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Pancreatic Fine Needle Aspiration: To Do or not To Do?

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Introduction

The aspiration of a pancreatic mass can provide tissue for the diagnosis of a malignancy. Traditionally, computed tomography (CT) and trans-abdominal ultrasonography (US) have been used to guide the aspiration of a pancreatic mass. Recently, endoscopic ultrasound (EUS) has been introduced as an alternative to CT/US guidance because of superior imaging of the pancreas achieved by EUS.

The most common technique for tissue acquisition from a pancreatic mass is fine needle aspiration (FNA). The use of a small gauge needle for aspiration cytology of the pancreas has increased the safety and ease of FNA compared to the traditional core tissue biopsy using large gauge needles. The tissue obtained during FNA is evaluated with cytological techniques whereas core tissue specimens are processed for histology.

The request for a tissue diagnosis of a pancreatic lesion may originate from a number of specialists caring for the patient. The primary care physician may request a tissue diagnosis in order to aid the patient and family in decision-making. The oncologist often requires a tissue diagnosis in order to provide chemotherapy. The surgeon may need a diagnosis for surgical planning. Lastly, the patient may request a biopsy in order to increase the certainty of a diagnosis. In this presentation, we will review the various techniques for obtaining tissue from a pancreatic lesion and evaluate the advantages and disadvantages.

The most common indication for a pancreatic 'biopsy' is the need for the documentation of a malignancy in a patient with a malignant-appearing pancreatic mass. In patients who are not operative candidates, a large pancreatic mass can be accessed with either cross-sectional imaging, US, or EUS. A tissue diagnosis is particularly important in patients who will be treated with chemotherapy. The cytological analysis of aspirated cytological material can readily differentiate between adenocarcinoma, islet cell malignancies, metastasis to the pancreas, and inflammatory lesions [1]. The result of a pancreatic 'biopsy' in operative candidates is important factor in the planning of surgery [2]. For example, the surgical approach to islet cell tumors is often quite different than adenocarcinomas.

A more compelling indication for a pancreatic mass 'biopsy' is the finding of an atypical pancreatic mass on imaging. The differential diagnosis of an atypical pancreatic mass is often quite wide and includes adenocarcinoma, islet cell tumor, pancreatic metastasis, focal chronic pancreatitis, and cystadenomas. The surgical approach as well as the overall management of the patient will often be altered depending on the results of the pancreatic 'biopsy'. For example, the management of a serous cystadenoma is quite different than an islet cell tumor.

Techniques of Pancreatic Biopsies and FNA

Surgical biopsies of the pancreas are usually performed during a laparotomy and are

guided by the surgeon's hands. The technique for intra-operative biopsy of the pancreas is very similar to non-operative techniques. A small gauge needle is placed into the pancreatic mass and the needle is moved to and fro within the mass, while suction is applied to the syringe. The complication rates and results of operative FNA are probably superior to large needle biopsy or wedge resections of pancreatic masses [3, 4]. False positive results are very rare, but false negative results occur at rates similar to other techniques. In a series of 37 patients, the sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy for intraoperative FNA cytologic results were 96%, 100%, 100%, 91%, and 97%, respectively [5]. The rate of complications is very low.

Intra-operative FNA of a pancreatic mass is used to determine if a lesion is malignant and to determine the type of malignancy. With rapid processing of cytologic material in the operating room, a tissue diagnosis may be provided to the surgeon in a timely manner and aid in the decision making. The disadvantage of this strategy is the time-consuming nature of the process and the prolongation of the operative time. The use of preoperative FNA avoids these issues.

CT/US-guided biopsies of the pancreas are usually performed as aspiration biopsies, using large or small gauge needles. The technique involves the use of a percutaneous approach with guidance from US or CT. The needle is passed through the abdominal structures intervening between the abdominal wall and the pancreatic mass. Core needle biopsies of the pancreas use a high-speed biopsy gun with 14, 16, or 18 gauge cutting-type needles [6]. In a recent series, a core biopsy of the pancreas resulted in a correct diagnosis in 51 of 63 biopsies, yielding a sensitivity for malignancy of 78.1%, a specificity of 100%, a positive predictive value of 100%, and an overall accuracy of 81.0%. One 57-year old patient developed an acute pancreatitis related to a biopsy (1.6%). The technique is easiest and most sensitive for detecting malignancies when the lesion is large and located in the body and tail of the pancreas [7]. CT-guidance is the most common technique, but US-guided pancreatic FNA have also been reported and is highly accurate [8]. In one series, CT-guided biopsies had an accuracy of 86%, and US-guided biopsies had an accuracy of 95%, but the study was not designed as a prospective, comparison trial [7]. Combining the techniques of CT and US guidance for pancreatic biopsies may increase the overall accuracy of the aspiration [7].

Despite the reports of highly diagnostic results of pancreatic FNA, other investigators have reported much lower diagnostic rates of CT-guided biopsies of pancreatic masses [9]. The accuracy of FNA of pancreatic lesions is dependent upon the type of lesion. For example the accuracy of FNA of cystic neoplasms is quite low (62%) [10]. The accuracy of FNA is dependent upon the adequacy of the tissue aspiration. In some series, inadequate tissue was obtained in 6-20% [11, 12].

Although complication rates of pancreatic FNA are very low, there are reports of pancreatitis and seeding of the biopsy tract [13]. In patients undergoing EUS-guided pancreatic FNA, abdominal pain occurs in 3%, but pancreatitis is seen in only 1% [11]. In large series of US-guided pancreatic biopsies of transplanted pancreatic tissue, pancreatitis or pain were not seen, but bleeding occurred in 2.6% [14].

EUS-Guided FNA of the pancreas has been performed over the past 5-10 years [15]. The technique involves the use of endoscopic

Figure 1. Linear echoendoscope with aspiration cytology needle.

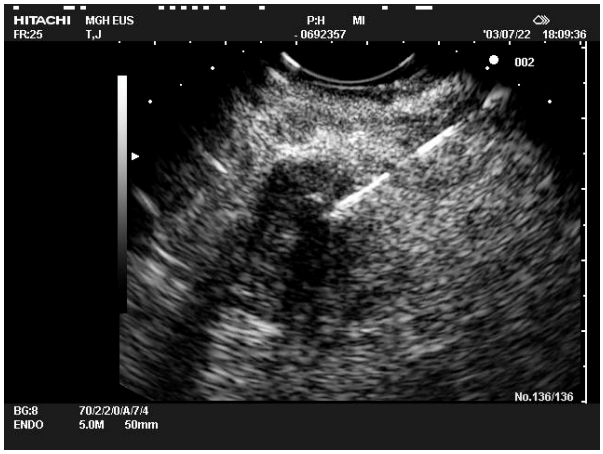

Figure 2. EUS image of FNA of a small pancreatic adenocarcinoma.

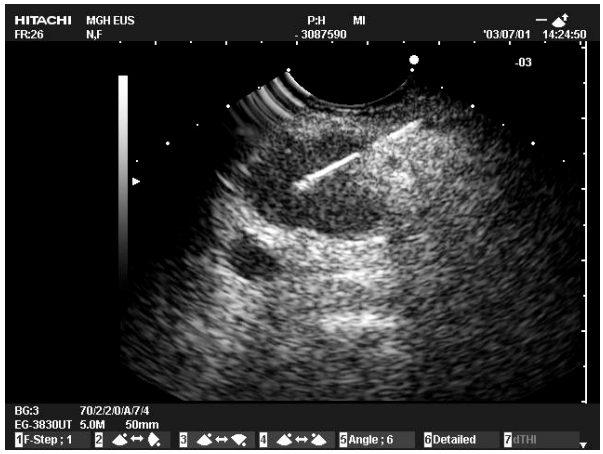

Figure 4. EUS image of FNA of malignant peri-pancreatic lymph node.

ultrasound, an endoscopic procedure in which an echoendoscope is placed into the stomach or duodenum (Figure 1). Using the guidance of the high frequency ultrasound transducer on the tip of the echoendoscope, a small gauge needle is passed through the wall of the gastrointestinal tract and into the pancreatic mass (Figure 2). A number of different sizes of needles are used, ranging from 25 to 19 gauge needles (Figure 3). A randomized trial of the two types of needles from two different manufacturers yielded similar results [16]. Peri-pancreatic lymph nodes can also be targeted for FNA (Figure 4) [17]. The accuracy of EUS-FNA for lymph nodes is similar to EUS-FNA of pancreatic masses [18]. It has been recommended that for optimal results, a pancreatic mass should be sampled with 7 aspirations and lymph nodes should be sampled with 5 aspirations. If an on-site cytologist is present, the number of aspirations can be reduced to whatever is necessary in order to obtain diagnostic tissue. Liver metastasis can also be aspirated by EUS and the tissue used as the basis for the diagnosis of the primary pancreatic lesion [19].

The chief advantage of EUS-guided FNA is the ability to target, small, intra-pancreatic masses. Nearly 25% of EUS targets of FNA in the pancreas cannot be seen with CT [20]. Similarly, EUS can also target low grade malignancies such a neuroendocrine tumors and metastatic lesions to the pancreas (Figure 5) [21]. These types of targets were not previously accessible by CT guidance [21]. EUS can also target lesions suspected with the findings of ERCP, such as a focal stricture

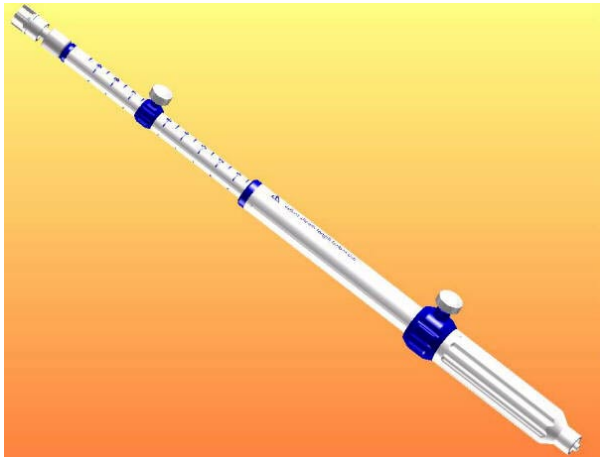

Figure 3. Two stage Medi-globe FNA needle handle.

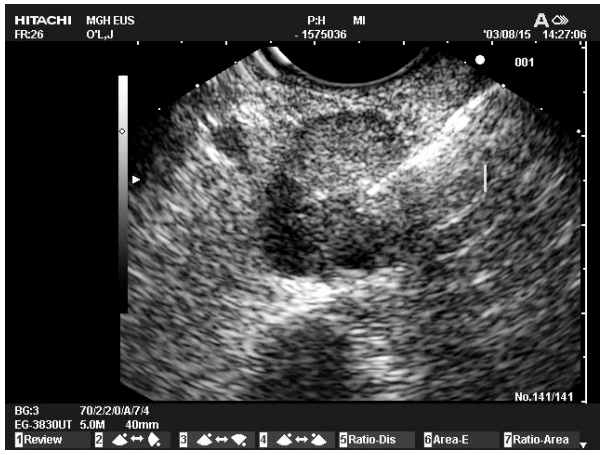

Figure 5. EUS images of an intra-pancreatic neuroendocrine tumor undergoing FNA.

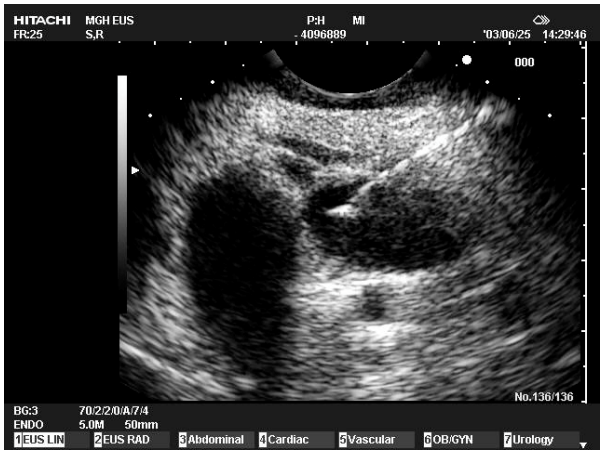

Figure 6. EUS image of a 1cm mucinous cystadenoma undergoing FNA.

[22]. FNA of cystic malignancies does not yield the accuracy commonly associated with the FNA of solid lesions (Figure 6). However, FNA-cytology of intra-ductal papillary mucinous tumors (IPMT) can yield diagnostic material, particularly when solid lesions associated with the cystic lesion are targeted [23, 24]. The greatest impact on patient care is the ability to avoid unnecessary surgery in non-operative candidates [20]. This strategy of providing endoscopic FNA has proven to be cost effective [20]. In 60% of patients, there was a change in patient management based on the results of the EUS FNA [25]. Most commonly the results of EUS and FNA result in a higher stage of malignancy [26]. With improved resolution offered by multi-detector, phased-array CT of the pancreas, the importance of EUS-guided FNA has increased. EUS-FNA was particularly accurate at identifying pancreatic malignancy in those patients presenting with obstructive jaundice [27]. However, falsely negative pancreatic FNA can result in inappropriate delays in surgical planning [28].

Recently, a new EUS-guided 'tru-cut' needle (Quik Core, Wilson-Cook Inc., Winston-Salem, NC, USA) has been used for obtaining tissue from benign and malignant lesions of the pancreas (Figure 7). This device is designed to provide tissue that can be processed histologically [29]. Although the device has been demonstrated to provide diagnostic tissue for pancreatic malignancies, the use of the device may be more important for diagnosing benign parenchymal diseases of the pancreas, such as autoimmune pancreatitis [30].

A decision analysis model has been used to compare the costs of three approaches to the diagnostic strategies of non-metastatic pancreatic head adenocarcinoma: EUS FNA versus CT-guided FNA versus surgery [31]. The endpoint was cost of management per patient. EUS FNA was the least costly strategy ($15,938) compared with CT FNA (US$ 16,378) and surgery (US$ 18,723). Sensitivity analysis revealed that EUS FNA remained the least costly option provided the frequency of malignant adenopathy was greater than 4%.

The complication rate of EUS-FNA is considered to be very low, between 1-2% [32]. The most common complication is bleeding and most commonly, the bleeding is self-limited and does not require transfusion. Pancreatitis is also rare and usually mild. Pancreatitis may occur more commonly after FNA of a cystic lesion as compared to FNA of a solid mass lesion (1.2%) [33]. Others have demonstrated a higher complication rate, but the complications were minor (bleeding and pancreatitis) and occurred within the first week after the procedure [11]. In the course of

Figure 7. 'Tru-cut' type of EUS needle designed to provide a core of tissue.

FNA, the endosonoscope can cause duodenal perforation in patients with duodenal stenosis, but this is a rare complication [34]. One of the major advantages of EUS-guided FNA of pancreatic lesions may be the decreased risk of peritoneal contamination with malignancy. In a recent series, 16.3% of patients undergoing CT-guided FNA developed peritoneal carcinomatosis, compared to 2.2% patients undergoing EUS-FNA [35].

Training of specialists in EUS-FNA is one of the most important issues in increasing the availability of this technique at major centers. Focused mentoring can significantly improve the accuracy of EUS-FNA [36]. The American Society of Gastrointestinal Endoscopy (ASGE) has recommended mentoring of 50 cases of pancreatic FNA in order for endoscopists to achieve competence [37]. The false positive rate of FNA cytology is extremely low, approaching zero. However, there are reports of falsely positive interpretations of pancreatic cytology [38]. An on-site cytologist will improve the results of FNA cytology [39]. In one series, only 2% of EUS-FNA specimens were inadequate for diagnosis [40].

There are no large, prospective trials comparing the ability of CT and EUS in the aspiration of pancreatic lesions. Qian and Hecht suggested that US/CT-guided biopsies may be more accurate and sensitive for documenting malignancy than EUS, but noted that EUS-guidance was used in more difficult lesions [41]. In contrast, in a small series, Jhala *et al*. demonstrated that EUS-FNA was superior to CT-FNA in obtaining adequate cells from neuroendocrine tumors of the pancreas for the diagnosis and performing additional immunohistochemical stains [42]. Mallery *et al*. compared 149 FNA samples (in 128 patients) over a 5 year period of time performed with surgical, CT, and EUS guidance at Massachusetts General Hospital [43]. There was no significant difference in accuracy rates for EUS (76.4%), CT/US (81.4%), and surgically guided (81.8%) pancreatic biopsies. However, EUS was used when masses were smaller as compared with CT/US and surgery. In univariate analyses, factors associated with greater accuracy regardless of technique were as follows: 1) older age, 2) larger size of the mass, and 3) participation by a cytologist during the procedure.

Conclusion

In summary, there are two major indications for pancreatic FNA, the need for documentation of malignancy prior to chemotherapy and the evaluation of an atypical pancreatic mass lesion. There are two common methods for the obtaining a tissue diagnosis, CT/US-guided FNA and EUS-guided FNA. In patients with a large unresectable pancreatic mass, either technique may be used to obtain diagnostic tissue. Small, intra-pancreatic masses often have a wide differential diagnosis and should be evaluated with EUS and FNA.

Keywords Biopsy; Biopsy, Fine-Needle; Endosonography; Pancreas; Pancreatic Neoplasms

Abbreviations CT: computed tomography; US: trans-abdominal ultrasonography; EUS: endoscopic ultrasound; FNA: fine needle aspiration

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References

1. Klapman JB, Logrono R, Dye CE, Waxman I. Clinical impact of on-site cytopathology interpretation on endoscopic ultrasound-guided fine needle aspiration. Am J Gastroenterol 2003; 98:1289-94. [PMID 12818271]

2. Gines A, Vazquez-Sequeiros E, Soria MT, Clain JE, Wiersema MJ. Usefulness of EUS-guided fine needle aspiration (EUS-FNA) in the diagnosis of functioning neuroendocrine tumors. Gastrointest Endosc 2002; 56:291-6. [PMID 12145615]

3. Schadt ME, Kline TS, Neal HS, Scoma RS, Naryshkin S. Intraoperative pancreatic fine needle aspiration biopsy. Results in 166 patients. Am Surg 1991; 57:73-5. [PMID 1992872]

4. Saez A, Catala I, Brossa R, Funes A, Jaurrieta E, Ferrer JE. Intraoperative fine needle aspiration cytology of pancreatic lesions. A study of 90 cases. Acta Cytol 1995; 39:485-8. [PMID 7762337]

5. Edoute Y, Lemberg S, Malberger E. Preoperative and intraoperative fine needle aspiration cytology of pancreatic lesions. Am J Gastroenterol 1991; 86:1015-9. [PMID 1858737]

6. Zech CJ, Helmberger T, Wichmann MW, Holzknecht N, Diebold J, Reiser MF. Large core biopsy of the pancreas under CT fluoroscopy control: results and complications. J Comput Assist Tomogr 2002; 26:743-9. [PMID 12439309]

7. Brandt KR, Charboneau JW, Stephens DH, Welch TJ, Goellner JR. CT- and US-guided biopsy of the pancreas. Radiology 1993; 187:99-104. [PMID 8451443]

8. Di Stasi M, Lencioni R, Solmi L, Magnolfi F, Caturelli E, De Sio I, et al. Ultrasound-guided fine needle biopsy of pancreatic masses: results of a multicenter study. Am J Gastroenterol 1998; 93:1329-33. [PMID 9707060]

9. Rodriguez J, Kasberg C, Nipper M, Schoolar J, Riggs MW, Dyck WP. CT-guided needle biopsy of the pancreas: a retrospective analysis of diagnostic accuracy. Am J Gastroenterol 1992; 87:1610-3. [PMID 1442684]

10. Sperti C, Pasquali C, Di Prima F, Rugge M, Petrin P, Costantino V, et al. Percutaneous CT-guided fine needle aspiration cytology in the differential diagnosis of pancreatic lesions. Ital J Gastroenterol 1994; 26:126-31. [PMID 8061338]

11. Eloubeidi MA, Chen VK, Eltoum IA, Jhala D, Chhieng DC, Jhala N, et al. Endoscopic ultrasound-guided fine needle aspiration biopsy of patients with suspected pancreatic cancer: diagnostic accuracy and acute and 30-day complications. Am J Gastroenterol 2003; 98:2663-8. [PMID 14687813]

12. David O, Green L, Reddy V, Kluskens L, Bitterman P, Attal H, et al. Pancreatic masses: a multi-institutional study of 364 fine-needle aspiration biopsies with histopathologic correlation. Diagn Cytopathol 1998; 19:423-7. [PMID 9839131]

13. Torreggiani WC, Lyburn I, Harris AA, Zwirewich CV. Seeding of pancreatic cancer along the path of a surgical drain: case report and literature review. Can Assoc Radiol J 2000; 51:241-3. [PMID 10976244]

14. Atwell TD, Gorman B, Larson TS, Charboneau JW, Ingalls Hanson BM, Stegall MD. Pancreas Transplants: Experience with 232 Percutaneous US-guided Biopsy Procedures in 88 Patients. Radiology 2004; 231:845-9. [PMID 15163821]

15. Chang KJ, Albers CG, Erickson RA, Butler JA, Wuerker RB, Lin F. Endoscopic ultrasound-guided fine needle aspiration of pancreatic carcinoma. Am J Gastroenterol 1994; 89:263-6. [PMID 8304315]

16. Fritscher-Ravens A, Topalidis T, Bobrowski C, Krause C, Thonke E, Jackle S, Soehendra N. Endoscopic ultrasound-guided fine-needle aspiration in focal pancreatic lesions: a prospective intraindividual comparison of two needle assemblies. Endoscopy 2001; 33:484-90. [PMID 11437040]

17. Cahn M, Chang K, Nguyen P, Butler J. Impact of endoscopic ultrasound with fine-needle aspiration on the surgical management of pancreatic cancer. Am J Surg 1996; 172:470-2. [PMID 8942546]

18. Williams DB, Sahai AV, Aabakken L, Penman ID, van Velse A, Webb J, et al. Endoscopic ultrasound guided fine needle aspiration biopsy: a large single centre experience. Gut 1999; 44:720-6. [PMID 10205212]

19. Prasad P, Schmulewitz N, Patel A, Varadarajulu S, Wildi SM, Roberts S, et al. Detection of occult liver metastases during EUS for staging of malignancies. Gastrointest Endosc 2004; 59:49-53. [PMID 14722547]

20. 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]

21. Fritscher-Ravens A, Izbicki JR, Sriram PV, Krause C, Knoefel WT, Topalidis T, et al. Endosonography-guided, fine-needle aspiration cytology extending the indication for organ-preserving pancreatic surgery. Am J Gastroenterol 2000; 95:2255-60. [PMID 11007226]

22. Harewood GC, Wiersema MJ. Endosonography-guided fine needle aspiration biopsy in the evaluation of pancreatic masses. Am J Gastroenterol 2002; 97:1386-91. [PMID 12094855]

23. Maire F, Couvelard A, Hammel P, Ponsot P, Palazzo L, Aubert A, et al. Intraductal papillary mucinous tumors of the pancreas: the preoperative value of cytologic and histopathologic diagnosis. Gastrointest Endosc 2003; 58:701-6. [PMID 14595305]

24. Brandwein SL, Farrell JJ, Centeno BA, Brugge WR. Detection and tumor staging of malignancy in cystic, intraductal, and solid tumors of the pancreas by

EUS. Gastrointest Endosc 2001; 53:722-7. [PMID 11375578]

25. Frazee RC, Singh H, Erickson RA. Endoscopic ultrasound for peripancreatic masses. Am J Surg 1997; 174:596-8; discussion 598-9. [PMID 9409580]

26. Suits J, Frazee R, Erickson RA. Endoscopic ultrasound and fine needle aspiration for the evaluation of pancreatic masses. Arch Surg 1999; 134:639-42; discussion 642-3. [PMID 10367874]

27. 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; 99:844-50. [PMID 15128348]

28. Nakamura R, Machado R, Amikura K, Ruebner B, Frey CF. 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. [PMID 7806910]

29. Larghi A, Verna EC, Stavropoulos SN, Rotterdam H, Lightdale CJ, Stevens PD. EUS-guided trucut needle biopsies in patients with solid pancreatic masses: a prospective study. Gastrointest Endosc 2004; 59:185-90. [PMID 14745390]

30. Varadarajulu S, Fraig M, Schmulewitz N, Roberts S, Wildi S, Hawes RH, et al. Comparison of EUS-guided 19-gauge Trucut needle biopsy with EUS-guided fine-needle aspiration. Endoscopy 2004; 36:397-401. [PMID 15100946]

31. Harewood GC, Wiersema MJ. A cost analysis of endoscopic ultrasound in the evaluation of pancreatic head adenocarcinoma. Am J Gastroenterol 2001; 96:2651-6. [PMID 11569690]

32. Gress FG, Hawes RH, Savides TJ, Ikenberry SO, Lehman GA. Endoscopic ultrasound-guided fine-needle aspiration biopsy using linear array and radial scanning endosonography. Gastrointest Endosc 1997; 45:243-50. [PMID 9087830]

33. O'Toole D, Palazzo L, Arotcarena R, Dancour A, Aubert A, Hammel P, et al. Assessment of complications of EUS-guided fine-needle aspiration. Gastrointest Endosc 2001; 53:470-4. [PMID 11275888]

34. Raut CP, Grau AM, Staerkel GA, Kaw M, Tamm EP, Wolff RA, et al. Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration in patients with presumed pancreatic cancer. J Gastrointest Surg 2003; 7:118-26; discussion 127-8. [PMID 12559193]

35. Micames C, Jowell PS, White R, Paulson E, Nelson R, Morse M, et al. Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA vs. percutaneous FNA. Gastrointest Endosc 2003; 58:690-5. [PMID 14595302]

36. Harewood GC, Wiersema LM, Halling AC, Keeney GL, Salamao DR, Wiersema MJ. Influence of EUS training and pathology interpretation on accuracy of EUS-guided fine needle aspiration of pancreatic masses. Gastrointest Endosc 2002; 55:669-73. [PMID 11979248]

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

38. Schwartz DA, Unni KK, Levy MJ, Clain JE, Wiersema MJ. The rate of false-positive results with EUS-guided fine-needle aspiration. Gastrointest Endosc 2002; 56:868-72. [PMID 12447300]

39. Afify AM, al-Khafaji BM, Kim B, Scheiman JM. Endoscopic ultrasound-guided fine needle aspiration of the pancreas. Diagnostic utility and accuracy. Acta Cytol 2003; 47:341-8. [PMID 12789912]

40. Eloubeidi MA, Jhala D, Chhieng DC, Chen VK, Eltoum I, Vickers S, et al. Yield of endoscopic ultrasound-guided fine-needle aspiration biopsy in patients with suspected pancreatic carcinoma. Cancer 2003; 99:285-92. [PMID 14579295]

41. Qian X, Hecht JL. Pancreatic fine needle aspiration. A comparison of computed tomographic and endoscopic ultrasonographic guidance. Acta Cytol 2003; 47:723-6. [PMID 14526668]

42. Jhala D, Eloubeidi M, Chhieng DC, Frost A, Eltoum IA, Roberson J, Jhala N. Fine needle aspiration biopsy of the islet cell tumor of pancreas: a comparison between computerized axial tomography and endoscopic ultrasound-guided fine needle aspiration biopsy. Ann Diagn Pathol 2002; 6:106-12. [PMID 12004358]

43. Mallery JS, Centeno BA, Hahn PF, Chang Y, Warshaw AL, Brugge WR. Pancreatic tissue sampling guided by EUS, CT/US, and surgery: a comparison of sensitivity and specificity. Gastrointest Endosc 2002; 56:218-24. [PMID 12145600]