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PERFORMANCE OF EUS-FNB IN SOLID PANCREATIC MASSES: LESSON FROM 463 CONSECUTIVE PROCEDURES AND A PRACTICAL NOMOGRAM

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INTRODUCTION AND BACKGROUND: EUS FOR PANCREATIC CANCER

Pancreatic cancer has a 5-year survival rate of less than 9%, being one of the major causes of cancer-related death [1, 2]. The only curative chance is surgical resection with clear

margins and negative lymph nodes, and this is possible only when pancreatic cancer is detected at early stage, but the majority of patients with pancreatic adenocarcinoma are diagnosed when the disease is locally advanced or metastatic. Detection of small cancers could reduce the mortality from pancreatic cancer. In the staging and evaluation of the resectability of pancreatic cancer, it is important that vascular invasion, lymph node metastases, and liver metastases are appropriately evaluated. CT scan, PET scan, MRI, transabdominal ultrasound are important tools in the diagnosis and staging of pancreatic cancer. Endoscopic ultrasonography (EUS) is an ultrasound (US) technique in which the tip of the endoscope is equipped with an ultrasound probe, allowing imaging of the pancreas without the interference of intestinal gas. A wide number of studies support the use of EUS, contrast-enhanced EUS (CE-EUS), EUS elastography, and EUS-guided fine needle aspiration or biopsy (EUSFNA/B). in this setting

EUS probe can be radial and linear. Radial-type EUS provides circumferential images in a plane perpendicular to the tip of the scope, similar to those provided by CT scan. Linear EUS provides a scan in the same plane as the scope tip, similar to those obtained with transabdominal US. Pancreas can be observed from 4 main stations including body of the stomach, and bulb and the second portion of the duodenum, distal to the Vater papilla or at the level of papilla.

Contrast-enhanced-EUS was first reported in 1995 with an intra-arterial CO2 infusion [3]. Contrast-enhanced harmonic EUS was developed in 2008 [4]. Contrast agents consist of gas-filled microbubbles encapsulated by a phospholipid or lipid shell [5]. The contrast agents are injected through a peripheral vein and the microbubbles are disrupted or stimulated to resonate, producing a low artifact signal. CE-EUS is very useful for the characterization of solid pancreatic lesions.

Endoscopic ultrasonography elastography for the evaluation of pancreatic tissue was first reported in 2006 [6]. There are two types of EUS elastography, strain and shear wave.

Strain elastography estimates the stiffness of the target tissue by measuring the degree of strain produced in response to compression. Shear wave elastography involves the emission of focused US from the probe to the target tissue, the so-called ‘acoustic radiation force impulse’ (ARFI), and the stiffness of the target tissue is then estimated by measuring the propagation speed of the shear wave. Only strain elastography is so far available for EUS. EUS elastography is used to characterize pancreas masses and lymph node metastases of pancreatic cancer with evaluation of lesion elasticity.

EUS is at present the most sensitive imaging modality for the detection of pancreatic lesions. Tipically, pancreatic cancers are hypoechoic mass. Across 22 studies covering 1170 patients, the median sensitivity of EUS for the detection of pancreatic tumors was 94%, superior to that of computed tomography (CT; 98% vs 74%) in 19 studies. EUS performs better than CT scan in particular when dealing with small pancreatic lesions. Comparing the performance of imaging technique in the detection of pancreatic lesions with a diameter minor than 30 mm, the sensitivities of EUS, CT, and MRI were 93%, 53%, and 67%, respectively. For lesions < 20 mm, the difference between EUS and CT was higher (94.4 vs. 50.0) [7-30]. Several reports show that EUS could detect pancreatic tumors that were not identified on other modalities and a meta-analysis reported that the sensitivity of EUS for detecting pancreatic malignancy when multidetector CT findings were indeterminate was 85%, with a specificity of 58% [31-34]. EUS can detect the pancreatic masses < 1 cm with a sensitivity of over 80%. Unfortunately these lesions represent the 0.8% of all the pancreatic lesions, but the 5-year survival is about 80% [35,36]. Canto and colleagues screened 225 asymptomatic individuals considered at high risk because of hereditary and familial pancreatic cancer [37,38]. They compared CT, MRI, and EUS and found that EUS was more sensitive for detecting pancreatic abnormalities (42%) than CT (11%) and MRI (33%). The specificity of EUS for the diagnosis of malignant pancreatic diseases is reported as 53%, with sensitivity of 95% (n = 115) [39]. CE-EUS depicts most pancreatic cancers as a solid

lesion with hypo-enhancement and can increase specificity. CE-EUS have an estimated specificity and sensitivity of 88% and 90%, respectively [40–56]. In two meta-analysis, the pooled sensitivity and specificity of CE-EUS were 93–94% and 88–89%, respectively [57, 58]. The overall sensitivity and specificity of EUS elastography were 93% and 63% [59–73]. In 7 meta-analyses, the pooled sensitivity and specificity were 95–99% and 67–76%, respectively [74–80].

The sensitivity and specificity of EUS for the detection of tumor vascular invasion range from 42% to 91% and 89% to 100%, respectively [111–127]. In meta-analyses, the pooled sensitivity and specificity were 66–86% and 89–94%, respectively [128–130]. The sensitivity of EUS is different for different vessels being over 80% for evaluation of portal vein invasion, consistently superior to CT-scan; for the evaluation of the superior mesenteric vein, superior mesenteric artery and celiac artery, the sensitivity of EUS is lower than CT [131-133]. CE-EUS increases the sensitivity of detection of PV involvement up to 100%. [126]

EUS is useful for the nodal staging of pancreatic cancer. In a meta-analysis the pooled sensitivity and specificity of EUS were 69% and 81%, respectively [128]. EUS showed higher sensitivity for nodal staging than CT (58% vs 24) [128]. The most used criteria for nodes malignancy are a round shape, hypo-echogenicity, a smooth border, and a short axis size greater than 5 mm [10, 18]. The sensitivity and specificity of CE-EUS for the diagnosis of metastatic lymph nodes were 83% and 91%, respectively. [134] For the detection of metastasis, CT and MRI are superior to EUS, however, EUS can detect small hepatic lesions of the left lobe, undetected on other imaging modalities [138]. EUS may also identify and sample ascites in case of suspected peritoneal carcinosis [136, 137].

EUS-guided fine needle aspiration (EUS-FNA) was first reported in the early ‘90s, and since then it has been used as technique of choice for obtaining histology in pancreatic masses. [7]. The overall complication rate of EUS-FNA is 0.82%, including pain, bleeding, and pancreatitis, which is the most common one, with an incidence of less than 1% [8]. The

range of reported sensitivities and specificities of EUS-FNA for the diagnosis of pancreatic cancer are 85–92% and 96–98%, respectively [81–85].

CE-EUS and elastography allow targeting EUS-FNA, improving the outcome [44, 52,70].

For typing the para-aortic lymph node, the sensitivity and specificity of EUS-FNA are 96.7% and 100% respectively, much better than PET -scan [135]. EUS elastography is able to identify the smallest metastatic changes in tissue hardness and CE-EUS is potentially useful for target selection prior to EUS-FNA, as suggested in the European guidelines. Malignant ascites or liver metastases preclude surgical resections and indicate poor survival [139]. EUS-FNA has a sensitivity of 82–94% for the diagnosis of malignant ascites or liver metastasis [140–143]. Endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) has become an indispensable tool for acquiring pancreatic lesion tissue, replacing percutaneous FNA. [140-145] A meta-analysis of 33 studies between 1997 and 2009 recently showed that EUS-FNA has a pooled sensitivity for malignant cytology of 85-91%, specificity of 94-98%, positive predictive value of 98-99%, and negative predictive value of 65-72%.[146,147,148,149] In a recent meta-analysis, the accuracy of EUS-FNA in diagnosing solid pancreatic masses was analyzed. Pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were 86.8%, 95.8%, 15.2, and 0.17, respectively. [150-165]

The rapid on-site evaluation (ROSE) involves the immediate evaluation of the smears obtained in the endoscopy suite.[166] This is usually done by a cytopathologist using a light microscope with immediate feedback about the diagnostic quality of the specimen. Numerous studies have confirmed the superiority of ROSE in terms of increasing the diagnostic yield by limiting the number of passes and decreasing the number of inadequate samples. [167-169] In a 3-year period the percentage of repeat procedures on the non-ROSE group was 5.8%, higher than in the ROSE group (2.9%).

The use of ROSE decreased the number of repeated procedures by approximately 50% (P = 0.024). [170] The diagnostic yield of cytology obtained by EUS-FNA with ROSE in most studies exceeds 90%.[171] In a meta-analysis involving 34 studies evaluating EUS-FNA, the pooled sensitivity and specificity for EUS-FNA of pancreatic ductal adenocarcinoma were 88.6% and 99.3%, respectively[171-173] Although there is evidence to support ROSE, there cost-effectiveness of implementing the procedure is debated. [174] Alternative strategies such as gross inspection and ROSE performed by an endosonographer, had worse results compared to ROSE by a dedicated cytotechnician (89%).175, 176] The need for ROSE may be obviated if core tissue can be obtained.[178] The specially designed biopsy needles cannot guarantee reliable histology with accuracy greater than 95%[179]. In a recent study, sixty consecutive patients referred for EUS-fine-needle biopsy (FNB) were evaluated to determine the additive value of ROSE on diagnostic accuracy. On-site specimen adequacy and final diagnostic accuracy were 58% and 83%, respectively.

Three sizes of EUS-FNA needles are available: 19G, 22G, and 25G. The most commonly used is the 22G needle.[182] The 25G needle may perform better in sampling lesions of the pancreatic head or uncinate process, because it is more flexible.[183] The diagnostic accuracy for pancreatic masses when using the 22G needles is up to 95% [184]. There are two randomized controlled trial comparing 22G and 25G needles performance, showing no significant differences in sample adequacy and complications [185,186,187] A recent randomized controlled trial comparing flexible 19G and 25G needles for EUS-FNA of solid pancreatic masses also found that there was no significant difference in the performance of flexible 19G and 25G needles in terms of technical failure (0% vs 2%, P = 0.99) or adverse events (2% vs 0%, P = 0.99).[188, 189,190, 191] There used to be an assumption that the use of a stylet during EUS-FNA prevents clogging of the needle lumen as the needle passes through the gastrointestinal wall.[199,200] Several

randomized controlled trials reported that the use of the stylet increases the blood in the specimen without augmenting the diagnostic yield in FNA.[189-195] Air flushing is superior to reinsertion of the stylet to collect EUS-FNA aspirates, except when there is clotting.[200]

There is no consensus on the use of suction: it is supposed to improve the diagnostic yield during EUS-FNA. EUS-FNA without suction uses the fine-needle capillary sampling technique to achieve the same result [200] In a randomized control trial the diagnostic yield during EUS-FNA of pancreatic masses with suction was higher than without suction (72.8% vs 58.6%, *P* = 0.001). In another study, EUS-FNA with suction was associated with higher sensitivity, and negative predictive value (85.7% vs 66.7%). In a pilot study continuous high negative pressure mechanical suction (35 mL of a 60 mL syringe) with a 22G needle yielded a tissue core adequate for histologic evaluation in 96% of solid masses. [195] The use of suction during EUS-FNA of lymph nodes was associated with excessive bloodiness. 187] The European Society of Gastrointestinal Endoscopy (ESGE) technical guidelines recommend the application of continuous suction for EUS-FNA of solid masses but no suction for lymph nodes.[141] Capillary aspiration technique by slow withdrawal of the stylet, may have higher sensitivity than conventional suction. Studies comparing slow pull versus suction in EUS-FNA of pancreatic masses found that the slow-pull technique had higher diagnostic yield, in particular using 25G needle.[201] In contrast, Kin *et al*. found no difference between suction and slow pull in EUS-FNA of solid pancreatic lesions using a standard 22G needle.[202] The “multipass” technique involves sampling widely through the lesion many times, before removing the needle. The needle is moved through the entire diameter of the lesion for 5-10 strokes.[210] In contrast, the fanning technique involves sampling multiple areas within a lesion with each pass. A sufficient number of passes must be performed to provide enough material for analysis.[211] A randomized trial comparing fanning to the conventional technique, found no significant difference in diagnostic accuracy although the fanning technique facilitated a

first-pass diagnosis (85% vs 60%) [212] Regarding learning curve in performing EUS-FNA of pancreatic lesions, current ASGE guidelines recommend 25 supervised EUS-FNA. The sensitivity rises with the number of procedures performed. [160] Most experts recommend a 6-24 month “hands-on” training in EUS before achieving competency.[161,165] The number of needle passes needed to obtain diagnostic material varies by site, size, and type of lesion, and potentially may be optimized by immediate cytological assessment of the adequacy of specimens [213-220]. If ROSE is not available, five to six passes may be required for pancreatic masses; well-differentiated pancreatic adenocarcinoma require a higher number of passes as compared to moderately and poorly differentiated tumors. In tumors that are very vascular, increasing the number of passes may decrease the diagnostic yield due to increasing blood contamination. [220-245] Gross examination of the specimens by the EUS endoscopist for cytological and histological sensitivities required only one to two passes in 92% of the cases with solid pancreatic masses.[246-248,249] In a prospective study involving a 25G needle, four passes were found to be sufficient for EUS-FNA of solid pancreatic lesions.[250] The ESGE recommends performing three needle passes when sampling lymph nodes and liver lesions and five passes when sampling solid pancreatic masses.[251]

In recent years, many studies have focused on the use of the EUS-core biopsy needle to obtain more tissue. These needles allow a larger specimen with preservation of tissue architecture. Possible indications for the use of FNB include failure of FNA with a 22G or 25G needle, suspicion of metastatic tumors requiring special studies for identification, and diagnosis of neuroendocrine tumors, lymphoma, or autoimmune pancreatitis. Histologic specimen should have higher diagnostic accuracy and provides more material for ancillary technique, such as immunohistochemistry. [146] When ROSE is not available, combining EUS-FNA cytology and histology significantly increases the sensitivity, compared with cytology or histology alone.[149] To obtain a core a large 19G

FNA needle or a “tru-cut” needle have been used, but this devices have a high rate of failure, especially in the pancreatic head or uncinate process.[182,183,184] In the last years, new biopsy needles were designed. A multicenter study reported that the ProCore 19G needle was technically feasible in 95% of cases, with an accuracy of 89.4%.[185] A study compared the 22G core biopsy needle to a standard 25G FNA needle, finding no differences in diagnostic yield, but fewer passes in the procore needle group.[186] Other studies showed no significant difference in the yield or quality of the histologic core between 22G FNA and 22G biopsy needles, but the biopsy needle provided an adequate sample with fewer passes.[187,189] A retrospective study using a 25G core biopsy needle showed a high cytological yield and histologic core tissue.[188]

The total complication rate of EUS-FNA in published series ranges from 0% to 13%.[252] The most common complications are perforation, pancreatitis, infection, tumor seeding and bleeding, with no correlation with the type of needle or the site of the lesion.[104,253,254,255]

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Performance of EUS-FNB in solid pancreatic masses: a lesson from 463 consecutive procedures and a practical nomogram

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Abstract

Objectives: The study's main goal was the diagnostic adequacy of pancreatic EUS-FNB and associated predictive factors. The secondary objective was to define the diagnostic accuracy of EUS-FNB in the diagnosis of pancreatic masses and pancreatic malignancies.

Methods: We retrospectively identified patients with solid pancreatic lesions that underwent EUS-FNB between 2013, and 2018. We calculated diagnostic adequacy and related factors. Using definitive histology on the surgically resected specimen as the gold standard, we calculated diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of EUS-FNB.

Results: We identified a total of 463 procedures. Diagnostic specimens were adequate in 436 procedures (94.1%), while 27 biopsies provided insufficient samples (5.9%). The multivariate analysis showed that lesion size and needle caliper were the only factors influencing diagnostic adequacy. The use of a biopsy needle (OR=0.69, 95% IC 0.30-0.1.63, p=0.400) did not improve sample adequacy. We calculated sensitivity (89%), specificity (100%), diagnostic accuracy (91.9%), positive predictive value (100%), and negative predictive value (76.6%) using resected specimen as the gold standard. We found no significant complications.

Conclusions: EUS-FNB is a reliable technique for the histological characterization of solid pancreatic masses.

Keywords: endoscopic ultrasound fine needle biopsy; pancreatic neoplasm; diagnostic yield

Introduction

Pancreatic solid lesions comprise many different diseases, malignant as pancreatic ductal adenocarcinoma (PDAC), neuroendocrine tumors (NET), lymphomas, metastasis, or benign, such as chronic pancreatitis (CP) and autoimmune pancreatitis (AIP)[1–3]. EUS-

guided sampling represents the technique of choice for tissue acquisition in most gastrointestinal lesions, including pancreatic lesions, liver nodules, lymph nodes, and subepithelial lesions[4]. At the beginning of the EUS era, the sampling was mostly cytological. In the last years, thanks to advances in technology, we can acquire real tissue cores by EUS[5]. Tissue samples, with preserved histological architecture, allow a better classification of pancreatic malignancies that is fundamental in the choice of personalized treatments[6]. Our study aim was to report the diagnostic adequacy of EUS-FNB in a tertiary center.

Material and Methods

We conducted a retrospective study based on a prospectively maintained database, which included all EUS-guided pancreatic tissue acquisition performed in the endoscopy center of the Gastroenterology Unit at IRCCS (Scientific Institute for Research, Hospitalization and Health Care) S. Orsola-Malpighi Hospital between January 1 2013 and October, 31 2018. The informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The local ethics committee approved data acquisition and analysis (code 401/2019/Oss/AOUBo). Enrolment criteria included aged ≥18 at the time of the procedure, solid pancreatic masses, availability of endoscopy and histologic reports, and informed consent. The flow-chart of the selection process is reported in **Figure 1**. Briefly, we report the endoscopic ultrasound sampling procedures. We performed EUS-FNB in outpatients and inpatients, with a fastening period of at least 8 hours and managing anticoagulant and antiaggregant therapy according to current guidelines[7,8]. During the procedures, the patients were in left lateral decubitus and received oxygen support. Conscious or deep sedation was provided by the endoscopist or the anesthesiologist when present, with continuous monitoring of vital signs. We employed a conventional linear EUS scope for all procedures (GF-UCT 180 Olympus Medical System Europe). We used both a trans-gastric and a trans-duodenal approach for

biopsy, depending on the lesion's site. We chose the type of needle according to lesion's size and site (available needles at the time of the study: Expect™ Slimline (SL) 19G/22G/25G, Acquire™ 22G, EchoTip ProCore™ HD 19G/20G/22G/25G). According to the macroscopic visual examination of the collected samples (MOSE), we decided the number of needle passes on a case-by-case basis. We used a single administration of antibiotics (ceftriaxone 2 g or levofloxacin 500 mg) only when considered necessary according to the patient's clinical situation, as current guidelines do not recommend routine antibiotic prophylaxis[9,10]. At the end of the procedure, patients were stationed under observation in the Endoscopy Unit for 1 hour, after which they were dismissed if no symptoms suggestive of a complication occurred. The outpatients were contacted by phone at home the day after the procedure according a pre-established protocol. An experienced endoscopist (NP) performed all the procedures. The study's main goal was to define the diagnostic adequacy of EUS-FNB and the associated clinical and technical factors. The secondary endpoints were: 1) to evaluate the diagnostic accuracy using surgical specimen as the gold-standard reference, 2) to evaluate procedure-related adverse events such as bleeding, pancreatitis, infection, and perforation. The demographic characteristics of patients are descriptive. We presented quantitative variables as proportion and mean ± SD, while categorical variables as relative and absolute frequencies. We used a backward logistic regression model to determine predictive variables of diagnostic adequacy (defined as the percentage of patients in whom EUS-FNB obtained a histologically interpretable specimen). A P value > 0.10 was used to remove the variables in backward multivariate, and a $P < 0.05$ was considered statistically significant. The multivariate analysis was reported as an odds ratio (OR) with a 95% confidence interval (CI 95%). Basing on the β coefficient of logistic regression and using a dedicated algorithm, we generated a nomogram predicting the diagnostic adequacy. Starting from nomogram, we obtained a score that was

calibrated using logistic regression and margin estimation. We used Stata 15 software (Stata Corp LP, TX) for statistical analysis.

Results

The flow-chart of patients' selection is reported in **Figure 1**: starting from 698 cases, we excluded 95 patients because they had a cystic lesion and 140 because only cytology was available. In the final analysis, we included only 463 patients whose baseline characteristics are reported in **Table 1**. The overall diagnostic adequacy was 94.1%. The histologic diagnosis of the 436 adequate sample were: 255 (58.5%) pancreatic ductal adenocarcinoma (PDAC), 83 (19%) neuroendocrine Tumors (NET), 40 (9.2%) chronic pancreatitis/autoimmune pancreatitis (CP/AIP), 21 (4.8%) metastasis/lymphomas, 14 (3.2%) intraductal papillary mucinous neoplasia (IPMN), 3 (0.7%) serous neoplasia and 2 (0.5%) atypia. In 18 cases (4.1%) the specimen resulted in normal pancreatic parenchyma. The histological diagnosis is reported in **Supplementary Table 1**. The multivariate analysis showed that the only factors influencing sample adequacy were: the size of the lesion with an OR of 1.05 (1.01 - 1.10; P=0.019) for each mm and the needle caliper in Gauge with an OR of 0.45 (0.57 - 0.99; P=0.049). Sex, age, size, and needle type were not significantly related to diagnostic accuracy. The lesion site did not reach a statistical relevance but showed a trend: the diagnostic adequacy seems to drop comparing head-isthmus vs. body-tail location (OR 0.44; 0.17 – 1.16; P=0.088) (**Table 2**). The nomogram derived from the multivariate model is plotted in **Figure 2**. Three parameters contributed to the final score: i) needle caliper (from 0 points of 25 Gauge to 2.4 points of 19 Gauge); ii) lesion location (from 0 points of lymph-nodes to 1.9 points of head); iii) lesion size (from 0.8 points of 10 mm to 7.8 points of 100 mm). The final score ranged from 0 to 21 points. The calibration of the score was graphically reported in **Figure 3** and exhaustively described in **supplementary Table 2**. Starting from 0 value, for each incremental point, we observed a statistically significant increase in diagnostic adequacy. For a score greater than 9 points, the diagnostic

adequacy was constantly higher than 90 %. From 9 points on, for every further increase, the gain was progressively smaller. A definitive diagnosis, based on the analysis of surgically resected specimens, was available in 136 patients. The results showed 84 (61.8%) cases of pancreatic ductal adenocarcinoma, 30 (22.1%) cases of neuroendocrine tumors, 15 (11%) cases of metastasis/lymphoma, 3 (2.2%) cases of IPMNs, 3 (2.2%) cases of CP/AIP and 1 (0.7%) case of serous lesion (**supplementary Table 3**). Based on the above findings, EUS-FNB for malignant lesions of the pancreas showed 89% sensitivity, 100% specificity, 91.9% diagnostic accuracy, 100% positive predictive value, and 76.6% negative predictive value (**Table 3**).

Discussion

Our study shows that EUS-FNB achieves an adequate sample for histological diagnosis in more than 94% of the cases. Endoscopic ultrasound-guided sampling has a fundamental role in the diagnosis and management of gastrointestinal lesions, and it is considered the first choice to biopsy pancreatic masses[4,11]. When EUS affirmed its position in the clinical context, the first technique used for tissue sampling was EUS-FNA with cytology assessment[12]. A recent meta-analysis found no significant difference in diagnostic adequacy between EUS-FNA and EUS-FNB when rapid onsite evaluation (ROSE) was available during FNA. Without ROSE, FNB showed better diagnostic adequacy in the characterization of solid pancreatic lesions[13]. FNB also seems to require fewer needle passes than FNA to establish malignancy diagnosis [14–17]. Endoscopic ultrasound-guided fine-needle biopsy (FNB) primary goal is to overcome FNA limitations, and besides

adequacy issues, the major pitfall of EUS-FNA is the inability to preserve tissue architecture[18,19]. Immunohistochemical and molecular characterization is possible only on tissue cores, so tissue sampling allows the choice of optimal treatment for each patient with a personalized approach[4,5]. In our series, we had a diagnostic adequacy on the lower end of the range reported in the literature[5]. A plausible explanation is that our series included a significant rate of non-malignant pancreatic masses, reducing the pre-test probability of pancreatic malignancy, and a high number of chronic pancreatitis, in which the diagnostic accuracy for pancreatic malignancies is reduced[20]. The analysis of the factors influencing adequacy showed that lesion size and needle caliper are the only factors reaching statistical significance. We observed an increase in the diagnostic adequacy of 5% for each mm of lesion's size. This result confirms previous studies showing better adequacy of the specimen in larger lesions, which was also reported in EUS-FNA studies[21]. The more interesting result is the correlation between needle caliper and diagnostic adequacy. We observed a significant increase in adequacy between the use of minor caliper needles and larger ones. This is a remarkable result, and previous studies showed this trend[22]. Technological advancement allowed the development of biopsy needles, improving, in theory, the ability to obtain a tissue core[23]. We found no impact of the dedicated needles in increasing adequacy rate compared to the standard needle, and the number of needle passes did not correlate with an improvement in diagnostic yield, as previously reported in other studies[20]. In our data, we also observed a trend towards incremental diagnostic yield from the body-tail to isthmus-head, though not statistically significant. We used the dataset to generate a nomogram able to predict the probability of diagnosis. After creating and calibrating the nomogram, we created a score for the adequacy probability. Observing the nomogram, a message arises: given the non-modifiable variables such as location and size, the choice of the needle caliper is crucial. In particular, the smaller the lesion the larger must be the needle to acquire enough tissue to obtain a diagnosis.

It seems fair to affirm that this study explores the diagnostic performance of EUS-FNB in a real-world practice of non-selected patients so that these results can apply to everyday practice.

For what concerns FNB performance, diagnostic accuracy is lower compared to previous studies[24–26], but still good, being over 90%. This is related to the application of stringent criteria to declare correct a diagnosis: even a little discrepancy in histology between EUS biopsy and the surgical specimen was considered a diagnostic failure. We did not test the mere capacity of EUS-FNB to obtain a diagnosis but to make a correct classification of the lesion with definitive histology as the gold standard. As we can see from table 3 we had a correct classification of the lesion most of the time, even with rare diagnoses such as a solid pseudopapillary tumor. This means that EUS-FNB is a reliable method to characterize a lesion, obtaining a tissue core that allows not only histological diagnosis but also ancillary methods, like the immunohistochemical analysis.

In all adequate specimens, immunohistochemical analysis was feasible, granting a complete diagnostic definition, thus confirming that EUS-FNB samples had a preserved tissue architecture. This is fundamental in FNB and differentiates this approach from FNA, in which samples usually consist of macro cell-aggregates, often not suitable for further characterization[27].

Regarding safety and feasibility, EUS-FNB was performed both in outpatients and in hospitalized patients, no significant adverse events occurred during or after the biopsy, showing that this is a safe procedure, especially if we consider the high number of cases and the absence of technical failures.

We found no significant difference in diagnostic yield between head and body/tail lesion, so there is no difference in performance between trans duodenal and trans gastric approach, confirming a recent study [28].

Our study has some limitations. First, it is a retrospective study and could be affected by selection bias, but it is worth noticing that our database was maintained prospectively, so this kind of bias should be limited. In the second place, long-time follow-up was not available for all patients, but the use of histology as a gold standard overcome this limitation, though narrowing the evaluation of diagnostic accuracy only to patients undergoing surgery. In conclusion, our data confirm current evidence that EUS-FNB is a feasible procedure defined by a high safety profile and a high technical success rate. Diagnostic yield was 94%, and in most cases, the material allowed histological and immunohistochemical analysis. We must consider that pancreatic pathologists, especially in Europe, are more confident with histologic samples than with cytology so that the biopsy approach can be considered more applicable in clinical practice. Avoiding the need for ROSE, EUS-FNB leans the endoscopic suite workflow; moreover, reducing the number of needles passes, the technique is less time consuming and, virtually, safer [9,29,30]. In the attempt to obtain an adequate tissue sample, the use of needles with a large caliper is related, in our experience, to a higher success rate with no difference between dedicated and standard needles. In particular, our nomogram shows that the smaller the lesion, the larger has to be the needle to compensate for the lower adequacy probability. Our experience suggests that EUS-FNB is a reliable technique for obtaining tissue samples that can be processed as histology with all the related implications.

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Figure legends

Figure 1: Flow chart of patient selection

Figure 2: Nomogram

Figure 3: Nomogram score calibration

FIGURES AND TABLES

Figure 1- Flow chart of patient selection for the analysis.

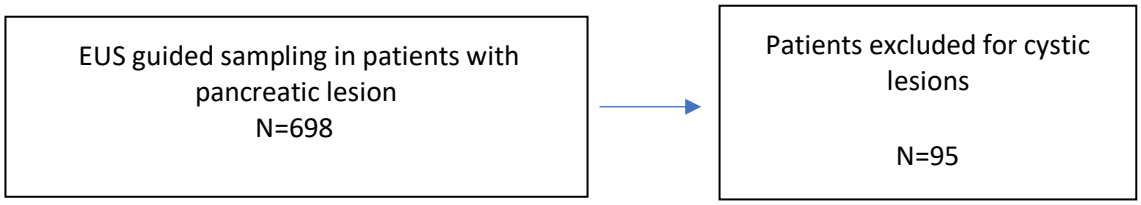


Table 1. Baseline characteristics (data are reported as absolute/relative frequencies and mean plus standard deviation).

EUS-FNB parameters	Patients (n=463)
Sex, n (%)	
M	231 (49.9)
F	232 (50.1)
Age [years], mean (SD)	66.0 (13.5)
Lesion dimensions [mm], mean (SD)	25.6 (13.6)
Lesion site, n (%)	
Head	267 (57.7)
Isthmus	35 (7.5)
Body-Tail	161 (34.8)
Needle type, n (%)	
Traditional needle	283 (61.1)
Biopsy needle	180 (38.9)
Needle caliper [Gauge], n (%)	
19	207 (44.7)
20	18 (3.9)
22	226 (48.8)
25	12 (2.6)
Number of passages, mean (SD)	2.1 (0.9)
Diagnostic adequacy, n (%)	
Adequate sample	436 (94.1)
Inadequate sample	27 (5.9)

Table 2. Multivariate analysis for predictive factors of diagnostic adequacy

Comparison between EUS-FNB and resected specimen		Biopsy							
		Carcinoma	IPMN	NET	Metastasis	PSC	CP	SPT	**Total**
Surgical specimen	Carcinoma	81 95.29	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	**81** **59.56**
	IPMN	2 2.35	2 100.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	**4** **2.94**
	NET	0 0.00	0 0.00	28 100.00	0 0.00	0 0.00	0 0.00	0 0.00	**28** **20.59**
	Metastasis	0 0.00	0 0.00	0 0.00	15 100	0 0.00	0 0.00	0 0.00	**15** **11.03**
	PSC	0 0.00	0 0.00	0 0.00	0 0.00	1 100	0 0.00	0 0.00	**1** **0.74**

Parameters	OR (95% CI)	P value	Step exclusion
Sex			
F	1		4th
M	2.05 (0.78 - 5.38)	0.156	
Age [years]	1.01 (0.98 - 1.10)	0.780	1st
Size [mm]	1.05 (1.01 - 1.10)	0.019	Final
Localization			
Head	1		
Isthmus	0.70 (0.18 – 2.73)	0.605	Final
Body-Tail	0.44 (0.17 – 1.16)	0.088	
Lymph-node	0.30 (0.05-1.83)	0.194	
Needle type			
Traditional needle	1		2nd
Biopsy needle	0.69 (0.29 - 1.63)	0.408	
Needle caliper [Gauge]	0.45 (0.57 - 0.99)	0.049	Final
Number of passages	1.39 (0.85 - 2.27)	0.221	3rd

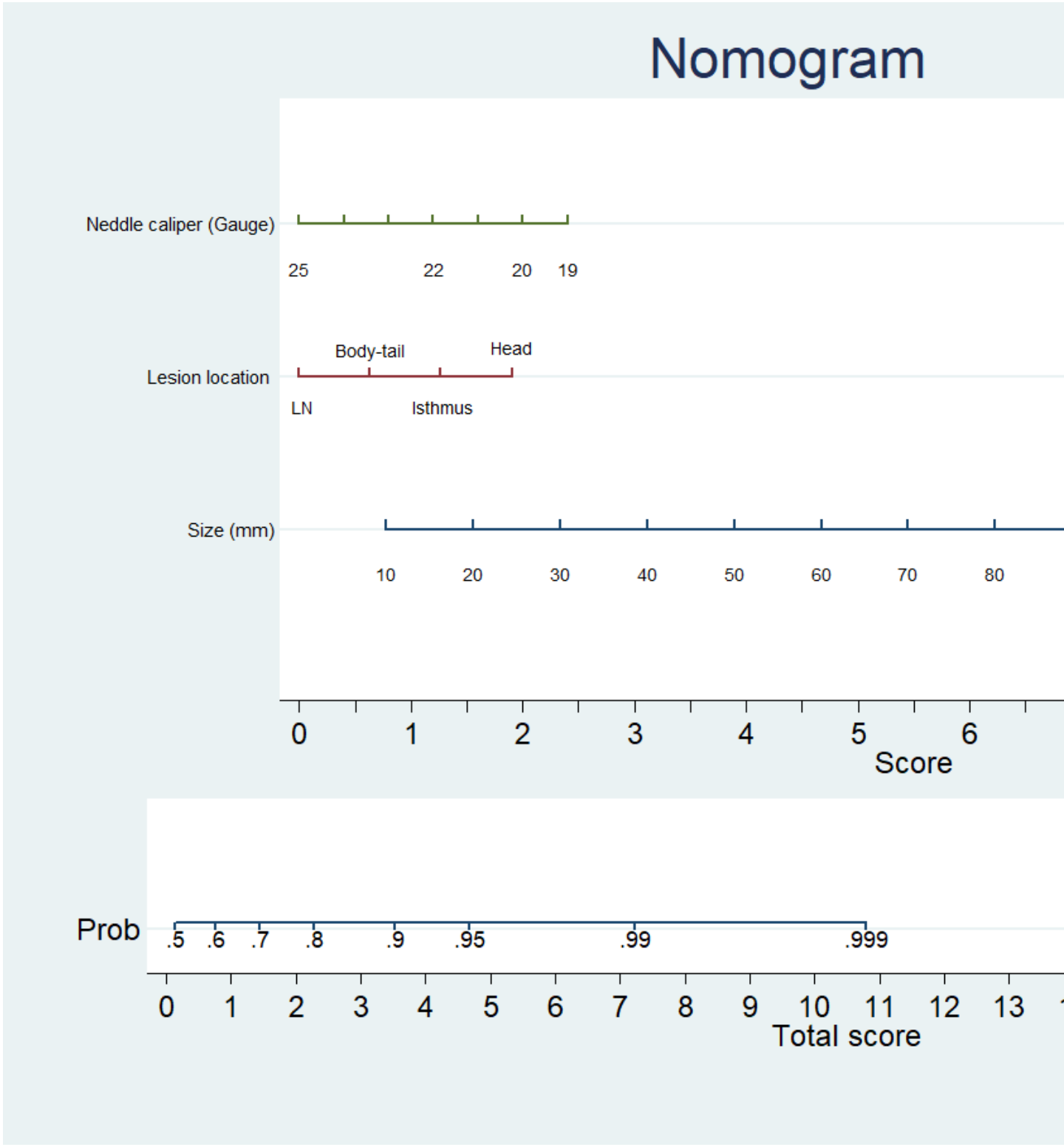
	CP	2 2.35	0 0.00	0 0.00	0 0.00	0 0.00	3 100.00	0 0.00	**5** **3.68**
	SPT	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	2 100.0	**2** **1.47**
	Total	**85** **100.00**	**2** **100.00**	**28** **100.00**	**15** **100.00**	**1** **100.00**	**3** **100.00**	**2** **100.00**	**136** **100.00**

PSC: Pancreatic Serous Cystadenoma
CP chronic pancreatitis
SPT: Solid pseudopapillary tumor

Agreement	Expected agreement	Kappa	Std. Err.	Z	Prob>Z
97.06%	42.83%	0.9486	0.0556	17.07	0.0000

Table 3. OR adequacy

Figure 2. Nomogram


Nomogram
Neddle caliper (Gauge)
25
22
20
19
Lesion location
Body-tail
Head
LN
Isthmus
Size (mm)
10
20
30
40
50
60
70
80
0
1
2
3
4
5
6
Score
Prob
.5
.6
.7
.8
.9
.95
.99
.999
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Total score

Supplementary Table 1. Histologic diagnosis of echo endoscopic-guided fine-needle biopsies (data are reported as absolute/relative frequencies).

EUS-FNB diagnosis	N (%)
Normal parenchyma	18 (4.1)
Atypia	2 (0.5)
PDAC	255 (58.5)
IPMN	14 (3.2)
NET	83 (19.0)
Metastasis/Lymphoma	21 (4.8)
Serous neoplasia	3 (0.7)
CP/AIP	40 (9.2)
Total	436 (100)

PDAC= Pancreatic Ductal Adenocarcinoma; IPMN= Intrapapillary Mucinous Neoplasia; NET= Neuroendocrine Tumor; CP= Chronic pancreatitis; AIP= Autoimmune pancreatitis

Supplementary Table 2. Probability of Adequacy

Cutoff -Points of Score	Probability of adequacy (%; 95CI)	P value*
0	53.7 (22.3 to 85.2)	0.001
1	59.7 (31.9 to 87.5)	<0.001
2	65.4 (41.7 to 89.0)	<0.001
3	70.6 (51.2 to 90.0)	<0.001
4	75.4 (60.0 to 90.8)	<0.001
5	79.6 (67.9 to 91.4)	<0.001
6	83.3 (74.5 to 92.1)	<0.001
7	86.4 (80.0 to 92.8)	<0.001
8	89.0 (84.4 to 93.6)	<0.001
9	91.1 (87.8 to 94.5)	<0.001
10	92.9 (90.3 to 95.5)	<0.001
11	94.3 (92.2 to 96.5)	<0.001
12	95.5 (93.5 to 97.4)	<0.001
13	96.4 (94.6 to 98.2)	<0.001
14	97.2 (95.5 to 98.8)	<0.001
15	97.7 (96.2 to 99.3)	<0.001
16	98.2 (96.8 to 99.6)	<0.001
17	98.6 (97.4 to 99.8)	<0.001
18	98.9 (97.8 to 100)	<0.001
19	99.1 (98.2 to 100)	<0.001
20	99.3 (98.5 to 100)	<0.001
21	99.4 (98.7 to 100)	<0.001

Supplementary Table 3. Definitive diagnosis based on surgical resected specimens (data are reported as absolute/relative frequencies).

Definitive diagnosis	N (%)
PDAC	84 (61.8)
IPMN	3 (2.2)
NET	30 (22.1)
Metastasis/Lymphoma	15 (11.0)
Serous neoplasia	1 (0.7)
CP/AIP	3 (2.2)
Total	136 (100)