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EUS Diagnosis of Vascular Invasion in Pancreatic Cancer: Surgical and Histologic Correlates

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BACKGROUND: Endoscopic ultrasound (EUS) has been compared to intraoperative surgical palpation for diagnosis of vascular invasion by pancreatic cancer. This study compares EUS with vascular resection and histologic evidence of vascular invasion in resected pancreatic masses.

METHODS: All patients with solid pancreatic masses who underwent both preoperative EUS and surgery at 1 hospital over a 7 year period were identified. The relationship of pancreatic masses to adjacent vessels was prospectively assessed by EUS. EUS findings were compared to surgical and pathology gold standards. "Vascular adherence" was defined as tumor adherence requiring vascular resection during surgery, and "vascular invasion" as histologic invasion of vessel wall by tumor.

RESULTS: 30 of 68 patients were resectable. Among these 30, vascular adherence was present in 8, including 18% of patients with an intact echoplane between tumor and adjacent vessels at EUS, 29% of those with loss of echoplane alone, and 50% of those with additional EUS features of vascular involvement. Vascular invasion was present in 4, including 12% of patients with an intact echoplane, 0% of those with loss of echoplane alone, and 33% of those with additional EUS features. Sensitivity, specificity, PPV, and NPV of EUS were 63%, 64%, 43% and 80% for vascular adherence and 50% 58%, 28% and 82% for vascular invasion. NPV rose to 90% for vascular adherence if only the portal confluence vessels were considered.

CONCLUSIONS: EUS has poor sensitivity, specificity, and positive predictive value for diagnosis of venous involvement by pancreatic cancer.

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INTRODUCTION

Endoscopic ultrasound (EUS) is commonly performed for diagnosis and staging of pancreatic masses. EUS has been considered the most accurate preoperative test for diagnosis of vascular invasion by pancreatic cancer, and in some centers patients with EUS findings of vascular invasion have been deemed unresectable. Recent studies have questioned the accuracy and interobserver reliability of EUS for diagnosis of vascular invasion by pancreatic cancer (1, 2). Previous EUS studies utilized intraoperative surgical palpation in nonresected patients as an independent standard for diagnosis of vascular invasion, but the accuracy of this means of diagnosis is unknown. This study compares EUS with the surgical finding of vascular adherence (defined as tumor adherence to vessels requiring vascular resection during surgery) and the pathology finding of vascular invasion (histologic evidence of invasion) among patients undergoing resection of pancreatic masses.

METHODS

We identified all patients with solid pancreatic masses treated at Yale-New Haven Hospital between November 1995 and June 2002 who underwent both preoperative EUS and surgery for possible resection. Patients were identified by review of EUS and pathology databases. All EUS exams were performed under supervision of one endosonographer, who performed 1,800 EUS exams during the study period. All EUS exams were interpreted prospectively and preoperatively, and with knowledge of previous CT and/or MR findings. CT and MR exams were performed at various referring hospitals and without a uniform protocol.

EUS was performed under conscious sedation with GF-UM20, GF-UM130, and GF-UC30P echoendoscopes (Olympus America, Inc., Melville, NY). The relationship of pancreatic masses to adjacent vessels was prospectively assessed for the following features: presence of normal tissue between the tumor and vessel, presence of an intact echo-rich interface

(echoplane) between the tumor and vessel, irregularity of the vessel wall, narrowing of the vessel lumen, echogenic material in the vessel lumen, presence of collateral vessels, and partial or complete encasement of the vessel by the tumor. In 2003, EUS videotapes were reviewed for all subjects with sonographic features of vascular invasion, but for study purposes the original prospective EUS interpretation was used.

During the study period patients were considered unresectable if they had documented nodal metastases outside the peripancreatic area, complete encasement of the portal vein or SMV, or loss of echoplane between tumor and the superior mesenteric artery or celiac artery on EUS. Patients with other features of venous invasion were considered potentially resectable. Patients with metastases demonstrated preoperatively by any method were excluded.

Most potentially resectable patients initially underwent staging laparoscopy. Those without metastatic disease underwent immediate laparotomy and exploration; pancreatic resection was performed when no metastatic disease, arterial invasion, or extension of tumor beyond the pancreas was found. The relationship of pancreatic masses to the major vessels of the portal confluence was assessed. Venous resection was performed when tumor masses were densely adherent to the underlying vein. Vascular repair or venous grafting were performed as appropriate.

"Vascular adherence" was defined as the surgical finding of tumor adherence to a vessel requiring vascular resection or repair. "Vascular invasion" was defined as the histologic finding of tumor in the vessel wall. Tumor staging is reported using the 2002 revision of the AJCC TNM staging system (3). Patients underwent surgery within a median of 2 wk after EUS, and all but 4 patients were operated upon within 4 wk. The study was approved by the Yale University Human Investigation Committee.

Statistical Analysis

Categorical variables are reported as percentages and continuous variables as medians and ranges. χ^2 and linear trend tests of statistical significance were calculated using SAS software (version 8.2, Cary, NC). The overall sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of EUS were assessed by considering the presence of any EUS feature (including loss of echoplane) as diagnostic for vascular involvement by tumor. For purposes of calculating predictive values, the prevalence of vascular adherence and invasion in resectable patients with pancreatic cancer was estimated at 30% and 20%, respectively (4).

RESULTS

Sixty-eight subjects were identified. The median age was 61 yr (range: 25–81 yr). Thirty-one (46%) patients were female. Final histologic diagnosis was adenocarcinoma in 58, other malignancies in 9, and chronic pancreatitis in 1. Tumor characteristics are shown in Table 1. One patient underwent neoadjuvant therapy prior to surgery. This patient's pretreatment EUS showed multiple features of SMV invasion, and SMV invasion was confirmed histologically in the resection specimen. In 20% of cases a focal pancreatic mass was not seen at EUS; these patients had a hypoechoic and heterogeneous region of pancreatic parenchyma without definable margins, often with an associated biliary or pancreatic duct stenosis.

Table 1. Tumor Characteristics for the 68 Subjects

	Total	No. Resectable at Surgery (%)
Mass location		
No focal mass	13	8 (62)
Head/uncinate	42	17 (40)
Neck/body/tail	13	5 (38), $p = 0.37$
T stage: EUS		
T4	1	0 (0)
T3	24	6 (25)
T2	23	10 (43)
T1	7	7 (100)
Tx	13	7 (54), $p = 0.008$
N stage: EUS		
N1	17	4 (24)
N0	51	26 (51), $p = 0.048$
Tumor size: EUS		
<2 cm	8	7 (88)
2–3 cm	13	6 (46)
>3 cm	28	10 (36), $p = 0.035$
Histology		
Adenocarcinoma	58	21 (36)
Nonadenocarcinoma	10	9 (90), $p = 0.002$

Thirty-eight of 68 (56%) cases were not resectable at the time of surgical exploration due to metastases (23), nodal disease (9), suspected arterial involvement (2), and tumor extension beyond the pancreas (4). Forty patients underwent laparoscopy that detected liver metastases in 11 (28%), all of whom had masses in the pancreatic head. Of the 38 unresectable cases, 11 underwent a jejunal bypass procedure.

Thirty of 68 cases (44%) were resected (10 Whipple, 14 pylorus preserving Whipple, and 6 body/tail resection). Eight of 30 resected cases underwent vascular resection (5) or repair (3). Vessels involved included the portal vein (4), SMV (2), celiac axis (1), and IVC (1).

Pathology specimens were available in all 8 patients undergoing vascular resection. Pathologic examination of the resected specimens revealed 7 pancreatic ductal adenocarcinomas and one leiomyosarcoma. The named vessels were infiltrated by tumor in 4 of 8 cases (3 adenocarcinoma, 1 leiomyosarcoma).

EUS Predictors of Vascular Involvement

EUS findings of vascular involvement are shown in Table 2. EUS showed an intact echoplane or normal pancreas between tumor and vessels of the portal confluence in 17 resected patients. Three of these 17 (18%) had vascular adherence. Resected vessels were intrapancreatic celiac axis (1), IVC (1), and SMV (1). Two of these 3 (IVC and SMV) had vascular invasion on histologic assessment of the resected vessel.

Table 2. Vascular Findings at EUS and Presence of Vascular Adherence or Invasion

	Total	Resectable(%)	Vascular Adherence (%)	Vascular Invasion (%)
Intact echoplane	29	17 (59)	3 (18)	2 (12)
Loss of echoplane only	18	7 (39)	2 (29)	0
Additional vascular findings*	21	6 (29)	3 (50), $p = 0.09^{\dagger}$	2 (33)
Irregular wall	12	4 (33)	3	2
Partial encasement	6	3 (50)	1	1
Narrowed lumen	8	3 (37)	1	1
Echogenic material in lumen	2	1 (50)	1	0
Multiple findings	7	2 (29)	1	1

*All subjects with additional vascular findings also had loss of echoplane.
†Comparison among intact echoplane, loss of echoplane, and additional vascular findings.

Review of EUS videotape for these 3 cases showed poor visualization of the involved vessel in 2 cases (IVC and celiac axis) and, in the third case, features of vascular invasion of SMV (loss of echoplane and partial encasement) that had been misinterpreted prospectively.

EUS showed loss of echoplane between a tumor and a vessel without other features of vascular invasion in 7 resected patients. Two of these 7 (29%) had vascular adherence. Both patients with vascular adherence required resection of an ellipse of the portal vein. Neither of these 2 cases had vascular invasion, although both resected vessels had histologic evidence of tumor adjacent to the vessel. Examples are shown in Figure 1 and Figure 2. Retrospective review of EUS videotape from these cases showed loss of echoplane along the involved vessel wall for >1 cm in 6 of 7 resected cases.

EUS showed additional features of vascular invasion in 6 resected patients. Three of these 6 (50%) had vascular adherence. Resected vessels included the portal vein (1), SMV (1), and splenic vein (1). Two of these 3 cases had histologic evidence of tumor invasion into the resected vessel. Examples are shown in Figure 3 and Figure 4. The 3 cases that did not require vascular resection included 1 with vessel wall irregularity, 1 with partial encasement, and 1 with both. The presence of these features was verified on videotape review.

The performance of EUS was assessed statistically by considering the presence of any EUS feature (including loss of echoplane) as diagnostic for vascular involvement by tumor. Sensitivity, specificity, PPV, and NPV of EUS for vascular adherence were 63%, 64%, 43%, and 80%. When only the vessels of the portal confluence were considered (portal vein, splenic vein, and SMV), these values changed to 83%, 67%, 52%, and 90%. Sensitivity, specificity, PPV, and NPV of EUS for vascular invasion were 50%, 58%, 28%, and 82%. When only the vessels of the portal confluence were considered these values changed to 66%, 59%, 35%, and 87%.

DISCUSSION

Endoscopic ultrasound has been considered the most accurate preoperative method for the diagnosis of vascular involvement by pancreatic cancer, and has been used to determine the resectability of pancreatic masses. While initial studies found EUS to be highly sensitive and specific for vascular invasion, they relied on a diagnostic standard of intraoperative surgical palpation in patients deemed to be unresectable (5–8). The accuracy of this method for diagnosis of vascular invasion is unknown and may be susceptible to substantial interobserver variability and bias. One more recent report using this same diagnostic standard concluded that EUS was

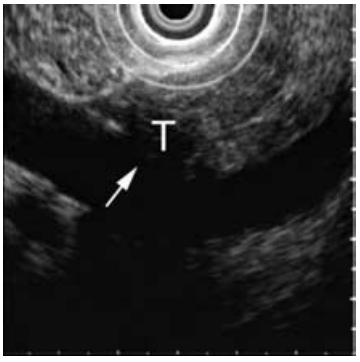

Figure 1. Loss of echoplane without vascular adherence or invasion. EUS demonstrates loss of echoplane (arrow) between the portal vein and a pancreatic head adenocarcinoma (T). At resection the tumor was not adherent to the portal vein and venous resection was not required.

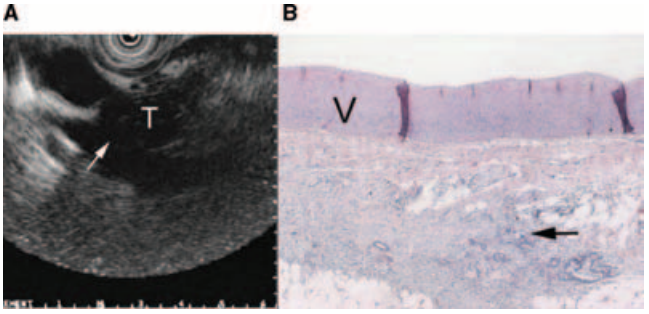

Figure 2. Loss of echoplane with vascular adherence but no vascular invasion. (*A*) EUS demonstrates loss of echoplane (arrow) between the portal vein and a pancreatic head adenocarcinoma (T). At resection the tumor was adherent to the portal vein and venous resection was required. (*B*) Histology demonstrates the tumor (arrow) adjacent to the vessel (V) but without invasion of the vessel wall.

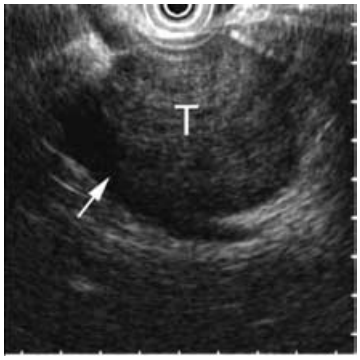

Figure 3. Multiple worrisome echofeatures without vascular adherence or invasion. EUS demonstrates loss of echoplane, irregular vessel wall, and narrowing of the vessel lumen (arrow) between the portal vein and a metastatic melanoma of the pancreatic head (T). At resection the tumor was not adherent to the portal vein and venous resection was not required.

inaccurate for predicting resectability of pancreatic masses (2). Another recent study found that no single sonographic feature of vascular invasion yielded sensitivity and specificity values greater than 80% when EUS images were blindly reviewed (1). These reports have forced a reassessment of the ability of EUS to determine vascular invasion. In this context we report a comparison of EUS with both surgical and histologic gold standards, defining "vascular adherence" as the need for vascular resection or repair during resection of a pancreatic mass, and defining "vascular invasion" as histologic evidence of tumor invasion into a resected vessel wall.

In most previous studies, various EUS findings were considered equally important indicators of vascular invasion by pancreatic cancer (5–10). These findings include close contact of the tumor and the vessel, loss of echo-rich interface (echoplane) between the tumor and vessel, abnormal contour of the vessel wall, tumor within the vessel lumen, peripancreatic venous collaterals, and encasement. Brugge *et al.* identified an irregular venous wall, loss of echoplane, and

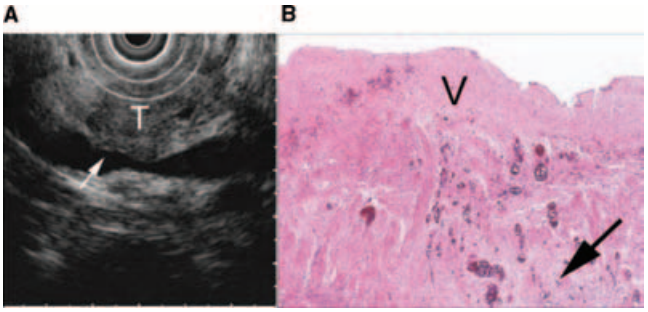

Figure 4. Multiple worrisome echofeatures with vascular adherence and invasion. (*A*) EUS demonstrates loss of echoplane, irregular vessel wall, and narrowing of the vessel lumen (arrow) between the portal vein and a pancreatic head adenocarcinoma (T). At resection the tumor was adherent to the portal vein and venous resection was required. (*B*) Histology demonstrates the tumor (arrow) invading the vessel wall (V).

proximity of the tumor mass (<3 mm) to be the most accurate predictors of vascular invasion, demonstrating 73–87% accuracy (10). In all of these studies surgical palpation of the pancreas and adjacent vessels was the independent standard for diagnosis, and histologic findings of vascular invasion were compared to EUS in only a minority of cases in one prior study (6).

In the current study of 68 patients with pancreatic masses, 30 of 68 were actually resectable at the time of surgery. The most common surgical finding precluding resection was the presence of previously undetected metastases, usually in the liver. Among the 30 resected patients, 8 had vascular adherence at the time of surgery, and only 4 of these had histologic evidence of vascular invasion. Similar findings were reported by Bold *et al.*, who identified tumor invasion of the vein wall in 71% of pancreatic masses requiring vascular resection (4).

In this study EUS had poor specificity and PPV for diagnosis of vascular adherence or invasion. Many prior studies have utilized loss of echoplane as a criterion for vascular invasion, but we found loss of echoplane to be a poor predictor of vascular involvement. Only 29% of cases with loss of echoplane alone had vascular adherence, and none had vascular invasion histologically. It has been postulated that the length over which the echoplane is lost may be an important factor (10). We found that all but one resected tumor exhibiting loss of echoplane did so for greater than 1 cm along the vessel wall.

EUS may be more accurate for diagnosis of vascular adherence and invasion when other worrisome echofeatures are present, such as an irregular vessel wall, narrowing of the vessel lumen, and partial encasement of the vessel. Of the tumors exhibiting these features that were resected, 50% had vascular adherence and 33% had vascular invasion. However, we were surprised that half of these patients did not require vascular resection despite the presence of these additional worrisome echofeatures. The specificity and PPV of these additional echofeatures for vascular adherence are too low for reliable preoperative diagnosis. The presence of multiple worrisome echofeatures (such as loss of echoplane with vessel wall irregularity and narrowing of the vessel lumen) may be more specific for venous invasion, but we were unable to evaluate this hypothesis due to the low number of such patients undergoing resection.

EUS did have good NPV for involvement of the portal confluence vessels (90% for vascular adherence and 87% for vascular invasion). Similar values have been reported in other studies (1, 9, 10). EUS missed SMV involvement in only one case, and on retrospective videotape review features of vascular involvement were seen in that case that had not been recognized prospectively. EUS was less useful, however, for visualization of other vessels, missing cases of IVC and intrapancreatic celiac artery involvement. The overall NPV EUS for involvement of any major vessel was 80% for vascular adherence and 82% for vascular invasion.

Our results support recent reports of the inaccuracy of EUS in predicting local vascular involvement by a pancreatic mass.

In our experience most tumors showing echofeatures of vascular invasion were not adherent to or invading the vessel in question. Retrospective review of EUS videotapes did not reveal a "learning curve" phenomenon or systematic misinterpretation. Peritumoral pancreatitis, edema, and fibrosis may in part explain the lack of specificity of EUS for diagnosis of vascular adherence or invasion in pancreatic malignancy (11). It is also possible that newer generation EUS instruments, with better tissue penetration and resolution, will improve the accuracy of EUS for diagnosis of vascular involvement.

EUS tends to overdiagnose vascular involvement by pancreatic cancer. In contrast, computed tomography and magnetic resonance imaging lack sufficient sensitivity in most series (12, 13). Thus, the combination of EUS with CT or MR might provide improved accuracy over EUS alone, particularly when the imaging studies are in concordance (14). We did not test this hypothesis in this study.

The weaknesses of our study include the low number of patients with vascular adherence or invasion. However, the diagnostic accuracy of EUS was sufficiently poor that a doubling of the study size would be unlikely to result in satisfactory EUS performance. Although this was a retrospective study, all EUS exams were interpreted preoperatively and prospectively, according to a standardized protocol. Since all exams were performed with knowledge of prior CT or MR findings, we could not evaluate the effect of these imaging tests on EUS interpretation. CT and MR were performed at various referring institutions, so the accuracy of these tests for diagnosis of vascular involvement could not be meaningfully assessed.

The preoperative diagnosis of venous invasion has become less important since venous resection is now an accepted surgical strategy for accomplishing resection of pancreatic head tumors. Nevertheless, preoperative diagnosis of vascular involvement may assist surgical planning and may affect the decision to operate in some patients. In addition, our findings have implications for EUS diagnosis of arterial invasion (currently considered a contraindication to surgery) and for EUS findings of vascular invasion in other clinical settings.

In conclusion, when sonographic features of vascular invasion are absent, EUS usually excludes involvement of the portal confluence vessels by pancreatic cancer. When sonographic features of vascular invasion are present, however, they may not be reliable for diagnosis. Many patients with loss of echoplane do not have vascular adherence or invasion. Other more worrisome echofeatures are indicative of an increased likelihood of vascular involvement but appear to lack the accuracy required for confident preoperative diagnosis.

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