Endoscopic Ultrasound in Pancreatic adenocarcinoma

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INTRODUCTION

Endoscopic ultrasound involves placing small, high-frequency ultrasound transducers on the tips of fiberoptic or video-endoscopes (1). A variety of transducer designs are used, but the two main varieties are a 270 to 360 degree rotating or non-rotating radial transducer and non-moving, convex longitudinal array transducers. By placing the transducer within the gut lumen, EUS overcomes the two major technologic problems for pancreatic imaging by transcutaneous ultrasound; obscuring overlying gas filled bowel and the necessity to use low frequency and therefore low resolution ultrasound to penetrate to the depth of the pancreas. Using ultrasonic imaging through the stomach and duodenum, the whole of the pancreas can be brought to within a few centimeters of a 5 to 20 MHz ultrasound transducer providing resolutions in the sub-millimeter range. Like transcutaneous ultrasound, EUS is also a "live" procedure which offers the advantage of being an interactive examination of the pancreas and surrounding tissues where subtle abnormalities can be imaged by the endoscopist from different perspectives, at different frequencies and ultimately cytologically sampled if necessary. In addition, as clinicians, endosonographers usually have the advantage of bringing much more clinical information to the procedure than the radiologist typically has in performing an abdominal CT or MRI. Furthermore, EUS now allows combining the biopsy (EUS-guided fine needle aspiration) and therapeutic capabilities of EUS (eg. tumor injection therapy or celiac neurolysis) with the initial diagnostic procedure. Finally, when EUS is combined with its sister endoscopic procedure, therapeutic ERCP, it results in a powerfully efficient combination of diagnostic, staging and therapeutic techniques that are very difficult to match with any other set of procedures.

EUS IN THE DIAGNOSIS OF PANCREATIC NEOPLASMS

The utility of EUS in visualizing pancreatic neoplasms was apparent soon after its clinical introduction in the mid-1980s in Japan (2) and Germany (3). Since then, there have been many series demonstrating the diagnostic superiority of EUS to CT and MRI in pancreatic neoplasms (4-12). Even for lesions less than 3 cm, EUS diagnosis rates have been consistently in the range of 95-100%. Another powerful aspect of EUS is that its specificity for ruling out pancreatic neoplasia is nearly 100% as long as the patient does not have underlying chronic pancreatitis (13). Although, ERCP is not generally used as a diagnostic technique anymore for pancreatic neoplasms, EUS is also superior to ERCP in the diagnosis of small pancreatic neoplasms (14) although they have similar sensitivities in detecting pancreatic head lesions (15).

With the advent of multidetector, high speed spiral CT, the advantage of EUS over CT in the diagnosis of pancreatic cancer is now narrowing. Series comparing state-of-the-art helical CT with high quality endoscopic ultrasound are still few (13). Spiral CT have overall detection rates above 90%; however, EUS still seems to be superior at detecting small (<2 to 3 cm) pancreatic carcinomas (8). There are a number of problems confounding series comparing EUS and CT. Rarely do institutions have similar levels of expertise in both procedures. In addition, in almost all series, the endosonographers are not blinded to the results of prior imaging or clinical information whereas radiologists rarely have access to the EUS information since it is usually performed after CT (17). It has been shown that clinical assessment has similar accuracy to imaging procedures in patients with suspected pancreatic cancer (18). Patient groups may also not be the same when comparing studies of the two procedures. In endosonographic series, patients presenting with metastatic liver disease (about one third of patients) or large, unresectable tumors are generally not included because there is less indication for EUS in these patients. However, these patients are often included in series assessing the diagnostic accuracy of CT (19,20). This inclusion can increase the overall diagnostic sensitivity of CT in pancreatic cancer detection by 5-15% compared to series focused only on those patients undergoing both EUS and CT (21).

There is little comparative data for EUS versus MRI in pancreatic cancer (22). Since series comparing CT to MRI for pancreatic masses show CT to currently have a slight advantage over MRI, it would be reasonable to presume EUS is superior to MRI at least for small masses. MRI has the additional advantage of being able to show

ductal anatomy using Magnetic Resonance Cholangiopancreatography (MRCP).

When patients have underlying chronic pancreatitis, all diagnostic modalities (CT, MRI, EUS, ERCP, and PET) are poor at detecting a superimposed pancreatic malignancy. EUS rarely misses pancreatic neoplasm when the pancreas is normal; however, this does not hold when chronic pancreatitis is present (10,11,23-26). When faced with this kind of patient, one has to use multiple diagnostic modalities, fine needle aspiration (27), tumor markers (28), close clinical follow-up and occasionally empiric resection (29) to find underlying pancreatic cancers in chronic pancreatitis. Molecular diagnostic techniques on FNA specimens may hold some promise in this area (30,31).

Despite the superior diagnostic capabilities of EUS, the frequency of its use in patients with suspected pancreatic neoplasms in the United States is still disappointingly low (4-9). This is a multifactorial problem. Initially this was primarily secondary to a lack of expert endosonographers at many institutions. However, in the last few years, high quality EUS has become available at most major institutions caring for significant volumes of cancer patients. Education of primary care practitioners, oncologists, radiologists and surgeons as to the capabilities of EUS and its appropriate role in patients with suspected pancreatic cancer is a current priority.

EUS GUIDED FINE NEEDLE ASPIRATION:

Technique:

The first EUS-FNA of a pancreatic cancer was reported in 1994 (32) and there have been numerous series since then (4,11,24,26,33-44). EUS-FNA techniques has been described extensively elsewhere (26,38,41,45-47) and involve passing an 18 to 25 (usually 22) gauge stainless steel, echogenic aspiration needle through the biopsy port of an echoendoscope under real-time guidance into an endosonographically visualized pancreatic mass, lymph node, liver metastasis or fluid collection. The needle is moved back and forth through the lesion with varying degrees of suction applied to it and the sample is deposited on a cytology slide(s) for immediate staining and cytopathologic examination.

Yield of EUS-guided fine needle aspiration:

EUS-FNA can provide a cytologic diagnosis in 80-95% of pancreatic malignancies (4,11,24,26,33-46) even in patients with previously negative attempts at tissue diagnosis (46). As with fine needle aspiration techniques in other organs (49), the diagnostic yield of EUS-FNA is dependent on technique (56), especially the training of the endosonographer (50) and the active involvement of a cytopathologist (51). Having a cytopathologist available in the room or close enough to give immediate feedback on the adequacy and preliminary cytologic diagnosis of an aspirate is a common clinical practice in endosonography centers in the United States (24,26,33,34,37-40,51,52). Cytopathologic feedback during the EUS-FNA probably increases the yield of a definitive cytologic diagnosis by about a 10% (26,36,40,51). As long as the lesion is visible, similar definitive cytologic yields are possible with transcutaneous ultrasound or CT-guided FNA of pancreatic masses, especially if a cytopathologist participates in the procedure. However, since EUS still seems superior for small lesions, the net overall yield of a definitive cytologic diagnosis will be higher with EUS-FNA than with CT guided techniques. An additional advantage of EUS-FNA is that being a real-time procedure, when an abnormality is found in the pancreas, one can proceed directly on to FNA at that time rather than scheduling a separate procedure as with CT. This may just be a matter of patient inconvenience in an ambulatory setting, but add additional days of hospitalization for inpatients. False positive EUS-FNA cytologies of the pancreas do occur rarely mainly because of interpretation errors (53).

It takes an average of three to four passes to provide a definitive cytologic diagnosis of a pancreatic malignancy (26,36,48,50,54). However, malignant lymph nodes and liver metastases generally require only one or two EUS-FNA passes for a definitive diagnosis (26). There are no clinical or endosonographic features that predict when a patient's lesion may take more FNA passes to make a diagnosis. The major determinant of FNA pass number is the differentiation of the tumor (26,55) with some masses taking up to ten or more passes or more to make a diagnosis to make a definitive diagnosis in well-differentiated tumors (56). If a cytopathologist is not immediately available, generally five to six passes into the lesion are recommended, realizing that this approach may still result in a non-diagnostic specimen 15-20% of the time (26,45). Larger needles and "Tru-cut" designs have been used obtain actual tissue biopsies (57-59); however, these larger needles have failed to significantly improve diagnostic accuracy (59,60) except perhaps in the case of unusual histology (46). Using cell surface markers also makes it possible to make a cytologic characterization of pancreatic lymphomas as long as enough cells are obtained (61,62). EUS-FNA of cystic tumors of the pancreas present special challenges, as cytology is often non-diagnostic and must be supplemented by chemical analysis of fluid for tumor markers such as CEA or CA19-9 and amylase (63-66).

Whether a cytologic diagnosis is necessary in all patients with a pancreatic mass seen by EUS, CT, MRI or ERCP is a topic of significant debate (4-9,68) with some physicians (69,70) feeling that attempts at obtaining a tissue diagnosis in potentially resectable pancreatic masses does not change management and therefore is of little use.

Other physicians (21,71), feel there are numerous rationales for attempting to make a preoperative tissue diagnosis in all of these patients.

Complications of EUS-guided fine needle aspiration:

The overall complication rate of EUS-FNA appears to be about 0.5-3% (4,11,24,33-48,52,54), similar to that reported with CT or ultrasound-guided FNA or biopsy (72-74). The major complications reported with EUS-FNA (47) are pancreatitis (75) and bleeding (45,76) with rare deaths having been reported from cholangitis associated with biopsy of a liver metastasis in a patient with poorly drained biliary obstruction from a pancreatic cancer (77) and uncontrolled bleeding from a pseudoaneurism (37). Bile peritonitis (78) and acute portal vein thrombosis (79) have also been reported with pancreatic EUS-FNA. As of yet, there has been only one published case of tumor seeding with EUS-FNA (80). This has also been reported with CT-guided biopsy or US-guided biopsy (81). In addition, a recent study reported peritoneal recurrence significantly higher in patients having had CT or US guided pancreatic biopsy than with EUS-FNA (82). Clinically significant bacteremia following EUS-FNA is rare (83); however, EUS-FNA of cystic lesions may have a higher risk complication due to the risk of infecting the cyst with luminal bacteria (84). Because of this intravenous antibiotics with oral antibiotics are routinely used for a few days for EUS-FNA of pancreatic cystic lesions (4-9,62,66). In addition, we use transluminal povidine iodine solution to minimize bacterial contamination during EUS-FNA of cystic pancreatic lesions (85).

EUS FOR PANCREATIC CANCER STAGING:

Overview:

The primary impact of endosonography on the management of pancreatic cancer is in detection and cytologic diagnosis. Early in its introduction there was considerable excitement for EUS as an accurate staging tool in these patients (4-9,86-89). However, more recent studies (17,90) have tempered the initial enthusiasm for EUS as a staging procedure. In addition, the progressive technologic advances in cross-sectional imaging have largely overshadowed many of the perceived advantages of EUS staging. Despite this, EUS does offer some potentially unique staging information in patients with pancreatic cancer primarily in the detection of occult metastatic disease and evaluation of splanchnic venous involvement by tumor near the portal vein-superior mesenteric vein-splenic vein confluence.

There are a number of staging systems for pancreatic cancer, but the most frequently used in the United States is the recently modified (91), sixth edition of the American Joint Committee on Cancer (AJCC) TNM-based staging system. To address the evolution of surgical approaches to pancreatic cancer (92-94), the most recent modification of this staging system has made involvement of the splanchnic venous system less relevant to advanced staging. How this modification will affect the accuracy and utility of EUS in overall staging is unclear.

T- staging: The accuracy of EUS for T staging of pancreatic cancer is generally reported to be about 80-85% at all stages (50,86-89,95-97) although other studies put this accuracy at only 70% (98). This is similar to CT and MRI; however, this degree of accuracy is dependent on the experience of the endosonographer (86) and the fact that clinical data is accessible to the endosonographer at the time of the procedure (17,90). Since the small (< 2cm) T1 lesions are difficult to even image by other cross-sectional techniques, EUS by default would be expected to have an advantage in T staging these lesions. Patients presenting with jaundice generally have bile duct compression by encasement or direct invasion. The region of the ampulla and pancreatic portion of the common bile duct is very easily seen by EUS, although distinguishing between encasement (T1 or T2) and invasion of the bile duct (T3) can be difficult. However, this distinction is largely irrelevant to management. Duodenal wall invasion also is a T3 criteria and this is usually easily visualized both endoscopically and endosonographically at EUS.

Many major oncologic centers no longer consider splanchnic venous involvement as an absolute contraindication to resection (93,94,99) since these patients appear to have the same post-operative survival rates as successful resections without venous involvement in some institutions. To reflect this trend, the new AJCC staging criteria changed splanchnic venous involvement from a T4 stage to a T3 stage lesion (92). However, a number of surgeons consider significant splanchnic involvement a relative or absolute contraindication to an attempt at curative resection because of poor survival outcomes (96,100,101). Thus, depending on the local institution, accurate information regarding splanchnic involvement with tumor may still significantly affect there management although it may not affect their staging.

The interface between the portal and superior mesenteric vein and a pancreatic head tumor is usually well visualized by both radial and linear endosonography. The overall accuracy of various endosonographic criteria for invasion have been assessed in detail (102) and include an irregular venous wall (87%), loss of acoustic interface

(78%), proximity of mass to the portal vein (73%), and absolute tumor size (39%). Using these criteria, EUS was more accurate (78%) than angiography (60%) at assessing portal vein involvement (102). Another recent large study reported an overall accuracy of 93% for vascular invasion (86) but also noted a considerably poorer accuracy for endosonographers having staged less than one hundred tumors. The presence of collateral formation as evidenced by the presence of peripancreatic head or periportal venous collaterals invariably indicates extensive portal vein involvement with tumor. The presence of gastric varices can indicate portal or splenic vein obstruction by tumor. As discussed in the previous chapter, dual phase spiral CT and gadolinium contrasted MRI show similar or better accuracies at assessing major venous invasion (102,103).

Some anatomical regions relevant to T staging are difficult to assess by EUS. The distal superior mesenteric vein and especially the superior mesenteric artery are often too far from the duodenal lumen to visualize adequately by EUS. Since major arterial (superior mesenteric, hepatic or celiac) invasion is a T4 stage criteria, the ability to consistently assess these vessels is a significant advantage of CT or MRI over EUS. EUS also has trouble assessing colonic invasion because most of this organ is out of range of the echoendoscope or visualization is limited because ultrasound cannot penetrate the air in the colonic lumen. Peritumor edema or pancreatitis can result in overstaging by EUS (86); however, this problem is not unique to ultrasound. The above T staging criteria have not been validated for non-adenocarcinomas. Thus, my own practice is to be very conservative in calling portal vein invasion with neuroendocrine tumors.

In summary, T staging of pancreatic cancer by EUS is correct about 80-85% of the time (104), similar to CT and MRI. It has unique staging advantages in small tumors and lesions of the pancreatic head but has the disadvantage of being highly operator dependent and unable to see deep areas of mesenteric root and pancreatico-colonic interface. EUS provides T stage information that is often complimentary to CT, MRI, and angiography but it cannot usually replace these procedures.

N Staging: EUS can detect very small (<0.5 cm) lymph nodes in the regions around the celiac axis, porta hepatis and pancreatic head, neck, body and tail. However, nodes at the root of the small bowel mesentery and subduodenal periaortic regions are often poorly seen. Just visualizing a lymph node by EUS does not make it malignant. For example, benign nodes around the porta-hepatis are a common finding, especially in the setting of previous inflammatory processes such as cholecystitis or pancreatitis. Endosonographic criteria for malignant adenopathy have been established (105,106) and include lymph node size greater than 1 cm, echolucency, homogeneity, round shape, and sharp edges. However, even if all these criteria are present, they have an overall accuracy of only about 80 to 90%. Using computerized analysis of nodal appearance has not improved this accuracy (107).

Although uniformly superior to CT or MRI, there have been multiple series showing the N stage accuracy of EUS in pancreatic cancer to be disappointingly low at 65-70% (86-89). This poor result is due to the lack of specificity of endosonographic criteria for malignant adenopathy, undetectable micrometastatic nodal disease and the inability to visualize some areas of metastatic nodes, especially the small bowel mesenteric root. The addition of EUS-FNA has greatly enhanced the specificity of N staging by EUS for pancreatic and other cancers (88,106) even in nodes as small as five millimeters.

Pancreatic surgeons debate the relevance of cytologically documented nodal disease (99). Some argue that cytologically documented nodal metastases is a contraindication to resection because of the poor survivals in such patients (108,109). However, others argue that although survivals are poorer with nodal metastases, it is still better than with no resection at all (110,111). All agree that nodal disease remote to the primary tumor such as the mediastinum (112) should mitigate against resection. Thus, the significance of EUS-FNA documentation of nodal spread will depend on the institutional approach to such patients. If malignant adenopathy is considered a contraindication to resection, EUS and EUS-FNA can result in significant cost savings when used for pancreatic cancer assessment (40). In our own series of EUS-FNA for pancreatic cancer, approximately 8% of patients undergoing diagnostic and staging EUS were found to have nodal spread by EUS-FNA (26). The relevance of EUS and EUS-FNA nodal staging may be significantly increased by the advent of molecular diagnosis of occult malignancy within nodes that are cytologically negative by EUS-FNA (113,114). In addition, as effective neoadjuvant regimens are developed for locally advanced disease, EUS-FNA demonstration of nodal metastases may have even more impact.

M Staging: EUS is limited in its ability to assess metastatic disease to only those regions that are accessible to EUS-FNA. About 80% of the liver is visible to EUS with the far right lobe and high dome of the liver usually being inaccessible to endosonographic imaging. However, only 4-6 cm of the left lobe and periduodenal right lobe are

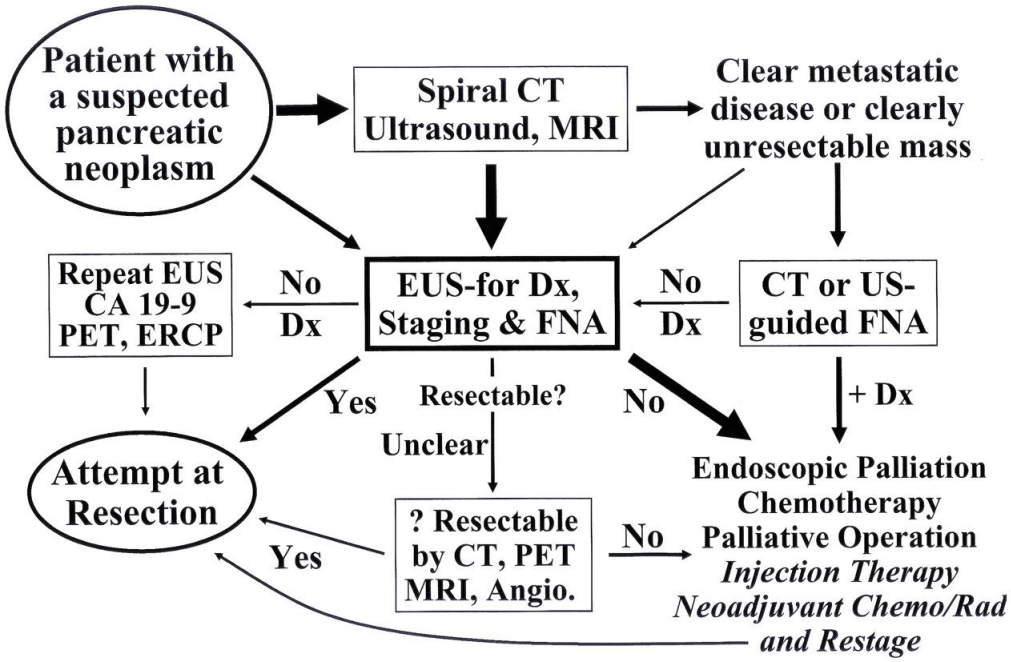
amenable to EUS-FNA. Liver metastases as small as 5 mm can be seen by EUS and sampled by EUS-FNA (26,35,77,88,115-117). If cytologically positive, these findings would obviate any attempt at curative resection and thus dramatically change the approach to managing that patient. Likewise, small amounts of peritoneal fluid can be easily aspirated by EUS-FNA (116,117) and if found to contain malignant cells represent metastatic, inoperable disease. However, only about 10% of peritoneal aspirates will have a positive cytology (117). Because ultrasound does not penetrate into air, the lungs cannot be examined for metastatic disease. Small right pleural effusions are, however, easily seen and tapped by EUS-FNA. Again, in our series (26), we found occult metastatic disease in about 7% of our patients, primarily small liver metastases.

Summary:

EUS is probably now inferior to CT and MRI in overall T staging accuracy because of its inability to visualize the superior mesenteric artery. EUS may still have an advantage over these procedures in detecting occult malignant adenopathy. It can only be considered a supplementary procedure for M staging. If it will obviate operative intervention, cytologically documenting occult remote nodal disease or metastatic disease can dramatically and cost-effectively (38,118,119) affect the future management of the patient with pancreatic cancer. If EUS is used purely as a staging procedure, it has to be considered complimentary, not superior, to findings on CT and MRI. However, if EUS is being used primarily for its diagnostic, biopsy and/or therapeutic capabilities, then the staging information obtained is an added bonus of the procedure.

THERAPEUTIC EUS IN PANCREATIC CANCER:

EUS also has therapeutic applications in pancreatic cancer. Celiac neurolysis can be performed through the posterior gastric wall under direct endosonographic guidance using bupivacaine and absolute alcohol injected on either side of the celiac artery (120,121). This is a relatively simple approach to the procedure compared to the radiologic transabdominal or anesthesiologic transthoracic approaches to celiac neurolysis. EUS celiac neurolysis takes about 10 minutes and can be done under the same sedation after a diagnostic EUS or EUS-FNA. EUS-guided fine needle injection (EUS-FNI) is now also being used experimentally for tumor injection therapy using activated



lymphocytes (122) and viral gene vectors (123,124). Finally, now that therapeutic channel echoendoscopes are available, transduodenal or transgastric biliary (125-128) and pancreatic (129) stent placement is possible by EUS in the patient when ERCP has failed.

SCREENING FOR PANCREATIC CANCER IN HIGH RISK PATIENTS

5-10% of all pancreatic cancer appears to be familial (130). There are rare kindreds where the risk of developing pancreatic cancer is very high (131). How to screen for presumed precursors (132) of neoplastic transformation, pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasms (IPMNs) in these families is unclear. Both imaging, cytologic, and molecular techniques are being used (131,133) with EUS and EUS-FNA usually being the cornerstone of this kind of surveillance. Decision analysis studies have suggested that this type of survey can be cost-effective compared to other accepted forms of cancer screening (134).

THE ROLE OF ENDOSCOPIC ULTRASOUND IN PANCREATIC CANCER:

Where high quality EUS and EUS-FNA is readily available, EUS can play a central and early role in the evaluation of the patient with suspected pancreatic cancer (4-9,13,14,97,135-137). Its superiority as a diagnostic tool and very high high specificity make it a ideal definitive test for patients suspected to have any pancreatic abnormality by CT, transcutaneous US or clinical evaluation. Since cytologic diagnosis and staging information can also be obtained at the same time, EUS with EUS-FNA usually provides most, if not all, of the data needed to go on to definitive stage-specific therapy. State-of-the-art staging CT or MRI can be used before or after EUS to compliment the EUS staging information provided, especially in equivocal operative cases and to rule out occult liver metastases. In the rare situation where CT, EUS and EUS-FNA have failed to provide a definitive diagnosis, other modalities such as CA 19-9 (138), ERCP, repeat EUS in a month or two, PET or laparoscopy can be used depending on the clinical situation. Our own approach to incorporating EUS and EUS-FNA into the management of pancreatic cancer is summarized in the above figure. Using EUS as an imaging procedure of last resort minimizes the clinical impact and cost effectiveness of this powerful procedure by placing it at the end of the evaluation instead of near the beginning.

REFERENCES:

1. Dancygier H, Lightdale CJ, Stevens PD. Endoscopic ultrasonography of the upper gastrointestinal tract and colon. In: Dancygier H, Lightdale CJ, editors. Endosonography in gastroenterology. Principles, techniques, findings. Stuttgart:Thieme, 1999:13-22.
2. Yasuda K, Mukai H, Fujimoto S, et al. The diagnosis of pancreatic cancer by endoscopic ultrasonography. Gastrointest Endosc 1988;34:1-8
3. Rösch T, Lorenz R, Braig C, et al. Endoscopic ultrasound in pancreatic tumor diagnosis. Gastrointest Endosc 1991;37:347-52.
4. Chang KJ. Endoscopic ultrasound-guided fine needle aspiration in the diagnosis and staging of pancreatic tumors. Gastrointest Endosc Clinics North Amer 1995;5:723-34.
5. Hawes RH. Endoscopic ultrasound. Gastrointest Endosc Clin N Am 2000 ;10 ;161-74.
6. Antillon MR, Chang KJ. Endoscopic and endosonography guided fine-needle aspiration. Gastrointest Endosc Clin N Am 2000;10:619-36.
7. Bhutani MS. Endoscopic ultrasonography. Endoscopy 2000;32:853-62.
8. Kochman ML. EUS in pancreatic cancer. Gastrointest Endosc 2002;56:S6-S12.
9. Hunt GC, Faigel DO. Assessment of EUS for diagnosing, staging, and determining resectability of pancreatic cancer: a review. Gastrointest Endosc 2002;55:232-7.
10. Muller MF, Meyenberger C, Bertschinger P, Schaer R, Marincek B. Pancreatic tumors: evaluation with endoscopic US, CT and MR imaging. Radiology 1994;190:745-51.
11. Bhutani MS. Endoscopic ultrasonography in pancreatic disease. Seminars in Gastrointestinal Disease 1998;9:51-60.
12. Yasuda K, Mukai H, Nakajima M. Endoscopic ultrasonography diagnosis of pancreatic cancer. Gastrointest Endosc Clinics North Amer 1995;5:699-712.
13. Wiersema MJ Identifying contraindications to resection in patients with pancreatic carcinoma: the role of endoscopic ultrasound. Can J Gastroenterol 2002;16:109-14.
14. Baron PL, Kay C, Hoffman B. Pancreatic imaging. Surg Oncol Clin N Am 1999;8:35-58.
15. Glasbrenner B, Schwarz M, Pauls S, et al. Prospective comparison of endoscopic ultrasound and endoscopic retrograde cholangiopancreatography in the preoperative assessment of masses in the pancreatic head. Dig Surg 2000;17:468-74.
16. Legmann P, Vignaux O, Dousset B, et al. Pancreatic tumors: comparison of dual-phase helical CT and endoscopic sonography. Am J Radiol 1998;170:1315-1332.
17. Meining A, Dittler HJ, Wolf A, et al. You get what you expect? A critical appraisal of imaging methodology in endosonographic cancer staging. Gut 2002;50:599-603.
18. Rosch T, Schusdziarra V, Born P, et al. Modern imaging methods versus clinical assessment in the evaluation of hospital in-patients with suspected pancreatic disease. Am J Gastroenterol 2000;95:2261-70.
19. Van Hoe L, Baert AL. Pancreatic carcinoma: applications for helical computed tomography. Endoscopy 1997;29:539-60.
20. Qian X, Hecht JL. Pancreatic fine needle aspiration. A comparison of computed tomographic and endoscopic ultrasonographic guidance. Acta Cytol 2003;47:723-6.
21. Erickson RA. Endoscopic diagnosis and staging: endoscopic ultrasound, endoscopic retrograde cholangiopancreatography. In: Evans DB, Pisters PWT, Abbruzzese eds. Pancreatic Cancer. New York: Springer, 2002:97-114.
22. Das A, Sivak MV, Chak A. Cervical esophageal perforation during EUS: a national survey.

Gastrointest Endosc 2001;53:599-602.
23. Vilman P, Jacobsen GK, Henriksen FW, et al. Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreatic disease. Gastrointest Endosc 1992;38:172-3.
24. Bhutani MS, Hawes RH, Baron PL, et al. Endoscopic ultrasound guided fine needle aspiration of malignant pancreatic lesions. Endoscopy 1997;29:854-58.
25. Barthet M, Portal I, Boujaoude J, et al. Endoscopic ultrasonographic diagnosis of pancreatic cancer complicating chronic pancreatitis. Endoscopy 1996;28:487-91.
26. Erickson RA, Sayage-Rabie L, Beisner RS. Factors impacting endoscopic ultrasound-guided fine needle aspiration passes for pancreatic malignancies. Gastrointest Endosc 2000;51:184-90.
27. Marchevsky AM, Nelson V, Martin SE, et al. Telecytology of fine-needle aspiration biopsies of the pancreas: a study of well-differentiated adenocarcinoma and chronic pancreatitis with atypical epithelial repair changes. Diagn Cytopathol 2003;28:147-52.
28. Hayakawa T, Naruse S, Kitagawa M, et al. A prospective multicenter trial evaluating diagnostic validity of multivariate analysis and individual serum marker in differential diagnosis of pancreatic cancer from benign pancreatic diseases. Int J Pancreatol 1999;25:23-9.
29. Abraham SC, Wilentz RE, Yeo CJ, et al. Pancreaticoduodenectomy (Whipple resections) in patients without malignancy: are they all 'chronic pancreatitis'? Am J Surg Pathol 2003;27:110-20.
30. Tada M, Komatsu Y, Kawabe T, et al. Quantitative analysis of K-ras gene mutation in pancreatic tissue obtained by endoscopic ultrasonography-guided fine needle aspiration: clinical utility for diagnosis of pancreatic tumor. Am J Gastroenterol 2002;97:2263-70.
31. Buchler P, Conejo-Garcia JR, Lehmann G, et al. Real-time quantitative PCR of telomerase mRNA is useful for the differentiation of benign and malignant pancreatic disorders. Pancreas 2001;22:331-40.
32. Chang KJ, Albers CG, Erickson RA, et al. Endoscopic ultrasound guided fine needle aspiration of pancreatic carcinoma. Am J Gastroenterol 1994;89:263-6.
33. Chang KJ, Katz KD, Durbin TE, et al. Endoscopic ultrasound guided fine needle aspiration. Gastrointest Endosc 1994;40:694-9.
34. Wiersema JM, Kouchman ML, Cramer HM, et al. Endosonography-guided real-time fine-needle aspiration biopsy. Gastrointest Endosc 1994;40:700-7.
35. Giovannini M, Seitz JF, Monges F, et al. Fine-needle aspiration cytology guided by endoscopic ultrasonography: results in 141 patients. Endoscopy 1995;27:171-7.
36. Wiersema MJ, Vilmann P, Giovannini M, et al. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. Gastroenterology 1997;112:1087-95.
37. Gress FG, Hawes RH, Savides TJ, et al Endoscopic ultrasound-guided fine-needle aspiration biopsy using linear array and radial scanning endosonography. Gastrointest Endosc 1997;45:243-50.
38. Erickson RA, Sayage-Rabie L, Avots-Avotins A. Clinical utility of endoscopic ultrasound-guided fine needle aspiration. Acta Cytol 1997;41:1647-53.
39. Faigel DO, Ginsberg GG, Bentz JS, et al. Endoscopic ultrasound-guided real-time fine-needle aspiration biopsy of the pancreas in cancer patients with pancreatic lesions. J Clin Oncol 1997;15:1439-43.
40. Chang KJ, Nguyen P, Erickson RA, et al. The clinical utility of endoscopic ultrasound-guided fine-needle aspiration in the diagnosis and staging of pancreatic carcinoma. Gastrointestinal Endoscopy 1997;45:387-93.
41. David O, Green L, Reddy V, et al. Pancreatic masses: a multi-institutional study of 364 fine-needle aspiration biopsies with histopathologic correlation. Diagn Cytopathol 1998;19:423-7.
42. Afify AM, al-Khafaji BM, Kim B, et al. Endoscopic ultrasound-guided fine needle aspiration of the pancreas. Diagnostic utility and accuracy. Acta Cytol 2003;47:341-8.
43. Harewood GC, Wiersema MJ Endosonography-guided fine needle aspiration biopsy in the evaluation of pancreatic masses. Am J Gastroenterol 2002;97:1386-91.
44. Ylagan LR, Edmundowicz S, Kasal K, et al. Endoscopic ultrasound guided fine-needle aspiration cytology of pancreatic carcinoma: a 3-year experience and review of the literature. Cancer 2002;96:362-9.
45. Erickson RA. Endoscopic ultrasound guided fine needle aspiration of the pancreas. Visible human Journal of Endosonography. 2002;1 (Vol. 3) (electronic journal @ vhjoe.com).
46. Binmoeller KF, Rathod VD Difficult pancreatic mass FNA: tips for success. Gastrointest Endosc 2002;56:S86-91.
47. Erickson RA. Technical review: EUS-guided fine needle aspiration. Gastrointest Endosc 2004:50:267-79.
48. Gress F, Gottlieb K, Sherman S, Lehman G. Endoscopic ultrasonography-guided fine-needle aspiration biopsy of suspected pancreatic cancer. Ann Intern Med 2001;134:459-64.
49. Frable WJ. Needle aspiration biopsy: past, present, and future. Hum Path 1989;20:504-17.
50. Harewood GC, Wiersema LM, Halling AC, et al. Influence of EUS training and pathology interpretation on accuracy of EUS-guided fine needle aspiration of pancreatic masses. Gastrointest Endosc 2002;55:669-73.
51. Klapman JB, Logrono R, Dye CE, et al. Clinical impact of on-site cytopathology interpretation on endoscopic ultrasound-guided fine needle aspiration. Am J Gastroenterol 2003;98:1289-94.
52. Raut CP, Grau AM, Staerkel GA, et al. Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration in patients with presumed pancreatic cancer. J Gastrointest Surg 2003;7:118-26.
53. Schwartz DA, Unni KK, Levy MJ, et al. The rate of false-positive results with EUS-guided fine-needle aspiration. Gastrointest Endosc 2002;56:868-72.
54. O'Toole D, Palazzo L, Arotcarena R, et al. Assessment of complications of EUS-guided fine-needle aspiration. Gastrointest Endosc 2001;53:470-4.
55. Molino D, Perrotti P, Antropoli C, et al. Analysis of factors influencing the diagnostic failure of intraoperative fine needle aspiration cytology in pancreatic cancer. Chir Ital 2002;54:289-94.
56. Lin F, Staerkel G. Cytologic criteria for well differentiated adenocarcinoma of the pancreas in fine-needle aspiration biopsy specimens. Cancer 2003;99:44-50.
57. Harada N, Kouzu T, Arima M, et al. Endoscopic ultrasound-guided histologic needle biopsy: preliminary results using a newly

developed endoscopic ultrasound transducer. Gastrointest Endosc 1996;44:327-30.
58. Matsui M, Goto H, Niwa Y, et al. Preliminary results of fine needle aspiration biopsy histology in upper gastrointestinal submucosal tumors. Endoscopy 1998;30:750-55.
59. Binmoeller KF, Thul R, Rathod V, et al. Endoscopic ultrasound-guided 18-gauge, fine needle aspiration biopsy of the pancreas using a 2,8 mm channel convex array echoendoscope. Gastrointest Endosc 1998;47:121-7.
60. Solmi L, Muratori R, Bacchini P, Primerano A, Gandolfi L. Comparison between echo-guided fine needle aspiration cytology and microhistology in diagnosing pancreatic masses. Surg Endosc 1992;6:222-4.
61. Henrique RM, Sousa ME, Godinho MI, et al. Immunophenotyping by flow cytometry of fine needle aspirates in the diagnosis of lymphoproliferative disorders: A retrospective study. J Clin Lab Anal 1999;13:224-8.
62. Bouvet M, Staerkel GA, Spitz FR, et al. Primary pancreatic lymphoma. Surgery 1998;123:382-90.
63. Bounds BC, Brugge WR. EUS diagnosis of cystic lesions of the pancreas. Int J Gastrointest Cancer 2001;30:27-31.
64. Brandwein SL, Farrell JJ, Centeno BA, et al. Detection and tumor staging of malignancy in cystic, intraductal, and solid tumors of the pancreas by EUS. Gastrointest Endosc 2001;53:722-7.
65. Hernandez LV, Mishra G, Forsmark C, et al. Role of endoscopic ultrasound (EUS) and EUS-guided fine needle aspiration in the diagnosis and treatment of cystic lesions of the pancreas. Pancreas 2002;25:222-8.
66. Bounds BC. Diagnosis and fine needle aspiration of intraductal papillary mucinous tumor by endoscopic ultrasound. Gastrointest Endosc Clin N Am 2002:12;735-45.
67. Frossard JL, Amouyal P, Amouyal G, et al. Performance of endosonography-guided fine needle aspiration and biopsy in the diagnosis of pancreatic cystic lesions. Am J Gastroenterol 2003;98:1516-24.
68. Brugge WR Fine needle aspiration of pancreatic masses: the clinical impact. Am J Gastroenterol 2002;97:2701-2.
69. Warshaw AL, Fernandez-del Castillo C. Pancreatic carcinoma. N Engl J Med 1992;326:455-65.
70. Nakamura R, Machado R, Amikura K, et al. Role of fine needle aspiration cytology and endoscopic biopsy in the preoperative assessment of pancreatic and peripancreatic malignancies. Int J Pancreatol 1994;16:17-21.
71. Evans DB, Staley CA, Lee JE, et al. Adenocarcinoma of the pancreas: recent controversies, current management, and future therapies. GI Cancer 1996;1:149-61.
72. Smith EH. Complications of percutaneous abdominal fine-needle biopsy. Radiology 1991; 178:253-8.
73. Fornari F, Buscarini L. Ultrasonically-guided fine-needle biopsy of gastrointestinal organs: indications, results and complications. Dig Dis 1992;10:121-33.
74. Brandt KR, Charboneau JW, Stephens DH, et al. CT- and US-guided biopsy of the pancreas. Radiology 1993;187:99-104.
75. Gress F, Michael H, Gelrud D, et al. EUS-guided fine-needle aspiration of the pancreas: evaluation of pancreatitis as a complication. Gastrointest Endosc 2002;56:864-7.
76. Affi A, Vazquez-Sequeiros E, Norton ID, et al. Acute extraluminal hemorrhage associated with EUS-guided fine needle aspiration: frequency and clinical significance. Gastrointest Endosc 2001;53:221-5.
77. ten Berge J, Hoffman BJ, Hawes RH, et al. EUS-guided fine needle aspiration of the liver: indications, yield, and safety based on an international survey of 167 cases. Gastrointest Endosc 2002;55:859-62.
78. Chen HY, Lee CH, Hsieh CH Bile peritonitis after EUS-guided fine-needle aspiration.
Gastrointest Endosc 2002;56:594-6.
79. Matsumoto K, Yamao K, Ohashi K, Watanabe Y; Sawaki A; Nakamura T; Matsuura A; Suzuki T; Fukutomi A; Baba T; Okubo K; Tanaka K; Moriyama I; Shimizu Y. Acute portal vein thrombosis after EUS-guided FNA of pancreatic cancer: case report. Gastrointest Endosc 2003;57:269-71.
80. Paquin SC, Chua TS, Tessier G, et al. A first report of tumor seeding by EUS-FNA. Gastrointest Endosc 2004;59:AB235.
81. Lundstedt C, Stridbeck H, Andersson R, et al. Tumor seeding occurring after fine-needle biopsy of abdominal malignancies. Acta Radiol 1991;32:518-520.
82. Micames CG, Jowell P, White R, et al. Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosied with EUS-guided FNA vs. percutaneous FNA. Gastrointest Endosc 2003;58:690-5.
83. Levy MJ, Norton ID, Wiersema MJ, et al. Prospective risk assessment of bacteremia and other infectious complications in patients undergoing EUS-guided FNA. Gastrointest Endosc 2003;57:672-8.
84. Catalano MF, Hoffman B, Bhutani M, et al. American Endosonography Club. Endoscopic ultrasound (EUS) guided fine needle aspiration (FNA) of gastrointestinal (GI) tract lesions: multicenter assessment of accuracy, complication rate and technical competence. Gastrointest Endosc 1997;45:AB26 (abstract).
85. Sing JT, Erickson RA, Fader R. An in-vitro analysis of microbial transmission during endoscopic ultrasound guided fine-needle aspiration and the utility of sterilization agents. Am J Gastroenterol 2003;98:S284 (abstract).
86. Gress FG, Hawes RH, Savides TJ, et al. Role of EUS in the preoperative staging of pancreatic cancer: a large single-center experience. Gastrointest Endosc 1999;50:786-91.
87. Rösch T. Staging of pancreatic cancer. Analysis of literature results. Gastrointest Endosc Clin N Amer 1995;5:735-9.
88. Chang KJ. Endoscopic ultrasound-guided fine needle aspiration in the diagnosis and staging of pancreatic tumors. Gastrointest Endosc Clin N Am 1995;5:723-34.
89. Tio TL, Sie LH, Kallimanis G, et al. Staging of ampullary and pancreatic carcinoma: comparison between endosonography and surgery. Gastrointest Endosc 1996;44:706-13.
90. Rosch T, Dittler HJ, Strobel K, et al. Endoscopic ultrasound criteria for vascular invasion in the staging of cancer of the head of the pancreas: a blind reevaluation of videotapes. Gastrointest Endosc 2000;52:469-77.
91. Exocrine Pancreas. In: Greene FL, Page DL, Fleming ID, et al. AJCC Cancer staging handbook. New York: Springer-Verlag, 2002:179-188.
92. Harrison LE, Brennan MF. Portal vein resection for pancreatic adenocarcinoma. Surg Oncol Clin N Am 1998;7:165-81.
93. Harrison LE, Klimstra DS, Brennan MF. Isolated portal vein involvement in pancreatic adenocarcinoma. A contraindication for resection? Ann Surg 1996;224:342-7.

94. Leach SD, Lee JE, Charnsangavej C, et al. Survival following pancreaticoduodenectomy with resection of the superior mesenteric-portal vein confluence for adenocarcinoma of the pancreatic head. Br J Surg 1998;85:611-7.
95. Protiva P, Sahai AV, Agarwal B Endoscopic ultrasonography in the diagnosis and staging of pancreatic neoplasms. Int J Gastrointest Cancer 2001;30:33-45.
96. Mertz HR, Sechopoulos P, Delbeke D, et al. EUS, PET, and CT scanning for evaluation of pancreatic adenocarcinoma. Gastrointest Endosc 2000;52:367-71.
97. Levy MJ, Wiersema MJ. Endoscopic ultrasound in the diagnosis and staging of pancreatic cancer. Oncology 2002;16:29-38.
98. Ahmad NA, Lewis JD, Ginsberg GG, et al. EUS in preoperative staging of pancreatic cancer. Gastrointest Endosc 2000;52:463-8.
99. Sasson AR, Hoffman JP, Ross EA, et al. En bloc resection for locally advanced cancer of the pancreas: is it worthwhile? J Gastrointest Surg 2002;6:147-57.
100. Roder JD, Stein HJ, Siewert JR. Carcinoma of the periampullary region: who benefits from portal vein resection? Am J Surg 1996;171:170-4.
101. Launois B, Franci J, Bardaxoglou E, et al. Total pancreatectomy for ductal adenocarcinoma of the pancreas with special reference to resection of the portal vein and multicentric cancer. World J Surg 1993;17:122-6.
102. Brugge WR, Lee MJ, Kelsey PB, et al. The use of EUS to diagnose malignant portal venous system invasion by pancreatic cancer. Gastrointest Endosc 1996;43:561-7.
103. Bluemke DA, Fishman EK. CT and MR evaluation of pancreatic cancer. Surg Oncol Clin N Am 1998;7:103-24.
104. Gorelick AB, Scheiman JM, Fendrick AM. Identification of patients with resectable pancreatic cancer: at what stage are we? Am J Gastroenterol 1998;93:1995-6.
105. Catalano MF, Sivak MV Jr, Rice T, et al. Endosonographic features predictive of lymph node metastasis. Gastrointest Endosc 1994;40:442-6.
106. Bhutani MS, Hawes RH, Hoffman BJ. A comparison of the accuracy of echo features during endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration for diagnosis of malignant lymph node invasion. Gastrointest Endosc 1997;45:474-9.
107. Loren DE, Seghal CM, Ginsberg GG, et al. Computer-assisted analysis of lymph nodes detected by EUS in patients with esophageal carcinoma. Gastrointest Endosc 2002;56:742-6.
108. Nitecki SS, Sarr MG, Colby TV, et al. Long-term survival after resection for ductal adenocarcinoma of the pancreas. Is it really improving? Ann Surg 1995;221:59-66.
109. Johnstone PA, Sindelar WF. Lymph node involvement and pancreatic resection: correlation with prognosis and local disease control in a clinical trial. Pancreas 1993;8:535-9.
110. Delcore R, Rodriguez FJ, Forster J, et al. Significance of lymph node metastases in patients with pancreatic cancer undergoing curative resection. Am J Surg 1996;172:463-8.
111. Huguier M, Baumel H, Manderscheid JC. Cancer of the exocrine pancreas. A plea for resection. Hepatogastroenterology 1996;43:721-9.
112. Hahn M, Faigel DO. Frequency of mediastinal lymph node metastases in patients undergoing EUS evaluation of pancreaticobiliary masses. Gastrointest Endosc 2001;54:331-5.
113. Wallace MB, Block M, Hoffman BJ, et al. Detection of telomerase expression in mediastinal lymph nodes of patients with lung cancer. Am J Respir Crit Care Med 2003:167;1670-5.
114. Mitas M, Cole DJ, Hoover L, et al. Real-time reverse transcription-PCR detects KS1/4 mRNA in mediastinal lymph nodes from patients with non-small cell lung cancer. Clin Chem 2003:49;312-5.
115. Nguyen P, Feng JC, Chang KJ. Endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration (FNA) of liver lesions. Gastrointest Endosc 1999;50:357-61.
116. Chang KJ, Albers CG, Nguyen P. Endoscopic ultrasound-guided fine needle aspiration of pleural and ascitic fluid. Am J Gastroenterol 1995;90:148-50.
117. Nguyen PT, Chang KJ. EUS in the detection of ascites and EUS-guided paracentesis. Gastrointest Endosc 2001;54:336-9.
118. Powis ME, Chang KJ Endoscopic ultrasound in the clinical staging and management of pancreatic cancer: its impact on cost of treatment. Cancer Control 2000;7:413-20.
119. Mortensen MB, Pless T, Durup J, et al. Clinical impact of endoscopic ultrasound-guided fine needle aspiration biopsy in patients with upper gastrointestinal tract malignancies. A prospective study. Endoscopy 2001:33;478-83.
120. Harada N, Wiersema MJ, Wiersema LM. Endosonography-guided celiac plexus neurolysis. Gastrointest Endosc Clin N Am 1997;7:237-45.
121. Gunaratnam NT, Sarma AV, Norton ID, et al. A prospective study of EUS-guided celiac plexus neurolysis for pancreatic cancer pain. Gastrointest Endosc 2001;54:316-24.
122. Chang KJ, Nguyen PT, Thompson JA, et al. 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.
123. Hecht JR, Bedford R, Abbruzzese JL, et al. A phase I/II trial of intratumoral endoscopic ultrasound injection of ONYX-015 with intravenous gemcitabine in unresectable pancreatic carcinoma. Clin Cancer Res 2003;9:555-61.
124. Chang KJ, Senzer N, Chung T, Hecht R, Vogel S, Rosemurgy A, et al. A novel gene transfer therapy against pancreatic cancer (TNFerade) delivered by endoscopic ultrasound (EUS) and percutaneous guided fine needle injection. Gastrointest Endosc 2004;59:AB92.
125. Mallery S, Matlock J, Freeman ML. EUS-guided rendezvous drainage of obstructed biliary and pancreatic ducts: Report of 6 cases. Gastrointest Endosc 2004;59:100-7.
126. Kahaleh M, Yoshida C, Kane L, et al. Interventional EUS cholangiography: A report of five cases. Gastrointest Endosc 2004;60:138-42.
127. Burmester E, Niehaus J, Leineweber T, et al. EUS-cholangio-drainage of the bile duct: report of 4 cases. Gastrointest Endosc 2003;57:246-51.
128. Kahaleh M, Wang P, Shami VM, et al. EUS-guided transhepatic cholangiography: Report of 6 cases. Gastrointest Endosc 2005;61:307-13.
129. Kahaleh M, Yoshida C, Yeaton P. EUS antegrade pancreatography with gastropancreatic duct stent placement: Review of two cases. Gastrointest Endosc 2003;58:919-23.

130. Rulyak SJ, Lowenfels AB, Maisonneuve P, et al. Risk factors for the development of pancreatic cancer in familial pancreatic cancer kindreds. Gastroenterology 2003;124:1292-9.
131. Rulyak SJ, Brentnall TA Inherited pancreatic cancer: surveillance and treatment strategies for affected families. Pancreatology 2001;1:477-85.
132. Biankin AV, Kench JG, Dijkman FP, et al. Molecular pathogenesis of precursor lesions of pancreatic ductal adenocarcinoma. Pathology 2003;35:14-24.
133. Kimmey MB, Bronner MP, Byrd DR, Brentnall TA. Screening and surveillance for hereditary pancreatic cancer. Gastrointest Endosc 2002;56:S82-6.
134. Rulyak SJ, Kimmey MB, Veenstra DL, et al. Cost-effectiveness of pancreatic cancer screening in familial pancreatic cancer kindreds. Gastrointest Endosc 2003;57:23-9.
135. Soetikno RM, Chang KJ. Endoscopic ultrasound-guided diagnosis and therapy in pancreatic disease. Gastrointest Endosc Clin N Am 1998;8:237-47.
136. Stevens PD, Lightdale CJ. The role of endosonography in the diagnosis and management of pancreatic cancer. Surg Oncol Clin N Am 1998;7:125-33.
137. Barkin JS, Goldstein JA. Diagnostic approach to pancreatic cancer. Gastroenterol Clin North Am 1999;28:709-22.
138. Ritts RE, Pitt HA, CA 19-9 in pancreatic cancer. Surg Oncol Clin N Am 1998;7:93-101.