Computed tomography, endoscopic, laparoscopic, and intra-operative sonography for assessing resectability of pancreatic cancer

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Abstract

Pancreas cancer is the fourth leading cancer killer in adults. Cure of pancreas cancer is dependent on the complete surgical removal of localized tumor. A complete surgical resection is dependent on accurate preoperative and intra-operative imaging of tumor and its relationship to vital structures. Imaging of pancreatic tumors preoperatively and intra-operatively is achieved by pancreatic protocol computed tomography (CT), endoscopic ultrasound (EUS), laparoscopic ultrasound (LUS), and intra-operative ultrasound (IOUS). Multi-detector CT with three-dimensional (3–D) reconstruction of images is the most useful preoperative modality to assess resectability. It has a sensitivity and specificity of 90 and 99%, respectively. It is not observer dependent. The images predict operative findings. EUS and LUS have sensitivities of 77 and 78%, respectively. They both have a very high specificity. Further, EUS has the ability to biopsy tumor and obtain a definitive tissue diagnosis. IOUS is a very sensitive (93%) method to assess tumor resectability during surgery. It adds little time and no morbidity to the operation. It greatly facilitates the intra-operative decision-making. In reality, each of these methods adds some information to help in determining the extent of tumor and the surgeon's ability to remove it. We rely on pancreatic protocol CT with 3–D reconstruction and either EUS or IOUS depending on the tumor location and operability of the tumor and patient. With these modern imaging modalities, it is now possible to avoid major operations that only determine an inoperable tumor. With proper preoperative selection, surgery is able to remove tumor in the majority of patients.
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1. Introduction

Pancreatic cancer is the tenth most common malignancy and the fourth highest cancer killer in adults [1]. It has an overall cumulative 5-year survival rate below 1% [2]. The process of tumor initiation, progression and metastasis is still not well understood. Although newer chemotherapeutic regimens show promise, surgical resection offers the only chance for cure with a 5-year survival rate of approximately 20%. Thus, pancreatic cancer remains an exceedingly difficult tumor to cure in its advanced form making early diagnosis and accurate staging an essential part of patient assessment. Accurate imaging permits correct staging and therapeutic planning. As physicians and patients will attest, there is as yet no single best diagnostic or staging modality. Patients with pancreatic cancer must, therefore, submit to two or more imaging tests in the majority of cases.

Computed tomography (CT) is a widely available and very accurate abdominal imaging study. Its resolution and clarity have recently been increased with the use of multi-detectors and intravenous contrast. Further, curved planar reformations are now being used to

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precisely define tumor relationships to the pancreatic duct, common bile duct and major mesenteric blood vessels. These new methods of CT imaging have greatly enhanced its ability to detect tumors and their relationships to vital structures. Certainly, CT is the most common tool used by surgeons to assess tumor operability.

Diagnostic ultrasound is another important and widely used imaging tool. It is inexpensive and minimally invasive with a wide range of applications from the thyroid to the rectum. Because of its location in the retroperitoneum, the pancreas is not well visualized using standard transcutaneous abdominal ultrasound. In an effort to overcome these limitations of ultrasound for pancreatic imaging, alternative approaches have been developed including endoscopic ultrasound (EUS), laproscopic ultrasound (LUS), and intra-operative ultrasound (IOUS). This review will focus on the role of multi-detector CT and each of these sonographic imaging techniques in determining resectability of patients with pancreatic cancer.

2. Surgical management of pancreatic cancer

Approximately 26,000 Americans are diagnosed and die from pancreatic adenocarcinoma each year [3]. If not removed surgically, the 5-year survival is 0%. Presenting symptoms include jaundice with or without abdominal pain and/or unexplained weight loss. When present, pain occurs as a dull intermittent ache in the upper abdomen that often radiates to the back. Jaundice may be associated with pruritus, acholic stools, and dark urine. Weight loss is usually associated with anorexia [4,5]. Surgical management remains the only potentially curative treatment [6]. Pancreaticoduodenectomy, first described by Walter Kauch [7] in 1912 and later by Allan Whipple [8] in 1934, remains the standard surgical management for pancreatic cancer located in the pancreatic head. The operation or modifications of it involve resection of the pancreatic head, distal gastrectomy, duodenectomy, cholecystectomy, common bile duct resection, and resection of the first 15 cm of jejunum. Reconstruction involves stomach, pancreas, and bile duct anastamoses to jejunum. The goal of surgery is to remove all tumors with the lowest morbidity and mortality. Whipple procedures are

associated with notable morbidity and mortality [9]. However, recent advances in surgical technique and peri-operative management have led to improved operative survival, and less morbidity [10–13]. Pathological margins free of tumor are the primary objective for all cancer surgeries. Accurate imaging with CT, EUS, LUS, and IOUS is critical for curative tumor resection (Table 1). Although standards for determining resectability for patients with pancreatic cancer are still debated, many surgical and medical oncologists accept the conditions outlined by Czito et al. in which there is no involvement of the superior mesenteric vein (SMV), SMV portal vein confluence, (defined as occlusion or encasement), direct extension to the superior mesenteric artery (SMA), inferior vena cava, aorta, or celiac axis; distant metastases (liver, peritoneal, etc...); or extensive peri-pancreatic or celiac nodal involvement [14]. Accurate preoperative assessment and staging is thus essential for resection with curative intent.

3. Staging of pancreatic cancer using CT and EUS

Early in its development, EUS demonstrated some superiority over other imaging modalities for staging pancreatic tumors. However, advances in endosonographic imaging over the past decade have had to compete with advances in other imaging modalities such as helical CT-scan, multi-detector CT-scan, pancreas protocol CT-scan, CT-scan with three-dimensional (3-D) image reconstruction, magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), and positron emission tomography (PET). Pancreatic protocol CT remains an essential initial step in the evaluation of pancreatic tumors. It is very reproducible and has a sensitivity of 90% and a specificity of 99% (Table 1). One of the main imaging advantages of a dedicated pancreatic protocol CT using multi-detector technology is the ability to create high resolution 2-D and 3-D imaging displays such as curved planar images, maximum and minimum image projections and volume rendering images. These types of imaging displays provide unique diagnostic information that cannot be gained from axial images alone [15,16]. Nonetheless, EUS at some centers remains the preferred imaging modality in many instances by virtue of its

Table 1
Sensitivity and specificity of computed tomography (CT), endoscopic ultrasound (EUS), laparoscopic ultrasound (LUS) and intraoperative ultrasound (IOUS) for staging pancreatic cancer

Method	Years	Mean sensitivity (%)	Mean specificity (%)	References
CT	2002, 2004	90	99	[15,16]
EUS	1999, 2004	77	96	[20,21,36]
LUS	1999	78	100	[31,36]
IOUS	1993,1999	93	89	[56,57]

ability to detect even the smallest lesions, determine the presence of vascular involvement, and acquire tissue from primary tumors, lymph nodes and even distant mestastases [17,18]. However, EUS is slightly less sensitive and specific than CT (Table 1).

Vascular involvement by tumor continues to be an important factor in determining surgical resectability in patients with pancreatic cancer. During the past decade, advances in computed tomographic technology (hardware and software) have improved pancreatic imaging capability. Brugel et al. used multi-planar reconstruction of pancreatic imaging to assess the vascular involvement in patients with pancreatic cancer [19]. Forty patients with pancreatic head tumors underwent high-resolution imaging with multi-slice helical CT prior to attempted surgical resection. Multi-planar reconstructions followed the course of major vessels in proximity to the tumor. Radiographic criteria were established and used to determine the likelihood of vascular invasion in 52 vessels in the 40 patients. Radiographic analysis was compared with surgical and histopathological reports. Sensitivity and specificity were in the range of 50–75% and 91–97%, respectively. Continued refinements in the use of high-resolution CT-scanners with multi-planar image reconstruction have continued to enhance the radiographic sensitivity for the detection of vascular involvement in patients with pancreatic cancer (Fig. 1). Recent studies show that the accurate assessment of vascular involvement is 90% [15,16].

Many well-designed comparative trials have attempted to determine the superiority of one or the other pancreatic imaging modalities. Soriano et al. studied 62 consecutive patients with pancreatic cancer deemed fit for surgery [20]. Patients underwent EUS, CT, MRI and angiography. Each imaging test was judged on its ability to image primary tumor, loco-regional extension, lymph node involvement, vascular invasion, distant metastases, TNM stage, and tumor resectability. Results were compared with surgical findings. Helical CT-scan had the highest accuracy in determining the extent of the primary tumor (73%), loco-regional extension (74%), vascular invasion (83%), distant metastases (88%), and tumor resectability (83%) (Fig. 1). EUS was most accurate in determining tumor size and lymph node involvement. The most cost effective strategy for assessing patients with pancreatic cancer was helical CT-scan followed by EUS in patients thought to be resectable by the first test [20]. A recently published report by Maluf-Filho et al. evaluated radial EUS and helical CT-scan in 61 patients with suspected pancreatic cancer or ampullary cancer [21]. EUS was found to be more accurate than helical CT-scan for diagnosing patients presenting with obstructive jaundice (87.0% vs 67.4%, $p = 0.04$). EUS and helical CT-scan were equally effective in detecting pancreatic cancer. However, EUS was more accurate in detecting tumor involvement of

Fig. 1. A and B: High-resolution pancreatic protocol computed tomography (CT) of normal pancreas and pancreatic cancer. (A) curved planar reformation of the normal pancreas with a normal pancreatic duct (arrow). (B) Maximum intensity image demonstrates pancreatic tumor (T) in tail of the pancreas encasing the splenic artery (arrow).

the portal-mesenteric vasculature and it allows fine needle aspiration biopsy to make diagnosis (Fig. 2A and B). EUS was also superior in detecting ampullary tumors.

The determination of resectability in patients with pancreatic cancer is one of the most important contributions of accurate staging. As noted previously, patients with pancreatic cancer have been evaluated using thin-slice, multi-planar reconstructions obtained with a multi-slice helical CT. This new technology provides an exact depiction of the spatial relation between tumor and the potentially invaded vessels [22]. When compared with advanced helical CT technology,
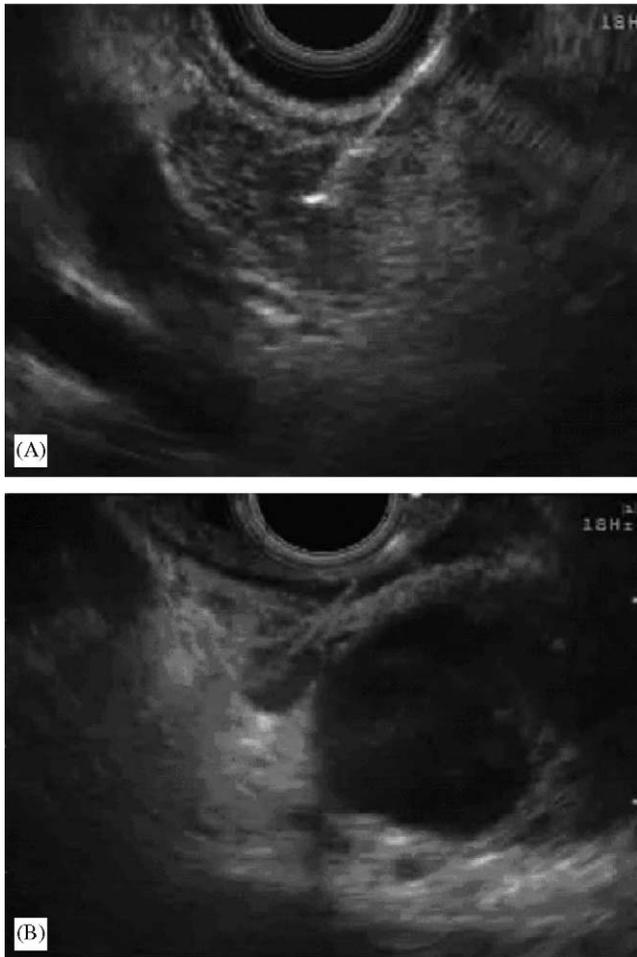
Fig. 2. (A) Endoscopic ultrasound (EUS) guided fine needle aspiration (FNA) of pancreatic head cancer. Tumor abuts the portal vein. (B) EUS-guided FNA of small (< 1 cm) lymph node near pancreatic cystic tumor. The endoscopic approach is transduodenal.

EUS is accurate at determining the vascular involvement of the portal venous system but is less accurate than helical CT-scan in detecting tumor involvement of the superior mesenteric artery [17,21].

Continued advances in ultrasound imaging and fine needle aspiration may improve the yield of EUS. One method to enhance ultrasound imaging is the use of contrast agents. Although not yet widely studied in endoscopic ultrasonography, such adjuvant imaging aids may increase the sensitivity of EUS. Rickes and Malfertheiner noted that echo-enhanced sonography has the potential to differentiate between different types of pancreatic tumors [23]. For example, pancreatic ductal carcinomas are often hypovascular while neuroendocrine tumors are hypervascular. The vascularity of tumors associated with pancreatitis may differ with respect to the degree of pancreatic inflammation and necrosis. Finally, pancreatic cystadenomas frequently demonstrate increased vascularity along fibrotic strands.

4. Staging of pancreatic cancer using laparoscopic ultrasonography (LUS)

Because of its wide availability, CT is often the first imaging modality used to assess patients suspected of having pancreatic cancer. However, CT is neither 100% sensitive nor accurate in this regard. Early studies reported CT to be 45% accurate in determining resectability. In one early report, liver metastases and vascular encasement went undetected in 23 cases [24]. Freeny et al. reported that CT accurately predicted resectability in only 67% of patients, failing to detect tumor invasion into small and large bowel mesentery, stomach, the presence of portal lymphadenopathy, and posterior tumor extension [25]. However, recent CT with multi-detectors and curved planar reconstruction can accurate image tumor extension into adjacent structures like the stomach (Fig. 3A) and the superior mesenteric vein (Fig. 3B).

LUS gained wide acceptance in the 1990s with the advent of flexible ultrasound probes that were made to be used through a laparoscopic port [26]. Since then studies have shown staging LUS is capable of revealing tumors, especially hepatic, peritoneal, and local extension by primary tumors, otherwise not detected preoperatively. However, LUS is less sensitive than multi-detector CT (Table 1). Prospective studies have shown that staging laparoscopy increases the rate of resection in patients with pancreatic cancer [27,28]. For example, Conlon et al. reported an accuracy of 94% in determining resectability using LUS [29]. Furthermore, John et al. demonstrated that of 40 patients with pancreatic and periampullary carcinoma, LUS suggested that 59% had unresectable lesions, which changed the operative management plan. In addition, LUS was significantly more specific in determining tumor resectability than laparoscopy alone [30,31]. In a later prospective study of 50 patients, the same group of researchers compared staging LUS with US and CT. They concluded that the sensitivity and negative predictive value of LUS in predicting tumor resectability were roughly comparable to those of US and CT, but LUS had significantly improved specificity and positive predictive value in defining tumor resectability [29]. Callery et al. also reported that LUS improved staging laparoscopy by identifying an additional 22% of patients with unresectable disease [32].

In 1995 another group of investigators reported that 19% of patients thought to be resectable preoperatively had occult metastases detected at staging LUS that allowed avoidance of unnecessary laparotomy [33] (Fig. 4). Hann et al. found that LUS altered management in 17% of patients [34]. Minnard et al. showed LUS altered management in 14% of cases [35]. In 1999, Catheline et al. reported LUS modified treatment in 41% of patients and spared an open procedure in 46%
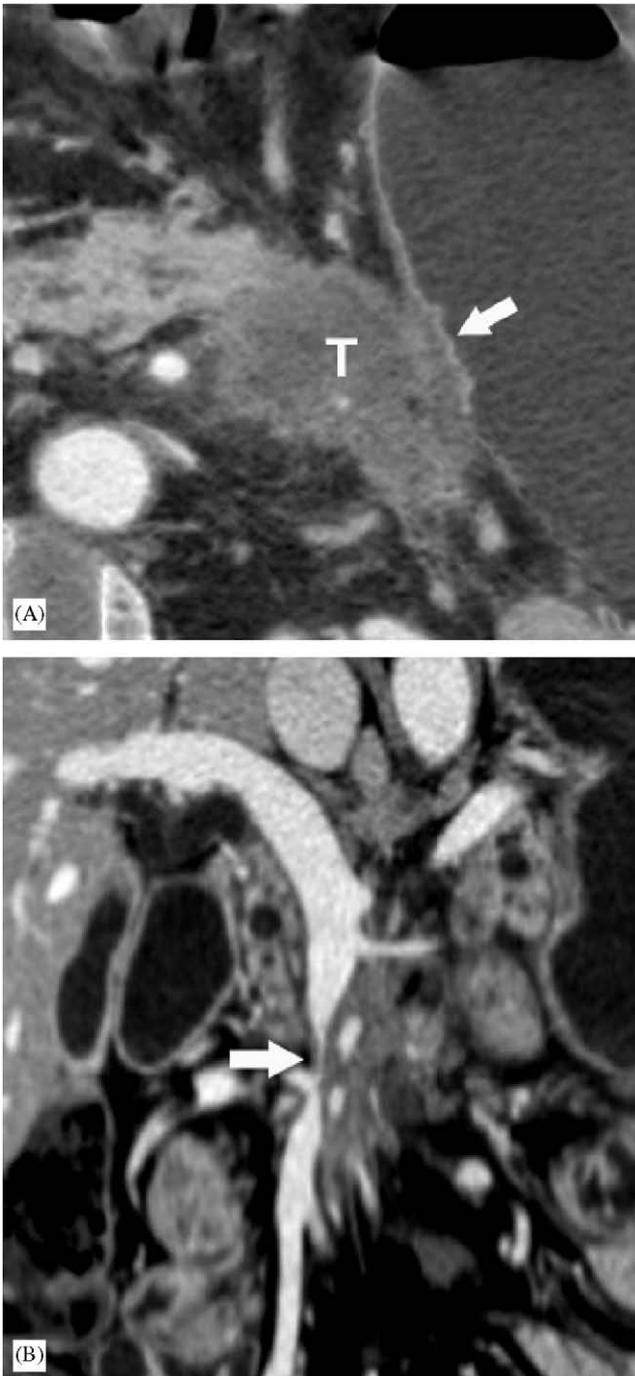
(A)

(B)

Fig. 3. A and B: Pancreatic protocol CTs of unresectable pancreatic carcinomas. (A) Minimum intensity image of a pancreatic tumor (T) in the tail of the pancreas invading the body of the stomach (arrow). (B) curved planar reformation of the superior mesenteric vein demonstrating circumferential encasement
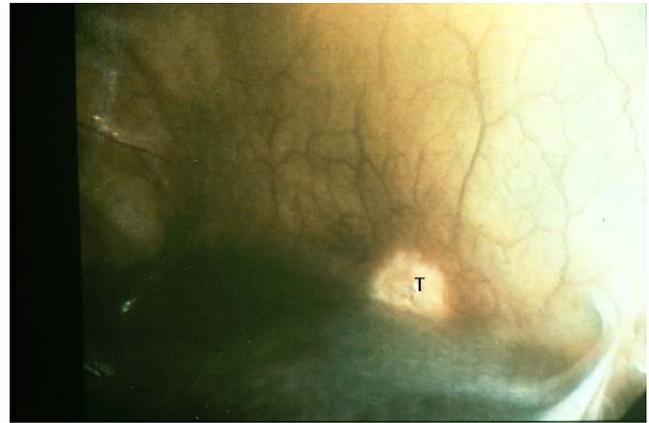

Fig. 4. Laparoscopic view of tumor implant (T) on surface of liver near diaphragm. This was an unexpected finding as CT showed no metastases.
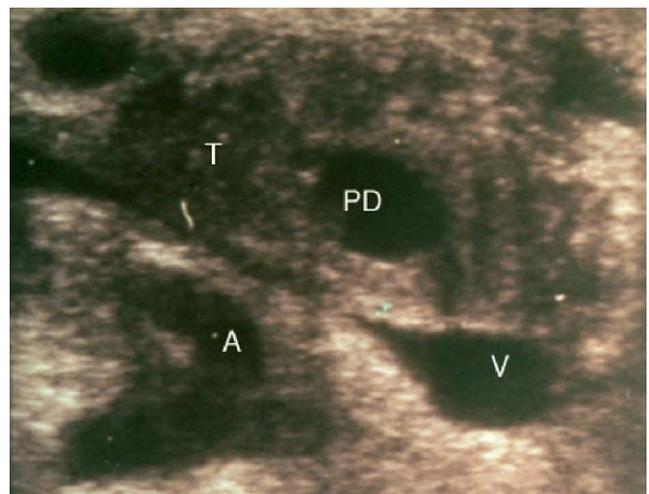

Fig. 5. Laparoscopic ultrasound image of tumor (T) in body of pancreas obstructing the dilated pancreatic duct (PD). Tumor is anterior to superior mesenteric artery (A) and splenic vein (V). Laparoscopic ultrasound predicted that this tumor was resectable and it was removed by a subtotal pancreatectomy-splenectomy.

of patients. They reported a 90% sensitivity for assessing positive lymph nodes, 100% for liver and peritoneal metastases (Fig. 4), and 100% for venous invasion [36]. Yet another group of investigators demonstrated that the addition of US to laparoscopic staging changed the surgical plan in 12% of patients

[37]. LUS is superior to laparoscopy alone because conventional laparoscopy prevents the surgeon from palpating intra-abdominal organs and retroperitoneal structures (Fig. 5). The addition of ultrasound imaging to standard laparoscopy adds minimal time (15–20 min) and is therefore recommended where the technology and expertise are available [38]. An added benefit to staging laparoscopy is the ability to perform palliative measures should a patient be found un-resectable. Palliation includes biliary enteric bypass, gastrojejunostomy, and neurolytic celiac plexus block. Palliation can improve jaundice, weight loss, abdominal pain and even survival [39–41].

With so many benefits to LUS, what are the arguments against its use? Rare reports demonstrating

a negative impact on cost-effectiveness have been published. In one study, LUS was shown to change management in only 7% of patients failing to justify its use from a cost perspective [42]. Holzman reported that laparoscopy may not be beneficial for all patients as the sensitivity for detecting metastatic disease is increasing [43]. As multi-detector CT protocols are becoming more widely available, the use of staging laparoscopy with ultrasound is becoming less valuable. We do not routinely use staging laparoscopy except for pancreatic tail tumors that have a high probability of occult distant metastases (Fig. 4).

5. Intra-operative ultrasonography (IOUS)

The use of IOUS is still relatively uncommon in the United States. IOUS may find tumors missed by CT or endoscopic ultrasonography. It can alter a planned operation, convert a curative resection to a palliative bypass, or vice versa. IOUS can also help delineate anatomy essential to an operation thereby avoiding complications due to blood vessel injury or help identify and thus preserve native anatomy obscured by tumor. With a sensitivity of 93%, it is as sensitive as any other method (Table 1).

It is well known that ultrasound waves cannot penetrate through air or gas. The limitations of standard transcutaneous ultrasound have been primarily overcome by closer application of the ultrasound probe to the target tissue. The advent of IOUS with placement of the near-field, high-resolution transducer on or adjacent to the organ of interest permits improved clarity and resolution of pancreatic masses. First described by Schlegel et al in 1961 [44], and Knight and Newell in 1963 [45] using A-mode ultrasonography (one-dimensional (1-D) image), IOUS was used to study kidney stones and gallbladder stones. Current IOUS is B-mode using frequencies that oscillate at 1–30 MHz [46]. The use of B-mode ultrasound employs the brightness of grayscale to demonstrate the amplitude of echo, and is thus easier to interpret. Immediate (real time) imaging is now possible. A primary indication for IOUS is to detect the precise location of pancreatic endocrine tumors: gastrinomas, insulinomas, glucagonomas, VIPomas, somatostatinomas [47–49]. Numerous studies have reported detection rates for insulinomas with IOUS ranging from 95 to 100% [50–52]. IOUS has also been used to guide surgery for chronic pancreatitis [53] and in the assessment of pancreatic adenocarcinoma.

When treating adenocarcinoma of the pancreas, IOUS is most useful in resectable patients. The use of IOUS was first described for resection of pancreatic cancer by Sigel et al. [54] and later by Plainfosse et al. [55] In these studies, IOUS was used to diagnose malignant invasion of the mesenteric venous system
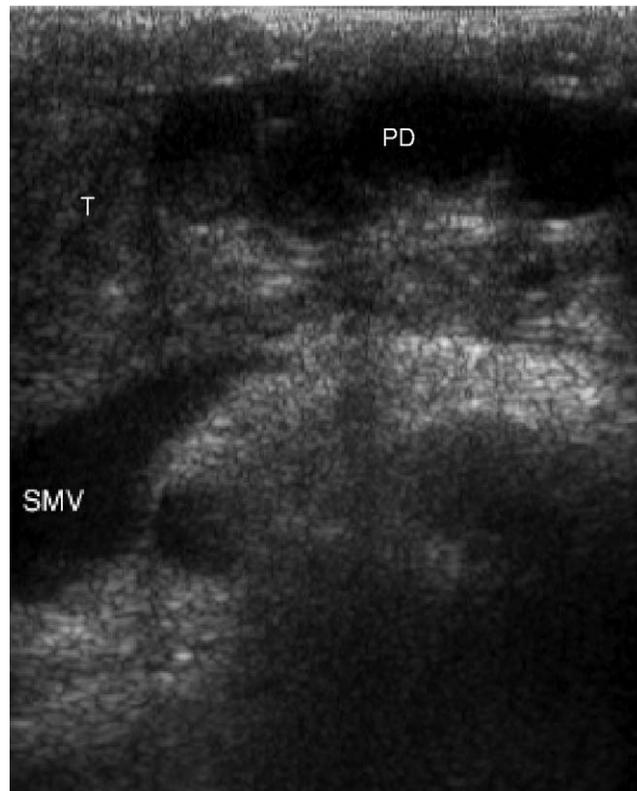

Fig. 6. Intraoperative ultrasound (IOUS) of pancreatic tumor (T) that was thought to be unresectable based on its relationship with the confluence of the superior mesenteric vein (SMV) and the splenic vein. However, IOUS demonstrated that the tumor was separate from the vein and that it obstructed the pancreatic duct (PD). Based on IOUS resection was performed and the tumor was removed with negative margins.

and the presence of extra-pancreatic spread (Fig. 6). Machi et al. showed IOUS to be more accurate in determining portal vein invasion than preoperative ultrasonography, CT, and portal phase superior mesenteric angiography [56]. Another study reported IOUS to provide the best assessment of portal venous involvement [57]. This is an important observation as the presence of portal vein involvement is a clear contraindication to surgical resection.

A recent study of the clinical utility of IOUS separated patients into three groups: those in whom IOUS was thought to be *very useful* (it changed management) (Fig. 6) those in whom IOUS was thought to be *useful* (the operative procedure was carried out under IOUS) and those in whom IOUS was thought to be *not useful*. In a group of patients (26) operated on for pancreatic carcinoma, the IOUS information was *very useful* in 16%, and *useful* in 42% [58]. An additional study on the subject concluded that "IOUS is now indicated for planning and guiding the surgeon in resection of pancreatic cancer" [59]. IOUS has also been shown to be capable of detecting metastatic liver lesions. A study in patients with colorectal cancer
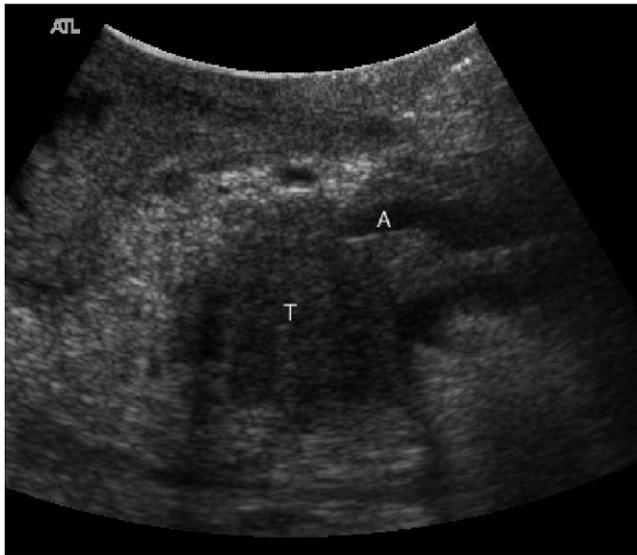
Fig. 7. IOUS of pancreatic head tumor (T) with common hepatic artery (A) coming off the superior mesenteric artery and coursing around the tumor making this tumor inoperable.

showed that 94% of metastatic lesions were accurately detected [60]. IOUS has also been used for detection of metastases in other locations [61–63]. The additional information provided by IOUS reduces operative time and tissue trauma in patients undergoing pancreatic surgery [64]. Further, IOUS can help in the identification of unusual operative anatomy like this example of the hepatic artery arising from the superior mesenteric artery. It also showed the artery at the anterior border of the mass in the head of the pancreas, curving over the portal vein (Fig. 7).

6. Conclusion

With advances in medical imaging, the evaluation of patients with pancreatic cancer is changing. During the last decade, endoscopic investigators established that EUS was superior to all other imaging modalities for the detection and staging of pancreatic cancer. EUS also permits the safe needle biopsy of tumors and lymph nodes. Most recently, significant improvements in multi-detector CT-scanning, particularly the introduction of three-dimensional image reconstruction, have re-established CT as the primary imaging modality for staging pancreatic cancer. Further, the roles of LUS and IOUS are being expanded. It is likely that these high-resolution imaging techniques, when used in combination, will offer patients and their surgeons the best and most cost-effective approach for effective management. Resectability of pancreatic tumors is likely to increase and complications and mortality decrease with improved imaging resolution.

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