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Abdominal Imaging

Preoperative assessment of pancreatic malignancy using endoscopic ultrasound

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Abstract
Background: Endoscopic ultrasound (EUS) has been regarded as the most accurate modality for locoregional staging of pancreatic malignancy. However, several recent studies have questioned this. The current study assessed the accuracy of EUS in determining preoperative resectability of pancreatic neoplasia.
Methods: A retrospective review was performed of patients with pancreatic malignancy who had preoperative EUS and underwent surgery. EUS-predicted resectability was compared with surgical resectability. Where available, accuracies of vascular and nodal staging were also assessed.
Results: Forty-five patients were identified (mean age = 60 years, age range = 36–79 years). All patients underwent surgical exploration; vascular staging was available in 32 cases and 17 cases underwent surgical resection. The sensitivity, specificity, and accuracy of EUS in determining unresectability were 66%, 100%, and 78% respectively. Overall EUS stage concurred with surgical stage in 56%, greater than surgical stage in 4%, and less than surgical stage in 40%. Vascular staging on EUS had a sensitivity of 69% and a specificity of 100%. Accuracy of nodal staging was 71%.
Conclusion: EUS had a high specificity for assessing unresectable pancreatic malignancy. This technique should be used to avoid unnecessary surgical exploration of incurable lesions. However, EUS had only a moderate sensitivity, and a proportion of patients staged preoperatively as having resectable disease will not be surgically resectable.

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Key words: Endoscopy—Pancreas—Neoplasms—Tumor staging—Ultrasonography.

Pancreatic ductal adenocarcinoma (PDA) is the fifth most common cause of cancer-related deaths in Western countries; in the United States its 5-year survival rate is 3%, the lowest of any cancer [1, 2]. Although surgery is the only curative treatment, the main determinant of outcome is tumor stage and unfortunately 80–90% of tumors present late in their natural history and are unresectable [2]. Until earlier diagnosis becomes a possibility, the challenge for diagnostic imaging techniques is to accurately and safely stage PDA to determine resectability. Staging is most frequently performed with computed tomography (CT), which does have limitations in this setting. Reports of the use of dual-phase imaging after intravenous contrast with helical CT scanners have shown improved performance compared with earlier reports and have shown the technique to be accurate in predicting unresectability [3, 4]. However, CT remains less accurate at predicting resectability [3–6]. There are also limitations of CT in detecting small lesions [7]. Over the past decade, endoscopic ultrasound (EUS) has increasingly been used for locoregional staging of PDA, and it has been shown to be highly accurate in selected study populations from specialized centers, particularly in patients with small tumors [8–11]. However, data are still limited and concerns remain regarding possible significant interobserver variability of EUS and the applicability of previous studies outside high-volume expert centers. Added to this are several recent studies that have questioned the accuracy of EUS for staging pancreatic cancer [12–14]. We assessed the accuracy of preoperative EUS in deter-

mining the resectability of pancreatic malignancy, with surgical findings as the gold standard.

Materials and methods

All EUS examinations were performed at Royal Perth Hospital, a tertiary referral hospital in Perth, Australia. EUS came into use at the hospital in 1990, and from 1991 all procedures were recorded prospectively onto a secure electronic database. We searched the database and identified all patients who underwent EUS for suspected pancreatic malignancy from January 1995 to December 2000. Cases were then selected where the patient underwent surgery within 4 weeks of the EUS examination. Patients with ampullary carcinoma, cholangiocarcinoma, and duodenal carcinoma were excluded from this study. The case notes of the selected patients were then reviewed. The following information was collected:

- Patient sex and demographics
- EUS findings, stage, and resectability (based on the EUS criteria outlined below)
- Findings at surgery, procedure performed, surgical stage, and surgical resectability
- Histologic diagnosis and stage (where available)
- Complications of EUS

Tumors were staged according to the current TNM classification [15] (Table 1). If this was not performed at the time of EUS, it was established from the EUS report. Figure 1 illustrates a typical T1 lesion. Criteria for unresectability were (a) distant metastases (including lymph node metastases, e.g., celiac axis metastases as opposed to locoregional lymph node spread; Fig. 2), (b) involvement of major vascular structures (including the portal vein, superior mesenteric vein and artery, celiac axis, and hepatic artery), (c) peritoneal disease or malignant ascites, and (d) Direct invasion of peripancreatic organs or major retroperitoneal structures. The EUS criteria used for vascular involvement were loss of hyperechoic vessel wall/tumor interface and direct visualization of tumor within the vessel [16] (Figs. 3, 4).

Using the findings at surgery and histology as the gold standard, 2×2 tables were constructed, and performance characteristics for EUS in determining resectability, vascular invasion, and lymph node status were determined. Specifically, values were calculated for sensitivity, specificity, accuracy, and positive and negative predictive values.

All EUS examinations were performed under conscious sedation with the use of a radial echoendoscope (Olympus GF-UM3, GF-UM20, or GF-UM 130, Olympus Japan, Inc., Japan) by one of three experienced endoscopic ultrasonographers. The Human Research Ethics Committees at both participating centers sanctioned this study.

Table 1. TNM 1997 classification of exocrine pancreatic cancer

Primary tumor (T)			
Tx	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	In situ carcinoma		
T1	Tumor limited to the pancreas ≤2 cm in greatest dimension		
T2	Tumor limited to the pancreas >2 cm in greatest diameter		
T3	Tumor extends directly into any of the following: duodenum, bile duct, peripancreatic tissues		
T4	Tumor extends directly into any of the following: stomach, spleen, colon, adjacent large vessels		
Regional lymph nodes (N)			
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph nodes metastases		
N1	Regional lymph nodes metastases		
Distant metastases (M)			
Mx	Distant metastases cannot be assessed		
M0	No distant metastases		
M1	Distant metastases		
Group staging criteria			
Stage I	T1	N0	M0
Stage II	T2–3	N0	M0
Stage III	T1–3	N1	M0
Stage IVa	T3	N1	M0
	T4	Any N	M0
Stage IVb	Any T	Any N	M1

Results

Demographics

We identified 45 patients who had preoperative EUS for staging pancreatic malignancy and subsequently underwent surgery within 4 weeks. Mean age was 60 years (range = 36–79 years). There were 28 men and 17 women. The tumor was in the pancreatic head in 43 patients and in the body or tail in two patients. Surgical resection was possible in 17 patients, and surgical vascular staging was available in 32 patients. The operative procedure performed was diagnostic laparoscopy alone in five patients, exploratory laparotomy in four patients, palliative bypass (choledochojejunostomy with or without gastrojejunostomy) in 19 patients, pancreaticoduodenectomy in 15 patients, and distal pancreatectomy in two patients. Histology revealed adenocarcinoma in 43 patients and neuroendocrine tumor in two patients. The numbers of patients in each TNM stage were: one (26%) in stage I, seven (16%) in stage II, eight (18%) in stage III, 15 (33%) in stage IVa, and 14 (31%) in stage IVb. These findings are summarized in Table 2.

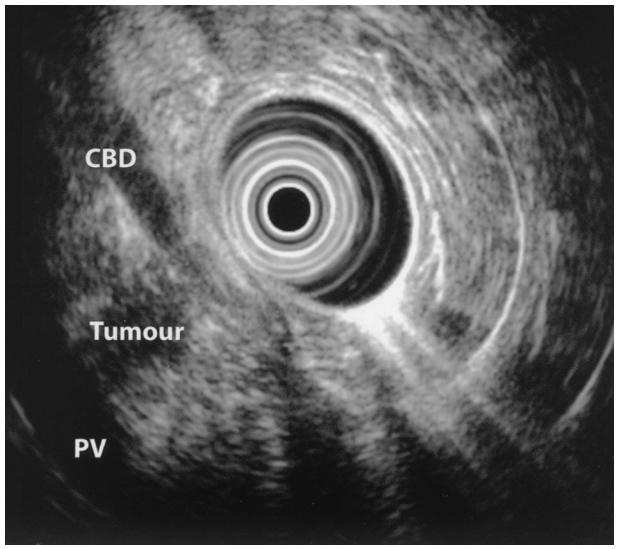

Fig. 1. A pancreatic adenocarcinoma staged correctly as T1N0 on EUS. This tumor was not clearly identified on other imaging. *CBD* common bile duct, *PV* portal vein.

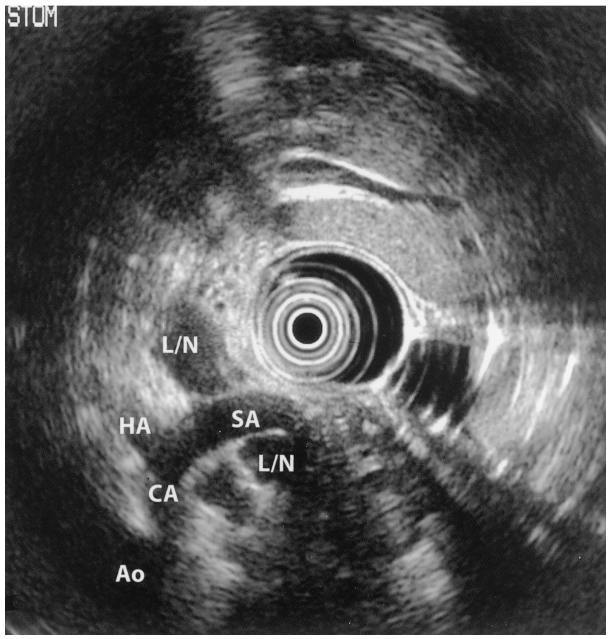

Fig. 2. Celiac axis lymphadenopathy (M1 disease). *Ao* aorta, *CA* celiac axis, *HA* hepatic artery, *L/N* lymph node, *SA* splenic artery.

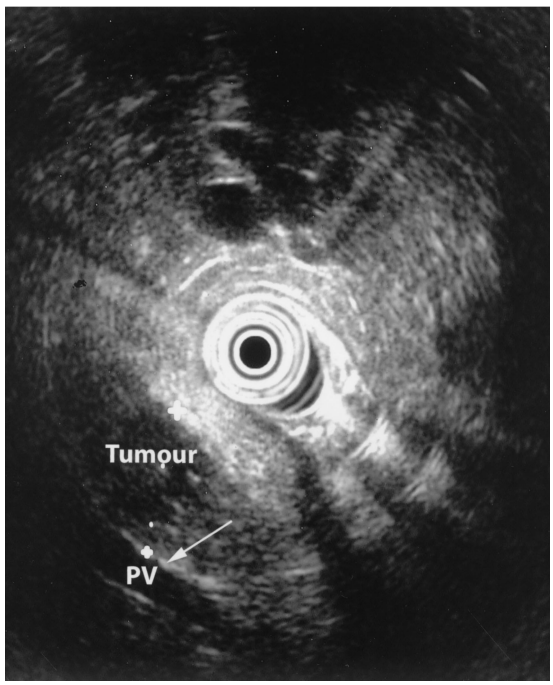

Fig. 3. Tumor adjacent to the portal vein (*PV*) with preservation of the hyperechoic interface between the tumor and vessel (*arrow*).

EUS performance

There were 29 tumors classified at operation as surgically unresectable and 16 tumors classified as surgically resectable based on the aforementioned criteria. One patient classified as having surgically unresectable disease by the study criteria due to superior mesenteric vein involvement actually had a pancreaticoduodenectomy with resection and reconstruction of a portion of the side wall of the vein. This was done because the patient had a neuroendocrine tumor with potential for cure. This patient was correctly staged on EUS as having venous involvement and, hence, was classified as unresectable on EUS and the surgical criteria in this study. Of the 16 patients with surgically resectable disease on criteria, all were resectable on EUS criteria. Of the 29 patients with unresectable disease on criteria, 19 (66%) were unresectable on EUS and 10 (34%) were resectable on EUS criteria. All 19 patients with unresectable disease on EUS criteria were unresectable by surgical criteria (as discussed above, one of these patients underwent a pancreaticoduodenectomy with superior mesenteric vein reconstruction), whereas, of the 26 patients classified as resectable on EUS, only 16 were resectable surgically (Table 3). Overall sensitivity, specificity, and accuracy of EUS in detecting unresectable disease were 66%, 100%, and 78%, respectively. Positive and negative predictive values were 100% and 62%, respectively. False negative rate was 34% and false positive rate was 0%. In the 10 patients in whom the tumor was resectable on EUS but unresectable at surgery, the reasons were: vascular involvement (five patients), hepatic metastases (three patients), nonhepatic metastases (three patients), and advanced local disease with inferior vena cava involvement (one patient; Table 4).

Surgical vascular staging was possible in 32 patients (Table 5). There were 11 patients in whom major vascular structures were involved on EUS and in all patients this

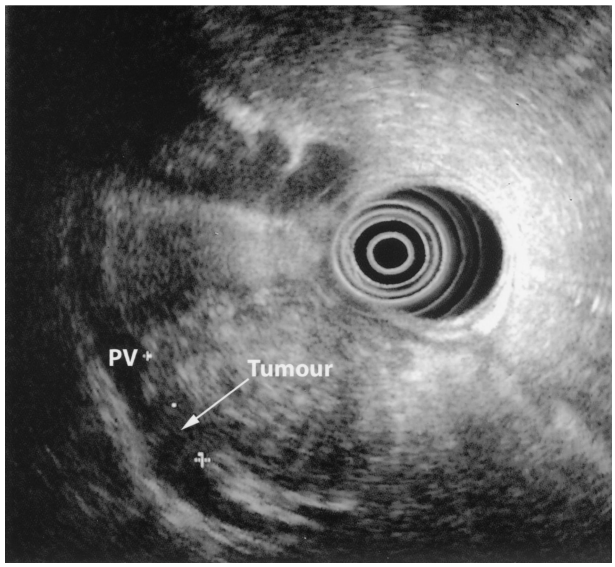

Fig. 4. Tumor involvement of the portal vein (*PV, arrow*).

Table 2. Patient demographics

Demographics	Patients (%)
Total number	45 (100)
Male	28 (62)
Female	17 (38)
Mean age, range	60 years, 36–79
Tumor location	
Head	43 (96)
Body/tail	2 (4)
Histology	
Adenocarcinoma	43 (96)
Neuroendocrine	2 (4)
Operation	
Pancreaticoduodenectomy	15 (33)
Distal pancreatectomy	2 (4)
Bypass	19 (42)
Exploratory laparotomy	4 (9)
Diagnostic laparoscopy	5 (11)
Surgical stage	
I	1 (2)
II	7 (16)
III	8 (18)
IVa	15 (33)
IVb	14 (31)

was confirmed surgically. Of the 16 patients in whom there was vascular involvement at surgery, EUS detected 11 (69%) of these. Of the 16 patients in whom there was no vascular involvement at surgery, all patients were clear at EUS. Hence, for vascular involvement, the sensitivity, specificity, and accuracy of EUS were 69%, 100%, and 85%, respectively. Positive and negative predictive values were 100% and 76%, respectively.

Lymph node staging was possible in 17 patients (Table 6). EUS detected six of the nine patients with histologic lymph node involvement. Of the eight patients with lymph node involvement on EUS, this was confirmed histologically in six patients. EUS sensitivity, specificity, and accuracy for detecting locoregional lymph node involvement were 67%, 75%, and 71%, respectively.

Table 3. Unresectability on EUS versus surgical criteria

	Surgically unresectable	Surgically resectable	Total
EUS unresectable	19	0	19
EUS resectable	10	16	26
Total	29	16	45

Table 4. Patients with resectable disease on EUS but unresectable surgically

Patient no.	Reasons for unresectability
1	Locally advanced (including inferior vena cava involvement)
2	Peritoneal metastases
3	Hepatic metastases
4	Portal vein involvement
5	Colonic metastases
6	Hepatic metastases
7	Hepatic metastases and vascular involvement
8	Lymph node metastases and portal vein involvement
9	Portal vein involvement
10	Portal vein involvement

Table 5. EUS vascular staging versus surgical vascular staging

	Vascular involvement at surgery	No vascular involvement at surgery	Total
Vascular involvement on EUS	11	0	11
No vascular involvement on EUS	5	16	21
Total	16	16	32

EUS stage and resectability

Overall, EUS stage concurred with surgical stage in 25 patients (56%), was greater than surgical stage in two patients (4%), and was less than surgical stage in 18 patients (40%; Table 7). In the two patients in whom EUS overstaged the malignancy, it was due to misclassification of a N0 lesion as N1. Resectability by EUS stage is outlined in Table 8. The only patient with EUS stage I disease was surgically resectable. No patient with EUS stage IV disease (20 patients) was surgically resectable. Of EUS stage II patients, 67% were resectable surgically; of EUS stage III patients, 58% were surgically resectable.

Table 6. EUS locoregional lymph node staging

	Lymph nodes involved histologically	Lymph nodes uninvolved histologically	Total
Lymph nodes involved on EUS	6	2	8
Lymph nodes uninvolved on EUS	3	6	9
Total	9	8	17

Table 7. EUS stage versus surgical stage

EUS stage versus surgical stage	*n* (%)
EUS stage = surgical stage	25 (56)
EUS stage > surgical stage	2 (4)
EUS stage < surgical stage	18 (40)

Table 8. Resectability by EUS stage

EUS stage	*n*	Resectable by surgical criteria, *n* (%)
I	1	1 (100)
II	12	8 (67)
III	12	7 (58)
T1 N1	0	0
T2 N1	4	3 (75)
T3 N1	8	4 (50)
IV	20	0 (0)

Discussion

Despite improvements in medical and surgical therapies, the overall 5-year survival rate of patients with PDA is lower than 5%, and there has been limited progress in developing suitable methods of screening to detect earlier stage disease [2, 17]. The overall poor outcome of patients with PDA makes accurate preoperative staging critical to optimize patient outcome and limit unnecessary investigations and surgery [18]. The main aim of preoperative imaging is to accurately identify patients with resectable disease and allow patients with inoperable disease to be appropriately referred for minimally invasive palliative therapy such as endoscopic stent or laparoscopic bypass [19, 20]. CT is usually the initial modality used for staging pancreatic cancer because of its ability to noninvasively detect metastatic disease and accurately identify unresectable disease [2–4], but it is limited in predicting resectability. However, accuracy of CT has improved with the introduction of faster, higher resolution helical scanners and the use of multiphase intravenous contrast-enhancement techniques [3, 5, 6]; indeed, a recent study reported the accuracy of CT to be greater than 80% in assessing resectability of PDA [6]. The introduction of multidetector array helical CT should improve results even further, but large studies have yet to be reported. Over the past 5–10 years, EUS has been regarded as the most accurate method of T and N staging of PDA, with early reports of accuracy of 78–94% for T staging and 64–82% for nodal staging [9, 21–24].

The initial enthusiasm for EUS has been dampened recently for several reasons. First, pancreatic cancer staging is technically one of the most difficult aspects of EUS, and expertise has been slow to spread outside a small number of expert centers [2, 17]. Consequently, there is concern that the results from expert institutions may not be reproducible elsewhere. Indeed, Australia is a prime example of a country where there has been slow dissemination of EUS, with only a handful of EUS units nationwide. To address the issue of expertise and a possible long learning curve, we elected to include patients only after our center had built up considerable experience of pancreaticobiliary EUS.

Second, there have been several recent reports that suggest EUS may not be as accurate as previously believed. Ahmad et al. retrospectively reviewed 89 patients with PDA who underwent preoperative EUS after imaging had demonstrated potentially resectable disease [12]. They found overall accuracies of 69% and 46% for T and N staging, respectively. Similarly, Rösch et al. reassessed the ability of EUS to detect vascular invasion and compared it with a combination of surgical and "unequivocal angiographic" stages [13]. They found a sensitivity of 43% and a specificity of 91% for EUS in detecting mesenteric vascular invasion. A recent Japanese study of PDA reported EUS accuracies of 64% for T stage and 50% for N stage [14]. We found EUS to have a sensitivity of 66% for detecting unresectable disease, with an accuracy of 78%. Our accuracies were 85% for determining local vascular invasion and 71% for lymph node status. Together these four studies strengthen the argument that EUS is less accurate than previously thought in staging PDA because it has only moderate sensitivity for determining local stage. Our study demonstrated that the major reason for this is understaging of local vascular disease. Of the 10 false-negative cases incorrectly classified as resectable on EUS, local disease was understaged in six. In five of these six cases, it was due to local vascular understaging. The other four false-negative cases in this study had metastatic disease that EUS would not be expected to detect.

There are several factors that may explain the discrepant results between the various staging studies of EUS in pancreatic malignancy. First, many of the early studies had limited sample sizes, often with fewer than 40 patients. Second, not all studies had histologic confirmation of staging, and as such the gold standard has varied between studies. For example, angiography has been used as the gold standard, but it has been shown that angiography is inferior to histologic staging because it does not

detect early adventitial vessel involvement [8, 13]. Third, surgical assessment of vascular invasion does not accurately assess vessel involvement unless a detailed dissection is undertaken of the portal and superior mesenteric vessels, and even then there may be difficulty distinguishing inflammatory from tumor involvement of vessels. Fourth, selection bias probably affects many studies of PDA staging because patients with advanced disease may be less likely to enter trials and less likely to have histologic confirmation. Indeed, selection bias could have been present in the current study because a proportion of patients not proceeding to surgery would have been staged as being unresectable on EUS (and other imaging), with the assumption that the imaging was accurate. Further, it is likely that patients with unequivocally unresectable disease on other imaging would not have been referred for EUS in our study. This could have resulted in a higher prevalence of patients with difficult-to-stage disease in the study population. Fifth, tumor size and stage have varied between studies. Smaller tumors are more accurately staged by EUS [25, 26]. In two studies suggesting that EUS has a high accuracy [8–11], more than half the patients had T1 or T2 tumors (which would be unusual in clinical practice). Conversely, in the current study and that by Ahmad et al. [12], most tumors were stage T3 and T4. Taken together, we feel the current evidence suggests that in clinical practice EUS is likely to have only moderate sensitivity in staging pancreatic malignancy. The exception to this is when the tumor is small, and in these cases EUS appears to be consistently a sensitive tool.

Despite these shortcomings, one of the great strengths of EUS in staging pancreatic malignancy is its high specificity for detecting unresectable disease. We found EUS to be 100% specific for unresectable pancreatic malignancy. Similarly, specificity for detecting local vascular involvement was 100%, and this result is consistent with previous reports [8, 13]. Had we used more liberal criteria to diagnose vascular invasion (such as minor tumor vessel interface irregularity) [17], our sensitivity might have risen but at the cost of reduced specificity. This clearly would be self-defeating. It should be reiterated that detecting unresectability is one of the strengths of CT and will improve with advancements in CT technology; hence, the specific question of what EUS adds to CT will need to be readdressed in the future.

We believe EUS still has a role in the preoperative algorithm for staging pancreatic malignancy. EUS is highly sensitive and specific for detecting and staging small pancreatic lesions, which may not be visible on CT or magnetic resonance imaging, and it should continue to be used when a small pancreatic lesion is suspected or needs to be staged. For the majority of patients with pancreatic malignancy, the accuracy of CT in staging locoregional disease and distant metastases is acceptably high and this should be the first-line staging investigation. EUS should be reserved for patients whose tumors appear resectable on CT or staging is uncertain. Our study has shown that in this setting EUS is only moderately sensitive but is highly specific for detecting unresectable disease. As such, it should be used as a triage tool after CT to allow preoperative diagnosis of unresectable disease. Given its moderate sensitivity, a proportion of patients with resectable disease on EUS will be surgically unresectable, and this issue remains the Achilles' heel of all current imaging techniques.

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