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World Journal of Gastrointestinal Surgery (*World J Gastrointest Surg*, *WJGS*, online ISSN 1948-9366, DOI: 10.4240) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGS covers topics concerning micro-invasive surgery; laparoscopy; hepatic, biliary, pancreatic and splenic surgery; surgical nutrition; portal hypertension, as well as associated subjects. The current columns of *WJGS* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal surgery diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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Perspective of laparoscopic liver resection for hepatocellular carcinoma

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Abstract

Liver resection (LR) for hepatocellular carcinoma (HCC) in patients with chronic liver disease (CLD) is associated with high risks of developing significant postoperative complications and multicentric metachronous lesions, which can result in the need for repeated treatments. Studies comparing laparoscopic procedures to open LR consistently report reduced blood loss and transfusions

requirements, lower postoperative morbidity, and shorter hospital stays, with no differences in oncologic outcomes. In addition, laparoscopic LR is associated with reduced postoperative ascites and a lower incidence of liver failure for HCC patients with CLD, due to the reduced surgery-induced parenchymal injury to the residual liver and limited destruction of the collateral blood/lymphatic flow around the liver. Finally, this procedure facilitates subsequent repeat LR due to minimal adhesion formation and improved vision/manipulation between adhesions. These characteristics of laparoscopic LR may lead to an expansion of the indications for LR. This editorial is based on the review and meta-analysis presented at the 2nd International Consensus Conference on Laparoscopic Liver Resection in Iwate, Japan, in October 2014 (Chairperson of the congress is Professor Go Wakabayashi from the Department of Surgery, Iwate Medical University School of Medicine), which is published in the *Journal of Hepato-Biliary-Pancreatic Sciences*.

Key words: Laparoscopic; Liver resection; Hepatocellular carcinoma; Chronic liver disease; Liver failure; Ascites; Indication; Repeat hepatectomy

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Core tip: Liver resection (LR) for hepatocellular carcinoma patients with chronic liver disease has high risks for developing significant postoperative complications and multicentric metachronous lesions with need of repeated treatments. Laparoscopic LR has advantages of reduced surgery-induced parenchymal injury and destruction of the collateral blood/lymphatic flow, which leads to reduced production of postoperative ascites, and facilitates repeat LR because of reduced adhesion formation and improved vision/manipulation between adhesions. These characteristics of laparoscopic LR may lead to expansion of the indications for LR.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is among the most common primary cancers and causes of cancer-related deaths^[1,2]. The options for HCC treatment include transarterial chemoembolization and local ablation therapy^[3], but the best chance for cure is with liver resection (LR)^[4] or liver transplantation^[5]. Liver transplantation should be considered in patients with deteriorating liver function who are within the Milan criteria^[6], whereas LR should be considered for those with preserved liver function^[7,8]. However, most HCC patients are at high risk for developing significant postoperative complications and multicentric metachronous lesions with underlying chronic liver disease (CLD). For these patients, the oncologic therapeutic effects and degree of invasive surgical stress, especially to the impaired liver, should be considered during the treatments. The variety of symptoms in patients with CLD^[9] raises the risks associated with anesthesia and surgery^[10], which increase according to the preoperative Child-Pugh class^[11]. For severe CLD patients, refractory ascites often develop even with limited LR, which then leads to fatal liver failure^[12,13].

Currently, the treatment choice for an HCC patient with CLD depends on the combination of tumor and liver conditions^[14]. Nevertheless, there are still a considerable number of these patients who are unable to undergo one of the treatment modalities listed above. Such patients may benefit from less-invasive laparoscopic LR (LLR)^[15] compared to open LR (OLR)^[16]. Indeed, this procedure has recently been evaluated in a review and meta-analysis^[17], which was presented at the 2nd International Consensus Conference on Laparoscopic Liver Resection in Iwate, Japan, in October 2014 (the Chairperson of the Congress is Professor Go Wakabayashi from the Department of Surgery, Iwate Medical University School of Medicine).

OVERVIEW OF LLR

For the review and meta-analysis^[17], 2183 and 466 articles were identified under a PubMed search of "laparoscopic liver resection" and "laparoscopic liver resection + hepatocellular carcinoma," respectively. No randomized trials were available. All data were reported as case series, case-control studies, reviews, and meta-analyses. Of these, there was one Cochrane review and 81 comparative studies for LLR, as well as 12 meta-analyses for all types of indications^[18-22], colorectal metastases^[23,24], left lateral sectionectomy^[25], and HCC^[26].

In the absence of randomized studies, the Cochrane study could not draw any conclusions. The meta-analyses generally showed that LLR reduced blood loss, transfusion requirements and complication rates, shortened the hospital stay, and resulted in identical or better surgical margins than OLR. Several analyses examined long-term results and showed no differences in oncologic outcomes between LLR and OLR.

The indications for LLR are essentially the same as those for OLR. However, the centers reported in these studies identified technical feasibilities related to tumor conditions (such as size, and location) and extent of resection as the limiting factors. Typically, giant tumors (> 10-15 cm in diameter) are excluded from the indications for LLR due to the lack of appropriate view of operative field in the small abdominal cavity. Also, LR combined with major vessel resection and reconstruction and living-donor LR for transplantation are performed at only a few experienced centers. A previous international survey^[27] reported a relatively small percentage (approximately 40%) of LLR procedures with some groups of higher rates over 80%. Although the low rate and disparity of LLR application could lead to selection bias in the reported results, the studies showed that LLR generally produced better perioperative outcomes without compromising long-term oncologic outcome for the patients selected to undergo these procedures.

LLR FOR HCC WITH CLD

Patients who undergo LR are exposed to three different types of stresses that are of particular importance in patients with CLD: (1) general, whole-body surgical stress; (2) reduced liver function due to resected liver volume; and (3) surgery-induced injury to the area around the liver (caused by destruction of the collateral blood and lymphatic flow with laparotomy and mobilization of the liver) and residual liver parenchyma (caused by mesenchymal injury from the compression of the liver). With LLR, the reduced surgery-induced injury can lower the risk of refractory ascites, leading to less successive complications and a smooth recovery without liver failure.

Among the studies in the review, HCC cases were included in four meta-analyses^[26,28-30] (with 494 to 1238 patients) and 23 comparative studies^[31-53], 13 of which^[31-36,41,43,44,49-51,53] examined the rates of postoperative ascites and liver failure. We conducted a meta-analysis for postoperative ascites and liver failure in nine and six of these studies that were of a high quality^[17]. The analysis showed reduced incidences of postoperative ascites (odds ratio 0.26, 95%CI: 0.14-0.49; $P < 0.001$) and liver failure (odds ratio 0.24, 95%CI: 0.10-0.56; $P = 0.001$), which are associated with LLR.

The impact of LLR on ascites production and liver failure depends on the severity of the background CLD, extent of the resection, and the operative technique (extent of dissection of the peritoneal attachments

Table 1 Possible conditions for the expansion of liver resection indication with laparoscopic liver resection

Patient group	Indications
Patients with severe liver dysfunction (Child-Pugh B/C)	LLR for subcapsular HCCs, particularly for the tumors on suspended ruptures LLR as the bridging therapy to liver transplantation, with the advantage of examination and evaluation of tumor pathology before transplantation LLR for HCCs in the patients with hepatitis B virus-related severe liver dysfunction without previous antiviral treatments who could acquire the recovery of liver function after antiviral treatments ^[62]
Patients with repeat lesions	Repeat LLR for the patients with deteriorated liver function and multicentric metachronous HCCs who have undergone multiple treatments and are usually treated with local ablation therapy, transarterial chemoembolization, or sorafenib

HCC: Hepatocellular carcinoma; LLR: Laparoscopic liver resection.

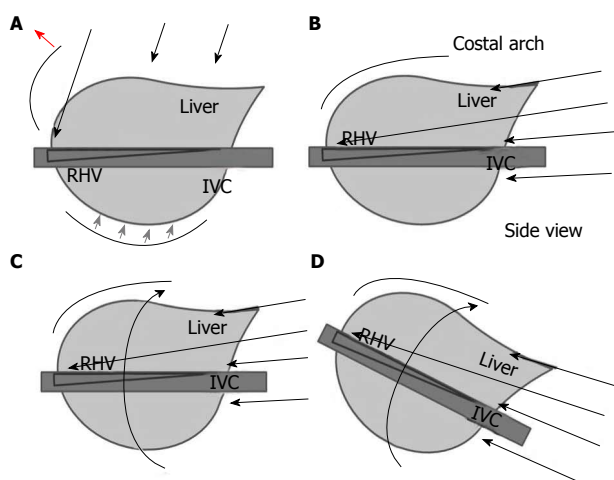


Figure 1 Specific view and approach/manipulation of laparoscopic liver surgery. A: The long arrow shows the direction of view and approach for open liver surgery. The subphrenic space is opened with a large subcostal incision plus lifting of the costal arch (red arrow) and the liver is picked up with the dissection of retroperitoneal attachments (gray arrows); B: Arrows show the direction of approach of the laparoscope and forceps; C,D: In laparoscopic liver resection, adjustments of laparoscopic view allow for fine operative fields and handling of large-volume liver/tumors by postural changes/rotation, which reduce compression of the liver parenchyma. IVC: Inferior vena cava; RHV: Right hepatic vein.

and adhesions). There are six comparative studies from five institutions in which all patients with HCC had liver cirrhosis^[31,33,36,42,45,53]. Among them, all three studies^[31,33,53] that examined postoperative ascites production showed a significant reduction with LLR. Another study compared the perioperative results after LLR between patients with severe cirrhosis (Child-Pugh B/C and ICG R15 \geq 40%) and with mild-moderate cirrhosis^[54]. Although it was a retrospective small-sized non-matched study, it showed comparable short-term outcomes, including postoperative ascites production, in these patients. The positive results from these well-designed studies examining the outcome of LLR for severe cirrhotic patients could lead to expansion of the indications for LLR.

Additional benefits of LLR in other aspects were found in other studies. The development of fewer adhesions with laparoscopic surgery was found to facilitate subsequent surgeries^[55]. With the initial LR

performed in laparoscopic approach, the subsequent salvage transplantation requires a shorter operative time, with reduced blood loss and fewer transfusions^[56]. Furthermore, recurrence with potential multicentric metachronous lesions is an important issue for HCC patients with CLD. Repeat LR increases the difficulty of LR as a result of modifications to the anatomy and the formation of adhesions. Two studies^[57,58] compared laparoscopic and open procedures with regard to repeat LR. The operating time of repeat LLR was significantly shorter with previous LLR compared to OLR. In addition, repeat LLR was associated with reduced blood loss and postoperative morbidity, and a shorter hospital stay compared with repeat OLR regardless of the approach used in the previous LR. The benefit of LLR for repeat procedures may be due to a reduced need for adhesiolysis because of the specific view and approach/manipulation of LLR (Figure 1)^[59-61]. This may also cause the reduction of surgery-induced injury on the liver and the area surrounding it.

CONCLUSION

The advantages of LLR for HCC patients with CLD include reductions of surgery-induced parenchymal injury and destruction of the collateral blood/lymphatic flow around the liver. LLR also minimizes the production of postoperative ascites and results in fewer subsequent fatal complications. The formation of fewer adhesions and improved vision and manipulation between adhesions facilitates subsequent repeat LR procedures. These characteristics of LLR may lead to expansion of the indications for LR for these patients (Table 1). However, further investigations are required to document the benefits of LLR in specific conditions.

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Is gall bladder cancer a bad cancer *per se*?

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Abstract

Gall bladder cancer (GBC) has one of the poorest outcomes of all cancers. Early GBC is difficult to diagnose on even computed tomography. GB has no submucosa and the cancer infiltrates directly into the muscularis propria. GB wall is thin and important adjacent organs viz. liver, duodenum and pancreas get easily infiltrated. Tumor in the GB neck often needs extended right hepatectomy. Infiltration of duodenum/pancreas may necessitate pancreato-duodenectomy or even

hepato-pancreato-duodenectomy. Mortality of surgical procedures, when performed for GBC, is higher than when performed for other cancers. Survival in GBC, even after R0 resection, is poor. There is no proven role of neo-adjuvant or adjuvant therapy for loco-regionally advanced GBC. There is no role of palliative surgery in metastatic GBC. Early GBC is diagnosed incidentally after cholecystectomy for stones and requires reoperation for completion extended cholecystectomy but unfortunately, most surgeons are not aware of this. GBC has a peculiar epidemiology and is uncommon in the West and has, therefore, not received much attention. Preventive cholecystectomy for asymptomatic stones is not recommended and there is no serum marker for screening. With all factors pitched against it, it does appear that GBC is a bad cancer *per se*!

Key words: Gall bladder neoplasms; Cholangiocarcinoma; Cholecystectomy; Hepatectomy; Hepato-pancreato-duodenectomy

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Core tip: Gall bladder (GB) wall is thin and important adjacent organs get easily infiltrated. Tumor in GB neck needs hepatectomy and infiltration of duodenum/pancreas necessitates pancreato-duodenectomy; mortality of these procedures is high. Survival in gall bladder cancer (GBC), even after R0 resection, is poor. There is no role of neo-adjuvant or adjuvant therapy. Early GBC, diagnosed incidentally after cholecystectomy for stones, requires reoperation but most surgeons are not aware of this. GBC, uncommon in the West, has not received much attention. Preventive cholecystectomy is not recommended and there is no marker for screening. GBC is a bad cancer *per se*!

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Gall bladder cancer (GBC), the commonest malignancy of the biliary tract, has one of the poorest outcomes of all cancers.

Early GBC has symptoms indistinguishable from gall stone disease (GSD). Diagnosis of early GBC is almost impossible on ultrasonography (US) and difficult on even computed tomography (CT) cf. hepatocellular carcinoma (HCC) and peri-ampullary cancers; endoscopic ultrasonography (EUS) is better but is not available easily and everywhere. Magnetic resonance imaging (MRI) too has no role in the diagnosis of GBC (cf. cholangio-carcinoma). GBC is PET avid but its use is restricted mainly to detect spread than for diagnosis. Laparoscopy again is to look for peritoneal dissemination than for diagnosis.

Even the anatomy of the gall bladder (GB) is against it. Unlike the intestines, GB wall has no submucosa so that a mucosal cancer infiltrates directly into the muscularis propria. Normal GB wall is thin (< 3 mm) and important adjacent organs viz. liver, duodenum and pancreas get easily infiltrated. The hepatic surface of the GB has no peritoneal cover (serosa) so a GB tumor easily infiltrates the liver parenchyma. Surgical resection for GBC involves lymphadenectomy and one (liver) or more organs. A 2 cm liver margin is required for GBC (cf. colo-rectal cancer liver metastases CRLM where even 1 mm margin is acceptable). Liver resection is usually in the form of a wedge but a major liver resection may be required if there is significant liver infiltration. For tumors in the GB neck, CBD has to be resected to achieve a negative margin; right portal pedicle lies at a distance of just a few mm from the GB bed and has to be sacrificed to achieve a 2 cm liver margin thus needing extended right hepatectomy (ERH). Infiltration of duodenum/pancreas may necessitate pancreato-duodenectomy (PD) and some patients with loco-regionally advanced disease may even require hepato-pancreato-duodenectomy (HPD). Involvement of main portal vein and proper hepatic artery contraindicates resection. While minimally invasive surgery has been shown to be technically safe and oncologically adequate for several cancers, *e.g.*, esophagus, stomach and CRC, its role and place in GBC is yet to be established.

Mortality of surgical procedures for GBC is high; mortality of the same surgical procedures when performed for GBC is higher than when performed for other cancers, *e.g.*, mortality of major hepatectomy for GBC is 16% vs 4% for cholangio-carcinoma CC^[1]. Mortality of HPD for GBC is much higher than that for CC^[2]. In a recent review, the Nagoya group observed that HPD, which can be performed for CC remains controversial for GBC^[3].

Survival in GBC, even after R0 resection, is poor. In many reports, no T3/T4 or node positive patient survived for 5 years. Even actuarial survival of GBC is much poorer, probably the poorest of all, than every other cancer - 5 year survival of stage III GBC is 7%-8% cf. 72% for breast, 38%-74% for CRC and 9%-20% for stomach cancer in stage III^[4]. In many cancers, the survival curve plateaus after the first two years and very

few late recurrences occur, *e.g.*, 5 year survival in CRC is 65% and drops to only 58% at 10 years^[4]. In GBC, disease recurs and patients die even after five years; in a report of 165 patients with T3/T4 GBC, 25 patients survived for 5 years but only 11 survived for 10 years^[5]. A critical review of major resections, *e.g.*, ERH, PD and HPD for GBC, reported mostly from Japanese centers, reveals that more patients died of these procedures than actually lived for 5 or 10 years because of them.

A large majority of GBCs are metastatic or loco-regionally advanced. In some cancers, *e.g.*, genito-urinary, breast and CRC, cure is possible even in presence of metastases; even repeat resections are indicated. In GBC, there is no role for resection in presence of metastases. Unlike some other cancers, *e.g.*, CRC and stomach, where the primary tumor should be resected for palliation even if metastases are unresectable, there is no role of palliative surgery in metastatic GBC. Total hepatectomy and transplant are options for unresectable HCC and CC and for neuro-endocrine tumors (NETs) with liver metastases but not for GBC. For loco-regionally advanced GBC, there is no proven neo-adjuvant treatment (cf. unresectable pancreatic, esophageal and rectal cancers). As opposed to breast cancer and CRC, where personalized chemotherapy is being increasingly used, the role of even adjuvant therapy is not well established in GBC. No molecular targets have so far been identified for GBC hence no biologicals are suitable for use.

GBC is resectable for cure only when it is confined to the GB and has spread to a few regional lymph nodes. Such early stage disease is invariably an incidental finding on histopathology of the GB removed for GSD. Most such patients need a reoperation for completion extended cholecystectomy (CEC)^[6]; unfortunately, most surgeons are not aware of this and the patient is denied a possible attempt at cure. This is reflected in poor (50% for stage I and 28% for stage II) 5 year survival in more than 10000 patients treated between 1989 and 1996^[4].

Injustice has been done to GBC as it was clubbed with liver in the 6th International Classification of Diseases ICD (1950), with other biliary cancers in the 7th ICD (1957) and with extra-hepatic bile duct and ampulla in the 8th ICD (1967); it was only in the 9th ICD (1977) that GBC received an identity of its own as 156 and recently as C 23.9 in the 10th ICD (2007).

The peculiar epidemiology of GBC is also its own enemy. GBC is a "non-western disease" - rare in United States/Canada, United Kingdom/Western Europe and Australia/New Zealand but common in Central/South America, Central/Eastern Europe, South Asia (India) and East Asia (Japan and South Korea)^[7]. Not much funding is available and very little investigative work has, therefore, been done for GBC. Even rarer tumors, *e.g.*, cystic pancreatic neoplasms (CPN) and gastrointestinal stromal tumors (GIST) have received more attention because of the populations they afflict. GBC is one of the few non-gender related cancers which are

more common in women than in men; in many under developed and developing economies, women tend to receive less optimal health care as compared to men.

Prevention, therefore, becomes important. Primary prevention remains a dream as the etiology of GBC is not yet known (cf. tobacco for lung and oral cavity, hepatitis for HCC). Secondary prevention, cholecystectomy for asymptomatic GSD, is invasive, expensive and risky and is not recommended. There is no serum marker (cf. PSA for prostate) for screening; surveillance of high risk groups viz. those with asymptomatic GS using US (cf. alfa-feto protein AFP for HCC in patients with cirrhosis or endoscopic, *e.g.*, for esophageal cancer in Barrett's and for CRC in inflammatory bowel disease IBD) is not an option as US detects the disease in advanced stage (II or more) only.

With all factors pitched against it, it does appear that GBC is a bad cancer *per se*!

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Retrospective Cohort Study

Capillary refill time as a guide for operational decision-making process of autoimmune pancreatitis: Preliminary results

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Abstract

AIM: To investigate the efficacy of a novel intraoperative diagnostic technique for patients with preliminary diagnosis of autoimmune pancreatitis (AIP).

METHODS: Patients with pancreatic surgery were reviewed to identify those who received a preliminary diagnosis of AIP between January 2010 and January 2014. The following data were collected prospectively for patients with a pathological diagnosis of AIP: clinical and demographic features, radiological and operative findings, treatment procedure, and intraoperative capillary refill time (CRT) in the pancreatic bed.

RESULTS: Eight patients (six males, two females; mean age: 51.4 years) met the eligibility criteria of pathologically confirmed diagnosis. The most frequent presenting symptoms were epigastric pain and weight loss. The most commonly conducted preoperative imaging studies were computed tomography and endoscopic retrograde pancreaticododenography. The most common intraoperative macroscopic observations were mass formation in the pancreatic head and diffuse hypervascularization in the pancreatic bed. All patients showed decreased CRT (median value: 0.76 s, range: 0.58-1.35). One-half of the patients underwent surgical resection and the other half received medical treatment without any further surgical intervention.

CONCLUSION: This preliminary study demonstrates a novel experience with measurement of CRT in the pancreatic bed during the intraoperative evaluation of patients with AIP.

Key words: Autoimmune pancreatitis; Pancreatic mass;

Inflammation; Hypervascularity; Capillary refill time

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Core tip: Autoimmune pancreatitis is still a diagnostic dilemma, and there is a way to go, especially differentiating from pancreatic malignancy. Hence the debate: to cut or to observe. We hypothesized that this infrequent inflammatory event causes increased vascularity on pancreatic tissue. Thus, we aimed to display whether there was a remarkable vascularity on the pancreatic surface or not by using capillary refill time. Preliminary results showed decreased capillary refill time demonstrating hypervascularity on the pancreatic surface and this inspired that capillary refill time could be an additional tool to guide the operational decision-making process of autoimmune pancreatitis.

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INTRODUCTION

Autoimmune pancreatitis (AIP) is clinically defined as chronic inflammatory pancreatitis with irregular narrowing of the main pancreatic duct, presenting with hyperglobulinaemia (especially IgG4)^[1,2]. Since its first description^[3], this infrequently recognized pathology has posed a diagnostic dilemma; its initial clinical symptoms are generally non-specific (abdominal pain, weight loss and obstructive jaundice) and commonly lead to a misdiagnosis of pancreatic cancer.

Differentiating AIP from malignant pathology in the pancreas requires some clinical judgment in assessing the findings of the diagnostic workup and can be dependent upon the treating physician's surgical experience with both conditions. Although imaging methods, such as computed tomography (CT), magnetic resonance imaging (MRI) and endosonography could provide differential findings, the accuracy is not consistent among all patients. Furthermore, there are many pitfalls in the frozen section diagnosis of pancreatic lesions and AIP patients may remain undiagnosed, so that sometimes, experience of the surgeon can play a remarkable role in determination of which management strategy will be performed.

Intraoperative observations may be useful for diagnosing AIP and determining the approach best suited for clinical management of a particular case; for example, surgeons may use macroscopic observations, such as that of a tumoral mass, to differentiate pancreatic cancer from AIP, and consider a pancreatoduodenectomy as treatment. However, it is important to remember that at

least 5% of patients undergoing surgery for a preliminary diagnosis of pancreatic cancer are found to have benign inflammatory disease according to their histopathological findings^[4]. Although a few policies have been published to help guide the surgeon's decision for managing such borderline cases, this entity remains a diagnostic challenge in general.

For the current study, we were inspired by the inflammatory nature of AIP pathology to investigate whether there is an association between changes in the pancreatic vascular pattern in patients with AIP, and whether such an association would be related to a measurable increase in blood flow in the pancreatic bed due to ongoing inflammation. We hypothesized that such an increase (reflective of the circulatory status) may be measurable as capillary refill time (CRT). Thus, this preliminary report presents our initial experience with measurement of CRT in the pancreatic bed during the intraoperative evaluation of patients with AIP.

MATERIALS AND METHODS

For this study, the medical records of patients undergoing pancreatic surgery were searched to identify patients who received a preliminary diagnosis of AIP between January 2010 and January 2014. All patients provided informed written consent prior to study enrollment and were consented for surgical procedure, as well. Those patients with a pathologically confirmed diagnosis of AIP were selected for study inclusion. All data recorded prospectively were retrieved from an IRB approved database. Clinical and demographic features of the patients, diagnostic methods and radiological findings, intraoperative observations, surgical procedures and outcomes were analyzed. Although systemic disease was investigated in three cases, increased IgG4 levels was detected in only one patient.

A single clinician using the following procedure made all measurements of CRT: First, the patient's core temperature was evaluated (nasopharynx, normal range: 36.5 °C - 37.5 °C) and proper thermoregulation was ensured. Then, the CRT was determined by pressing a gloved finger against the pancreatic surface, particularly on the most vascularized portion, until the region turned white (pressing time ranged between 4 and 7 s). The finger pressure was then fully released and the time it took for the pancreatic surface to return to its previous color was measured to the nearest second using a chronometer (generally carried out by the anesthesia care team). None of the patients received inotropic agents at the time of the CRT measurement. Each patient's vital signs were recorded during the CRT measurement; in the case of abnormal vital signs, treatment was immediately initiated to restore the hemodynamic profile, after which a repeat measurement was taken. The normal values for CRT are well established and defined as < 2 s, with prolonged refill defined as ≥ 2 s. A digital video camera was used

Table 1 Demographic features of the patients with autoimmune pancreatitis

Sex	Age (yr)	Presentation	Diagnostic tests	Findings	CRT (s)	Surgery
Patient 1, F	69	Jaundice, epigastric pain	Doppler US, CT	4 cm × 4 cm solid mass, Pancreatic head, LAPs	0.80	PPPD
Patient 2, M	61	Epigastric pain, weight loss, jaundice	ERCP, CT	Pancreatic head mass (4 cm × 3 cm), obstruction of the CBD, invasion of SMV	1.35	PPPD
Patient 3, M	34	Jaundice, pruritis, fatigue	ERCP, CT	Periampullary solid mass 2 cm × 3 cm in size	0.68	Biopsy
Patient 4, M	56	Fatty stool, epigastric pain, weight loss	Doppler US, PET-CT	Diffuse swelling of the pancreas	0.58	Biopsy
Patient 5, M	42	Epigastric pain, weight loss, fatty stool	Doppler US, CT, EU	Periampullary solid mass (2 cm × 2 cm)	0.75	Biopsy
Patient 6, F	58	Mild epigastric pain, weight loss	CT, MRI,	Diffuse swelling and 2 cm × 2.5 cm solid mass in pancreatic head	0.77	PPPD
Patient 7, M	45	epigastric and back pain, weight loss	CT, MRI, EU	Diffuse swelling and mass formation 2 cm × 3 cm in size	0.69	Biopsy
Patient 8, M	53	Epigastric pain, weight loss, jaundice	ERCP, MRI	Pancreatic head mass (3 cm × 3 cm), obstruction of the CBD	1.26	PPPD

F: Female; M: Male; CRT: Capillary-refill time; US: Ultrasound; CT: Computed tomography; ERCP: Endoscopic retrograde cholangio-pancreatography; MRI: Magnetic resonance imaging; EU: Endoscopic ultrasound; LAP: Lymphadenopathy; SMV: Superior mesenteric vein; CBD: Common bile duct; PPPD: Pylorus-preserving pancreaticoduodenectomy.

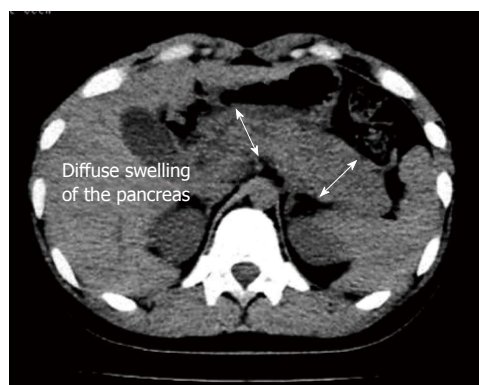


Figure 1 Diffuse swelling and enlargement of the pancreas (double-head arrow).

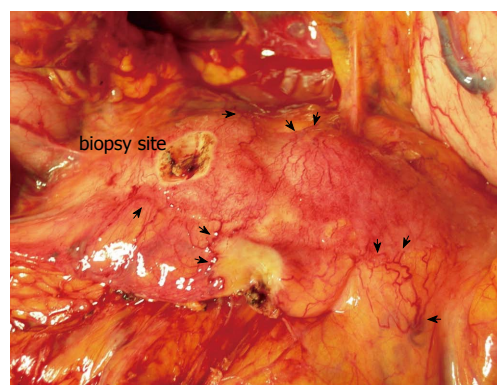


Figure 2 Intraoperative findings of diffusely increased vascularity on the pancreatic surface (black arrows), picture was taken after.

to record the CRT during the operation, and the study investigators reviewed the recorded tape, along with use of a chronometer, to confirm the recorded CRT measurement.

The criteria used by the surgical team to determine whether resection should be performed were standardized and included suspicious findings from endoscopic ultrasound (EU)-guided biopsy, malignant cells detected by frozen section assessment, older age (which increases the possibility of malignancy), and severe obstruction of the common bile duct (CBD) that could not be managed by endoscopic retrograde pancreaticoduodenography (ERCP).

RESULTS

Eight patients with pathologically diagnosed AIP were included in the study; this group was composed of two females and six males, with a mean age of 51.4 years (range: 34-69 years). The duration of symptoms ranged from 2 wk to 3 mo, and the most frequent presenting symptoms were epigastric pain and weight loss. All patients showed mildly elevated levels of liver function enzymes. Among the three patients

examined for IgG level, only one (patient 4) showed an elevated level. The methods of and findings from preoperative imaging studies are shown in Table 1. For patient 2, the CBD cannulation failed during ERCP and the pancreatic mass was observed to have invaded the superior mesenteric vein. Patients 3 and 8 also underwent ERCP, to address the CBD dilatation and relieve the obstruction. For some patients, the CT scan revealed diffuse swelling of the pancreatic tissue (Figure 1). The tumor masses were most frequently located in the pancreatic head (6/7 cases). EU-guided fine needle aspiration biopsy (FNAB) was performed in two patients, with both cases showing non-specific inflammatory changes.

For all patients, the intraoperative macroscopic pancreas assessment revealed diffuse hypervascularization (Figure 2). The median CRT was 0.76 s (range: 0.58-1.35 s). Six patients had a CRT of < 1 s, with four of those patients undergoing only a biopsy before the surgical procedure was suspended. Five patients had inconclusive findings of malignancy from the histological analysis of the frozen section biopsy specimens, while four of these patients had findings compatible with inflammatory changes. When the surgical team

considered the accumulated findings from each patient's preoperative work-up along with their intraoperative findings, surgical resection (pylorus-preserving pancreaticoduodenectomy) was carried out for one-half of the patients (4/8 cases; Table 1).

All patients experienced an uneventful postoperative recovery. Patients who underwent biopsy only (without further surgery) were administered corticosteroids on a 3-wk 1 mg/kg course followed by a life-long 5 mg maintenance course. In all patients but one, the medical treatment led to symptom improvement. Any patient required pain management was referred to an algologist. The mean follow-up period was 26.4 mo, during which none of the cases showed signs of malignancy. In addition, none of the patients who underwent pylorus-preserving pancreaticoduodenectomy showed symptomology or abnormal findings related to other organ systems, leading to their classification as type 2 AIP cases.

DISCUSSION

We investigated the clinical importance of CRT measurement for patients with a prediagnosis of AIP. In these patients, a decreased CRT was found as an operative observation when the cut-off value of 2 s was used. Half of the patients underwent surgical resection (in accordance with the criteria explained in Methods section). It is well-known that not all pathologically diagnosed AIP cases have preoperative findings consistent with the set of specifications and criteria in the literature, highlighting the clinical dilemma facing physicians treating this disease^[5]. In particular, AIP patients present with remarkable variation and no single diagnostic test has been established as the gold standard^[6,7].

In the present study, preoperative diagnostic work-up, including imaging methods such as CT, MRI and EU, were not adequate to establish a definitive diagnosis. It is possible that the technical limitations of EU related to tissue sampling, particularly when the head of the pancreas is involved^[8], may explain the inadequacy of this method in diagnosing our AIP cases. Moreover, the negative predictive value of EU-guided FNAB for pancreatic cancer has been reported as about 75%^[9,10]. However, the focal type of AIP that the majority of our patients were ultimately diagnosed with also presented a diagnostic challenge for ERCP, emphasizing the technical difficulty in diagnosing this condition prior to surgery.

Dominance of elderly patients among AIP cases and presentation with severe jaundice contribute to the diagnostic difficulty or misdiagnosis of AIP^[11,12]. Although the clinical manifestation of AIP may vary from patient to patient, most cases mimic the symptoms of pancreatic cancer. Hence, the high suspicion of malignancy leads treating physicians to prefer surgical removal as the treatment, particularly for patients with focal AIP. It is important to note that the case series reported herein included only AIP cases for whom the decision to perform

surgery had already been made due to suspicion of malignancy or obstructive pathology which were deemed inappropriate for conservative management. Surgeons frequently need more information, apart from laboratory and radiological findings, demonstrating diffuse enlargement or focal masses in the pancreas, to diagnose AIP^[11,13,14]. Therefore, we suggest that some intraoperative findings may help to guide the operational decision-making process.

The "inflammatory hypervascularization" character of the pancreas in AIP was the basis of our hypothesis and CRT was used in our study to evaluate this entity. Findings from this study demonstrated increased blood flow in response to the existing inflammation and subsequent decrease in CRT. It is well known that both malignant and benign pancreatic tissues may be reflected by changes in the vascularization patterns. Central hypervascularization caused by increased flow in the main artery of the organ or local neovascularization is more likely to be present in malignant lesions. However, a carcinoma may also present hypovascularization as desmoplastic changes and vascular encasement leading arterial stenosis or obstruction^[15]. On the contrary, benign lesions, especially in inflammatory conditions, increase the propensity to develop diffuse hypervascularization and the capillary flow rate increases due to the associated increase in metabolic activity. Likewise, Hocke *et al*^[16] reported that contrast-enhanced EU shows hypervascularization of AIP lesions, whereas pancreatic cancer lesions appear to be more hypovascular masses. In this study, diffuse hypervascularization was observed along the anterior surface of the pancreatic body and confirmed by the CRT measurements. With regard to the CRT results, all cases in our series were diagnosed with a value lower than the normal range reported in the literature. The normal value for CRT should be 2 s^[17,18] and, on average, CRT increases 3.3% per decade increase in age. The median CRT for pediatric patients is 0.8 s, while that of adults is 1.0 to 1.5 s^[19]. In our case series, the average CRT was 0.76 s.

Most of the focal AIP cases reported in the literature have been diagnosed only when swelling has become diffuse or after surgical observation^[20]. In our case series, the definitive diagnosis was achieved according to accumulated findings from histological analyses of frozen section specimens, CRT, the intraoperative observations of pancreatic vascular pattern (particularly diffuse peripheral hypervascularization), and pathological findings (periphlebitis, dense lymphoplasmocytic infiltration, and/or fibrotic changes). For four of our cases, the surgery was halted due to pathological confirmation of notable inflammatory changes and markedly decreased CRT; consequently, each case was referred for non-surgical medical treatment.

Several limitations to our study design exist and must be considered when interpreting our findings. First, the small sample size (eight cases) prevented us from establishing a significant causal relation between decreased CRT and AIP; a comparative study

between suspected AIP patients and those with definitive pancreatic cancer might allow strong conclusions to be drawn. Second, the CRT measurement was made using a chronometer and based on visual inspection; this measurement may be more accurate using a standardized method, such as digitalized CRT techniques. Intraoperative ultrasonography-based elastography is an emerging concept and may be also useful in addressing this clinical dilemma. However, this study aimed to describe CRT as an additional tool to lead surgeon to examine the patient for possibility to have AIP in the light of the surgeon's experience and intraoperative observations.

This paper demonstrates preliminary results of a novel experience with measurement of CRT in the pancreatic bed during intraoperative evaluation of patients with AIP. The main finding of this prospective analysis of patients with a prediagnosis of AIP is that changes in macroscopic vascular pattern and decreased CRT, in conjunction with frozen section analysis, can help to guide the treatment approach. Large-scale clinical trials are needed to determine its role in clinical decisions making for this very complicated entity.

COMMENTS

Background

Autoimmune pancreatitis (AIP) remains a diagnostic challenge for both clinicians and surgeons. Differentiating AIP from malignant pathology in the pancreas requires some clinical judgment in assessing the findings of the diagnostic workup and can be dependent upon the treating physician's surgical experience with both conditions.

Research frontiers

The authors aimed to introduce a novel intraoperative diagnostic technique for patients with preliminary diagnosis of AIP.

Innovations and breakthroughs

This preliminary study demonstrating a novel experience with measurement of capillary refill time in the pancreatic bed during the intraoperative evaluation of patients with AIP provided a decreased capillary refill time which can be attributable to hypervascularity.

Applications

Hypervascularization of AIP lesions radiologically inspired us to investigate the efficacy of this feature. It was evaluated by measurement of capillary refill time in the operating theatre. Preliminary results showed that it can be an additional tool in the surgical decision-making process.

Terminology

Pancreatic hypervascularity: increased vascular web secondary to pancreatic inflammation; Capillary refill time: the time taken for color to return to an external capillary bed after finger pressure is applied to cause blanching on pancreatic tissue.

Peer-review

An interesting novel method of assessing of this difficult pancreatic condition. The paper will be of interest to our readers interested in pancreatic problems.

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Retrospective Study

Accuracy of computed tomography in nodal staging of colon cancer patients

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Abstract

AIM: To predict node-positive disease in colon cancer using computed tomography (CT).

METHODS: American Joint Committee on Cancer stage I - III colon cancer patients who underwent curative-intent colectomy between 2007-2010 were identified at a single comprehensive cancer center. All patients had preoperative CT scans with original radiology reports from referring institutions. CT images underwent blinded secondary review by a surgeon and a dedicated abdominal radiologist at our institution to identify pericolic lymph nodes (LNs). Comparison of outside CT reports to our independent imaging review was performed in order to highlight differences in detection in actual clinical practice. CT reviews were compared with final pathology. Results of the outside radiologist review, secondary radiologist review, and surgeon review were compared with the final pathologic exam to determine sensitivity, specificity, positive and negative predictive values, false positive and negative rates, and accuracy of each review. Exclusion criteria included evidence

of metastatic disease on CT, rectal or appendiceal involvement, or absence of accompanying imaging from referring institutions.

RESULTS: From 2007 to 2010, 64 stage I - III colon cancer patients met the eligibility criteria of our study. The mean age of the cohort was 68 years, and 26 (41%) patients were male and 38 (59%) patients were female. On final pathology, 26 of 64 (40.6%) patients had node-positive (LN+) disease and 38 of 64 (59.4%) patients had node-negative (LN-) disease. Outside radiologic review demonstrated sensitivity of 54% (14 of 26 patients) and specificity of 66% (25 of 38 patients) in predicting LN+ disease, whereas secondary radiologist review demonstrated 88% (23 of 26) sensitivity and 58% (22 of 38) specificity. On surgeon review, sensitivity was 69% (18 of 26) with 66% specificity (25 of 38). Secondary radiology review demonstrated the highest accuracy (70%) and the lowest false negative rate (12%), compared to the surgeon review at 67% accuracy and 31% false negative rate and the outside radiology review at 61% accuracy and 46% false negative rate.

CONCLUSION: CT LN staging of colon cancer has moderate accuracy, with administration of NCT based on CT potentially resulting in overtreatment. Active search for LN+ may improve sensitivity at the cost of specificity.

Key words: Colon cancer; Lymph nodes; Clinical staging; Computed tomography; Neoadjuvant therapy

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Core tip: Clinical staging to determine eligibility for neoadjuvant trials requires accurate imaging. This study compares lymph node identification on preoperative computed tomography (CT) scans by outside radiologists, a tertiary cancer center radiologist and a surgeon, mirroring referral patterns to tertiary care facilities. While re-review of CT scans by a tertiary center radiologist improved sensitivity of lymph node detection, CT staging of colon cancer demonstrated moderate accuracy overall. Our findings suggest that the administration of neoadjuvant chemotherapy based on preoperative CT staging would potentially result in overtreatment of colon cancer patients.

Choi AH, Nelson RA, Schoelhammer HF, Cho W, Ko M, Arrington A, Oxner CR, Fakih M, Wong J, Sentovich SM, Garcia-Aguilar J, Kim J. Accuracy of computed tomography in nodal staging of colon cancer patients. *World J Gastrointest Surg* 2015; 7(7): 116-122 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v7/i7/116.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v7.i7.116>

INTRODUCTION

Adjuvant chemotherapy is well-established for treating

colon cancer patients with American Joint Committee on Cancer (AJCC) stage III disease^[1]. More recently, there has been growing interest in administering neoadjuvant chemotherapy (NCT) prior to planned surgical resection to reduce disease recurrence in high-risk tumors. Preliminary results from the Fluoropyrimidine, Oxaliplatin and Targeted-Receptor preOperative Therapy (FOxTROT) trial for patients with high-risk operable colon cancer, an ongoing phase III randomized controlled trial in the United Kingdom, have demonstrated that NCT for operable, locally-advanced colon cancer can downstage tumors^[2]. Patients for the study were selected on the basis of having either T3 tumors with ≥ 5 mm extramural tumor depth or T4 tumors by computed tomographic (CT) imaging. Nodal stage was not specifically used as inclusion criteria for the study and only 52% of patients randomized to the adjuvant chemotherapy group demonstrated nodal involvement on final pathologic exam.

Unlike rectal cancer, where neoadjuvant chemoradiation is frequently utilized based on staging with endorectal ultrasound (ERUS) or magnetic resonance imaging (MRI)^[3,4], the administration of NCT for patients with resectable colon cancer is controversial. In order to appropriately select colon cancer patients for NCT, an accurate and reliable imaging modality for detecting involved lymph nodes (LN) is mandatory. Due to low sensitivity, MRI and positron emission tomography (PET) are not favorable imaging studies for preoperative pathologic LN detection^[5-8]. In contrast, CT is currently the most commonly used imaging study used to stage colon cancer patients preoperatively, particularly to identify liver, lung, and other sites of distant metastases that may exclude patients from NCT trials^[9-11]. Our objective was to determine the utility and accuracy of preoperative CT scan in detecting regional colon cancer LN metastases by comparing outside CT reports to independent imaging review at a referral center in order to highlight differences in detection in actual clinical practice.

MATERIALS AND METHODS

Patient selection

After obtaining approval from the Institutional Review Board, we identified and analyzed the medical records of 64 colon cancer patients with AJCC stage I - III disease who underwent curative resection between 2007 and 2010 at City of Hope Comprehensive Cancer Center. Exclusion criteria included evidence of metastatic disease on CT, rectal or appendiceal involvement, or absence of accompanying imaging from referring institutions. Medical records were reviewed for demographic and treatment-related variables.

Data collection

Prior to treatment at our institution, patients had CT imaging performed at outside community hospitals or imaging centers. Outside CT images and radiology reports were obtained on all patients. Secondary

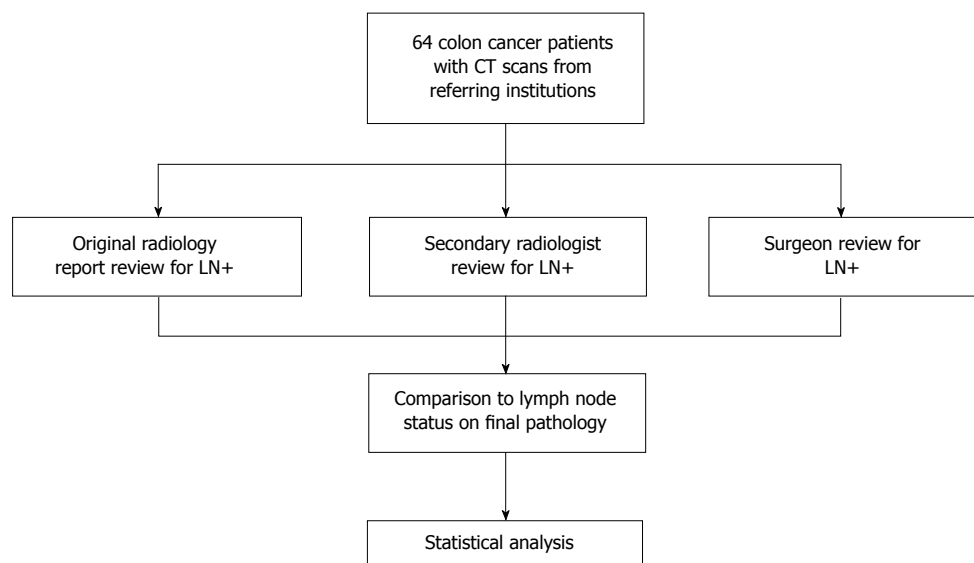


Figure 1 Study design. CT: Computed tomography; LN+: Lymph node positive.

imaging review of the original outside CT scans was conducted by a surgeon and an abdominal imaging radiologist at our institution. They were blinded to the original radiologic report final pathology exam and reviewed the images with the specific goal to identify mesenteric LNs (Figure 1). Once reviewed, each observer's results were compared with the final pathology.

Imaging review

Patients were staged according to the AJCC 7th edition TNM classification system. Variables examined in our study included age, sex, location of primary tumor, T stage, and N stage. Radiographic LN involvement was defined when the longest LN diameter was > 1.0 cm or was 0.7-1.0 cm in size with round shape, heterogeneity, eccentricity, hilar thinning, calcification, central necrosis, or perinodal infiltration. Based on the radiographic review, each patient was designated either lymph node positive (LN+) or lymph node negative (LN-). The reports from outside radiologists were reviewed and the absence of pathologic LN identification was recorded as LN-.

Statistical analysis

Results of the outside radiologist review, secondary radiologist review, and surgeon review were compared with the final pathologic exam to determine sensitivity, specificity, positive (PPV) and negative predictive values (NPV), false positive and negative rates, and accuracy of each review. Both binomial 95%CI and asymptotic *P*-values were calculated to determine the statistical significance of each observer's results compared to a null hypothesis of 50% (*i.e.*, results expected due to random chance). The association between clinical factors and the accuracy of LN detection was also examined.

RESULTS

Study population

From 2007 to 2010, 64 stage I-III colon cancer patients met the eligibility criteria of our study (Table 1). The mean age of the cohort was 68 years, and 26 (41%) patients were male and 38 (59%) patients were female. Tumors were located in the sigmoid colon ($n = 18$, 28%), the ascending colon ($n = 16$, 25%), or the cecum ($n = 14$, 22%). On final pathology, 19 (30%) patients were stage I, 19 (30%) were stage II, and 26 (40.6%) patients were stage III. LN- disease was diagnosed in 38 patients and LN+ disease in 26 patients. In the LN+ cohort, 17 patients had N1 disease and 9 patients had N2 disease. All patients in our study had ≥ 12 LNs removed with a median of 22 LNs.

Nodal identification by different reviewers

Outside radiology review only identified 14 of 26 LN+ patients and 25 of 38 LN- patients (Table 2). The sensitivity, specificity, and accuracy for the original radiology review for predicting LN disease were calculated, as were PPV, NPV, false positive rate, and the false negative rate (Table 3). The original radiology review had the lowest sensitivity and highest false negative rate compared with the secondary radiologist and surgeon review. Figure 2 shows an example of a LN- CT by the original radiologist; however, this case was LN+ on final pathology, secondary radiology, and secondary surgical reads.

The secondary radiologist correctly identified 23 of 26 LN+ cases and 22 of 38 LN- cases (Table 2). Of the three observers, the secondary radiologist demonstrated the highest sensitivity and accuracy for LN+ detection, 88% (95%CI: 76%-100%, $P < 0.01$) and 70% (95%CI: 59%-82%, $P < 0.01$), respectively. The accuracy of the secondary radiologist

Table 1 Patient demographic and final pathologic characteristics

Characteristics	n = 64 (%)
Age (yr) ¹	67.6 ± 12.8
Sex	
Male	26 (40.6)
Female	38 (59.4)
Tumor location	
Cecum	14 (21.9)
Ascending colon	16 (25.0)
Transverse colon	6 (9.4)
Splenic flexure	1 (1.6)
Descending colon	6 (9.4)
Sigmoid colon	18 (28.1)
Rectosigmoid	3 (4.7)
Pathologic stage	
Stage I	19 (29.7)
Stage II	19 (29.7)
Stage III	26 (40.6)
N stage	
N0	38 (59.4)
N1	17 (26.5)
N2	9 (14.1)

¹Mean ± SD.

was approximately 10% higher than that of outside radiologist review (Table 3).

Surgeon review correctly predicted 18 of 26 LN+ patients and 25 of 38 LN- patients (Table 2). Of the three observers, sensitivity and accuracy of the surgeon review were better than the original radiology review, but not as high as the secondary radiology review (Table 3). The surgeon review had comparable specificity to original radiology review.

Clinical predictors of lymph node identification accuracy

Location of the tumor, sex, body mass index (BMI), and number of LN examined on final pathology were analyzed to determine whether these variables correlated with improved accuracy of LN detection on preoperative CT scan reviewed by the secondary radiologist. LN detection in female patients tended to be more accurate than male patients (76% vs 63%, $P = 0.27$) and BMI < 25 also tended to improve accuracy of LN detection (84% vs 67%, respectively; $P = 0.16$). Total number of LNs examined and location of the tumor did not predict LN detection accuracy ($P = 0.91$ and $P = 0.87$, respectively).

DISCUSSION

Given the promising outcomes of preoperative and perioperative therapies in other gastrointestinal malignancies^[4,12,13], NCT for node-positive colon cancer remains of great interest. The theoretical benefits of NCT include the reduction of micrometastatic disease and tumor shedding during surgery, and use of tumor response to neoadjuvant chemotherapy to guide further adjuvant therapies if needed after surgery. In addition, patients may be better able to tolerate full-dose chemotherapy regimens in the preoperative rather than

Table 2 Comparison of lymph node status prediction by computed tomography against final pathologic examination for three observers

	Final pathology (n = 64)	
	LN+ (n = 26)	LN- (n = 38)
Original radiologist		
LN+	14	13
LN-	12	25
Secondary radiologist		
LN+	23	16
LN-	3	22
Surgeon		
LN+	18	13
LN-	8	25

LN+: Lymph node positive; LN-: Lymph node negative.

postoperative setting. To determine which patients may benefit most from NCT, accurate preoperative imaging to assess nodal disease is essential.

Our study compared CT reviews by the original radiologist and two secondary reviewers (a radiologist and a surgeon) with the final pathology. While the original radiology reviews had low sensitivity, the results from the secondary radiologist and surgeon reviews were comparable to contemporary studies on LN staging by CT. For example, in a meta-analysis of 19 studies that included 907 patients, the overall sensitivity of CT for LN+ detection was 70% and the specificity was 78%^[14]. While the majority of prior reports used results obtained only by dedicated abdominal radiologists^[10,11,15,16], our study sought to investigate CT reviews performed by three different clinical perspectives in order to compare and contrast the reading results. This approach was designed to mirror actual clinical practice, particularly in tertiary care and referral centers, as patients frequently arrive for initial consultation with outside imaging and reports of variable quality. The sensitivity rates from the original radiology reviews were lower than those from the secondary reviewers, and it is possible that these higher rates of false negatives exist because LN+ detection and staging were not the primary focus of the original review. Compared with the outside radiology review, sensitivity and accuracy for lymph node detection improved with active search for lymphadenopathy on secondary review, while specificity tended to decrease. These findings highlight the importance of independently reviewing outside imaging studies prior to clinical decision making. Of note, in order to avoid multiple insurance charges for preoperative imaging, the majority of patients did not undergo repeat CT scans at our institution. Thus, we were unable to make comparisons in LN detection between outside CT scans and our institutional CT scans.

While CT is the most commonly utilized imaging modality for preoperative staging in colon cancer, the use of PET and MRI for metastatic lymph node detection has been studied by other investigators. PET/CT generally

Table 3 Statistical analysis of lymph node status prediction by computed tomography against final pathologic examination for three observers (*n* = 64)

	Sensitivity (95%CI, <i>P</i> -value)	Specificity (95%CI, <i>P</i> -value)	PPV (95%CI, <i>P</i> -value)	NPV (95%CI, <i>P</i> -value)	FPR (95%CI, <i>P</i> -value)	FNR (95%CI, <i>P</i> -value)	Accuracy (95%CI, <i>P</i> -value)
Original radiologist	54% (35%-73%, <i>P</i> = 0.69)	66% (51%-81%, <i>P</i> = 0.05)	52% (33%-71%, <i>P</i> = 0.85)	68% (52%-83%, <i>P</i> = 0.03)	34% (19%-49%, <i>P</i> = 0.05)	46% (27%-65%, <i>P</i> = 0.69)	61% (49%-73%, <i>P</i> = 0.08)
Secondary radiologist	88% (76%-100%, <i>P</i> < 0.01)	58% (42%-74%, <i>P</i> = 0.33)	59% (44%-74%, <i>P</i> = 0.26)	88% (75%-100%, <i>P</i> < 0.01)	42% (26%-58%, <i>P</i> = 0.33)	12% (0%-24%, <i>P</i> < 0.01)	70% (59%-82%, <i>P</i> < 0.01)
Surgeon	69% (51%-87%, <i>P</i> = 0.05)	66% (51%-81%, <i>P</i> = 0.05)	58% (41%-75%, <i>P</i> = 0.37)	76% (61%-90%, <i>P</i> < 0.01)	34% (19%-49%, <i>P</i> = 0.05)	31% (13%-49%, <i>P</i> = 0.05)	67% (56%-79%, <i>P</i> = 0.01)

P-value indicates significance of the observer's statistic compared null hypothesis of 0.5. PPV: Positive predictive value; NPV: Negative predictive value; FPR: False positive rate; FNR: False negative rate.



Figure 2 Computed tomography image showing positive nodal disease. This computed tomography image read by outside radiologist as lymph node (LN) negative disease was confirmed to be LN positive by final pathology (arrow head). Contiguous with the base of the appendix, an irregular cecal soft tissue mass (4.5 cm × 2.2 cm × 3.2 cm) can be seen (arrow).

demonstrates lower sensitivity than CT alone^[5-7]. Because PET lacks the spatial resolution of CT, even when combined with CT, increased fluorodeoxyglucose (FDG) uptake in lymph nodes can be difficult to interpret, particularly when nodes are in close proximity to a primary tumor with high standardized uptake value (SUV). Similarly, MRI is associated with lower sensitivity, but increased specificity for LN involvement when compared to CT^[8], and this may in part due to the fact that MRI criteria for lymph node positivity other than size, such as border criteria or signal criteria, can be subjective and have less reliable inter-observer differences^[17].

CT appears to have comparable sensitivity and specificity to ERUS for LN+ detection, although preoperative ERUS staging for rectal cancer depends on the combination of the T and N stage^[18]. The ability of ERUS to accurately determine the T stage in rectal cancer is likely better than the ability of CT to determine the T stage for colon cancer. CT can differentiate tumor invasion through the muscularis propria (T1/T2 vs T3/T4) in colon cancer with high accuracy^[19], but depending on the operator, ERUS better distinguishes invasion of rectal tumors through the layers of the rectal wall with

very high accuracy^[20]. For these reasons, CT staging for lymph node involvement in colon cancer has not been utilized to select patients for neoadjuvant chemotherapy administration, in contrast to the use of ERUS in rectal cancer staging.

Other groups have also examined the role of preoperative staging with CT in colon cancer patients. Currently, the FOxTROT trial is randomizing patients on the basis of preoperative T staging by CT to determine whether administration of neoadjuvant oxaliplatin, folinic acid and fluorouracil prior to surgical resection impacts long-term outcomes when compared with the current standard of surgical resection followed by adjuvant chemotherapy^[2]. Preliminary results showed 91% of patients who were classified as high risk by CT had T3 tumors or above confirmed by final pathology. Of the 99 patients randomized to the preoperative chemotherapy group, 39.4% (39/99) were LN+ on final pathology^[2]. Stratification by T stage on CT scan may result in the administration of neoadjuvant chemotherapy to LN- patients, particularly because CT tends to overstage nodal disease compared with the final pathologic diagnosis. In the preliminary results of the FOxTROT trial, 48% of patients were LN- in the postoperative chemotherapy group, but would have received neoadjuvant chemotherapy according to the trial's CT T staging criteria.

The current clinical staging of colon cancer by CT has moderate sensitivity and specificity for detecting lymph node involvement. By implementing a study design that mirrors actual clinical practice, our study demonstrated that although sensitivity increases by actively re-reviewing CT imaging from referral centers for metastatic nodal disease, specificity may be negatively impacted. The patient derived benefit of accurate preoperative CT identification of LNs would be the reliable diagnosis of stage III disease prior to surgery with the potential eligibility for neoadjuvant treatment strategies. However, at the current level of CT technology, administration of neoadjuvant chemotherapy based on preoperative CT LN involvement would potentially result in overtreatment of these selected

colon cancer patients. Currently, CT scanning is used to determine T stage as entry criteria for clinical trials of neoadjuvant chemotherapy for colon cancer, but the results of these trials are needed before CT becomes the standard imaging modality for detecting presumed LN+ colon cancer and guiding neoadjuvant therapy.

COMMENTS

Background

Adjuvant chemotherapy is well-established for treating colon cancer patients with American Joint Committee on Cancer stage III disease. More recently, there has been growing interest in administering neoadjuvant chemotherapy (NCT) prior to planned surgical resection to reduce disease recurrence in high-risk tumors. In order to appropriately select colon cancer patients for NCT, an accurate and reliable imaging modality for detecting involved lymph nodes (LN) is mandatory. The authors' objective was to determine the utility and accuracy of preoperative computed tomography (CT) scan in detecting regional colon cancer LN metastases by comparing outside CT reports to independent imaging review at a referral center in order to highlight differences in detection in actual clinical practice.

Research frontiers

Currently, there is growing interest in preoperatively identifying colon cancer patients who would benefit from neoadjuvant therapy. One such study (Fluoropyrimidine, Oxaliplatin and Targeted-Receptor preOperative Therapy trial) is randomizing patients on the basis of preoperative T staging by CT to determine whether administration of neoadjuvant oxaliplatin, folinic acid and fluorouracil prior to surgical resection impacts long-term outcomes when compared with the current standard of surgical resection followed by adjuvant chemotherapy.

Innovations and breakthroughs

Although previous studies have also demonstrated that CT has modest accuracy for preoperative identification of LNs, this study utilizes comparison of three different clinical perspectives to highlight differences in LN detection in actual clinical practice.

Applications

From a practical standpoint, this results highlight the importance of independently reviewing outside imaging studies prior to surgical resection. The authors have demonstrated that sensitivity for LN detection increases with active search on re-review by the authors' surgeon and dedicated abdominal radiologist compared to the original outside radiology assessments.

Terminology

Node-positive disease in colon cancer involves the metastatic spread of cells from the primary tumor to the regional mesenteric LNs.

Peer-review

This is a timely presentation of important results in clinical oncology.

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Delayed esophageal perforation occurring with endoscopic submucosal dissection: A report of two cases

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Abstract

We report two cases of delayed esophageal perforation occurring with endoscopic submucosal dissection. Our cases involved delayed perforation after 10 d in case 1 and after 6 d in case 2. Both cases were related to solid food. We performed subtotal esophagectomy with gastric tube reconstruction of the esophagus *via* the subcutaneous route anterior to the thoracic wall without conservative treatment because both cases involved chest pain and major leakage of food into the mediastinum. Postoperative complications were a local factor (including suture failure and esophageal stricture) in case 1, and we performed endoscopic balloon dilatation five times for esophageal stricture. There was no intrathoracic and mediastinal infection in either case. Surgical treatment for delayed esophageal perforation can be performed safely and surely if diagnosis and assessment are not delayed.

Key words: Esophageal cancer; Endoscopic submucosal dissection; Delayed perforation

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Core tip: Patients with early esophageal cancer often experience endoscopic submucosal dissection with complications, including bleeding, perforation, and stenosis. Although most cases are successfully treated conservatively, perforation is a life-threatening complication and can require surgical intervention. In our cases, we performed surgery approximately three hours after the patients' complaints. Postoperative

complications were a local factor (including wound infection and esophageal stricture) and did not include intrathoracic and mediastinal infection. Surgical treatment for delayed esophageal perforation can be performed safely and surely if diagnosis and assessment are not delayed.

Matsuda Y, Kataoka N, Yamaguchi T, Tomita M, Sakamoto K, Makimoto S. Delayed esophageal perforation occurring with endoscopic submucosal dissection: A report of two cases. *World J Gastrointest Surg* 2015; 7(7): 123-127 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v7/i7/123.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v7.i7.123>

INTRODUCTION

Patients with early esophageal cancer often undergo endoscopic submucosal dissection (ESD) as a standard treatment. ESD for the esophagus has a high rate of complete resection and a low complication rate^[1]. However, performing this procedure on the esophagus is technically difficult because the wall of the esophagus is thin. The risk is particularly high for superficially spreading esophageal cancer. The complications of ESD include bleeding, perforation, and stenosis. The most frequent ESD complication is stenosis (11.6%). Another complication, perforation, is not uncommon (5.0%), and is life threatening. These complications can be successfully treated without surgery in most cases^[2]. However, delayed perforation is rare and can require surgical intervention. In this report, we describe our experience with the surgical treatment of delayed esophageal perforation after ESD, and we discuss management strategies.

CASE REPORT

Case 1 was an 83-year-old man with diabetes mellitus who complained of heartburn. Esophagogastroduodenoscopy (EGD) was performed, and middle thoracic esophageal cancer was found (Type 0-IIc). The location was 25-28 cm from the incisor teeth, and the lesion covered three-quarters of the circumference (Figure 1). The depth of tumor invasion indicated that the tumor was in contact with or invaded the muscularis mucosa (M3), as revealed by endoscopic diagnosis. Enhanced computed tomography (CT) did not show a main lesion or lymph node metastases (cT1aN0M0 cStage I). We chose to perform ESD, and after resection of the lesion, we injected a steroid (triamcinolone acetonide; Kenacort®-A, Bristol-Myers Squibb, New York, NY, United States) into an artificial ulcer (Figure 1). The histopathological findings were 45 cm × 34 mm, SCC, pT1a-LPM, pHM (2 mm), pVM0, INFa, ly0, v0, and CurA. On day 6 after ESD, the patient began to eat a meal, and esophageal obstruction was

suspected due to a complaint of a feeling of blockage while swallowing solid food. Although we performed EGD, stenosis was not found, and the resected area was cured. On day 10, the patient had sudden chest pain during dinner. Enhanced CT showed food residue in his mediastinum, and we diagnosed perforation of the esophagus (Figure 2). After approximately 3 h, we performed subtotal esophagectomy with gastric tube reconstruction of the esophagus *via* the subcutaneous route anterior to the thoracic wall without lymph node dissection. The operative duration was 385 min. The blood loss was 1040 cc (including pleural effusion), and 4 units of red cell concentrate were administered. The perforation extended from the right side to the posterior wall of the esophagus at the inferior mediastinum. The postoperative complications were wound infection and esophageal stricture. The patient did not have an intrathoracic and mediastinal infection. We performed endoscopic balloon dilatation (EBD) for esophageal stricture five times, and the patient was discharged 88 d after surgery.

Case 2 was a 75-year-old man who had experienced ESD three times for upper and middle thoracic esophageal cancer over three years. Ten months after the last ESD, postoperative follow-up found middle thoracic esophageal cancer (Type 0-IIb). The location was 25-28 cm from the incisor teeth, and the extent of the lesion ranged over half of its circumference. The depth of tumor invasion was intraepithelial (M1) as revealed by endoscopic diagnosis. Enhanced CT did not show a main lesion or lymph node metastases (cT1aN0M0 cStage I). Although we performed ESD, we could not completely resect the lesion due to marked fibrosis (Figure 3). On postoperative day 3, the patient ate a meal and had no symptoms. On day 6, the patient had sudden chest pain during breakfast. Enhanced CT showed food residue in his mediastinum, and we diagnosed perforation of the esophagus (Figure 4). After approximately 3 h, we performed subtotal esophagectomy with gastric tube reconstruction of the esophagus *via* the subcutaneous route anterior to the thoracic wall with lymph node dissection. The operative duration was 390 min. The blood loss was 270 cc, and no transfusion was administered. The perforation involved the right side of the esophagus below the tracheal bifurcation. Histological examination revealed IIc, 4 mm × 4 mm, SCC, pT1a-EP, ly0, v0, pPM0 (100 mm), and pDM0 (150 mm). There were no postoperative complications in the hospital. The patient did not have an intrathoracic and mediastinal infection and was discharged 47 d after surgery.

DISCUSSION

ESD is a popular endoscopic procedure for the stomach and colon. ESD in the esophagus is accompanied by technical difficulties. Recently, the application of ESD for esophageal lesions has been reported. In the 2007

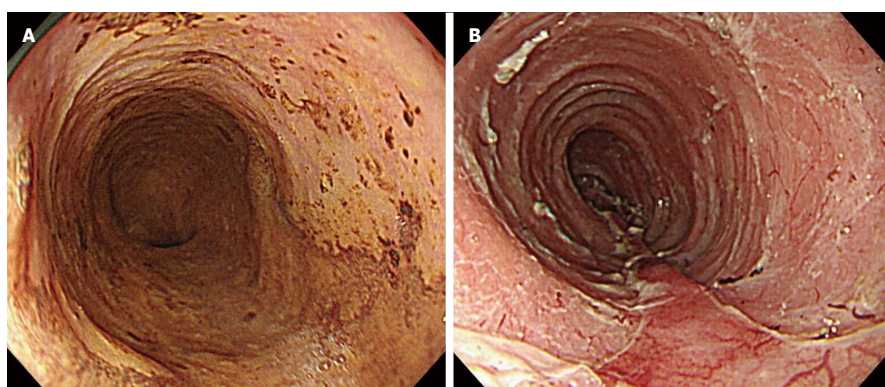


Figure 1 Endoscopic findings in case 1. A: Before endoscopic submucosal dissection (ESD). The lesion covered three-quarters of the circumference; B: After ESD. We injected a steroid into an artificial ulcer.

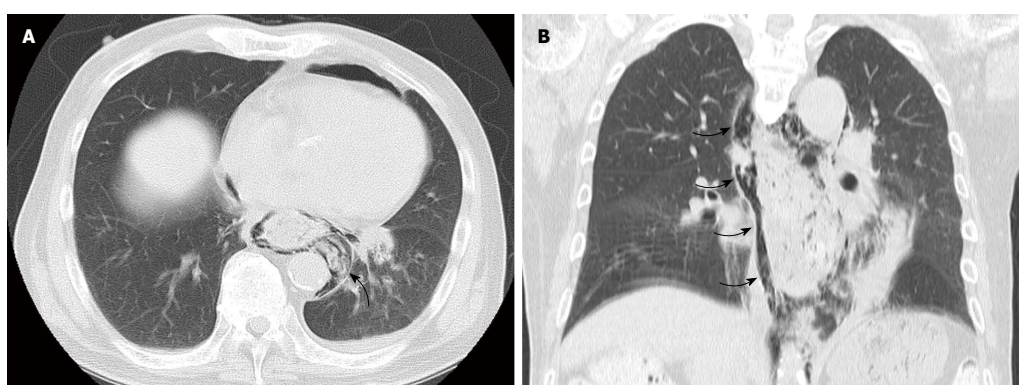


Figure 2 Enhanced computed tomography showed food residue in his mediastinum (arrow) (A) and mediastinal emphysema (arrow) (B).

guidelines of the Japanese Esophageal Society, the absolute indications for this procedure were M1 and tumors invading the lamina propria (M2) that spread to less than two-thirds of their circumference. The relative indication for this procedure was M3 without clinical lymph node involvement^[3]. In case 1, the depth of tumor invasion was M3, and the lymph nodes had no metastases. We selected ESD because the patient was elderly. In case 2, we performed ESD because the depth of tumor invasion was M1, and the lymph nodes had no metastases.

The complications of ESD in the esophagus are bleeding, perforation, and stenosis. The most common complication is stenosis, which is reported in 11.6% of cases^[2]. Near-circumferential lesions are a risk factor for stenosis, which has been reported in 45% of such cases^[4]. Takeuchi *et al.*^[5] reported that a steroid injected into the remaining submucosal layer of the post-ESD ulcer base was very effective at preventing postoperative stricture after esophageal ESD.

The rate of perforation is low (5.0%) and is caused by perioperative perforation of the ESD and dilation of esophageal strictures^[2,6]. Delayed perforation has been reported following the injection of steroids into the deeper layer of the ulcer base and food bolus obstruction^[5,7]. Tumor size was not shown to influence the incidence of perforation^[1]. In our cases, both perforations were related to solid food. Additionally, a steroid might have been involved in case 1, and fibrosis from a past ESD might have been involved in case 2.

Most perforation cases are treated conservatively, and surgery is rare^[2]. Conservative treatment can be selected in cases of effective endoscopic clipping, non-severe mediastinitis related to minor leaks, and stable vital signs. When conservative treatment (such as fasting, intravenous administrations of antibiotics, and drainage) has been ineffective for several days, surgical treatment should be selected^[8,9]. Otherwise, the patient is at a risk. Lee *et al.*^[10] reported that their patient with a perforation developed unstable vital signs during endoscopic clipping, which resulted in an urgent operation. We selected surgery from the outset because the reported chest pain was strong, and enhanced CT showed major leakage of food into the mediastinum. There was no delay in diagnosis or in treatment in either case. Although the surgery was an invasive treatment, postoperative complications were the only local factor (wound infection and esophageal stricture), and the patients' general conditions were stable after surgery. Conservative treatment should not be performed without safety and surety because of the attendant risks^[8-10].

In conclusion, surgical treatment for delayed esophageal perforation occurring with ESD can be performed safely when diagnosis and assessment are not delayed.

COMMENTS

Case characteristics

Case 1 was an 83-year-old man with diabetes mellitus who complained of

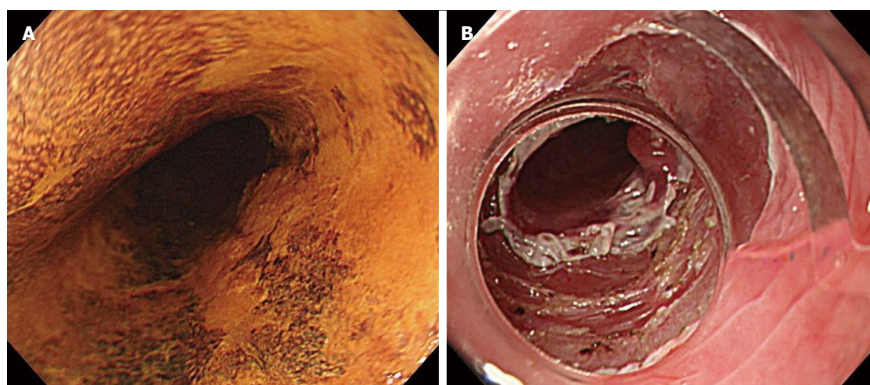


Figure 3 Endoscopic findings in case 2.
A: Before endoscopic submucosal dissection (ESD). The extent of the lesion ranged over half of its circumference; B: After ESD. We could not completely resect the lesion due to marked fibrosis.

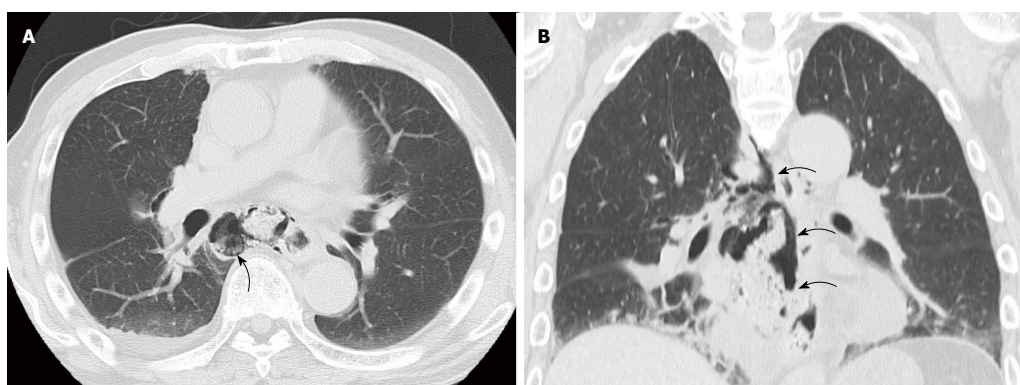


Figure 4 Enhanced computed tomography showed food residue in his mediastinum (arrow) (A) and mediastinal emphysema (arrow) (B).

heartburn. Case 2 was a 75-year-old man who had experienced endoscopic submucosal dissection (ESD) three times for upper and middle thoracic esophageal cancer over three years.

Clinical diagnosis

Delayed esophageal perforation occurring with endoscopic submucosal dissection.

Differential diagnosis

Mediastinitis, empyema, pneumonia.

Laboratory diagnosis

Tumor makers were within normal limits.

Imaging diagnosis

Computed tomography scan did not show a main lesion or lymph node metastases (cT1aN0M0 cStage I).

Pathological diagnosis

In case 1, the histopathological findings were 45 mm × 34 mm, SCC, pT1a-LPM, pHM (2 mm), pVM0, INFa, ly0, v0, and CurA. In case 2, histological examination revealed lIc, 4 mm × 4 mm, SCC, pT1a-EP, ly0, v0, pPM0 (100 mm), and pDM0 (150 mm).

Treatment

The authors performed sub total esophagectomy with gastric tube reconstruction of the esophagus via the subcutaneous route anterior to the thoracic wall.

Related reports

Delayed esophageal perforation occurring with endoscopic submucosal dissection is rare.

Term explanation

In the 2007 guidelines of the Japanese Esophageal Society, the absolute indications for this procedure were M1 and tumors invading the lamina propria (M2) that spread to less than two-thirds of their circumference.

Experiences and lessons

Food bolus obstruction may be related to delayed esophageal perforation occurring with ESD.

Peer-review

This is a nice case report on the subject of esophageal perforation after endoscopic submucosal dissection.

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