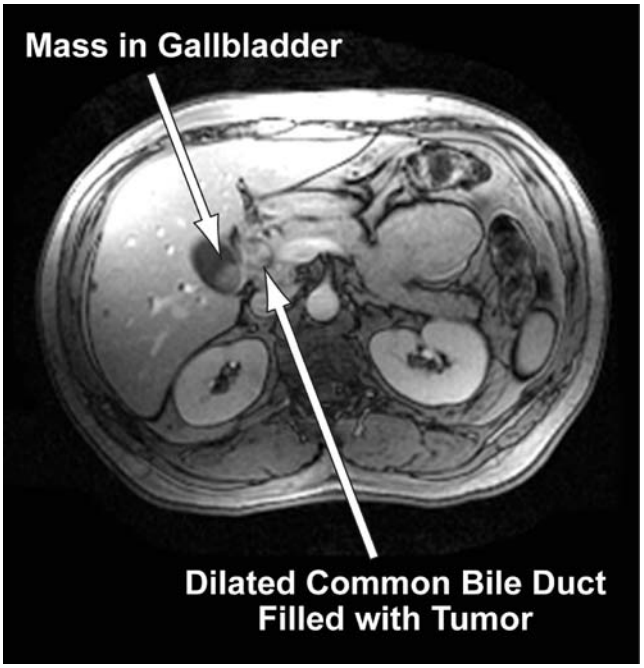

Figure 1 An axial cut from the MRCP. The *arrows* point to the obstructing mass in the gallbladder and common bile duct.

course of radiation therapy. Follow-up CT in June 2007 was negative for recurrence.

Discussion

Currently, no other cases of a synovial cell sarcoma primary to the common bile duct/gallbladder have been reported. Therefore, all information regarding etiology and prognosis refer to synovial cell sarcomas of the soft tissues. Limited information regarding synovial cell sarcomas of the lung is also available.

Synovial sarcoma is a rare malignant neoplasm that comprises ~10% of all soft tissue sarcomas.[2] Morphologically, this tumor predominantly presents in two histologic forms: a monophasic form comprised mainly of spindle-shaped cells and a biphasic form that is comprised of spindle-shaped cells with some epithelial differentiation and gland formation present. The chromosomal translocation t (X;18)(p11;q11) has been found in over 90% of synovial cell sarcomas. Chromosome 18 breaks at a gene named SYT, a ubiquitous nuclear protein believed to be involved in transcription. Chromosome X breaks on two points near by each other, SSX1 and SSX2.[3]

Kawai and colleagues found a correlation of the translocation and the histologic type: all biphasic tumors contained the SYT–SSX1 translocation and all SYT–SSX2 translocations were present in the monophasic tumors.[3] The SYT–SSX1 translocation is associated with a poorer prognosis.[4]

Synovial cell sarcomas most often occur in adolescents and young adults in close proximity to large joints in both

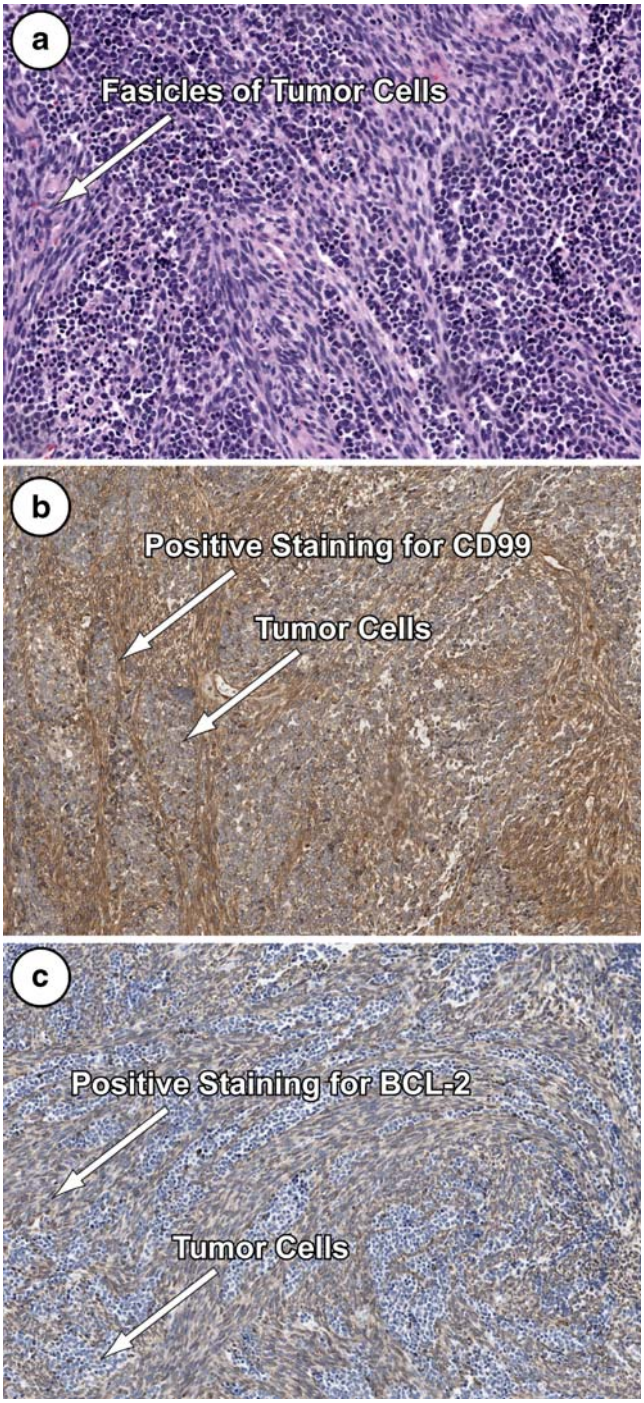

Figure 2 **a** A hematoxylin–eosin stain of the tumor showing fascicles of infiltrating tumor cells. **b** A pathology slide stained for CD-99. The tumor cells are shown in *blue* and the stroma stains positive for CD-99, which helped differentiate the tumor as a high grade, poorly differentiated monophasic synovial cell sarcoma. **c** This slide is stained for BCL-2. The tumor cells are shown in *blue* and the stroma stains positive for BCL-2, which also helped differentiate the tumor as a high grade, poorly differentiated monophasic synovial cell sarcoma.

the upper and lower extremities. The tumor usually presents as a painless, slow-growing mass. The tumor has also been described in numerous locations unrelated to joint structures, including the head and neck, chest, buttocks, and abdominal wall. The tumor is, in fact, not derived from synovial cells but primitive mesenchymal cells.[5]

In the few reported cases of primary synovial sarcomas of the lung, patients have presented with chest wall pain, cough, shortness of breath, or hemoptysis. The average age at presentation is 25 years. All patients had large pleural-based intrathoracic masses at presentation. Intraoperatively, necrosis and hemorrhage were almost uniformly present.[1]

The majority of data regarding prognosis is based on studies of synovial cell sarcomas of the extremities. Overall, survival rates of extremity synovial cell sarcomas at 5 and 10 years are ~60 and ~40%, respectively. The large difference in survival reflects the high rate of late metastasis of this neoplasm.[6] Factors predicting a worse prognosis for patients with synovial sarcomas include tumor size (>5 cm); male gender; older age (>20 years); extensive tumor necrosis; high grade; large number of mitotic figures (>10 per 10 high-powered fields); neurovascular invasion; local recurrence; distant metastasis; and, recently, the SYT–SSX1 variant.[4] The location of the tumor can also be an important prognostic factor. Tumors located on the distal extremities have a more favorable prognosis than tumors located more proximally on the extremities. Tumors located on the trunk have the worst prognosis. This characteristic could also be due to size distribution of the tumor. Distal tumors are much more likely to be smaller than more proximal tumors. The majority of tumors identified on the truck are larger than 5 cm. The favorable prognosis of distally located tumors could also be due to the increased ease of diagnosis at smaller size.[6] The prognosis for patients with pulmonary synovial sarcoma is poor, with an overall 5-year survival rate of 50%. The main prognostic factor is the ability to achieve a complete resection.[1]

There is no standardized therapy; most patients are treated with surgery or with surgery and adjuvant radiation therapy. The rarity of this tumor has not permitted controlled studies of adjuvant chemotherapy. Synovial sarcomas are chemosensitive to ifosfamide and doxorubicin, with an overall response rate of approximately 24%. In a meta-analysis, adjuvant chemotherapy improved the time to local recurrence and recurrence-free survival rate.[4] To our knowledge, this is the first report of a synovial cell sarcoma primary to the common bile duct.

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Combined Resection of the Pancreas and Inferior Vena Cava for Pancreatic Metastasis from Renal Cell Carcinoma

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Abstract Indications for pancreatic resections for metastatic disease have not yet been defined to date, and few guidelines exist for the management of these lesions. However, most authors recommend surgery as the treatment of choice for pancreatic metastasis (PM). Resection of the inferior vena cava (IVC) is rarely done during removal of peripancreatic cancer. This report presents the first case of metachronous PM from renal cell carcinoma (RCC) with IVC involvement successfully treated by en-bloc resection in a 70-year-old asymptomatic woman. The abdominal computed tomography (CT) scan showed a 4.0-cm mass in the tail and a 5.0-cm mass in the head of the pancreas with a suspected involvement of vena cava. An en-bloc total pancreatectomy was performed with excision of the involved portion of the cava vein. Histology confirmed the presence of two metastases from RCC with neoplastic infiltration of the IVC and without lymph node involvement. All surgical margins were tumor-free. At most recent follow-up 12 months after pancreatectomy, the patient has no evidence of disease. We believe that a multidisciplinary approach and careful evaluation and treatment of these patients is a mandatory component for patient selection. IVC resection should be performed only when a margin-negative resection is expected to be achieved.

Keywords Pancreas · Renal cancer · Pancreas secondary · Cava vein · Vein resection

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Introduction

Pancreatic metastases (PM) are rare, comprising 3% of pancreatic tumors removed in sizable series of operations.[1] Indications for pancreatic resections for metastatic disease have not been yet defined to date, and few guidelines exist for the management of these lesions. However, most authors recommend surgery as the treatment of choice for PM.[1–5] Resection of the inferior vena cava (IVC) is rarely done during removal of peripancreatic cancer. This report presents the first case of metachronous PM from renal cell carcinoma (RCC) with IVC involvement successfully treated by en-bloc resection.

Case Report

A 70-year-old asymptomatic woman was admitted to our department of digestive surgery with two lesions in her pancreas found on routine follow-up computed tomography

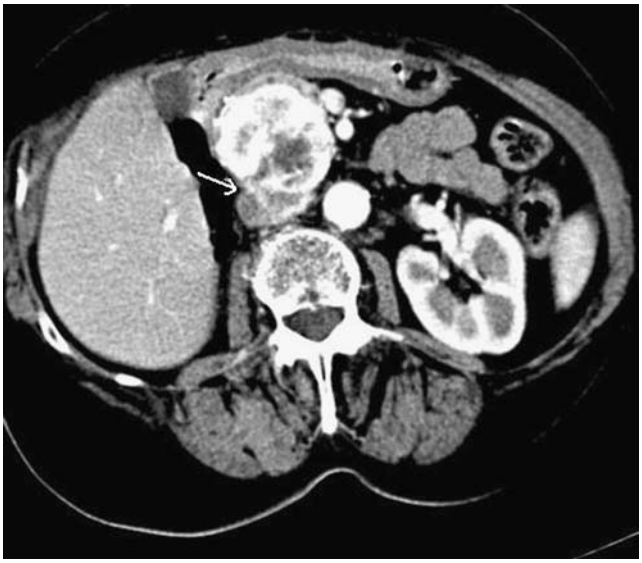

Figure 1 The abdominal CT scan showed a 5.0-cm mass in the head of the pancreas with a suspected involvement of vena cava (*arrow*).

(CT) scan. She had undergone a right nephrectomy 13 years earlier for RCC and had surveillance abdominal and chest CT scans the last 18 months that were unremarkable. Physical examination was unremarkable; clinical laboratory studies were unrevealing and included a normal complete blood count and chemical profile, as well as normal alkaline phosphatase and CA 19-9.

The abdominal CT scan showed a 4.0-cm mass in the tail and a 5.0-cm mass in the head of the pancreas with a suspected involvement of vena cava (Fig. 1). A metastatic work-up disclosed no evidence of any extrapancreatic lesions. Based on the patient's history and investigations, a diagnosis of a metastatic pancreatic tumor from RCC was made, and a laparotomy was performed. After initial exploration to rule out hepatic metastases or serosal implants, the portal and superior mesenteric veins were dissected to rule out local involvement. The bulky nature of the tumor inhibited our ability to do the Kocher maneuver, and the total pancreatectomy was performed from the left to the right. The pancreas and the spleen were gently mobilized from the underlying left adrenal and kidney with special care. Via a further gentle dissection on the right, we reached the level of the spleno–mesenteric junction. The gastroduodenal artery and splenic artery and vein were ligated and transacted. The gallbladder was dissected; the common bile duct, the stomach, and the jejunum were transacted. After the ligation and transaction of the various venous branches originating from the posterior surface of portal vein and superior mesenteric vein, the specimen was then attached only to the involved vena cava. Therefore, the right internal jugular vein was resected through a cervical incision and incised longitudinally. Vascular clamps were placed 2–3 cm proximal and distal to the involved venous segment and on the left renal vein. An en-bloc total pancreatectomy was performed with excision of the involved portion of the cava vein, removing the involved vein and a 0.5-cm segment of grossly uninvolved vessel (Fig. 2). The anterior wall (half of the venous diameter) of the cava vein has been resected and reconstructed using an internal jugular vein graft. The anastomosis was carried out with three running sutures of 5/0 polypropylene under temporary clamping. Systemic hemodynamics were stable throughout the IVC reconstruction and clamp time of 9 min. The jugular vein flap was first sutured to the upper and left part of the IVC defect; by this procedure, we were able to replace the upper clamp in order to restore rapidly the rena–caval flow. After reconstruction of the IVC, a standard technique was used to re-establish gastric and biliary continuity.

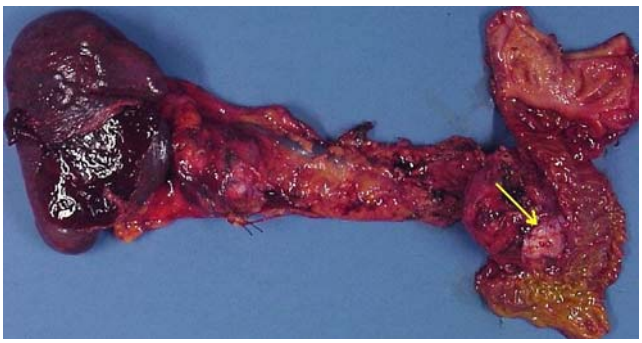

Figure 2 Total pancreatectomy with en-bloc resection of the anterior wall of the vena cava (*arrow*).

Histology confirmed the presence of two metastases from RCC with neoplastic infiltration of the IVC and without lymph node involvement. All surgical margins were tumor-free.

The postoperative course was uneventful, and the patient was discharged on the 18th postoperative day; at that time she was asymptomatic, and a postoperative Doppler examination demonstrated patency of the IVC. Postoperative anticoagulant therapy with heparin was replaced by warfarin potassium within 2 weeks and was continued for 6 months.

At most recent follow-up 12 months after pancreatectomy, the patient has no evidence of disease.

Discussion

Isolated PM from RCC are rare, most of them are solitary; some are multiple. Treatment recommendations for multiple isolated PM vary. Whereas some advise total pancreatectomy, others critically reject surgery[6–8] on the assumption that multiple PM signals incipient fatal disseminated disease. Sellner et al.[9] in a systematic review of the literature reported that solitary or multiple isolated PM did not differ

in terms of treatment outcome. This is reflected by a comparable actuarial 5-year survival rate of 64% for resected solitary PM and 78% for resected multiple PM.

Due to its proximity to a number of important regional vascular structures, pancreatic carcinoma is often associated with regional invasion. However, isolated direct extension of a pancreatic head neoplasm to the anterior surface of the IVC is uncommon. Bold et al.[10] reported 63 patients who underwent pancreaticoduodenectomy with en-bloc resection of adjacent vascular structures. Among them, only three patients that were otherwise resectable required resection of the IVC. To our knowledge, this is the first report of a total pancreatectomy with en-bloc resection of the IVC for PM from RCC.

The role of IVC resection and replacement for the treatment of malignant disease is limited to a small number of selected patients, and only few surgeons have focussed on its development.[11–13]

Indications for IVC replacement in patients who are treated surgically for extensive neoplasms remains controversial. IVC replacement may not be necessary for patient with complete IVC obstruction because collateral circulation provides sufficient venous drainage. Caval replacement was mandatory because in our case, the IVC was infiltrated but with no collateral circulation. The risk involved in not performing IVC reconstruction is renal dysfunction, particularly in nephrectomized patients. Even if the left renal vein has multiple collateral branches,[14,15] such as gonadal vein and renal azygos communications, these collateral branches drain venous return from the left kidney and preserve left renal function.[16,17]

There are a variety of options for replacement of the IVC when it cannot be reconstructed primarily.[18,19] In case of patients undergoing simultaneous digestive resection–reconstruction and prosthetic IVC replacement, postoperative graft infection should be taken into consideration. For this reason, we prefer complete venous anastomosis using autologous tissue. The autointernal jugular vein is an ideal graft for vein reconstruction because it has a sufficient length and does not require reconstruction after unilateral resection. Moreover, because of the rich connections between the ipsi- and contralateral descending vein in the neck, unilateral resection or ligation of an internal jugular vein does not cause any venous insufficiency in the head. Another significant advantage of the internal jugular vein is that it has no major branches, except for the superior and middle thyroid veins between the level of the hyoid bone and the venous angle, so that a sufficiently long graft is easily and quickly obtained through a cervical incision.

Replacement for malignant involvement of the IVC has been performed rarely because of the magnitude and risk of the operation; nevertheless, in the absence of surgical resection, patient survival is limited. This is particularly true in PM from RCC; Sellner et al.[9] showed a significantly longer survival time of patients with resected versus nonresected metastatic lesions. We believe that a multidisciplinary approach and careful evaluation and treatment of these patients is a mandatory component for patient selection. IVC resection should be performed only when a margin-negative resection is expected to be achieved.

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