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ROUND TABLE

Endoscopic Ultrasonography: Impact in Diagnosis, Staging and Management of Pancreatic Tumors. An Overview

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Pancreatic Adenocarcinoma

The incidence of pancreatic adenocarcinoma (PA) is increasing and represents the fourth leading cause of cancer death in Western countries. The aggressive nature of the disease and late diagnosis make incidence rates almost identical to mortality rates.
This malignancy is currently difficult to treat, because only a few patients (5-20%) have resectable disease at the moment of diagnosis, with a 5-year survival rate of less than 25%.
In the last few years, much effort has been made to achieve an optimal standard algorithm for pancreatic cancer staging. Careful preoperative staging is essential in order to plan the best treatment, selecting patients who can benefit from surgery and those who will need palliative treatment.
The regional anatomy of the pancreas is complex to study and cytology samples are difficult to obtain because of its retroperitoneal location.
Endoscopic ultrasonography (EUS), a technique in which an ultrasonographic probe is placed at the tip of an oblique viewing endoscope, was introduced in the early '80s to overcome the limitations of trans-abdominal ultrasonographic imaging of the pancreas caused by intervening air, fat and bone.
The ability to position the echographic transducer in direct proximity to the pancreas by means of the stomach and duodenum, combined with the use of high-frequency probes, produces detailed high-resolution images of the pancreas which far surpass those of other imaging techniques such as computed tomography (CT) and magnetic resonance (MR).
Even if new radiological devices such as dual-phase helical-CT (h-CT) have been introduced, EUS still remains the best instrument for studying pancreatic cancer, with a T-stage accuracy of 78-94% and an N-accuracy of 64-82% [1, 2].
In a review comparing EUS versus h-CT in staging pancreatic cancer, Hunt and Faigel [3] found EUS to be more accurate in detecting (97% vs. 73%) and predicting tumor resectability (91% vs. 83%) and more sensitive in detecting vascular invasion (91% vs. 64%).
A recent retrospective study comparing multi-detector spiral CT to EUS and EUS-FNA has shown an overall accuracy of CT of 74% while EUS had an accuracy of 94% [4].
Maybe, with the introduction of a multi-detector CT scanner with a narrow collimator and faster scanning, the ability of CT to show the pancreas will improve, but more studies are needed to establish the real applications of multi-detector CT.
We have to remember that EUS is operator-dependent and several factors can influence its staging accuracy, such as the experience of the endosonographer, imaging artifacts, and

the knowledge of the results of previous imaging tests, while CT accuracy may be influenced by the cut-section thickness which can vary from 3.2 mm to 5 mm thick slices in different studies, so standardized protocols of images reconstruction are required.
A recent prospective study [5] comparing EUS, h-CT, magnetic resonance imaging (MRI) and angiography, found that h-CT showed the highest overall accuracy and negative predictive value for assessing tumor resectability, whereas EUS and angiography had the highest positive predictive value. EUS shows good accuracy for detecting vascular invasion of the portal vein system, while the visualization of the superior mesenteric artery may be more difficult.
The Authors conclude that, in those cases with a potentially resectable tumor, a sequential approach consisting of h-CT as an initial test and EUS as a confirmatory technique seems to be the most reliable and cost minimizing strategy.
Thus, despite the improvement in technology, no consensus about the best approach of staging pancreatic cancer and assessing tumor resectability has been reached. A reasonable conclusion from different studies and review may be that EUS and h-CT are complementary in preoperative staging: EUS is more accurate for local T-staging, in particular for tumors less than 3 cm, whereas h-CT is better for the evaluation of larger tumors and the detection of distant metastasis.

EUS-FNA

The development of a linear-array echoendoscope has expanded the utility of EUS by permitting operative procedures such as fine needle aspiration biopsy (FNA).
Many reports regarding the feasibility and safety of EUS-guided FNA have been published; after localizing the target lesion with endosonography, a needle device which allows cytological specimens, is advanced into the mass under real-time control.
So, EUS is able to identify lesions with a diameter of 3 mm and can guide the biopsy of the lesion, improving the sensitivity and specificity of EUS alone to 80% and 100% respectively, with an adequate cellularity of the specimen in 75-95% of cases [6].
The complication rate, including mild pancreatitis and self-limiting bleeding, is negligible and the risk of tumoral seeding is low; in fact, EUS-FNA is performed through the retroperitoneum.
EUS-FNA is a useful and safe method for the investigation of pancreatic masses, with a high feasibility rate even when lesions are small. However, EUS-FNA is technically challenging and requires long training in centers where the volume of EUS procedures is high [7].
A debated issue is the presence of the cytopathologist in the endoscopic room to evaluate the adequacy of the specimen. There are no data available which assess any significant beneficial effect either on specimen adequacy or on FNA sensitivity and accuracy as a result of the cytopathologist being present during EUS-FNA procedures. For this reason, US groups usually prefer to have a cytopathologist being present on site while European experts send the smears directly for the final diagnosis.
The theory sustaining the presence of a cytopathologist is derived from the idea that aspirated material has to be rapidly smeared and stained to be directly examined by optical microscope; this could minimize the number of FNA passages and eventually improve the accuracy of the procedure, reducing the number of inadequate specimens.
In addition, tissue samples from metastatic lymph nodes may increase the overall diagnostic accuracy of EUS [6].
Selecting who should undergo EUS-FNA is a controversial issue [8]. EUS-FNA should be performed to diagnose patients with unresectable cancer in order to program adjuvant therapy (chemotherapy or radiotherapy). Another important point is the exclusion of other types of tumors such as lymphoma, neuroendocrine tumors, metastasis, or benign lesions such as groove pancreatitis.

Recently, there has been increased attention paid to the economic impact of different procedures in medical decision making.
EUS-FNA may change the management of a patient with pancreatic adenocarcinoma, and the avoidance of surgery by EUS-FNA results in a substantial cost saving.
EUS-FNA can be used for identifying patients with suspected pancreatic cancer who do not actually have cancer, thereby avoiding surgery.
In a recent retrospective study, Agarwal *et al*. [4] showed that the absence of focal mass lesion on EUS excluded pancreatic cancer with a negative predictive value (NPV) of 100%, irrespective of clinical presentation.
On the other hand, in patients showing a visible mass on EUS and a stent in the common bile duct, the NPV of EUS-FNA was only 38% due to the inability to identify tumoral cells in a background of reactive cellular atypia secondary to the stent. So, patients with a strong clinical suspicion of cancer must be followed and EUS-FNA has to be repeated after about 3 months. In the same study, the Authors show that by excluding all 9 patients with stent placement, the EUS-FNA NPV rose up to 89%. These data are in favor of always performing EUS-FNA before either a diagnostic or a therapeutic palliative ERCP procedure.
Moreover, a benign tissue diagnosis does not exclude malignancy; a marked desmoplastic reaction is often present in pancreatic adenocarcinoma, so tissue sampling can be difficult and may give a false negative result.

Cystic Tumors of the Pancreas

The improvement of imaging techniques has increased the detection of pancreatic cystic lesions in patients who are often asymptomatic.
Pancreatic cystic lesions encompass a wide variety of pathologic entities; it is important to distinguish neoplastic from benign lesions. The clinical aspect may guide the diagnosis; in a patient without a previous history of acute pancreatitis, a cystic lesion is always suspected and must be investigated. On the other hand, a cystic neoplasm may cause acute recurrent pancreatitis.
EUS provides detailed information regarding the morphology of cystic lesions, thanks to its high resolution and its ability to guide FNA of fluid and cells from the internal wall.
Serous cystadenoma is typically microcystic, with multiple "honeycomb-like" compartments and thin wall; these lesions usually have no malignant potential.
Mucinous cystic neoplasms are typically macrocystic and they can have a malignant evolution.
The presence of mural nodules or thickening of the wall suggests malignancy.
Intraductal papillary mucinous tumors (IPMTs) of the pancreas are characterized by dilatation of the main pancreatic duct (MPD) and/or cystic dilatations of the branch ducts, with a large production of mucin.
Viscous mucin and protein plugs may cause intermittent obstruction of the pancreatic duct and, consequently, acute recurrent pancreatitis. Tumor progression leads to the development of mural nodules and masses which can be limited to the duct wall or can infiltrate pancreatic parenchyma. While an IPMT at an early stage has a good prognosis, invasive carcinoma has identical life expectancy as compared to ductal adenocarcinoma. For this reason, an early diagnosis is essential in this setting; furthermore, it is often difficult to distinguish an IPMT from chronic pancreatitis solely on the basis of a diffusely dilated MPD. A patulous papilla, visible mucus and mural nodules of the MPD help in orienting the diagnosis.
EUS-guided FNA can be helpful in patients in whom the diagnosis still remain uncertain. By analyzing different studies on cystic lesions of the pancreas, Brugge [9] concludes that imaging alone is not sufficient to provide a diagnosis; cystic fluid analysis is an important diagnostic tool and the utility of neoplastic markers such as CA-19.9 and CA-125 is under investigation.
In a study regarding the role of cystic fluid obtained by CT and abdominal US-guidance, Hammel *et al*. [10] reported a sensitivity of

75% and a specificity of 90% for CA-19.9 levels greater than 50,000 U/mL in differentiating mucinous tumors from other cystic lesions.

Neuroendocrine Tumors

The majority of neuroendocrine tumors (NET) can be primarily diagnosed on the basis of clinical presentation and measurement of secretory products. However, NET may be nonfunctional in 15-30% of cases.
Precise localization of the tumor is important for the surgical approach, but these tumors are often small and difficult to detect.
EUS can correctly image small NET, even those in the range of 5 mm seen in multiple endocrine neoplasia (MEN) [11].
A multicenter study [12] verified the ability of EUS to detect pancreatic NET in patients where transabdominal ultrasonography and CT were negative, but the clinical presentation was oriented to a neuroendocrine disease.
EUS localized 32 of 39 tumors, showing a sensitivity of 82%, and it was more sensitive than angiography (82% vs. 27%).
Moreover, EUS showed a good correlation with the pathologic findings as far as the dimensions of the tumor were concerned.
There are non specific endosonographic characteristics and the differentiation between other neoplastic forms or benign findings and NET may be difficult. There seem to be no ultrasonographic differences between functional and non-functional NET.
In most cases, these tumors are homogeneous, relatively hypoechoic, with regular margins.
They can be echo-rich, showing a sonographic pattern similar to that of peripancreatic lymph nodes; in these cases, a differential diagnosis can be difficult and a misdiagnosis may lead erroneously to unnecessary surgery.
The ability to sample these lesions by EUS-FNA improves the diagnostic accuracy of EUS and avoids false positive results.
The evaluation of the vascular pattern with sonographic microbubble contrast agents may be helpful in the diagnosis; because of the rich vascularization of NET, the tumor shows bright echoes a few seconds after the endovascular injection of the contrast, with a spreading and homogeneous vascular image [13]. In MEN, the primary role of EUS is preoperative localization of the tumor in order to plan the best surgical treatment.
It must also be determined whether the lesion is isolated or whether multiple lesions are present.
Another important role of EUS in the preoperative setting is its ability to tattoo lesions by fine-needle injection using India ink [14]; this procedure makes the surgical steps easier, obviating the need to localize the tumor by palpation.

Therapeutic EUS

EUS is emerging not only as an imaging technique, but also as a modality for guiding the delivery of new therapies for pancreatic cancer, such as immunotherapy and radiofrequency, and can be helpful in the palliation of pancreatic cancer.
Celiac plexus neurolysis (CPN) is an effective technique for the treatment of pancreatic cancer pain.
Up to the present, percutaneous techniques have been used under X-ray or CT-guided, with serious side effects such as paraplegia and spleen injury.
EUS-guided neurolysis (EUS-CPN) is simple to perform and has less side effects thanks to its endoabdominal approach. The Celiac ganglion is located near the origin of the celiac artery from the aorta and it is easily visualized at EUS; a needle is positioned inside the ganglia, and chemical neurolysis is carried out with bupivacaina and absolute ethanol.
Data from the literature report a significant reduction of pain in 85-90% of patients, with a reduction in analgesic drug use.
In a study on 45 patients with pancreatic cancer or malignant celiac nodes, Wiersema [15] reported that after the EUS-CPN, 52% of

patients no longer needed to increase their doses of morphine and 30% decreased their doses of oral morphine.
Among the palliative application of operative EUS, biliary and pancreatic duct drainage have been described [16].
A fistulous track through the bowel wall is created under ES guidance, followed by transmural stent placement through the accessory channel of the echoendoscope, or via a duodenoscope after a guidewire placement.
Advances in understanding the biological basis of tumors have allowed the identification of many alterations in oncogenes and tumor suppressor genes.
In gene therapy, vectors, such as virus or liposome, are used to transfer genes in the DNA of neoplastic cells.
After the genetic transfer, the expression of the gene product may alter the biological behavior of the tumor.
EUS can guide the injection of the viral system and chemotherapeutic agents into the tumor.
The immunologic therapy of tumors is based on the activation of host immune effector cells (cytotoxic T-lymphocytes) by cytokines.
Cytokines may be installed directly within the tumor or can be produced by a mixed lymphocyte reaction generated by the incubation of the allogenic donor peripheral blood mononuclear cells.
Chang *et al*. [17] reported the first application of EUS to the immunologic therapy of pancreatic cancer; using a 22 G needle, a cytoimplant of mixed lymphocytes was injected into unresectable pancreatic cancer in 8 patients. Tumor regression occurred in 3 of 8 patients, no change in 3 and increased growth in 2 of the 8 patients.
EUS-guided radiofrequency (RF) ablation has been studied in normal porcine pancreases [18].
A modified needle electrode is inserted into the tissue under real-time imaging guidance and RF is applied for a previously decided upon amount of time.
Parameters, such as application time and electrode tip temperature, impedance and wattage, have to be standardized in human pancreatic cancer to optimize the diameter of coagulation necrosis.
In Goldberg's report [18], the correlation between EUS or CT and the pathologic findings was excellent for lesions larger than 5 cm.
In the pancreas, the main fields of application of EUS-RF would be palliation of large unresectable adenocarcinomas, multiple metastases and small endocrine tumors.
EUS-RF is a promising therapeutic device which requires future development and clinical trials.
Tumor ablation techniques, such as RF, also provide the immune system with an antigen source which can induce antitumor immunity.
Many other EUS-guided treatment modalities have been tested in preliminary animal studies, checking their feasibility and safety.
This field of clinical application of EUS has greatly increased in the past few years, giving promising results for a wider clinical application of this technique.

Conclusions

In conclusion, EUS is an accurate technique for staging pancreatic malignancies.
The development of the linear-array echoendoscope has expanded the utility of EUS by enabling operative procedures such as FNA biopsy and celiac plexus neurolysis.
Other therapeutic applications of EUS, such as radiofrequency and injection therapy of genetic or immunologic agents, have to be confirmed by large and multicenter trials in order to define the real clinical utility of these new techniques.

Keywords Biopsy, Fine-Needle; Catheter Ablation; Celiac Plexus; Diagnosis; Diagnostic Imaging; Endosonography; Neoplasm Staging; Pancreatic Neoplasms; Radiography, Interventional; Therapeutics

Abbreviations CPN: celiac plexus neurolysis; h-CT: helical computed tomography; IPMT: intraductal papillary

mucinous tumor; MEN: multiple endocrine neoplasia; MPD: main pancreatic duct; NET: neuroendocrine tumors; NPV: negative predictive value; PA: pancreatic adenocarcinoma; RF: radiofrequency

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References

1. Gress FG, Hawes RH, Savides TJ, Ikenberry SO, Cummings O, Kopecky K, et al. Role of EUS in preoperative staging of pancreatic cancer: a large single-center experience. Gastrointest Endosc 1999; 50:786-91. [PMID 10570337]

2. Yasuda K, Mukai H, Nakajima M, Kawai K. Staging of pancreatic carcinoma by endoscopic ultrasonography. Endoscopy 1993; 25:151-5. [PMID 8491131]

3. Hunt GC, Faigel DO. Assessment of EUS for diagnosing, staging, and determining resectability of pancreatic cancer: a review. Gastrointest Endosc 2002; 55:232-7. [PMID 11818928]

4. Agarwal B, Abu-Hamda E, Molke KL, Correa AM, Ho L. Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the diagnosis of pancreatic cancer. Am J Gastroenterol 2004; 99 (5):844-50. [PMID 15128348]

5. Soriano A, Castells A, Ayuso C, Ayuso JR, de Caralt MT, Gines MA, et al. Preoperative staging and tumor resectability assessment of pancreatic cancer: prospective study comparing endoscopic ultrasonography, helical computed tomography, magnetic resonance imaging, and angiography. Am J Gastroenterol 2004; :492-501. [PMID 15056091]

6. Chang KJ, Nguyen P, Erickson RA, Durbin TE, Katz KD. The clinical utility of endoscopic ultrasound-guided fine-needle aspiration in the diagnosis and staging of pancreatic carcinoma. Gastrointest Endosc 1997; 45:387-93. [PMID 9165320]

7. Mertz H, Gautam S. The learning curve for EUS-guided FNA of pancreatic cancer. Gastrointest Endosc 2004; 59:33-7. [PMID 14722544]

8. Varadarajulu S, Wallace MB. Applications of Endoscopic Ultrasonography in Pancreatic Cancer. Cancer Control 2004; 11:15-22. [PMID 14749619]

9. Brugge WR. Evaluation of pancreatic cystic lesions with EUS. Gastrointest Endosc 2004; 59:698-707. [PMID 15114319]

10. Hammel P, Levy P, Voitot H, Levy M, Vilgrain V, Zins M, et al. Preoperative cyst fluid analysis is useful for the differential diagnosis of cystic lesions of the pancreas. Gastroenterology 1995; 108:1230-5. [PMID 7535275]

11. Lees WR. The pancreas: differential diagnosis and pancreatitis. In: Lightdale CJ, ed. Endoscopic Ultrasonography. Gastrointestinal Endoscopy Clinics of North America. Philadelphia, PA, USA: WB Saunders, 1992:657-72.

12. Rosch T, Lightdale CJ, Botet JF, Boyce GA, Sivak MV Jr, Yasuda K, et al. Localization of pancreatic endocrine tumors by endoscopic ultrasonography. N Engl J Med 1992; 326:1721-26. [PMID 1317506]

13. Nagase M, Furuse J, Ishii H, Yoshino M. Evaluation of contrast enhancement patterns in pancreatic tumors by coded harmonic sonographic imaging with a microbubble contrast agent. J Ultrasound Med 2003; 22:789-95. [PMID 12901406]

14. Gress FG, Barawi M, Kim D, Grendell JH. Preoperative localization of a neuroendocrine tumor of the pancreas with EUS-guided fine needle tattooing. Gastrointest Endosc 2002; 55:594-7. [PMID 11923783]

15. Wiersema MJ. Endosonographic guided celiac plexus neurolysis. In:B hutani M, ed. Interventional Endoscopic Ultrasonography. Chapter 15. Amsterdam, The Netherlands: Harwood Academic Publisher, 1999:117-23.

16. Giovannini M, Moutardier V, Pesenti C, Bories E, Lelong B, Delpero JR. Endoscopic ultrasound-guided bilioduodenal anastomosis: a new technique for biliary drainage. Endoscopy 2001; 33:898-900. [PMID 11571690]

17. Chang KJ, Nguyen PT, Thompson JA, Kurosaki TT, Casey LR, Leung EC, Granger GA. Phase I clinical trial of allogeneic mixed lymphocyte culture (cytoimplant) delivered by endoscopic ultrasound-guided fine-needle injection in patients with advanced pancreatic carcinoma. Cancer 2000; 88:1325-35. [PMID 10717613]

18. Goldberg SN, Mallery S, Gazelle GS, Brugge WR. EUS-guided radiofrequency ablation in the pancreas: results in a porcine model. Gastrointest Endosc 1999; 50:392-401. [PMID 10462663]