Peer reviewed article

# Vascular invasion in pancreatic cancer

**Evaluation of endoscopic ultrasonography, computed tomography, ultrasonography, and angiography**

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## Summary

*Principles:* current methods for detecting vascular invasion in pancreatic cancer can be inaccurate, invasive, and expensive. The aim of this study is to assess the value of current imaging modalities in determining vascular invasion by pancreatic cancer.

*Methods:* the results of Endoscopic Ultrasonography (EUS), Computed Tomography (CT), Ultrasonography (US), and Angiography performed in 170 patients, suffering from pancreatic cancer, were retrospectively studied and correlated with intra-operative findings and surgical anatomopathological diagnosis after resection. We assessed sensitivity, specificity, positive and negative predictive values, and accuracy for detecting vascular invasion.

*Results:* EUS turned out to be the most reliable imaging technique for detecting vascular invasion in pancreatic cancer, with a sensitivity of 55%, specificity of 90%, positive predictive value of 61.1%, negative predictive value of 87.5%, and accuracy of 82.2%. CT results were 39.4%, 90%, 52%, 84.4%, and 79.1% for the respective categories, with however, better results with multi-slice CT. The US results were 3.7% for the sensitivity, 96.3% for the specificity, 25% for the positive predictive value, 75.2% for the negative predictive value, and 73.4% for the accuracy. For angiography, the sensitivity, the specificity, the positive predictive value, the negative predictive value, and the accuracy were 52.6%, 72.3%, 43.5%, 79.1%, and 66.7% respectively.

*Conclusion:* in this study, EUS was the most valuable imaging modality in assessing vascular invasion (especially for venous invasion) for pancreatic cancer, with an accuracy of more than 80%. A further prospective study should be carried out to evaluate the combination of imaging modalities for the detection of vascular involvement, especially with multi-slice CT which almost reached the performances obtained by EUS.

*Key words: pancreatic cancer; vascular invasion; endoscopic ultrasonography; computed tomography; ultrasonography; angiography*

## Introduction

Pancreatic cancer is associated with a poor prognosis, with less than 5% of patients surviving 5 years after diagnosis [1].

Surgical resection remains the only chance for curative therapy in these patients [2–4]. Accurate preoperative staging of pancreatic cancer is essential to avoid unnecessary surgery in those patients with unresectable disease and, by the same token, not to deny the opportunity for cure in patients with resectable disease [2, 3, 5]. However, upon surgical exploration, only 5% to 25% of the tumours are amenable to curative resection [3, 4, 6–8].

There is as yet no evidence-based consensus on the optimal preoperative imaging assessment of patients with suspected pancreatic cancer [3, 5].

However in the absence of metastatic disease precluding curative therapy, assessment of vascu-

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lar invasion is an important parameter for determining resectability of pancreatic cancer [2]. A frequent error is to misdiagnose an involved major vessel [8]. Limited venous invasion does not represent an absolute contraindication for surgery [1, 9]. From the point of view of arterial vessels, the large trunks must be analysed with care because they can constitute in themselves a contraindication to surgery. However, isolated involvement of smaller branches such as the gastro-duodenal artery does not preclude surgical resection [10]. Venous resection can be performed safely, in order to obtain a margin-negative resection [11]. However, the survival does not differ between patients with venous resection and patients who undergo standard operations [12]. Recently, Fukuda et al. [13] reported that the depth of portal vein invasion significantly alters survival after pancreatic resection with curative intent combined with portal vein resection. The survival rate was similar for patients with no portal invasion and those with superficial invasion. However, a deeper portal invasion was associated with a poorer survival rate, similar to that of patients undergoing non-curative resection.

Echoendoscopic Ultrasonography (EUS) is useful for the evaluation of pancreatic cancers [14]. This evaluation is crucial for determining T and N stage and feasibility of operative resection [15]. Computed Tomography (CT) has become an important method for preoperative staging, however, alone, it has been shown too inaccurate for the evaluation of resectability [16].

Among the most widely available imaging techniques for evaluation of vascular invasion in pancreatic cancer, EUS, CT, abdominal Ultrasonography (US), and angiography are the most commonly used techniques in our clinical setting.

To our knowledge, few studies have compared EUS, CT, US, and angiography for vascular invasion in pancreatic cancer.

The aim of this study is to evaluate in the same group of patients the sensitivity, the specificity, the positive and negative predictive value, and the accuracy of EUS, CT, US, and angiography in assessing vascular involvement. The gold standards used here are surgical exploration and anatomopathological investigations after resection.

## Materials and methods

Between January 1994 and December 2005, some 800 patients suffering from pancreatic cancer were registered in Geneva. During this period, 170 consecutive patients were operated on for suspicion of pancreatic cancer with curative intent. All examinations (EUS, CT, US, and angiography) were interpreted prospectively and preoperatively, with the knowledge of the results of the previous radiological findings. The original prospective interpretations were used.

CT was performed in all cases (except in cases of clear contraindication). EUS was performed in all cases since the technique could be performed with sufficiently accuracy. Angiography was performed in cases where a doubt remained concerning an anatomical variation or an arterial invasion.

These data were reviewed retrospectively.

There was no neoadjuvant therapy prior to surgery in this study.

The criteria for exclusion were: the presence of organ metastasis, involvement of the peritoneal cavity, an evident arterial invasion (ie, superior mesenteric artery, hepatic artery, and / or coeliac trunk), a contraindication to anaesthesia, and refusal of surgery.

A venous invasion was not considered a contraindication for surgery. An arterial involvement not confirmed by at least 2 radiological modalities was not considered a formal contraindication.

The surgical and the anatomopathological findings were correlated with the results of imaging, assessing the accuracy of EUS, CT, US, and angiography for the evaluation of vascular invasion. When there was a discrepancy between the surgical and the anatomopathological findings, the gold standard was the histological result.

We postulate that the presence of any one of the criteria described below for vascular invasion would be sufficient for a diagnosis of vascular involvement.

### Operative techniques

2 surgeons (PM, GM) operated all patients. A standard pancreaticoduodenectomy or pylorus-preserving variant was done for tumours located in the head of the pancreas or in the uncinate process. For tumours located in the body or tail, a caudal splenopancreatectomy was performed. In the case of disseminated disease, a total pancreatectomy was performed.

Regional lymph nodes were routinely resected *en bloc* with the tumour specimen.

Vascular resection with reconstruction was performed in patients if adequate vascular control could be achieved and a high probability of disease free margins was anticipated.

### Endoscopic ultrasonography imaging

Patients underwent EUS of the pancreato-biliary system by experienced endoscopists (GIF-EUM-20, GIF-EUM 30 and 160, Olympus, Zurich, Switzerland) [17]. Endoscopy was performed under conscious sedation using intravenous midazolam.

EUS criteria of vascular invasion were: loss of the normal hyperechoic interface between the tumour and the vessel, irregular tumour and vessel interface, tumour within vessel lumen, vessel encasement, or collaterals with associated venous occlusion [3, 5, 8, 15, 18–20].

### Computed tomography imaging

Various techniques were used during this study period due to changing CT technology. From 1994 to 2002, images were obtained on a single-slice CT (GE High Speed CT, General Electric) and from 2002 to 2005 images were obtained on a multi-slice CT (MX-8000, Marconi Medical Systems).

Helical CT was initially performed with and without intra-venous (IV) contrast medium using the following parameters: nominal section thickness of 3 mm, reconstruc-

tion field of view of 40 cm, reconstruction intervals of 3 mm, X-ray tube potential of 120 kV, and current of 240 mAs from the top of the liver to the bottom of the pancreas. Two series were acquired after IV injection of a 140-mL bolus of 300 mg I/mL of iopamirol (Iopamiro 300; Bracco, Milan, Italy) at a rate of 3.5 mL/second, with identical thickness and interval parameters during the arterial phase (35 seconds after the start of contrast infusion) and the venous phase (65 seconds after the start of contrast infusion).

From 2002 to 2005, there was a progressive shift to a 2 mm section thickness, and 1 mm reconstructions intervals, permitting obtaining 2D multiplanar (MPR) reconstructions and 3D vascular reconstructions.

CT criteria of vascular invasion were: encasement with a fatty plane obliteration of greater than or equal to 180 degrees of the vessel's diameter, tumour within the vessel lumen, thrombosis or occlusion of the vessel, or presence of venous collaterals [3, 5, 18, 19, 21–23].

### Ultrasonography imaging

Percutaneous abdominal ultrasound (Aloka ProSound 5500, Aloka Inc, Japan) was performed using a multi-frequency probe.

Morphology and haemodynamic function of the peripancreatic arteries and veins were studied by duplex ultrasound.

US criteria of vascular invasion were: loss of normal hyperechoic tissue between the tumour and the vessel, obstruction, thrombosis, or encasement by tumoral tissue over more than half the circumference of any vessel [24, 25].

### Angiography imaging

Transfemoral intra-arterial digital substraction angiography of the coeliac axis and the superior mesenteric artery was performed using a standard angiography technique, previously described [5].

The angiographic criteria of vascular invasion were: occlusion or stenosis of vessels [5].

### Statistical analysis

Sensitivity, specificity, positive and negative predictive value, and accuracy of EUS, CT, US, and angiography in detecting vascular invasion were assessed by considering the presence of any radiological feature as diagnosis for vascular invasion by tumour.

## Results

In the current study, adenocarcinomas represented 80% of all cases, and more than 90% in the vascular invasion subgroup. Main characteristics of the population are summarised in the table 1.

**Table 1**

Baseline characteristics and pathological findings in patients after surgery for pancreatic cancer (n = 170).

| Characteristic | |
|---|---|
| Age, years | |
| Median | 65 |
| Range | 17–82 |
| Sex, n (%) | |
| Women | 87 (51,2) |
| Men | 83 (48,8) |
| Pathology, n (%) | 170 (100) |
| Adenocarcinoma | 136 (80) |
| Head | 77 (45,3) |
| Body | 6 (3,5) |
| Tail | 8 (4,7) |
| Disseminated | 2 (1,2) |
| Periampullary | 43 (25,3) |
| Mucinous Cystadenoma | 11 (6,5) |
| Mucinous Cystadenocarcinoma | 2 (1,2) |
| Insulinoma | 7 (4,1) |
| Paraganglioma | 2 (1,2) |
| Gastrinoma | 1 (0,6) |
| Pseudocyst | 1 (0,6) |
| Carcinoid tumour | 1 (0,6) |
| Intraductal papillary tumour | 4 (2,4) |
| Acinar-cell carcinoma | 1 (0,6) |
| Neuroendocrine tumour | 2 (1,2) |
| PTH like tumour | 1 (0,6) |
| Mucinous carcinoma | 1 (0,6) |

We excluded 15 patients (8.8% of patients) because they presented clearly benign tumours (paraganglioma, mucinous cystadenoma, intraductal papillary tumour).

Pancreatic cysts represented less than 8% of all cases.

There were 32 cases (18.8%) of accompanying pancreatitis in this series.

Specifically, the final anatomopathological evaluation of the series identified 33 patients having vascular invasion (19.4%). Most of the cancers were located in the head of the pancreas (45% for the overall group and 63.3% for the vascular invasion subgroup). The superior mesenteric vein was the most frequently involved vessel (47%). The hepatic artery and the splenic vein were the less commonly affected vessels (4%) (table 2).

Comparison of the performances of CT scan (153 patients), EUS (90 patients), percutaneous US (109 patients), and angiography (66 patients) in detecting vascular invasion in this series are given in table 3.

The sensitivity for the detection of venous invasion was 55.6% for EUS, 47% for angiography, 40.7% for CT, and 4.4% for US. For the detection of arterial involvement, the sensitivity rate was 42%, 66.7%, 40%, and 0% respectively (US did not detect any arterial involvement). When only the vessels of the portal confluence were considered these values changed to 60% for EUS, 43.8% for angiography, 40% for CT, and 0% for US. US detected only one splenic vein's involvement.

Forty-five invaded vessels were surgically and pathologically proven so in 33 patients. These involved vessels included: 21 superior mesenteric veins (47%), 11 superior mesenteric arteries

**Table 2**

Characteristics in patients with proven vascular invasion (n = 33).

| Characteristic | |
|---|---|
| Age, years | |
| Median | 63 |
| Range | 23–80 |
| Sex, n (%) | |
| Women | 17 (51.5) |
| Men | 16 (48.5) |
| Pathology, n (%) | 33 (100) |
| Adenocarcinoma | 30 (90.9) |
| Head | 21 (63.6) |
| Body | 1 (3) |
| Tail | 4 (12.1) |
| Disseminated | 1 (3) |
| Periampullary | 3 (9.1) |
| PTH like tumour | 1 (3) |
| Carcinoid tumour | 1 (3) |
| Intraductal papillary tumour | 1 (3) |
| Vessels involved, n (%) | 45 (100) |
| Portal vein | 6 (13.3) |
| Superior mesenteric vein | 21 (46.7) |
| Superior mesenteric artery | 11 (24.4) |
| Splenic vein | 1 (2.2) |
| Splenic artery | 5 (11.1) |
| Hepatic artery | 1 (2.2) |

(24%), six portal veins (13%), five splenic arteries (11%), one splenic vein (2%), and one hepatic artery (2%).

We performed 21 venous resection-reconstructions and 2 arterial resection-reconstructions during this study.

Twenty patients with vascular invasion had benefited from EUS, with a detection rate of 14 of the 29 (48.3%) proven involved vessels. CT correctly diagnosed 19 of the 45 surgically and pathologically proven invaded vessels (42.2%) in 33 patients. Of the 39 proven invaded vessels in 27 patients, only one was correctly diagnosed by US. Finally, angiography correctly diagnosed 12 of the 24 proven involved vessels (50%) in 19 patients.

From 1994 to 2002, images were obtained on a single-slice CT (108 patients). In this period, the sensitivity was 31.8% in the detection of vascular involvement. The specificity was 89.5%; the positive and negative predictive values were 43.75% and 83.7% respectively. The accuracy was 77.8%.

From 2002 to 2005, images were obtained on a multi-slice CT (45 patients). The sensitivity was then 54.5%, the specificity 91.2%, the positive predictive value 66.7%, the negative predictive value 86.1%, and the accuracy 82.2%.

2 patients did not benefit from CT because of contraindication to intravenous iodine.

**Table 3**

Comparison of CT, EUS, US, and angiography in the detection of vascular invasion (n = 155).

| | Sensitivity, n (%) | Specificity, n (%) | Positive predictive value, n (%) | Negative predictive value, n (%) | Accuracy, n (%) |
|---|---|---|---|---|---|
| EUS | 11/20 (55%) | 63/70 (90%) | 11/18 (61.1%) | 63/72 (87.5%) | 74/90 (82.2%) |
| CT overall | 13/33 (39.4%) | 108/120 (90%) | 13/25 (52%) | 108/128 (84.4%) | 121/153 (79.1%) |
| CT single-slice | 7/22 (31.8%) | 77/86 (89.5%) | 7/16 (43.75%) | 77/92 (83.7%) | 84/108 (77.8%) |
| CT multi-slice | 6/11 (54.5%) | 31/34 (91.2%) | 6/9 (66.7%) | 31/36 (86.1%) | 37/45 (82.2%) |
| US | 1/27 (3.7%) | 79/82 (96.3%) | 1/4 (25%) | 79/105 (75.2%) | 80/109 (73.4%) |
| Angiography | 10/19 (52.6%) | 34/47 (72.3%) | 10/23 (43.5%) | 34/43 (79.1%) | 44/66 (66.7%) |

EUS: endoscopic ultrasonography; CT: computed tomography; US: ultrasonography

## Discussion

Although there are many studies evaluating the accuracy of EUS, CT, US, and angiography in the staging of pancreatic cancer [3, 7, 15, 16, 18, 26–28], few have evaluated these imaging modalities for the detection of vascular invasion based on surgical and anatomopathological data. A consensus regarding the reliability of these techniques in predicting vascular invasion is still lacking.

In the current study, 19.4% of patients with potentially operable pancreatic cancer had vascular invasion. The literature reports vessel involvement in 18–64% of the cases, depending on the population studied [4, 28].

In this study, an accuracy of more than 80% was reached in the detection of vascular invasion for both EUS and multi-slice CT. The accuracy for US and angiography was 73.4% and 66.7%, respectively. Similar results are reported in the literature [4, 5, 15, 29].

EUS is a relatively new technique in the assessment of vascular invasion in pancreatic cancer and requires a trained endoscopist [30]. Thus not all patients benefited from this exam in our study. However, EUS has for several years been integrated into the management of all patients with a suspicion of pancreatic cancer.

Indeed, EUS seems to be the most accurate imaging modality in the detection of vascular invasion. These results are confirmed by several studies [2, 15, 16, 19, 20]. For example, Ahmad et al. [2]

reported a sensitivity of 86%, a specificity of 71%, a positive predictive value of 86%, and a negative predictive value of 71%.

As in our series, Aslanian et al. [20] found better results when only the vessels of the portal confluence were considered with performance reaching 66%, 59%, 35%, and 87% respectively.

Interestingly, EUS detects venous invasion with more sensitivity (55.6%) than arterial involvement (42%). This may be due the technical difficulty in reaching this vessel when the head of the pancreas is deformed by cancer. Similar findings were reported by Midwinter et al. [18], who showed sensitivity for venous invasion of 81%, and 17% for the arterial involvement.

In this study, EUS had poor sensitivity and positive predictive value for diagnosing vascular invasion. However, the specificity, the negative predictive value, and the accuracy were good (more than 80%); similar values have been reported in other series [29].

EUS provides excellent views of peripancreatic vasculature and also shows the relationship between the tumour and the vessels [2]. However, a bias remains in the inter-observer variability. EUS tends to over-diagnose vascular involvement [20] (7 false positives in our series, which might prevent a potentially resectable patient from undergoing surgery). Furthermore the learning curve is long [29]. On the another hand, concomitant pancreatitis (32 cases in our study) accompanying a cancer is a well known limitation [15, 29] in correctly diagnosing a pancreatic mass. False positive results for vascular involvement may be due to change in peritumoural inflammation [7].

In contrast, CT lacks sufficient sensitivity for detecting vascular invasion in several published series [5, 15, 19, 28, 29]. Previous studies reported sensitivity values between 15–97% [15, 19, 28, 29, 31], specificity between 69–100% [5, 28, 31], positive predictive value of 55–89% [16, 28, 31], and negative predictive value of 28-95% [5, 28, 31]. Our results were within the reported range by these studies. These findings depend on the type of vessels studied and on the CT technology. McCarthy et al. [16] showed better results for the detection of arterial involvement: sensitivity of 84% for arterial invasion and 66% for venous invasion, similar findings were noted by House et al. [32].

One of the weaknesses of our study is the varying CT technique used over the study period. Indeed, since the introduction of the multi-slice CT, allowing three-dimensional reconstruction, the results have improved and almost reached the performance of EUS. Recently Squillaci et al. [31] reported a sensitivity of 97%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 95%, with CT detection of vascular invasion. The discrepancy between these results and our findings may be explained by the progressive alteration of radiological protocols since the introduction of the multi-slice CT in our centre.

Our results for angiography in the detection of vascular invasion were within the ranges reported by previous series [2, 7]. However, our sensitivity and negative predictive value were higher than Ahmad et al. [2], and Soriano et al. [5], although the latter reported a better specificity and positive predictive value; similar findings were reported in other series [25, 31].

The angiography detects arterial invasion with more sensitivity than the venous involvement. It had a higher sensitivity in detecting infiltration of arteries than EUS or CT (66.7%, 42%, and 40% respectively).

Confirmation of vascular invasion is clear when the vessel is occluded or eroded on imaging. The same is only suspected when vessel course is deviated or disturbed. Furthermore, the tumour may completely encase and invade the small amount of fat surrounding the vessel and, yet, not cause a distortion of the contour of the vascular lumen, which is required for detection on angiography. This feature can be visualised during EUS or CT. Thus, angiography requires more extensive vascular involvement to be detected [2, 14].

In this study, we used this exam in all cases where a doubt remained concerning an anatomical variation or an arterial invasion.

Our results for US are consistent with those previously reported by Böttger et al. [7], regarding the specificity, the negative predictive value, and the accuracy, but do not support the findings reported by Ishida et al. [25], and by Minniti et al. [24]. The latter found that US' accuracy is similar to that of CT in detecting vascular involvement.

Recently, US has developed to include 3D vascular reconstructions, allowing an accuracy of 93% in the diagnosis of portal vein invasion [33].

Magnetic resonance imaging (MRI) is a good alternative to CT, with results for vascular invasion detection similar to the latter [4, 34]. We reserve MRI for cases with contraindication to CT (allergy to iodine, renal insufficiency, and pregnancy).

In this study, the imaging modalities had a poor sensitivity and positive predictive value for diagnosing vascular invasion. However, the specificity, the negative predictive value, and the accuracy were good, especially with EUS and multi-slice CT. Our overall accuracy for the detection of vascular involvement was within the range reported by previous series [4, 5, 15, 29].

We remind the reader that only operated cases with a curative aim were analysed. However, this study allowed us to use only strong data based on concurrent surgical and anatomopathological findings.

Although, this study was retrospective, all diagnostic procedures were performed in the same group of patients, and were interpreted preoperatively and prospectively, according to a standardised protocol. Finally, to the best of our knowledge, the size of the group reported is larger than previous published series [2, 4, 19, 20].

EUS appears to be complementary to CT, because EUS identifies additional unresectable cases [5, 29]. The preoperative diagnosis of vascular invasion may assist surgical planning [20]. But a certain

diagnosis of vascular invasion may be difficult to obtain, and a place for explorative surgery reamins.

In conclusion, EUS is the most valuable imaging modality with an accuracy of 83%, compared with single-slice CT, US, and angiography, in the detection of vascular involvement in pancreatic cancer. However, in this study, multi-slice CT has almost reached the performances obtained by EUS in detecting vascular invasion.

Clearly additional prospective studies are needed to determine the optimal investigational tools for detecting vascular invasion. We therefore propose and have designed a prospective study including EUS and positron emission tomography coupled with multi-slice CT to assess vascular involvement and distant metastasis.

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