REVIEW ARTICLE

Optimizing Endoscopic Ultrasound Guided Tissue Sampling of the Pancreas

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ABSTRACT

Endoscopic ultrasound is an important innovation in the field of gastrointestinal endoscopy and allows evaluation of many organs in the vicinity of the gastrointestinal tract. Endoscopic ultrasound-fine needle aspiration has been established to be an important tool in the management of pancreaticobiliary disease and is used for screening, staging, biopsy confirmation, and palliation. The accuracy of endoscopic ultrasound-fine needle aspiration is affected by several factors such as different needle sizes and types and fine needle aspiration techniques. Several comparative studies have been published on various techniques, such as the use of a stylet and suction during fine needle aspiration. Although most studies demonstrate high accuracy across techniques and equipment, various fine needle biopsy histology needles have been studied to compare the advantage of fine needle biopsy over fine needle aspiration. Although fine needle biopsy needles provide better tissue architecture and require fewer numbers of passes, there is no significant evidence of the superiority of fine needle biopsy over fine needle aspiration with regard to diagnostic yield and core tissue procurement. The main aim of this article is to review the various methodologies for improving the practice of endoscopic ultrasound-fine needle aspiration and endoscopic ultrasound- fine needle biopsy tissue sampling for cytological and histological analysis.

INTRODUCTION

Pancreatic cancer is the fourth most common cause of cancer-related death in United States and has an overall five year survival rate is about 5-6% [1]. These poor outcomes are likely due to the aggressive behavior of these tumors, the advanced stage of presentation, and the lack of options for early detection. Early detection, proper staging, and tissue sampling for individualized therapy for pancreatic cancer is important for increasing overall survival and optimizing patient care. Endoscopic ultrasound (EUS) can be used for early detection, screening in high risk individuals, staging, and minimally invasive tissue sampling. Together with cross-sectional imaging, EUS has become a standard tool for the evaluation of pancreatic cancer. Results from the Surveillance Epidemiology and End Results (SEER) database, a US-population based study, have demonstrated that pre-operative EUS evaluation is associated with increased survival in patients who have pancreatic cancer. This is likely due to stage-targeted therapy with chemoradiation and curative-intent surgery compared to populations who did not undergo EUS [2].

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Abbreviations EUS endoscopic ultrasound; EUS-FNA endoscopic ultrasound-fine needle aspiration; EUS-FNB endoscopic ultrasound-fine needle biopsy; EUS-TCB endoscopic ultrasound–Trucut biopsy; OCE onsite cytological evaluation; RCTs randomized controlled trail
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EUS is one of several high resolution imaging modalities for pancreatico-biliary disease along with pancreas specific Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). EUS-guided fine needle aspiration (FNA) has an important role in the cytological and morphological diagnosis of pancreatic cancers. The procedure is minimally invasive and relatively safe [3]. For the last twenty-five years EUS-FNA has evolved in terms of diagnostic and therapeutic management of gastrointestinal (GI) lesions. Tissue can also be obtained with EUS- FNA techniques from different lesions, such as the liver, gall bladder, adrenal glands, and retroperitoneal and mediastinal lymph nodes [4-7]. Adequate tissue is essential for initiating chemotherapy, and thus pre-operative EUS-FNA or other tissue-sampling methods are increasingly necessary in the setting of neo-adjuvant therapy where surgical tissue is not available [8]. The quality indicators for the EUS-FNA technique include accurate staging of the malignancy, the diagnostic yield, and optimal tissue acquisition (adequacy) with few adverse events [9]. Several clinical trials and observational studies have been published to establish the effectiveness of EUS-FNA on pancreatic masses, but challenges and limitations associated with the techniques still exist. To optimize the outcomes associated with EUS-FNA, different factors should be considered. These include effectiveness of different sizes of EUS-FNA needles, the number of fine-needle core biopsy (FNB) histology needles, various novel sampling techniques, and the availability of onsite cytological evaluation (OCE) for rapid evaluation and operator performance [10-18]. The main objective

of this review is to describe the methods for optimizing the practice of EUS-FNA and EUS-FNB tissue sampling methodology for cytological analysis.

EUS-FNA

Adequate sample acquisition by EUS-FNA has become an essential tool for the accurate diagnosis of pancreatic cancer. EUS procedures are similar to those of standard upper endoscopy with moderate or deep sedation. The endoscope is passed orally to the stomach and duodenum. The pancreas body and tail are best visualized through the posterior stomach wall and the pancreas head via the second and third duodenum. Depending on the site of the lesion, different needle sizes and approaches are considered. The tumor is targeted with the EUS endoscope, and a needle is passed via the instrument channel. The needle apparatus is unlocked, and the sharp tip is punctured into the tumor. A stylet may be used to provide negative pressure by slow withdrawal of the stylet, or it may be removed completely and negative pressure applied with a syringe. The needle is passed to-and-fro typically for 20-30 seconds while moving the position of the needle in a "fanning" pattern to maximize sampling volume. The needle is then removed from the endoscope, and the tissue is prepared for pathological examination. All the FNA material is expressed onto glass slide or placed in a preservative material for pathological analysis. When making thin smears, one sample is typically prepared for OCE by making an air-dried slide and staining with a modified Romanowsky stain. Matching thin smears are made, alcohol fixed, and prepared with Papanicolaou stain. Visible core tissue can be placed in formalin and paraffin embedded for Hematoxylin and Eosin staining. After each pass of the needle, the on-site cytotechnician, when available, evaluates the adequacy and degree of the pathological changes in the obtained material. Based on the information provided by the cytotechnician, the operator repeats the FNA until sufficient tissue is obtained. The role of OCE is important because it provides real-time feedback on specimen adequacy and allows the endoscopist to continue or modify the sampling to ensure an adequate specimen. After complete staining, all EUS- FNA specimens are evaluated for cytological diagnosis and cellular preservation by a pathologist. The cytologic diagnoses are classified according to established guidelines [19].

Role of On-Site Cytological Evaluation

Meta-analysis of several randomized controlled trials (RCTs) and observational studies have revealed that EUS-FNA has an overall sensitivity of 85% (95% CI, 84-86) and a specificity of 98% (95% CI, 97-99) for pancreatic malignancies [20]. The false positive rate of EUS-FNA is about 1.1-5.3% and false negative rate is about 4-45% [20-25]. The main reasons for the high false negative rate are sampling errors, which occur more frequently for cystic lesions than solid lesions. There are few data comparing the diagnostic yield, specimen adequacy, and accuracy with and without OCE [26-27]. In one RCT, patients with pancreatic masses who had undergone EUS-FNA with and without OCE were evaluated for diagnostic yield of malignancy and proportion of inadequate specimens. The results showed no difference in the diagnostic yield of malignancy (OCE absent: 71.6% *vs*. OCE present: 75.2%, P=0.45) or the proportion of inadequate specimens between the two groups (OCE absent, 13.3% *vs*. OCE present, 9.9%, P=0.4). Fewer passes were required for obtaining an adequate specimen in the OCE group (median, OCE present: 4 *vs*. OCE absent: 7) [27]. Similarly, results from one observational study revealed that OCE was associated with fewer passes (with OCE 2 *vs*. without OCE 3.5, p<0.001), increased diagnostic yield for malignancy (96.2% *vs*. 78.2%, p=0.002), fewer inadequate samples (1% *vs*. 12.6%, P=0.002), and improved overall accuracy (OCE 96.8% *vs*. OCE absent 86.2%, P=0.01) [28]. In another RCT, the diagnostic yield of pancreatic masses with OCE-guided EUS-FNA was compared with seven passes of EUS-FNA without OCE. The study reported that there was no difference in diagnostic yield or the duration of procedure (P=0.944) between those two groups [29]. There were fewer passes required in the OCE arm than in the seven passes of the no-OCE arm. Therefore, the use of OCE allows fewer FNA passes but has less impact on diagnostic yield and number of inadequate specimens on EUS-FNA on pancreatic cancer. However, the use of OCE may be important in some centers where there adequacy of specimens is very low (<90%) [8].

Role of Negative Pressure/Suction during EUS FNA

Suction aspiration is widely used in standard EUS-FNA techniques. In one RCT, both the capillary suction (by slow removal of the needle stylet) and standard suction (with -10 cc to -20 cc of suction) had a comparable diagnostic sensitivity of 90% with fewer than two passes for the diagnosis of pancreatic masses [30]. Similarly, results from a pilot study demonstrated that the capillary technique was associated with higher diagnostic yield and less contamination with blood than the EUS-FNA suction technique of pancreatic masses. Sample adequacy of the capillary technique was 72% *vs*. 52% with suction technique, contamination of blood was 48% with the capillary technique *vs*. 71% with the suction technique, and the diagnostic yield with the capillary technique was 76% *vs*. 64% with the suction technique, but these results were not significant. However the small numbers of cases provide insufficient power to detect the clinically relevant differences. Therefore larger RCTs are needed to confirm this result with greater precision [31].

Several trials have evaluated the need to keep the stylet in the needle during EUS-FNA of pancreatic masses. Hypothetically, the stylet may reduce cellular contamination from the organs (stomach or duodenum) when the needle is passing through to reach the pancreas. However, the results from large studies showed no difference in the diagnostic yield or adequacy when comparing EUS-FNA with or without the use of a stylet [13, 15].

Role of Different Needle Gauges

Several studies have been conducted to evaluate the performance of 19-gauge, 22-gauge, and 25-gauge needles for the sampling of pancreatic mass lesions [10-12]. Results from pooled data from various observational studies and randomized trials by Wani *et al.* [8] demonstrated that a 25-gauge needle was associated with higher diagnostic yield compared with a 22-gauge needle in patients undergoing EUS-FNA of pancreatic masses. One observational study demonstrated that the diagnostic yield of a 19-gauge needle was higher than that of 22-gauge needle [32]. When one needle fails to obtain an adequate specimen, changing to a different size needle may be helpful. One observational study demonstrated that changing a needle was required for 5% of cases, and there was no difference between pancreatic and non-pancreatic cases [33]. Thus results are mixed regarding whether larger or smaller needles are preferred, but there is generally good diagnostic yield with all needles.

Complication of EUS- FNA

EUS-FNA is generally a safe procedure with few adverse events. Postprocedural pain, pancreatitis, bleeding, infection, and fever episodes are the most commonly reported adverse events, with a cumulative morbidity risk of 0.98% [34]. The overall mortality for EUS-FNA is 0.02% and pancreatitis rate is about 0.44% [35-37]. Aggressive tissue sampling of pancreatic cysts with methods such as intracystic brush cytology may be associated higher rates of intracystic bleeding and hemosuccus pancreaticus [38, 39]. The risk of bacteremia is low after EUS-FNA for both the upper and lower GI tract and is comparable to EUS without FNA [40, 41]. The routine use of antibiotics is generally not recommended during the procedure of EUS-FNA for solid lesions. However, the use of antibiotics for EUS-FNA pancreatic cystic lesions is recommended. In one case series, the rate of cystic infection was reported to be as high as 14% [42]; however, retrospective data from another cohort study showed a decreased risk of infection in patients treated with antibiotic use than without antibiotic use [43]. Tumor seeding in the needle tract has been reported only in rare cases. However large, population-based and single-center studies have not shown a detectable increased risk of tumor seeding with EUS-FNA [44, 45].

EUS-FNB

Acquisition of core biopsy specimens theoretically may improve histopathological analysis, immunostaining, and cost effectiveness, and it may eliminate the need for OCE [8]. Several benign conditions such as serous cystic pancreatic tumors, chronic pancreatitis, and autoimmune pancreatitis require histological morphology assessment for definitive diagnosis [46-48]. Several studies have evaluated the advantage of EUS-FNB over EUS-FNA. New needle technologies with various forms and diameters have been studied to overcome some of the limitations associated with EUS-FNA. Initially histology core procurement was started with a trucut needle biopsy (EUS-TNB, Quickcore; Cook Medical, Limerick Ireland) [49]. Due to the lack of flexibility of TNB needle and the anatomical location of pancreatic tumors, EUS-TNB was limited to use for pancreatic masses in the body and tail region of the pancreas where the endoscopic approach was more straightforward [50].

There have been several RCTs comparing newer core biopsy FNB needles to conventional FNA needles for the sampling of pancreatic. Although advancements have been made in terms of technical and novel instruments for adequate tissue acquisition, the multiple randomized controlled trials and observational studies have failed to show improvement in the diagnostic yield of FNB *vs*. FNA for pancreatic lesions [8]; however, FNB required fewer needle passes, preserved tissue integrity, was a shorter procedure, and allowed immunostaining [51-61].

Unlike EUS-FNA, routine use of OCE has not been widely evaluated in EUS-FNB. The nature of the bulk tissue acquired by FNB makes it less amenable to thin smear preparation and OCE. Alternative assessments include "touch preparation" in which the core biopsy is lightly touched or rolled onto a glass slide to exfoliate cells for cytological analysis and a gross inspection for bulk tissue. Results from one study revealed that the overall accuracy of FNA was 76%, the overall accuracy TCB was 76% (P=ns), and the overall accuracy of the combination of FNA and TCB was 95% (P=0.07) [62]. There were no differences in EUS-TCB accuracy compared to the accuracy of FNA with OCE similarly one retrospective study that evaluated formalin fixed-paraffin embedded (FFPE) cores only (Procore needle, Cook Medical) demonstrated no additional diagnostic yield compared to conventional EUS-FNA [63] .The routine use of OCE for EUS-FNB is thus not recommended because the available evidence suggests that it does not improve diagnostic yield [8]. Therefore improved needle design and more prospective RCTs are needed to evaluate the effectiveness of EUS-FNB with or without OCE. However, EUS-FNB can be used as a salvage technique when the results from the conventional EUS-FNA are inadequate [8]. Several studies have reported that show EUS-FNB is safe with comparable adverse events to those of EUS-FNA [64, 65].

Perspectives: How to Assess Specimen Adequacy

Most trials have shown that gross specimen evaluation by the endosonographer at the time of the procedure is important for evaluating the specimen's adequacy. The biopsy specimens are carefully retrieved from the needle lumen by air push or advancing the stylet. The specimen is then placed in buffered formalin, embedded in paraffin, and stained with Hematoxylin and Eosin for histological evaluation. Several factors determine the adequacy of the specimen, such as tumor cellularity, the presence of necrosis, the presence of blood, and the ratio of tumor cells to stroma [26, 66]. In one prospective study on pancreatic neuroendocrine tumors, the specimens obtained by EUS-FNA were sufficient for histological diagnosis in 93.3%. The primary outcome of the study was Ki-67 immunostaining

determination, which was accomplished by 92.9% [64]. However, in one study, histology quality and diagnostic yield was compared between procore FNB and standard FNA needle. The results showed that the overall diagnostic rate for the FNA group was 90%, but it was 100% for the FNB group. In most studies, the maximum length of the tissue core was measured after the procedure. At least 4-5 mm length of sample core or more is needed to make a histological assessment, and this is more likely to produce a diagnosis than the sample core, which are smaller [67-71]. In some studies adequacy has been described as when the specimen contains whitish material (presumed core tissue) obtained by EUS-FNB. Results from such studies have demonstrated that there is a high correlation between this visible core and adequate histologic specimens [7, 71, 72]. Inadequacy is also defined in some studies as specimens that contain no representative or useful tissue for rendering a pathologic diagnosis [73]. The tissue derived from the EUS FNB was judged adequate for obtaining a histology-based diagnosis, while retrieved material was judged inadequate if it was not sufficient to firmly establish a diagnosis [64]. However, most core biopsies are directly placed into formalin without evaluation of adequacy by touch preparation at the time of procedure. On site touch preparation assessment of core biopsies is often performed to direct the procedure and identify the appropriate time to conclude the procedure. Its utility, however, is debatable. In one study, the diagnostic yield was equal or greater for the needle biopsies without touch preparation relative to FNA [52]. In another observational study, touch preparation of core tissue improved the diagnostic accuracy of EUS-FNB when compared to EUS-FNB alone [74]. Therefore larger, well controlled studies are needed to evaluate the effectiveness and diagnostic yield of EUS-FNB with touch preparation.

Summary and Future Directions

Pancreatic cancer is characterized by several variations in biological behaviors and genes. Adequate tissue acquisition will be essential for exploring potential molecular markers and their role in individualized cancer therapy. Short-term goals include determining whether RNA and DNA can be extracted and profiled from FNA/FNB samples. Preliminary studies suggest that EUS-FNA allows the extraction of sufficient RNA to allow molecular tests such as K-*ras* mutation analysis, Ki-67 determination and realtime polymerase chain reactions [67, 75]. In summary, EUS-FNA has been demonstrated to be effective and safe for sampling the pancreas and related tissues. Advances in techniques and needles have improved specimen adequacy and procedural efficiency. Recent evidence suggests that EUS-FNA and FNB are likely to enable personalized therapy by allowing the characterization of genomic alterations and predictors of optimal therapy. In addition, well designed RCTs will be beneficial for defining the role of OCE in the field of EUS-FNB and efficacy of histology needles.

Conflicts of interest

Michael Wallace reports consulting income from Olympus Corp and grant support from Boston Scientific and Cosmo pharmaceuticals.

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