

# Endoscopic ultrasound-guided fine needle aspiration: How to obtain a core biopsy?

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## ABSTRACT

Endoscopic ultrasound (EUS)-guided fine needle aspiration has emerged as the procedure of choice to obtain samples to reach a definitive diagnosis of lesions of the gastrointestinal tract and of adjacent organs. The obtainment of a tissue core biopsy presents several advantages that can substantially contribute to the widespread diffusion of EUS utilization in the community and in countries where cytology expertise may be difficult to be achieved. This article will review the EUS-guided fine needle biopsy techniques developed so far, the clinical results, their limitations as well as their future perspective.

**Key words:** Core biopsy, endoscopic ultrasound, fine needle aspiration, fine needle biopsy, histology, tissue acquisition

## INTRODUCTION

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) has emerged as the procedure of choice to obtain samples to reach a definitive diagnosis and proper staging of lesions of the gastrointestinal (GI) tract and of adjacent organs.<sup>[1,2]</sup> The sensitivity of EUS-FNA, however, is strongly dependent on the availability of an on-site cytopathology, which has been clearly demonstrated to significantly influence the diagnostic accuracy as well as the proportions of indeterminate and unsatisfactory samples.<sup>[3-6]</sup> Unfortunately, access to on-site cytopathology and the availability of a Cytopathologist specifically trained to interpret EUS specimens is not available in many centers.<sup>[7]</sup> This has created a barrier to the widespread use of EUS-FNA, because the lack of

cytopathology expertise has strongly compromise the overall perceived utility of EUS.<sup>[8]</sup>

The obtainment of a tissue biopsy specimen for histologic examination may overcome this main limitation of EUS-FNA. The advantages of a biopsy core specimen are well-known, since the evaluation of tissue architecture improves both the diagnostic accuracy and reproducibility. Of note, a tissue core biopsy with preserved architecture is critical to diagnose and fully characterize certain neoplasms, such as lymphomas and GI stromal tumors (GIST). Moreover, tissue specimens for histologic examination also provides the opportunity to immunostain the tissue, further increasing differential diagnostic capabilities; reach a specific diagnosis for benign diseases not always obtainable with a cytological sample, thus sparing patients from more invasive and risky sampling procedures or costly and unnecessary follow-up examinations; perform tissue profiling and/or cell culture needed to guide targeted therapies for individualized treatment of patients with cancer of the GI tract.<sup>[9-11]</sup>

This article will review the EUS-guided fine needle biopsy (EUS-FNB) techniques developed so far, the

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clinical results, their limitations as well as their future perspective.

### EUS-GUIDED TRU-CUT BIOPSY (EUS-TCB)

In 2002, the first experiences using the Quick-Core® (Cook Medical Inc., Bloomington, in, United States), a 19-gauge needle capable of collecting an 18-mm tissue specimen sufficient for histologic examination [Figure 1], were performed in animals and humans.<sup>[12,13]</sup> Since then, a number of studies were conducted in order to examine the feasibility and safety of EUS-TCB, as well as, to compare its performance with other EUS-guided sampling techniques. Overall, studies that evaluated the performance of EUS-TCB reported disappointing results, characterized by a wide variation in both diagnostic accuracy (ranging from 52% to 100%)<sup>[14,15]</sup> and yield (50-100%),<sup>[16,17]</sup> with the worst performances reported when punctured where performed through the duodenum.<sup>[16,18]</sup> In addition, no clear advantage for EUS-TCB over EUS-FNA has been demonstrated,<sup>[16,19-22]</sup> even in patients with suspected lymphomas or subepithelial lesions, which are considered a class IIa indication for the use of EUS-TCB.<sup>[23]</sup> Moreover, the Tru-cut needle is very difficult to handle and the technique is less intuitive than



**Figure 1.** Non-handle portion of the Tru-cut needle demonstrating the following: Outer “catheter sheath,” an internal 19-gauge “cutting sheath” that shaves off the tissue specimen; an 18-mm-long “specimen tray,” which contains the tissue core; and a 5-mm-long “stylet tip.” Adapted with permission from Levy and Wiersema

EUS-FNA. For these reasons, this technically demanding and cumbersome to use needle, especially when the procedure is performed from the duodenum, has failed to reach widespread use outside of tertiary care centers. On the other hand, it should be considered as the primer to present and future developments in EUS-FNB.

### EUS-FNB USING A STANDARD 22-GAUGE NEEDLE

#### *With negative suction pressure*

In an article in 2000, Voss *et al.*<sup>[24]</sup> in an attempt to overcome some of the limitations of EUS-FNA, described their experience in gathering tissue specimens from pancreatic solid masses using a standard 22-gauge FNA needle in association with high negative suction pressure obtained by using a 30 mL syringe. Overall, the procedure was successful in 90 of the 99 patients (91%), with the achievement of material for histologic evaluation in 81% of the patients in whom the procedure was feasible, which was diagnostic in 75% of them. Interestingly, diagnostic accuracy was significantly better for adenocarcinomas than for neuroendocrine tumors (81% *vs.* 47%,  $P = 0.02$ ), whereas tumor size did not influence the results.

In an article in 2005, Larghi *et al.*,<sup>[25]</sup> performed a prospective, observational study implementing the Alliance II inflation system (Boston Scientific Corp., Natick, Mass, US), which was attached to a standard 22-gauge FNA needle. The Alliance II Inflation system allowed achieving a high steady and continuous negative suction and the authors named this technique as EUS-guided fine needle tissue acquisition (EUS-FNTA) to distinguish it from standard EUS-FNA.

In the EUS-FNTA technique, once the needle is advanced into the target lesion under real-time EUS imaging, the stylet is withdrawn and the Alliance II system is attached to the proximal end of the needle. The Alliance II system is then turned into the suction mode and a high negative continuous suction pressure corresponding to 35 mL of the 60 mL syringe, a value arbitrarily chosen, is applied. The lock of the syringe is then opened to apply steadily and continuously high negative suction pressure during the to- and- from movements of the needle inside the target lesion.

In the experience with this technique, Larghi *et al.* included 27 patients with heterogeneous indications (pancreatic, mediastinal, left adrenal, liver, gallbladder

and gastric wall masses).<sup>[26]</sup> All patients first underwent EUS-FNA with a total of five passes performed. Using the same 22-gauge FNA needle an extra pass was done with the technique described above and in all but one patient a tissue specimen for histologic examination was procured, with no complications. EUS-FNA and EUS-FNTA reached the same diagnostic accuracy of 77%, prompting the authors to speculate that EUS-FNTA could have the potential for a better performance if done as the starting sampling technique, with more needle passes performed.<sup>[25]</sup> This inference, however, was partially disproved by the only other study that further investigated the role of this technique,<sup>[26]</sup> which involved mainly patients with enlarged lymph nodes. The content of the needle after EUS-FNTA was directly placed into formalin for histologic examination and tissue core biopsy specimens were found in only 28% of the 36 patients evaluated. On the other hand, overall diagnostic accuracy of 78% was reported, a result very similar to the one described by Larghi *et al.*,<sup>[25]</sup> thus implying that a sample for at least cytologic evaluation was obtained.

#### *Without negative suction pressure*

Several studies have assessed the capability to obtain tissue core biopsy specimens using a standard 22-gauge needle without applying high negative suction pressure [Table 1]. Iglesias-García *et al.*<sup>[27]</sup> assessed value of an extra pass performed using the same 22-gauge needle utilized after two previous FNA passes in obtaining tissue core specimens in 62 patients with pancreatic masses. Histologic samples were adequate in 84% of the cases with a  $6.5 \pm 5.3$  mm mean length of the retrieved specimens. Overall, correct diagnosis from the samples collected with this additional needle pass was 89%, meaning that a few samples had some cells that made possible to reach a cytologic diagnosis but not sufficient to render a biopsy core for full histologic evaluation. In a subsequent study, Möller *et al.*<sup>[28]</sup> further investigated the capability of collecting tissue samples from 192

patients with pancreatic masses using a 22-gauge needle without high negative suction pressure. The material, which was retrieved by reinserting the stylet in the needle, was first visually evaluated for the presence of core tissue specimens that were subsequently carefully harvested by syringe suction and placed in formalin. The remaining liquid material was placed in saline solution or smeared onto glass slides for cytologic analysis. Using this technique, adequate samples for histologic evaluation were found in 86% of patients with only one or two passes performed. In these cases, an adequate cytologic specimen was also available in 93% of the cases. Overall, diagnostic accuracy was 71% and 78% for histologic and cytologic samples, respectively, with an extremely high accuracy (88%) when both histologic and cytologic results were combined.<sup>[28]</sup> Finally, Noda *et al.*<sup>[29]</sup> performed a similar study on 33 patients with pancreatic masses where samples were half evaluated for cytology and half for histology by the cell-block method. Reading of the cell-block was diagnostic in 25 of the 33 patients (76%) and in 31 out of the 33 (94%) after immunostaining was performed.

#### **EUS-FNB USING A STANDARD 19-GAUGE NEEDLE**

Between 2005 and 2006, two Japanese investigators first reported their experiences in using a standard 19-gauge needle to gather core biopsy specimens for histologic examination in patients with solid pancreatic masses and with mediastinal and/or intra-abdominal lymphadenopathy of unknown origin.<sup>[30,31]</sup> They reported overall diagnostic accuracy of 69% and 98%, respectively. This discrepancy in the overall reported accuracy was due to the high rate of failure (5 out of 8 patients, 63%) reported in one of the two studies of the sampling procedure when performed through the duodenum that is required for patients with pancreatic head and uncinate process masses.<sup>[30]</sup> However, the impressively high capability (88%) to correctly subtype

**Table 1. Studies evaluating the possibility of acquiring a tissue biopsy sample for histologic examination using a standard 22-G needle**

Author (year)	No. of patients	Patient population	Yield of core tissue (%)	Diagnostic accuracy (%)
Voss <i>et al.</i> <sup>[24]§</sup>	99	Pancreatic masses	81	68
Larghi <i>et al.</i> <sup>[25]*®</sup>	27	Solid masses	96	76.9
Iglesias-García <i>et al.</i> <sup>[27]</sup>	62	Pancreatic masses	83.9	88.7
Gerke <i>et al.</i> <sup>[26]*</sup>	120	Solid masses and lymph nodes	27.8	77.8^
Möller <i>et al.</i> <sup>[28]</sup>	192	Pancreatic masses	86.5	71.4
Noda <i>et al.</i> <sup>[29]</sup>	32	Solid masses and lymph nodes	NA	93.9

§Using high negative suction pressure with a 30 mL syringe, \*Using high negative suction pressure obtained using the alliance II inflation system, ®Results obtained with a single needle pass for tissue acquisition was performed at the end of a standard FNA, ^Diagnostic accuracy calculated based on both histologic and cytologic specimens, FNA: Fine needle aspiration

lymphomas in patients with lymphadenopathy of unknown origin reported in the study by Yasuda *et al.*<sup>[31]</sup> clearly showed that tissue specimens acquired with a standard 19-gauge needle could have a primary role in establishing a definitive diagnosis in selected patient populations.

In Table 2 are summarized the results of all studies in which a standard 19-gauge needle has been used to gather samples for histologic analysis, independently of the sampling technique utilized.<sup>[30-41]</sup> Excluding the study from Itoi *et al.*<sup>[30]</sup> in which a high technical failure rate was found when the procedure was performed through the duodenum, the overall technical success and yield in all the published studies were above 90%. Similarly, overall diagnostic accuracy was found to be above 90%, with the only exception of the study by Iwashita *et al.*<sup>[36]</sup> in which patients with a pancreatic mass suspicious for autoimmune pancreatitis (AIP) were evaluated. In the latter study, despite specimens for histologic analysis were obtained in 93% of the patients, a definitive histologic diagnosis of AIP based on lymphoplasmacytic infiltration around pancreatic ducts, obliterative phlebitis and/or positive immunoglobulin G4 immunostaining could be possible in only 43% of the cases. In the remaining 50% of the patients, tissue for histologic analysis was

available but specific histologic findings of AIP could not be found and a diagnosis of idiopathic chronic pancreatitis was made.<sup>[36]</sup> This low diagnostic accuracy can be attributed to the patchy distribution of the specific histologic changes of AIP,<sup>[42]</sup> thus rendering the amount of tissue obtained with EUS-guided biopsy insufficient to establish a definitive diagnosis. Importantly, in all patients with available tissue, a malignant etiology could be excluded that is extremely important in order to safely start empirical therapy for AIP with steroids.<sup>[36]</sup>

After the first publication in 2006,<sup>[31]</sup> the Japanese group from Gifu University Hospital published their experiences in patients with mediastinal lymphadenopathy and a clinical presentation suggestive of sarcoidosis<sup>[37]</sup> and in a larger cohort of patients with mediastinal and abdominal lymph nodes/lesions suspicious for lymphoma.<sup>[38]</sup> Both studies demonstrated the value of using a standard 19-gauge needle to confirm the clinical suspicion of sarcoidosis<sup>[37]</sup> and to establish a diagnosis of lymphoma with subclassification in a very high percentage of patients, thus sparing them from more invasive diagnostic procedures.<sup>[38]</sup> These results highly suggest that 19-gauge needle should be used as the sampling procedure of choice in these patient populations.

**Table 2. Studies evaluating the possibility of acquiring a tissue biopsy sample for histologic examination using a standard 19-gauge needle**

Author (year)	No. of patients	Patient population	Technical success (%)	Yield (%)	Diagnostic accuracy (%)
Itoi <i>et al.</i> <sup>[30]^</sup>	16	Pancreatic masses	81	68.8	68.8
Yasuda <i>et al.</i> <sup>[31]</sup>	104	Mediastinal and/or abdominal lymphadenopathy	100	100	98.1; 88 accuracy in subclassification of lymphoma
Iwashita <i>et al.</i> <sup>[37]</sup>	41	Mediastinal lymphadenopathy suspicious for sarcoidosis	100	95.1	95.1
Larghi <i>et al.</i> <sup>[32]@#</sup>	120	Heterogeneous patient population	99.2	96.7	93.2
Larghi <i>et al.</i> <sup>[33]#</sup>	30	Pancreatic masses suspicious for non-functional neuroendocrine neoplasia	100	93.3	93.3
Iwashita <i>et al.</i> <sup>[36]</sup>	44	Pancreatic masses suggestive of autoimmune pancreatitis	100	93	43.2
Yasuda <i>et al.</i> <sup>[38]</sup>	152	Mediastinal and/or lesions suspicious for lymphoma	97	97	93.4; 95 accuracy in abdominal subclassification of lymphoma (142 patients)
Varadarajulu <i>et al.</i> <sup>[41]</sup>	38	Pancreatic masses/subepithelial lesions	100	94.7	94.7
Stavropoulos <i>et al.</i> <sup>[39]*</sup>	31	Patients with abnormal liver tests undergoing EUS to rule out biliary obstruction	100	91	91
Eckardt <i>et al.</i> <sup>[40]</sup>	46	Gastric subepithelial lesions		59	52
Gor <i>et al.</i> <sup>[44]</sup>	10	Patients with abnormal liver tests	100	100	100
Larghi <i>et al.</i> <sup>[34]5#</sup>	121	GI subepithelial lesions	99.2	93.4	93.4

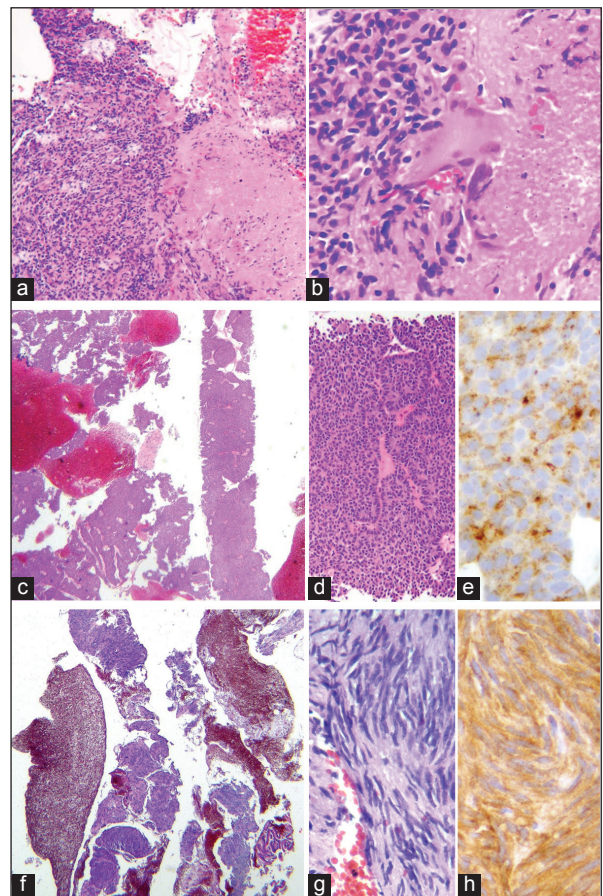
^All failures occurred when sampling was performed from the duodenum, @Consecutive patients with subepithelial lesions, esophagogastric wall thickening, mediastinal and abdominal masses/lymphadenopathy of unknown origin, pancreatic body or tail lesions after a negative FNA were included in the study, \*Adequate specimen defined as a length of 15 mm with the presence of at least 6 portal tracts, <sup>5</sup>All procedures were performed using the forward viewing EUS scope, #The EUS-FNTA technique was used, EUS-FNTA: Endoscopic ultrasound-fine needle tissue acquisition, GI: Gastrointestinal



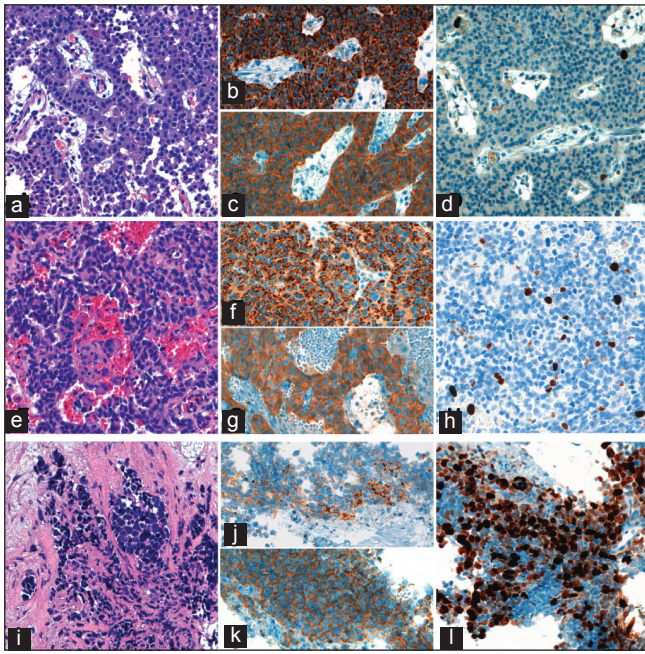
In order to overcome the limitation of using a standard 19-gauge needle through the duodenum, the technique described by Itoi *et al.*<sup>[30]</sup> and by Yasuda *et al.*<sup>[31]</sup> has been modified by removing the stylet before insertion of the needle into the working channel of the EUS scope to increase needle flexibility and improve its performance.<sup>[32]</sup> When using this technique after removing the stylet, a 10-mL syringe already preloaded with 10 mL of negative pressure is attached to the proximal end of the needle and used to apply moderate negative suction pressure. The needle is then advanced under EUS guidance few millimeters inside the target lesion. After opening the lock of the syringe to apply negative pressure, two or three to- and- from motions inside the lesion using the fanning technique<sup>[43]</sup> are made, which together account for one needle pass. The needle is removed after closing the lock of the syringe and the collected specimens are placed directly in formalin by flushing the needle with saline or by and sent for histologic examination. The authors continued to call the technique EUS-FNTA to distinguish it from EUS-FNA, as previously mentioned.

In the first experience using the modified EUS-FNTA technique, Larghi *et al.*, included patients with mediastinal and abdominal lymphadenopathy or masses of unknown origin and with subepithelial lesions, esophagogastric wall thickening and with pancreatic body or tail solid lesions after a negative FNA.<sup>[32]</sup> Overall, in the cohort of 120 patients consecutively enrolled, the procedure was technically successful in all but one patient without any complication, with a yield of 97% and diagnostic accuracy of 93%. Remarkably, not only specimens gathered with the EUS-FNTA could be of help to make a diagnosis of malignancy, but also a definitive diagnosis of a benign disease in 20 patients who were spared from more invasive diagnostic procedures and from unnecessary follow-up examinations<sup>[32]</sup> [Figure 2]. Subsequently, the same group performed a second study in patients with pancreatic lesions suspicious for non-functional neuroendocrine neoplasia (NF-NEN).<sup>[33]</sup> In these patients, the rationale was to attempt to gather tissue specimens to determine Ki-67 proliferation index, which is an important prognostic information that can help in management decisions.<sup>[33]</sup> A total of 30 consecutive patients with a mass located throughout the pancreas were enrolled. The procedure was technically successful in all cases (27% of the cases performed transduodenally) and in 28 out of the 30 patients a specimen for histologic examination was retrieved and confirmed the suspicious

diagnosis of NF-NEN. Moreover, in 26 patients (93% of those with an available specimen and 87% of the entire cohort), Ki-67 determination could be performed [Figure 3]. Comparison with the Ki-67 determination on surgical specimens, which represent the gold standard, was feasible in 12 patients and when a cut-off of 5% was used to differentiate G1 and G2 tumors an agreement was found in all patients.<sup>[33]</sup> These results indicate that pre-operative Ki-67 determination on EUS-FNTA specimens is feasible and can give important information to be used in the discussion with each single patient regarding the available therapeutic options.



**Figure 2.** Representative cases of specimens obtained by Endoscopic ultrasound-guided fine needle tissue acquisition. (a-b) Mediastinal lymphnode: (a) Abundant tissue fragments, at higher magnification; (b) Showing caseous material (left part of the micrograph) and polynucleated giant cells consistent with a tubercular granuloma, as also later confirmed by polymerase chain reaction methods; h and e; (c-e) Body-tail of the pancreas: (c and d) Multiple large tissue fragments of a well-differentiated, non-functioning, neuroendocrine tumor, with a typical trabecular structure, low grade histology void of necrosis and mitotic figures (d) and chromogranin A expression at immunohistochemistry (e); c, d, h and e; e, immunoperoxidase. (f-h) Perigastric lesion: (f), abundant, large fragments of neoplastic tissue with solid structure, in absence of necrosis, composed of regular, fused cell with mild atypia (g) Intense immunoreactivity for c-Kit and consistent gastrointestinal stromal tumor; f, g, h and e, h, immunoperoxidase



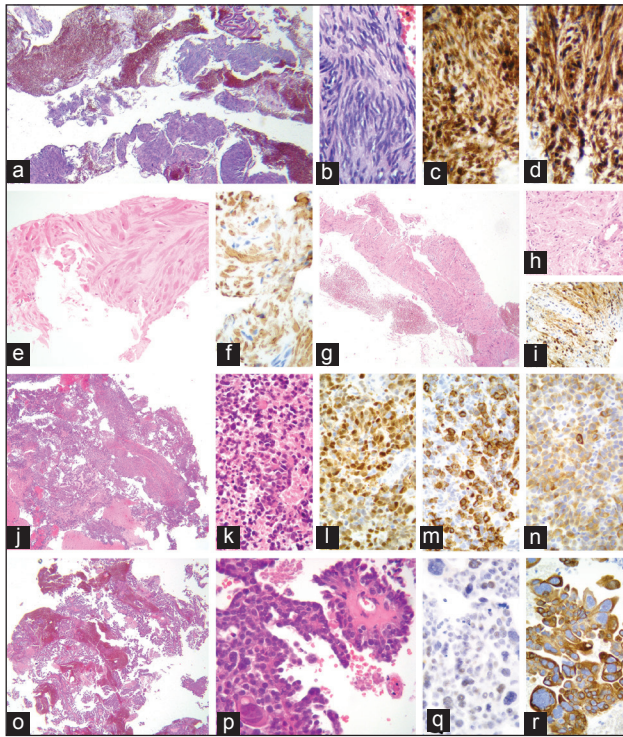
**Figure 3.** Examples of grading for neuroendocrine neoplasms in EUS-FNTA samples. a-d, Grade 1 p-NET showing trabecular histology, mild atypia (a), intense immunoreactivity for chromogranin A (b) and synaptophysin (c) and rare cells with nuclear labeling for Ki-67 (d). E-H, Grade 2 p-NET showing large trabecular structure, moderate cell atypia (e), intense immunoreactivity for chromogranin A (f) and synaptophysin (g) and discrete cells with nuclear labeling for Ki-67 (h) I-L, High grade, G3, p-NEC fragmented sample showing abundant desmoplasia and solid islets of cells with severe atypia and scarce cytoplasm (i), focal and often faint immunoreactivity for chromogranin A (j), intense and diffuse immunoreactivity for synaptophysin (k) and diffuse nuclear labeling for Ki-67 (l). a, e, i, h and e; b-d, f-h and j-l, immunoperoxidase

Two other patient populations in which the use of a standard 19-gauge needle has been evaluated are patients with abnormal liver function tests of unclear etiology referred for EUS to exclude biliary obstruction and those with subepithelial lesions.<sup>[34,39,40]</sup> In the first patient population, after an unrevealing EUS Stavropoulos *et al.*<sup>[39]</sup> investigated the value of EUS-guided liver biopsy performed in the same session using a standard 19-gauge needle. An adequate specimen was defined as a specimen of at least 15 mm in length and with a minimum of 6 complete portal tracts. Among the 22 patients evaluated, a specimen with these characteristics could be retrieved in 20 of them (91%) and was diagnostic in all cases. Importantly, there were no procedural complications, including five higher risk patients with relative coagulopathy (platelets <100,000/ $\mu$ L, international normalized ratio >1.3). More recently, Gor *et al.*<sup>[44]</sup> using a standard 19-gauge needle have replicated these results in a case series of 10 patients in whom diagnostic tissue core specimens were obtained in all included patients, with a mean length of 14.4 mm and a mean of 9.2 complete portal tracts per sample.<sup>[44]</sup>

In patients with subepithelial lesions, two studies have reached opposite conclusions reporting diagnostic accuracy of 52%<sup>[40]</sup> versus 93% respectively.<sup>[34]</sup> The reason for this discrepancy is unclear. We speculated that in the recently published study of Larghi *et al.*,<sup>[34]</sup> the employment of the EUS-FNTA technique with removal of the stylet before the procedure, which renders the needle more flexible and easy to operate, coupled with the utilization of the forward viewing therapeutic linear echoendoscope that seems to ensure easier deployment of a 19-gauge needle<sup>[45-47]</sup> could accounted for the better results reported. Representative cases of histologic samples from subepithelial lesions gathered with the EUS-FNTA technique are shown in [Figure 4]. Interestingly in the latter study,<sup>[34]</sup> in three patients in whom immunohistochemical studies were negative despite histopathologic features that were suggestive of GIST, the authors were able to perform genetic analysis for diagnostic purposes [Figure 5]. The capability of performing genotype profiling of GISTs is relevant beyond its diagnostic significance because it has a prognostic impact and allows optimizing chemotherapy for unresectable cases and for other selected cases where neoadjuvant therapy may be a useful option.<sup>[48,49]</sup>

Finally, Varadarajulu *et al.*<sup>[41]</sup> recently published their experience in using a newly developed flexible 19-gauge needle (Expect™ 19 Flex, Bost Scientific Corp., Natick, MA, US) made of nitinol, which is supposed to have a better performance for transduodenal puncture. They evaluated 32 patients with pancreatic head/uncinate or peripancreatic masses approached from the duodenum and 6 patients with subepithelial lesions in the stomach (five cases) and in the rectum (one case). On-site cytopathology evaluation and cell-block analysis were performed. The procedure was successful in all patients and examination of cell-block specimens revealed optimal histologic core tissue in 36 of 38 (94%) patients, which was diagnostic in all cases. Based on these results,<sup>[41]</sup> the same group proposed an algorithm in which they recommended the use of a standard 19-gauge needle for lesions approached from the esophagus, stomach and rectum, and the use of the flex 19-gauge needle for transduodenal puncture.<sup>[50]</sup> In our opinion, there are insufficient data to make this suggestion and further experiences with this needle is necessary before a definitive conclusion on the value of the proposed algorithm can be drawn.

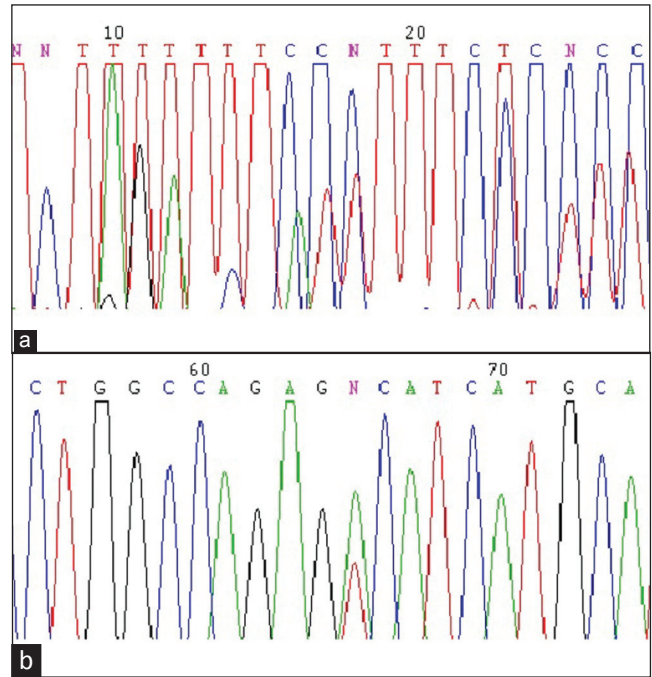




**Figure 4.** Representative cases of tissue type and amount obtained by Endoscopic ultrasound-guided fine needle tissue acquisition in subepithelial lesions. (a-d) Gastric gastrointestinal stromal tumor (GIST): Abundant tissue fragments (a) at higher magnification showing a spindle-cell neoplasm (b) whose strong and diffuse immune positivity for CD117 (c) and DOG1 (d) unequivocally qualified as a GIST (a and b, h and e; c, CD117 IHC; D, DOG1 IHC; original magnification: a, ×20, b, c and d, ×400). (e, f) Esophageal leiomyoma. The abundance of the available fragments allowed not only to detect the presence of spindle cells with abundant eosinophilic cytoplasm with bland nuclei and no mitotic activity, but also to appreciate their arrangement in intersecting fascicles (e); these findings, together with an intense desmin reactivity (f) in the absence of staining with CD117 and DOG1 (not shown) led to a straight forward diagnosis of leiomyoma (e, h and e; f, desmin IHC; original magnification: e, ×200, F, ×400). G-I Gastric schwannoma: The bioptic specimen showed a spindle cell neoplasm (g and h); the preservation of architectural details such as the presence of hyaline thickening of vessel walls (h) and the diffuse S-100 positivity (i) in the absence of CD117 and DOG1 staining (not shown) were diagnostic for a schwannoma (g, h, h and e; i, S-100 IHC; original magnification: g, ×40, h, i, ×400). J-N Gastric metastasis of melanoma: The bioptic sample was composed of fragments of highly cellular neoplasm composed of atypical epithelioid cells (j, k) intensely and diffusely positive for S-100 (l), HMB-45 (m) and Melan-A (n), typical features of melanoma (j, k, h and e; l, S-100 IHC; M, H MB-45 IHC; N, Melan-A IHC ;original magnification: j, ×40, k, l, m, n, ×400). O-R Gastric metastasis of ovarian serous papillary carcinoma: The bioptic fragments showed a neoplasm composed of epithelioid cells with marked atypia arranged in papillae (o, p), with nuclear WT1 immunoreactivity (q) and intense staining for cytokeratin 7 (r) (o, p, h and e; q, WT1 IHC; r, cytokeratin 7 IHC; original magnification: o, ×20, p, q, r, ×400)

### EUS-FNB USING PROCORE® NEEDLES

Although the Quick-Core® needle failed to reach widespread use due to technical difficulty associated with its utilization and the relative lack of advantages over standard FNA needles, the same manufacturer

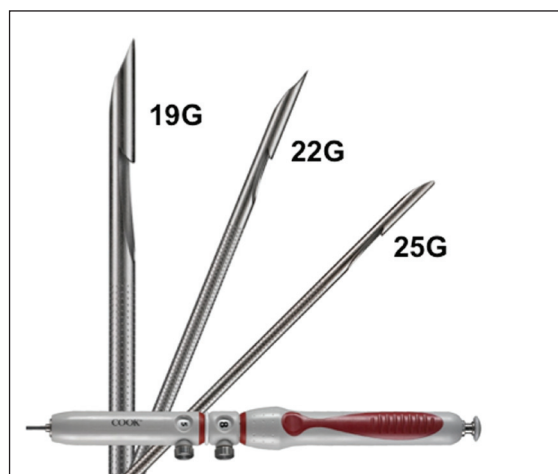


**Figure 5.** Mutational analyses performed on tissue core biopsy specimens obtained by Endoscopic ultrasound-guided fine needle tissue acquisition in two patients with a subepithelial lesion after histologic features were consistent with the diagnosis of gastrointestinal stromal tumor but with negative immunohistochemical studies. Partial nucleotide sequence of exon 11 of *KIT* gene showed a reading-frame shift mutation caused by a heterozygous deletion of 6 nucleotides (from position 1666-1671) (a) This determines a deletion of two amino acids (glutamine and tryptophan at position 556 and 557, respectively) (Q556-W557). Partial nucleotide sequence of exon 18 of *PDGFRA* gene showed a heterozygous A→T change at base 2526 (b) This determines a substitution of an aspartic acid with a valine at position 842 (D842V)

developed a new needle with a different design, the ProCore™ needle.<sup>[51]</sup> To meet all the needs and have a needle to cover for any different clinical scenarios and difficulty, three needle sizes have been developed, the 19-gauge, the 22-gauge and the 25-gauge ProCore™ needles.

The main characteristic of this needle is represented by the presence of a lateral opening of varying length depending on the needle size, which presents a reverse bevel to hook and cut the tissue entrapping it into the needle. This reverse bevel is located at a different distance from the tip of the needle depending on the needle size [Figure 6].

In the first published study,<sup>[51]</sup> which involved five European Centers, each participating center used a different sampling technique. However, site of the puncture (duodenum *vs.* other sites), use or not of the stylet, number of to- and- from movements, 3-4 versus 1 number of needle passes, 2-3 versus 1 and modality of sample retrieval (air, stylet or saline



**Figure 6.** Novel 19-G, 22-G and 25-G ProCore™ needles with reverse bevel technology for acquisition of tissue sample

solution) did not have any impact on the tissue sample acquisition.<sup>[51]</sup> At multivariate analysis, the presence of an experienced pathologist to evaluate the sample was the only variable associated with the obtainment of an optimal sample for histologic analysis and to make a correct final diagnosis.

The same European group<sup>[52]</sup> subsequently proposed a standardized sample acquisition protocol as follows:

1. The 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 the needle was finally removed. Tissue samples were recovered in formalin or cytolyt by flushing the needle with saline.<sup>[52]</sup>

A different sampling technique, the so-called slow pull technique, has been proposed for the tissue acquisition procedure performed using the 25-gauge ProCore™ needle.<sup>[53]</sup> With this technique once the needle is inside the lesion, the negative suction pressure is obtained by slowly and continuously pulling out the stylet from the needle while 10-20 to-and-fro movements are performed. Preliminary data<sup>[54]</sup> have reported a significantly higher yield of this technique when compared to the suction method used in both the European ProCore studies.<sup>[51,52]</sup>

The performance of the 19-gauge ProCore™ needle in the diagnosis of intra- and extra-intestinal lesions

was evaluated in a large multicenter study by Iglesias-Garcia *et al.*<sup>[51]</sup> Among 109 patients with 114 very heterogeneous lesions, EUS-FNB using this newly developed biopsy needle was technically feasible in 112 cases (98%), with no complications. The only two technical failures occurred when the sampling procedure was performed through duodenum, accounting for an overall success rate of 94% for transduodenal sampling. Overall, in all lesions in which the procedure was technically successful a sample suitable for pathological evaluation was obtained, which was adequate for histologic examination in about 90% of cases. Diagnostic accuracy was 86% for all lesions and 93% only considering malignant lesions, respectively.<sup>[51]</sup>

A study evaluating the interobserver agreement in grading the quality of specimens obtained with the 19-gauge ProCore™ needle among five expert pathologists from the five participating centers was also performed.<sup>[55]</sup> Overall, an excellent interobserver agreement in the assessment of the histologic material was found among the involved pathologists, and this was particularly high (91%) with regard to sample adequacy.<sup>[55]</sup> Moreover, when the same samples were evaluated by non-expert pathologists, the interobserver agreement substantially decreased, thus suggesting the paramount importance of a pathologist dedicated to read EUS samples. It is our opinion that efforts to establish pathology expertise by combining their educational activities with those of endosonographers should be strongly encouraged.

The same study group subsequently evaluated the performance of the 22-gauge ProCore™ needle in a cohort of 61 patients with pancreatic masses, which were localized in the pancreatic head/uncinate in 57% of the cases, thus requiring a transduodenal approach.<sup>[52]</sup> Only one needle pass was performed using the protocol described above. In one patient with an uncinate process mass the procedure failed due to inability to extend the needle out of the working channel of the echoendoscope. In the remaining patients with a successful sampling procedure, tissue specimens for histologic examination were retrieved in 55 patients (90%), which in all but one patient (88.5%) were judged adequate to make a definitive diagnosis. All adequate specimens were found to be diagnostic, thus accounting for overall accuracy of 88.5%. These very promising results prompted another group to design a randomized trial to compare the performance of this needle with that of a standard 22-gauge FNA needle



in the obtainment of cytologic and histologic samples in 56 patients with pancreatic masses.<sup>[56]</sup> No significant difference in the median number of passes required for establishing the on-site diagnosis, rates of diagnostic accuracy, or technical failure between the FNA and FNB needles were detected. Moreover, no significant difference between the two groups was found in the proportion of samples in which histologic core tissue was present (FNA 100% *vs.* FNB 83.3%,  $P = 0.26$ ).<sup>[56]</sup> More importantly, histologic core of optimal quality was present in 66.7% of FNA specimens and 80% of FNB specimens ( $P = 0.66$ ).<sup>[56]</sup>

In a study with a similar design that included not only pancreatic masses but also patients with enlarged lymph nodes and intra- and extra-intestinal solid lesions, the 22-gauge ProCore™ required significantly fewer needle passes when compared with a standard 22-gauge FNA needle to achieve adequacy.<sup>[57]</sup> Despite similar cytologic interpretability, diagnostic accuracy, and amount of cell-block material between the two needles, this finding can result in less procedural time and cost savings.<sup>[57]</sup> Future multicenter studies in large patient population with heterogenous indications are needed to better clarify if the 22-gauge ProCore™ has any advantage over a standard 22-gauge FNA needle.

More recently, the performance of the 22-gauge ProCore™ needle has been evaluated in pancreatic cystic lesions.<sup>[58]</sup> Samples for cyto-histologic diagnosis were retrieved in 65% of the cysts, with adequacy that reached 94.4% and 100% for lesions with a solid component and with already malignant transformation.

Finally, Iwashita *et al.*<sup>[53]</sup> reported the first experience in using the 25-gauge ProCore™ needle for the evaluation of 50 consecutive patients with solid pancreatic lesions. They applied the slow pull technique described above. After FNB, the obtained material was expressed onto a glass slide by reinsertion of the stylet and any visible core was lifted off and placed in formalin, whereas smears for on-site cytopathologic evaluation were made from the residual material. The authors found an impressively high sensitivity (83%) for cytologic diagnosis on the first needle pass, which increased to 91% and 96% at the second and third pass, respectively. On the first pass, where the histologic analysis was performed on a per pass basis, they found a sensitivity of 63%. This value increased to 87% at the subsequent two to four passes. Interestingly, the presence of a histologic core was found in only 12% of the patients after the first

needle pass and in 32% of the patients at the subsequent two to four passes. In our opinion, these results indicate that the 25-gauge ProCore™ needle is a proficient needle to gather diagnostic cytologic specimen, probably even more efficient than a standard 25-gauge FNA needle, but cannot be used when a tissue core biopsy specimen is required to make the diagnosis.

A new Olympus prototype side-port needle (Olympus Medical Corp., Tokyo, Japan) has been recently developed and tested in one pilot study and one prospective multicenter study.<sup>[59,60]</sup> This needle is identical to the standard 22-gauge EUS-FNA needle, but has a second opening located 4 mm from the tip on the opposite side to the bevel. Available studies have shown encouraging results, with cytologic diagnosis achieved in more than 94% of cases. However, at the moment, there are no data regarding the ability of this needle to obtain histologic biopsy core samples.

## CONCLUSIONS AND FUTURE PERSPECTIVE

In the last decade in an attempt to overcome some of the limitations of EUS-FNA, alternative sampling techniques and dedicated needles to obtain core tissue biopsy specimens for histologic examination under EUS guidance have been developed.

The obtainment of a tissue core biopsy presents several advantages that can substantially contribute to the widespread diffusion of EUS utilization in the community and in countries where cytology expertise may be difficult to be developed. Histology is easier to interpret and in the era of individualized medicine, a tissue core biopsy can provide information that can facilitate and target personalized treatment of most GI malignancies. Indeed, tissue samples for histologic examination seem to be more adequate to perform predictive molecular markers or cell culture with chemosensitivity testing to guide individualized therapies.

Based on these premises, a change in our way of thinking is needed and we should put all our efforts in search of the right technique and/or the right needle that will provide enough tissue to perform all assessment necessary to reach the diagnosis and allow tailored treatments.

We firmly believe that a very close collaboration between endosonographers and pathologists is of paramount importance to succeed in this balanced

effort to develop the right EUS-FNB needle and technique and should be strongly encouraged.

## REFERENCES

- Vilmann P, Jacobsen GK, Henriksen FW, *et al.* Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreatic disease. *Gastrointest Endosc* 1992;38:172-3.
- Dumonceau JM, Polkowski M, Larghi A, *et al.* Indications, results, and clinical impact of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2011;43:897-912.
- Iglesias-Garcia J, Dominguez-Munoz JE, Abdulkader I, *et al.* Influence of on-site cytopathology evaluation on the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) of solid pancreatic masses. *Am J Gastroenterol* 2011;106:1705-10.
- Alsohaibani F, Girgis S, Sandha GS. Does onsite cytotechnology evaluation improve the accuracy of endoscopic ultrasound-guided fine-needle aspiration biopsy? *Can J Gastroenterol* 2009;23:26-30.
- Hébert-Magee S, Bae S, Varadarajulu S, *et al.* The presence of a cytopathologist increases the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration cytology for pancreatic adenocarcinoma: A meta-analysis. *Cytopathology* 2013;24:159-71.
- Eloubeidi MA, Tamhane A, Jhala N, *et al.* Agreement between rapid onsite and final cytologic interpretations of EUS-guided FNA specimens: Implications for the endosonographer and patient management. *Am J Gastroenterol* 2006;101:2841-7.
- Jhala NC, Jhala DN, Chhieng DC, *et al.* Endoscopic ultrasound-guided fine-needle aspiration. A cytopathologist's perspective. *Am J Clin Pathol* 2003;120:351-67.
- Kalaitzakis E, Panos M, Sadik R, *et al.* Clinicians' attitudes towards endoscopic ultrasound: A survey of four European countries. *Scand J Gastroenterol* 2009;44:100-7.
- Braat H, Bruno N, Kuipers EJ, *et al.* Pancreatic cancer: Promise for personalised medicine? *Cancer Lett* 2012;318:1-8.
- Wakatsuki T, Irisawa A, Terashima M, *et al.* ATP assay-guided chemosensitivity testing for gemcitabine with biopsy specimens obtained from unresectable pancreatic cancer using endoscopic ultrasonography-guided fine-needle aspiration. *Int J Clin Oncol* 2011;16:387-94.
- Brais RJ, Davies SE, O'Donovan M, *et al.* Direct histological processing of EUS biopsies enables rapid molecular biomarker analysis for interventional pancreatic cancer trials. *Pancreatol* 2012;12:8-15.
- Wiersema MJ, Levy MJ, Harewood GC, *et al.* Initial experience with EUS-guided trucut needle biopsies of perigastric organs. *Gastrointest Endosc* 2002;56:275-8.
- Levy MJ, Jondal ML, Clain J, *et al.* Preliminary experience with an EUS-guided trucut biopsy needle compared with EUS-guided FNA. *Gastrointest Endosc* 2003;57:101-6.
- Shah SM, Ribeiro A, Levi J, *et al.* EUS-guided fine needle aspiration with and without trucut biopsy of pancreatic masses. *JOP* 2008;9:422-30.
- Wahnschaffe U, Ullrich R, Mayerle J, *et al.* EUS-guided Trucut needle biopsies as first-line diagnostic method for patients with intestinal or extraintestinal mass lesions. *Surg Endosc* 2009;23:2351-5.
- Sakamoto H, Kitano M, Komaki T, *et al.* Prospective comparative study of the EUS guided 25-gauge FNA needle with the 19-gauge Trucut needle and 22-gauge FNA needle in patients with solid pancreatic masses. *J Gastroenterol Hepatol* 2009;24:384-90.
- Ribeiro A, Pereira D, Escalón MP, *et al.* EUS-guided biopsy for the diagnosis and classification of lymphoma. *Gastrointest Endosc* 2010;71:851-5.
- Larghi A, Verna EC, Stavropoulos SN, *et al.* EUS-guided trucut needle biopsies in patients with solid pancreatic masses: A prospective study. *Gastrointest Endosc* 2004;59:185-90.
- Varadarajulu S, Fraig M, Schmulewitz N, *et al.* Comparison of EUS-guided 19-gauge Trucut needle biopsy with EUS-guided fine-needle aspiration. *Endoscopy* 2004;36:397-401.
- Wittmann J, Kocjan G, Sgouros SN, *et al.* Endoscopic ultrasound-guided tissue sampling by combined fine needle aspiration and trucut needle biopsy: A prospective study. *Cytopathology* 2006;17:27-33.
- Aithal GP, Anagnostopoulos GK, Tam W, *et al.* EUS-guided tissue sampling: Comparison of "dual sampling" (Trucut biopsy plus FNA) with "sequential sampling" (Trucut biopsy and then FNA as required). *Endoscopy* 2007;39:725-30.
- Storch I, Shah M, Thurer R, *et al.* Endoscopic ultrasound-guided fine-needle aspiration and Trucut biopsy in thoracic lesions: When tissue is the issue. *Surg Endosc* 2008;22:86-90.
- Levy MJ, Wiersema MJ. EUS-guided Trucut biopsy. *Gastrointest Endosc* 2005;62:417-26.
- Voss M, Hammel P, Molas G, *et al.* Value of endoscopic ultrasound guided fine needle aspiration biopsy in the diagnosis of solid pancreatic masses. *Gut* 2000;46:244-9.
- Larghi A, Noffsinger A, Dye CE, *et al.* EUS-guided fine needle tissue acquisition by using high negative pressure suction for the evaluation of solid masses: A pilot study. *Gastrointest Endosc* 2005;62:768-74.
- Gerke H, Rizk MK, Vanderheyden AD, *et al.* Randomized study comparing endoscopic ultrasound-guided Trucut biopsy and fine needle aspiration with high suction. *Cytopathology* 2010;21:44-51.
- Iglesias-Garcia J, Dominguez-Munoz E, Lozano-Leon A, *et al.* Impact of endoscopic ultrasound-guided fine needle biopsy for diagnosis of pancreatic masses. *World J Gastroenterol* 2007;13:289-93.
- Möller K, Papanikolaou IS, Toerner T, *et al.* EUS-guided FNA of solid pancreatic masses: High yield of 2 passes with combined histologic-cytologic analysis. *Gastrointest Endosc* 2009;70:60-9.
- Noda Y, Fujita N, Kobayashi G, *et al.* Diagnostic efficacy of the cell block method in comparison with smear cytology of tissue samples obtained by endoscopic ultrasound-guided fine-needle aspiration. *J Gastroenterol* 2010;45:868-75.
- Itoi T, Itokawa F, Sofuni A, *et al.* Puncture of solid pancreatic tumors guided by endoscopic ultrasonography: A pilot study series comparing Trucut and 19-gauge and 22-gauge aspiration needles. *Endoscopy* 2005;37:362-6.
- Yasuda I, Tsurumi H, Omar S, *et al.* Endoscopic ultrasound-guided fine-needle aspiration biopsy for lymphadenopathy of unknown origin. *Endoscopy* 2006;38:919-24.
- Larghi A, Verna EC, Ricci R, *et al.* EUS-guided fine-needle tissue acquisition by using a 19-gauge needle in a selected patient population: A prospective study. *Gastrointest Endosc* 2011;74:504-10.
- Larghi A, Capurso G, Carnuccio A, *et al.* Ki-67 grading of nonfunctioning pancreatic neuroendocrine tumors on histologic samples obtained by EUS-guided fine-needle tissue acquisition: A prospective study. *Gastrointest Endosc* 2012;76:570-7.
- Larghi A, Fuccio L, Chiarello G, *et al.* Fine-needle tissue acquisition from subepithelial lesions using a forward-viewing linear echoendoscope. *Endoscopy* 2013; [Epub ahead of print].
- Larghi A, Lococo F, Ricci R, *et al.* Pleural tuberculosis diagnosed by EUS-guided fine-needle tissue acquisition. *Gastrointest Endosc* 2010;72:1307-9.
- Iwashita T, Yasuda I, Doi S, *et al.* Use of samples from endoscopic ultrasound-guided 19-gauge fine-needle aspiration in diagnosis of autoimmune pancreatitis. *Clin Gastroenterol Hepatol* 2012;10:316-22.
- Iwashita T, Yasuda I, Doi S, *et al.* The yield of endoscopic ultrasound-guided fine needle aspiration for histological diagnosis in patients suspected of stage I sarcoidosis. *Endoscopy* 2008;40:400-5.
- Yasuda I, Goto N, Tsurumi H, *et al.* Endoscopic ultrasound-guided fine needle aspiration biopsy for diagnosis of lymphoproliferative disorders: Feasibility of immunohistological, flow cytometric, and cytogenetic assessments. *Am J Gastroenterol* 2012;107:397-404.
- Stavropoulos SN, Im GY, Jlayer Z, *et al.* High yield of same-session EUS-guided liver biopsy by 19-gauge FNA needle in patients undergoing EUS to exclude biliary obstruction. *Gastrointest Endosc* 2012;75:310-8.
- Eckardt AJ, Adler A, Gomes EM, *et al.* Endosonographic large-bore biopsy of gastric subepithelial tumors: A prospective multicenter study. *Eur J Gastroenterol Hepatol* 2012;24:1135-44.

41. Varadarajulu S, Bang JY, Hebert-Magee S. Assessment of the technical performance of the flexible 19-gauge EUS-FNA needle. *Gastrointest Endosc* 2012;76:336-43.
42. Zamboni G, Lüttges J, Capelli P, et al. Histopathological features of diagnostic and clinical relevance in autoimmune pancreatitis: A study on 53 resection specimens and 9 biopsy specimens. *Virchows Arch* 2004;445:552-63.
43. Bang JY, Magee SH, Ramesh J, et al. Randomized trial comparing fanning with standard technique for endoscopic ultrasound-guided fine-needle aspiration of solid pancreatic mass lesions. *Endoscopy* 2013;45:445-50.
44. Gor N, Salem SB, Jakate S, et al. Histological adequacy of EUS-guided liver biopsy when using a 19-gauge non-Tru-Cut FNA needle. *Gastrointest Endosc* 2013; [Epub ahead of print]
45. Larghi A, Lecca PG, Ardito F, et al. Evaluation of hilar biliary strictures by using a newly developed forward-viewing therapeutic echoendoscope: Preliminary results of an ongoing experience. *Gastrointest Endosc* 2009;69:356-60.
46. Trevino JM, Varadarajulu S. Initial experience with the prototype forward-viewing echoendoscope for therapeutic interventions other than pancreatic pseudocyst drainage (with videos). *Gastrointest Endosc* 2009;69:361-5.
47. Larghi A, Seerden TC, Galasso D, et al. EUS-guided therapeutic interventions for uncommon benign pancreaticobiliary disorders by using a newly developed forward-viewing echoendoscope (with videos). *Gastrointest Endosc* 2010;72:213-5.
48. Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumours: Origin and molecular oncology. *Nat Rev Cancer* 2011;11:865-78.
49. Eisenberg BL, Smith KD. Adjuvant and neoadjuvant therapy for primary GIST. *Cancer Chemother Pharmacol* 2011;67 Suppl 1:S3-8.
50. Bang JY, Ramesh J, Trevino J, et al. Objective assessment of an algorithmic approach to EUS-guided FNA and interventions. *Gastrointest Endosc* 2013;77:739-44.
51. Iglesias-Garcia J, Poley JW, Larghi A, et al. Feasibility and yield of a new EUS histology needle: Results from a multicenter, pooled, cohort study. *Gastrointest Endosc* 2011;73:1189-96.
52. Larghi A, Iglesias-Garcia J, Poley JW, et al. Feasibility and yield of a novel 22-gauge histology EUS needle in patients with pancreatic masses: A multicenter prospective cohort study. *Surg Endosc* 2013;27:3733-8.
53. Iwashita T, Nakai Y, Samarasena JB, et al. High single-pass diagnostic yield of a new 25-gauge core biopsy needle for EUS-guided FNA biopsy in solid pancreatic lesions. *Gastrointest Endosc* 2013;77:909-15.
54. Iwashita T, Nakai Y, Samarasena JB, et al. Endoscopic ultrasound-guided fine needle aspiration and biopsy (EUS-FNAB) using a novel 25-gauge core biopsy needle: Optimizing the yield of both cytology and histology. *Gastrointest Endosc* 2012;75:AB183.
55. Petrone MC, Poley JW, Bonzini M, et al. Interobserver agreement among pathologists regarding core tissue specimens obtained with a new endoscopic ultrasound histology needle; a prospective multicentre study in 50 cases. *Histopathology* 2013;62:602-8.
56. Bang JY, Hebert-Magee S, Trevino J, et al. Randomized trial comparing the 22-gauge aspiration and 22-gauge biopsy needles for EUS-guided sampling of solid pancreatic mass lesions. *Gastrointest Endosc* 2012;76:321-7.
57. Witt BL, Adler DG, Hilden K, et al. A comparative needle study: EUS-FNA procedures using the HD ProCore™ and EchoTip® 22-gauge needle types. *Diagn Cytopathol* 2013;41:1069-74.
58. Barresi L, Tarantino I, Traina M, et al. Endoscopic ultrasound-guided fine needle aspiration and biopsy using a 22-gauge needle with side fenestration in pancreatic cystic lesions. *Dig Liver Dis* 2013; [Epub ahead of print]
59. Kaffes A, Corte C. Fine needle aspiration at endoscopic ultrasound with a novel side-port needle: A pilot experience. *Therap Adv Gastroenterol* 2012;5:89-94.
60. Kaffes AJ, Chen RY, Tam W, et al. A prospective multicenter evaluation of a new side-port endoscopic ultrasound-fine-needle aspiration in solid upper gastrointestinal lesions. *Dig Endosc* 2012;24:448-51.

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