

Radial Endoscopic Ultrasonography in the Preoperative Staging of Pancreatic Cancer

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Abstract

Background. Endoscopic ultrasonography (EUS) is a diagnostic method that aims to detect and stage tumors of the pancreas more accurately. It has a high predictive role regarding tumor resectability. **Aim.** The present paper aims to assess the diagnostic accuracy of radial EUS in the staging of pancreatic cancer as well as the role of EUS to predict tumor resectability. **Material and methods.** 30 patients (22 males, 8 females, mean age 61 ± 12 years) with pancreatic masses staged by both radial EUS and surgery (17 patients with intraoperative exploration and 13 with pathological examination of surgical specimens) and with histologically proved adenocarcinoma were included in the study. Surgical examination was indicated in patients with pancreatic masses evidenced by imaging methods other than EUS, without distant metastases proved preoperatively, and without taking into consideration the staging obtained by EUS. Resectability criteria for pancreatic tumors as assessed by EUS were invasion of superior mesenteric artery or invasion of celiac trunk. **Results.** The accuracy of EUS T staging was 86.6%, that of N staging was 93.3% while that of the vascular invasion was 80%. The accuracy of EUS for predicting tumor stage had a direct impact on the assessment of tumor resectability (83.3%, CI 95%: 81.5- 85.2). It had a sensitivity of 100%, specificity of 75%, PPV of 91.6% and NPV of 100%. **Conclusion.** The radial EUS of the pancreas is an accurate method for tumor staging. For establishing tumor resectability, association with other imaging methods is advisable for arterial assessment.

Key words

Pancreatic carcinoma – endoscopic ultrasonography – staging - resectability.

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Introduction

Pancreatic cancer is the fourth cancer-related cause of death. As it is asymptomatic for a long time, over 95% of the patients are diagnosed in advanced stages of the disease, when their 5-year survival rate is about 10% [1]. The main issue when making a diagnosis is to select the therapy that ensures the best survival. The prognosis depends on tumor stage, and surgery is not an option for T4 or M1 tumors.

Many studies have evaluated the efficiency of the various preoperative imaging diagnostic methods. Endoscopic ultrasonography (EUS) is a diagnostic method implemented to better detect and stage pancreatic tumors in order to reach a higher tumor resectability prediction. The literature considers both CT and EUS as having high accuracy, while the studies conducted so far have been rather heterogeneous in terms of staging classification, surgery option and employed EUS techniques.

The aim of the present study was to establish staging accuracy of radial EUS in pancreatic cancer and how well EUS can predict tumor resectability.

Material and methods

Included in the study were patients with pancreatic masses staged by both radial EUS and surgery (intraoperative exploration or pathology examination of surgical specimens) and with histologically proved adenocarcinoma. Patients with other histology than adenocarcinoma or without surgical assessment were excluded.

Surgical examination was indicated in patients with pancreatic masses established by other imaging methods than EUS, without distant metastases proved preoperatively, and without considering staging obtained by EUS.

EUS was performed by the same physician, using a radial mechanical scanning echo endoscope (GF-UM160; Olympus Corp., Tokyo, Japan) unblinded in relation to the results of US and /or CT. Fasting patients were examined after sedation with 2-7 mg Midazolam intravenously. In order to perform a thorough pancreatic exploration, the endoscope was first introduced into the duodenum to study the uncinate process, the head of the gland, and the biliary tree, and was

subsequently withdrawn into the stomach for visualization of the pancreatic body and tail. The echoendoscopic criteria for malignant tumor included hypoechoic inhomogeneous mass, with irregular margins. The presence of peripancreatic and regional malignant lymph nodes was also investigated according to standard criteria (size > 1 cm, echo-poor, round shape, and regular margins). Nodal staging was based on appearance alone. Even though this approach has limited accuracy, it was deemed sufficient as the locoregional nodal stage (N stage) has no significant impact on therapy. Locoregional staging was performed according to the modified UICC criteria (TNM 2003). Vascular invasion was defined as direct visualization of loss of hyperechoic vascular wall, tumor ingrowth with complete vascular obstruction, peripancreatic venous collaterals [2] (Figs. 1-3). No biliary stents were used preoperatively in any of the evaluated tumors. Resectability criteria for pancreatic tumors assessed by EUS were invasion of superior mesenteric artery or celiac trunk.

The patients with visceral invasion, liver metastases or ascites evaluated by preoperative transabdominal ultrasonography or CT scan (without considering EUS

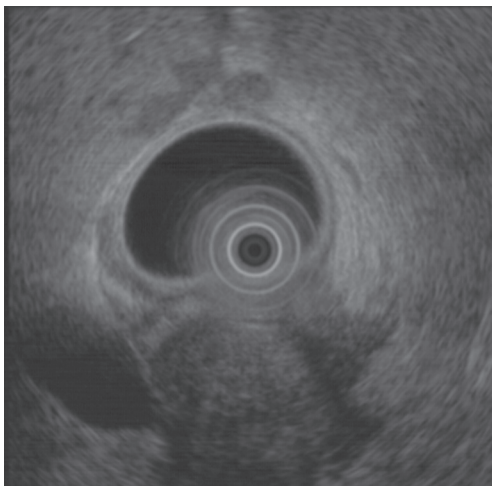


Fig 1. Adenocarcinoma of the pancreatic body with invasion of portal vein.

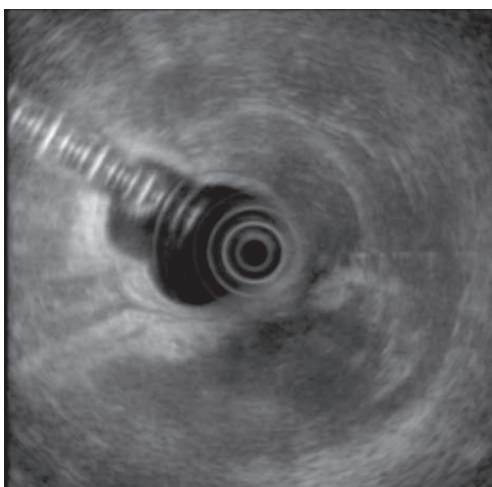


Fig 2. Adenocarcinoma of the pancreatic head with invasion in superior mesenteric vein.

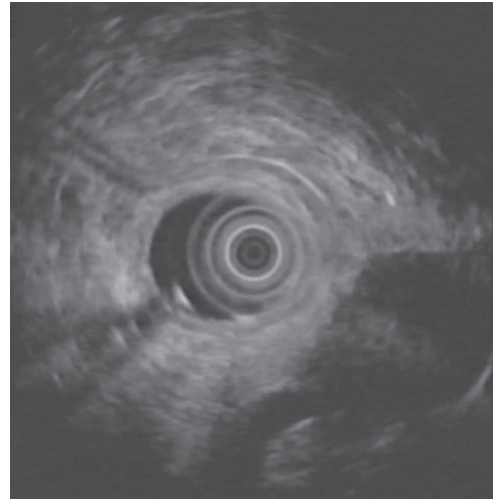


Fig 3. Adenocarcinoma of the pancreatic body with invasion of splenic artery nearby its origin from celiac axis.

results) were not included in the study. All the patients included in the study underwent exploratory laparotomy for staging, which was performed by two surgeons who had expertise in pancreatic tumor pathology, unblinded regarding the preoperative EUS staging. The EUS and the surgical intervention were performed within two weeks' time maximum.

Extensive dissection was performed to exclude major organ or vessel invasion. Biopsies were prelevated when suspicious nodules were observed on the liver capsule, peritoneum, or the omentum.

The standard for the diagnosis of resectability was the result of surgical exploration. The surgical criteria for unresectability included biopsy-proven peritoneal carcinomatosis, liver metastases, arterial invasion of superior mesenteric artery and celiac axis. Venous invasion of superior mesenteric vein, portal vein or splenic vein and arterial invasion of the splenic artery were not considered contraindications for surgery.

The surgical resectability was defined by macroscopic complete (R0) resection after explorative laparotomy. Extended lymphadenectomy was a part of radical surgery.

In tumor cases, TNM staging using EUS was compared with the results of histopathological or intraoperative staging. The patients were followed-up and the date and cause of death were recorded.

Statistical methods

The diagnostic performance analyses were carried out using the Chi square test or Fischer test. Whenever required, the performance indices were also calculated according to standard formulae: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy (Ac).

Results

Patient characteristics

We retrospectively reviewed 45 consecutive patients

referred to our hospital for EUS between June 2004 and March 2007 for the diagnosis and staging of a pancreatic tumor suspected to be malignant. The final diagnosis was based on surgery (n=20), intraoperative biopsy (n=17), endoscopic biopsies (n=1), percutaneous biopsies (n=1) or follow-up exceeding 6 months (n=6). Thirty seven patients underwent surgery and out of them three patients had neuroendocrine tumors, while 4 of them had chronic pancreatitis. Adenocarcinoma was confirmed histologically in the remaining 30 patients and they were included in this study (22 male patients, 8 female patients, mean age 61 ± 12 years). The tumor mass was located in the head of the pancreas in 21 (70%) cases, in the body in 8 (26.6%) cases and in the tail in one case (3.3%).

Thirteen patients underwent curative intent resection: 12 cephalic duodenopancreatectomies (CPD) and one distal splenopancreatectomy, in a patient who presented one liver metastasis and metastasectomy was also performed. The histological examination of surgical specimen showed 2 pT1 cases, 2 pT2 cases and 9 pT3 cases and 5pN0 and 8 pN1 cases. Seventeen patients underwent explorative surgery and five of them had a biliary bypass; chemotherapy was given in 14 cases and best supportive care in one case. Surgery

revealed hepatic metastases (n=6), peritoneal carcinomatosis and ascites (n=7), as well as both peritoneal metastases and peritoneal carcinomatosis (n=2). In one case the curative intention surgery was not possible because of malignant arrhythmias (n=1). The intraoperative exploration showed the following staging of pancreatic tumors: 3 pT2, 8 pT3, 6 pT4 cases and 3 pN0 and 14 pN1 cases. In total there were 2 pT1 cases, 5 pT2 cases, 17 pT3 cases, 6 pT4 cases and 8 pN0 and 22 pN1 cases (Fig. 4). Chemotherapy was done in 14 cases and best supportive care in one case.

The mean follow-up was 10 months (median 7 months, range 1-40 months) in the whole series.

Diagnostic accuracy of EUS for staging

One T1 case was overstaged because the duodenal invasion was wrongly assessed. One T3 case was understaged as T2 because portal invasion was underestimated. Two T3 cases were overstaged as being T4 because the invasion of the superior mesenteric artery was overestimated.

In comparison with the pathological results of tumor staging on surgical specimens, the EUS found that one case was T1, 3 cases were T2, 8 cases T3 and one case was T4. EUS overstaged one T3 case and one T4 case, but staged accurately 11 cases. In cases assessed only by explorative

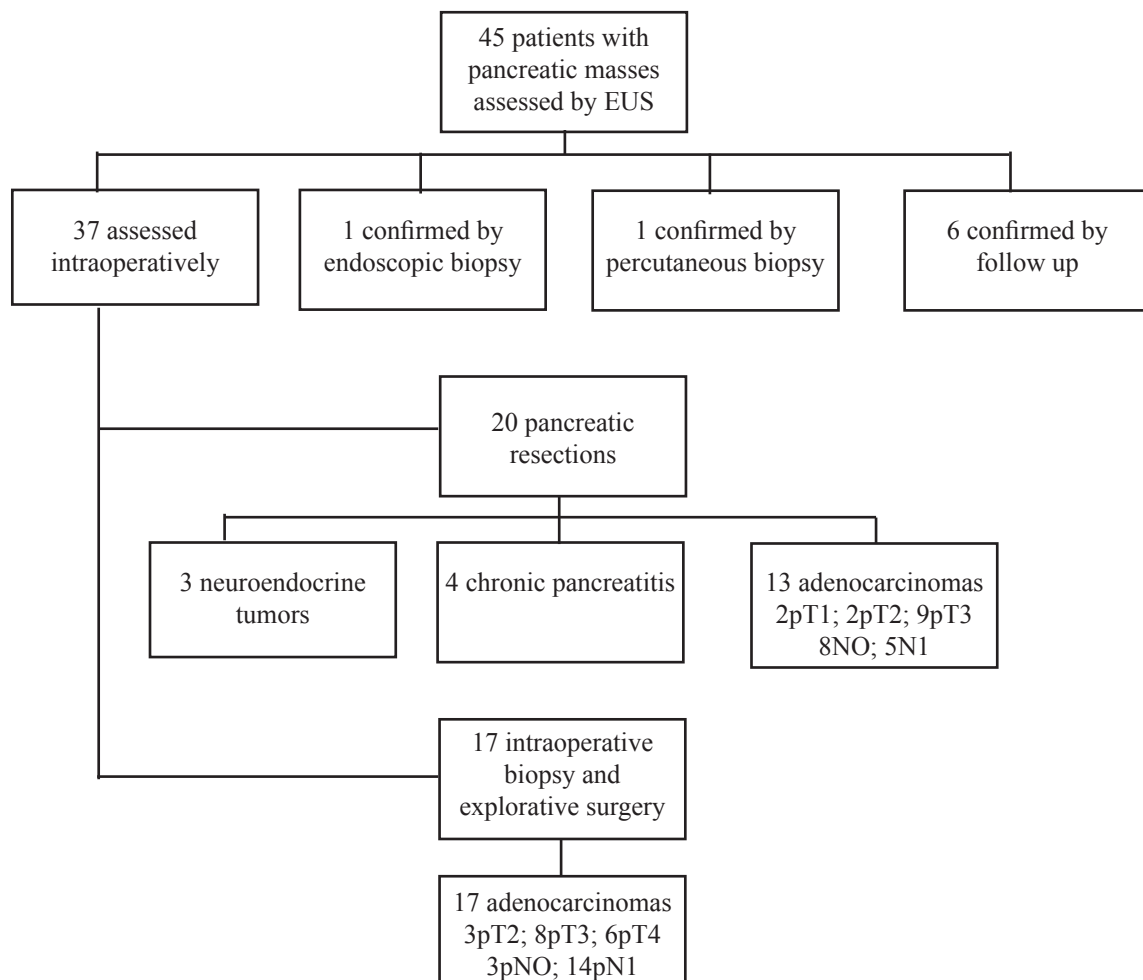


Fig 4. The pathology of patients with pancreatic masses included in the study

surgery, EUS staged 2 of these patients as T2, 8 patients as T3 and 7 patients as T4. One T3 case was understaged while one T4 case was overstaged and 15 cases were accurately staged.

For the T3 stage, the sensitivity was 82.35% (CI 95%: 80.04-86.81) and the specificity was 92.31% (CI 95%: 87.32-94.43) while for the T4 stage the sensitivity was 100% (CI 95%: 93.89-100%) and the specificity was 91.67% (CI 95%: 88.67-93.45) (Table I).

EUS staged correctly all N1 cases but overstaged 2 N0

Table I. Accuracy of EUS for tumor (T) staging of pancreatic cancer

T stage EUS	Intraoperative histopathologic stage				Accuracy (CI 95%)
	T1	T2	T3	T4	
T1	1 (3.3%)	0 (0%)	0 (0%)	0 (0%)	96.67% (92.39-98.54)
T2	0 (0%)	5 (16.6%)	1 (3.3%)	0 (0%)	96.67% (94.58-98.98)
T3	1 (3.3%)	0 (0%)	14 (%)	0 (0%)	86.67% (82.45-89.23)
T4	0 (0%)	0 (0%)	2 (6.6%)	6 (20%)	93.33% (90.23-96.71)
Total	2 (6.6%)	5 (16.6%)	17 (56.6%)	6 (20%)	86.67% (80.87-88.29)

According to TNM 2003 classification of pancreatic cancer: T1-tumor limited to the pancreas, 2 cm or less in greatest dimension; T2- tumor limited to the pancreas, more than 2 cm in greatest dimensions; T3- tumor extends beyond the pancreas, but without involvement of the celiac axis or the superior mesenteric artery; T4- tumor involves the celiac axis and the superior mesenteric artery

cases (25% of them). The sensitivity for N1 staging was 75% (CI 95%: 72.6-80.2), the specificity was 100% (CI 95%: 94.7-100), the PPV was 100% (CI 95%: 93.9-100) while the NPV was 91.6% (CI 95%: 90.3-93.4) (Table II). For N0 staging sensitivity was 75% (CI 95%: 72.4-77.6), the specificity was 100% (CI 95%: 87.4-100), the PPV was 100% (CI 95%: 92.4-100%) and NPV was 91.7% (CI 95%: 89.2-94.5).

Diagnostic accuracy of EUS for resectability

The accuracy of vascular invasion assessment was 80% (CI 95%: 78.7-82.2), the sensitivity and specificity were 100% (CI 95%: 95.7-100) and 53% (CI 95%: 50.4-60.8) respectively. The PPV and NPV were 74% (CI 95%: 70.0-

Table II. Accuracy of EUS for tumor (N) staging of pancreatic cancer

N stage EUS	Intraoperative histopathologic stage		Accuracy (CI 95%)
	N0	N1	
N0	6 (20%)	0 (0%)	93.3% (92.1/96.2)
N1	2 (6.6%)	22 (73.33%)	93.3% (91.43/92.18)

According to TNM 2003 classification of pancreatic cancer: N0- no regional lymph node metastasis; N1- Regional lymph node metastasis

76.4) and 100% (CI 95%: 92.5-100) respectively. The EUS overstaged the invasion of the superior mesenteric vein (n=1), of the portal vein (n=2) and of the superior mesenteric artery (n=2). There were no understaged cases. The accuracy of EUS for arterial invasion was 86.6% (CI 95%: 83-88.2) and for venous invasion 80% (CI 95%: 77.8-83.2).

The accuracy of EUS for predicting tumor stage had a direct impact on the assessment of tumor resectability (83.3%, CI 95%: 81.5- 85.2), sensitivity of 100%, specificity of 75%, PPV of 91.6%, NPV of 100%. All cases considered as T3 stage were resectable; 25% of cases considered as stage T4 and unresectable by EUS were wrongly overstaged and could have been omitted from surgery.

Survival

The survival was 5 months in unresected patients (median 3 months, range 0-21 months) and 16 months (median 13 months, range 4-40) in resected patients. The 5 year survival was 5.6% and 12% in non-resected and resected patients, respectively (Fig. 5). The difference in survival was statistically significant (p=0.0009).

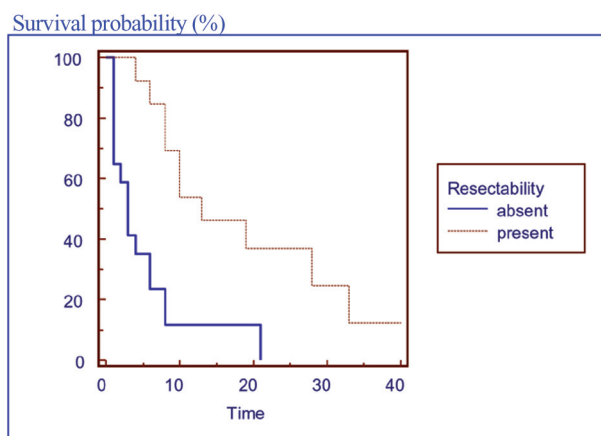


Fig 5. Overall survival curves of resected patients (n=13) and nonresected patients (n= 17).

Discussion

Many studies have evaluated the efficiency of the various preoperative imaging diagnostic methods in pancreatic cancer. Endoscopic ultrasonography is a well-known method of preoperative staging in pancreatic cancer that is recommended for assessing tumor resectability. The literature has provided different results on this topic. The first studies about radial EUS staging carried out before 1997 used the 1987 TNM staging that did not include stage T4 but included the involvement of adjacent vessels (both arteries and veins) and of neighbouring organs in stage T3. Although the studies were carried out on a limited number of cases, the accuracy of T staging was of 73-94% [3-6]. The division according to stage revealed that the accuracy of EUS ranged from 33 to 100% for stage T1, 78 to 100% for stage T2 and 71 to 85% for stage T3. Large tumor sizes that weakened

the ultrasounds were considered the main drawback [3, 4, 7]. Mechanical radial EUS was gradually replaced by linear and digital radial EUS. Studies that compared the accuracy of mechanical and radial EUS were carried out. Their findings indicated that the two examinations had similar accuracy: 88% T staging accuracy for the radial examination and 75% N staging accuracy. These results are similar to our results but there was a higher accuracy for assessing vascular invasion (100%) [8].

Later studies were carried out on patients who underwent EUS according to TNM 1997 classification which included invasion of the portal vein, celiac trunk and mesenteric vessels as T4 stage. The results of EUS T staging were better than for PET or MRI, but poorer than those published before (62-69%), probably related to the type and resolution of the scope used [9-11]. The authors found an accuracy for T3 staging of 61- 74%, and for T4 staging of 78-88% [10-12], close to our results. One of these studies which showed better results by EUS staging than CT scan staging predicted that the use of the 2003 TNM classification would improve the global accuracy of the EUS examination [12]. This has recently been confirmed by a review of five relevant studies on endoscopic staging of pancreatic tumors, which concluded that EUS offered better results as compared with CT [13].

Our study, although limited to a small number of patients, demonstrated excellent EUS staging with an accuracy of 86.6%, which was due to the use of the 2003 TNM staging. It is also one of the few studies that use this classification to evaluate the value of EUS. The comparison with surgical T staging was performed whenever distant tumor spread was not revealed ultrasonographically. In such cases the EUS was disregarded and T4 tumors were also included. This could explain why the accuracy of T4 staging (over a quarter of all examined patients), and consequently global accuracy, registered very good values. Studies published since 2000 have selected pancreatic tumors for resection based on the results of multidetector-row CT with contrast substance. Therefore, tumors with arterial vascular invasion were not surgically explored. This limited the statistical analysis and underestimated endoscopic global accuracy.

Currently, the presence of metastatic lymph nodes does not change the management of pancreatic tumors although the postoperative prognosis of operated tumors with distant lymph nodes (retroperitoneal, celiac) is usually poor. Therefore, the identification of stage N1 does not modify the therapeutical option. In this study the accuracy of N staging was over 90%, which is higher than in other studies that obtained results of 41-86% [14], due to the uneven use of lymph node malignancy criteria according to the above-mentioned criteria. However, in our patients lymph node assessment was carried out only intraoperatively, and not histologically, in more than half of the studied patients, which represents a drawback of the study.

The assessment of vascular invasion is the key to T staging in pancreatic cancer. EUS has proved to offer better results than angiography [11]. The accuracy of EUS in assessing

vascular invasion, an examination operator-dependent, varies between 67 and 100% and may be lower due to the lack of complete scanning of the pancreatic parenchyma in the duodenum [2, 6, 15, 16] or the use of different assessment criteria for vascular invasion. A recent meta-analysis of 29 studies on vascular invasion assessed with EUS concluded that the specificity and sensitivity were of 90% and 79%, respectively, and that no differences between the radial and linear examinations were registered [17]. Tridimensional linear EUS may bring additional information, as indicated by a study carried out on 17 pancreatic adenocarcinoma cases [18]. Our study, which used the vascular invasion criteria created by Snady et al in 1992 [2], obtained an 80% accuracy of global vascular invasion assessment, close to the 87.5% obtained in a 1999 prospective analysis that used the same criteria [6]. The NPV was higher than that obtained by other studies [6, 9, 11, 19], due to the reduced number of patients included in the study and perhaps influenced by unblinded examination by other imaging methods.

In our center, the criteria for pancreatic tumor resection are quite liberal and include T3 stage without involvement of celiac axis and superior mesenteric artery. Using these criteria for resectability, assessment of venous invasion is less important, and our data show that the EUS evaluation of venous invasion assessment was less accurate than for arterial invasion. We found a high sensitivity of EUS for assessment of tumor resectability, especially in stage T3. The specificity and PPV were lower and, considering only EUS results for preoperative staging, some resectable tumors could have escaped radical surgery. The explanation of our results relies on the criteria used for vascular invasion despite the resolution of the mechanical EUS. Some authors consider that the signs of arterial invasion in EUS include only altered arteries, occluded arteries or wall irregularities and not the loss of the artery-tumor interface, in which case the tumor could be resected, situation responsible for overstaging of the invasion of the superior mesenteric artery in our study [20]. If EUS would have indicated tumor resection, 25% of tumors considered T4 were truly resectable. Therefore, we found a higher accuracy for arterial invasion than published in other studies [21], but this could be due to the number of cases evaluated with arterial involvement. That is why it is important to combine EUS with CT scan, which is considered to be better than EUS in the assessment of arterial invasion in pancreatic cancer. However, CT examination should also be carefully considered since there could be tumor lesions that this examination is unable to detect [21]. Our assessment of venous invasion was according to other data published (accuracy 83-93%) [21, 22].

The main limitations of our study are the small number of patients and the lack of unblinded evaluation in relation with previous imaging examinations.

Conclusions

The radial EUS of the pancreas is an accurate method for evaluation of tumor staging when using TNM 2003

classification. For predicting tumor resectability, the sensitivity of EUS is high, but the specificity is low. For arterial invasion and resectability assessment, the association with other imaging methods is advisable.

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Conflicts of interests

Nothing to declare.

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