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**Role of the preoperative usefulness of the pathological diagnosis of pancreatic diseases**

Matsumoto K *et al*. Role of EUS-FNA and pancreatic juice cytology

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**Abstract**

Pancreatic cancer is the fifth leading cause of cancer death and has the lowest survival rate of any solid cancer. Endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNA) is currently capable of providing a cytopathological diagnosis of pancreatic malignancies with a higher diagnostic power, with a sensitivity and specificity of 85%-89% and 98%-99%, compared to pancreatic juice cytology (PJC), whose sensitivity and specificity are only 33.3%-93% and 83.3%-100%. However, EUS-FNA is not effective in the cases of carcinoma *in situ* and minimally invasive carcinoma because both are undetectable by endoscopic ultrasonography, although PJC is able to detect them. As for the frequency of complications such as post endoscopic retrograde cholangiopancreatography pancreatitis, EUS-FNA is safer than PJC. To diagnose pancreatic cancer appropriately, it is necessary for us to master both procedures so that we can select the best methods of sampling tissues while considering the patient’s safety and condition.

**Key words:**Endoscopic ultrasound-guided fine-needle aspiration biopsy; Pancreatic juice cytology; Pancreatic cancer; Cytology; Pathology

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**Core tip:** In the era of cyto-pathological diagnosis of pancreatic cancer, endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNA) and pancreatic juice cytology (PJC) represent the most promising procedures for diagnosing pancreatic malignancies. However, there haven’t been any reports that compared the utilities and faults of these procedures. In this review we have highlighted the current role of EUS-FNA and PJC in the diagnosis process for pancreatic malignancies.

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**INTRODUCTION**

Pancreatic ductal adenocarcinoma (PDAC) currently ranks fifth when it comes to death involving cancer. It also, when it comes to solid cancers, has the lowest survival rate[1,2]. The current survival rate for patients with PDAC after 5 years with the condition is less than 3.5%[3,4]. An early diagnosis is crucial to improve the prognosis. However, for a number of reasons, including the inaccessibility of the pancreas and the highly malignant property of the disease, an early diagnosis is still difficult to obtain, despite the constant improvements in diagnostic imaging. Furthermore, it is especially difficult to distinguish between a PDAC and a pancreatic inflammatory lesion, which includes chronic pancreatitis (CP), or a benign stricture of the main pancreatic duct (MPD), and between intra-ductal papillary mucinous carcinoma (IPMC) and intra-ductal papillary mucinous neoplasm (IPMN). Being able to differentiate PDAC from other conditions is important, because not only are the treatments for each of these conditions different, but the prognosis for CP and other rare tumors is better than that for PDAC. A cyto-pathological diagnosis is desirable before beginning therapy in cases in which a qualitative diagnosis for the pancreatic mass by various imaging studies is not possible. In fact, 5-10 percent underwent pancreatoduodenectomy based on a diagnosis that was made before surgery. However, after performing surgery of the primary pancreatic or periampullary malignancy, it is later proven histopathologically to be CP, a benign fibrous common bile duct stricture or so on[5-7]. After performing endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNA) for a pancreatic mass, the frequency of a PDAC does not reach 80%[8,9], which is very important because the treatment strategy for a resection case and an unresectable case are different between PDAC and pancreatic neuroendocrine tumor cases[10-14].

There are many diagnostic procedures in cytopathological treatment including, abdominal ultrasound guided fine-needle aspiration biopsy, computed tomography guided fine-needle aspiration biopsy, EUS-FNA, pancreatic juice cytology (PJC), and Endoscopic pancreatography guided biopsy. I will give an outline mainly on EUS-FNA and PJC in this review.

**PROCEDURE OF AN EUS-FNA**

Vilmann P was the first person to describe the EUS-FNA of a pancreatic mass in 1992[15]. These days, EUS-FNA is the preferred method to sample pancreatic mass lesions, replacing for the most part other methods because EUS-FNA is considered the best diagnostic modality for pancreatic masses with a higher accuracy than that of biopsies under CT or US guidance.

There is a door knocking method and a fanning method in EUS-FNA. The door knocking method is a nice procedure that is useful in obtaining a specimen from a mass, especially one with fibrotic tissue, and, as for the fanning method, the utility is proved by RCT[16].

FNA needles, which are available in sizes from 19 to 25 gauge (G), are available commercially. A recent meta-analysis suggests that a 22-G and a 25-G needle have a similar specificity rate after being used with 1292 patients being diagnosed with pancreatic malignancies[17]. The same study showed that the 25-G needle did appear to have a higher sensitivity when compared to the 22-G needle. Another study found that 25-G needles seemed to be more advantageous over the 22-G needles when it comes to the adequacy of passes. No difference in accuracy, number of passes or complications was found[18]. However, 25-G needles should be considered first in cases in which one must sample from the pancreatic head or uncinated process lesions, as in some studies it has appeared that the 25-G needle has a reduced chance of experiencing technical failures over 22-G needles in such situations[19,20]. 19-G needles, on the other hand, are not often used in the duodenum because of their natural rigidity. However, recently, a more flexible needle has been made of nitinol to improve its ability to function well (Flex 19, Boston Scientific, Natick, MA). An initial study using these new and improved needles included 38 patients. 32 of the 38 patients had pancreatic head/ uncinate lesions. The use of the needles provided adequate samples for cytological analysis in all 32 patients. There were no reported technical failures or procedure related complications[21]. Ramesh J reported that there is no significant difference in the performance of flexible 19G and 25G needles although the procurement of histological core tissue with the flexible 19-G needles was significantly higher (88% *vs* 44%, *P* < 0.001)[22].

As for aspiration, there is a report that compared non-aspiration, aspiration of 10 mL, the aspiration of the slow pull method, and 10-20 mL, but a constant opinion was not obtained from the sampling rate about accuracy[23-27].

EUS-FNA accuracy is also impacted by the skill level and whether or not a cytopathologist is available [28-30]. It has recently been shown, in a meta-analysis that covered 34 studies, that rapid on-site evaluation had a significant determinant on the accuracy of EUS-FNA when it comes to the diagnosis of pancreatic masses[28]. 2 studies have evaluated the optimal number of EUS-FNA passes[29,31] to be 5-7 passes for pancreatic masses in order to get the best diagnostic yield. For situations in which rapid pathology interpretation is not possible, this information may prove to be useful.

It is considered that the white specimens in EUS-FNA samples include histological evidence, and, as for the red specimen, it is thought to be the blood component. When inspected by a 19G needle, a histologic core was found to be present in white specimens 78.9% of the time, and in red specimens 9.3% of the time[32]. It is reported in multiple meta-analysis that ROSE is useful in solving the problem mentioned above [28,33].

Whereas, a meta-analysis suggests 25 G needles have a higher sensitivity rate than 22 G needles when it comes to diagnosing pancreatic malignancy[17], it is expected in the future that EUS-FNA by using a 25G needle will become more mainstream because of the ease of its puncture. At that time, reexamination re-examination may be required if it is necessary to perform immunohistochemical staining after performing ROSE, due to the smaller sample size meaning a decreased chance of there being a histologic core in the sample. Furthermore, there is a fundamental problem in that globally, there are not enough pathologists capable of performing ROSE.

We developed the target sample check illuminator (TSCI)to be a device that would solve the above problem[34]. The mean number of needle punctures was 2.4 (range, 1–5), and the agreement rate between TSCI and histopathology in 142 samples was 93.7% (133/142). No differences in detection capacity were observed in cancerous or non-cancerous lesions. When presence of the target specimen was confirmed by TSCI, 91.4% (53/58) of the patients were able to finish the tests, and the mean number of needle punctures was 1.2 (67/58).

**DIAGNOSTIC POWER OF EUS-FNA**

Two recent studies reported a sensitivity of 85% and 89% based on cytology for the diagnosis of malignancy. The specificity for the same was found to be 98% and 99% respectively[28,35].

It is useful in the improvement of the diagnostic ability of EUS-FNA to use a genetic analysis from EUS-FNA samples. Recent meta-analysis reported that combining K-ras mutation analysis with routine cytology moderately improves the ability of EUS-FNA to differentially diagnose between PDAC and pancreatic inflammatory masses. In a total of eight studies, with 696 cases of PDAC and 138 cases of pancreatic inflammatory masses, the pooled sensitivity, specificity, positive likely ratio and negative likely ratio of K-ras mutation analysis combined with cytopathology for diagnosis of PDAC versus pancreatic inflammatory masses were 90%, 95%, 13.45, and 0.13, respectively. Especially, among total 123 patients whose EUS-FNA results were inconclusive or negative, fifty-nine had K-ras mutations and were finally diagnosed with PDAC (48%, 59/123)[36]. In addition, there are several possible means of processing aspirated samples obtained by EUS-FNA for molecular and other ancillary tests[37].

**COMPLICATION WITH EUS-FNA**

Complications from EUS-FNA include pain, bleeding, fever, and infection. Rare complications such as, acute portal vein thrombosis[38], peritoneal seeding of tumor cells[39], and ruptured pseudoaneurysm of the splenic artery[40] have also been reported. A recent systematic review by Wang *et al*[41], who identified 51 articles with a total of 10941 patients, reported that the mortality rate attributable to EUS-FNA-specific morbidity was 0.02% (2/10941) and that out of 8246 patients with pancreatic lesions only 60 (0.82%) patients reported any complications. About 36/8246 patients had pancreatitis. Of those patients, 75% of the cases were mild. Out of the total number of patients, one of them with severe pancreatitis died. The total rates of pain, bleeding, fever and infection were 0.38%, 0.10%, 0.08% and 0.02% respectively. 2.2% of patients were reported to have peritoneal seeding of tumor cells after receiving EUS-FNA. However, it seems to be lower than that caused by CT-guided FNA (16.3%)[42]. There was no increase in the risk of peritoneal carcinomatosis in pancreatic masses to be found[43]. Beane *et al*[44] found there to be no difference in the survival rate of patients with PDAC who underwent EUS-FNA than with those who did not. Not only was there no difference, but a recent study that looked at the risk of gastric/peritoneal recurrence in cases were EUS-FNA was performed found EUS-FNA was not associated with increased needle track seeding[45]. Furthermore, preoperative EUS-FNA was evaluated in 498 patients, and it was found that it had no negative effect on the survival rate of patients with resected pancreatic cancer[46].

**LIMITATION FOR EUS-FNA**

Even though EUS-FNA has an excellent accuracy and a low incidence of major complications, it does have several limitations. We cannot perform EUS-FNA when we cannot detect a tumor in EUS. Actually, we cannot identify the carcinoma in situ in EUS[47]. Secondly, even though EUS-FNA has a very high sensitivity rate, when in comes to pancreatic tumors, its negative predictive value is only 55-65%[35, 48]. As such, EUS-FNA does not allow us to rule out the possibility of a malignancy. Third, if the patient has chronic pancreatitis the diagnostic accuracy of EUS-FNA decreases[49,50]. It might also hinder cytological interpretation of pancreatic FNA, thus giving EUS-FNA a decreased sensitivity[51]. Fourth, EUS-FNA for pancreatic cancer has a false-positive rate of 1.1%, usually in patients with chronic pancreatitis[52]. Fifth, we may not be able to perform EUS-FNA when we cannot discontinue the use of an antithrombotic drug.

**PROCEDURE, DIAGNOSTIC POWER, AND COMPLICATION OF PJC**

McCune developed the ERCP process in 1968[53]. As for the sampling of the pancreas lesion, Endo was the first person to perform a collection of pancreatic juice under the ERP[54]. The process of PJC is used in all of the following procedures: brushing cytology, cytodiagnosis with pancreatic duct lavage fluid (PDLF), cytodiganosis by using endoscopic nasopancreatic drainage (ENPD), and cytodiagnosis by using secretin. Now I will present the methods, diagnosis results, and complications of each procedure.

***Brushing cytology***

A cytopathological diagnosis by using brushing cytology is easier than conventional aspiration cytology because it can collect fresh cells.

However, the sensitivity (33.3%-65.8%) and the accuracy (46.7%-76.4%) are not so good because it is difficult to perform and collect enough cells[55,56]. Recently, scraping cytology with a guide-wire yielded 71.4%-93% sensitivity, 100% specificity, 100% positive predictive value, 75%-84.4% negative predictive value, and 88.8%-94% accuracy[8,57].

However, this diagnosis rate is shown to improve by mastering the procedure[56].

When we diagnose a carcinoma in situ (CIS) by PJC for a pancreatic duct stenosis case, when we are unable to see the pancreatic mass in imaging studies, and resected it, it is usually the case that there is no cancer at the site of stenosis in the MPD. The stenosis is caused by inflammation due to a CIS, which was derived from a branch duct. For this reason, the diagnostic power of brushing cytology is uncertain. As for the complications rate of brush cytology, it has been reported that acute pancreatitis is a possible complication with a rate of 4.2%-33.3%[8, 55-57].

***ENPD method***

The ENPD method places 5 or 6-French ENPD tubes in the patient for up to 2-3 d[58,59]. Iiboshi *et al*[58] diagnosed 15 CIS using this method. Sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of the ENPD method for pancreatic cancer were 80%-100%, 83.3%-100%, 93.3%-100%, 71%-100%, and 87%-95%, respectively, revealing significantly higher sensitivity than the conventional method (*P* = 0.0001)[58]. As for the complications of the ENPD method, post endoscopic pancreatitis (PEP) has a rate of 7.5%. In particular, the incidence rate of PEP of ENPD method for BD-IPMN is higher than the conventional method[60].

***Cytodiagnosis by using secretin***

Due to the fact that secretin stimulates pancreatic exocrine function, we are able to obtain more pancreatic juice when secretin is present than without it. Finally, we can obtain pancreatic epithelial cells by using secretin. Administration of secretin was performed conventionally before collecting pancreatic juice for cytodiagnosis[54,60]. Secretin may be required in cases in which a sufficient amount of material was not able to be obtained by conventional methods or it may be needed to aspirate mucous fluid in intraductal papillary mucinous neoplasm[57]. Nakaizumi reported that the sensitivity for PDAC was 76% in PJC by using secretin[61]. As for the complications of secretin, at the top of the attached document, it shows a rate of 1.9% for nausea, 0.7% for flushing, and 0.5% for stomachache and vomiting[62]. We have not experienced any adverse events with the secretin administration. Also, we confirmed that the quantity of pancreatic juice significantly increases even though the secretin load in diluted form is 1/32.

***Cytodiagnosis with pancreatic duct lavage fluid***

Imamura’s process requires us to inject a saline from injection lumen, before aspirating it by the negative pressure from a guide-wire lumen with a different syringe at the same time by using double or triple-lumen cannule after brushing cytology in ERP. The sensitivity of pancreatic cancer diagnosis by this procedure is 83%, and pancreatitis was not a side-effect due to PDLF[63]. We choose to do PJC by using secretin if a catheter is able to pass through the narrow segment of the main pancreatic duct, and PDLF if the catheter cannot pass.

If secretin is used in cases where a catheter is unable to pass the stenosis of the main pancreatic duct, the pancreatic ductal pressure in the caudad area past the stenosis increases, and this causes pancreatitis.

**GENETIC ANALYSIS WITH PANCREATIC JUICE**

It is useful in the improvement of the diagnostic ability of PJC to use a genetic and molecular analysis from PJC samples in cases in which a small quantity of specimen was obtained from PJC and the adjuvant diagnosis of the cytodiagnosis is negative. In a diagnosis for pancreatic cancer, sensitivity improves by adding the *K-ras* mutation analysis with routine cytology[64]. There are some reports about the utilities of telomerase activity[65], DNA methylation[66], Smad4[67], and KL-6[68,69] measurement in pancreatic juice.

**LIMITATION OF PJC**

First, the accuracy of PJC is generally only around 40%-70%[55,56] except in some institutions[8,57,58]. Second, we cannot diagnose pancreatic neuroendocrine tumor, solid pseudopapillary neoplasm, or pancreatic acinar cell carcinoma, because they are not connected to the main pancreatic duct. Third, it is hard to perform immunostaining because it is difficult to obtain a specimen as compared with EUS-FNA. Fourth, around 4.2%-33.3% of complications such as post ERCP pancreatitis (PEP) can occur after PJC[8,55-57,60], but it is reported that the risk decreases for PEP with diclofenac administration.  Elmunzer reported that post-ERCP pancreatitis developed in 27 of 295 patients (9.2%) in the indomethacin group and in 52 of 307 patients (16.9%) in the placebo group (*P* = 0.005). Moderate-to-severe pancreatitis developed in 13 patients (4.4%) in the indomethacin group and in 27 patients (8.8%) in the placebo group (*P* = 0.03)[70].

**USE OF EUS-FNA AND PJC**

Generally, EUS-FNA is better in diagnostic ability and adverse events than PJC. Therefore, if we can perform EUS-FNA, we should choose EUS-FNA, and it is desirable to only choose PJC in the following cases: (1) We can not detect a mass in EUS; (2) It is difficult to perform EUS-FNA when avoiding blood vessels and the main pancreatic duct; (3) It is difficult to stop use of antithrombotic medicine; and (4) There aren’t any institutions capable of performing EUS-FNA in the neighborhood.

Furthermore, there are some reports that the diagnostic accuracy of EUS-FNA and/or PJC was significantly higher than that of EUS-FNA or PJC alone[8,71].

In conclusion, although there are some complications such as acute pancreatitis and dissemination, if the frequency of complications and the physical burden of surgery for patients are taken into consideration, it is perhaps better to obtain tissue before treatment begins. Since there are various methods of sampling tissue, it is important to choose the procedure while considering the patient’s condition and safety.

**REFERENCES**

1 **DiMagno EP**, Reber HA, Tempero MA. AGA technical review on the epidemiology, diagnosis, and treatment of pancreatic ductal adenocarcinoma. American Gastroenterological Association. *Gastroenterology* 1999; **117**: 1464-1484 [PMID: 10579989 DOI: 10.1016/S0016-5085(99)70298-2]

2 **Jemal A**, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer statistics, 2003. *CA Cancer J Clin* 2003; **53**: 5-26 [PMID: 12568441 DOI: 10.3322/canjclin.53.1.5]

3 **Gudjonsson B**. Cancer of the pancreas. 50 years of surgery. *Cancer* 1987; **60**: 2284-2303 [PMID: 3326653 DOI: 10.1002/1097-0142(19871101)60:9<2284::AID-CNCR2820600930>3.0.CO;2-V]

4 **Warshaw AL**, Fernández-del Castillo C. Pancreatic carcinoma. *N Engl J Med* 1992; **326**: 455-465 [PMID: 1732772 DOI: 10.1056/NEJM199202133260706]

5 **Smith CD**, Behrns KE, van Heerden JA, Sarr MG. Radical pancreatoduodenectomy for misdiagnosed pancreatic mass. *Br J Surg* 1994; **81**: 585-589 [PMID: 7911387 DOI: 10.1002/bjs.1800810435]

6 **van Gulik TM**, Reeders JW, Bosma A, Moojen TM, Smits NJ, Allema JH, Rauws EA, Offerhaus GJ, Obertop H, Gouma DJ. Incidence and clinical findings of benign, inflammatory disease in patients resected for presumed pancreatic head cancer. *Gastrointest Endosc* 1997; **46**: 417-423 [PMID: 9402115 DOI: 10.1016/S0016-5107(97)70034-8]

7 **Abraham SC**, Wilentz RE, Yeo CJ, Sohn TA, Cameron JL, Boitnott JK, Hruban RH. Pancreaticoduodenectomy (Whipple resections) in patients without malignancy: are they all 'chronic pancreatitis'? *Am J Surg Pathol* 2003; **27**: 110-120 [PMID: 12502933 DOI: 10.1097/00000478-200301000-00012]

8 **Matsumoto K**, Takeda Y, Harada K, Horie Y, Yashima K, Murawaki Y. Effect of pancreatic juice cytology and/or endoscopic ultrasound-guided fine-needle aspiration biopsy for pancreatic tumor. *J Gastroenterol Hepatol* 2014; **29**: 223-227 [PMID: 23869654 DOI: 10.1111/jgh.12332]

9 **Haba S**, Yamao K, Bhatia V, Mizuno N, Hara K, Hijioka S, Imaoka H, Niwa Y, Tajika M, Kondo S, Tanaka T, Shimizu Y, Yatabe Y, Hosoda W, Kawakami H, Sakamoto N. Diagnostic ability and factors affecting accuracy of endoscopic ultrasound-guided fine needle aspiration for pancreatic solid lesions: Japanese large single center experience. *J Gastroenterol* 2013; **48**: 973-981 [PMID: 23090002 DOI: 10.1007/s00535-012-0695-8]

10 **Sarmiento JM**, Que FG. Hepatic surgery for metastases from neuroendocrine tumors. *Surg Oncol Clin N Am* 2003; **12**: 231-242 [PMID: 12735141]

11 **Gourgou-Bourgade S**, Bascoul-Mollevi C, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Boige V, Bérille J, Conroy T. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. *J Clin Oncol* 2013; **31**: 23-29 [PMID: 23213101 DOI: 10.1200/JCO.2012.44.4869]

12 **Von Hoff DD**, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369**: 1691-1703 [PMID: 24131140 DOI: 10.1056/NEJMoa1304369]

13 **Raymond E**, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, Valle J, Metrakos P, Smith D, Vinik A, Chen JS, Hörsch D, Hammel P, Wiedenmann B, Van Cutsem E, Patyna S, Lu DR, Blanckmeister C, Chao R, Ruszniewski P. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011; **364**: 501-513 [PMID: 21306237 DOI: 10.1056/NEJMoa1003825]

14 **Yao JC**, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, Hobday TJ, Okusaka T, Capdevila J, de Vries EG, Tomassetti P, Pavel ME, Hoosen S, Haas T, Lincy J, Lebwohl D, Öberg K. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011; **364**: 514-523 [PMID: 21306238 DOI: 10.1056/NEJMoa1009290]

15 **Vilmann P**, Jacobsen GK, Henriksen FW, Hancke S. Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreatic disease. *Gastrointest Endosc* 1992; **38**: 172-173 [PMID: 1568614]

16 **Bang JY**, Magee SH, Ramesh J, Trevino JM, Varadarajulu S. Randomized trial comparing fanning with standard technique for endoscopic ultrasound-guided fine-needle aspiration of solid pancreatic mass lesions. *Endoscopy* 2013; **45**: 445-450 [PMID: 23504490 DOI: 10.1055/s-0032-1326268]

17 **Madhoun MF**, Wani SB, Rastogi A, Early D, Gaddam S, Tierney WM, Maple JT. The diagnostic accuracy of 22-gauge and 25-gauge needles in endoscopic ultrasound-guided fine needle aspiration of solid pancreatic lesions: a meta-analysis. *Endoscopy* 2013; **45**: 86-92 [PMID: 23307148 DOI: 10.1055/s-0032-1325992]

18 **Affolter KE**, Schmidt RL, Matynia AP, Adler DG, Factor RE. Needle size has only a limited effect on outcomes in EUS-guided fine needle aspiration: a systematic review and meta-analysis. *Dig Dis Sci* 2013; **58**: 1026-1034 [PMID: 23086117 DOI: 10.1007/s10620-012-2439-2]

19 **Sakamoto H**, Kitano M, Komaki T, Noda K, Chikugo T, Dote K, Takeyama Y, Das K, Yamao K, Kudo M. Prospective comparative study of the EUS guided 25-gauge FNA needle with the 19-gauge Trucut needle and 22-gauge FNA needle in patients with solid pancreatic masses. *J Gastroenterol Hepatol* 2009; **24**: 384-390 [PMID: 19032453 DOI: 10.1111/j.1440-1746.2008.05636.x]

20 **Camellini L**, Carlinfante G, Azzolini F, Iori V, Cavina M, Sereni G, Decembrino F, Gallo C, Tamagnini I, Valli R, Piana S, Campari C, Gardini G, Sassatelli R. A randomized clinical trial comparing 22G and 25G needles in endoscopic ultrasound-guided fine-needle aspiration of solid lesions. *Endoscopy* 2011; **43**: 709-715 [PMID: 21611946 DOI: 10.1055/s-0030-1256482]

21 **Varadarajulu S**, Bang JY, Hebert-Magee S. Assessment of the technical performance of the flexible 19-gauge EUS-FNA needle. *Gastrointest Endosc* 2012; **76**: 336-343 [PMID: 22817786 DOI: 10.1016/j.gie.2012.04.455]

22 **Ramesh J**, Bang JY, Hebert-Magee S, Trevino J, Eltoum I, Frost A, Hasan MK, Logue A, Hawes R, Varadarajulu S. Randomized Trial Comparing the Flexible 19G and 25G Needles for Endoscopic Ultrasound-Guided Fine Needle Aspiration of Solid Pancreatic Mass Lesions. *Pancreas* 2015; **44**: 128-133 [PMID: 25232713 DOI: 10.1097/MPA.0000000000000217]

23 **Wallace MB**, Kennedy T, Durkalski V, Eloubeidi MA, Etamad R, Matsuda K, Lewin D, Van Velse A, Hennesey W, Hawes RH, Hoffman BJ. Randomized controlled trial of EUS-guided fine needle aspiration techniques for the detection of malignant lymphadenopathy. *Gastrointest Endosc* 2001; **54**: 441-447 [PMID: 11577304]

24 **Lee JK**, Choi JH, Lee KH, Kim KM, Shin JU, Lee JK, Lee KT, Jang KT. A prospective, comparative trial to optimize sampling techniques in EUS-guided FNA of solid pancreatic masses. *Gastrointest Endosc* 2013; **77**: 745-751 [PMID: 23433878 DOI: 10.1016/j.gie.2012.12.009]

25 **Puri R**, Vilmann P, Săftoiu A, Skov BG, Linnemann D, Hassan H, Garcia ES, Gorunescu F. Randomized controlled trial of endoscopic ultrasound-guided fine-needle sampling with or without suction for better cytological diagnosis. *Scand J Gastroenterol* 2009; **44**: 499-504 [PMID: 19117242 DOI: 10.1080/00365520802647392]

26 **Nakai Y**, Isayama H, Chang KJ, Yamamoto N, Hamada T, Uchino R, Mizuno S, Miyabayashi K, Yamamoto K, Kawakubo K, Kogure H, Sasaki T, Hirano K, Tanaka M, Tada M, Fukayama M, Koike K. Slow pull versus suction in endoscopic ultrasound-guided fine-needle aspiration of pancreatic solid masses. *Dig Dis Sci* 2014; **59**: 1578-1585 [PMID: 24429514 DOI: 10.1007/s10620-013-3019-9]

27 **Kudo T**, Kawakami H, Hayashi T, Yasuda I, Mukai T, Inoue H, Katanuma A, Kawakubo K, Ishiwatari H, Doi S, Yamada R, Maguchi H, Isayama H, Mitsuhashi T, Sakamoto N; Japan EUS-FNA Negative Pressure Suction Study Group. High and low negative pressure suction techniques in EUS-guided fine-needle tissue acquisition by using 25-gauge needles: a multicenter, prospective, randomized, controlled trial. *Gastrointest Endosc* 2014; **80**: 1030-7.e1 [PMID: 24890422 DOI: 10.1016/j.gie.2014.04.012]

28 **Hébert-Magee S**, Bae S, Varadarajulu S, Ramesh J, Frost AR, Eloubeidi MA, Eltoum IA. The presence of a cytopathologist increases the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration cytology for pancreatic adenocarcinoma: a meta-analysis. *Cytopathology* 2013; **24**: 159-171 [PMID: 23711182 DOI: 10.1111/cyt.12071]

29 **Erickson RA**, Sayage-Rabie L, Beissner RS. Factors predicting the number of EUS-guided fine-needle passes for diagnosis of pancreatic malignancies. *Gastrointest Endosc* 2000; **51**: 184-190 [PMID: 10650262]

30 **Iglesias-Garcia J**, Dominguez-Munoz JE, Abdulkader I, Larino-Noia J, Eugenyeva E, Lozano-Leon A, Forteza-Vila J. Influence of on-site cytopathology evaluation on the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) of solid pancreatic masses. *Am J Gastroenterol* 2011; **106**: 1705-1710 [PMID: 21483464 DOI: 10.1038/ajg.2011.119]

31 **LeBlanc JK**, Ciaccia D, Al-Assi MT, McGrath K, Imperiale T, Tao LC, Vallery S, DeWitt J, Sherman S, Collins E. Optimal number of EUS-guided fine needle passes needed to obtain a correct diagnosis. *Gastrointest Endosc* 2004; **59**: 475-481 [PMID: 15044881]

32 **Iwashita T**, Yasuda I, Mukai T, Doi S, Nakashima M, Uemura S, Mabuchi M, Shimizu M, Hatano Y, Hara A, Moriwaki H. Macroscopic on-site quality evaluation of biopsy specimens to improve the diagnostic accuracy during EUS-guided FNA using a 19-gauge needle for solid lesions: a single-center prospective pilot study (MOSE study). *Gastrointest Endosc* 2015; **81**: 177-185 [PMID: 25440688 DOI: 10.1016/j.gie.2014.08.040]

33 **Schmidt RL**, Witt BL, Lopez-Calderon LE, Layfield LJ. The influence of rapid onsite evaluation on the adequacy rate of fine-needle aspiration cytology: a systematic review and meta-analysis. *Am J Clin Pathol* 2013; **139**: 300-308 [PMID: 23429365 DOI: 10.1309/AJCPEGZMJKC42VUP]

34 **Matsumoto K**, Ueki M, Takeda Y, Harada K, Onoyama T, Kawata S, Ikebuchi Y, Imamoto R, Horie Y, Murawaki Y. Development of a device for detecting the target specimens from EUS-guided FNA samples. *Endosc Int Open* 2015; **3**: E662-4 [PMID: 26716133 DOI: 10.1055/s-0034-1393076]

35 **Hewitt MJ**, McPhail MJ, Possamai L, Dhar A, Vlavianos P, Monahan KJ. EUS-guided FNA for diagnosis of solid pancreatic neoplasms: a meta-analysis. *Gastrointest Endosc* 2012; **75**: 319-331 [PMID: 22248600 DOI: 10.1016/j.gie.2011.08.049]

36 **Xu Y**, Hu D, Zhu Q, Sun Y. Performance of K-ras mutation analysis plus endoscopic ultrasound-guided fine-needle aspiration for differentiating diagnosis of pancreatic solid mass: a meta-analysis. *Chin Med J (Engl)* 2014; **127**: 3296-3301 [PMID: 25266530]

37 **Tadic M**, Stoos-Veic T, Kusec R. Endoscopic ultrasound guided fine needle aspiration and useful ancillary methods. *World J Gastroenterol* 2014; **20**: 14292-14300 [PMID: 25339816 DOI: 10.3748/wjg.v20.i39.14292]

38 **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**: 269-271 [PMID: 12556803]

39 **Hirooka Y**, Goto H, Itoh A, Hashimoto S, Niwa K, Ishikawa H, Okada N, Itoh T, Kawashima H. Case of intraductal papillary mucinous tumor in which endosonography-guided fine-needle aspiration biopsy caused dissemination. *J Gastroenterol Hepatol* 2003; **18**: 1323-1324 [PMID: 14535994]

40 **Matsumoto K**, Hara K, Sawaki A, Mizuno N, Hijioka S, Imamura H, Niwa Y, Tajika M, Kawai H, Kondo S, Inaba Y, Yamao K. Ruptured pseudoaneurysm of the splenic artery complicating endoscopic ultrasound-guided fine-needle aspiration biopsy for pancreatic cancer. *Endoscopy* 2010; **42 Suppl 2**: E27-E28 [PMID: 20073006 DOI: 10.1055/s-0029-1215323]

41 **Wang KX**, Ben QW, Jin ZD, Du YQ, Zou DW, Liao Z, Li ZS. Assessment of morbidity and mortality associated with EUS-guided FNA: a systematic review. *Gastrointest Endosc* 2011; **73**: 283-290 [PMID: 21295642 DOI: 10.1016/j.gie.2010.10.045]

42 **Micames C**, Jowell PS, White R, Paulson E, Nelson R, Morse M, Hurwitz H, Pappas T, Tyler D, McGrath K. Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA vs. percutaneous FNA. *Gastrointest Endosc* 2003; **58**: 690-695 [PMID: 14595302]

43 **Ikezawa K**, Uehara H, Sakai A, Fukutake N, Imanaka K, Ohkawa K, Tanakura R, Ioka T, Tanaka S, Ishikawa O, Katayama K. Risk of peritoneal carcinomatosis by endoscopic ultrasound-guided fine needle aspiration for pancreatic cancer. *J Gastroenterol* 2013; **48**: 966-972 [PMID: 23065024 DOI: 10.1007/s00535-012-0693-x]

44 **Beane JD**, House MG, Coté GA, DeWitt JM, Al-Haddad M, LeBlanc JK, McHenry L, Sherman S, Schmidt CM, Zyromski NJ, Nakeeb A, Pitt HA, Lillemoe KD. Outcomes after preoperative endoscopic ultrasonography and biopsy in patients undergoing distal pancreatectomy. *Surgery* 2011; **150**: 844-853 [PMID: 22000199 DOI: 10.1016/j.surg.2011.07.068]

45 **Ngamruengphong S**, Xu C, Woodward TA, Raimondo M, Stauffer JA, Asbun HJ, Wallace MB. Risk of gastric or peritoneal recurrence, and long-term outcomes, following pancreatic cancer resection with preoperative endosonographically guided fine needle aspiration. *Endoscopy* 2013; **45**: 619-626 [PMID: 23881804 DOI: 10.1055/s-0033-1344216]

46 **Ngamruengphong S**, Swanson KM, Shah ND, Wallace MB. Preoperative endoscopic ultrasound-guided fine needle aspiration does not impair survival of patients with resected pancreatic cancer. *Gut* 2015; **64**: 1105-1110 [PMID: 25575893 DOI: 10.1136/gutjnl-2014-307475]

47 **Maguchi H**. The roles of endoscopic ultrasonography in the diagnosis of pancreatic tumors. *J Hepatobiliary Pancreat Surg* 2004; **11**: 1-3 [PMID: 15747027]

48 **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**: 844-850 [PMID: 15128348]

49 **Fritscher-Ravens A**, Brand L, Knöfel WT, Bobrowski C, Topalidis T, Thonke F, de Werth A, Soehendra N. Comparison of endoscopic ultrasound-guided fine needle aspiration for focal pancreatic lesions in patients with normal parenchyma and chronic pancreatitis. *Am J Gastroenterol* 2002; **97**: 2768-2775 [PMID: 12425546]

50 **Varadarajulu S**, Tamhane A, Eloubeidi MA. Yield of EUS-guided FNA of pancreatic masses in the presence or the absence of chronic pancreatitis. *Gastrointest Endosc* 2005; **62**: 728-36; quiz 751, 753 [PMID: 16246688]

51 **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**: 868-872 [PMID: 12447300]

52 **Siddiqui AA**, Kowalski TE, Shahid H, O'Donnell S, Tolin J, Loren DE, Infantolino A, Hong SK, Eloubeidi MA. False-positive EUS-guided FNA cytology for solid pancreatic lesions. *Gastrointest Endosc* 2011; **74**: 535-540 [PMID: 21737075 DOI: 10.1016/j.gie.2011.04.039]

53 **McCune WS**, Shorb PE, Moscovitz H. Endoscopic cannulation of the ampulla of vater: a preliminary report. *Ann Surg* 1968; **167**: 752-756 [PMID: 5646296]

54 **Endo Y**, Morii T, Tamura H, Okuda S. Cytodiagnosis of pancreatic malignant tumors by aspiration, under direct vision, using a duodenal fiberscope. *Gastroenterology* 1974; **67**: 944-951 [PMID: 4372126]

55 **Wakatsuki T**, Irisawa A, Bhutani MS, Hikichi T, Shibukawa G, Takagi T, Yamamoto G, Takahashi Y, Yamada Y, Watanabe K, Obara K, Suzuki T, Sato Y. Comparative study of diagnostic value of cytologic sampling by endoscopic ultrasonography-guided fine-needle aspiration and that by endoscopic retrograde pancreatography for the management of pancreatic mass without biliary stricture. *J Gastroenterol Hepatol* 2005; **20**: 1707-1711 [PMID: 16246190]

56 **Uchida N**, Kamada H, Tsutsui K, Ono M, Aritomo Y, Masaki T, Kushida Y, Haba R, Nakatsu T, Kuriyama S. Utility of pancreatic duct brushing for diagnosis of pancreatic carcinoma. *J Gastroenterol* 2007; **42**: 657-662 [PMID: 17701129]

57 **Uehara H**, Tatsumi K, Masuda E, Kato M, Kizu T, Ishida T, Takakura R, Takano Y, Nakaizumi A, Ishikawa O, Takenaka A. Scraping cytology with a guidewire for pancreatic-ductal strictures. *Gastrointest Endosc* 2009; **70**: 52-59 [PMID: 19249043 DOI: 10.1016/j.gie.2008.09.059]

58 **Iiboshi T**, Hanada K, Fukuda T, Yonehara S, Sasaki T, Chayama K. Value of cytodiagnosis using endoscopic nasopancreatic drainage for early diagnosis of pancreatic cancer: establishing a new method for the early detection of pancreatic carcinoma in situ. *Pancreas* 2012; **41**: 523-529 [PMID: 22504379 DOI: 10.1097/MPA.0b013e31823c0b05]

59 **Mikata R**, Ishihara T, Tada M, Tawada K, Saito M, Kurosawa J, Sugiyama H, Sakai Y, Tsuyuguchi T, Miyazaki M, Yokosuka O. Clinical usefulness of repeated pancreatic juice cytology via endoscopic naso-pancreatic drainage tube in patients with pancreatic cancer. *J Gastroenterol* 2013; **48**: 866-873 [PMID: 23053424 DOI: 10.1007/s00535-012-0684-y]

60 **Harada R**, Kawamoto H, Fukatsu H, Kato H, Hirao K, Kurihara N, Mizuno O, Ogawa T, Ishida E, Okada H, Yamamoto K, Yamamoto H. Nonprevention of post-endoscopic retrograde cholangiopancreatographic pancreatitis by pancreatic stent after aspiration of pure pancreatic juice in patients with intraductal papillary mucinous neoplasms of the pancreas. *Pancreas* 2010; **39**: 340-344 [PMID: 19823100 DOI: 10.1097/MPA.0b013e3181bb8da1]

61 **Nakaizumi A**, Tatsuta M, Uehara H, Yamamoto R, Takenaka A, Kishigami Y, Takemura K, Kitamura T, Okuda S. Cytologic examination of pure pancreatic juice in the diagnosis of pancreatic carcinoma. The endoscopic retrograde intraductal catheter aspiration cytologic technique. *Cancer* 1992; **70**: 2610-2614 [PMID: 1423189]

62 **ChiRhoStim**. Indications. Available from: URL: http: //www.human-secretin.com/html/index.aspx?p32sda=indications&psdge87d=269&tl97abi=73

63 **Imamura T**, Koizumi Y, Koyama R, Okuda C, Takeuchi K, Matsuda M, Hashimoto M, Watanabe G, Yoshida H and Imawari M. Effectiveness of cytodiagnosis with pancreatic duct lavage fluid for pancreatic ductal carcinoma –new sampling technique.　*Gastroenterological* *Endosc* 2009; **51**: 84-90

64 **Ha A**, Watanabe H, Yamaguchi Y, Ohtsubo K, Wang Y, Motoo Y, Okai T, Wakabayahi T, Sawabu N. Usefulness of supernatant of pancreatic juice for genetic analysis of K-ras in diagnosis of pancreatic carcinoma. *Pancreas* 2001; **23**: 356-363 [PMID: 11668203]

65 **Suehara N**, Mizumoto K, Muta T, Tominaga Y, Shimura H, Kitajima S, Hamasaki N, Tsuneyoshi M, Tanaka M. Telomerase elevation in pancreatic ductal carcinoma compared to nonmalignant pathological states. *Clin Cancer Res* 1997; **3**: 993-998 [PMID: 9815776]

66 **Matsubayashi H**, Canto M, Sato N, Klein A, Abe T, Yamashita K, Yeo CJ, Kalloo A, Hruban R, Goggins M. DNA methylation alterations in the pancreatic juice of patients with suspected pancreatic disease. *Cancer Res* 2006; **66**: 1208-1217 [PMID: 16424060]

67 **Fukushige S**, Furukawa T, Satoh K, Sunamura M, Kobari M, Koizumi M, Horii A. Loss of chromosome 18q is an early event in pancreatic ductal tumorigenesis. *Cancer Res* 1998; **58**: 4222-4226 [PMID: 9766641]

68 **Ito H**, Endo T, Oka T, Matumoto T, Abe T, Toyota M, Imai K, Satoh M, Maguchi H, Shinohara T. Mucin expression profile is related to biological and clinical characteristics of intraductal papillary-mucinous tumors of the pancreas. *Pancreas* 2005; **30**: e96-102 [PMID: 15841035]

69 **Matsumoto K**, Takeda Y, Harada K, Onoyama T, Kawata S, Horie Y, Sakamoto T, Ueki M, Miura N, Murawaki Y. Clinical Impact of the KL-6 Concentration of Pancreatic Juice for Diagnosing Pancreatic Masses. *Biomed Res Int* 2015; **2015**: 528304 [PMID: 26451373 DOI: 10.1155/2015/528304]

70 **Elmunzer BJ**, Scheiman JM, Lehman GA, Chak A, Mosler P, Higgins PD, Hayward RA, Romagnuolo J, Elta GH, Sherman S, Waljee AK, Repaka A, Atkinson MR, Cote GA, Kwon RS, McHenry L, Piraka CR, Wamsteker EJ, Watkins JL, Korsnes SJ, Schmidt SE, Turner SM, Nicholson S, Fogel EL. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. *N Engl J Med* 2012; **366**: 1414-1422 [PMID: 22494121 DOI: 10.1056/NEJMoa1111103]

71 **Noma Y**, Kawamoto H, Kato H, Iwamuro M, Hirao K, Fujii M, Tsutsumi K, Horiguchi S, Yamamoto N, Sakakihara I, Tomoda T, Matsumoto K, Okada H, Yamamoto K. The efficacy and safety of single-session endoscopic ultrasound-guided fine needle aspiration and endoscopic retrograde cholangiopancreatography for evaluation of pancreatic masses. *Hepatogastroenterology* 2014; **61**: 1775-1779 [PMID: 25436378]

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