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Pancreatic cancer: diagnosis and endoscopic staging

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Abstract. – Early diagnosis and appropriate staging of pancreatic adenocarcinoma is of vital importance to possibly detect this otherwise lethal disease at a curable phase and to stratify patients who would benefit the most from surgical resection. The availability of endoscopic ultrasound (EUS) with its unique capability of obtaining refine images of the pancreas has represented a major breakthrough in the management of these difficult tasks. Furthermore, the ability to perform fine needle aspiration (FNA) under real time EUS guidance has offered the possibility to reach a definite diagnosis which has a major impact on the decision making process in the care of patients with both resectable and unresecectable pancreatic cancer. In parallel to the widespread importance of diagnostic EUS, the therapeutic applications of EUS are increasing and may further expand the role of this procedure in the management of pancreatic cancer. This article focuses on the current role of EUS and EUS-FNA in the diagnosis and staging of solid pancreatic lesions in different clinical scenarios, including those individuals at a high risk of developing pancreatic cancer and who may be candidates for a EUS-based screening and surveillance program. Data on the emerging therapeutic role of EUS for pancreatic cancer treatment will also be reviewed.

Key Words:

Pancreatic cancer, Staging, Endoscopic ultrasound.

Introduction

Pancreatic adenocarcinoma is the forth leading cause of cancer death in men and women in most western countries[1]. In 2000, there were approximately 216,400 new cases diagnosed worldwide, and 213,500 cancer-related deaths[2]. The dismal prognosis of this disease is clearly depicted by its virtually uniform fatality, with an overall 5-years survival rate of less than 5%[1]. The only chance for cure is currently surgical resection, which can be extremely effective for lesions detected at a very early stage as demonstrated by a series from Japan in which all patients with a tumor smaller than 1 cm survived long-term[3]. Unfortunately, at the time of diagnosis only 10% to 15% of patients have a disease amenable for potential curative resection, defined by negative margins (R0) and no residual tumor at histopathological examination of the resected specimen[4]. Nonetheless in these patients the 5-years survival rate approaches 20% with post-operative chemo-radiation therapy, while in most of the cases disease will recur in the first two years after the diagnosis[5,6]. Optimally, earlier detection through screening and precise pre-operative staging would best stratify patients who would benefit the most from surgery, while sparing the remaining from unnecessary interventions that carry significant morbidity and mortality.

In the last 20 years, the role and the importance of the endoscopist in the diagnosis and staging of pancreatic cancer has greatly evolved due to the development of endoscopic ultrasound (EUS). The intragastric and intraduodenal position of the EUS probe in close proximity to the pancreas allows the obtainment of high-resolution images and the visualization of local anatomic details not detected by other imaging techniques. This peculiarity, coupled with the ability to perform EUS-guided fine needle aspiration (EUS-FNA) to acquire tissue samples[7], has rapidly made EUS one of the most important and accurate tool for the evaluation of pancreatic cancer.[8] More recently, the precision of EUS in targeting the pancreas and then thrusting a needle into it has stimulated investigators to consider EUS not only for tissue acquisition, but also for direct injection and delivery of anti-neoplastic or radiosensitizer agents into pancreatic solid lesions as a form of therapy[9].

This paper will review the current role of EUS and EUS-FNA in the diagnosis and stag-

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ing of solid pancreatic lesions, with particular emphasis on the data regarding the performance of EUS in pancreatic cancer screening for high-risk individuals, in subjects with equivocal results on previous imaging modalities, and in the diagnostic and staging algorithm of pancreatic masses. Data on the emerging therapeutic role of EUS for pancreatic cancer treatment will also be presented.

EUS for Pancreatic Cancer Screening in High-Risk Individuals

It is now known that about 3-16% of pancreatic cancers are either syndromic or familial[10-12]. These high-risk individuals with known genetic syndromes that predispose them to the disease or with a strong family history may be offered screening and surveillance in an attempt to detect pancreatic neoplasia at a curable stage. An inherited risk for pancreatic malignancy is believed to occur in three distinct clinical settings: familial multi-organ cancer syndromes, genetically driven chronic diseases not directly associated with cancer syndromes, and in familial groupings of pancreatic cancer with yet unidentified genetic abnormalities, termed familial pancreatic cancer (FPC) (Table I)[13]. The familial multi-organ cancer syndromes that predispose to pancreatic cancer include Peutz-Jeghers syndrome (PJS), familial atypical multiple mole melanoma (FAMMM), familial breast-ovarian cancer (FBOC), hereditary non-polyposis colorectal cancer (HNPCC), and familial adenomatous polyposis (FAP). Among the genetically driven chronic disease states not directly associated with multiorgan malignancy, the one clearly associated with pancreatic cancer development is hereditary pancreatitis (HP) that has the highest penetrance of any genetic pancreatic cancer syndrome[14]. Finally, the third clinical setting is FPC, which is generally defined as families in which two or more first degree relatives are affected by pancreatic cancer, without fulfilling the criteria for one of the above described cancer syndromes[15].

Consensus practice recommendations on who should be screened among high-risk individuals have been recently developed during the Fourth International Symposium of Inherited Diseases of the Pancreas in 2003[16]. A threshold of a >10-fold increased risk for developing pancreatic cancer was chosen to select individuals who may benefit from screening. This threshold includes family members with ≥ 3 first-degree relatives with pancreatic cancer, and patients with FAMMM, PJS, and HP. Moreover, individuals with 3 pancreatic cancer cases among first-, second-, and third degree relatives, with at least one of these being a first-degree relative, and subjects with *BRCA2* mutations and at least one case of pancreatic cancer within second-degree relatives

Table I. Clinical settings associated with an increased risk of inherited pancreatic cancer.

Clinical setting	Gene	Risk
Familial multi-organ cancer syndromes:		
Peutz-Jeghers (PJS)	STK 11/LKB1	RR = 132 CLR = 36%
Familial atypical multiple mole melanoma (FAMMM)	CDKN2a	CLR = 17%
Familial breast-ovarian cancer (FBOC)	BRCA2 BRCA1	RR = ~ 5% ?
Hereditary non-polyposis colorectal cancer (HNPCC)	MLH1, MSH2, MSH6, PMS1, PMS2	?
Familial adenomatous polyposis (FAP)	APC	?
Genetically driven chronic diseases:		
Hereditary pancreatitis	PRSS1	CLR = 40%
Cystic fibrosis	CFTR	RR = 3.5
Fanconi anemia	FA gene	?
Ataxia telangiectasia	ATM	?
Familial pancreatic cancer:		
PC in 3 or more first-degree relatives		RR = 32
PC in 2 first-degree relative		RR = 6.4
PC in 1 first-degree relatives		RR = 4.5

Abbreviations: RR, relative risk; CLR, cumulative lifetime risk, PC, pancreatic cancer.

Table II. Available studies on EUS-based screening and surveillance for pancreatic cancer in high-risk individuals.

Author (ref)	Country	No. of individuals evaluated (underlying condition)	No. with definitive diagnosis	Definitive diagnosis
Kimmeye et al, 2002[19]	USA	46 (all with FPC)	12	All with widespread dysplasia on resected specimens but no invasive carcinoma
Canto et al, 2004, 2006[20,21]	USA	116 (109 FPC, 7 PJS)	15	8 IPMN 1 T2N1 adenocarcinoma 1 PanIN 1A-1B lesions 5 benign lesions (2 serous cystadenomas, 1 accessory spleen, 1 pancreatic abscess and 1 focal fibrosis) Diffuse areas of PanIN 1 to 3 were incidentally discovered in the resected specimens
Poley et al,* 2009[22]	The Netherlands	42 (21 FPC, 13 FAMMM, 3 HP, 2 PJS, 4 other)	10	7 IPMN 3 adenocarcinoma (2 T3N1, 1 T1N0)
Langer et al, 2009[23]	Germany	76 (66 FPC, 10 FAMMM)	6	3 serous cystadenomas 1 PanIN1 lesions with lobular fibrosis 1 PanIN2 lesion 1 IPMN with PanIN2 lesion

*The lesions were all detected at baseline evaluation, while in the other studies surveillance is also considered. Abbreviations: FPC, familial pancreatic cancer; PJS, Peutz-Jeghers syndrome; FAMMM, familial atypical multiple mole melanoma; HP, hereditary pancreatitis; IPMN, intraductal papillary mucinous neoplasm.

were considered to be at high risk by expert opinion and were also felt to be candidates for screening[16].

The available published data comparing different imaging techniques in this difficult to care for population, suggest that EUS-based screening and surveillance has the highest potential to detect pancreatic neoplasms at a curable stage[17,18]. All the experiences from four major academic centers in both the United States and Europe are summarized in Table II. EUS was empirically used for the first time to screen high-risk individuals for pancreatic cancer by physicians at the University of Washington caring for a large pedigree of patients with pancreatic cancer, the Family X[24]. In non-affected family members they found that EUS was able to detect abnormalities not seen on computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) examinations[25]. The most frequent observed findings were clusters of 2- to 8-mm hypoechoic lobules, echogenic foci and strands, and hyperchoic pancreatic duct walls, all features resembling those found in chronic pancreatitis[19,25]. In most cases the EUS findings were confirmed at ERCP, which led to an empiric approach using EUS followed by ERCP when needed in this family and others with FPC. A total of 46 subjects have been evaluated with this approach so far[19]. Twelve of the 13 patients with both chronic pancreatitis-like EUS abnormalities and an abnormal pancreatogram underwent pancreatectomy (10 total, 2 distal) and all of them were found to have widespread dysplasia, involving primarily small and medium size ducts, with no cases of invasive carcinoma[19].

The same screening protocol using EUS with ERCP limited to those patients with abnormal EUS findings has subsequently been adopted by investigators at Johns Hopkins (CAPS 1 study)[20], with the addition of dual-phase, multidetector, thin-section CT scan after 2001 (CAPS 2 study)[21]. A total of 116 subjects have been evaluated in these two series. Overall, "neoplastic-type lesions" were identified in 29 patients (25%) of whom 15 had definitive diagnoses made (14 on surgical resection and one on clinical follow-up). Overall, 8 patients (53%) had an intraductal papillary mucinous neoplasms (IPMN), one a T2 N1 adenocarcinoma, and one with dysplasia on EUS-FNA had diffuse PanIN 1A-1B lesions upon resection. Five patients with a cystic or a solid

lesion on EUS as their indication for surgery had benign lesions at resection: 2 serous multiloculated cystadenomas, one accessory spleen, one pancreatic abscess and one focal fibrosis. Interestingly, in all but 3 subjects who underwent surgery areas of PanIN 1 to 3 were incidentally discovered in the resected specimens, mostly with a diffuse distribution throughout the pancreas[20,21].

The data from the Johns Hopkins investigators provide evidence that, in a highly selective population of high-risk individuals, screening and surveillance by EUS may detect early pancreatic lesions, allowing for curative resection. EUS performed better than CT, which missed one pancreatic head mass, two cystic lesions, and a pancreatic abscess, and even better than ERCP, which missed most of the lesions[20,21]. On the other hand, EUS also led to resection of benign lesions in several patients who went to surgery, emphasizing the difficult balance between undertreating individuals before they develop an untreatable disease versus overtreating and exposing them to the high risks of morbidity and mortality associated with pancreatic surgery[20,21].

Data supporting the conclusions of the two American experiences have been recently published form The Netherlands, where first time screening EUS of high-risk individuals was able to detect asymptomatic cancer and premalignant IPMN-like lesions in 7% and 16% of the subjects, respectively[22]. Conversely, data from Germany, where an EUS and MRI/-magnetic resonance colangiopancreatography (MRCP)-based screening program has evaluated 76 FPC families over a 5 years period, found a low yield of potential pancreatic precursor lesions during both screening and surveillance, thus questioning the overall value of this costly strategy[23].

At present time, when the highest risk patients are selected, one time screening with EUS has been modeled to be relatively cost-effective with a ratio of $16,885/life-years saved, but with many assumptions and without accounting for the repeated surveillance examinations currently being used in practice[26]. On the other hand, a recent Markov modeling analysis concluded in favour of no screening when selecting first-degree relatives of FPC kindreds with EUS findings of chronic pancreatitis[27]. Future multicenter international studies are needed to solve this controversy and to really assess the cost-effectiveness of a screening program in this patient population. In addition, to enhance the specificity of EUS it can be of value its use in combination with new generation imaging such as contrast-enhanced multi-detector row helical CT, as well as MRI/MRCP[28,29]. These additional imaging tests may also be helpful in detecting extrapancreatic neoplasms located beyond the imaging range of EUS, which appear to occur more frequently in these patients[17]. Lastly, due to the poor interobserver agreement for EUS findings in this patient population, even between experienced endosonographers[30], longitudinal follow up of patients by the same operator may be of great importance[31].

EUS for Diagnosis and Staging of Pancreatic Solid Masses

EUS has a diverse role in the evaluation of patients with a suspicious of a pancreatic mass and in those in whom a pancreatic solid lesion have already been identified by other previously performed imaging modalities. Despite the recent technological advances of both CT and MRI, EUS still remains the most accurate diagnostic test for the detection of pancreatic lesions, particularly those smaller than 2 cm[32]. For this reason, when other noninvasive cross-sectional imaging modalities have reported equivocal results, EUS should always be strongly recommended and where available performed[33,34]. The major advantage of EUS in this clinical setting is its very high negative predictive value approaching 100%, which reliably excludes pancreatic cancer when a focal mass is not detected during the examination[35,36]. Missed lesions in patients with underlying chronic pancreatitis, diffuse infiltrating carcinoma, prominent ventral/dorsal anlage, or a recent episode of acute pancreatitis have been, however, reported even in very expert hands[37]. Thus, in cases with a strong clinical suspicious a follow up EUS is recommended and of clinical value[38].

One frequent reason for referral patients to a tertiary high volume EUS center is the evaluation of the presence of pancreatic cancer after the discovery of non-specific changes on CT, such as an enlarged or a prominent pancreatic head. Three studies evaluating this clinical setting have been recently published and found pancreatic cancer in 8%, 8.7%, and 22% of the patients, respectively[39-41]. In the latter study[41], the mean size of the pancreatic lesions discovered was 3.5 cm, that is surprisingly large not to be detected by CT and may just reflect the poor quality of the CT technique and interpretation offered in some of the

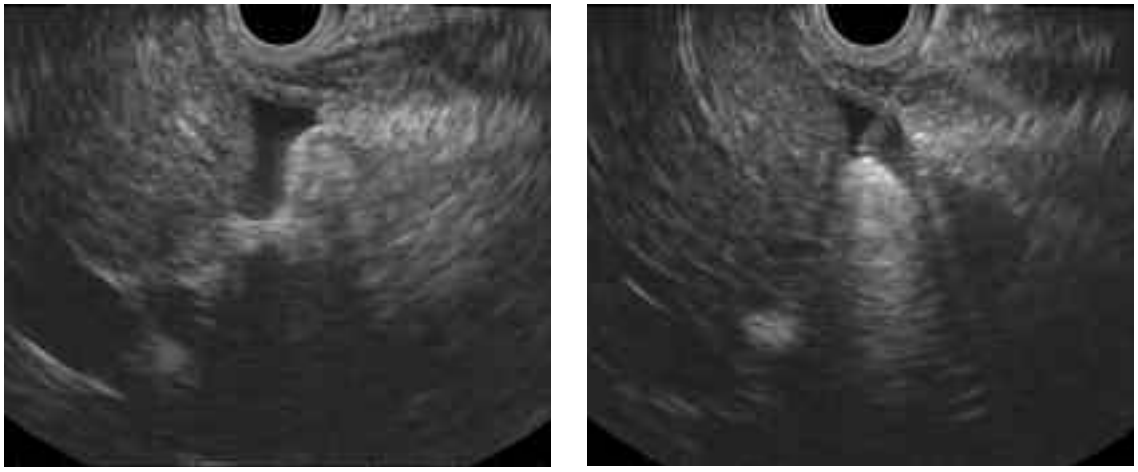

Figure 1. Low volume ascites (LVA). ***A,*** Linear EUS view of a small pocket of LVA. ***B,*** Fine needle aspiration of the LVA.

community hospitals, where most of these exams where performed.

A different clinical scenario is represented by a patient in whom a pancreatic mass has been detected on cross-sectional imaging studies. When the mass is clearly unresectable based on CT or MRI results and the patient is in good clinical conditions, tissue sampling to reach a definitive diagnosis and offer proper treatment should be performed either by the percutaneous route or by EUS-FNA[42]. The choice between one or the other sampling method is highly dependent on the local expertise and the availability of EUS or interventional radiology. In patients who are at risk for sedation-related complications and in those with surgically altered upper GI anatomy the percutaneous route may be preferred. EUS, however, is advantageous because it provides additional staging informations, i.e. the presence of lymph node metastases in the celiac, lumboaortic, retroduodenopancreatic and superior mesenteric regions and of small pocket of previously undetected ascites that may be sampled (Figure 1). Moreover, it offers the possibility of performing EUS-guided celiac plexus neurolysis (EUS-CPN) in patients with significant pain not controlled by narcotics during the same session[43]. In cases of negative results by other biopsy techniques or by EUS-FNA not performed in a tertiary center, the use or the repetition of EUS-FNA is strongly supported[44,45]. In expert hands, EUS-FNA of pancreatic masses is a safe procedure[46], has a mean accuracy of about 85% that can be even higher in the presence of an on-site cytopathology[47,48], and carries a lower risk of tumor seeding than percutaneous techniques[49].

When resectability of a pancreatic mass at previously performed CT or MRI is equivocal, EUS±FNA is the next logical step to establish the patients who may benefit the most from a major surgical intervention[50]. If EUS demonstrates the mass to be clearly unresectable (Figure 2), one can proceed with FNA for tissue acquisition. In potentially resectable lesions, on the other hand, the argument for a definitive diagnosis before undergoing surgery is debated[51]. Arguments made for EUS FNA in potentially respectable lesions (Figure 3) include an established protocol of preoperative neoadjuvant therapy, a demand by the patient for a conclusive diagnosis of cancer before consenting to surgery, and lastly to exclude unusual neoplasms other than adenocarcinoma (lymphoma, acinar cell car-

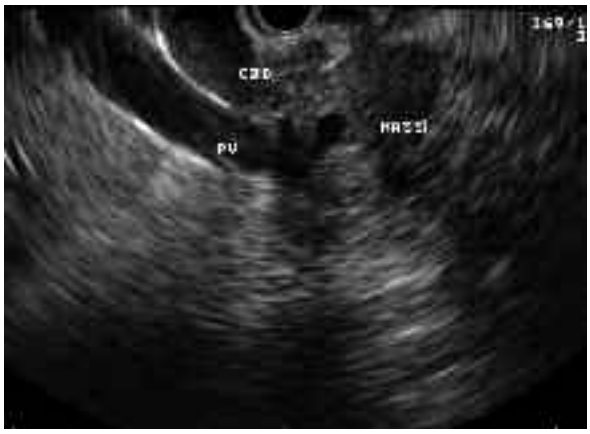

Figure 2. Unresectable pancreatic mass causing common bile duct dilatation (CBD) with encasement of the portal vein (PV) and the superior mesenteric vein.

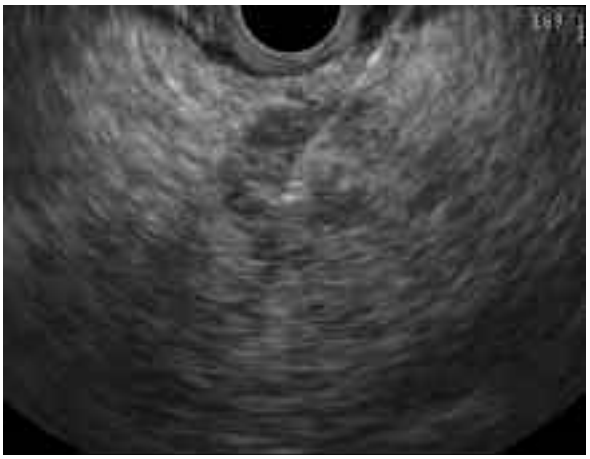

Figure 3. Fine needle aspiration of a 15 mm pancreatic T1 head mass EUS image of a pancreatic neuroendocrine tumor after contrast enhancement with SonoVue that enhance tumor vascularisation.

cinoma, solid pseudopapillary tumor and pancreatic metastases) (Figure 4) that can be found in up to 5% of individuals with pancreatic masses and would not benefit from operation[52]. Moreover, the degree of tumor differentiation gathered with EUS FNA, which has an important prognostic value[53], can provide an additional information that can help in deciding the proper therapeutic strategy for each single patient. A proposed algorithm for the evaluation of solid pancreatic masses is shown in Figure 5.

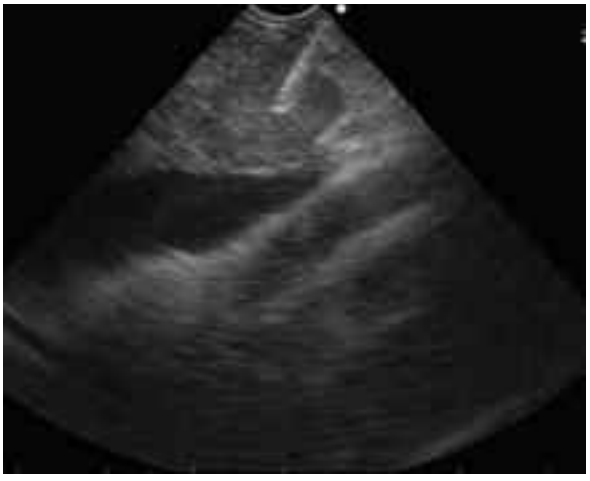

Figure 4. Fine needle aspiration of a small rounded T1 pancreatic mass using a newly developed forward viewing therapeutic EUS scope (GF-UCT160J-AL5, Olympus Medical System Europe, Hamburg, Germany). Histology showed the mass to be a metastasis from a epidermoid sarcoma located in the arm.

A particularly difficult task is the differentiation of pancreatic cancer from inflammatory masses due to focal chronic pancreatitis, for which EUS has not proven to be reliable. In an attempt to overcome this limitation of EUS, new techniques such as contrast-enhanced EUS and elastography have been developed[54]. Contrast-enhanced EUS to better assess the perfusion inside the pancreatic mass has been evaluated in one study using Levovist[55] and more recently using the second generation contrast agent SonoVue.[56] Both studies reported pancreatic cancer to be relatively hypoenhancing and inflammatory masses hyperenhancing compared with the surrounding pancreatic tissue, while the latter study clearly showed benefit from the use of contrast agent with an increase in the sensitivity and specificity from 73.2% and 83.3% to 91.1% and 93.3% after its administration[56]. Better results may be obtained using the contrast harmonic imaging technique as preliminary reported by Kitano et al,.[57] The second new imaging technique under evaluation is elastography, which is capable to distinguish the hardness of the tissue under examination by calculating and visualizing real-time tissue elasticity. This method has been proved to be feasible to distinguish neoplastic pancreatic "hard" tissue from inflammatory pancreatic "soft" tissue[58], even though recent studies have reported conflicting results on its accuracy[59-61]. Finally, DNA analysis of FNA aspirates[62] and digital imaging analysis of EUS images[63] seem promising additional techniques to solve this important clinical challenge, but need further confirmation in larger cohort of patients.

Interventional EUS for Pancreatic Cancer

The most well established interventional procedure for pancreatic cancer performed under EUS guidance is EUS-CPN[64]. The plexus is composed of two ganglia, usually located anterior and lateral to the aorta at the level of the celiac trunk. Using a curvilinear array echoendoscope, this region can be easily visualized from the lesser curve of the stomach by following the aorta to the origin of the main celiac artery. With careful inspection it also possible to directly visualize the celiac ganglia as 1 to 5 elongated hypoechoic structures[65, 66].

EUS-CPN is done using a 19-gauge needle or a dedicated 20-gauge needle with multiple side holes. The procedure involves the injection of the anesthetic bivucaine followed by a second injection at the same site of absolute alcohol, which

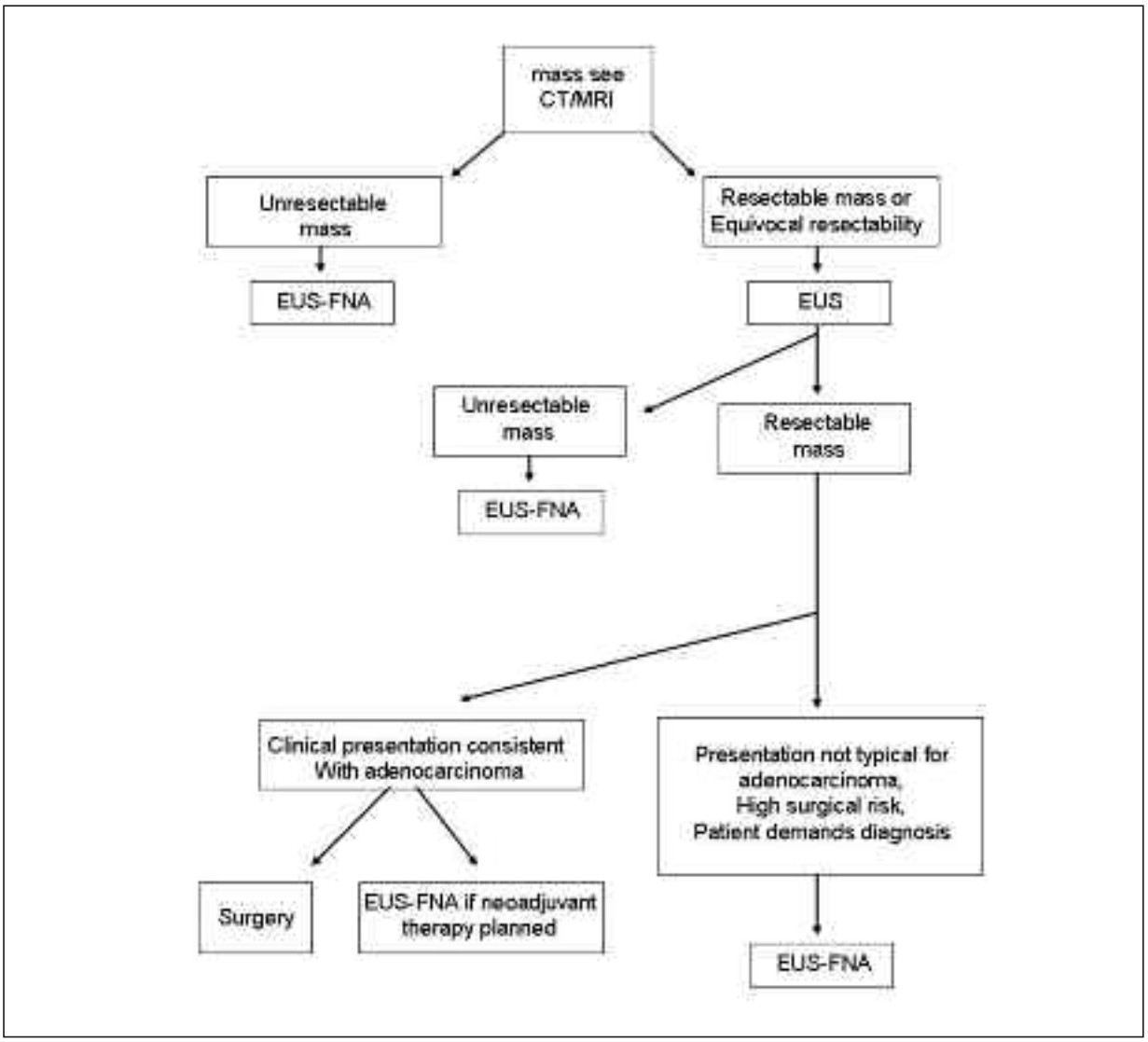

Figure 5. Fine needle aspiration of a small rounded T1 pancreatic mass using a newly developed forward viewing therapeutic EUS scope (GF-UCT160J-AL5, Olympus Medical System Europe, Hamburg, Germany). Histology showed the mass to be a metastasis from a epidermoid sarcoma located in the arm.

can done at the base (central) only or on either side (bilateral) of the celiac axis. The effect of direct injection into the ganglia has been retrospectively evaluated in a recent study[67], which needs a prospective confirmatory study before it can become part of routine practice.

Despite the first report was published more than 10 years ago[68], there is a paucity in good quality data and most of the evidence on the effectiveness of this procedure is mainly based on observational and uncontrolled studies[69,70]. To overcome this limitation, a meta-analysis of the published studies have been recently performed and found EUS-CPN to be able to relief pain in about 80% of patients with pancreatic cancer[71]. Based on this Authors recommended EUS-CPN as a valid treatment for pancreatic cancer pain, with a trend versus a better pain relief with bilateral injection than injecting at one site, results confirmed in a more recent comparative study[72]. Moreover, preliminary results from the first randomized, double blind, sham-controlled trail have reported that early EUS-CPN (performed at the time of tissue diagnosis) reduces abdominal pain score in all patients and narcotic use in the subset of patients who did not undergo subsequent chemotherapy[73].

In parallel to the growing importance and widespread use of EUS FNA for the evaluation of pancreatic masses, efforts have been made to develop a role for this procedure in the therapy of pancreatic cancer. The first approach involved the injection of anti neoplastic agents under EUS guidance directly into the pancreatic tumor. Chang et al.,[74] demonstrated the feasibility and safety of the injection of an allogenic mixed lymphocyte culture (cytoimplant) in 8 patients with unresectable pancreatic adenocarcinoma. Subsequently, Hecht et al.[75] delivered an anti-tumor viral therapy, the ONYX-015 (dl1520) repeatedly into the tumor of 21 patients with advanced adenocarcinoma. The ONYX-015 (dl1520) is an E1B-55kD gene-deleted replication-selective adenovirus that preferentially replicates in and kills malignant cells, This therapy in association with intravenous administration of gemcitabine during the last 4 sessions resulted in partial disease regression in 2 patients, stabilization in 6, minimal changes in 2 and progression in 11. Major complications were sepsis in 2 patients and duodenal perforation in 2 other patients. These complications were subsequently avoided by administration of antibiotics prophylaxis and performance of transgastric injection, respectively[75]. At the present time, we await for the publication of the long-term results presented at DDW in 2006 of a multicenter American trial involving EUS or CT guided injection of TNFerade, a replication-deficient adenovector containing human TNFα gene, regulated by a radiation-inducible promoter Egr-1[76]. TNFerade was injected weekly for 5 weeks in combination with continuous intravenous 5-FU (200 mg/m^2/d × 5d/wk) and radiation (50.4 Gy) in 50 patients with unresectable tumor. The preliminary results were encouraging and reported that four of the five patients whose tumors became surgically resectable had pathologically negative margins and 3 survived longer than 24 months[76].

More recently other EUS-guided treatment strategies have been attempted. Two series by Sun et al.,[77] and Jin et al.,[78] have reported EUS-guided direct instillation of radioactive seeds (brachytherapy) in 15 and 22 patients, with modest benefit only related to reduction of pain. On the other hand, EUS has been also used to place fiducial markers in pancreatic tumors for image-guided radiotherapy with a very high rate of successful placement even in patients with head or uncinate lesions[79]. Other form of therapies such as EUS-guided pancreatic photodynamic therapy and radiofrequency ablation have been evaluated in animal models[80-83], but are still awaiting clinical trials.

Conclusions

EUS with or without FNA is a major advance in the evaluation of individuals at high risk of developing pancreatic cancer and has been incorporated worldwide in the diagnostic and staging algorithm of patients with a suspected or already identified pancreatic solid lesion. Efforts are now directed towards the exploration of the therapeutic potential of EUS that will hopefully bring EUS to the next level moving it from a purely diagnostic to a mostly therapeutic procedure.

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