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Do we really need fine-needle biopsy needle for an ultrasound-guided biopsy of pancreatic adenocarcinoma? A retrospective study

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Abstract. – OBJECTIVE: Endoscopic ultrasound (EUS)-guided FNB was not demonstrated to be better than EUS fine-needle aspiration (FNA) to obtain adequate samples for diagnosis of pancreatic tumors. We report our experience using a 22-gauge needle aspiration to obtain both cytologic and histologic samples.

PATIENTS AND METHODS: In a total of 232 patients (51% men), 22-gauge needles (Cook Medical) were used to obtain a cytological sample (between 2008 and 2016, Cohort A) and a cytologic and a histologic sample (between 2016 and 2019, Cohort B) to evaluate the usability of this needle to collect material for cytologic and histologic examination. MOSE was used.

RESULTS: Pancreatic adenocarcinoma was diagnosed in 76/113 (68%) patients in Cohort A and in 88/119 (74%) in Cohort B. Non-diagnostic sampling occurred in 30/113 (26%) patients in Cohort A and in 25/119 (21%) in Cohort B. The median number of passages was three in both cohorts. Lesions were in the head/uncinated process 57% *vs.* 51% and body/tail 43% *vs.* 49% in Cohorts A and B, respectively; the mean tumor size was 34.5 mm (SD 10.7) in Cohort A and 35.4 mm (SD 14.7) in Cohort B.

CONCLUSIONS: FNA needle (22-gauge) with adequate passes, MOSE determination and adequate processing of specimens, provided FNA and FNB specimen collection.

Key Words:
Fine-needle biopsy, Endoscopic ultrasound, Pancreatic adenocarcinoma, Diagnostic accuracy.

Introduction

Despite its relatively low incidence, pancreatic cancer (>95% with features consistent with adenocarcinoma) is recognized as a leading cause of cancer-related death in Western countries[1]. According to the Cancer Statistics Center of the American Cancer Society, approximately 60,000 people will be diagnosed with pancreatic cancer in 2021 in the USA, with 48,000 estimated deaths[1].

Diagnosis of pancreatic adenocarcinoma (PAC) relies on imaging modalities; endoscopic ultrasound (EUS) is used with a tissue acquisition technique, such as fine-needle aspiration (FNA). Evidence indicates that, at the time of diagnosis, approximately 80% of patients have regional spread or metastatic disease. Therefore, effective and safe modalities to diagnose pancreatic cancer at an early, and therefore more likely curative stage are needed to improve outcomes and reduce the high mortality (5-year survival: 6%)[2].

EUS-guided FNA (EUS-FNA) is a minimally invasive method for tissue sampling from solid masses. Since its introduction in the mid-1990s, EUS-FNA has been a key diagnostic tool in patients with suspected solid pancreatic masses, thanks to high sensitivity and specificity, increasing accuracy over time, and a very low rate of complications[2-4]. However, EUS-FNA often requires multiple passes to obtain an adequate quantity of the tissue.-

Endoscopic ultrasound guided tissue acquisition by MOSE (macroscopic on site evaluation) and ROSE (rapid on-site evaluation) have been introduced in the clinical practice in order to guide sampling collections process. MOSE evaluation by the endosonographer has been advocated to estimate the adequacy of specimens of samples from target lesion for histological diagnosis. ROSE is provided by a pathologist or an experienced cytotechnologist providing im-

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mediate real-time evaluation of a FNA biopsy or touch imprints of a core biopsy. ROSE may be useful to improve diagnostic accuracy, but it is not widely available due to limited resources. In addition, ROSE impact on diagnostic accuracy is still unclear[5].

The technique of fine-needle biopsies (FNBs) was developed to increase the amount of tissue acquisition and, consequently, the diagnostic accuracy of samples). The features of fine-needles, such as a different tip design and side fenestration, allow core biopsies with preserved architecture, enabling not only a cytological but also a histological analysis (including tumor genomic profile) and avoiding ROSE[6,7]. Therefore, EUS-FNB and EUS-FNA needles have been recently compared in three clinical studies (two perspectives and one retrospective); however, they could not demonstrate a conclusive benefit of the newer and more expensive tools[6-8].

The aim of the present study is to demonstrate that, in a center with a remarkable experience in EUS-FNA procedures, it is possible to acquire both cytological and histological samples with the same EUS needle (EchoTip Ultra; Cook Medical, Limerick, Ireland) thanks to a different modality of handling the collected material.

Patients and Methods

This retrospective, monocentric cohort study was conducted at the Regina Elena Cancer Institute of Rome, a center with a >15-year experience in EUS-FNA procedures. The local Ethical Committee has approved the study design and all patients had signed an informed consent to the use of their data for research purposes before enrolment.

Patients

Data from consecutive patients who, from September 2008 to December 2019, underwent EUS-FNA on solid pancreatic masses with a conventional 22-gauge FNA needle (EchoTip Ultra) by the same expert endosonographer were retrieved.

All patients who had a suspected solid malignant pancreatic mass according to clinical symptoms (pain, jaundice, weight loss, etc.) and/or radiological findings (a solid pancreatic mass exposed by CT and/or MRI and/or EUS) were considered. Procedures in patients with masses with a predominantly cystic component (>50%), extra pancreatic gastrointestinal masses of uncertain origin (gastric or duodenal masses infiltrating pancreas), suspected masses originating from other organs or peri-pancreatic-lymphadenopathy were excluded from the analysis as well as procedures where ROSE was employed.

Patients who underwent EUS-FNA from September 2008 to March 2014 (Cohort A) and from April 2014 to December 2019 (Cohort B) were identified. In Cohort A, only cytological analysis was performed whilst in Cohort B, patients had both cytological and histological analysis on tissue samples collected with the same needle (FNA needle).

Endoscopic Ultrasound Fine-Needle Aspiration/Fine-Needle Biopsy Procedure

EUS was performed with a curved linear array echoendoscope (GF-UCT 140, Olympus; and EG-3570 UTK, Pentax, Japan) by an expert endoscopist on a patient positioned in the left lateral decubitus position under moderate sedation (midazolam and fentanyl i.v.). Pancreatic masses were visualized by endoscopic ultrasonography and FNA or FNB procedures were conducted from the duodenum when masses were located in the pancreatic head or uncinate process, while EUS were conducted from the stomach for masses located in the body or tail of the pancreas.

The needle was advanced into the target with the stylet in place; then the stylet was removed, and suction was applied by a 5 mL syringe while moving the needle 15-20-times to and from within the lesion. We always performed funning technique by using the elevator and vertical knob of the endoscope to sampling different portions of the lesion. Suction was stopped before removing the needle. In absence of an on-site cytologist, three to six needle passes were performed for each lesion to increase diagnostic yield.

Specimen Management

All aspirated material was collected immediately into liquid-based cytology tubes (ThinPrep) and, successively, the core tissue was moved from cytolytic solution to the formalin-containing bottle (Figure 1). Macroscopically on-site evaluation (MOSE) was made by the endosonographer immediately after the collection to evaluate the number of needed passes. However, a minimum of three passes for every lesion was made. The first evaluation of the tissue sampling adequacy was evidenced by the presence of a long strain of tissue (>1 cm), without the presence of large amount of blood.

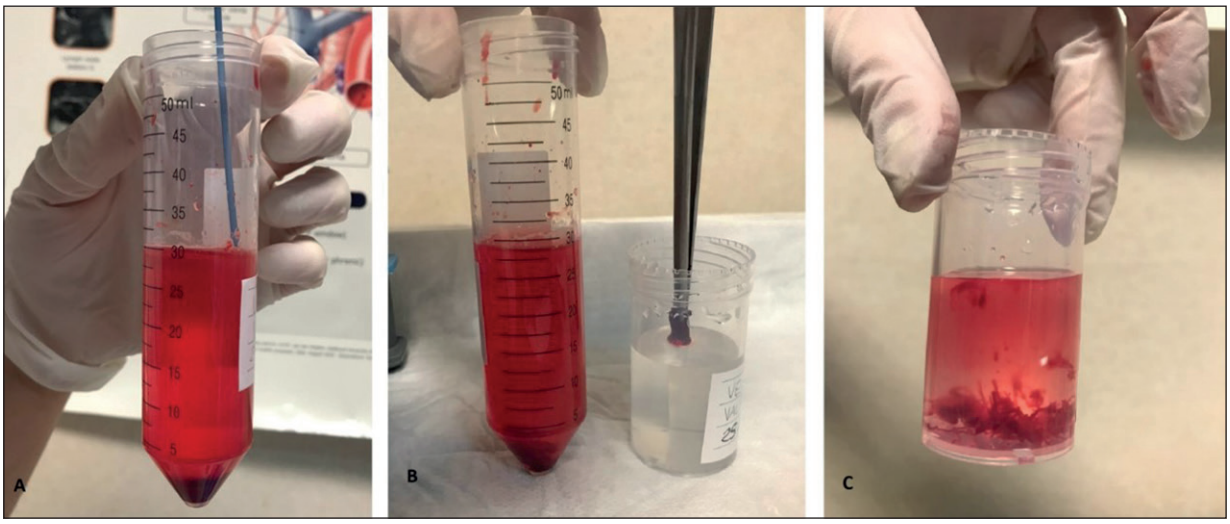

Figure 1. Management of the collected samples on site. **A,** First step, flush all aspirated material in the ThinPrep solution. **B,** Displacement at formalin recipient. **C,** Both samples delivery to the Pathology Unit.

Both cytological samples and material placed in a formalin solution were delivered to the cytopathology unit within 48 hours. A standardized procedure was developed for the cytological sample: all specimens prepared were resuspended into a methanol-based preservative (PreserverCyt); subsequently, the ThinPrep processor yields an alcohol-fixed slide preparation. The processor disperses cells and collects them on a polycarbonate filter, and finally transfers cells to a glass slide. The slide is then immersed in 95% alcohol and stained with Papanicolau technique. The core tissue obtained was fixed in formalin 10% solution. All histological samples were processed as described: fixed, dehydrated and embedded in paraffin in order to obtain blocks of paraffin tissue for histological examinations. Routine staining was performed. All samples were analyzed by a pathologist with a large experience in cytology and histology of gastrointestinal diseases.

Statistical Analysis

Data were analyzed by descriptive statistics. The association between categorical variables was estimated with chi square test or Fisher exact test, as appropriate. Sensitivity, specificity and accuracy were calculated and reported with their 95% confidence intervals. $p<0.05$ was regarded as statistically significant. Statistical analysis was performed with SPSS version 21.0 (SPSS Inc., Chicago, IL, USA)

Results

Data from a total of 232 patients (119 men) with a mean age of 65.9 years (standard deviation [SD]: 10.9) were evaluated. All patients had pancreatic solid masses and underwent EUS-FNA/B consecutively between September 2008 and December 2019 (Figure 2). Patients' demographic data and lesion characteristics are reported in Table I.

Demographic and Lesions Characteristics

Overall, the analyzed cohorts were comparable in terms of demographic and lesions characteristics. The mean tumor size was 35 mm (SD: 12.9),

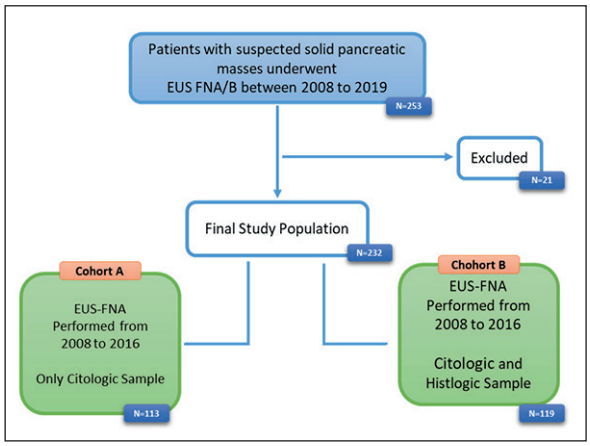

Figure 2. Case series.

Table I. Patient demographic and tumor data, final diagnosis of 232 patients with pancreatic solid masses.

Parameters	n (%)/mean (SD)
Age (years)	65.9 (SD: 10.9)
Sex (n), male/female	119/113
Tumor size (mm)	35 (SD: 12.9)
Location:	
• Head/uncinate	126 (54%)
• Body/tail	106 (45%)
Final diagnosis:	
• Positive for PAC	164 (71%)
• Negative for malignancy	13 (6%)
• Non diagnostic	55 (23%)

with a comparable distribution for location (head/uncinate process *vs.* body/tail).

EUS-FNA/B was feasible in all patients with a median of three needle passes in both cohorts.

Final diagnosis was PAC in 164/232 (71%) patients: 76 (68%) in Cohort A and 88 (74%) in Cohort B, respectively. Negative diagnosis for neoplastic disease, confirmed by surgery, or clinical and imaging follow up, was made in 13 (6%) patients: of these, 7 (6%) were in Cohort A and 6 (5%) were in Cohort B.

Diagnostic Accuracy

In 30/113 (26%) patients in Cohort A and in 25/119 (21%) patients in Cohort B, EUS-FNA/B was non-diagnostic and confirmed by other diagnostic procedures (ultrasound or CT-guided biopsy) or surgery.

Total diagnostic accuracy was 75% with a sensibility of 73.1%. There was no statistically significant difference in diagnostic accuracy between Cohort A and Cohort B (71.7% *vs.* 78.2%, respectively; p=0.32).

Sensibility of FNA/B in Cohort A and B was 68.9% and 77%, respectively (p=0.29).

In lesions ≥20 mm, diagnostic accuracy was 76.7%, with a sensibility of 75.3%; in lesions ≤20 mm, accuracy was 59.1% with a sensibility of 50%.

Calculation for location total accuracy was 74.1% in head–uncinate tumors and 76.5% in body-tail lesions. From 2010 to 2019, accuracy calculated by years showed a progressive increase, with the highest rate (78.8%) in 2019 and the lowest rate in 2010 (66.7%) (Table II.

Discussion

Currently, EUS-FNA is the gold standard for EUS-guided sampling of PAC[8]. However, this procedure still has several limitations.

EUS-FNA samples provide a relatively small amount of tissue specimens, without preserving the core tissue architecture, which is essential for histological diagnosis of pancreatic masses[10,11]. Cytological analysis alone may not diagnose malignancies, such as stromal cell tumors, lymphomas, or well-differentiated adenocarcinoma[12].

Frequently, to obtain more tissue for an accurate diagnosis or detection of biomolecular markers, it is necessary to increase the number of passes. This may increase the risk of adverse events and prolong the procedure.

ROSE has been considered to improve diagnostic yield and accuracy with a limited number of passes. To date, its advantages are not demonstrated, even in centers with highly trained personnel, because costs are increased and an on-site cytopathologist is not easily available[13]. Many studies did not show an actual imple-

Table II. Comparison of demographic, tumor and endoscopic procedure data between Cohort A and B.

Parameters	Cohort A	Cohort B	*p*-value
Age (years), mean (SD)	65.3 (10.9)	66.5 (SD 11.1)	0.41
Sex (n), male/female	64/49	55/64	0.15
Tumor size (mm), mean (SD)	34.5 (10.7)	35.4 (14.7)	0.61
Location, n (%):			0.41
• Head/uncinate	65 (57%)	61 (51%)	
• Body/tail	48 (43%)	58 (49%)	
Needle passes (n)	3	3	0.99
Final diagnosis, n (%)			0.27
• Pancreativ adenocarcinoma	76 (68%)	88 (84%)	
• Negative for malignancy	7 (6%)	6 (5%)	
• Non diagnostic	30 (26%)	25(21%)	
Diagnostic accuracy (%)	71.7%	78.2%	0.32

mentation in diagnostic rate in EUS-FNA with ROSE, but only a better evaluation of the sample adequacy.

Recently, the FNB needle (such as EchoTip-Procoreneedle, Cook Medical) or the novel fork tip biopsy needle have been developed to obtain core biopsy and a large amount of collected specimen. Nevertheless, their price is higher than that of traditional needles, such as EchoTip Ultra needle, with a great impact on the total cost of the procedure[14].

In our study, we used a traditional 22-gauge needle (EchoTip Ultra). In the first period (until March 2014), we collected only cytological samples (ThinPrep solution), while more recently (from April 2014 onwards), we changed the procedure to obtain cytological and histologic samples with the same type of needle. Our data showed that the distribution of pancreatic lesions by size and location, and the accuracy of malignancy detection are comparable in the two cohorts. There is no difference in diagnostic accuracy for pancreatic masses in Cohort A (cytologic samples only) and in Cohort B (cytologic and histologic samples). We found no differences between the two cohorts in the number of passes and in the time of procedure, since the handling of the sample is carried out by the nurse in the operating room during the procedure. We think that our data add a new perspective to results from previous studies comparing FNA *vs.* FNB or newer *vs.* standard needles. Interestingly, with the same standard needle, we obtained high-quality tissue by just modifying the way of handling the collected samples. Furthermore, when using a FNA standard needle, we could obtain both cytologic and histologic samples.

Notably, as already described by Karsenti et al[15], the use of MOSE is mandatory in order to limit needle passes by accurately estimating the quantity of histologic core fragment in the absence of ROSE[7,16].

Biomolecular diagnosis requires a large amount of cellular material and tissue; its introduction induced a new modality of collecting samples for. Nevertheless, the routine passage of the sample, with the ThinPrep solution and then with the formalin buffer, permits to collect a large number of cells (after treatment in PreserverCyt solution) separated and well-purified. Such a sample can be excellent for the study of biomolecular markers; at the same time, it may provide a tissue fragment for immuno-histochemistry.

The increasing use of the funning technique permits to enlarge the field of sampling during the same pass. So, by always flushing the aspirated material before in ThinPrep solution and then moving it in formalin it is possible to obtain both cytologic and histologic samples. Both samples are equally representative of every area collected in a single or in further passes. This is very important because many intralesional necrotic and inflammatory infiltrated areas are frequently present in pancreatic carcinoma. So, it is important to analyze all kinds of tissues and cells deriving from different areas of the solid lesion.

This study has several limitations. First of all, the lack of ROSE, mainly in Cohort A, may decrease the rate of diagnostic accuracy of all the study population, while the same diagnostic rate becomes higher in the last part of the series (Cohort B).

Moreover, in Cohort A, a lower degree of experience of endoscopist and pathologist was responsible for a low rate of diagnosis, which increased rapidly over time.

In this setting, it could also be helpful to perform a comparative histopathological study concerning the morphology of the histological fragment obtained with the described procedure and the core biopsy needle fragments.

However, several studies demonstrated the better performance of the novel type of needle, both core biopsy needle (such as EchoTipProcore) and novel fork needle (such as Acquire, Boston Scientific). Indeed, this approach allows the collection of a sample more representative of the entire lesion. This is relevant for diseases in which it is difficult to reach diagnosis with a single biopsy specimen (such as lymphoma, neuroendocrine tumor or auto-immune pancreatitis)[4,6,10,13,14,17,18].

Our histological samples were adequate to allow a histologic and molecular characterization of PAC. Biomolecular diagnosis will likely become crucial in the near future as demand for a more personalized therapy is growing[19].

Our results suggest that using a FNA standard 22-gauge Cook needle with an adequate number of passes, a MOSE determination of the sample before ending the procedure allows to collect sufficient material for cytological and histological analysis. A close collaboration between the echo-endoscopist and the pathologist is crucial to standardize the correct processing of specimens, from sampling to histologic evaluation.

Our experience suggests that beyond the size and the type of the needle (useful in most cases) also the collecting modality and management of the samples during the EUS-FNA are crucial.

The modality of collection must be standardized in every tertiary center according to pathologists' requirements, and a close collaboration between echo-endoscopist and endoscopy service team should be encouraged.

In conclusion, our data suggest that use of a 22-gauge FNA needle with an adequate number of passes, a MOSE determination of the sample, and an adequate management of the sample, permits to obtain both FNA and FNB specimen collection.

A validated collecting modality, such as implementation of funning technique with adequate number of passes guided by MOSE evaluation, and correct management of the samples allows to collect both cytological and histological analysis using a 22-gauge FNA needle.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

(1) Conceptualization: DA. (2) Data curation: FM, PV. (10) Supervision: DA. (11 Validation: DO, FG, DF, FM, PV, EV, FP, DA. (13) writing original draft: DA. (14) Writing-review and editing: DO, FG, DF, FM, PV, EV, FP, DA.

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