ROLE OF ENDOSCOPIC ULTRASOUND IN THE DIAGNOSIS AND STAGING OF PANCREATIC CANCER

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1. ABSTRACT

Endoscopic Ultrasound (EUS) is a relatively new modality. Its high resolution makes it possible to detect tumors of 5mm in diameter otherwise missed by other imaging modalities. It is more accurate than computerized tomography (CT) scan, Transabdominal Ultrasound (US) and Magnetic Resonance Imaging (MRI) in diagnosing pancreatic lesions, especially those less than 20mm in diameter. EUS can be used to obtain pancreatic and nodal tissue using ultrasound- guided fine needle aspiration increasing the diagnostic yield and helping determining further management. It can also determine vascular involvement by pancreatic cancer with a sensitivity of more than 90%. The current indications for EUS in the diagnosis and management of pancreatic cancer will be reviewed.

2. INTRODUCTION

Pancreatic carcinoma has a poor prognosis. This is due to a variety of factors including advanced stage at diagnosis, rapid local spread and the anatomical location of the tumor. Therefore, early diagnosis, accurate staging and assessment of tumor resectability are of major importance. Early diagnosis of pancreatic cancer is difficult. Ultrasound, CT scan and Endoscopic Retrograde Pancreatic Cholangiography (ERCP) have been the conventional radiographic modalities in the management of pancreatic cancer. However, their utility is limited by the lack of sensitivity in detecting small lymph nodes and vascular invasion.

EUS can overcome the limitations of a transabdominal US in the visualization of the pancreas from the overlying bowel (1). EUS offers a technique, which by way of placing an ultrasound probe in very close proximity (1-2cm) to the pancreas, allows visualization of the pancreatic parenchyma and surrounding tissue as well as assessment of nodal status. In experienced hands, EUS is the single most accurate test for diagnosing and staging pancreatic cancer (2). This review will discuss the techniques of EUS and its role in surgical staging, determining resectability and its evolving use to obtain tissue via EUS-guided fine needle aspiration (FNA).

3. EUS INSTRUMENTS

The concept of EUS is an ultrasonic transducer with specific frequencies, placed at the tip of a side-viewing endoscope. It is covered with a balloon that creates a tight water interface between the tissue and the transducer. There are two types of EUS instruments: Radial scanning and linear array.

3.1. Radial Scanning

Radial Scanning (mechanical sector) consists of a single piezoceramic element mechanically rotated around the long axis of the endoscope creating a 360-degree sector scan. The transducer frequencies range from 5 to 20 MHz. Higher frequencies allow better picture resolution but have poor depth of penetration. The image obtained permit the acquisition of transverse sections of the organs. The radial scanning is not suitable for biopsy of pancreatic lesions.

3.2. Linear Array

This second transducer consists of multiple small piezoceramic elements configured as a rectangle and mounted on a curved surface. Instead of the

Table 1. Sensitivity of EUS compared to other imaging modalities in the diagnosis of pancreatic cancer.

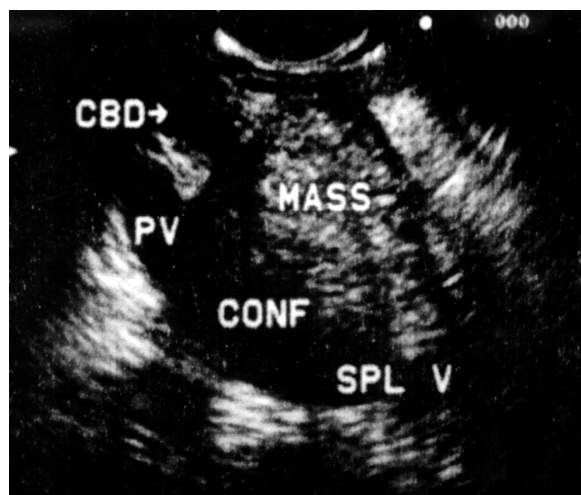| Author (ref)	Patients	EUS (%)	US(%)	CT (%)	MRI (%)	ERCP (%)	Angiography (%)
Nakaizumi (2)	49	94	78	65			
Muller (10)	49	94		9	83		
Rosch (7)	102	99	67	77		90	
Yasuda (6)	146	98	75	80		86	89
Palazzo (8)	64	91	64	66			
Giovannini(9)	94	100	48	69			

Figure 1. Hypoechoic and slightly heterogeneous mass in the head of the pancreas. (CBD: common bile duct, PV: portal vein, CONF: portal confluence, SPL V: splenic vein).

360 degrees image seen with the radial scanning, the picture given by the linear array is pie- shaped and parallel to the shaft of the endoscope. This EUS modality permits pulsed as well as color doppler and US- Guided fine needle placement for tissue sampling.

4. EUS TECHNIQUES

By placing the ultrasound probe in the second portion of the duodenum and gradually withdrawing it into the bulb, the head of the pancreas, lymph nodes, bile ducts, portal vein as well as the portal confluence can be visualized as shown in Figure 1. By positioning the tip of the endoscope in specific locations in the stomach, the body and tail of the pancreas, lymph nodes, splenic vessels and the celiac trunk can be imaged (3, 4).

5. EUS IN DIAGNOSING PANCREATIC LESIONS

Endoscopic ultrasound is extremely accurate in detecting pancreatic masses. Its spacial resolution makes it possible to detect tumors of 5mm in diameter and allows detailed examination of their echotexture (5). Pancreatic lesions can be simply classified as solid or cystic. Solid masses include adenocarcinoma, neuroendocrine tumors and focal pancreatitis. Cystic lesions include benign cysts, cystic neoplasms and pseudocysts. The use of EUS to identify, stage and sample pancreatic lesions is now established. Small pancreatic lesions of less than 20mm in size are readily detected by EUS. They usually appear homogenous and hypoechoic. Larger lesions are generally observed as hypoechoic, slightly heterogeneous with relatively irregular outer margins, sometimes associated with cystic changes. If the tumor contains mucin- secreting cells, it tends to give a hyperechoic picture (2, 6). These echographic appearances can sometimes confound even the experienced endosonographer since malignant lesions can have smooth borders, while benign inflammatory masses may be hypoechoic and heterogeneous.

Multiple studies have compared EUS to other imaging modalities (2, 6- 10) (table 1). The sensitivity of EUS ranges from 91- 100%, compared to US 48- 75%, MRI: 83%, ERCP: 86- 90% and angiography 89%. CT scan detection rate for pancreatic tumor of any size is approximately 70 %, whereas for lesions less than 3cm it is 55% and for masses less than 2cm is 20- 30 %.

Cystic lesions of the pancreas can be broadly classified into primary cystic neoplasms and pseudocysts. Primary cystic neoplasms (Figure 2) can be further subclassified into serous and mucinous. EUS has the greatest ability to delineate detailed structure of these lesions, and with the advent of the fine needle aspiration; it can assist in differentiating serous from mucinous neoplasms (11).

Focal pancreatitis may present as a discrete pancreatic mass. Therefore, despite excellent sensitivity in detecting pancreatic tumors, EUS without fine needle aspiration and cytology, is limited by its ability to reliably differentiate neoplastic from benign inflammatory lesions solely based on the sonographic appearance. In one study, its specificity was only 76% in the diagnosis malignant tumors (7).

5.1. EUS – Guided- Fine Needle Aspiration

Percutaneous CT or US- guided FNA are the most commonly used methods for obtaining pancreatic tissue. However, the ability to successfully obtain a diagnostic pathologic material ranges from 20- 70% (12- 15). This is due to technical difficulties with both visualization and access of the mass and inadequate sampling due to the surrounding focal pancreatitis.

EUS- guided FNA is emerging as an important modality in obtaining a pathologic diagnosis. Radial scanning echoendoscopes should not be used to perform FNAs since the needle is only seen in cross section, appearing as a dot in the EUS field which makes advancing the needle tip into the target tissue very difficult (16). However, with the development of

Table 2. Accuracy of EUS- guided FNA in the diagnosis of pancreatic cancer.

Author (ref)	Patients	Sensitivity (%)	Specificity (%)	Accuracy
Chang (18)	38	91	100	87
Chang (19)	44	83	80	88
Wiersema (20)	14	82		90
Bhutani (21)	47	64	100	
Gress (22)	48			77
Chang (17)	20	91	100	94

Table 3. Comparison of EUS, abdominal CT scan and transabdominal US in detecting regional lymphadenopathy in pancreatic cancer

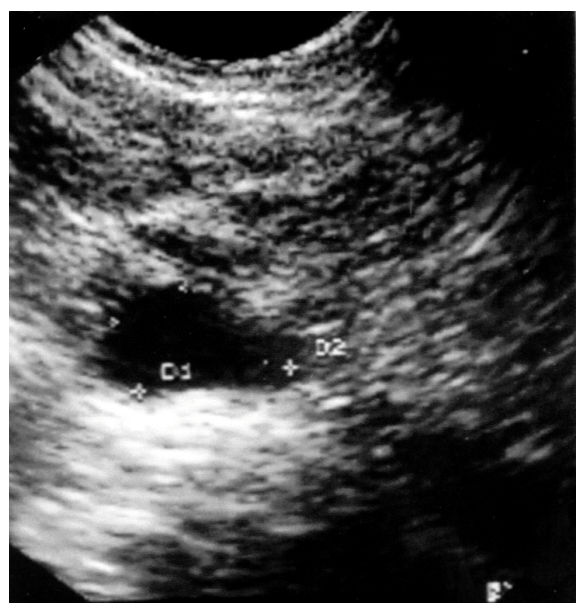| Author (ref)	EUS (%)	CT (%)	US (%)
Palazzo (8)	74	42	37
Yasuda (3)	66	38	55
Rosch (26)	72	36	12
Muller (10)	64	50	56
Giovannini (9)	92	69	53

Figure 2. Pancreatic cystic lesion with the hyperechoic shadow produced by the fluid in the cyst.

the linear array transducers, EUS- guided FNA became feasible since the entire needle track can be visualized under real time ultrasonography.

EUS-guided FNA is considered a very safe technique. In a multicenter study of 164 consecutive patients with a variety of pancreatic lesions, the FNA complication rate were 1% for bleeding and perforation, 1% minor bleed and fever (1). It is now becoming apparent that cystic lesions have a significantly higher complication rate compared to solid ones (22). The need for antibiotics is still uncertain. Although most of the studies used prophylactic antibiotics, randomized studies may be needed to determine their usefulness. Malignant seeding is a small but significant concern of percutaneous

FNA. This concern is reduced with the EUS- guided FNA since the track that could be seeded, will eventually be resected if surgery is attempted.

6. EUS IN DETERMINING RESECTABILITY

The high resolution of EUS in detecting pancreatic tumors has led endosonographers to explore the accuracy of this technique in staging pancreatic cancer. Original studies compared EUS with surgical staging. EUS sensitivity is approximately 80% (64- 94%) for T stage. It was accurate in 33- 100% for T1, 75- 83% for T2 and 83- 100% for T3. Because the initial results were encouraging, multiple studies compared it to other diagnostic modalities. The overall detection rate of EUS for T stage was 89- 100% compared to 50- 70% for CT scan, 50- 85% for US and 70- 80 % for angiography (3, 6). This suggests that endosonography is highly accurate in predicting T stage in assessing resectability.

6.1. EUS in Detecting Lymph Nodes

The sensitivity for EUS in visualizing lymph nodes is 89- 92% with a specificity of 26- 75%. It was more sensitive than CT scan (40 –50%) and US (12- 57%). (3, 6, 8- 10, 21, 23-26) (table 3). Although the sensitivity for detecting regional lymph nodes is high, it is sometimes very difficult to discern whether the adenopathy is malignant or inflammatory (18, 27). Catalano et al. (25) suggested four features predictive of lymph node metastases: a) homogenous and hypoechoic appearance, b) sharply demarcated borders, c) rounded shape and d) size >10mm. If all features are present, the lymph node was metastatic in all cases, whereas if none of the predictors were present, metastases were found in 20% of the cases. Although elongated shape, heterogeneous, hyperechoic lymph node with indistinct borders are suggestive of a benign lymph node; these endosonographic features may be evident in malignant involvement (especially in micrometastasis) (25). The results of Catalano could not be reproduced by Bhutani et al. (28) in a study involving 35 patients with lymphadenopathy; the four features could not differentiate between benign and malignant involvement. Furthermore, 75% of the lymph node did not have all four features at the same time. The only feature that was statistically significant in predicting malignancy was mixed echogenicity. This appearance was present in 31% of malignant lymph node compared to 0% of benign ones. There are additional difficulties utilizing endoscopic ultrasound to distinguish benign from malignant lymphadenopathy: First, the echogenicity does not depend solely on the histologic characteristics, but also on the

Table 4. Comparison between EUS, US CT and Angiography in detecting portal system invasion

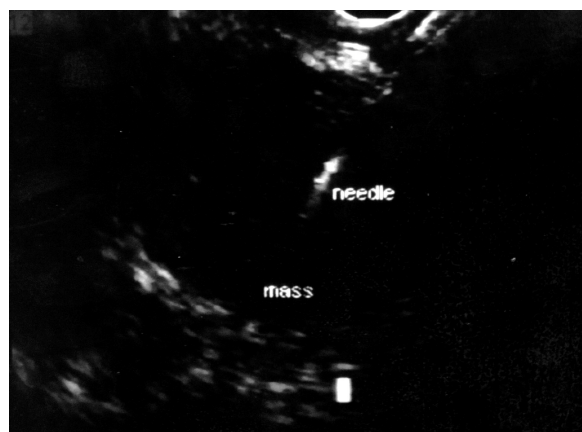| Author	EUS (%)	US (%)	CT (%)	Angiography (%)
Rosch (26)	Sensitivity: 91	9	36	85
	Specificity: 97	72	85	100
Palazzo (8)	Sensitivity: 100	17	71	
Giovannini (9)	Sensitivity: 92	22	46	
	Specificity: 83	81	96	
Nakaizumi (2)	Accuracy: 79	54	48	

Figure 3. Fine needle aspiration of a pancreatic mass.

transducer frequency. Second, the criteria proposed are subjective and therefore may suffer from interobserver variability (28, 29).

EUS- guided FNA of the lymph node plays an important role in increasing the specificity of the EUS in detecting metastatic lymphadenopathy. The technique of endoscopic aspiration is similar to that of pancreatic masses. EUS- guided FNA has a sensitivity of 64- 83% with a specificity close to 100% (1, 20, 30). A false negative could exist if the lymph node is focally infiltrated by malignant cells.

6.2. EUS in Detecting Venous Involvement

Invasion of the peripancreatic vessels is one of the most important criteria for determining resectability of pancreatic cancer. Traditionally, the detection of vascular involvement has relied mainly on angiography and CT scan. EUS has emerged as a new, more accurate modality for detecting vascular involvement (table 4).

6.2.1. Venous Obstruction

Pancreatic masses can sometimes totally occlude any of the three branches of the portal venous system. This can be suggested either by the lack of blood flow on doppler EUS and/ or indirectly by the presence of collaterals. In the case of portal vein obstruction, the collaterals may be seen along the duodenal wall, bile ducts and later, as esophageal varices. With splenic vein occlusion, collaterals are apparent along the gastric wall and may appear later as fundic varices (30). The sensitivity of detecting these collaterals by EUS is variable. Rosch et al (26) found evidence of collaterals in 83% in patients

with portal- splenic infiltration whereas for Snady et al (31), this criteria was sensitive in only 21%.

6.2.2. Venous Invasion

Four endosonographic criteria have been proposed to reflect venous invasion.

In a series of 28 patients (32), irregular venous wall was the most specific sign (100%) for diagnosing venous invasion. The sensitivity varied according to the vessel studied: 60% for the portal vein, 67% for the splenic vein and 17% for the superior mesenteric vein. The significantly lower sensitivity for the superior mesenteric vein was due to the difficulty in visualizing it.

Yasuda et al (33) studied this criterion (called rough- edged vessel with compression). The sensitivity for detecting portal vein and splenic vein invasion was 93% and 64% respectively. Loss of the hyperechoic interface between the vessel and the mass is another criterion for venous invasion. The tissue line situated between the pancreatic parenchyma and the portal confluence appears as hyperechoic. This line probably represents the vessel wall either alone or in combination with the perivascular fat. It is mainly seen surrounding the major arteries and to a lesser extent the venous structures (30, 31). The detail with which EUS visualize the tumor- vessel interface is the reason why EUS is more accurate than angiography. The tumor may indent the portal vein on angiography and thus interpreted as invasion whereas if the echorich plane is still well preserved by EUS, the tumor is amenable to resection. Tumor size has been advocated to reflect tumor invasion. A lesion size of >3cm was associated with higher frequency of vascular involvement.

Tumor- vessel contiguity may also predict resectability. Contiguity is defined as the length of which the tumor mass is in contiguity with blood vessel. Snady et al (31) suggested that a compression of more than 3 cm in length may prove to be another criterion of unresectability for pancreatic adenocarcinoma.

6.2.3. EUS in Detecting Arterial Invasion

Evaluation of arteries for malignant invasion using EUS is more difficult than assessing venous structure (30). This is probably due to the fact that arteries are smaller than veins and follow a more tortuous course. This may make it difficult to trace their entire paths. Also, with larger tumors, the superior mesenteric artery may be difficult to locate as it runs deep to the pancreatic head. In many cases, it appears that tumors encase rather than invade the artery probably because arteries have thicker walls. Encasement is probably more easily assessed with

angiography. Sandy at al (31) suggested that alteration in vessel course and caliber may be a sign of arterial involvement. Rosch *et al* (26) found EUS to be less sensitive than angiography for assessing invasion of the celiac trunk in 28 patients with pancreatic and ampullary carcinomas (50 versus 83% respectively).

7. RADIAL SCANNING VERSUS LINEAR ARRAY TRANSDUCERS FOR PANCREATIC CANCER STAGING

EUS has proven to be a highly accurate technology for local staging for pancreatic cancer. Most of the staging procedures using EUS have been performed using the radial scanning endosonography. Gresset et al. (21) compared the two types of transducers for staging of pancreatic cancer in 33 patients. In both modalities, the accuracy did not differ for T or N staging or vascular involvement.

8. FUTURE PERSPECTIVES

Endoscopic ultrasound is the most accurate imaging modality for pancreatic cancer. Its main indications are to diagnose pancreatic cancer with great precision especially for masses less than 2 cm in size, which are frequently missed by CT scan or transabdominal US. It is also the most accurate method to determine resectability by delineating vascular invasion and provides a mean to obtain pathologic information suspicious lymphadenopathy. EUS is rapidly becoming a standard procedure in the diagnosis and management of patients with pancreatic cancer.

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