Endoscopic ultrasound-guided fine-needle aspiration with on-site cytopathology versus core biopsy: a comparison of both techniques performed at the same endoscopic session

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Background: Endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) with bedside cytopathology is the gold standard for assessment of pancreatic, subepithelial, and other lesions in close proximity to the gastrointestinal tract, but it is time-consuming, has certain diagnostic limitations, and bedside cytopathology is not widely available.

Aims: The goal of this study is to compare the diagnostic yield of EUS-guided FNA with on-site cytopathology and EUS-guided core biopsy.

Methods: Twenty-six patients with gastrointestinal mass lesions requiring biopsy at a tertiary medical center were included in this retrospective analysis of a prospective cohort. Two core biopsies were taken using a 22 gauge needle followed by FNA guided by a bedside cytopathologist at the same endoscopic session. The diagnostic yield and test characteristics of EUS core biopsy and EUS FNA with bedside cytopathology were examined.

Results: The mean number of passes was 3.2 for FNA, and the mean procedure time was 39.4 minutes. The final diagnosis was malignant in 92.3%. Sensitivity and specificity were 83% and 100%, respectively, for FNA, and 91.7% and 100%, respectively, for core biopsy. Diagnostic accuracy was 92.3% for FNA and 84.6% for core biopsy. The two approaches were in agreement in 88.4% with a kappa statistic of 0.66 (95% confidence interval 0.33 – 0.99).

Conclusions: An approach using two passes with a core biopsy needle is comparable to the current gold standard of FNA with bedside cytopathology. The performance of two core biopsies is time-efficient and could represent a good alternative to FNA with bedside cytopathology.

Introduction

Endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) is a widely available, commonly used, and effective modality for the evaluation of various gastrointestinal and peri-intestinal masses including pancreatic, submucosal, and lymphatic lesions [1 – 3]. Despite the diagnostic utility of EUS-guided FNA in the evaluation of mass lesions, there are several limitations to the procedure. The diagnostic yield of EUS-FNA is highly variable and influenced by the presence of an on-site cytopathologist. For example, EUS-FNA of pancreatic lesions has a diagnostic accuracy ranging from 78% to 95% [4], but these rates have been reported to be even lower for other targets [5, 6]. Inadequate specimens are obtained in as many as 29% of patients who undergo EUS-FNA without immediate review by a bedside cytopathologist [7]. On-site cytopathological evaluation of FNA samples significantly decreases the number of inadequate samples as well as the number of needle passes needed [8, 9]. Despite these advantages, many institutions lack immediate on-site interpretation by a cytopathologist during EUS-FNA.

Another limitation of EUS-FNA is the inherent inadequacies of cytology itself. The absence of tissue architecture with FNA makes it difficult to diagnose stromal tumors and lymphomas [10, 11]. More recently, studies have examined the utility of performing EUS-guided core biopsies as a way to overcome such limitations [12]. In the last decade, many studies have been published comparing the diagnostic yield of EUS-FNA (without on-site cytopathology) and EUS core needle biopsy for various gastrointestinal lesions. To our knowledge, there has not been a study comparing EUS-guided core biopsy and EUS-FNA utilizing immediate bedside cytopathologist review. We hypothesize that the diagnostic yield of EUS core biopsy is comparable to the diagnostic yield of EUS-FNA combined with on-site cytopathology.

Methods

Study design

This study was conducted at a tertiary referral medical center. With the aim of increasing diagnostic yield, all patients who were referred for EUS-guided biopsy at the Michael E. DeBakey VA Medical Center (MEDVAMC) between October 2011 and January 2013 were considered for both FNA and core biopsy during the same endoscopic session. Core biopsy was not performed if patients had cystic lesions, small lesions (defined as <1 cm) legions with overlying vascular structures that precluded safe intervention, or if the advanced endoscopist performing the procedure felt the risks of multiple biopsies outweighed the benefits. Data for this study was prospectively collected as part of a database that includes all EUS procedures performed in our endoscopy unit. Informed consent was obtained from each patient. The protocol was approved by the Baylor College of Medicine IRB and the MEDVAMC Research and Development Committee.

EUS-FNA and core biopsy

In this study, back-to-back EUS-FNA and core biopsy were performed on all patients during the same endoscopic session. All procedures were performed by a single, experienced advanced endoscopist (YS). YS has performed over 1000 cases of EUS and EUS-FNA. A gastroenterology fellow partially assisted in some of these cases. The mass lesions were identified using endoscopic ultrasound and sampled via two core biopsies (Cook 22-gauge Pro-Core core biopsy needle, Cook Endoscopy Inc; Limerick, Ireland) followed by two FNA passes (Cook 22-gauge FNA needle, Cook Endoscopy Inc; Limerick, Ireland). Suction was used to enhance cell capture. A bedside attending cytopathologist was present during the procedure and evaluated all FNA samples. A minimum of two FNA passes were made and more passes were obtained as needed based on the bedside cytopathologist's assessment of the initial FNA samples. Core biopsies were processed and evaluated by a pathologist (LG) blinded to the FNA results. All FNA and core biopsy specimens felt to be malignant were reviewed and confirmed by a second pathologist. LG has over 25 years of experience as a cytopathologist. She is a consultant cytopathologist for the entire VA system. At the completion of the procedure, patients were monitored in the post-anesthesia care unit for adverse events. Adverse events occurring after the immediate post-procedure period were determined based on chart review.

Outcomes

The primary objective of this study was to determine the diagnostic accuracy of EUS-guided core biopsy when compared with the accuracy of the gold standard, EUS-FNA with a bedside cytopathologist. Accuracy was defined as the percentage of specimens in which the biopsy diagnosis was consistent with the final diagnosis (i.e. sum of true positives and true negatives). The final diagnosis was determined based on a combination of surgical pathology; biopsy of primary tumor or metastatic lesions; serial imaging including computed tomography (CT), magnetic resonance imaging (MRI), X-ray, ultrasound, and positron emission tomography (PET) imaging; labs such as tumor markers; and clinical course. For example, if pathological diagnosis could not be obtained after multiple attempts with various modalities, metastatic or rapidly growing lesions were considered to be malignant. Patients were monitored for at least 1 year following their EUS procedure. Secondary outcomes examined in this study included procedure time and adverse events. Procedure time was defined as the time from insertion of the endoscope to removal. Data for secondary outcomes were collected based on a review of anesthesia, post-anesthesia care unit, and electronic medical records.

Statistical analysis

The diagnostic accuracy, sensitivity, and specificity were calculated for both techniques. Diagnostic accuracy (defined as true positives and true negatives) was compared using the Chi-squared test. Agreement in diagnostic yield of EUS-guided core biopsy and EUS-FNA with bedside cytopathologist was assessed using the kappa statistic. A multivariate analysis was conducted to examine potential predictors of an accurate diagnosis. Data analysis was performed using JMP 7 software (SAS Institute, Cary, NC).

Results

During the period between October 2011 and January 2013, 45 patients were referred for EUS-guided biopsy at the MEDVAMC. Both interventions could not be performed on 19 of the 45 patients for the following reasons: seven cystic lesions, five lesions smaller than 1 cm, four masses not seen during EUS, and three which were technically difficult to sample. Twenty-six patients were included in the final analysis. Nineteen (73.1%) of the sampled lesions were pancreatic masses. Extrapancreatic lesions included peripancreatic lymph nodes, gastric lesions, para-aortic lymph nodes, mediastinal masses, and liver lesions. Patient demographics and other relevant clinical characteristics are provided in **Table 1**.

Results from the procedure are displayed in **Table 2**. The mean number of passes was 3.2 for FNA. Mean procedure time was 39.4 minutes. There were no adverse events during or immediately following the procedure.

The final diagnosis was malignant in 92.3% of the cases and benign in 7.7% of the cases. Diagnostic accuracy was 84.6% (95%CI: 66.4–93.8%) for EUS core biopsy and 92.3% (95%CI: 75.5–97.8%) for EUS-FNA. The difference in accuracy between the two approaches was not statistically significant ($P=0.14$). The kappa statistic, which was calculated to measure the agreement in yield between EUS-FNA and EUS-guided core biopsy, was 0.62 (95%CI 0.33–0.91). The sensitivity and specificity for EUS-FNA were 83% and 100%, respectively. The sensitivity and specificity for EUS core biopsy were 91.7% and 100%, respectively.

Table 1 Patient characteristics.

Characteristics	
Age, mean ± SD, years	66.8 ± 8.9
Sex, male, n (%)	25 (96.2)
Race, Non-Hispanic White, n (%)	16 (61.5)
Site of lesion	
Pancreas, n (%)	19 (73.1)
Other, n (%)	7 (26.9)

Table 2 Endoscopic ultrasound (EUS) characteristics.

Diagnosis	
Benign, n (%)	2 (7.7)
Malignant, n (%)	24 (92.3)
Diagnostic accuracy	
FNA, n (%)	24 (92.3)
Core biopsy, n (%)	22 (84.6)
EUS-FNA test characteristics	
Sensitivity, %	83
Specificity, %	100
EUS core biopsy test characteristics	
Sensitivity, %	91.7
Specificity, %	100
Number of passes for FNA, n	
Mean	3.2
Range, min, max	2, 7
Procedure time, min	
Mean	39.4
Range, min, max	15, 80

EUS, endoscopic ultrasound; FNA, fine-needle aspiration.

Discussion

Endoscopic ultrasound-guided FNA with on-site cytopathology has become the gold standard in the evaluation of gastrointestinal and peri-intestinal mass lesions. This practice is not only cost-effective [13] but immediate review of FNA by an on-site cytopathologist has been shown to increase diagnostic yield by as much as 18 – 26 % [6, 7]. Unfortunately, this practice has not been universally embraced, most likely due to cost as well as lack of the necessary expertise and personnel. As such, there have been more and more studies published which examine alternatives to the on-site cytopathologist. One such alternative is the use of EUS-guided core biopsy [14]. Based on the results of our study, the diagnostic yield of two passes with a 22-gauge core biopsy needle is comparable to EUS-FNA with on-site cytopathology. The yield of EUS-FNA with a bedside cytopathologist in our study, irrespective of EUS-guided core biopsy, is similar to the yields published in other studies, which range from 78 % to 89 % [15 – 17]. For institutions which cannot afford or do not have access to an on-site cytopathologist, performing two core biopsies may improve yields and prevent unnecessarily repeating the procedure. As far as we can tell, this is the only study which compares EUS core biopsy to our current gold standard of EUS-FNA in the same patients with on-site cytopathology review.

At this time, most of the published studies compare the diagnostic yield of EUS core biopsy using a 19-gauge needle and EUS-FNA without bedside cytopathology [16 – 19]. While diagnostic accuracy tends to vary depending on the site, there is generally no significant difference between the two modalities [17 – 19]. While the 19-gauge Trucut core biopsy needle appears to operate well at certain sites such as the esophagus and portions of the stomach, it was more difficult to use in the antrum/fundus of the stomach as well as the duodenal bulb [20]. Even with the new, European-designed 19-gauge fine needle biopsy device, which was designed to overcome the limitations of obtaining transduodenal samples from the pancreatic head, this process continues to be technically difficult [21]. As a result, other types of FNA and core biopsy needles are being developed and compared [22]. Bang et al. published a randomized trial which compared the diagnostic yield of the 22-gauge FNA needle and a new 22-gauge biopsy needle for EUS-guided sampling of solid pancreatic masses [23]. With the new 22-gauge biopsy needle, they were able to obtain transduodenal biopsies without difficulty, thus overcoming the limitations of the 19-gauge core biopsy needles. Interestingly, the new 22-gauge core biopsy needle was capable of obtaining cytology and histology specimens. Their study concluded that the diagnostic yield of the new 22-gauge biopsy needle is comparable to the 22-gauge FNA needle. The authors commented that the yield of histologic core tissue was unsatisfactory with the biopsy needle, but there was no statistically significant difference in the number of passes for diagnosis or number of cases where there was a failure to achieve the diagnosis between the two diagnostic modalities. Another study examined 62 patients with solid pancreatic lesions which were sampled by EUS-guided 22-gauge core biopsy needle and 25-gauge FNA needle at the same endoscopic session [24]. There was no difference in adequacy of the specimens obtained through FNA and core biopsy needles. Additionally there was a significant agreement between EUS-FNA and core biopsy (88.5 % for positive agreement and 62.5 % for negative agreement).

In our study, EUS-guided core biopsies were obtained before EUS-FNA of the same lesion. As previously discussed, one of the inherent limitations of FNA is the lack of architecture which can be important in making certain diagnoses. This decision was made because we did not want the FNA to disrupt the underlying architecture and diminish the yield of core biopsy although this is only a theoretical risk. Additionally, we did not alternate the two modalities in an effort to keep more variables constant. It would be interesting to see whether results would be similar if EUS-FNA preceded the EUS-guided core biopsies.

There are several advantages to our study. It includes a wide spectrum of disease which is not limited to solid pancreatic mass lesions. It compares the yield of EUS-FNA and EUS core biopsy performed on the same lesion during a single endoscopic session. Studies which compare the yield of these two modalities generally use a criterion-standard reference method. While patients with suspected malignancies based on either of these diagnostic tests generally undergo a subsequent surgical resection whereby the final diagnosis may be confirmed, those with benign cytology or histology are followed clinically. The final diagnosis in these "benign" cases is generally determined after a certain period of time based on a patient's clinical course and/or subsequent studies which may include imaging or repeat endoscopy with or without sampling. The criterion-standard reference method is used in our study as well, but mass lesions were sampled simultaneously using EUS-FNA and core biopsies. In this manner, patients serve as their own control. Also, all core biopsy specimens were reviewed by a single pathologist who was blinded to the results of the preceding FNA specimens.

Despite performing EUS-guided core biopsies followed by multiple passes for FNA during the same endoscopic session, the procedure was performed safely and efficiently. There were no adverse events during or immediately following the procedure. Mean procedure time was 39.4 minutes. EUS-FNA has been accepted to be a safe intervention with a low post-procedural adverse events rate [25]. EUS-guided core biopsy (using the 19-gauge Trucut needle) has also been shown to be safe, with an adverse events rate of approximately 2 % [26]. Although more studies are needed, the EUS-guided core biopsy may eventually supplant EUS-FNA with on-site cytopathology as the gold standard.

Limitations

Much like other published studies examining the diagnostic yield of EUS-FNA and EUS core biopsy, the primary limitation of this study is the small size of the study population. Additionally, we examined a heterogenous population of lesions in this study. Also, some patients referred for biopsy were not included because core biopsy could not be performed. As such, results are biased towards patients in whom core biopsy was technically feasible. While all EUS procedures were performed by a single, experienced endoscopist in our study which allows for standardization, diagnostic yield may vary at other institutions when endoscopy is performed by multiple physicians or less experienced physicians. This study was conducted at a single tertiary referral center, and as such, there was a disproportionate amount of malignant lesions. Also, a cost analysis was not performed in this study but it would be interesting to see whether EUS core biopsies are cost effective when compared with EUS-FNA + on-site cytopathologist. Lastly, our study was not designed or powered to show significant differences between EUS-FNA and core biopsies but to compare the accuracy of both approaches.

Conclusion

Based on our study, the diagnostic yield of two passes with a 22-gauge core biopsy needle may be comparable to the current gold standard of FNA with a bedside cytopathologist when sampling gastrointestinal lesions. Large, prospective, randomized studies are still needed to further compare these two modalities. Eventually, an approach with two core biopsies could represent a time efficient and widely available alternative to FNA with a bedside cytopathologist.

Competing interests: There are no disclosures or conflict of interest for any of the authors.

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