

Feasibility and yield of a novel 22-gauge histology EUS needle in patients with pancreatic masses: a multicenter prospective cohort study

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Abstract

Background The option of obtaining tissue samples for histological examination during endoscopic ultrasound (EUS) has theoretical and practical advantages over cytology alone. The aim of this study was to evaluate the feasibility, yield, and diagnostic accuracy of a new EUS 22-G fine-needle biopsy (FNB) device in patients with solid pancreatic masses in a multicenter, prospective study. **Methods** All consecutive patients who underwent EUS-guided fine-needle biopsy (EUS-FNB) using a newly developed 22-G FNB needle between September 2010 and October 2010 were enrolled in the study. The EUS-FNB

technique was standardized among the participating endoscopists. Only a single needle pass was performed.

Results A total of 61 patients (35 males, mean age 64.2 ± 12.4 years) with solid pancreatic masses with a mean size of 32.4 ± 8.5 mm (range 13–90 mm) participated. EUS-FNB was performed through the duodenum in 35 cases (57.4 %) and was technically feasible in all but one of the 61 (98.4 %) patients without complications. Tissue samples for histological examination were obtained from 55 patients (90.2 %) and were deemed adequate in 54 of the cases (88.5 %). The diagnoses established by EUS-FNB were adenocarcinoma (39 patients), neuroendocrine tumors (5), chronic focal

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pancreatitis (5), sarcoma (2), lymphoma (1), acinar cellular tumor (1), and pancreatic metastasis from renal cell carcinoma (1). In an intention-to-treat (ITT) analysis, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for the histologic diagnosis of a pancreatic mass were 87.5, 100, 100, 41.7, and 88.5 %, respectively.

Conclusions EUS-FNB was technically feasible in 98 % of patients with a solid pancreatic mass. A suitable sample for histological evaluation was obtained in 88.5 % of the cases after only one single needle pass. The apparently low negative predictive value is likely to be improved by increasing the number of needle passes.

Keywords Endoscopic ultrasound · Fine-needle biopsy · Histology

Pancreatic mass lesions can present a true diagnostic challenge to physicians, particularly in regard to establishing a tissue diagnosis, as therapeutic decisions are often based on the ability to reliably establish or exclude the presence of malignancy [1]. Although most mass lesions prove to be ductal adenocarcinoma, a variety of other neoplasms and benign conditions with various prognoses and differential treatment options can arise within the pancreas [2]. Thus, the establishment of a tissue diagnosis is of primary importance.

Since the initial report in 1992 [3], endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) has emerged as an important tool in the evaluation of patients with pancreatic lesions [4]. EUS-FNA of pancreatic masses can be considered a safe procedure [5, 6], with an overall diagnostic accuracy between 60 and 90 % [5, 7–11], and with a lower risk of tumor seeding than percutaneous techniques [12]. The usefulness of EUS-FNA in this clinical setting, however, is somewhat limited by the need for an on-site cytopathologist to improve diagnostic yield [13], and by the low negative predictive value of the procedure, i.e., a negative FNA in a patient with a pancreatic mass does not reliably rule out the presence of a pancreatic malignancy [14]. There is, therefore, a clear need for alternative techniques that can improve the diagnostic yield, accuracy, and negative predictive value of EUS.

Theoretically, obtaining a pancreatic core biopsy tissue sample that permits both histological analysis and the use of immunostaining might have many advantages over aspiration of cytological specimens. Various EUS-guided techniques to retrieve tissue specimens have been explored, including FNA and Tru-Cut needles, with variable success and complication rates [15–21]. Importantly, the diagnostic yield of these procedures has been strongly limited for lesions located in the pancreatic head/uncinate process due

to mechanical friction of the needle-firing mechanism ensuing from the bended scope position [22–25].

We recently presented the results of a multicenter cohort study in which the performance of a new 19-gauge needle, specifically designed to acquire tissue samples, was evaluated in patients with both intestinal and extraintestinal mass lesions and peri-intestinal lymphadenopathy, with very promising results [26]. The relatively large diameter of this 19-gauge needle makes its use in the duodenum still somewhat difficult. For this reason, a similarly designed but smaller 22-gauge fine-needle biopsy (FNB) device has been developed. In a small, randomized, single-center study, with its primary aim to assess the median number of passes required to establish a diagnosis, this needle showed promising accuracy for pancreatic masses. However, technical feasibility and diagnostic yield were limited to only 28 patients [27].

The aim of the present study was to evaluate the feasibility, yield, and diagnostic accuracy of this newly developed needle in the evaluation of solid pancreatic masses.

Patients and methods

Patients, procedure, and examination technique

For this multicenter study, the performance data from the use of a newly designed 22-gauge FNB needle from five centers (Marseille, Milan, Rome, Rotterdam, and Santiago de Compostela) were pooled. The FNB needle was used for EUS-guided tissue acquisition in patients with pancreatic mass lesions who were referred over a 2-month period.

EUS-FNB was performed by eight different expert endosonographers (AL, JIG, JWP, MCP, PGA, EB, MB, MG) using a convex array echoendoscope (Olympus UCT-140/180[®] or Pentax EG-3870UTK[®]). Tissue acquisition was done with the newly designed 22-gauge EchoTip[®] ProCore[™] FNB needle (Cook Medical Inc., Bloomington, IN, USA), featuring ProCore[™] reverse bevel technology (Fig. 1). The differences between the 19- and 22-gauge ProCore[™] needles are given in Table 1.

Tissue acquisition was done according to a standardized protocol. After the target lesion was endosonographically visualized and the region scanned for interposing vessels using color and pulsed Doppler, FNB was performed as follows: (1) the FNB needle was advanced into the target lesion under EUS guidance, (2) once inside the lesion, the stylet was removed and negative suction pressure was applied using a 10-mL syringe for 30 s, (3) three to-and-fro movements within the lesion were made, (4) suction was then released by closing the lock of the syringe, and (5) the needle was finally removed. In all cases only a single needle pass with the 22-gauge FNB needle was performed.



Fig. 1 Detailed image of the tip of the new histology needle showing the notch in which the tissue sample is caught during puncture

Table 1 Main characteristics of the new 22-G EUS needle and the previously used 19-G [26]

	ECHO-HD-22-C	ECHO-HD-19-C
Needle outer diameter (mm)	0.71	1.07
Needle inner diameter (mm)	0.51	0.94
Needle length (mm)	1.705	1.705
Needle bevel	Lancet	Lancet
Stylet tip design	Lancet	Lancet
Reverse bevel length (mm)	2	4
Sheath size	5.2 Fr	5.2–4.2 Fr
Needle material	Stainless steel	Stainless steel
Stylet material	Nitinol	Nitinol

Tissue samples were recovered in formalin or cytolyt by flushing the needle with 5 cc of saline. All samples were processed at the Pathology Departments of the centers for histological analysis. There was no pathologist present in the endoscopy room, and FNB samples were recovered and stored for further processing by the endoscopist.

Samples were embedded in paraffin. Tissue sections of 3–4 μ m were stained with hematoxylin & eosin for morphological evaluation and/or different immunohistochemical analysis. If pathologists were not able to obtain a core for histological evaluation, they processed the same material as cell-block for cytological evaluation.

Gold standard reference diagnosis of malignant versus benign disease

When histological examination was diagnostic for malignancy, this was considered the definitive diagnosis. For patients with EUS-FNB nondiagnostic for malignancy or

for a specific benign disease, the presence or exclusion of malignancy was based on the histopathological examination of the surgically resected specimen or on the long-term clinical follow-up, including follow-up imaging. For this purpose, patients were evaluated for a minimum of 12 months.

Outcome parameters

The primary outcome parameter was diagnostic accuracy. This parameter depends on the technical success in obtaining a sample and on the adequacy and rightness of the final pathological diagnosis. Secondary outcomes were technical feasibility and the percentage of cases in which a final histological diagnosis was obtained.

The study was approved by each local institutional review board and conducted in accordance with the Declaration of Helsinki and its amendments and the Good Clinical Practice guidelines. All patients provided written informed consent to participate in the study.

Data analysis

Results are given as a percentage and 95 % confidence interval (CI). Normally distributed variables are presented as mean with standard deviation and range. A descriptive analysis was performed. Results are compared by a χ^2 test or Fisher's exact test, as appropriate. Sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy were also calculated based an ITT analysis, where patients from whom a tissue specimen was not retrieved were considered false negative. Because historical information on the performance of a FNB needle was not available, a formal sample size calculation was not performed. In order to minimize the impact of a potentially insufficient sample size, accuracy data are given with a 95 % CI.

Results

A total of 61 patients (35 males, mean age = 64.2 \pm 12.4 years, range = 34–85 years) with a solid pancreatic mass were enrolled. Lesions were located in the uncinate process (4 cases, 6 %), the pancreatic head (31 cases, 51 %), the pancreatic body (17 cases, 28 %), and the pancreatic tail (9 cases, 15 %). Mean size of the pancreatic masses was 32.4 \pm 8.5 mm (range 13–90 mm).

Overall, EUS-FNB was performed transduodenally in 35 cases (57.4 %) and transgastrically in 26 cases (42.6 %) and was technically feasible in all but one of the 61 patients enrolled in the study (98.4 %; 95 % CI: 95, 100 %). In one patient with an uncinate process mass, the needle could not be extended out of the working channel of the scope

because of the bent position. Tissue samples for histological examination were obtained in 55 patients (90.2 %; 95 % CI: 83, 98 %), while no core biopsy tissue samples were retrieved in 5 patients. There were no complications related to the procedure.

At pathological examination, the tissue retrieved by EUS-FNB was judged adequate to obtain an histology-based diagnosis for 54 patients (88.5 %; 95 % CI: 82, 97 %), while for 1 patient the retrieved material was not enough to firmly establish a diagnosis. In the 54 patients with adequate tissue specimens, diagnoses made by EUS-FNB were adenocarcinoma in 39 patients, neuroendocrine tumors in 5, chronic focal pancreatitis in 5, sarcoma in 2, and 1 case each of lymphoma, acinar cellular tumor, and pancreatic metastasis from renal cell carcinoma in the remaining three patients (representative cases are shown in Fig. 2). In the five cases of chronic pancreatitis, a subsequent EUS-FNA was performed in three of them with no evidence of malignancy, while long-term follow-up of at least 12 months proved the diagnosis to be correct in all. In the seven patients in whom a tissue specimen was not retrieved (5) or inconclusive (1), or in whom the procedure failed (1), a definitive diagnosis of adenocarcinoma was obtained in all by EUS-FNA ($n = 3$) and by histological examination of the surgical specimen ($n = 4$).

When evaluating the performance of the needle in detecting malignancy on an ITT basis, the sensitivity, specificity, positive predictive value, negative predictive

value, and overall accuracy were 87.5, 100, 100, 41.7, and 88.5 %, respectively.

Discussion

We performed the first multicenter prospective cohort study of patients with pancreatic masses to evaluate the technical and diagnostic performance of a newly developed 22-gauge needle specifically designed to acquire tissue specimens for histological examination. We found that the procedure was technically feasible in all but one patient and had an overall diagnostic accuracy close to 90 %. This result confirms the 89 % diagnostic accuracy shown by the same needle in a very preliminary single-center study limited to 28 cases, in which a higher number of needle passes were performed [27].

In general, cytological evaluation of all FNA samples acquired under EUS guidance requires a high degree of expertise and a close collaboration between the endoscopist and the cytopathologist [28]. This is especially true for pancreatic EUS-FNA. Diagnostic accuracy strongly depends on the presence of a cytopathologist in the EUS suite during the procedure to perform rapid on-site cytological examination (ROCE), which also decreases the number of inadequate diagnoses with a possible reduction of costs [29, 30]. ROCE, however, is available in only a limited number of centers throughout the world, thus

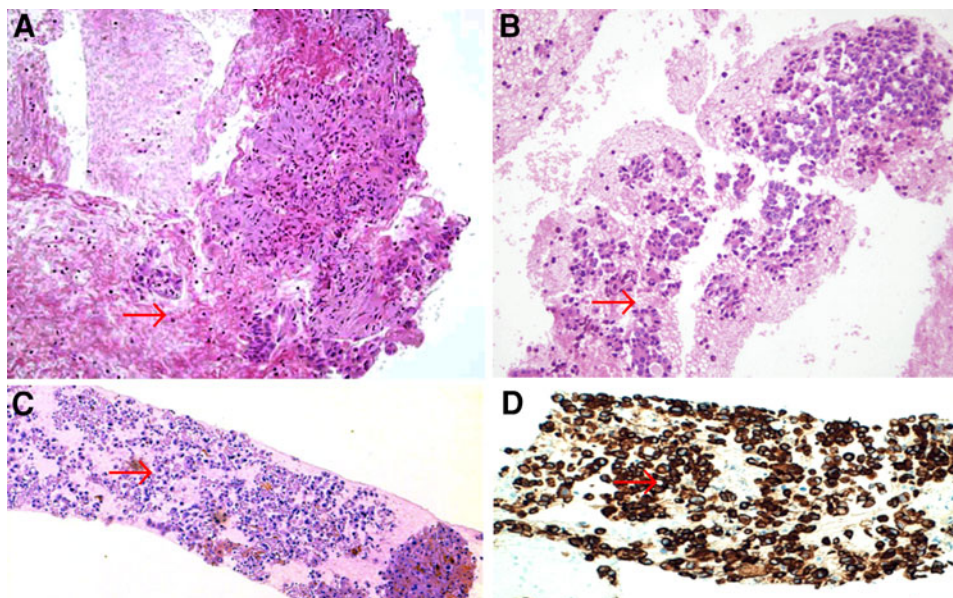


Fig. 2 Example of tissue samples as obtained by the 22-gauge ProCore™ needle from different pancreatic masses. **A** Blood, compressed fibrous tissue, and evident (center and lower right part of the micrograph, arrows) epithelial cells with severe atypia in glandular structures diagnostic for ductal adenocarcinoma. **B** Blood and abundant moderately atypical epithelial cells in ribbons (center of

the micrograph, arrows) indicative of acinar cell adenocarcinoma. **C**, **D** Blood cells with fibrin clot and abundant and dispersed severely atypical cells (arrow in C) positive for vimentin at immunohistochemistry (D) and thus consistent with a diagnosis of sarcomatoid carcinoma. A–C Hematoxylin and eosin. D Immunoperoxidase, scale bar 5 mm

reflecting the difficulty in setting up the logistics of such a service. Of note, in the randomized trial comparing a standard 22-gauge FNA needle with the same 22-gauge FNB needle adopted in the present study and ROCE, FNB not appear to be inferior to ROCE, showing that it may lead to a substantial economical saving [27].

An alternative way to theoretically increase diagnostic accuracy of EUS without the need to establish a ROCE service but have a close collaboration with a dedicated pathologist is by obtaining tissue core biopsy specimens for histological examination. Such specimens would allow detailed analysis of preserved tissue architecture, including the relationship of cells to the stroma. Importantly, histology also provides the opportunity to immunostain the tissue, further increasing differential diagnostic capabilities, including the advent for future tissue profiling to guide individualized therapies [31].

With these considerations in mind, we recently performed a study evaluating the feasibility and yield of a newly developed 19-gauge biopsy needle specifically designed for tissue retrieval [26]. Moreover, one of us independently developed a technique of tissue acquisition using a standard 19-gauge needle with the stylet removed before its insertion into the working channel to increase needle flexibility [32]. Both studies were performed in two patient populations with heterogeneous indications and showed very good diagnostic accuracy (around 93 %) [26, 31]. Transduodenal biopsies were performed in only 12 patients in one of the studies, with one failure [32], and in 35 lesions in the second study [26], with two failures. In general, puncturing from the duodenal position was more difficult, and in many cases the EUS-FNB needle needed to be pushed out of the scope in the stomach before advancing the scope into the duodenum.

To overcome this limitation of the use of large 19-gauge needles, we used a smaller needle featuring the ProCore™ reverse bevel technology in the present study to acquire tissue samples in 61 consecutive patients with pancreatic masses. The procedure was technically feasible in all but one patient, despite that in 57 % of cases the puncture was carried out transduodenally. In all cases in which FNB technically succeeded in obtaining an adequate sample, a correct diagnosis was obtained. Importantly, as previously pointed out by our group, tissue samples provided a valuable means to obtain an alternative benign diagnosis which is not always possible with a cytological sample, thus preventing these patients from undergoing more invasive and risky surgical explorations and biopsies.

It could be argued that in the ITT analysis (i.e., also including the technical failures), a sensitivity of slightly less than 90 % is suboptimal, particularly when considering the very high prevalence of malignancies in the present series, resulting in a low negative predictive value. However, all false-negative cases occurred due to the technical failure to

obtain an adequate tissue sample via FNB while no false negative occurred in technically successful cases, resulting in a 100 % accuracy at per-protocol analysis. With inadequate tissue sampling the main reason for failure to reach a definitive diagnosis, it is important to note that our standardized protocol allowed only a single needle pass. It is conceivable that more needle passes would have increased the yield of tissue acquisition and hence diagnostic accuracy, and increase the low negative predictive value found in our study, with just few more minutes added to the overall examination time. For cytological evaluation of pancreatic masses in the absence of ROSE, it is, in fact, recommended that at least five needle passes be performed [33]. Of note, penetration of the needle into the pancreatic mass was achieved in all cases, and also in those patients in whom the puncture was performed from the duodenal bulb, because of the flexibility of the new needle. This represents a major improvement over the most widely used needle for obtaining histological samples by EUS, i.e., the Quick-Core® needle, which is associated with a less than 50 % success rate when used transduodenally [22]. No comparative data are available with the ProCore™ 19-gauge needle that we used previously.

The main limitation of the present study is the use and definition of the gold-standard reference method. Ideally, when the pathological results of the EUS-FNB are negative, histological confirmation from surgical specimens should serve as the gold standard. Obviously, for ethical reasons this is not possible in patients in whom surgery is not indicated. In these particular cases, clinical follow-up for at least 12 months with repeated imaging procedures (EUS and CT), albeit not ideal, is a well-accepted surrogate reference standard. Second, we did not randomize FNB with FNA or other FNB techniques. However, based on reference and historical data, it becomes readily apparent that the accuracy values of the new needle compare favorably with those of other techniques. Third, we did not standardize post-FNB management in the cases in which there was FNB technical failure, although FNA was successfully adopted in some cases. It is quite conceivable that an adapted algorithm with multiple FNB needle passes would result in further improvement of diagnostic accuracy.

The safety of EUS-FNA is well established [34] and complication rates range between 1 and 2.5 % [35]. Small case series have reported complication rates of EUS-guided Quick-Core® biopsies to range from 2 to 4 %, with the largest study showing a complication rate of 2.4 % [25]. In our present series of 61 cases, and in the previously published study that used a larger needle [26], there were no complications associated with the procedure. However, we do not know if targeting lesions other than solid masses, i.e., cysts, in order to get tissue from the cystic wall can increase the risk of bleeding and pancreatitis. However, based on the

present results, the use of these EUS-FNB needles seems at least as safe as the standard FNA or Quick-Core® needle.

In conclusion, EUS-guided biopsy of pancreatic mass lesions with the new 22-gauge ProCore™ histology needle is feasible and safe. It provides tissue specimens for histological evaluation in the majority of cases, with an overall diagnostic accuracy close to 90 % after a single needle pass.

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