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SSAT STATE-OF-THE-ART CONFERENCE

Introduction: Esophagus, Dysplasia, and Early Esophageal Adenocarcinoma: Managing the Transition

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There has been a marked increase in the incidence of esophageal adenocarcinoma in the Western world over the last three decades.[1] Once an uncommon histological subtype of esophageal cancer, the majority of cases of esophageal cancer diagnosed this year will be adenocarcinoma.[2] Most cases of esophageal adenocarcinoma are thought to arise in the setting of Barrett's esophagus and obesity. Barrett's esophagus is a metaplastic transformation of the lining of the distal esophagus with a transformation from the normal squamous epithelium to a columnar metaplasia with intestinal features.[3] Barrett's esophagus is thought to be a consequence of chronic, severe gastroesophageal reflux. Although not all cases of Barrett's esophagus will progress to invasive esophageal cancer, the presence of Barrett's esophagus is associated with a 0.5–1.0% annual risk of developing esophageal cancer.[4] Unfortunately, Barrett's esophagus appears to be an increasingly common condition, with a prevalence of as high as 1.6% in Western countries.[5]

The current consensus is that once identified, a patient with Barrett's esophagus should undergo endoscopic surveillance of their esophagus for evidence of dysplasia. If dysplasia or adenocarcinoma is identified, the current conservative recommendation is removal of the dysplastic mucosa, traditionally by esophagectomy.[6] However, the last decade has seen a number of advances in our understanding of the pathobiology of Barrett's esophagus and esophageal adenocarcinoma and the development of new therapies for the patient with these conditions. These advances have allowed us to pose a number of important questions regarding the management of a patient with Barrett's esophagus that may challenge the current consensus management of this condition. With our increased understanding of the molecular pathogenesis of Barrett's esophagus, are there molecular markers of cancer risk which are more sensitive predictors of cancer risk in Barrett's than dysplasia? Can control of the underlying cause of Barrett's metaplasia, gastroesophageal reflux, by medical or surgical means reduce the risk of cancer or even cause regression of Barrett's esophagus? Have advances in endoscopic therapy including endoscopic mucosal resection of Barrett's metaplasia and endoscopic ablation of metaplasia eliminated the need for surgical resection of the esophagus in cases with dysplasia? Finally, has the development of minimally invasive approaches to esophagectomy and our understanding of the risk of occult cancer in patients with high-grade dysplasia made esophagectomy the treatment of choice for Barrett's with high-grade dysplasia?

The accompanying articles address these issues in more detail, reviewing the dilemmas confronting GI surgeons as they manage patients with Barrett's esoph-

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agus. With an increased understanding of the "state of the art" in Barrett's esophagus, GI surgeons can strive to provide individualized care to patients with this complex condition.

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SSAT STATE-OF-THE-ART CONFERENCE

The Molecular Basis of Carcinogenesis in Barrett's Esophagus

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Our current management of cancer risk in Barrett's esophagus is to perform endoscopic surveillance for the detection of dysplasia. However, dysplasia is an imperfect predictor of cancer risk for a variety of reasons including biopsy sampling error, poor intra- and inter-observer reproducibility of dysplasia interpretations and the poor predictive value for negative, indefinite, low-grade, and even high-grade dysplasia.[1–3] Dysplasia is a conglomerate of histologic abnormalities that suggest that clones of cells have acquired neoplastic properties that predispose them to cancer formation. Therefore, dysplasia is a surrogate marker for cells that have accumulated enough genetic damage that they now possess some of the physiologic properties of cancer cells. Therefore, a better indicator of cancer risk would be detection of the genetic damage itself before the histologic manifestations of dysplasia are even apparent. In addition, the identification of molecular biomarkers may offer easy reproducibility and standardization in addition to the truly early detection of neoplastic progression.

In the traditional phenotypic model, carcinogenesis in Barrett's esophagus is viewed as occurring in discrete steps from metaplasia to dysplasia and finally to carcinoma. In the genetic model, neoplastic progression is envisioned as a continuum over which cells progressively accumulate genetic abnormalities until they acquire the six essential physiologic hallmarks of cancer.[4] These cancer hallmarks include the ability of cells (1) to provide their own growth signals, (2) to avoid growth inhibitory signals, (3) to avoid apoptosis, (4) to replicate without limit, (5) to sustain angiogenesis (the formation of new blood vessels), and (6) to invade and metastasize. These hallmarks represent the physiologic traits that must be acquired by cells during the genesis of all human tumors and, therefore, are not specific for neoplastic progression of Barrett's esophagus. However, there are differences among human tumors regarding the specific genetic alterations acquired that endow the cell with each of these physiologic hallmarks and we will highlight some of the genetic alterations that occur in Barrett's esophagus which allow the cell to acquire each of the hallmarks.

Hallmark 1: The Ability to Provide Growth Signals In general, this occurs by the activation of oncogenes. Genes that stimulate cell growth in normal cells are termed proto-oncogenes. When these same genes become overactive as a

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result of certain types of mutations, they are called oncogenes. Thus, oncogene activation leads to uncontrolled cell growth. Examples of oncogenes implicated in Barrett's carcinogenesis include cyclins D1 and E, transforming growth factor-α, epidermal growth factor, and the epidermal growth factor receptor.[5]

Hallmark 2: The Ability to Avoid Growth Inhibitory Signals In general, growth inhibitory signals are transmitted by tumor suppressor genes. Tumor suppressor genes are normal genes that restrain cell proliferation. When tumor suppressor genes are inactivated, the cells are able to avoid growth inhibitory signals allowing for uncontrolled proliferation. Mutation, deletion of the chromosomal region containing the gene (called loss of heterozygosity (LOH)), and attachment of methyl groups to the promoter region of genes (called promoter hypermethylation) are ways in which tumor cells can inactivate tumor suppressor genes. Examples of tumor suppressor genes inactivated during neoplastic progression of Barrett's esophagus include p53, p16, and the adenomatous polyposis coli (APC) gene.[5]

Hallmark 3: The Ability to Avoid Apoptosis Apoptosis is a pre-programmed mechanism for normal cells to self-destruct. This is beneficial to normal cells, in that it prevents cells with damaged, mutated DNA from undergoing replication. However, to cancer cells, apoptosis is detrimental, and cancer cells must find ways to avoid self-destruction. Barrett's cells have found a variety of ways to overcome triggering apoptosis. For example, as already discussed, inactivation of p53 is one way in which Barrett's cells avoid inducing apoptosis in response to DNA damage or mutation. Another way Barrett's cells avoid apoptosis is by the upregulation of cycloxygenase-2, a gene whose protein product exerts antiapoptotic effects. Finally, Barrett's cancer cells have been found to express Fas-ligand, a death-promoting ligand that can activate the apoptotic cascade within the tumor killing immune cells resulting in their destruction.[6,7]

Hallmark 4: The Ability to Replicate without Limit Normally, as cells undergo successive cell divisions, they reach senescence. Senescence is an intrinsic mechanism of cells that limits their normal proliferative capacity. The triggering of senescence involves the loss of telomeres which are repetitive pieces of DNA located at the ends of chromosomes. When telomeres become too short, senescence ensues. Telomerase is the enzyme that allows for the synthesis and stabilization of telomeres.[8] Stable telomeres confer immortality to the cell. In contrast to normal esophageal tissues, benign Barrett's esophagus expresses low levels of telomerase, which appears to increase as the metaplastic cells progress to high-grade dysplasia and cancer.[9]

Hallmark 5: The Ability to Sustain Angiogenesis In order for a tumor to increase in size, it must maintain an adequate blood supply. The synthesis of new blood vessels is termed angiogenesis. One way in which tumor cells synthesize new blood vessels is by secreting vascular endothelial growth factors (VEGFs) which promote the proliferation and migration of endothelial cells upon binding to their receptors, the vascular endothelial growth factor receptors (VEGFRs). The expression of VEGFs and VEGFRs has been found in metaplastic Barrett's esophagus as well as in neoplastic Barrett's tissues.[10,11]

Hallmark 6: The Ability to Invade and Metastasize Although the mechanisms of cancer cell invasion and metastasis are poorly understood, abnormalities in cell–cell interaction mediated by cadherins and catenins are thought to play a role.[12] In the neoplastic progression of Barrett's esophagus, the normal membraneous location of E-cadherin and β-catenin decreases, and the cytoplasmic and nuclear staining for these proteins increases as the degree of dysplasia increases.[13] In addition, Barrett's cancers have been found to express matrix metalloproteases which degrade the extracellular matrix and facilitate invasion.[14]

Status of Biomarkers to Predict Cancer Risk in Barrett's Esophagus

Some of the individual abnormalities described above have been proposed as biomarkers for cancer risk in Barrett's esophagus, and it is likely that a few of these will eventually become clinically useful. The National Cancer Institute's Early Detection Network has proposed five phases of study that biomarkers must undergo for validation.[15] It is only in the latter three phases that clinical studies are carried out to (1) evaluate retrospectively the predictive ability of the biomarker and to define a "positive" test (phase 3), (2) prospectively determine the predictive ability of the biomarker (phase 4), and (3) estimate the reduction in mortality by action taken based on the biomarker assay (phase 5).[16] The majority of the biomarkers proposed for Barrett's esophagus have been evaluated in phase 3 studies, and none of these potential biomarkers have been evaluated in phase 5 studies. The Barrett's biomarkers that have shown the most promise thus far include aneuploidy and increased tetraploidy, 17p LOH, and 9p LOH.

Aneuploidy and Increased Tetraploidy Aneuploidy does not indicate a single genetic abnormality but rather refers to an alteration in the normal diploid (2n) or tetraploid (4n) (where n refers to the number of chromosomes) DNA content of a cell. Thus, aneuploidy reflects the accumulation of multiple genomic abnor-

malities like the ones discussed above. Aneuploidy can be detected by flow cytometry or by fluorescence in situ hybridization (FISH); however, FISH may be less sensitive than flow cytometry in the detection of chromosomal abnormalities.[17,18] A number of large prospective studies have found that aneuploidy and/or increased tetraploidy (>6% of cells within a tissue with 4n) are significant predictors of cancer risk in Barrett's esophagus.[3,19,20]

17p LOH 17p is the chromosomal locus for p53, and a number of studies have investigated the ability of 17p LOH to predict neoplastic progression of Barrett' esophagus.[17,21–23] In two large prospective studies 17p LOH, as detected by flow cytometry, in baseline biopsy specimens of Barrett's esophagus was found to be a significant predictor of neoplastic progression regardless of the degree of dysplasia.[21,22] More recently, a number of cross-sectional studies have reported promising results on the ability of 17p LOH, detected by FISH in biopsy tissues and in brush cytology specimens of Barrett's esophagus, to predict neoplastic progression.[17,23]

Aneuploidy/Increased Tetraploidy, 17p LOH, and 9p LOH in Combination In a large, prospective study, the ability of this combination of biomarkers to predict neoplastic progression in Barrett's esophagus was found to be better than any of the biomarkers used alone.[22] The incidence of cancer was 80% at 6 years in those patients whose biopsies contained all three abnormalities, whereas the incidence of cancer was 12% at 10 years in those patients whose biopsies did not demonstrate any of these abnormalities.[22] Thus, it is likely that a panel of biomarkers will be better predictors of neoplastic progression in Barrett's esophagus than a single individual genetic abnormality.

Overall, although the results of these studies are promising, the use of these biomarkers in routine clinical practice is not yet recommended. In light of the recent advances in biomarker discovery, it is likely that combinations of molecular biomarkers will eventually be better predictors of neoplastic progression than dysplasia. Large, prospective clinical trials of candidate biomarkers (phases 4 and 5 studies) for detecting cancer arising in Barrett's esophagus are eagerly awaited.

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Reflux, Barrett's, and Adenocarcinoma of the Esophagus: Can We Disrupt the Pathway?

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Gastroesophageal reflux disease (GERD) is simply defined as increased or abnormal exposure of the esophageal mucosa to refluxed gastric juice. GERD is recognized as a spectrum, and it begins with symptoms without mucosal injury and extends through erosive disease to Barrett's esophagus and ultimately in some patients to adenocarcinoma of the esophagus. The severity of GERD can be correlated with the pathophysiologic derangements that allow reflux to occur, including the presence and size of a hiatal hernia and the degree of incompetence of the lower esophageal sphincter.[1,2] Further, the composition of the refluxed gastric juice is an important factor in the severity of reflux disease. Esophageal squamous mucosal injury is most likely to occur with reflux of very low pH material (acid) where pepsin is most active or when there is mixed reflux of both acid and bilious material.[3,4] The majority of patients with GERD have mixed reflux but those with Barrett's tend to have the greatest amount of bilious reflux.[5,6] These findings, initially made using Bilitec monitoring and aspiration studies for esophageal bilirubin exposure, have been confirmed with impendence technology showing significantly increased non- or weak acid reflux events in patients with Barrett's esophagus compared to those with reflux without Barrett's.[7] Further, exposure to refluxed bile has been shown by multivariable analysis to be the leading factor associated with the presence of Barrett's esophagus in a large group of patients with GERD.[8]

The transformation of normal esophageal squamous mucosa into Barrett's likely takes years of exposure to refluxed gastric juice. The hallmark of Barrett's esophagus is an endoscopically visible segment of columnar mucosa in the distal esophagus. However, in the United States, in addition to an endoscopically visible segment of columnar mucosa, the diagnosis of Barrett's esophagus requires a biopsy demonstrating intestinal metaplasia characterized by the presence of goblet cells. A significant issue in the pathophysiology of Barrett's is how the normal squamous esophageal mucosa is transformed into columnar mucosa with intestinal metaplasia. Longitudinal follow-up studies in individual patients suggest that it is a two-step process, where squamous mucosa is first changed into cardiac mucosa and subsequently, cardiac mucosa becomes intestinalized.[9,10] The best clinical evidence for the initial step being the development of cardiac mucosa without intestinal metaplasia can be found in patients after an esophagectomy and gastric pull-up. In these patients, columnar cardiac mucosa has been shown to develop above the anastomosis in mucosa that had been histologically proven to be squamous at the time of the esophagectomy.[11–13] In the distal esophagus, the presence and length of cardiac columnar mucosa has been correlated with the severity

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of reflux disease and particularly reflux of acid.[14] This initial step, from squamous to cardiac mucosa, is either a result of transdifferentiation, whereby differentiated squamous cells undergo a phenotypic change to become columnar cells, or secondary to transformation of the stem cells to produce columnar rather than squamous progeny.[15] While either mechanism is possible, the favored theory is that stem cells are transformed by exposure to luminal contents, as a consequence of reflux-induced squamous mucosal injury.

The second step in the development of Barrett's esophagus is intestinalization of the cardiac columnar mucosa. There is evidence that this second step is in part related to the nature of the refluxed gastric juice, with bile being an important, probably ever critical, component.[16] In addition, the likelihood of finding intestinal metaplasia is correlated with the length of the columnar lining in the distal esophagus and the duration of follow-up.[2,11] Once segments of columnar lining in the distal esophagus approach 3 cm nearly 100% of patients will have intestinal metaplasia. Importantly, the location of intestinal metaplasia within a columnar-lined segment is not random. In the classic 1976 report by Paull et al., the mucosal histology of the columnar-lined esophagus was evaluated in biopsies obtained using manometric control.[17] They showed that intestinal metaplasia, if present, was always located at the proximal portion of the columnar segment, adjacent to the squamocolumnar junction. While the intestinal metaplasia could extend distally to the gastroesophageal junction, often it did not, and either junctional (cardiac) or oxyntic mucosa was located distally. These findings have been confirmed and extended by Chandrasoma et al. who showed that not only is intestinal metaplasia, when present, always located in the proximal portion of a columnar segment, but that the density of goblet cells, the hallmark feature of intestinal metaplasia, is also highest proximally.[18] Thus, when trying to confirm the presence of intestinal metaplasia within a columnar-lined segment, biopsies should be focused proximally near the squamocolumnar junction rather than distally near the gastroesophageal junction.

The explanation for this distribution pattern of intestinal metaplasia is gradually becoming understood. The lowest pH and the longest duration of exposure to refluxed gastric juice occur in the most distal part of the esophagus, and with movement up the esophagus, the duration of acid exposure decreases. Thus, there is a gradient of exposure to reflux in the esophagus. This gradient has been shown in a patient with Barrett's esophagus using a catheter with multiple pH probes, and the percent time pH<4 varied from 26.5% near the gastroesophageal junction to 6.7% 16 cm proximally.[19] It is becoming evident that the pH and nature of the refluxed material play a critical role in the distribution of intestinal metaplasia within a columnar-lined esophagus, probably by modulating stem cells both directly and by altering the expression of master switch genes which regulate stem cell activity. Master switch genes, including Wnt, BMP-4, hedgehog, and Cdx-2, regulate stem cells during embryogenesis. While it was thought that after development the expression of these genes was shut off, it is now clear that these signaling pathways continue to have a vital role in adult life by directing differentiation, maintaining stem cell niches, and coordinating cellular responses to injury, particularly in the mucosa of the gastrointestinal tract.[20] Expression of Wnt appears to participate in the development of normal squamous mucosa, while the hedgehog proteins, particularly sonic, are critical for fundic gland differentiation and maintenance of normal gastric epithelium.[21] The homeobox proteins cdx1 and cdx2 have a major role in the development and maintenance of normal intestinal mucosa.[22] While an acidic pH is necessary for maximal sonic hedgehog expression, the expression of cdx2 is down-regulated by exposure to an acidic environment.[23] Expression of cdx2 has been linked to intestinal metaplasia in the esophagus, and similar to the gradient of esophageal acid exposure and of intestinal metaplasia, there is also a gradient of cdx2 expression with the highest expression proximally in long-segment Barrett's esophagus where acid exposure is lowest (authors data, publication pending). Similarly, there is a gradient of sonic hedgehog expression, with the highest expression distally near the gastroesophageal junction where acid exposure is greatest (authors data, publication pending). The interplay of sonic hedgehog and cdx2 expression likely participates in the phenotype of the columnar segment, with cardiac mucosa most likely to be present distally near the gastroesophageal junction where there is increased acid exposure and high sonic hedgehog expression. In contrast, intestinal metaplasia is most likely to be present proximally near the squamocolumnar junction where there is less acid exposure and high cdx2 expression.

There is some controversy regarding the necessity of intestinal metaplasia for the diagnosis of Barrett's esophagus. Recently, it has been suggested in the United Kingdom that the mere presence of a columnar-lined esophagus is a risk factor for adenocarcinoma.[24] However, controversy remains about how adequately these patients were biopsied to exclude the presence of intestinal metaplasia and whether or not the biopsies were focused at the squamocolumnar junction where intestinal metaplasia is most likely to be present. In the United States, patients with a columnar-lined esophagus without intestinal metaplasia are not considered to have a premalignant lesion, are not given the diagnosis of Barrett's, and are not recommended to undergo routine surveillance endoscopy.[25] In contrast to reports from past decades, though, it is rare to not have intestinal metaplasia in a 2–3-cm segment of columnar mucosa in the distal

esophagus, making the controversy somewhat of a moot point.

While the tendency is to think of Barrett's esophagus as a global condition, something that is either present or absent, there is evidence that all Barrett's is not equal, even in an individual patient. Aside from the issue of whether intestinal metaplasia extends throughout the columnar segment or is limited to the proximal portion, Fitzgerald et al. have shown that gene expression varies between the proximal and distal portions of a long segment of Barrett's esophagus, with inflammatory gene expression highest near the squamocolumnar junction.[26] It is likely that the interplay of master switch gene expression and the expression of other genes including COX-2, interleukins 1 and 8, VEGF, and cyclin D1 regulates the development and progression of Barrett's, dysplasia, and adenocarcinoma. The importance of this interplay is demonstrated by evidence suggesting that cancers often do not occur proximally in the area of highest inflammatory gene expression and greatest goblet cell density. Goblet cells are known to be typically absent in areas of high-grade dysplasia and in a pathologic review of the mucosa adjacent to small tumors resected endoscopically; Takubo et al. reported that cardiac mucosa rather than intestinal metaplasia was typically present.[27] Interestingly, in cell culture, Kong et al. found that insertion of the cdx2 gene into cultured keratinocytes led to a significant reduction in proliferation of the cells.[28] Consequently, while intestinal metaplasia appears to be a marker for malignant potential, the areas of intestinal metaplasia may in fact be those that are better differentiated and less likely to progress to cancer.

Although important insights have been gained into the pathways whereby reflux can lead to Barrett's esophagus and esophageal adenocarcinoma, it is less clear if antireflux therapies can halt or potentially reverse the disease once it has started. Logically, in the absence of reflux, there should be no cardiac mucosa in the distal esophagus. However, the normal mucosa in the region of the gastroesophageal junction remains disputed, with evidence that perhaps up to 4 mm of cardiac mucosa can be normally found.[29,30] Longer lengths correlate with reflux disease, but it is unclear whether aggressive antireflux therapy can prevent the development of cardiac mucosa in the esophagus or if cardiac mucosa can be reversed back to squamous mucosa with eradication of reflux. In contrast, there is clear evidence that cardiac mucosa often progresses to intestinal metaplasia over time. Oberg and colleagues followed 69 patients with 1–4-cm segments of cardiac mucosa and found that intestinal metaplasia developed in 35 patients at a median of 6.2 years.[31] Interestingly, they also evaluated the impact of the type of therapy for reflux on progression of cardiac mucosa and showed that antireflux surgery was associated with a reduced likelihood of progression to intestinal metaplasia as compared to medical therapy.[11] Wetscher et al. compared 83 patients with reflux disease treated with proton pump inhibitors to 42 patients that underwent an antireflux operation for reflux disease and noted that during follow-up, 12 patients (14.5%) in the medical therapy group compared to no patient in the surgical group developed Barrett's esophagus.[32] These studies suggest that elimination of reflux with an antireflux operation can alter the natural history of reflux disease and prevent the development of intestinal metaplasia in the esophagus.

A controversial and important issue is whether medical or surgical antireflux therapy can alter the natural history of Barrett's esophagus once it is present. Clinical follow-up in patients after standard medical or surgical therapy for reflux disease has shown that regression of short tongues of intestinal metaplasia back to cardiac mucosa or squamous mucosa occurs in up to 30% of patients, but longer lengths seldom disappear.[25] However, Csendes and colleagues showed that after vagotomy, partial gastrectomy and duodenal diversion intestinal metaplasia regressed back to cardiac or fundic mucosa in over 60% of patients with Barrett's esophagus during long-term follow-up.[33] Further, compared to medical therapy, antireflux surgery has been associated with a greater likelihood of regression of dysplasia.[34] The impact of medical and surgical therapy for reflux on progression of Barrett's to dysplasia and cancer has also been studied. The dramatic increase in the incidence of esophageal adenocarcinoma in the setting of better and more available acid suppression therapies, certainly at a superficial level, would not indicate that acid suppression alone is likely to have a significant impact on Barrett's progression. The efficacy of acid control may be an important issue, and certainly experimental evidence has suggested that exposure of *ex vivo* cultured Barrett's tissue to pulsed acid exposure led to increased proliferation, whereas either continuous acid exposure or effective acid suppression was associated with decreased proliferation and increased differentiation.[35–37] There is limited retrospective evidence that acid suppression with proton pump inhibitors may be associated with a reduced incidence of dysplasia in patients with Barrett's esophagus.[38] The efficacy of antireflux surgery for preventing progression of Barrett's to dysplasia or cancer has been evaluated in a number of single institution studies, and a reduction in the number of patients that would have been expected to develop dysplasia or cancer has been observed.[25] Further, a functioning fundoplication has been shown in a randomized trial to be associated with a significantly reduced incidence of Barrett's progression compared to medical therapy.[39] Similar findings have been reported in nonrandomized studies.[40,41] However, undisputable evidence that antireflux surgery reduces the risk of Barrett's progression to

adenocarcinoma is lacking. An often quoted paper suggesting that antireflux surgery does not alter the risk of adenocarcinoma is the large retrospective Swedish registry study by Lagergren et al. which showed that the adenocarcinoma risk in patients with reflux disease was similar for those treated medically and surgically.[42] This trial has been criticized for the methodology of selecting the study population from an inpatient registry with a discharge diagnosis of heartburn, hiatal hernia, or reflux esophagitis and then dividing the patients based on whether or not they also had a diagnosis code indicating antireflux surgery. The timing of the surgery in relation to the hospital admission for heartburn, hiatal hernia, or reflux esophagitis was not considered and would indicate that patients with a failed procedure were analyzed and likely muddied the water on the issue of whether antireflux surgery is able to protect against Barrett's progression. However, the greatest flaw in the study is that the inpatient registry did not have a code for Barrett's esophagus, and therefore, the authors did not have information on the prevalence of Barrett's in the two groups. Even worse, there is evidence to suggest that antireflux surgery was the preferred therapy in Sweden for patients with Barrett's esophagus.[43] This would be like comparing the risk of lung cancer in two groups of patients without knowing if the two groups were comparable for the number of smokers and how much they smoked daily. Therefore, without knowing that the medical and surgical therapy groups in Lagergren's study had a similar prevalence of the leading risk factor for esophageal adenocarcinoma, Barrett's esophagus, it is not possible to conclude with any authority that antireflux surgery does not reduce the incidence of progression to cancer.

If therapy for reflux disease was to have an impact on the natural history of reflux disease, then there should be evidence that the therapy is affecting gene expression alterations induced by reflux. Two of the genes associated with the reflux to Barrett's to adenocarcinoma sequence are COX-2 and interleukin-8, and antireflux surgery has been shown to normalize the expression of both of these genes in patients with reflux disease.[44,45] Thus, at the molecular level, evidence is accumulating in support of the intuitive concept that stopping reflux of both acid and bilious material could alter the natural history of reflux disease in patients who might otherwise develop Barrett's esophagus and perhaps adenocarcinoma.

In summary, the pathway from reflux to Barrett's and adenocarcinoma is gradually becoming understood, and variations in gene expression are providing potential explanations for the histologic findings that have been documented within a columnar-lined esophagus for over 30 years. As the genes involved in the progression of Barrett's to adenocarcinoma are identified, they can be used as markers to assess the impact of antireflux therapy in these patients. To date, no therapy has proven efficacy in preventing progression of Barrett's, but given the available evidence, the possibility that an antireflux operation may alter the natural history of Barrett's esophagus should be considered.

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SSAT STATE-OF-THE-ART CONFERENCE

Endoscopic Treatment for Barrett's Esophagus and Early Esophageal Cancer

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Barrett's esophagus offers two unique opportunities to endoscopically study neoplasia in the esophagus. The first is the effect of chronic inflammatory change produced by reflux of acid and bile into the distal esophagus, producing a partially intestinalized metaplastic epithelium. Most endoscopic therapies for neoplasia do not address this issue since the significance of this process in neoplastic progression is unclear. The pre-neoplastic condition though allows investigators the opportunity to examine the pathogenesis of metaplasia and to assess potential biomarkers. The second opportunity is the ability to treat the metaplasia producing normal appearing squamous mucosa using endoscopic therapies. These techniques have been adapted from the strategies developed from squamous cancers of the esophagus. However, the apparent reversal of the metaplastic process is unique to Barrett's esophagus. The epidemiology of this disease suggests that it is rapidly increasing in Western populations and may be increasing in Asian countries as well.

This paper was originally presented as part of the SSAT/AGA/ASGE State-of-the-Art Conference, Barrett's Esophagus, Dysplasia, and Early Esophageal Adenocarcinoma: Managing the Transition, at the SSAT 50th Annual Meeting, June 2009, in Chicago, Illinois. The other articles presented in the conference were Sarosi GA, Introduction: Barrett's Esophagus, Dysplasia, and Early Esophageal Adenocarcinoma: Managing the Transition; Souza RF, The Molecular Basis of Carcinogenesis in Barrett's Esophagus; DeMeester SR, Reflux, Barrett's and Adenocarcinoma of the Esophagus: Can We Disrupt the Pathway?; and Pennathur A and Luketich JD, Minimally Invasive Esophagectomy for Barrett's with High Grade Dysplasia and Early Adenocarcinoma of the Esophagus

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Like most epithelial malignancies, the inflammatory process is believed to be critical in the generation of a cancer-like stem cell. Although the pathogenesis of the intestinal phenotype has still not been totally elucidated, it seems clear that inflammatory pathways can upregulate cytosolic phospholipase A2 which is known to increase prostaglandin E2 production leading to increased cell proliferation.[1] In addition, the EGFR pathway is also upregulated by these inflammatory mediators. Transcriptional regulators such as BMP4 and CDX2 have been found to be involved in the phenotypic transformation of the squamous mucosa to intestinal-type mucosa. It is believed that the esophageal cancer stem cell is a small nearly quiescent population that then differentiates into a intestinal phenotype under the influence of inflammatory mediators such as IL-6 and the STAT3 pathway.[2] IL-6 has been found to be important in other cancer stem cells as well as interactions between mesenchymal stem cells. These cells are typically translocated from the bone marrow to regions of inflammation or neoplastic growth. The interactions between cancer stem cells and mesenchymal stem cells produce increased growth. It is important that any therapies that treat Barrett's esophagus also address these issues.

Endoscopic treatment is focused on destruction of the existing metaplastic tissue using thermal or photochemical treatments that eliminate the mucosa. It is unclear why the removal of the metaplastic epithelium almost always results in squamous epithelium, although this effect may not be durable. In addition, it is unclear if the stem cells that gave rise to Barrett's esophagus are affected by this therapy. Genetic abnormalities are not found in the squamous mucosa, although they may be present in non-dysplastic appearing metaplastic mucosa after ablative therapy. Current treatment requires combinations of mucosal resection techniques to eliminate visible lesions followed by ablation of

residual metaplastic tissue.[3] Endoscopic resection can be accomplished by either single or multiple mucosal resection cap devices. It is important that all mucosal abnormalities are first eliminated with mucosal resection devices, since this provides critical information regarding the presence of a malignancy and important information regarding depth of invasion of an existing cancer. Mucosal resection is the only ablative technique that actually acquires histology. After the areas of mucosal abnormality are removed, ablation of the residual Barrett's mucosa is most commonly performed with radiofrequency ablation, though photodynamic and recently cryotherapy have also been used. Results are similar with ablation rates over 80% for all of these therapies. Side effects of these therapies include stricture formation and chest pain after treatment. Photodynamic therapy has the unique adverse event of cutaneous photosensitivity. Photodynamic therapy also is known to have an increased depth of penetration and stricture formation. Long-term results are only available for photodynamic therapy, revealing that durable remission of Barrett's esophagus and high grade dysplasia (HGD) is possible.[4]

Each of the ablative therapies have certain strengths. Radiofrequency ablation is associated with the fewest complications since it has a limited depth of injury, although stricture formation is approximately 6% in a prospective series.[6] This prospective randomized controlled radiofrequency ablation study with 12-month follow-up found that the success rate in patients with high grade dysplasia was 81%. A patient with a straight esophageal segment without strictures is ideal for this modality. Patients with a tortuous esophagus may well do better with a treatment like photodynamic therapy that can be applied more readily in this situation. In addition, Barrett's segments that do not seem to respond to one form of ablation often respond well to another. Cryotherapy has been used in the situation of pre-existing strictures, with some anecdotal success.

However, recurrence of cancer and dysplasia (HGD), is not well established after ablative therapy. After combination photodynamic therapy and endoscopic mucosal resection for high grade dysplasia, the risk of recurrence is 8% in patients treated for HGD.[4] The risks increase with length of Barrett's esophagus, number of treatments required to eliminate the metaplasia, and the presence of p16 LOH.[5] Lifetime continued surveillance is still required. Biomarkers that would predict recurrence and identify best patients for treatment are needed.

At the current time, it appears that the best candidates for ablative therapy have shorter segments of Barrett's esophagus with high grade dysplasia (<8 cm), are p16 negative, have straight esophagus, and are compliant with physician instructions. Surgical resection is favored for patients with longer segments, healthier patients (as most endoscopic therapy is performed in patients with significantly more co-morbidities), and in patients who do not have a tolerance for treatment failure.

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SSAT STATE-OF-THE-ART CONFERENCE

Minimally Invasive Esophagectomy for Barrett's with High-grade Dysplasia and Early Adenocarcinoma of the Esophagus

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There has been a dramatic increase in the incidence of esophageal cancer in the Western population over the last two to three decades.[1] Further, the pattern of esophageal cancer has changed, with an increase in the incidence of adenocarcinoma, while the incidence of squamous cell carcinomas has declined. The reason for this increase is not clear, but gastroesophageal reflux disease, obesity, and Barrett's esophagus have been identified as risk factors.[2] High-grade dysplasia (HGD) in Barrett's esophagus is a premalignant condition which can progress to invasive adenocarcinoma. We have previously reviewed the important issues with regard to the treatment of HGD and early cancer.[2,3]

In this paper, we summarize some of the important aspects of HGD, the incidence of adenocarcinoma in resected specimens, issues regarding the clinical behavior of T1 adenocarcinomas, and the surgical aspects in the treatment of HGD and early-stage adenocarcinoma (T1) with a particular focus on minimally invasive esophagectomy (MIE).

High-grade Dysplasia

High-grade dysplasia is defined as intraepithelial neoplasia that has not yet penetrated the basement membrane and represents the final step in the metaplasia–dysplasia–carcinoma sequence in the transformation of Barrett's esophagus to adenocarcinoma.[4] The optimal approach to the treatment of HGD is controversial.

There are relatively few studies which address the rate of progression of HGD to adenocarcinoma.[2,5–7] In one study, Reid and colleagues reported a 59% 5-year cumulative risk of cancer among 76 patients with HGD.[6] In addition, there are difficulties in the diagnosis of HGD. First, there are sampling errors in the diagnosis of HGD and early neoplasia. Cameron mapped the esophagectomy specimens in patients with HGD and detected areas of microscopic carcinoma, which were frequently small (<1.1 cm^2).[8] Thus, even with a vigorous biopsy protocol, carcinomas can be missed.

Further, pathologists differ on their opinion as to whether or not HGD is present, and interobserver disagreement among experienced pathologists for the differentiation of HGD versus intramucosal carcinoma is significant.[9] In a study by Ornsby and colleagues, the interobserver agreement among pathologists was only fair and did not improve with establishment of standard criteria.[2,10]

This paper was originally presented as part of the SSAT/AGA/ASGE State-of-the-Art Conference, Barrett's Esophagus, Dysplasia, and Early Esophageal Adenocarcinoma: Managing the Transition, at the SSAT 50th Annual Meeting, June 2009, in Chicago, Illinois. The other articles presented in the conference were Sarosi GA Jr., Introduction: Barrett's Esophagus, Dysplasia, and Early Esophageal Adenocarcinoma: Managing the Transition; Souza RF, The Molecular Basis of Carcinogenesis in Barrett's Esophagus; DeMeester SR, Reflux, Barrett's and Adenocarcinoma of the Esophagus: Can We Disrupt the Pathway?; and Wang KK, Endoscopic Treatment for Barrett's Esophagus and Early Esophageal Cancer."

Society of Surgery of the Alimentary Tract 2009 Session on: Barrett's Esophagus, Dysplasia, and Early Esophageal Adenocarcinoma: Managing the Transition

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Occult Adenocarcinoma in Patients with HGD

Surgical series evaluating the incidence of occult adenocarcinoma in patients who had undergone an esophagectomy for HGD show an incidence of up to 75%.[2] Pelligrini and Collard have summarized several series of patients who underwent esophagectomy for high-grade dysplasia.[11,12] We have also presented an update of several series comprising 371 patients, with the incidence of occult carcinoma being 42%.[2]

Some of the drawbacks of these studies are that they are retrospective and do not define the endoscopy protocol followed prior to the diagnosis of HGD. Nevertheless, the incidence of missed adenocarcinoma in these patients is very high, despite an intensive biopsy protocol.[2] Therefore, because the detection of invasive adenocarcinoma in the resected specimens of patients with a pre-resection diagnosis of HGD being very high, one can make a strong argument for esophagectomy in fit patients.[2]

Korst and Altorki summarized the findings in 140 patients who underwent esophagectomy for HGD, 59 (42%) of those had adenocarcinoma in the resected specimen. Of these patients, 43 had T1 lesions, nine had T2 lesions, and six had T3 lesions. Thus, in 25.4% of patients with invasive cancer, the tumors invaded beyond the muscularis propria.[4] Thus, mucosal ablation therapy alone is inadequate to treat a significant percentage of these patients.

Impact of Earlier Diagnosis and Survival After Esophagectomy

Esophageal cancer, when diagnosed, has an overall 5-year survival of approximately 10–15%.[1] The main reason for this poor prognosis is the advanced stage at diagnosis. In contrast, patients who are diagnosed early and have surgical resection have a good prognosis. For example, the 5-year survival among patients with Stage 0 lesions (tumor in situ) is greater than 95% and in Stage 1 patients is 50–80%. Thus, treatment at an earlier stage is associated with a better outcome.[1,2] Surgical intervention via esophagectomy in patients with HGD, many of whom may be harboring early invasive cancer, or early-stage T1 lesions, offers the best chance for cure in fit patients.

The Role for Esophagectomy in HGD and T1 Esophageal Cancer

Esophagectomy offers the most definite treatment in that it eliminates all of the Barrett's epithelium and the mucosa at risk. On the other hand, critics point out that the morbidity and mortality has been considered high[13] and many of these patients may not harbor cancer at the time of resection. One of the main concerns for recommendation of esophagectomy is the risks associated with surgery. Certainly, one of the most important factors in lowering the risk of esophagectomy is the experience of the surgeon doing the esophagectomy. In an effort to decrease the morbidity and mortality from this surgery, recent advances in minimally invasive surgery have allowed us to develop and refine the technique of minimally invasive esophagectomy at the University of Pittsburgh.

We have reported our results of a series of 222 consecutive MIEs.[14] The median ICU stay was 1 day, the hospital stay 7 days and the operative mortality was only 1.4%. In addition, stage-specific survival was similar to open esophagectomy series. Thus, in our center, we observed a short hospital stay, low mortality, and good oncologic results after MIE.

Esophagectomy for T1 Esophageal Cancer

T1 esophageal cancers encompass a very heterogenous group of patients. This heterogeneity includes not only depth of the tumor (intramucosal or submucosal) but also other prognostic factors such as the length of the tumor, the presence of angiolymphatic invasion, nodal metastases, and the degree of differentiation, even in these superficial tumors. Although, it is commonly stated that patients with T1 intramucosal cancer can be managed with endoscopic therapies, due to the lower chance of lymph node metastases, these associated factors may in fact preclude adequate treatment with endoscopic therapies.[3]

We recently reported our experience in 100 consecutive patients who underwent esophagectomy for T1 esophageal carcinoma. A minimally invasive approach was used in 80% of the patients.[3] This series included all patients with T1 tumors, including those with adverse prognostic factors. In our study, the 30-day mortality was zero. The resection margins were microscopically negative in 99% (99/100) of patients. N1 disease was present in 21 patients [T1a:2/29 (7%); T1b:19/71 (27%)], associated high-grade dysplasia in 64/100 (64%) and angiolymphatic invasion in 19/100 (19%) patients. At a median follow-up of 66 months, the estimated 3 year disease-free survival for all patients (including N1) was 80%. Nodal status and size/length were significantly associated with overall survival and disease-free survival, respectively. Patients with T1 cancer have the best chance for cure and esophagectomy can be performed safely in these patients in experienced centers.[3]

Quality of Life

With advances made in surgical techniques, and perioperative surgical critical care, the mortality and morbidity from esophagectomy have decreased.[2] However, the long term quality of life (QOL) after esophagectomy is being increasingly recognized as an important factor. Despite potential problems, such as dysphagia, or dumping that may be associated with esophagectomy, studies suggest that the long-term impact on the QOL is minimal.[2,3,14,15] In an effort to decrease the morbidity and preserve the QOL, we have adopted a minimally invasive approach. In one of our studies on outcomes after MIE, the general QOL was assessed by the Short-Form 36. There was no significant differences when the preoperative and post-operative scores were compared, indicating preservation of QOL. In addition, the reflux-related QOL was evaluated with the Gastroesophageal Reflux Disease-Health Related Quality of Life (HRQOL). The range of this score varies from 0 (no symptoms) to 45 (most severe symptoms). The mean HRQOL score was 4.6 indicating a normal score. Further, the dysphagia scores were excellent with a mean score of 1.4 using a scale of 1 (no dysphagia) to 5 (severe dysphagia). More recently, we evaluated the QOL in patients who undergone an esophagectomy for T1 esophageal cancer.[3] At a mean follow-up of 48.2 months, the median HRQOL score was 3. Thus the QOL after minimally invasive esophagectomy appears to be well preserved.

Conclusion

In summary, the management of HGD is controversial. There is a significant risk of occult invasive cancer being already present or subsequently developing in patients with HGD.[2,16] Many patients with T1 esophageal cancer have several risk factors which may preclude adequate treatment with endoscopic therapy. Esophagectomy can be performed safely in patients with T1 cancer, with good long-term results.[3] Esophagectomy should entail removal of all of the Barrett's mucosa and the anastomosis is commonly performed in the high chest or in the neck. Strong consideration should be given for the performance of surgery in a high-volume hospital. With esophagectomy for early-stage esophageal cancer, the long-term survival is excellent and these patients have a good quality of life.[2,3]

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ORIGINAL ARTICLE

Surgical Outcomes Associated with Oesophagectomy in New South Wales: An Investigation of Hospital Volume

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Abstract
Introduction Resection remains the standard treatment for curable oesophageal cancer. By linking the NSW Central Cancer Registry (CCR) and the NSW Admitted Patient Data Collection (APDC) databases, mortality, post-resection complication and survival associated with oesophagectomy were investigated.
Methods All patients diagnosed with oesophageal cancer from 2000 to 2005 as recorded in the CCR (n=2,082) were linked with records in the APDC, giving a total of 17,205 episodes of care. Over 15% (n=321) of all patients underwent an oesophagectomy.
Results and Discussion The overall 30-day mortality rate following resection was 3.7%, ranging from 2.6% in high volume hospitals to 6.4% in low volume hospitals. Three-year absolute survival for localised-regional disease following oesophagectomy was 64% (95%CI 54–73%) in high-volume hospitals, 58% (95%CI 46–68%) in mid-volume and 45% (95%CI 23–65%) in low-volume hospitals. The post-resection complication rate was 19% (95%CI 13–26%) for high-volume hospital, 24% (95%CI 13–40%) in low-volume and 31% (95%CI 22–41%) in mid-volume hospitals.
Conclusion Oesophagectomy in NSW is performed with satisfactory results. However, there is a suggestion that higher- rather than lower-volume hospitals have better post-resection outcomes.

Keywords Mortality · Survival · Hospital volume · Complications · Oesophagectomy

Introduction

The increase in incidence of oesophageal cancer has been well documented throughout the world and within Australia.[1–6] In developed countries, this increase is seen predominantly in histological subgroup of adenocarcinomas.[2–6] The incidence rate of oesophageal cancer in New South Wales (NSW) is more than two and a half times higher in males than females. Unfortunately, at diagnosis, only approximately a third of patients with oesophageal cancer have localised disease.[2] In addition, prognosis of the disease is poor, with 5-year relative survival for patients diagnosed with localised disease at diagnosis being 25% whilst that for distant degree of spread is 4%.[7] In NSW, 5-year absolute survival for adenocarcinoma ranges from 22% for localised disease to 2% for metastatic disease.[6]

Resection remains the standard of care for curable oesophageal cancer. Stage I, II and III cancers (based on the tumour node metastasis classification)[8] are potentially resectable; however, patients should be assessed for physiologic ability to undergo resection. Accurate and comprehensive preoperative staging with computed tomography, positron emission tomography (PET) scanning, endoscopic ultrasound (EUS) and laparoscopy improves patient selection for surgery by excluding those with metastases and may increase postoperative survival.[8–10]

Determinants of outcomes from oesophageal cancer surgery include hospital volume (as a proxy measure for

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surgeon and/or facility experience), hospital peer group classification, tumour stage and location and patient comorbidity.[11–15] Outcomes which are frequently measured include in-hospital mortality, morbidity and survival. Previous studies have shown that mortality rate post-surgery decreased as surgeon or hospital volume increased.[11–16] Overall survival has also been demonstrated to be better for patients treated in high-volume compared with low-volume (less than eight resections per year) hospitals, but only attains statistical significance when only patients with stages I and II are considered.[15] This indicates that overall survival is worsened by the poorer survival of oesophageal cancer in the more advanced stages of disease. Authors have also noted the importance of adjusting for comorbidity in the analyses as patients with comorbidity may be unevenly distributed between hospital peer groups.[11,15]

After adjusting for tumour stage and patient age, a recent study failed to show better survival in patients treated in high-volume hospitals (classified as >20 resections per year), but the authors did show that oesophagectomies performed in a university hospital, rather than a non-university hospital or non-teaching hospital, resulted in better survival.[17]

This study investigated (1) hospital characteristics in which an oesophagectomy occurred in NSW; (2) the outcomes (including 30-day mortality, post-resection complications and survival) following oesophagectomy; and (3) survival differences between patients receiving surgical resection and those who did not.

Materials and Methods

Data Sources

The Central Cancer Registry (CCR) receives notifications of cancer in NSW and maintains a record of all cases of cancer diagnosed in NSW residents since 1972. The registry is run according to the International Association of Cancer Registries (IACR) rules[18] and is one of the few Australian Cancer Registries to record degree of spread at first diagnosis for all solid malignant tumours.[19] Degree of spread is assigned by the NSW CCR into one of four summary stages (localised, regional, distant or unknown).[6] It is defined as the maximum extent of disease based on all diagnostic and therapeutic evidence received within 4 months of diagnosis and follows the international coding guidelines for summary stage adopted by several international groups including the World Health Organisation and the IACR.[20] For example, morphological data ending with a '3' is invasive cancer localised to the tissue of origin and hence classified as 'B' and grouped as 'localised'. Cancers which have spread into an adjacent organ or lymph nodes are classified as 'C' and 'D' and are grouped into 'regional', whilst a classification of 'E' indicates 'distant' metastasis. Histological subgroups were based on Berg groupings of International Classification of Diseases-Oncology v3 (ICD-O3) morphologies.

The Admitted Patients Data Collection (APDC) includes records for all hospital separations from all NSW public and private hospitals and day procedure centres and for data linkage purposes, data commence from 1 July 2000.

Master Linkage Key

Identifying information from the CCR and the APDC was included in the Master Linkage Key (MLK) maintained by the Centre for Health Record Linkage (www.cherel.org.au). Records were matched using probabilistic record linkage methods and 'Choice Maker' software.[21]

A total of 17,205 APDC records from 1 July 2000 to 30 June 2006 were matched to 2,082 primary invasive oesophageal cancer cases on the CCR (ICD-O3 codes C15.0-C15.9) diagnosed between 1 July 2000 and 31 December 2005, this being the data available at the time of the study. The parameters for the extract from the MLK were such that the false positive and false negative rates were each <0.1%.

Other Variables

Accessibility/Remoteness Index for Australia (ARIA+) values were applied to cases via the local government area (LGA).[22] Due to small populations in the remote and very remote categories, cases in these locations were combined with outer regional locality. Sensitivity analysis was performed excluding people resident in LGAs near the NSW borders at the time of cancer diagnosis (due to the potential for these people to attend at interstate hospitals) and examining the effect on the modelling. Socioeconomic status was estimated using the Index of Relative Socioeconomic Disadvantage (IRSD), one of four Socio Economic Indexes for Areas created by the Australian Bureau of Statistics.[23]

English and non-English-speaking backgrounds (CALD) were determined by country of birth data from the CCR, with English-speaking comprising countries of birth of Australia, New Zealand, UK, USA, Canada and South Africa.

International Classification of Diseases (ICD-10-AM) procedural block codes used for determining if an oesophagectomy was performed (by abdominal and thoracic/transthoracic/cervical mobilisation) were 0858-0860.[24] Time between surgery date and date of diagnosis was accounted for in statistical modelling. Post-resection complications were derived from ICD-10-AM diagnostic codes and included any post-procedural disorders or complications of procedures, haemorrhages, pulmonary and cardiac complications.

Comorbidities were used as a surrogate measure for patient general health status and ability to undergo a resection. A person was counted as having a particular comorbidity if any hospital admission in the 5.0-year period mentioned any comorbidity code defined for cardiovascular disease, impaired glucose metabolism or diabetes mellitus, chronic lower respiratory disease or renal disease.[24] Hence, this was not an extensive measure of comorbidity and would underestimate the true extent of comorbidity in the cohort; however, given the availability of data, it was the best possible method of measure.

Hospitals in which an oesophagectomy was performed were arbitrarily grouped by total number of oesophagectomies performed from Jul 2000 to Jun 2006. Groupings were 'Low volume' if ≤10 oesophagectomies, 'Mid volume' if the number of oesophagectomies were between 11 and 20 (inclusive) and 'High volume' for greater than 20 oesophagectomies.

Statistical Analyses

Survival analysis was undertaken to examine for localised-regional disease: (1) the association between undergoing an oesophagectomy or not and (2) survival following the oesophagectomy. People diagnosed with oesophageal cancer in the NSW CCR were followed to 31st December 2005 for death from the cancer. Survival estimates are reported using the Kaplan–Meier product limit method, and Cox proportional hazard regression was used to estimate hazard ratios. Adjusted logistic regression was used to determine which factors were associated with post-resection complication. Statistical significance for hazard regression was taken at the $p \leq 0.10$ level and at $p < 0.05$ for logistic regression analysis. All statistical analysis was performed using SAS version 9.

This research was performed with approval from the NSW Population and Health Service Research Ethics Committee (2008/02/057).

Results

From 1 July 2000 to 31 December 2005, 2,082 cases of oesophageal cancer were diagnosed in NSW. Of these, 781 (37.5%, 95%CI 35.4–39.6%) were classified as having localised disease, 484 (23.2%, 95%CI 21.5–25.1%) with regional spread and 481 (23.1%, 95%CI 21.3–25.0%) with distant metastases within 4 months of diagnosis by the NSW CCR

Over 15% (95%CI 13.9–17.1%) of all patients ($n=321$) were identified as undergoing an oesophagectomy, of which 83.8% ($n=269$, 95%CI 79.2–87.6) were diagnosed with localised and regional spread of disease. Sensitivity analyses showed that adjusting for border LGAs had no effect on the statistical analyses. Low- and mid-volume hospitals undertook resections on a greater proportion of patients with metastatic disease (10.6%; 95%CI 4.0–23.9% and 13.7%; 95%CI 8.3–21.6% respectively) compared with high-volume hospitals (3.2%, 95%CI 3.3–11.7%).

The overall 30-day mortality rate following resection was 3.7% (12/321; 95%CI 2.0–6.6%). Low-volume hospitals recorded 3 in 47 (6.4%, 95%CI 1.7–18.6%) fatalities within 30 days of surgery, mid-volume hospitals recorded 5 in 116 (4.3%, 95%CI 1.6–10.3%) fatalities, whilst high-volume hospitals had the lowest rate with 4 in 155 (2.6%, 95%CI 1.0–6.4%) recorded. When surgical procedure was examined, using thoracotomy, 10 in 278 (3.6%, 95%CI 1.8–6.7%) fatalities occurred within 30 days of surgery, whilst 2 in 43 (4.9%, 95%CI 1.3–15.4%) occurred for transhiatal oesophagectomies. Due to the small number of fatalities within 30 days of surgery, modelling was not possible.

The overall post-resection complication rate was 24.0% (95%CI 20.2–29.0%). Mid-volume hospitals had the highest complication rate (31.0%, 95%CI 23.0–40.3%) compared with low-volume (23.4%, 95%CI 12.8–38.4%) and high-volume hospitals (18.7%, 95%CI 13.1–25.9%). For surgical procedure, transhiatal oesophagectomies had a slightly higher complication rate (27.9%, 95%CI 15.8–43.9%) than thoracotomies (23.4%, 95%CI 18.6–28.9%). When adjusted for all factors, the overall association between hospital volume and complication rate was significant, with difference in complication rate significantly higher in mid-volume (OR 2.89, 95% CI 1.29–6.46, $p=0.01$) compared to high-volume hospitals (Table 1).

Three-year absolute survival for localised-regional disease following oesophagectomy was 45.1% (95%CI 23.4–64.6%) for low-volume hospitals, 58.0% (95%CI 46.1–68.2%) for mid-volume hospitals and 64.4% (95%CI 53.8–73.2%) for high-volume hospitals. Similar absolute survival was seen for thoracotomy (58.2%, 95%CI 50.3–65.2%) versus transhiatal procedures (66.9%, 95%CI 45.2–81.6%).

As modelling localised and regional spread of disease separately failed validity, when all factors including age, gender, CALD, comorbidity and accounting for time-to-resection-after-diagnosis were modelled, 3-year survival from localised-regional cancer for patients following an oesophagectomy was not significantly different between hospital volume nor surgical procedure (Table 2). Tumours located in the upper third (HR 3.71, 95%CI 1.26–10.9, $p=0.02$) and middle third oesophagus (HR 2.12, 95%CI 0.94–4.80, $p=0.07$) had worse survival than tumours of the distal third/overlapping oesophagus.

Further hazard regression analysis showed that after adjusting for potential confounding factors, patients undergoing oesophagectomy for localised-regional disease had statistically significant better cancer cause 1-year survival

Table 1 Factors Associated with Post-resection Complication Using Logistic Regression Analysis

Group	No complication (*N*=244, %)	Complication (*N*=77, %)	Adjusted OR	*p* value
Age				
<60 years	83 (33.9)	19 (24.7)	0.90 (0.42–1.92)	0.78
≥60 years	161 (66.1)	58 (75.3)	Referent	
Sex				
Male	184 (75.5)	54 (69.9)	1.38 (0.58–3.28)	0.47
Female	60 (24.5)	23 (30.1)		
Surgical methods				
Thoracotomy	213 (87.1)	65 (84.9)	Referent	0.61
Transhiatal oesophagectomy	31 (12.9)	12 (15.1)	1.29 (0.49–3.43)	
Hospital volume				0.04[a]
Low	36 (14.0)	11 (14.1)	1.75 (0.63–4.88)	0.29
Mid	50 (32.5)	36 (46.5)	2.89 (1.29–6.46)	0.01
High	127 (53.5)	29 (39.4)	Referent	

Adjusted for all factors in the table plus co-morbidity, ARIA+, IRSD, CALD, degree of spread, histology, tumour location, year of diagnosis, time since diagnosis and AHS of residence

[a] Indicates overall *p* value

after diagnosis than those who did not undergo resection (HR 0.39, 95%CI 0.28–0.56, $p<0.001$). Residing in an inner regional area (HR 1.17, 95%CI 1.06–1.29, $p<0.001$) or outer regional/remote area (HR 1.53, 95% CI 1.30–1.81, $p<0.001$) rather than a major city was associated with worse 1-year survival. Patients aged 60 years and above (1.68, 95% CI 1.50–1.89, $p<0.001$) also had significantly poorer 1-year survival, and trend analysis showed worse survival for patients with lower socioeconomic status ($p<0.001$). Survival from localised-regional cancer has improved over time (HR 0.96, 95%CI 0.94–0.99, $p=0.002$), and tumours located in the distal third/overlapping oesophagus had better survival than the cervical/upper third (HR 0.87, 95% CI 0.76–0.99, $p=0.04$).

Discussion

Oesophagectomy is the mainstay of curative treatment for patients with oesophageal cancer.[8] Oesophagectomy is associated with significant operative morbidity and operative mortality, however offers the only form of cure particularly for patients with adenocarcinoma, which, in recent years, has become the dominant histological subtype in Western society.[1–6,17]

Over 15% of 2,082 patients diagnosed with oesophageal cancer were identified has having undergone an oesophagectomy in NSW from 2000 to 2006, and of these, over 83% were diagnosed with localised-regional spread of disease. This is a lower resection rate than that reported in

Table 2 Three-Year Absolute Survival from Localised-Regional Oesophageal Cancer After Oesophagectomy

Variable	Number (%, *n*=269)	Adjusted hazard ratio[a] (±95% CI)	*p* value
Age group			
<60 years	86 (31.8)	0.65 (0.36–1.20)	0.17
60+years	183 (68.2)	Referent	
Sex			
Male	188 (70.0)	2.35 (1.20–4.62)	0.01
Female	65 (24.2)	Referent	
Surgical method			
Thoracotomy	231 (86.0)	Referent	0.32
Transhiatal oesophagectomy	38 (14.0)	0.66 (0.30–1.49)	
Hospital volume			0.32[b]
Low	39 (14.5)	0.66 (0.25–1.76)	0.41
Mid	97 (36.1)	1.45 (0.69–3.06)	0.33
High	130 (48.5)	Referent	
Tumour location			0.05[b]
Cervical/upper third	10 (3.6)	3.71 (1.26–10.9)	0.02
Thoracic/middle third	28 (10.3)	2.12 (0.94–4.80)	0.07
Distal third/overlapping	171 (63.6)	Referent	
NOS	60 (22.4)	0.77 (0.35–1.65)	0.50

[a] Adjusted for all factors in the table plus comorbidity, ARIA+, IRSD, CALD, histology, time since diagnosis and AHS of residence

[b] Indicates overall *p* value

other studies, and hence, the lower number of resections undertaken is a limitation of this study.[13,15,25]

A very low rate of 30-day postoperative mortality (3.7%) was reported for this study. This mortality rate falls within suggested international benchmarks,[26] but may be a reflection of the lower number of oesophagectomies performed. Nevertheless, contemporary published Australian mortality results for oesophagectomy compare favourably with those published in both the UK and USA.[11,12,14,16,25,27] Operative mortality for single surgeons, multiple surgeons in a single institution and multicentre data report operative mortalities well within acceptable international benchmarks.[26,28–33] In general, operative mortality rates across all institution types in NSW were reassuring particularly given the mortality rates in low-volume hospitals in the USA and UK.[11,16] There may be a number of reasons for this. It may be speculated that surgical training in Australia is accepted to be of a high standard. It may be further speculated that surgeons in NSW performing oesophagectomy are likely to have had subspecialist training in upper gastrointestinal surgery units in Metropolitan Australia and internationally. The relative low incidents of oesophagectomy and the low number of surgeons performing oesophagectomy may facilitate communication between surgeons locally, which may then lead to a collective improvement in technique. It is generally accepted within the Australasian surgical community that there is no place for surgeons performing occasional oesophageal resections. This principle may be at least partially responsible for the low mortality rates presented in this study, although no evidence can be provided and the overall number of oesophagectomies was low.

Although statistical distinction in 30-day mortality between hospital volume was not able to be ascertained in the study reported here (due to lower numbers and lack of power), there was a suggestion that mortality was worse in lower volume hospitals, which is similar to that reported.[13,15,25] Wouters et al.[15] reported that in-hospital mortality was significantly worse in low-volume hospitals when compared with high-volume hospitals. The study reported here was able to demonstrate an association between lower hospital volume and increased post-resection complications, showing further agreement with other studies.[13,15] Wouters et al. adjusted for important factors such as comorbidity, cancer stage, surgery type and neoadjuvant therapy received. Other studies have demonstrated that doctor/hospital volume was associated with improved survival and/or postoperative mortality in patients with oesophageal cancer, but adjustment for comorbidity was not always undertaken.[11,14,25]

In a review of operative outcomes following oesophagectomy (among other high equity procedures) in the USA, poor operative mortality rates ranged from approximately 10% in institutions which frequently performed oesophagectomies to 20% in institutions which performed infrequent resections.[16] The authors concluded that real differences existed between so-called high-volume and low-volume hospitals in the quality of surgery undertaken and the resulting surgical outcomes. Similar conclusions have been reached in the UK. In 2002, the UK National Health Executive produced guidelines for the commission of cancer services advising that treatment for oesophagogastric cancer should be limited to hospitals serving minimum populations of one to two million.[34] These recommendations were based on data from the UK, suggesting that a critical number of oesophagectomies needed to be performed in a given institution to maintain a high standard of care.[26] However, other studies have failed to demonstrate statistically significant relationships between hospital surgery volume and long-term outcomes.[35,36]

Of those patients in NSW who underwent an oesophagectomy, 10% were classified as having distant metastases, which seems unusual as metastatic disease is regarded as a contraindication for oesophagectomy. The CCR defines summary stages as the maximum extent of disease received from all notifications up to 4 months after diagnosis. Hence, it is quite plausible that patients may have had localised-regional disease at the time of surgery and then reclassified with metastatic disease post-surgery. This requires further investigation of individual case files so that time between procedure date and stage classification date can be accounted. Tumour node metastases staging information was also not available, and investigation of the 'staging' codes assigned to these patients is also necessary. These deficiencies in data available for evaluation are an intrinsic limitation of registry-based evaluation of treatment outcomes. More detailed evaluation of surgical/oncological outcomes will be made possible with the adoption of more detailed population health datasets at a jurisdictional and Australasian level. This process is underway within the community of upper gastrointestinal surgeons of Australia and New Zealand under the auspices of the Australian and New Zealand Gastro-oesophageal Surgeons Association.[37]

Low- and mid-volume hospitals had the highest proportion of patients classified with distant and unknown degree of spread undergoing resection. These results may indicate a lack of staging or diagnostic ability of smaller hospitals or again may be reflective of the low number of oesophagectomies performed. Due to a lack of resections undertaken and hence statistical power, neither hospital volume nor surgical procedure was related to survival from loco-regional disease in this study, contrary to findings in previous studies;[11,14,17,25] however, absolute survival was greater in higher volume hospitals, agreeing with the literature. In order to undertake analyses with larger numbers and hence attain statistical power and to allow

for stage-by-stage survival analyses, this study should be repeated in another 10 years.

Patients residing in outer regional/remote areas had worse 1-year survival from localised-regional oesophageal cancer following diagnosis. Similarly, trend analysis suggested worse 1-year survival for patients with poorer socioeconomic status. This may indicate reduced access to services and delayed presentation of the disease for both factors.

In addition to the low number of resections performed over the 5 years and an underestimation of comorbidity, major limitations of this study also include a lack of pre-staging information. The APDC is a database of all in-patient hospital procedures; hence, treatment which occurs as an outpatient such as pre-staging techniques, chemotherapy and radiotherapy is not available, and these variables may affect patient survival. Computed tomography of chest, pelvis and abdomen, EUS, PET and laparoscopy are utilised to stage patients prior to resection.[8,10] Similarly, adjuvant and neoadjuvant therapy which may have been used in the treatment regimen for patients also cannot be accounted for. Although debated with regards to the outcome benefit, neoadjuvant chemotherapy is considered standard care by many.[38]

Conclusion

In summary, this study demonstrates that oesophagectomy for oesophageal cancer is being performed in NSW with satisfactory operative mortality and survival rates, especially when compared to mortality rates of low-volume hospitals reported in the USA and UK. There is, however, some suggestion that higher volume hospitals have better mortality, post-resection complication rates and better survival than lower volume hospitals.

Patients residing in regional or remote locations or those with poorer socioeconomic status have lower 1-year survival from localised-regional oesophageal cancer.

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ORIGINAL ARTICLE

A Meta-Analysis of Randomized Controlled Trials that Compared Laparoscopy-Assisted and Open Distal Gastrectomy for Early Gastric Cancer

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Abstract
Background We conducted a meta-analysis to evaluate and compare the advantages of laparoscopy-assisted distal gastrectomy (LADG) over open distal gastrectomy (ODG) for treating early gastric cancer (EGC).
Methods We searched MEDLINE, EMBASE, Science Citation Index, and Cochrane Controlled Trial Register for relevant papers published between January 1990 and January 2010 by using the following search terms: laparoscopy-assisted gastrectomy, laparoscopic gastrectomy, and early gastric cancer. The following data were analyzed: operative time, estimated blood loss, number of harvested lymph nodes, time required for resumption of oral intake, duration of hospital stay, frequency of analgesic administration, complications, tumor recurrence, and mortality.
Results We selected four papers reporting randomized control studies (RCTs) that compared LADG with ODG for EGC. Our meta-analysis included 267 patients with EGC; of these, 134 and 133 had undergone LADG and ODG, respectively. The volume of intraoperative blood loss, frequency of analgesic administration, and rate of complications were significantly lesser for LADG than for ODG. However, the time required for resumption of oral intake and duration of hospital stay did not significantly differ between LADG and ODG. The operative time for LADG was significantly longer than that for ODG; further, the number of harvested lymph nodes was significantly lesser in the LADG group than in the ODG group.
Conclusion LADG is advantageous over ODG because it results in lesser blood loss, is less painful, and is associated with a low risk of complications. Additional RCTs that compare LADG and ODG and investigate the long-term oncological outcomes of LADG are required to determine the advantages of LADG over ODG.

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Keywords Laparoscopy-assisted distal gastrectomy (LADG) · Meta-analysis · Early gastric cancer

Introduction

Gastric cancer is the second leading cause of cancer-specific mortality worldwide,[1] and every year, 930,000 new cases are diagnosed and 700,000 deaths occur.[2] Recently, the World Health Organization reported a reduction in worldwide gastric cancer mortality.[3,4] Early gastric cancer (EGC) is defined as adenocarcinoma confined to the mucosa or submucosa, irrespective of lymph node involvement.[5] Recently, in Japan, with advancements in diagnostic modalities and mass examination techniques, the incidence of EGC has increased

to more than 50% of the overall incidence of gastric cancer.[6] In countries with a high incidence of EGC, such as Japan and Korea, focus is shifting from radical treatments for cure to the development of new technologies such as laparoscopy-assisted surgery or endoscopic resection for treating gastric cancer.[5] Since it was first reported in 1994,[7] laparoscopy-assisted distal gastrectomy (LADG) has been widely used for EGC treatment.[8] LADG has the following advantages over open distal gastrectomy (ODG) for treating gastric cancer: LADG is a minimally invasive technique, allows for rapid recovery of bowel movement, is less painful, requires shorter hospital stay, and has good cosmetic outcome.[9–12] Only four randomized control studies (RCTs)[13–16] that compared LADG with ODG for EGC have been published; however, the sample sizes in these RCTs were not adequate to examine the advantages and disadvantages of LADG. Therefore, we conducted a meta-analysis of the data from the four RCTs and compared LADG and ODG by considering several factors.

Materials and Methods

The papers were identified by searching the major medical databases such as MEDLINE, EMBASE, Science Citation Index, and Cochrane Controlled Trial Register for relevant papers published between January 1990 and January 2010. The following search terms were used: laparoscopy-assisted gastrectomy, laparoscopic gastrectomy, and early gastric cancer. Furthermore, our literature search was limited to articles that described the design of the RCT.

Three researchers (HO, YT, and KH) extracted data from each article by using a structured sheet and entered the data into a database. Data regarding the following factors were considered: operative time, estimated blood loss, number of harvested lymph nodes, time required for resumption of oral intake, duration of hospital stay, frequency of administration of analgesics, complications, tumor recurrence rate, and mortality.

The extent of the lymph node dissection was determined according to the Japanese guidelines for the treatment of gastric cancer.[17] Mortality was defined as 30-day mortality.

Statistical Analysis

Weighted mean differences (WMDs) and odds ratios (ORs) were used for the analysis of continuous and dichotomous variables, respectively. Random-effects models were used to identify heterogeneity between the studies.[18] Heterogeneity was assessed using the χ^2 test. The confidence interval (CI) was established at 95%. *P* values of less than 0.05 were considered to indicate statistical significance. Statistical analyses were performed using the Review Manager software version 5.0.23 provided by the Cochrane Collaboration.

Results

In this study, we identified four papers on RCTs that compared LADG and ODG for EGC. The characteristics of the four RCTs are presented in Table 1. Our meta-analysis included 267 patients with EGC; of these, 134 and 133 had undergone LADG and ODG, respectively. The results of this meta-analysis are shown in Fig. 1.

Operative Time

In all the four RCTs, the operative time for LADG was significantly longer than that for ODG. Moreover, analysis of the pooled data revealed that the operative time for LADG was significantly greater by 96.47 min (WMD= 96.47; 95% CI=61.28–131.66; $p<0.00001$).

Blood Loss

The volumes of intraoperative blood loss were recorded in all the four RCTs. In three RCTs, the estimated intraoperative blood loss was significantly lower in the LADG group than in the ODG group. Analysis of the pooled data revealed that intraoperative blood loss in the LADG group was significantly lesser by 108.57 ml (WMD=−108.57; 95% CI=−175.12 to −42.02; $p=0.001$).

Number of Harvested Lymph Nodes

Only one RCT reported that the number of harvested lymph nodes was significantly lesser in the LADG group than in the ODG group. In addition, analysis of the pooled data revealed that the number of harvested lymph nodes was significantly lesser by 4.88 in the LADG group (WMD=−4.88; 95% CI=−6.94 to −2.82; $p<0.00001$).

Table 1 Characteristics of the Selected Four Randomized Clinical Trials

Authors	Year	Country	Number of patients		Depth of invasion	Reconstruction
			LADG	ODG		
Kitano et al.[13]	2002	Japan	14	14	EGC	B-I
Lee et al.[14]	2005	Korea	24	23	EGC	B-I
Hayashi et al.[15]	2005	Japan	14	14	EGC	B-I
Kim et al.[16]	2008	Korea	82	82	EGC	B-I

EGC early gastric cancer, *B-I* Billroth I

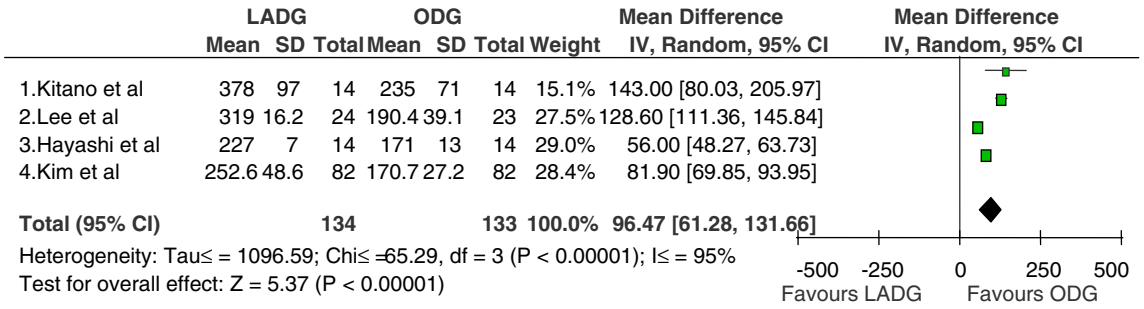
Resumption of Oral Intake

In two RCTs, the time required for resumption of oral intake was significantly lesser in the LADG group than in the ODG group. Analysis of the pooled data revealed that the two groups did not differ significantly in this regard (WMD=−0.45; 95% CI=−1.40 to 0.50; p=0.35).

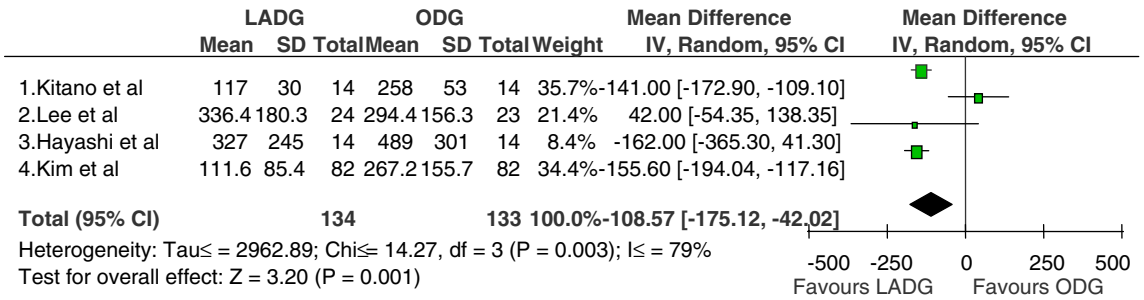
Duration of Hospital Stay

In two RCTs, the duration of hospital stay was significantly shorter in the LADG group than in the ODG group. However, analysis of the pooled data revealed no significant difference between the LADG and ODG groups (WMD=−2.03; 95% CI=−4.73 to 0.67; p=0.14).

1. duration of operative time (minutes)



2. volume of blood loss (ml)



3. number of harvested lymph nodes

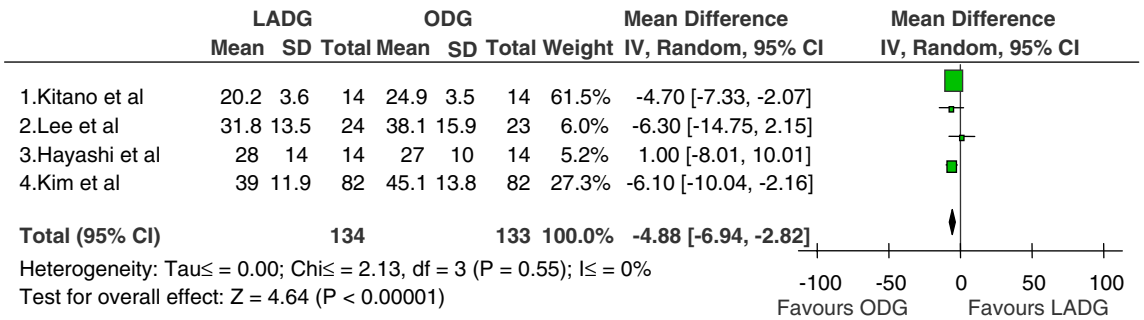
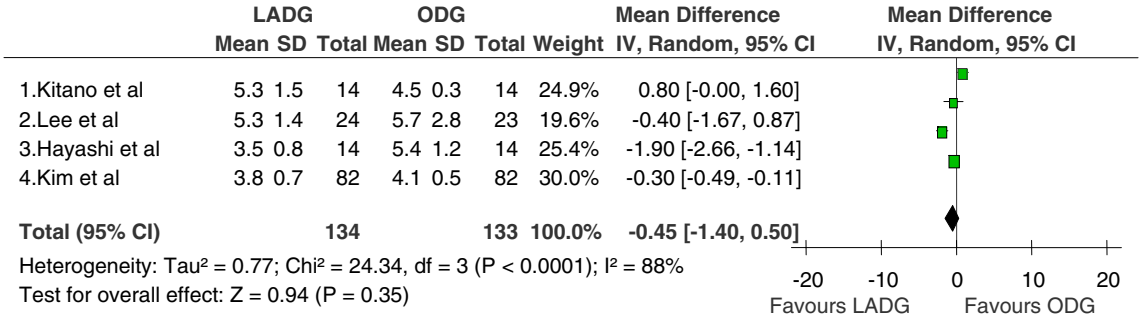
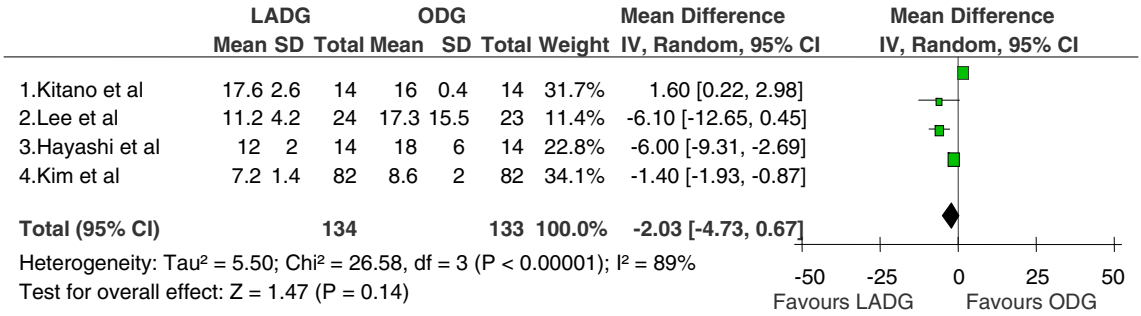


Figure 1 Meta-analysis of laparoscopy-assisted distal gastrectomy (LADG) and open distal gastrectomy (ODG) for early gastric cancer. *SD* standard deviation, *n* number of patients, *WMD* weight mean difference, *OR* Odds Ratio

4. time to oral intake (days)



5. period of hospital stay (days)



6. frequency of analgesic administration (times)

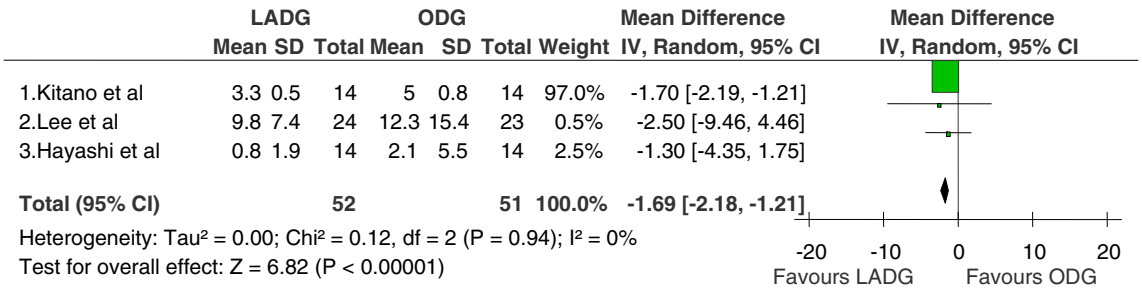


Figure 1 (continued.)

Frequency of Analgesic Administration

In all the RCTs, the patients received analgesic injections after the operation. Epidural anesthesia was achieved in patients in three of the RCTs. Of the four RCTs, the number of RCTs that recorded the frequency of analgesic administration,[13–15] dose of analgesics,[13,16] and duration of anesthesia[14,15] was three, two, and two, respectively. The frequency of analgesic administration did not differ significantly between the two groups. However, analysis of the pooled data revealed that this frequency was 1.69-fold lower in the LADG group (WMD=−1.69; 95% CI=−2.18 to −1.21; $p<0.00001$).

Complications

All the four RCTs reported postoperative complications. The total number of patients who developed wound

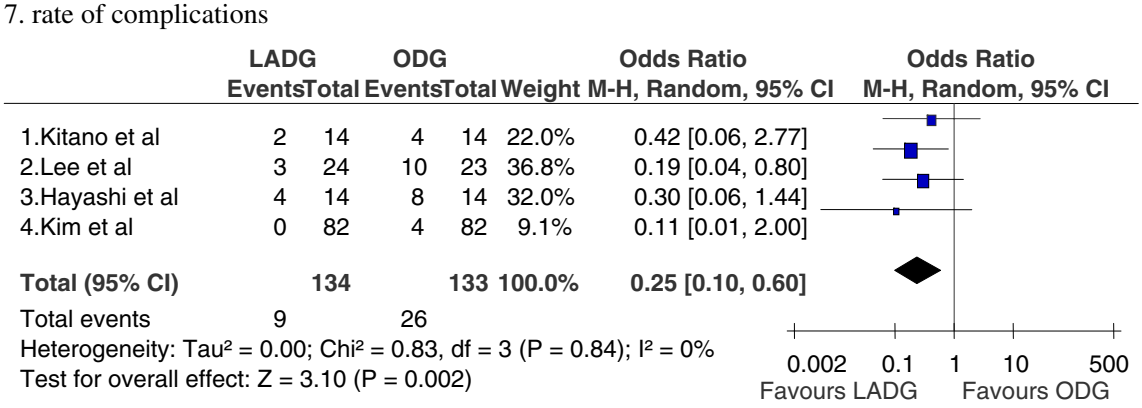


Figure 1 (continued.)

infections, anastomotic leakage, pulmonary atelectasis, and pleural effusion after LADG was one, zero, four, and two, respectively; the corresponding numbers for the abovementioned complications after ODG were two, two, 12, and two, respectively. The results of one RCT indicated that the complication rate was significantly higher after ODG than after LADG. Analysis of the pooled data revealed that the incidence of all the abovementioned complications was significantly higher in the ODG group than in the LADG group (OR=0.25; 95% CI=0.10-0.60; p=0.002); in particular, the incidence of pulmonary ateectasis tended to be higher in the ODG group than in the LADG group (p= 0.05).

Tumor Recurrence

Tumor recurrence was observed in one patient after ODG; computed tomography revealed liver metastasis during the 1-year follow-up.

Mortality

Thirty-day mortality was not observed in any of the RCTs.

Heterogeneity

Significant heterogeneity was detected between the studies with respect to the four following factors: operative time, intraoperative blood loss, time required for resumption of oral intake, and duration of hospital stay.

Discussion

Several retrospective studies have analyzed the short-term outcome of LADG;[10,19,20] however, the advantages of LADG for treating malignancies remain controversial because of a lack of large-scale studies.[7] The aim of this study is therefore to determine the advantages of LADG over ODG by analyzing the data pooled from the four RCTs.

This meta-analysis revealed that the operative time for LADG was significantly greater than that for ODG. This finding could be attributable to the lack of tactile sensation, complexity, and the advanced techniques required for LADG involving systemic lymphadenectomy.[21] LADG with systemic lymphadenectomy is considered to be technically more complicated than other laparoscopic procedures such as laparoscopic cholecystectomy and colectomy because it necessitates identification of a number of major vessels and extensive lymph node dissection. Further, learning curves are associated with LADG. The operative time for LADG for treating gastric cancer depends on the following factors: LADG experience, knowledge of the laparoscopic system and instruments and familiarity with the same, and the skill of the surgeon.[22] Furthermore, when this technique is performed by a skilled and experienced surgeon, the operative time for LADG is similar to that for ODG.[23] In the near future, the operative time for LADG is expected to reduce with advancements in surgical techniques and laparoscopic devices.

As observed in three RCTs, intraoperative blood loss was significantly lesser in the LADG group than in the ODG group. This difference may be attributable to the use of a laparoscopic device and better detection of large and small vessels due to the greater field of view in the former procedure. The decreased intraoperative blood loss in LADG may reduce the need for transfusions and may thus lower the risk of recurrence in patients.[24]

Analysis of the pooled data revealed that the number of harvested lymph nodes was significantly smaller in the LADG group than the ODG group, although this difference was significant only in one of the four RCTs. Miura et al. showed that the number of lymph nodes retrieved from the perigastric region along the major curvature and the retroperitoneal region (second-tier nodes) along the celiac

and splenic arteries was significantly smaller in the LADG group than in the ODG group.[25]

Further, two of the four RCTs reported that resumption of oral intake was significantly earlier in the LADG group than in the ODG group. However, analysis of the pooled data did not reveal any significant difference in this regard. In two RCTs, the duration of hospital stay was found to be shorter for the LADG group than for the ODG group, and analysis of the pooled data did not reveal any significant difference in this regard. These findings imply that the time required for patients to resume daily activities may not be lesser after LADG than after ODG.

Although the frequency of analgesic administration between the LADG and ODG groups in three RCTs was not significant, analysis of the pooled data revealed that the frequency was significantly lower in the LADG group than in the ODG group. The wounds created during LADG are smaller than those created during ODG, and this may necessitate less analgesic administration. The perioperative stress level is lower when surgery is less painful and the patients require less time to resume their daily life activities. Kim et al. reported that along with cosmetic advantages, LADG provides psychological and physical benefits.[16]

This meta-analysis revealed that the rate of complications in the LADG group was significantly lower than that in the ODG group (75%). A small number of patients developed surgical site infections such as wound infection and anastomotic leakage. Analysis of the pooled data revealed that the rate of pulmonary atelectasis tended to be higher in the ODG group than in the LADG group. Lee reported that the incidence of pulmonary complications was significantly lesser after LADG than after ODG.[15] Kitano showed that pulmonary function was impaired to a lesser degree after LADG.[13] The lower level of the perioperative pain after LADG than after ODG may be related with a lower tendency of pulmonary atelectasis. Thus, LADG may be advantageous over ODG because the former results in a lesser degree of pulmonary function impairment and is associated with a lower risk of complications.

The results of this study indicate that LADG is less invasive than ODG because the former results in decreased blood loss and is associated with a decreased frequency of analgesic administration and a low risk of complications; however, the results do not indicate that patients who underwent LADG recover earlier than those who underwent ODG because the time required for resumption of oral intake and duration of hospital stay did not significantly differ between the two groups. Further, the operative time for LADG was found to be significantly greater and the number of harvested lymph nodes lesser as compared to ODG.

A significant heterogeneity was observed between the four RCTs with regard to the operative time, intraoperative blood loss, time required for resumption of oral intake, and duration of hospital stay, and this finding may be attributable to variations in surgeon skill, extent of lymph node dissection, and the stage of the learning curve at which the surgeries were performed. There were no incidences of 30-day mortality in all the studies. However, recurrence was observed in only one patient during the short-term follow-up period after ODG.

Therefore, additional RCTs that compare LADG and ODG and investigate the long-term oncological outcomes of LADG are required to determine the advantages of LADG over ODG.

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ORIGINAL ARTICLE

Single-Incision Pediatric Endosurgical (SIPES) Versus Conventional Laparoscopic Pyloromyotomy: A Single-Surgeon Experience

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Abstract
Background Pyloromyotomy by single-incision pediatric endosurgery (SIPES) is a new technique that leaves virtually no appreciable scar. So far, it has not been compared to conventional laparoscopic (CL) pyloromyotomy. This study compares the results of the first 15 SIPES pyloromyotomies of a surgeon to his last 15 CL cases.
Methods Data were collected on all SIPES pyloromyotomies. Age, gender, operative time, estimated blood loss, conversion/complication rate, and outcome in the SIPES patients were compared to the CL cohort.
Results There was no difference in age, weight, gender, blood loss, or hospital stay. A trend toward shorter operating time was found in the CL group (21.7 ± 9.9 versus 30.3 ± 15.8, $p=0.08$, 95%CI 20.9–39.7 min). Two mucosal perforations occurred in the SIPES cohort. Both cases were converted to conventional laparoscopy, the defect was repaired, and both patients had an uncomplicated postoperative course. There were no wound infections or conversions to open surgery. Parents were uniformly pleased with the cosmetic results of SIPES.
Conclusion SIPES pyloromyotomy may have a higher perforation rate than the CL approach. If recognized, a laparoscopic repair is feasible. Improved cosmesis must be carefully weighed against the potentially increased risks of SIPES versus conventional laparoscopic pyloromyotomy.

Keywords Single incision · Laparoscopy · Pyloromyotomy · Infant

Introduction

Pyloromyotomy by single-incision pediatric endosurgery (SIPES) has recently been described[1] and is a new laparoscopic approach that leaves virtually no appreciable scar. More than 25 of these procedures have been performed in our hospital so far. To date, studies comparing conventional laparoscopic and SIPES pyloromyotomy have not been published.

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In order to evaluate the risks and benefits of SIPES pyloromyotomy and whether improved cosmesis is worth giving up the advantages of conventional laparoscopic instrument triangulation, the results of the first 15 SIPES pyloromyotomies of a single surgeon were compared to those of the surgeon's last 15 conventional laparoscopic cases.

Material and Methods

After IRB approval (protocol no. X090814001), data were prospectively collected on all SIPES pyloromyotomies performed at our institution, including age, gender, operative time, estimated blood loss, conversion and complication rate, as well as time to hospital discharge reflecting time to full oral feeds. Clinical outcome and parent satisfaction at ambulatory follow-up 1 to 4 weeks later was assessed as well. Data for the conventional laparoscopic pyloromyotomies were collected by retrospective

chart review. The parameters of the surgeon's first 15 SIPES cases were compared to his last 15 conventional laparoscopic cases. Dichotomous variables were compared using Fischer's exact test. Continuous variables were analyzed by Student's t test. A p value of <0.05 was considered significant.

The diagnosis of pyloric stenosis was confirmed by ultrasound in all patients. A muscular wall thickness of over 4.0 mm or a pyloric length of 1.6 cm or greater was considered positive for the diagnosis. The patients were admitted for iv hydration and the surgery was performed once the serum bicarbonate level was below 30 mg/dl and the chloride concentration was above 90 mmol/l. The technique for SIPES pyloromyotomy has been previously described,[1] while the technique of laparoscopic pyloromyotomy has been well established and evaluated at our institution.[2,3] The main difference of the two techniques was the location of the 3-mm working instruments. In the conventional laparoscopic approach, these were placed into the abdomen through separate full-thickness stab incisions in the right and left upper quadrants. In the SIPES procedure, they were introduced through a single 1-cm horizontal skin incision in the umbilicus, lateral on both sides of the optical port (Fig. 1).

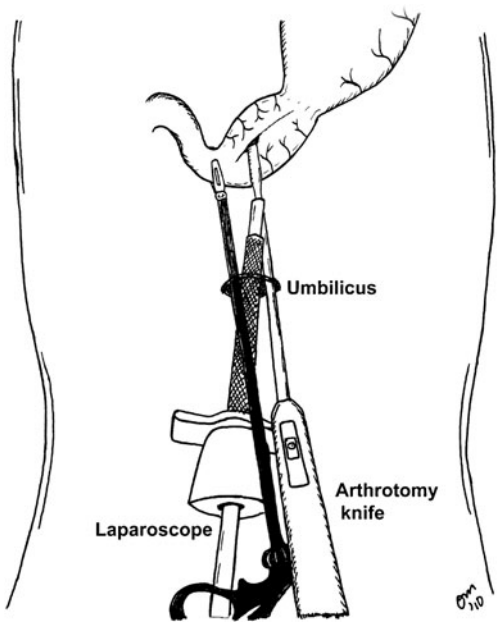

Figure 1 Instrument configuration for SIPES pyloromyotomy. The pylorus is stabilized by holding the proximal duodenum with a grasper in the surgeon's left hand. This orients the pylorus in an oblique fashion toward the left upper quadrant, which facilitates incising the serosa longitudinally. The arthrotomy knife is then replaced by a second grasper to bluntly spread the muscle layer down to the submucosa.

Results

There was no significant difference between the groups in age, weight, gender, pyloric dimensions, blood loss, complication rate, or length of stay (Table 1). A trend toward shorter operating time was found in the conventional laparoscopic group (21.7 ± 9.9 versus 30.3 ± 15.8 min, p=0.08, 95%CI 20.9–39.7 min).

Two perforations occurred in the SIPES cohort. In one case, after completing the spread of the muscular layers, there was a small perforation visible in the pyloric mucosa at the duodenal aspect. The case was immediately converted to angulated conventional laparoscopy with two 3-mm stab incisions in the right and left upper quadrants. The defect was closed using two simple 4–0 polyglactin sutures using intracorporeal knot tying. Fibrin glue was applied to the muscular gap and an omental patch was placed onto the pylorus for reinforcement. In the second patient, the pyloromyotomy was completed using the single-incision approach without difficulty. Upon inspecting the pylorus, a small traumatic full-thickness perforation was noticed in the anterior proximal duodenum where the left-hand grasper had been placed to stabilize the pylorus during the cut and spread. After converting to conventional laparoscopy, the defect was sutured using three inverting (Lambert-type) 4–0 polyglactin sutures. Both patients were kept NPO overnight with a nasogastric tube in place to gravity drainage. The following morning, an upper gastrointestinal contrast study was obtained, which showed normal passage of contrast and no leak in both cases. The patients were given ad lib feeds and discharged home in the afternoon of the first postoperative day.

When both patients with perforation were excluded from the statistical analysis, the operation times for SIPES and laparoscopic pyloromyotomy were more similar (25.2 ± 9.4 versus 21.7 ± 9.9 min, respectively, p=0.34).

There were no wound infections or conversions to open surgery in either group. One patient was readmitted with persistent vomiting after conventional laparoscopy, but eventually discharged home on ranitidine and metoclopramide for gastroesophageal reflux.

All patients were seen in our ambulatory clinic 1 to 3 weeks after the operation. Parents were uniformly pleased with the cosmetic results of SIPES. Upon questioning, the parents of all 15 patients in whom the SIPES approach was attempted said they would chose the procedure again if a future sibling required a pyloromyotomy.

Discussion

Single-incision laparoscopy is becoming a routine approach for many standard surgical procedures such as appendecto-

Table 1 Comparison of SIPES Versus Conventional Laparoscopic Pyloromyotomy

	SIPES (n=15)	Laparoscopic (n=15)	p
Age (days)	43 ± 25	38 ± 15	0.48
Gender (female)	3	3	1
Weight (kg)	4.1 ± 0.5	4.0 ± 1.2	0.77
Pyloric length (mm)	22.1 ± 4.7	21.5 ± 4.8	0.73
Pyloric width (mm)	4.7 ± 0.6	4.5 ± 0.9	0.48
OP time cut-to-close (min)	30.3 ± 15.8	21.7 ± 9.9	0.08
Perforation rate	2/15	0/15	0.24
Readmission rate	0/15	1/15	0.50
EBL (ml)	1.3 ± 0.5	1.3 ± 0.6	1
LOS (days)	1.1 ± 0.3	1.3 ± 0.5	0.2

my[4] and cholecystectomy.[5] Pyloromyotomy is one of the most frequently performed operations in pediatric surgery. Since March 2009, we have offered single-incision endosurgical pyloromyotomy to our patient, and our initial experience has recently been published.[1]

In this study, the cases of a single surgeon were included to minimize the effect of technical variability, personal experience, and instrumentation preference on the outcomes and thereby make the study cohorts more comparable. Because the single-incision approach was offered to all parents after March 2009, and all parents agreed to it, selection bias was avoided. This is confirmed by the comparable preoperative characteristics of both groups.

Likewise, there was no statistical difference in the outcome variables. The longer mean operating time in the SIPES group was mostly due to conversion to triangulated laparoscopy and the repair of the defect in the patients with perforation. However, the SIPES operating times were within the mean operating times of conventional laparoscopic pyloromyotomy (20 to 31 min) reported in the literature.[6–8]

Although not statistically proven, SIPES pyloromyotomy may have a higher perforation rate than the conventional laparoscopy. A high index of suspicion for this problem is warranted because if it is recognized intraoperatively, a laparoscopic repair can be performed without postoperative sequellae. It is crucial to inspect the antrum, the pylorus along with the exposed mucosa, as well as the duodenum for any potential injuries after the completed pyloromyotomy. As in the laparoscopic procedure, care must be taken not to crush or stab the duodenal wall when stabilizing it with the left-hand grasper.

In the literature, a perforation rate as high as 8% to 9% has been reported for conventional laparoscopic pyloromyotomy.[9–11] Nevertheless, the rate of two perforations in the 15 SIPES patients seem quite high, especially when comparing it to the conventional laparoscopic control group in this study. Partially, they may be attributed to the initial learning curve of a new technique. According to a study by Kim,[12] the learning curve for conventional laparoscopic pyloromyotomy is the steepest in the first 15 cases and plateaus after about 30 cases. If this is correspondingly applicable to SIPES pyloromyotomy, the complication rate should decrease in the future.

Due to the possibility of perforation, SIPES pyloromyotomy should be done in centers where laparoscopic management of complications is possible. Otherwise, conversion to an open procedure would be necessary, which could increase morbidity and ultimately decrease parent satisfaction. When obtaining informed consent, it should be clearly stated that there may be a higher complication rate for SIPES and that conversion to conventional triangulated laparoscopy or an open surgical procedure is possible.

Correspondingly, a surgeon should not hesitate to convert if the SIPES operation becomes difficult or endoscopic vision is impaired. Some suggestions that may help facilitate the SIPES procedure are the use of a long endoscope with 45° optical angulation (to spatially separate the cameraman's hand from the surgeon's as much as possible) and working instruments of different lengths (to separate the surgeon's hands from each other). In general, a more longitudinal working axis can be beneficial in SIPES cases as well. This can be accomplished by lining up the pylorus for the cut and spread in an oblique fashion, with the antral side pointing toward one to two o'clock instead of the more conventional horizontal alignment.[1]

Interestingly, one set of parents had heard of single-incision laparoscopy from a popular press article they had encountered on the Internet. The other parents did not comment on their knowledge of single-incision endosurgery preoperatively. None specifically asked for a single-incision approach.

A drawback of this study is that parent satisfaction was not formally quantitated in the SIPES group. Furthermore, data on parent satisfaction were not consistently queried or recorded in the retrospective conventional laparoscopic patients.

Conclusion

If performed with care, SIPES pyloromyotomy is a reasonable alternative to the standard laparoscopic approach, leaving almost no appreciable scar. Parent satisfaction is extremely high. However, improved cosmesis must be carefully weighed against a potentially higher perforation rate. A decline in the complication rate should be observed before SIPES pyloromyotomy can be universally recommended. The introduction of novel angulated instruments may help simplify the operation in the future. Ultimately, the parent's expectations and choices will determine whether SIPES pyloromyotomy will become a popular treatment option.

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ORIGINAL ARTICLE

Benefit of Post-operative Surveillance for Recurrence after Curative Resection for Gastric Cancer

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Abstract
Background Although most clinicians perform surveillance after gastrectomy, there is no consensus on the optimal follow-up schedule. This study aimed to evaluate the benefit of postoperative surveillance for recurrence after curative resection for gastric cancer.
Method We retrospectively studied 110 patients who had recurrences after undergoing curative gastrectomies between 2000 and 2004 at Korea University Hospital. We analyzed the clinico-pathologic factors and oncologic results according to the presence of recurrence symptoms.
Results Fifty-five (50%) patients had symptomatic recurrences. There were significant differences in recurrence patterns; locoregional (29.1%) and peritoneal recurrences (27.3%) were dominant in asymptomatic group; peritoneal (47.3%) and hematogenous recurrences (25.5%) were dominant in symptomatic group. The median recurrence-free survival was not different for both groups ($p=0.054$). However, median overall and post-recurrence survival was poor in the symptomatic group ($p=0.004$, $p<0.001$). The presence of symptoms and short disease-free survival were independent poor prognostic factors for post-recurrence survival.
Conclusion Patients with asymptomatic recurrences could have increased survival compared to symptomatic patients. Although our post-operative surveillance could not be any benefit to improve outcomes for recurrent gastric cancer, it is important to discriminate the nature of recurrent gastric cancer by the presence of symptoms for planning further treatment.

Keywords Gastric cancer · Recurrence · Surveillance

Introduction

Although the value of post-operative surveillance remains controversial in cancer management, post-operative follow-up program is recommended for nearly all cancers in the National Comprehensive Cancer Network.[1] Three main reasons for follow-up are to detect complications associated with the surgery, to collect outcome data, and to diagnose recurrent disease. Many surgeons and medical units endeavor to detect recurrences at an earlier and asymptomatic stage in the hope that this will lead to improve outcomes. However, the evidence is weak, and many surgeons have questioned the use of intensive follow-up programs.[2–4] In colorectal cancer, several randomized controlled trials and meta-analyses have demonstrated an overall survival advantage associated with detection of recurrences through intensive follow-up.[3,5,6] Follow-up guidelines are available for other cancers, such as breast[7,8] and lung,[9] for the detection of early recurrences to achieve survival advantage, as compared with patients who present later with symptomatic recurrences. In some studies, an intense post-operative surveillance program for gastric cancer patients has been successful in detecting asymptomatic recurrences earlier than symptomatic recurrences. However, the overall survival was not increased in these studies and the survival after recurrence seemed to be increased because of lead time bias.[10–12] In another study,

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follow-up could not identify early asymptomatic recurrences and patients with symptomatic recurrences had more aggressive disease with a poorer survival.[13] Therefore, the value of intensive follow-up for gastric cancer patients after curative resection was not determined and there is no consensus regarding the follow-up program. Also the treatment program was not established and the result was poor in recurrent gastric cancer patients.[14,15] Anyway, most clinicians perform surveillance after gastrectomy for recurrent gastric cancer treatment. We retrospectively reviewed the long-term outcomes of patients undergoing follow-up and determined whether or not a routine intensive follow-up program enhances survival after curative resection of gastric carcinoma.

Methods

A prospectively compiled database was searched for patients with gastric carcinoma who had recurrences after undergoing a curative (R0) resection between 2000 and 2004 at Korea University Hospital. Of 738 patients undergoing curative resection, 112 patients were confirmed to have recurrent disease in May 2009; of these 112 patients, two were lost to follow-up. The remaining 110 patients were enrolled in this study and they were divided into two groups according to the presence of cancer-related symptoms at the time of a recurrence diagnosed. Curative resection was performed as subtotal or total gastrectomy in accordance to the location of tumor for secure sufficient free resection margin and we performed D2 or more lymph node dissection in all patients. Postoperative adjuvant chemotherapy was performed for pathologically advanced case but no radiation therapy was done.

Symptomatic recurrence was defined as a patient-initiated finding or complaint that resulted in a work-up documenting recurrence, most often detected at a patient-initiated visit. Asymptomatic recurrence was defined as a recurrence discovered by a routine or unprovoked radiographic, laboratory, or endoscopic test, usually in the context of a physician-scheduled visit. The clinicopathologic factors and patterns of recurrence were compared between the two groups. The resected specimens had been examined by pathologists and tumor and lymph node stages were determined by the International Union against Cancer Classification system.[16] The patterns of recurrence were classified as peritoneal, hematogenous, locoregional and distant metastases. Peritoneal recurrences included positive cytology in the ascitic fluid, carcinomatosis, or ovarian metastasis. Hematogenous recurrences were defined by organic metastases including liver, lung, and bone. Locoregional recurrences were in the gastric bed and regional lymph nodes and remnant gastric cancer at the anastomotic site or gastric stump. Distant metastases were defined by the organ site or as distant lymph nodes outside of the regional basin. Recurrences were categorized by the site at initial presentation after an extent of disease evaluation was completed. Patients with multiple tumors within a single category were documented as single-site disease in that category. Patients with recurrent disease in more than one of the categories were documented as having multiple site recurrences, and each of the appropriate categories was recorded. The follow-up program schedule consisted of history and physical examination every 3 months in the first postoperative year, every 6 months in the second post-operative year, and annually thereafter for at least 5 years. Hematologic and blood chemistry panels, and blood tests for tumor markers were examined every 6 months in the first and second years, and annually thereafter. Chest radiography was performed annually and abdominal computed tomography was performed every 6 months in the first year and annually thereafter until 5 years. Endoscopy was performed annually to screen for cancer in the gastric remnant. The length of follow-up was defined as the interval between surgery and review of patients in May 2009; and for those patients who had died from recurrences of gastric cancer, the length of follow-up was defined as the interval between surgery and death. The recurrence-free survival from curative gastrectomy to recurrence, the post-recurrence survival from recurrence to death, and the overall survival from curative gastrectomy to death were estimated using the Kaplan-Meier method and for each of these time intervals, patients with symptomatic recurrences were compared with asymptomatic recurrences using a log-rank test. For statistical evaluation of the differences between the two groups, a chi-square test was used for comparison of percentage frequencies, and student's t test was used for comparison of means in continuous variables. Univariate analysis was performed using the log-rank test to determine the prognostic variables associated with early death after recurrence. Multivariate analysis was performed using Cox proportional hazards regression for variables with statistical significance in univariate analysis. The SPSS software for Windows program was used for statistical analyses and a P value$\leq$ 0.05 was considered to be statistically significant.

Results

Clinico-pathologic Factors and Patterns of Recurrence According to the Presence of Symptoms

Fifty-five patients (50%) were asymptomatic when the recurrence was detected, whereas 55 patients had symptoms

suggesting recurrence at the time they sought evaluation at the hospital. Patient demographics and clinico-pathologic variables at the time of the initial surgery were compared between patients with asymptomatic and symptomatic recurrences, and are shown in Table 1. The average number of resected lymph nodes between two groups showed no significant difference (49.02±17.34 vs. 43.69±11.49, p=0.06). No differences in clinico-pathologic variables were evident between the two groups with the exception of lymph node metastases. Specifically, the asymptomatic group had more prevalent N1 lymph node metastases (43.6%), whereas N2 lymph node metastases were most prevalent (41.8%) in the symptomatic group. In our study group, we performed adjuvant chemotherapy in 56 patients and no radiation therapy. In asymptomatic group, more patients had postoperative adjuvant chemotherapy comparing symptomatic patients (p=0.02). When the patterns of recurrence were compared between two groups, the asymptomatic group had mainly locoregional (29.1%) and peritoneal recurrence (27.3%). In the symptomatic group, the most prevalent pattern of recurrence was peritoneal (47.3%) and hematogenous (25.5%) which showed a statistical difference between two groups (Table 2).

When the tumor was divided into differentiated and undifferentiated by histologic type, the recurrence pattern was closely associated with tumor differentiation. In undifferentiated tumor, the more prevalent recurrence patterns were peritoneal seeding and locoregional recurrence. Otherwise, hematogenous spreading was more prevalent in differentiated type tumor.

Table 1 Clinico-pathologic Factors According to the Presence of Symptoms at the Detection of Gastric Cancer Recurrence

Variable	Asymptomatic recurrence (n=55)	Symptomatic recurrence (n=55)	p value
Gender			
Male	38 (69.1%)	30 (54.5%)	0.116
Female	17 (30.9%)	25 (45.5%)	
Age, mean	55.36±12.02	56.22±14.84	0.741
Location			
Upper	10 (18.2%)	8 (14.5%)	0.809
Middle	21 (38.2%)	20 (36.4%)	
Lower	24 (43.6%)	27 (49.1%)	
Extent of resection			
Subtotal	27 (49.1%)	25 (45.5%)	0.538
Total	28 (50.9%)	29 (52.7%)	
Other	0	1 (1.8%)	
Number of dissected lymph nodes (mean ± SD)	49.02±17.34	43.69±11.49	0.060
Adjuvant chemotherapy			
No	19 (34.5%)	35 (63.6%)	0.002*
Yes	36 (65.5%)	20 (36.4%)	
Depth of invasion			
T1	4 (7.3%)	1 (1.8%)	0.456
T2	9 (16.4%)	7 (12.7%)	
T3	37 (67.3%)	43 (78.2%)	
T4	5 (9.1%)	4(7.3%)	
Lymph node metastasis			
N0	3 (5.5%)	7 (12.7%)	0.02*
N1	24 (43.6%)	15 (27.3%)	
N2	11 (20.0%)	23 (41.8%)	
N3	17 (30.9%)	10 (18.2%)	
UICC stage			
IA	1 (1.8%)	1(1.8%)	0.084
IB	3 (5.5%)	2(3.6%)	
II	7 (12.7%)	7 (12.7%)	
IIIA	16 (29.1%)	14 (25.5%)	
IIIB	7 (12.7%)	20 (36.4%)	
IV	21 (38.2%)	11 (20.0%)	
Lymph-vascular invasion			
No	26 (47.3%)	25 (45.5)	0.848
Yes	29 (52.7%)	30 (54.5)	

*p<0.05; statistically significant

Median Time-to-recurrence and Post-recurrence Survival

Table 3 summarizes the median time-to-recurrence and post-recurrence survival time according to the presence of symptoms at the time of detection of gastric cancer recurrence. Figure 1 demonstrates the recurrence-free survival from curative resection to recurrence for both asymptomatic and symptomatic patients. The median time from resection to recurrence was not significantly different between the two groups (asymptomatic group, 27.0±7.5 months; and symptomatic group, 24.0±3.3 months; p=0.054). Figure 2 demonstrates the post-recurrence survival from recurrence to death. Asymptomatic patients had a longer median post-recurrence survival time after recurrence (15.1±2.1 months) than symptomatic patients (7.2±1.6 months; p<0.001). As demonstrated in Fig. 3, the median overall survival from resection to death was 43.3±

Table 2 Main Pattern of Recurrence According to by the Presence of Symptoms at the Detection of Gastric Cancer Recurrence

Recurrence	Asymptomatic recurrence (n=55)	Symptomatic recurrence (n=55)
Peritoneal recurrence	15 (27.3%)	26 (47.3%)
Hematogenous recurrence	10 (18.2%)	14 (25.5%)
Locoregional recurrence	16 (29.1%)	11 (20.0%)
Distant lymph node	14 (25.5%)	4 (7.3%)

*P=0.018; statistically different

Table 3 Median Time to Recurrence and Post-recurrence Survival Time According to the Presence of Symptoms at the Detection of Gastric Cancer Recurrence

	Asymptomatic	Symptomatic	p value
Resection ↕ Recurrence	**27.0±7.5 months**	**24.0±3.3 months**	**0.054**
Recurrence ↕ Death	**15.1±2.1 months**	**7.2±1.6 months**	<0.001*
Overall	**43.3±15.5 months**	**34.0±4.1 months**	0.004*

*p<0.05 ; statistically significant

15.5 months for asymptomatic patients and 34.0±4.1 months for symptomatic patients (p=0.004).

Treatment Patterns and Prognostic Factors for Post-recurrence Survival

Table 4 demonstrates the treatment patterns after the detection of gastric cancer recurrence. Curative resection was achieved in five patients. Four patients had remnant gastric cancer; these patients were asymptomatic and recurrence was detected through routine endoscopic examination. One patient had clinical symptoms suggestive of acute appendicitis and a solitary appendiceal metastasis was suspected at the time of surgery. He underwent a curative right hemicolectomy and post-operative adjuvant chemotherapy, and had no recurrence until a recent follow-up evaluation. Two patients underwent adjuvant chemotherapy after re-operation among patients who underwent curative resection. Palliative resection was performed in ten patients; four patients had asymptomatic recurrences and six patients

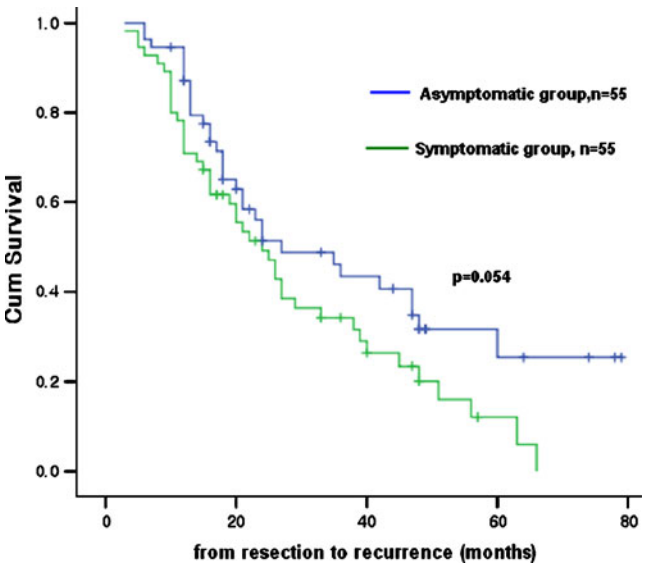

Figure 1 Recurrence-free survival curves from resection to recurrence according to the presence of symptom at the detection of gastric cancer recurrence.

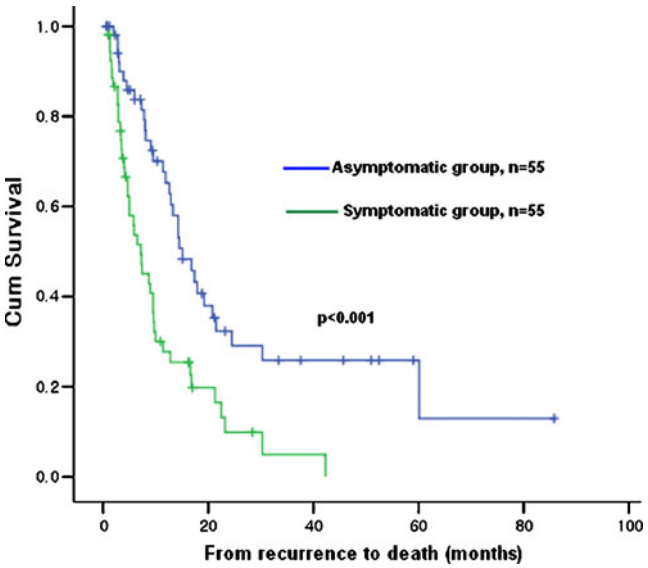

Figure 2 Post-recurrence survival curves from recurrence to death according to the presence of symptom at the detection of gastric cancer recurrence.

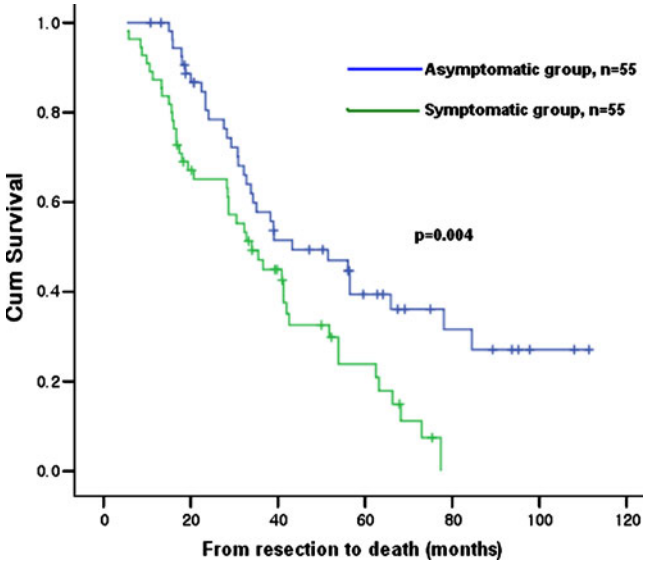

Figure 3 Overall survival curves from resection to death according to the presence of symptom at the detection of gastric cancer recurrence.

had symptomatic recurrences. Eight patients underwent adjuvant chemotherapy after re-operation among patients who underwent palliative resection. Thirteen patients underwent palliative bypass or diverting procedures; six patients in the asymptomatic group underwent palliative bypass surgery, ileostomy, or colostomy. Seven patients in the symptomatic group also underwent the same operative procedure for relieving symptoms of malignant obstruction. Six patients underwent adjuvant chemotherapy after re-operation among patients who underwent palliative bypass or diverting procedures. The total number of patients who underwent chemotherapy was 56. Among the 56 patients, the number of patients who underwent post-recurrence chemotherapy alone was 40 (36.4%); 28 patients (50.9%) had asymptomatic recurrences and 12 patients (21.8%) had symptomatic recurrences.

Forty-two patients had no treatment after recurrence: 13 patients (23.6%) had asymptomatic recurrences and 29 patients (52.7%) had symptomatic recurrences.

Table 5 demonstrates the potential predictors of post-recurrence survival, including characteristics of the primary tumor and factors associated with recurrence, such as the presence of symptoms, the patterns of recurrence, and post-recurrence treatment. By univariate analysis, predictors of poor post-recurrence survival were advanced stage (UICC III/IV versus I/II), the presence of lymphatic and/or vascular tumor invasion, the presence of recurrence symptoms, the pattern of re-operation, multiplicity of recurrence sites and ≤12 month disease-free interval. Among these six variables that predict poor post-recurrence survival as determined by univariate analysis, the presence of recurrent symptoms and ≤12 month disease-free interval were independent prognostic factors by multivariate analysis ($p=0.003$ and $p<0.001$, respectively).

Discussion

In general, the potential value of a routine surveillance program in patients who have undergone curative resection for gastric cancer is to detect recurrences in the early and asymptomatic period. Early detection of cancer recurrence may be associated with improved survival because it may provide an opportunity for treatment to be initiated while the patient's condition is sufficiently stable to receive effective therapy. However, there have been no effective treatments for recurrent gastric cancer, except curative resection. Kodera and colleagues[10] attempted to identify the survival benefit of follow-up surveillance for recurrence after curative gastric cancer surgery. In their study, a defined group of patients with asymptomatic recurrence was identified earlier than patients who presented with symptomatic recurrences, although no survival advantage was provided. Bennett et al.[13] reported that follow-up surveillance could not identify asymptomatic recurrences earlier than symptomatic recurrences and the median recurrence-free survival was the same in patients in both groups. They also found that asymptomatic patients had a

Table 4 Treatment of Recurrence According to the Presence of Symptoms at the Detection of Gastric Cancer Recurrence

Treatment	Total ($n=110$)	Asymptomatic ($n=55$)	Symptomatic ($n=55$)
Curative resection + chemotherapy	2 (1.8%)	1 (1.8%)	1 (1.8%)
Curative resection	3 (2.7%)	3 (5.5%)	0 (0%)
Palliative resection + chemotherapy	8 (7.3%)	4 (7.3%)	4 (7.3%)
Palliative resection	2 (1.8%)	0 (0%)	2 (3.6%)
Bypass operation + chemotherapy	3 (2.7%)	1 (1.8%)	2 (3.6%)
Ileostomy or colostomy + chemotherapy	3 (2.7%)	2 (3.6%)	1 (1.8%)
Ileostomy or colostomy	7 (6.4%)	3 (5.5%)	4 (7.3%)
Chemotherapy	40 (36.4%)	28 (50.9%)	12 (21.8%)
No treatment	42 (38.2%)	13 (23.6%)	29 (52.7%)

Table 5 Univariate and Multivariate Analysis of the Prognostic Factors for Post-recurrence Survival

Variable	No. of patients	Univariate *p* value	Multivariate *p*value	Hazard ratio (95% CI)
Gender				
Male	68	0.702		
Female	42			
Age				
<40	15	0.826		
40~70	78			
>70	17			
Tumor size				
<7 cm	68	0.315		
≥7 cm	42			
UICC stage				
I/II	21	0.021*	0.100	0.539
III/IV	89			(0.258~1.126)
Adjuvant chemotherapy				
No	54	0.124		
Yes	56			
Recurrence symptom				
Asymptomatic	55	0.004*	0.003*	0.472
Symptomatic	55			(0.286~0.779)
Recurrence pattern				
Peritoneal	41	0.053		
Hematogenous	24			
Locoregional	27			
Distal lymph node	18			
Post-recurrence chemotherapy				
No	54	0.124		
Yes	56	0.047*		
Reoperation			0.226	1.125 (0.598~2.507)
No	82			
Curative resection	5			
Palliative resection	10			
Bypass or diverting operation	13			
Tumor differentiation				
Differentiated	40	0.652		
Undifferentiated	70			
Lymphovascular invasion				
No	51	0.004*	0.068	0.589
Yes	59			(0.333~1.040)
Recurrence sites				
Single	28	0.016*		
Multiple	82			
Peritoneal recurrence				
No	69	0.299		
Yes	41			
Disease-free interval				
≤12 month	26	<0.001*	<0.001*	7.518
>12 month	84			(4.187~13.498)

*$p<0.05$; statistically significant

longer post-recurrence and disease-specific survival than symptomatic patients. They therefore suggested that symptomatic recurrences could be one of the biologically aggressive markers and the impact of detecting asymptomatic recurrences could not be distinguished from the effects of other biologic variables. In our study, the time to relapse in asymptomatic recurrences was not different than symptomatic recurrences.

Almost symptomatic recurrences were detected by routine follow-up consisted with history taking and physical examination and confirmed by further study. Also, the recurrence-free survival in the two groups was not statistically different in two groups. This result is similar to that of the above study and symptomatic recurrence itself is of biological importance. The symptomatic group had more prevalent N2 groups in lymph node metastasis, although no difference was noted in cancer stage between the two groups. Also, the original clinical and pathologic variables were not different in the two recurrent groups. Therefore, the presence of symptoms at the time of detection of recurrence may be an important factor that could affect the post-recurrence outcome in our study group. Peritoneal seeding was considered to be the most common pattern of recurrence in recurrent gastric cancer.[15] However, in early gastric cancer, the hematogenous form was the most prevalent in recent reports.[17] In our study, most recurrent cases had advanced cancer stages when curative resection was done, so peritoneal recurrences were the most prevalent pattern (34.3%). Peritoneal carcinomatosis is usually detected based on symptoms from bowel obstruction and ascites in the follow-up period, because current diagnostic modalities, including conventional computed tomography (CT) and PET/CT scans, cannot reliably detect peritoneal deposits in the early asymptomatic postoperative period.[18] Peritoneal recurrences were more prevalent in the symptomatic group, followed by the hematogeous recurrences. For the asymptomatic group, locoregional recurrences, especially remnant gastric cancer, could be detected by regular endoscopic follow-up in our protocol because the cost of gastroscopy was less expensive in our country when compared with Western countries. Four of five cases of remnant gastric cancer recurrences underwent curative surgery; a routine follow-up surveillance program supplied survival benefit for these patients. Because the life expectancy is prolonged and the incidence of long-term follow-up cases after distal gastrectomy is increased, there has been increased concern about remnant gastric cancer. The diagnosis and curative resection of remnant gastric cancers at the early stage through appropriate follow-up is important to improve survival.[19] When considering no effective treatment exists, except curative resection in recurrent gastric cancer, an appropriate follow-up program for detecting remnant gastric cancer is

important to improve outcomes for gastric cancer surveillance. In the treatment of hepatic metastases; in colorectal cancer, hepatic resection is accepted and survival is achieved in up to 40% of cases.[20,21] However, in gastric cancer, the results of resections for hepatic metastases are poor because the majority of hepatic recurrences are incurable and disseminated through other pathways.[22] In our cases, no resection was done for hepatic metastasis; rather palliative chemotherapy was done considering the performance status of the patients. Previous randomized trials demonstrated that chemotherapy has improved survival in patients with recurrent and unresectable gastric cancer when compared with supportive treatment.[23,24] In our cases, palliative chemotherapy was performed in about 50% of recurrences and more frequent in asymptomatic recurrences, but no survival benefit was achieved when compared with other treatment modalities. In many centers, chemotherapy has become the standard treatment for recurrent gastric cancer in the hope of improving survival and quality of life. However, there is no evidence that treatment at an earlier stage improves outcomes and chemotherapy cannot improve survival in the group with recurrences detected prior to becoming symptomatic in the context of aggressive follow-up to detect asymptomatic disease.[10,12] In our study, the prognostic factors for post-recurrence survival in recurrent gastric cancer were investigated and the presence of recurrent symptoms and short (≤12 months) disease-free interval were shown to be independent prognostic factors. The characteristics of the two factors associated with recurrence are in agreement with the more aggressive nature of tumor biology and they are associated with faster dissemination of tumor emboli in the systemic circulation and progressing to end-stage tumor status. Other variables that have significance by univariate analysis, such as advanced tumor stage and lympho-vascualr invasion are also representative of aggressive tumor biology, although they have a marginal significance in multivariate analysis. Therefore, the results of this study suggest that the presence of symptoms in postoperative surveillance for recurrence after curative resection for gastric cancer is ultimately a good marker for biologic aggressiveness and an important determinant of post-recurrence survival. Our study was retrospective and did not compare surveillance to no surveillance or compare different surveillance protocols; therefore, no critical data was provided to confirm the benefit of post-operative surveillance program in gastric cancer. Also, most recurrent gastric cancer had no definite treatment except curative resection until now. Therefore, more intensive or frequent surveillance could not benefit these symptomatic recurrent gastric cancer patients in our study.

In our study, asymptomatic patients had more benefit from curative resection and post-recurrence chemotherapy and curative resection of recurrent gastric cancer was almost performed in remnant gastric cancer except one case. However, in multivariate survival analysis, the presence of recurrent symptom was the independent prognostic factor in our study. Therefore, when considering these biases, symptomatic group had a more biologically aggressive disease and poor survival than asymptomatic group.

Although a large randomized trial is needed to determine whether or not the intensive follow-up program has survival and economic benefit, our results suggested that the discrimination of recurrence according to the presence of symptoms could be beneficial for a post-recurrence therapeutic plan.

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ORIGINAL ARTICLE

Anastomotic Sealing by Extracellular Matrices (ECM) Improves Healing of Colonic Anastomoses in the Critical Early Phase

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Abstract
Background Extracellular matrices have proven potential for in vivo tissue regeneration at gastrointestinal luminal organs. In this study, small intestinal submucosa (SIS) was tested as a sealant for colonic anastomoses in a rodent model.
Methods In the rodent model, standard colonic anastomoses in the control group (CG; $n=30$) and anastomoses sealed by omentum ($n=30$) were compared to SIS-sealed anastomoses in the study group (SG; $n=30$). After 4-, 30-, and 90-day macroscopic and microscopic healing, bursting pressure and anastomotic stricture rate were evaluated.
Results The rate of anastomotic dehiscence was 1/10 after 4 days and 0/10 after 30 and 90 days in all groups. In the SG, the bursting pressure was significantly increased after 4 days compared to CG (148±9 vs. 108±8 mmHg; $p>0.05$). Histologically, after 4 days of neovascularization, fibroblast ingrowth and collagen deposition were significantly increased in SG compared to CG. After 30 days, nonsignificant differences were noted in all three parameters. Adhesion rate and anastomotic stricture rate were not significantly affected by SIS sealing after 4, 30, and 90 days.
Conclusion Especially in the critical phase of anastomotic healing up to day 4, anastomotic healing was improved by SIS sealing. SIS sealing did not cause long-term complications.

Keywords Extracellular matrix · Small intestinal submucosa · Anastomosis · Colon · Reinforcement

Introduction

Colonic anastomoses are among the most frequently performed surgical operations in general surgery. Anastomotic leaks are serious complications and a major factor of morbidity and mortality. In the literature, the incidence of anastomotic failure reaches from 0.5–1% at the right hemicolon to 8–23% for low colorectal anastomoses.[1–3] The estimated mortality from anastomotic leakage can be greater than 20% in colorectal anastomoses.[4]

Even though technical modifications have decreased the rate of leakage in these operations, the high mortality and severe morbidity in patients suffering from anastomotic leakage justify the necessity for evaluation of additional methods for decreasing the rate of anastomotic failure in colonic anastomoses. Reinforcement of the anastomosis by wrapping it with an artificial or biological graft has been claimed to be useful.[5] A promising approach for protection of gastrointestinal anastomosis is anastomotic sealing with so-called extracellular matrices (ECM). ECM are acellular, collagenous resorbable scaffolds of biological origin. ECM have been introduced as bioscaffolds for in vivo tissue engineering and regeneration of intestinal tissues. Especially small intestinal submucosa (SIS) has been experimentally evaluated for intestinal tissue engineering by our group and others.[5–8] SIS is a biodegradable, commercially available, acellular, immunologically inert collagen matrix, which is extracted from the submucosal layer of porcine

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small bowel. Different regulatory proteins which play important roles in the promotion of wound healing have been expressed on SIS. Molecules responsible for cellular migration and attachment, like fibronectin and heparin sulfate proteoglycan, and different growth factors, like fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and transforming growth factor (TGF)-β, have been identified in SIS.[9–11] Several experimental studies have been performed to evaluate SIS in substitution and remodeling of defects in various gastrointestinal luminal organs. Recently, our group could demonstrate the feasibility and safety of anastomotic reinforcement by SIS in a large animal model with an observation period of up to 30 days.[12] The aim of this study was to concentrate on the early phase of anastomotic healing and on the long-time effects of ECM sealing on large-bowel anastomotic healing.

Materials and Methods

Animals

The study was approved by the animal care and use committees at the University of Freiburg and the local district government in Freiburg, Germany. All procedures in this study were performed under strict adherence to the German Law of Animal Welfare and met the standards set in the "Guide for care and use of laboratory animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (National Institutes of Health (NIH) Publication No. 86-23, revised 1985). Ninety male Wistar rats (Charles River, Sulzfeld) weighing 180 to 290 g were used for the experiments. They were housed two per cage and were allowed free access to chow until 12 h before operation. During the first four postoperative days, the animals had free access to water and were fed a liquid diet (Osmolite®, Abbot Nutrition, Wiesbaden, Germany) to avoid postoperative impairment of bowel passage.

Experimental Design

The 90 animals were randomly assigned to three groups of 30 animals each:

1. Control group (control)—standard colocolonic anastomosis group
2. Omental group (omentum)—colocolonic anastomosis wrapped by pedunculated omentum
3. SIS group (SIS)—colocolonic anastomosis sealed by a 20×10 mm one-layer SIS patch

In each of the experimental groups, ten rats were sacrificed at fourth, 30th, and 90th postoperative day for investigation of early anastomotic healing and stability and for access and comparison of the long-time course in ECM-sealed anastomoses.

Preparation of SIS

SIS was prepared as previously described.[13] Sections of porcine jejunum were obtained from the local slaughterhouse and immediately after slaughtering placed in 0.9% saline solution. Jejunal sections were then cut into 10-cm lengths and luminally cleaned with 0.9% saline solution. First, the mesenteric tissues were removed from the segment of the small intestine, followed by mechanical removal of the tunica serosa and tunica muscularis from its outer surface by gentle abrasion using a scalpel handle and saline-moistened gauze. The segment was then inverted, and the tunica mucosa was mechanically removed by similar mechanical abrasion and then reverted to its original orientation. The remaining 0.1- to 0.2-mm-thick translucent tube actually consisted of the tunica submucosa. The stratum compactum that originally was in contact with the more superficial luminal mucosa was now the luminal surface of the SIS graft. After sterilization of the SIS graft by 2 h of incubation in 0.1% perchloric acid, it was subsequently rinsed with sterile normal saline and stored in refrigerated 0.05% gentamicin at 4°C. Storage time for the graft materials ranged from 3 days to a maximum of 7 days until the material was used for anastomotic sealing. For evaluation of acellularity and structural surface integrity of each prepared porcine jejunal segment, one 5×5-mm sample was examined by scanning electron microscopy. Only acellular pieces of SIS, without evidence of damage to surface structure on both sides in scanning electron microscope (SEM) were used for further experiments.

Scanning Electron Microscopy

After rinsing in PBS, SIS samples were fixed with 4% buffered formaldehyde for 24 h at room temperature. The samples were then dehydrated in a graded series of acetone, dried in a critical-point dryer, mounted for SEM, and coated with gold in an evaporator unit. Examination was then performed in an LEO 435 VP (LEO Electron Microscopy Ltd., Cambridge, England) scanning electron microscope.

Operative Procedure

The operative procedure was performed under sterile laboratory conditions. The abdomen was shaved and disinfected with polyvidone (Betaisodonna®, Mundipharma, Limburg, Germany). A 3-cm lower midline incision was performed. The descending colon and rectum were identified and exposed. Transection of the descending colon and adjacent

mesentery was performed. Fecal contents were carefully removed with iodine gauze. The anastomosis was performed end to end using 12 inverting interrupted sutures (PDS 6/0, Ethicon, Germany). The distance of the single sutures to the resection margins and the distance between the single sutures were 1–2 mm. In the control group, the anastomosis was anatomically placed in the free abdominal cavity without intentional sealing by any tissue. In the omental group, the anastomosis was wrapped 360° by pedunculated omentum. In order to prevent any early dislocation of the pedunculated omentum, it was fixed with a single 6/0 suture to the colonic segment below the anastomosis. In the SIS group, the anastomosis was wrapped by a 20×10-mm one-layer SIS patch. In order to allow some swelling during early healing, 360° anastomotic sealing was achieved by a 5-mm overlapping of the two ends of the SIS patch at the mesenterial side of the anastomosis without fixing the ends to each other. The porous abluminal surface of the SIS patch was orientated towards the colonic serosa. The dense stratum compactum surface of SIS was adjusted towards the free abdominal cavity. After physiological rearrangement of the abdominal organs, the abdominal cavity was closed in layers with absorbable sutures. The abdominal cavity was closed in the same manner in all groups after completion of the anastomoses.

On the fourth, 30th, or 90th postoperative day, the animals underwent relaparotomy. After induction of anesthesia in a box with isoflurane (4%), animals were killed by cardiac puncture and potassium injection in a lethal dose. The abdomen was opened with a complete midline incision and additionally with a horizontal incision, generating optimal exposure of the operative situs. After exploration for signs of intra-abdominal inflammation, peritonitis, and intra-abdominal abscess, the intra-abdominal adhesions were noted and graded (score 0–3; Table 1). The adhesions around the anastomosis were not dissected, and a 4-cm-long segment containing the anastomosis was removed and carefully cleaned of fecal remnants. After 4 days, the mechanical stability of the anastomoses was determined by measurement of bursting pressure. After 30 or 90 days, information on anastomotic obstruction or stenosis, which could be a long-term complication of anastomotic sealing, was gained by contrast enemas of the anastomotic segments.

Measurement of Bursting Pressure

Mechanical testing of the anastomosis was performed by measuring the bursting pressure. An 18-Fr catheter was inserted into both ends of the anastomotic bowel segment and secured by purse-string sutures. Air was insufflated via one catheter; the other one was connected to a digital manometer (Codman ICP Express, Ethicon, Norderstedt, Germany). The bowel segment was plunged into water, and the bursting pressure was detected by the presence of ascending air bubbles and the abrupt fall of intraluminal pressure.

Radiographic Examination

Contrast enemas of the descending colon were performed by filling the colon with water-soluble contrast agent (Gastrografin®, Fa. Schering, Berlin, Germany). The diameters of the anastomosis and the preanastomotic and postanastomotic segments were evaluated by X-ray analysis. X-rays were performed within 15 min after sacrifice ex situ on the isolated and transected large-bowel segment. Both ends were clamped, and the bowel was filled by cannulation of the proximal segment and enema with contrast agent. X-rays were digitalized, and diameters were measured 1 cm above, at the level of and 1 cm below the anastomosis using an image analysis program (Image J®,

Table 1 Macroscopic Results and Mean Adhesion Scores on the Fourth, 30th, and 90th Postoperative Day

	Control			Omentum			SIS		
	4th POD	30th POD	90th POD	4th POD	30th POD	90th POD	4th POD	30th POD	90th POD
n	10	10	8	9	10	10	10	10	10
Anastomotic dehiscence	1/10	0/10	0/8	1/9	0/10	0/10	1/10	0/10	0/10
Anastomotic obstruction	0/10	0/10	0/8	1/9	0/10	0/10	0/10	0/10	0/10
Intra-abdominal abscess	0/10	0/10	0/8	0/9	0/10	0/10	0/10	0/10	0/10
Adhesion score (0–3)[a]	1.70 (0.26)	0.80 (0.25)	0.89 (0.31)	0.80 (0.26)	1.10 (0.35)	0.33 (0.24)	1.10 (0.29)	1.20 (0.39)	1.10 (0.32)

POD postoperative day

[a] Adhesion score: 0 = no adhesion, 1 = adhesions with one structure, 2 = adhesions with two structures, 3 = adhesions with three or more structures; mean scores with SEM in brackets

NIH, Bethesda, USA). Ex situ radiologic evaluation does not represent physiological conditions; therefore, the findings were judged as artificial, although the conditions were comparable and the radiological observations allow assessment of the degree of stenosis or dilatation at the anastomotic site independent of functional spasms of the colon. An anastomotic index (AI) was calculated for each animal.

$$\mathrm{AI} = \frac{2 \times \text{anastomotic diameter}}{\text{proximal diameter} + \text{distal diameter}}$$

A straight tube will have AI=1.0. Anastomotic stricture and/or proximal dilatation will result in a decreased AI.[14]

Macroscopic Examination

During ex situ examination, the specimen was kept moist by superfusion with 0.9% saline. The descending colon was cut longitudinally along the mesenteric border. At first, the serosal site was checked. Condition and location of the SIS patch, macroscopic vascularization of the patch, and occurrence of bowel necrosis or fistula were assessed. The specimen was everted, and the mucosal surface was examined.

Microscopic Examination

For histological examination, 2-mm-wide tissue strips were cut out at 90° angles to the anastomotic line. The strips were fixed in phosphate-buffered 4% formaldehyde for 4 days and subsequently embedded in paraffin. The sections were cut in 5-μm slides and stained with hematoxylin and eosin and sirius red according to standard protocols. In each animal, two sections were used for histological assessment. One was taken from the antimesenterial side of the anastomosis, the other one from the mesenterial side. Inflammatory cell infiltration, blood vessel ingrowth, fibroblast ingrowth, and collagen deposition in the bowel wall were assessed and scored from 0 to 4 according to the method of Phillips et al.[15]

The following parameters were employed for scoring:

No evidence	Score 0
Occasional evidence	Score 1
Light scattering	Score 2
Abundant evidence	Score 3
Confluent cells or fibers	Score 4

Evaluation was carried out by a single pathologist blinded for the experimental protocol. The anastomotic collagen deposition was examined strictly in the bowel wall. The collagen content of the SIS patches and covering omentum were excluded. Furthermore, microscopic anastomotic presence of abscesses, necrosis, fistula, and foreign body reaction as features of impaired anastomotic healing was assessed.

Statistical Analysis

All results are expressed as mean ± standard error of mean (SEM). Differences in parameters among groups were examined using one-way analysis of variance (ANOVA) and post hoc analysis with Tukey's HSD test and Dunnett's *t* tests. p values<0.05 were assumed to be significant. SPSS 14.0.2. (SPSS Inc., Chicago, IL, USA) software was used.

Results

General

One rat with an anastomosis wrapped by omentum was sacrificed because of mesenteric ischemia of a 5-cm small-bowel segment caused by mesenterial strangulation on the second day after surgery. One other rat in the control group died of unknown reasons on day 45 and another on postoperative day 67. Postmortal abdominal examination did not reveal any abdominal pathology as a reason for death. All three animals were excluded from further analysis. In another three animals, abdominal examination on the scheduled date of sacrifice revealed covered anastomotic dehiscence (Table 1). Those animals were excluded from measurement of bursting pressure. No significant difference in postoperative weight change between the experimental groups was detected at any of the three observation points. The median weight change was +2.03 g (range −18 to +25 g) after 4 days, +182.4 g (range +121 to +270 g) after 30 days, and +388.5 g (range 303 to 503 g) after 90 days.

Macroscopic Examination

On the fourth, 30th, or 90th day after surgery, macroscopic examination of the abdominal cavity was performed before removal of the anastomotic segment. Four days after surgery, one animal in each group showed anastomotic leakage. All three leaks were covered by either small bowel in the control group, omentum in the omental group, and SIS in the SIS group. No free perforation or peritonitis was evident. No intra-abdominal abscess or anastomotic fistula was present in any of the animals. One animal in the omental group had macroscopically detectable anastomotic obstruction on the fourth day after surgery. After 30 or 90 days, no anastomotic leakage, intra-abdominal abscess, anastomotic fistula, or macroscopically visible obstruction was recognizable (Table 1).

Four days after surgery, all SIS patches were completely covering the anastomoses and clearly visible. After 30 days,

the SIS was visible as a thin gauzy membrane covering the anastomoses. Ninety days after implantation, the SIS membrane was no longer identifiable by macroscopic means (Fig. 1).

Intra-abdominal adhesions were frequently observed in all groups. Adhesive organs were omentum, lower intra-abdominal fat, and small-bowel segments. Adhesions with the abdominal wall were observed in only two animals in the control group. There were no significant differences in formation of adhesions between the control group and the SIS group at any time point in ANOVA analysis (Table 1). Quantity of adhesions after omental anastomotic wrapping increased over time. This phenomenon could not be seen in the control group and in SIS-sealed anastomoses (Table 1).

Microscopic Examination

Four days after surgery, no significant differences between the control group and the omental group were detected histologically. In the SIS group, the anastomotic inflammatory cell infiltrate was decreased compared to both other groups, however, without reaching significance. After 4 days, collagen deposition ($p<0.001$), vascular ingrowth ($p<0.05$), and fibroblast ingrowth ($p<0.01$) were significantly increased in SIS-sealed anastomoses compared the control group (Fig. 2). Compared to the omental group, the mean scores in all three parameters were increased in the SIS group, but significance was only reached for the factor collagen deposition ($p<0.01$; Fig. 2). The microscopic findings of the colonic anastomoses after 30 and 90 days are summarized in Table 2. Thirty days after surgery, collagen deposition, fibroblast infiltrate, and neovascularization of the SIS-sealed anastomoses were still increased compared to both other groups, although no significant differences were seen. After 90 days, histological examination revealed no significant differences in histological scoring between all three groups. Increased values for vascularization, fibroblast activity, and collagen deposition compared to both other groups were no longer evident in SIS-sealed anastomoses after 90 days (Fig. 3).

The SIS patches covering the anastomoses were microscopically visible below the serosal layer after 4, 30, and 90 days. Sirius red staining revealed decreasing thickness and decreasing collagen content over time (Fig. 3). After 90 days, a thin collagenous layer, measuring in average one fifth of the original thickness of the SIS patch, was visible only directly below the serosal layer as a residuum of the collagenous structures of SIS. Lymphocytes and macrophages infiltrated the SIS patches without any indication of abscess or infection after 4, 30, and 90 days. The quantity of inflammatory cell infiltration of the SIS patch was clearly decreasing over time. Cellular infiltration by activated fibroblasts was visible in the complete thickness of the SIS patches. Furthermore, distinct neovascularization of the patches was observed (Fig. 4).

Radiographics

No relevant anastomotic obstruction was detected, either in the control group or in the two experimental groups. Thirty days and 90 days after surgery, no significant difference in anastomotic index could be noted between the control group (0.97±0.02/0.98±0.05), the omental group (1.05±0.06/1.01±0.03), and the SIS group (0.91±0.03/1.02±

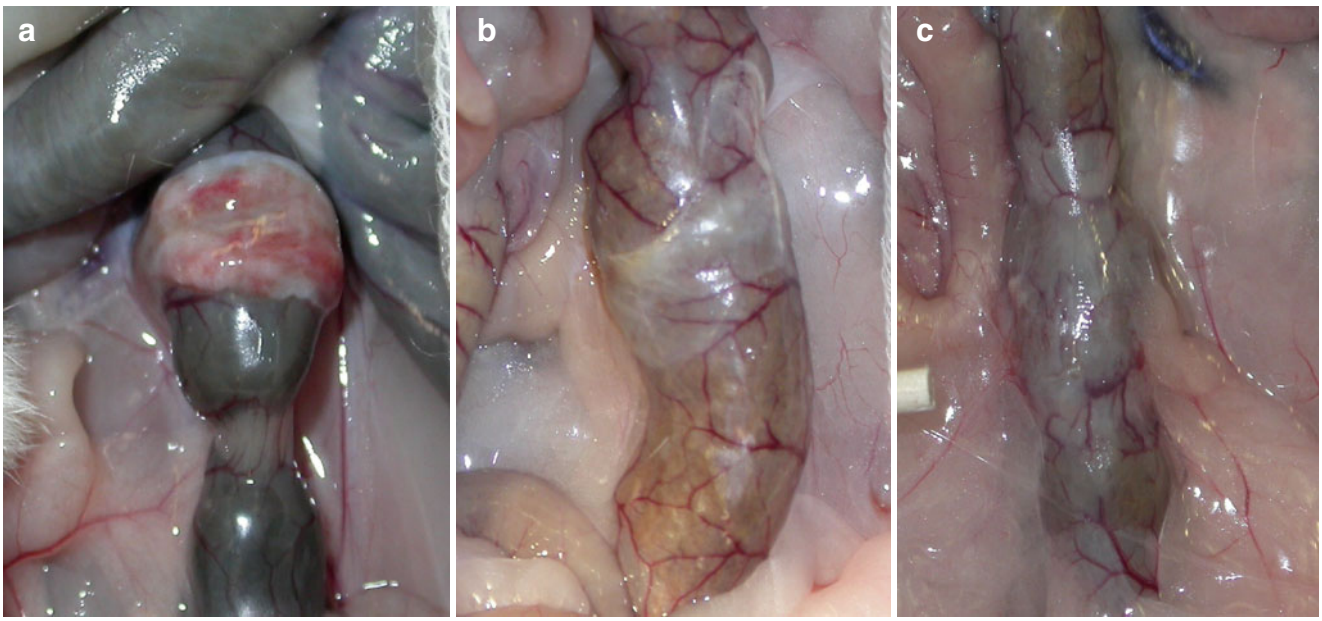

Figure 1 Macroscopic appearance of SIS-sealed colonic anastomoses on fourth day (**a**), 30th day (**b**), and 90th day (**c**) after surgery.

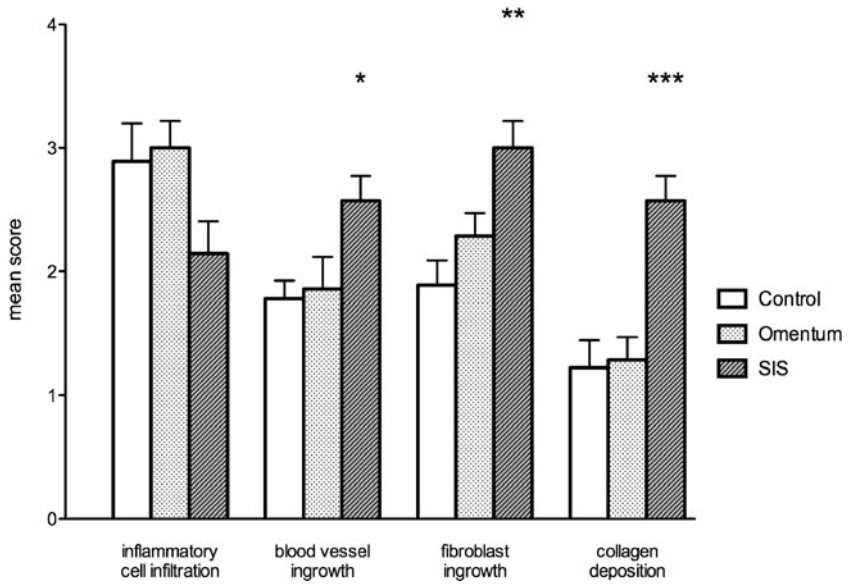

Figure 2 Microscopic scoring of colonic anastomoses on fourth postoperative day. Mean scores with SEM. *$p<0.05$ compared to control group; **$p<0.01$ compared to control group; ***$p<0.001$ compared to control group; $p<0.01$ compared to omentum group.

0.01). Furthermore, no leakages or anastomotic fistulas were found in radiographic examination.

Bursting Pressure

The bursting pressure was measured only in the animals sacrificed 4 days after surgery. Mean bursting pressure in the control group was 108 mmHg, whereas the values in the experimental group with omental wrapping was 111 mmHg, without any significant difference ($p>0.05$). Mean bursting pressure in the SIS group was 148 mmHg. A significant difference was detected between control group ($p<0.05$) and the SIS group. No significant differences were found in comparing the omental group and the control group (Fig. 5).

Discussion

Anastomotic dehiscence is a common complication and a substantial factor of morbidity and mortality in colorectal surgery. Extensive experimental efforts have been undertaken to evaluate mechanical methods which promote anastomotic healing, especially at the site of the colon. Various biological and artificial materials have been tested for anastomotic sealing. Although many influencing factors for anastomotic healing are known, there is no widely used substance or material in surgical practice which is able to reduce the rate of anastomotic dehiscence. ECM seem to be a very promising approach for improving anastomotic healing. ECM are nonimmunogenic, cell-free biological collagenous matrices which induces host responses for tissue regeneration, neovascularization, and restoration of tissue structure that is specific to the implantation site.[9] The mechanisms for this response of site-specific repair are not specifically known; however, it is assumed that the three-dimensional architectural structure of the fibrillar collagens and adhesive glycoproteins in the naturally occurring biopolymers is a key factor for structured tissue regeneration induced by ECM.[9]

The most experimental and clinical work concerning the application of ECM in surgery has been performed on SIS. SIS is commercially available and already in clinical use for treatment of anal fistula,[16,17] hernia repair,[18,19] and staple-line reinforcement in gastrointestinal anastomoses. Recently, we were able to demonstrate the promoting effects of

Table 2 Microscopic Findings and Scoring of Colonic Anastomoses of the Long-Term Groups on 30th and 90th Postoperative Day

	30th POD			90th POD		
	Control ($n=10$)	Omentum ($n=10$)	SIS ($n=10$)	Control ($n=8$)	Omentum ($n=10$)	SIS ($n=10$)
Inflammatory cell infiltration (0–4)	1.50 (0.17)	1.22 (0.15)	1.56 (0.18)	1.38 (0.18)	1.38 (0.18)	1.70 (0.26)
Blood vessel ingrowth (0–4)	2.50 (0.18)	2.11 (0.20)	2.67 (0.17)	3.00 (0.00)	2.38 (0.26)	2.60 (0.16)
Fibroblast ingrowth (0–4)	2.20 (0.13)	2.00 (0.17)	2.56 (0.18)	2.38 (0.26)	2.00 (0.00)	2.20 (0.20)
Collagen deposition (0–4)	3.20 (0.2)	3.22 (0.15)	3.78 (0.15)	3.25 (0.25)	3.50 (0.19)	3.50 (0.17)

Mean scores with SEM in brackets

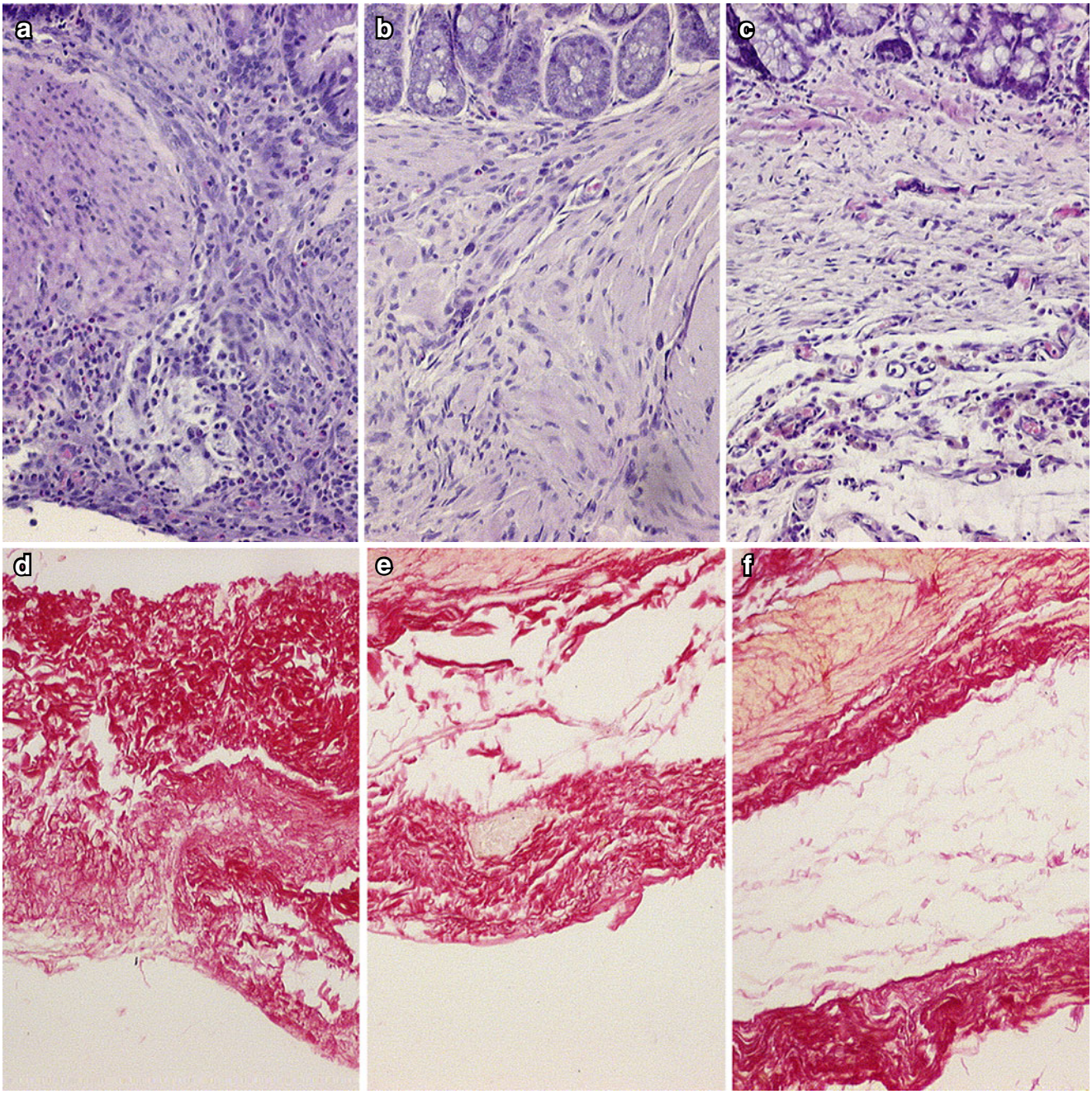

Figure 3 **a**–**c** Histologic appearance of SIS-sealed colonic anastomoses on fourth day (**a**), 30th day (**b**), and 90th day (**c**) after surgery (hematoxylin and eosin stain; magnification ×100). The luminal side of the anastomoses is oriented to the upper picture side. **a** 4 days. The anastomotic area is infiltrated by inflammatory cells. Blood vessel ingrowth and fibroblast activation are clearly visible. **b** 30 days. By 30 days, collagen deposition is clearly increasing. Inflammatory infiltrate is decreasing. **c** 90 days. Not only complete mucosal covering but also the regeneration of muscularis mucosae is detectable. A rich neovascularization of the anastomotic area especially on the abluminal side of the bowel wall, near the former SIS sealing, is visible. **d**–**f** Histologic appearance of SIS sealing of colonic anastomoses on fourth day (**d**), 30th day (**e**), and 90th day (**f**) after surgery (sirius red stain; magnification ×100). Collagenous fibers are stained red. The side of the SIS patch which is adjacent to the bowel wall is oriented to the upper picture side. The density of the collagenous fibers of the SIS is decreasing by the time especially in the center of the former extracellular matrix.

ECM sealing on the healing of colonic anastomoses in a porcine model.[20] The SIS patches covering the colonic anastomoses showed marked neovascularization and migration of fibroblasts into the SIS matrix within 30 days. In bowel wall healing, an increased amount of granulation tissue and an increased rate of complete mucosal coverage at the anastomotic site were observed. These results, however, were not significant compared to standard

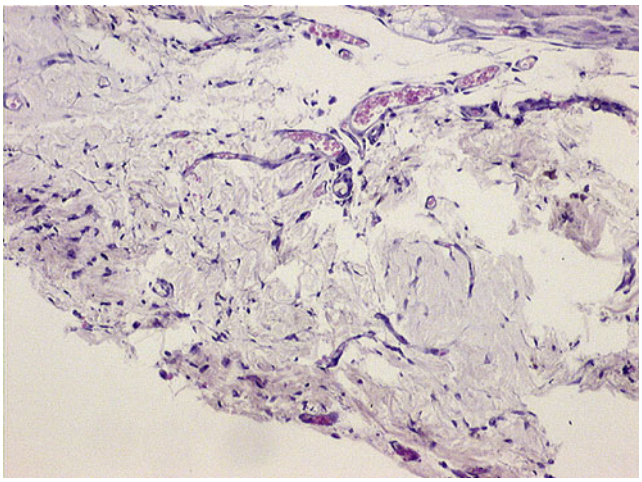

Figure 4 Histologic appearance of SIS 30 days after anastomotic sealing (hematoxylin and eosin stain; magnification ×100). Blood vessel ingrowth and vascularization of the former extracellular matrix are visible. Fibroblast ingrowth and de novo collagen synthesis are detectable at the outer side of the matrix.

anastomoses 30 days after creation of anastomoses. Although no information about the impact of SIS on early anastomotic healing and on long-term effects of SIS on colonic anastomoses beyond 30 days were gained, the feasibility and safety of anastomotic sealing by SIS were demonstrated.

In this current observation, we focused on the critical time point of early anastomotic healing on day 4. It is known that colonic anastomoses are most fragile on days 3 and 4 because of low collagen content mediated by high activity of colonic collagenase induced by injury to the bowel wall during the healing phase of the anastomosis.[21] On day 7 after anastomosis, collagenolytic activity reverts to normal values.[22] The early effects of SIS sealing on the healing of colonic anastomoses were determined by measuring the bursting pressure and evaluating macroscopic and microscopic characteristics in the critical window of anastomotic healing of colonic anastomoses on the fourth postoperative day. We used uncovered standard anastomoses and colonic anastomoses sealed with pedunculated omentum as controls. Specific effects on anastomotic sealing by SIS were assessed compared to the experimentally and clinically best-investigated method of anastomotic protection, the pedunculated omental wrapping, since several studies in the past have reported beneficial effects of omental reinforcement on rate of anastomotic leakage.[20,23–25]

In our study, the rates of anastomotic dehiscence, anastomotic fistula, and intra-abdominal abscess formation as a result of anastomotic leakage were not affected by anastomotic sealing with pedunculated omentum or SIS. Generally, in rodent and other animal models, the rate of spontaneous anastomotic failure in technically perfect anastomoses is very low and not comparable to colonic anastomoses under clinical conditions in humans, where we are confronted with rates of leakage of up to 23%.[1–3] The reasons for this might be the use of young healthy animals and species-dependent physiological differences in wound healing compared to the human situation. In rodent and porcine models, even primary dehiscent colonic anastomoses failed to reproduce the natural history of anastomotic leakage and its serious consequences comparable to the human scenario.[26–28] Therefore, if tested in animal models, other criteria need to be utilized to determine the effectiveness of anastomotic sealing in colonic healing. In this regard, besides macroscopic examination, anastomotic healing was evaluated by histological examination, applying an established scoring system for colonic wound healing. Furthermore, the mechanical strength of the anastomoses was measured by determination of anastomotic bursting pressure.

For microscopic evaluation of anastomotic healing, inflammatory cell infiltration, anastomotic fibroblast ingrowth, anastomotic neovascularization, and collagen deposition were assessed. In early anastomotic healing, colonic anastomoses sealed by SIS showed significantly increased fibroblast ingrowth compared to standard anastomoses or anastomoses sealed by omentum. This stimulation of fibroblast proliferation was also seen in an in vitro model of SIS which also proved stimulation of fibroblast VEGF secretion by SIS.[29] This pathophysiological phenomenon might be the reason for the increased neovascularization in SIS-sealed colonic anastomoses on the fourth and 30th postoperative day. These findings are confirmed in an in vivo angiogenesis model in which SIS or an artificial cellulose/collagen matrix was implanted subcutaneously in mice, and vessel outgrowth was proven to be stimulated by SIS.[29] The presence of different proteins responsible for cellular migration and attachment, like fibronectin and

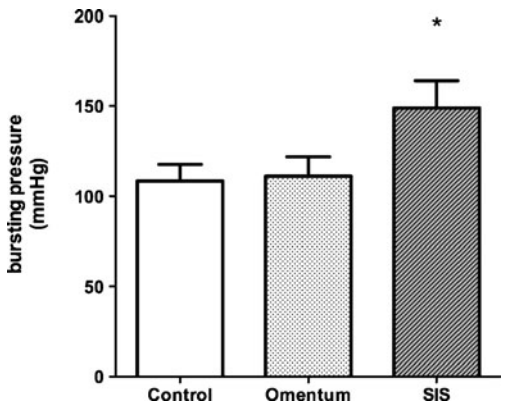

Figure 5 Measurement of bursting pressure after 4 days in mmHg ± SEM. *The SIS group (149±9 mmHg) showed significantly higher values compared to the control group (108±9 mmHg); $p<0.05$. No significant difference occurred between the control group and the omental group (111±11 mmHg).

heparin sulfate proteoglycan, and different growth factors, like FGF-2, VEGF, and TGF-β, which have been identified in SIS,[9–11] could be one reason for the phenomenon of increased anastomotic fibroblast and vessel ingrowth.

In our model, the content of collagen in the anastomosis, excluding the collagen of the covering SIS patch, was increased with high significance in early anastomotic healing. Since the anastomotic collagen content is critical for regaining tissue integrity and mechanical anastomotic strength,[30] the increase in mechanical resistance of the anastomoses could be explained by the increase of anastomotic collagenous fibers in SIS-sealed anastomoses. A possible mechanism for increased anastomotic collagen deposition is the stimulation of de novo collagen synthesis by FGF-2 which has been detected on SIS.[10] Growth factors accelerate wound healing by stimulation of ingrowth of granulation tissue and enhancing epithelialization.[31] In rodent esophageal anastomoses, locally administrated FGF has been shown to increase mechanical strength and anastomotic collagen deposition.[32] In colonic anastomoses, direct administration of FGF has not been evaluated yet, but it is known that other growth factors like EGF increase anastomotic collagen content here.[33] Another mechanism for the elevated concentration of anastomotic collagen may be a decreased expression of matrix metalloproteases (MMP) at the anastomotic site. Degradation of preexisting collagen and collagenolysis are mediated by MMP.[34] The anastomotic infiltration by inflammatory cells was decreased in SIS-sealed anastomoses compared to both control groups. Inflammatory cells are one main source of MMP.[34] The increased collagen anastomotic content was still detectable 1 month after surgery, which means that the integrity and resistance of the SIS-sealed anastomoses is enhanced for nearly the complete critical period of anastomotic healing. In clinical practice, the climax in the rate of anastomotic leakage in colorectal surgery traditionally is assumed to occur around the fifth to seventh postoperative day. In the present study, not only was the histological content of anastomotic collagen increased in early healing but the bursting pressure was also significantly increased in anastomoses which were sealed by SIS compared to standard anastomoses. Compared to anastomoses protected by omental sealing, the bursting pressure was also increased, however, without reaching a significant level in SIS-sealed anastomoses.

In the present observation, long-term effects of anastomotic covering were investigated by macroscopic, histologic, and radiographic examination after 30 and 90 days. The mechanical properties of the anastomoses were not assessed in these periods because it is known that these parameters are not suitable for evaluation of anastomotic healing beyond 1 week.[35] The use of SIS does not lead to significant long-term complications. SIS did not cause relevant luminal colonic narrowing in a follow-up period up to 90 days. Luminal obstruction following anastomotic wrapping has been reported for anastomotic sealing with other biomaterials like Dacron, PGA, and Dura mater.[26,36,37] Adverse effects like formation of low-grade lymphoma of the bowel wall at the anastomotic site, as has been reported in anastomotic reinforcement with synthetic materials like Dacron,[36] were not seen in the present study. After 90 days, SIS was extensively biodegraded, histologically thinned away, and macroscopically no longer visible. Contraction of SIS, which has been reported in other studies,[5] could cause bowel obstruction in the long term if gastrointestinal anastomoses are sealed by SIS. In view of the complete absence of luminal narrowing in SIS-protected anastomosis after 90 days and the large degree of degradation of the material within this period, we cannot confirm these drawbacks. Various materials which have been evaluated for anastomotic reinforcement caused relevant increase of anastomotic adhesions.[37] SIS did not significantly affect the formation of intra-abdominal adhesions in our study in observation periods of up to 3 months.

In conclusion, SIS sealing promotes processes of colonic wound healing and increases early mechanical stability of colonic anastomoses around the critical period of anastomotic healing. Promoting effects of SIS on colonic wound healing were microscopically significant, and mechanical stability was significantly increased. The use of SIS in this context is effective and safe, since adverse effects of anastomotic reinforcement, like strictures, increased formation of adhesions and anastomotic abscesses were absent for up to 90 days of follow-up, a period in which the SIS patch was nearly completely degraded. Although further experimental evaluation, especially in animal models with impaired anastomotic healing, is needed, SIS is a promising approach for promotion of wound healing in high-risk colonic anastomoses.

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ORIGINAL ARTICLE

Ultimate Fate of the Leaking Intestinal Anastomosis: Does Leak Mean Permanent Stoma?

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Abstract
Background The ultimate fate of the leaking intestinal anastomosis is unknown. We sought to analyze long-term outcomes of anastomotic leak with an emphasis on identifying the likelihood of re-establishing intestinal continuity and the potential for releak with corrective surgery.
Methods All consecutive subjects treated for clinical anastomotic leak from January 2001 through December 2007 were retrospectively reviewed. Patients were stratified by management of leak: (1) drainage alone, (2) proximal loop diversion, (3) repair/revision without diversion, (4) end stoma, or (5) tube enterostomy. We then determined management of anastomotic leak, mortality, corrective procedures, releak, and re-establishment of intestinal continuity.
Results In a database of 2,627 intestinal procedures, 79 patients had 88 anastomotic leaks with a final overall mortality of 10.1%. The aggregate rate of re-establishment of intestinal continuity was lowest for the patients treated by end stoma (44.4%) as compared to other initial management options ($p<0.01$). Of the patients who survived their initial anastomotic leak, 20.5% had another leak (releak).
Conclusions Patients who underwent resection of the leaking anastomosis and end stoma or proximal loop diversion have a high rate of long-term fecal diversion. The proportion of patients who experience an anastomotic releak is substantial following further corrective surgery to re-establish intestinal continuity.

Keywords Anastomosis · Postoperative complication · Gastrointestinal tract · Leak

Introduction

Anastomotic leak remains a troubling clinical challenge with substantial morbidity and mortality.[1] Patients who experience anastomotic leak have prolonged hospital stay and an associated mortality ranging from 6% to 39%.[2-7] Patients who suffer anastomotic leak are difficult to manage, particularly because their desire to maintain intestinal continuity must be balanced with their risk of further septic complications. In the last two decades, advances in both radiologic and surgical techniques have significantly changed the management of anastomotic leak. Minimally invasive methods to treat anastomotic leak have given clinicians more management options. For example, CT-guided drainage of a contained leak in a patient with localized peritonitis, and low-grade sepsis is a viable option, permitting local control of pelvic sepsis without the loss of intestinal continuity. In addition, laparoscopic abdominal washout has also been described for non-septic patients with pelvic abscess not amenable to percutaneous drainage.[8] Although these advances have altered the care of some patients with anastomotic leak, patients with sepsis due to anastomotic leak often have no option except operative intervention that results in intestinal discontinuity.

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Little is known about long-term outcomes following management of anastomotic leak complications. In this paper, we sought to analyze our clinical experience with anastomotic leaks to determine long-term outcomes with a particular emphasis on identifying the likelihood of re-establishing or maintaining intestinal continuity and the potential for releak when an anastomosis is re-attempted. In particular, does prior anastomotic leak increase the risk for another leak? These data would be particularly useful in discussions with patients about the risks and benefits of re-anastomosis.

Methods

Patients

We abstracted patient information from our prospective intestinal surgery database dating from January 1, 2001 through December 31, 2007. Our database includes all patients with gastrointestinal anastomoses distal to the ligament of Treitz and performed by attending surgeons in the Department of Colon and Rectal Surgery. Patients were entered into the study if they met the following criteria: (1) presence of an anastomosis to the small intestine, colon, rectum, or anus; (2) laparoscopic or conventional open surgery; and (3) elective or emergency procedure.

Intra- and Postoperative Variables

We retrospectively examined the medical record of all patients to obtain information regarding patient demographics, reason for surgery, management of leak, vital status, outcome, and presence of stoma at last contact. Patients who had not been followed up were contacted by phone as part of routine quality control and postoperative care.

Definitions

Clinical leak We used the definition of clinical leak derived from recommendations of a recent systematic review[2] and from the Surgical Infection Study Group.[8] A clinical leak was defined as the presence of luminal contents through a drain or wound site or abscess cavity causing inflammation (i.e., fever, leukocytosis, or fecal discharge). Anastomotic leaks may be detected by radiologic studies but must have clinical signs of leak to be considered a clinical leak. Data regarding leak were prospectively collected and retrospectively reviewed.

Corrective Surgery This is any procedure performed to re-establish intestinal continuity after documented anastomotic clinical leak including loop ileostomy reversal, end stoma reversal, and/or any revision or reconstruction of the prior leaking anastomosis.

Releak The rate of releak is the number of patients who had another anastomotic clinical leak at the site of the original leaking anastomosis divided by the total number of patients who underwent further corrective surgery multiplied by 100. Releak includes those patients who leaked again at the original anastomotic site after diversion takedown but only when they had been considered healed by imaging and/or endoscopy. Leaks occurring at the site of the proximal loop diversion (after the closure) were not classified as a releak.

Anastomotic Leak Management Procedures

Drainage and/or Antibiotics Alone This included percutaneous, laparoscopic, or open surgical drainage of pus of succus and/or antibiotics.

Re-exploration and Proximal Loop Diversion This included laparotomy or laparoscopy to re-explore the abdomen, drain or washout the abdomen/pelvis, and perform diverting stoma.

Anastomotic Resection and End Stoma This included laparotomy or laparoscopy to re-explore the abdomen, resect the anastomosis, and perform an end stoma.

Repair/Revision of the Anastomosis Without Diversion This included laparotomy or laparoscopy to re-explore the abdomen, drain or washout the abdomen/pelvis as needed, and repair or revise the anastomosis without a proximal diversion.

Tube Enterostomy (n=1) This included laparotomy followed by washout and placement of a silastic tube into the intestinal anastomosis. This was performed in one patient who could not have stoma creation.

Statistical Analysis

Data analysis was performed with SAS 9.1.3. Fisher's exact test was used to compare rates of intestinal continuity among patients treated with drain alone, re-exploration and proximal diversion, resection of the anastomosis and end stoma, or redo or repair of the anastomosis without diversion. All study protocols were approved by our institution's review board.

Results

From a database of 2,627 intestinal resections with anastomosis, 79 patients had one or more clinical leaks

Table 1 Characteristics of All 79 Patients Treated for Anastomotic Leak During the Study Period (Results Include (*n*) and Proportion of Total)

Characteristic	Drainage/antibiotics (*n*=25)	Diversion (*n*=25)	Resection and end colostomy (*n*=20)	Repair/reconstruct anastomosis (*n*=8)	Tube enterostomy (*n*=1)	All patients (*n*=79)
Age (mean)	53.7	55.8	56.4	49.6	NA	55.3
Female sex (%)	9 (36%)	13 (52%)	4 (20%)	5 (62.5%)	0	31 (39%)
Current smoker	6 (24%)	5 (20%)	5 (25%)	0	1 (100%)	17 (21.5%)
Prior steroid use	8 (32%)	3 (12%)	3 (15%)	1 (13%)	1 (100%)	16 (20%)
Pelvic anastomosis	10 (40%)	5 (20%)	4 (20%)	2 (25%)	0	21 (27%)
HTN	8 (32%)	16 (64%)	5 (25%)	1 (13%)	0	30 (38%)
Arthritis	3 (12%)	2 (8%)	1 (5%)	0	0	6 (8%)
Kidney disease	2 (8%)	0	1 (5%)	0	0	3 (4%)
Liver disease	3 (12%)	0	2 (10%)	0	0	5 (6%)
PVD	1 (4%)	2 (8%)	0	0	0	3 (4%)
Radiation	0	2 (8%)	1 (5%)	2 (25%)	0	5 (6%)

accounting for 88 total leaks. Age and patient characteristics are listed in Table 1. In these 79 patients, the majority of confirmed pathologic diagnoses for surgery were neoplasm, ulcerative colitis, Crohn's disease, or diverticular disease (Table 2). The majority of patients underwent left-sided anastomoses or anorectal (64%) and a small number underwent small bowel anastomosis (Table 3). Mean follow-up was 31.7±26.2 months for the entire cohort.

The 79 patients with anastomotic leak were categorized into five groups based on initial management. Management included drainage and/or antibiotics alone (*n*=25), operative re-exploration and proximal loop diversion (*n*=25), anastomotic resection and end stoma (*n*=20), repair/revision of the anastomosis without diversion (*n*=8), or tube enterostomy (*n*=1) (Table 3). Eight patients died after leak for an overall in-hospital mortality of 10.1%. Of the 71 patients who survived their anastomotic leak, 44 required further corrective surgery to re-establish intestinal continuity and nine patients releaked (20.5±11.7%) at the original anastomotic site. Of the 71 patients who were discharged from the hospital, intestinal continuity was re-established in 51 of 71 patients (71.8±10.3%) by study end (Table 4).

Management

Drainage and/or Antibiotics Twenty-five patients were initially managed by antibiotics and/or drainage as first-line therapy for anastomotic leak. One patient died, and seven patients had a proximal loop ileostomy created at the time of the original operation but required further drainage because of signs and symptoms attributed to clinical anastomotic leak. Following initial management, takedown of preexisting diversion was ultimately performed in five of seven patients, but one patient developed an enterocutaneous fistula from the area of the initial anastomosis and was re-diverted. In addition to the five patients with preexisting stomas, another six required some form of corrective surgery to re-establish intestinal continuity. Overall, 45.8% (*n*=11) of patients treated initially with drainage and/or antibiotics alone underwent corrective surgery (takedown of ileostomy and/or revision of the anastomosis or both) with a releak rate of 27.3±23.5% (*n*=3) from the original anastomosis. At the end of follow-up, intestinal continuity was restored in 21 of 24 patients (87.5±13.4%) (Table 4) who survived the initial leak.

Table 2 Indication for Index Operation and Management of First Anastomotic Leak for Each Patient (Results Include (*n*) and Proportion of Total)

Surgery indication	Drainage/antibiotics alone *n*=25	Loop diversion *n*=25	Resection and end colostomy *n*=20	Repair or reconstruct anastomosis *n*=8	Tube enterostomy *n*=1	All patients *n*=79
Crohn's	5 (20%)	5 (20%)	2 (10%)	2 (25%)	1 (100%)	15 (19%)
Ulcerative colitis	8 (32%)	5 (20%)	1 (5%)	2 (25%)	0	16 (20%)
Diverticulitis	8 (32%)	2 (8%)	4 (20%)	0	0	14 (18%)
Neoplasm	4 (16%)	9 (36%)	10 (50%)	2 (25%)	0	25 (32%)
Other	0	4 (16%)	3 (15%)	2 (25%)	0	9 (11%)

Table 3 Anastomosis Type at Index Operation and Management of First Anastomotic Leak for Each Patient (Results Include (*n*) and Proportion of Total)

Surgical procedure	Drainage/antibiotics alone *n*=25	Loop diversion *n*=25	Resection and end colostomy *n*=20	Repair or reconstruct anastomosis *n*=8	Tube enterostomy *n*=1	All patients *n*=79
Small bowel	3 (12%)	2 (8%)	0	2 (25%)	1 (100%)	8 (10%)
Right sided	5 (20%)	6 (24%)	6 (30%)	4 (50%)	0	21 (26%)
Left sided	7 (28%)	7 (28%)	10 (50%)	1 (13%)	0	25 (32%)
Rectal/anal	10 (40%)	10 (40%)	4 (20%)	1 (13%)	0	25 (32%)

Anastomosis can be made to the small bowel, right sided (anastomosis to the colon proximal to the splenic flexure), left sided (anastomosis to the colon distal to the splenic flexure), and rectal/anal (anastomosis to the distal rectum or anus)

Proximal Loop Diversion Proximal diversion was utilized to manage anastomotic leak in 25 patients, of which one patient died of abdominal sepsis. Of the 24 remaining patients, seven had no further surgery and maintained the diverting loop. Seventeen patients underwent further corrective surgery, and 13 had only their stomas reversed. Four patients required reconstruction of their anastomoses in addition to stoma reversal. One patient died following corrective surgery. Of the 16 patients who survived corrective attempts to re-establish intestinal continuity, two patients had another anastomotic leak requiring further surgery, and the patient releak rate was 12.5±16.3%. One of the patients with a releak underwent further surgery, and ultimately, intestinal continuity was re-established by study end. Of those patients who survived all reconstruction attempts, 69.5±17.7% have intestinal continuity re-established (Table 4).

Resection of Anastomosis Twenty patients underwent resection of the anastomosis and creation of an end stoma. Two patients died within the postoperative period. Eight patients had their stomas reversed of which one patient releaked (12.5±16.9%). All patients who underwent attempted reversal ultimately had re-establishment of intestinal continuity (Table 4). However, only 44.4±20.9% of all patients treated initially by resection and end stoma for anastomotic leak had re-establishment of intestinal continuity by study end.

Repair or Revision Eight patients underwent repair or revision of the anastomosis without diversion. Three patients developed leaks after reconstructive surgery, two of whom died secondary to overwhelming sepsis. There were a total of three leaks in all patients requiring further surgery resulting in a releak rate of 37.5±27.9%. Of those patients who survived all corrective operations, all (*n*=6) remain with intestinal continuity intact (Table 4).

Tube Enterostomy One patient underwent tube enterosotomy because of operative findings in an attempt to control sepsis. This patient expired during his hospital course.

Restoration of Intestinal Continuity

A total of 71 patients were discharged from the hospital after their first anastomotic leak, and intestinal continuity was re-established in 51 of 71 patients (71.8±10.2%) by study end. The aggregate rate of re-establishment of intestinal continuity was lowest for the patients treated by end stoma (44.4±20.9%) or proximal loop diversion (69.5±17.7%) as compared to those treated by drainage

Table 4 Total Number of Patients who Died, Required Further Corrective Surgery, Experienced "Releak," or Re-establishment of Intestinal Continuity as Related to Management During Anastomotic Leak (Results Include (*n*) and Proportion of Total)

Variable	Drainage/antibiotics alone *n*=25	Loop diversion *n*=25	Resection and end colostomy *n*=20	Repair or reconstruct anastomosis *n*=8	Tube enterostomy *n*=1	All patients *n*=79
Deaths	1	2	2	2	1	8
Attempted further corrective surgery	11	17	8	8[a]	N/A	44
"Releak"	3 (27.3%)	2 (12.5%)	1 (12.5%)	3 (37.5%)	N/A	9 (20.5%)
Intestinal continuity re-established	21 (87.5%)	16 (69.5%)	8 (44.4%)	6 (100%)	N/A	51 (71.8%)

[a] Please note that eight patients had repair or reconstruction as their procedure to manage anastomotic leak, which was also identified as the procedure to attempt further corrective surgery

and/or antibiotics alone (87.5±13.4%) or repair/revision of the anastomosis (100±19.6%) (Fisher's test; $p<0.01$) (Fig. 1). It should be understood that the analysis of restoration of intestinal continuity only includes patients who survived surgical therapy.

Discussion

Despite significant advances in management of anastomotic leak, our data reveal that fecal diversion is still commonly employed to control septic complications. Although, diversion is still commonly used in the modern management of anastomotic leak, we do not have data to either support or refute its continued use. However, we do note that patients who require excision of the anastomosis and end stoma or washout and proximal loop diversion have a high rate of chronic fecal diversion. Conversely, the majority of patients treated by drainage and/or antibiotics alone did not require further surgery and were able to maintain intestinal continuity. Last, our data reveal a high rate of anastomotic releak for those requiring further corrective surgery to re-establish intestinal continuity after stoma creation.

It is clear that anastomotic leak following intestinal anastomosis is associated with substantial increased morbidity and mortality.[1] Others have also described high rates of recurrent abscess, enterocutaneous fistula, and anastomotic stricture in those patients who experience anastomotic leak.[9] In addition, there are inherent morbidities associated with stoma construction including dehydration, renal failure, and para-stomal hernia.[10,11] Despite patient preferences to avoid stoma and recent advances in laparoscopic surgery and interventional radiology to avert stoma in certain circumstances, our study reveals that stoma creation is frequently utilized by our group during management of anastomotic leak, as has been previously described by others.[8,12]

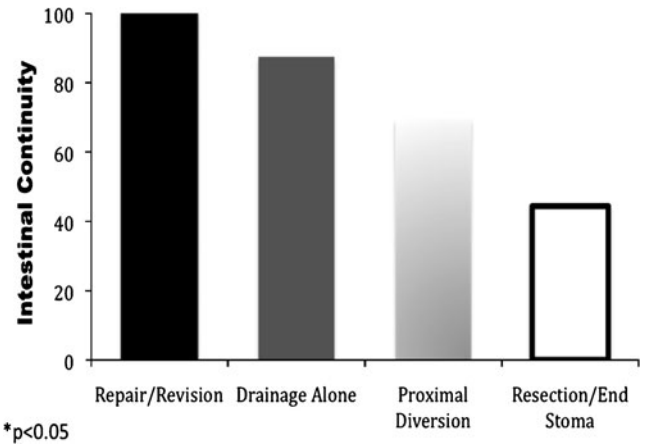

Figure 1 Proportion of patients that had re-establishment of intestinal continuity during a mean follow-up of 31.7 months as related to management during anastomotic leak.

Clinical indications for stoma creation following anastomotic leak are somewhat subjective; thus, we sought to determine long-term outcomes in those patients who "required" a stoma compared to those treated with other techniques. In our study, we found that a large number of patients, 56% of patients with an end stoma and 31% of patients with proximal diversion, retained their stoma over a long follow-up period of 31.7 months. While higher reversal rates are reported for elective proximal diversion, our data are consistent with previous reported rates in emergency settings such as perforated diverticulitis.[13-15] We noted that patients were more likely to retain intestinal continuity if drainage of contained anastomotic leak (88%) was effective. It is likely that the reason for creating the stoma may have similarly affected the decision to keep the stoma, but a clear picture as to what makes patients keep their stoma is unavailable from our dataset.

We had a small number of patients who were treated with repair or revision of the anastomosis without diversion. Although the clinical findings at the time of re-exploration led the operating surgeon to consider no diversion, it is difficult to determine if this technique is a viable option. We do know that these patients were more likely to maintain intestinal continuity, but a mortality of 25% ($n=2$) makes this management method somewhat controversial. It is possible that this mode of therapy is possible with proper patient selection, but further data are needed before it can be recommended or condemned. We do know that primary anastomosis without diversion is safe for some destructive colon injuries in select trauma patients.[16] Although it may be inferred that there are some clinical similarities between trauma surgery and reoperative surgery for anastomotic leak, a randomized trial or other objective data are needed before management strategies can be extrapolated across indications.

Patients who have been unfortunate enough to experience anastomotic leak often inquire about the likelihood of releak with corrective attempts. In our study, we found that 20.5% of patients experienced releak following further corrective attempts. Releak rates were also high for those patients who had an end colostomy performed and resection of their anastomosis (12.5%) and in the group that had their anastomosis redone or repaired at the time of the first leak (37.5%). Although the releak rate is less than half as common in the diverted patients as compared to the patients that underwent repair or revision, the small sample size precludes accurate statistical comparisons. Yet, all of the releak rates calculated after an initial leak are comparatively higher than the average published rate.[14,17] The releak rate after stoma takedown for anastomotic leak is also higher than the leak rate reported for reversal of end colostomy in

the setting of diverticulitis.[15] Again although a small sample, these data may help the physician in counseling the patient who requires reconstructive surgery after anastomotic leak.

There are a number of strengths and limitations of this study. First, conclusions from our study must be considered with the caveat that there are limitations related to the retrospective nature of our data analysis. There are a number of technical details and clinical facts, including surgeon decision making and surgeon preferences, which were not reviewable during data analysis. Importantly, it should be understood that our results do not answer the question of how to best treat an anastomotic leak. Despite these limitations, the data were prospectively collected, and thus, we were able to review a large number of patients who underwent treatment for a variety of conditions, rendering the results applicable to most surgeons. In addition, the data do provide valuable information concerning clinical questions of long-term results in patients with clinical leak as well as the likelihood of "releak" following further corrective surgery.

In conclusion, our data raise some interesting questions regarding the subsequent management of anastomotic leak. It is clear that the patient's chances to avoid leak are best during the first procedure, as subsequent procedures to re-establish intestinal continuity are often complex in the subset of patients who have a clinical need for diversion. Although our study has small numbers of anastomotic leaks, it appears that patients who undergo diversion for anastomotic leak are at high risk of releak. Reasons for this may be related to the primary procedure or underlying patient comorbidities, i.e., steroids, difficult anatomy, and poor nutrition. Further understanding regarding mechanisms to avoid releak in this subgroup of patients is needed in order to avoid the potentially devastating septic complications of a second or third anastomotic leak.

Author contributions Dr Ricciardi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Francone, Saleem, Roberts, and Ricciardi.

Analysis and interpretation of data: Francone, Saleem, Roberts, Marcello, Schoetz, Read, and Ricciardi.

Critical revision of the manuscript for important intellectual content: Francone, Saleem, Roberts, Marcello, Schoetz, Read, and Ricciardi.

Statistical analysis: Francone, Saleem, Roberts, Marcello, Read, and Ricciardi.

Study supervision: Ricciardi.

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ORIGINAL ARTICLE

Ileal Pouch Prolapse: Prevalence, Management, and Outcomes

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Abstract
Aim The study aim is to review the prevalence, management, and outcomes for patients diagnosed with ileal pouch prolapse after restorative proctocolectomy.
Materials and Methods Patients were identified retrospectively from a prospectively maintained pouch database. Parameters analyzed included presenting symptoms, indications for pouch surgery, type of ileal pouch-anal anastomosis, treatment modalities, and outcomes.
Results Of 3,176 patients who underwent ileal pouch surgery, 11 were diagnosed with pouch prolapse (0.3%). Seven had full-thickness prolapse and four mucosal prolapse. Six were male, and five were female. Indication for index surgery was ulcerative colitis (nine patients), familial adenomatous polyposis (one patient), and colonic inertia (one patient). Median age at pouch prolapse was 34 years. Median time from index surgery to prolapse diagnosis was 2 years. Two patients with mucosal prolapse responded to conservative management; two required mucosal excisions. An abdominal approach was successful in four out of seven patients with full thickness prolapse. The three failures subsequently underwent continent ileostomy formation and prompted us to add biological mesh to future pouchpexy repairs.
Conclusions Pouch prolapse is rare, and there are no obvious predisposing factors. Mucosal prolapse may be treated by stool bulking or a local perineal procedure. Full thickness prolapse requires definitive surgery and is associated with risk of pouch loss.

Keywords Ileal pouch prolapse · Ulcerative colitis · Familial adenomatous polyposis · Continent ileostomy · Biological mesh

Introduction

Since its initial description in 1978, ileal pouch-anal anastomosis (IPAA) is considered the gold standard for the definitive surgical treatment of most patients with ulcerative colitis (UC) and familial adenomatous polyposis (FAP).[1] When successful, an IPAA restores intestinal continuity, avoiding the need for a permanent ileostomy. Studies with long-term follow-up have documented good outcomes and quality of life.[2,3]

However, restorative proctocolectomy is a complex procedure that creates a new and unnatural anatomy and physiology. It is therefore no surprise that there are problems and pathologies unique to this surgery, which may occur early or late. Recognized complications include anastomotic leakage, peri-pouch sepsis, pouch strictures, portal vein thrombosis, and development of Crohn's disease in the pouch.[4–6] Ileal pouch prolapse is a rarely reported

Some data pertaining to this article was presented in poster format, American Society of Colon and Rectal Surgeon, St Louis, June 2–6, 2007.

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complication. One previous study,[7] reported the condition in 83 patients in a survey of colorectal surgeons in North America. While there was a 94% success rate reported with surgical repair, there were no data on long-term follow-up with associated recurrences.

The aim of our study was to report our experience from a single high-volume center on this rare condition.

Methods

Using a prospectively maintained, Institution Review Board approved pelvic pouch database, all patients who underwent IPAA and were subsequently diagnosed with ileal pouch prolapse were identified. Patients with both mucosal and full thickness pouch prolapse were included. A review of patient charts and electronic medical records was performed. All patients signed an informed consent allowing use of their data at the time of enrollment into the pouch registry. Data abstracted included demographic information (gender, indication for surgery and time from pouch formation to prolapse), presenting symptoms, technique used for anastomosis, treatment, and outcomes. In terms of treatment outcomes, we wished to determine if the treatment modality used was successful or resulted in recurrence of full thickness prolapse or persistence of mucosal prolapse. The operative notes were reviewed to determine surgical treatment.

All patients who have undergone ileal pouch or related surgery at this institute are followed up by office visits and were ask to fill in a self-administered, structured, questionnaire. This is then uploaded to the ileal pouch database. Continuous data are reported as medians and ranges.

Results

The overall incidence of ileal pouch prolapse in this study population was 0.3% (11 out of 3,176 patients), indicating the rarity of the condition. Seven patients had full-thickness pouch prolapse, four were diagnosed with mucosal prolapse. In contrast to rectal prolapse, there was no female predominance. Patient demographics including indications for ileal pouch formation, type of pouch configuration, technique for IPAA, and presenting symptoms are outlined in Table 1. Ten patients had pouch prolapse diagnosed based on symptoms and examination (Figs. 1 and 2) with one patient diagnosed after pouchography for the investigation of pouch dysfunction.

The first line of treatment for patients with mucosal prolapse only was stool bulking agents and biofeedback to avoid excessive straining. In two patients, this was successful in relieving symptoms. The other two patients underwent a local perineal procedure in the form of pouch advancement with excision of redundant mucosal tissue. None of these patients developed full-thickness prolapse. The follow-up time period was a median of 5 years (range, 4–7).

Patients with full thickness pouch prolapse were treated with definitive transabdominal surgery. Pouchpexy using a transabdominal approach, with fixation of pouch to the sacrum using non-absorbable sutures, was used in the first six patients. In these patients, the mesentery of the pouch lay in the curvature of the sacrum with the pouch lying anteriorly. Three patients developed recurrence. Given the high recurrence rate, we subsequently modified our procedure for the seventh patient with full-thickness prolapse. This patient had already failed a pouchpexy performed at an outside institute. In this patient, we sutured

Table 1 Patient Demographics

Age	Gender	Indication for pouch	Pouch type	Time to prolapse (years)	symptoms	Treatment	Pouch loss
34	M	UC	J, DS	6	Anal pain, mucosal prolapse	Stool bulking Biofeedback	No
32	F	FAP+Ca	J, M	1	Anal pain, solitary pouch ulcer	Pouchpexy hysterectomy	No
15	F	UC	J, DS	4	External prolapse	Pouchpexy	No
48	M	UC+Ca	S, M	1	External prolapse	Mucosal excision	No
38	F	Dysmotility	J, DS	2	Pouch dysfunction	Pouchpexy	Yes[a]
21	F	UC	J, DS	4	External prolapse	Pouchpexy	No
40	M	UC	S, M	1.5	External mucosal prolapse	Stool bulking Biofeedback	No
22	M	UC	Redo J, M	1	External prolapse	Pouchpexy	Yes[a]
34	M	UC	J, M	6	External prolapse	Pouchpexy	Yes[a]
23	F	UC	J, DS	0.5	External prolapse	Pouchpexy / Biological mesh	No
41	M	UC	Redo J, M	2	Mucosal prolapse	Local procedure	No

[a] J-pouch converted to continent ileostomy

UC ulcerative colitis, *Ca* carcinoma, *FAP* familial adenomatous polyposis, *IndC* indeterminate colitis, *J* J-pouch configuration, *S* S-pouch configuration, *DS* double stapled, *M* mucosectomy (thus handsewn anastomosis)

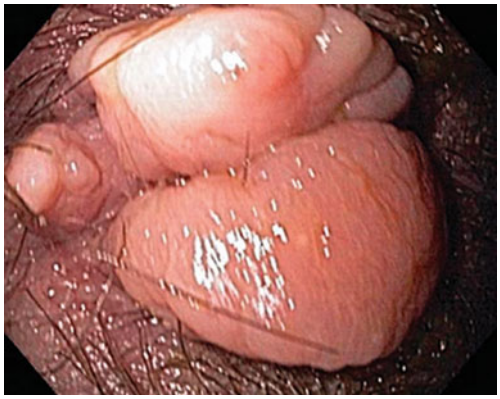

Figure 1 External pouch prolapse.

a biological mesh posterior to the pouch with subsequent fixation of this mesh to the sacrum using heavy non-absorbable Ticron (US Surgical) sutures. At 9 months follow-up, there is no recurrence.

All patients who failed definitive pouch prolapse surgery elected to undergo conversion of the ileal pouch to a continent ileostomy. In one patient, the full-thickness prolapse occurred after re-do ileal pouch surgery. At the time of pouch excision, it was noted that the posterior aspect of the pouch was densely adherent to the sacrum, and our clinical suspicion was that the origin of the prolapse involved the afferent limb of the pouch. The second patient had undergone ileal pouch surgery for colonic inertia with obstructed defecation. The third patient, in addition to recurrence of the prolapse, had associated problems with seepage and urgency. The typical histopathological finding on examination of pouch tissue excised showed surface mucosal hemorrhagic changes with thickening of the muscularis mucosae consistent with prolapse (Fig. 3),

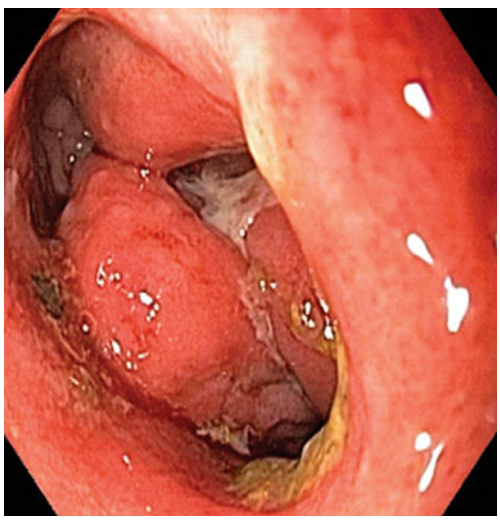

Figure 2 Prolapse of pouch tissue is evident when the patient is asked to strain at pouchoscopy.

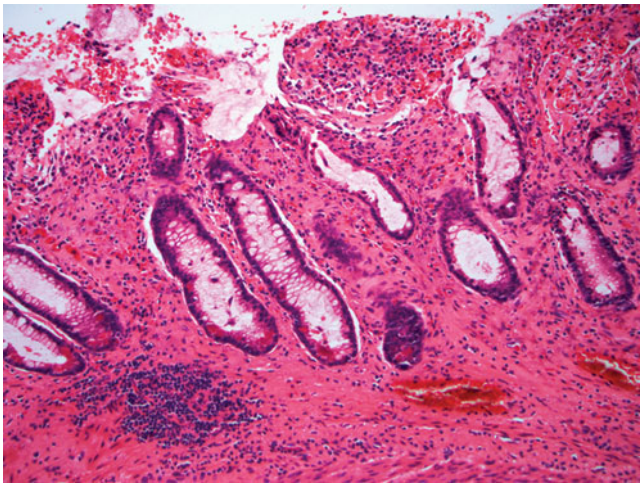

Figure 3 Histopathological examination of the excised pouch showed mucosal prolapse changes, characterized by fibromuscular obliteration of the lamina propria, crypt distortion, and superficial ischemic changes.

correlating with solitary pouch ulceration. Figure 4 provides a summary of the different treatment pathways used.

Discussion

This study shows that ileal pouch prolapse is rare. The rarity of this condition may be due to the fact that the mesentery of the small bowel puts tension on the pouch, limiting the potential for distal intussuception. Given the relatively rare incidence of pouch prolapse and in contrast difficulties with reach of the pouch that are often encountered during IPAA creation, we do not advocate any maneuvers to prevent this problem. The diagnosis of pouch prolapse is suggested by a history of the patient feeling tissue coming out of the anus, often associated with anal pain, and sometimes with seepage and difficult defecation. The potential for pouch prolaspe should be considered in the differential for any patient presenting with pouch dysfunction. Physical examination may show the prolapsing mucosa or pouch. Anoscopy reveals redundant tissue above the anastomosis, and when the patient is asked to bear down, this tissue can be seen to descend toward the outside. One may identify a solitary pouch ulcer. Pouchoscopy with a rigid scope can also be revealing, while pouchoscopy with a flexible scope is less so, due to the tension on the pouch walls caused by the distension. In some cases, defecating pouchography may be used to confirm the diagnosis.

Awareness of the two types of prolapse is essential to ensure appropriate treatment, which consequently determines outcomes. Patient with mucosal prolapse can be initially managed with stool bulking agents and biofeed-

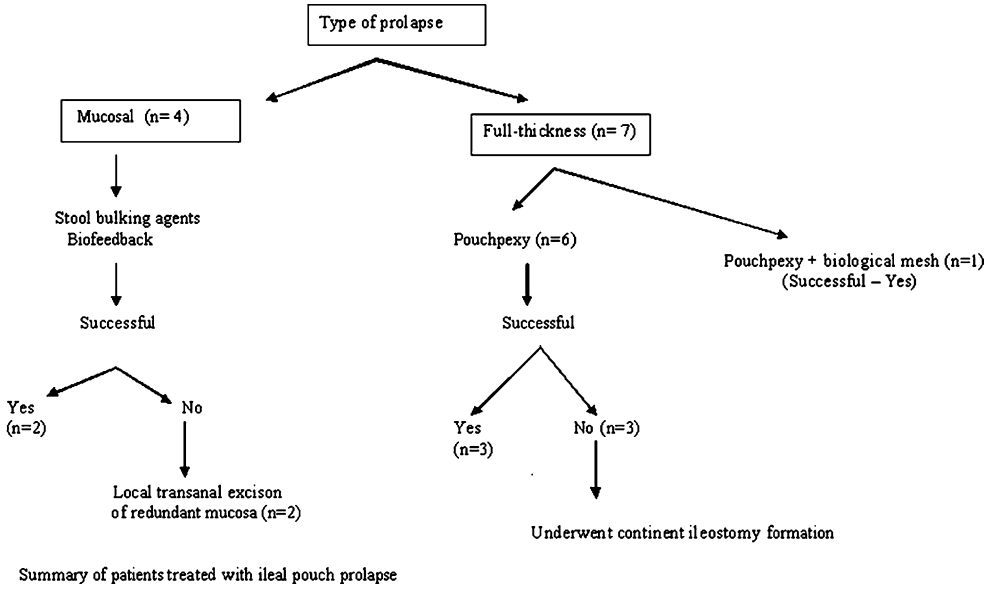

Figure 4 Summary of treatment modalities used in patients treated with ileal pouch prolapse.

back to avoid excessive straining. In contrast, most patients with full-thickness prolapse require definitive repair or pouch excision. In the above series, all pouch fixations were performed posteriorly between the pouch and sacrum. However, we appreciate that, on occasion, anterior pouch fixation or more novel techniques may be required.

Technically, we approach these patients in a similar manner to those undergoing repeat pouch surgeries.[8] We insert ureteric stents and place the patient in a lithotomy position. The pelvic dissection should begin posteriorly after one has identified a plane between the sacral promontory and mesentery of the pouch. The pouch is mobilized to the level of the pelvic floor. As described above, we believe that the addition of a biological mesh to the repair may be prudent. One should be conscious that the pouch wall is quite thin and vulnerable to transmural penetration with a needle. Thus, we would recommend to fix a biological mesh such as Permacol (Covidien, USA) to the pouch wall using 3/0 non-absorable sutures. If the mesentery of the pouch lies posteriorly, then this is encompassed by the mesh. Other authors have used GoreTex for this purpose.[9] The biological material is then fixed to the sacrum using a heavier non-absorable suture. A long-term follow-up of treated patients will be required to determine outcomes, but in the absence of any definitive data, our experience is that the pouchpexy alone using sutures is associated with a high failure rate. In those patients who suffer recurrence particularly when associated with significant sphincter dysfunction, there is the option of converting the ileal pouch to a continent ileostomy or end ileostomy.

In 2003, Ehsan et al.[7], reported on 83 patients with pouch prolapse. These data were based on a survey of all North American members and fellows of The American College of Surgeons and included 23,541 pouches for an incidence of 0.3%. Their data provide a useful background to our study. The majority of patients presented within 2 years of pouch construction. Most had a "J" pouch configuration with a stapled IPAA. Similar to our study group, most patients described the external prolapse of tissue. Others reported straining to evacuate, seepage, and incontinence. Many patients were misdiagnosed as pouchitis before the diagnosis was established. Surgery was carried out in 52 patients, with a transanal approach in 52% and transabdominal in 48%. They reported that 94% of pouches were salvaged, although there is no data on follow-up and no recurrence rates reported. We believe that our series is representative of the general pouch population who suffer ileal pouch prolapse. Based on our 50% failure rate with pouchpexy alone, we have taken the decision to add a biological mesh to subsequent abdominal repairs but appreciate that long-term data will be required to confirm the validity of this approach. The small number of patients in this cohort means that one is unable to identify any significant risk factors associated with ileal pouch prolapse.

Conclusion

While ileal pouch prolapse is relatively rare, all physicians and surgeons involved in the care of ileal pouch patients must be aware of its existence. A differentiation of the types is important to ensure appropriate treatment. Mucosal prolapse can be successfully managed using bulking agents or mucosal excision techniques. Full-thickness pouch prolapse requires pouch fixation using an abdominal or perineal approach. While insertion of a biological mesh has

the potential for infection, we do believe that it will reduce the incidence of recurrences. Those who recur have the option of a further repair or conversion of the ileal pouch to a continent ileostomy.

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SSAT POSTER PRESENTATION

Optimal Technical Management of Stump Closure Following Distal Pancreatectomy: A Retrospective Review of 215 Cases

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Abstract
Background Pancreatic fistula (PF) is a major source of morbidity following distal pancreatectomy (DP). Our aim was to identify risk factors related to PF following DP and to determine the impact of technique of transection and stump closure.
Methods We performed a retrospective review of 215 consecutive patients who underwent DP. Perioperative and postoperative data were collected and analyzed with attention to PF as defined by the International Study Group of Pancreatic Fistula.
Results PF developed in 36 patients (16.7%); fistulas were classified as Grade A (44.4%), B (44.4%), or C (11.1%). The pancreas was transected with stapler (n=139), cautery (n=70), and scalpel (n=3). PF developed in 19.8% of remnants which were stapled/oversewn and 27.7% that were stapled alone (p=0.4). Of the 69 pancreatic remnants transected with cautery and oversewn, a fistula developed in 4.3% (p=0.004 compared to stapled/oversewn; p=0.006 compared to stapled/not sewn). The median length of postoperative hospital stay was significantly increased in patients who developed PF (10 vs. 6 days, p=0.002)
Conclusion The method of transection and management of the pancreatic remnant plays a critical role in the formation of PF following DP. This series suggests that transection using electrocautery followed by oversewing of the pancreatic remnant has the lowest risk of PF.

Keywords Distal pancreatectomy · Pancreatic fistula · Complications

Introduction

Distal pancreatectomy (DP) is the procedure of choice for benign or malignant lesions in the pancreatic body or tail. The typical procedure consists of resection of the pancreatic parenchyma at a variable point to the left of the superior mesenteric vein–portal vein axis and may include concomitant removal of the spleen. For decades, DP had been associated with high morbidity and low but measurable mortality. In recent years, the mortality rate after DP has been reduced to less than 5% in high volume centers;[1–5] however, morbidity rates remain high ranging from 10–47%.[3,6–8] Pancreatic fistula is the most frequently reported complication and the primary cause of postoperative morbidity following DP.[6–10] Development of pancreatic fistula often leads to further complications such as intra-abdominal abscess, sepsis, hemorrhage, delayed gastric emptying, and occasionally malabsorption. These additional complications have important implications for the healthcare system, often with additional procedures, increased length of hospital stay, and increased cost.[9–11]

While it is clear that pancreatic fistula remains a problem following DP, the risk factors for development of fistula are not well-defined. Obesity, patient age, trauma, malignancy, duct obstruction, and texture of the pancreatic parenchyma

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have all been implicated as potential risk factors.[9,12] However, surgical technique is also considered an important risk factor for the development of pancreatic fistula.[9] A wide variety of surgical techniques for parenchymal transection and closure of the pancreatic remnant have been described in an effort to reduce the occurrence of fistula. These techniques include stapled closures, sutured closures, combined stapled and sutured closures, ultrasonic dissection, sealing with fibrin glue, application of mesh, seromuscular flaps, pancreaticoenteric anastomosis, and ligation of the main pancreatic duct at the transection line.[3,6–9,11–21] Currently, there is no consensus as to the optimal surgical technique for pancreatic transection and stump closure during distal pancreatectomy. The purpose of this study is to determine the impact of the type of pancreatic transection and closure of the pancreatic remnant on the formation of pancreatic fistula.

Material and Methods

Our Institutional Review Board approved this retrospective review of all patients who underwent distal pancreatectomy at Thomas Jefferson University Hospital from January 1996 through July 2008. Patients who underwent distal pancreatectomy were identified using electronic search of a surgical database. The indications for distal pancreatectomy included primary pancreatic processes, non-pancreatic malignancies, and trauma. No patients were excluded from the study. Octreotide was rarely used in the preoperative, prophylactic setting, but was often used in patients with documented pancreatic fistulae.

Patient data including demographics, comorbidities, additional procedures, method of pancreatic transection, management of the pancreatic remnant, operative time, blood loss, pathology, and postoperative complications were collected using hospital electronic record and chart review. These data were compiled and further analyzed. The primary endpoint was pancreatic fistula. Pancreatic fistula was defined using the International Study Group on Pancreatic Fistula (ISGPF) definition: drainage of any measurable volume after postoperative day 3, with an amylase content of greater than three times the normal serum value.[22] Pancreatic fistulas were retrospectively graded according to the ISGPF grading system.[22] Secondary endpoints were all complications.

Statistical Analysis

Continuous variables (such as length of postoperative hospital stay) were compared using a two-sided Student's *t* test. Qualitative variables (such as pancreatic fistula rates) were compared using Fisher's exact test. Bivariate cross-tabulations, with chi-square statistics, to assess bivariate associations between selected risk factors and the occurrence of fistulas were performed. A multivariate logistic regression analysis which modeled the occurrence of fistulas as a function of all risk factors with significant bivariate associations and also selected other variables (i.e., age group, sex, body mass index, and estimated blood loss) to assess and control for confounding was performed. A p value less than 0.05 was considered significant. SAS Release 9.2 statistical software (SAS Institute, Inc., Cary, NC, USA) was used for all analyses.

Results

From January 1996 to July 2008, 215 patients underwent distal pancreatectomy. There were more females (n=125; 58%) than males (n=90; 42%). The mean age of patients was 58.8 years (range 18–87 years). Indications for distal pancreatectomy are listed in Table 1. More patients were

Table 1 Indications for Distal Pancreatectomy

Indications for distal pancreatectomy (n=215 patients)	No. of patients (%)
Benign	
Cystadenoma (serous and mucinous)	27 (12.6)
IPMN	21 (9.8)
Neuroendocrine	21 (9.8)
Solid pseudopapillary neoplasm	13 (6.0)
Pseudocyst	8 (3.7)
Trauma	8 (3.7)
Chronic pancreatitis	7 (3.3)
Cysts	7 (3.3)
Microcystic adenoma	6 (2.8)
Abscess	2 (0.9)
Pancreatic intraepithelial neoplasia	2 (0.9)
Inflammatory myofibroblastic tumor	1 (0.5)
Miscellaneous	9 (4.2)
Total benign	132 (61%)
Malignant	
Ductal adenocarcinoma	41 (19.0)
Neuroendocrine	21 (9.8)
Metastatic tumors	8 (3.7)
Mucinous cystadenocarcinoma	3 (1.4)
Gastric cancer	3 (1.4)
Adenosquamous carcinoma	2 (0.9)
Anaplastic carcinoma	2 (0.9)
Acinar cell carcinoma	1 (0.5)
Lymphoma	1 (0.5)
Liposarcoma	1 (0.5)
Total malignant	83 (39%)

operated on for benign lesions (61%) than for malignancies (39%). The most frequent benign lesions were cystadenomas (12.6%), intra-ductal papillary mucinous neoplasms (9.8%), and neuroendocrine tumors (9.8%). Eight patients (3.7%) underwent distal pancreatectomy for pancreatic trauma. Of the malignant lesions, pancreatic ductal adenocarcinoma (19%) and neuroendocrine tumors (9.8%) were the most frequent indications.

Open distal pancreatectomy with splenectomy was performed in 84% of patients (Table 2). Open distal pancreatectomy with splenic preservation was performed in 9%. Laparoscopic resection was attempted in 16 patients (7.4%) and completed in 13 patients (6%). Additional organs, excluding the spleen, were resected in 108 patients (50%); the majority of these were incidental cholecystectomies (Table 3). The mean operative time was 274 min (range 83–665), and the average blood loss was 621 ml (range 0–5400). The pancreas was transected using a stapler in 139 patients, electrocautery in 70 patients, and scalpel in three patients (unknown in three patients; Fig. 1). Of the 139 patients who were transected with stapler, the pancreatic remnant was oversewn in 91 patients, not oversewn in 47 patients, and sealed with tissue glue in one patient. Of the 70 patients who were transected with electrocautery, the pancreatic remnant was oversewn in 69 patients and not oversewn in one patient. For the three patients who were transected with scalpel, the remnant was oversewn in one patient, not oversewn in one patient, and pancreaticojejunostomy was performed in one patient.

Pancreatic fistula was the most common complication, occurring in 36 patients (16.7%). Pancreatic fistula occurred in 50% of patients undergoing laparoscopic spleen preserving distal pancreatectomy, 44.4% of patients undergoing laparoscopic distal pancreatectomy and splenectomy, 15.6% of patients undergoing open distal pancreatectomy and splenectomy, and 10.0% of patients undergoing open spleen preserving distal pancreatectomy. The characteristics of patients who developed a pancreatic fistula are described in Table 4. Fistulas were classified as Grade A in 16 patients (44.4%), Grade B in 16 patients (44.4%), and Grade C in four patients (11.1%). Pancreatic fistula developed in 27.7% of patients that were stapled and not oversewn, 19.8% of patients where the remnants were stapled and oversewn, and only in 4.3% of remnants that were divided by cautery and oversewn (Fig. 1). The fistula rate for remnants that were cauterized and oversewn was significantly lower as compared to the leak rate in both stapled and oversewn ($p=0.004$) and stapled and not oversewn ($p=0.0006$). There was no difference in the incidence of pancreatic fistula between patients who had additional organs (excluding spleen) resected compared to those where no additional organs were resected (13% vs. 20.6%; $p=0.15$). Of the 13 laparoscopic cases (all stapled and none oversewn), six (46.2%) developed pancreatic fistula.

The median length of postoperative hospital stay was significantly increased in patients who developed pancreatic fistula, as compared to those who did not develop a fistula

Table 2 Demographics and Clinical Characteristics

Demographic and clinical characteristics (total=215 patients)	
Mean age in years (range)	58.8 (18–87)
Female	125 (58%)
Male	90 (42%)
Race	
Caucasian	194 (90.2%)
African American	13 (6.0%)
Hispanic	3 (1.4%)
Other	5 (2.3%)
Mean Body Mass Index (range)	26.9 (16.4-60.1)
Procedure	
Open distal pancreatectomy and splenectomy	180 (83.7%)
Open distal pancreatectomy (spleen preserving)	20 (9.3%)
Laparoscopic distal pancreatectomy and splenectomy	9 (4.2%)
Laparoscopic distal pancreatectomy (spleen preserving)	4 (1.9%)
Open subtotal pancreatectomy	2 (0.9%)
Patients with additional organs resected	108 (50.2%)
Mean operative time in minutes (range)	274 (83–665)
Mean blood loss in milliliters (range)	621 (0–5,400)
Median length of postoperative hospital stay in days (range)	6 (2–61)

Table 3 Additional Operative Procedures Performed

Additional operative procedures[a]	No. of patients (%)
Cholecystectomy	66 (30.1)
Gastrectomy	22 (10.2)
Partial colectomy	10 (4.7)
Wedge resection of liver	8 (3.7)
Nephrectomy	8 (3.7)
Adrenalectomy	6 (2.8)
Small bowel resection	3 (1.4)
Hysterectomy and bilateral salpingo-oophorectomy	2 (0.9)
Oophorectomy	1 (0.5)
Resection of omental mass	1 (0.5)
Orthotopic liver transplant	1 (0.5)
Pancreatico-jejunostomy	1 (0.5)
Resection of retroperitoneal mass	1 (0.5)

[a] Some patients had more than one additional procedure

(10 days vs. 6 days; $p=0.002$; Table 4). Pancreatic fistula was treated with maintenance of JP drainage alone in 41.7% of patients and maintenance of JP drainage plus octreotide in 30.6% of patients. Percutaneous drain placement by interventional radiology was required in 22.2% of fistulas. Three patients who developed fistula required reoperation; all three had Grade C fistulas.

Fifty-five patients (25.6%) developed at least one postoperative complication (Table 5). There were two perioperative deaths (0.9%). One was a patient with malignant pheochromocytoma adherent to the pancreas and spleen, who developed postoperative sepsis and multi-system organ failure (death on postoperative day 48). The other mortality was a patient with metastatic melanoma who expired from unexpected cardiac arrest in the postoperative period (death on postoperative day 21).

We also examined fistula rates based on surgical volume at the entire institution. As one can see from Fig. 2, the volume of pancreatic surgery increased by several-fold beginning in 2006. Prior to this point, there were a total of 93 distal pancreatectomies, while starting in 2006, there were a total of 120 distal pancreatic resections. When calculating leak rates pre- and post-2006, there is a significant decrease in leak rates (26% vs. 10%, $p=0.003$).

Bivariate analyses showed that pancreatic transection using a stapler, not oversewing the pancreatic remnant, and low surgeon volume (fewer than 20 total cases performed) were all significantly associated with the development of pancreatic fistula (Table 6). While the bivariate analyses show significant differences in the likelihood of a pancreatic fistula, as noted, none of these differences remained significant in the multivariate logistic regression analysis (Table 7), although the method of pancreatic transaction was borderline significant ($p=0.058$) with a hazard ratio of 3.2.

Discussion

In the present study, we analyzed the morbidity and mortality associated with DP, with particular attention to pancreatic fistula and surgical technique. For the 215 patients in this series, we report a mortality rate of 0.9% and a morbidity rate of 25.6%. Pancreatic fistula was the most frequent complication, occurring in 16.7% of patients. We found a significantly lower fistula rate in pancreatic remnants that were transected by cautery and oversewn (4.3%), as compared to remnants that were stapled and oversewn (19.8%; $p=0.004$) or stapled and not oversewn (27.7%; $p=0.0006$). In our relatively small laparoscopic group, 46.2% developed pancreatic fistula. Median length of stay was significantly increased in patients who developed pancreatic fistula compared to those who did not (10 days vs. 6 days; $p=0.002$).

Our data support the claim that DP can be performed with low mortality,[1–5] however, morbidity remains high largely due to pancreatic fistula. Our pancreatic fistula rate falls within the range of 3–26% reported in the literature.[3,6–8] This wide variability of fistula rates is likely due to discrepancy in the diagnostic criteria used to define pancreatic fistula across the various studies. A review by Bassi et al. identified more than 25 definitions of pancreatic fistula that vary based on the daily amount of drain output, amylase level of the fluid and duration of drainage.[23] In this

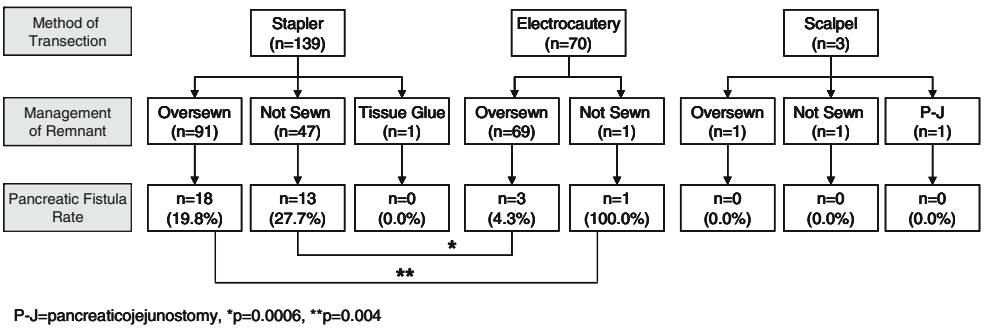

Figure 1 Legend—flowsheet demonstrating the breakdown of patients by method of transection of pancreatic remnant, management of the remnant, and fistula rates.

Table 4 Characteristics of Patients with Pancreatic Fistula

Clinical characteristics of patients with pancreatic fistula (n=36)	
Mean age (years, range)	53.8 (21–77)
Gender	
Female	20 (55.6%)
Male	16 (44.4%)
Mean body mass index (range)	26.5 (17.9–43)
Procedure	
Open distal pancreatectomy and splenectomy	28 (77.8%)
Open distal pancreatectomy (spleen preserving)	2 (5.6%)
Laparoscopic distal pancreatectomy and splenectomy	4 (11.1%)
Laparoscopic distal pancreatectomy (spleen preserving)	2 (5.6%)
Additional organs resected	14 (39%)
Median length of postoperative hospital stay days (range)	10 (4-61)
Grade of Fistula	
Grade A	16 (44.4%)
Grade B	16 (44.4%)
Grade C	4 (11.1%)
Management of fistula	
JP drain alone	15 (41.7%)
JP drain+octreotide	11 (30.6%)
Interventional radiology drainage	8 (22.2%)
Endoscopic cystgastrostomy	1 (2.8%)
Reoperation	3 (8.3%)

study, pancreatic leaks were defined and classified according to the standard definitions outlined by the ISGPF.[22] Pancreatic fistula was defined as a drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than three times the serum amylase content. Grade A fistulas, or "transient fistulas," have little clinical impact. Grade B fistulas require a change in management, usually have persistent drainage after 3 weeks and may be associated with signs of infections. Grade C fistulas are associated with a major change in clinical pathway and patient stability may be borderline. The ISGPF definition has resulted in an internationally accepted standard definition of pancreatic fistula that allows for better comparisons between fistula rates from different institutions. Using the ISGPF definition, our pancreatic fistula rate of 16.7% falls in the middle of the range of reported rates in the literature. Given the fact that the ISGPF definition was not published until 2005, many leaks were identified and graded in a retrospective fashion by reviewing inpatient medical records.

Table 5 Postoperative Complications

All postoperative complications (total patients=215)	No. of patients (%)
Pancreatic fistula	36 (16.7)
Intra-abdominal abscess	22 (10.2)
Small bowel obstruction	8 (3.7)
Respiratory	6 (2.8)
Cardiac	5 (2.3)
Sepsis	4 (1.9)
Wound infection	3 (1.4)
Delayed gastric emptying	2 (0.9)
Mortality	2 (0.9)
Patients with complication	55 (25.6)
Patients without complication	160 (74.4)

Management of pancreatic fistula following DP has not been standardized. The majority of the pancreatic fistulas that occurred in our series were either Grade A or Grade B. All of these were managed conservatively. Intra-operatively placed drains were maintained and additional percutaneous drains were placed when necessary for undrained collections. Octreotide was administered to patients at the discretion of the surgeon. Patients were additionally supported with parenteral nutrition when indicated. Most patients had a delay in hospital discharge as a result of their fistula. With conservative management, all Grade A and B fistulas closed spontaneously. Four Grade C fistulas occurred in our study. Three of these required reoperation for either hemorrhage or abdominal sepsis. Mortality occurred in two patients with Grade C fistulas; both of these patients had malignant tumors with metastatic disease. The increased utilization of healthcare resources and

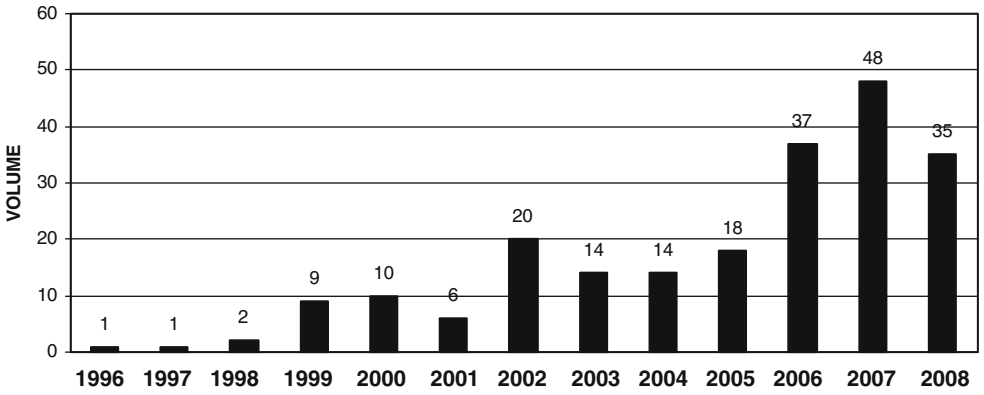

Figure 2 Graph demonstrating increasing volume of distal pancreatectomies by year at Thomas Jefferson University Hospital.

potential severity of disease associated with pancreatic fistula illustrates the need for effective methods to reduce their incidence.

The optimal surgical technique for both pancreatic transection and closure of the pancreatic remnant remains a debate. A multitude of surgical techniques and instruments have been proposed for reducing the occurrence of pancreatic fistula. A partial list of techniques includes hand-sutured closure, stapled closure, sutured plus stapled closure, sealing with fibrin glue, application of mesh, seromuscular flaps, ultrasonic dissection, bipolar scissors, pancreaticoenteric anastomosis, and ligation of the main pancreatic duct.[3,6–9,11–21] The most frequently used techniques are the suture and stapler closures of the pancreatic remnant. Kleeff et al. have observed a significantly increased risk of pancreatic fistula with stapled closure.[9] In contrast, other investigators have reported increased pancreatic fistula rates with sutured closure of the pancreatic remnant.[3,14,15,24] Many have concluded that the method of stump closure has no impact on the incidence of pancreatic fistula.[12,13,21,25,26]

In our study, the surgical technique most commonly involved transection of the pancreatic parenchyma with a stapler or electrocautery. The pancreatic remnant was then either oversewn or not oversewn at the discretion of the attending surgeon. We found a significantly lower fistula rate in pancreatic remnants that were cauterized and oversewn (4.3%), as compared to remnants that were stapled and oversewn (19.8%; $p=0.004$) or stapled and not oversewn (27.7%; $p=0.0006$). Bivariate analysis confirmed the importance of method of transaction ($p=0.012$), type of remnant closure/sealing ($p=0.012$), and surgeon volume ($p<0.001$) for pancreatic fistula after distal pancreatectomy. Multivariate analysis failed to demonstrate one single independent factor, although the method of pancreatic transection showed a nearly significant increase in risk of fistula ($p=0.058$, hazard ratio=3.2) with the use of non-stapled transection. It is likely that if there were more patients in our study, this factor would have reached statistical significance.

Interestingly, surgeon volume was a significant factor in the determination of pancreatic fistula. We used a cutoff of <20 procedures during the period of this study. This left us with groups that were relatively equal in size. There were a total of 24 surgeons who performed distal pancratectomies in this series, with a volume range of 1 to 67. The median number of cases performed was 2.5, and there were three surgeons who performed more than 20 procedures with a leak rate of 10% in the high volume group, as compared to 28% for the lower volume surgeons. This factor was not, however, significant on multivariate analysis. Surgeon volume has not been thoroughly examined as a specific risk factor for pancreatic fistula after pancreatic resection, and in fact, ours is the first one that we could find that addressed its potential importance for leaks after distal pancreatectomy. Another fact that we found to be significant was institutional volume. Starting at the beginning of 2006, there was a dramatic increase in the number of pancreatic resections performed. In 2006, 2007, and half of 2008, there were a total of 120 distal pancreatectomies a

Table 6 Bivariate Analysis

Bivariate analysis: proportion of cases with pancreatic fistula by selected risk factors			
Method of pancreatic transection	Not stapled 4/73=5.48%	Stapled 31/139=22.30%	chi-square=9.83, df=1, $p=0.002$
Method of sealing pancreatic remnant	Oversewn 21/161=13.04%	Not oversewn 15/54=27.78%	chi-square=6.30, df=1, $p=0.012$
Surgeon volume	High 14/136=10.29%	Low 22/79=27.85%	chi-square=11.05, df=1, $p<0.001$

Table 7 Multivariate Logistic Regression Analysis

Multivariate logistic regression analysis

Variable	Effect	Odds ratio	95% LCL	95% UCL	df	Wald X^2	p value
Age	50–59 vs. 18–49	0.565	0.188	1.696	3	2.0570	0.5607
	60–69 vs. 18–49	0.524	0.175	1.564			
	70+ vs. 18–49	0.521	0.174	1.563			
Gender	Male vs. female	1.137	0.485	2.666	1	0.0870	0.7680
Body Mass Index	25–29.99 vs.<25	1.238	0.498	3.081	2	1.3065	0.5203
	>=30 vs. <25	0.658	0.237	1.825			
Estimated Blood Loss	200–499 vs. <200	2.023	0.684	5.981	3	1.7330	0.6296
	500–799 vs. <200	1.744	0.440	6.903			
	800+ vs. <200	1.407	0.395	5.014			
Method of pancreatic transection	Stapled vs. non-stapled	3.242	0.962	10.928	1	3.5980	0.0578
Method of sealing pancreatic remnant	Not oversewn vs. oversewn	1.570	0.669	3.686	1	1.0744	0.2999
Surgeon volume	Low vs. high	1.881	0.785	4.510	1	2.0066	0.1566

year (mean=40 per year), while in the prior years of the study, there were 93 distal resections (mean=9.5). As one would expect, the increased institutional volume lead to a significant decrease in the number of pancreatic fistulae (26% vs. 10%, p=0.003).

Several authors state that the texture of the pancreatic parenchyma is an important risk factor associated with the development of postoperative pancreatic fistula.[3,12,13] Fibrotic pancreatic tissue is believed to be less likely to leak as compared to soft pancreatic parenchymal tissue, as long as the continuity of the main pancreatic duct is not compromised. Due to the retrospective nature of our study, we were unable to include pancreatic texture as a variable in our analysis as we found that it was not consistently reported in the operative reports and medical records that were reviewed.

The administration of prophylactic octreotide to reduce the incidence of postoperative pancreatic fistula remains controversial. Several studies have shown that prophylactic octreotide reduces the rate of pancreatic fistula following elective pancreatic resection.[27–30] In contrast, other authors have shown no benefit to the use of prophylactic octreotide.[31,32] Prophylactic octreotide was not included as a variable in our study. The retrospective nature of our study precluded its use as a variable for analysis, as we found that it was not consistently reported in the reviewed medical records.

Laparoscopic surgery has quickly been adopted as the standard for a variety of solid organ resections. In the surgical treatment of pancreatic disease, laparoscopic resections are becoming increasingly popular. To date, most reports of laparoscopic distal pancreatectomy are small series from single institutions.[33–38] The occurrence of pancreatic fistula following laparoscopic distal pancreatectomy in these studies has been reported as ranging from 13% to 50%.[33–38] A large, multi-center retrospective review comparing laparoscopic distal pancreatectomy with open distal pancreatectomy reported shorter length of hospital stay with laparoscopic distal pancreatectomy and no significant differences in major complication rate or pancreatic fistula rate when compared to open distal pancreatectomy.[39] In our series, laparoscopic distal pancreatectomy was attempted in 16 patients and completed in 13 patients. Pancreatic fistula occurred in six (42.6%) of these 13 patients. This fistula rate is at the higher end of the reported ranges in the literature. We expect that as this technique becomes more widely used and newer techniques are developed, the incidence of pancreatic fistula will decrease.

Our institution has recently opened a randomized, prospective clinical trial evaluating the method of pancreatic stump closure following distal pancreatectomy (NCT00889213). In this trial, patients are stratified by pancreatic texture and randomized to one of two methods of closure—standard closure (investigator's choice of stapler, cautery, or sharp transaction with suture closure at surgeon's discretion) or experimental closure which adds an autologous falciform patch and the placement of fibrin glue (Vitagel) between the parenchyma and the patch. This trial began accruing patients in August 2008 and has an accrual goal of 190 patients. We hope that this trial will help to resolve the controversy around management of the pancreatic stump after distal pancreatectomy.

In summary, pancreatic fistula remains a significant cause of the morbidity associated with distal pancreatectomy. The method of transection of the pancreatic parenchyma and management of the pancreatic remnant appear to be related to the formation of pancreatic fistula. This series suggests that transection using electrocautery followed by oversewing of the pancreatic remnant minimizes the formation of pancreatic fistula. Additional prospective,

randomized studies are needed in order to determine the optimal surgical technique for parenchymal transection and remnant closure during distal pancreatectomy to minimize the occurrence of postoperative pancreatic fistula.

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SSAT POSTER PRESENTATION

Pancreatic Exocrine Function Is Preserved After Distal Pancreatectomy

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Abstract
Introduction Our objective was to measure human stool elastase-1 to determine the effect of distal pancreatectomy on exocrine function.
Methods During a 72-month period, 115 patients underwent resection. Stool elastase values were measured preoperatively in 83 patients and repeated at 3, 12, and 24 months. The amount of pancreas resected was divided into two categories—limited to the left of the portal vein and those resections over or extended to the right of the vein.
Results Elastase values were normal in 84% (n=70) of cases prior to resection (33% if chronic pancreatitis, 70% if pancreatic adenocarcinoma). In the 70 patients with normal preoperative values, exocrine function was maintained in those with resection that was limited to the left of the portal vein at 3, 12, and, 24 months. If the resection was over or extended to right of the portal vein, then 88% maintained normal exocrine function at 3 months, 92% at 12 months, and 100% were normal at 24 months.
Conclusion Of patients undergoing distal pancreatectomy, one sixth will have preoperative pancreatic insufficiency, most commonly those with pancreatic adenocarcinoma or chronic pancreatitis. Postoperative pancreatic insufficiency was seen transiently in those with resection that extended to the portal vein or beyond.

Keywords Pancreas · Pancreatectomy · Exocrine function · Elastase · Function test pancreatic

Introduction

Pancreatic exocrine function after pancreatectomy is infrequently considered, yet exocrine function may have far-reaching nutritional implications in patients before or after surgery. The malabsorption resulting from exocrine insufficiency leads to poor nutritional status and can have a significant impact on our patient's ability to tolerate their disease, the resection, and potential chemotherapy/radiotherapy protocols. Previously, assessment of pancreatic exocrine function has been time-consuming and unreliable. In 2001, an assay for human stool elastase-1 (HSE-1) became commercially available and had several advantages over traditional testing.[1–7] These advantages included simplicity of testing and accuracy—the test did not require a 24-h stool collection or a special diet, HSE-1 specifically measures human elastase so it is not affected by oral enzyme supplementation which is from an animal source, and HSE-1 results in few false positives with a normal value having >99% sensitivity.

We have previously reported on the effect of pancreaticoduodenectomy (PD) on pancreatic exocrine function using HSE-1.[8] We found that 78% of patients with pancreatic cancer already had exocrine insufficiency before resection and that PD resulted in exocrine insufficiency in 50% of patients with normal function pre-resection. To our knowledge, no study has assessed exocrine function after

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distal pancreatectomy (DP) using HSE-1. If this information was available, the following questions could be addressed. How frequently do patients with disease in the distal pancreas present with exocrine insufficiency? Will resection of the distal pancreas lead to short- or long-term postoperative exocrine insufficiency? Does the extent of resection during DP have an effect on postoperative exocrine function? Should central (middle) pancreatectomy be prioritized over distal pancreatectomy for neck and body tumors to preserve exocrine function?

Materials and Methods

Soon after HSE-1 analysis became commercially available, use of the assay was implemented in our institution. In November of 2001, we began to analyze for HSE-1 in patients that were candidates for pancreatic resection. HSE-1 level was measured at the following time periods—preoperatively, and then postoperatively at 3±2, 12±3, and 24±6 months. These postoperative sample times were utilized as they are designated times for follow-up imaging in patients that are resected for cystic neoplasms of the pancreas; the majority of our cases were resected for this indication. We searched an Institutional Review Board (IRB)-approved single-surgeon database for all distal pancreatic resections performed between July 2002 and June 2008. A preoperative HSE-1 was required to enter this study, since each patient acted as their own control. During this period, 115 patients underwent distal pancreatectomy; 31 (27%) cases were excluded due to a lack of a preoperative HSE-1 test, while one case was excluded because of a previous pancreaticoduodenectomy. The medical records of these remaining 83 patients were then analyzed in detail for demographics, pathologic tissue diagnosis, amount of pancreas resected, and all pre- and postoperative HSE-1 levels.

Human Stool Elastase-1

HSE-1 was defined as "normal" if it is >200 μg/g stool. The value of >200 μg/g stool has a >99% sensitivity (few false positives).[9] The laboratory that analyzes our samples, as well as other laboratories nationwide, divides results into several categories of normal and abnormal. Severely abnormal is defined as <100 μg/g stool, moderately abnormal 100–200 μg/g stool, low normal 201–480 μg/g stool, and normal >480 μg/g stool. We chose, however, to use a cutoff of >200 μg/g stool for normal based on the >99% sensitivity and the lack of available data of similar strength to support stratifying the results into more subgroups. While the test has a high sensitivity for "normal" results, the same is not necessarily true for the sensitivity with respect to "abnormal" results. Therefore, if the value was abnormal at <200 μg/g of formed stool, it may have been that the patient was not truly exocrine insufficient, i.e., the result could have been falsely low as with loose watery stool from ulcerative colitis without exocrine insufficiency, and the stool weight had been falsely increased due to excess water in the stool. The caveat is that a "normal" test appears reliable and our analysis focused on these patients.

Therefore, if patients had a HSE-1 that was abnormal, they were asked if the stool sample was formed or loose. If it was formed, then all patients with an abnormal HSE-1, either preoperatively or postoperatively, were placed on exocrine enzyme supplementation regardless of symptoms that might suggest enzyme insufficiency such as weight loss, diarrhea, or steatorrhea. In patients with loose stool, the test was repeated, and if they could not produce a formed stool, then clinical judgment was used to determine if enzyme supplementation should be recommended. To emphasize, because of the inaccuracy of an "abnormal" HSE-1 value, we focused our study on an analysis of just those with preoperative normal levels.

Surgical Technique

DP was performed with or without splenectomy. The pancreas was transected in all cases with a #15 blade and the pancreatic duct oversewn with 6–0 monofilament non-absorbable suture. The pancreatic stump was then closed in a fish-mouth fashion with 3–0 silk suture. The cases were divided into two groups depending on the amount resected—those where resection was limited to the left of the portal vein and those where the transection was directly over or to the right of the portal vein.

Data Analysis

Statistical significance was established using chi-square or Fisher's Exact test, where appropriate. Some patients did not provide a stool sample at each of the three postoperative time periods. We initially dealt with the missing data by comparing each post-resection time period's value to that patient's preoperative stool HSE-1 value. To further minimize bias due to cases that did not have postoperative samples, we used an actuarial method to evaluate the cumulative incidence of normal postoperative stool HSE-1 values in those cases where the preoperative stool HSE-1 was normal. We first established that an actuarial event curve would examine for the following event—the achievement of a normal test much like a Kaplan Meier curve would examine for mortality. Once a normal test was achieved, then the case would be censored (similar to mortality). We decided that "normal" would be restricted to the time when all low measurements had ended, i.e., in a

case that was normal at 3 months, low at 1 year, and normal at 24 months, then "normal" was designated at 24 months and not 3 months. With fewer samples, the confidence interval would be wider, and perhaps the actuarial method might help define the confidence in this method. A p value of <0.05 was considered to be statistically significant.

Results

Of the 83 patients with preoperative HSE-1 in the study, the average age was 57±15 years (range 16–90), and 53 (64%) were female. In Table 1, the final pathologic tissue diagnosis is listed by order of frequency. Note that 55% (n=46/83) were cystic neoplasms (serous cystadenoma, intraductal papillary neoplasm, or mucinous cystadenoma).

Preoperative HSE-1 values were normal in 84% (70/83). Normal preoperative HSE-1 values were seen less commonly in cases with pancreatic adenocarcinoma or chronic pancreatitis (PC and CP). Normal HSE-1 levels preoperatively were observed in 56% (9/16) of cases with PC and CP versus cases with other diagnoses, where 91% (61/67) were normal preoperatively (p=0.0006).

Note that preoperatively, we requested a stool sample from all 115 cases. Only 83 samples were obtained for two reasons—we did not request the sample in a timely manner (a computerized checklist had to be devised), and the remainder was due to lack of patient compliance. The latter two reasons resulted in 27% of the 115 cases not providing a stool sample and ineligibility for this study.

Since abnormal stool HSE-1 values are not reliable and each patient acted as their own control, we then focused our analysis on the 70 cases with normal preoperative results. In these 70 patients with preoperative HSE-1 samples, there were 84 postoperative HSE-1 stool values available—at 3 months (n=45), at 12 months (n=23), and at 24 months (n=16). There were three reasons for not having a postoperative sample for the 83 patients—the patient was not far enough postoperative at each time period, patient compliance, and not following the computerized checklist.

Table 2 shows the rate of maintained normal HSE-1 values at each of the postoperative testing periods for all cases and then those that had resection to the left of the portal vein or extended onto the portal vein or to the right of the portal vein. By 24 months postoperatively, all patients with HSE-1 values had maintained their normal exocrine status. Of patients whose resection was limited to the left of the portal vein, again, all patients had normal postoperative HSE-1 values at 3, 12, and 24 months. Of those with resection extended over or beyond the portal vein, 88% had normal postoperative HSE-1 at 3 months (p=0.10), 92% at 12 months (p=0.33), and 100% at 24 months (p=1.0).

When using the more restricted definition of "normal" only if no subsequent sample was abnormal, the actuarial cumulative incidence of maintained "normal" values for all HSE-1 samples were normal at 2 years after resection. Regardless of the extent of resection, no difference was observed in the maintenance of normal HSE-1 at any of the time periods.

Discussion

Human pancreatic elastase is ideal to assess the ability of the pancreatic parenchyma to excrete digestive enzymes as it passes unaltered from the pancreas into the gut, is not digested or absorbed, and appears in the stool concentrated greater than five-fold.[3,6] The enzyme is stable at room temperature for many days and can be shipped to diagnostic centers without special precautions.[3] Timed stool samples, invasive duodenal tubes, and special diets are not required. The HSE-1 test is an immunoreactive process (ELISA against human elastase-1) and is a specific test for just human elastase in the stool. HSE-1 is therefore not affected by oral enzyme supplementation, which is from an animal source. Finally, the test is highly sensitive to detect normal

Table 1 Pathologic Tissue Diagnosis

Disease	Number of patients (n=83)	Normal preoperative HSE-1 (n)
Serous cystadenoma	23% (19)	84% (16)
IPMN	22% (18)	94% (17)
Islet cell tumor	17% (14)	93% (13)
Pancreatic adenocarcinoma (PC)	12% (10)	70% (7)
Mucinous cystadenoma	11% (9)	100% (9)
Chronic pancreatitis (CP)	7% (6)	33% (2)
Other	8% (7)	86% (6)
All cases	100% (83)	84% (70)
Not PC, Not CP	81% (67)	91% (61)
PC and CP	19% (16)	56% (9)*

IPMN intraductal papillary mucinous neoplasia

*p=0.0006 PC and CP versus not PC, not CP

Table 2 In Those 70 Cases with Normal Preoperative HSE-1 Levels, the Percent of Those Who Maintained a Normal Postoperative HSE-1 at Varying Postoperative Measurement Periods, also Sorted by the Amount of Pancreas Resected

Extent of resection	3months (n=45)	12months (n=23)	24months (n=16)
70 cases with normal preoperative HSE-1			
Actual data			
Left of PV (43%, n=30)	100%	100%	100%
Right side or over PV (57%, n=40)	88%	92%	100%
All cases (100%, n=70)	96%	100%	100%
Actuarial data			
Left of PV	87% (70%, 97%)	96% (82%, 99%)	100%[a]
Right side or over PV	78% (61%, 91%)	89% (72%, 98%)	100%[a]
All cases	82% (70%, 91%)	92% (82%, 98%)	100%[a]

PV portal vein

[a] No abnormal cases remaining at 24 months, so confidence interval cannot be estimated

elastase activity. Any value >200 μg/g of stool indicates satisfactory exocrine function. In our experience, HSE-1 may not be accurate when the stool cannot be weighed accurately. HSE-1 measurements on unformed stool should be observed with caution, as they will be falsely low, suggesting low pancreatic exocrine function when it is not present (as in diarrhea from ulcerative colitis). For this reason, sensitivity is decreased in patients with small intestinal disease, such as Crohn's and short-gut syndrome (of which there were none in our study).[1–6] Valid interpretation can be made when a preoperative stool sample is normal, and it remains normal after the operation. Therefore, our analysis focused on the cases that had normal stool for elastase which should be considered to have >99% sensitivity.[9]

As HSE-1 is only recently commercially available, exocrine function after distal pancreatic resection has not been assessed using HSE-1. Our group has previously published the evaluation of pancreatic exocrine function with HSE-1 after pancreaticoduodenectomy (PD).[8] We found that 78% of all patients about to undergo PD had normal exocrine function, while only 32% of those with pancreatic adenocarcinoma had normal preoperative HSE-1. Additionally, we found a significant reduction in those able to achieve normal exocrine function at 3, 12, and 24 months after PD to 52%, 27%, and 50%, respectively. Of note, there appeared to be some return towards normal HSE-1 levels in the second year after PD where values might have been low at the 1-year test period.

In the current study, we attempted to assess the impact of distal pancreatectomy (DP) on exocrine function using HSE-1. Specifically, do patients undergoing DP have the same trend as PD towards preoperative pancreatic insufficiency secondary to disease? As with PD, might they experience further pancreatic insufficiency due to loss of pancreatic parenchyma from their operation? This information should help surgeons determine the importance of parenchymal preservation to plan the most appropriate resection, i.e., distal pancreatectomy or central (middle) pancreatectomy for a lesion in the neck or body of the pancreas.

We observed a similar rate of normal HSE-1 in the preoperative period during the current DP study as compared to our previous PD study. Normal exocrine function was observed in 84% of our distal pancreatectomy patients and 78% in the previous PD study. Two items seem to validate our use of HSE-1 in the assessment of exocrine function. First, in cases with pancreatic adenocarcinoma, we saw a significant reduction in the frequency of normal preoperative exocrine function before PD (32%), with 70% of patients normal before DP. This suggested that HSE-1 was able to discern if the tumor was blocking the main pancreatic duct in head lesions, but not in distal lesions. Second, HSE-1 was able to discern the diffuse disease of chronic pancreatitis before DP, where only 33% had normal preoperative HSE-1 values. We therefore believe that normal HSE-1 values should be assumed to indicate normal exocrine function in our DP patients.

After DP, most patients did not experience loss of exocrine function. Since the HSE-1 results are less reliable when abnormal, we chose to include only the 70 cases with normal values before DP—a subgroup that contained 84% of the original patients in the study. All patients whose distal pancreatic resection was limited to the left of the portal vein continued to have normal exocrine function at all postoperative time periods. In patients whose resections extended over or beyond the portal vein, a large majority (88% and 92%, respectively) maintained normal exocrine function 3 and 12 months after DP. All measured HSE-1 samples at 24 months were normal or had returned to normal after DP or extended DP. This data indicates that permanent postoperative pancreatic insufficiency, as a result of parenchymal loss from resection of the distal pancreas, was not observed. In the few cases where lower values were observed, the effect was transient. Using an actuarial method to compensate for the bias of missing samples, we found no difference in this trend for maintaining a normal HSE-1 after any type of DP. The random events that contributed to the missing samples did not change the cumulative incidence of a “normal” test in this group of 70 patients. The random events leading to missing samples

were that the patient was not far enough postoperatively at each time period, patient compliance, or not having and then not following a computerized checklist for the range of time to collect a stool sample.

Previous studies of the effect on exocrine function by DP have not utilized HSE-1 but rather defined exocrine insufficiency in a variety of ways—by clinical symptoms or the need for exocrine enzymes,[10,11] used timed stool collections for chymotrypsin,[12] serum detection of orally administered synthetic peptide bentiromide followed by measurement of free *p*-aminobenzoic acid in the urine or blood (BT-PABA),[13] and serum detection of pancreolauryl after oral administration of fluorescein dilaurate together with a standardized breakfast.[14] These reports are summarized in Table 3, but it is important to realize that only two of these studies measured preoperative exocrine function in 12 and 63 patients, respectively, and none of them used HSE-1.

Trauma patients needing DP (n=74) were studied by Cogbill and colleagues.[11] They observed no clinical symptoms or need for enzyme replacement after DP; however, preoperative exocrine testing was not possible and the follow-up time was not noted. Sato and colleagues[13] studied a variety of cases of tumors of the pancreas treated with DP (n=12). The Sato study used objective testing BT-PABA and did not observe a significant decline in exocrine function after DP. Probably, the best study to relate to our study is the one by Falconi and coworkers.[12] They used 72-h fecal chymotrypsin in 50 patients with benign tumors. All had normal preoperative fecal chymotrypsin levels, and they were observed at 1-year post DP that 28% excreted less chymotrypsin and therefore qualified for exocrine insufficiency. The two remaining studies assessed patients with chronic pancreatitis (CP), the majority of which should already have exocrine insufficiency. Hutchins and coworkers[14] showed no change after DP in 63 patients with CP using detection of serum pancreolauryl after oral dilaurate, a test thought to be the best "tubeless" exocrine assessment. The majority of these cases with CP did not have normal exocrine function preoperatively. Riediger and colleagues[10] studied the outcomes of all types of resection for CP. In the group having DP, they found 38% with postoperative insufficiency in 21 CP patients at approximately 56 months after DP, but did not state the preoperative percentage of insufficiency. This review of these heterogeneous reports suggests minimal effect on exocrine function by DP, if exocrine function was thought to be normal before DP and the patients were followed for more than 1 year.

The implications of this review and our results with HSE-1 testing have two considerations—first, detection and treatment of exocrine function, and second, the choice of central pancreatectomy (also called middle pancreatectomy) to preserve exocrine function. The first consideration is to focus on exocrine function before and after pancreatic resection. A significant number of cases are exocrine insufficient before surgical resection, implying malabsorption. Our focus should be to seek the presence of malabsorption and malnutrition and then reverse them preoperatively. We recommend that all patients presenting with disease in their distal pancreas, and especially patients with pancreatic adenocarcinoma and chronic pancreatitis, undergo preoperative screening, using HSE-1 for pancreatic insufficiency.

If HSE-1 is normal, then preoperative enzyme supplementation is not required. If HSE-1 is not normal and the patient submitted a formed stool, then enzyme supplementation should be recommended to improve nutritional status and decrease subsequent morbidity related to the pancreatic operation. The same logic is recommended for use of postoperative HSE-1 testing. In those patients who underwent a distal resection that extended over or beyond the portal vein, we recommend close monitoring for 2 years, both by HSE-1 testing and symptom evaluation and subsequent enzyme supplementation as necessary. HSE-1 values may return to normal at 2 years after operation.

Second, regards central pancreatectomy. The lack of impact on long-term exocrine function in a person with

Table 3 Review of Pancreatic Insufficiency After Distal Pancreatectomy

First author	Number of patients	Disease	Follow-up time	Exocrine function assessed	Preop exocrine insufficiency (%)	Postop exocrine insufficiency (%)
Cogbill[11]	74	Trauma	Unknown	Symptoms/need for pancreatic enzymes	Not assessed	0
Sato[13]	12	Various	2 months	Oral BT-PABA	50	42
Falconi[12]	50	Benign tumors	12 months	72-h fecal chymotrypsin	0	28
Hutchins[14]	63	Chronic Pancreatitis	34 months (mean)	Pancreolauryl assay or 72-h fecal fat	65	61
Riediger[10]	21	Chronic pancreatitis	56 months (median)	Symptoms/need for pancreatic enzymes	Not stated	38

BT-PABA bentiromide ρ-amino benzoic acid cleaved by chymotrypsin to be excreted in urine as PABA

normal exocrine function before DP (even extended DP) may assist decision-making. Support for the latter operation has been that preservation of the tail and body of the pancreas would theoretically prevent exocrine insufficiency secondary to parenchymal loss.[15,16] Since leak rates, operative times, and other complications are higher after central pancreatectomy than for DP,[17] our data would not support central pancreatectomy for preservation of exocrine function. Consideration for central pancreatectomy should therefore be focused on preserving endocrine rather than exocrine function.

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ORIGINAL ARTICLE

Impact of Splenectomy on Thrombocytopenia, Chemotherapy, and Survival in Patients with Unresectable Pancreatic Cancer

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Abstract
Background Patients with unresectable pancreatic cancer (PDAC) or endocrine tumors (PET) often develop splenic vein thrombosis, hypersplenism, and thrombocytopenia which limits the administration of chemotherapy.
Methods From 2001 to 2009, 15 patients with recurrent or unresectable PDAC or PET underwent splenectomy for hypersplenism and thrombocytopenia. The clinical variables of this group of patients were analyzed. The overall survival of patients with PDAC was compared to historical controls.
Results Of the 15 total patients, 13 (87%) had PDAC and 2 (13%) had PET. All tumors were either locally advanced (n=6, 40%) or metastatic (n=9, 60%). The platelet counts significantly increased after splenectomy (p<0.01). All patients were able to resume chemotherapy within a median of 11.5 days (range 6–27). The patients with PDAC had a median survival of 20 months (range 4–67) from the time of diagnosis and 10.6 months (range 0.6–39.8) from the time of splenectomy.
Conclusions Splenectomy for patients with unresectable PDAC or PET who developed hypersplenism and thrombocytopenia that limited the administration of chemotherapy, significantly increased platelet counts, and led to resumption of treatment in all patients. Patients with PDAC had better disease-specific survival as compared to historical controls.

Keywords Pancreatic cancer · Palliative splenectomy · Pancreatic endocrine tumors

Introduction

The pancreas has a diverse cellular heterogeneity and function, and can give rise to a number of histologically distinct malignancies. Most malignant cancers originate from the ductal epithelium or endocrine cells and include pancreatic ductal adenocarcinomas (PDAC) and malignant endocrine tumors (PETs). Each histologic type has a different molecular signature and clinical course; PDACs are associated with the worst prognosis, and PETs are usually less aggressive.[1,2] Most patients with PDAC (85%) present with locally advanced or metastatic tumors that are unresectable. Treatment with gemcitabine-based chemotherapy has been shown to significantly improve survival, albeit to only a small degree.[3] In contrast, PETs usually present at an earlier stage. Chemotherapy is determined by the grade of the tumor, with high-grade tumors more likely to respond.[4–6] Thus, the goal of treatment for unresectable PDAC or PET is treatment with chemotherapy.

By virtue of the anatomic location of the pancreas, locally advanced PDAC or PETs can lead to thrombosis or

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occlusion of the splenic, superior mesenteric (SMV), and/or portal (PV) vein(s) with resultant hypersplenism. As in patients with cirrhosis and portal hypertension, the enhanced splenic function often produces thrombocytopenia. In addition, cytotoxic chemotherapeutic regimens, especially gemcitabine, often induce bone marrow suppression, which results in thrombocytopenia. When this occurs, many patients must stop their treatment, since serious and potentially lethal side effects could develop.

We hypothesized that a palliative splenectomy for patients with locally advanced unresectable PDAC or PETs who developed hypersplenism and thrombocytopenia that limited the administration of chemotherapy, would extend the duration of treatment and improve disease-specific survival (DSS). To investigate our hypothesis, we analyzed our experience with 15 patients who were managed with this novel treatment strategy and compared the survival of the PDAC subgroup of patients with stage-matched historical controls.

Material and Methods

Patients

Approval from the University of California, Los Angeles Office for the Protection of Research Subjects Institutional Review Board was obtained prior to initiating this study. Using a prospectively collected pancreatic cancer database, we performed a review of all patients from 2001 to 2009 with locally advanced or metastatic fine needle aspirate or biopsy (core needle, incisional, or excisional) confirmed PDAC or PET who were unresectable and underwent a splenectomy for severe thrombocytopenia that developed during administration of chemotherapy. The pathology reports were generated by one of four gastrointestinal pathologists on faculty at UCLA. The clinical, radiographic, and histopathologic findings; treatment and perioperative variables; and DSS of these patients were examined.

Clinical variables analyzed included gender, age, and stage at the time of diagnosis, and tumor histology (PDAC and PET). Radiographic variables analyzed included location of the tumor and PV/SMV/splenic vein status (patent vs. nonpatent) on high resolution computed tomography (CT) or magnetic resonance imaging (MRI) scans. Treatment variables analyzed included the pre- and post-splenectomy chemotherapeutic regimen administered and tumor response. Variables directly related to splenectomy that were examined included length of hospital stay, need for conversion to an open operation, white blood cell count and hemoglobin immediately after surgery (postoperative day 1), and pre- and postoperative platelet counts. Preoperative platelet counts were recorded at the last clinic visit prior to surgery. Postoperative platelet counts were recorded on the day of hospital discharge. The time to resumption of chemotherapy after splenectomy was also examined.

Survival Analysis

For survival analysis, the DSS of all patients with PDAC from the time of diagnosis or splenectomy was examined. For those patients who died, the date of death was determined from the clinic charts when available, or alternatively, the social security death index (http://ssdi.rootsweb.ancestry.com/cgi-bin/ssdi.cgi) by an exact match between the patient's name and birth date. If alive, the date of last follow-up was taken as the last time the patient was seen in clinic. The two patients with PET were not included in the survival analysis, as PET are less clinically aggressive than PDAC.

Statistical Analysis

For significance analysis, X^2 and Fisher's exact test were used as appropriate. DSS was estimated using the Kaplan–Meier method. All statistical analyses were performed using JMP statistical software (SAS Corporation, Cary, NC). Significance was assigned at the 0.05 level.

Results

Clinical, Radiographic, and Histopathologic Findings

From 2001 to 2009, 15 patients with unresectable pancreatic cancer who developed hypersplenism and thrombocytopenia, which limited the administration of their chemotherapy, underwent a splenectomy at UCLA Medical Center. The distribution of the clinical, radiographic, and histopathologic findings for these patients is listed in composite in Table 1 and individually in Table 2. Thirteen patients (87%) had primary disease; two patients (13%) recurred after a Whipple operation. The median age of patients was 56 years (range 25 to 62 years). Nine patients were male (60%) and 6 (40%) were female. Most patients had PDAC (n=13, 87%), while only two patients had PET (13%). All patients had locally advanced, stage 3 (n=6, 40%) or metastatic, stage 4 (n=9, 60%) disease. Nine tumors (60%) were located in the head/uncinate process and 6 (40%) were located in the body/tail. On high-resolution CT/MRI, the portal or splenic veins were thrombosed in 12 (80%) patients (Fig. 1); the three other patients had documented splenomegaly on CT/MRI. In fact, splenomegaly was not routinely reported in the radiology report per the usual practice of the UCLA gastrointestinal

Table 1 Composite Patients' Clinical, Radiographic, Treatment, and Histopathologic Characteristics

Age (median years)	56 (25–62)
Gender	
Male	9 (60%)
Female	6 (40%)
Histopathology	
PDAC	13 (87%)
PET	2 (13%)
Location	
Head/uncinate	9 (60%)
Body/tail	6 (40%)
Vein thrombosed	12 (80%)
Splenectomy (procedure type)	
Laparoscopic	11 (73%)
Laparoscopic converted to open	4 (27%)
Hospital stay (median days)	3 (2–6)
Platelet count	
Preoperative (median $\times 10^3$)	87 (66–160)
Postoperative (median $\times 10^3$)	425 (229–994)*

*$p<0.01$

radiologists for pancreas-protocol CT scans or MRIs. The median spleen weight was 348 g (range 164–525) but may be an underestimate of the actual spleen size due to morcellation prior to extraction. The spleen volumes are likewise not reported for similar reasons.

Treatment and Procedure Variables

The median time from the initial diagnosis of cancer to splenectomy was 9.8 months (0.3–58) during which all patients were administered chemotherapy. Chemotherapy was stopped due to thrombocytopenia within 2 weeks of surgery for all patients. Most patients with PDAC were administered a gemcitabine-based combination therapy (n=9, 69%) both before and after splenectomy; a 5-fluorouracil (5-FU)-based combination regimen was used less frequently (n=4, 31%). All patients had at least a partial tumor response to both drug treatments; there were no complete responses.

There was minimal morbidity associated with the splenectomy. A laparoscopic splenectomy was successfully performed for 11 (73%) patients, while the procedure was converted to an open operation for 4 (27%) patients. Excess blood loss was the primary reason for conversion. The median hospital stay was 3 days (range 2–6) and did not differ between the laparoscopic and open groups ($p>0.05$). Recorded immediately after surgery, the white blood cell count (median 11.05×10^3/μL, range 4.26×10^3–21×10^3) and hemoglobin (median 11.75 g/dL, range 9.2–13.3) did not reveal evidence of bone marrow suppression due to preoperative chemotherapy. At the time of splenectomy, 12 patients had National Cancer Institute (NCI)/Eastern Cooperative Oncology Group (ECOG) Grade 1 thrombocytopenia (defined by 75×10^3–150×10^3), two patients had NCI/ECOG Grade 2 (defined by 50×10^3–74×10^3), and one patient had impending NCI/ECOG-defined thrombocytopenia. The platelet counts significantly responded to splenectomy in all patients, preoperative (median 87×10^3/μL, range 66×10^3–160×10^3) vs. postoperative taken immediately prior to discharge (median 425×10^3/μL, range 229×10^3–994×10^3), ($p<0.01$). All patients were able to resume full dose of the same chemotherapy regimen after splenectomy within a median of 11.5 days (range 6–27).

Survival Analysis

The median follow-up for all survivors was 35 months (range 13–63) from the time of diagnosis and 25 months (range 0.6–51) from the time of splenectomy. The 13 patients with PDAC had a median survival of 20 months (range 4–67) with a 5-year DSS of 25% from the time of diagnosis, and a median DSS of 10.6 months (range 0.6–39.8) from the time of splenectomy (Fig. 2). Both patients with PET had well-differentiated tumors. One patient died of disease after 107 months, and the other is still alive with disease after 60 months.

Discussion

PDAC is the fourth leading cause of cancer-related deaths in the United States, with an overall 5-year survival of 4%. In 2009, 42,770 patients in the USA were diagnosed with PDAC and 35,240 died from their disease.[7] The poor outcome of patients with PDAC has been attributed to the advanced stage of disease at diagnosis, the poor response to current systemic and local therapies, and the aggressive biologic nature of the disease. Resection for PDAC provides the only chance for cure, but only about 15% of patients are eligible for surgery.[8] Even those patients who undergo a "curative resection" have a 5-year survival rate of 35% in the best series.[9] Most patients (85%) present with locally advanced or metastatic tumors, and they have a median survival of less than 12 or 5 months, respectively.[7] Chemotherapy can significantly extend DSS and decrease disease-related morbidity.[3]

PETs have been studied much less frequently than PDAC primarily due to their low prevalence; only about 2,500 new PETs are diagnosed annually in the United States.[10–12] PETs are categorized as functional or nonfunctional depending on whether the secreted peptide is biologically active and produces a clinical syndrome; about 50% of nonfunctional PETs secrete peptides that are

Table 2 Individual Patient's Clinical, Radiographic, Treatment, Histopathologic, and Survival Characteristics

Patient	Location	Histology	Stage	Chemo	Preop Plts ($\times 10^3$)	Postop Plts ($\times 10^3$)	Time to chemo (days)	Status at last F/U	Diagnosis to surgery (months)	Survival from Dx (months)	Survival from surgery (months)
1	H/U	PDAC	3	CiFU/LV+MitoC	82	370	13	DOD	1.37	4.2	2.8
2	H/U	PDAC	3	Gemzar	96	555	6	DOD	38.3	48.2	40
3	H/U	PDAC	4	GTX	87	425	14	DOD	57	15.7	5.9
4	H/U	PDAC	3	GTX	86	321	14	DOD	57.03	67.2	9.4
5	H/U	PDAC	3	GFLIP	87	533	22	AWD	38.3	63.5	25.2
6	B/T	PDAC	4	GFLIP	81	403	–	AWD	4.4	17.9	13.4
7	H/U	PDAC	4	CiFU/LV/MitoC/ Persantine	81	447	9	DOD	9.2	20.4	10.6
8	B/T	PDAC	3	CiFU/LV/MitoC/ Persantine	91	361	20	DOD	9.3	11.2	1.9
9	B/T	PET (well-diff.)	4	Temodar/Xeloda	66	864	10	AWD	9.6	60.3	50.7
10	H/U	PDAC	3	Gemzar	113	300	–	DOD	10.3	20.4	10.1
11	B/T	PET (well-diff.)	4	VP16/Cisplatin	111	679	27	DOD	5.03	107	95.8
12	H/U	PDAC	3	CiFU/LV/MitoC	86	541	–	DOD	10.6	28.3	17.3
13	B/T	PDAC	4	GTX	88	994	8	AWD	2.2	34.9	32.7
14	H/U	PDAC	4	GTX	73	237	6	DOD	9.13	17.4	17.1
15	B/T	PDAC	4	GTX	160	229	11	AWD	4.05	13.3	0.67

H/U head or uncinate tumor, *B/T* body or tail, *DOD* died of disease, *AWD* alive with disease, *CiFU* continous infusion 5FU, *LV* leukovorin, *MitoC* mitomycin C, *Gemzar* gemcitabine, *GFLIP* gemcitabine+5FU+leukovorin+irinotecan+persantine, *Temodar* temozolomide, *GTX* gemcitobine+taxotere

clinically silent.[13] Insulinomas are the most common type of PET, and a majority are benign.[14] In contrast, approximately 60% of non-insulin-secreting PETs are malignant.[11,15] Due to their less aggressive clinical behavior than PDAC and resistance to most current chemotherapeutic agents, PETs are treated aggressively with resectional therapy. However, cytotoxic chemotherapy is given to patients with unresectable PETs. Therapy is determined by the grade of the tumor.[4–6] Thus, chemotherapy is the primary goal of treatment for unresectable PET or PDAC for as long as the patient can tolerate it.

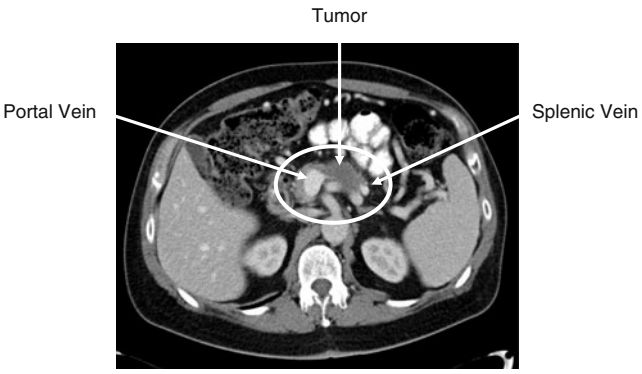

Figure 1 Representative pancreas-protocol CT scan from a patient with a PDAC located in the body/tail who has complete occlusion of the splenic vein and an enlarged spleen.

Locally advanced or recurrent pancreatic tumors of either histologic type in the head of the gland can involve the splenic vein, SMV, or PV. Tumors in the body or tail can involve the splenic vein. Either can cause venous

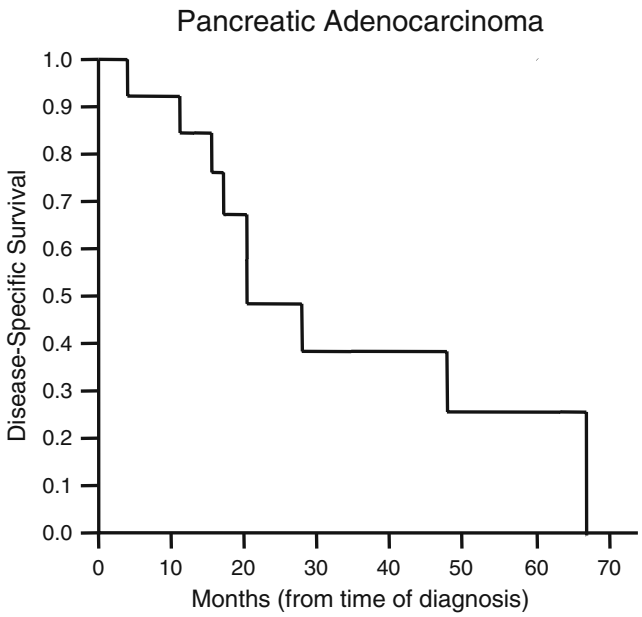

Figure 2 Disease-specific survival of 13 patients with PDAC. Median survival was 20 months (range 4–67 months).

occlusion from compression by the tumor mass or thrombosis of the vessel.[16] Left-sided portal hypertension, hypersplenism, and thrombocytopenia may result, which limits the patients' ability to tolerate aggressive chemotherapy. In this study, we examined the perioperative morbidity and effectiveness of splenectomy on restoring platelet counts to normal, administration of chemotherapy, and survival in our small series of 15 patients. A similar analysis was performed on 11 patients with hepatitis C, cirrhosis, and portal hypertension.[17] In this series, splenectomy reversed the hypersplenism-induced thrombocytopenia, and patients could resume pegylated interferon therapy.

A recent meta-analysis[3] of 50 trials (7,043 participants) on the effectiveness of 5-FU- or gemcitabine-based chemotherapy and radiotherapy for inoperable pancreatic cancer found that chemotherapy can significantly improve 1-year mortality ($p<0.00001$) in patients with locally advanced or metastatic PDAC and can also significantly decrease morbidity. Gemcitabine–platinum combinations significantly reduced 6-month mortality on subgroup analysis ($p<0.001$) and currently are the standard of care for the disease. Unfortunately, a number of factors often limit administration of chemotherapy to patients with pancreatic cancers. These include a poor functional or nutritional status; an unresponsive tumor and thus no clinical benefit to giving the drugs; bone marrow suppression that can result in severe anemia, leucopenia, and thrombocytopenia,[18] or isolated thrombocytopenia. The potential causes of isolated thrombocytopenia include hypersplenism, bone marrow suppression with preferential inhibition of platelet production, or other very rare causes such as gemcitabine-associated thrombotic microangiopathy,[19] or capecitabine (Xeloda)-induced idiopathic thrombocytopenic purpura. In fact, a major side-effect profile listed on the gemcitabine package insert includes thrombocytopenia. Thus, patients who are receiving chemotherapy, particularly gemcitabine-based regimens, are at risk of developing thrombocytopenia. With concurrent hypersplenism, the risk is even higher, as bone marrow production of platelets is usually be suppressed. Hypersplenism may unmask subclinical thrombocytopenia.

A recent study to develop a prognostic score that would predict survival after resection for PETs, using 3,851 patients from the National Cancer Data Base (1985–2004), found that age, grade, and distant metastases were the most significant predictors.[20] Administration of adjuvant chemotherapy was not associated with increased survival. Nevertheless, cisplatin and etoposide combination therapy is effective in treating patients with poorly differentiated PETs, while streptozocin, doxorubicin, and 5-fluorouracil is the standard cytotoxic regimen for functional PETs.[21] In fact, several studies suggest that PETs are more responsive to chemotherapy than endocrine tumors in other parts of the gastrointestinal tract, most notably carcinoid tumors. Our two patients with PETs who underwent splenectomy and aggressive chemotherapy have had excellent survival outcomes. As listed in Table 2, one patient is still alive with disease after 60 months and recently underwent an extensive resection of the primary tumor and multiple liver metastases. The other patient eventually died of disease after a rather long 9-year course.

Patients, with either PDAC or PET, who are offered splenectomy must demonstrate a good functional status, preferably with thrombocytopenia as the only factor limiting treatment. A complete blood cell count should be obtained preoperatively to exclude cytotoxic chemotherapy-induced bone marrow suppression as the primary cause of thrombocytopenia. If other blood elements are also low, particularly the absolute neutrophil count, then the chemotherapy should be considered as the primary cause of thrombocytopenia and splenectomy deferred. In this case, the dose of chemotherapy should be lowered or combination changed; alternatively, one might elect to give drugs that stimulate bone marrow production, such as granulocyte colony-stimulating factor or erythropoietin. If isolated thrombocytopenia is present, with the other elements normal, and there is evidence of hypersplenism on high-resolution imaging (e.g., portal vein thrombosis or an enlarged spleen), then splenectomy should be pursued. Ideally, we prefer that patients have a good response to chemotherapy, as measured by a decrease in tumor size or extent of disease on imaging and tumor markers; although, this was not the case in the present series, as patients underwent splenectomy over a wide time range from the time of diagnosis. CA19-9 is the best serum marker of response for PDAC;[22] chromogranin, synaptophysin, pancreatic polypeptide, or gastrin can be used for PET.[23] Patients must not have end-stage disease and severe malnutrition. We require that patients have a preoperative abdominal CT or MRI scan, which are usually being done for disease surveillance during treatment. The primary tumor is evaluated to ensure that it is not growing into the splenic hilum or to note additional features (varices, etc.) that will help in planning the procedure. In addition, the abdomen is evaluated for any signs of carcinomatosis and/or ascites. By using these stringent preoperative criteria prior to splenectomy, perioperative morbidity and mortality can be minimized, and platelet counts are likely to respond.

Patients who are not operative candidates can alternatively undergo splenic artery embolization or external beam splenic irradiation, as these two treatments can also potentially reverse hypersplenism-induced thrombocytopenia.[24] Embolization should be considered as second-line treatment after splenectomy because it can be associated with significant postoperative pain and splenic abscesses.[25] Furthermore, splenic irradiation is rarely performed for

hypersplenism but can be effective for relief of pain associated with splenomegaly in patients with hematologic disorders.[26] In our experience, as discussed previously, splenectomy is safe and can be performed with minimal morbidity and a short hospital stay.

There were no deaths in our series; hospital stay was short (median 3 days), and patients' platelet counts responded rapidly with quick resumption of chemotherapy (median 11.5 days). The median follow-up for all survivors was 35 months (range 13–63) from the time of diagnosis. The 13 patients with PDAC had a median survival of 20 months (range 4–67) with a 5-year DSS of 25% from the time of diagnosis, and a median survival of 10.6 months (range 0.6–39.8) from the time of splenectomy.

Conclusion

In conclusion, while the optimal treatments for patients with locally advanced or metastatic PDAC or PET are in evolution, we found that our novel strategy of splenectomy for the development of hypersplenism-induced thrombocytopenia that limited chemotherapy treatment was effective. Splenectomy was performed with minimal morbidity, and was associated with a rapid increase in platelet counts and a short time before resuming chemotherapy. In addition, patients with PDAC who underwent this novel treatment strategy had significantly improved DSS as compared to historical controls.

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ORIGINAL ARTICLE

‘Slowing Down When You Should’: Initiators and Influences of the Transition from the Routine to the Effortful

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Abstract
Background ‘Slowing down when you should’ has been described as marking the transition from ‘automatic’ to ‘effortful’ functioning in professional practice. The ability to ‘slow down’ is hypothesized as an important factor in expert judgment. This study explored the nature of the ‘slowing down’ phenomenon intraoperatively and its link to surgical judgment.
Methods Twenty-eight surgeons across different surgical specialties were interviewed from four hospitals affiliated with a large urban university. In grounded theory tradition, data were collected and analyzed in an iterative design, using a constant comparative approach. Emergent themes were identified and a conceptual framework was developed.
Results Surgeons recognized the ‘slowing down’ phenomenon acknowledging its link to judgment and described two main initiators. Proactively planned ‘slowing down’ moments were anticipated preoperatively from operation-specific (tying superior thyroid vessels) or patient-specific (imaging abnormality) factors. Surgeons also described situationally responsive ‘slowing down’ moments to unexpected events (encountering an adherent tumor). Surgeons described several influencing factors on the slowing down phenomenon (fatigue, confidence).
Conclusions This framework for ‘slowing down’ assists in making tangible the previously elusive construct of surgical judgment, providing a vocabulary for considering the events surrounding these critical moments in surgery, essential for teaching, self-reflection, and patient safety.

Keywords Judgment · Nontechnical skills · Expertise · Automaticity · Slowing down

Introduction

Surgeons face many challenges and uncertainties in the course of their daily clinical activities. Medicine is not an exact science, and when clinicians find themselves in the ‘muddy zones’ of practice, they must be able to detect, understand, and respond effectively to essential, relevant, yet sometimes subtle cues in the environment.[1,2] Effective responding requires a transition from a relatively routine or ‘automatic’ mode of practice implicit in expertise, whereby one is simply ‘doing what they know to do’,[3] into the more attentive mode of practice, requiring more cognitive effort and often intentional problem solving.

We have argued previously that this transitional process of ‘slowing down when you should’ is a crucial part of expert surgical judgment, and failing to transition during critical moments may lead to medical error and patient harm.[4] As an example, a postoperative tachycardia may be explained as uncontrolled pain rather than considering and recognizing the subtle cues of a pulmonary embolus. This study was designed to explore the factors that initiate and influence this transition from the routine to the effortful in operative surgical practice.

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Research Design and Methods

This study took place with institutional review board approval at four tertiary care academic hospitals associated with a single large urban medical school. Semistructured 60-min interviews were conducted with 28 surgeons who, by reputation, had sound operative judgment and were considered experts in their field (nine general surgery, four neurosurgery, three orthopedics, three cardiac surgery, three vascular, two otolaryngology, two plastics, one thoracic, and one trauma surgeon). Each interview was conducted by the principal investigator (a surgeon, CAM) and a research assistant (CEM). Interviews explored surgeons' general perceptions of expertise as it relates to operative judgment, as well as their perceptions and experiences of these transitions from the routine to the effortful in their operative practice (see Table 1). Elaboration of recent events and experiences was encouraged. Interviews were conducted individually (n=10) or in pairs of surgeons (n=9) within the same specialty. Both were valuable in exploring different aspects of this phenomenon, with paired interviews evoking a lively discussion of the details of recent operative experiences and individual interviews capturing a more personal reflection of the surgeon's individual experiences of this phenomenon.

This study used a constructivist approach to qualitative grounded theory methodology.[5,6] Consistent with the key elements of grounded theory, the study utilized an iterative design, with data collection and data analysis occurring concurrently to encourage theoretical ideas to emerge and then be explored further with subsequent data collection. As well, purposeful sampling was used. This allows for the phenomenon (in this study 'slowing down') to be explored in the desired population to maximize the richness of the data. Interviews from this study were audiotaped and recorded and then transcribed generating 458 pages of transcript. Coding was performed by two researchers (CEM and CM) who read the entire data set. A constant comparative approach to data analysis[5,7] was employed, consistent with grounded theory, to allow new instances from subsequent data collection to be compared with existing codes and categories. This coding structure and the emergent theoretical framework were discussed, refined, and confirmed by other members of the research team, consisting of a surgeon (HM), a qualitative researcher (LL), and a cognitive psychologist (GR). Sampling continued until saturation of the key emergent themes (the point in qualitative research where ongoing data collection fails to change or add to the existing theoretical framework) was achieved.[8] The final coding structure was applied to the complete data set, using NVivo software (2007, QSR International Pty Ltd), to facilitate cross-referencing.[9] A reflexive approach was used throughout the study. Confirmability was ensured by maintaining an audit trail of all analytical memos, minutes of the meetings, and revisions to the coding structure. This paper focuses on two emergent themes—the 'initiators' and 'influences' of the 'slowing down' phenomenon identified within a larger program of research, with other themes explored and published elsewhere.[10]

Results

When introduced to the concept of a transition from a routine mode to an effortful mode during surgery, all

Table 1 The Semistructured Interview Template

Introduction	
Theme 1: General thoughts on judgment	Preoperative, operative, postoperative judgment.
Theme 2: General approach to surgery	What is your routine preparation for a case?
	Do you use visual imagery or mental rehearsal, and if so, how?
	What does this preparation do for the case?
'Slowing down' phenomenon	
Theme 1: Recognition of the 'slowing down' phenomenon	Is this phenomenon recognizable?
	If yes, describe the details of a recent example.
	What are your telling signs of being in a transition?
	Do you notice it in others?
Theme 2: Understanding the 'slowing down' phenomenon	What causes the phenomenon to occur?
	What might inhibit or prevent it from occurring?
	Describe ways you manage the 'slowing down' moments.
Theme 3: Failure to 'slow down'	Describe events of previous 'mistakes'.
	Could they have been prevented?
	Do you remember a time you have said, "I can't believe I just did that"?
	If so, describe it and explain why you think it happened.

participants recognized this as a phenomenon occurring in their operative practice and described details of related events. As one surgeon described, "The change to that sort of state usually goes along with where I stop talking to the resident and focus very intently on what's going on and I may, again, ask for quiet in the room or to reduce distractions, that sort of thing." Surgeons related to the term 'slowing down', using it in their descriptions of events prior to the term being introduced in the interview. For example, one surgeon described the phenomenon in the following way: "… if I'm not in the right plane or if I haven't got the right exposure, I might slow down, rethink where I am." A framework for considering the initiators and influences of the phenomenon in practice evolved from this study and is represented in Fig. 1.

Initiators of Slowing Down

Surgeons described their experiences of 'slowing down' intraoperatively as either planned or unplanned. Planned transitions occurred at critical points that were flagged as requiring special attention—the *proactively planned* 'slowing down' transitions. Unplanned transitions were described as occurring in response to unexpected events caused by a variety of situations—the *situationally responsive* 'slowing down' transitions.

Proactively Planned 'Slowing Down' Transitions

Surgeons described critical points of operative procedures that were recognized and anticipated prior to commencing the operation. When these anticipated critical points were approaching, surgeons described themselves as becoming more focused, intentionally transitioning from the routine to the more effortful. These anticipated moments seemed to originate from cues that were either 'procedural specific', occurring each and every time the surgeon performed that procedure, or 'patient specific', occurring as a result of preemptive planning for the unique intricacies and potential hazards of the particular patient.

Procedural Specific In most, if not all operations, the surgeons recognized critical points where they experienced a tendency to pay more attention. Even for routine operations and for very experienced surgeons, there were critical parts identified that elicited a transition in the

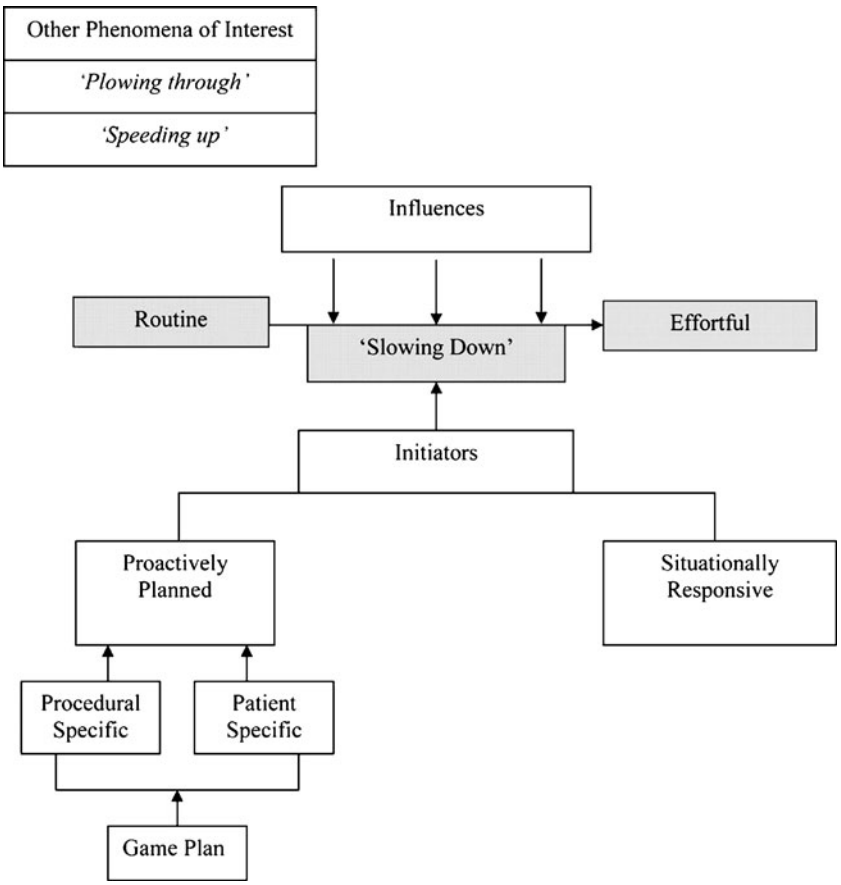

Figure 1 Conceptual framework for the 'slowing down' phenomenon.

surgeon from the routine to the effortful. As one example, a surgeon stated,

> "If we're doing a lung resection…dissecting pulmonary artery branches, that tends to be a quiet time, so we stop talking and just kind of focus on what we're doing, because there is potential for getting into big trouble. So, when we're at critical points where you could get into trouble, you know, the chatter stops." Interview 12, B03

Patient Specific In addition to the procedural-specific 'slowing down' moments, surgeons described patient-specific 'slowing down' moments that were identified preoperatively. As one surgeon explained, "I try and think through—now, what are the parts of this case that are going to be particularly difficult, if there are any, and try to think those through in advance." A general surgeon described a recent procedure in which a patient had previous abdominal surgery and was requiring further surgery; "Like the game plan starts right when you open up the abdomen and say it's a re-do, I say to the residents, 'do not cut until I'm in the room'." Recognizing the potential for injuring bowel upon entering the abdomen, the surgeon changed her routine. Rather than allowing the fellow to start the laparotomy without her supervision, which was her standard practice, she insisted on being present for it to ensure there was adequate care at that critical moment.

Game Plan The participants often described this activity of identifying *procedural-specific* and *patient-specific* checkpoints as the development of the "game plan". One surgeon stated that immediately prior to every case, he asks himself, "Where are the landmines? What's going to prevent me from getting my usual good result?" Through the preparation of understanding where these "landmines" are for any given procedure, surgeons felt better prepared to not only manage them appropriately but to also, in some cases, avoid them altogether. This anticipation of the "landmines" or checkpoints—both *procedural specific* and *patient specific*—was considered key to expert judgment based on the model of a surgeon who avoids getting into trouble rather than a surgeon who is forced to get out of trouble. As one participant said, "I have to say, you know, I think the people that I've worked with who have unbelievable judgment is because they're unbelievable at anticipating what's going to happen." This game plan often included techniques of mental rehearsal and visual imagery and provided a forum for the surgeon to consider the unusual and difficult parts of the procedure in advance.

Situationally Responsive 'Slowing Down' Transitions

Despite preplanning, surgeons made reference to the experience of having to react to the unexpected—to deal with intraoperative 'surprises'. They describe becoming more focused—transitioning from the routine mode to the more effortful mode in response to these situations. The *situationally responsive* 'slowing down' transitions were recognized and acknowledged by all surgeons and epitomized by one who said, "It's when you're looking at something you haven't seen before or you weren't expecting, then what do you do at that point? And so, obviously stopping to regroup and decide what to do." Participants used terms like "slowing down", "stopping", "regrouping", and "reassessing" to describe their experience with this unanticipated transition. The uncertainty surrounding unexpected events seemed to evoke a need to stand back and reassess the situation, slowing the pace of the operation or even stopping. Unlike the proactively planned transitions, where much of the thinking takes place preoperatively, situationally responsive 'slowing down' transitions seemed to involve a more elaborated intraoperative problem solving process, often leading to impromptu readjustments of the game plan.

Some surgeons talked about the transition as being initiated by cues that only become obvious after time: "… there's sometimes a series of cues and you know as sort of the captain of the ship you have to kind of decide when the cues have reached the level that you've got to, the frame shift occurs." Others described a sensation of recognizing the responsive transition only after the situation that caused it was over, having lacked awareness of actually being in a more effortful mode as it was unfolding. This was experienced as a 'sense of relief' after the fact, as with one surgeon's description; "Sometimes you don't even know you're there until it's over and you've done some stressful component to the operation, and as soon as it's done everybody kind of breathes a sigh of relief." The transition from the routine to the effortful, therefore, seems not always to be abrupt, intentional or consciously directed by the surgeon.

Influences on Slowing Down

Several factors were recognized as having the potential to influence whether the surgeon appropriately 'slows down' (Table 2; Fig. 1). They were considered to be different than the initiators which focused more on factors that caused the initial transition from the routine mode to the more effortful mode (e.g., bleeding, abnormal anatomy, categorized above into either *proactively planned* or *situationally responsive* 'slowing down' moments). Some were transitory 'internal' factors, such as fatigue; "my decision making and judgment

Table 2 Influences on the 'Slowing Down' Phenomenon

Transitory "internal" factors	'Personality' factors	Situational factors
Fatigue	Adaptability	Time pressure
Endurance	Confidence	Hierarchical pressure
Physical ailments	Humility	Distractions
	Fear of doing harm	Availability of resources
	Willingness to learn	Teaching pressures
	Fear of losing reputation	Team considerations
	Mindfulness	Social pressure
	Ego	
	Greed	

when I was tired or frustrated at one or two in the morning was not as crisp". Others factors were perceived to be related more to personality factors such as a lack of adaptability, with those who had the ability "to change directions based on receiving new information or information in a way that they hadn't considered it previously" being considered more likely to transition out of the routine when required, or overconfidence, which could often lead to surgeons "getting over their heads". Other factors affecting this process were seen to be more situational, such as time pressures ("I think the pressure of the clock is distracting…"), hierarchical pressures ("even if it is my case…you let the person do something and you think, gee, I hope we didn't do that… more out of respect for the surgeon, instead of respect for the patient."), or social pressures to create a "fun" operating room ("There is a social environment that you find yourself in").

Contrasts to the Experience of Slowing Down

During the interviews, surgeons also described details of situations that were distinctly different from the experience of successfully 'slowing down when they should'. Two such categories of experience were articulated in the interviews, categories we have labeled 'plowing through' and 'speeding up' (Fig. 1). They are mentioned here for completeness but will require exploration and elaboration with further study.

Plowing Through

Surgeons described operative experiences that they felt, in retrospect, were moments where they perhaps should have slowed down, but did not. Two broad forms of this 'plowing through' phenomenon were suggested by the participants. First, surgeons described 'plowing through' as a result of being unaware, or not appreciating, all pertinent, available information in their surroundings. These situations were construed by participants as a 'failure to slow down', occurring because of a failure to obtain an accurate or complete picture of the environment, or a lack of situation awareness. As one surgeon described,

> "I think, once in a while, you'd be working along a structure and you don't realize you were working with an anatomic variation and you hit something. Umm, and you say to yourself, geez, I didn't think I'd get into that vein or that artery…I mean you're sort of not listening to the anatomic cues that are presenting themselves to you…"
> Interview 7, A13

Although surgeons considered themselves to be paying attention to their environment, they recognized a failure to accurately read the cues that were available in an appropriate and timely manner. This became obvious to them in retrospect once the 'plowing through' had occurred.

A second form of 'plowing through' was associated with routine cases where participants thought they became complacent, failing to pay due diligence when necessary. As explained by one surgeon,

> "I think that's the other time you get burned. It's the easy ones, because the difficult ones you're going slow all the time. And that's exactly what happened here. It was an easy lobectomy—you're not going slow, you're maybe chit-chatting, you're maybe not paying as much attention."
> Interview12, B03

Surgeons admitted that because of the routine nature of the particular case, or part thereof, they allowed their concentration to drift and did not maintain the level of attention necessary to prevent a mishap from occurring.

Both of these forms of 'plowing through' were recognized causes not only of surgical mishaps ("injuring the facial nerve" or "compromising a tumor margin") but also of 'near misses'. As one participant described,

> "There will be times where you take a needle and you stab the surface of the heart because you weren't looking…you burn too close to the aorta when you're

> cutting through the pericardium and, you'll not get into the aorta, but it leaves a little mark and I think 'it's a good thing I didn't go deeper'…certainly there are times you say, 'oh yeah, that wasn't sharp'"
> Interview 10, B02

Regardless of whether this resulted in a mishap or a 'near miss', surgeons acknowledged that there was information available prior to the event that had been incorrectly interpreted or simply unattended and was therefore experienced by them as 'plowing through'.

Speeding Up

Another contrast to the experience of 'slowing down' was the sudden presence of an immediate, emergent life-threatening event such as a significant bleed or a cardiac arrest. This moment was described frequently by surgeons as a sense of 'speeding up' rather than 'slowing down'. The urgency required of the situation and the stresses associated with it were identified as the reasons for this subjective experience of 'speeding up'. Some participants recognized that sensing this urgency to act can lead to a cascade of errors and described an attempt to counteract this experience by purposefully slowing the pace and their movements down. As one surgeon stated, "Your mind speeds up but you have to force yourself to slow down because I recognise in myself if I go faster I will make more mistakes." Thus, in these circumstances, making a conscious effort to be more deliberate, slowing the pace of the operation down, seemed to be a mechanism used to prevent further trouble and regain control.

Discussion

Increasingly, the research focus related to the prevention of medical error has been shifting away from factors and actions related to the individual and toward an articulation of the systemic pressures and factors that enable human fallibilities and undermine structural fail safes.[11–15] This refocusing of the field on sociological and environmental human factors has offered an important step forward in understanding how error occurs despite the best intentions of humans within the system. At the same time, this refocus has placed very little research emphasis on understanding the ways in which individual expert performance functions as an integral part of a robust error checking system. The results of this study, therefore, have the opportunity to provide an important supplement to the literature on systemic factors in medical error with our exploration of how experts effectively self-regulate their activities and (often) avoid errors through a process of appropriately increasing attention to a task when unusual or complicating circumstances are present.

Professional expertise and cognitive psychology literatures indicate that experts engage in two different types of thought processes during their daily activities. First, through an accumulation of automatic resources, such as pattern recognition and cognitive scripts and schemas, professional experts spend the majority of their time in a nonanalytic, automatic, or 'routine' mode.[3,16–18] Activities in this routine mode are carried out with little cognitive effort.[19] In contrast, the analytic or effortful mode of processing is engaged when the expert is confronted with nonroutine aspects of practice, requiring recruitment of cognitive resources to deliberatively deal with the issue at hand.[20–22] Much attention in the judgment literature has focused on this dual-processing model, with researchers discussing the values of both the automatic and intentional processes.[23,24] However, little effort has been directed toward understanding the transition from one mode to the other in professional expertise.

Through an exploration of surgical experiences, our study provides a taxonomy and framework for considering the transition from the routine to the effortful—'slowing down when you should'—in surgical practice. This work is currently limited to interviews with surgeons in one educational institution, so requires further research to explore its transferability to other venues or disciplines. Nonetheless, the development of such a taxonomy has potential for guiding some important steps in improving practice and safety. It has been suggested that words not only allow us to express our thoughts but also shape them.[25,26] In this sense, our taxonomy has the potential to make explicit an activity that was, at best, implicit in experts' practice, a way of thinking intentionally about these important aspects of safe and effective practice. Combined with an understanding of the various levels involved with attaining and maintaining situation awareness in dynamic environments,[27,28] this framework may be a significant step toward developing a meaningful taxonomy for surgical error. Along these lines, many surgeons, following their interview, stopped the interviewer (CAM) in corridors to discuss subsequent 'slowing down' moments, their successes, *and* their failures. This suggests not only that the taxonomy has resonance with the participants but also that it offers a language for discussing such events that likely was not afforded our participants before their having participated in this reflective exercise. It also suggests that having the language increases the likelihood of awareness and recognition of 'slowing down' moments (both successes and failures), creating opportunities to address such events explicitly—enhancing them where they are occurring and increasing their occurrence in situations where they may not have taken place. Finally, it provides an important opportunity to teach about this

critical skill set, moving such educational experiences from the implicit curriculum (whereby learners are expected to simply absorb these lessons over extended observation)[29] to the explicit curriculum, with its attendant discussion and intentional efforts at improvement.

This study also generates a set of interesting opportunities for further exploration of the phenomenon. For example, several surgeons in this study noted that this transition can sometimes be recognized only through the 'sense of relief' felt after the events that initiated it are over. This raises the possibility that experts may not always be aware of the transition while it is occurring, forming the basis of our reference to this phenomenon as 'slowing down *when you should*', rather than '*knowing* when to slow down'. It is possible that surgeons respond to cues they perceive in their environment on a subliminal level without necessarily being aware of having done so.[30,31] If so, we might wonder about the extent to which this transition is intentional and conscious and the place of metacognitive theory in these processes.[32] In the psychology literature, a 'consciousness continuum' has been described whereby thoughts arising from information stored in the unconscious (automatic processing) are brought to the subconscious, available for full construction by the conscious using more effortful and intentional processing.[33] Awareness of the information occurs at some stage along the continuum depending on available cognitive resources. Given our limited attention capacity, it is possible that information is processed from the unconscious and influences behavior without us being aware prior to fully formed constructions of what that information means to us.[33] Complicating this issue, it is likely that many of these slowing down moments themselves become automated with repeated experience and therefore require a less fully formed construction of the process with growing expertise. Thus, the professional's evolving ability to respond to these fluctuations as well as maintaining an ability to monitor both the situation and themselves is an interesting area for future research.[34,35]

As a first step in this program of research, the current study has provided a taxonomy for the phenomenon of 'slowing down when you should' as it relates to expert surgical judgment. A future study might look at a population of surgeons who have a reputation for poor surgical judgment. What would the phenomenon 'slowing down' look like in this population and where would the differences lie when compared to the expert population? With language to represent the phenomenon and an ability to recognize it in surgical practice, we have a valuable framework to begin to develop a better understanding of what is involved when surgeons make, or fail to make, this transition from the routine to the effortful. Further studies could build upon this framework to develop a more comprehensive theoretical foundation for exploring surgical error.

From an educational perspective, this taxonomy and framework provides an opportunity to teach surgical judgment in a structured and explicit manner, taking advantage of the critical moments—both planned and unplanned—in every case. Making these 'slowing down' moments explicit, with an ability to recognize them in daily practice, provides opportunities for critical self-reflection, both 'in the moment' with implications for self-regulation and patient safety and following the event, leading to continuing improvements in surgical practice.

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CASE REPORT

Gastric Venous Reconstruction After Radical Pancreatic Surgery: Case Report and Review of the Literature

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Abstract Vascular resection during surgery for adenocarcinoma of the pancreas is being performed with increasing frequency in order to achieve an R0 resection. With increasingly radical operations come challenges for reconstruction. Generally, these are related to reconstruction of the portal vein; this is particularly true of long-segment vein involvement by the tumor, in which venous outflow from dependent organs can become compromised. We report the first case of left gastric vein to inferior mesenteric vein bypass during a radical total pancreatectomy with long-segment portal vein resection for pancreatic adenocarcinoma, performed to relieve severe gastric venous congestion.

Keywords Pancreatectomy · Vein · Reconstruction · Adenocarcinoma

Case Report

The patient was a 42-year-old female who presented with a 3-week history of jaundice, pruritis, dark urine, and clay-colored stool. She also complained of early satiety, constipation, lethargy, and 4 kg of weight loss. Physical examination was unremarkable but for the jaundice. Initial computed tomography (CT) scan revealed a 3-cm solid mass in the head of the pancreas, with intrahepatic and extrahepatic biliary dilatation. The portal vein was severely narrowed for a length of at least 3 cm as it coursed through the head of the pancreas (Fig. 1); there was no evidence of locoregional or distant metastasis.

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The initial bilirubin was 124 with an obstructive pattern to her liver function tests. A preoperative endoscopic retrograde cholangiopancreatography was performed, and a common bile duct stent was placed. Following this procedure, the patient developed moderately severe pancreatitis with CT evidence of peripancreatic fluid collections and edema of the gland. A pancreaticoduodenectomy with en bloc excision of the retropancreatic superior mesenteric vein (SMV)–splenic–portal vein confluence was planned. In the event that the extent of the tumor was difficult to define at the time of the operation, the possibility of a total pancreatectomy was raised preoperatively and informed consent was obtained for same.

The operation was performed through a midline incision; there were no peritoneal or visceral metastases. A Cattell–Braasch maneuver[1] was performed with mobilization of the entire root of the mesentery. This allows for excellent freedom of movement of the portal vein and also simplifies dissection of the neurolymphatic tissue along the posterior aspect of the superior mesenteric artery (SMA) and anterior aorta. The duodenum was completely kocherized, and the lesser sac was entered by dividing the gastrocolic omentum, enabling inspection of the entire pancreas.

On palpation, a large mass was felt in the head of the pancreas with extension into the neck and proximal body of the pancreas. Given the preoperative episode of pancreatitis, we were unsure whether this truly represented tumor or whether it was inflammatory tissue. Intraoperative frozen

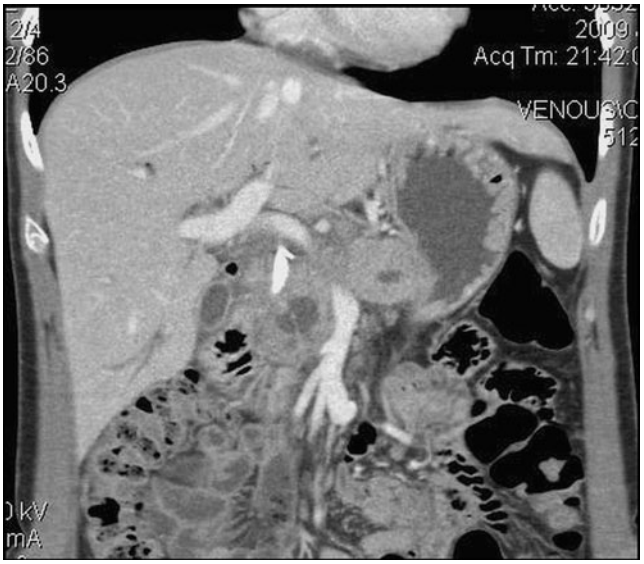

Figure 1 Portal vein compressed by tumor.

section from a Tru-Cut biopsy confirmed the presence of cancer and a decision was made to perform a total pancreatectomy, splenectomy, portal vein resection and reconstruction, and para-aortic lymphadenectomy. The neurolymphatic tissue encircling the first 15 cm of SMA was divided, and the pancreaticoduodenal vessels ligated and divided. We then mobilized the tail of the pancreas from left to right (dividing the short and posterior gastric vessels), including all fibrofatty tissue overlying the retroperitoneum in the lesser sac. The left side of the aorta was exposed, and all neurolymphatic tissue around the

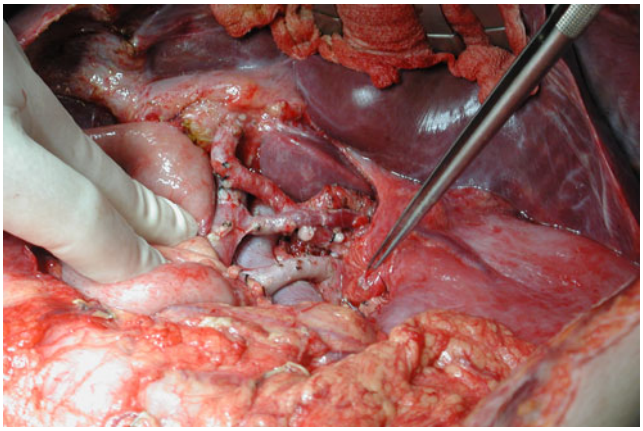

Figure 3 Patent LGV to IMV anastomosis and decompressed stomach.

celiac axis was dissected. We then mobilized all the lymph nodes along the right crus and aortocaval groove. As we mobilized the celiac vessels, the left gastric vein (LGV) was encountered and divided, leaving only the esophageal collaterals to provide venous outflow to the stomach. The periportal lymph nodes were taken en bloc with the bile duct. The proximal jejunum was separated from the mesentery, and the first jejunal tributary to the SMV was ligated and divided.

At this point, the pancreas was held only by a length of portal vein. Five thousand units of systemic heparin was administered, and Satinsky clamps were applied to the portal vein and SMV prior to resection. The inferior mesenteric vein (IMV), which drained into the distal SMV, had been identified and preserved in continuity

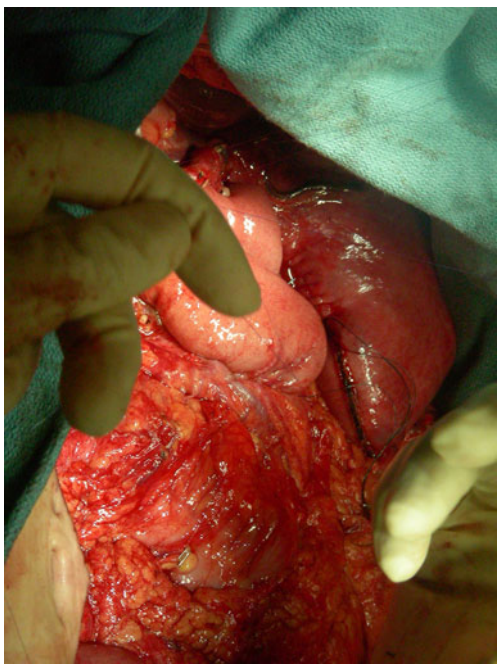

Figure 2 Gastric remnant congested after tumor resection.

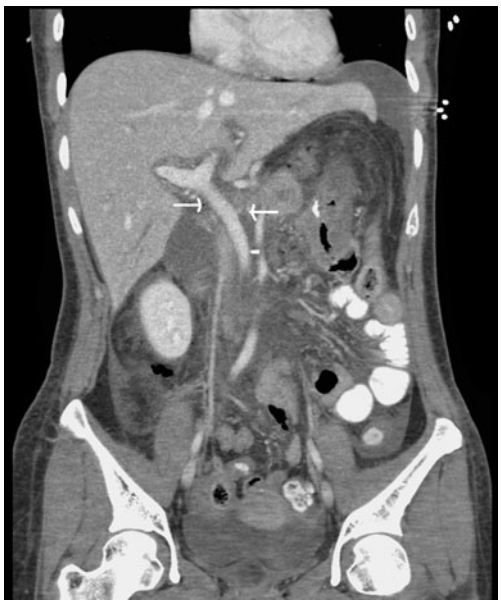

Figure 4 Postoperative CT scan with multiplanar reconstruction of patent portal vein reconstruction and insertion of the anastomosed IMV.

throughout the dissection. After resection, the portal vein was reconstructed with an end-to-end anastomosis using 6-0 prolene. We then performed a choledochojejunostomy followed by an isoperistaltic retrocolic gastroenterostomy.

As we performed the gastric anastomosis, we noted that the stomach appeared discolored and extremely edematous. The mucosa was hemorrhagic and congested, and it appeared as though the paraesophageal veins were not functioning adequately (Fig. 2). We had concerns about perioperative hemorrhage and also viability of the stomach without adequate venous outflow. In order to ameliorate the congestion, we divided the IMV proximally and flipped it superiorly to reach the remnant of the left gastric vein. We then performed an end-to-end anastomosis using 7-0 prolene between the LGV and IMV to allow gastric inflow into the reconstructed portal vein. The congestion of the stomach was immediately relieved, and the wall appeared to have normal compliance (Fig. 3).

The patient had an uneventful postoperative recovery. A CT was performed on postoperative day 5 to confirm patency of the vascular reconstruction (Fig. 4).

The pathology revealed a T3N1M0 tumor with peripancreatic invasion and 7/22 lymph nodes positive for malignancy. All resection margins were negative. The patient was discharged home on day 10 and referred for consideration of adjuvant chemotherapy and radiotherapy.

Discussion

Extended resections of the pancreas for adenocarcinoma including venous resection and reconstruction are technically demanding but are indicated in order to achieve an R0 resection.[2–4] Such operations also should only be contemplated when they can be done with a low morbidity and mortality. The technical challenges that arise during these operations relate in part not only to the tumor resection but also to the organs that remain in situ. During the course of the operation described in this report, all of the draining veins from the stomach were removed, including the coronary vein (LGV) and the short and posterior gastric veins. Although this can usually be performed safely,[5] in this case, it resulted in an extremely congested gastric remnant with significant submucosal edema and a hemorrhagic mucosa. In our opinion, there was a high risk of gastric mucosal compromise with severe gastric bleeding in the postoperative period; the preservation of the IMV suggested a novel and effective solution to this problem: decompression of the stomach by reestablishing portal venous drainage with a LGV–IMV bypass.

The left gastric vein has been used for several applications in portosystemic shunt surgery, either alone or in combination with an autogenous interposition vein graft or ringed PTFE graft.[6–9] The mesenterico-left portal vein (SMV, IMV, LGV to LPV) shunt is a durable shunt with good patency rates and low rates of encephalopathy,[10] with similar patency report in animal and human models of left gastric vein diversion either to the renal vein or the inferior vena cava.[11] Other variations of portosystemic anastomosis using the left gastric vein also exist with all reporting high long-term patency rates.[9]

Unlike shunt surgery, there are limited studies on the efficacy and utility of preservation, and no studies in the reconstruction, of gastric venous outflow during oncologic operations. Kurosaki et al. reported that preservation of the left gastric vein during pylorus-preserving pancreaticoduodenectomy was associated with an accelerated return of gastric function, earlier removal of the nasogastric tube and return to a solid diet.[12] This paper suggests that the preservation of gastric venous outflow can be important to the restoration of normal motility and function of the stomach.

To our knowledge, this is the first report on the use of the left gastric vein remnant joined to an inverted inferior mesenteric vein in order to minimize complications following radical total pancreatectomy. This reconstruction can be performed safely with good early patency, with the intent of avoiding the complications associated with venous hypertension of the stomach. This reconstruction should be considered when such an operation is contemplated and care should be taken to preserve the inferior mesenteric vein in continuity, with the portal vein thus allowing it to function as a conduit for gastric venous outflow.

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CASE REPORT

Autoimmune Esophagitis: IgG4-related Tumors of the Esophagus

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Abstract We present a case of a 23-year-old gentleman who presented with dysphagia, weight loss, and recurrent esophageal strictures requiring multiple dilatations. An endoscopic ultrasound with esophagogastroduodenoscopy revealed a mass present in the distal esophagus. Fine needle aspiration suggested that the mass in the lower esophagus resembled a gastrointestinal stromal tumor. After surgical resection, final pathologic analysis revealed that the tumor was comprised of benign-appearing fibroinflammatory cells with an increase and predominance of IgG4-positive plasma cells. The microscopic appearance was consistent with a benign condition as a result of an IgG4-related process. He did not, however, have any other symptoms indicative of systemic autoimmune disease or connective tissue disorders. We present the pre-operative imaging, operative management, pathologic diagnosis, and literature review of this rare condition and the first known report of autoimmune esophagitis as part of the IgG4 spectrum of diseases.

Keywords IgG4 · Autoimmune disorders · Esophagus · Autoimmune esophagitis

Introduction

IgG4-related disorders represent a disease process that has in the past decade gained much attention due to the proclivity of physicians to confuse it with and treat it as a malignant tumor. This disease process is known to manifest in many organs and has been reported in the pancreas, biliary tree, salivary glands, kidneys, lungs, pituitary, and prostate, as well as the soft tissues, retroperitoneum, and lymph nodes. There is considerable clinical, laboratory, and histopathological overlap between IgG4-related diseases and known autoimmune disorders, which have likewise been shown to lead to intrinsic damage to a multitude of organ systems. On occasion, IgG4-related lesions may affect only one organ and unfortunately presents both clinically and radiologically with symptoms that mimic a malignancy. As our recognition of the potential for IgG4-related disorders to mimic malignant tumors increases and the diagnostic criteria become further elucidated, patients may be spared unnecessary surgical procedures and subsequent loss of organ function.

Case Report

A 23-year-old Caucasian gentleman with a 6-year history of esophageal strictures, presumed to be secondary to gastro-esophageal reflux disease, presented to our clinic with debilitating dysphagia and significant weight loss over the last 12 months. His past medical history is non-contributory and there was no evidence of other autoimmune diseases or connective tissue disorders. As his symptoms progressed, he required multiple esophageal dilatations by his local gastroenterologist for symptomatic relief.

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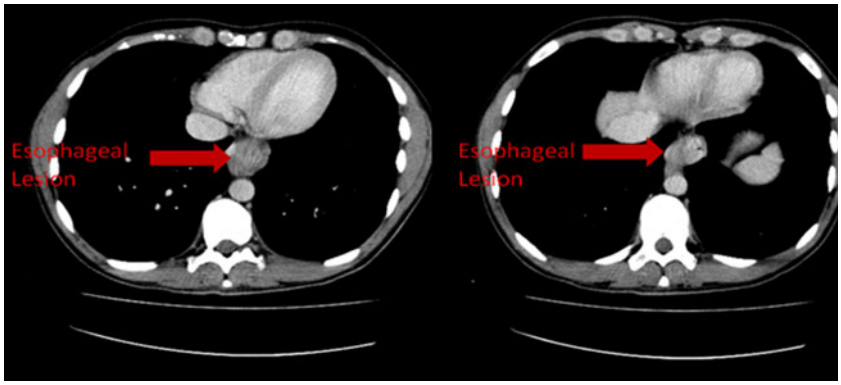

Fig. 1 Cat scan demonstrating distal esophageal lesion.

Due to the lack of significant pathology explaining the esophageal stricture, an endoscopic ultrasound (EUS) was performed to evaluate for a mass. At EUS, a subepithelial lesion was identified that had characteristics of a mass. A fine needle aspiration of this subepithelial lesion located in the distal esophagus demonstrated a submucosal spindle cell tumor with immunostains that were positive for CD4 and CD117. This was believed to be consistent with the diagnosis of a gastrointestinal stromal tumor (GIST).

Pre-operative workup included an esophagram, computed axial tomography (cat) scan and an esophagogastroduodenoscopy (EGD). The cat scan (Fig. 1) demonstrates a large esophageal lesion in the lower third of the esophagus. Pooling of contrast in the lower third of the esophagus secondary to a presumed large, circumferential esophageal mass was seen on the esophagram. The remainder of the study showed that there was significantly delayed emptying of the esophagus with poor peristalsis. The EGD (Fig. 2) confirmed the esophagram findings, demonstrating a moderate stenosis measuring 20 (in length)×8 mm (inner diameter) at 42 cm from the incisors. An EGD performed 2 months post-dilation showed a persistent intra-luminal lesion with mass effect.

Due to his debilitating symptomatology, the multitude of dilatations, recurrent stricturing, poor peristalsis in the proximally dilated esophagus, and a distal subepithelial mass, he was counseled about a minimally invasive esophagectomy with a cervical anastomosis. Unfortunately, because preoperative immunohistochemical staining showed positivity for C-kit and the preoperative diagnosis was possible GIST, pre-operative IgG4 levels were not obtained prior to embarking on surgical therapy.

Consequently, he underwent a successful thorascopic and laparoscopic esophagectomy with a cervical anastomosis. His post-operative course was uneventful and was discharged home on post-operative day 8 tolerating a diet by mouth. He is currently 4 months post-operatively, doing well and without evidence of disease progression to other organs.

Gross examination of the surgical specimen revealed a 1.2 cm mucosal ulceration in the distal esophagus just proximal to the gastro-esophageal junction. Beneath the ulceration in the submucosa was a poorly defined, firm, white–tan mass that measured 1.5×0.8×0.4 cm. It extended deep through the muscularis, but did not involve the surgical margin. Histologic findings showed a spindle cell proliferation with prominent lymphoplasmacytic inflammation and venulitis. These features were confined to the submucosal tumor and did not extend in either direction submucosally. Additionally, there were no mucosal changes identified adjacent to the ulcer or at any distance from the ulcer, to suggest an underlying tumor of any sort.

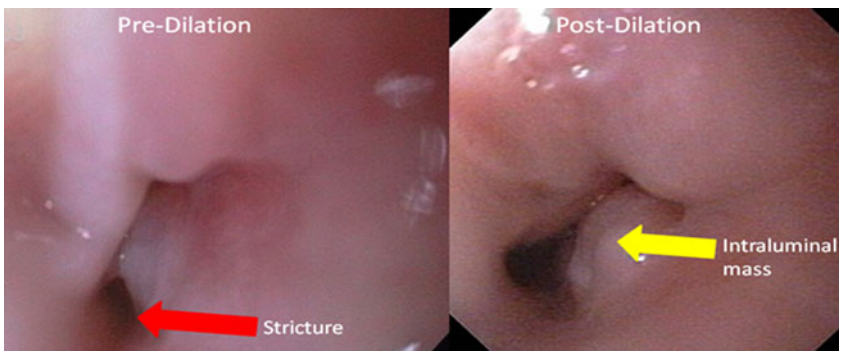

Fig. 2 Esophagogastroduodenoscopy (EGD) demonstrating distal esophageal stricture prior to dilation. Persistent post-dilation mass is seen in follow-up EGD.

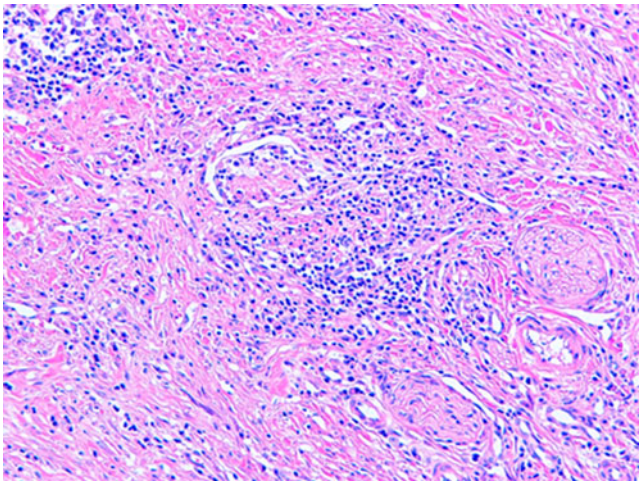

Fig. 3 Dense chronic inflammatory infiltrate with plasma cells and a prominent myofibroblastic response. Focal venulitis was identified.

Immunohistochemistry (Fig. 2) revealed IgG4 positive plasma cells as high as 75 per high powered field and fibroblastic spindle cells staining with SMA. Stains for S-100 and ALK-1 were negative (Fig. 3). Additionally, staining for C-kit showed focal staining of interstitial cells with no evidence of GIST. Given the heightened numbers of IgG4-positive plasma cells and the lack of c-kit staining, the lesion was considered to be part of a spectrum of IgG4-related disease rather than a GIST (Fig. 4).

Discussion

Autoimmune disorders are characterized by multisystem involvement and the ability to affect any organ[1]. Many investigators have described a wide variety of gastrointestinal manifestations with generalized autoimmune disorders. Others have shown that autoimmune disorders results in a chronic form of inflammation that can permanently damage the organ resulting in a pseudotumor effect[2–5].

Multiple reports have demonstrated that autoimmune disorders of the pancreas can present with lesions that resemble malignancy, both clinically and radiographically[2–5]. In fact, Sarles et al.[6] reported a case of pancreatic involvement associated with hypergammaglobulinemia as early as 1960. Since then, many cases have been described, with the highest volume of literature coming out of Japan, which has led to the concept of autoimmune pancreatitis[2–11].

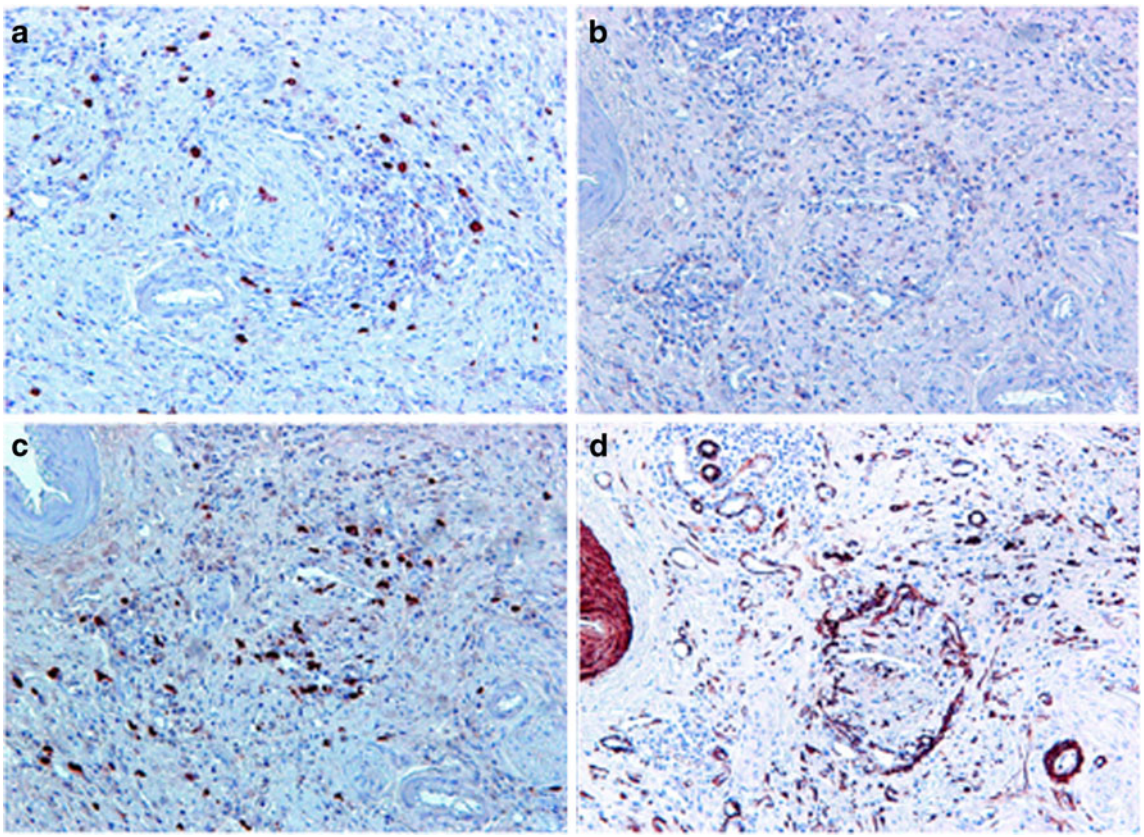

Fig. 4 **a** c-Kit stains the interstitial cells, **b** ALK-1 is negative, **c** IgG4 stains the majority of the plasma cells in the field, **d** SMA stains the smooth muscle in the vessel walls.

Despite the first description of solid organ involvement with autoimmune disorders over 50 years ago, the precise pathogenesis and pathophysiology of autoimmune disorders-associated dysfunction remains unclear. Autoimmune disorders vary in clinical presentation based on the organ system involved and present with a wide spectrum of radiologic features with characteristic imaging seen only in a minority of cases. Hence, diagnosis is most accurately made through pathologic evaluation, with unique histologic features consistent with abundant IgG4-positive cells[7].

In the majority of patients with autoimmune disorders, there are increased serum levels of IgG4, but this is not specific to any particular organ system[5,9–11]. In fact, elevated levels of serum IgG4 have been observed in other disorders such as asthma and atopic dermatitis[8,9]. The lack of specificity of serum IgG4 only adds to the difficulty in establishing the preoperative diagnosis of autoimmune disorders. Since autoimmune disorders have been shown to mimic malignancy in organ systems both clinically and radiographically, it is not surprising that patients with autoimmune disorders are still commonly offered aggressive treatment options, including resection. It is important to try to make the diagnosis prior to attempted surgery because it has been shown that autoimmune disorders may respond to conservative management including the use of steroids, resulting in decreased inflammatory pseudotumor effect. Thus, it is imperative that there is accurate detection of the autoimmune disorders process in order to avoid surgery and spare the patient the loss of function, morbidity, and possible mortality that comes with surgical resection.

This is the first reported case of a patient with autoimmune esophagitis secondary to IgG4 that resulted in a pseudotumor causing symptomatic dysphagia and esophageal stricture. This presentation is unique, in that patients with esophageal manifestation of their autoimmune disease rarely present with an esophageal mass resulting in strictures. Furthermore, patients plagued with esophageal manifestations of their connective tissue disorder often present with a wide range of symptoms unlike those described in our case presentation[12]. Patients with systemic lupus erythematosus may present with esophageal dysmotility as seen on manometry, as well as reflux esophagitis secondary to decreased lower esophageal sphincter tone[13]. Scleroderma, on the other hand, affects the lower esophageal sphincter which will eventually lead to lower esophageal strictures but does not have any associated esophageal masses[1]. Sjogrens syndrome can lead to achalasia-like symptoms and upper esophageal webs[14]. Hence, esophageal manifestations of autoimmune disorders are most commonly ulcerations, erosions or dysmotility—not necessarily inflammatory pseudotumors[1].

Conclusions

IgG4-related organ dysfunction is an inflammatory condition that frequently mimics malignancy. We present the first reported case of isolated esophageal involvement secondary to IgG4 plasma cell infiltration. Preoperative diagnosis remains difficult in this disease and is best done through biopsy and histologic analysis. A high index of suspicion is necessary to accurately make the diagnosis prior to resection. It is anticipated that as our experience with serum IgG4 testing and knowledge of the systemic nature of autoimmune disorders increases, patients with autoimmune disease with organ anomalies will be diagnosed promptly and be spared potentially unnecessary surgery.

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MULTIMEDIA ARTICLE

Transumbilical Totally Laparoscopic Single-Port Nissen Fundoplication: A New Method of Liver Retraction: *The Istanbul Technique*

Ismail Hamzaoglu · Tayfun Karahasanoglu · Erman Aytac · Adem Karatas · Bilgi Baca

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Abstract
Introduction Mustafa Kemal Atatürk, founder of the Turkish Republic, had guarded many German scientists of a Jewish descent before the Second World War. Dr. Rudolf Nissen was one of the outstanding surgeons who had served in the Turkish university hospitals. He had created an antireflux procedure which is named after his own name while he was working in our clinic, the Cerrahpaşa Hospital. From a laparoscopic approach, the Nissen fundoplication was the gold standard intervention for the surgical treatment of gastroesophageal reflux disease (GERD). Currently, video laparoscopic surgery is evolving quickly with the guidance of new technology. Single-port (SP) laparoscopic transumbilical surgery is one of the newest branches of advanced laparoscopy.
Discussion Simple or complex manipulations may be performed with SP laparoscopic transumbilical surgery. The advantages, which are gained from conventional laparoscopy, can be invigorated by an SP laparoscopic approach. The retraction technique of the liver and the optical system were the most important factors, which made the Nissen fundoplication possible via single port. Here, we report that totally laparoscopic transumbilical SP Nissen fundoplication procedure was performed in three patients for sliding hiatal hernia with GERD.
Conclusion Totally laparoscopic transumbilical SP Nissen fundoplication is a safe and feasible technique for the surgical treatment of GERD.

Keywords Nissen fundoplication · Single port · Laparoscopy · Transumbilical · Gastroesophageal reflux

Introduction

Mustafa Kemal Atatürk, who is the founder of the Turkish Republic, had invited many German scientists of a Jewish descent to Turkey before the Second World War. Dr. Rudolf Nissen was one of those precious medical doctors who had accepted Atatürk's invitation and came to live and work in Turkey.[1–3]

He was enthusiastically welcomed in Turkey and appointed as the Chief of the First Surgery Clinic in Istanbul University, the Cerrahpaşa Hospital, in 1933.

Nissen performed his first Nissen fundoplication operation in Istanbul on a 28-year-old man with a bleeding distal esophageal ulcer in 1936. He resected the distal esophagus and proximal stomach and reconstructed it in a fashion that embedded the esophageal stump into the wall of the stomach. He had noticed that the patient had not complained from reflux symptoms. He had described his technique in 1936 in Turkish and in 1937 in German.[4] He developed this technique and he described this antireflux procedure called gastroplication in 1956.[5] Dr. Nissen had worked on the antireflux procedure and published an improved version of the technique. He has given this

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technique its currently known name, fundoplication.[6] His student Rosetti and later Deemester and Donahue improved this 360° fundoplication.[7–9] Different types of antireflux procedures have been published afterwards. However, laparoscopic approach has made the Nissen fundoplication the gold standard intervention for the surgical treatment of gastroesophageal reflux disease (GERD) since its application in the early 1990s with the development of minimally invasive techniques.[10,11]

Single-port (SP) laparoscopic surgery is one of the newest branches of advanced laparoscopy. Simple or complex surgical procedures such as appendectomy, sleeve gastrectomy, or colorectal resections may be currently performed with SP laparoscopic surgery.[12–15]

Herein, we present a transumbilical totally laparoscopic SP Nissen fundoplication procedure that was performed in three patients for sliding hiatus hernia and GERD symptoms. A cholecystectomy procedure had been performed in one of the patients because of symptomatic cholelithiasis at the same time.

Patient and Methods

All patients were complaining about reflux symptoms. During the evaluation process, sliding type hiatus hernia causing GERD was diagnosed in all patients. One of the patients had also symptomatic cholelithiasis with multiple gallstones confirmed by liver ultrasonography. The blood biochemistries of the patients were in the normal limits.

The patients fully consented to the operation and a detailed information consent form was also signed by each patient. They were aware of being our initial cases for this specific procedure. We explained to the patients that, as an initial procedure, this technique would bring them no benefit, but it would reduce the wound size relatively. Furthermore, they were fully aware that we would need to use an additional port or would convert the operation to open surgery in the event of intraoperative difficulty or complication.

Surgical Procedure of Transumbilical Totally Laparoscopic SP Nissen Fundoplication

The patients were placed in supine position with the sacrum at the edge of the table and the two legs abducted on the boards were fixed to the operating table. The surgeon stood between the patient's legs and the first assistant stood on the patient's right side. Under general anesthesia, the SILS Port™ (SILS™ Port 12 mm, Covidien AG, Norwalk, Connecticut, USA) was introduced (open technique) into the abdomen through the umbilicus. All surgical procedures were performed intracorporeally. A 5-mm flexible laparoscope with integrated camera (Olympus®, Orangeburg, New York) using the HD-TV EXERA 2 System (LTF-VH, Olympus) was used to allow two 5-mm instruments to work in a synchronized way. Under the guide of the laparoscope, a routine exploration was performed.

The Istanbul Technique Retraction of the liver without inserting an additional trocar is a problem for making SP transumbilical interventions for upper gastrointestinal tract surgery. Various liver retraction techniques have been described before.[16] The main principle of the *Istanbul Technique* is an atraumatic suspension of the liver with a mechanism like a hammock. A Penrose drain 8 cm long and 1 cm wide was prepared for this retraction method. Two silk sutures in 10 cm lengths were tied to the two different ends of the Penrose drain. Then, it was inserted through a 10-mm trocar of the SILS Port. The left triangular ligament was opened by Ultracision (Harmonic Ace, Ethicon Endosurgery®, Cincinati, OH), leaving approximately 1 cm intact to prevent the slipping of the retraction mechanism. The Penrose drain was passed through the foramen in the left triangular ligament with the guidance of the silk laces and placed below the lateral segment of the liver. The silk laces tied on the edges of a Penrose drain were taken out of the abdomen with a device that was created from an 18-gauge Spinocan. This percutaneous suture-passing technique had been described previously by Dunning and Kohli.[17] These silk laces were taken out of an appropriate place to retract the left lateral segment of the liver and fixed above the skin with the help of a clamp. We called this maneuver the *Istanbul Technique* (Fig. 1).

An articulating endograsper (Roticulator Endo Grasp™ with Lock, Covidien AG, Norwalk, Connecticut, USA) was used for retracting the stomach during the dissection.

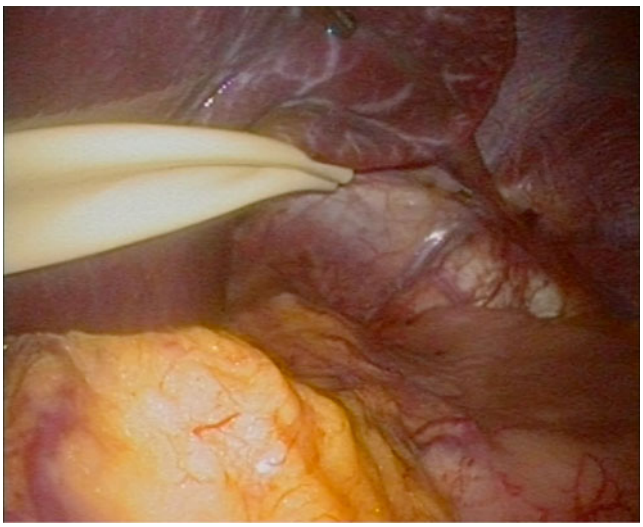

Fig. 1 Laparoscopic view of the retraction of the left lateral lobe of the liver with the Penrose drain (the *Istanbul Technique*).

Portions of the right and the left crus of the diaphragm and the distal part of the esophagus were dissected. The whole dissection was performed with Harmonic Ace. Dissection of the fundus was started where the short gastric vessels appeared. Crurorraphy was performed with two silk stitches before creating the fundoplication. A 10-mm endoscopic suturing device (SILS™ STITCH, Covidien® AG, Norwalk, Connecticut, USA) was used for stitching. The floppy Nissen fundoplication was created without difficulty after finishing the dissection. Because we prefer a floppy fundoplication, we do not use any size of orogastric bougie for calibration. The fundoplication was performed with two silk stitches. One of the two stitches passing from the muscular layer of the esophagus was performed using an endoscopic needle holder. Finally, the fundoplication was fixed to the right crus of the diaphragm (Fig. 2). The Penrose drain was retrieved with the SILS Port after releasing the silk laces and the SILS Port site was closed. Entire operation could be watched in electronic supplementary material section.

Surgical Procedure of Transumbilical Totally Laparoscopic SP Cholecystectomy

The gall bladder was hung from the corpus to the abdominal wall with a silk suture after inserting the SILS Port. An articulating endograsper was used to create triangulation during the dissection of the cystic duct and the cystic artery. All the dissection was performed with Harmonic Ace. The cystic duct and the cystic artery were ligated by use of 5-mm polymer endoclips (Hem-O-Lock, Weck Closure Systems, North Carolina, USA) and transected. The gall bladder was separated from the liver. The gall bladder was taken out of the abdominal cavity from the umbilicus.

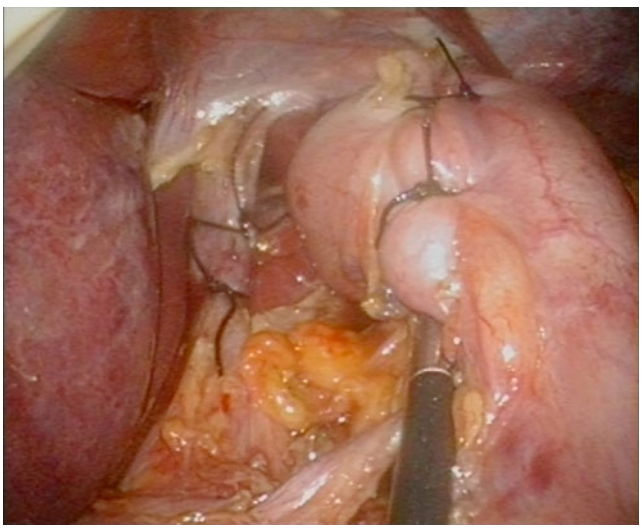

Fig. 2 Laparoscopic view of performed transumbilical SP Nissen fundoplication.

Table 1 Patients' Characteristics

	Case 1	Case 2	Case 3
Age	23	40	58
Gender	Female	Male	Female
Operating time (min)	180	180	210
Body mass index (kg/m^2)	23	24	32
Blood loss (ml)	20	50	20
Post operative hospital stay (days)	2	2	2

Results

There were three patients who underwent transumbilical totally laparoscopic SP Nissen fundoplication. One of these also had a SP laparoscopic cholecystectomy. Patients' characteristics were shown in Table 1. Mean operative time was 190 min (180–210 min). Operative time was longer in the patient who underwent cholecystectomy. Mean blood loss was 30 ml (20–50 ml). No drain was used. The patients started a soft oral diet 12 h after the surgery and were discharged uneventfully on postoperative day2. Umbilical scar was almost invisible 1 week after the operation (Fig. 3).

Discussion

Prior to GERD surgery, the patients can be gathered in three separate groups such as nonerosive reflux disease, erosive esophagitis, or Barrett's esophagus. In nonerosive GERD patients, pH study should be performed. Manometric studies are very helpful during the evaluation of patients,

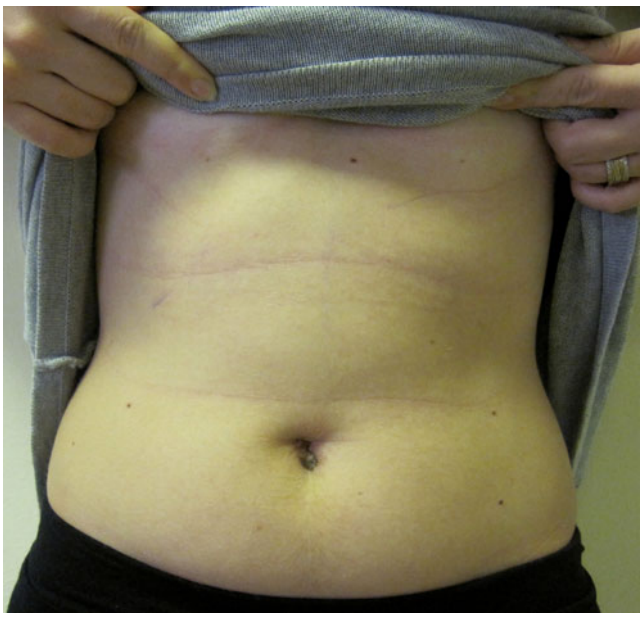

Fig. 3 Photograph of the patient 1 week after the operation.

especially those who show atypical symptoms and patients suspected of having esophageal motor disorders. In each of the three patients who showed typical GERD symptoms, the diagnosis was made by esophagogastroduodenoscopy. All of the patients were diagnosed with grade I–II erosive esophagitis and small hiatal hernia (type I). The patients' symptoms showed a good response to medical treatment. However, the symptoms started showing again when medical therapy was discontinued. In patients with dysphagia, upper gastrointestinal imaging can be performed before anything else. It is recommended that a gastric emptying study should be performed in selected patients.

Video laparoscopic surgery is evolving quickly with the guidance of new technology. SP transumbilical laparoscopy is the threshold technique during the adaptation period of the abdominal surgical interventions to the natural orifice transluminal endoscopic surgery. Umbilicus is a natural scar tissue and is an access for performing the SP transumbilical surgery, which preserves the body image perfectly with a lesser scar.

The superiority of the laparoscopic Nissen fundoplication has been proved against the open techniques for the surgical treatment of GERD.[18] The advantages, which are gained from the conventional laparoscopy, can be invigorated by the SP laparoscopic approach.

In this initial experience, we reported three patients who underwent transumbilical laparoscopic SP Nissen fundoplication and found that this novel technique was safe and feasible comparing with the other minimally invasive techniques. The patient satisfaction was superior and they were very happy to preserve their body image with this almost scarless surgery. To our knowledge, this is the first peer-reviewed publication describing transumbilical laparoscopic SP Nissen fundoplication.

SP laparoscopic surgery requires more advanced laparoscopic skills. There is only one access and the use of the instruments may complicate to continue the operation. For this kind of difficult surgical interventions, surgeons have developed some techniques which make operation safe and easy. In this study, the authors improved a new retraction method for liver retraction. The retraction technique of the liver is the most important factor which makes the Nissen fundoplication, obesity surgery, and gastric surgery applicable via a single port. We also think this technique can be applied during multiport laparoscopy and will prevent bleeding from the liver due to retraction. The *Istanbul Technique* can provide an atraumatic liver retraction and can fully expose the esophagogastric region. SP laparoscopic Nissen fundoplication can be performed safely with the help of this retraction technique.

The GERD patients who have no or small hiatal hernia could be good candidates for single-port antireflux surgery (SPARS). When the surgeons complete the learning curve period for SPARS, they could perform more complicated procedures with the help of new techniques and technology.

This procedure can be done using transumbilical or epigastric incision. The distance between the xiphoid edge and the umbilicus could be an important factor for performing the transumbilical laparoscopic SP Nissen fundoplication. In our older patient, this distance was very long and this factor caused difficulties during the surgery. It becomes harder to reach the area of the surgery, to make manipulations, and to visualize. In these patients who have longer xiphoid–umbilicus distances, an epigastric incision can be used. However, another incision far away from umbilicus for laparoscopic SP access will not be as scarless as transumbilical access.

From a cosmetic perspective, it leaves an almost invisible scar. It is almost impossible to see the scar a few months after the surgery. It preserves the patients' body image. This is especially important for younger patients such as our 23-year-old patient. The patients feel less traumatized and feel as if they are not ill because they do not have any scars on their abdomen. Because of this, they feel better about the procedure from the first moment on. It is not a hundred percent certain, but it is predicted that there is less pain as well. It is expected there will be less bleeding from the postoperative trocar sites.

There are two limitations of the SP laparoscopic Nissen fundoplication. One of them is the incisional hernia risk and the other one is the longer operation time. There is a concern about the incisional hernia risk of this larger incision of the fascia comparing with the conventional laparoscopic surgery. However, there has been no published data regarding increased incisional hernia risk in transumbilical SP laparoscopic surgery. Currently, the probability of this complication can be only an issue for further prospective randomized controlled trials. The other limitation is the longer operation time. Current surgical devices of the SP surgery and the experience of the laparoscopic surgeons are not sufficient to perform these procedures as fast as the conventional minimally invasive procedures. Improved instruments like articulating energy devices will make these procedures easier to perform. More complicated procedures such as bariatric operations will be performed with the help of these developing devices and with the help of the newly discovered techniques like the *Istanbul Technique*.

Totally laparoscopic transumbilical SP Nissen fundoplication is a safe and feasible technique for the surgical treatment of GERD. Prospective randomized trials are required to assess the long-term results comparing transumbilical laparoscopic SP Nissen fundoplication with laparoscopic Nissen fundoplication.

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HOW I DO IT

An Alternative Surgical Technique for Caval Preservation in Liver Transplantation

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Abstract
Introduction The results of orthotopic liver transplantation in patients with end-stage liver disease continue to improve. Refinements in surgical techniques represent an important part of this improvement.
Materials and Methods With the advent of split-liver and living-donor liver transplantation, inferior vena cava (IVC) preservation transitioned from being a potential option to being mandatory for many cases. Preserving the IVC can be a demanding technical maneuver in many liver transplants and several different approaches have been developed. When utilizing IVC preservation, there are several options for implantation of the graft. The piggyback technique, when feasible, is considered safe and provides hemodynamic stability for the recipient.
Results and Discussion In some cases it may be difficult to perform the piggyback technique if intense inflammatory adhesions and severe significant collateral circulation exist between the IVC and the posterior segments of the liver. In these cases, the retro-hepatic dissection can be carried out with a different approach: the infrahepatic vena cava and the confluence of the three hepatic veins can be cross-clamped en-bloc without dissection.
Conclusion This technique broadens the transplant surgeons' armamentarium and can be used in the setting of a very difficult retro-hepatic dissection. It is safe, and allows a shorter anhepatic phase with caval preservation.

Keywords Transplantation · Liver · Surgical technique · IVC preservation

Introduction

Orthotopic liver transplantation (OLT) has become a common procedure.[1,2] There are two main surgical techniques that can be used to accomplish a liver transplant: the standard technique and the piggyback (PB) technique. Both techniques may be done with or without veno-venous bypass (VVB). VVB in OLT shunts portal and inferior vena cava (IVC) blood into the superior vena cava to ensure adequate cardiac preload during the venous clamping phase. The choice of whether the IVC is preserved or fully clamped strongly impacts whether VVB is used or required. With the standard technique, the recipient's retro-hepatic IVC is removed and the allograft is transplanted with a segment of the IVC above and below the liver. In the piggyback technique, the recipient's IVC is preserved and the IVC of the donor is anastomosed to the recipient's hepatic veins or to the IVC, based upon the surgeon's preference. The perioperative outcome may be impacted by the different surgical techniques used. The duration of surgery (in particular the length of the anhepatic phase), the amount of blood loss, platelet and volume replacement, as well as the warm ischemia time for the graft are just a few of the many variables that may increase the rate of perioperative complications.[3,4] The use of VVB can also influence the volume of blood products required because of the platelet derangements that are typically attendant with the use of such an extracorporeal circuit. For all of these reasons, the IVC-preserving piggyback technique compares favorably to the standard approach when readily achievable.

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Background

The "caval phase" of liver transplantation, extending from the dissection of the cava to the vascular anastomosis of the allograft, represents a crucial time of the procedure. The retro-hepatic portion of the IVC, including the entire segment between the renal vein and the diaphragm, can be either removed, as in the standard technique, or preserved, as in the piggyback technique.

With the standard technique, two vascular clamps are placed on the infra- and suprahepatic IVC, then the IVC is resected and removed together with the native liver. To prevent hemodynamic instability, a veno-venous bypass circuit usually is used, where the femoral vein and the portal vein constitute the venous outflow while the axillary vein or the internal jugular vein, comprise the inflow. One of the bypass cannulas is placed directly into the recipient portal vein, after it has been divided, in order to remove the native liver.[5] The reconstruction of the IVC is performed by two end-to-end cavo-caval anastomoses between the donor and the recipient IVC.[6]

The piggyback technique was first described by Calne and Williams in 1968. [7] The initial operation was done in a 46-year-old woman diagnosed with cholangiocarcinoma complicated by obstructive jaundice and gastrointestinal bleeding. The donor was a 5-year-old child who died of mumps encephalitis. The donor's operation started 15 min after cardiac death, since at the time the thought was that livers could be safely used if cooled within 15 min of cardiac death. The allograft was perfused with cold heparinized Ringer's solution. The recipient's operation was done on bypass, where the portal flow was shunted into the right internal jugular vein using an intravenous infusion set. Due to the size discrepancy between the donor and the recipient, the decision was made to leave the recipient's IVC intact after suture ligating all the retro-hepatic branches and clamping the hepatic veins. The suprahepatic IVC of the allograft was anastomosed end-to-end to the hepatic vein. The portal vein anastomosis was done end-to-end, and the donor's celiac trunk was anastomosed end-to-end to the recipient hepatic artery. The biliary reconstruction was a choledocho-choledochostomy with interposition of the gallbladder. The recipient died 11 weeks after the operation with a partial liver infarction thought to be secondary to a thrombus arising from the recipient hepatic artery where it had been clamped at the time of the surgical anastomosis. In 1989, Tzakis popularized IVC preservation when he described the "piggyback" technique which he used in 24 consecutive cases over 4 months.[8] At that time three different anastomoses of the allograft's suprahepatic IVC were described: one using a common cuff of the recipient's three hepatic veins, another at the confluence of the recipient's right and middle hepatic veins, and the third where the recipient's left and middle hepatic veins were connected and then jointly used for the anastomosis. The techniques used for the intra-parenchymal exposure of the hepatic veins were described in this paper. Retransplantation of patients in which the PB technique was used was also discussed. This was cited as a major advantage of PB to the standard technique, in that retransplantation was simpler in terms of caval control. The PB technique requires peeling the native liver off of the IVC. All the retro-hepatic veins are divided between ties. Many current practitioners of this technique divide and oversew the right hepatic vein. The hepatectomy is completed by dividing the portal vein, cross-clamping the confluence of the left and middle hepatic veins, and dividing them as distal from the IVC as possible within the liver parenchyma.

In the PB technique, the caval anastomosis is performed using a cuff of the middle and left hepatic veins which is sewn to the donor's suprahepatic IVC. This approach can be vulnerable to torsion or stenosis of the suprahepatic anastomosis (leading to a secondary Budd–Chiari syndrome). Some surgeons will combine all three hepatic veins to create a very large orifice for performing the suprahepatic IVC anastomosis, but this usually necessitates full caval clamping and increases the likelihood that VVB will be needed.

Another version of the PB technique has been described by Belghiti et al. [9–11] which minimizes the risk of outflow obstruction, but still only requires partial caval clamping and thus usually allows VVB to be avoided. This technique consists of a side-to-side cavo-caval anastomosis in the setting of a PB procedure in conjunction with the closure of the upper and lower caval stumps of the allograft during back bench surgery.

Since these techniques were first performed, several studies have analyzed their effects on the perioperative and postoperative outcomes.[3,4,12,13] The results show less blood transfusion requirement, shorter operative time and anhepatic phase duration, decreased costs, better intraoperative hemodynamics, shorter ICU length of stay, and better patient outcomes using the PB technique, as compared to the standard technique.

Currently, the PB technique is considered a safe and effective procedure that can easily be performed in almost all cases. Moreover, it can make retransplantation easier if necessary. However, there are circumstances where a liver transplant surgeon plans to use the PB technique but finds that intense retro-hepatic inflammatory adhesions and/or severe collateral circulation (varices) leads to a situation that makes use of the standard technique unavoidable.[13] In these instances the PB technique may still be used if there is proper timing with the institution of VVB or if the surgeon is able to execute rapid maneuvers to complete the hepatectomy and has an expert anesthesia team. Below we

describe a technique for caval preservation that may be used in patients who have intense retro-hepatic inflammatory adhesions and severe collateral circulation, where the dissection of the liver off the retro-hepatic vena cava, as typically performed with the PB technique, may be more difficult than usual.

Surgical Technique

After the abdominal cavity is entered, the suitability for a PB technique is determined during the exploratory laparotomy phase of the recipient hepatectomy. A caudate lobe densely encasing the IVC, retroperitoneal fibrosis, intense retro-hepatic inflammatory adhesions, or severe collateral circulation represent the most important relative contraindications to the PB technique.

The dissection and division of the biliary tree and vascular structures in the porta hepatis are conventionally completed. First, the peritoneum overlying the hepatic hilum is incised. Subsequently, the common bile duct is divided between ties, followed by skeletonization of the proper hepatic artery which is, also, divided between ties. Finally, the main portal vein is dissected and left intact. At this stage the hepatic artery is dissected down towards the celiac trunk to expose a segment of the common hepatic artery at least 1 cm below the take off of the gastroduodenal artery. The next maneuvers are designed to free the liver from its natural attachments: the left and right triangular, the falciform, and the hepato-gastric ligaments are all divided with electrocautery. In cases of an accessory or completely replaced left hepatic artery taking off from the left gastric or splenic artery and running in the substance of the hepato-gastric ligament, this structure should be divided between ties. The liver is then rotated and peeled off the IVC. In doing this, all of the small hepatic veins are divided between ties, whereas the right hepatic vein is skeletonized, double clamped, divided, and oversewn. Alternatively, it may be divided using a mechanical stapler. At this stage the portal vein as well as the confluence of the left and middle hepatic veins are ready to be clamped and divided for the final stage of the hepatectomy.

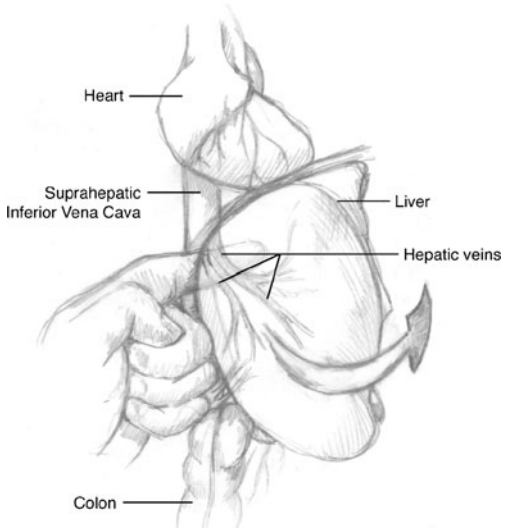

Figure 2 Medial rotation of the right lobe of the liver during the blunt dissection facilitates the progression and the completion of the blunt dissection (illustration: courtesy of Mr. Paul Schiffmacher).

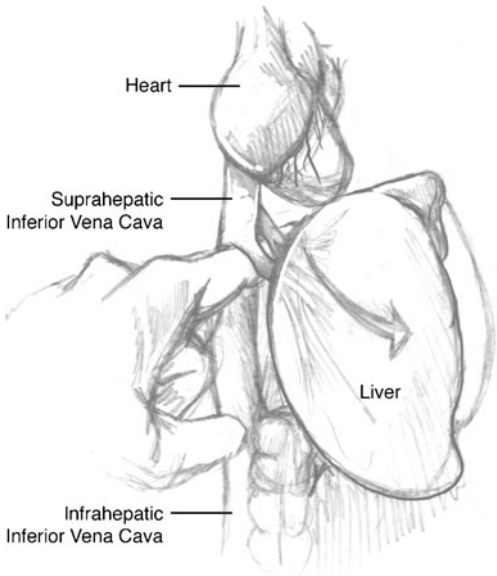

Figure 1 After the right and left triangular ligaments of the liver are divided, the diseased liver is pulled anteriorly, while the left index finger bluntly dissects a plane between the three hepatic veins and the retro-hepatic IVC (illustration: courtesy of Mr. Paul Schiffmacher).

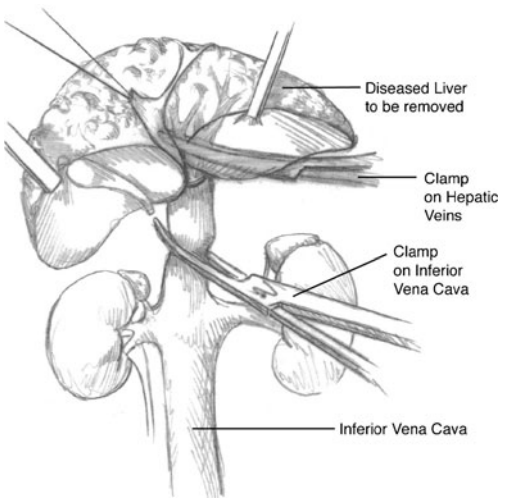

Figure 3 Dual cross-clamping of the infrahepatic IVC and hepatic veins en-bloc. This maneuver limits the blood loss from the stumps of the retro-hepatic veins that are divided without ligation, and allows the diseased liver to be removed from the surgical field (illustration: courtesy of Mr. Paul Schiffmacher).

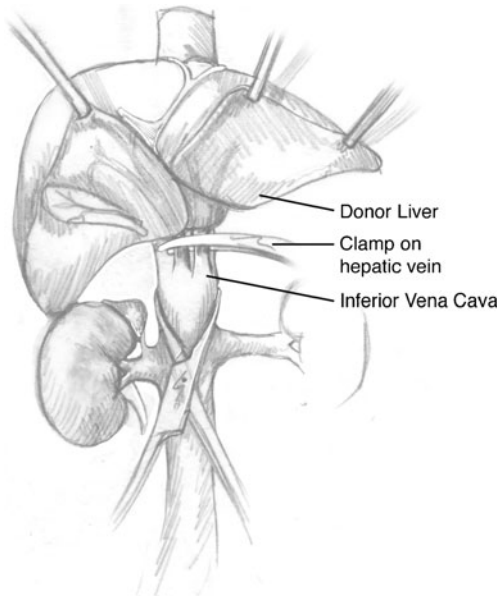

Figure 4 Allograft re-vascularization: the clamps on the hepatic artery, portal vein, and hepatic veins are removed in this sequence (illustration: courtesy of Mr. Paul Schiffmacher).

If the mobilization of the hepatic parenchyma from the retro-hepatic portion of the IVC becomes unsafe because of the degree of portal hypertension or a substantial degree of collateral circulation, a plane between the suprahepatic IVC and the three hepatic veins can be bluntly developed with finger dissection, after division of the right and left triangular ligaments. This maneuver is accomplished by gently pulling the liver anteriorly (Fig. 1), and rotating the right lobe medially (Fig. 2) while gently advancing the left index finger into the dissection plane. Subsequently, the three hepatic veins are clamped en-bloc. At this stage the infrahepatic IVC is temporarily cross-clamped, to allow removal of the diseased liver from the recipient (Fig. 3), without ligation and division of the retro-hepatic veins. This portion of the operation needs to be done quickly in order to maintain hemodynamic stability. It cannot be understated that the reduction in preload which accompanies caval clamping requires judicious anesthesia management and communication between the surgical and anesthesia teams. Once the liver is removed from the surgical field, a second vascular clamp is placed longitudinally on the retro-hepatic IVC, and the infrahepatic IVC cross-clamp is released. This sole remaining longitudinal clamp will only partially occlude the retro-hepatic IVC; therefore, this maneuver will restore blood flow in the IVC and, at the same time, allow suturing of the stumps of the retro-hepatic veins. After the completion of this portion of the operation, the IVC's longitudinal clamp is released, and the allograft is sewn in place, using the PB technique (Fig. 4).

Discussion

There are known advantages of the PB technique as compared to the standard technique that can be briefly divided into surgical and medical parameters (Table 1). The surgical advantages include: decreased blood loss, the need for only one caval anastomosis which shortens the warm ischemia time, more effective hemostasis post-graft reperfusion from better platelet and liver graft function, a safer approach in cases of retransplantation, a shorter anhepatic phase and warm ischemia time, and decreased total operative time.

The medical advantages include: better hemodynamic stability and preservation of renal function due to conservation of blood flow in the IVC at all times, easier maintenance of core body temperature, and more normal fluid balance due to decreased blood loss.[3,4] Furthermore, by preserving the caval flow with the PB technique, VVB-related complications, such as the potential for thromboembolic events, air embolism, extremity wound seromas, bypass site infections, and brachial plexus injury may be avoided.[3]

A difficult retro-hepatic dissection represents the most common cause for conversion from PB to standard technique. The retro-hepatic dissection can be extremely complicated in cases of: caudate lobe hypertrophy wrapping completely around the IVC, native liver excessively large and firm, difficult exposure of the retro-hepatic vena cava, presence of dense inflammatory adhesions, or extensive collateral circulation secondary to severe portal hypertension. Furthermore, changes in hepatic vein integrity, such as those secondary to surgical damage during the transplant,

Table 1 Major Advantages of the Piggyback Versus the Standard Technique Used for Orthotopic Liver Transplantation

Piggyback technique without VV bypass	Standard technique with VV bypass
Decreased blood loss	Easy model for training of junior surgeons
Shorter anhepatic phase and warm ischemia time	Easy model for training of junior anesthesiologists
Decreased total surgical time	Fast procedure in expert hands
Better hemodynamic stability	The bypass circuit maintains the patient's temperature constant

VV veno-venous

and anatomical variations may be considered further relative contraindications to PB. These may occur in patients who have undergone TIPS, those with aberrant hepatic veins, or in cases of a small common cuff of the left and middle hepatic veins.[12]

The PB technique can be used successfully in the face of diffuse and tenacious peri-hepatic adhesions, along with the presence of giant collaterals in the retro-hepatic area. In fact, dangerous and long dissections can be minimized by following, in rapid sequence, a seven-step modified PB technique:

1. Developing a tunnel between the three hepatic veins and the IVC to allow en-bloc cross-clamping of the three hepatic veins.
2. Short cross-clamping of the infrahepatic IVC.
3. Removing the recipient native liver.
4. Applying a longitudinal clamp on the retro-hepatic IVC, and at the same time removing the intrahepatic IVC cross-clamp.
5. Oversewing the stumps of the retro-hepatic veins.
6. Sewing in the allograft.
7. Reperfusing the liver.

We have found this variation of the PB technique to be safe, fast, and easy to replicate for experienced transplant surgeons, and we have used it successfully in four cases. Use of this technique eliminates the barriers to the PB technique which some anatomic situations might create. For this reason the procedure described herein has become our method of choice in cases of very complex retro-hepatic dissections.

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REVIEW ARTICLE

The Impact of Intestinal Failure on Oral Drug Absorption: A Review

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Abstract
Introduction Intestinal failure is a complex gastroenterological condition that occurs as a result of reduced intestinal absorption of nutrients and/or water and electrolytes. Without treatment, nutritional depletion and/or dehydration will result. It can be acute or chronic and occurs secondary to a variety of causes, including massive bowel resection, inflammatory bowel diseases of the bowel, and small bowel dysfunction.
Results and Discussion Resection of the small bowel results in a range of physiological changes that affect the absorption of nutrients, water, and electrolytes. In addition, these changes may also affect the absorption of orally administered medication. However, there is only minimal published literature regarding this, with the publications limited to case reports of failure or efficacy of certain medicines such as digoxin and warfarin in individual patients. Due to the highly heterogeneous nature of intestinal failure patients, there is little generalizability of the information within these articles to other patients. Only one article seeks to provide limited practical advice regarding prescribing in this complex patient group.
Conclusion The input of specialist pharmacists is necessary in the management of these patients to ensure that appropriate drugs and formulations are prescribed in a timely manner to optimize absorption and resultant efficacy.

Keywords Oral drug administration · Absorption, intestinal · Short bowel syndrome · Stomas, surgical

Introduction

Intestinal failure may be caused by obstruction, dysmotility, surgical resection, congenital defect, or disease-associated loss of absorption and is characterized by the inability to maintain protein energy, fluid, electrolyte, or micronutrient balance.[1] A subgroup of these patients are those with short bowel syndrome resulting from surgical resection, congenital defect, or disease-associated loss of absorption and are characterized by the inability to maintain protein energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted, normal diet.[1]

It is obvious that massive resection or widespread disease of the gastrointestinal tract is not going to be without consequence for the absorption of orally administered medication. The American Gastroenterological Association has published a position statement regarding the management of patients with short bowel syndrome recognizing this problem, stating: "Oral medication absorption is often impaired and larger doses, intravenous, or sublingual delivery may be required; significant interpatient variability may be observed".[2] This poses some difficult clinical management problems as many drugs are only available in oral dosage forms and there is a lack of published information regarding medication use in this patient group. Therapeutic failure may result in significant morbidity and inconvenience for the patient while an efficacious dosage form, route, or dosing schedule is established, often on a basis of trial and error. Some efforts have been made in the literature to make some suggestions regarding alternative routes of administration in

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short bowel syndrome.[3] However, this strategy of total avoidance of the oral route is not always practical.

In order to understand to what extent drug absorption may be affected by intestinal failure, it is essential to initially gain a brief overview of the usual drug absorption process.

Drug Absorption

Absorption of orally administered drugs is possible throughout the gastrointestinal tract, from stomach to rectum, although the principal site for absorption is the upper small intestine. This is primarily because of the large surface area and potential for a long contact time for the drug with the permeable intestinal surface. In addition, there is high peristalsis, high blood flow, and an optimal pH for the absorption of most drugs. The stomach acts as mainly a repository organ, ejecting pulses of drug in solution by peristalsis onto drug absorption sites in the small intestine.

Gastrointestinal drug absorption is mostly a passive, first-order process. The drug–response relationship is partly dependent on bioavailability or the rate and extent of drug absorption into the systemic circulation. A low bioavailability may result from losses occurring during any one or a combination of the processes described above. If a drug is highly permeable, then resultant absorption is rapid and potentially complete within the small intestine. Absorption of less permeable, usually polar drugs, still usually occurs in the small intestine, but absorption is likely to be incomplete during the usual transit time of 2–4 h through the small intestine. The oral route is generally avoided for many of these polar drugs, such as gentamicin due to their resultant poor bioavailability.

Many factors influence the absorption of drugs from the gastrointestinal tract. The most important of these are summarized in Table 1.

The absorption rate may ultimately affect the extent of absorption and is dependent on elimination. The extent of absorption is of the utmost importance in clinical situations. If gastric emptying is altered, intestinal membrane permeability, integrity, or surface area is affected then the extent of absorption will change. These changes can be difficult to predict.

Table 1 Summary of Main Factors that May Influence Drug Absorption

Physicochemical characteristics of the drug
Drug formulation (tablet, capsule, elixir, enteric coated, sustained release)
Disintegration and dissolution time
Drug concentration
Excipients in tablet or capsule formulations
Lipophilicity
pK_a
Stability in gastrointestinal tract
Patient characteristics
Residual intestinal length—hence, absorptive surface area
Mucosal integrity of remaining bowel, including presence of disease
Gastric emptying time
Intestinal motility and transit
pH of gastric and intestinal lumen
Mesenteric blood flow
Presence of bile salts
Presence of interacting substances in gastrointestinal tract
Concurrent medication
Nutritional intake
Pharmacokinetic characteristics of drug
Site of release of active drug
Drug metabolism by gut bacteria and in gut wall
Extent and rate of absorption
Method of absorption (passive, active—may also depend on presence of drug transporters such as P-GP)
First-pass metabolism
Pharmacodynamics

Potential Chronic Changes in Intestinal Failure Patients

Length of Functional Small Intestine

Any changes that affect the surface area, permeability, or integrity of the intestinal membrane may affect the *extent* of drug absorption as these factors are all interrelated. In both jejunostomy patients and those with a jejuno-colic anastomosis, the surface area available for drug absorption has been *significantly* reduced. This may be a particular problem for drugs or formulations with a relatively low or variable oral bioavailability, even in healthy patients, such as levothyroxine or ciclosporin.

The majority of drugs are absorbed in the duodenum due to the high surface area and favorable pH (6–6.5). In some patients, certain important drug absorption sites for specific drugs or formulations (such as enteric-coated or sustained-release preparations, which often rely on an intact colon being present) may have been completely resected.

Gastric Emptying

The initial rapid transit of gastric contents, such as that seen in patients with a jejunostomy, may reduce dissolution times for solid oral medicines and reduce the time that the drug is exposed to an acid pH, which may be a particular problem for drugs with narrow absorption time windows. Therefore, changes in gastric emptying times may directly influence the rate of absorption of a given drug. The effect of rapid transit of gastric contents on the absorption of specific drugs is illustrated by observing the effects of concurrent

metoclopramide administration.[4] The rate of absorption of digoxin is reduced, while the absorption rate of aspirin, paracetamol, and tetracycline is increased.

Small Bowel Transit

Rapid transit through the small bowel may reduce the duration of contact of a drug with its absorption site—the intestinal wall. The extent of absorption of a given drug is related to small intestinal transit time. Transit may also be affected by whether the drugs are taken with food or just liquid. Rapid intestinal transit can have major implications for moderately soluble, such as digoxin, or permeable drugs or those in a controlled release or enteric-coated formulation, resulting in reduced bioavailability and potential therapeutic failure. It may have less impact on drugs that are highly permeable or soluble and presented in an instant-release dosage form.

One method of trying to optimize the absorption of solid oral medicines in patients with a rapid small bowel transit is administering the medicines in liquid dosage form. However, many commercial liquids have osmolalities over 1,000 mOsm/kg.[5] The osmolality of gastrointestinal secretions ranges from 100 to 400 mOsm/kg. The administration of hyperosmolar liquids may result in dose-related osmotic diarrhea, abdominal cramps, and vomiting. In addition, many oral liquids are sweetened with sorbitol, maltitol, or xylitol, which are all poorly absorbed polyalcohol sugars. Sorbitol is occasionally used as an osmotic laxative in doses of 7.5 to 30 g. Sorbitol frequently causes bloating and flatulence with daily doses of 10 g and abdominal cramps occur with 20 g per day.[6] While individual preparations contain relatively small amounts, patients receiving multiple medications in maximum doses are more likely to experience diarrhea, which can result in serious morbidity.[7]

Pancreatico-biliary Secretions

Most lipid digestion occurs in the duodenum and jejunum. If the terminal ileum is resected, then disruption of the enterohepatic recirculation of bile acids may occur and fat absorption capacity may be reduced. In extreme cases, this manifests as steatorrhoea.[8] Any reduction in fat absorption will affect the absorption of fat-soluble drugs, such as ciclosporin or alfacalcidol.

Enterohepatic Circulation

Drugs that circulate in the enterohepatic circulation after absorption, particularly those that are converted to active metabolites in the liver, such as digoxin or loperamide, will have their metabolism disrupted, and dose adjustments may be necessary.

Lactobacilli

Patients with a short bowel and an intact colon may rarely have an unusually high level of lactobacilli in their gastrointestinal tract, producing lactic acid from sugars.[8] The enteral absorption of drugs that must be protonated may be affected due to this excessive lactic acid production. In addition, drug formulations that are pH-dependent may not be effectively absorbed if the colonic pH was more acidic.

Nutritional Intake

The presence of food in the stomach will lengthen gastric emptying times, with the implications discussed above. The majority of short bowel patients will receive a modified diet to meet their nutritional needs. This may involve oral supplements, enteral feeding, or parenteral nutrition. Sip feeds are unlikely to cause problems with oral drug therapy, apart from known drug–food interactions. There are also interactions associated with the co-administration of drugs such as phenytoin with enteral feeds via enteral feeding tubes.[9] Most intestinal failure patients are on overnight enteral feeding regimens; hence, it would be possible to give any medication during the day and hence minimize drug–feed interactions.

Drugs Used in the Management of Intestinal Failure Patients

Many intestinal failure patients are on H_2 antagonists and/or proton pump inhibitors to reduce the volume of gastrointestinal secretions. These drugs will also alter the gastric pH. Therefore, any drugs dependent on an acidic pH for absorption or dissolution, such as ketoconazole, may have these processes disrupted, particularly their *rate* of absorption.[10]

Effects of GI Disease

Diseases such as inflammatory bowel disease and coeliac disease affect the mucosal surface of the intestinal lumen and may also alter the gastric emptying time.[10] It has also been noted that the colonic pH in patients with malabsorption secondary to ulcerative colitis may drop below 5, resulting in potential problems in effectively absorbing enteric-coated drugs.

Evidence for Changes in Drug Handling

Drugs Used in Management of Intestinal Failure

Of the drugs used to manage intestinal failure, there is only one case report that contains any evidence for altered

handling after oral ingestion. While papers regarding the use of omeprazole and loperamide note that increased doses, or even intravenous administration, may be required, no evidence is provided to substantiate the proposition that bioavailability be reduced in these patients. Reduced cimetidine bioavailability after a massive bowel resection was observed in one patient.[11] The author also noted that slowing the gastric emptying time might improve bioavailability.

Warfarin

It is known that warfarin has a pK_a of 5.05 and is predominantly unionized at a low pH; hence, it is extensively absorbed through the stomach and proximal small intestine. It is suggested, therefore, that the reduced surface area may reduce absorption from the gastrointestinal tract and affect drug bioavailability. Despite this, some cases report successful anticoagulation.

Successful oral anticoagulation therapy has been achieved with in patients with jejuno-colic anastomoses.[12,13] A rapid (t_{max} = 30 min) and complete warfarin "absorption" of 92.8% and 96% on two occasions was reported in a patient with only 12–15 cm of jejunum.[14] One factor to consider that may influence the successful anticoagulation of patients with short bowel syndrome is the possibility of coexisting vitamin K deficiency in these patients.

Other cases report failure of attaining therapeutic anticoagulation in patients with short bowel syndrome and suggest various mechanisms for this apparent acquired warfarin resistance. Exogenous vitamin K was identified as the causative agent in two case reports, either administered directly[15] or within a parenteral nutrition regimen.[16–18] Failure to achieve a therapeutic international normalized ratio (INR) was observed in a patient with total duodenectomy with gastrojejunostomy.[19] No mention was made in any report of an attempt to administer warfarin as syrup or via the buccal route. All but one study used an indirect measure of absorption—either the INR or prothrombin time—rather than measuring serum warfarin levels.

Digoxin

Orally administered digoxin is thought to be absorbed primarily in the duodenum and proximal jejunum. Oral bioavailability varies from 66% to 90% depending on the formulation, with the critical rate-limiting factor being its solubility. Doses of 250–500 μg have produced therapeutic serum concentrations in patients with jejunocolic anastomoses,[20,21] with an in vivo study demonstrating 50% absorption.[20]

Changing formulation to elixir or gel capsules may improve digoxin bioavailability, as demonstrated in patients with small intestine malabsorption.[22] The compensatory ability of the colon to absorb digoxin may enable therapeutic concentrations to be achieved in patients after resection of the small intestine.[23] However, a case report of a patient with an end jejunostomy demonstrated poor absorption, resulting in failure to achieve therapeutic serum concentrations from tablets, gel capsules, and elixir at doses up to 750 μg/day.[24]

Beta-blockers

Sotalol is usually completely absorbed after oral administration. Sotalol has been successfully utilized to manage atrial fibrillation in two patients with short bowel syndrome.[25] Drug doses were adjusted, above usual dosage guidelines, utilizing serum drug concentrations as a guide.

The pharmacokinetics of intravenous and oral pindolol were investigated in short bowel syndrome, and no significant differences were observed in bioavailability compared to healthy controls.[26]

Tricyclic Antidepressants

Amitriptyline is extensively absorbed through the stomach and small intestine and is hepatically metabolized to nortriptyline. Oral absorption is >95%. Buccal administration of amitriptyline has demonstrated therapeutic serum concentrations from 75 mg/day.[27] Therapeutic serum concentrations of nortriptyline have also been achieved while receiving the drug via the oral route in short bowel patients.[28]

Paracetamol

Paracetamol is usually rapidly absorbed from the small intestine. Dissolution and gastric emptying are the rate-limiting steps. A decreased absorption of paracetamol in patients with a short bowel has been observed, suggesting that the main absorption site is the jejunum distal from the duodenojejunal flexure.[29]

Levothyroxine

Levothyroxine is incompletely and variably absorbed (40–75%) from the gastrointestinal tract even in healthy individuals. It is known not to be absorbed in the duodenum but is suggested that there may be malabsorbed drug in short bowel patients and increased doses may be necessary.[30]

Tacrolimus and Ciclosporin

Oral absorption of ciclosporin is variable (35–45%), with all absorption occurring in the first 3 h after oral ingestion, with absorption thought to occur over a relatively short segment of the upper small intestine. It has been suggested

that factors altering small intestine transit time or the area or integrity of the absorptive surface would be expected to alter ciclosporin absorption.[10]

Variable bioavailability between different patients and brands of ciclosporin has been reported, needing increasingly higher doses being required.[31,32] Therapeutic concentrations were also achieved with tacrolimus.

Antimicrobial Agents

Aciclovir malabsorption is reported in a patient with genital herpes following the removal of 0.6 m of terminal ileum.[33] Recurring symptoms were observed with increasing doses, until 800 mg four times daily was given. The C_{max} was still less than half that observed in healthy volunteers.

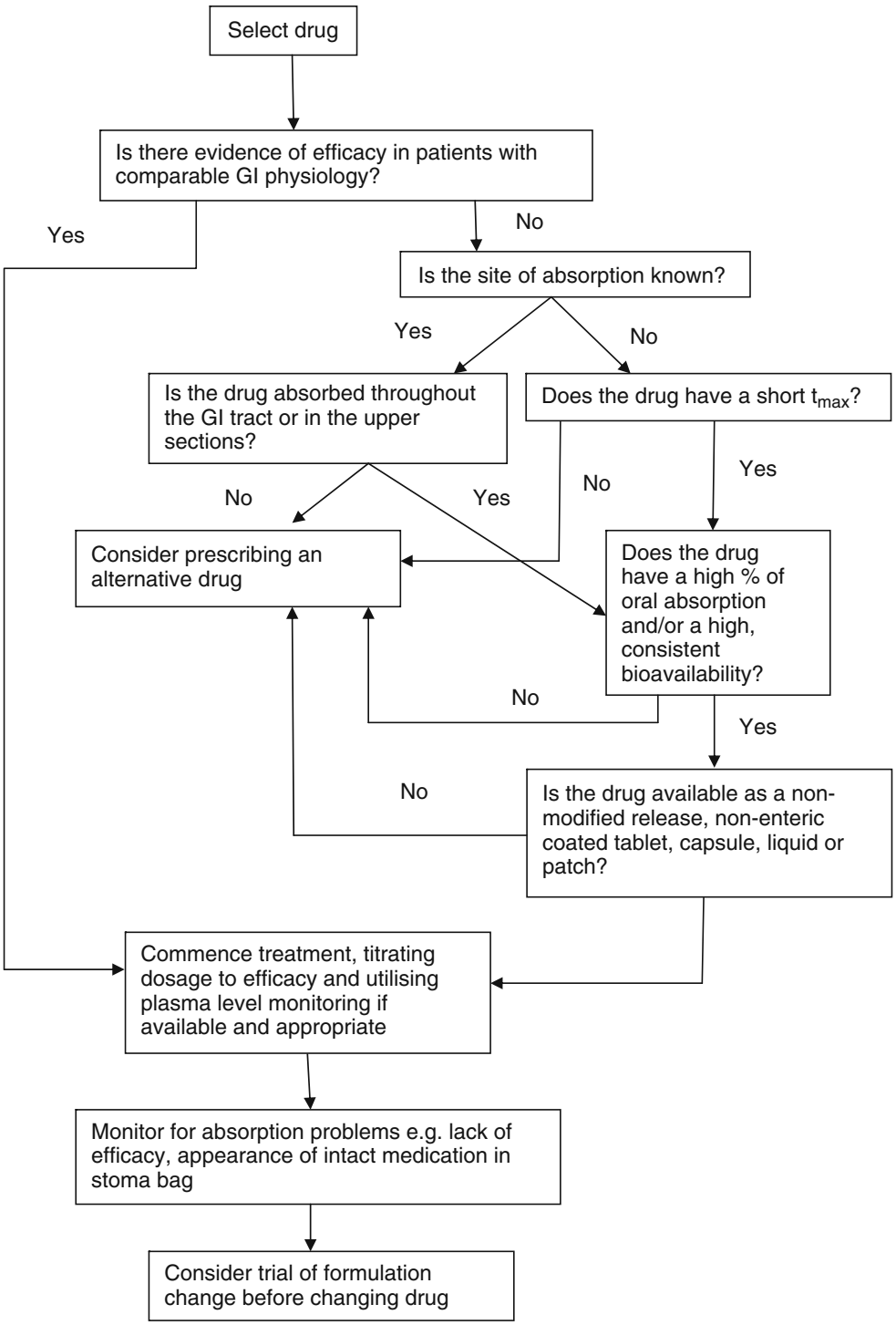

Figure 1 Prescribing algorithm for intestinal failure patients.

Rapid absorption of fluconazole is reported in a patient in whom the gastric antrum, duodenum, and ileum had been removed.[34] Fluconazole is usually rapidly absorbed from the gastrointestinal tract, with approximately 90% bioavailability.

Reduced absorption of cefaclor, cefalexin, and co-trimoxazole has been reported in children with a short bowel.[35,36] The investigators also found that oral penicillins and macrolides are not absorbed sufficiently in children with resection of >100 cm small intestine and advise that these medicines are given parenterally to ensure efficacy.

Prescribing Strategy

Due to the highly heterogeneous nature of this patient population, it is difficult to directly apply the findings of the published literature to specific patients. Where evidence exists, this should be examined alongside a careful consideration of a patients functioning bowel physiology. Where no evidence exists, a systematic approach is suggested, as shown in Fig. 1.

A consideration of these factors should enable the selection of a drug that is most likely to be sufficiently absorbed in order to be efficacious. Plasma level monitoring may be utilized for the adjustment of doses for certain drugs, but plasma levels do not correlate to efficacy for all drugs, so dosages may need to be carefully titrated to balance efficacy and potential side effects. Utilizing liquids in preference to tablets or capsules enables the bypass of disintegration and dissolution, but is unlikely to significantly improve bioavailability.

Conclusions

Patients with intestinal failure requiring chronic medication will need multidisciplinary input, particularly from pharmacists, in order to facilitate appropriate prescribing and targeted selection of appropriate drugs and formulations. It is essential for all involved in their care to be aware of the potential of unpredictable drug absorption and the likelihood of treatment failure.

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REVIEW ARTICLE

Periampullary and Duodenal Neoplasms in Neurofibromatosis Type 1: Two Cases and an Updated 20-Year Review of the Literature Yielding 76 Cases

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Abstract
Background Patients with neurofibromatosis type 1 (NF1) are at increased risk to develop tumors throughout the gastrointestinal tract, including neuromas, gastrointestinal stromal tumors (GIST), and periampullary somatostatin-rich carcinoids. Here, we briefly describe two male patients with NF1 and review the recent literature on this topic.
Methods Databases for PubMed and MEDLINE were searched for English-language articles since 1989 using a list of keywords, as well as references from review articles.
Results The results generated by the search yielded 50 articles and 74 cases. Patients most commonly presented with jaundice, weight loss, GI bleeding, or anemia. The mean age at presentation was 47.9 years, with 59% of patients being female. Mean tumor size was 3.8 cm (range 0.9–27 cm). Tumor location was the duodenum (60%), ampulla (31%), pancreas (5%), or bile duct/gallbladder (4%). Tumor type was reported as somatostatinoma (40%), GIST (34%), adenocarcinoma (8%), carcinoid (6%), neurofibroma (5%), schwannoma (4%), or gangliocytic paraganglioma (3%). Treatment included classic Whipple procedure (42%), local excision (25%), pylorus-preserving pancreaticoduodenectomy (17%), and other resection (6%). Mean follow-up was 31 months postresection (range 0–99 months): 75% of patients were alive with no evidence of disease.
Conclusions These results underscore the importance of a thorough evaluation for tumors in NF1 patients with gastrointestinal symptoms, as well as subsequent surgical management when findings suggest a tumor in the periampullary region, as resection remains the mainstay of treatment.

Keywords Neurofibromatosis · Periampullary neoplasm · Gastrointestinal stromal tumor · Carcinoid · Somatostatinoma

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Introduction

Neurofibromatosis type 1 (NF1) is an autosomal-dominant disorder occurring in one in 3,000 births characterized by cutaneous neurofibromas, café au lait macules, axillary and inguinal freckling, Lisch nodules (pigmented hamartomatous nevus of the iris), and bony lesions. NF1 is also associated with multiple benign and malignant neoplasms, including tumors of the nervous system (central and peripheral) and gastrointestinal tract. The most common gastrointestinal tumors occurring in patients with NF1 include neurofibromas, gastrointestinal stromal tumors (GISTs) of the small bowel, and periampullary carcinoid tumors. The incidence of GI tract involvement is difficult to assess in NF1 patients, although reports have indicated the presence of tumors in 10–25% of patients,[1–5] causing symptoms in less than 5% of patients. GISTs alone have been reported in 5–25% of NF1 patients,[6–8] with the largest series indicating a 7% incidence of GIST.[9]

Klein et al. reviewed the literature in 1989 for periampullary neoplasms in NF1 patients and reported the most common tumors to be carcinoid tumors, followed by neurofibromas.[1] This association has been further substantiated with multiple reports of somatostatin-producing carcinoid tumors originating in the periampullary region.

GISTs are the most common tumors of mesenchymal origin in the gastrointestinal (GI) tract. NF1 has been associated with the presence of multiple GISTs throughout the GI tract, most commonly in the small bowel and stomach, with approximately 60% of patients having multiple tumors or multiple tumor sites.[7] GISTs in non-NF1 patients are commonly associated with gain-of-function mutations of the proto-oncogene c-kit, as well as platelet-derived growth factor receptor α (PDGFRA). These mutations are not typically seen in NF1 patients. Multiple previous case series of NF1 patients with GISTs have shown that none had the c-kit or PDGFRA mutation.[10–13]

Although the incidence of GI tumors in NF1 patients has been well-documented, the pathogenesis of these tumors remains unclear. Neurofibromatosis (von Recklinghausen's disease) results from mutations of the NF1 gene (a tumor suppressor) on chromosome 17 (17q11.2), which encodes the protein neurofibromin. Half of these mutations are believed to be sporadic. Neurofibromin is one of many proteins involved in downregulating the proto-oncogene RAS pathway, as a member of the GTPase-activating protein family. Over 300 mutations in NF1 have been reported.[12] The relationship of tumors in the GI tract and NF1 gene mutations remains an area of investigation.[4,10,14–17]

We briefly report two cases of NF1 patients with periampullary tumors. The first patient underwent successful resection by pylorus-preserving pancreaticoduodenectomy of a periampullary GIST. The second patient was diagnosed with an ampullary endocrine tumor that was amenable to local excision. We include an updated review of the English-language literature in the 20 years following the initial review by Klein et al., which has yielded 74 cases of periampullary and duodenal tumors in NF1 patients.

Clinical Material

Patient 1

A 43-year-old male with a past medical history of neurofibromatosis diagnosed in childhood presented to an outside hospital with melena, fatigue, and shortness of breath. He was found to be anemic (Hgb=9.0 g/dl) and was transfused. A colonoscopy had been performed 6 months prior, which revealed only two benign colonic polyps that were removed. The patient underwent an esophagogastroduodenoscopy (EGD) which revealed a bulging periampullary mass and periampullary clot. A magnetic resonance cholangiopancreatogram was performed which showed a normal bile duct and a periampullary mass. At that time, the patient was transferred to our hospital for further workup.

A repeat EGD showed a 2.5-cm deeply ulcerated and actively bleeding mass in the second portion of the duodenum just distal to the ampulla, with an associated blood clot (Fig. 1). The ampulla appeared normal. An abdominal computed tomography (CT; Fig. 2) showed a 2.4×1.8-cm heterogenous mass in the periampullary region of the duodenum.

At exploration, multiple small spherical lesions were found on the serosal surface of the small bowel, the largest of which was approximately 20 cm distal to the ligament of Treitz, on the antimesenteric border of the proximal jejunum. The patient had a 2-cm palpable mass at the level of the ampulla of Vater, infiltrating into the pancreas, which was not amenable to local excision. The patient underwent a resection of the proximal jejunum, cholecystectomy, and pylorus-preserving pancreaticoduodenectomy (PPPD) with routine reconstruction.

The patient's early postoperative course was uncomplicated. He was discharged to home from the hospital on postoperative day 6, without drains, on a regular diet. He was readmitted 7 days following hospital discharge for an upper GI bleed, shown on endoscopy to be a Mallory-Weiss tear. This was managed conservatively and did not rebleed.

Gross examination of the PPPD specimen (Fig. 3a) revealed a 1.8×2×2-cm ulcerated, circumscribed tumor located near the ampulla of Vater. In addition, multiple firm white-tan subserosal nodules ranging in size from 0.2 to 0.7 cm were located in the duodenum and jejunum (Fig. 3b), and a dominant 2-cm mass was present in the jejunum. Microscopically, all tumors were GISTs, consisting of plump spindle cells forming a vague fascicular pattern (Fig. 4a). The nuclei were elongated without any significant pleomorphism; the cytoplasm was variably abundant, and the cell borders were indistinct. Mitotic figures were not readily seen, and necrosis was not present. Multiple skeinoid fibers were identified in these duodenal and jejunal GISTs. Immunohistochemical (IHC) staining was strongly positive for anti-CD34 and anti-CD117(c-kit), supporting the diagnosis of GISTs (Fig. 4b, c). S-100 stain, seen in tumors of neural origin, was negative. Subsequent molecular studies for c-kit mutations revealed a normal c-kit gene, without the presence of activating mutations in exons 9, 11, 13, and 17. Molecular analysis for activating mutations in PDGFA was not performed.

The patient was seen at 2 months follow-up and was doing well. A recent telephone call to him revealed that he has been in good health, without GI symptoms or complications in the 18 months since his successful resection.

Patient 2

A 31-year-old male with neurofibromatosis diagnosed in childhood presented with multiple episodes of solid-food

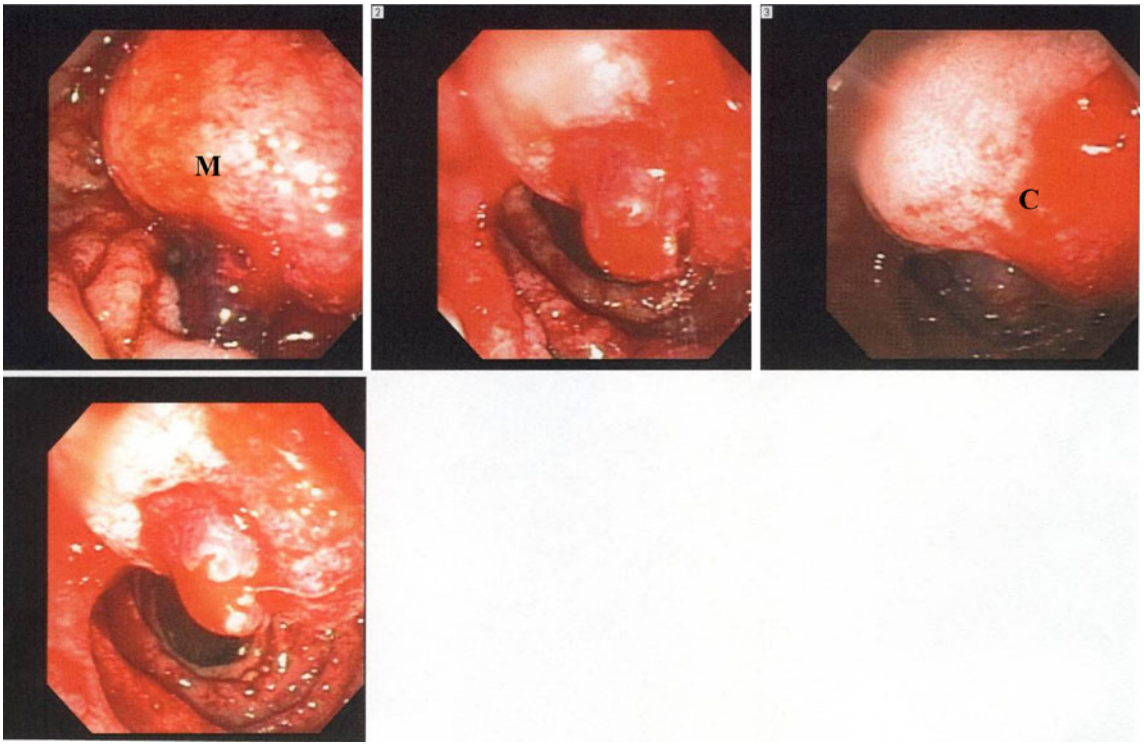

Figure 1 The EGD for patient 1 shows a bulging mass (*M*) at the periampullary region, with associated blood clot (*C*).

dysphagia as well as abdominal discomfort. Upper endoscopy revealed gross and histologic changes compatible with severe eosinophilic esophagitis. During the procedure, a prominent ampulla of Vater was noted (Fig. 5), and biopsies revealed a well-differentiated endocrine tumor of uncertain malignant potential. Endoscopic ultrasound (Fig. 6) revealed a 1.5×1.0-cm hypoechoic ampullary mass confined to the mucosa and submucosa (T1N0M0) with minimal dilation of the pancreatic duct in the head of the pancreas. CT scan did not detect the ampullary lesion, nor did it reveal an evidence of metastatic disease. A multidisciplinary team that included gastroenterologists and hepatobiliary surgeons ultimately decided with the patient and his family that open surgical extirpation was appropriate.

At surgery, multiple small lesions were seen throughout the serosal surface of the small bowel, scattered every 10–20 cm through the jejunum and ileum, with the two largest of these being at the ligament of Treitz and 10 cm distal. These two lesions were locally excised. A transduodenal local resection of the ampullary mass was then performed, using standard technique. The spherical lesion was resected with negative lateral and deep margins, and the bile duct and pancreatic duct were reconstructed via sphincteroplasty and septoplasty, respectively.

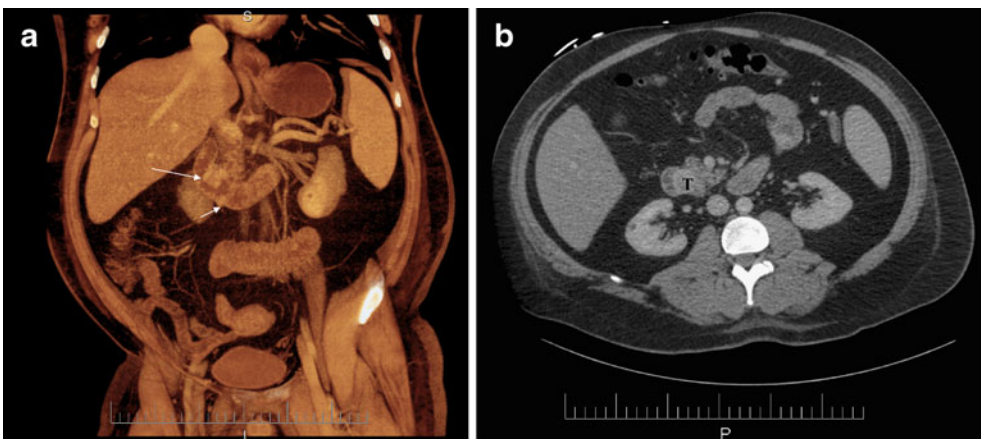

Figure 2 **a** This coronal CT scan image of patient 1 nicely reveals the large periampullary mass (*large arrow*), as well as a smaller duodenal wall mass (*small arrow*) at the junction of D_2 and D_3. **b** This axial CT image for patient 1 reveals the large periampullary tumor (*T*) mass.

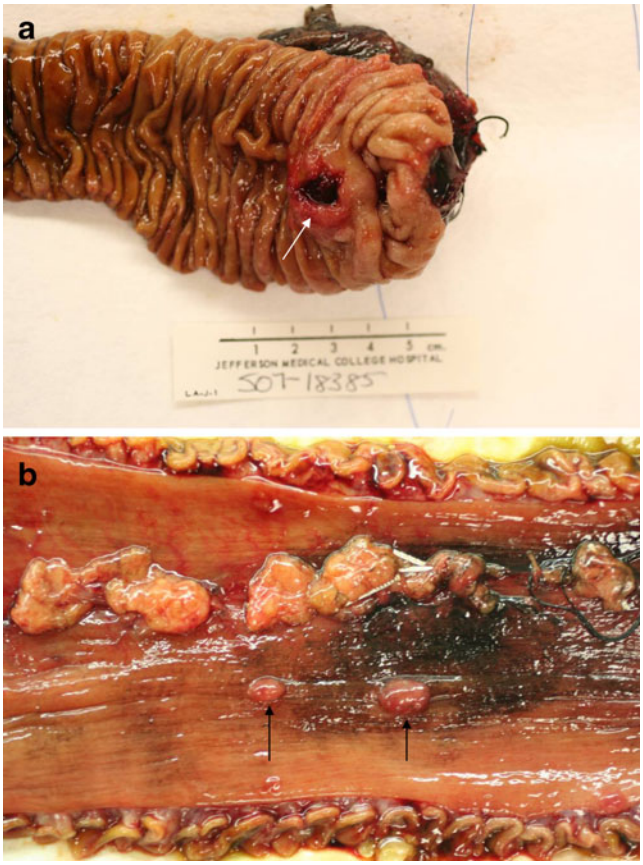

Figure 3 **a** This image shows the gross appearance of the duodenal ulceration (*arrow*) associated with the underlying mass of patient 1. **b** Two small GISTs are shown (*arrows*) in the proximal jejunal serosa from patient 1.

Gross examination of the ampullary specimen (Fig. 7) revealed a 0.7×0.4×0.4-cm firm, well-circumscribed tumor mass. Microscopically, sections of the mass showed solid groups and nests of polygonal neoplastic cells, having moderately pleomorphic nuclei with small central nucleoli and a moderate amount of granular eosinophilic cytoplasm (Fig. 8). Neoplastic cells infiltrated the duodenal smooth muscle wall around the ampulla, extending into the overlying duodenal mucosa. Only rare mitotic nuclei were seen (less than one mitosis per ten high-powered fields) with no evidence of necrosis. IHC staining was strongly positive for chromogranin A and synaptophysin (Fig. 9). Somatostatin staining could not be performed. The neoplastic cells showed a perinuclear dot-like staining pattern with pancytokeratin AE1/AE3. This histology and IHC profile were consistent with the diagnosis of well-differentiated ampullary endocrine neoplasm.

Gross examination of the two serosal small-bowel tumors revealed a 1.2-cm mass at the ligament of Treitz and a 0.5-cm mass from the jejunum. Microscopically, these were low-grade spindle-cell neoplasms. IHC stains were strongly positive for CD117 and had moderate

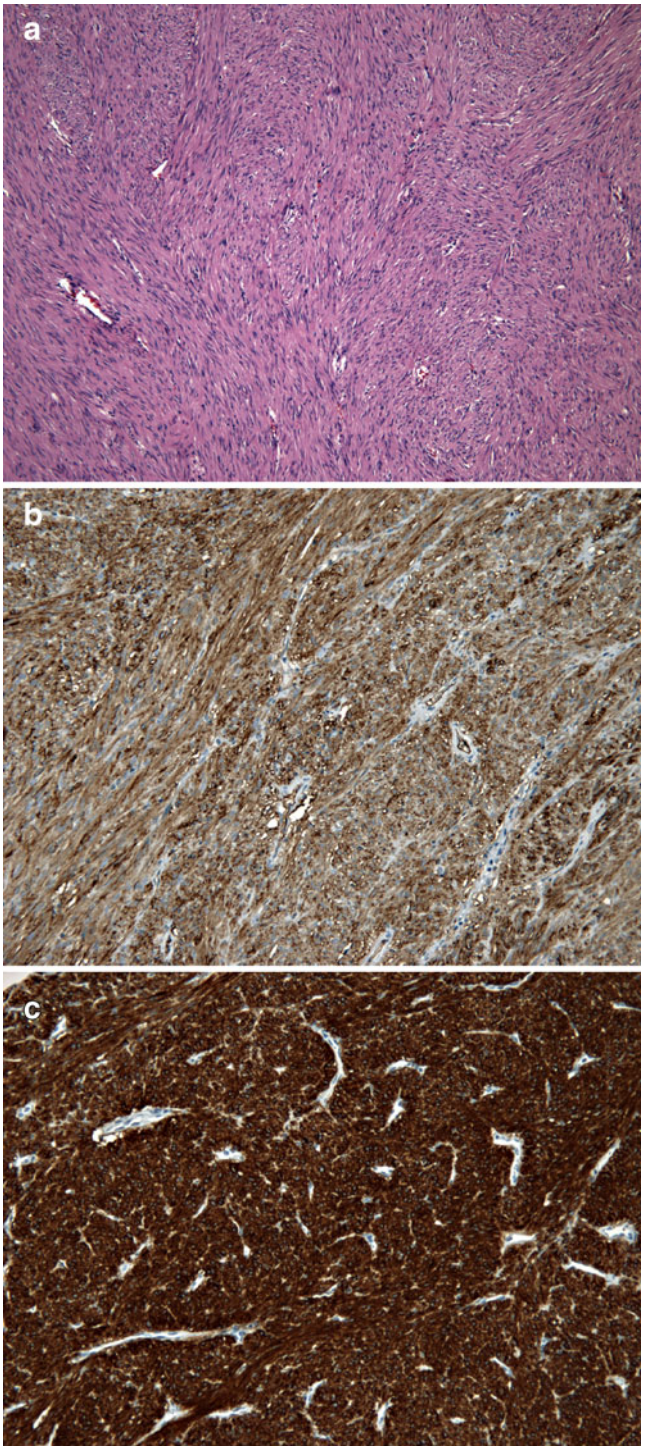

Figure 4 **a** Microscopic appearance of the periampullary GIST removed from patient 1 consisting of bland spindle cells forming fascicles (hematoxylin–eosin, original magnification ×10). **b**, **c** For patient 1, immunohistochemical stains were strongly positive for CD34 (**b**) and CD117/c-KIT (**c**), supporting the diagnosis of GIST.

staining with CD34. The spindled neoplastic cells were negative for pancytokeratin AE1/AE3, S100, and alpha smooth muscle actin. This histology and IHC profile are consistent with GIST.

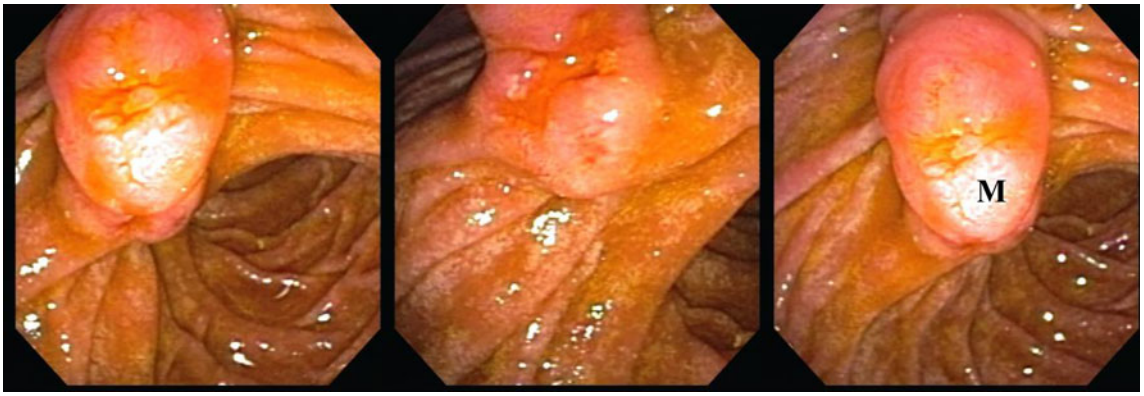

Figure 5 The EGD from patient 2 shows an ampullary mass (*M*) with raised erythematous mucosa, 1 cm distal to the ampulla.

The patient's postoperative course was without complication. He was discharged home on postoperative day 6 and at 6 months follow-up was doing well.

Discussion and Literature Review

Background

Patients with NF1 are predisposed to developing benign and malignant neoplasms, particularly those of neurogenic or neuroendocrine origin.[18] Zoller et al. reported a fourfold increase in risk of developing a malignancy in patients with NF1 (24%), as compared to the general population.[9]

GI tract involvement has been reported to occur in 12–25% of patients with NF1, although only 5% are symptomatic.[1,3,5] These tumors typically occur in three forms[19]: hyperplasia of intestinal neural plexuses (neuromas and neurofibromas), GISTs, and periampullary endocrine tumors (somatostatin-producing carcinoids) occasionally associated with pheochromocytomas.[12,20] GISTs are believed to be the most common GI tumor in NF1 patients,[6] with 1.5% of all GISTs occurring in NF1 patients.[7]

Association of NF1 and Periampullary Tumors

The most extensive previous review of periampullary and gallbladder tumors in patients with NF1 was reported in 1989 by Klein et al.[1] The authors identified 37 cases in patients with NF1 and noted that 54% were found in the ampulla, 38% in the duodenum, 5% in the pancreas, and 3% in the gallbladder. Histologically, most tumors were carcinoids (41%), followed by neurofibroma (30%), neurofibrosarcoma (malignant peripheral nerve sheath tumor) and adenocarcinoma (8% each), neurilemoma (schwannoma) and paragangliomas (5% each), and ganglioneuroma (3%). Of the 20 tumors found at the ampulla of Vater, 60% were carcinoids.

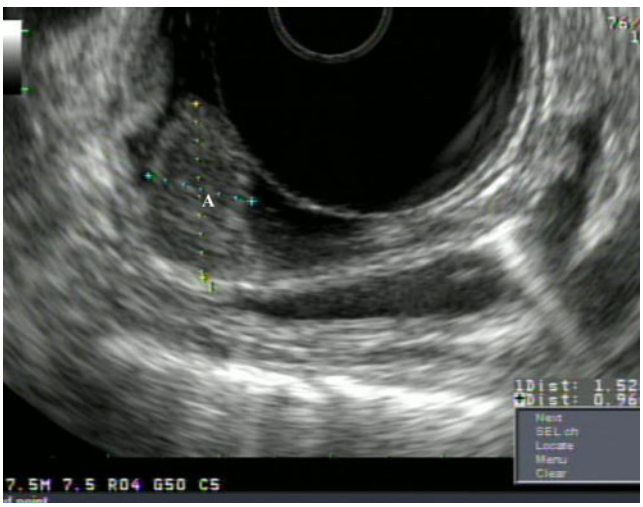

Figure 6 For patient 2, endoscopic ultrasound at the ampulla revealed a 1.0-by-1.5 cm hypoechoic ampullary mass (*A*) confined to the mucosa and submucosa.

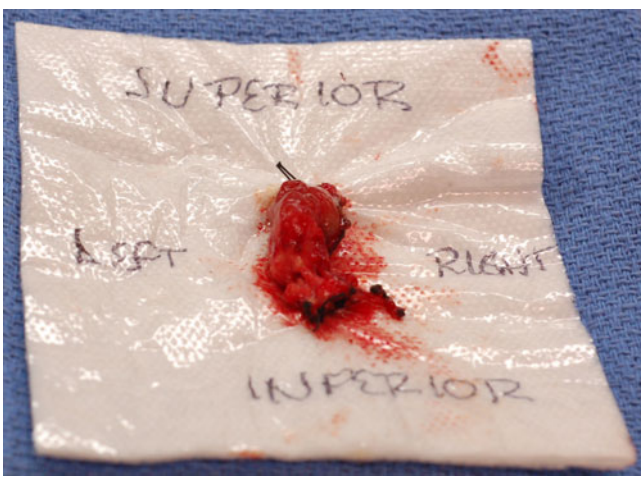

Figure 7 Gross pathology of the specimen from patient 2 shows a 0.7×0.4×0.4-cm tan-white, firm, well-circumscribed tumor which was locally resected from the periampullary region.

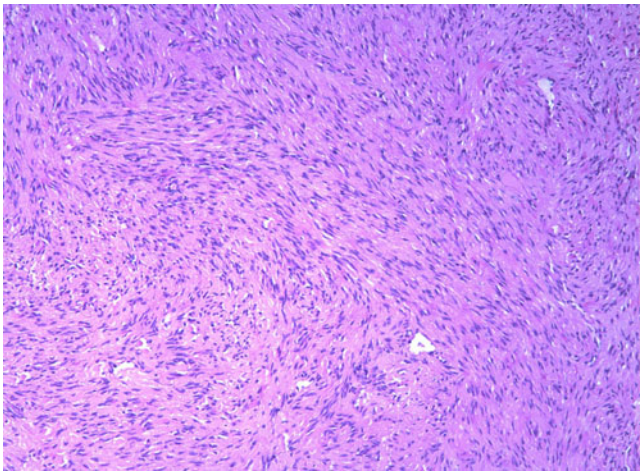

Figure 8 Microscopic evaluation of the ampullary lesion from patient 2 revealed neoplastic cells showing a perinuclear dot-like staining pattern with pancytokeratin AE1/AE3.

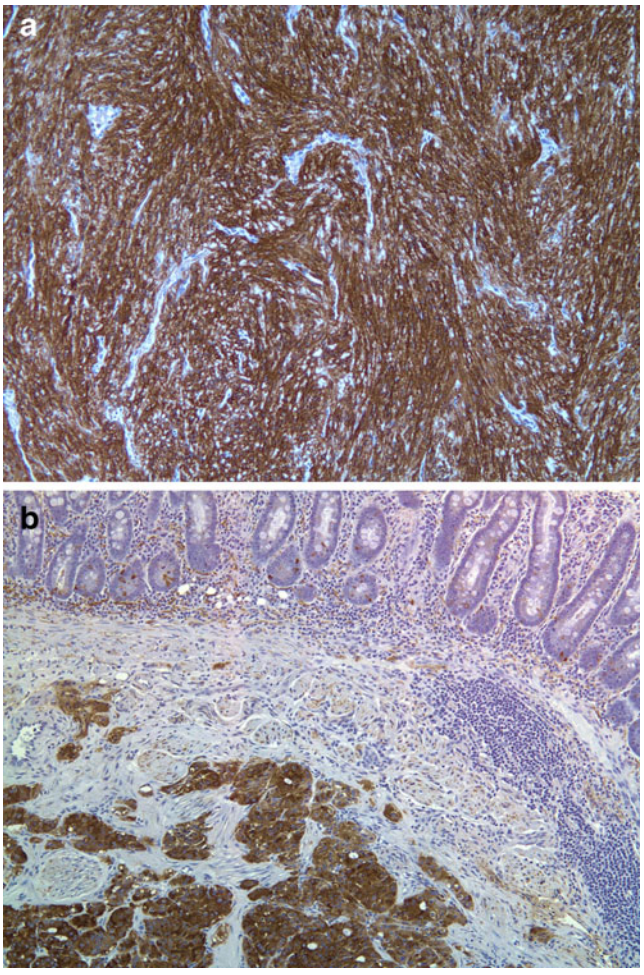

Figure 9 **a**, **b** Immunohistochemical staining of the specimen from patient 2 was strongly positive for chromogranin A (**a**) and synaptophysin (**b**), consistent with the histologic diagnosis of a well-differentiated endocrine neoplasm.

Our extensive 20-year review of the English-language literature since 1989 was conducted using the search terms neurofibromatosis, periampullary, gastrointestinal stromal tumor, gallbladder, pancreas, bile duct, and ampulla. In addition, we examined references from relevant articles. This yielded 74 reported cases of periampullary tumors in patients with neurofibromatosis, which, when added to our two cases, totals 76 cases. In these 76 cases, the most common symptoms at presentation were jaundice, weight loss, pain, GI bleeding, and anemia (Table 1). Only 8% of the reported patients were asymptomatic. This is consistent with previous reports on ampullary carcinoids in both NF1 and non-NF1 patients.[21,22] In contrast to previous reviews, adenocarcinomas (8%) were reported more frequently in our 20-year review than neurofibromas (5%).

Association of NF1 and Periampullary Somatostatin-Staining Carcinoid Tumors

Our review found that 47% of periampullary tumors were neuroendocrine in origin (Table 2), with 40% being reported as somatostatinoma, 6% as carcinoid, and 1% as malignant endocrine tumor. Periampullary carcinoid tumors were first described in association with NF1 in 1982 by Cantor et al.[23] A review of the literature in 2002 found 25 cases reported since that initial description.[24] These tumors are most commonly located in the duodenum or ampulla of Vater and tend to be pure somatostatin-staining tumors (as

Table 1 Review of Literature: Demographics and Symptoms[42–76]

	Number (%), n=76	
Age (years)	47.9 years	
Gender (m/f)	31/45	(41/59)
Symptoms (n=59)		
Symptomatic	54	(92)
Asymptomatic	5	(8)
Pain	20	(37)
Weight loss	17	(32)
Jaundice	15	(28)
Anemia	12	(22)
Melena/GI bleed	11	(20)
Nausea/vomiting	7	(13)
Diarrhea	6	(11)
Abdominal mass	4	(7)
Pancreatitis	3	(6)
Cholangitis	2	(4)
Duodenal ulcer	2	(4)
Bowel obstruction	1	(2)
Hematemesis	1	(2)
Somatostatinoma syndrome	1	(2)

Table 2 Review of Literature: Tumor Location, Size, and Type[42–76]

	Number (%), $n=80$[a]	
Tumor location		
Duodenum	48	(60)
Ampulla of Vater	25	(31)
Pancreas	4	(5)
Bile duct/gall bladder	3	(4)
Multiple GI tumors[b]	21	(26)
Mean tumor size (cm), 3.8 cm (range 0.9–27 cm)		
Tumor <5 cm	15	(22)
Tumor ≥5 cm	54	(78)
Type		
Somatostatinoma	32	(40)
GIST	27	(34)
Adenocarcinoma	6	(8)
Carcinoid	5	(6)
Neurofibroma	4	(5)
Schwannoma	3	(4)
Gangliocytic paraganglioma	2	(3)
Malignant endocrine tumor	1	(1)

GIST gastrointestinal stromal tumor

[a] Four patients each had two different tumors that could be included in the review

[b] At least one additional tumor located throughout the GI tract in addition to the periampullary or duodenal lesion

compared to the multihormonal variety seen in non-NF1 patients).[25–27] It has been reported that 26–41% of periampullary somatostatinomas are associated with NF1.[25,28]

Periampullary somatostatinomas are often characterized pathologically by psammoma bodies and tend to present with size-dependent local symptoms in the absence of the somatostatinoma syndrome (diabetes mellitus, steatorrhea, cholelithiasis) often seen with pancreatic primaries.[29,30] Additionally, pancreatic somatostatinomas are more likely to present with metastases at the time of operation (possibly due to differences in size at the time of detection) and do not have the same association with NF1.[29]

Much is known about carcinoids in the general population, including the relation of metastatic potential to size and site of origin and the generally favorable 5-year survival rate of 90%.[31] It is not known if these conclusions apply in the context of NF1. A 2004 review of 56 duodenal somatostatinomas in NF1 (n=27) and non-NF1 (n=29) patients showed that the non-NF1 patients were less likely to have tumors with multihormonal production (4.7% vs. 16%).[32] Otherwise, with respect to the somatostatinoma syndrome, tumor size, and psammoma body presence, the two groups were similar. A 50% incidence of lymph node metastases has been reported for carcinoids >2 cm, arguing for a regional resection even when technically locally resectable.[18,21]

Association of NF1 and GISTs

GISTs are the most common GI tumors found in NF1 patients, typically occurring in the stomach and jejunum. This association has been well described,[14,15] particularly by the Armed Forces Institute for Pathology (AFIP).[7,33,34] GISTs in NF1 tend to be multiple, may be benign or malignant, and can have both muscular and neural differentiation.[2,6] At the time of Klein's review[1], GISTs were classified as leiomyomas, leiomyosarcomas, leiomyoblastomas, or schwannomas due to their histologic appearance and relation to the muscularis propria. With the advent of immunohistochemical staining, GISTs became recognized as a distinct subset of mesenchymal tumors. They are thought to originate from the interstitial cells of Cajal or their stem cell precursors.

Zöller et al. reported that GISTs are detected in 7% of patients with NF1.[9] A review of 167 duodenal GISTs from the AFIP found that 6% were associated with NF1, that these were more likely to be multiple small intestinal GISTs, and that, although usually clinically indolent, severe GI bleeding was a distinctive complication of this group.[7,32] Histopathologically, these NF1-associated tumors tended to be mitotically active, showed more significant focal nuclear atypia, and demonstrated diffuse Cajal cell hyperplasia, as compared to the non-NF1-associated tumors. GISTs in NF1 patients also have shown increased skeinoid fibers as compared to those seen in non-NF1 patients.[35,36] Previous reports have found that 22–31% of GISTs in NF1 patients are found in the duodenum, and approximately 60% of patients harbor tumors at multiple sites.[7,14]

Based on light microscopic features, the prediction of aggressive behavior for GISTs remains difficult. Features associated with malignant behavior include tumor size (>5 cm), extragastric location within the GI tract, invasion of adjacent organs, cytologic grade/cell type (mixed cell type more aggressive than spindle or epithelioid alone), foci of unequivocal tumor necrosis, tumor infiltration of the overlying mucosa, and high mitotic activity (at least five mitoses per 50 high-power fields).[37] It is generally accepted that the presence of two or more of these features can be quite predictive of aggressive or malignant behavior. The tumors in our two patients did not fulfill any of the above criteria. Occasionally, however, an apparently benign GIST that lacks any of the above criteria of malignancy has been observed to metastasize.

Molecular Pathogenesis of Sporadic vs. NF1-Associated GISTs

In non-NF1 patients, GISTs are thought to result from a gain-of-function mutation of the c-kit proto-oncogene, resulting in constitutive activation of the transmembrane

Table 3 Review of Literature: Treatment and Outcome[42–76]

	Number (%)	
Treatment (n=47)		
Classic Whipple	20	(42)
Local excision	12	(25)
PPPD	8	(17)
Nonoperative	5	(10)
Other resection	3	(6)
Outcomes (n=65)		
ANED	49	(75)
DOD	6	(9)
DOPC	4	(6)
DUC	3	(5)
DUNC	2	(3)
AWD	1	(2)
Mean follow-up	31 months	

PPPD pylorus-preserving pancreaticoduodenectomy, *ANED* alive no evidence of disease, *DOD* died of disease, *DOPC* died of perioperative condition, *DUC* died of unrelated causes, *DUNC* died of unknown causes, *AWD* alive with disease

type III receptor tyrosine kinase KIT (CD117). This receptor binds and mediates the growth factor called stem cell factor. In non-NF1 patients, the c-kit mutation is seen in 90% of GISTs.[2,15] These mutations may be on exon 11, 9, 13, or 17, which encode respectively the juxtamembrane, extracellular, TKI, and TK2 domains. The expression of CD34 and CD117 on both GISTs and the interstitial cell of Cajal suggests a common origin of these cells.

Additionally, 5% of non-NF1-associated GISTs are believed to have mutations in the PDGFRA tyrosine kinase. These mutations have been demonstrated on exons 12 and 18, which encode for the kinase activation loop and the juxtamembrane domain, respectively.[15]

Several recent studies have detected no mutations in either KIT or PDGFRA in NF1 patients with GISTs.[7,10,15] Although a recent review of 15 duodenal GISTs from NF1 patients showed that 20% of these tumors demonstrated c-kit point mutations, these were not the mutations typically associated with GISTs from the non-NF1 population. This underscores the likelihood of a different molecular mechanism for the development of GISTs arising in NF1 patients.

Treatment and Outcome

Resection remains the mainstay of treatment for periampullary tumors in NF1. As can be seen in Table 3, the most common methods of resection have included classic Whipple resection (42%), local excision (25%), and pylorus-preserving pancreaticoduodenectomy (17%). Of those 65 patients where outcome data were reported, 75% were alive with no evidence of disease; 9% had died of disease; and 6% had died of a perioperative complication or condition. As it is hard to determine the regional spread of these tumors by imaging or gross inspection and there is a 50% rate of metastases of carcinoid tumors to local lymph nodes,[2,38] a wide resection with lymph node harvest appears indicated in patients with large carcinoid tumors (perhaps >2 cm in diameter). Nonsurgical treatment for periampullary tumors is limited. GISTs in the non-NF1 patient population have shown responses to imatinib and sunitinib,[17,39] although such drugs would not be expected to be active in NF1-associated GISTs.

Radiologic imaging is important in evaluating the resectability of periampullary tumors. CT or MRI offers the best radiologic evaluation of these lesions for lymphadenopathy, local invasion, and visceral metastasis.[5]

Carcinoid tumors less than 2 cm have a low risk of lymph node metastasis and may be amenable to local excision with enucleation with an excellent prognosis. Tumors greater than 2 cm have a high propensity for local or lymph node invasion and may require formal pancreaticoduodenectomy.[28,40] Gastrointestinal somatostatinomas are also larger in size on presentation and are commonly located within the head of the pancreas or the duodenum. Therefore, pancreaticoduodenectomy is the preferred surgical procedure for these lesions as well.[41] Although these have a high rate of metastases on presentation, surgical exploration may be useful in staging, debulking, or palliation of obstruction. Periampullary adenocarcinomas require pancreaticoduodenectomy for adequate margins of the lesion.

Summary

In summary, we have reviewed periampullary, duodenal, and gallbladder neoplasms occurring in NF1 patients. Patients with NF1 who present with gastrointestinal symptoms, including jaundice, weight loss, pain, and GI bleeding, should be evaluated for the typical causes, with increased suspicion for periampullary and duodenal tumors. These tumors are most often small-bowel GISTs, periampullary somatostatin-producing endocrine tumors, and adenocarcinomas. Definitive treatment will often include surgical management.

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GI IMAGE

Large Epiphrenic Diverticulum

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Keywords Esophageal diverticulum · Paraesophageal hernia · Esophageal dysphagia

Case Presentation

A 53-year-old man with a history of intractable gastroesophageal reflux disease (GERD) presented to the ER with dysphagia to solids, regurgitation of solids and liquids, and worsening reflux symptoms, accompanied by a 20-lb weight loss in 2 months. On admission, he denied odynophagia, hematemesis, or melena. He reported no history of tobacco use, and he had never had an esophagogastroduodenoscopy (EGD). Lab results were within normal limits, and physical exam result was significant for decreased breath sounds at the right lung base and epigastric tenderness.

Computed tomography (CT) of the chest and abdomen showed a markedly dilated esophagus and, distally, an 8-by-9-cm contrast-filled hollow structure in the right thorax (Fig. 1). Barium swallow suggested that both the structure and gastroesophageal junction were above the diaphragmatic hiatus (Fig. 2). On EGD, the esophagus was filled with liquid and solid food. A large luminal structure was entered at the distal esophagus and was inundated with undigested food. It had a narrow neck leading to the normal stomach.

The patient underwent a laparoscopic exploration for a presumed type III paraesophageal hernia. Intraoperatively, only a moderately sized hiatal hernia was found. At that time, the surgeons felt that the paraesophageal hernia was easily reduced with traction on the distal stomach and freeing of the hernia sac from the diaphragmatic attachments. The hernia was then repaired primarily, and partial fundoplication was performed. Postoperative esophagram redemonstrated a contrast-filled structure in the right chest. Consideration was given to an acute recurrence of the hernia; however, further review of the case concluded that the actual diagnosis was a large epiphrenic diverticulum.

The patient returned to the operating room. Through a laparoscopic abdominal approach, the fundoplication was taken down, and an esophagocardiomyotomy was performed. A right thoracotomy was performed, and the giant diverticulum was confirmed and resected. The patient recovered uneventfully.

Discussion

Epiphrenic esophageal diverticula are rare. They are classified as “pulsion” diverticula in the distal-most 10 cm of the esophagus. They are believed to arise in areas of increased intraluminal pressure and are more common on the right.[1] Motility disorders are posited to underlie their

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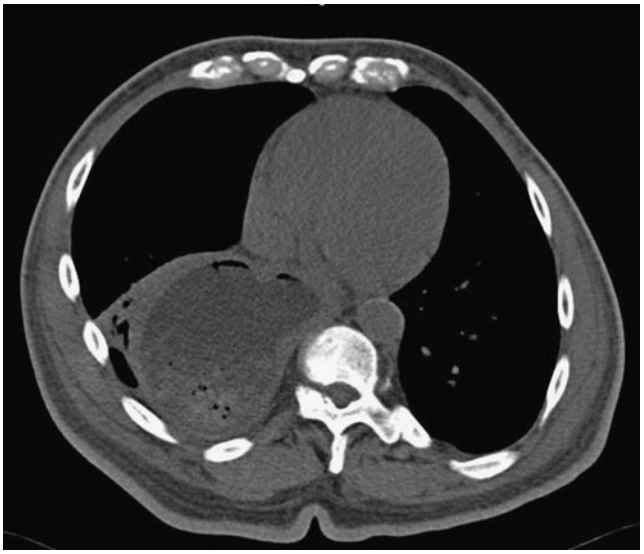

Figure 1 CT chest showing 8×9-cm structure in right hemithorax.

development and are demonstrated in up to 81% of patients.[2] Non-specific motility disorder and all primary motility disorders have been implicated, including diffuse esophageal spasm, hypertensive lower esophageal sphincter, and vigorous achalasia.[3] Less frequently, the increased intraluminal pressure may be the result of other esophageal lesions, including masses or stricture.[4]

Epiphrenic diverticula are often asymptomatic and discovered incidentally. When present, symptoms include dysphagia, regurgitation, chest pain, and significant weight loss.[5,6] Assessment of these patients includes EGD with biopsy, CT of the chest and abdomen, and barium esophagram for diagnosis of the diverticulum and estimation of its size. Additionally, esophageal manometry may identify an underlying motility disorder, though significant technical difficulty in passing the probe past the diverticulum may preclude this diagnosis.[6]

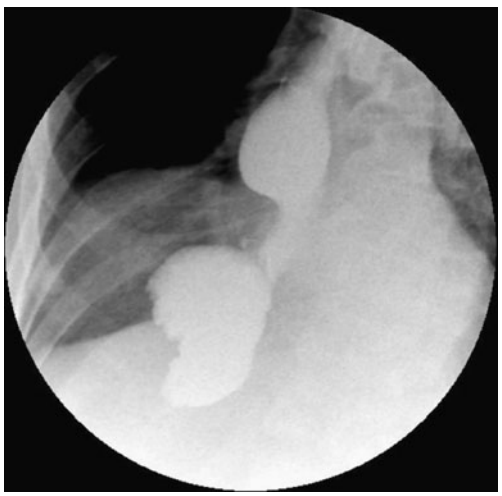

Figure 2 Esophagram showing a large structure above the diaphragmatic hiatus.

The surgical management of epiphrenic diverticula is a controversial topic. There is no consensus regarding indications for surgical intervention, given the significant morbidity and mortality associated with these procedures. While some series advocate surgery for all epiphrenic diverticula due to high rates of pulmonary sequelae (25–45%), a recently published study of long-term outcomes suggests that watchful waiting may be acceptable for small diverticula presenting with mild symptoms.[7]

When surgery is indicated, the choice of an optimal surgical procedure is also controversial. Diverticulectomy with esophagomyotomy and partial fundoplication is supported by several studies, given the lower rates of recurrence when the underlying motility problem is addressed by long myotomy.[6] The approach is typically via left thoracotomy, as this facilitates the performance of long myotomy and fundoplication. Other approaches include plication of the diverticulum and Nissen fundoplication, instead of partial fundoplication.

In the case presented above, consideration was given to other surgical approaches for repair of the large diverticulum. A laparoscopic abdominal approach was used to perform the takedown of the partial fundoplication and esophagocardiomyotomy simultaneously. For this reason, a left thoracotomy approach was not necessary, and right thoracotomy was utilized for better access to the large, right-sided diverticulum. Postoperatively, a repeat partial fundoplication procedure could be considered in the future if the patient's GERD symptoms do not respond well to medical therapy.

In our patient, preliminary imaging and a history of GERD were consistent with a type III paraesophageal hernia; confusing anatomy and difficult visualization of the mucosal "Z-line" given significant debris in the esophagus made diagnosis by EGD challenging. The barium swallow was also difficult to correlate with both CT and EGD findings. Nonetheless, the right-side location of the mass and the intraoperative finding of a small hernia, likely too small to account for the preoperative imaging, were clues to the correct diagnosis.

We suggest that cinematographic esophagram would have facilitated the identification of the diverticulum. By providing a dynamic study, unlike the still images seen using fluoroscopic exams, the misdiagnosis of a paraesophageal hernia could have been avoided; this method is already in use in the assessment of esophageal diverticula.[8] Intraoperatively, endoscopy during the paraesophageal hernia repair would have been helpful by confirming the extent and location of the herniated fundus and raising suspicion for another possible etiology.

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GI IMAGE

Paper Pica: An Unusual Cause of Colonic Ischemia

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Abstract
Introduction Pica as an eating disorder is uncommonly associated with surgical complications. Paper as the consumed substance has been previously reported twice in the literature.
Discussion We present a case of bowel obstruction and ischemia secondary to paper pica. The pathophysiology, histology, and characteristics of this entity are presented, and emphasis is placed on clinical suspicion in patients with psychiatric history.

Keywords Paper pica · Colonic ischemia · Bowel obstruction · Bezoar

Case Report

A 51-year-old woman was accepted in transfer with a 2-day history of diffuse abdominal pain, followed by emesis and obstipation. Her past medical history was significant for depression, anorexia nervosa (requiring hospitalization), and osteoarthritis. On presentation, physical examination revealed her to be cachectic and malnourished. She was afebrile, with stable vital signs. Her abdomen was soft, moderately distended with minimal tenderness to palpation, and no signs of peritoneal irritation. Digital rectal examination revealed no palpable masses or occult blood. Laboratory studies on admission were unremarkable except for a white cell count of 10,400 with 33% bands.

Computed tomography of the abdomen and pelvis demonstrated massively dilated loops of bowel with stasis of fecal material in the right colon. There was also a small amount of ascites and mesenteric edema (Fig. 1). The following day, the patient became progressively distended and profoundly tender with evidence of peritonitis. She was brought to the operating room where laparotomy demonstrated large amount of dark bloody fluid in the peritoneal cavity. The ascending, transverse, and proximal descending colon was noted to be markedly dilated and necrotic. Total abdominal colectomy with end ileostomy was performed (Fig. 2). Histopathology revealed transmural necrosis (Fig. 3, arrow).

Microscopic examination of the specimen revealed ischemic colitis with transmural necrosis, and the dilated lumen was found to contain copious amounts of polarized material most consistent with paper (Fig. 3, arrowhead). Postoperatively, the patient admitted to consuming a large amount of paper. It is noteworthy that pieces of paper were observed to emerge from her ileostomy for several days after the surgery.

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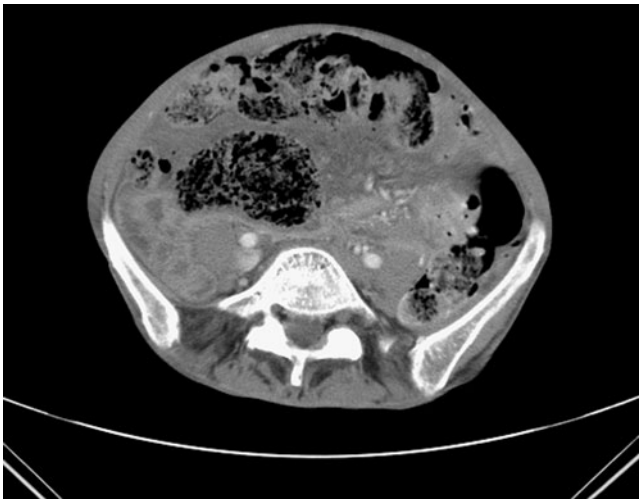

Figure 1 Computed tomography of the abdomen and pelvis shows colonic distention, fecal matter, and mesenteric edema.

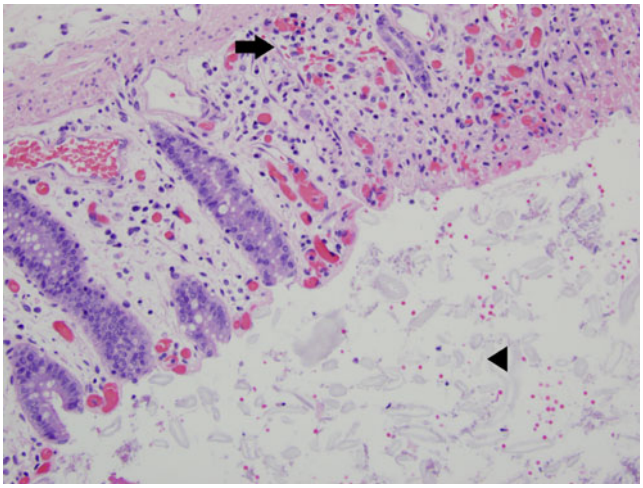

Figure 3 Microscopic view of the specimen with hematoxylin and eosin staining.

Discussion

Pica is an eating disorder characterized by excessive consumption of unprepared food products (e.g., flour, raw rice, and salt) or most commonly non-food substances (e.g., soil, coal, chalk, and soap). In a literature review of 43 patients with surgical complications secondary to pica, all cases were related to non-food consumption.[1] Intestinal obstruction was the most common complication, with the most frequent location being the ileum followed by the colon. Anatomically, the ileum, due to its narrower lumen, is more prone to pica obstruction, but often times, the slow accumulation of the consumed material, followed by colonic water absorption leads to high concentration of the undigested matter and the formation of very hard dry stool that cause complete colonic obstruction.

Paper pica is extremely rare, and this report represents only the second published case of colonic obstruction. A thorough review of the literature revealed two previously described cases of paper pica with surgical complications. The first was a 30-year-old woman who presented with clinical and radiographic findings consistent with small bowel obstruction.[2] At laparotomy, she was found to have an obstructed terminal ileum, and enterotomy released a large paper bezoar. The second was a 31-year-old woman who presented with progressively worsening abdominal pain and constipation.[3] During laparotomy, she was found to have a large 5 cm sigmoid perforation, 680 g of paper was extracted, and the perforation was repaired primarily. The patient postoperatively confessed the habit of eating paper since the age of 12.

Surgical complications of pica are rare. Although careful history may hint at the diagnosis, most patients conceal their unusual eating habits, and diagnosis is most often made at celiotomy.

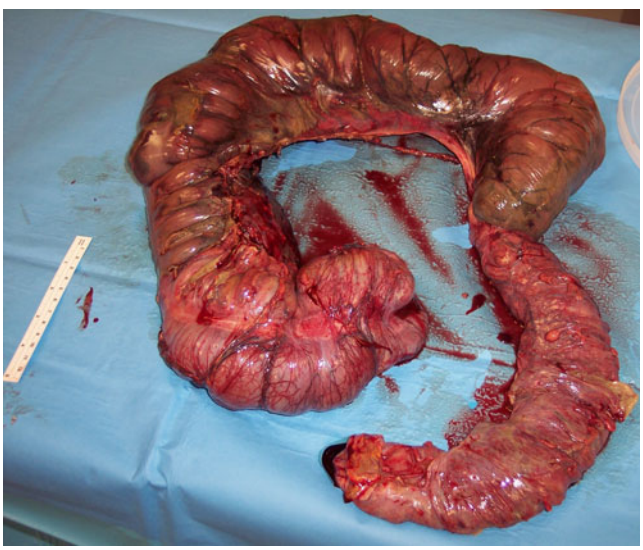

Figure 2 Surgical specimen involving the entire colon.

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