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Laparoscopy with Laparoscopic Ultrasonography in the TNM Staging of Pancreatic Carcinoma

Timothy G. John, M.D.,[1] Andrew Wright, M.D.,[2] Paul L. Allan, M.D.,[2] Doris N. Redhead, M.D.,[2] Simon Paterson-Brown, M.D.,[1] David C. Carter, M.D.,[1] O. James Garden, M.D.[1]

[1]University Department of Surgery, The Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW, UK
[2]University Department of Radiology, The Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW, UK

Abstract. A prospective study was performed comparing laparoscopy with laparoscopic ultrasonography (LapUS), transabdominal ultrasonography (USS), computed tomography (CT), and selective visceral angiography with portal phase venography (SVA) for the assessment of resectability in 50 patients with pancreatic or periampullary cancer. The results were stratified by TNM stages. Tumor unresectability was demonstrated in 36 patients (72%). The sensitivity of LapUS for demonstrating the index lesion was 96%. Laparoscopic ultrasonography failed to predict factors precluding resection by T stage in six patients, and there were no significant differences in the ability of any modality to predict local resectability (predictive value 58–73%). Laparoscopic ultrasonography did not overestimate T stage and was significantly more specific for assessing unresectability compared with USS (100% vs. 64%, $p < 0.05$) and CT (100% vs. 47%, $p < 0.005$). No imaging investigation was able to assess the N stage accurately. Metastases were confirmed in 16 patients (32%), with LapUS proving significantly more sensitive than USS (94% vs. 29%, $p < 0.001$) and CT (94% vs. 33%, $p < 0.005$). The addition of LapUS to the laparoscopic examination did not change the M stage in any patient, as all metastases were superficially located. Laparoscopy with LapUS was the most reliable method for assessing overall tumour resectability and was significantly more predictive than CT (97% vs. 79%, $p < 0.005$). These results confirm that laparoscopy is indispensable for detecting occult intraabdominal metastases. LapUS reliably predicts tumor unresectability, offsetting the tendency of USS and CT to overestimate T stage. Methods of accurate N staging remain elusive, and the use of routine SVA is not justified.

Pancreatic cancer is one of the most commonly diagnosed malignancies. Patients often present at a late stage with obstructive jaundice, gastric outflow obstruction, or both; and they have a poor prognosis. Whereas surgical resection with curative intent represents the only chance for long-term survival, the main options for palliation are endoscopic or percutaneous biliary stent insertion (or both) or surgical biliary or duodenal bypass (or both). Careful patient selection is fundamental to the management of such patients to avoid unnecessary and potentially morbid intervention in patients with unresectable tumors who would benefit from a nonoperative approach and to ensure appropriate selection of those with potentially resectable lesions for pancreatoduodenectomy. Although the stakes remain high in this regard, precise imaging of pancreatic malignancies is fraught with difficulty owing to the retroperitoneal location of the pancreas and the complexity of its immediate anatomic relations.

Correspondence to: O.J. Garden, M.D.

Although the armamentarium of diagnostic and staging investigations continues to undergo expansion and refinement, no consensus exists as to the optimal investigative algorithm for such patients. Laparoscopic ultrasonography (LapUS) is a relatively recent addition to the range of methods available for staging patients with pancreatic and periampullary cancer. Its attraction is twofold. Staging laparoscopy has been shown to be unrivaled for demonstrating previously unsuspected, small-volume intraabdominal metastases typically affecting the liver and peritoneum [1–5]. Also, the use of a high-frequency contact ultrasound transducer during laparoscopy facilitates generation of high-resolution, real-time sonographic images of the area of interest [6, 7]. Initial reports of laparoscopy with LapUS for staging pancreatic cancer appeared to confirm its utility in assessing metastatic disease and locoregional invasion [8–10], primarily in patients already considered potential candidates for surgery following other investigations. Data regarding its performance in direct comparison with conventional staging modalities is lacking.

Having previously relied on "traditional" radiologic modalities, such as transabdominal ultrasonography (USS), contrast-enhanced computed tomography (CT), and selective visceral angiography with portal phase venography (SVA) to assess such patients in our hospital, a prospective study comparing LapUS with these techniques was performed. In particular, evaluation of tumor resectability with reference to the TNM staging system was undertaken to evaluate the strengths and weaknesses of the various investigations in this role.

Methods

Patients with carcinoma of the pancreatic head or periampullary region were prospectively evaluated by an investigative algorithm consisting of USS, CT, LapUS, and SVA prior to laparotomy. A prospective blind comparison of the diagnostic accuracies of these investigations for defining tumor resectability was performed with reference to the UICC TNM classification [11]. All patients provided written consent prior to the LapUS examination.

Strict differentiation between cancers of the pancreas and those arising in the peripapillary region can be difficult. Although the UICC staging classification strictly distinguishes between these entities, it was recognized that tumors which infiltrate both papilla and the pancreatic head could be classified pathologically as T4 peripapillary cancers, or alternatively, as T2 pancreatic cancers. For the purposes of this study, all carcinomas of the pancreas and peripapillary region were considered together and classified according to the UICC TNM classification of pancreatic cancer [11]. This approach was justified for the purposes of determining an endpoint of tumor resectability, rather than the outcome of treatment.

Transabdominal Ultrasonography

Transabdominal USS was performed after a fast of at least 6 hours using an Acuson 128 ultrasound machine (Mountain View, CA, USA) with 3.5- or 4.0-MHz transducers. All scans were performed by one experienced radiologist (P.L.A.). Color Doppler and Doppler spectral analysis were used to assess the major peripancreatic blood vessels for tumor involvement. The presence of significant turbulence or an increase in velocity $> 100\%$ at or beyond the region of the tumor was taken as evidence of vascular invasion. The examinations were performed "blind," and a protocol form was completed.

Computed Tomography

The CT scans of the abdomen were obtained under the direction of one radiologist (A.R.W.) or by a nominated deputy according to the following protocol. If CT scans had recently been obtained at a referring hospital, the films were reviewed and the examination repeated only if the quality of the original scans were regarded as unsatisfactory. The scans were interpreted "blind," and a protocol form was completed.

Abdominal CT scanning was performed using a General Electric 9800 whole-body CT scanner (General Electric Medical Systems, Milwaukee, WI, USA). Contiguous 10 mm slices were acquired through the entire liver and pancreas before the administration of intravenous contrast. The examination was repeated following the injection of a 100 ml bolus of iodinated contrasted medium (Iopamidol 370). Contiguous slices of 10 mm were obtained, with scan acquisition performed in a cranial direction to optimize contrast opacification of the superior mesenteric and portal veins. Recently, several CT scans were obtained using the technique of spiral CT scanning with a Siemans Somatom Plus spiral-acquisition CT scanner. Scans were performed before and during intravenous contrast enhancement with 100 to 120 ml of Iopamidol 300. For the precontrast scans, the liver and pancreas were scanned during a single breath-hold using 10 mm nominal slice thickness and a 10 mm/s table speed. For the postcontrast scan, 5 mm slice thickness and 5 mm/s table speed or 10 mm slice thickness with 10 mm/s table speed was used depending on the volume of interest.

Selective Visceral Angiography

All angiographic examinations were performed and interpreted "blind" by one radiologist (D.N.R.). A protocol form was completed for each examination. A 7F Cordis superior mesenteric or Sidewinder catheter was introduced percutaneously into the right common femoral artery by the Seldinger technique and advanced into the abdominal aorta. The celiac axis was initially selected, and 60 to 70 ml of nonionic contrast (Niopam 370E, Merck Pharmaceuticals) was injected at a rate of 6 ml/s and at a pump pressure of 600 psi. Following an initial delay of 1 second, 10 films were obtained at a speed of one film every 2 seconds. This provided an anatomic display of the branches of the celiac axis and, during the venous phase, visualization of the splenic and portal veins.

The catheter was then placed within the superior mesenteric artery, and 70 ml of contrast is again injected at the same rate and pressure settings. A long film delay of 9 to 10 seconds was employed, and 10 radiographs were obtained at a rate of one film every 2 seconds. This sequence of films demonstrated any arterial anomalies involving the superior mesenteric artery, such as an accessory or replaced right or common hepatic artery. The longer delay ensured optimal visualization of the superior mesenteric and portal veins. When the mesoportal venous pathway lay across the plane of the vertebral column and imaging was consequently impaired, the examination was repeated with a 17-degree right posterior oblique view with the catheter still in the superior mesenteric artery and employing the same settings. Thus the opacified veins were projected away from the bony structures, and clearer images were obtained.

Laparoscopy with Laparoscopic Ultrasonography

The technique of staging laparoscopy with LapUS has been described in detail elsewhere [9, 12]. In brief, laparoscopy was performed under general anesthesia as a separate procedure in advance of any planned laparotomy. Two 10 mm ports were utilized, usually at the umbilicus and the right flank. A systematic examination of the abdominal cavity was performed using a 30 degree telescope, examining the serosal surfaces of the anterior abdominal wall, diaphragm, falciform ligament, omentum, pelvic viscera, bowels, and their mesenteries. No attempts were made to insufflate or enter the lesser sac, nor was dissection or mobilization of the pancreatic head or mesenteric root performed.

Laparoscopic ultrasonography was performed using a variety of commercially available systems. A 7.5-MHz multielement linear-array LapUS probe was used in every case (Aloka UST-5521-7.5 or Aloka, UST-5523L-7.5, KeyMed, Southend-on-Sea, UK; or Tetrad 8A, Englewood, CO, USA) and was connected by a sterile cable to a portable ultrasound machine (Aloka SSD-500 or Aloka SSD-680; or Tetrad 2200 imaging system). Simultaneous viewing on the operating theater monitors of both the laparoscopic view of the abdominal cavity and the sonographic images was achieved by "picture-in-picture" video mixing using a Panasonic WJ-AVE5 audiovisual mixing desk (KeyMed).

The thin film of moisture covering the abdominal organs usually provided excellent acoustic coupling with the LapUS transducer. Installation into the peritoneal cavity of up to 500 ml normal saline solution at room temperature was used to optimize transducer contact and minimize down-pressure. This instilled fluid also served as peritoneal washings for peritoneal cytologic analysis, which is the subject of a separate report [13].

An anatomic survey of the liver, biliary tree, pancreas, and peripancreatic structures was performed with reference to stan-

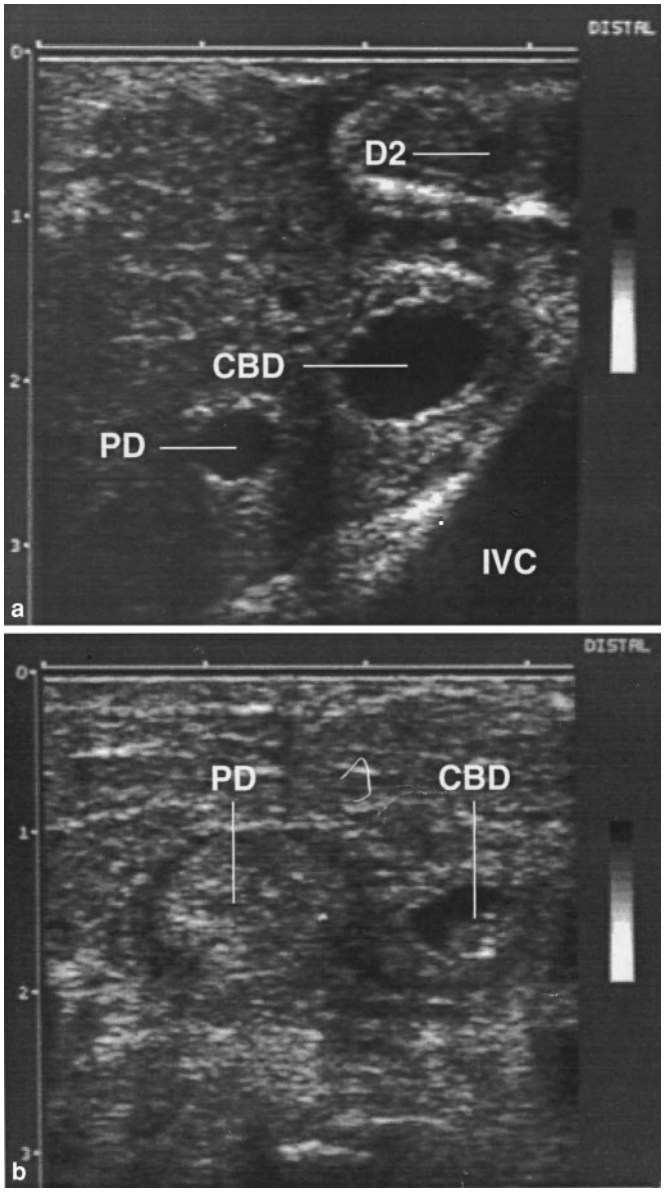

Fig. 1. Laparoscopic ultrasound scans of a patient presenting with obstructive jaundice secondary to a periampullary tumor. **a.** This transverse scan through the head of the pancreas shows a prominent lower common bile duct (CBD) and pancreatic duct (PD), the second part of the duodenum (D2), and inferior vena cava (IVC). **b.** This image, which is proximal to the ampulla, demonstrates a tumor infiltrating the pancreatic duct and within the lumen of the lower common bile duct.

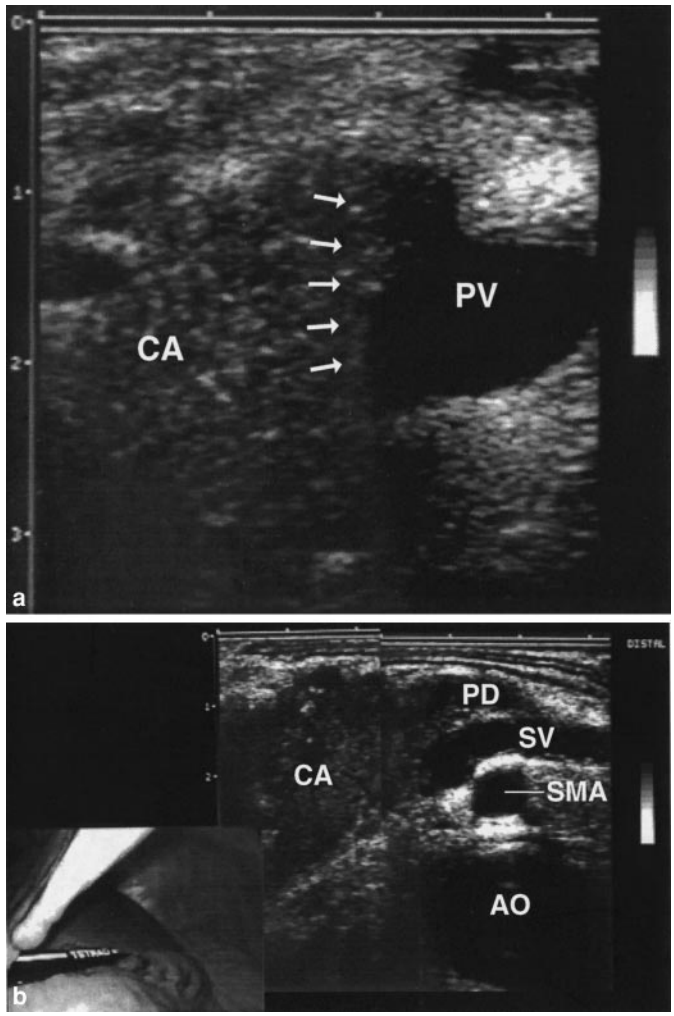

Fig. 2. Transverse laparoscopic ultrasound images of a patient presenting with an apparently resectable carcinoma in the head of the pancreas on CT scan. **a.** The pancreatic cancer (CA) is hypoechoic relative to the surrounding tissues. There is apparent infiltration (arrows) within the portal vein (PV). **b.** This composite image shows the transducer placed on the antrum of the stomach underneath the left lobe of the liver. The hypoechoic tumor (CA), which measured approximately 3 cm in maximal diameter, extended across the neck of the pancreas toward a dilated pancreatic duct (PD). The splenic vein (SV) and superior mesenteric artery (SMA) lie anterior to the aorta (AO).

dard anatomic landmarks with the LapUS probe operated via umbilical and right flank ports to achieve scanning in two planes. Having characterized the primary pancreatic lesion, its local resectability was assessed. Tumor invasion of the portal vein was the main consideration when determining local resectability of pancreatic or periampullary cancer, with particular attention to the right lateral aspect of the splenoportal venous junction (Figs. 1, 2). The following criteria were adopted to indicate vascular invasion: (1) obliteration or thrombosis of the vein, as evidenced by failure of the laparoscopic ultrasonographer to demonstrate a patent vessel in the expected anatomical location, with or without venous collateralization; (2) a fixed stenosis of the vessel wall; (3) loss of the hyperechoic vessel–tumor interface with encroachment of hypoechoic tumor to the vessel margin; (4) vessel encasement as evidenced by tumor encirclement and "rigidity"; (5) the presence of invading tumor within the vessel lumen. Care was taken to avoid creating artifactually the impression of portal vein compression by excessive probe pressure.

Other evidence for local unresectability was sought by examining for tumor extension into adjacent soft tissue planes, such as the mesenteric root, hepatoduodenal ligament, or retropancreatic fascia. Regional lymph node enlargement (> 10 mm maximum node diameter) was arbitrarily regarded as being suspicious of malignant involvement (Fig. 3).

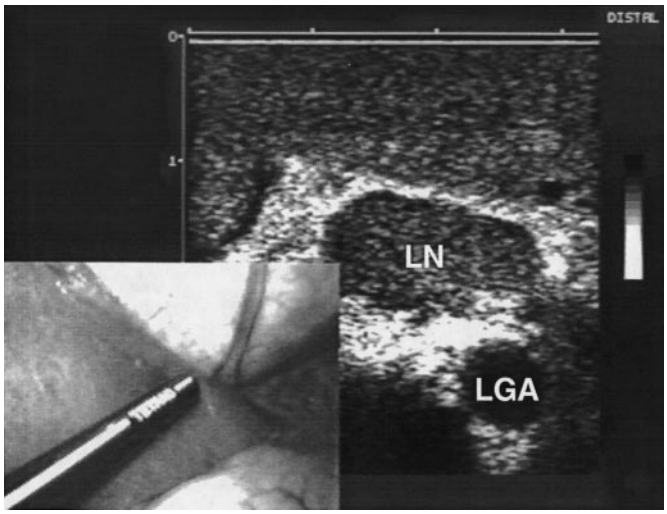

Fig. 3. The transducer has been placed on the left lobe of the liver to look for possible celiac lymphadenopathy. A lymph node (LN) measuring 1 × 2 cm in diameter is seen lying anterior to the left gastric artery (LGA).

Validation of Tumor Unresectability

Validation of the study endpoint of tumor unresectability was achieved in a number of ways. (1) By laparoscopy when distant intraabdominal metastases or malignant regional lymphadenopathy were discovered with histologic confirmation by laparoscopic needle biopsy, fine-needle aspiration (FNA) cytology, or scissor biopsy of the lesion. (2) By surgical assessment. Exploratory laparotomy was the ultimate arbiter of tumor resectability in most patients and was always performed by a consultant surgeon experienced in pancreatic surgery (D.C.C., O.J.G., S.P.B.). The findings were documented on a standardized proforma. Examination of the peritoneal cavity and viscera was performed, with palpation of the liver, mesenteries, peripancreatic tissues, and serosal surfaces for metastases, malignant lymphadenopathy, or extrapancreatic tumor invasion. Histologic proof of such findings was sought in each case by biopsy. Intraoperative ultrasonography of the liver was performed using a 7.5-MHz "T-probe" to search for intrahepatic metastases (Aloka UST-576-T or Tetrad 6C). Trial dissection of the pancreas was performed to assess local tumor resectability by a standardized technique [14]. Palliative resections comprising gross transection of tumor in patients with locally invasive disease were not performed. In general, patients with cancers of the pancreatic head or periampullary region were treated by a Whipple pancreaticoduodenectomy; patients with cancers of the pancreatic body and tail underwent distal pancreatectomy; and total pancreatectomy was reserved for patients with carcinoma of the head and body. Patients with periampullary tumors apparently localized to the papilla and considered potentially resectable by local excision were evaluated superficially by means of a longitudinal duodenotomy. Such tumors were regarded as resectable when transduodenal local excision or ampullectomy could be achieved with tumor-free resection margins. (3) By nonoperative findings, when portal-superior mesenteric vein invasion was accepted on the basis of concurring radiologic findings of USS, CT, LapUS, or SVA, together with the clinical observation of a rapid death from carcinomatosis. Independent validation of these findings during laparotomy was not obtained in a number of cases because an a priori clinical decision had been made to palliate the patient nonoperatively by means of biliary stent insertion. Combined evidence from the various staging investigations and clinical findings were accepted as validation of tumor unresectability in these cases. (4) By histopathologic findings. Validation of tumor resectability for cure required the demonstration of microscopically tumor-free resection margins and regional lymph nodes following routine histopathologic examination of the resection specimens. Particular attention was paid to the surgical transection lines of the stomach, common duct, pancreas, duodenum, and retropancreatic fascia.

Breaches of protocol occurred inasmuch as some patients failed to undergo all four investigative modalities. Eleven patients did not undergo USS according to protocol. CT scans performed at the original hospital within 2 months prior to referral and regarded as being of satisfactory quality were not repeated in 12 cases (27%). Thirty-three of fifty patients underwent SVA. Laparoscopic evidence of metastases precluded operative intervention in these patients, and SVA was accordingly regarded as unjustified.

Evaluation of T Stage

Patients were considered to have pancreatic or periampullary cancers that were resectable with curative intent when there was no evidence of extrapancreatic tumor invasion (T1) or when local tumor invasion was limited to the distal common bile duct or medial duodenal wall (T2). However, local tumor invasion of the peripancreatic fat or tissues of the hepatoduodenal ligament was regarded as indicating unresectable tumor (also T2). Similarly, tumor invasion or encasement of major peripancreatic blood vessels, stomach, spleen, or colon indicated tumor unresectability (T3). Local tumor resectability by T stage was validated by surgical staging in 29 of 50 patients and by nonoperative means in 6 patients when all four staging modalities and the patients' clinical course were indicative of advanced cancer. For the purposes of this study, lesions with positive resection margins were regarded as having been "unresectable" in the context of "cure." Fifteen patients in whom metastases had been discovered and who were assessed by neither laparotomy nor SVA were not evaluable by T stage (Tx).

Evaluation of N and M Stages

For the purposes of this study, patients with distant metastases (M1) or malignant regional lymphadenopathy (N1) documented by laparoscopic or operative biopsy (Fig. 4), including patients found to have lymph node metastases following histologic examination of the pancreatic resection specimen, were regarded as having "unresectable" tumors. The absence of distant metastases (M0) or regional lymph node spread (N0) was accepted only after full operative staging, including examination of suspicious lesions by frozen section histology where appropriate. Lymph node status was unevaluable in 23 patients in whom operative staging was not performed, and the M stage of three patients could not be validated for similar reasons (i.e., Nx and Mx).

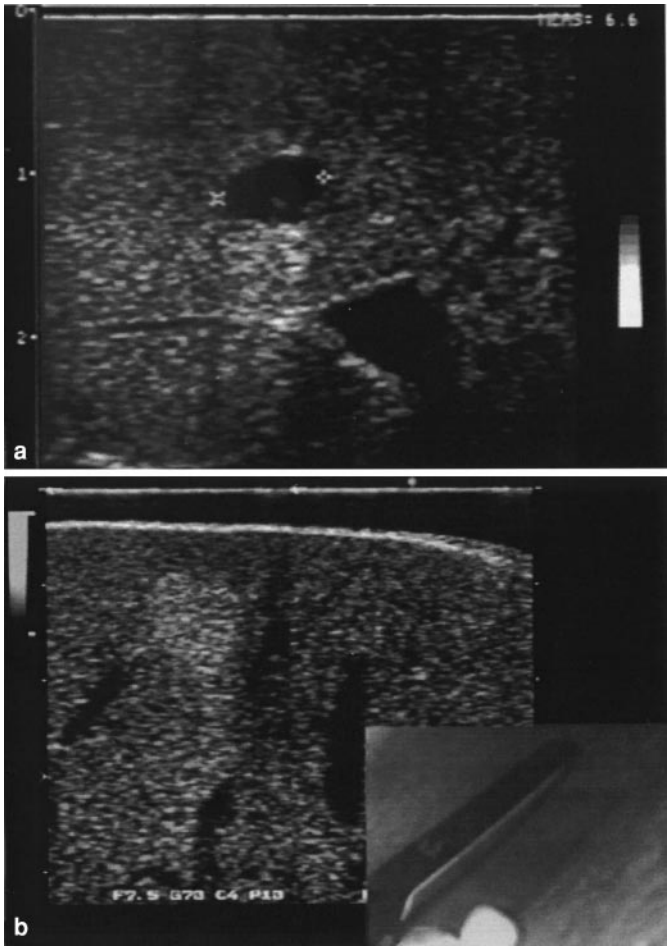

Fig. 4. a. Laparoscopic ultrasonography has demonstrated that a potential metastatic deposit in the liver on CT scanning measures 6.6 mm in maximal diameter but has ultrasound features typical of a benign hepatic cyst. Note the posterior acoustic enhancement typical of a hepatic cyst. **b.** The transducer has been positioned in the right subphrenic space in a pool of instilled saline. The resultant ultrasound image demonstrates a hyperechoic lesion measuring approximately 1 cm in diameter lying just underneath the capsule of the liver. Ultrasound-guided biopsy confirmed the presence of an "occult" metastasis.

Overall Staging

All 50 patients were classified overall as having "resectable" or "unresectable" lesions, taking into account the findings for each of the T, N, and M stages. Overall unresectability was therefore denoted by the demonstration of defined criteria contraindicating tumor resection for any aspect of the TNM staging system, recognizing that other TNM criteria may have classified them as being "resectable" in the same patient.

Analysis of Results

Summary measures of diagnostic accuracy were calculated using 2×2 contingency tables. The predictive values of positive results for determining tumor unresectability and negative findings for predicting tumor resectability were calculated. Statistical comparisons between summary measures of diagnostic accuracy were performed using the continuity-corrected chi-square method or Fisher's exact test when expected frequencies were less than five. Statistical significance was taken as $p < 0.05$.

Results

Fifty consecutive patients presenting with carcinoma of the pancreas or periampullary region were studied [31 men with a median age of 62 years (range 42–78 years)]. Staging laparoscopy with LapUS was performed in all patients between March 1993 and April 1995. A histologic diagnosis of pancreatic or periampullary carcinoma was obtained in 44 patients by percutaneous ($m = 4$) or operative ($n = 10$) needle biopsy of the pancreas; laparoscopic ($n = 15$) or operative ($m = 1$) biopsy of metastatic lesions in the liver, serosal surfaces, or regional lymph nodes; histopathologic examination of the pancreatic resection specimen ($n = 14$); or endoluminal biopsy of periampullary lesions ($n = 10$). No biopsy diagnosis was obtained in the other six patients, although a pancreatic mass lesion was documented by imaging investigations, and death due to carcinomatosis was observed in each case [crude mean survival 34 weeks (range 12–67 weeks)]. The primary tumor was situated in the pancreatic head (33 patients), pancreatic body (5 patients), pancreatic head and body (1 patient), and periampullary region (11 patients). A biliary stent had been inserted in 30 patients by the endoscopic route (22 patients) or percutaneous route (8 patients); and a cholecystjejunostomy had previously been performed in one patient at the referring hospital.

Patient Outcome

Exploratory laparotomy was performed in 29 patients, 14 of whom underwent tumor resection (Whipple operation in 9 patients; transduodenal local resection for periampullary carcinoma in 3 patients; total pancreatectomy in 1 patient; distal pancreatectomy in 1 patient). Palliative bypass surgery was performed in 14 patients (duodenal and biliary bypass in 8 patients; duodenal bypass alone in 5 patients; biliary bypass alone in 1 patient); and laparotomy with tumor biopsy was performed in one patient found to have invasion of the posterior wall of the stomach by a pancreatic body carcinoma. Three patients who underwent tumor resection had either peripancreatic lymph node metastases (two patients), or invasion of the peripancreatic soft tissues with tumor involvement of the posterior resection margin (one patient); for the purposes of this study these tumors were considered "unresectable" for cure. Conversely, three patients in whom transduodenal local resections were not possible owing to pancreatic tumor infiltration were nevertheless judged as having tumors that were potentially resectable by pancreaticoduodenectomy. However, it was elected to forego pancreatic resection in these frail patients of high cardiovascular risk status, and palliative bypass operations were performed instead. Therefore for the purposes of this study, the prevalence of patients with "unresectable" tumors was 72% (36 of 50 patients).

Postoperative morbidity following LapUS was encountered in one patient with carcinoma of the pancreatic body who previously had undergone percutaneous needle biopsy. Peritoneal carcinomatosis was revealed at laparoscopy, and the patient developed an umbilical port-site metastasis 6 weeks later. The general health of another two patients deteriorated rapidly after LapUS had revealed histologically proven disseminated pancreatic cancer, with death occurring 6 days and 2 weeks later, respectively.

Table 1. Diagnostic accuracy of staging investigations for predicting tumor unresectability according to T stage in 35 patients with pancreatic or periampullary carcinoma.

Test	Sensitivity	Specificity	PPV	NPV
USS	0.60	0.64*	0.66	0.58
CT	0.71	0.47**	0.61*	0.58
LapUS	0.68	1.00	1.00	0.73
SVA	0.67	0.69	0.72	0.64

USS: transabdominal ultrasonography; CT: computed tomography; LapUS: laparoscopic ultrasonography; SVA: selective visceral angiography; PPV: positive predictive value; NPV: negative predictive value.

*$p < 0.05$; **$p < 0.005$ (USS/CT versus LapUS).

Table 2. Diagnostic accuracy of staging investigations for predicting tumor unresectability according to N stage in 27 patients with pancreatic or periampullary carcinoma.

Test	Sensitivity	Specificity	PPV	NPV
USS	0.67	0.85	0.61	0.88
CT	0.83	0.71*	0.50	0.92
LapUS	0.71	0.80	0.56	0.89
SVA	0.20	1.00	1.00	0.78

*$p < 0.05$ (SVA versus CT).

Diagnosis of Primary Tumor

A focal mass lesion within the pancreas or periampullary region was revealed by USS in 32 of 39 patients (82%) and by CT in 42 of 45 patients (93%). Definition of a primary tumor mass was possible in 48 of 50 patients (96%) using LapUS. The tumor typically appeared as a discrete, irregular, hypoechoic mass in cases of pancreatic cancer or as an isoechoic or hypoechoic lesion prolapsing into the lumen of the second part of the duodenum or infiltrating the pancreatic head in patients with periampullary carcinoma. There were two false-negative LapUS examinations where focal tumor could not be demonstrated. Both patients had diffuse isoechoic carcinomas of the pancreatic head, and in one the examination was limited by adhesions associated with a cholecystojejunostomy performed at the referring hospital.

The presence of the primary tumor was inferred from displacement of the pancreaticoduodenal arteries or by displacement or invasion of the portal or superior mesenteric veins in 21 of 32 patients (66%) studied by SVA ($p = 0.005$, SVA vs. CT; $p = 0.0008$, SVA vs. LapUS). An anomalous right or common hepatic artery arising from the superior mesenteric artery or aorta was demonstrated in 8 of 32 patients (22%); it had been recognized using LapUS in four cases. Severe obliterative vascular disease with occlusion of the celiac and superior mesenteric arteries was shown in one patient.

Evaluation of T Stage

Validation of T stage status was achieved in 35 patients: by surgical staging in 29 patients and by nonoperative criteria in 6. Sixteen lesions were staged as T1, three as T2 (invasion of retropancreatic fat in one patient, invasion of mesenteric root in one patient, and invasion of hepatoduodenal ligament in one patient) and sixteen as T3 (vascular invasion in 15 patients and invasion of the posterior wall of the stomach in 1 patient). Tumor unresectability according to T stage was therefore documented in 19 of 35 evaluable patients (prevalence 54%). The derived summary measures of diagnostic accuracy for T staging are summarized in Table 1.

There were six instances where LapUS failed to identify tumor unresectability due to T2-T3 local tumor invasion. Invasion of the portal–superior mesenteric vein was not predicted in three patients, one of whom had a diffusely infiltrating isoechoic carcinoma of the pancreatic head, the extent of which was difficult to define; another had a 5 cm diameter tumor in which dense posterior acoustic shadowing largely obscured in the vein–tumour interface. In the third case, marked distortion of the portal-superior mesenteric vein by a 3 cm diameter carcinoma of the uncinate process was identified, although no direct venous invasion was identified and diagnosis of a potentially resectable "pushing" tumor was predicted. However, during surgical exploration the tumor was deemed to have extended too far posterior to the superior mesenteric vein to enable resection without necessitating gross tumor transection.

Infiltration of the posterior wall of the stomach was undetected in one patient with an 8 cm diameter pancreatic body cancer in which the tumor was discovered to have extended into the lesser sac to infiltrate the serosa during laparotomy. Retrospective review of the LapUS images in this patient revealed loss of the normal hyperechoic interface between the stomach serosa and the pancreas, which had not been recognized during the procedure. Infiltration of the retroperitoneal soft tissues alongside the inferior vena cava was discovered in one case. Retropancreatic fat invasion was discovered by histopathologic examination of the distal pancreatectomy specimen of one patient. The sensitivities (60–71%) and negative predictive values (58–73%) of all investigations for identifying tumor unresectability due to direct extrapancreatic invasion did not differ significantly.

There were 16 instances where overestimation of T stage by one or more investigations was demonstrated. These "false positive" findings were attributable to USS in four patients [invasion of the portal vein ($n = 2$), common bile duct ($n = 2$), or peripancreatic fat ($n = 1$)], CT in eight patients [invasion of peripancreatic fat ($n = 6$), portal vein invasion ($n = 3$), or colonic invasion ($n = 1$)], and SVA in four patients (slight narrowing of the superior mesenteric–portal vein junction leading to the diagnosis of "encasement"). All these patients were subsequently shown to have resectable tumor by surgical validation and histopathologic examination of the resected specimen. There were no instances of overstaging the T stage by LapUS; accordingly, its specificity and positive predictive value were significantly superior to that of both USS and CT (Table 2).

Angiography failed to detect local tumor unresectability due to proven portal vein invasion or encasement in two of six cases. The other false-negative examinations were due to invasion of the peripancreatic soft tissues (hepatoduodenal ligament, mesenteric root, retropancreatic/retroduodenal fascia).

Evaluation of N Stage

Nodal status was evaluable in 27 patients, 7 of whom had proven regional lymph node metastases at laparoscopy (3 patients), laparotomy (2 patients), or on histopathologic examination of the pancreatic resection specimen (2 patients) (prevalence of N1 stage 26%). The sites of the involved nodes were paraaortic (three

Table 3. Diagnostic accuracy of staging investigations for predicting tumor unresectability according to M stage in 43 patients with pancreatic or periampullary carcinoma.

Test	Sensitivity	Specificity	PPV	NPV
USS	0.29****	1.00	1.00	0.71**
CT	0.33***	0.96	0.83	0.59*
LapUS	0.94	1.00	1.00	0.96
SVA	0.00****	1.00	—	—

*$p < 0.05$; **$p < 0.01$; ***$p < 0.005$; ****$p < 0.001$ (USS/CT/SVA versus LapUS).

Table 4. Diagnostic accuracy of staging investigations for predicting overall tumor unresectability in 50 patients with pancreatic or periampullary carcinoma.

Test	Sensitivity	Specificity	PPV	NPV
USS	0.67	0.56	0.80	0.40
CT	0.66	0.54**	0.79*	0.38
LapUS	0.83	0.93	0.97	0.68
SVA	0.62	0.64	0.82	0.40

*$p < 0.05$; **$p < 0.005$ (CT versus LapUS).

patients), hilar (two patients), retroduodenal (two patients), mesenteric root (two patients), or peripancreatic tissues (two patients). The derived summary measures of diagnostic accuracy for N staging are summarized in Table 2.

Failure to detect lymph node metastases was associated with all four investigations (sensitivity range 20–83%), and "false positive" results were also obtained with USS (two patients), CT (five patients), and LapUS (four patients), where histopathology revealed lymph node enlargement > 10 mm to be due to reactive hyperplasia.

Evaluation of M Stage

The M stage was evaluable in 43 patients, of whom 16 were shown to have liver or peritoneal metastases (or both) following biopsy at laparoscopy (15 patients) or laparotomy (1 patient) (prevalence of M1 stage 37%). Metastatic lesions were visible during laparoscopy in 15 patients. A small malignant lesion on the edge of hepatic segment IV that inexplicably had not been detected during laparoscopy was discovered at laparotomy in one patient. Laparoscopic ultrasonography was the only modality to have detected small intraparenchymal liver metastases in 7 of 15 patients, although laparoscopically visible surface lesions were also present in all these cases. In 10 patients, both USS and CT failed to detect intraabdominal metastatic lesions, which were frequently small (1–15 mm diameter). There was one "false positive" CT examination in which a patient with intrahepatic duct dilatation was interpreted as having liver metastases. The derived summary measures of diagnostic accuracy for M staging are summarized in Table 3. The sensitivity and predictive value of a negative result were significantly superior for laparoscopic staging of metastatic disease compared with either USS or CT. Of the four patients with metastases who underwent SVA, none was identified, and there were no false-positive results.

Evaluation of Overall Tumor Resectability

Fourteen patients were considered to have resectable tumors (i.e., 72% prevalence of unresectability). Laparoscopy with LapUS was the most reliable modality for determining overall tumor unresectability with overall positive and negative predictive values of 97% and 68%, respectively (Table 4). Laparoscopic ultrasonography correctly upstaged disease following a "negative" laparoscopy in patients with unresectable tumors due to nodal metastases or local invasion in 14 patients (28%). One patient was staged overall as "false positive" by LapUS on account of enlarged hilar lymph nodes (12 mm maximum diameter), incorrectly interpreted as metastatic.

There were six instances where LapUS failed to identify factors that precluded curative resection when all factors were taken into consideration. Invasion of the portal vein had not been predicted in three patients, infiltration of the posterior wall of the stomach was undetected in one patient, retropancreatic fat invasion was discovered in the distal pancreatectomy specimen of one patient, and malignant peripancreatic lymphadenopathy (14 mm maximum node diameter) was demonstrated in the pancreaticoduodenectomy specimen of the remaining patient. The derived summary measures of diagnostic accuracy for overall staging are summarized in Table 4.

Discussion

Staging laparoscopy with LapUS was shown to be a safe and effective means of assessing patients with pancreatic and periampullary carcinoma under consideration for definitive surgical intervention. The postoperative deaths of two patients at 6 days and 2 weeks, respectively, reflected their poor general health and advanced malignancy rather than any specific complication of the laparoscopic procedure. The instance of malignant port-site seeding was also a cause for concern. There have been two other case reports of malignant seeding to the parietes following laparoscopy in patients with pancreatic cancer [15, 16]. The patient reported herein should be considered in the context of established malignant ascites and peritoneal carcinomatosis, and therefore at increased risk of seeding. Although the incidence and mechanisms of laparoscopic malignant seeding continue to attract close scrutiny, we believe that the benefits of staging laparoscopy presently outweigh this risk.

In this study, the high sensitivity (96%) of LapUS for defining focal pancreatic or periampullary tumor masses was similar to that reported from studies of endoscopic ultrasonography (EUS), in which reported diagnostic sensitivities of 98% to 100% have been obtained [17, 18]. This underscores the utility of high-resolution contact sonography for imaging the pancreas and periampullary region. However, it does not address the ongoing dilemma of differentiating between patients with malignancy and those with focal nonneoplastic lesions (e.g., chronic pancreatitis), which remains a challenge common to all current imaging methods [19].

The failure in two cases to identify pancreatic cancers, which in retrospect appeared echographically diffuse and isoechoic, has identified a diagnostic pitfall for LapUS. Interestingly, periampullary cancers were readily identified despite their isoechoity and relatively small dimensions, and LapUS was probably aided by concomitant pancreatic and bile duct dilatation in these patients. It was also noteworthy that USS, CT, and SVA were less performant than LapUS in imaging the primary lesion. The sensitivities of USS (82%), CT (93%), and SVA (66%) were not at variance with those reported in previous studies, which have cited corre-

sponding figures in the range of 51% to 98% [17, 18, 20–28], 69% to 99% [17, 18, 20, 21, 23–26, 28–31], and 33% to 72% [26, 32–35].

We have reproduced our earlier findings [8, 9] and those of others [1–5, 10, 36–39] indicating that staging laparoscopy is highly sensitive for detecting "occult" intraabdominal metastases in patients with pancreatic or periampullary cancer. Furthermore, the significant advantage of laparoscopy in this role was established by prospective blind comparison with USS, CT, and SVA, as most previous reports have comprised patients selected retrospectively by USS or CT (or both) as being free of metastatic disease. In the present study, prospective standardization of the methods of scanning and reporting had little impact on the failure of USS and CT to detect metastases in approximately two-thirds of cases examined. These results concur with those of a multicenter study comparing dynamic CT with MRI in which sensitivities for the detection of metastatic disease were 26% and 42%, respectively [40].

The advent of more refined CT scanning techniques, in particular helical CT scanning, raises the question of whether this technology would have been more succesful in identifying metastatic disease than the conventional intravenous contrast-enhanced CT utilized herein. Nevertheless, of the two patients examined using helical CT scanning in the present study, a laparoscopically detected liver metastasis of the left hepatic lobe was missed in one patient. Also, available reports indicate that helical CT remains fallible in this aspect of pancreatic cancer staging [41, 42]. Alternatively, other authorities have reported such findings as rare following examination with helical CT and consequently regard the benefits of staging laparoscopy as marginal [43]. A role for angiography in the detection of metastases can no longer be supported. Previous studies have demonstrated angiography to be poorly sensitive in this regard [34, 35, 44], and it was reemphasized herein.

The principle that LapUS may identify intrahepatic metastases that are imperceptible to USS, CT, and laparoscopy was illustrated in 7 of the 16 patients with M1 stage disease on a lesion-by-lesion basis. However, the impact of LapUS as the only means of diagnosing metastatic disease on a patient by patient basis was only marginal and concurs with the experience of Hann and colleagues [39]. These findings differ from those of Bemelman and colleagues for whom LapUS was the sole means of detecting intrahepatic metastases in approximately one-third of such cases [10]. Whereas the overall incidence of liver metastases in the present series was similar to that reported by Bemelman et al., the relatively higher sensitivity of laparoscopy observed in our study may reflect a rigorous laparoscopic technique using a 30 degree telescope to scrutinize the subphrenic spaces and inferior aspects of the left and right hepatic lobes. Our routine use of intraoperative ultrasonography at laparotomy makes it unlikely that overt hepatic lesions had been "missed" with LapUS. Additionally, Hann and colleagues reported the important role of laparoscopic ultrasonography in downgrading a CT diagnosis of liver metastasis by the demonstration of benign lesions such as cysts [39].

Laparoscopic ultrasonography was found to be at least as predictive as USS, CT, and SVA in determining resectability by T stage. However, the identification of six false-negative results among 19 cases (32%) of T2-T3 tumor unresectability (due to peripancreatic soft tissue invasion or portal vein involvement) has indicated the fallibility of LapUS in this role. As regards the diagnosis of portal vein invasion, large hypoechoic tumors and diffusely infiltrative, isoechoic tumors have been identified as pitfalls. The former scenario has also been identified as limiting EUS in the staging of vascular invasion [28, 45]. Extrapancreatic soft tissue invasion also prove to be difficult to define reliably by LapUS. Whereas loss of the hyperechoic serosal–tumour interface was apparent in retrospect following IOUS in the patient with a pancreatic body carcinoma infiltrating the posterior wall of the stomach, no sonographic features for the identification of diffuse retropancreatic infiltration were apparent. This is probably because the sonographic interface between the pancreatic parenchyma and the retroperitoneal tissues is less well defined than those delineating vascular and ductal structures. This aspect of the LapUS examination remains, therefore, a potential weakness, although overall it was of clinical significance in a few patients.

The decision of an experienced pancreatic surgeon during exploratory laparotomy and trial pancreatic dissection was adopted as the arbiter of local tumor resectability. Although it is an essentially subjective measure, this surgical decision is the endpoint that matters most to the patients' immediate fate in clinical practice. Although other workers have been prepared to perform portal vein resections when confronted with apparent locally invasive tumor [46, 47], our departmental philosophy remains one of avoidance of this aggressive approach. The fallibility of early trial pancreatic dissection in identifying tumor invasion of the lateral aspect of the splenoportomesenteric venous junction has also been cited, along with the need to perform portal vein resection when this is discovered unexpectedly following transection of the pancreatic neck (i.e., "the point of no return") [14, 48, 49]. However, there were no such instances where this scenario occurred unexpectedly because of prior understaging, nor were positive resection margins documented in this site.

Reassuringly, LapUS did not overstage local tumor status in this study. Features of portal–superior mesenteric vein invasion, such as occlusion, stenosis, loss of the hyperechoic vein–parenchymal interface, luminal invasion, and vessel encasement, proved reliable in this respect. This high specificity for LapUS is in agreement with the findings of others. Bemelman and colleagues correctly identified locally unresectable tumors in 13 of 14 cases, their one false-positive result occurring in a patient with retroperitoneal radiation fibrosis [10]. The Memorial Sloan-Kettering Cancer Center investigators also reported one such instance of overstaging of superior mesenteric vein encasement among 10 patients, a finding that may have been attributable to the "learning curve" [39].

The rationale for LapUS in the local staging of pancreatic and periampullary cancer appears to have been strengthened by the parallel experience of those working with EUS, inasmuch as the two techniques share the fundamental principle of high-resolution contact sonography. The observations of the present study appear to concur with those investigating EUS criteria for vascular invasion where few false-negative examinations were observed (sensitivity 88–100%, NPV 89–100%) [17, 18, 24, 28, 50, 51]. However, a tendency by EUS to overstage vascular invasion remains a cause for concern in some centers [28, 42]. Such errors have been attributed to large tumor size and duodenal infiltration with failure of duodenal intubation, a reliance on oblique sonograms and failure to image the tumor periphery. Laparoscopic ultrasonography should theoretically be less prone to such limitations, as the transducer is not limited to the duodenal lumen and has a far greater range of maneuverability.

No evidence was provided in this study to support a definitive role for USS in the locoregional staging of patients with pancreatic or periampullary cancer. Although Campbell and Wilsons' retrospective study concluded that USS was an effective staging tool in their institution, having correctly identified vascular invasion in 12 of 16 patients (75%) with no false positives [22], the results of the present study did not reproduce these findings. Nor did our findings agree with those of van Delden and colleagues, who reported Doppler USS to have efficacy similar to that of LapUS for assessing vascular invasion of pancreatic cancers [52]. Both under- and overestimation of T stage were observed, giving respective positive and negative predictive values of 66% and 58% and a specificity that was significantly inferior to that of LapUS. Operator dependence and technical considerations should not have been an issue in this study, as USS examinations were performed by an experienced sonographer using state-of-the-art equipment including Doppler and color Doppler techniques to evaluate the peripancreatic vasculature. Rather, these findings reflect more closely the reported experience of others [17, 18, 23, 24, 26, 28]. Nevertheless, this experience does not detract from the utility of USS as a first-line method for confirming the diagnosis and defining the level of extrahepatic biliary obstruction and for screening the liver for overt metastases.

Although the performance of CT in predicting tumor resectability was shown to have been similar to that of LapUS, and in this respect was not at variance with the results reported by Freeny and colleagues [29, 31], the present study did identify a tendency for CT to overstage local tumor status, particularly with regard to peripancreatic fat invasion (six patients) and portal vein invasion (three patients). Although other workers have expressed similar concerns regarding the specificity of CT in the staging of pancreatic cancer [25, 30, 53], these studies were retrospective, and confounded by suboptimal scanning techniques, such as the use of nonenhanced CT. These flaws were largely avoided in the present study, which observed a technique similar to that described by Freeny et al. [29, 31], whereas other workers utilizing updated CT protocols have also documented false-positive CT examinations during locoregional staging of pancreatic and periampullary cancer [4, 17, 28, 39, 40, 54].

Proponents of CT cite its reliability for staging pancreatic cancer with high specificity, with no false positives reported among those patients evaluated surgically [29, 31]. Accordingly, the CT features of tumor unresectability have come to be regarded by some authorities as "almost, by definition, absolute" [55] and "the only accurate method" for the preoperative evaluation of vascular invasion [46]. Although more advanced CT techniques have superseded the methods used in this study, which nevertheless remain the mainstay of cross-sectional imaging in many hospitals, our findings challenge such perceptions. Using state-of-the-art helical CT for evaluating vascular invasion in 38 patients with pancreatic cancer, Gmeinwieser and colleagues reported the technique to have performed well when assessing portal vein involvement (sensitivity 91%, specificity 94%) [41]. However, complete avoidance of both false-negative and false-positive examinations proved elusive, which may reflect the wider experience with helical CT scanning. Although excellent results continue to be reported with sophisticated modern CT protocols in the staging of pancreatic cancer [42, 56], awareness to the possibility of tumor overstaging should be encouraged. In this regard, Hann and colleagues reported the utility of LapUS for refuting CT diagnoses of vascular encasement in 2 of 10 patients reported as such [39]. The significantly superior specificity of LapUS for T staging of pancreatic cancer reported herein concurs with such observations.

The routine use of SVA for preoperative assessment of patients with pancreatic and periampullary malignancy has again been shown to be unjustified. Understaging was largely due to the inability of SVA to identify peripancreatic soft tissue invasion, whereas the diagnosis of vascular encasement from the appearance of subtle narrowing in the vicinity of the superior mesenteric–portal venous junction yielded four false positives. This scenario has been documented previously [42, 44, 48, 57], and Dooley and colleagues have described "notching" in the vicinity of the portal–superior mesenteric venous junction as a "normal variant" of SVA that could be misconstrued as tumor encasement [58]. Therefore, while SVA contributed little additional useful information regarding T stage compared with less invasive investigations, serious concern has again been raised regarding its propensity to overestimate local tumor stage and so risk denying "curative" resections to patients with potentially resectable disease.

The difficulty of accurately staging regional lymph node metastases in patients with pancreatic and periampullary cancer has again been demonstrated. Also, the relatively small number of patients defined as having positive regional nodes inhibits the formulation of definite conclusions regarding the diagnostic accuracies of the various investigations. The occurence of both false-positive and false-negative results for all modalities concurs also with the experience of those evaluating EUS for confirming that malignant lymph node enlargement cannot be reliably identified on the basis of lymph node size alone [28, 59–61]. Nodal enlargement is frequently the result of reactive hyperplasia; and, conversely, smaller nodes may harbor micrometastases. Consequently, patients with pancreatic or periampullary cancer should not be denied surgical assessment of resectability on the basis of regional lymphadenopathy alone in the absence of biopsy confirmation of nodal malignancy. This was not the case with any of the patients in this study.

In summary, critical evaluation of LapUS compared with USS, CT, and SVA has broadly reproduced our own previous results [9] and those of others [10, 38, 39, 52] in the overall staging of patients with pancreatic and periampullary cancer. The advantage of laparoscopy and LapUS over USS, CT, and SVA in the overall staging of patients with pancreatic and periampullary carcinoma lies predominantly with the significantly superior sensitivity of laparoscopy for identifying intraabdominal metastases and facilitating their biopsy. The unique role of laparoscopy in this respect has again been proved and justifies its mandatory use prior to laparotomy in patients with potentially resectable lesions, irrespective of the results of USS and CT. Despite an initial benefit for laparoscopic staging of 15% in avoiding unnecessary laparotomy in patients with periampullary cancers, the risk of late laparotomy for palliation of duodenal obstruction has been reported as being relatively high (30%) following laparoscopic staging [62]. Although the sensitivity and NPV of LapUS for predicting tumor resectability were roughly comparable to those of USS and CT, its superior specificity and PPV for defining the stigmata of unresectability support its adoption in the staging algorithm for such patients. Its utility in comparison with newer techniques such as helical CT and EUS, and its influence on the longer-term man-

agement of patients with pancreatic and periampullary cancer, awaits further study.

Résumé

Par une étude prospective, on a comparé la coelioscopie à l'échographie laparoscopique (EcL), à l'échographie transcutanée (ETC), à la tomodensitométrie (TDM) et à l'angiographie viscérale sélective avec temps veineux de la phase portale (AVS) dans l'évaluation de la résecabilité chez 50 patients ayant un cancer pancréatique ou périampullaire. Les résultats ont été stratifiés selon les stades TNM. La tumeur n'a pas été résecable chez 36 patients (72%). La sensibilité de l'EcL pour détecter la lésion primitive a été de 96%. Dans six cas, l'EcL n'a pas permis de prédire la non-resecablité selon le stade T. On n'a pas pu mettre en évidence de différence significative en ce qui concerne la possibilité de prédire la résecabilité locale selon l'une ou l'autre modalité diagnostique (valeurs prédictives 58–73%). L'EcL n'a jamais surestimé le stade T et était plus spécifique (de façon significative) pour évaluer la résecabilité par rapport à l'ETC (100% vs 64%, $P < 0.05$) et à la TDM (100% vs 47%, $P < 0.005$). Aucun de ces moyens diagnostiques n'était performant en ce qui concerne le stade N. Des métastases ont été observées chez 16 patients (32%), l'EcL étant plus sensible que l'ETC (94% vs 29%, $P < 0.001$) et que la TDM (94% vs 33%, $P < 0.005$) pour détecter les métastases ganglionnaires. L'utilisation de l'EcL n'a pas apporté un plus par rapport à la laparoscopie simple en ce concerne le stade M car toutes les métastases à distance étaient superficielles. L'EcL était la méthode la plus fiable pour évaluer la résecablité globale des tumeurs, et la prédictabilité était significativement meilleure que pour la TDM (97% vs 79%, $P < 0.005$). Ces résultats confirment que la coelioscopie est indispensable pour détecter des métastases occultes intra-abdominales. Parmi les moyens à notre disposition, l'EcL prédit avec fiabilité la non-résecablité des tumeurs, rattrapant la surestimation du stade T caractérisée par l'ETC et la TDM. Des méthodes précises pour déterminer l'état ganglionnaire (N) nous échappent encore, mais le recours à l'AVS systématique n'est pas justifié.

Resumen

Se efectúa un estudio prospectivo en 50 pacientes con cáncer periampular de páncreas. El objetivo es averiguar el valor de: la laparoscopia, laparoscopia con ultrasonografía (LapUS), ecografía transabdominal (USS), tomografía computerizada (CT) y angiografía visceral selectiva de los venogramas portales (SVA), en la resecabilidad del cáncer de cabeza de páncreas. Los resultados se estatificaron de acuerdo con la clasificación TNM. Se constató que el cáncer no era resecable en 36 pacientes (72%). La sensibilidad de la LapUS en la valoración del grado de lesión fue del 96%. En 6 pacientes, la LapUS fue insuficiente para predecir factores dependientes del estadio T que imposibilitaron la resección tumoral. No hubo ninguna diferencia significativa entre las exploraciones antes mencionadas para predecir la resecabilidad local (valor predictivo 58–73%). La LapUS no sobrevaloró el estadio T y fue mucho más precisa, incluso desde el punto de vista estadístico, al evaluar la irresacabilidad tumoral que la USS (100% vs 64%, $p < 0.05$) y que la CT (100% vs 47%, $p < 0.005$). Ningún método diagnóstico por imagen fue capaz de evaluar con precisión el estadio N. En 16 pacientes (32%) se detectaron metástasis con la LapUS, que demostró una sensibilidad mayor que la USS (94% vs 29%, $p < 0.001$) y la CT (94% vs 33%, $p < 0.005$). Al completar la exploración laparoscópica con LapUS, no se produjo modificación alguna, por lo que al estadio M se refiere, en ningún paciente ya que todas las metástasis estaban localizadas superficialmente. La laparoscopia con LapUS es el método más fiable para evaluar la resecabildiad tumoral, siendo su valor predictivo mucho más significativo que la CT (97% vs 79%, $p < 0.005$). Estos resultados confirman que la laparoscopia es indispensable para detectar metástasis intraabdominales ocultas. La LapUS permite establecer un pronóstico exacto de irresecabilidad tumoral, compensando la tendencia de la USS y de la CT a sobrevalorar el grado del estadio T. Parece difícil encontrar métodos capaces de evaluar de forma precisa el estadio N. No está justificado el empleo rutinario de la SVA.

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