

# World Journal of *Gastrointestinal Surgery*

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**CASE REPORT**

- 1 Associating liver partition and portal vein ligation for staged hepatectomy for extensive alveolar echinococcosis: First case report in the literature

*Akbulut S, Cicek E, Kolu M, Sahin TT, Yilmaz S*

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## Associating liver partition and portal vein ligation for staged hepatectomy for extensive alveolar echinococcosis: First case report in the literature

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### Abstract

Alveolar echinococcosis (AE) is a zoonotic disease that is caused by *Echinococcus multilocularis* that affects liver and a variety of organs and tissues. It differs from other echinococcal disease because it shows tumor like behavior in the affected organ and tissues. The treatment of choice is concomitant medical therapy and resection with negative margins. Nevertheless, resection with the intent of negative margins (R0) may lead to serious complications such as liver failure. In the present case report, we used Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) procedure, which was defined in 2012 by Schnitzbauer *et al*, in a 28-year-old male patient to avoid complications of major liver resection in order to treat alveolar echinococcosis. Until now, we have not encountered any study using ALPPS procedure for the treatment of alveolar echinococcosis. In the present case report we aimed to show that ALPPS procedure can be safely performed for margin-negative resection of primary or recurrent AE that shows a tumor like behavior. It is our opinion that this procedure should be performed in centers that have expertise and sufficient technical capacity to perform liver transplantation and advanced liver surgery.

**Key words:** Alveolar echinococcosis; Extensive disease;

Associating liver partition portal vein ligation; Curative management

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**Core tip:** We have shown the feasibility and efficacy of Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) procedure -initially described for the resection of advanced tumors including colorectal liver metastasis, hilar cholangiocarcinoma and to a lesser extent hepatocellular carcinoma-in resection of recurrent hepatic alveolar echinococcosis in a young patient. In selected patient groups with benign liver disease with extensive hepatic involvement ALPPS can be safely used in centers which have expertise in liver transplantation and major hepatic surgery. According to our knowledge, the present patient is the first extensive hepatic AE case that ALPPS procedure has been applied in the literature.

Akbulut S, Cicek E, Kolu M, Sahin TT, Yilmaz S. Associating liver partition and portal vein ligation for staged hepatectomy for extensive alveolar echinococcosis: First case report in the literature. *World J Gastrointest Surg* 2018; 10(1): 1-5 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v10/i1/1.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v10.i1.1>

## INTRODUCTION

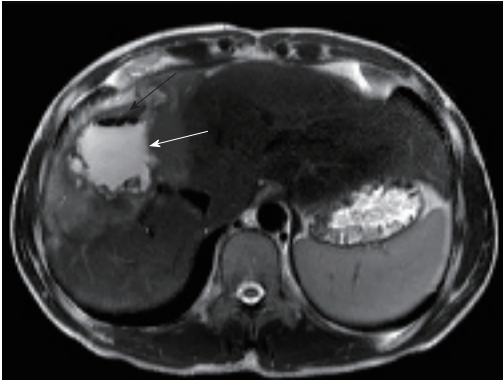
Alveolar echinococcosis (AE) is a zoonotic disease that primarily affects the liver but has the potential for local invasion and metastasis to brain, lung and bones. Therefore; although it seems to be a parasitic disease, it has the clinical behavior of a malignancy<sup>[1]</sup>. The growth pattern of the parasite determines the biologic behavior of the disease. Usually the disease exceeds the pseudo-membrane formed by the compressed fibrotic liver tissue and compresses the intrahepatic biliary and vascular structures. This causes diverse clinical presentation including adjacent organ compression symptoms, portal hypertension or hepatic outflow obstruction. In addition to all; invasion of the main vascular structures cause metastasis of the parasite<sup>[2]</sup>. Conservative treatment options include benzimidazole derivatives and percutaneous therapy such as puncture-aspiration-injection-reaspiration, percutaneous evacuation, modified catheterization technique, dilatable multi-function trocar. However, parasite can be dormant for a long time before overt symptoms emerge and most of the patients are diagnosed in the late stages of the disease. Therefore; radical resection and/or liver transplantation seems to be the only sustainable definitive treatment of the disease. However the operation is hard and time consuming requiring multiple organ resection and intraoperative transfusions<sup>[3]</sup>. Liver resection is often precluded by the fact that disease reaches extensive

sizes and reduces the remnant functional liver volume.

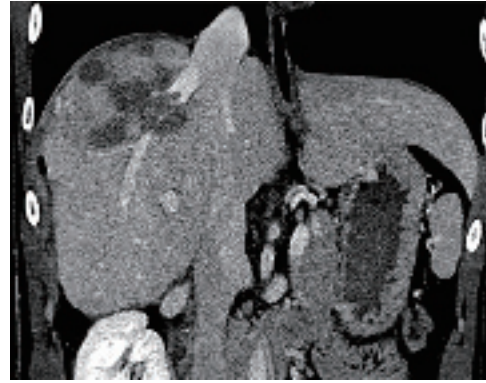
Associating liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) was initially described in 2012 by Schnitzbauer *et al*<sup>[4]</sup> for the resection of advanced tumors including colorectal liver metastasis, hilar cholangiocarcinoma and to a lesser extent hepatocellular carcinoma<sup>[3]</sup>. It provides the means for resection of tumors that is not possible by single stage procedure due to insufficient hepatic reserve postoperatively<sup>[5]</sup>. Although there are technical variations and controversies the conventional ALPPS procedure includes full mobilization of the liver from its attachments, dissection of the retro-hepatic vena cava, ligation of the right main branch of the portal vein and transection of the liver parenchyma at the Falciform ligament or the Cantlie's line together with isolation of the right and left livers by polyester or bio-absorbable synthetic material as the initial stage. The second stage that includes the resection of the right lobe is usually performed  $7 \pm 2$  d later after evaluation of the hypertrophy of the remnant liver<sup>[6]</sup>. The procedure causes enhanced hypertrophy of the remnant liver (60%-90%) in a shorter period when compared to conventional radiologic portal vein occlusion (10 d vs 40 d)<sup>[7]</sup>. Its use in hepatic EA has not been previously. In the present study, we report a successful ALPPS procedure in 28 years old male patient with hepatic alveolar echinococcosis which is the first report of use of ALPPS in a hepatic hydatid disease.

## CASE REPORT

A 28-year-old male patient with recurrent AE was referred to our Liver Transplant Center. Patient history revealed that patient had been on medical therapy for a long time and had been operated twice 1 year prior to admission to our center. In addition, he had received two percutaneous hepatic abscess drainage by interventional radiology. Physical examination of the patient showed that there was subcostal incision and distal to the incision there were two 7 Fr drainage catheters. Laboratory evaluation of the patient was as follows: hemoglobin: 12.6 g/dL; white blood cell count: 27.400; platelet count 480.000, galactosylhydroxylsyl: 113 U/L; ALP: 104 U/L, total bilirubin: 1.13 mg/dL, AST: 373 U/L, ALT: 268 U/L ve INR: 1.3. In order to evaluate the extent of the resectability of the disease both contrast enhanced multidetector computerized tomography (MDCT) and dynamic liver magnetic resonance imaging were obtained (Figures 1-3). In the MDCT, it was seen that there was a hypodense, lobulated masses in segment 4-8 that was 13 cm × 7.5 cm in diameter and had peripheral contrast enhancements in the post-contrast images. Furthermore, the right hepatic vein and the anterior branch of the right portal vein could not be identified. MDCT and the patient's clinical situation was evaluated all together and decided that an extended right hepatectomy may result in hepatic failure and organ allocation in the emergency setting may be difficult. Therefore, we decided to



**Figure 1** T2 axial dynamic liver magnetic resonance imaging. A mass lesion with heterogeneous signal density that completely occupies segment 4 and right hepatic lobe and contains air densities (black arrow) and infected collection (white arrow).



**Figure 3** Preoperative reconstructed coronal multidetector computerized tomography images. The lesion is invading the right hepatic vein but did not extend to the retrohepatic inferior vena cava.



**Figure 2** Preoperative axial venous phase multidetector computerized tomography image. A percutaneous drainage catheter to drain the infected content of the lesion is seen (white arrow). Furthermore, it is observed that the cystic lesion causes a retraction in the hepatic capsule and shows invasion to surrounding tissue with millimetric amorphous calcification foci (black arrow).



**Figure 4** Postoperative axial phase multidetector computerized tomography image. Extended right hepatectomy involving the right lobe and segment IV is performed, remaining segments II and III. Segment III bile duct is dilated (white arrow) and an external biliary drainage catheter is seen inside the bile duct (black arrow).

perform ALPPS procedure in order to provide segment 2-3 hypertrophy in this patient. A laparotomy was performed through the old incision of the patient and dissection and mobilization of the liver took 4 h. The right hepatic lobe was completely dissected away from the inferior vena cava and the right hepatic vein was completely identified to perform ALPPS procedure. This was followed by the hilar dissection and identification of the right hepatic artery originating from the superior mesenteric artery and the bile duct bifurcation was identified and marked by a vascular tape. The right branch of portal vein was identified and transected using a vascular stapler. Hepatic parenchyma transection was performed using a cavitron ultrasonic surgical aspirator (CUSA; ValleyLab, Boulder, CO, United States) so that extended right hepatectomy can be performed leaving segment 2 and 3 intact. In order to prevent parenchymal adhesion a drape covered sheet barrier was inserted into the transection plane. The postoperative course was uneventful and the patient was re-operated for definitive procedure in the postoperative eighth day. The right

hepatic artery, right hepatic vein and the bile duct was transected without any problem.

Serum bilirubin and GGT levels of the patient were elevated in the postoperative course. Endoscopic retrograde cholangio-pancreatic ductography was attempted but failed and a percutaneous trans-hepatic cholangiogram (PTC) guided drainage catheter was inserted. PTC showed severe stenosis of the biliary tract and the guide wire could not be inserted into the common bile duct. The patient was discharged with an external biliary drainage catheter (Figure 4). PTC guided intervention was repeated after the patient's general condition improved and again showed severe stenosis preventing any intervention. A surgical exploration was planned. A guide wire was inserted through the drainage catheter and the left branch of the bile duct was identified. Roux-en-Y Hepaticojejunostomy was performed. A control cholangiogram performed on the postoperative 6<sup>th</sup> week showed that contrast flow through the anastomosis was normal. The drainage catheter was extracted and patient was followed up with a six months course of albendazole therapy (Figure 5).



**Figure 5** Intraoperative cholangiography through the external biliary drainage catheter following hepaticojejunostomy is seen. The images following contrast injection demonstrates patent bile ducts and no leakage from the anastomosis site.

## DISCUSSION

AE can be located in almost every organ or tissue of the body, although the liver is the most commonly involved organ. It has a multi-vesicular and invasive clinical behavior. Furthermore, it shows hematogenous metastasis to distant organs such as the brain, lung and bone<sup>[8]</sup>. Mortality rate is high in untreated, extensive or distant organ metastasis cases (90% within 10 years, about 100% within 15 years after the onset of 15 years)<sup>[1]</sup>. It is an extensive disease of the liver and in 70% of the cases right lobe is affected and 20% of the cases show bilateral involvement. At the time of the diagnosis, in 40% of the cases hepatic hilum is involved<sup>[9]</sup>. Margin negative resection and medical therapy provides the only chance of cure. Radical resection rates have been reported to be between 15%-85% changing according to the extent of the disease<sup>[10]</sup>. In Turkey, Aydinli *et al*<sup>[11]</sup> have reported the resection rate to be 47% in their series. Otherwise, patients with unresectable lesions, liver failure, recurrent cholangitis are bound for liver transplantation which accounts for 14% of the cases<sup>[11,12]</sup>. In the majority of patients with unresectable alveolar echinococcosis cases require lifelong medical therapy with antihelminthics and amphotericine B, all of which have only modest efficacy in disease control. Therefore, we thought that ALPPS treatment may be an alternative treatment modality in approach to extensive AE disease in cases where surgical treatment is thought to be impossible.

ALPPS is the procedure of choice in the extensive liver lesions with marginal resectability and borderline future remnant liver volumes. Schadde *et al*<sup>[13]</sup> have reported that ALPPS provided margin negative (R0) resection in 91% of the cases with various hepatic malignancies. They reported the morbidity and mortality of ALPPS was 40% and 11%; respectively<sup>[13]</sup>. Therefore; it should be performed in centers with experience in liver surgery and transplantation such as our liver transplant center. Our Liver Transplant Center is highly experienced in liver surgery and has an average of 400 liver operations per year including 210-220 liver transplantation and

180-200 liver resection. Our experience on ALPPS procedure has begun to increase in the last year and we often apply it to primary and metastatic tumors of the liver. According to our knowledge, the present patient is the first extensive hepatic AE case that ALPPS procedure has been applied in the literature.

Embolization of the portal vein branches have been used for induction of hypertrophy of the future remnant liver. ALPPS seems to be superior in degree of induction of remnant liver hypertrophy and it seems to induce this hypertrophy in shorter period when compared to portal vein embolization<sup>[14]</sup>. Therefore, in hepatic tumors with borderline resectability ALPPS is a good alternative to portal vein embolization that provide high resectability rates in cases with hepatic tumors who can tolerate major abdominal surgery. Use of ALPPS procedure for benign liver tumors or parasitic infestations have not been reported until now.

In the present case, our patient was a twenty-eight years old male patient with extensive hepatic AE occupying right lobe and segment 4 of the liver. There are several reasons regarding our choice of ALPPS procedure in our patient. First of all, our patient was young and his medical condition tolerated such a major hepatic surgery. Secondly, attempt to perform embolization of the right branch of portal vein could have failed because the MDCT images showed invasion and occlusion of right portal and right hepatic veins. Furthermore, there have been two attempts for surgery in the medical history which did not succeed. Therefore, we believed that ALPPS procedure could provide necessary hypertrophy in the future liver remnant in a considerably shorter period and provide means for radical resection.

In conclusion, in the present study we have shown the feasibility and efficacy of ALPPS procedure in resection of recurrent hepatic alveolar echinococcosis in a young patient. In selected patient groups with benign liver disease with extensive hepatic involvement ALPPS can be safely used in centers which have expertise in liver transplantation and major hepatic surgery.

## ARTICLE HIGHLIGHTS

### Case characteristics

A 28-years-old male patient was referred to our Liver Transplant Center because of recurrent advanced alveolar echinococcosis.

### Clinical diagnosis

The patient was diagnose with extensive hepatic alveolar echinococcosis.

### Differential diagnosis

The different diagnosis was many malignant liver tumors.

### Laboratory diagnosis

An elevated blood AST and ALT levels suggested parenchymal damage.

### Imaging diagnosis

Both multidetector computerized tomography and dynamic liver magnetic

resonance imaging demonstrated extensive hepatic alveolar echinococcosis.

### Pathological diagnosis

Alveolar echinococcosis.

### Treatment

Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy.

### Related reports

According to our knowledge, the present patient is the first extensive hepatic AE case that ALPPS procedure has been applied in the literature.

### Term explanation

ALPPS: Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy.

### Experiences and lessons

In selected patient groups with benign liver disease with extensive hepatic involvement ALPPS can be safely used in centers which have expertise in major hepatic surgery.

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## Dolichocolon revisited: An inborn anatomic variant with redundancies causing constipation and volvulus

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### Abstract

The objective of this review is to examine whether a redundant colon gives rise to symptoms like constipation and volvulus. In 1820, Monterossi made drawings of colons with displacements and elongation of the colon found during autopsy. In 1912, Kienböck first visualized a redundant colon using bismuth, and Lardennois and Auborg named the anatomic variant dolichocolon in

1914. The criteria were later: A sigmoid loop rising over the line between the iliac crests, a transverse colon below the same line and extra loops at the flexures. The incidence of dolichocolon is 1.9%-28.5%. Dolichocolon seems to be congenital, as fetuses, newborns, and infants exhibit colonic redundancies. Studies have identified a triade of constipation, abdominal pain, and distension. Colon transit time was recently shown to increase significantly with increased number of redundancies, which increases abdominal pain, bloating and infrequent defecation. The diagnosis of dolichocolon is established by barium enema or CT-colonography. Treatment is conservative, or surgical in case of volvulus or refractory constipation.

**Key words:** Dolichocolon; Colon elongatum; Functional gastrointestinal disorders; Constipation; Volvulus

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**Core tip:** Dolichocolon is an inborn anatomic variant, where redundancies may be located in the right, middle and left part of the colon and at the flexures. This review investigated the literature on dolichocolon. The prevalence is not known. The incidence is 1.9%-28.5% in patient series. The dominating symptoms of dolichocolon are constipation, abdominal pain and volvulus. Colon transit time is prolonged and increases significantly with increased number of redundancies, which increases abdominal pain, bloating and infrequent defecation. The diagnosis is established by a barium enema or CT-colonography. Treatment is conservative, or surgical in case of volvulus or refractory constipation.

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## INTRODUCTION

The redundant colon represents an unusually lengthened large bowel folded up upon itself, forming extra loops, tortuosities and kinks. The redundancy may involve the entire colon or it may be limited to certain areas as the hepatic flexure, transverse colon, splenic flexure, but the distal colon especially the region of the sigmoid is the most commonly affected. There has long been a debate about whether a redundant colon gives rise to symptoms like constipation and volvulus. The objective of this review is to critically examine this issue.

### *Embryological development of the colon*

The development of the midgut in the embryo is characterized by a rapid elongation of the gut and its mesentery, resulting in formation of the primary intestinal loop. The cephalic limb of the loop develops into the distal part of the duodenum, the jejunum, and part of the ileum. The caudal limb becomes the lower portion of the ileum, the caecum, the appendix, the ascending colon and the proximal two-thirds of the transverse colon. In adults, the junction of the cranial and caudal limb can only be recognized if a portion of the vitelline duct persists as a Meckel's diverticulum<sup>[1]</sup>. Coinciding with the growth in length, the primitive intestinal loop rotates around an axis formed by the superior mesenteric artery. Subsequently, elongation of the small intestinal loop continues, forming coiled loops. Similarly, the large intestine grows considerably in length, but fails to participate in the coiling phenomenon. At the end of the third month, the intestinal loops return to the abdominal cavity from the extra-embryonic coelom. The caecal bud is temporarily located in the right upper quadrant below the liver before it descends into the right iliac fossa, thereby forming the ascending colon and hepatic flexure. The distal end of the caecal swelling forms a narrow diverticulum, the appendix. As the intestine returns to the abdominal cavity, their mesenteries are pressed against the posterior abdominal wall where they fuse with the parietal peritoneum, fixing the right and left colon. The colon is now as it is in the adult.

## ANCIENT ANATOMIC OBSERVATIONS OF THE COLON

In 1820, Monterossi<sup>[2]</sup> noted from autopsies an increased length of the colon, which was depicted in handmade drawings showing sigmoid loops and duplication of the right and left colonic flexure (Figure 1). Treves<sup>[3]</sup> dissected the bodies of patients who died from reasons other than abdominal diseases. He was convinced that the length of the bowel was independent of age, height, and weight. In the full-term fetus, he found that the length of the intestine, and especially the colon, was significantly constant. Shober<sup>[4]</sup> reported 18 cases selected from different investigators between 1826 and

1896 in which the sigmoid flexure was found on the right side of the pelvis. Various other abnormalities were reported, including a caecum in the right hypochondriac region with extensive mesentery. It seems that the colon was likely to vary in length and in mode of disposition more than any other part of the intestinal canal<sup>[5]</sup>. This was further demonstrated by Black<sup>[6]</sup> in a series of drawings from textbooks and journal papers between 1836 and 1911, showing a multitude of displacement and elongation of the left colon. The hepatic and splenic flexures were permanently in place.

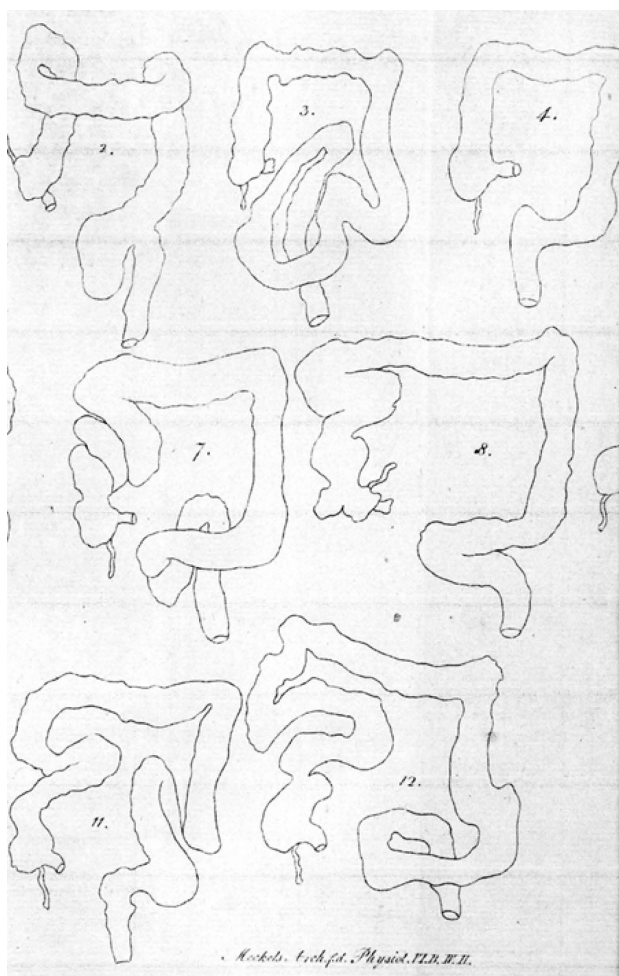
Bryant<sup>[7]</sup> measured the intestines after removed from the body. His data showed that Treves<sup>[3]</sup> was incorrect in stating that all children start life with practically the same length of intestine. He found great variations in the small intestine and colon before the fifth month of fetal life. At the age of 10 years, the child has a length of colon considered normal for the adult. He also found that the colon varied in length from 1.25 to 2.00 m, with an average length of 1.52 m. Furthermore, he reported that the length of the colon increased about 20 cm between 20 and 80 years of age.

## NEWER OBSERVATIONS OF COLON LENGTH

Phillips *et al*<sup>[8]</sup> reported colon length from several studies of cadavers, using laparotomy, barium enema or CT-colonography, between 1955 and 2015. The mean length of the colon varied between 109.0 cm and 169.0 cm. A redundant colon with loops was not mentioned. In their own study, they found a significant proportion of colons had mobility of the ascending and descending segments, with the length of the latter being highly variable. This may indicate loose redundancies.

## RADIOLOGY OF DOLICHOCOLON

By combining a bismuth meal and a bismuth clysm, Kienböck<sup>[9]</sup> was the first to visualize a redundant colon. An extremely long mobile descending colon and sigmoid ran from the left flexure through the abdomen up under the liver and then distally superimposed to the ascending colon and caecum, before joining the rectum. A few years later, Lardennois and Aubourg<sup>[10]</sup> using the same technique demonstrated various redundancies in all parts of the colon, in both adults and children. These investigators named the anatomic variant dolichocolon (dolicho-, Greek: long). During the following years, many case-series with all positions of colonic redundancies were published, using this new X-ray technique<sup>[11-14]</sup>. The colon length or that of the redundancies was not measured. Years later, the redundant colon was characterized by the following criteria: a sigmoid loop rising over the line between the iliac crests, a transverse colon below the same line and extra loops at the hepatic and splenic flexure. A fully developed dolichocolon occurs when all redundancies



**Figure 1** Handmade drawings of dolichocolon forming tortuosities, loops and kinks. From Monterossi<sup>[2]</sup>, 1820.

are present simultaneously<sup>[15-17]</sup> (Figures 2 and 3).

A long colon may result in an incomplete colonoscopy, as demonstrated in a study in which the colorectal length was 45 cm longer than the length in a group who underwent complete colonoscopy<sup>[18]</sup>.

## ETIOLOGY OF DOLICHOCOLON

Redundancy of the colon is a far from seldom variant. In 1934, Kantor<sup>[19]</sup> reported 258 cases from 1614 patients who underwent roentgenography, an incidence of 16.0%. However, Moeller<sup>[13]</sup> found redundant colon in 18 out of 744 cases, an incidence of 2.4%. A high incidence of 28.5% was found among 562 cases reported by Larimore<sup>[12]</sup>, and in 116 newborn infants, he found redundancy with the same frequency and variation as in adults. In cadavers, Bryant<sup>[7]</sup> reported an incidence of 14% among 242 subjects. Thus, redundancy seems to occur at any age, in either sex, and without special preference to any habitus<sup>[20]</sup>.

For the next half century, the interest in redundant colon seemed to wane. The prevalence of dolichocolon in a population is not known, because healthy people have not been investigated for that purpose. The closest

to such an evaluation is a study by Brumer<sup>[21]</sup> in which 53 patients had a barium enema for reasons other than constipation; one patient (1.9%) had a redundant colon. In 2009, Raahave *et al*<sup>[17]</sup> published a study of 236 patients with constipation disorders, finding high frequencies of colonic redundancies.

The question for many authors has been whether dolichocolon is a congenital anatomic variant, an abnormal growth, or pathological stretching. Treves<sup>[3]</sup> and Bryant<sup>[7]</sup> assumed that colon growth is associated with activity and function depending on the diet. Very recently, the large bowel was shown in mice to undergo substantial changes in length, as it fills with fecal matter, and that the stretching of longitudinal muscles results in slow colonic transit<sup>[22]</sup>. However, using barium enema, several authors have shown that fetuses, newborns, and infants exhibit colonic redundancies<sup>[10,12,23]</sup>. Recently, colonic elongation has been shown in children by nuclear transit scintigraphy<sup>[24]</sup>. A familiar occurrence of dolichocolon has also been observed<sup>[25]</sup>. In general, there are great variations in the frequency and positions of redundancies. Most investigators have found them to occur in the middle and left side of the colon<sup>[11,12,17,23]</sup>.

Thus, dolichocolon is mainly congenital, but function and fecal transport may also promote some changes.

## SYMPTOMS FROM THE REDUNDANT COLON

The dominating symptom of dolichocolon is constipation<sup>[4,6,9,13,14,19,23,25,26]</sup>, and patients have died from it<sup>[5]</sup>. In 1962, Brumer<sup>[21]</sup> examined 106 patients with chronic constipation using barium enema and found 32 (30.2%) had a redundant colon. Among 53 controls, only one (1.9%) had a colon with redundancies. He concluded that a causal connection must exist between this anomaly and constipation. The most common related cause of constipation after anorectal myectomy was later found to be a redundant colon<sup>[27]</sup>. When evaluating patients with slow transit constipation, the cause was always associated with dolichocolon<sup>[28]</sup>. Recently, a high proportion of patients with constipation disorders was shown to have redundant colon<sup>[17]</sup>.

Pain sometimes cramp-like, often occurs in the lower abdomen<sup>[4,11,13,17,19,23,25]</sup>, where a tender mass may sometimes be felt<sup>[6,17,19]</sup>. Constipation and pain are often followed with distension, and many cases demonstrate how much these patients have suffered.

Non-specific symptoms have also been linked to redundant colon, such as general weakness, headache, and mild fever attacks suggested to be caused by a toxic condition because of fecal stasis<sup>[4,10,23,29]</sup>. In the beginning of the 20<sup>th</sup> century, a theory of autointoxication was formulated<sup>[30]</sup>, but then discredited among little proof of bacterial toxin production. However, immune activation is detected in constipated patients based on levels of CD3<sup>+</sup>, CD4<sup>+</sup>, CD8<sup>+</sup>, and CD25<sup>+</sup> T-cells and by spontaneous proliferation of lymphocytes. T-cell activation, elevated

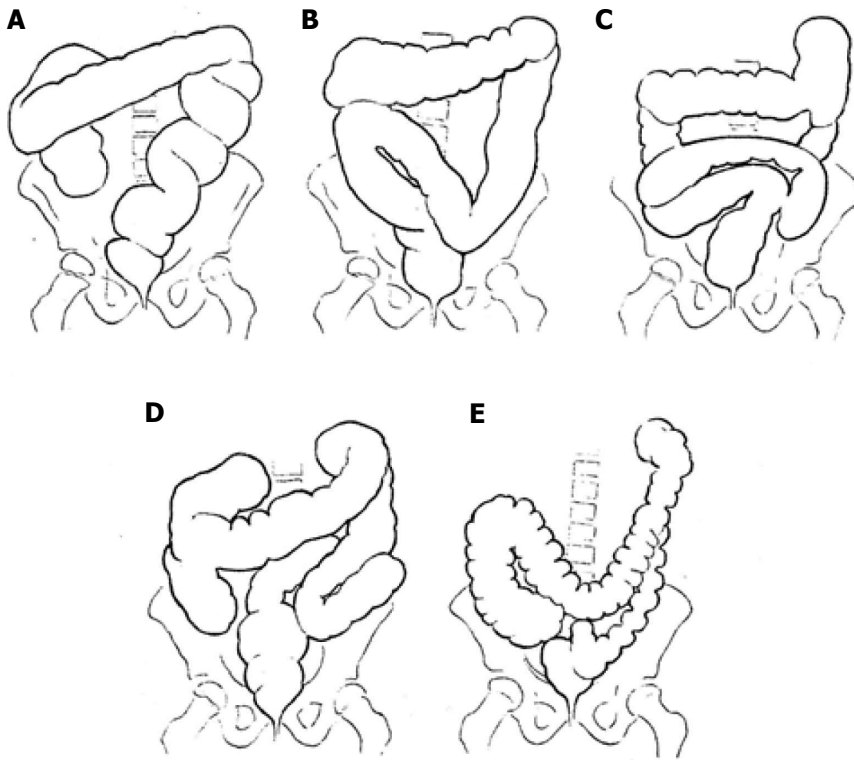


Figure 2 Different types of dolichocolon. A-C: Redundancies in the sigmoid; D: Generalized redundancies; E: Low transverse colon. From Caffey<sup>[16]</sup>, 1961.



Figure 3 Barium enema showing a fully developed dolichocolon: A sigmoid loop rising over the line between the iliac crests, a transverse colon below the same line and extra loops at the flexures.

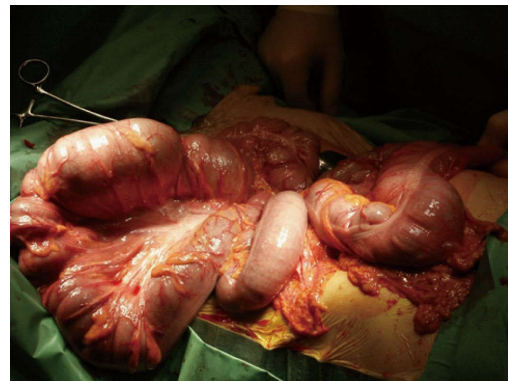


Figure 4 Dolichocolon with loose mesenteries allowing the colon to be drawn out of the abdomen: The transverse colon is localized at the right, and the sigmoid loop at the left.

levels of antibacterial antibodies, and a tendency towards elevated concentrations of IgG, IgM, and circulating immune complexes, provide evidence of the stimulation of systemic cellular and humoral immunity in chronic constipation<sup>[31]</sup>.

An elongated colon is often associated with a failure of agglutination of the mesentery with the parietal peritoneum. Consequently, the elongated colon is not fixed to the dorsal wall and can swing free on a long mesentery (Figure 4), and loose redundant loops have a potential risk of volvulus.

## FUNCTION OF A REDUNDANT COLON

Information to the function of a redundant colon is

scarce. Atony and a weak muscular tone may be limited to the site of the redundancy<sup>[14]</sup> or dysfunction may be the result of derangement of the autonomous intestinal nervous system<sup>[32]</sup>. Kantor<sup>[19]</sup> suggested that constipation varies directly with colon length, and Metcalf *et al*<sup>[33]</sup> later stated that transit is largely proportional to the length and volume of a colon segment. In an overview, Müller-Lissner *et al*<sup>[34]</sup> stated that, although a long colon could prolong stool residence time, no studies have correlated colonic transit time with colon length. Subsequently, Raahave *et al*<sup>[17]</sup> demonstrated that the mean colon transit time was 36.26 h in patients without redundancies, 43.80 h in those with one redundancy, 41.65 h in those with two redundancies, and 52.27 h in those with three to

four redundancies. The mean colon transit time of 44 controls was 24.75 h. The difference in colon transit time between the four levels of redundancies was significant. Abdominal pain, bloating, and infrequent defecation increased significantly with an increased number of redundancies. A separate analysis found a significant positive correlation between colon transit time and fecal load and a redundant sigmoid colon.

In studies of patients undergoing subtotal colectomy for slow transit constipation, the majority of colon specimens were significantly redundant<sup>[35-38]</sup>. Colon transit time is meant to be a measure of the speed of fecal propulsion through the colon, and an even distribution of radiopaque markers suggests the same function of all parts of the colon, including redundancies. Possible reasons for dysmotility are disorders of the enteric nervous system, neuroendocrine system or brain-gut axis, including lack of interstitial cells of Cajal<sup>[39]</sup>.

## DIAGNOSIS OF DOLICHOCOLON

A redundant colon should be suspected in patients with constipation, abdominal pain, distension and seldom defecation, especially when symptoms have been present from childhood. However, these symptoms may also come from pure functional colonic disorders, which is why many patients with dolichocolon have not received a diagnosis. A colon transit study and a barium enema or CT-colonography is needed to confirm the diagnosis. This is essential in guiding therapy.

## TREATMENT OF CONSTIPATION

From the very beginning, chronic constipation was suggested to be treated with enemas, mineral oil, other laxatives, abdominal massage, a supporting corset, and eventually sedatives<sup>[4,10,11]</sup>. Murray<sup>[40]</sup> focused on diet and advocated cereals containing husk, as well as the use of salads, raw fruits and vegetables, that grow above the ground. Large quantities of water must be taken, and moderate use of weak tea and coffee is allowed, but no alcoholic beverages. The colonic content was lubricated with oil and a tincture of belladonna given three times a day to increase the intestinal tone. In addition, abdominal electrotherapy was used over the abdomen, just as an afternoon siesta took place since the patients tire very easily. Short walks were advised as exercise. A mild sedative was eventually added<sup>[14]</sup>. The intervention was discontinued, when the function of the colon was restored, except the retention enema with oil and high residue diet may be more or less a permanent part of the regimen. The majority of patients with a redundant colon who are given this treatment will then return to a state of approximate well-being. In the subsequent years, most authors agreed with these principles<sup>[23,29,32,41]</sup>. A gap of interest in redundant colon then followed for nearly half a century. In general, redundancy of the colon was regarded as an unimportant observation.

Redundant colon is not mentioned in a European Perspective of Diagnosis and Treatment of Chronic Constipation<sup>[42]</sup> or in the current American Gastroenterological Association Medical Position Statement on Constipation<sup>[43]</sup>. This is a surprise, considering existing knowledge. Patients with constipation disorders and a redundant colon have had improvements in their quality of life by a fiber-rich diet supplemented with husk, sufficient water intake, a prokinetic drug, and physical activity<sup>[39]</sup>. Apart from the prokinetic drug, current treatment resembles the regimen of a hundred years ago.

## SURGERY FOR DOLICHOCOLON

Immediate surgery was advocated when a sigmoid loop is twisted (volvulus)<sup>[11,20,23,29,41]</sup>. In this context, it is notable that sigmoid volvulus accounts for a disproportionally high number of cases of intestinal obstruction in developing countries such as Africa (20%-45%) compared to developed countries (1%-7%). In addition, sigmoid volvulus occurs in much younger patients<sup>[44]</sup>. Today, it will first be tried to straighten out the twisted loop by an endoscopic maneuver. If this fails, acute surgery is necessary.

Most authors advise against surgery for dolichocolon<sup>[11,19,23,32,41]</sup>. Lane<sup>[30]</sup> introduced colectomy for chronic constipation with a death rate of 20.5%, but without giving any information with regard to colon anatomy among 39 patients. Subtotal colectomy for a redundant colon was mentioned as a possibility in 1914<sup>[10]</sup>. However, resection of colonic segments was performed with satisfactory results in five cases<sup>[45]</sup> and without improvement in three cases<sup>[13]</sup>. In 1960, Davis<sup>[46]</sup> presented the results of 14 children operated on for symptomatic dolichocolon resistant to conservative treatment. No failures occurred, and the results were excellent in eight patients, good in three, and fair in three. Hollender<sup>[25]</sup> reported good functional results after various colonic resections in 11 patients with dolichocolon. In other studies of patients who underwent subtotal colectomy for slow transit constipation, the majority of colon specimens were significantly redundant<sup>[35-37]</sup>.

In 15 patients, the cause of constipation was slow colonic transit, which was associated with dolichocolon<sup>[28]</sup>. After hemicolectomy or colectomy, the patients received daily evacuations and experienced less pain. Recently 31 patients with slow transit constipation and a dolichocolon underwent colectomy<sup>[38]</sup>. At follow-up, most patients reported daily defecation and no uncontrolled diarrhea. Abdominal pain was very seldom and patient satisfaction high.

## FUTURE PERSPECTIVES

The prevalence of dolichocolon is not known, because population based investigations have not been made. However, in projects with colonoscopic screening for cancer it may be possible to estimate the number and

localization of colonic redundancies. Colorectal length may be determined by magnetic resonance imaging or by tracking the progression of an electromagnetic capsule<sup>[47]</sup>. It will hopefully then be possible to determine the prevalence of dolichocolon and a causal relationship to constipation and volvulus.

## CONCLUSION

Dolichocolon is an anatomic variant with redundancies of the colonic segments and flexures. The diagnosis is established by barium enema or CT-colonography. Accumulating data from 200 years shows dolichocolon is congenital and causes constipation. Treatment is conservative, and only patients refractive to this therapy may undergo a subtotal colectomy. A redundant loop may cause volvulus, requiring an endoscopic maneuver or surgery. Future research has to show the prevalence of dolichocolon in a population and to determine whether it always gives rise to constipation.

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Clinical Trials Study

# Transcutaneous electroacupuncture alleviates postoperative ileus after gastrectomy: A randomized clinical trial

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**Author contributions:** Chen KB, Lu YQ, Chen JD, Chen L, Shi DK and Huang ZH designed and established the study process; Chen KB, Lu YQ, Chen L and Shi DK performed the study, collected and analyzed the data and wrote and revised the manuscript; Wang ZF, Huang Y, Wu ZW and Jiang YH contributed to patient recruitment and performing the study; Zheng YX assisted with protocol development and patient management; Zhang GP assisted with acupuncture techniques; Chen KB and Lu YQ contributed equally to this research.

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## Abstract

### AIM

To investigate the efficacy and safety of transcutaneous

electroacupuncture (TEA) to alleviate postoperative ileus (POI) after gastrectomy.

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## METHODS

From April 2014 to February 2017, 63 gastric cancer patients were recruited from the Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China. After gastrectomy, the patients were randomly allocated to the TEA ( $n = 33$ ) or control ( $n = 30$ ) group. The patients in the TEA group received 1 h TEA on Neiguan (ST36) and Zusanli (PC6) twice daily in the morning and afternoon until they passed flatus. The main outcomes were hours to the first flatus or bowel movement, time to nasogastric tube removal, time to liquid and semi-liquid diet, and hospital stay. The secondary outcomes included postoperative symptom assessment and complications.

## RESULTS

Time to first flatus in the TEA group was significantly shorter than in the control group ( $73.19 \pm 15.61$  vs  $82.82 \pm 20.25$  h,  $P = 0.038$ ), especially for open gastrectomy ( $76.53 \pm 14.29$  vs  $87.23 \pm 20.75$  h,  $P = 0.048$ ). Bowel sounds on day 2 in the TEA group were significantly greater than in the control group ( $2.30 \pm 2.61/\text{min}$  vs  $1.05 \pm 1.26/\text{min}$ ,  $P = 0.017$ ). Time to nasogastric tube removal in the TEA group was earlier than in the control group ( $4.22 \pm 1.01$  vs  $4.97 \pm 1.67$  d,  $P = 0.049$ ), as well as the time to liquid diet ( $5.0 \pm 1.34$  vs  $5.83 \pm 2.10$  d,  $P = 0.039$ ). Hospital stay in the TEA group was significantly shorter than in the control group ( $8.06 \pm 1.75$  vs  $9.40 \pm 3.09$  d,  $P = 0.041$ ). No significant differences in postoperative symptom assessment and complications were found between the groups. There were no severe adverse events related to TEA.

## CONCLUSION

TEA accelerated bowel movements and alleviated POI after open gastrectomy and shortened hospital stay.

**Key words:** Transcutaneous electroacupuncture; Gastrectomy; Postoperative ileus

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**Core tip:** Transcutaneous electroacupuncture (TEA) is a non-invasive and portable device. We applied TEA on postoperative gastric cancer patients to promote the bowel motility recovery. As far as we are concerned, it was the first attempt to investigate the efficacy and safety of TEA to alleviate postoperative ileus after gastrectomy.

Chen KB, Lu YQ, Chen JD, Shi DK, Huang ZH, Zheng YX, Jin XL, Wang ZF, Zhang WD, Huang Y, Wu ZW, Zhang GP, Zhang H, Jiang YH, Chen L. Transcutaneous electroacupuncture alleviates postoperative ileus after gastrectomy: A randomized clinical trial. *World J Gastrointest Surg* 2018; 10(2): 13-20 Available from:

## INTRODUCTION

Gastric cancer is one of the most common malignancy burdens in China, especially in economically less developed regions. The standard surgery is total or subtotal gastrectomy with D2 lymph node dissection for gastric cancer with radical-cure intention. However, postoperative ileus (POI) is not rare and causes symptoms such as abdominal pain, distention, nausea and vomiting due to the accumulation of gas and secretions<sup>[1]</sup>. This probably affects patient recovery, prolongs hospital stay, and increases cost. The treatment for POI includes fasting, nasogastric depression, maintenance of fluid and electrolyte balance, parenteral nutrition, and exercise<sup>[2]</sup>. There is no clinical evidence for the use of prokinetic agents in POI and they may have severe adverse effects<sup>[3]</sup>.

Modern electroacupuncture (EA) was developed from traditional Chinese medicine, which has been shown to accelerate gastric emptying and colonic motility<sup>[4,5]</sup>. A clinical study showed that electroacupuncture reduced the duration of POI after laparoscopic surgery for colorectal cancer<sup>[6]</sup>. A study in dogs indicated that transcutaneous EA (TEA) on Neiguan (ST36) is as effective as EA in improving rectal distention-induced intestinal dysmotility<sup>[7]</sup>. It is non-invasive and more portable.

Therefore, we applied the novel technique of TEA in gastric cancer patients to promote postoperative recovery of bowel motility. To the best of our knowledge, this was the first attempt to investigate the efficacy and safety of TEA to alleviate POI after gastrectomy.

## MATERIALS AND METHODS

### Patients

From April 2014 to February 2017, 63 patients were recruited from the Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China. All the patients underwent total or partial gastrectomy. Inclusion criteria were as follows: (1) Gastric cancer patients without distal metastases; (2) age 18-85 years; (3) no severe history of cardiovascular, hepatic, hematological and renal diseases; (4) Eastern Cooperative Oncology Group (ECOG) performance status score  $\leq 2$ ; and (5) written informed consent was obtained before the study. Exclusion criteria were as follows: (1) Bile leakage or acute peritonitis; (2) cardiac pacemaker; (3) medication, such as metoclopramide, that affects bowel function; (4) history of chronic constipation; (5) history of abdominal surgery; (6) palliative gastrectomy; and (7) postoperative enema.

### Procedures and TEA

This study was designed collaboratively by doctors from

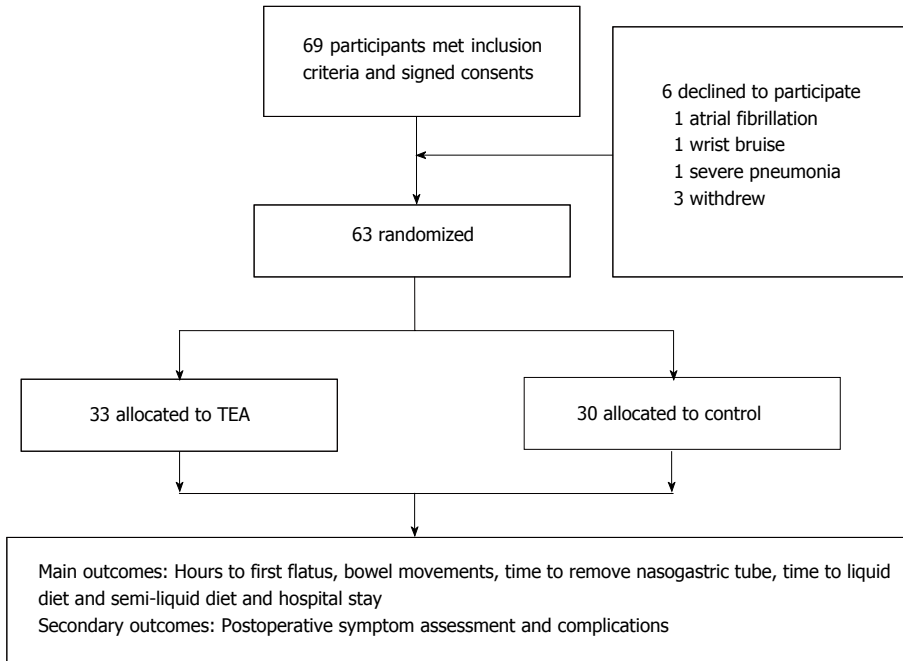


Figure 1 Flow chart of study participants. TEA: Transcutaneous electroacupuncture.

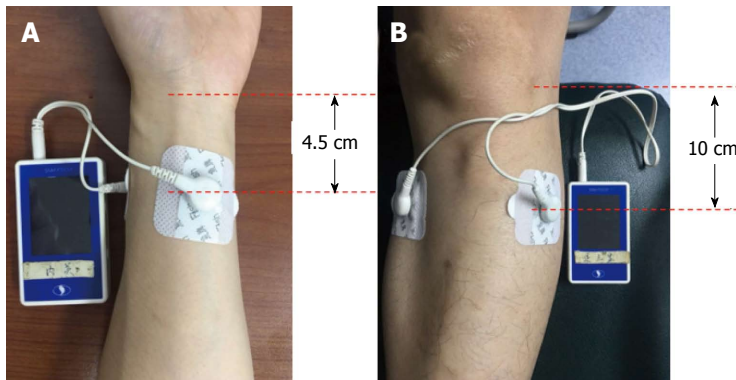


Figure 2 Transcutaneous electroacupuncture sites used in this study. A: Neiguan (ST36): Two electrodes were oppositely attached on the skin approximately 4.5 cm below the wrist wrinkle; B: Zusanli (PC6): Two electrodes were oppositely attached on the skin 10 cm below the lateral patella pit.

the Second Affiliated Hospital of Zhejiang University and Division of Gastroenterology and Hepatology, Department of Medicine, Johns Hopkins University, United States. TEA was developed by Professor Jian-De Chen in the Clinical Gastrointestinal Motility Laboratory, Johns Hopkins University School of Medicine, and gained safety certification in Zhejiang Province. The doctors who participated in the study were all trained in the TEA technique in Pace Translational Medical Research Center, Ningbo, China.

Sixty-nine patients were initially recruited but six declined to participate because of atrial fibrillation ( $n = 1$ ), wrist bruise ( $n = 1$ ), severe pneumonia ( $n = 1$ ) and withdrawal without any reasons ( $n = 3$ ). The remaining 63 patients were randomly allocated by computer algorithm to the TEA ( $n = 33$ ) or control ( $n = 30$ ) group (Figure 1). The TEA group started treatment on day 1 after surgery, until passing flatus or on day 5. They had

1 h TEA on ST36 and Zusanli (PC6) twice daily in the morning (09:00-10:00) and afternoon (14:00-15:00). The EA sites of ST36 and PC6 were consistent with other studies (Figure 2). The parameters for ST36 were 2 s on, 3 s off, 25 Hz, 0.5 ms, 2-6 mA; while for PC6 it was 0.1 s on, 0.4 s off, 100 Hz, 0.25 ms, 2-6 mA. The electric current was gradually increased just below the patient's pain threshold, and could be minimally adjusted during the procedure. The patients were allowed to sit even walk during the treatment as long as the TEA was continuously functioning well. The control group received no treatment and without any TEA being binded. The main outcomes were hours to the first flatus or bowel movement, time to nasogastric tube removal, time to liquid and semi-liquid diet, and hospital stay. And the secondary outcomes included postoperative symptom assessment based on each patient's subjective scale (0-10, including pain, tiredness, nausea, shortness of

**Table 1** Baseline patient characteristic

	TEA ( <i>n</i> = 33)	Control ( <i>n</i> = 30)	<i>P</i> value
Age (yr)	63.0 ± 9.70	59.0 ± 8.30	0.103
Sex (M/F)	22/11	24/6	0.183
Chronic gastritis	8/25	9/21	0.409
Diabetes	1/32	0/30	0.524
Hypertension	10/23	9/21	0.599
BMI	22.32 ± 3.23	21.85 ± 3.21	0.561
ECOG score (1/2)	27/6	24/6	0.553
Preoperative activity level	1.18 ± 0.392	1.17 ± 0.46	0.888
Preoperative albumin (g/L)	40.70 ± 3.38	40.08 ± 5.09	0.564
Preoperative chemotherapy (Y/N)	2/31	2/28	0.657
Surgery (Open/laparoscopic)	10/23	7/23	0.369
Surgery (Billroth-I/II/Rou-en-Y)	10/11/12	11/13/6	> 0.05
Surgery time (min)	210.79 ± 53.40	213.36 ± 69.12	0.868
pT staging (T0/1/2/3/4)	1/7/14/8/3	0/8/7/10/5	-
pN staging (N0/1/2/3a/3b)	1/7/14/8/3	11/5/4/10/0	-
Nasal enteral nutrition (Y/N)	11/22	9/21	0.496
PCIA/PCEA	32/1	29/1	0.833

TEA: Transcutaneous electroacupuncture; BMI: Body mass index.

breath, and wellbeing according to Edmonton Symptom Assessment System), and postoperative complications and hospital stay. Prolonged POI was defined as not passing flatus at > 5 d after surgery.

### Statistical analysis

Statistical analysis was performed using SPSS version 24.0, using Student's *t* test and  $\chi^2$  test, and variables were expressed as mean ± SD. *P* < 0.05 was considered as statistically significant.

## RESULTS

A total of 63 patients (46 male, 17 female, age range: 37-75 years) were recruited and randomized to the TEA group (*n* = 33) and control group (*n* = 30). In the TEA group, 23 patients underwent open gastrectomy and 10 underwent laparoscopic gastrectomy. In the control group, 23 patients underwent open gastrectomy and 7 patients underwent laparoscopic gastrectomy. The baseline characteristics did not differ significantly between the groups (Table 1). The operating time in the TEA group was 210.79 ± 53.40 min compared with 213.36 ± 69.12 min in the control group (*P* = 0.868).

Time to first flatus in the TEA group was significantly shorter than in the control group (73.19 ± 15.61 vs 82.82 ± 20.25 h, *P* = 0.038), especially for open gastrectomy (76.53 ± 14.29 vs 87.23 ± 20.75 h, *P* = 0.048). Bowel sounds on day 2 in the TEA group were significantly greater than in the control group (2.30 ± 2.61/min vs 1.05 ± 1.26/min, *P* = 0.017). For open gastrectomy, bowel sounds on day 2 and day 3 in the TEA group were significantly greater than in the control group (*P* = 0.006, 0.028, respectively) (Table 2). Time to nasogastric tube removal was earlier in the TEA than control group (4.22 ± 1.01 vs 4.97 ± 1.67 d, *P* = 0.049). Time to starting liquid diet was shorter in the TEA than control group (5.00 ± 1.34 vs 5.83 ± 2.10 d, *P* = 0.039).

Hospital stay was significantly shorter in the TEA than in the control group (8.06 ± 1.75 vs 9.40 ± 3.09 d, *P* = 0.041) (Table 2). Then, we excluded patients with complications of pneumonia, chyle leakage and pancreatic leakage, the hospital stay in the TEA group was still significantly shorter compared to the control group (7.73 ± 1.14 vs 8.59 ± 1.67 d, *P* = 0.026) (Table 2).

There was no significant difference in symptoms between the two groups including pain, tiredness, nausea, shortness of breath and wellbeing (Table 3).

There was no significant difference in postoperative complications between the two groups (*P* = 0.270) (Table 4). There was no prolonged ileus in TEA group, while there were three such cases in the control group. An adverse event of bruising on the wrist due to TEA was reported and the patient withdrew from the study. However, there was no severe adverse event.

## DISCUSSION

In this prospective and randomized clinical study, we confirmed the role of TEA in the treatment of post-gastrectomy bowel motility recovery for the first time. TEA in gastric cancer patients significantly increased postoperative bowel movement; shortened time to first flatus, nasogastric tube removal, liquid diet and hospital stay, and it was safe.

POI is caused by impaired motility of the whole gastrointestinal tract due to abdominal or extra-abdominal surgery, which is the main reason for symptoms of discomfort and prolonged hospital stay. POI costs \$1.5 billion annually in the United States<sup>[8]</sup>. Pathophysiologically, it is explained by release of inhibitory neural reflexes and inflammatory mediators from the site of injury<sup>[1]</sup>. However, the complex pathogenesis remains incompletely understood. Treatment for POI includes fasting, nasogastric depression, maintenance of fluid and electrolyte balance, and ambulation. Recent evidence supports that early oral or

**Table 2 Main outcomes**

	TEA (n = 33)	Control (n = 30)	P value
Time to first flatus (h)			
Total	73.19 ± 15.61	82.82 ± 20.25	0.038 <sup>b</sup>
Open	76.53 ± 14.29	87.23 ± 20.75	0.048 <sup>b</sup>
Laparoscopic	65.52 ± 16.53	68.31 ± 9.08	0.692
Bowel sound on day 1 (/min)	0.96 ± 1.80	0.63 ± 1.63	0.461
Bowel sound on day 2 (/min)	2.30 ± 2.61	1.05 ± 1.26	0.017 <sup>b</sup>
Bowel sound on day 3 (/min)	4.30 ± 3.11	2.85 ± 2.19	0.068
Bowel sound on day 1 (open) (/min)	0.70 ± 1.29	0.70 ± 1.83	1.000
Bowel sound on day 2 (open) (/min)	2.52 ± 2.56	0.80 ± 1.0	0.006 <sup>b</sup>
Bowel sound on day 3 (open) (/min)	4.74 ± 3.10	2.77 ± 2.23	0.028 <sup>b</sup>
Walk independently (h)	27.10 ± 15.24	36.73 ± 25.91	0.074
Walking duration per day (min)	10.36 ± 6.65	9.13 ± 6.16	0.452
Remove nasogastric tube (POD)	4.22 ± 1.01	4.97 ± 1.67	0.049 <sup>b</sup>
Liquid diet (POD)	5.00 ± 1.34	5.83 ± 2.10	0.039 <sup>b</sup>
Semiliquid diet (POD)	6.68 ± 1.78	7.60 ± 2.33	0.087
Hospital stay (POD)	8.06 ± 1.75	9.40 ± 3.09	0.041 <sup>b</sup>
Modified liquid diet (POD)	4.73 ± 0.94 (30)	5.30 ± 1.23 (27)	0.057
Modified semiliquid diet (POD)	6.30 ± 1.12 (30)	7.11 ± 1.74 (27)	0.039 <sup>b</sup>
Modified hospital stay (POD)	7.73 ± 1.14 (30)	8.59 ± 1.67 (27)	0.026 <sup>b</sup>

<sup>b</sup>P: Significant difference. TEA: Transcutaneous electroacupuncture; POD: Postoperative day.

**Table 3 Secondary outcomes according to Edmonton Symptom Assessment System**

	TEA (n = 33)	Control (n = 30)	P value
Pain on day 1	3.79 ± 1.35	3.38 ± 1.50	0.266
Pain on day 2	2.79 ± 1.10	2.55 ± 1.08	0.391
Pain on day 3	2.39 ± 1.20	2.14 ± 0.90	0.416
Tiredness on day 1	5.29 ± 2.13	5.42 ± 2.21	0.815
Tiredness on day 2	4.17 ± 2.01	4.53 ± 1.96	0.467
Tiredness on day 3	3.41 ± 2.58	4.33 ± 1.77	0.162
Nausea on day 1	0.88 ± 1.77	0.55 ± 0.90	0.352
Nausea on day 2	0.49 ± 1.50	0.38 ± 0.72	0.730
Nausea on day 3	0.43 ± 1.72	0.32 ± 0.61	0.764
SOB on day 1	0.73 ± 1.66	0.30 ± 0.97	0.213
SOB on day 2	0.52 ± 1.60	0.35 ± 1.33	0.657
SOB on day 3	0.55 ± 1.74	0.19 ± 0.96	0.391
Wellbeing on day 1	5.97 ± 1.54	5.68 ± 1.75	0.494
Wellbeing on day 2	6.88 ± 1.24	6.62 ± 1.57	0.469
Wellbeing on day 3	7.41 ± 1.69	6.83 ± 1.64	0.225

TEA: Transcutaneous electroacupuncture; SOB: Shortness of breath.

parenteral nutrition could be an option<sup>[2]</sup>, but for gastric cancer patients, oral nutrition may increase anastomotic leakage rate in the early stage, and parenteral nutrition cannot be tolerated postoperatively. The use of prokinetic agents for treatment of POI is still controversial<sup>[3]</sup>. In short, there is currently no effective way to accelerate bowel motility recovery.

Acupuncture has been widely used for treatment of gastrointestinal diseases for thousands of years in China, and several studies have demonstrated that it helps gastric and colon cancer patients recover from POI<sup>[9,10]</sup>. A modern method of EA, which is modified from the traditional acupuncture, also controls postoperative pain and improves gastrointestinal motility after surgery. A randomized controlled trial indicated that EA reduced duration of POI after laparoscopic surgery for colorectal cancer<sup>[6]</sup>. Animal experiments found that EA at ST36

accelerated colonic motility and transit in freely moving rats<sup>[11]</sup>, and improved restraint-stress-induced delay of gastric emptying *via* central glutamatergic pathways in conscious rats<sup>[12]</sup>. Jun-fan Fang *et al.*<sup>[13]</sup> revealed that EA affected the patients by activating the vagus nerve instead of regulating local inflammation. EA also has a therapeutic effect on diabetic gastroparesis<sup>[14]</sup>.

TEA is a new method of electrical stimulation *via* cutaneous electrodes placed at acupoints without needles. It is a non-invasive method that can be easily accepted by patients and even self-administrated at home. Chen *et al.*<sup>[4,15,16]</sup> has proved that electroacupuncture improves impaired gastric, small intestinal<sup>[17]</sup> and colonic<sup>[18]</sup> motility, ameliorates gastric dysrhythmia<sup>[19]</sup>, and accelerates gastric emptying<sup>[5,20]</sup>, and it is used to treat gastroesophageal reflux, functional dyspepsia and irritable bowel syndrome<sup>[4]</sup>. TEA is effective in

**Table 4 Postoperative complications**

	TEA ( <i>n</i> = 33)	Control ( <i>n</i> = 30)	<i>P</i> value
Prolonged postoperative ileus	0	3	0.102
Wound infection	1	1	0.730
Pneumonia	1	1	0.730
Chyle leakage	2	1	0.182
Ventricular premature beat	1	0	0.524
Liver impairment	1	0	0.524
Pancreatic leakage	0	1	0.476
Total	6	7	0.270

TEA: Transcutaneous electroacupuncture.

treatment of functional dyspepsia<sup>[21]</sup> and chemotherapy-induced nausea and vomiting<sup>[22]</sup>. Experiments in dogs have shown that EA and TEA at ST36 both improve the rectal distention-induced impairment of intestinal contraction, transit and slow waves mediated *via* the vagal mechanism<sup>[7]</sup>, and needleless TEA is as effective as EA in ameliorating intestinal hypomotility<sup>[7]</sup>. Huang *et al.*<sup>[23]</sup> investigated the effects of TEA on healthy volunteers, and found that TEA improved impaired gastric accommodation and slow waves induced by cold drinks.

Acupuncture seems promising for treating POI after gastrectomy<sup>[9,24]</sup> and control of emesis during chemotherapy<sup>[25]</sup>. To the best of our knowledge, this was the first attempt to investigate the effectiveness of TEA to alleviate POI after gastrectomy. We found that TEA shortened the time to first flatus, along with more bowel sounds on days 2 and 3 in subgroup analysis of patients with open gastrectomy. There may be an approximate correlation between quantity or quality of bowel sounds and bowel function, but it has not been established as a definitive association. Some studies have inserted a Sitz marker capsule into the distal anastomosis to evaluate bowel movements<sup>[9,26]</sup>. As we noted, bowel sounds became more frequent and louder during the recovery period and increased to more than 2-4/min on days 2 and 3, which could be a good predication of normal bowel function transition.

In contrast, postoperative pain results in stress and affects the mobilization of patients after surgery. Early mobility or activity is recognized as a critical step in enhanced recovery after surgery (ERAS)<sup>[27]</sup>. The anesthetists would like to perform patient-controlled epidural analgesia (PCEA) or patient-controlled intravenous analgesia (PCIA) after surgery in our center, and we routinely give patients analgesics to relieve abdominal pain. As a consequence, the postoperative pain score was < 4 on day 1, and there was no significant difference between the two groups; it gradually decreased to < 3 on days 2 and 3. Several studies have proved that acupuncture or EA reduces pain in patients undergoing thoracic<sup>[28]</sup>, abdominal<sup>[6]</sup>, inguinal hernia surgery<sup>[29]</sup>, breast cancer<sup>[30]</sup>, or kidney<sup>[31]</sup> surgery. The postoperative patients in our study had less pain because of PCEA or PCIA, most of the patients tolerated pain well, they could even sit up and stand on the morning of day 1 after operation, thus

the pain-control availability of TEA was not validated.

Epidural anesthesia might diminish the positive effects of acupuncture by blocking the afferent and efferent neural pathways<sup>[32]</sup>. Administration of local anesthetic through a thoracic epidural catheter may decrease POI by reducing sympathetic neural input<sup>[1]</sup>. Based on these reasons, Simon *et al.*<sup>[6]</sup> excluded patients who received epidural anesthesia or analgesia, and revealed that EA significantly reduced the duration of POI and postoperative analgesic requirement after laparoscopic surgery for colorectal cancer. Several laboratory and clinical studies have also proved that parasympathetic nerve activity was involved in the process of EA or TEA. Nevertheless, as mentioned before, PCEA or PCIA was routinely used in our center for pain control, which might have affected the outcomes, although there was no significant difference between the two groups.

This study had several limitations. First, the number of patients may have been inadequate to make the results convincing. Second, we did not apply ERAS to the postoperative recovery, which had been proved effective to reduce POI<sup>[27]</sup>. Third, the mechanisms underlying perioperative gastrointestinal waves or vagal tone associated with TEA should be confirmed in the future. Fourth, it was not a double-blind research, thus we could not exclude the placebo effect.

In conclusion, TEA accelerated bowel movements and alleviated POI and decreased hospital stay after open gastrectomy. It is a safe and convenient treatment for recovery from POI.

## ARTICLE HIGHLIGHTS

### Research background

Postoperative ileus (POI) after gastrectomy is not rare and causes various symptoms, which probably affects patient recovery, prolongs hospital stay, and increases cost. However, there is no effective way to alleviate POI until now.

### Research motivation

Transcutaneous electroacupuncture (TEA) is a new-developed, non-invasive and portable device. It has been validated to improve intestinal dysmotility in dog experiment. But it remains unknown whether it is useful to alleviate POI for post-gastrectomy patients clinically.

### Research objectives

The aim of this article was investigating the efficacy and safety of TEA to alleviate POI after gastrectomy.

### Research methods

From April 2014 to February 2017, 63 gastric cancer patients were recruited from the Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China. After gastrectomy, the patients were randomly allocated to the TEA (*n* = 33) or control (*n* = 30) group. The patients in the TEA group received 1 h

TEA on Neiguan (ST36) and Zusanli (PC6) twice daily in the morning and afternoon until they passed flatus. The main outcomes were hours to the first flatus or bowel movement, time to nasogastric tube removal, time to liquid and semi-liquid diet, and hospital stay. The secondary outcomes included postoperative symptom assessment and complications.

### Research results

Time to first flatus in the TEA group was significantly shorter than in the control group ( $73.19 \pm 15.61$  vs  $82.82 \pm 20.25$  h,  $P = 0.038$ ), especially for open gastrectomy ( $76.53 \pm 14.29$  vs  $87.23 \pm 20.75$  h,  $P = 0.048$ ). Bowel sounds on day 2 in the TEA group were significantly greater than in the control group ( $2.30 \pm 2.61/\text{min}$  vs  $1.05 \pm 1.26/\text{min}$ ,  $P = 0.017$ ). Time to nasogastric tube removal in the TEA group was earlier than in the control group ( $4.22 \pm 1.01$  vs  $4.97 \pm 1.67$  d,  $P = 0.049$ ), as well as the time to liquid diet ( $5.0 \pm 1.34$  vs  $5.83 \pm 2.10$  d,  $P = 0.039$ ). Hospital stay in the TEA group was significantly shorter than in the control group ( $8.06 \pm 1.75$  vs  $9.40 \pm 3.09$  d,  $P = 0.041$ ). No significant differences in postoperative symptom assessment and complications were found between the groups. There were no severe adverse events related to TEA.

### Research conclusions

In this prospective and randomized clinical study, we confirmed the role of TEA in the treatment of post-gastrectomy bowel motility recovery for the first time. TEA in gastric cancer patients significantly increased postoperative bowel movement; shortened time to first flatus, nasogastric tube removal, liquid diet and hospital stay, and it was safe.

### Research perspectives

The authors proved that TEA was effective and safe to recovery post-gastrectomy patients from POI. So it will probably provide clinical surgeons with a novel non-invasive device to accelerate bowel function recovery and reduce hospital stay, which satisfies the concept of enhanced recovery after surgery (ERAS). Besides, TEA could be considered to be applied on other abdominal surgeries as well.

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Observational Study

# Perioperative liver and spleen elastography in patients without chronic liver disease

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## Abstract

### AIM

To investigate changes in hepatic and splenic stiffness in patients without chronic liver disease during liver resection for hepatic tumors.

### METHODS

Patients scheduled for liver resection for hepatic tumors were considered for enrollment. Tissue stiffness measurements on liver and spleen were conducted before and two days after liver resection using point shear-wave elastography. Histological analysis of the resected liver specimen was conducted in all patients and patients with marked liver fibrosis were excluded from further study analysis. Patients were divided into groups depending on size of resection and whether they had received preoperative chemotherapy or not. The relation between tissue stiffness and postoperative biochemistry was investigated.

### RESULTS

Results are presented as median (interquartile range). 35 patients were included. The liver stiffness increased in patients undergoing a major resection from 1.41 (1.24-1.63) m/s to 2.20 (1.72-2.44) m/s ( $P = 0.001$ ). No change in liver stiffness in patients undergoing a minor resection was found [1.31 (1.15-1.52) m/s vs 1.37

(1.12-1.77) m/s,  $P = 0.438$ ]. A major resection resulted in a 16% (7%-33%) increase in spleen stiffness, more ( $P = 0.047$ ) than after a minor resection [2 (-1-13) %]. Patients who underwent preoperative chemotherapy ( $n = 20$ ) did not differ from others in preoperative right liver lobe [1.31 (1.16-1.50) *vs* 1.38 (1.12-1.56) m/s,  $P = 0.569$ ] or spleen [2.79 (2.33-3.11) *vs* 2.71 (2.37-2.86) m/s,  $P = 0.515$ ] stiffness. Remnant liver stiffness on the second postoperative day did not show strong correlations with maximum postoperative increase in bilirubin ( $R^2 = 0.154$ , Pearson's  $r = 0.392$ ,  $P = 0.032$ ) and international normalized ratio ( $R^2 = 0.285$ , Pearson's  $r = 0.534$ ,  $P = 0.003$ ).

## CONCLUSION

Liver and spleen stiffness increase after a major liver resection for hepatic tumors in patients without chronic liver disease.

**Key words:** Chemotherapy; Adjuvant; Colorectal neoplasms; Elasticity imaging techniques; Hepatectomy; Liver neoplasms

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**Core tip:** Point shear-wave elastography is an ultrasound-based technique which lets the user measure tissue stiffness. The technique has previously mostly been used to study patients with chronic liver disease and cirrhosis. In the current study we investigate changes in liver and spleen stiffness in patients without chronic liver disease undergoing chemotherapy and liver resection for liver tumors. A major liver resection resulted in a 42% increase in liver stiffness. Also, spleen stiffness increased more in a major than a minor resection. However, there was no difference in tissue stiffness between patients who received preoperative chemotherapy or not.

Eriksson S, Borsini H, Öberg CF, Brange H, Mijovic Z, Stureson C. Perioperative liver and spleen elastography in patients without chronic liver disease. *World J Gastrointest Surg* 2018; 10(2): 21-27 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v10/i2/21.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v10.i2.21>

## INTRODUCTION

Liver elastography implies reporting metrics related to the mechanical stiffness of the liver, using either ultrasound or magnetic resonance techniques<sup>[1]</sup>. Ultrasound-based techniques include virtual touch tissue quantification (VTTQ) (Siemens, Erlangen, Germany) which is a software based on point shear-wave elastography (SWE) technology, used to measure tissue elasticity<sup>[2-4]</sup>. Using standard ultrasound equipment, an acoustic pulse is applied to a region of interest within the tissue under investigation<sup>[5]</sup>. The pulse will cause small displacements

of the tissue and generate shear waves perpendicular to the original pulse. The shear wave propagation velocity will differ depending on the elastic properties, *i.e.*, stiffness, of the tissue<sup>[6]</sup>. High shear wave velocity denotes a stiffer tissue. In relation to surgical resection of liver tumors, a high preoperative liver stiffness has been shown to increase the risk of postoperative liver failure after resection of hepatocellular carcinoma in patients with chronic liver disease<sup>[7]</sup>.

Changes in perioperative liver stiffness in patients without chronic liver disease undergoing liver resection for tumors have not been previously investigated. Surgical resection offers a potential cure for both primary liver tumors and liver metastasis<sup>[8,9]</sup>. The risk of postoperative liver failure is the most important factor for postoperative mortality limiting the size of the resection<sup>[10]</sup>. An otherwise healthy liver can withstand a larger resection than a liver with parenchymal damage, which requires a larger liver remnant to ensure a sufficient postoperative liver function. Parenchymal damage can be due to chronic liver disease because of hepatitis or alcohol abuse but also occurs in non-alcoholic fatty liver disease or because of chemotherapy<sup>[11-13]</sup>. Chemotherapy associated parenchymal damage include steatosis, steatohepatitis and sinusoidal obstruction syndrome which all have been suggested to increase postoperative morbidity or mortality<sup>[12,14,15]</sup>.

The current study aimed to investigate changes in hepatic and splenic stiffness during liver resection for hepatic tumors in patients without chronic liver disease, effects of preoperative chemotherapy on tissue stiffness and its relation to early postoperative biochemistry with the aim to detect postoperative liver failure.

## MATERIALS AND METHODS

### Patient selection

The study protocol was approved by the Regional Ethical Review Board. Patients scheduled for liver resection for hepatic tumors at a single center were considered for enrollment. Patients were given both written and oral information about the study and gave their written consent prior to enrollment. Patients' clinical data were recorded from patient medical records. Patients with marked liver fibrosis were excluded from study analysis.

To study the effect of liver resection on liver stiffness patients were divided into two groups depending on whether they underwent a major resection (hemihepatectomy or extended hemihepatectomy) or a minor resection. Liver resection was performed as previously described<sup>[16]</sup>. If necessary, the blood flow of the portal vein and hepatic artery was temporarily occluded (Pringle's maneuver). Preoperative chemotherapy was defined as receiving chemotherapy within 3 mo prior to surgery<sup>[17]</sup>.

### Liver stiffness measurements

Measurements of liver and spleen stiffness were made

**Table 1 Patient characteristics**

	No resection	Minor resection	Major resection
No. of patients	4	16	15
Gender (male:female)	1:3	8:8	8:7
Age (yr)	69 (56-76)	75 (66-79)	66 (50-74)
BMI (kg/m <sup>2</sup> )	23.5 (21.4-28.6)	24.7 (21.8-26.8)	26.8 (25.2-28.7)
Weight (kg)	64 (53-86)	72 (63-83)	78 (70-90)
ASA physical status (1/2:3/4)	3:1	10:6	10:5
Preoperative bilirubin (μmol/L)	5 (4-7)	6 (5-10)	7 (6-11)
Preoperative INR	1.0 (0.9-1.0)	1.0 (0.9-1.1)	1.0 (1.0-1.1)
Diagnosis			
Colorectal metastases	3	13	11
Other malignant tumors	0	2	3
Benign tumors	1	1	1
Number of hepatic tumors	5 (1-7)	1 (1-2)	2 (2-6)
Largest hepatic tumor (mm)	42 (17-57)	30 (10-45)	30 (23-51)
Preoperative chemotherapy	2	6	12
Oxaliplatin-based therapy	2	4	9
Liver lobe operated (right lobe:left lobe:both lobes)	-	7:4:5	7:0:8
Operating time (h)	2.5 (2-3)	3 (3-5.5)	6 (4.5-7)
Operative bleeding (mL)	125 (100-150)	275 (150-500)	650 (400-1100)
Length of hospital stay (d)	3 (2-6)	6 (3-9)	6 (5-7)
Liver parenchyma damage			
Steatosis	-	0	1
Steatohepatitis	-	0	0
SOS	-	0	0

Data are presented as number or median (interquartile range). BMI: Body mass index; ASA: American Society of Anesthesiologists; INR: International normalized ratio; SOS: Sinusoidal obstruction syndrome.

using a Siemens ACUSON S2000 ultrasound system (Siemens Medical Solutions Inc., Mountain View, CA, United States) accompanied by the VTTQ software package. A 4C1 transducer (Siemens Medical Solutions Inc., Mountain View, CA, United States) was used. Patients were fasting 4 h before examination. To decrease movement artefacts patients were asked to hold their breath during the seconds of measurement. Measurements were conducted before and after liver resection.

Preoperative measurements were conducted in both the right and the left liver lobe as well as in the spleen. A region of interest within the respective parenchyma was chosen at a depth of 3-6 cm from the transducer<sup>[3]</sup>. The regions were chosen so that major blood vessels and bile ducts were avoided. For measurements in the right liver lobe intercostal transducer placement was used. Each region was measured 10 times and a median of the 10 measurements was calculated. Comparison between the pre- and postoperative measurements were made on the spleen and the remnant liver lobe, *e.g.*, on the right liver lobe if the patient was undergoing a left hemihepatectomy. Tissue stiffness data was presented as the shear wave velocity (m/s).

### Histological analyses

Histological analysis of the resected liver specimen was conducted in all patients. The pathologist was blinded to stiffness results. Steatosis was graded (0-3), steatohepatitis (0-8) and fibrosis (0-4), according to the non-alcoholic fatty liver disease activity score, NAS<sup>[18]</sup>. A steatosis grade  $\geq 2$  was defined as steatosis. A NAS

$\geq 5$  was defined as steatohepatitis and fibrosis  $> 2$  was defined as marked fibrosis. Sinusoidal obstruction syndrome was defined as a sinusoidal dilatation grade  $\geq 2$  according to Rubbia-Brandt *et al*<sup>[11]</sup>.

### Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 23 (IBM, Armonk, NY, United States). The statistical methods were reviewed by a biomedical statistician. To compare continuous data the Mann-Whitney *U*-test or the Wilcoxon test for paired samples was used. Categorical data was compared with a  $\chi^2$  test. Correlations were made using linear regression analysis and by calculating a Pearson's correlation coefficient, *r*. A *P*-value  $< 0.05$  was considered statistically significant. All results are presented as median (interquartile range) if not stated otherwise.

## RESULTS

### Patient enrollment and preoperative measurements

About 47 patients were enrolled in the study. Nine patients failed to complete the study protocol and were excluded from the study; 6 patients declined to participate after enrollment, mostly due to postoperative pain and 3 patients were transferred to a different hospital before the second measurement. In addition, 3 patients were excluded from study analysis because of marked fibrosis on histological analysis of the liver specimen, leaving 35 patients included for study analysis.

**Table 2** Liver and spleen stiffness measurements for the minor and major resection groups

	Minor resection	Major resection	P value
No. of patients	16	15	-
Future liver remnant (m/s)	1.31 (1.15-1.52)	1.41 (1.24-1.63)	0.318
Right liver lobe preoperative (m/s)	1.29 (1.12-1.49)	1.38 (1.14-1.57)	0.423
Left liver lobe preoperative (m/s)	1.35 (1.06-1.71)	1.41 (1.29-1.63)	0.667
Spleen preoperative (m/s)	2.76 (2.36-2.91)	2.69 (2.33-3.11)	0.984
Liver remnant postoperative (m/s)	1.37 (1.12-1.77)	2.20 (1.72-2.44)	< 0.001
Spleen postoperative (m/s)	2.83 (2.44-3.18)	2.90 (2.63-3.50)	0.216
Relative difference in liver remnant (%)	4 (-16-24)	42 (33-71)	0.001
Relative difference in the spleen (%)	2 (-1-13)	16 (7-33)	0.047

Data are presented as median (interquartile range).

Postoperative liver measurements were made typical on postoperative day 2 (postoperative day 1-3). Patient characteristics are presented in Table 1. Median preoperative shear wave velocity in all patients in the right liver lobe was 1.33 (1.15-1.50) m/s and in the left liver lobe 1.41 (1.20-1.66) m/s. The shear wave velocity in the left lobe was higher than in the right,  $P = 0.026$ . Median preoperative shear wave velocity of the spleen was 2.76 (2.37-3.02) m/s.

Four patients did not undergo resection because of intraoperatively discovered unexpected excessive liver tumor disease precluding resection ( $n = 2$ ) and two patients without intraoperatively detectable tumor disease. No difference in pre- and postoperative liver or spleen stiffness was found for these patients (results not shown).

#### Tissue stiffness in minor vs major resection

Liver and spleen stiffness measurements for the minor and major resection groups are presented in Table 2. There were no differences between groups regarding gender ratio, body mass index, American Society of Anesthesiologists (ASA) physical status classification or diagnosis. However, patients who underwent a minor resection were older than patients undergoing a major resection [75 (66-79) vs 66 (50-74) years,  $P = 0.033$ ] and did not undergo preoperative chemotherapy as frequent as the patients who underwent a major resection (6 vs 12 patients,  $P = 0.017$ ).

The stiffness of the liver remnant increased in patients undergoing a major resection ( $P = 0.001$ ) as compared to preoperative measurements. There was no difference for patients undergoing a minor resection ( $P = 0.438$ ).

#### Chemotherapy

Patients who underwent preoperative chemotherapy ( $n = 20$ ) did not differ from others in preoperative right liver lobe [1.31 (1.16-1.50) vs 1.38 (1.12-1.56) m/s,  $P = 0.569$ ] or spleen [2.79 (2.33-3.11) vs 2.71 (2.37-2.86) m/s,  $P = 0.515$ ] stiffness.

There was no difference between patients preoperatively treated with oxaliplatin ( $n = 15$ ) compared to others in preoperative right liver [1.31 (1.16-1.50) vs 1.38

(1.14-1.61) m/s  $P = 0.670$ ] or spleen [2.76 (2.34-2.97) vs 2.76 (2.37-3.07) m/s,  $P = 0.892$ ] stiffness.

#### Correlation between tissue stiffness and postoperative bilirubin and international normalized ratio

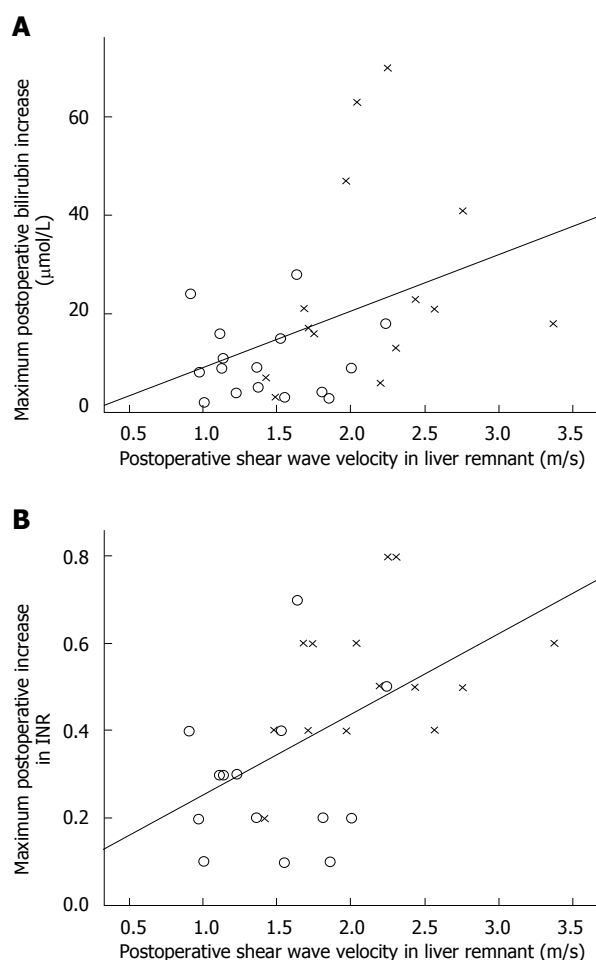
The correlation between shear wave velocity in the liver remnant and maximum postoperative increase of bilirubin and international normalized ratio (INR) are presented in Figure 1 respectively.

## DISCUSSION

The current study presents data on changes in liver and spleen stiffness after liver resection for hepatic tumors in patients without chronic liver disease. In patients who underwent a major resection, the stiffness of the liver remnant increased by 42% as measured with point SWE. No change in liver stiffness was found in patients who underwent a minor resection. The spleen stiffness increased by 16% after a major resection, more than after a minor resection (Table 2).

Liver elastography is most frequently used to non-invasively quantify the degree of liver fibrosis in patients with chronic liver disease<sup>[2]</sup>. As patients with liver fibrosis were excluded in the present study, the reasons for increase in liver stiffness found must be unrelated to histological fibrosis. The increase in tissue stiffness may be explained by a postoperative increase in portal pressure which causes a congestion in the smaller liver remnant<sup>[19]</sup>. In comparison, an elevated liver stiffness has been shown in patients with acute decompensated heart failure<sup>[20]</sup> and also in patients with extrahepatic biliary obstruction<sup>[21]</sup>. No comparative measurements of portal pressure were conducted in the current study. In animal models, increase in hepatic perfusion in small-for-size liver grafts has shown to be of importance in both liver regeneration and liver damage<sup>[22]</sup>. However, the significance of liver stiffness on liver regeneration is yet to be investigated. A postoperative increase in liver stiffness has previously been demonstrated after liver resection for living donor transplantation<sup>[19]</sup>.

Mean shear wave velocity in healthy livers range about 0.8-1.7 m/s<sup>[5]</sup>. The present preoperative measurements are in alignment with these values. In addition, there



**Figure 1** Correlation between maximum postoperative bilirubin increase (A), international normalized ratio (B) and stiffness in liver remnant for patients who underwent minor (O) and major (X) resection. A:  $R^2 = 0.154$ , Pearson's  $r = 0.392$ ,  $P = 0.032$ ; B:  $R^2 = 0.285$ , Pearson's  $r = 0.534$ ,  $P = 0.003$ . INR: International normalized ratio.

was a significant difference between measurements in the right and left liver lobes. This has been observed previously<sup>[23]</sup>, and may be due to the smaller volume of the left lobe or its close position to the heart, causing movement artefacts. The same authors have suggested that more reliable measurements are obtained at a greater depth than superficial measurements. For that reason measurements in the current study was conducted at a depth of 3–6 cm from the transducer<sup>[23]</sup>.

Point SWE measurements allow fast and non-invasive measurements of tissue stiffness. Compared to transient elastography with Fibroscan®, another ultrasound-based tissue stiffness diagnostic technique, point SWE can be made using standard ultrasound equipment, without the need for an extra examination and a region of interest within the tissue can easily be defined by the operator using a real-time conventional B-mode image<sup>[5,24]</sup>.

Measurements were done on the second postoperative day as earlier measurements were found difficult to make due to postoperative pain.

No differences in liver or spleen stiffness were found in patients undergoing preoperative chemotherapy. Chemotherapy-induced liver parenchyma damage

could worsen outcome after a liver resection<sup>[12,14,15]</sup> and perioperative identification of parenchymal damage would be desirable. Oxaliplatin, often included in preoperative treatment of colorectal liver metastasis, has previously been shown to induce splenic enlargement<sup>[25]</sup>, proposed as a result of induced sinusoidal obstruction syndrome<sup>[26]</sup>. In the present study, no differences were found in preoperative splenic or liver stiffness in patients who received oxaliplatin. However, only one patient showed histological signs of steatosis and none presented with sinusoidal obstruction syndrome or steatohepatitis, which is a considerably lower frequency than previously reported<sup>[11–13]</sup>. One limitation of the current study is the relative small number of patients included, which may explain the differences.

Postoperative liver failure has high morbidity and mortality rates and early detection is of great interest to rapidly initiate treatment measures<sup>[27]</sup>. There is currently no good method for its early diagnosis and signs of liver failure are first detected several days after surgery when patients develop high bilirubin and INR values<sup>[28]</sup>. The present measurements on the second postoperative day showed weak but significant correlations with maximum postoperative increase in bilirubin and INR, as shown in Figure 1. A study on living liver donors have presented similar results on maximum bilirubin<sup>[19]</sup>. In a small report on 3 patients with acute liver failure due to intoxication, liver stiffness was suggested to be higher than healthy controls but similar to patients with liver cirrhosis<sup>[29]</sup>. Point SWE measurements may play a role in the early detection of liver failure, however further study is needed on the dynamics of normal and pathological liver stiffness after liver resection.

In conclusion, liver and spleen stiffness changes after liver resection for hepatic tumors using point SWE measurements have been presented. The size of resection matters to the dynamics of liver stiffness. The potential of point SWE in the detection of chemotherapy induced liver damage and postoperative liver failure needs further investigation.

## ARTICLE HIGHLIGHTS

### Research background

Surgical resection offers a potential cure for both primary liver tumors and liver metastases. The risk of postoperative liver failure is the most important factor for postoperative mortality and limits the size of the resection. An otherwise healthy liver can withstand a larger resection than a liver with parenchymal damage, which requires a larger liver remnant to ensure sufficient postoperative liver function. Liver elastography implies reporting metrics related to the mechanical stiffness of the liver. Liver elastography is most frequently used to non-invasively quantify the degree of liver fibrosis in patients with chronic liver disease. Changes in perioperative liver stiffness in patients without chronic liver disease undergoing liver resection for tumors have not been investigated.

### Research motivation

Postoperative liver failure has high morbidity and mortality rates and early detection is of great interest to rapidly initiate treatment measures. There is currently no good method for its early diagnosis and signs of liver failure are first detected several days after surgery when patients develop high bilirubin and international normalized ratio values.

### Research objectives

The current study aimed to investigate the changes in hepatic and splenic stiffness during liver resection for hepatic tumors in patients without chronic liver disease; and to investigate effects of preoperative chemotherapy on tissue stiffness and its relation to early postoperative biochemistry with the aim to detect postoperative liver failure.

### Research methods

Tissue stiffness measurements on liver and spleen were conducted before and two days after liver resection for hepatic tumors using point shear-wave elastography (SWE). Patients were divided into groups depending on size of resection and whether they had received preoperative chemotherapy or not.

### Research results

The stiffness of the liver remnant increased by 42% as measured with point SWE in patients who underwent a major resection. In patients who underwent a minor resection, no change in liver stiffness was found. The spleen stiffness increased by 16% after a major resection, more than after a minor resection. In patients undergoing preoperative chemotherapy, no differences in liver or spleen stiffness were found. Remnant liver stiffness on the second postoperative day did not show strong correlations with maximum postoperative increase in bilirubin and international normalized ratio.

### Research conclusions

Liver and spleen stiffness increase after a major liver resection for hepatic tumors in patients without chronic liver disease. The potential of point SWE in the detection of chemotherapy induced liver damage and postoperative liver failure needs further investigation.

### Research perspectives

Point SWE measurements may play a role in the early detection of liver failure; however, further study is needed on the dynamics of normal and pathological liver stiffness after liver resection.

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**REVIEW**

- 28 Evolution of transanal total mesorectal excision for rectal cancer: From top to bottom

*Emile SH, de Lacy FB, Keller DS, Martin-Perez B, Alrawi S, Lacy AM, Chand M*

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## Evolution of transanal total mesorectal excision for rectal cancer: From top to bottom

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**Author contributions:** Emile SH, de Lacy FB, Keller DS, Martin-Perez B, Alrawi S, Lacy AM and Chand M contributed to the conception and design of the study, literature review and analysis, drafting and critical revision and editing and final approval of the submitted version.

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### Abstract

The gold standard for curative treatment of locally advanced rectal cancer involves radical resection with a total mesorectal excision (TME). TME is the most effective treatment strategy to reduce local recurrence and improve survival outcomes regardless of the surgical platform used. However, there are associated morbidities, functional consequences, and quality of life (QoL) issues associated with TME; these risks must be considered during the modern-day multidisciplinary treatment for rectal cancer. This has led to the development of new surgical techniques to improve patient, oncologic, and QoL outcomes. In this work, we review the evolution of TME to the transanal total mesorectal excision (TaTME) through more

traditional minimally invasive platforms. The review the development, safety and feasibility, proposed benefits and risks of the procedure, implementation and education models, and future direction for research and implementation of the TaTME in colorectal surgery. While satisfactory short-term results have been reported, the procedure is in its infancy, and long term outcomes and definitive results from controlled trials are pending. As evidence for safety and feasibility accumulates, structured training programs to standardize teaching, training, and safe expansion will aid the safe spread of the TaTME.

**Key words:** Rectal cancer; Total mesorectal excision; Transanal total mesorectal excision; Transanal total mesorectal excision; Sphincter sparing surgery; Colorectal surgery

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**Core tip:** The evaluation and management of rectal cancer have evolved remarkably over the last few decades. Total mesorectal excision (TME) has been recognized as the standard surgical management for curative radical treatment of rectal cancer. While abdominal procedures, whether by the open or minimally invasive approaches, apply the classical concept of “top-to-bottom” dissection, the transanal TME (TaTME) uses the opposite approach of “bottom-to-top” dissection. In this review we discuss the evolution of TME for rectal cancer to the TaTME, its technical aspects, advantages, shortcomings, and current needs. The research and education initiatives as well as future directions of TaTME were also highlighted.

Emile SH, de Lacy FB, Keller DS, Martin-Perez B, Alrawi S, Lacy AM, Chand M. Evolution of transanal total mesorectal excision for rectal cancer: From top to bottom. *World J Gastrointest Surg* 2018; 10(3): 28-39 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v10/i3/28.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v10.i3.28>

## INTRODUCTION

Despite the current multidisciplinary modern management, rectal cancer remains a formidable challenge for the colorectal surgeon. Surgical therapy for rectal cancer has evolved since Dr. Ernest Miles described the abdominoperineal resection in 1908. With this radical resection and the realization that rectal cancer must be tackled from the both abdomen and perineum, Miles reduced the local recurrence rate from nearly 100% to 30%<sup>[1]</sup>. Defining the “zone of upward spread” he introduced the concept of surgical oncology whereby the tumor, blood supply and nodal tissue needed to be excised.

With better surgical tools enabling a low anastomosis, a shift toward sphincter-saving approaches began, with the anterior resection replacing abdominoperineal resection as the standard curative resection, when possible. These approaches resulted in poor oncologic outcomes for recurrence and overall survival. Technical advancement came to light in 1982, when Heald *et al*<sup>[2]</sup> published the total mesorectal excision (TME) technique. The TME entails sharp, nerve-sparing dissection in the avascular plane between the mesorectum and surrounding structures circumferentially. A complete TME with intact fascia and no invasion into the muscular coat or mucosa is an important, positive prognosticator against locoregional tumor recurrence<sup>[3]</sup>.

TME became the gold standard for curative resection from proven better local control and survival<sup>[4]</sup>. Neoadjuvant and adjuvant chemotherapy and radiotherapy serve as adjuvants to improve the outcome after surgery; the dose and timing of these adjuncts are variable based on the disease stage and patient-related factors<sup>[5-14]</sup>. However, these adjuncts are not a substitute for a proper TME, with poor surgery yielding an inadequate surgical specimen invariably leading to local recurrence<sup>[15]</sup>. Additional evidence from the Medical Research Council of United Kingdom CR07 and National Cancer Institute of Canada-CTG CO16 (CR07) trial highlighted the importance of good quality surgery, and how inadequate surgery can be only minimally compensated for by chemoradiotherapy<sup>[3,16]</sup>. In the early 1990's, laparoscopic surgery was introduced, and gradually become applied to colon and rectal cancer. While there were initial concerns about the oncological safety of laparoscopy, the Clinical Outcomes of Surgical Therapy (COST) Trial demonstrated the safety, oncologic equivalency, and clinical benefits over open surgery<sup>[17]</sup>. Abundant support has reported comparable oncologic outcomes and improves short-term benefits of laparoscopic over open surgery for rectal cancer<sup>[3,18-21]</sup>. The safety of laparoscopy for rectal cancer was less clearly defined initially, as early controlled trials concentrated on the oncologic safety of colon cancer<sup>[17,20]</sup>. While skepticism remained, the improved outcomes with TME were shown to be generalizable in both open and minimally invasive approaches<sup>[3,6,22-28]</sup>. Then recent studies further questioned the oncologic equivalence of the laparoscopic approach for rectal cancer. The ALaCaRT and ACOSOG Z6051 trials failed to establish the non-inferiority of laparoscopy compared to open rectal cancer surgery<sup>[29,30]</sup>. The authors of ALaCaRT recommended using a different platform in low rectal cancers than pure abdominal laparoscopy, as working in the deep pelvis with rigid, straight laparoscopic instruments from difficult angles was challenging and required complex maneuvers<sup>[29]</sup>. Technical limitations exist with the laparoscopic approach, especially during the distal transection of the rectum, due to limited visualization and restriction working in the confined, bony pelvis<sup>[31]</sup>. These limitations highlighted the need for other approaches to

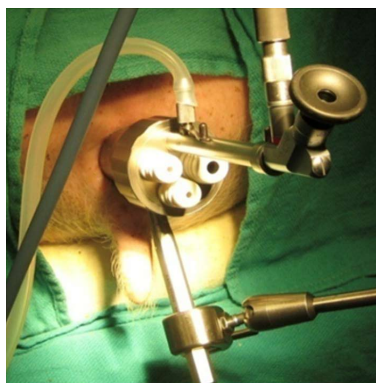


Figure 1 Transanal endoscopic microsurgery platform.

rectal cancer. Robotic assisted surgery was introduced to address the limitations of laparoscopy, and gained acceptance from the improved visualization, lower conversion rates, better TME quality lower positive CRM rate, and earlier recovery of genitourinary functions<sup>[32-34]</sup>. Studies reported equivalent oncologic and functional outcomes of both approaches, which raise the issue about the cost-effectiveness of the robotic platform, and the need for more effective and cost-efficient platforms<sup>[35-37]</sup>.

### Literature search

For this review, three of the authors reviewed published data regarding rectal cancer surgery, with attention to surgical techniques over the last several decades leading to the transanal TME. With the defined focus, PubMed and MEDLINE databases and the #colorectal research hashtag on Twitter were searched from database inception through September 15, 2017 for articles and data published with relevant evidence regarding the evolution of surgery for rectal cancer. The following search terms were used: "total mesorectal excision", "transanal excision", "local excision", "laparoscopic colorectal surgery", and "transanal total mesorectal excision", "TaTME", "rectal carcinoma" and "rectal cancer". Reference lists were manually searched and relevant articles were added if pertinent to the scope of the study. Articles were included if in English and the full content was available. Conference proceedings and videos were not included.

### Evolution of surgical approaches in rectal cancer towards the TaTME

Despite significant advances in technology and use of minimally invasive approaches in many other surgical disciplines, open surgery remains the gold standard for rectal cancer. Technical challenges and subsequent low uptake of laparoscopy in low rectal cancer surgery and contention on the value of robotic platforms have left the door open for a new approach. An ideal approach would involve a short learning curve, low relative cost,

reproducibility and clear evidence of patient safety.

### Local excision

To leverage the benefits of a minimally invasive approach, intraluminal, endoscopic, transanal, and hybrid techniques have been expanded in recent years. Additional desire to improve not only oncological outcomes but also function and quality of life outcomes led to investigation of local excision techniques<sup>[38,39]</sup>. While local excision has improved functional outcomes compared with radical resection, the lack of lymphadenectomy and higher rates of positive resection margins, locoregional recurrence, and lower overall survival means that it may not be directly comparable to TME in terms of oncological outcomes<sup>[38-45]</sup>. Therefore, it is currently recommended for benign and early (T1) rectal lesions, unless on clinical trial<sup>[46,47]</sup>. With these outcomes, it was necessary to develop more precise methods for local excision<sup>[48]</sup>.

### Transanal endoscopic surgery

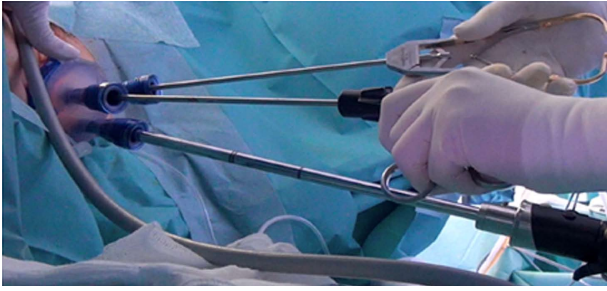
Advanced endoscopic platforms, combining the transanal and minimally invasive approaches addressed the limitations of conventional transanal resections, and allowed precise dissection of low and mid rectal tumors, a limitation of other platforms to date.

### Transanal endoscopic microsurgery

In 1983, Dr. Gerhard Buess developed Transanal Endoscopic Microsurgery (TEM), (Figure 1), offering improved visualization from a stereoscopic magnified view in the gas-dilated rectum for precise excision in an operative space that would be otherwise difficult to reach, as well as significantly lower morbidity, lower local recurrence rates, with a higher rate of negative resection margins than traditional TAE<sup>[49-52]</sup>. Widespread adoption was limited due to the cost of the specialized instrumentation, additional learning curve, and limited indications for the technique<sup>[53-56]</sup>.

### Transanal minimally invasive surgery

Dr. Sam Atallah introduced Transanal Minimally Invasive Surgery (TAMIS), (Figure 2) as an alternate advanced videoscopic transanal platform that also combines minimally invasive benefits with transanal resection, but addresses some limitations of TEM<sup>[55]</sup>. The same superior visualization and reach of TEM is offered but using standard laparoscopic equipment reduces the cost and learning curve<sup>[55,57,58]</sup>. The TAMIS platform may also be less traumatic to the anal sphincter than TEM<sup>[57]</sup>. A recent systematic review described low conversion rate of 2.3%, and low rates of positive margins, tumor fragmentation, and overall complications of 4.36%, 4.1% and 7.4%, respectively<sup>[54]</sup>. Both TEM and TAMIS have limitations in patient selection, lack of adequate lymphadenectomy inability to adequately stage the pelvis, and prohibitively high recurrence rates with



**Figure 2** Transanal minimally invasive surgery platform. Photo courtesy of Antonio Lacy, Hospital Clinic and AIS Channel.

T2 and more advanced rectal tumors<sup>[55,59-62]</sup>. TEM and TAMIS remain important in the evolution of the TaTME platform.

### **Natural orifice transluminal endoscopic surgery**

Natural orifice transluminal endoscopic surgery (NOTES) further pushed the boundaries of minimally invasive surgery, eliminating the extraction wound, associated pain, risk of wound infection and incisional hernia. The per-oral transgastric approach was first developed in animal models, and then intensely explored across transoral, transanal, transurethral, and transvaginal routes, before being cautiously tested in clinical practice<sup>[63,64]</sup>. Dr. Mark Whiteford reported a successful NOTES transanal sigmoid colectomy cadaver series in 2007<sup>[65]</sup>, while Dr. Patricia Sylla combined the transgastric endoscopic and TEM platform in a swine rectosigmoid resection series<sup>[66]</sup>.

Dr. Antonio Lacy was instrumental in moving the concept of NOTES out of the “lab” and into potential practise, reporting a sigmoid resection using transvaginal mini-laparoscopic-assisted natural orifice surgery for sigmoid adenocarcinoma<sup>[67]</sup>. Using the TEM platform in a human rectal cancer series, there seemed to now be a safe alternative to open and laparoscopic TME<sup>[68]</sup>. Several colorectal series followed, affirming the feasibility of NOTES<sup>[69-76]</sup>. However for the majority NOTES remains experimental, with concerns over the operative platform, accidental organ injury and viscerotomy closure<sup>[64,73]</sup>. The potential of performing complex colorectal dissection using existing transanal endoscopic platforms fueled the movement towards the TaTME.

### **Trans abdominal trans anal proctosigmoidectomy**

Hybrid approaches to rectal cancer were occurring long before NOTES. For sphincter preservation and conservation of adequate function in very distal lesions, Dr. Gerald Marks developed the TransAnal Abdominal TransAnal Proctosigmoidectomy with colo-anal anastomosis (TATA) technique in 1984, a transanal initiated TME dissection that offers a direct, precise distal dissection, assuring adequate distal margins<sup>[77,78]</sup>. Dr. John Marks routinely integrated laparoscopic and robotic approaches with TATA, adding the advantages of minimally invasive surgery to this groundbreaking procedure. The TATA introduced the concept of “bottom-

up” technique, in contrast to the “top-down” traditional technique followed in the abdominal procedures.

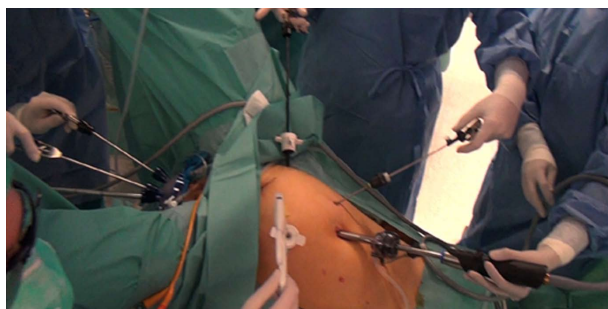
### **Transanal TME**

TaTME extends the TATA’s principle of initiating the TME dissection transanally (bottom-up) and accomplishes the most difficult part of the dissection from the caudal side<sup>[77]</sup>. Sylla and Lacy first described the TaTME in 2010<sup>[79]</sup> followed by an early case series of 20 patients<sup>[68]</sup>, and a further validated series in 140 patients<sup>[80]</sup>. Since these early reports, numerous series have described the safety and feasibility of taTME even in challenging patients. The theoretical advantages of access and visualization have established this technique as not only a credible alternative to more traditional approaches which has the potential to provide optimal outcomes for oncologic resection of low rectal cancers<sup>[81-91]</sup>.

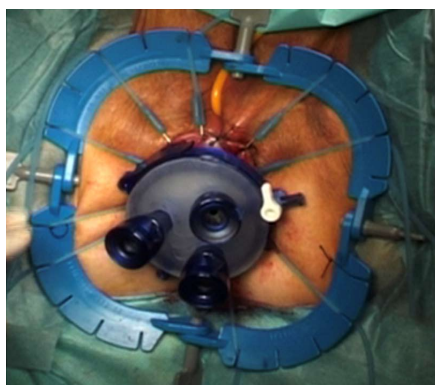
**Indications for TaTME:** TaTME is mainly indicated for treatment of malignant tumors affecting the middle and lower third of the rectum. Moreover, it can be applied in benign conditions affecting the rectum such as Crohn’s disease and ulcerative colitis. Benign indications for TaTME may include reversal of Hartmann’s procedure, restorative proctocolectomy or completion proctectomy and ileal-pouch anal anastomosis<sup>[92]</sup>.

**Technical points of the TaTME:** Briefly, the procedure is performed in the modified lithotomy (Lloyd-Davies) position. It can be performed by a single team or, as originally described by Lacy, two-team (“Cecil Approach”), which allows for shorter operative times, improved visualization, and better traction and counter-traction to facilitate the resection (Figure 3). The abdominal approach is determined by surgeon preference, and entails full left colon and splenic flexure mobilization, high ligation of the inferior mesenteric artery (with identification and preservation of the pelvic nerve plexuses), and division of the inferior mesenteric vein was divided at the inferior pancreas border, and a TME performed.

For TaTME, the rectum is irrigated, a purse-string suture placed to occlude the rectum, then the Transanal Access Platform inserted as shown in Figure 4, and pneumorectum established. Performing a tight purse-string suture is imperative to prevent translocation of liquid stool and cancer cells while the dissection is being carried out. Adequate rectal irrigation and the purse-string suture may help reduce the potential for implantation of cancer cells and/or bacteria inherent in the transanal dissection plane that could result in abscesses or local recurrence. While long-term outcomes will need to be assessed for these risks, measures to prevent the risk include standard manipulations and appropriate case selection as well as rectal irrigation with a cytotoxic solution<sup>[93]</sup>. Under endoscopic visualization, the rectum is circumferentially



**Figure 3** Two-teams working simultaneously for transanal total mesorectal excision ("Cecil Approach"). Photo courtesy of Antonio Lacy, Hospital Clinic and AIS Channel.



**Figure 4** Transanal access platform with trocar insertion in an inverted triangle shape. Photo courtesy of Antonio Lacy, Hospital Clinic and AIS Channel.

mobilized, and the dissection continued proximally in the avascular TME plane towards the peritoneal reflection to meet the abdominal mobilization (Figure 5)<sup>[82,92]</sup>. The extraction can be performed transanally, or through a Pfannenstiel or stoma-site incision, depending on the abdominal approach used and the bulk of the specimen.

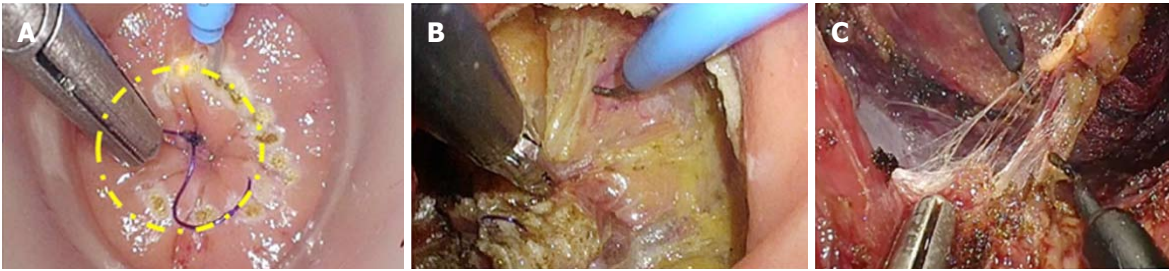
**Safe implementation of TaTME:** TaTME may enhance distal rectal access and visualization, allowing optimal margins, adequate lymph node yield, and high quality resection, even in the most difficult patients<sup>[94-96]</sup>. Denost *et al.*<sup>[97]</sup> showed that the perineal approach reduces the risk of positive CRM compared to an abdominal approach, and may be an oncologically superior approach for low rectal cancer. Report from the International TaTME Registry suggests the procedure is oncologically safe and effective<sup>[83]</sup>. Since TaTME is in its infancy, longer follow-up and controlled trials needed. It is important to note that the TaTME is technically challenging, and formal training through a hands-on course is recommended, with active proctoring during the first year and ongoing participation within multicenter registries, for quality improvement and long term follow up<sup>[98]</sup>. Consensus for standardization of the technique and structured training are ongoing, to facilitate safe, appropriate implementation into clinical practice<sup>[92,98-101]</sup>.

**Advantages of TaTME:** In general, transanal approaches allow better visualization of the distal rectum and clearly demonstrates the distal resection margin. The TaTME furthers these benefits, uniquely allowing deep pelvic dissection without the need for traction on the rectum. The plane of resection is clearly identified, even in obese and male patients with narrow pelvis, which were considered unfavorable conditions for laparoscopic TME<sup>[102]</sup>.

**Oncological benefits:** The major potential benefit of TaTME is its theoretical ability to obtain a higher quality TME specimen. Results from the international TaTME registry showed complete or almost complete mesorectal excision rate of 96%, CRM positive rate of 2.4% and DRM positive rate of 0.3%<sup>[83]</sup>. Similarly, Xu *et al.*<sup>[103]</sup> and colleagues concluded that TaTME provided lower rate of positive CRM compared to laparoscopic TME (OR: 0.34, 95%CI: 0.12-0.93;  $I^2 = 0\%$ ). A recent meta-analysis reinforced the previous results, demonstrating that TaTME attained significantly higher rate of complete and near complete mesorectal excision than laparoscopic TME<sup>[104]</sup>. Additionally, TaTME had wider CRM with a significantly lower number of patients with positive CRM (OR: 0.39,  $P = 0.02$ ). However, more controlled trials including larger number of patients are required to validate the oncologic and pathologic outcomes with TaTME.

**Functional benefits:** Bowel, bladder, and sexual dysfunctions are among the most common and devastating complications of rectal cancer surgery. TaTME decreases the number of permanent stomas, but at the cost of increasing the rate of coloanal anastomoses. With this, there is the theoretical risk of impaired continence and functional outcomes. Few studies have addressed long-term functional outcomes to date. Preliminary results demonstrate similar postoperative sphincter function when compared with laparoscopic or open TME<sup>[105-107]</sup>. A recent review of 30 patients evaluating functional outcomes 6 mo after TaTME showed acceptable quality of life and functional outcomes, comparable to published results after conventional laparoscopic low anterior resection<sup>[108]</sup>. In this study, deterioration for all domains was observed at one month after surgery compared to baseline, but returned to baseline at 6 mo for all areas except social function and anal pain. More studies with larger sample sizes and longer follow up are needed. A lower rate of urinary dysfunction has been observed after TaTME, which can be attributable to the enhanced visualization that improves definition of anatomic landmarks and allows nerve-sparing dissection in the presacral plane<sup>[109]</sup>.

The risk of urethral injury is a real concern, and a unique complication of the procedure; Studies have shown an incidence of more than 10%, in addition, injury of the urethral sphincter can lead to urinary



**Figure 5 Transanal total mesorectal excision.** A: Circumferential mucosal tattoo after pure-string placement; B: Bottom-up dissection; C: "Rendez-vous" with the abdominal team. Photo courtesy of Antonio Lacy, Hospital Clinic and AIS Channel.

incontinence and dysfunction<sup>[83]</sup>. The membranous urethra is put at risk if the posterior prostatic lobe is deflected downwards inadvertently, or during the perineal phase of an abdominoperineal resection. Urethral injury may be prevented with adequate training and mentoring of the technique and following a meticulous technique of dissection in the anterior plane<sup>[110]</sup>. Methods to better identify the urethra intraoperatively and reduce injury rates, such as with fluorescence imaging, have been described and may also be beneficial with this new technique<sup>[111,112]</sup>.

#### Perioperative benefits

Technical benefits of TaTME include having significantly shorter operation time than laparoscopic TME<sup>[103]</sup>. A plausible explanation is that the bottom-up approach overcomes the technical limitations associated with laparoscopic TME, enabling surgeons to proceed more easily and efficiently. Also, the simultaneous two-team technique can help reducing the operation time significantly<sup>[25]</sup>. Another technical advantage of TaTME is having lower rates of conversion to open surgery compared to laparoscopic TME (OR: 0.29,  $P = 0.02$ )<sup>[104]</sup>. The overall conversion rate of laparoscopic TME was almost four-times that of TaTME (8.6% vs 2.6%). On analysis of the reasons for conversion, technical difficulties accounted for 25% of conversions in the TaTME group vs 47% in the laparoscopic TME group. Technical difficulties necessitating conversion in the laparoscopic group were related to high BMI and narrow pelvis as previously implied. TaTME also allows for transanal specimen extraction, thus decreasing the need for an abdominal assist incision.

**Safety:** The safety and feasibility of TaTME for short and midterm outcomes has been extensively described<sup>[80,89,91,113-115]</sup>. A report from the TaTME International Registry reported postoperative morbidity, anastomotic leakage and mortality rates of 32.6%, 6.7% and 2.6%, respectively<sup>[83]</sup>. A pooled analysis in a recent systematic review had similar rates of intraoperative complications and lower rate of postoperative morbidity compared to laparoscopic TME, with no significant difference between the TaTME and laparoscopic TME in regards to anastomotic leak<sup>[104]</sup>. However, there

remain some concerns about the rapid development of this new technique and critics would point to the more catastrophic complications including prostate and urethral injuries. But this had led to design and implementation of detailed national training programs which have been initiated in the United States and Europe. This may help safe expansion of the technique and mitigate the safety issues.

#### Other side of the coin: Shortcomings of TaTME

Although TaTME has achieved promising oncological and functional results in treatment of rectal cancer as reported in several studies, the technique does have certain limitations that need to be addressed. Firstly, the bottom-to-up dissection approach followed in TaTME can be quite difficult since the majority of surgeons are not familiar with such different anatomical perspective for dissection, therefore adequate training under expert supervision is imperative before employing the technique in practice. Secondly, with new techniques new complications may arise, this is true with TaTME as a number of complications were recognized after the procedure. Complications specific to TaTME include formation of local collection or abscess secondary to bacterial contamination due to transection of the rectum at the start of the procedure. In one report<sup>[116]</sup>, TaTME was found to be associated with positive cultures in more than one-third of the patient, with development of pre-sacral abscess in 17% of the patients.

As aforementioned, the risk of injury of the urethra and urethral sphincter, which can occur in up to 10% of patients, is a unique complication of TaTME compared to the abdominal approaches for rectal cancer<sup>[84]</sup>. The risk of urinary retention and transient urinary dysfunction was previously reported and minimal detrusor activity was documented in urodynamic studies implying neurogenic bladder dysfunction<sup>[82]</sup>. It is also worthy to note that the CO<sub>2</sub> insufflation used to aid dissection might expose planes beyond the scope for dissection particularly during lateral and posterior dissection of the mid rectum which can lead to extending the dissection too deep into the pre-sacral space which carries a significant risk of injuring the autonomic nerves and venous plexus in this plane<sup>[96,117]</sup>.

**TaTME: Research and education initiatives**

In order to establish the efficacy of a new surgical treatment, well-designed controlled experiments must be performed. Trials such as the COLOR III<sup>[118]</sup> and the TaTME trial in United States are currently recruiting, with the primary outcome of non-inferiority for local recurrence. While we wait for the definitive outcomes from large-scale controlled trials, multicentre registries are valuable for quality assurance and audits to optimize and standardize outcomes. The international TaTME registry, in which worldwide surgeons performing TaTME are invited to join, is a secure online database funded by the Pelican Cancer Foundation (<https://tatme.medicaldata.eu>). The analysis of this large population-based cohort is a joint effort with the objective of improving research and care of the patients with rectal cancer treated with TaTME.

In the last few years, there has been an increase in availability, quality, and utilization of online and social media resources for surgery. These platforms best feature offer instant and unlimited medical knowledge. Tools such as the online Advances in Surgery (AIS) Channel (<https://aischannel.com>) or iLappSurgery Foundation app ([www.ilappsurgery.com](http://www.ilappsurgery.com)) have gained favour in the surgical community. They have taken the next step by providing high-quality surgical education, which is clearly one of the keys to raise the standards of training. These two platforms are focused specifically on laparoscopic surgery and colorectal procedures, with TaTME being one of its cornerstones.

All these initiatives for TaTME research, training and education have experienced a great acceptance. This is based on the obvious theoretical benefits that can overcome problems such as the risk for increased non-complete specimens obtained by laparoscopy and the longer operative times and higher costs associated with robotics. The international TaTME registry, AIS Channel and iLappSurgery Foundation have been developed for being guidance not only for trainees but also for experienced surgeons. TaTME is a complex procedure to learn, so continuous quality improvement from data analysis as well as high-quality training programs are needed for correct standardization and safe implementation of the technique<sup>[98,100,101]</sup>.

**Future direction for TaTME**

The survival outcomes with respect to disease recurrence in rectal cancer surgery are directly related to the quality of resection<sup>[3]</sup>, and thus the success of TaTME must be held against this quality assurance measure to ensure oncological parity and perhaps superiority. This new technique is complex and requires exceptional anatomical knowledge to perform an unfamiliar dissection. Previous laparoscopic colorectal experience and a high case volume are essential to reach a standard in an acceptable amount of time. Nursing/operating room staff and anaesthesiology also require specific training to become familiar with the

new set up, particularly when performing a two-team approach, where the coordination among all operating room staff is crucial to avoid a potentially dangerous situation.

The learning curve of TaTME is yet to be established; however, according to estimation by expert groups approximately 20 consecutive cases are sufficient to develop an adequate learning curve for a surgeon proficient in laparoscopic and transanal surgery. In accordance with this appraisal, a minimum of five proctored cases is recommended in order to achieve an optimal level for the TaTME performance. However, establishing centres of excellence would allow surgeons to increase volume of cases and allow training of more junior surgeons in a safe manner. Different training courses taught by expert groups are available, which generally include didactic lessons, live cases, and hands-on cadaver labs. After completion of the courses, proctoring in the origin institutions should be the next step in the adoption process. Mentors should travel and proctor cases along with the trainees, to show on the spot the tips and tricks as well as adjusting the technique to the site's intrinsic characteristics. Validation and accreditation of the technique are also under development and a matter of discussion in the international surgical societies<sup>[98,100]</sup>.

**CONCLUSION**

The TaTME was developed from existing platforms and as an attempt to resolve the challenges of minimally invasive low rectal cancer surgery. As evidence for safety and feasibility accumulates, and with the implantation of structured training programs in order to standardize training, teaching, and safe expansion, TaTME seems on course for further uptake. The improved visibility of the pelvic structures and better accessibility for ultralow anastomoses may render the transanal approach ideal for a wide variety of cases. The indications for TaTME are currently expanding beyond mid and low rectal cancers, and open up new possibilities to use the approach for different diseases. Although the initial results of TaTME are promising and encouraging, further controlled clinical trials including larger number of patients with long-term follow-up are required to validate the oncologic and pathologic outcomes of TaTME. With the international registry and ongoing controlled trials, we look forward to long-term outcomes with this innovative approach.

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## Retrospective Study

**Adherence to surveillance endoscopy following hospitalization for index esophageal variceal hemorrhage**

Brendan T Everett, Steven D Lidofsky

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**Author contributions:** Everett BT acquired and analyzed the data, and wrote the manuscript with Lidofsky SD, who designed the study.

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**Abstract****AIM**

To investigate patient adherence to surveillance endoscopy after index esophageal variceal hemorrhage and the extent to which adherence influences outcomes.

**METHODS**

We reviewed the records of patients with cirrhosis admitted to the medical intensive care unit between 2000 and 2014 for first time esophageal variceal hemorrhage treated with endoscopic variceal ligation who were subsequently discharged and scheduled for surveillance endoscopy at our medical center. Demographic and clinical data were obtained through the medical records, including etiology of cirrhosis, completion of variceal obliteration, attendance at surveillance endoscopy, zip code of primary residence, distance from home to hospital, insurance status, rehospitalization for variceal hemorrhage, beta-blocker at discharge, pharmacologically treated psychiatric disorder, and transplant free survival.

**RESULTS**

Of 99 consecutive survivors of esophageal variceal bleeding, the minority (33) completed variceal obliteration and fewer (12) adhered to annual surveillance. Completion of variceal obliteration was associated with fewer rehospitalizations for variceal rebleeding (27% vs

56%,  $P = 0.0099$ ) and when rehospitalizations occurred, they occurred later in those who had completed obliteration (median 259 d *vs* 207 d,  $P = 0.0083$ ). Incomplete adherence to endoscopic surveillance was associated with more rehospitalizations for variceal rebleeding compared to those fully adherent to annual endoscopic surveillance (51% *vs* 17%,  $P = 0.0328$ ). Those adherent to annual surveillance were more likely to be insured privately or through Medicare compared to those who did not attend post-hospital discharge endoscopy (100% *vs* 63%,  $P = 0.0119$ ).

## CONCLUSION

Most patients do not complete variceal obliteration after index esophageal variceal hemorrhage and fewer adhere to endoscopic surveillance, particularly the uninsured and those insured with Medicaid.

**Key words:** Liver cirrhosis; Endoscopy; Esophageal varices; Secondary prevention; Patient adherence

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**Core tip:** We investigated adherence to surveillance endoscopy in 99 consecutive patients with cirrhosis who survived esophageal variceal bleeding, and the extent to which adherence influenced outcomes. We found that the minority (33%) completed variceal obliteration and fewer (12%) underwent annual surveillance. Completion of obliteration was associated with fewer and later rehospitalizations for variceal rebleeding. Those non-adherent to annual surveillance were more likely to be uninsured or to have coverage through Medicaid assistance. Our findings identify potential markers for socioeconomic factors that limit endoscopic adherence following variceal hemorrhage and lead to adverse outcomes. New approaches are needed to overcome barriers to adherence.

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## INTRODUCTION

Gastrointestinal variceal hemorrhage is a major and dramatic complication of cirrhosis, with a hospitalization-associated mortality rate of 15%-20%<sup>[1,2]</sup>. Survivors of initial variceal hemorrhage have a 60% probability of rebleeding within 1-2 years and a 33% mortality rate if no further treatment is sought after hemostasis<sup>[2,3]</sup>. Controlled clinical trials have demonstrated that the most effective strategy to reduce rebleeding from varices is serial endoscopic variceal ligation (EVL), with a goal of variceal obliteration, in combination with

non-selective beta adrenergic receptor blockers<sup>[2-4]</sup>. Combined endoscopic and pharmacologic therapy, in this way, reduces rebleeding rates to as low as 14%<sup>[5]</sup>. In a real-world setting, the success of this strategy is likely to be influenced by patient adherence to endoscopic surveillance, but this has not been formally studied.

There is growing evidence that cirrhotic patients often do not receive evidence-based treatments for disease related complications<sup>[6]</sup>. Despite recommendations to perform an esophagogastroduodenoscopy (EGD) to screen for gastroesophageal varices after a diagnosis of cirrhosis is made<sup>[2]</sup>, a study of United States military veterans with newly diagnosed cirrhosis due to hepatitis C found only a third of patients had an EGD within one year after diagnosis, and 46% had still not undergone an EGD at 6 years<sup>[7]</sup>. Moreover, in those with endoscopic evidence of esophageal varices but no history of hemorrhage, only 60% were either placed on beta-blockers or underwent EVL for primary prophylaxis of variceal bleeding<sup>[6]</sup>.

Similar gaps in care have been observed in cirrhotics with a history of gastrointestinal variceal bleeding. In one study, referral for surveillance endoscopy was placed in just 65% of patients at the time of discharge following hospitalization for esophageal variceal hemorrhage<sup>[8]</sup>. In another study, between 74%-93% of patients with an acute variceal hemorrhage had either post-hospital discharge esophageal variceal obliteration or were placed on a beta-blocker, while 44%-59% had post-discharge esophageal variceal obliteration alone<sup>[9]</sup>. Even if orders for beta-blockers and surveillance endoscopy are placed, patient-related factors may influence adherence to measures to prevent recurrent variceal hemorrhage. This study was undertaken in survivors of hospitalization for esophageal variceal hemorrhage to identify, in a real-world setting, potential factors that prevent patients from returning for surveillance endoscopy, and to examine if such patients have different outcomes than those who adhere to endoscopy following index variceal hemorrhage.

## MATERIALS AND METHODS

### Study population

We reviewed the medical records of patients (age  $\geq 18$  years) who were admitted consecutively to the medical intensive care unit of the University of Vermont Medical Center (UVMCC), a tertiary care center, with an admission diagnosis of gastrointestinal (GI) hemorrhage, melena, hematemesis, or bleeding esophageal varices, for which they underwent EGD from July 1, 2000 to December 31, 2014 with follow up through June 30, 2015. The medical records and EGD reports were then reviewed to identify those with esophageal varices on initial EGD<sup>[1]</sup>. Bleeding was attributed to esophageal varices if at least one of the following criteria was met: (1) Identification of

actively bleeding esophageal varices; (2) esophageal varices identified with stigmata of recent hemorrhage; or (3) clinical presentation consistent with upper GI hemorrhage (e.g., melena and/or hematemesis), large esophageal varices present, and no alternative etiology for GI bleeding identified on EGD. Patients treated for bleeding esophageal varices were provided information at discharge regarding the time of follow up endoscopy through patient instructions. Similar instructions were provided following each subsequent endoscopy.

Inclusion criteria were: (1) Cirrhosis (defined by any of the following International Classification of Diseases 9<sup>th</sup> Revision diagnostic codes: 571.2, 571.5, or 571.6); (2) index esophageal variceal hemorrhage (i.e., no prior history of variceal bleeding); and (3) EVL. Exclusion criteria were: (1) Transjugular intrahepatic portosystemic shunt (TIPS) for control of bleeding at index bleed; (2) primary residence in county outside of local endoscopy region; (3) death at index bleed; (4) age < 18 years; (5) presence of comorbid illness with limited survival (e.g., metastatic cancer, end stage heart or lung disease); (6) non-esophageal variceal bleed (e.g., gastric), and (7) sclerotherapy.

### Measurements and outcomes

The study design was approved by the University of Vermont Committee on Human Research in the Medical Sciences (CHMS 15-134). Demographic and clinical data were obtained through the medical records, including age, gender, date of index variceal hemorrhage, etiology of cirrhosis, recent significant alcohol consumption (greater than 7 drinks per week for women, greater than 14 drinks per week for men), completion of variceal obliteration, attendance at surveillance EGD, zip code of primary residence, distance from home to hospital, insurance status, re-hospitalization for variceal hemorrhage, beta-blocker at discharge, pharmacologically treated psychiatric disorder, and transplant free survival.

Completion of variceal obliteration was defined as endoscopic eradication of varices with the first EGD of the series occurring within 6 mo following hospital discharge. Adherence to surveillance endoscopy was defined as undergoing EGD at intervals no greater than every 1 year after completion of variceal obliteration. The severity of liver disease at the time of admission was assessed by the Model for End-stage Liver Disease (MELD) score<sup>[10]</sup> and Child-Turcotte-Pugh class<sup>[11]</sup>.

The following outcomes were assessed: (1) Beta adrenergic blockade at hospital discharge; (2) appearance at initially scheduled outpatient EGD; (3) completion of variceal obliteration; (4) adherence to surveillance EGD after variceal obliteration; (5) rehospitalization for gastrointestinal variceal bleeding; and (6) transplant free survival.

### Statistical analysis

Analyses were performed with GraphPad Prism (Version

6.0). Differences between groups were determined by Fisher's exact test for categorical variables, by Mann-Whitney *U* test for continuous non-parametric variables, and by Student's *t* test for continuous parametric variables. Kaplan-Meier curves for both survival and time to rehospitalization were compared using the log-rank test. A value of *P* < 0.05 was deemed statistically significant.

## RESULTS

### Characteristics of the Study population

Between July 1, 2000 and December 31, 2014, there were 347 consecutive individuals with cirrhosis admitted to the medical intensive care unit for gastrointestinal hemorrhage, melena, hematemesis, or bleeding esophageal varices. Of these, 205 had an esophageal variceal bleed. Ultimately, 99 met the study entry criteria. Reasons for exclusion included primary residence outside of local endoscopy region (63 admissions), death or TIPS at index bleed (17 admissions), incomplete records (14 admissions), and comorbid illness with limited survival (12 admissions).

As shown in Table 1, the median age of the study population was 55 years; 60% of the study population was male, the median admission MELD score was 13, 54% of the study population was Child-Turcotte-Pugh class B, and 39% had a pharmacologically treated psychiatric disorder. The most common etiology of liver disease was alcoholic cirrhosis (63%), of which 16% (10 of 62) had concomitant hepatitis C. The median distance from the hospital was 24.9 kilometers. Nearly a third of patients had no health insurance or had financial health coverage through Medicaid (a government-sponsored health plan that assists with medical costs in selected low income individuals). At hospital discharge, 87% of patients were on a beta-blocker.

### Completion of variceal obliteration and clinical characteristics

Overall, 53 of 99 patients (53%) came for an initial surveillance EGD after hospital discharge, as scheduled, and 33 patients (33%) completed variceal obliteration (Table 2). Achievement of obliteration required a median of 2 EGD sessions after hospital discharge (range 1-6). The median time to first surveillance EGD was 44 d (range 10 to 171 d). There were no significant differences in the proportion of patients who completed esophageal variceal obliteration with respect to gender, age, etiology of cirrhosis, length of index hospital stay, recent alcohol use, distance from residence to hospital, MELD score, Child-Turcotte-Pugh class, health insurance status, comorbid psychiatric disorders, or beta blocker at time of discharge (Table 3). Similarly, no significant differences in demographic features were observed between those completing variceal obliteration and those without endoscopic

**Table 1 Summary of baseline patient characteristics *n* (%)**

Demographics/baseline measures	Number ( <i>n</i> = 99)
Male	59 (60)
Age, median (range), yr	55 (31-82)
Etiology of cirrhosis	
Alcohol	62 (63)
Hepatitis C	12 (12)
Other	25 (25)
Recent alcohol use	46 (46)
Distance from hospital, median (range), kilometers	24.9 (0.8-95.1)
MELD score, median (range)	13 (6-27)
Child-turcotte-pugh classification	
A	24 (24)
B	53 (54)
C	22 (22)
Index bleed in 2007 or earlier	44 (44)
Insurance	
Medicaid <sup>1</sup> or uninsured	31 (31)
Medicare or private insurance	68 (69)
Comorbid psychiatric disorder	39 (39)
Length of stay, median (range), d	5 (2-75)
Beta-blocker at discharge	86 (87)

<sup>1</sup>Government-sponsored health plan that assists with medical costs in selected low income individuals. MELD: Model for end-stage liver disease.

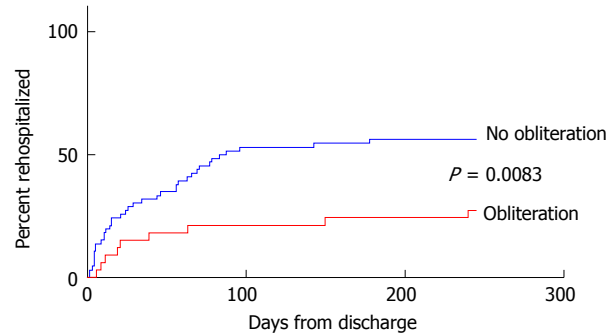
**Table 2 Outcomes of the study population *n* (%)**

Demographics/baseline measures	Number ( <i>n</i> = 99)
Incomplete obliteration	66 (66)
No post-discharge endoscopy	46 (46)
Completed obliteration	33 (33)
Adhered to 1-yr surveillance	12 (12)
Rehospitalized for variceal bleed	46 (46)

follow-up following hospital discharge (Supplemental Table 1). In addition, despite codification of guidelines for management of gastroesophageal varices by the American Association for the Study of Liver Diseases in 2007<sup>[2]</sup>, the proportion of patients who completed esophageal variceal obliteration before and after 2007 did not significantly differ.

### Adherence to surveillance endoscopy and clinical characteristics

Complete adherence to annual endoscopic surveillance was achieved in 12 of 99 patients (12%). Those adherent to annual endoscopic surveillance were more likely to be insured privately or through Medicare (a national health plan with universal coverage for age 65 or greater) when compared with those with incomplete adherence to annual surveillance (100% vs 64%,  $P = 0.016$ , Table 4) and to those without endoscopic follow up after hospital discharge (100% vs 63%,  $P = 0.0119$ , Table 5). Non-significant differences were observed in the proportion of patients who adhered to annual endoscopic surveillance (vs the proportion with incomplete adherence) when the index variceal bleed occurred in 2007 or earlier (17% vs 48%,



**Figure 1 Time until rehospitalization for variceal rebleeding.** The results shown represent the time from admission for index variceal esophageal variceal hemorrhage to rehospitalization for variceal rebleeding in those completing variceal obliteration (median 259 d to rehospitalization) and those not completing obliteration (median 207 d to rehospitalization,  $P = 0.0083$ ).

$P = 0.0607$ ). There were otherwise no significant differences in the proportion of patients who adhered to surveillance endoscopy with respect to gender, age, etiology of cirrhosis, length of hospital stay, distance from residence to hospital, MELD score, Child-Turcotte-Pugh Class, recent alcohol use at time of admission, comorbid psychiatric disorders, or beta-blocker at time of discharge.

### Rehospitalization for variceal bleeding

Rehospitalization for gastrointestinal variceal bleeding occurred in 46% of patients (median time to rehospitalization 250 d). More hospitalizations for variceal rebleeding occurred in those who did not complete obliteration (56% vs 27%,  $P = 0.0099$ ), and these rehospitalizations occurred earlier (median 207 d vs 259 d,  $P = 0.0083$ , Figure 1). Incomplete adherence to endoscopic surveillance was associated with more rehospitalizations for variceal rebleeding compared to those fully adherent to annual endoscopic surveillance (51% vs 17%,  $P = 0.0328$ ).

### Survival

Survival data were available for 88 of 99 (89%) patients. Of this population, 30 had transplant free survival at the close of the study (34%), 56 died (64%) and 2 patients underwent liver transplantation. Of the 66% who died or received liver transplantation, the median time to the event was 995 d (mean 1380 d). There were no significant differences in median time to death/transplant in those completing obliteration (median 1072 d, range 123 d-4917 d) compared with those not completing obliteration (median 1118 d, range 24-4549 d,  $P = 0.2585$ ) and those without post-discharge endoscopy (median 679 d, range 24-4401 d,  $P = 0.9601$ ).

## DISCUSSION

Despite abundant evidence summarized in practice

**Table 3 Characteristics of those completing variceal obliteration *n* (%)**

Measures	Obliteration ( <i>n</i> = 33)	No obliteration ( <i>n</i> = 66)	<i>P</i> value
Male	18 (55)	41 (62)	0.5186
Age, median (range), yr	53 (34-78)	54 (31-82)	0.3934
Etiology of cirrhosis			
Alcohol	19 (58)	43 (65)	0.5125
Hepatitis C	4 (12)	8 (12)	1.0000
Other	10 (30)	15 (23)	0.4657
Recent alcohol use	15 (45)	31 (47)	1.0000
Distance from hospital, median (range), kilometers	24.9 (0.8-80.3)	20.9 (1.4-95.1)	0.6892
MELD score, median (range)	12 (6-18)	13.5 (7-27)	0.1615
Child-turcotte-pugh classification			
A	11 (33)	13 (20)	0.1451
B	17 (52)	36 (54)	0.8325
C	5 (15)	17 (26)	0.3080
Index bleed in 2007 or earlier	15 (45)	29 (44)	1.0000
Medicaid <sup>1</sup> or uninsured	7 (21)	24 (36)	0.1687
Comorbid psychiatric disorder	9 (27)	30 (45)	0.1260
Length of stay, median (range), d	6 (2-33)	5 (3-75)	0.5619
Beta-blocker at discharge	30 (91)	56 (85)	0.5348

<sup>1</sup>Government-sponsored health plan that assists with medical costs in selected low income individuals. MELD: Model for end-stage liver disease.

**Table 4 Characteristics of those completing variceal obliteration and surveillance at 1-yr intervals *n* (%)**

Measures	1-yr surveillance ( <i>n</i> = 12)	Incomplete adherence ( <i>n</i> = 87)	<i>P</i> value
Male	7 (58)	52 (60)	1.0000
Age, median (range), yr	55 (45-78)	54 (31-82)	0.1936
Etiology of cirrhosis			
Alcohol	6 (50)	56 (64)	0.3560
Hepatitis C	2 (17)	10 (12)	0.6364
Other	4 (33)	21 (24)	0.4918
Recent alcohol use	15 (45)	42 (48)	0.3726
Distance from hospital, median (range), kilometers	30.4 (3.7-80.3)	13.7 (0.8-95.1)	0.3898
MELD score, median (range)	11.5 (6-17)	13 (7-27)	0.2543
Child-turcotte-pugh classification			
A	3 (25)	21 (24)	1.0000
B	6 (50)	47 (54)	1.0000
C	3 (25)	19 (22)	0.7259
Index bleed in 2007 or earlier	2 (17)	42 (48)	0.0607
Medicaid <sup>1</sup> or uninsured	0 (0)	31 (36)	0.0160
Comorbid psychiatric disorder	5 (42)	34 (39)	1.0000
Length of stay, median (range), d	6 (3-7)	5 (2-75)	0.8808
Beta-blocker at discharge	12 (100)	74 (85)	0.3572

<sup>1</sup>Government-sponsored health plan that assists with medical costs in selected low income individuals. MELD: Model for end-stage liver disease.

guidelines<sup>[2]</sup>, concerning the efficacy of endoscopic management in survivors of esophageal variceal bleeding, a striking finding of our study is that 66% of patients did not complete variceal obliteration and even fewer adhered to endoscopic surveillance for this major cirrhosis-related problem. Moreover, patients who did not complete variceal obliteration were more likely to develop recurrent variceal bleeding and were rehospitalized significantly sooner for this complication. Similarly, those non-adherent to annual endoscopic variceal surveillance had significantly more rehospitalizations for variceal rebleeding. Collectively, these observations reinforce the importance of variceal obliteration and annual endoscopic surveillance for prevention of variceal rebleeding<sup>[2,5,12]</sup>. The suboptimal

adherence to preventative therapies in the outpatient setting, as observed in our study, mirrors those of studies in hospitalized cirrhotic patients, which have demonstrated that a minority of such individuals receive evidence-based treatments to prevent disease related complications<sup>[13,14]</sup>. Two broad reasons may account for gaps in cirrhosis-related quality care: decisions made by health professionals, and decisions made by patients. In this study, the gaps were attributable to patient attendance at already scheduled endoscopic sessions. Our findings, in a real world setting, are consistent with the results of controlled clinical trials<sup>[2-4,12,15]</sup>, which have demonstrated that variceal obliteration and surveillance variceal ligation in patients who have recovered from esophageal variceal hemorrhage reduces

**Table 5** Characteristics of those adherent to surveillance at 1-yr intervals vs no endoscopic follow up *n* (%)

Measures	1-yr surveillance ( <i>n</i> = 12)	No post-discharge EGD ( <i>n</i> = 46)	<i>P</i> value
Male	7 (58)	29 (63)	0.7518
Age, median (range), yr	55 (45-78)	54.5 (31-82)	0.4237
Etiology of cirrhosis,			
Alcohol	6 (50)	28 (61)	0.5273
Hepatitis C	2 (17)	6 (13)	0.6649
Other	4 (33)	12 (26)	0.7200
Recent alcohol use	4 (33)	21 (46)	0.5255
Distance from hospital, median (range), kilometers	30.4 (3.7-80.3)	20.9 (1.5-95.1)	0.4965
MELD score, median (range)	11.5 (6-17)	13 (7-26)	0.1707
Child-turcotte-pugh classification			
A	3 (25)	9 (20)	0.6983
B	6 (50)	27 (59)	0.7455
C	3 (25)	10 (21)	1.0000
Index bleed in 2007 or earlier	2 (17)	19 (41)	0.1790
Medicaid <sup>1</sup> or uninsured	0 (0)	17 (37)	0.0119
Comorbid psychiatric disorder	5 (42)	19 (41)	1.0000
Length of stay, median (range), d	6 (3-7)	5 (3-75)	0.6455
Beta-blocker at discharge	12 (100)	38 (80)	0.1851

<sup>1</sup>Government-sponsored health plan that assists with medical costs in selected low income individuals. MELD: Model for end-stage liver disease; EGD: Esophagogastroduodenoscopy.

hospitalizations for recurrent bleeding from esophageal varices. In addition, our observations, which suggest that adherence to endoscopic surveillance did not influence transplant-free survival over the duration of the study, are consistent with the results of a large meta-analysis, which suggested that beta-blocker use (and not endoscopic intervention) is the dominant factor that improves survival rates following hospitalization for esophageal variceal bleeding<sup>[16]</sup>.

The principal factor we found to be associated with decreased adherence to surveillance EGD and variceal obliteration was health plan coverage. In particular, we found that those uninsured or insured by Medicaid were significantly less likely to maintain full adherence to annual surveillance endoscopy. This observation mirrors an association between Medicaid and/or lack of health plan coverage and reduced adherence to health care interventions in other contexts. Specifically, among patients with cirrhosis, those insured by Medicaid have been shown to have a greater all-cause 30 d rehospitalization rate<sup>[17]</sup> and reduced adherence to hepatocellular carcinoma (HCC) surveillance imaging, with just 17% undergoing follow-up ultrasound in a 15-mo period<sup>[18]</sup>. Suboptimal utilization of preventative care is not unique to those with cirrhosis and Medicaid, as screening modalities for cervical cancer, breast cancer, and colon cancer<sup>[19-21]</sup> have all been shown to be under-utilized by those insured by Medicaid when compared to those privately insured. In 2012, the United States passed the Patient Protection and Affordable Care Act which allowed states to choose whether to expand Medicaid coverage. States which chose not to expand Medicaid had lower cancer screening rates, particularly amongst federally qualified health centers, while those expanding Medicaid had an

increase in early stage cancer diagnosis in the working-age population<sup>[22]</sup>, suggesting that reducing financial barriers to care by expanding public health insurance coverage increases utilization of services that have been shown to improve healthcare outcomes<sup>[23]</sup>. Additional socioeconomic factors that may interfere with utilization of preventative measures in this population include lack of transportation<sup>[24,25]</sup>, work hours conflicting with medical office hours<sup>[26]</sup>, and reduced health literacy<sup>[27]</sup>. Additionally, patient knowledge of their medical problems has been shown to correlate with improved adherence to HCC surveillance ultrasound<sup>[24]</sup>, creating another barrier to adherence for a population at risk for reduced health literacy.

By contrast, factors shown in other contexts to influence adherence to medical management regimens, such as distance to the hospital<sup>[28,29]</sup>, psychiatric comorbidities<sup>[30]</sup>, and alcohol use<sup>[31]</sup>, were not found to be associated with adherence to surveillance or completion of variceal obliteration in our study. This latter conclusion must be taken with caution, given that our study took place at a single center with a large rural referral population and the population's median distance from residence to the hospital was small for a rural region. Additionally, the sample size may not have been sufficiently powered to detect a significant association between psychiatric disorders and endoscopic non-adherence.

Lessons can be learned from studies that have addressed suboptimal adherence to guideline-based measures in other health conditions. For example, cardiac rehabilitation after an index myocardial infarction, a class I A recommendation from the American College of Cardiology and American Heart Association, has been shown to reduce both mortality and rehospitalization

at 1 year<sup>[32]</sup>. Cardiac rehabilitation utilization after a qualifying hospitalization has been shown to be low, with just 18.7% attending at least 1 session after hospital discharge<sup>[33]</sup>. In response, tools and programs have been developed to address this gap in care. One such tool has been an automatic electronic medical record based “opt out” referral system, which was shown to double cardiac rehabilitation attendance<sup>[34]</sup>. A similar increase in utilization of ultrasound screening for HCC was seen by mailing invitations to patients<sup>[35]</sup>. Financial incentives have been shown to increase cardiac rehabilitation adherence<sup>[32]</sup> and to increase smoking abstinence during pregnancy with high rates of sustained abstinence at 24 wk post-partum<sup>[36]</sup>. Another intervention that may improve adherence is minimizing lead-time between visits with providers and subsequently scheduled studies. Adherence to HCC surveillance ultrasound has been shown to correlate with shortened lead-times, prompting the authors to recommend scheduling ultrasounds on the same day as appointments with health professionals as a means to improve adherence by both reducing lead-time and transportation barriers<sup>[28]</sup>. These and other approaches should be considered to improve endoscopic adherence among patients with cirrhosis after an index esophageal variceal hemorrhage. This area is ripe for future study and is likely to translate into long term improvement of disease-related outcomes.

## ARTICLE HIGHLIGHTS

### Research background

Esophageal variceal hemorrhage is a significant complication of cirrhosis and is associated with a high mortality rate. Current guidelines recommend a combination of non-selective beta adrenergic receptor blockers with endoscopic variceal ligation as the most effective way of reducing variceal rebleeding. It is increasingly recognized that cirrhotic patients often do not receive evidence-based treatments for disease related complications.

### Research motivation

Whereas prior studies have focused on gaps in cirrhosis-related quality care attributable to decisions made by healthcare professionals, this study focused specifically on patient factors which may impact adherence to endoscopic variceal surveillance. By identifying a patient population at risk of poor adherence, we hope to spur future studies which will assess interventions to promote adherence to improve disease-related outcomes.

### Research objectives

We sought to identify potential factors, in a real world setting, which may prevent patients from completing variceal obliteration and adhering to surveillance endoscopy following their first esophageal variceal hemorrhage.

### Research methods

We performed a retrospective review of the records of patients with cirrhosis admitted to the medical intensive care unit between 2000 and 2014 for first time esophageal variceal hemorrhage treated with endoscopic variceal ligation who were subsequently discharged and scheduled for surveillance endoscopy at our medical center. Demographic and clinical data were obtained through the medical records. Differences between groups were determined by Fisher's exact test for categorical variables, by Mann-Whitney *U* test for continuous non-parametric variables, and by Student's *t* test for continuous parametric variables. Kaplan-Meier curves for both survival and time to rehospitalization

were compared using the log-rank test.

## Research results

Of 99 patients included in the study, 33% completed variceal obliteration and 12% adhered to annual surveillance. Completion of variceal obliteration was associated with fewer rehospitalizations for variceal rebleeding (27% vs 56%,  $P = 0.0099$ ) and when rehospitalizations occurred, they occurred later in those who had completed obliteration (median 259 d vs 207 d,  $P = 0.0083$ ). Incomplete adherence to endoscopic surveillance was associated with more rehospitalizations for variceal rebleeding compared to those fully adherent to annual endoscopic surveillance (51% vs 17%,  $P = 0.0328$ ). Those adherent to annual surveillance were more likely to be insured privately or through Medicare (a national government-sponsored health plan that provides universal coverage for age 65 or greater) compared to those who did not attend post-hospital discharge endoscopy (100% vs 63%,  $P = 0.0119$ ).

## Research conclusions

We found that the minority of survivors of esophageal variceal bleeding completed variceal obliteration and fewer adhered to annual surveillance. Those completing variceal obliteration had fewer and later rehospitalizations for variceal rebleeding. Incomplete adherence to endoscopic surveillance was associated with more frequent rehospitalizations for variceal rebleeding. Collectively, these observations reinforce the importance of variceal obliteration and annual endoscopic surveillance for prevention of variceal rebleeding. Incomplete adherence to endoscopic surveillance was associated with lack of health care insurance or health care insurance through Medicaid (a government-sponsored health plan that defrays medical expenses in selected low income individuals). This population has been shown in prior studies to have greater financial barriers to healthcare, poor health literacy, and limited transportation, all of which may be contributing to the decreased endoscopic adherence observed in our study.

## Research perspectives

This study provides a link between health care coverage vulnerability, a marker of lower socioeconomic status, and reduced adherence to endoscopic surveillance following esophageal variceal bleeding. Future research should attempt to improve adherence in this population using interventions which have been shown to be successful in other fields, such as scheduling procedures on the same day as a preexisting appointment, using text message appointment reminders, or even using financial incentives.

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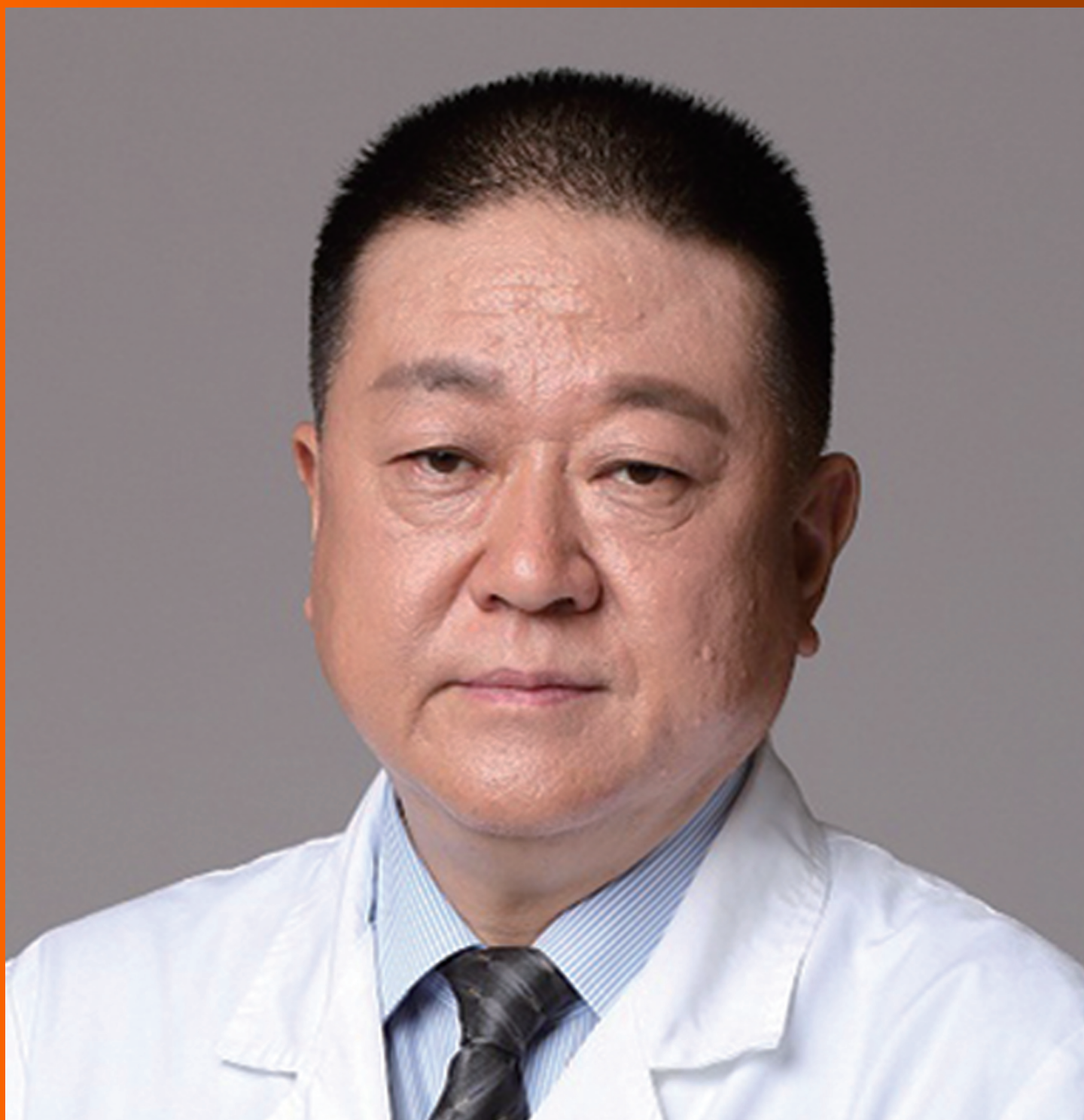


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**MINIREVIEWS**

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## Approach to pseudomyxoma peritonei

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### Abstract

Pseudomyxoma peritonei (PMP) is a mucinous tumour of the appendix that spreads into the peritoneal cavity in the form of gelatinous deposits. The incidence of PMP is believed to be approximately 1-3 out of a million per year. Nonetheless, due to its indolent nature, it is usually discovered at an advanced stage and severely impacts quality of life. Curative treatment for PMP is complete cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC). An extensive literature review was conducted searching EMBASE, MEDLINE, PubMed, and Google Scholar databases for PMP in aims to delineate a clinical approach to diagnosis and treatment. Literature was limited to the years 2007-2018. We found the 5-year overall survival with CRS and HIPEC estimated to be between 23%-82% and rates of major complications as high as 24%. Therefore, it is important to appropriately stage and select patients that should undergo CRS with HIPEC. Modalities like MDCT radiological scores have been shown to have sensitivity and specificity of 94% and 81%, respectively, in being able to predict resectability and survival. Despite treatment, the disease often recurs. Tumor markers have significant potential for establishing prognosis pre-operatively, and this paper will review the most recent evidence in support of them.

**Key words:** Pseudomyxoma peritonei; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Mucocoele; Appendix

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**Core tip:** This paper highlights the most recent evidence in the clinical approach to pseudomyxoma peritonei. Diagnosis, treatment, complications of treatment, overall survival, and post-operative follow-up will be explored.

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## INTRODUCTION

Although neoplasms of the appendix are rare, they carry a significant disease burden. Upwards of 58% of malignant tumors arising from the appendix are mucinous in origin<sup>[1]</sup>. When these mucinous tumours are able to penetrate through the appendicular wall and spread into the peritoneal cavity in the form of gelatinous deposits, the condition is termed pseudomyxoma peritonei (PMP)<sup>[1]</sup>. The incidence of PMP is believed to be approximately 1-3 out of a million. Nonetheless, due to its indolent nature, it is usually discovered at an advanced stage and severely impacts quality of life<sup>[2]</sup>. PMP is targeted *via* a multidisciplinary approach involving surgical oncologists, pathologists, radiation and medical oncologists. Curative treatment for PMP is complete cytoreductive surgery (CRS), with hyperthermic intraperitoneal chemotherapy (HIPEC)<sup>[3]</sup>. However, this procedure is not without its significant post-operative morbidity and mortality. Recent studies have developed preoperative tools to assess for appropriate surgical candidates who will benefit from this treatment. This review will outline an approach to diagnosis, pre-operative assessment, treatment, and post-operative follow-up for PMP.

## LITERATURE SEARCH STRATEGY

An extensive literature review was conducted searching EMBASE, MEDLINE, PubMed, and Google Scholar databases using the following key words: "pseudomyxoma peritonei", "cytoreductive surgery", "hyperthermic intraperitoneal chemotherapy", "mucocoele", and "appendix." Papers were limited to the years 2007-2018. The reference lists of all retrieved articles were manually reviewed to further identify potentially relevant studies.

## PATHOGENESIS

The pathological process of PMP starts similar to most primary tumors of the alimentary tract<sup>[1]</sup>. Neoplastic transformation of the goblet cells results in the formation of a primary mucinous tumor. As mucin levels increase within the mucocoele, there is eventual rupture<sup>[2]</sup>. The rupturing of the mucocoele is the initiating event that leads to the development of PMP<sup>[4]</sup>. The rupture allows tumor cells to access the peritoneal cavity, and given their lack of cell adhesion molecules, they passively circulate with ease. This seeding of tumor cells eventually leads to bulky mucinous deposits all along the abdominal cavity, which causes an increase in intraabdominal pressure. This pressure can lead to compression of visceral organs and even bowel obstruction. PMP deposits are consistently seen within the greater omentum, lesser omentum, and

beneath the right hemi-diaphragm<sup>[4]</sup>. However, the tumor is absent on the peritoneal surfaces of the intestine and mesentery due to peristaltic activity.

## DISEASE BURDEN

The exact incidence of the disease is unknown but has been estimated at 1-3 out of a million, per year<sup>[5]</sup>.

## CLINICAL PRESENTATION

PMP is typically diagnosed between the ages of 40-55, and is often found incidentally in patients undergoing laparotomy, laparoscopy, or imaging for other medical conditions. Due to its indolent nature and non-specific symptoms, most are found with advanced disease. The clinical presentation of the disease is dependent on the progression of the disease, as is the prognosis<sup>[6]</sup>. Localized disease typically presents with appendicitis-like symptoms or a pelvic mass due to mucinous deposits on adjacent organs. More advanced disease presents with abdominal distension, bowel obstruction, and ascites. The classic sign termed "jelly belly" is an increase in abdominal girth caused by an accumulation of gelatinous ascites. Figure 1 demonstrates mucinous ascites on computed tomography (CT). This is often in the late stage when most of the abdomen is filled with tumour and mucinous ascites. Often the chief complaint is a new-onset hernia due to increased intra-abdominal pressure<sup>[7]</sup>.

## HISTOLOGY

In 1995, Ronnett *et al*<sup>[8]</sup> attempted to correlate the histology of PMP with prognosis. Their classification scheme is summarized in Table 1. Diffuse peritoneal adenomucinous (DPAM) is classic PMP with mucinous ascites on the surface of the peritoneum without invasion and has an indolent course. Peritoneal mucinous adenocarcinoma (PMCA) represents a class with a higher percentage of malignant cells, and thus has a worse prognosis. The third group, PMCA with intermediate features (PMCA-I), is described as a hybrid between DPAM and PMCA and has features of both<sup>[8]</sup>. Figure 2 depicts histology of the three types of PMP in further detail.

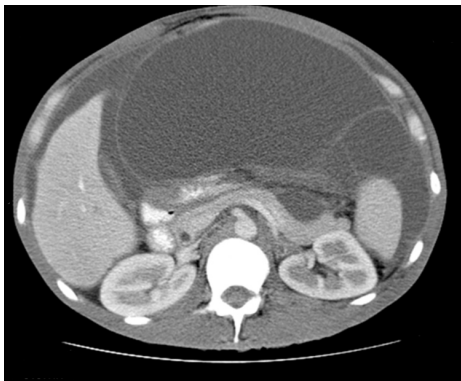
Misdraji *et al*<sup>[9]</sup> found this classification to be correlated with and representative of the disease prognosis. Ninety-six percent of those with DPAM were found to be disease-free 52 mo after treatment, whereas only 33% of those with features of PMCA were disease-free<sup>[9]</sup>. They concluded that tumors limited to the appendicular wall or mesoappendix are curable with appendectomy (T1). However, anything beyond the muscularis propria is at risk for dissemination and the development of PMP.

To further simplify classification, the World Health Organization proposed a classification scheme based on histogenesis and clinical behavior. The WHO classification divides PMP into two groups<sup>[10]</sup>: low and high grade.

**Table 1** Classification of pseudomyxoma peritonei

System	Classification
Ronnett <i>et al</i> <sup>[8]</sup>	DPAM: PMP with mucinous ascites on the surface of peritoneum. No invasion. Indolent course. Best prognosis PMCA: Higher percentage of malignant cells. Poorer prognosis PMCA-I: Intermediate hybrid between DPAM and PMCA
WHO	Low grade: Mucin pools with low grade dysplasia. Eighty-three percent of five-year OS High Grade: Mucin pools with high grade dysplasia. More likely for rupture and spillage into the peritoneal cavity. Sixty-eight percent of five-year OS

PMP: Pseudomyxoma peritonei; DPAM: Diffuse peritoneal adenomucinosis; PMCA: Peritoneal mucinous carcinomatosis; PMCA-I: Peritoneal mucinous carcinomatosis-intermediate; OS: Overall survival; WHO: World Health Organization.



**Figure 1** Mucinous ascites on computed tomography<sup>[24]</sup>. This computed tomography scan demonstrates mucinous ascites. We also see characteristic findings of pseudomyxoma peritonei: Scalloping of the liver and spleen.

## DIAGNOSIS

CT is the primary mechanism of diagnosis for PMP. CT is able to identify an appendiceal mucocoele in the early course of this disease. This is often seen as a calcified mass near the ileocecal valve<sup>[11]</sup>. Progressive disease is seen on CT as a characteristic pattern of high density mucinous patches with bowel and mesenteric sparing. Figure 3 demonstrates PMP on CT. What is interesting to note is that the primary tumor is rarely visualized at this stage<sup>[11]</sup>. CT is as good as magnetic resonance imaging (MRI) in describing both location and morphology of the mucocoele<sup>[1]</sup>. However, MRI is more sensitive at identifying whether the mucocoele is mucin- or fluid-filled<sup>[1]</sup>.

The diagnostic challenge with PMP is being able to identify resectable versus unresectable disease. CRS with HIPEC is associated with significant postoperative complications, and mortality is estimated to be 15%-20%<sup>[3]</sup>. It is therefore imperative that we select only appropriate candidates for surgery. A study published by Bouquot *et al*<sup>[3]</sup> aimed to create a preoperative score based on CT findings that would assess the extent of the disease and predict resectability. They suggest that perihepatic involvement, especially involvement of the hepatic pedicle, lesser omentum, and vena cava are associated with incomplete CRS. The MDCT score is a simple preoperative radiographic score that measures tumor burden in the perihepatic region and is able to predict resectability and survival in PMP patients. The

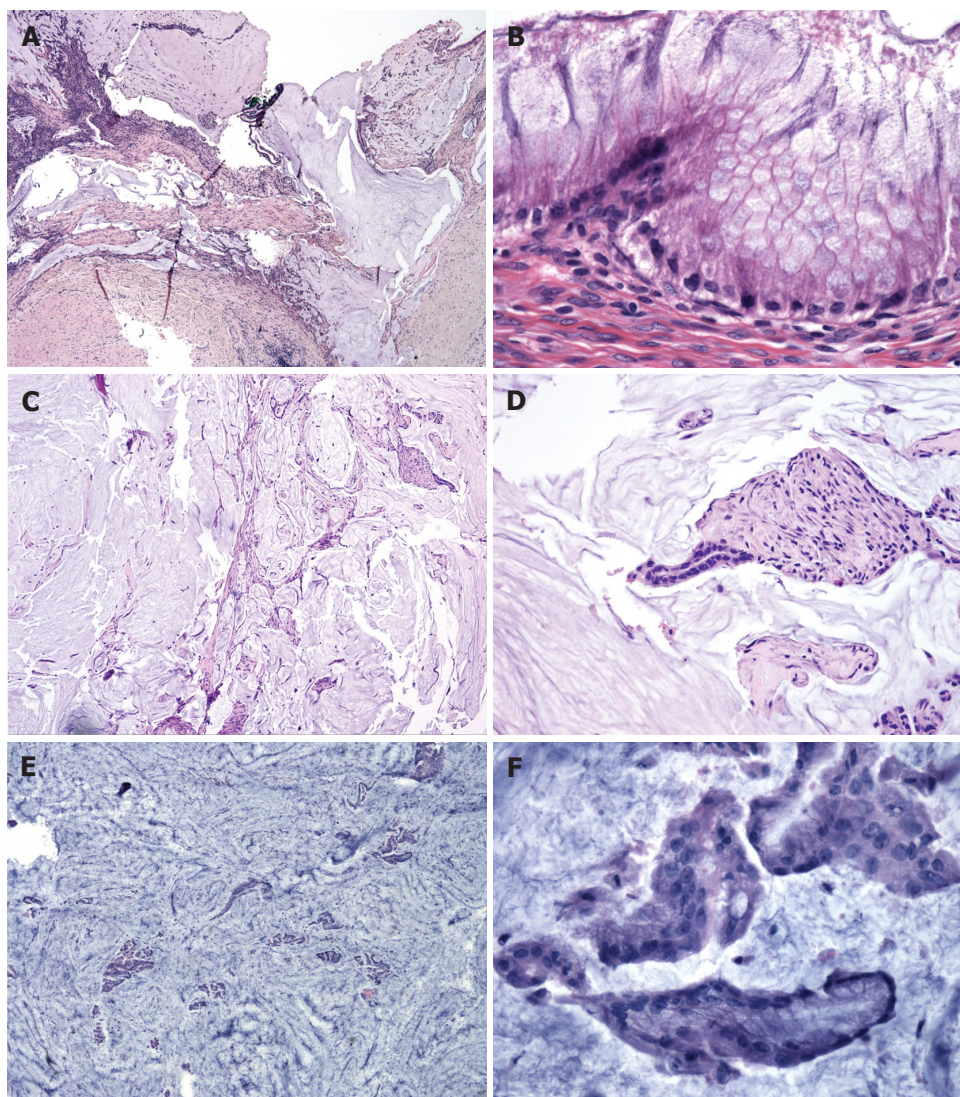
sensitivity and specificity of this score is 94% and 81% respectively, although it requires further study and refinement. It is evident by this study that thickness of the tumour burden and involvement of the right upper quadrant on CT are poor prognostic factors and should be taken into consideration before committing to CRS and HIPEC.

Despite treatment with CRS combined with HIPEC, disease often recurs. Tumor markers have been found to have prognostic value in PMP. Although not diagnostic, they can be used like CEA in colorectal carcinoma in post-operative follow-up to monitor for recurrence.

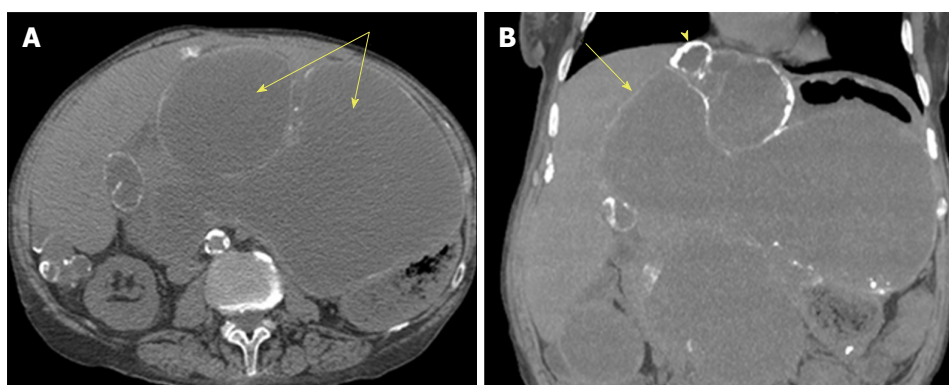
Taflampas *et al*<sup>[12]</sup> analyzed recurrence and survival correlated with pre-operative levels of CEA, CA-125, and CA19-9 in 519 patients who underwent CRS with HIPEC for PMP. They found that overall survival (OS) and disease-free survival were lower when preoperative levels of all three tumor markers were elevated.

Rangarajan *et al*<sup>[13]</sup> conducted a retrospective study looking at pre-operative inflammatory markers in predicting survival in patients undergoing CRS and HIPEC for PMP. Their study included 699 patients who underwent CRS and HIPEC between 1994 and 2015 for PMP. They found that patients with an elevated neutrophil-lymphocyte ratio (NLR, an inflammatory marker) had poor long-term survival. As NLR is both inexpensive and easily calculated, it has strong potential to be used in determining prognosis for patients with PMP.

Additionally, Bong *et al*<sup>[14]</sup> conducted a study aimed at examining the prognostic significance of inflammatory markers in patients undergoing CRS/HIPEC for colorectal peritoneal carcinomatosis. Although distinct from PMP, the findings of this study illustrate the effectiveness of CRS/HIPEC for peritoneal carcinomatosis. They looked at NLR, platelet-lymphocyte ratio (PLR) and CEA. Their study found that preoperative levels of PLR and CEA were significant prognostic factors for peritoneal carcinomatosis for patients undergoing CRS/HIPEC<sup>[11]</sup>. An elevated PLR was associated with shorter OS. Furthermore, there is increasing evidence that suggests platelets facilitate tumor development by promoting tumor cell proliferation, angiogenesis, and metastasis<sup>[11]</sup>. Furthermore, Di Fabio *et al*<sup>[15]</sup> found that there was a significant decrease in CEA levels post-operatively after significant tumor burden had been removed *via* CRS and HIPEC.



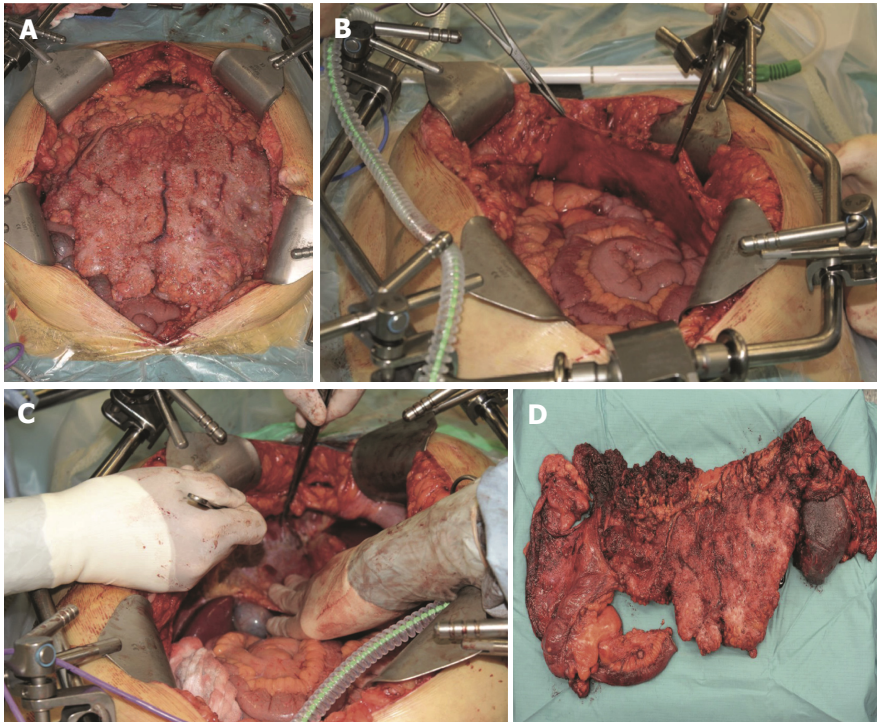
**Figure 2 Histological classification of pseudomyxoma peritonei<sup>[25]</sup>**. This figure highlights some of the characteristic findings in the different histological types of pseudomyxoma peritonei. A, B: Disseminated peritoneal adenomucinosis (DPAM) is demonstrated in (A and B) with paucicellular mucin pools (A) and scant strips of low-grade neoplastic epithelium (B); C, D: Peritoneal mucinous carcinomatosis-intermediate (PMCA-I) is demonstrated in (C and D). PMCA-I is less cellular than PMCA, but the degree of atypia exceeds that of DPAM (D); E, F: Highlight PMCA, with mucin cells with abundant epithelium (E) and malignant cytological features (F).



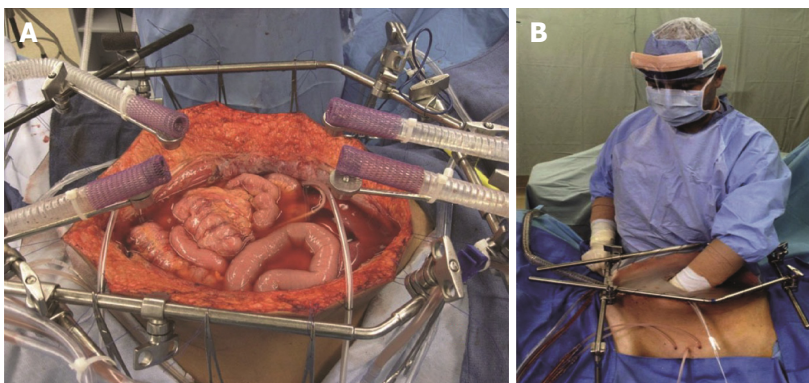
**Figure 3 Computed tomography of pseudomyxoma peritonei<sup>[26]</sup>**. This is an axial computed tomography scan. A: Cystic accumulations of mucus (arrows) surrounded by calcified rims; B: A coronal reconstruction representing cystic accumulations in the upper abdomen and the liver.

In summary, tumor markers have significant potential in establishing prognosis pre-operatively, and with

further investigation and research, may eventually be used for diagnostic purposes.



**Figure 4** Intraoperative pictures of cytoreductive surgery<sup>[11]</sup>. This is a figure depicting various stages of cytoreductive surgery. A: A view of a pseudomyxoma patient's abdominal cavity immediately after laparotomy; B: Stripping of the right anterior peritoneum; C: Depicts stripping of the right subphrenic peritoneum; D: An image of the resected terminal ileum, colon, and spleen affected by pseudomyxoma peritonei.



**Figure 5** Hyperthermic intraperitoneal chemotherapy after complete cytoreductive surgery<sup>[27]</sup>. This figure demonstrates the hyperthermic intraperitoneal chemotherapy (HIPEC) setup after cytoreductive surgery has been completed. A: HIPEC administered using an open technique; B: After placement of tubes, drains and temperature probes, the skin edges are elevated onto the rim of the self-retaining retractor using a running suture. A plastic sheet covers the abdomen to prevent splashing and loss of chemotherapy agent. A slit in the sheet allows the surgeon to access the abdominal cavity. Continuous mixing by the surgeon ensures all abdominal surfaces are uniformly coated with doses of heated chemotherapy.

**Table 2** Cytoreductive score

Score	Tumor burden
CC0	No residual tumor
CC1	Residual tumor < 2.5 mm
CC2	Residual tumor between 2.6 mm and 2.5 cm
CC3	Residual tumor > 2.5 cm

## TREATMENT AND OUTCOME

Initially described by Sugarbaker *et al.*<sup>[16]</sup> in 1995, CRS consists of six resections that aim to decrease tumor

burden from peritoneal surfaces. The resections include: greater omentectomy-splenectomy, left upper quadrant peritonectomy, right upper quadrant peritonectomy, lesser omentectomy-cholecystectomy, pelvic peritonectomy with resection of the sigmoid colon, and antrectomy<sup>[16]</sup>. The current practice is to follow CRS with HIPEC (Figures 4 and 5).

The goal of CRS is to remove all visible tumor. Thus, the amount of tumor burden resected is used to score the effectiveness of the procedure. Table 2 depicts the scoring system<sup>[17]</sup>. The importance of this grading system is that tumors larger than 2.5 cm, if not resected during

**Table 3** Five-year overall survival

Ref.	Year	Type of study	No. of patients	Five-year OS (%)
Baratti <i>et al</i> <sup>[27]</sup>	2018	Retrospective	265	74.5
Pallas <i>et al</i> <sup>[28]</sup>	2017	Retrospective	100	43
Chia <i>et al</i> <sup>[29]</sup>	2016	Systematic Review	NA	13-23
Moran <i>et al</i> <sup>[30]</sup>	2015	Retrospective	956	84
Gupta <i>et al</i> <sup>[10]</sup>	2014	Retrospective	791	68-83
Chua <i>et al</i> <sup>[31]</sup>	2012	Retrospective	2020	82
Smeenk <i>et al</i> <sup>[20]</sup>	2007	Retrospective	103	59.5

NA: Not available; OS: Overall survival.

**Table 4** Complications of complete cytoreductive surgery/hyperthermic intraperitoneal chemotherapy

Ref.	Year	Type of study	No. of patients	Complication(s)
Hamilton <i>et al</i> <sup>[32]</sup>	2016	Retrospective	42	Intrabdominal abscess: 9.5% Bleeding: 9.1% Pleural effusion: 7.1% Anastomotic leak: 7.1% Renal failure: 2.4% Post-op mortality 2%
Chua <i>et al</i> <sup>[18]</sup>	2012	Retrospective	2020	Major complications grade III/IV: 24% Recurrence: 19% Hematological toxicity: 28% Reoperation rates: 23% Sepsis: 14% Fistula: 23%
Chua <i>et al</i> <sup>[31]</sup>	2009	Systematic Review	NA	Abscess: 37% Ileus: 86% Perforation: 10% Anastomotic leak: 9% DVT/PE: 9% Renal insufficiency: 7%

NA: Not available; DVT/PE: Deep vein thrombosis/pulmonary embolism.

CRS, will not be eliminated by HIPEC<sup>[18]</sup>. Resections are deemed complete if surgeons are able to achieve CC0 or CC1.

Once the abdominal cavity has been entered and CRS completed, the surgeon has an open abdomen. The coliseum technique describes elevating the edges of the abdomen with retractors to essentially create a barrel. The chemotherapeutic agent most often used is mitomycin C (MMC). It is heated to 41-42 degrees Celsius outside of the abdomen. Once the target temperature is achieved, the abdomen is manually perfused by the surgeon or assisted for 90 min. After 90 min, MMC is flushed out from the abdomen and the abdomen is washed with normal saline<sup>[19]</sup>.

The rationale for heating the chemotherapy was described by Sugarbaker *et al*<sup>[17]</sup>. In essence, it increases tissue penetration, cytotoxicity of the chemotherapeutic, and heat has an inherent anti-tumor effect. Furthermore, the manual distribution of chemotherapy for 90 min allows for all surfaces of the abdomen and pelvis to be adequately exposed to the chemotherapeutic agent. Ninety minutes is described to be ideal as it is enough time to cause cytotoxicity to cancer cells without causing disturbances to renal function and hemodynamics<sup>[19]</sup>.

The initial management of PMP was debulking

surgery. However, CRS/HIPEC has been shown to be superior in the long-term. Järvinen *et al*<sup>[7]</sup> showed in a retrospective analysis of 120 patients from 1984-2011 that the 5-year OS was similar: 67% for debulking group and 69% for CRS/HIPEC. However, the reoperation rates were much higher in debulking, 54% compared to 9%<sup>[7]</sup>. Very few studies have actually done a direct comparison. In the last 30 years, there have been several single center and multicenter reports that detail the outcomes of CRS and HIPEC, but no randomized control trials have been published. Nonetheless, CRS and HIPEC are accepted as first-line treatment for selected PMP patients.

In 2007, Smeenk *et al*<sup>[20]</sup> conducted a retrospective study in the Netherlands on 103 patients who underwent CRS/HIPEC for PMP between 1996-2004. They found the 5-year OS to be 59.5%<sup>[20]</sup>. Our paper aimed to look at more recent literature and studies published that outline the success, defined by five-year OS in patients who underwent CRS/HIPEC.

Gupta *et al*<sup>[10]</sup> analyzed the outcomes following CRS and HIPEC for appendiceal tumours. They looked at five-year OS and disease-free survival (DFI). It was found that CRS and HIPEC achieve 83% five-year OS if the tumor is low grade, and 68% if the tumor is high

grade<sup>[10]</sup>.

Table 3 illustrates the five-year OS reported over the years for CRS/HIPEC for patients with PMP. All authors reported that the five-year OS is highly dependent on the pathology of the disease. Nonetheless, Chua *et al.*<sup>[18]</sup> looked at an outstanding 2020 patients who underwent CRS/HIPEC for PMP and found that the five-year OS was 82%. This, along with the reported outcomes from other studies, highlights that CRS with HIPEC is an effective tool for the treatment of PMP.

Table 4 outlines both surgical and nonsurgical complications associated with CRS and HIPEC. Chua *et al.*<sup>[18]</sup> found the rates of major complications to be as high as 24%. Sugarbaker *et al.*<sup>[17]</sup> outlined that hematological (28%) and gastrointestinal (26%) to be the major complications associated with CRS/HIPEC. Complications seen include neutropenia, sepsis, pleural effusion, respiratory insufficiency, increased risk for thromboembolism, anastomotic leak, bowel perforation, fistula formation, abscess, and wound dehiscence<sup>[21]</sup>.

Thromboembolism risk, including DVT and PE, should be taken into consideration, and post-operative patients should be started on anti-thrombotic treatment. Anastomotic leak seems to be the major gastrointestinal complication. This may be associated with intraperitoneal HIPEC. Potential for further study includes assessing whether creating a temporary stoma and revisiting a primary anastomosis at a later date decreases the amount of anastomotic leak.

In the absence of a more effective way of treating PMP and other peritoneal carcinomatosis, the morbidity and mortality needs to be weighed against benefits of survival. More radical surgical procedures (*i.e.*, Whipple) have similar complications to CRS/HIPEC but not nearly as significant of a benefit.

Bevan *et al.*<sup>[4]</sup> recommend a baseline CT scan to be completed 3 mo post-operatively and then every 6 mo to monitor for recurrence. Routine bloodwork looking at tumor markers discussed in this review can also be compared with that of baseline to facilitate the detection of recurrence. Our recommendation is to do baseline CT, CEA, NLR, and PLR at 3 mo, and then every 6 mo post-operatively.

Despite these outcomes after CRS and HIPEC, there is significant recurrence of the disease. Yan *et al.*<sup>[22]</sup> found recurrence to be as high as 28%, and the majority of these patients underwent repeat surgery. Lord *et al.*<sup>[5]</sup> conducted a retrospective analysis of 512 patients undergoing CRS with HIPEC for PMP, and they found that 26.4% (137/512) developed recurrence and 25.5% (35/137) underwent repeat surgery. Complete tumor removal was achieved in 20/35 (57.1%). They found that there was no significant difference in early post-operative complications in comparison to primary CRS surgery. The five-year OS in the 375 without recurrence was found to be 90.9%, and the 35 that had repeat CRS had a five-year OS of 79%<sup>[5,23]</sup>. The literature suggests that if recurrence does occur, a second CRS procedure is feasible; however, the data

are limited due to small sample sizes. Continued data collection is needed to draw stronger conclusions on how to approach a patient with recurrence.

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## Systematic review of cystic duct closure techniques in relation to prevention of bile duct leakage after laparoscopic cholecystectomy

Aafke H van Dijk, Stijn van Roessel, Philip R de Reuver, Djamila Boerma, Marja A Boermeester, Sandra C Donkervoort

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**Author contributions:** van Dijk AH, Donkervoort SC, Boerma D, Boermeester MA and de Reuver PR conceptualized and designed the review together; van Dijk AH and van Roessel S carried out analysis; van Dijk AH, van Roessel S and de Reuver PR drafted the manuscript; all authors reviewed and approved the final manuscript as submitted.

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### Abstract

#### AIM

To study the effect of different techniques of cystic duct closure on bile leakage after laparoscopic cholecystectomy (LC) for biliary disease.

#### METHODS

A systematic search of MEDLINE, Cochrane and EMBASE was performed. Rate of cystic duct leakage (CDL) was the primary outcome. Risk of bias was evaluated. Odds ratios were analyzed for comparison of techniques and pooled event rates for non-comparative analyses. Pooled event rates were compared for each of included techniques.

#### RESULTS

Out of 1491 articles, 38 studies were included. A total of

47491 patients were included, of which 38683 (81.5%) underwent cystic duct closure with non-locking (metal) clips. All studies were of low-moderate methodological quality. Only two studies reported separate data on uncomplicated and complicated gallbladder disease. For overall CDL, an odds ratio of 0.4 (95%CI: 0.06-2.48) was found for harmonic energy *vs* clip closure and an odds ratio of 0.17 (95%CI: 0.03-0.93) for locking *vs* non-locking clips. Pooled CDL rate was around 1% for harmonic energy and metal clips, and 0% for locking clips and ligatures.

## CONCLUSION

Based on available evidence it is not possible to either recommend or discourage any of the techniques for cystic duct closure during LC with respects to CDL, although data point out a slight preference for locking clips and ligatures *vs* other techniques. No separate recommendation can be made for complicated gallbladder disease.

**Key words:** Biliary surgery; Cholecystectomy; Outcomes; Cystic duct leakage; Prevention

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**Core tip:** Cystic duct leakage (CDL) is an unwanted, potential life threatening complication of laparoscopic cholecystectomy (LC). Several techniques have been described to securely close the cystic duct during cholecystectomy. Based on available evidence from this systematic review, it is not possible to either recommend or discourage any of the techniques for cystic duct closure during LC with respect to CDL, although data point out a slight preference for locking clips and ligatures *vs* other techniques. No separate recommendation can be made for complicated gallbladder disease.

van Dijk AH, van Roessel S, de Reuver PR, Boerma D, Boermeester MA, Donkervoort SC. Systematic review of cystic duct closure techniques in relation to prevention of bile duct leakage after laparoscopic cholecystectomy. *World J Gastrointest Surg* 2018; 10(6): 57-69 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v10/i6/57.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v10.i6.57>

## INTRODUCTION

Laparoscopic cholecystectomy (LC) is the standard treatment for gallstone disease and associated with low morbidity and mortality. Cystic duct leakage (CDL) is reported in 0.5%-3% of patients following LC<sup>[1,2]</sup>. Recent articles show that CDL increases to 4%-7% in patients with complicated gallstone disease, such as cholecystitis, pancreatitis, cholangitis and stones in the common bile duct<sup>[3-5]</sup>.

Adequate closure of the cystic duct is essential to prevent CDL, especially in patients with complicated gallstone disease having a higher risk of bile leakage. Although CDL is classified as a minor injury of the bile ducts, it is associated with significant re-intervention rate, increased morbidity and even mortality<sup>[6-8]</sup>. The most common closure technique during LC is by simple (non-locking) metallic clips. Alternatives are locking clips (e.g., Hem-o-Lok®, Teleflex, Wayne, United States; Lapro-Clip®, Medtronic, Minneapolis, United States; Click' aV®, Grena, Nottingham, United Kingdom) or ligatures (e.g., ENDOLOOP®, Ethicon, Somerville, United States)<sup>[4,5]</sup>. Locking clips differ from metallic clips as they are made of polymers, are usually absorbable and are designed to lock in place with comparable locking pressure and therefore are thought to provide a more secure closure.

With the introduction of vessel sealing devices, such as LigaSure™ (Medtronic, Minneapolis, United States) and the Harmonic scalpel® (Ethicon, Somerville, United States), their feasibility and outcome in closing the cystic duct during LC are of interest. The aim of this systematic review was to assess the risk of CDL and the CDL rate for different techniques of cystic duct closure after LC, both in uncomplicated and complicated gallbladder disease.

## MATERIALS AND METHODS

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), No review protocol was devised before the commencement of this review<sup>[9]</sup>.

### Eligibility criteria

Studies were eligible for inclusion when: (1) patients receiving LC for gallstone disease were included; (2) the technique of closure of the cystic duct was described; (3) leakage of the cystic duct was described as an outcome; (4) the article reported original data and the full-text was available; and (5) the study included a minimum of 50 patients per closure technique given the estimated low event rate of CDL. Only studies published following the introduction of LC (1985 and later) were included. No further limits, such as study design and language were predefined. The original author was contacted when the full text of an article was not available in the clinical library.

### Search

The databases of PubMed/MEDLINE, the Cochrane Library and EMBASE were systematically searched (in July 2018). The complete search is listed in Appendix 1. In summary, the following search terms and synonyms were used; LC, closure of the cystic duct and CDL. All possible techniques of the closure of the cystic duct were also included separately, such as "clips" and "loops". Free text words were also searched for every keyword.

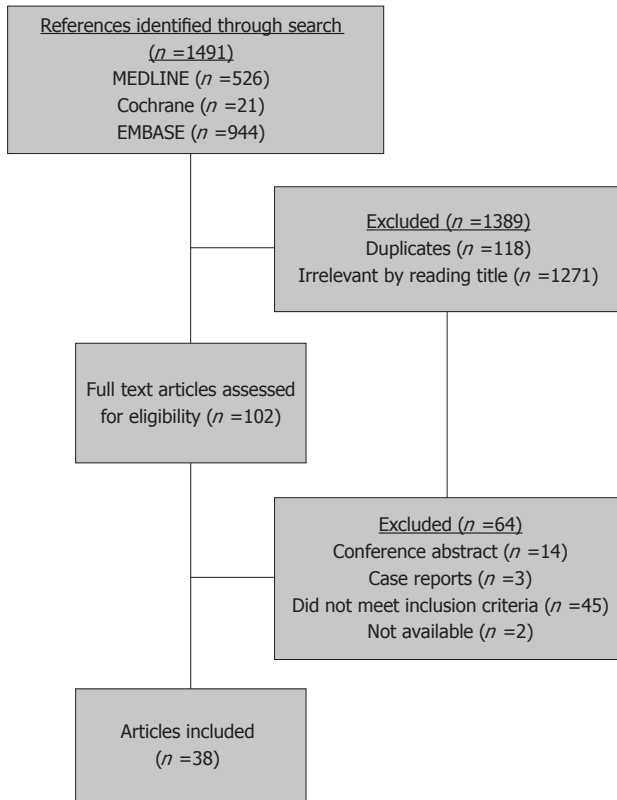


Figure 1 PRISMA flow diagram of the inclusion process (last search July 5, 2018).

References of the included articles were searched for possible relevant studies.

### Selection of studies

Available articles were independently screened for inclusion by two reviewers (van Dijk AH and van Roessel S) on title and abstract. All duplicates were removed. After selection of eligible articles, full-text was assessed independently by both reviewers according to the eligibility criteria.

### Collection of data

The following data was extracted from the articles by both reviewers independently; authors, year and country of publication, study design, number of included patients, number of patients with complicated gallstone disease, type of closure technique, failure of closure technique, operating time, duration of hospital stay, leakage of the cystic duct, biloma, bile duct injuries, and intra-abdominal abscesses.

Complicated gallstone disease was defined as patients with cholecystitis, biliary pancreatitis, cholangitis or patients that underwent ERCP prior to LC with or without choledocholithiasis. The failure of the closure technique was defined as the need to use another technique to safely secure the cystic duct during LC, such as placing extra clips or adding a loop. Bile duct injuries were classified according to the Amsterdam classification<sup>[10]</sup>. Patients who underwent cystic duct

closure with an endoloop, a ligature or intracorporeal knot were analyzed in the "ligature" group.

Both reviewers assessed risk of bias. The MINORS score was used to assess bias in non-randomized studies, of which the maximum score is 16<sup>[11]</sup>. When a study ranked 0-5 points it was listed as high risk of bias, 6-10 as moderate risk of bias and higher than 10 of low risk of bias. For the randomized studies the risk of bias in accordance with the Cochrane Library guideline<sup>[12]</sup>.

### Main outcomes

The main outcome of this study was overall CDL and for the subgroups of uncomplicated and complicated gallbladder disease for each technique used to close the cystic duct during LC. Secondary outcomes were the failure of the technique, defined as the need for another technique to safely close the cystic duct, and the occurrence of short-term complications such as a biloma, bile duct injury or intra-abdominal abscess. Operating time and duration of hospital stay were also collected for comparative studies.

### Statistical analysis

A proportion of events and a 95%CI were calculated for the main outcome. Comparative studies were grouped per study design and analyzed with the Peto method using Review Manager by the Cochrane Library (RevMan, version 5.3, the Cochrane Collaboration, 2014). This was displayed in a forest plot. The Peto odds ratio methods is commonly used in rare events and was found to be the best performing method<sup>[12]</sup>. The non-comparative studies were analyzed using R-biomedical statistics (version 3.1.1) and an estimated pooled event rate was calculated with a random effects model and displayed in a forest plot.

A subgroup analysis was planned for the main outcome in the subgroup of complicated vs non-complicated patients. Data from one single arm of a randomized study was used for meta-analysis, if only one single arm of a study could be included for one of the outcomes. Statistical heterogeneity between studies was assessed by viewing the forest plots and the  $I^2$  test and shown per study design. An  $I^2$  test with a value of 45% and lower was considered as low heterogeneity, of 46%-75% of moderate and above 75% as high. To assess publication bias funnel plots were created.

## RESULTS

### Selection of studies

A total of 1491 articles were defined by searching the databases of MEDLINE, EMBASE and the Cochrane Library. The flow diagram is depicted in Figure 1. After removing 118 duplicates 1271 references were deemed irrelevant after reading the title and abstract. The remaining 102 full texts were assessed for eligibility according to the eligibility criteria. A total of 38 articles met the inclusion criteria and were included in present

systematic review. A total of 64 articles were excluded, as they did not meet the inclusion criteria (e.g., case report or conference abstract, see Appendix 2).

### Included studies

Of the 38 included studies, 14 were used in the comparative analysis and 24 in the non-comparative analysis. Of the comparative studies, 4 were randomized controlled trials<sup>[13-16]</sup>, 3 were prospective<sup>[17-19]</sup> and 7 had a retrospective design<sup>[20-27]</sup> (Tables 1 and 2). Six studies compared the harmonic energy with metal clips<sup>[13-15,22,23,26]</sup>, locking vs non-locking clips were the subject of four studies<sup>[20,21,24,25]</sup> and the other three covered either ligatures<sup>[16,19]</sup> or a vessel sealing device<sup>[17,18]</sup>.

Non comparative analysis consisted of data from one single arm of a randomized trial (25), sixteen retrospective studies<sup>[28-43]</sup> and 7 studies with a prospective design<sup>[44-50]</sup>. A single arm of an RCT and 5 other studies reported on harmonic energy<sup>[27-29,44-47]</sup>. Closure with ligatures was described in six articles<sup>[36-38,48-50]</sup> and the use of metal clips in nine<sup>[30-33,35,40-43]</sup>. Only one article described locking clips as a closure technique<sup>[39]</sup> and one study reported on the LigaSure technique<sup>[34]</sup>. Only one study with a sufficient number of patients on the use of a stapler as closure technique was available<sup>[28]</sup>.

### Risk of bias

Not one of the studies scored higher than 10 on the Minors score. All studies were of low to moderate methodological quality, as shown in Appendix 2A and B. The 5 randomized studies were of a high risk of bias, as shown in Figure 2. The funnel plots in Appendix 4 showed some asymmetry, indicating that publication bias cannot be excluded.

### Outcomes

In this review a total of 47491 patients were included, all of which underwent LC. In 38683 (81.5%) patients the cystic duct was closed with (metal, non-locking) clips, a ligature was used in 3604 (7.6%) patients, 1853 (3.9%) patients received locking clips, in 1692 (3.6%) patients the cystic duct was closed by harmonic energy, 1299 received an absorbable clip (2.7%) and 230 (0.5%) cystic ducts were divided by LigaSure. In 130 patients (0.2%) harmonic energy and a ligature were used simultaneously.

The patient and operative characteristics of the comparative analysis are shown in Table 2. Eight of 14 studies included patients with complicated gallstone disease, but none reported separate data on the effect of the used technique in patients with complicated vs uncomplicated gallstone disease. Also, only five studies reported failure of the used technique.

Table 3 shows the clinical outcome of the 14 comparative studies and shows that the morbidity rate after LC is low. Table 4 shows the patient and operative characteristics and clinical outcomes for the non-comparative studies. Eleven of 24 studies did not report

patients with complicated gallstone disease and 6 out of 24 did not report failure of the technique. The overall morbidity rate was low.

### CDL

The overall incidence of CDL ranged from 0% to 4% in all 38 studies. The pooled CDL rate was around 0%-1% for each of the techniques (Figures 3-8). Figure 3 shows the forest plot of the comparison of harmonic energy vs metal clips for closing the cystic duct in six studies<sup>[13-15,22,23,26]</sup>. The overall pooled Peto odds ratio for CDL was 0.4 (95%CI: 0.06-2.48), with low heterogeneity. The use of locking clips vs non-locking clips was compared in three studies (Figure 4); the pooled Peto odds ratio was 0.17 (95%CI: 0.03-0.93)<sup>[20,24,25]</sup>. Figure 5 depicts the CDL rate for closure of the cystic duct by metal (non-locking) clips in 20 studies (also including the relevant single group from the comparative studies) including 38573 patients; the overall pooled event rate is 0.01% (95%CI: 0-0.01)<sup>[13-17,19,21-26,30,31,33,35,40-43]</sup>. Harmonic energy was used to close the cystic duct in 14 non-comparative analysis including 1692 patients (Figure 6); the pooled event rate for CDL was 0.01% (95%CI: 0.01-0.02)<sup>[13-15,18,22,26-29,44-47]</sup>. The overall pooled CDL event rate after application of a ligature to the cystic duct was 0.00% (95%CI: 0-0.01), calculated from eight studies including 3604 patients (Figure 7)<sup>[16,36-38,48-50]</sup>. Locking clips were used in four studies (including the relevant group from the comparative studies) (in 1853 patients) to close the cystic duct (Figure 8); the overall pooled event rate of CDL was 0.00% (95%CI: 0-0.01)<sup>[20,24,25,39]</sup>.

### CDL in uncomplicated and complicated disease

Sixteen studies of the 38 studies did not specify whether patients had complicated or uncomplicated disease, and seven studies only included patients with uncomplicated disease. Of the 16 studies that did report on complicated and uncomplicated patients, only 2 specified the outcomes per disease entity. Analysis on effectiveness of various techniques of cystic duct closure in patients with uncomplicated vs in those with complicated gallbladder disease could therefore not be performed.

### Operating time and hospital stay

Operating time and hospital stay data are listed in Table 2. Five studies compared harmonic energy with metal clips reported on operating time<sup>[13-15,23,26]</sup>. In four studies operating time was significantly shorter in the harmonic energy group than in the clip group<sup>[13-15,23]</sup>. In the remaining study the operating time was non-significantly shorter in the harmonic group<sup>[26]</sup>. The operating time was significantly shorter in the absorbable clip group compared to non-absorbable clips<sup>[21]</sup>. In one study locking clips were associated with a significantly shorter duration of surgery compared to non-locking clips in one study<sup>[25]</sup>.

Hospital stay was discussed in six studies, two

**Table 1** Characteristics of included comparative studies, descending in year of publication

Study, year, country	Study design	Intervention	Control	Aim study
Jain <sup>[27]</sup> , 2011, India	RCT	Ultrasonic shears	Electrocautery	To test the benefit of ultrasonic shears in LC
Redwan <sup>[13]</sup> , 2010, Egypt	RCT	Harmonic shear (Olympus Keymed Sono surg version G2 220–240V 3A)	Titanium clips	To demonstrate the efficiency and safety of the harmonic scalpel
Kandil <sup>[14]</sup> , 2010, Egypt	RCT	Harmonic scalpel (Harmonic ACE, Ethicon Endo-Surgery)	Metal clips	To compare metal clips <i>vs</i> the harmonic scalpel on safety and efficacy in LC
Bessa <sup>[15]</sup> , 2008, Egypt	RCT	Harmonic scalpel (Harmonic ACE, Ethicon Endo-Surgery)	Clip and cautery	To compare the safety and efficacy of the harmonic scalpel <i>vs</i> clip and cautery in LC
Seenu <sup>[16]</sup> , 2004, India	RCT	Absorbable ligature (Vicryl <sup>1</sup> , Ethicon)	Titanium clips (Ligacip, Ethicon)	To compare postoperative outcomes after occlusion of the cystic duct with tied knots <i>vs</i> titanium clips
Singal <sup>[19]</sup> , 2018, India	PS	Non-absorbable ligature (Filasilk, Meril)	Titanium clips (Ligacip, Ethicon)	To study safety and efficacy of silk ligatures compared to clips of closure of the cystic duct
Schulze <sup>[17]</sup> , 2010, Denmark	PS	LigaSure (ForceTriad system, Valleylab)	Titanium clips	To evaluate the safety of the LigaSure system in cholecystectomy
Hüscher <sup>[18]</sup> , 2003, Italy	PS	Harmonic shears (Ultracision, Ethicon Endo-Surgery)	Harmonic shears and absorbable endo-loop	To verify the advantages if ultrasonic dissection
Yang <sup>[21]</sup> , 2014, China	RS	One absorbable clip	Titanium clips	The effectiveness and safety of electrocoagulation after occlusion of the cystic duct and artery with an absorbable clip
Wills <sup>[22]</sup> , 2013, USA	RS	Harmonic scalpel (Harmonic ACE, Ethicon Endo-Surgery) in pts with a cystic duct > 5 mm	Single surgical clip in pts with cystic duct < 5 mm	The comparison of the Harmonic scalpel <i>vs</i> surgical clips in the occlusion of the cystic duct
Matsui <sup>[20]</sup> , 2012, Japan	RS	Locking absorbable clips (Laproclip 8 mm, 12mm, Tyco Healthcare)	Endo-loop (SURGITIE, Tyco Healthcare)	To evaluate the effect of locking clips on the leakage from the cystic duct in cholecystectomy
		Locking non-absorbable clip (Hem-o-lok XL, Teleflex Medical)	Metallic clip (ENDO CLIP III, Tyco Healthcare)	
Wu <sup>[26]</sup> , 2011, China	RS	Ultrasonic shears (Harmonic ACE, Ethicon Endo-Surgery)	Clips	To compare conventional LC to SILC
Gelmini <sup>[23]</sup> , 2010, Italy	RS	Harmonic scalpel (Harmonic-Ethicon Endo Surgery)	Clips	To demonstrate that the harmonic scalpel is safe in LC
Rohatgi <sup>[24]</sup> , 2006, United Kingdom	RS	Absorbable locking clips (Laproclip, USS-DG, Tyco)	Titanium clips (Ligacip, Ethicon)	To compare the efficacy of the locking absorbable clip <i>vs</i> clips in LC
Yano, 2003, Japan <sup>[25]</sup>	RS	Locking absorbable clips (Laproclip, Davis and Geck)	Ligacip (metal clip, Ethicon)	To assess if locking clips are safer and less invasive than metal Ligacips

RS: Retrospective study design; RCT: Randomized controlled trial; PS: Prospective study design; LC: Laparoscopic cholecystectomy.

randomized, one prospective and 3 retrospective studies<sup>[13,14,18,21,23,25]</sup>. In the three studies<sup>[13,14,23]</sup> reporting on the comparison of harmonic energy and metal clips, two studies showed a significantly shorter hospital stay in the harmonic group<sup>[13,14]</sup>, but in one study the hospital stay was comparable in the harmonic and clip groups<sup>[23]</sup>.

### Failure of technique

Only 4 studies described failure of the harmonic scalpel during surgery, mostly resulting in the need to add either clips or ligatures<sup>[22,23,29,46]</sup>. The failure of the harmonic scalpel was reported in 24 patients from a total of 352 patients (6.7%). Locking clips failed in 52 patients from a total of 1853 (2.8%) during surgery, reported in 4 studies<sup>[20,24,25,39]</sup>. In 1270 patients 18 ligatures failed (1.4%), which was reported in three studies<sup>[19,37,50]</sup>. Failure of closure technique usually meant the need to switch to a different closure technique. None of the studies describing failure of technique noted the consequences of failure, such as an increase in

complications.

### Short term morbidity

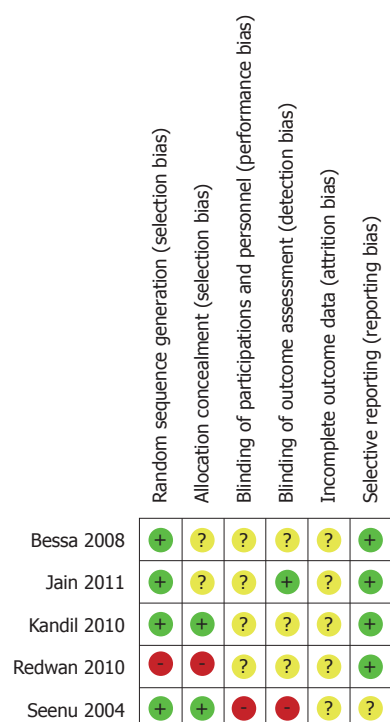
Following closure of the cystic duct with harmonic energy 4 of 863 (0.46%) patients developed a biloma or intra-abdominal abscess. After closure with metallic clips four of 3122 patients (0.13%) were diagnosed with a biloma or abscess, compared to 5 of 907 patients (0.55%) who received a locking clip. After closure with a ligature no biloma or abscess was seen in 1096 patients.

The rate of BDI was reported in 20 studies<sup>[13–15,17,18,22,23,25,26,28,29,33–36,42,45,49,50]</sup>. Overall, only 20 of 17180 patients were diagnosed with BDI (0.12%). Seven BDI were reported in the harmonic group (7 of 1085 patients, 0.65%), all type D. In the patients who had closure of their cystic duct with metal clips 8 BDI were seen (8 of 13421 patients, 0.06%), of which the severity (type D) was reported in only two patients. Two of 328 patients (0.61%) who received a locking clip were diagnosed with a BDI of unknown severity. Two bile duct injuries

**Table 2 Patient and operative characteristics of included comparative studies**

Study, year, country	No. of patients	No. of complicated cases	Failure of technique in intervention group	Operating time	Hospital stay
Harmonic scalpel/ shears <i>vs</i> metal clips					
Wills <sup>[22]</sup> , 2013, United States	57 <i>vs</i> 148	NR	3	NR	NR
Wu <sup>[26]</sup> , 2011, China	100 <i>vs</i> 100	0 (exclusion criterium)	NR	Mean in minute (SD) 49.2 (13.8) <i>vs</i> 53.3 (24)	NR
Redwan <sup>[13]</sup> , 2010, Egypt	80 <i>vs</i> 80	NR	NR	Mean in minute (SD) 20 (6.8) <i>vs</i> 45 (6.5)	Mean in days (SD) 1 (0.0) <i>vs</i> 1.5 (0.51)
Kandil <sup>[14]</sup> , 2010, Egypt	70 <i>vs</i> 70	NR	NR	Mean in minute (SD) 33.2 (9.6) <i>vs</i> 51.7 (13.8)	Mean in hours (SD) 23.4 (2.29) <i>vs</i> 267.0 (8.94)
Gelmini <sup>[23]</sup> , 2010, Italy	95 <i>vs</i> 90	28 <i>vs</i> 22	17	Median in minute (range) 60 (20-140) <i>vs</i> 80 (45-130)	Median in days (range) 2 (1-16) <i>vs</i> 2 (1-12)
Bessa <sup>[15]</sup> , 2008, Egypt	60 <i>vs</i> 60	0 (exclusion criterium)	NR	Median in minute (range) 32 (18-75) <i>vs</i> 40 (21-85)	NR
Absorbable <i>vs</i> non-absorbable clips					
Yang <sup>[21]</sup> , 2014, China	635 <i>vs</i> 728	545 <i>vs</i> 626	NR	Mean in minute (SD) 41.6 (16.5) <i>vs</i> 58.9 (19.4)	2.6 (0.4) <i>vs</i> 2.7 (0.6)
Locking <i>vs</i> non-locking clips					
Matsui <sup>[20]</sup> , 2012, Japan	907 <i>vs</i> 110	85 (unknown in which group)	5	NR	NR per group
Rohatgi <sup>[24]</sup> , 2006, United Kingdom	346 <i>vs</i> 148	NR	2	NR	NR
Yano, 2003, Japan <sup>[25]</sup>	328 <i>vs</i> 444	8 <i>vs</i> 9	0	Mean in minute (SD) 84.6 (1.6) <i>vs</i> 112.7 (2.3)	Mean in days (SD) 7.9 (0.2) <i>vs</i> 8.0 (0.1)
Other					
Singal <sup>[19]</sup> , 2018, India	70 silk ligature <i>vs</i> 70 titanium clips	0 (exclusion criterium)	0	NR	NR in detail ("similar")
Schulze <sup>[17]</sup> , 2010, Denmark	101 Ligasure <i>vs</i> 113 titanium clips	Only elective surgery	NR	NR	NR
Seenu <sup>[16]</sup> , 2004, India	53 absorbable ligature <i>vs</i> 52 titanium clips	NR	NR	Mean in minute 78 <i>vs</i> 66	NR
Hüscher <sup>[18]</sup> , 2003, Italy	331 harmonic shears <i>vs</i> 130 harmonic shears + endoloop	109 <i>vs</i> 68	NR	Mean in minute 76.8 <i>vs</i> 97.5	Mean in days 4.3 <i>vs</i> 5.1

NR: Not reported.

**Figure 2 Risk of bias of included randomized comparative studies.**

were found when Ligasure™ was used, one type B and one type D (2 of 230 patients, 0.87%). There was only one bile duct injury, type B, in the patients in whom the cystic duct was closed with a ligature (1 of 2296 patients, 0.04%).

### Subgroup analysis

It was not possible to identify the subgroup of patients with the highest incidence of CDL, such as patients with complicated gallstones disease, due to lack of subgroup data. Fifteen studies of the 38 studies did not report whether patients with complicated disease were included, and seven studies only included patients with uncomplicated disease. Of the 16 studies that did report complicated patients, only 2 specified the outcomes per subgroup. Therefore, an analysis of CDL associated with the cystic duct closure technique for high-risk patients was not possible.

## DISCUSSION

Based on the available evidence as appraised in this systematic review it is not possible to either recommend or discourage any of the techniques for cystic duct

**Table 3** Clinical outcomes of included comparative studies

Study, year, country	No. of patients	Leakage of the cystic duct	Bile duct injury	Biloma	Intra-abdominal abscess
Harmonic scalpel/shears <i>vs</i> metal clips					
Wills <sup>[22]</sup> , 2013, United States	57 <i>vs</i> 148	1 <i>vs</i> 1	1 (D) <i>vs</i> 0	1 <i>vs</i> 0	0 <i>vs</i> 0
Wu <sup>[26]</sup> , 2011, China	100 <i>vs</i> 100	0 <i>vs</i> 1	0 <i>vs</i> 0	0 <i>vs</i> 0	0 <i>vs</i> 0
Redwan <sup>[13]</sup> , 2010, Egypt	80 <i>vs</i> 80	0 <i>vs</i> 1	0 <i>vs</i> 0	0 <i>vs</i> 0	0 <i>vs</i> 0
Kandil <sup>[14]</sup> , 2010, Egypt	70 <i>vs</i> 70	0 <i>vs</i> 1	0 <i>vs</i> 0	NR	NR
Gelmini <sup>[23]</sup> , 2010, Italy	95 <i>vs</i> 90	0 <i>vs</i> 0	0 <i>vs</i> 0	NR	2 <i>vs</i> 0
Bessa <sup>[15]</sup> , 2008, Egypt	60 <i>vs</i> 60	0 <i>vs</i> 0	0 <i>vs</i> 0	NR	NR
Locking absorbable <i>vs</i> locking non-absorbable clips					
Yang <sup>[21]</sup> , 2014, China	635 <i>vs</i> 728	0 <i>vs</i> 7	NR	NR	1 <i>vs</i> 2
Locking <i>vs</i> non-locking clips					
Matsui <sup>[20]</sup> , 2012, Japan	907 <i>vs</i> 110	0 <i>vs</i> 0	NR	NR	NR
Rohatgi <sup>[24]</sup> , 2006, United Kingdom	344 <i>vs</i> 146	0 <i>vs</i> 3	NR	2 <i>vs</i> 2	NR
Yano <sup>[25]</sup> , 2003, Japan	328 <i>vs</i> 444	1 <i>vs</i> 2	2 <i>vs</i> 4 (severity not reported)	NR	NR
Other					
Singal <sup>[19]</sup> , 2018, India	70 silk ligature <i>vs</i> 70 titanium clips	0 <i>vs</i> 0	NR	NR	NR
Schulze <sup>[17]</sup> , 2010, Denmark	101 Ligasure <i>vs</i> 113 titanium clips	0 <i>vs</i> 0	0 <i>vs</i> 0	NR	NR
Seenu <sup>[16]</sup> , 2004, India	53 absorbable ligature <i>vs</i> 52 titanium clips	2 <i>vs</i> 2	NR	NR	NR
Hüscher <sup>[18]</sup> , 2003, Italy	331 harmonic shears <i>vs</i> 130 harmonic shears + endoloop	7 <i>vs</i> 3	1 (D) <i>vs</i> 0	NR	0 <i>vs</i> 1

Amsterdam classification was used to identify the severity of the bile duct injuries: B: Major bile duct leaks with or without concomitant biliary strictures; C: Bile duct strictures without bile leakage; D: Complete transection of the duct with or without excision of some portion of the biliary tree.

closure during LC with respect to CDL, although the data point out a slight preference for locking clips and ligatures *vs* harmonic energy or (non-locking) metal clips.

No separate recommendation could be made for complicated gallbladder disease as subgroup analysis was not possible due to a lack of reported data per subgroup of complicated and uncomplicated gallbladder disease. The patient populations of the studies included in this systematic review represented clinical practice and comprised a mix of patients with uncomplicated and complicated biliary disease (such as cholecystitis, pancreatitis, cholangitis and common bile duct stones). Several studies however excluded patients with complicated disease. Also, sample sizes are rarely large enough to allow subgroup analysis. When looking at clinical practice different closure techniques are used for different operative scenarios during LC. For example, it is likely that locking clips were used more often in "difficult cholecystectomies". Therefore, selection bias most likely affected results per technique. The higher bile duct injury rate in locking clips compared to non-locking metal clips may represent preference of locking clips in difficult cholecystectomies, rather than a technique related effect. Vice versa the low bile duct injury rate when ligatures were used may reflect use of this closure technique in less difficult cholecystectomies, or instead be a true favorable effect of this technique.

It is essential to prevent bile duct injuries, regardless of their nature. Type A bile duct injury (Amsterdam Classification<sup>[10]</sup>), which includes CDL, is previously classified as "minor" injury. Notwithstanding the cla-

ssification "minor", type A injuries can be associated with significant morbidity. A recent article shows that mortality related to a type A leakage is 4.2% and sepsis occurs in 15.7% of patients<sup>[7]</sup>. Although treatment, mostly endoscopically, is usually successful, it would be more prudent to prevent CDL altogether. Whichever closure technique was used, obtaining a critical view of safety (CVS) remains crucial, as can be seen in the occurrence of type D lesions in either technique.

A previous systematic review on the methods of cystic duct closure has been published in 2010, and included only 3 RCTs<sup>[51]</sup>. The primary outcomes of their Cochrane review include mortality and short term morbidity, but do not focus on CDL. Since then, two more RCT's, one prospective study and nine retrospective studies have been published, all of which were included in this systematic review. Present review added important information on CDL after various techniques of cystic duct closure and presented an up-to-date overview of all available evidence on the manner of closure of the cystic duct during LC.

This review is hampered by some important limitations. First, the already mentioned lacks of available studies in literature that supply separate data on complicated and uncomplicated gallbladder disease. Second, different study designs were included, such as RCTs, prospective and retrospective studies, to collect enough evidence in large sample sizes. Third, for the purpose of analysis we lumped some techniques into one group; for example, endoloops and intracorporeal knots were both in the "ligature" group. Fourth, reliable comparison of different techniques of cystic

**Table 4 Outcomes of non-comparative studies**

Study, year, country	Study design	Intervention	No. of patients	No. of complicated cases	CDL	Biloma/abscess	BDI	Failure of technique
Harmonic scalpel/ shears /stapler								
Jain <sup>[27]</sup> , 2011, India	RCT <sup>5</sup>	Harmonic shears	100	0 (exclusion criterium)	0	0	NR	NR
Ramos <sup>[44]</sup> , 2015, Brazil	PS	Harmonic shears	125	0 (exclusion criterium)	0	NR	NR	NR
Patel <sup>[45]</sup> , 2010, United Kingdom	PS	Harmonic scalpel (LCS-5, Ethicon) <sup>2</sup>	100	NR	1	NR	1 (D)	NR
Westervelt <sup>[46]</sup> , 2004, United States	PS	Harmonic scalpel (unknown)	100	NR	0	NR	NR	2
Power <sup>[47]</sup> , 2000, Ireland	PS	Harmonic scalpel (Ultracision, Ethicon Endo-Surgery) and clip	282	101	2	NR	NR	NR
Lee <sup>[28]</sup> , 2011, South Korea	RS	Endo-GIA (US Surgical Corp.) <sup>1</sup>	92 <sup>1</sup>	90	0	NR	4 (D)	NR
Tebala <sup>[29]</sup> , 2006, Italy	RS	Harmonic shears (Ultracision, Ethicon Endo- Surgery)	100	0 (exclusion criterium)	0	1/NR	0	2
Ligature								
Shah <sup>[48]</sup> , 2010, Nepal	PS	Intracorporeal single ligation	80	19	0	NR	NR	NR
Carvalho <sup>[49]</sup> , 2009, Brazil	PS	Surgical knots (2-0 polyester) <sup>4</sup>	1000	NR	0	NR	0	NR
Talebpour, 2007, Iran <sup>[50]</sup>	PS	Absorbable sutures and intracorporeal knots	200	25	0	NR	1 (B)	18
Suo <sup>[36]</sup> , 2013, China	RS	Absorbable thread (VICRYL_ W9215, Ethicon)	1096	296	0	NR / 0	0	NR
Golash <sup>[37]</sup> , 2008, Oman	RS	Intracorporeal ligation (3/0 Vicryl)	1000	NR	0	NR	NR	0
Fullum <sup>[38]</sup> , 2005, United States	RS	Two 2-0 PDS Endoloops (Ethicon Endo-Surgery)	105	22	0	NR	NR	NR
Locking clips								
Leung <sup>[39]</sup> , 1996, Hong Kong	RS	PDS-clip (Ethicon Endo-surgery)	272	94	3	4 intra-peritoneal collections	NR	45 (30 in complicated group)
Clips								
Sinha <sup>[40]</sup> , 2012, India	RS	Ligaclip (titanium clip, Ethicon) <sup>4</sup>	756	NR	4	NR	NR	NR
Agresta <sup>[41]</sup> , 2011, Italy	RS	Titanium clips <sup>4</sup>	932	123	1	NR	NR	NR
Feroci <sup>[32]</sup> , 2011, Italy	RS	Polymeric absorbable clip	664	NR	0	0	NR	NR
Ou <sup>[42]</sup> , 2009, China	RS	Clips	10000	NR	6	NR	0	NR
Ojima <sup>[35]</sup> , 2007, Japan	RS	Clips	1127	NR	3	NR	23	NR
Lee <sup>[33]</sup> , 2004, Taiwan	RS	Clips <sup>4</sup>	1009	78	5	NR/1	2 (D)	NR
Dolan <sup>[43]</sup> , 1999, Northern Ireland	RS	Titanium clips	303	18	0	1 / 0	NR	0
Wise Unger <sup>[30]</sup> , 1996, United States	RS	Clips	22165	NR	58	NR	NR	NR
Feussner <sup>[31]</sup> , 1991, Germany	RS	Clips	178	28	1	NR	NR	NR
Other								
Lewandowski <sup>[34]</sup> , 2006, Poland	RS	LigaSure (Valleylab)	129	NR	0	NR	2 (1B, 1D)	NR

Amsterdam classification was used to identify the severity of the bile duct injuries: B: Major bile duct leaks with or without concomitant biliary strictures; C: Bile duct strictures without bile leakage; D: Complete transection of the duct with or without excision of some portion of the biliary tree. <sup>1</sup>Only in patients with an inflamed and dilated cystic duct (> 1.0 cm); <sup>2</sup>Only in patients with a cystic duct < 5 mm; <sup>3</sup>severity unknown; <sup>4</sup>In patients undergoing MLC (mini LC: three ports) or SILC; <sup>5</sup>Method of closure not described in one study arm, therefore not used as comparative cohort. CDL: Cystic duct leakage; BDI: Bile duct injury; RS: Retrospective study design; PS: Prospective study design; CD: Cystic duct; LC: Laparoscopic cholecystectomy.

duct closure, with event rates around 1%, needs very large sample sizes per studied technique to show a clinically relevant difference. However, 38683 (81.5%) of the 47491 included patients underwent cystic duct

closure with non-locking metal clips, leaving the other techniques of interest possibly underpowered. Also, the Peto odds ratio methods are commonly used in rare events and were used in this review because it was

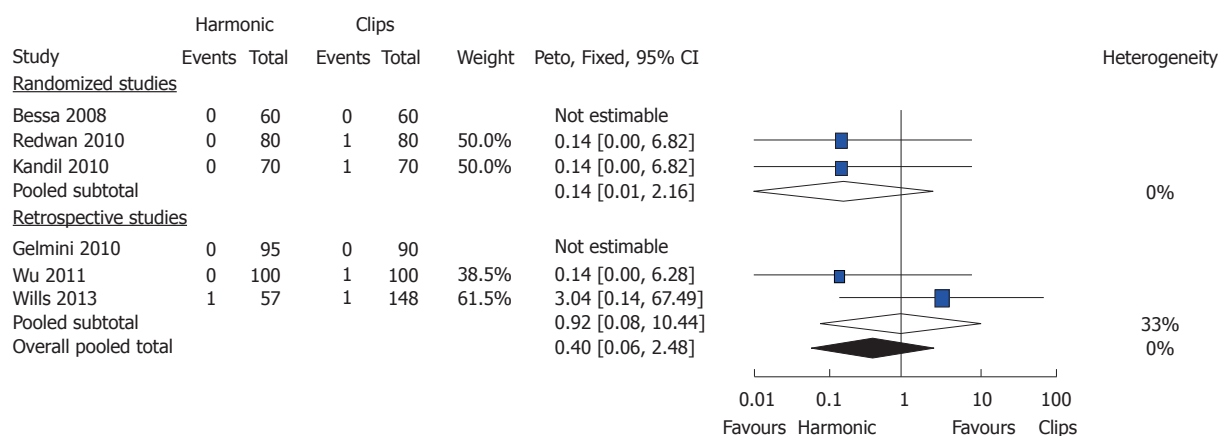


Figure 3 Forest plot on the comparison of harmonic scalpel and metal clips on cystic duct leakage.

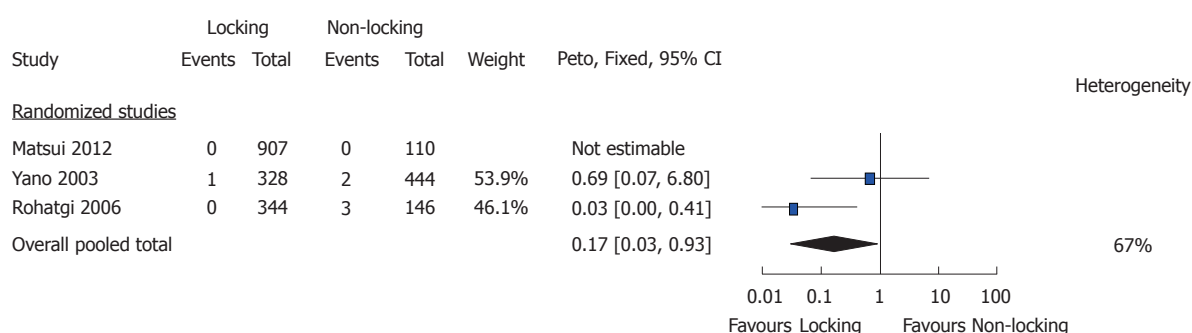


Figure 4 Forest plot on the comparison locking and non-locking clips on cystic duct leakage.

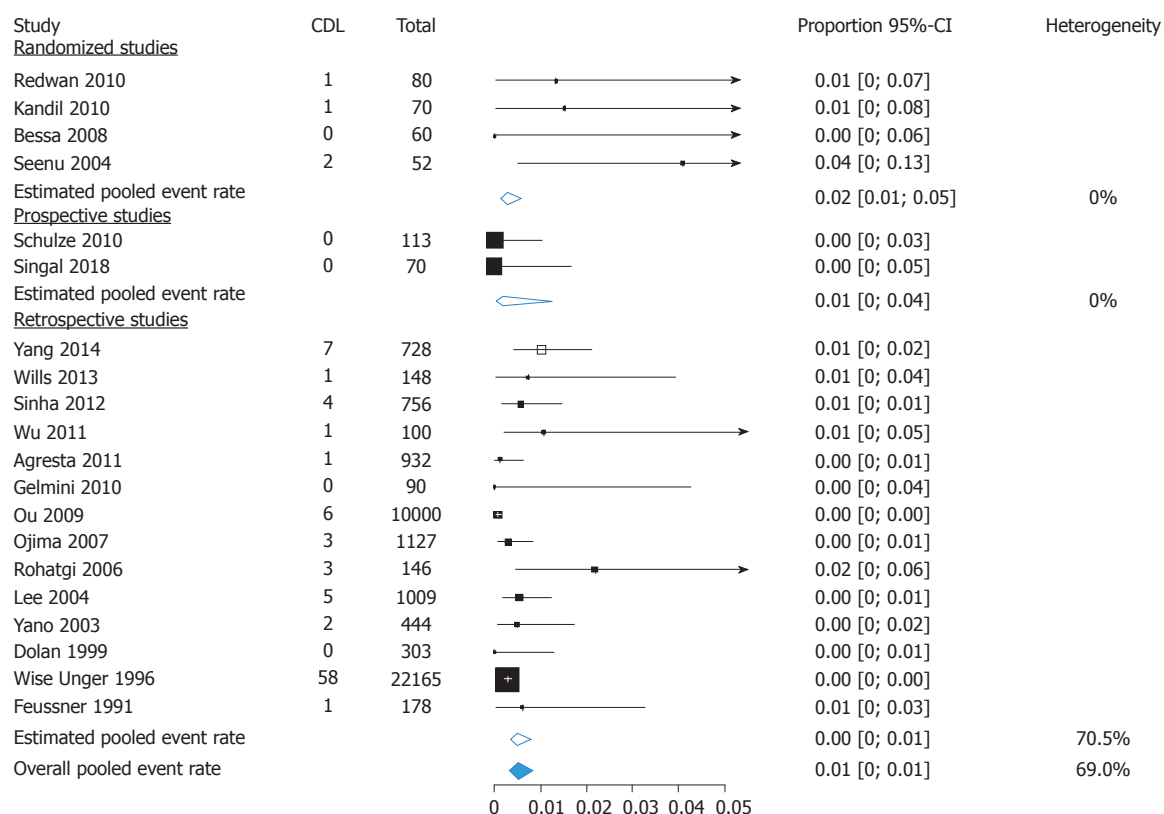


Figure 5 Forest plot of cystic duct leakage following the application of metal clips. CDL: Cystic duct leakage.

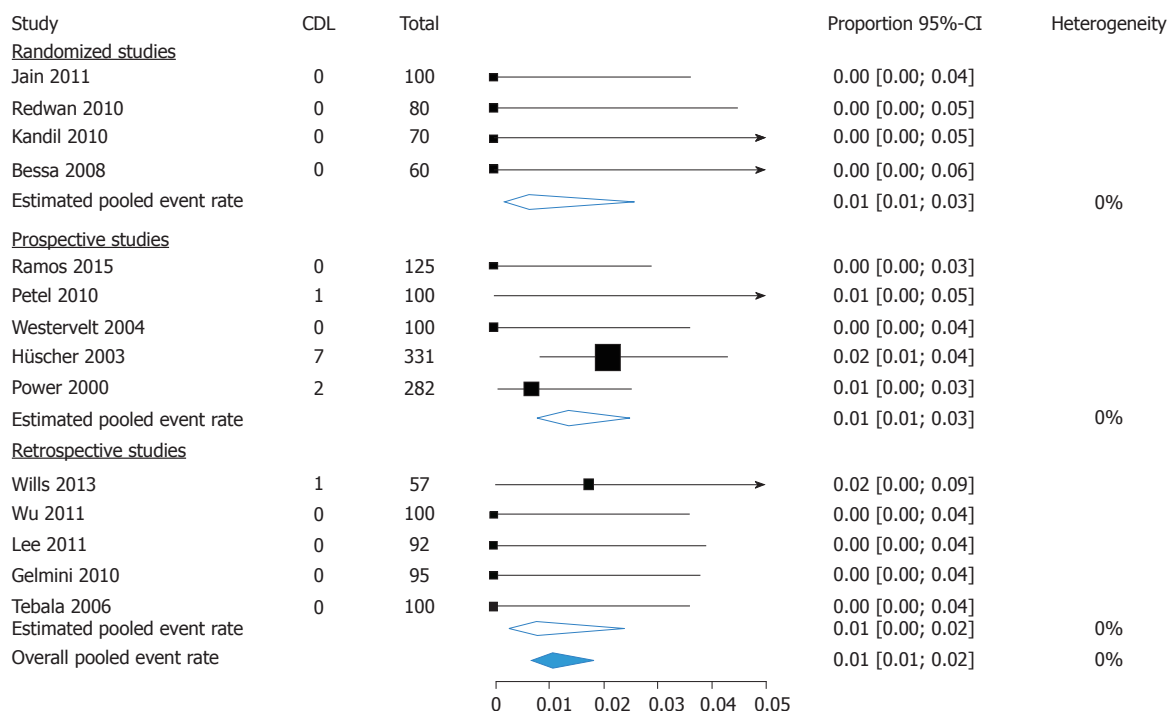


Figure 6 Forest plot of cystic duct leakage following the application of harmonic scalpel/shears. CDL: Cystic duct leakage.

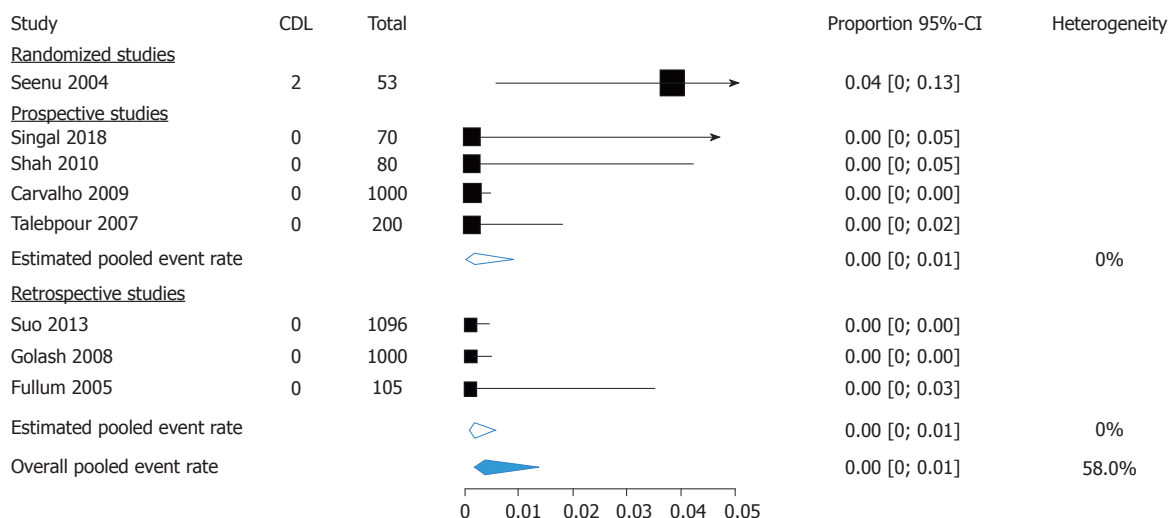


Figure 7 Forest plot of cystic duct leakage following the application of ligature. CDL: Cystic duct leakage.

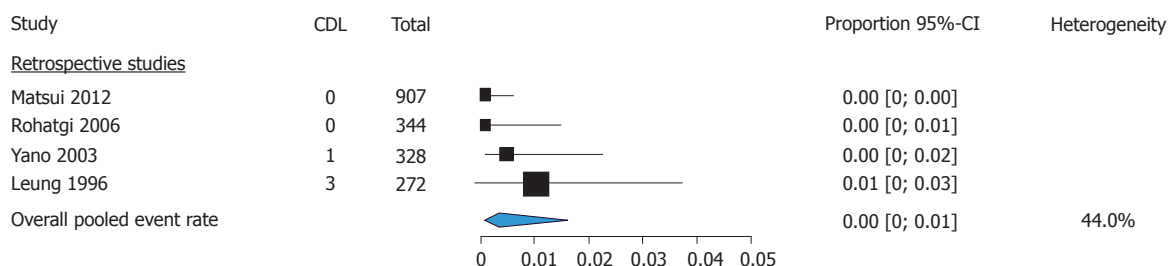


Figure 8 Forest plot of cystic duct leakage following the application of locking clips. CDL: Cystic duct leakage.

the best performing method for pooling our results. Unfortunately, this method does not allow zero events in a group when using it for a comparative analysis, so some included studies in this review could not be used in the pooled comparative analysis. To review the effect of using Peto odds, the same analysis was performed but with 1 event for every group that originally had no events. This resulted in a slightly higher overall pooled event rate, but the effect was very minimal. So, excluding the studies with zero events from the meta-analysis did not result in a big change in the overall pooled event rate. Finally, most studies did not specify cost per particular technique nor cost-effectiveness. Some techniques were clearly more expensive than others, such as the added costs of clip appliers and disposable scalpels/shears. With the ever increasing expenses of our health care system, the choice for a certain method depends in part on the extra costs incurred vs costs saved.

Our group has advocated to report studies on surgery in gallbladder disease in two different entities, uncomplicated and complicated disease<sup>[3]</sup>. In patients with complicated disease, LC is anticipated to be more difficult than in uncomplicated patients. Consequently, higher risk of complications during the procedure and postoperatively can be expected. We recently published that the risk of bile leakage, including CDL, in patients with complicated gallstone disease is underestimated in literature<sup>[3]</sup>. Generally, the rate of CDL is reported between 0.5%-3%, but complicated disease is associated with a CDL rate of 4%-7%<sup>[1,2]</sup>. Based on this risk difference, patients with a high probability of CDL (difficult cholecystectomy) should be included with sufficient high numbers when investigating which technique is superior in cystic duct closure.

It is remarkable that for such a frequently conducted surgical procedure as LC good quality evidence from high sample size trials is lacking to determine which cystic duct closure technique is superior with respect to prevention of CDL. Studies in large populations of patients undergoing LC with or without a high risk of CDL are needed.

## ARTICLE HIGHLIGHTS

### Research background

Cystic duct leakage (CDL) is reported in laparoscopic cholecystectomy (LC) in 0.5%-3% of patients, and is even reported to increase to up to 4%-7% in patients with complicated gallstone disease.

### Research motivation

Although CDL is classified as a minor injury of the bile ducts, it is associated with significant morbidity and even mortality, so adequate closure of the cystic duct is essential to prevent CDL.

### Research objectives

Several techniques are used during cholecystectomy to close the cystic duct, but it is currently unknown which technique has the lowest rate of CDL. The aim of this systematic review was to assess the risk of CDL and the CDL rate for

different techniques of cystic duct closure after LC, both in uncomplicated and complicated gallbladder disease.

## Research methods

A systematic review and meta-analysis was performed according to PRISMA guidelines. A search of MEDLINE, Cochrane and EMBASE was done. Studies were eligible for conclusion when patients underwent cholecystectomy and methods of closure of the cystic duct were described. The primary outcome was leakage of the cystic duct. The risk of bias was evaluated with the MINORS score for non-randomized studies and the Cochrane Library guide for the randomized studies. Odds ratios were analyzed for comparison of techniques and pooled event rates for non-comparative analyses. Pooled event rates were compared for each of included techniques.

## Research results

A total of 1491 articles were found by searching the databases. Out of 1491 articles 102 full texts were screened and 38 articles included. A total of 47491 patients were included, of which 38683 (81.5%) underwent cystic duct closure with non-locking (metal) clips. All studies were of low-moderate methodological quality. Only two studies reported separate data on uncomplicated and complicated gallbladder disease. For overall CDL, an odds ratio of 0.4 (95%CI: 0.06-2.48) was found for harmonic energy vs clip closure and an odds ratio of 0.17 (95%CI: 0.03-0.93) for locking vs non-locking clips. Pooled CDL rate was around 1% for harmonic energy and metal clips, and 0% for locking clips and ligatures.

## Research conclusions

Based on the available evidence as appraised in this systematic review it is not possible to either recommend or discourage any of the techniques for cystic duct closure during LC with respect to CDL. The data do point out a slight preference for locking clips and ligatures vs harmonic energy or (non-locking) metal clips. This is the first systematic review on methods of cystic duct closure that focuses on CDL. As CDL is an important and potentially serious complication of cholecystectomy, this subject should warrant further research.

## Research perspectives

It is interesting to see that no separate recommendation could be made for complicated gallbladder disease as subgroup analysis was not possible due to a lack of reported data per subgroup of complicated and uncomplicated gallbladder disease. It could be hypothesized that cystic duct closure is especially important in these patients and that data on this subject would be readily available. Future research should therefore focus on good quality evidence from high sample size trials that include patients with both uncomplicated and complicated gallstone disease.

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## Inverted Meckel's diverticulum: Two case reports and a review of the literature

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### Abstract

Gastrointestinal surgeons seldom encounter inverted Meckel's diverticulum in their clinical practice. We describe two cases of inverted Meckel's diverticulum. If the patient has a disease-related complication such as intussusception, as with our first case, it can be easily detected. However, if the patient has subacute or chronic symptoms, as with our second case, the diagnosis might be delayed. Regardless of the disease-related complication, intussusception of inverted Meckel's diverticulum can be easily managed with laparoscopic single-port surgery.

**Key words:** Inverted Meckel's diverticulum; Laparoscopic surgery; Intermittent hematochezia; Intussusception; Abdominal pain

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**Core tip:** When clinicians encounter an adult patient complaining of intermittent hematochezia and/or abdominal pain without any evidence of gastrointestinal bleeding after esophagogastroduodenoscopy and co-

lonoscopy, inverted Meckel's diverticulum and other small bowel pathologies must be considered to avoid unwanted complications related to these rare disease entities. Computed tomography scan is a beneficial diagnostic tool to identify small bowel pathology and to differentiate among diverse diseases, including lipomas, inflammatory fibroid polyps, vascular malformations, lymphomas, inverted diverticula and malignant tumors.

Chong EH, Kim DJ, Kim S, Kim G, Kim WR. Inverted Meckel's diverticulum: Two case reports and a review of the literature. *World J Gastrointest Surg* 2018; 10(6): 70-74 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v10/i6/70.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v10.i6.70>

## INTRODUCTION

Meckel's diverticulum is a congenital anomaly that results from persistence of the omphalomesenteric duct at its attachment site to the distal ileum. According to autopsy studies, this condition is found in 2% of the general population<sup>[1,2]</sup>. On average, the diverticulum is located two feet proximal to the ileocecal valve and often contains gastric or pancreatic tissue, causing mucosal bleeding. Patients with Meckel's diverticulum are usually asymptomatic. However, according to a population-based study, untreated Meckel's diverticulum cases are associated with as high as a 6.4% lifetime risk of developing complications requiring surgical treatment<sup>[3]</sup>. The most common presentation of complicated Meckel's diverticulum is gastrointestinal (GI) bleeding; less frequent symptoms include diverticulitis, volvulus and intestinal obstruction with or without intussusception, a condition in which a proximal segment of bowel rolls into a distal part<sup>[4]</sup>. To the best of our knowledge, inversion of a Meckel's diverticulum is rare and has been reported in only a few case series worldwide<sup>[5-8]</sup>.

## CASE REPORT

### Case 1

A 34-year-old man without any underlying disease visited our gastroenterology clinic on October 29, 2014 for melena beginning 5 d earlier. The initial laboratory findings were all within normal ranges, and subsequent esophagogastroduodenoscopy showed no remarkable findings except for several areas of erosive gastritis. The patient was diagnosed with irritable bowel disease, but the symptoms remained intractable after one year of follow-up. On March 16, 2016, the patient complained of hematochezia with left lower quadrant abdominal pain. Emergent sigmoidoscopy was performed but failed to reveal any focus of bleeding. Thereafter, computed tomography (CT) scans revealed small bowel intussusception with segmental thickening of the mucosa (Figure 1A). The patient was referred to the Depart-

ment of General Surgery, and laparoscopic single-port exploration was performed. During the operation, bowel edema at the distal ileum (50-60 cm upstream of the ileocecal valve) was observed, and an intraluminal mass was palpable. Securing the margin, segmental resection of the small bowel with side-to-side stapled anastomosis was performed. The delivered specimen was inspected, and the intraluminal polyp-like mass was exposed (Figure 1B). The patient had an uneventful postoperative course and was discharged 6 d after surgery. Final pathology revealed an inverted intussusception of Meckel's diverticulum with focal heterotopic gastric mucosa (Figure 1C).

### Case 2

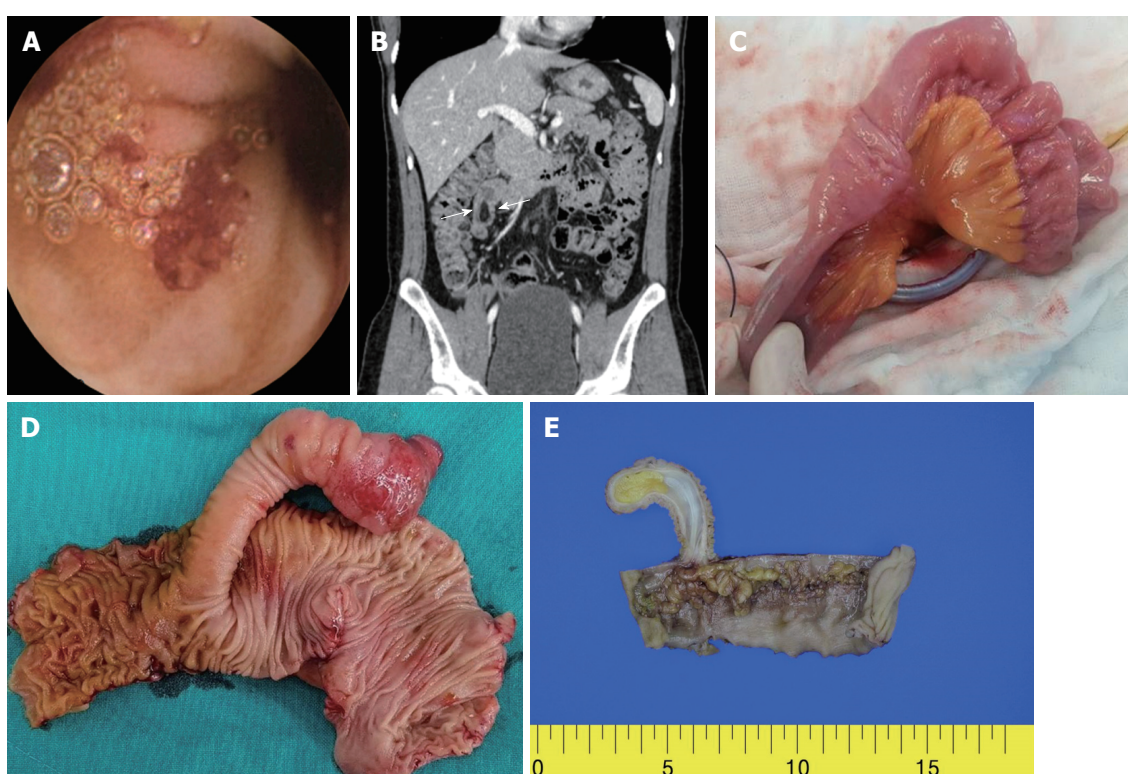
A 27-year-old man with a history of heavy alcohol consumption visited the emergency room on December 31, 2017 for hematochezia beginning 4 d earlier. The initial laboratory findings showed low hemoglobin levels (8.5 g/dL). Serial physical examinations revealed old clots on irrigation through a Levin tube and melena upon digital rectal examination. Upon admission, two pints of packed red blood cells were transfused, and emergent esophagogastroduodenoscopy with sigmoidoscopy failed to reveal intestinal pathology. Therefore, the gastroenterologist decided to perform capsule endoscopy. This procedure revealed small bowel bleeding, but failed to detect intestinal pathology due to low video quality (Figure 2A). A CT scan revealed small bowel intussusception at the distal ileum with a possible 2 cm lipoma (Figure 2B). After a diagnosis of intussusception, the patient was referred to the Department of General Surgery. On January 4, 2018, laparoscopic single-port exploration was performed. During surgery, the intussusception at the distal ileum with a palpable club-like intraluminal mass was detected (Figure 2C), and segmental small bowel resection with end-to-end anastomosis was performed. While exploring the specimen, a large polyp-like mass with mucosal ulceration at the tip was demonstrated in the small bowel (length 6 cm, width 1.5 cm). The patient had an uneventful postoperative course and was discharged 6 d after surgery. The final pathology revealed that the mucosa showed a finger-like projection with normal mucosa and a surface ulceration measuring 5 cm × 2 cm × 2 cm (Figure 2D). Upon sectioning of the finger projection, the cut surface showed serosa infolding with mesenteric tissue, consistent with an inverted diverticulum causing intussusception without heterotopic tissue (Figure 2E).

## DISCUSSION

The mechanism of inversion in Meckel's diverticulum is still not clearly understood. One possible explanation is that abnormal peristaltic movement around an ulceration or ectopic tissue at Meckel's diverticulum may cause inversion<sup>[9]</sup>. Inverted Meckel's diverticulum can cause two clinical manifestations: GI bleeding and intussusception,



**Figure 1** Inverted Meckel's diverticulum causing intussusception with focal heterotopic gastric mucosa. A: Computed tomography scan: small bowel intussusception with segmental thickening of mucosa at the distal ileum; B: Bowel edema at the distal ileum (50-60 cm upstream from ileocecal valve) with a polyp-like mass; C: Inverted intussusception of Meckel's diverticulum with focal heterotopic gastric mucosa. White arrow: typical target sign; yellow circle: goblet cells; yellow arrow: pyloric glands; red arrow: foveolar epithelium; blue arrow: small intestinal epithelium.



**Figure 2** Inverted Meckel's diverticulum causing intussusception without heterotopic tissue. A: Capsule endoscopy: small bowel bleeding, but failed to detect intestinal pathology; B: Computed tomography scan: small bowel intussusception at the distal ileum with possible 2 cm sized low-density mass (white arrow); C: Laparoscopic finding: the intussusception at the distal ileum with palpable club-like intraluminal mass; D: Finger-like projection with normal mucosa and surface ulceration; E: Section of finger-like projection: serosa in folding with mesenteric tissue, consistent with inverted diverticulum causing intussusception without heterotopic tissue.

as in our two cases. Most complaints are of hematochezia and/or melena due to ulceration of the inverted Meckel's diverticulum. Ulceration may be caused by ectopic gastric or pancreatic tissues in the inverted Meckel's diverticulum itself, but can also occur without accompanying abnormal ectopic tissues. The latter can be explained by repetitive mechanical trauma to the mucosa from the reversible intussusception.

CT is a common tool for diagnosing intussusception in the small intestine. A characteristic coiled spring appearance or target sign are well-known findings on CT scans. However, if the patient visits the clinic complaining

of melena or hematochezia without abdominal pain, as in Case 2, the diagnosis may be delayed. Pantongrag-Brown *et al*<sup>[8]</sup> reported that approximately 80% of patients with inverted Meckel's diverticulum complained of subacute or chronic symptoms, including GI bleeding, intermittent abdominal pain, or other signs of low-grade small bowel obstruction<sup>[8]</sup>. Although capsule endoscopy can help confirm small bowel bleeding, as in Case 2, routine use of this device for diagnosing small bowel bleeding must be done with caution. This caution is necessary not only due to low video quality and its limitations regarding exact location of the intestinal pathology<sup>[10]</sup>, but also

because of the increased risk of intestinal obstruction. On the other hand, CT scans are much more beneficial for the identification of small bowel pathology and differentiation of diverse diseases, including lipomas, inflammatory fibroid polyps, vascular malformations, lymphomas, inverted diverticula and malignant tumors. Inverted Meckel's diverticulum is sometimes confused with lipoma on CT scans. However, findings of an intraluminal polypoid lesion in the small intestine covered with a thick collar of enhancing soft tissue may be a decisive indicator of inverted Meckel's diverticulum as opposed to lipoma, which appears on CT scans only as a thin covering over the low-density fatty mass<sup>[5]</sup>.

Intermittent and/or small amounts of GI bleeding can be easily detected by Tc<sup>99m</sup> RBC scintigraphy, where the minimum detectable bleeding rate was reported as 0.05-0.2 mL/min; relatively stable persistence in the circulation made it possible to monitor patients with intermittent bleeding<sup>[11]</sup>. Scintigraphy could have been used to locate the bleeding focus in the first case. However, according to the gastroenterologist, they initially thought that the chronic intermittent hematochezia in this patient was due to a hemorrhoid. This was why the patient was followed by a local gastroenterology clinic for one year. Subsequently, the patient was admitted to the emergency room complaining of hematochezia with abdominal pain. CT scans were used to evaluate the cause of the left lower quadrant pain but not the hematochezia in this case. In the second case, scintigraphy could have been used to evaluate the cause of melena. However, the gastroenterologist decided on capsule endoscopy, revealing GI bleeding in the small intestine. According to the gastroenterologist, scintigraphy was not considered at that moment because the bleeding from the small intestine was already confirmed by capsule endoscopy and because CT scans are performed to reveal underlying pathologies causing GI bleeding in adults. CT angiography can be considered if the GI bleeding is active. The detection limit of CT angiography for active bleeding was 0.3 mL/min in porcine models<sup>[11]</sup>. Our cases were regarded as having chronic and intermittent GI bleeding, not active bleeding.

Although the gastroenterologist had 30 years of experience, they performed capsule endoscopy in the second case. They expected to find small bowel pathology but failed to do so. Apart from low video quality, if the capsule was obliterated by small bowel pathologies, the patient might experience intestinal obstruction, leading to increased morbidity related to surgery. Following this report, we hope clinicians worldwide will be cautious regarding the use of capsule endoscopy to evaluate the cause of GI bleeding in adults.

Currently, small bowel intussusception in adults, regardless of cause, requires prompt surgical management, such as segmental resection of the small bowel. A thorough appreciation of the characteristic CT scan findings of inverted diverticulum (as opposed to those of malignant tumors such as lymphoma) may help create

an appropriate surgical approach.

## ARTICLE HIGHLIGHTS

### Case characteristics

The chief complaint of adults with inverted Meckel's diverticulum is intermittent hematochezia, melena and/or abdominal colicky pain.

### Clinical diagnosis

If an adult patient has chronic intermittent abdominal pain, melena, hematochezia, and/or complaints of intestinal obstruction, inverted Meckel's diverticulum with intussusception should be considered.

### Differential diagnosis

CT scans would be beneficial for differentiating among other diseases such as lipoma, inflammatory fibroid polyps, vascular malformations, lymphoma, and malignant tumors.

### Laboratory diagnosis

In cases of intermittent hematochezia and/or melena, hemoglobin level would reveal anemia.

### Imaging diagnosis

A characteristic coiled spring appearance or target sign are well known findings on CT scans.

### Pathological diagnosis

Full-thickness inversion of diverticulum with or without heterotopic tissues such as stomach, pancreas *etc.* in hematoxylin and eosin staining would be the main finding of inverted Meckel's diverticulum.

### Treatment

Small bowel intussusception in adults, regardless of cause, requires prompt surgical management, such as segmental resection of the small bowel.

### Related reports

Meckel's diverticulum is a congenital anomaly of the omphalomesenteric duct remnant attached to the distal ileum and, when left untreated, the lifetime risk of developing complications requiring surgical treatment can be as high as 6.4%

### Term explanation

Intussusception means a condition in which a proximal segment of bowel rolls into a distal part and causes intestinal obstruction.

### Experiences and lessons

Following this report, we hope clinicians worldwide will be cautious regarding the use of capsule endoscopy to evaluate the cause of gastrointestinal bleeding in adults.

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- 75 Current role of palliative interventions in advanced pancreatic cancer

*Ciambella CC, Beard RE, Miner TJ*

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# Current role of palliative interventions in advanced pancreatic cancer

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## Abstract

Pancreatic adenocarcinoma is the third leading cause of cancer death in the United States. Unfortunately, at diagnosis, most patients are not candidates for curative resection. Surgical palliation, a procedure performed with the intention of relieving symptoms or improving quality of life, comes to the forefront of management. This article reviews the palliative management of unresectable pancreatic cancer, including obstructive jaundice, duodenal obstruction and pain control with celiac plexus block. Although surgical bypasses for both biliary and duodenal obstructions usually achieve good technical success, they result in considerable perioperative morbidity and mortality, even when performed laparoscopically. The effectiveness of self-expanding metal stents for biliary drainage is excellent with low morbidity. Surgical gastrojejunostomy for duodenal obstruction appears to be best for patients with a life expectancy of greater than 2 mo while endoscopic stenting has been shown to be feasible with good symptom relief in those with a shorter life expectancy. Regardless of the palliative procedure performed, all physicians involved must be adequately trained in end of life management to ensure the best possible care for patients.

**Key words:** Surgical palliation; Duodenal obstruction; Hepatojejunostomy; Gastrojejunostomy; Endoscopic stenting; Malignant ascites; Celiac block; Palliative triangle; Pancreatic cancer; Obstructive jaundice

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**Core tip:** Unfortunately, at the time of diagnosis most patients with pancreatic cancer are not candidates for curative resection. Surgical palliation, a procedure performed with the intention of relieving symptoms or improving quality of life, comes to the forefront of

management. The majority of palliative care focuses on three high burden symptoms: obstructive jaundice, duodenal obstruction and tumor-related pain. There exists a wide range of interventions including both operative and non-operative techniques. Regardless of the palliative procedure, all physicians involved must be adequately trained in end of life management to ensure the best possible care for patients.

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## PANCREATIC CANCER INTRODUCTION

The incidence of and number of deaths caused by pancreatic tumors have been slowly increasing. It is estimated that in 2018, 55440 new cases of pancreatic cancer will be diagnosed in the United States with a five-year survival of only 8.5%. Of newly diagnosed cancers, 29% will have regional spread and 52% will already be metastasized<sup>[1]</sup>. Patients with pancreatic cancer are often asymptomatic until the disease develops to an advanced stage and thus have a low cure rate. Surgery is the only curative treatment but only 20% of patients are suitable for a curative resection<sup>[2]</sup>. Therefore, surgeons must determine which patients have incurable disease, preoperatively or intraoperatively, and be well versed in surgical and nonsurgical options in regards to palliative care. Palliation for pancreatic cancer is often centered around three high burden symptoms: obstructive jaundice, duodenal obstruction and tumor-related pain.

## GOALS OF PALLIATIVE INTERVENTION

Surgeons by necessity manage many patients at the end of life and have been at the forefront in the movement toward palliative care for decades. There exists a wide range of multidisciplinary treatments and a surgeon must consider which palliative intervention may aid in symptom relief from the advanced malignancy. Important factors to consider are the likelihood of symptom improvement, quality of life, pain control, and cost-effectiveness. The palliative phase of care should focus on reducing morbidity, mortality and duration of treatment. Symptom palliation may improve survival but it is not appropriate to select a procedure for that reason alone<sup>[3-6]</sup>.

There have been a variety of definitions of palliative care put forth in the literature that has led to confusion in understanding the role of palliative operations. Historically, the term "palliative" has had an assortment of meanings. In an effort to help clarify the term the

World Health Organization (WHO) has put forth a definition of palliative care as "the total active care of patients whose disease is not responsive to curative treatment". Control of pain, of other symptoms, and of psychological, social, and spiritual problems is paramount. The goal of palliative care is the achievement of the best quality of life for patients and their families<sup>[7]</sup>. While this definition broadly characterizes palliative, it does not illuminate the diverse goals of surgical palliation. Patients with advanced malignancy comprise a range of diverse clinical scenarios requiring surgery that it makes valid comparisons of outcomes difficult. Emphasis on maintaining an individualized approach is crucial as the same palliative procedure may have very different aims for each patient.

Surgical palliation is best defined as "the deliberate use of a procedure in a patient with incurable disease with the intention of relieving symptoms, minimizing patient distress, and improving quality of life"<sup>[4,5,7-9]</sup>. Palliative care is total care and not the opposite of a cure. Palliative decision-making should focus on attainable results that improve quality of life and symptom control for patients<sup>[8]</sup>.

A customized approach requires effective communication between the patient, the family, and the surgeon. The palliative triangle has been put forth as a model to assist in the challenging clinical decision making when deliberating the most appropriate palliative surgical procedures<sup>[4,6]</sup>. The model was first created to explore high patient satisfaction after palliative operations even with poor rates of morbidity, mortality, and overall survival<sup>[4]</sup>. The palliative triangle enables the patient's symptoms, hopes, fears, beliefs, and psychological support to be considered with operative and non-operative options to craft a palliative intent agreed upon by all parties and thus fostering shared decision-making<sup>[4,5,8,9]</sup>. In a recent study including patients with pancreatic cancer, appropriate patient selection for palliative surgery was determined by the palliative triangle approach. Using this stratification there was improvement in symptom resolution, overall survival, 30-d morbidity and mortality compared to prior studies<sup>[9]</sup>.

The intent behind the procedure is what transforms a palliative operation into a tool to accomplish a goal<sup>[3]</sup>. At the crux of palliative decision-making is quality not quantity of life. The foundation of palliative care is built upon the compassion a physician has for his terminally ill patient and is predicated on effective communication. The palliative triangle model can guide surgeons as they address and relieve the most common and debilitating symptoms of advanced pancreatic cancer: obstructive jaundice, duodenal obstruction and pain. A successful palliative intervention is one that provides durable symptom relief for a patient.

## OBSTRUCTIVE JAUNDICE

Approximately half of newly diagnosed pancreatic

cancers occur within the head of the pancreas. Many of these patients present with jaundice, as the intra-pancreatic portion of the bile duct becomes obstructed by the mass<sup>[10]</sup>. The decrease excretion of bile acids into the duodenum results in pruritus and fat malabsorption that may increase risk of bleeding due to decreased absorption of fat soluble vitamin K and subsequently impaired synthesis of vitamin K dependent coagulation factors<sup>[11]</sup>. Patients require intervention as cholestasis can result in liver dysfunction and eventually failure. Interventions to decompress the obstructed bile duct include endoscopic stenting, percutaneous external drainage and operative biliary bypass.

### **Endoscopic stent placement**

In patients who are diagnosed with unresectable disease at initial encounter, placement of an endoscopic biliary stent for biliary obstruction is the favored palliative intervention. Endoscopic stenting may also be the best definitive therapy for patients with poor performance status or short life expectancy. The procedure involves cannulation of the bile duct and guidewire placement. Then endoscopic retrograde cholangiography is performed typically with sphincterotomy, which facilitates the insertion of the prosthesis. Since the 1990s endoscopic technology has improved with randomized studies demonstrating that endoscopic stenting is feasible in over 90% of patients<sup>[12]</sup>. However, stents can become occluded resulting in cholangitis or pancreatitis. Stents can also migrate leading to the need for re-intervention<sup>[13]</sup>.

Bliss *et al*<sup>[14]</sup> performed a retrospective analysis of unresected pancreatic cancer patients between 2007-2011 who received surgical bypass or endoscopic stenting for biliary obstruction. Among propensity score-matched patients mortality and readmission rates were similar. Patients in the endoscopic group had a lower median length of stay and cost. Also, those in the endoscopic group were more likely to be discharged home. However, 20.3% (63) of endoscopic compared to 4.5% (14) of surgical patients underwent reintervention, with endoscopic group having higher rate of obstructive complications including cholangitis, evidence of biliary obstruction, and acute pancreatitis<sup>[14]</sup>.

Advances in stent development have resulted in several available endostents including plastic, uncovered or partially covered metal. Walter *et al*<sup>[15]</sup> performed a multicenter randomized trial to explore which stent enables successful and durable palliation of extrahepatic biliary obstruction: a plastic stent, an uncovered self-expanding metal stent (SEMS) or a partially covered SEMS. The study included 219 patients in The Netherlands from February 2008 through February 2013. Functional durability of uncovered stents was 288 d and for partially covered metal stents was 299 d. However, the durability for plastic stents was only 172 d. Median survival was 109 d overall, 80 d in patients with metastatic disease. When examining cost from initial

endoscopic retrograde cholangiography until 1 year later there was no significant difference between the SEMS arms and the plastic stents. Thus, Walter *et al*<sup>[16]</sup> determine that SEMS should be used for palliation of malignant extrahepatic biliary obstruction. Furthermore health-related quality of life (HRQoL) scores remained stable over time in SEMS arms, whereas HRQoL deteriorated over time in patients with a plastic stent<sup>[15,16]</sup>. Reduction in jaundice and pruritus was seen in both groups but SEMS endorsed significantly less fatigue, decrease in nausea and vomiting resulting in improved appetite.

### **Transhepatic biliary drainage**

Percutaneous drainage is an alternative if endoscopic biliary stent placement is unsuccessful or technically not feasible. The placement of a transhepatic biliary catheter involves percutaneously entering the liver with a needle. Percutaneous access also allows for internal metal stent or drain placement once the guidewire is properly positioned. If an external drain is left additional procedures are common, including routine catheter changes, and major complications including hospitalization for catheter exchange due to malfunction or leakage. Despite this, percutaneous drain placement has been useful in significantly reducing pruritus<sup>[17]</sup>. New interventions such as endoscopic ultrasound (EUS)-guided biliary drainage are being explored as additional options for occasions when endoscopic retrograde cholangiography stent placement is unsuccessful<sup>[18]</sup>.

### **Surgical biliary bypass**

If unresectable disease is found during laparotomy, an open biliary-enteric bypass provides effective palliation of biliary obstruction. Also, if endoscopic or percutaneous palliation of jaundice is not feasible a palliative biliary bypass may be planned.

Open, laparoscopic and robotic techniques can be used to bypass malignant obstructions *via* anastomosis of bile duct to the duodenum or jejunum. Jejunal bypass is employed more frequently as cancer growth could dehiscence or obstruct a duodenal anastomosis. A Roux-en-Y reconstruction is typically used as it reduces the risk of cholangitis from enteric reflux into the biliary tree<sup>[19]</sup>.

The traditional biliary bypass is a Roux-en-Y choledochojejunostomy or hepaticojejunostomy. First a cholecystectomy is performed<sup>[19]</sup>. Then the common bile duct or hepatic duct is transected. The distal end of the bile duct is sutured closed. An approximately 40 cm to 60 cm in length roux limb is anastomosed end-to-side to a jejunal limb roughly 20 cm distal to the ligament of Treitz. The biliary-enteric anastomosis is created with interrupted 4-0 PDS or Vicryl suture or, if previous obstruction resulted in an enlarged duct the suture may be placed in a continuous fashion<sup>[20]</sup>. There are other options for creating a biliary enteric anastomosis, including using a side-to-side technique and a loop

hepaticojejunostomy (or choledochojejunostomy) can be performed. Patient anatomy, surgeon preference and operative modality all contribute.

The robotic system is emerging as a feasible and effective option for palliative biliary bypass. There are several unique advantages of the robotic system, which overcome the obstacles of conventional laparoscopic surgery such as improved visualization with a three-dimensional camera, increase dexterity with a platform that offers the seven degrees of movement as a human wrist does, and improved ergonomics<sup>[21]</sup>. A small study demonstrated robotic hepaticojejunostomy for advanced malignant biliary obstruction in nine patients, four with pancreatic head cancer. There were five patients who received Roux-en-Y hepaticojejunostomy and four patients who underwent double bypass. There was no procedure-related mortality<sup>[21]</sup>. The post-operative stay was 13.3 d. Future studies comparing laparoscopic and robotic approaches are needed.

## DUODENAL OBSTRUCTION

Duodenal obstruction can be caused by duodenal invasion of pancreatic head tumors or pancreatic body tumors invading the duodeno-jejunal junction. Intestinal obstruction causes nausea, vomiting and poor oral intake, which can compromise quality of life and put patients at risk of dehydration and malnutrition. It has been estimated that 10%-25% of all patients with pancreatic cancer will develop symptomatic duodenal obstruction<sup>[22]</sup>. Rates as high as 38% have been reported in patients with pancreatic head adenocarcinoma<sup>[23]</sup>. Duodenal obstruction usually occurs late in the disease process. Traditional management was centered on open gastrojejunostomy (GJ). More recently minimally-invasive surgical GJ and endoscopic stenting have been introduced as alternatives.

### Endoscopic stenting technique

Endoscopic stenting of the duodenum with SEMS is one option to relieve malignant obstruction. The stents are uncovered stents enabling them to lodge into the stricture and adjacent tissue. Metallic stent placement has been increasingly used as a minimally invasive method with the development of the through-the-scope stent placement (TTS) as opposed to earlier per-oral or percutaneous approach under fluoroscopic guidance. Once the stents are deployed they range from 18 to 12 mm in caliber and extend a length of 6 to 12 cm<sup>[24]</sup>.

The procedure is performed under conscious sedation. An upper endoscope is employed to identify the stenosis. A guidewire is then inserted through the working channel of the endoscope and advanced distal to the obstruction. To permit adequate stent margin the stent length should enable 2 cm of overlap in both directions. Then, the SEMS system can be delivered over the guidewire and positioned so the undeployed

stent covers the stenosis proportionately. Lastly, the stent is deployed and placement and luminal patency are verified endoscopically and fluoroscopically<sup>[25,26]</sup>.

Patients with malignant duodenal obstruction may also have concurrent biliary obstruction. It is advised to place a biliary stent, as detailed above, before duodenal stenting in patients with existing or imminent biliary obstruction. If the duodenal stent is done prior, biliary stenting is very difficult so the biliary drainage must always precede the duodenal stent placement<sup>[27]</sup>.

### Endoscopic stenting indications and outcomes

Endoscopic stenting provides a therapeutic option for patients who are poor surgical candidates. Presence of carcinomatosis or malignant ascites would result in patients being at high-risk category for surgery. Furthermore, the patient's expected survival based on their disease course must be considered. In a multi-center study involving 176 patients with predominately pancreatic tumors obstructing the stomach and duodenum, stent deployment was technically successful in 173 patients. Oral intake was sustained for a median of 146 d in 84% of patients<sup>[28]</sup>.

Mittal *et al*<sup>[29]</sup> compared outcomes for 16 patient who had open GJ, 14 patients who had laparoscopic GJ and 16 patients who underwent endoscopic stenting who were matched for age, sex, ASA grade and level of obstruction. Patients who underwent endoscopic stenting resumed oral intake the same day while it took 6 d in the open GJ group and 4 d in the laparoscopic GJ group ( $P < 0.001$ ). The surgical groups had higher rate of complications (pneumonia, ileus, wound infection and sepsis) compared with the endoscopically treated group ( $P = 0.016$ ). The length of stay after procedure was 2 d in the endoscopic stenting group, 7 d in laparoscopic GJ group and 10 d in the open GJ group<sup>[29]</sup>.

Several studies have demonstrated a decrease in the time to tolerate oral intake, shorter length of stay after the procedure and lower complication rate for stented patients compared to surgical GJ<sup>[29,30]</sup>. Although similar survival rates have been described a small study in 2006 comparing enteral stent (24 patients) to open GJ (17 patients) found the 30 d mortality rate was decrease in the enteral stent group (16.6% vs 29.4%)<sup>[26]</sup>.

Reinterventions have been shown to be higher after stent placement due to recurrent obstructive symptoms. Symptom recurrence is attributed to tumor ingrowth and stent migration<sup>[31]</sup>. Despite recurrence, additional duodenal stent placement has been shown to be feasible and effective<sup>[31,32]</sup>. Stent design continues to advance and covered stents were designed to mitigate tumor ingrowth, but were found to have a high rate of migration<sup>[33]</sup>. Now, partially covered stents are being investigated and outcomes may continue to improve. Furthermore, clinical trials are underway in patients with pancreatic cancer exploring if there is symptom

improvement with pyloric stent in addition to the duodenal stent<sup>[34]</sup>.

### **Palliative GJ surgical technique**

Traditionally, surgical GJ was performed for palliation of duodenal obstructions. The distal stomach is anastomosed to the jejunum in the antecolic approach. In the retrocolic approach a jejunal loop is positioned through the transverse colon mesentery.

An open approach begins with an incision in the upper midline of the abdomen. In an antecolic GJ a portion of the distal stomach is connected to a jejunal section located 15–20 cm distal to the ligament of Treitz. In a retrocolic GJ the transverse colon is raised cephalad to find an avascular section of mesentery to pass the jejunal loop through. A two-layer suture, single layer suture, or a stapled anastomosis can be performed depending on surgeon preferences. One option to decrease risk of bowel herniation is placement of sutures from mesentery to jejunum. Lastly, the midline incision is closed in the usual fashion<sup>[34,35]</sup>. GJ can also be performed laparoscopically or robotically.

As mentioned earlier, the robotic system is emerging as a feasible and effective option for palliative bypass. A small study performed double (hepaticojejunostomy, and GJ) in four patients with pancreatic head cancer. There was no procedure-related mortality<sup>[21]</sup>. The post-operative stay was 13.3 d. Future studies comparing laparoscopic and robotic approaches are needed.

### **Palliative GJ indications and outcomes**

Surgical duodenal bypass procedures may be preferred in a patient population with relatively longer life expectancy, as they would benefit from the durability of surgical palliation. A multicenter randomized trial, the SUSTENT study, was conducted in The Netherlands and found long-term relief was better after GJ compared to stent placement in regards to food intake, major complications, recurrent obstructive symptoms, and reinterventions. Patients were observed for a period of two months following operation. The authors determined a palliative GJ is preferable in patients expected to live at least two months, but recommended stenting for patients with a life expectancy less than that<sup>[36]</sup>. Importantly, delayed gastric emptying is a common complication after GJ that can lead to prolonged hospitalization and time without oral intake.

One study from 1998 compared the short-term outcomes of open GJ (22 patients) to laparoscopic GJ (9 diagnosis-matched controls) for the palliation of gastric outlet obstruction caused by advanced pancreatic cancer. Mortality, overall morbidity, operating time, time to oral solid food intake, and survival were not significantly different between the 2 groups. However, estimated blood loss and hospital stay were significantly reduced in the laparoscopic group<sup>[37]</sup>.

In 2004, Mittal *et al.*<sup>[29]</sup> found the laparoscopic surgery correlated with a lower complications, a shorter

hospital stay, and a shorter time to tolerate a diet vs an open surgery. Increased laparoscopic training likely contributed to improvement in short-term outcomes in the laparoscopic group. Much of the literature has patient cohorts with a variety of malignancies and studies comparing open GJ and laparoscopic GJ in patients with only pancreatic cancer are sparse.

### **Prophylactic GJ**

Even with thorough preoperative staging including three-dimensional imaging techniques, which have continued to improve over time, between 8% and 33% of patients, are found to be unresectable at the time of laparotomy<sup>[38]</sup>. There remains controversy over the best course when converting from a surgery with curative intent to a non-curative procedure for patients without duodenal obstruction symptoms pre-operatively.

In 1999, a prospective, randomized trial explored the need of prophylactic GJ in unresectable pancreatic cancer discovered at time of surgery. Eighty-seven patients with no evidence of intestinal obstruction were randomized to receive either a GJ or no GJ. Performing a GJ did not influence morbidity, mortality or length of hospital stay. No patients experienced late gastric outlet obstruction in the GJ group, but 19% of patients in the no-GJ group required subsequent bypass for gastric outlet obstruction<sup>[39]</sup>. Thus, the authors recommended prophylactic GJ in all patients found to be unresectable at laparotomy.

In another randomized study from 2003, 65 patients with unresectable periampullary cancer discovered at laparotomy were randomized to double bypass or hepaticojejunostomy only. Gastric outlet obstruction developed in (5.5%) who underwent double bypass as compared (41.4%) treated with hepaticojejunostomy alone. The postoperative hospital stay, morbidity, and survival between the two groups were not significantly different. The authors concluded that the most appropriate palliative surgery would include prophylactic GJ completed at the time of hepaticojejunostomy in all patients to minimize the risk of postoperative gastric outlet obstruction<sup>[40]</sup>. The trial was terminated early due to the superiority of the double bypass.

More recently, studies have shown increased morbidity and mortality among patients who receive a palliative procedure at the time of laparotomy. Spanheimer *et al.*<sup>[41]</sup>'s retrospective study published in 2014 found duodenal bypass compared to laparotomy only did not decrease the future need for intervention of gastric outlet obstruction in the cohort examined. Insulander *et al.*<sup>[42]</sup>'s retrospective observational cohort study from 2016 demonstrated longer overall survival in patients who received chemotherapy after laparotomy alone versus laparotomy with double bypass. This may be reflective of the improvement in chemotherapy options for pancreatic cancer in the past several years. Each patient is unique and most recent data suggests that surgical bypass procedures should be performed

only in selected patients.

## MALIGNANT ASCITES

Peritoneal carcinomatosis, which is one of the most frequently encountered modes of metastasis in pancreatic cancer, can result in symptomatic ascites<sup>[43]</sup>. Conventional modalities for managing malignant ascites include sodium restricted diets, diuretic therapy and serial paracentesis<sup>[44]</sup>. Paracentesis is used most frequently. Fischer described a simple technique of inserting a 14-gauge needle with a catheter into the peritoneal cavity enabling multiple liters to be drained<sup>[45]</sup>. However, symptom resolution is usually less than 72 h. Newer therapies are being investigated such as radical cytoreductive surgery combined with intraperitoneal chemotherapy with hyperthermia (known as HIPEC)<sup>[44]</sup>. Even in patients who are not candidates for cytoreductive surgery, hyperthermic intraperitoneal perfusion chemotherapy *via* a catheter placed by minimal invasive laparoscopic approach has been shown as a valuable treatment. A multi-institutional analysis in fifty-two patients with a variety of primary tumors demonstrated resolved ascites in 94% of patients using laparoscopic HIPEC. Mean hospital stay was 2.3 d with a median survival of 14 wk. Postoperative complications consisted of two minor wound infections and one deep vein thrombosis. Laparoscopic HIPEC has been well demonstrated as an effective intervention to palliate malignant ascites<sup>[44,46]</sup>.

## TUMOR RELATED PAIN

Approximately 75% of patients will present with abdominal or back pain<sup>[47]</sup>. Location of tumor is crucial in determining presenting symptoms as patients with pancreatic head tumors tend to have jaundice but those with tumors in the body or tail tend to have abdominal pain<sup>[48]</sup>. Tumor can invade into mesenteric or celiac nerve plexus which may result in the classic epigastric pain. Most cancer related pain is treated by pharmacological oral treatments. The WHO put forth an analgesic ladder, with a progressive administration of non-opioids then adding opioids in increasing strength as needed. Managing pain as best as possible is of utmost importance since uncontrolled pain has been correlated with depression and decrease quality of life<sup>[49]</sup>. Additional modalities must be considered to adequate control pain.

### Celiac plexus block

The celiac plexus is a nerve cluster in proximity to the celiac artery. Parasympathetic nerves to the viscera are located here in addition to pancreatic nociceptive fibers<sup>[50]</sup>. The block is chemical, usually consisting of ethanol or local anesthetic. The procedure can also be performed open, laparoscopically, percutaneously,

endoscopically or thoracoscopically<sup>[51]</sup>.

For patients with unresectable disease at presentation EUS-guided celiac plexus neurolysis is preferred. The neurolytic agent is injected around the celiac trunk using a linear-array echo endoscope. Celiac plexus neurolysis can also be performed during diagnostic EUS. Diagnostic EUS has been shown to result in improved pain relief and prevent progressive increases in opioid use<sup>[51]</sup>. Safety may be improved with EUS since color Doppler enables real-time visualization of blood vessels surrounding the gastric lumen can be imaged as opposed to traditional percutaneous technique<sup>[52]</sup>.

Celiac plexus block can be performed intra-operatively by a laparoscopic or open approach for patients found to have unresectable disease at laparotomy. The laparoscopic approach is performed under ultrasound guidance and the probe has a small channel to guide the needle directly. In the open technique, the non-dominant hand is placed on the aorta, with index and middle finger on either side. Then moving inferiorly the first branch encountered is the celiac trunk. The retroperitoneum is then infiltrated with a spinal needle<sup>[20]</sup>.

Randomized controlled trials of patients with pancreatic cancer showed significant pain reduction with regional neurolysis of celiac plexus and provides an adjunct for pain control<sup>[52]</sup>. A meta-analysis of 302 patients in randomized trials compared systemic opiate therapy with neurolytic celiac plexus block and found lower pain scores at 2, 4, and 8 wk after randomization for patients who underwent celiac plexus block, along with less systemic opiate use and constipation<sup>[53]</sup>. Adverse events reported include transient diarrhea and 20%-42% of patients can have transient orthostatic hypotension due to vasodilation<sup>[54]</sup>.

## PALLIATIVE CHEMOTHERAPY

For patients with advanced malignancy, a procedure that offers quicker recovery can lead to earlier palliative systemic or local therapy, and to an improved quality of life. Palliative chemotherapy has demonstrated a survival benefit and improved quality of life in patients with unresectable disease<sup>[55]</sup>. Gemcitabine monotherapy has been the standard in patients with metastatic pancreatic cancer. With new combination chemotherapy, such as nab-paclitaxel plus gemcitabine, demonstrating increased overall and progression free survival any factors leading to delay in chemotherapy may be detrimental<sup>[56]</sup>.

## CONCLUSION

Pancreatic cancer is an extremely aggressive disease with a five-year survival of only 8.5%. When a curable operation is not possible, treatment decisions should focus on reducing morbidity and improving quality of life. The success of a palliative treatment to provide durable symptom resolution should be at the forefront

of the discussion among physicians, patients and their families.

Palliative treatment of obstructive jaundice, duodenal obstruction and pain should be promptly addressed. The role of surgical palliation has evolved over the past several decades as there have been advances in non-operative palliative interventions. Although surgical bypasses for both biliary and duodenal obstructions usually achieve good technical success, they result in considerable perioperative morbidity and mortality, even when performed laparoscopically. The effectiveness of SEMS for biliary drainage is excellent with low morbidity and demonstrate reduction in jaundice and pruritus. Surgical GJ for duodenal obstruction appears to be best for patients with a life expectancy of greater than 2 mo while endoscopic stenting has been shown to be feasible with relief of nausea and emesis in those with a shorter life expectancy. Regional neurolysis of celiac plexus can serve as an adjunct for better tumor-related pain control. Regardless of the palliative procedure performed, all physicians involved must be adequately trained in end of life management to ensure appropriate and compassionate care for patients.

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**Retrospective Study**

- 84 Male gender and increased body mass index independently predicts clinically relevant morbidity after spleen-preserving distal pancreatectomy

*Dumitrascu T, Eftimie M, Aiordachioae A, Stroescu C, Dima S, Ionescu M, Popescu I*

**CASE REPORT**

- 90 Coexistence of duodenum derived aggressive fibromatosis and paraduodenal hydatid cyst: A case report and review of literature

*Akbulut S, Yilmaz M, Alan S, Kolu M, Karadag N*

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Retrospective Study

# Male gender and increased body mass index independently predicts clinically relevant morbidity after spleen-preserving distal pancreatectomy

Traian Dumitrascu, Mihai Eftimie, Andra Aiordachioae, Cezar Stroescu, Simona Dima, Mihnea Ionescu, Irinel Popescu

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## Abstract

### AIM

To identify risk factors for clinically relevant complications after spleen-preserving distal pancreatectomy (SPDP). No previous studies explored potential predictors of morbidity after SPDP.

### METHODS

The data of 41 patients who underwent a SPDP in a single surgical center between 2000 and 2015 were retrospectively reviewed from a prospectively maintained electronic database established in our Department of Surgery. The database included demographic, clinical, bioumoral, pathological, intraoperative and postoperative parameters. Uni- and multivariate ana-

lyses were performed to assess potential predictors of clinically relevant morbidity. Postoperative morbidity was defined as in-hospital complications and mortality was assessed at 90 d. Clinically relevant morbidity was defined as complication  $\geq$  grade 2 Dindo.

## RESULTS

Overall morbidity rate was 34.1% (14 patients): grade I (6 patients, 14.6%), grade II (2 patients, 4.8%), grade IIIa (1 patient, 2.4%), and grade IIIb (5 patients, 12.2%). A number of 5 patients (12.2%) required re-laparotomy for postoperative complications. There was no postoperative mortality. Thus, at least one clinically relevant complication occurred in 8 patients (19.5%). Univariate analysis identified male gender ( $P = 0.034$ ), increased body mass index ( $P = 0.002$ ) and neuroendocrine pathology ( $P = 0.013$ ) as statistically significant risk factors. Multivariate analysis identified male gender [odds ratio (OR): 1.29, 95%CI: 1.07-1.55,  $P = 0.005$ ] and increased body mass index (OR: 23.18, 95%CI: 1.72-310.96,  $P = 0.018$ ) as the only independent risk factors of clinically relevant morbidity after SPDP.

## CONCLUSION

Male gender and increased body mass index are independently associated with increased risk of clinically relevant morbidity after SPDP. These findings may assist a surgeon in clinical decision-making to better select patients suitable for SPDP.

**Key words:** Spleen-preserving distal pancreatectomy; Morbidity; Male gender; Body mass index

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**Core tip:** No previous studies explored potential predictors of morbidity after spleen-preserving distal pancreatectomy (SPDP). The study aims to identify risk factors for clinically relevant complications after SPDP. Data of 41 patients with SPDP were reviewed and uni- and multivariate analyses were performed to assess potential predictors of clinically relevant morbidity, defined as complication  $\geq$  grade 2 Dindo. The rate of clinically relevant complications was 19.5%. Male gender [odds ratio (OR): 1.29, 95%CI: 1.07-1.55,  $P = 0.005$ ] and increased body mass index (OR: 23.18, 95%CI: 1.72-310.96,  $P = 0.018$ ) were found as independent risk factors of clinically relevant morbidity after SPDP. These findings may assist a surgeon in clinical decision-making to better select patients suitable for SPDP.

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## INTRODUCTION

Pancreatic resections are widely considered to have increased risk of postoperative complications<sup>[1]</sup>. Although distal pancreatectomies (DP) are less complicated surgical procedures compared with pancreatico-duodenectomies, however, morbidity rates are still high: 27.2%-50.2%<sup>[2-8]</sup>.

DP can be performed with or without splenectomy, mainly depending on the type of pathology (benign or malignant) and surgeon's expertise. Recent meta-analyses have shown that preservation of spleen during DP was associated with decreased rates of intra-abdominal abscesses<sup>[9,10]</sup>, infectious complications<sup>[11]</sup>, overall<sup>[11]</sup> or clinically relevant<sup>[10]</sup> pancreatic fistula and overall morbidity<sup>[11]</sup>, particularly when the splenic vessels are preserved<sup>[9-11]</sup>.

Thus, it appears that there are some differences of morbidity between DP with and without splenectomy<sup>[9-11]</sup> and identification of potential predictors of morbidity in the subgroup of patients with spleen-preserving distal pancreatectomy (SPDP) would be a topic of interest. To date, several studies have explored potential predictors of postoperative complications after DP, but none included only patients with SPDP<sup>[2-8,12-26]</sup>.

The study aims to assess risk factors for clinically relevant complications after SPDP with spleen vessels preservation, in a single center experience.

## MATERIALS AND METHODS

### Study design

Between January 1, 2000, and December 31, 2015, a number of 41 SPDP were performed in our Department of Surgery. Data were retrospectively analyzed from a prospectively gathered electronic database and included demographic, clinical, bioumoral, pathological, intraoperative and postoperative parameters, as shown in Table 1.

### Surgical technique

Our technique of SPDP with splenic vessel preservation was described elsewhere<sup>[27]</sup>. Six patients (14.6%) underwent minimally invasive SPDP (2 laparoscopic and 4 robotic).

### Outcomes

The final pathological examination included 16 patients with neuroendocrine tumors (39%), 9 patients with serous/mucinous cystadenoma (22%), 6 patients with solid pseudopapillary tumors (14%), 5 patients with nodular chronic pancreatitis (12%), 4 patients with malignant pathology (10%) and one patient with pancreatic trauma (2%).

Postoperative morbidity was defined as in-hospital complications and mortality was assessed at 90 d. A complication  $\geq$  grade 2 was considered clinically relevant, according to Dindo-Clavien classification.

**Table 1** Demographic, clinical, bioumoral, intraoperative and pathology data of 41 patients with spleen-preserving distal pancreatectomy: A comparative analysis between patients with and without clinically relevant postoperative complications

Parameter	All patients	No complications (33 patients)	Clinically relevant complications (8 patients)	P value
Male gender	12 (29.3%)	7 (21.2%)	5 (62.5%)	0.03 <sup>1</sup>
Age, yr	41 (18–76)	39 (18–76)	51 (34–66)	0.067 <sup>2</sup>
Charlson comorbidity index	0 (0–4)	0 (0–4)	1.5 (0–3)	0.157 <sup>2</sup>
Body mass index, kg/m <sup>2</sup>	25 (19–42)	24 (19–37)	34.5 (24–42)	0.002 <sup>2</sup>
Overweight and obesity	22 (53.6%)	15 (45.4%)	7 (87.5%)	0.049 <sup>1</sup>
Overweight	8 (19.5%)	7 (21.2%)	1 (12.5%)	1 <sup>1</sup>
Obesity	14 (34.1%)	8 (24.2%)	6 (75%)	0.012 <sup>1</sup>
Diabetes mellitus	1 (2.4%)	0	1 (12.5%)	0.195 <sup>1</sup>
Chronic pancreatitis	6 (14.6%)	5 (15.1%)	1 (12.5%)	1 <sup>1</sup>
Preoperative leucocytes number <sup>3</sup> , /μL	7700 (4900–15300)	7700 (4900–15300)	7300 (5200–9200)	0.961 <sup>2</sup>
Preoperative neutrophil number <sup>3</sup> , /μL	4900 (2800–13200)	4900 (2800–13200)	4050 (3500–6400)	0.759 <sup>2</sup>
Preoperative lymphocyte number <sup>3</sup> , /μL	1800 (1000–3300)	1600 (1000–3300)	2200 (1100–2900)	0.291 <sup>2</sup>
Preoperative neutrophil-to-lymphocyte ratio <sup>3</sup>	2.9 (1.2–8.4)	2.9 (1.2–8.4)	2.2 (1.6–5.8)	0.137 <sup>2</sup>
Preoperative platelet number <sup>3</sup> , /μL	262500 (161000–464000)	264000 (161000–410000)	258000 (170000–464000)	0.735 <sup>2</sup>
Preoperative platelet-to-lymphocyte ratio <sup>3</sup>	134 (55.4–372.7)	134 (55.4–372.7)	141.9 (85–372.7)	0.550 <sup>2</sup>
ASA score 3	6 (14.6%)	4 (12.1%)	2 (25%)	0.577 <sup>1</sup>
Minimally invasive approach	6 (14.6%)	4 (12.1%)	2 (25%)	0.577 <sup>1</sup>
Soft pancreas texture	35 (85.3%)	28 (84.8%)	7 (87.5%)	1 <sup>1</sup>
Associated procedures	5 (12.2%)	4 (12.1%)	1 (12.5%)	1 <sup>1</sup>
Operative time, min	150 (70–330)	150 (70–320)	185 (120–330)	0.067 <sup>2</sup>
Estimated blood loss, mL	150 (50–600)	150 (50–600)	175 (50–300)	0.550 <sup>2</sup>
Intraoperative blood transfusions	1 (2.4%)	1 (3%)	0	1 <sup>1</sup>
Tumor diameter, cm	3.5 (0.4–14)	3 (0.4–14)	2.75 (0.4–3.5)	0.060 <sup>2</sup>
Length of resected pancreas, cm	9 (6–12)	9 (6–12)	8.5 (8–12)	0.784 <sup>2</sup>
Malignant pathology	4 (2.4%)	3 (9.1%)	1 (12.5%)	1 <sup>1</sup>
Neuroendocrine pathology	18	11	7	0.013 <sup>1</sup>

<sup>1</sup>Fisher's exact test (two-tailed); <sup>2</sup>Mann-Whitney test (two-tailed); <sup>3</sup>Assessed no more than one week prior to surgery. ASA: American Society of Anesthesiologists.

Postoperative pancreatic fistulae, hemorrhage and delayed gastric emptying were classified according to the International Study Group of Pancreatic Surgery definitions.

The patients were stratified according to the World Health Organization definitions for underweight [body mass index (BMI) < 18.5 kg/m<sup>2</sup>], normal weight (BMI: 18.5–24.9 kg/m<sup>2</sup>), overweight (BMI: 25–29.9 kg/m<sup>2</sup>) and obesity (BMI ≥ 30 kg/m<sup>2</sup>).

### Statistical analysis

Data are expressed as number (percentage) for categorical variables and median (range) for continuous variables. Fisher's exact test (two-tailed) and Mann-Whitney test (two-tailed) were used to compare categorical and continuous variables, respectively. Potential predictors of clinically relevant morbidity were tested in univariate analysis, and risk factors with *P*-values < 0.1 were included in a multivariate binary logistic regression model with the forwarding stepwise method.

*P*-values < 0.05 were considered statistically significant. Statistical analyses were performed with SPSS (Statistical Packages for Social Sciences) version 20.0 software (SPSS Inc., Chicago, IL, United States).

## RESULTS

### Morbidity

Overall morbidity rate was 34.1% (14 patients): grade

I (6 patients, 14.6%), grade II (2 patients, 4.8%), grade IIIa (1 patient, 2.4%), and grade IIIb (5 patients, 12.2%). A number of 5 patients (12.2%) required re-laparotomy for postoperative complications. There was no postoperative mortality. Thus, 8 patients (19.5%) developed clinically significant morbidity.

Postoperative pancreatic fistula was observed in 13 patients (31.7%): grade A (6 patients, 14.6%), grade B (5 patients, 12.2%), and grade C (2 patients, 4.8%).

Postoperative delayed gastric emptying was observed in 5 patients (12.2%): grade A (2 patients, 4.8%), grade B (2 patients, 4.8%), and grade C (1 patient, 2.4%).

Postoperative hemorrhage was observed in 5 patients (12.2%): grade B (1 patient, 2.4%), and grade C (4 patients, 10%).

Other complications included intra-abdominal abscess, wound infection and splenic vessels thrombosis (one patient each, 2.4%).

Patients who developed clinically significant postoperative complications required postoperative blood transfusion in high percent (6 patients, 75%), while no patients from the group without complications needed a blood transfusion (*P* < 0.001).

Overall median hospital stay was 8 d (5–45 d) and was significantly higher for patients with clinically significant morbidity (25 d, range 8–45 d), compared with patients without complications (7 d, range 5–24 d)

( $P < 0.001$ ).

### Uni- and multivariate analysis of predictors of clinically relevant morbidity after SPDP

Univariate analysis identified male gender ( $P = 0.034$ ), increased BMI ( $P = 0.002$ ) and neuroendocrine pathology ( $P = 0.013$ ) as statistically significant risk factors. Furthermore, the multivariate analysis also included age, operative time and tumor diameter ( $P$ -values  $< 0.1$ ) (Table 1).

Multivariate analysis identified male gender [odds ratio (OR): 1.29, 95%CI: 1.07-1.55,  $P = 0.005$ ] and increased BMI (OR: 23.18, 95%CI: 1.72-310.96,  $P = 0.018$ ) as the only independent risk factors.

## DISCUSSION

Morbidity rates after SPDP without splenic vessels removal vary between 18% and 71%<sup>[10,28]</sup> and pancreatic fistula represents the most frequent complication: 7.6%-40%<sup>[28]</sup>. Furthermore, pancreatic fistula is considered a risk factor for compromised patency of spleen vessels after SPDP and late complications such left portal hypertension<sup>[29]</sup>.

Severe or clinically relevant complications after SPDP occur in 11.6%-18% of patients<sup>[8,21,24]</sup>. In the present cohort overall, clinically relevant morbidity and pancreatic fistula rates were 34.1%, 19.5%, and 31.7%, respectively.

Male gender<sup>[3,15,21]</sup> or increased BMI<sup>[3,14,15,18,24]</sup> were previously found independent risk factors of overall morbidity or pancreatic fistulae in few studies including all together DP with and without splenectomy. However, most studies failed to demonstrate any correlation of male gender<sup>[2,6-8,14,16-20,22-26]</sup> or increased BMI<sup>[2,8,16,17,19,21-23,25,26]</sup> with morbidity after DP. In the present study, male gender and increased BMI was found the only independent risk factors for clinically relevant morbidity after SPDP.

Age<sup>[2,3,6-8,13,15-18,20-22,25,26]</sup>, diabetes<sup>[3,6,8,13-16,19,23,25,26]</sup>, chronic pancreatitis<sup>[2,6,15,16,19,26]</sup>, American Society of Anesthesiologists (ASA) score<sup>[3,13,14,16,18,20,23,24]</sup>, blood loss<sup>[7,12-14,17,19,20,22,26]</sup>, operative time<sup>[2,3,12,13,15,19,21,22,26]</sup>, soft pancreas texture<sup>[14,22,23]</sup>, pathology<sup>[3,6-8,13,15,18,21-26]</sup> and type of approach (open or minimally invasive)<sup>[14,15]</sup> does not appear to be independent risk factors of overall morbidity or pancreatic fistulae after DP in most published studies, as it was the case in the present study.

However, few studies identified age<sup>[14,19,23]</sup>, chronic pancreatitis<sup>[13]</sup>, ASA score<sup>[8]</sup>, increased operative time<sup>[7,16,20]</sup>, blood loss<sup>[18,21,23,25]</sup>, soft pancreas texture<sup>[18]</sup>, neuroendocrine pathology<sup>[14]</sup> and laparoscopic approach<sup>[25]</sup> as independent risk factor for postoperative complications after DP.

It is worth mentioning that a meta-analysis has shown that laparoscopic DP has been associated with significantly decreased morbidity rates, compared with

the open approach<sup>[30]</sup>.

Several studies have associated neuroendocrine pathology with an increased risk of postoperative complications (including pancreatic fistulae) after pancreatic resections<sup>[14,18,31]</sup>. In the present study patients with neuroendocrine pathology have had increased risk of clinically relevant complications only in univariate analysis.

Nevertheless, a recent meta-analysis has shown that soft pancreas texture, increased BMI, blood loss or operative time are high-risk factors for pancreatic fistulae occurrence after DP<sup>[32]</sup>.

The present study also explored the potential predictive value of surrogates of inflammatory markers such as the neutrophil-to-lymphocyte ratio or platelet-to-lymphocyte ratio for morbidity after SPDP but failed to identify any correlation. These inflammatory markers were previously demonstrated to predict morbidity after major surgery such as liver resections<sup>[33]</sup> but not for pancreatic resections<sup>[34]</sup>.

The results of the present study should be regarded with caution because there are a limited number of patients.

In conclusion, male gender and increased body mass index are independently associated with increased risk of clinically relevant morbidity after SPDP. Thus, the results of the present study may assist a surgeon in clinical decision-making to better select patients suitable for SPDP.

## ARTICLE HIGHLIGHTS

### Research background

Many studies have explored potential predictors of morbidity after distal pancreatectomy. All the reported studies included both patients with and without spleen preservation. Some studies have suggested that there might be some differences in outcomes between the patients with distal pancreatectomy, with and without spleen preservation. To date, there is no study to explore potential predictors of postoperative morbidity in a group of patients with only spleen-preserving distal pancreatectomy. The aim of the study is to identify risk factors for clinically relevant morbidity after spleen-preserving distal pancreatectomy in a single surgical center experience.

### Research motivation

Morbidity after spleen-preserving distal pancreatectomy remains a significant concern and preservation of the spleen during distal pancreatectomy might sometimes be technically challenging. Thus, identification of potential predictors of clinically relevant morbidity in patients with spleen-preserving distal pancreatectomy would be of interest for clinical practice to better select the patients for this type of surgical procedure.

### Research objectives

The primary objective of the study was to explore potential predictors of clinically relevant morbidity after spleen-preserving distal pancreatectomy in a single surgical center experience.

### Research methods

It was a retrospective analysis reviewing the data of 41 consecutive patients who underwent spleen-preserving distal pancreatectomy with spleen vessel preservation between 2000 and 2015 in our Department of Surgery. Appropriate statistical tests were used to compare potential risk factors between the groups

of patients with and without clinically relevant morbidity after spleen-preserving distal pancreatectomy, in uni- and multivariate analyses.

## Research results

To the best of our knowledge, this is the first study exploring potential predictors of clinically relevant morbidity in patients with spleen-preserving distal pancreatectomy. The study found male gender and increased body mass index as independent predictors of clinically relevant morbidity after spleen-preserving distal pancreatectomy.

## Research conclusions

This is the first study that identifies male gender and increased body mass index as risk factors of clinically relevant morbidity in a group of patients with only spleen-preserving distal pancreatectomy. Patient-related factors such as gender and body mass index should be taken into consideration when a spleen-preserving distal pancreatectomy is proposed. The data provided in the present study can be used for clinical decision-making, particularly when preservation of the spleen during distal pancreatectomy is technically demanding.

## Research perspectives

Preoperative evaluation of patients suitable for a spleen-preserving distal pancreatectomy is of utmost importance. The impact of male gender and body mass index on postoperative outcome after spleen-preserving distal pancreatectomy remains to be explored in future studies including more substantial number of patients.

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## Coexistence of duodenum derived aggressive fibromatosis and paraduodenal hydatid cyst: A case report and review of literature

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**Author contributions:** Akbulut S designed the report, analyzed the data and wrote the paper; Akbulut S and Yilmaz M performed the surgical procedure and collected the patient's clinical data; Alan S and Karadag N provided histopathological information; Kolu M provided radiological information.

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### Abstract

Intra-abdominal aggressive fibromatosis is a locally aggressive tumor mostly originating from the mesentery or retroperitoneal space, infiltrating adjacent tissues, and very rarely metastasizing to distant organs. There are only two case reports in the English language literature where intra-abdominal aggressive fibromatosis originated from the intestinal wall. In this study, we aimed to report a case of aggressive fibromatosis originating from the muscularis propria layer of the duodenum and invading pancreas. Another interesting aspect of this case is that a primary paraduodenal hydatid cyst was incidentally detected in the surgical specimen. A 46-year-old female patient presented to our clinic with postprandial nausea and vomiting. A contrast-enhanced abdominal computerized tomography revealed a mass lesion with a size of 100 mm × 80 mm which originated from the distal pancreas and compressed the gastric pilor externally. Upon exploration the distal part of duodenum, proximal

jejunum, and pancreatic mass were noted to form a conglomerated structure. Therefore, the fourth part of the duodenum, a 25 cm part of the proximal jejunum, distal pancreas, and the spleen were excised *en-bloc*. The pathology report of the specimen indicated fibromatosis with a diameter of 55 mm that originated from the muscularis propria of the duodenum and extended into the pancreatic parenchyma. There was also an incidentally detected 10 mm paraduodenal hydatid cyst. No tumor recurrence was detected at a follow-up period of 24 mo. In conclusion, the most ideal treatment of desmoid-type fibromatosis is surgical resection of the mass lesion with clean surgical borders. Although rare, this tumor may originate from the intestinal wall. Histopathological verification is of great significance for a proper diagnosis.

**Key words:** Duodenal wall; Hydatid cyst; Aggressive fibromatosis; Intra-abdominal fibromatosis; Desmoid tumor; Desmoid-type fibromatosis

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**Core tip:** Fibromatosis can be categorized into two broad categories depending on their localization: superficial and deep (aggressive fibromatosis or desmoid tumor). Desmoid-type fibromatoses can be categorized into three groups depending on their localization, namely extra-abdominal, abdominal wall, and intra-abdominal fibromatosis. Intra-abdominal desmoid-type fibromatosis may develop from the small intestinal mesentery, omentum, retroperitoneum, pelvis, and very rarely, the intestinal wall (such as our case). We aimed to report a case of aggressive fibromatosis originating from the muscularis propria layer of the duodenum and the invading pancreas. Another interesting aspect of this case is that a primary paraduodenal hydatid cyst was incidentally detected.

Akbulut S, Yilmaz M, Alan S, Kolu M, Karadag N. Coexistence of duodenum derived aggressive fibromatosis and paraduodenal hydatid cyst: A case report and review of literature. *World J Gastrointest Surg* 2018; 10(8): 90-94 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v10/i8/90.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v10.i8.90>

## INTRODUCTION

Intra-abdominal aggressive fibromatosis (desmoid tumor) is a locally aggressive tumor mostly originating from the retroperitoneal space or musculoaponeurotic tissues in the mesentery, showing fibroblast/myofibroblast proliferation, infiltrating adjacent tissues, and very rarely metastasizing to distant organs<sup>[1,2]</sup>. The most significant risk factors for intra-abdominal aggressive fibromatosis are positive family history, female gender, APC gene mutation, pregnancy, hormone therapy, and a history of surgical procedure and trauma. The tumor

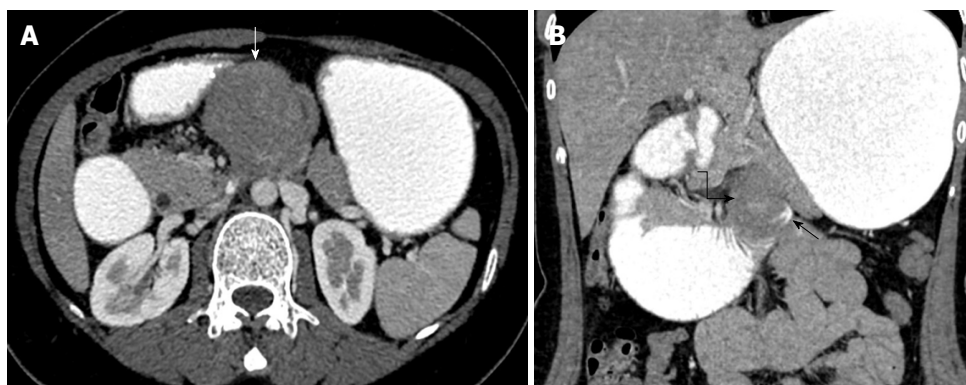
is mostly asymptomatic when it first emerges<sup>[1-5]</sup>. When it grows and starts to invade adjacent tissues or organs, however, it may produce signs and symptoms including abdominal discomfort, pain, palpable mass, intestinal obstruction, perforation, fistula, and inguinal hernia<sup>[1-3]</sup>. Depending on tumor size, growth pattern, and symptomatology, a staging model has been developed, which usually forms the basis for treatment planning<sup>[6]</sup>. The majority of publications about intra-abdominal aggressive fibromatosis have stated that the tumor originates from the mesentery. Despite this, only two papers have been published about aggressive fibromatosis originating from the intestinal wall<sup>[2,4]</sup>. In this paper, we report a case of aggressive fibromatosis originating from the muscularis propria layer of the duodenum and invading the pancreas.

## CASE REPORT

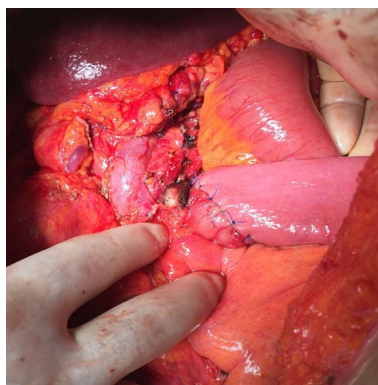
A 46-year-old female patient presented to our outpatient clinic with postprandial nausea and vomiting. She stated that these complaints had started 6 mo earlier and had recently become worse. Her past medical history was not remarkable. On physical examination she only had tenderness in the epigastric region. Her biochemical parameters and tumor markers were within normal limits. Oral and intravenous contrast enhanced computerized tomography revealed a mass lesion with an approximate size of 100 mm × 80 mm that originated from the body of the pancreas and extended inferiorly (Figures 1 and 2).

As the mass did not invade vascular structures, a surgical intervention was planned. The abdominal cavity was entered *via* midline incision. After opening the gastrocolic ligament, the diameter of the dense mass was approximately 120 mm × 100 mm. It was noted that it originated from the pancreatic body, caused severe adhesions with adjacent tissues, and formed a conglomerated structure together with the fourth part of the duodenum and proximal jejunal loops. The mass was also severely adhered to the prepyloric antrum of the stomach. First, dense adhesions between the stomach and the mass were dissected with sharp dissection. Then, the extremely close anatomic relations of the mass with both the portal vein and the superior mesenteric artery were cut with sharp dissection. The conglomerated fourth part of the duodenum, proximal jejunum, distal pancreas, and the spleen were removed *en-bloc*. Then, an end-to-end anastomosis was formed between the third part of duodenum and proximal jejunum (Figure 3). Supportive serosal stitches were placed along the anastomosis line. A jejunal tube extending to the proximal part of the anastomosis was placed in order to protect the anastomosis. The patient was discharged uneventfully.

The histopathological examination of the pathology specimen revealed a lesion with an approximate diameter of 55 mm and an appearance consistent with fibromatosis, which originated from the muscularis



**Figure 1 Oral and intravenous contrast-enhanced multidetector computed tomography.** A: Axial cross-sectional views of the multidetector computed tomography (MDCT) scan; B: Coronal reformant cross-sectional views of the MDCT scan. A space occupying mass lesion with homogenous density showing minimal contrast uptake is seen in the pre-aortic area in the abdominal midline (white arrow). Coronal reformant MDCT images show that the mass is in the fourth part of the duodenum (curved black arrow). There is only slight oral contrast passage to jejunal loops (thin black arrow), and the duodenum and stomach had a ptotic appearance due to mechanical obstruction caused by the mass.

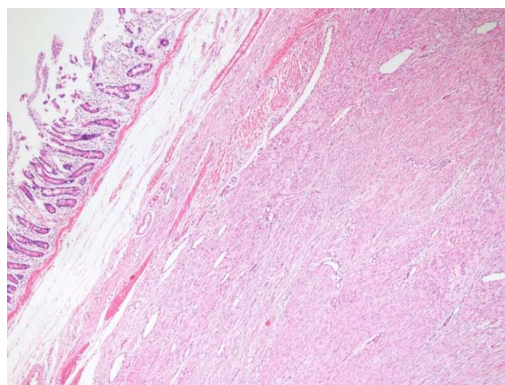


**Figure 2 Intraoperative views.** The image of the anastomosis formed with circular stapler between the third part of the duodenum and proximal jejunum after the resection. Circumferential serosal sutures with polyene were placed to reinforce the anastomosis.

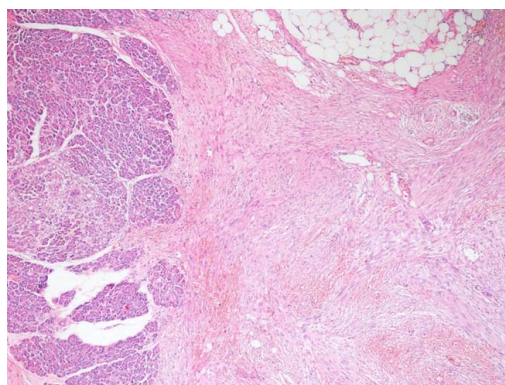


**Figure 3 Appearance of back-table stage of surgery.** The resected specimen after the transection of the pancreas. It was seen that the mass originated from the duodenum and invaded pancreas.

propria layer of the duodenum and extended into the pancreatic parenchyma (Figures 4 and 5). Immunohistochemically, the tumor was positive for vimentin (strong staining), beta catenin, cluster of differentiation 99 (CD99), smooth muscle actin (weak staining), calponin (patchy staining), and Ki67 proliferation index

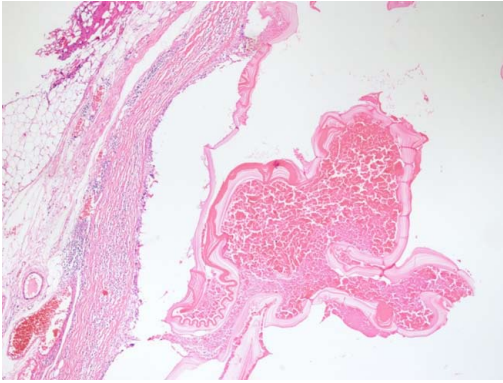


**Figure 4 Microscopic appearance of duodenal wall tissue stained with hematoxylin and eosin.** Spindle cell tumor originating from the muscularis propria under duodenal mucosa (HE × 40).



**Figure 5 Microscopic appearance of pancreatic tissue stained with hematoxylin and eosin.** It shows extension to pancreatic parenchyma (HE × 40).

(5%) whereas it was negative for B-cell lymphoma 2, CD68, low molecular weight keratin, high molecular weight keratin, CD117, and pan-cytokeratin. Additionally, a hydatid cyst lesion with a diameter of 10 mm was detected in the neighborhood of the tumor (Figure 6). The patient was administered etodolac for a total of 3 mo at the postoperative period. The tumor did not



**Figure 6** Microscopic appearance of the hydatid cyst tissue stained with hematoxylin and eosin. An acellular membrane of a hydatid cyst is shown here (HE  $\times$  40).

recur for a period of 24 mo postoperatively.

## DISCUSSION

Fibromatosis can be categorized into two broad categories depending on their localization: Superficial (palmar, plantar, and penile) and deep (aggressive fibromatosis = desmoid tumor = desmoid-type fibromatosis). Superficial fibromatoses are typically small and grow slowly. Deep fibromatoses are locally aggressive tumors that are bigger and grow more rapidly than superficial ones. Deep fibromatoses develop as a result of the proliferation of clonal fibroblasts found in deep soft tissues. The term aggressive fibromatosis was first defined by McFarlane in 1832<sup>[1,7]</sup>. In 1838, Mueller suggested the use of the term desmoid tumor instead of the term aggressive fibromatosis<sup>[1,7]</sup>. Finally, the World Health Organization categorized all the terms deep fibromatosis, aggressive fibromatosis, and desmoid tumor under the title “desmoid-type fibromatosis”. The World Health Organization put desmoid-type fibromatoses into the intermediate (locally aggressive) types of fibroblastic/myofibroblastic tumors.

Desmoid-type fibromatoses can be categorized into three groups depending on their localization, namely extra-abdominal (50%-60%), abdominal wall (25%), and intra-abdominal fibromatosis (12%-15%)<sup>[1,2]</sup>. Extra-abdominal desmoid-type fibromatoses most commonly originate from the shoulder, chest wall, neck, back, and soft tissues of the leg. Abdominal wall desmoid-type fibromatoses mostly develop from the rectus abdominis or internal oblique muscle fasciae. Intra-abdominal desmoid-type fibromatosis may develop from the small intestinal mesentery (80%), ileocolic mesentery, omentum, retroperitoneum, pelvis, and very rarely the intestinal wall<sup>[5]</sup>. Desmoid-type fibromatosis occurs sporadically in 85%-90% of cases whereas the remainders are related to *APC* gene mutation (Familial adenomatous polyposis (FAP), Gardner syndrome).

Desmoid-type fibromatosis constitutes 0.03% of all tumors and less than 3% of all soft tissue tumors in humans. The estimated annual incidence of desmoid-

type fibromatosis in the general population is 2-5 people per one million<sup>[5]</sup>. Although desmoid-type fibromatosis mostly affects persons aged 15 to 60 years, it peaks around the age of 30. It is more common in women than men<sup>[1]</sup>.

Demonstration of a mass showing an infiltrative growth pattern in contrast-enhanced computerized tomography or magnetic resonance imaging is of great value for making the provisional diagnosis of desmoid-type fibromatosis. Observing spindle cells with small and regular nuclei, which are surrounded by abundant collagen in biopsy material taken from the mass is typical for the disorder. Upon immunohistochemical staining the lesion is positive for muscle cell marker actin, vimentin, and desmin, while it is negative for CD34. However, definitive diagnosis is made by showing the mutation in the  $\beta$ -catenin gene (*CTNNB1*). Among cases with sporadic desmoid-type fibromatosis, 85% have been reported to have somatic mutations in the *CTNNB1* gene. The differential diagnosis of desmoid-type fibromatosis includes gastrointestinal stromal tumors, solitary fibrous tumors, inflammatory myofibroblastic tumors, sclerosing mesenteritis, retroperitoneal fibrosis, and lymphoma. Therefore, histopathological verification and demonstration of gene mutation if possible are of paramount importance prior to instituting treatment<sup>[8]</sup>.

In general, desmoid-type fibromatosis is treated with one or several of the treatment options including surgical resection, non-steroidal anti-inflammatory drugs (sulindac, meloxicam, etodolac, indomethacin), hormone therapy (tamoxifen, raloxifene, toremifene, progesterone, testolactone), chemotherapy (doxorubicin, doxorubicin + dacarbazine, epirubicin, methotrexate + vinblastine), radiotherapy (neoadjuvant, adjuvant), and targeted therapy with tyrosine kinase inhibitors (imatinib, sorafenib, pazopanib)<sup>[1,6]</sup>. Irrespective of tumor localization, the most ideal treatment approach is R0 surgical resection with 2-3 cm clean surgical borders<sup>[1,2]</sup>. In cases where R0 resection is not an option, recurrence rates could be dramatically reduced by combining one of the above mentioned treatment modalities with debulking tumor surgery.

Whereas almost all published cases of intra-abdominal desmoid-type fibromatosis originated from the gut mesentery, the tumor reported here originated from the intestinal wall itself. To our knowledge, a total of two such cases have been reported, one from the duodenal wall<sup>[2]</sup> and the other from the cecal wall<sup>[4]</sup>. Hence, it is difficult to make any suggestion on how to approach these cases. However, the general R0 resection rule also applies here. The tumor of duodenal origin gave a radiological appearance of pancreatic origin. This case indeed appeared as a pancreatic mass compressing the duodenum because proliferation in the duodenal wall extended to the pancreatic parenchyma. The back table appearance of the specimen was also compatible with a pancreatic mass. However, the histopathological examination revealed that this was in fact caused by the invasion of the pancreas by proliferation of duodenal

origin. Being female, having a history of four pregnancies, and using oral contraceptives for years are each risk factors for desmoid tumor development for the patient presented here. Both endoscopy and colonoscopy were performed in order to demonstrate any other risk factors such as FAP, but both failed to reveal any finding consistent with FAP. Another important point to consider is the anastomosis technique. To date, we placed a tube passing from the distal jejunum to the proximal part of the anastomosis in order to reduce anastomosis pressure in all three cases where we had to resect the fourth part of duodenum for various indications and then we performed end-to-end duodeno-jejunal anastomosis with the help of a stapler. We did not experience anastomosis leak problems in any of our patients.

It was quite interesting that a 10 mm paraduodenal hydatid cyst in the surgical specimen was incidentally detected. A postoperative serum echinococcus enzyme-linked immunosorbent assay test was negative. Additionally, the thoracoabdominal computed tomography images were retrospectively examined and no other hydatid cyst lesion could be identified in any other location. The cystic lesion detected in the patient was considered a primary paraduodenal hydatid cyst. Thus, postoperative albendazole treatment was not commenced. It is unclear whether the hydatid cyst triggered the desmoid reaction. However, it is a known fact that hydatid disease can cause inflammation in the surrounding tissue. It is clear that this case report needs to be supported by other studies.

In conclusion, desmoid-type fibromatosis is a locally aggressive tumor that does not metastasize to distant organs. The most ideal treatment is surgical resection of the mass lesion with clean surgical borders. Although rare, desmoid-type fibromatosis may originate from the intestinal wall. Histopathological verification is of great significance for a proper diagnosis.

## ARTICLE HIGHLIGHTS

### Case characteristics

A 46-year-old female patient presented to our outpatient clinic with postprandial nausea and vomiting.

### Clinical diagnosis

Upper gastrointestinal obstruction due to pancreatic/duodenal tumor.

### Differential diagnosis

Pancreatic mass, Duodenal mass.

### Laboratory diagnosis

Both biochemical parameters and tumor markers were within normal limits.

### Imaging diagnosis

A contrast-enhanced abdominal computerized tomography revealed a mass lesion with a size of 100 mm × 80 mm which originated from the distal pancreas.

### Pathological diagnosis

Aggressive fibromatosis also known as a desmoid tumor originated from the muscularis propria of the duodenum and a paraduodenal hydatid cyst.

### Treatment

The fourth part of the duodenum, proximal jejunum, distal pancreas, and the spleen were removed *en-bloc*. After then, an end-to-end anastomosis was performed between the third part of duodenum and proximal jejunum.

### Related reports

There are only two case report describing aggressive fibromatosis that originated from the intestinal wall.

### Term explanation

Fibromatosis can be categorized into two groups: superficial and deep. Deep fibromatosis also known as aggressive fibromatosis, desmoid tumor, and desmoid-type fibromatosis. Desmoid-type fibromatosis can be categorized into three groups: extra-abdominal, abdominal wall, intra-abdominal fibromatosis.

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## Molecular therapeutic strategies targeting pancreatic cancer induced cachexia

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### Abstract

Pancreatic cancer (PC) induced cachexia is a complex metabolic syndrome associated with significantly increased morbidity and mortality and reduced quality of life. The pathophysiology of cachexia is complex and poorly understood. Many molecular signaling pathways are involved in PC and cachexia. Though our understanding of cancer cachexia is growing, therapeutic options remain limited. Thus, further discovery and investigation of the molecular signaling pathways involved in the pathophysiology of cachexia can be applied to development of targeted therapies. This review focuses on three main pathophysiologic processes implicated in the development and progression of cachexia in PC, as well as their utility in the discovery of novel targeted therapies.

Skeletal muscle wasting is the most prominent pathophysiologic anomaly in cachectic patients and driven by multiple regulatory pathways. Several known molecular pathways that mediate muscle wasting and cachexia include transforming growth factor-beta (TGF- $\beta$ ), myostatin and activin, IGF-1/PI3K/AKT, and JAK-STAT signaling. TGF- $\beta$  antagonism in cachectic mice reduces skeletal muscle catabolism and weight loss, while improving overall survival. Myostatin/activin inhibition has a great therapeutic potential since it plays an essential role in skeletal muscle regulation. Overexpression of insulin-like growth factor binding protein-3 (IGFBP-3) leads to increased ubiquitination associated proteolysis, inhibition of myogenesis, and decreased muscle mass in PC induced cachexia. IGFBP-3 antagonism alleviates muscle cell wasting.

Another component of cachexia is profound systemic inflammation driven by pro-cachectic cytokines

such as interleukin-6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interferon gamma (INF- $\gamma$ ). IL-6 antagonism has been shown to reduce inflammation, reduce skeletal muscle loss, and ameliorate cachexia. While TNF- $\alpha$  inhibitors are clinically available, blocking TNF- $\alpha$  signaling is not effective in the treatment of cancer cachexia. Blocking the synthesis or action of acute phase reactants and cytokines is a feasible therapeutic strategy, but no anti-cytokine therapies are currently approved for use in PC. Metabolic alterations such as increased energy expenditure and gluconeogenesis, insulin resistance, fat tissue browning, excessive oxidative stress, and proteolysis with amino acid mobilization support tumor growth and the development of cachexia. Current innovative nutritional strategies for cachexia management include ketogenic diet, utilization of natural compounds such as silibinin, and supplementation with  $\omega$ 3-polyunsaturated fatty acids. Elevated ketone bodies exhibit an anticancer and anticachectic effect. Silibinin has been shown to inhibit growth of PC cells, induce metabolic alterations, and reduce myofiber degradation. Consumption of  $\omega$ 3-polyunsaturated fatty acids has been shown to significantly decrease resting energy expenditure and regulate metabolic dysfunction.

**Key words:** Cachexia; Muscle wasting; Pancreatic cancer; Cachexia therapies; Molecular signaling

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**Core tip:** Pancreatic cancer (PC) induced cachexia is a complex metabolic syndrome associated with increased morbidity, mortality and reduced quality of life. The complex pathophysiology of cachexia involves muscle wasting, systemic inflammation, and metabolic alterations. Molecular signaling pathways responsible for muscle wasting include TGF- $\beta$ , myostatin/activin, IGF-1/PI3K/Akt, and JAK-STAT. IL-6, TNF- $\alpha$ , and INF- $\gamma$  are the most well studied pro-cachectic cytokines that promote systemic inflammation. Metabolic alterations such as increased energy expenditure and glycolytic pathway dysfunction could be potentially improved with ketonemia, silibinin, and  $\omega$ 3-polyunsaturated fatty acids. Targeting molecular signaling pathways in PC induced cachexia could lead to discovery of effective therapies.

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## INTRODUCTION

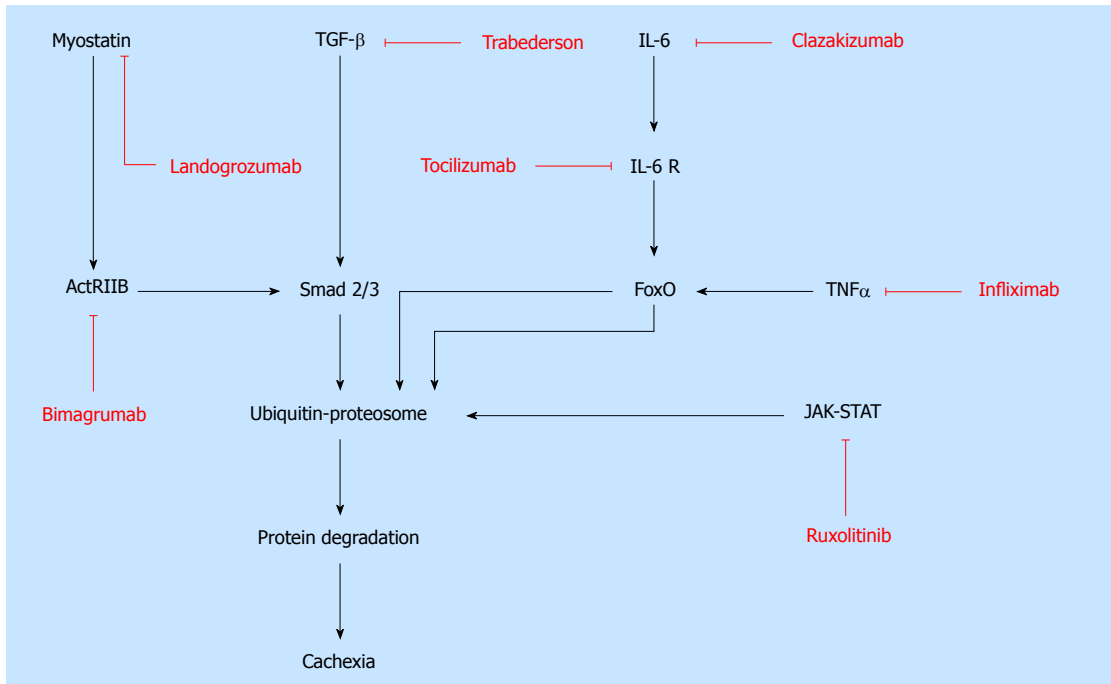
Cachexia is a systemic syndrome predominantly cha-

racterized by an increased catabolic drive that leads to the profound wasting of skeletal muscle and fat tissue. Though skeletal muscle and fat tissue degradation are the most prominent, other tissues are involved and contribute to cachexia syndrome. These include cardiomyocyte wasting (leading to heart failure) and an increased metabolic rate in the liver (leading to metabolic derangements increased energy expenditure)<sup>[1-4]</sup>. Cachexia is mediated by cytokines, tumor-derived factors, neuropeptides, and neurotransmitters, all of which lead to a pro-inflammatory and catabolic state<sup>[5]</sup>. Ultimately, such metabolic derangements provide metabolites and energy sources which support tumor growth.

Cancer cachexia affects 80% of patients with pancreatic cancer (PC), constituting the highest rate of cachexia in all malignancies<sup>[6-7]</sup>. The best available treatment for PC is radical resection, but cachectic patients are less likely to have surgery than non-cachectic patients<sup>[6]</sup>. In general, the appropriate treatment is precluded as cachectic and malnourished patients are poor surgical candidates. Furthermore, cachectic patients that undergo surgery have more post-operative complications, higher rates of intensive care unit admission, longer hospital stay and increased mortality<sup>[6]</sup>. Preoperative sarcopenia is associated with poor postoperative outcome, prognosis and overall survival in patients with surgically resectable PC<sup>[7-9]</sup>. Moreover, cachexia limits available treatment options due to reduced response and tolerance to chemotherapy and radiation. Overall, median survival and quality of life is significantly reduced in cachectic patients.

As the incidence of cachexia is particularly high in patients with PC, it is proposed that the biology of the pancreatic tumor and its systemic inflammatory sequelae are uniquely intensified in comparison to other malignancies. Gene expression is altered in PC tumorigenesis leading to tumor cell development, survival and symptoms of cachexia. Several signaling pathways are upregulated, including those involving transforming growth factor-beta (TGF- $\beta$ ), integrin, phenyl glycidyl ether 2, phosphatidylinositol 3-hydroxy kinase (PI3K), k-Ras and p53<sup>[10]</sup>. Furthermore, inflammatory and immune response genes are upregulated and mediate cell proliferation, migration, adhesion and angiogenesis; these genes are implicated in PC induced cachexia<sup>[10]</sup>. Tumor derived growth factors and secreted proteins cause muscle wasting and the other metabolic abnormalities seen in cachexia. In short, the catabolic and anabolic balance is disrupted leading to overtly cachectic symptoms.

The pathogenesis of cancer cachexia is convoluted and multifactorial. Although progress has been made in understanding molecular mechanisms, there remains a lack of clinical data for PC. Understanding the molecular signaling pathways involved in cachexia not only advances therapeutic approaches, but also advances our approach to treating cancer. Given the complexity and



**Figure 1 Signaling pathways involved in the pathophysiology of cachexia and targeted therapies.** Multiple molecular signaling pathways and mediators lead to protein degradation and cancer cachexia including myostatin/ActR II B, TGF- $\beta$ , Smad 2/3, IL-6, TNF $\alpha$ , FoxO and JAK-STAT. These molecular signaling pathways serve as therapeutic strategies for treatment of cachexia. Pharmacologic inhibitors that have been used clinically or experimentally are labelled in red and specific targets are notated. TGF- $\beta$ : Transforming growth factor-beta; IL-6: Interleukin-6; TNF- $\alpha$ : Tumor necrosis factor-alpha; ActR II B: Activin type II B.

multitude of potential molecular targets implicated in PC cachexia, the therapeutic strategies are limited and advances in this area have been limited.

Unfortunately, there are few preclinical cachexia models with appropriate complexity, and the development of therapies has thus been limited. Current therapeutic strategies for PC cachexia include appetite stimulation with megestrol acetate, ghrelin agonists, and serotonin agonists as well as interference with metabolic and inflammatory derangements with pro-cachectic cytokine antagonists such as cyclooxygenase 2 (COX-2) inhibitors,  $\beta$ 2 agonists, angiotensin converting enzyme inhibitors,  $\beta$ B, selective androgen receptor modulators, myostatin antagonists and  $\omega$ -3 fatty acids<sup>[11]</sup>. This review however focuses on the molecular pathways activated in PC cachexia that can serve as targets for pharmacologic interference and the recent advances in this field. In spite of our increased understanding of its pathogenesis, clinically reliable therapies for cachexia are not available.

## PANCREATIC CANCER INDUCED CACHEXIA

Unlike starvation, which causes adipose tissue wasting, cachexia involves the degeneration of many additional tissues, most notably skeletal muscle. Increased proteolysis, catabolism, and oxidative stress mediate muscle wasting, or myopenia. Muscle breakdown leads to an increase in circulating amino acids which are potentially utilized by the tumor to increase growth. Understanding the molecular pathways that mediate skeletal muscle

wasting is necessary to make advancements in targeted therapies for cachexia patients (Figure 1). Preventing muscle atrophy would lead to improved functional status and quality of life in patients with cachexia. Therefore, it is reasonable to target muscle wasting in cachexia.

### Tumor secreted TGF- $\beta$

The tumor-host interaction is a primary pathophysiologic mechanism of cancer cachexia. Investigating tumor secreted proteins that are involved in regulation of muscle integrity and function contributes novel insight into the development of therapies for PC cachexia. One such tumor secreted protein is transforming growth factor- $\beta$  (TGF- $\beta$ ), which is part of the superfamily of signaling proteins involved in pathways that regulate cell growth, differentiation, homeostasis, inflammation, immunomodulation and apoptosis<sup>[12,13]</sup>. It is well known that TGF- $\beta$  plays a key role in tumor development by acting as a tumor suppressor in the p21 cell cycle inhibitor signaling pathway<sup>[13,14]</sup>. Gene expression analysis has identified the overexpression of *TGFB1* and *TGFB2* which encode for TGF- $\beta$ 1 and TGF- $\beta$ 2 proteins in PC<sup>[10,14]</sup>. Interestingly, TGF- $\beta$  is thought to have a dual role depending on the tumor development stage. In both healthy and early tumor cells it is involved in tumor suppression. However, in advanced tumors with high expression, TGF- $\beta$  stimulates carcinogenesis and metastasis<sup>[12-14]</sup>. Furthermore, increased TGF- $\beta$  expression inactivates the tumor suppressor gene *Smad4/DPC4*, the loss of which is commonly implicated in PC tumor progression<sup>[15,16]</sup>. TGF- $\beta$  is also considered

to be a negative regulator of skeletal muscle *via* the Smad2/3 pathway, which contributes to myopenia *via* myostatin, activin and inhibin signaling<sup>[17]</sup>. Specifically, myostatin is involved in the regulation of muscle mass homeostasis by decreasing protein synthesis and increasing protein catabolism<sup>[13,17]</sup>. TGF- $\beta$  superfamily proteins have been implicated in pathogenesis of many cancers, cachexia, muscular dystrophies, and several other conditions<sup>[3,12,13,18]</sup>. TGF- $\beta$  is a potential therapeutic target.

Despite the clear implication of TGF- $\beta$  signaling between PC and cachexia, there are few studies that investigate the therapeutic efficacy of direct antagonism. Using a murine model, TGF- $\beta$  antagonism with a TGF- $\beta$  antibody reduced skeletal muscle breakdown and weight loss, while improving overall survival, lean body mass, and bone mineral in metastatic PC<sup>[13]</sup>. Mice with *Pan02* tumor cells had lower levels of TGF- $\beta$  and p-Smad2/3 signaling marker after TGF- $\beta$  inhibition with neutralizing antibody compared to control mice<sup>[13]</sup>. Furthermore, TGF- $\beta$  inhibition reduced motor impairment and improved function measured with rotarod running speed<sup>[13]</sup>. This is particularly interesting and worth further investigation as most patients with cachexia have severe functional impairment with poor motor skills contributing to a reduced quality of life. Limited clinical data available from studies involving TGF- $\beta$ 2 antagonism with trabedersen showed improved overall survival in patients with PC presumably due to disruption of tumor cytokine production and upregulation of host antitumor cytokines<sup>[14]</sup>. Further studies are necessary to definitively evaluate TGF- $\beta$  pathway inhibition as a treatment strategy for PC cachexia.

## MYOSTATIN AND ACTR II B

Myostatin and activin, both part of TGF- $\beta$  superfamily, are negative regulators of muscle growth and development *via* the activin type II B (ActR II B) receptor<sup>[19-21]</sup>. Myostatin signaling inhibits myogenesis, decreases protein synthesis, and activates ubiquitin ligase muscle degradation involving the Akt/mTOR pathway<sup>[12,22]</sup>. Likewise, genetic myostatin deficiency leads to significant skeletal muscle hypertrophy<sup>[21,22]</sup>. Several studies suggest that myostatin is upregulated and is one of the key drivers of muscle wasting in cachexia<sup>[12,21,22]</sup>. The myostatin signaling pathway is targeted in treatment of various muscle wasting disorders and has been shown to improve strength and functioning in animal models<sup>[21]</sup>. Thus, the therapeutic potential of myostatin and ActR II B inhibition in treatment of cachexia is worth investigating. ActR II B blockade has been studied as a therapy for inclusion body myositis, chronic obstructive pulmonary disease, and age-related sarcopenia with positive results<sup>[23]</sup>. Blocking ActR II B ligands improved survival and increased muscle mass in cachectic mice with colon cancer in a recent preclinical study<sup>[24]</sup>. Novartis Pharmaceuticals recently completed a randomized control trial of bimagrumab, an anti-ActR II B monoclonal

antibody, for treatment cachexia associated with PC and lung cancer<sup>[25]</sup>. Patients treated with bimagrumab had greater increase in lean body mass and thigh muscle volume, yet also had greater decrease in total body weight<sup>[25]</sup>. However, the literature is divided with regard to myostatin antagonism. A phase 2 trial of landogrozumab, a monoclonal anti-myostatin antibody, evaluated its efficacy in improving lean body mass, physical performance, and overall survival in patients with PC<sup>[26]</sup>. Landogrozumab was not superior to placebo since both groups had similar increase in lean body mass from baseline and improved physical performance measures using hand grip strength<sup>[26]</sup>. Indeed, the placebo group had higher overall survival compared to landogrozumab group<sup>[26]</sup>.

Proteinase-activated receptor 2 (PAR2) is a possible molecular linker between PC and cachexia. Serine proteinases released by tumor cells activate PAR2 and subsequent myostatin signaling *via* ALK5<sup>[12]</sup>. Thus, PAR2 has been identified as a target that could provide therapeutic benefit in cachexia.

In summary, myostatin and its associated signaling pathways have essential roles in skeletal muscle regulation and are all well studied in a variety of muscular pathologies. Its utility in attenuating progressive myopenia however remains unclear. There have been multiple animal and human studies that evaluate the myostatin, activin and actR II B signaling pathway in colorectal and lung cancer cachexia, but few that focus explicitly on PC. Therefore, the therapeutic potential of myostatin and activin inhibition for PC cachexia warrants further investigation.

## IGFBP-3 and IGF-1/PI3K/AKT signaling pathways

Insulin-like growth factor binding proteins (IGFBPs) 1-7 stabilize the insulin-like growth factor (IGF) complex, prolong its half-life, and increase its distribution to target tissues<sup>[27,28]</sup>. IGFBPs are involved in the regulation of various cellular processes *via* the IGF-1/PI3K/AKT, NF- $\kappa$ B, TGF- $\beta$ , and JAK-STAT signaling pathways<sup>[10,28]</sup>. However, overexpression of IGFBPs leads to decreased bioavailability of IGFs and disrupted intracellular signaling pathways necessary for myogenesis<sup>[27,28]</sup>. PC cachexia is characterized by a decrease in the level of circulating anabolic factors such as IGF-1<sup>[1]</sup>. Specifically, IGFBP-3 is the primary binding protein for IGF-1, and the IGF-1/PI3K/Akt signaling pathway is a key regulator of muscle mass<sup>[3,10,27,29]</sup>. Mechanistically, the IGF-1 receptor activates the PI3K-Akt pathway which leads to downstream sequelae including mTOR activation, increased protein synthesis and muscle growth, and decreased protein degradation by inhibiting the GSK3 $\beta$  and FoxO<sup>[29,30]</sup>. Furthermore, IGF-1 signaling leads to suppression of proteolysis and ubiquitin-proteasome system which prevents apoptosis of myocytes<sup>[10,31]</sup>. With overexpression of IGFBP-3, normal signaling is arrested and increased ubiquitination leads to proteolysis and a subsequent decrease in muscle mass<sup>[10,31]</sup>.

IGFBP-3 is significantly upregulated in PC tumor

**Table 1** Cytokines involved in cachexia, function, and specific targeted therapies

Cytokine	Function	Drug
TGF- $\beta$	Decreases protein synthesis; increases muscle catabolism	Trabectedin (binds TGF- $\beta$ mRNA)
TNF- $\alpha$	Generates radical oxygen species; increases ubiquitin-proteasome activity	Infliximab (anti-TNF- $\alpha$ mAb); etanercept (recombinant TNF- $\alpha$ R); thalidomide/lenalidomide (inhibits TNF- $\alpha$ ); pentoxifylline (inhibits TNF- $\alpha$ )
IL-6	Mediates systemic inflammation; increases muscle catabolism; regulates synthesis of acute phase reactants	Clazakizumab (anti-IL-6 mAb); tocilizumab (anti-IL-6 receptor mAb)

TGF- $\beta$ : Transforming growth factor-beta; IL-6: Interleukin-6; TNF- $\alpha$ : Tumor necrosis factor-alpha.

cells<sup>[10]</sup>. Likewise, it has been demonstrated that IGFBP-3 plays a role in the pathophysiology of cancer cachexia by inhibiting the myotubule proliferation and differentiation in naïve myoblasts. Excess IGFBP-3 seems to precipitate myopenia by suppressing the IGF-1/PI3K/AKT signaling pathway thereby inhibiting myogenesis and enhancing myotubule protein degradation<sup>[10]</sup>. Additionally, anti-IGFBP-3 antibody and *in vivo* IGFBP-3 knockdown significantly alleviates myocyte atrophy in PC<sup>[10]</sup>. Thus, preventing IGFBP-3 upregulation by tumor cells or inhibition may have utility in cachexia therapy. Interestingly, in cachectic mice with sarcoma, IGF-1 and IGFBP-3 injection improved cachexia by attenuating weight loss through improved caloric intake and enhanced glucose metabolism<sup>[31]</sup>. Blocking various downstream regulators in IGF-1/PI3K/AKT suppresses its activity and promotes muscle atrophy<sup>[10,32]</sup>.

## SYSTEMIC INFLAMMATION

Chronic inflammation is a primary driver of cachexia. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-1 (IL-1), IL-6, and interferon gamma produced by the tumor or host are well established promoters of cachexia (Table 1)<sup>[5,22]</sup>. Elevated nonspecific markers of inflammation such erythrocyte sedimentation rate and C-reactive protein (CRP) are commonly seen in patients with cachexia and are associated with poor prognosis<sup>[4]</sup>. Furthermore, cachexia is characterized by increased hepatic energy expenditure and the secretion of acute phase reactants with corresponding hypoalbuminemia is observed<sup>[1,3]</sup>. Overall, a robust inflammatory response leads to anorexia and hypercatabolic state<sup>[4,33]</sup>. Targeting inflammatory is therefore an important therapeutic strategy for the management of systemic inflammatory processes, such as cachexia. Broad anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs, corticosteroids, and other anti-inflammatory or immunomodulatory medications have been used to treat cachexia, but a novel and more effective approach would involve specific molecular targets.

### JAK2-STAT3 signaling pathway

The JAK-STAT signaling pathway is activated by various cytokines, involved in signal transduction and the mediation of inflammation, cancer development and progression, and cancer cachexia<sup>[2,34,35]</sup>. Current evidence

suggests that activation of the JAK-STAT signaling pathway contributes to skeletal muscle wasting and weight loss<sup>[36-39]</sup>. While the exact mechanism of this pathway's cachectic effect is unclear, it is likely due to an increase in pro-inflammatory cytokines, acute phase reactants, and catabolic factors. Intracellular JAK2-STAT3 pathway is activated by weight loss and inflammation associated cytokines IL-6, IL-11, leukaemia inhibitory factor, and TNF- $\alpha$ ; thus inhibition is both multifaceted and approachable<sup>[33,40,41]</sup>. Multiple studies have demonstrated attenuation of cachexia by inhibiting the JAK2-STAT3 pathway or its downstream signaling colorectal and lung cancer<sup>[36-39]</sup>.

Gene expression profiling of adipose, skeletal muscle and liver tissue in cachectic mice has shown activation of the JAK2-STAT3<sup>[2]</sup>. When treated with JAK2 inhibitor AG490, cachectic mice with PC had less weight loss and reduced blood IL-6 levels compared to controls<sup>[2]</sup>. AG490 also inhibited tumor growth, invasion, and reduced vascular endothelial growth factor (VEGF) and matrix metalloprotein-2<sup>[42]</sup>. Given that IL-6 is a major activator of JAK2-STAT3 signaling pathway, IL-6 has been shown to promote growth and invasion of pancreatic tumor cells<sup>[2,39,42]</sup>. Reduced secretion of IL-6 limits positive feedback in the pathway and further inflammatory signaling which plays an important role in cachexia mediation<sup>[2,33,38]</sup>.

Ruxolitinib, another JAK2 inhibitor, has been identified as a potential second line treatment in patients with PC<sup>[34,35]</sup>. Currently, there is an ongoing phase II clinical trial investigating ruxolitinib as a treatment of patients with cancer cachexia; however there are no ongoing studies specific to PC<sup>[43]</sup>. In all, the JAK2-STAT3 pathway presents several novel targets for therapy since it is implicated in the pathophysiology of both PC and cachexia, and it is pharmacologically targetable with a variety of antagonists<sup>[2,34,35,44]</sup>.

### IL-6

IL-6 is a cytokine produced by not only host cells such as hepatocytes and macrophages, but also PC cells<sup>[45,46]</sup>. It is involved in cellular proliferation, differentiation, and apoptosis<sup>[46]</sup>. IL-6 is overexpressed in PC and contributes to tumor development and progression, and, as it is a systemic mediator of inflammation, IL-6 is strongly correlated with cachexia<sup>[33,46,47]</sup>. IL-6 promotes growth and enhances the invasiveness of tumor cells<sup>[42]</sup>. Additionally, IL-6 is a central regulator of the hepatic

acute phase response by triggering muscle catabolism in order to mobilize amino acids in the synthesis of acute phase reactants<sup>[4,22]</sup>.

Multiple studies show elevated IL-6 level in patients and mice with PC cachexia<sup>[2,10,45,46,48]</sup>. Furthermore, elevated IL-6 levels seem to correlate with poor functional status, fatigue, increased weight loss, hypoalbuminemia, anemia, and reduced overall survival<sup>[4,45]</sup>. High IL-6 levels are associated with decreased skeletal muscle mass, increased weight loss, and severe fatigue<sup>[45]</sup>. Given this inflammatory state induced by tumor growth, heightened IL-6 secretion is also correlated with elevated CA19-9, CEA, AST, ALP, CRP and cortisol<sup>[45]</sup>.

In itself, cachexia contributes to immune dysfunction by lowering the native T cell response against cancer cells and subsequently impairing treatment response<sup>[33,48]</sup>. IL-6 significantly diminishes the ketogenic response to decreased caloric intake leading to systemic metabolic stress and marked glucocorticoid secretion. Such physiology hinders anti-tumor immunotherapy<sup>[48]</sup>. Cachectic mice with PC had lower plasma glucose and ketones suggesting impaired mitochondrial  $\beta$ -oxidation and free fatty acid metabolism compared to food restricted, or anorexic, healthy controls<sup>[48]</sup>. Based on this study, it would be useful to determine if IL-6 blockade leads to improved ketogenesis and normalization of the metabolic stress response to caloric deprivation. With regard to tumor cells, high serum levels of IL-6 correlates with chemoresistance<sup>[33,45,48]</sup>, while antagonism with IL-6R antibodies increases chemosensitivity<sup>[33]</sup>.

Implementing anti-IL-6 therapies could be useful in reducing inflammation and symptoms of cachexia, however there are currently no clinical trials of anti-IL-6 antibody use in PC models. Anti-IL-6 monoclonal antibodies, such as Tocilizumab, have however been used to treat autoimmune diseases including rheumatoid arthritis and giant cell arteritis. In cancer, anti-IL-6 antibody clazakizumab therapy has been evaluated as a potential cachexia treatment in patients with non-small cell lung cancer (NSCLC)<sup>[4,11]</sup>. A phase II randomized controlled trial (RCT) similarly reported improvements with regard to anemia, fatigue, and weight loss<sup>[4,23,49]</sup>. Likewise preclinical trials with tocilizumab (an anti-IL-6 receptor monoclonal antibody) have demonstrated improved survival and amelioration of cachexia in mice<sup>[50]</sup>. Attenuated IL-6 signaling lessens inflammation and reduces skeletal muscle loss. However, there are no anti-cytokine therapies currently approved for treatment of cachexia in PC patients.

### TNF- $\alpha$

Tumor necrosis factor-alpha (TNF- $\alpha$ ), a cytokine also appropriately known as cachectin, has been extensively studied in multiple pathways that promote lipolysis and myopenia<sup>[4]</sup>. Mouse models of cachexia demonstrate that TNF- $\alpha$  induces proteolysis *via* oxidative stress through reactive oxygen species (ROS) and increase activation of the ubiquitin-proteasome pathway<sup>[4,51,52]</sup>. Elevated

plasma TNF- $\alpha$  level have been observed in patients with PC, particularly those with advanced disease, cachexia, and poor nutritional status<sup>[53-55]</sup>. Similar to IL-6, elevated TNF- $\alpha$  correlates with anemia, hypoalbuminemia, low body weight and body mass index<sup>[53,55]</sup>.

While the inhibition of TNF- $\alpha$  seems an appealing strategy for treating cachexia and inhibitors are readily used in practice, targeting TNF- $\alpha$  has not been effective. One of the first clinical trials evaluated pentoxifylline which was thought to decrease TNF- $\alpha$ <sup>[56]</sup>. Pentoxifylline did not induce weight gain or improve appetite in cachectic patients<sup>[56]</sup>. In the same manner, infliximab, a monoclonal anti-TNF- $\alpha$  antibody, failed to prevent weight loss, increased fatigue, and reduced quality of life in patients with NSCLC<sup>[57]</sup>. In phase II clinical trials, adjunct infliximab to standard gemcitabine therapy showed no significant change in lean body mass, performance status, or survival<sup>[58,59]</sup>.

While not an inhibitor TNF- $\alpha$ , thalidomide down-regulates the expression of TNF- $\alpha$ , NF $\kappa$ B, COX 2, and other cytokines and was thought to reduce weight loss in patients with cachexia due to its immunomodulatory properties<sup>[60-62]</sup>. Indeed, thalidomide is effective at attenuating weight and lean body mass loss<sup>[60]</sup>. Additionally, studies have noted prolonged survival (148 vs 110 d) in patients receiving thalidomide, but it remains uncertain if weight loss control benefits survival<sup>[60]</sup>. A more recent trial did not observe any difference in plasma cytokine levels or cachexia symptoms between the thalidomide group and placebo group<sup>[11,63]</sup>. Furthermore, no benefit over placebo was observed in patients with esophageal cancer<sup>[61]</sup>.

Several more recent drugs have been investigated for their therapeutic potential. Lenalidomide is an immunomodulatory derivative of thalidomide that inhibits TNF- $\alpha$  and decreases inflammatory cytokines. It is FDA approved for myelodysplastic syndrome and multiple myeloma. Postulating that the anti-inflammatory action the drug could have an anti-cachectic effect, phase I and II clinical trials attempted to assess the efficacy of lenalidomide on lean body mass and muscle strength in patients with advanced tumors and inflammation-mediated cachexia<sup>[64]</sup>. Etanercept is a recombinant human TNF- $\alpha$  receptor which binds TNF- $\alpha$  to limit its action and it has been investigated as a potential adjunct to cancer therapy with varied results<sup>[65-67]</sup>. Combining etanercept with docetaxel in patients with advanced cancer has demonstrated improvement in chemotolerance and reduced fatigue<sup>[65,66]</sup>. Conversely, combination etanercept and gemcitabine therapy did not provide obvious benefit to PC patients in clinical trials<sup>[51]</sup>. Other studies similarly show negligible improvements in weight gain, appetite and quality of life<sup>[67]</sup>.

Based on the current pre-clinical and clinical data which demonstrated no benefit of TNF- $\alpha$  inhibition, targeting TNF- $\alpha$  alone as a therapy for PC-induced cachexia seems futile. However, combined TNF- $\alpha$  and IL-6 therapy warrants consideration. OHR/AVR118,

**Table 2 Dietary changes and observed effects in pancreatic cancer induced cachexia**

Ketogenic diet	Diminishes tumor growth and induces apoptosis Increases skeletal muscle mass
Silibinin	Inhibits IL-6, IL-8, TNF- $\alpha$ secretion Downregulates glycolysis proteins Increases skeletal muscle mass
$\omega$ 3 Fatty acid	Regulates metabolic dysfunction Lowers IL-6, TNF- $\alpha$ , CRP Improves host immune response

IL-6: Interleukin-6; TNF- $\alpha$ : Tumor necrosis factor-alpha; CRP: C-reactive protein.

an immunomodulatory peptide-nucleic acid used for anorexia in HIV/AIDS, in clinical trials as a potential therapy<sup>[68,69]</sup>. Significant improvement in appetite, body weight, physical performance and depression has been observed<sup>[68,69]</sup>. Further study should be conducted to assess whether multimodal cytokine inhibition is useful in PC.

### Fat tissue browning

Lipolysis and adipose tissue wasting play a key role in the development of cachexia syndrome. An interesting phenomenon of fat tissue browning has been observed in animal models of cancer cachexia<sup>[1,3,70]</sup>. It is hypothesized that a combination of pro-inflammatory microenvironment derived from factors such as IL-6, TNF- $\alpha$  and parathyroid-related peptide secreted by the tumor and the host as well as metabolic dysregulation leads to white adipose tissue browning as cachexia syndrome progresses<sup>[70,71]</sup>. Brown adipose tissue is characterized by high mitochondrial content and increased uncoupling protein 1 which is responsible for thermoregulation by uncoupling electron transport from adenosine triphosphate (ATP) generation. This causes increased energy expenditure, increased heat production, and lipolysis which leads to exilarated weight loss and contributes to the cachexia syndrome progression<sup>[70-72]</sup>. White adipose tissue wasting and fat browning seems to occur early during development of cachexia syndrome and independently from skeletal muscle wasting<sup>[70]</sup>. However, the complex molecular signaling pathways implicated in fat tissue browning and lipolysis is not well described. Further investigation to understand the mechanisms of how systemic metabolic and inflammatory alterations leads to switching of white adipose tissue to brown adipose tissues is necessary to advance our knowledge and treatment options for cachexia. Inhibition of fat tissue browning should be explored as a possible molecular therapeutic strategy for PC induced cachexia.

## ABERRANT METABOLISM

Anorexia and decreased food intake are commonly seen in cancer. However, cachexia is not driven by anorexia

alone, but by a variety of metabolic changes, both local and systemic, assumed during tumorigenesis<sup>[73]</sup>. There are several well established metabolic phenotypes typical to cancer, including increased energy expenditure and gluconeogenesis, insulin resistance, fat tissue browning, excessive oxidative stress, and proteolysis with amino acid mobilization<sup>[1,74]</sup>. Overall, metabolic dysfunction favors tumor growth and progression while inducing cachexia in the host. Due to the aberrant physiology, simple nutritional supplementation and increased caloric intake are not effective in treating cachexia<sup>[73]</sup>. Reversing metabolic alterations could be key to slowing the progression of cancer and improving survival in cachectic patients (Table 2).

### Ketone bodies and glucose metabolism

Aberrant energy metabolism is of the main pathophysiologic mechanisms of cachexia. Metabolic alterations in the host as well as tumor-derived factors lead to muscle wasting and fat degradation<sup>[74,75]</sup>. A ketogenic diet, one that is high in fats and low in carbohydrates, has been established to produce anticonvulsive, antioxidant and anti-inflammatory effect<sup>[74,75]</sup>. By altering the caloric source, tissues are relegated to performing lipid metabolism with mitochondrial enzymes which tumor cells often lack. In PC murine models, elevated ketone bodies (sodium hydroxybutyrate and lithium acetoacetate) diminish tumor growth and induce apoptosis<sup>[75]</sup>. Correspondingly, tumor cells displayed decreased glucose and glutamine uptake, lactate release, ROS levels, and intracellular ATP, altogether suggestive of metabolic adaptation<sup>[75]</sup>. Furthermore, ketone bodies inhibit degradation of myotubules and adipocytes thereby controlling weightloss<sup>[75]</sup>. In fact, mice that were treated with a ketogenic diet experienced a 45% increase in muscle weight and 20% increase in carcass weight<sup>[75]</sup>. Body and muscle mass are similarly preserved in colorectal cancer mouse models, interestingly with a significant reduction in plasma IL-6<sup>[74]</sup>. Thus, the metabolic alterations induced by the ketogenic diet lead to decreased secretion of pro-inflammatory cytokines and metabolites associated with cachexia involved in pathogenesis of cachexia syndrome. As ketogenic metabolism has been shown to suppress the progression of cancer and decrease systemic inflammation in animal models, it is appropriate to consider further investigation in PC patients with cachectic symptoms.

### Ghrelin

Ghrelin is a peptide hormone secreted by the stomach and pancreas and modulates energy homeostasis, increases appetite, and stimulates growth hormone (GH) secretion<sup>[76]</sup>. Ghrelin constitutes a promising novel therapeutic strategy since it plays a key role in appetite and energy expenditure regulation. Multiple studies reported that administration of ghrelin or ghrelin receptor agonists such as anamorelin improved food

intake, appetite, adiposity, and lean body mass in cachectic patients<sup>[76-78]</sup>. Three Phase 3 RCTs (ROMANA 1 - NCT01387269, ROMANA 2 - NCT01387282 and ROMANA 3 - NCT01395914) reported that anamorelin significantly increased lean body mass in cachectic patients with NSCLC<sup>[76,79]</sup>. A multicenter Japanese study examined the efficacy and safety of anamorelin in patients with NSCLC and concluded that anamorelin was safe, well tolerated and it significantly increased lean body mass, improved anorexia and nutritional state (mainly seen as an increase in prealbumin)<sup>[80]</sup>. In a recent Cochrane systematic review, Khatib *et al.*<sup>[81]</sup> stated that there is insufficient evidence to be able to support or refute the use of ghrelin in cancer cachexia and further investigation with adequately powered RCTs is warranted. Furthermore, no clinical trials to date have been conducted to evaluate effectiveness of ghrelin or ghrelin agonists in PC associated cachexia. Given the promising results of anamorelin in treatment of cancer cachexia across multiple studies, it is worth exploring this further as a treatment option for PC induced cachexia.

### Silibinin

Due to the toxicity of standard chemotherapy, which in itself initiates a significant inflammatory response and cachexia, attention has been given to alternative therapeutic options with anti-cancer and anti-cachectic properties. Silibinin is a bioactive compound from the *Silybum marianum* plant which demonstrates anti-proliferative and pro-apoptotic effect on various cancers *in vitro* and *in vivo* by inhibiting pro-cachectic cytokine production including TNF- $\alpha$ , IL-6 and IL-8<sup>[82-84]</sup>. Of note, silibinin also inhibits the growth of PC cells, induces metabolic alteration, and reduces myofiber degradation<sup>[84]</sup>. Administration of silibinin was associated with the downregulation of major glycolysis mediators such glucose transporter 1 and the consequent reduction in glucose and lactate flux<sup>[84]</sup>. Diminished proto-oncogene *c-myc* expression and STAT3 pathway deactivation is also associated with silibinin treatment<sup>[84]</sup>. Tumor-bearing mice treated with silibinin had significant reduction of weight loss and increase in carcass and muscle mass<sup>[84]</sup>. Silibinin alters pancreatic tumor metabolism mainly by inhibiting glycolysis, the pentose phosphate activity, and nucleotide synthesis<sup>[82,84]</sup>. Targeting glucose metabolism pathways leads to inhibition of tumor growth and could be a potential therapeutic option for cachexia amelioration of tumor induced cachexia.

### $\omega$ 3-polyunsaturated fatty acid supplementation

$\omega$ 3-polyunsaturated fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) exhibit immunomodulatory effects and lower the release of pro-inflammatory cytokines<sup>[85-87]</sup>. They are also involved in various biologic processes including the regulation of membrane integrity, transcription factor activity, and intracellular signaling<sup>[85,86]</sup>. Polyunsaturated fatty acids also play an important role in lipid metabolism

and modulate multiple signaling pathways in PC<sup>[85,87]</sup>. Consumption of  $\omega$ 3-polyunsaturated fatty acids has been shown to significantly decrease resting energy expenditure and regulate metabolic dysfunction<sup>[88]</sup>. Most enteral and parenteral nutritional formulas currently used for cachectic cancer patients provide  $\omega$ 3-polyunsaturated fatty acids supplementation. Data concurs that the addition of  $\omega$ 3-polyunsaturated fatty acids and increased protein improves quality of life and provides a therapeutic advantage in patients with PC cachexia<sup>[88-91]</sup>. Skeletal muscle mass is increased in patients receiving enteral  $\omega$ 3-polyunsaturated fatty acid formulas<sup>[92]</sup>, and fish oil or marine phospholipids supplementation leads to weight and appetite stabilization with fewer side effects<sup>[93]</sup>. Additionally, recent clinical trials report that  $\omega$ 3-polyunsaturated fatty acid supplementation also improves host immune response, quality of life, and survival<sup>[88,89,91-93]</sup>. For example, administration of intravenous  $\omega$ 3-polyunsaturated fatty acids in combination with gemcitabine for up to 6 cycles of chemotherapy improved quality of life and progression free survival in patients with advanced PC<sup>[91]</sup>. *In vitro* gemcitabine and Lipidem™, a combination of DHA and EPA, inhibited growth of PC further confirming anti-proliferative and anti-invasive effects of  $\omega$ 3-polyunsaturated fatty acids in PC<sup>[94]</sup>. Moreover, a systematic review of 11 RCTs concluded that consumption of  $\omega$ 3-polyunsaturated fatty acids improves weight loss, clinical outcomes and overall survival in cachectic PC patients<sup>[88]</sup>.

$\omega$ 3-Polyunsaturated fatty acids play an important role in inflammation, influencing the production of cytokines and ROS as well as suppressing the expression of VEGF and PDGF ultimately disturbing the tumor microenvironment and tumor proliferation<sup>[87]</sup>. A recent meta-analysis reported that patients with GI malignancies supplemented with parenteral  $\omega$ 3-polyunsaturated fatty acids had reduced levels of IL-6, TNF- $\alpha$  and CRP, decreased incidence of postoperative infection and overall better postoperative outcome compared to controls<sup>[89]</sup>. Overall,  $\omega$ 3-polyunsaturated fatty acids-enriched nutrition is safe and provides better outcomes in cachectic cancer patients<sup>[73,89]</sup>. Thus, combining nutritional supplementation with pharmacologic therapy is an ideal management strategy.

## CONCLUSION

Much progress has been made to clarify the pathophysiology of PC induced cachexia. Given the high prevalence of cachexia it is probable that the pancreatic tumor has a unique or exacerbated mechanism leading to cachexia when compared to other cancers. Several molecular signaling pathways have been identified as targets for treatment development. Several pre-clinical studies have provided a foundation of knowledge insight into development of cachexia therapies. However, the application of this data in a clinical setting is necessary to firmly establish potential therapies. Ultimately,

cachexia syndrome is complex and multifactorial. Combination therapy targeting muscle wasting, systemic inflammation, and metabolic alterations is the most effective approach. Further research is necessary to establish PC clinically applicable therapies for cachexia in PC patients.

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# Pancreaticoduodenectomy complicated by Budd-Chiari syndrome: A case report and review of literature

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## Abstract

### BACKGROUND

Pancreaticoduodenectomy (PD)-induced morbidity, consisting mainly of the pancreatic fistula and its hemorrhagic and infectious consequences, is well described in the literature, in terms of its definition, risk factors, preventive measures, and standardized management of complications. However, some life-threatening complications remain atypical and undescribed.

### CASE SUMMARY

We report here the case of a 69-year-old patient with Budd-Chiari syndrome that occurred after arterial embolization of postpancreatectomy hemorrhage. Diagnosis was established with biological findings (*i.e.*, acute liver failure) and radiological findings (*i.e.*, compressive hematoma of the retrohepatic vena cava). Emergency surgical revision was performed to evacuate the hematoma. The postoperative course was uneventful, with rapid recovery of liver function. To our knowledge, post-PD Budd-Chiari syndrome has never been described in the literature.

### CONCLUSION

Acute liver failure in early post-PD should prompt investigation to rule out Budd-Chiari syndrome.

**Key words:** Pancreaticoduodenectomy; Pancreatic fistula; Acute liver failure; Budd-Chiari syndrome; Case report

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**Core tip:** Pancreaticoduodenectomy (PD) is responsible for significant morbidity and mortality. Pancreatic fistula (PF), the main complication of this surgery, has been the subject of many clinical practice guidelines releases to recommend its definition, prevention, and management. However, some clinical presentations of severe PF after PD remain atypical and undescribed. We report here a case of acute Budd-Chiari syndrome in relation to a compressive hematoma of the retrohepatic vena cava due to massive postpancreatectomy hemorrhage. Emergency relaparotomy to remove the compressive hematoma enabled rapid improvement. Awareness of this potential life-threatening complication may help avoid a delay in diagnosis and to propose an appropriate therapeutic strategy.

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## INTRODUCTION

Pancreaticoduodenectomy (PD) is responsible for significant morbidity and mortality, mainly related to the occurrence of pancreatic fistula (PF)<sup>[1]</sup>. The consequent hemorrhagic and infectious complications of PF make it a life-threatening issue. While its definition, risk factors, prevention, and management are well described in the literature, some clinical presentations of severe PF after PD appear atypical and, to our knowledge, undescribed.

Acute liver failure following postpancreatectomy hemorrhage, arising from various etiologies, is widely reported in case series and reports. In the case reported herein, an acute Budd-Chiari syndrome developed due to the extrinsic compression of the inferior vena cava by a hematoma, which was diagnosed by computed tomography (CT) scan and was treated surgically.

## CASE PRESENTATION

A 69-year-old man with no significant history was admitted for ampullary adenocarcinoma. A PD was performed by laparotomy using the Whipple procedure, followed by a Child reconstruction. The patient was considered high-risk for PF, according to the Wirsung duct size of  $\leq 3$  mm and presence of soft pancreatic parenchyma; thus, a preventive treatment (octreotide) was given. The postoperative course was marked by PF development on the 3<sup>rd</sup> postoperative day, which

was treated with somatostatin and conservation of the nonaspirating drain placed intraoperatively. A control CT scan was performed on the 7<sup>th</sup> postoperative day and showed absence of active bleeding or pseudoaneurysm, absence of hematoma, and good placement of the drain (with contact with the pancreaticojejunal anastomosis). On the 12<sup>th</sup> postoperative day, the patient presented hemorrhagic shock with hemodynamic instability. The CT scan revealed an active bleeding arising from the stump of the gastroduodenal artery, with formation of a noncompressive hematoma. The drain had migrated and was no longer in the area of the pancreatic anastomosis. The PF was scored as grade C, according to International Study Group of Pancreatic Fistula classification. Endovascular exclusion of the gastroduodenal artery was performed by interventional radiology, along with placement of a covered stent in the hepatic artery.

Severe acute liver failure and acute renal failure developed immediately. Blood test showed cytolysis above 10 N (aspartate aminotransferase at 2000 UI/L, alanine aminotransferase at 1738 UI/L), cholestasis (alkaline phosphatase at 336 UI/L, gamma-glutamyltransferase at 388 UI/L), total hyperbilirubinemia (at 43.8  $\mu$ mol/L), decreased prothrombin rate (by 36%), decreased factor V (by 32%), and a creatinine rate of 152  $\mu$ mol/L. On the repeat CT (abdominal injection of iodinated contrast), the liver presented a heterogeneous enhancement, with a defect of enhancement in the left liver on portal time. Concerning liver vascularization, the portal trunk, the hepatic veins and the hepatic artery were permeable, with absence of intrastent thrombosis and of active bleeding. However, the inferior vena cava was compressed in its retrohepatic and suprahepatic segments by a hematoma located in the lesser omental sac (Figures 1 and 2).

## FINAL DIAGNOSIS

This presentation was consistent with a secondary acute Budd-Chiari syndrome, due to the extrinsic compression of the inferior vena cava by a compartmentalized hematoma in the lesser omental sac. This hematoma was linked to the abundant bleeding of the stump of the gastroduodenal artery.

## TREATMENT

A emergent relaparotomy was performed and confirmed the diagnosis, showing a congestive hepatomegaly and a compression on the inferior vena cava by the hematoma.

## OUTCOME AND FOLLOW-UP

Hemodynamic status and liver function improved rapidly after evacuation of this hematoma. Fifteen days later, CT showed hepatic segment I necrosis, with no clinical and biological consequences. Postoperative follow-up was progressively favorable, with the recovery of a correct general status and a normal liver function.

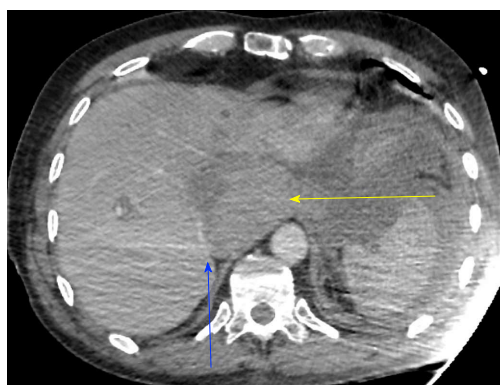


Figure 1 Injected abdominopelvic computed tomography showing extrinsic compression of the retrohepatic vena cava (blue arrow) by hematoma (yellow arrow).



Figure 2 Injected abdominopelvic computed tomography showing extrinsic compression of the inferior vena cava and cavohepatic confluence. Permeable hepatic veins are indicated by white lines.

## DISCUSSION

We report here a very atypical complication of a severe PF after PD: An acute Budd-Chiari syndrome secondary to a compressive hematoma of the retrohepatic vena cava.

The reported morbidity rates after PD range from 30% to 50%, and are mainly related to the occurrence of PF. PF can be life-threatening because of the hemorrhagic and infectious complications it induces<sup>[1]</sup>. Delayed postoperative hemorrhage is one of the most severe issue in pancreatic surgery. This dreaded complication is usually secondary to erosion of the visceral arteries, most often the gastroduodenal artery stump, following a PF<sup>[2]</sup>. In salvage hemorrhage treatment, transcatheter arterial embolization or stenting of the hepatic artery is an effective and safe treatment; whereas, open surgical hemostasis may cause remarkable decaying, be noneffective, and lead to ligation of the hepatic artery<sup>[2]</sup>.

The complication of liver failure in the postoperative period after PD occurs only seldomly, and is reported in the literature to the same low extent. Most of the reported cases are only described in cases reports; these include an underestimated or undiagnosed liver disease before surgery<sup>[3,4]</sup>, a nutritional origin related to exocrine pancreatic insufficiency<sup>[5,6]</sup>, an asymptomatic

median arcuate ligament not detected before and during surgery, or inefficiently treated<sup>[7,8]</sup>, a hepatic artery injury during the PD<sup>[9,10]</sup>, as secondary to adjuvant chemotherapy (mainly with gemcitabine)<sup>[11]</sup>, a proximal or selective hepatic arterial embolization or intrastent thrombosis<sup>[12-17]</sup>, and a portal vein occlusion<sup>[18,19]</sup>.

In the case presented herein, liver failure was probably multifactorial, but dominated by the inferior vena cava compression interfering with hepatic venous drainage. The migration of the drain may have favored misdrainage and the formation of consequently compressive hematoma. The delay between CT scan and endovascular exclusion was approximately 3 h, which may explain the increase in hematoma, becoming compressive on the inferior vena cava. This delay was due to the difficulty of the endovascular treatment. Surgical revision was preferred to radiological drainage, because of the severity and high-speed development of liver failure.

Budd-Chiari syndrome results from obstruction of hepatic venous drainage, regardless of the obstruction site (from hepatic venules to the inferior vena cava) and cause. It is classified into primary or secondary cases. Secondary Budd-Chiari syndrome is defined as endoluminal obstruction by extravascular lesion (*i.e.*, tumor, infection, or parasite) or by extrinsic compression (*i.e.*, tumor or hematoma). Clinically, Budd-Chiari syndrome is characterized by liver failure in a few days, sometimes severe or even fulminant. Hepatomegaly and elevated transaminases (greater than 5 N) are associated. Ascites and renal insufficiency are very common. In our case, the absence of ascites, which can be explained by the persistence of permeability of the hepatic veins, led to a delay in the diagnosis.

The treatment of Budd-Chiari syndrome consists of treating the cause (here, evacuation of compressive hematoma and control of hemostasis) and reestablishing hepatic venous drainage. The overall prognosis has improved significantly in recent years. Reportedly, when the entire therapeutic strategy is implemented, the 5-year overall survival rate is 89%<sup>[20]</sup>.

In our case, the patient presented a series of complications during the postoperative period. The main issue was grade C PF responsible for hemorrhage due to rupture of a pseudoaneurysm of the gastroduodenal artery stump, requiring emergent endovascular treatment. This sequence of complications, as well as its management, risk factors and prevention, have been well described in the literature. To our knowledge, extrinsic compression of the inferior vena cava by a compartmentalized hematoma in the lesser omental sac responsible for an acute Budd-Chiari syndrome with severe liver failure remains undescribed.

Conventionally, Budd-Chiari syndrome is associated with a compensatory hypertrophy of properly drained areas (most often segment I because of anatomy of venous drainage pathways) and ischemia that can progress to necrosis of obstructed venous drainage areas<sup>[20]</sup>. In our case, asynchronous venous obstruction by initial compression of the retrohepatic vena cava, and

therefore Spigelian veins, followed by compression of the cavohepatic return pathways explains the predominant segment I ischemia, causing its necrosis.

Awareness of this potential life-threatening complication may allow a rapid diagnosis by harvesting clinical evidence (*i.e.*, hemodynamic instability, hepatomegaly, and ascites), biological evidence (*i.e.*, hepatic cytolysis, acute liver failure, and acute renal failure), and radiological evidence (*i.e.*, extrinsic cavohepatic compression, ascites, and heterogeneous liver parenchyma). Undelayed diagnosis and appropriate therapeutic management will determine the prognosis of this complication.

More generally, it may be necessary to discuss the interest of a systematic surgery after endovascular treatment of hemorrhage for evacuation and drainage of ongoing or residual hematoma that could be a source of infectious or mechanical complications, such as gastroparesis, increasing morbidity, lengthening of hospital stay, and mortality.

## EXPERIENCES AND LESSONS

An acute liver failure following endovascular treatment of postpancreatectomy hemorrhage should lead to the ruling out of Budd-Chiari syndrome, justifying emergent diagnosis imaging, and addressed by surgical revision.

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