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Progress Report

EUS-FNB with or without on-site evaluation for the diagnosis of solid pancreatic lesions (FROSENOR): Protocol for a multicenter randomized non-inferiority trial

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ABSTRACT

Background: Rapid on-site evaluation (ROSE) of cytological specimensacquired with EUS-guided fine needle aspiration (EUS-FNA) represents the most accurate available technique to reach a definitive diagnosis in patients with pancreatic solid masses. Recently, needles with high histological yield have been developed for EUS-guided fine needle biopsy (EUS-FNB), with which the need for ROSE can be potentially overcome.

Aims: The primary aim is to compare the diagnostic accuracy of EUS-FNB with or without ROSE. The main endpoint will be measured against the gold standard diagnosis (surgical pathology whenever available or diagnostic work-up in agreement with a clinical course of at least six months). Secondary endpoints include: (a) safety; (b) presence of tissue core; (c) quality of specimens; (d) time of the sampling procedure. Reliability of macroscopic on-site evaluation (MOSE) by endosonographers will be also assessed.

Methods: FROSENOR is an international randomized non-inferiority ongoing study at sixteen centers in four continents. Eight hundred patients will be randomized in two arms (EUS-FNB + ROSE vs. EUS-FNB alone) and outcomes compared. Sample size has been calculated in order to demonstrate the non-inferiority of FNB alone. Randomization and data collection will be performed online.

Discussion: This study will ascertain if ROSE is still needed when performing EUS-FNB of solid pancreatic lesions.

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1. Rationale and aims

Since its initial report in 1992 [1], endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) has become the procedure of choice for sampling of lesions of the gastro-intestinal tract and of adjacent organs, with a diagnostic accuracy ranging from 60% to 90% [2]. The diagnostic accuracy of EUS-FNA is affected by several factors [3–8], but the availability of rapid on-site evaluation (ROSE) of the collected specimens is the most relevant [9–11]. ROSE can provide a real time definitive diagnosis, significantly reducing the diagnostic turnaround time and allowing earlier therapeutic/palliative procedure. Moreover during ROSE, the cytopathologist can also establish the need for additional sampling to perform ancillary studies that are required in some cases to reach an effective diagnosis [12–14]. A recent technical review article with an evidence-based approach has recommended ROSE for centers with a low diagnostic accuracy (<90%) or during the development of any EUS service [15].

Unfortunately, cytology requires a high degree of expertise rarely found outside high volume tertiary care centers and ROSE is not available in many countries [13,16]. Both these needs have created a barrier to the dissemination of EUS in the community and in many countries, because the lack of cytological expertise has resulted in a low diagnostic accuracy and, therefore, in a limited perceived utility of EUS [16,17].

Theoretically, this limitation of EUS-FNA can be overcome by the obtainment of a tissue core for histologic examination by EUS-fine needle biopsy (EUS-FNB). Histological specimens with preserved architecture are easier to be interpreted by a standard pathologist than cytological smears. Moreover, they also provide the opportunity to perform immunohistochemistry and molecular analyses. Ancillary studies facilitate malignancy detection in difficult cases and improve the possibility to reach a specific diagnosis even for benign diseases [18,19], thus sparing patients from more invasive and risky sampling surgical procedures and unnecessary follow-up examinations [20].

Recently, novel needles specifically designed to obtain histological specimens have become available. Two are end-cutting forward-acquiring needles (the SharkCore™ by Medtronic, Dublin, Ireland, and the Acquire™ by Boston Scientific Corp., Marlborough, MA, USA), whereas the third one is a side-fenestrated antegrade-cutting bevel needle (the ProCore™ 20-gauge, Cook Medical, Bloomington, IN, USA). Preliminary results for both pancreatic and non-pancreatic lesions are extremely encouraging [21–25]. Indeed, all these needles demonstrated a histological yield and accuracy rate >90% [26–28].

The EUS-FNB specimen does not preclude the possibility of performing ROSE through the touch imprint cytology technique (TIC) [21], which has been recently demonstrated to be comparable with samples from EUS-FNA in terms of both smear quality and diagnostic yield [29]. Moreover, a recently published large retrospective series including about three thousand patients demonstrated that the diagnostic yield of EUS-FNB is significantly higher than EUS-FNA. Furthermore, ROSE on EUS-FNB specimens performed equally to ROSE on standard EUS-FNA samples but adequacy is obtained with a lower number of passes when using an FNB needle [30].

Therefore, to investigate if ROSE is still needed in the evaluation of solid pancreatic lesions we designed a study to compare the diagnostic accuracy of EUS-FNB coupled with ROSE with that of EUS-FNB alone.

2. Study design

This is a prospective multicenter randomized non-inferiority trial. This study is carried out in Italy, Spain, Belgium, The Netherlands, USA, Japan, and Australia. The Ethics Committee (EC) of the provinces of Verona and Rovigo approved the study on 17 October 2017 (protocol number 50348). Subsequently, the study was approved by the EC/IRB of each participating center. Before starting enrollment, we registered the protocol on Clinical Trial.gov (NCT03322592). This study will be conducted according to the principles and the recommendations of the 2013 Declaration of Helsinki. The CONSORT study flowchart is illustrated in Fig. 1.

Study eligibility must fulfill the following criteria:

Inclusion criteria:

- Solid pancreatic mass referred for EUS-guided tissue acquisition.
- Lesion can be visualized with EUS and needle puncturing can be technically feasible.
- Age ≥18 years.
- Written informed consent.

Exclusion criteria:

- Known bleeding disorder that cannot be sufficiently corrected with co-fact or fresh frozen plasma.
- Use of anticoagulants that cannot be discontinued.
- International Normalized Ratio (INR) >1.5 or platelet count <50.000.
- Cystic lesions even with solid component.
- Previous inclusion in other or present study.
- Pregnancy.

2.1. Objectives

2.1.1. Primary aim and endpoint

To compare the diagnostic accuracy of EUS-FNB with or without ROSE in patients with solid pancreatic masses. Diagnostic accuracy will be calculated in comparison to the gold standard diagnosis: (1) in operated patients, based on the diagnosis of the surgical resected specimen; (2) in non-operated patients, based on the conclusions of the diagnostic work-up (combined outcomes of additional tissue sampling and imaging studies), and confirmed by a compatible clinical disease course of at least 6 months.

2.1.2. Secondary aims and endpoints

To compare EUS-FNB with or without ROSE in terms of:

a) Safety of the procedures, based on percentage of intra- and post-procedural adverse events (as defined in Cotton et al.) [31] in the 2 arms and using different needle types.
b) Procurement yield (percentage) of tissue core biopsy samples in the 2 arms and using different needle types.
c) Time of the sampling procedures (minutes) in the two arms.
d) Quality of samples acquired in the 2 arms and with the different needle types. Specimens quality will be measured applying predetermined scores [32,33] (see Table 1).

In the EUS-FNB without ROSE arm, to evaluate the reliability of specimens macroscopic on-site evaluation (MOSE) [34,35], determined by the percentage of concordance between the presence of core at MOSE by the echoendoscopist (a “core” is defined as a worm-like material whitish/yellowish or red, not including fluid-like specimens) and at histopathological evaluation (a “core” is defined as an intact piece of tissue of at least 550 μ in the greatest axis).

2.2. EUS-FNB procedures and cyto-histological assessment

After identification of the target lesion, the surroundings will be scanned with color-Doppler, to determine the optimal puncture

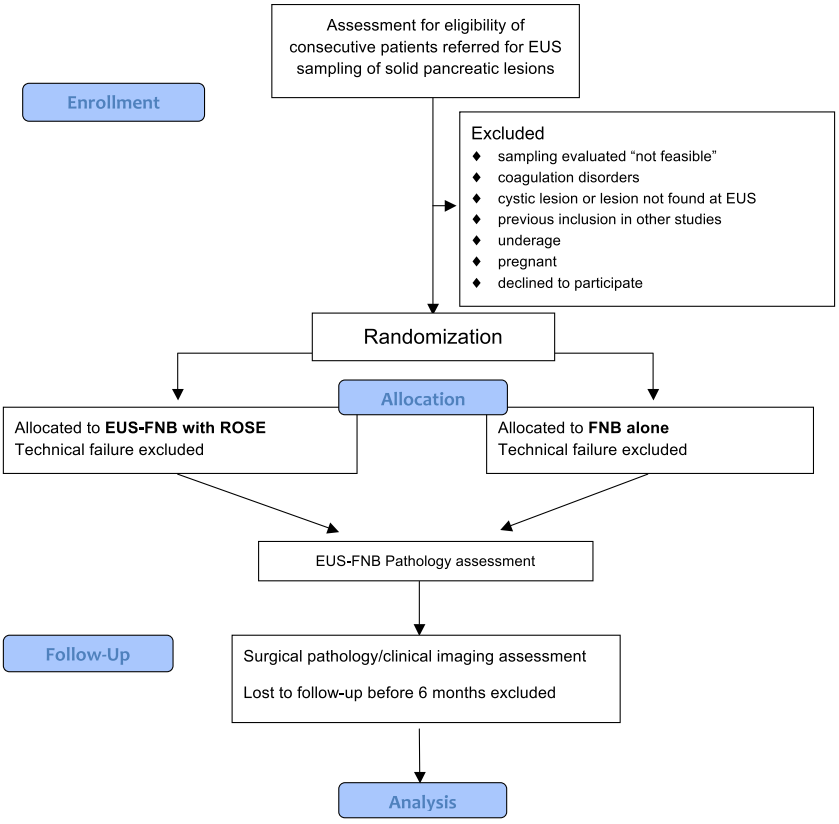

Fig. 1. CONSORT flow diagram illustrating the enrollment and the randomization process of the study.

Table 1
Scores utilized to evaluate the qualityof the tissue retrieved.

Tissue integrity score	
Score	Explanation
0	Insufficient material for interpretation
Cytology (1–2)	
1	Sufficient material for *limited* cytological interpretation; probably not representative
2	Sufficient material for *adequate* cytological interpretation
Histology (3–6)	
3	Sufficient material for *low quality* histological interpretation (microfragments <550 μ in greatest axis).
4	Sufficient material for *good quality* histological interpretation (1–5 cores >550 μ in greatest axis).
5	Sufficient material for *high quality* histological interpretation (6–10 cores >550 μ in greatest axis).
6	Sufficient material for *excellent quality* histological interpretation (more than 10 cores >550 μ in greatest axis or total tissue length >5.500 μ).
Blood contamination score	
Score	Explanation
0	Only blood
1	Much blood contamination, surface area >50% of the slide
2	Medium blood contamination, surface area 25–50% of the slide
3	Little blood contamination, surface area <25% of slide

trajectory, avoiding interposing vessels. If puncturing seems technically feasible, the endosonographer will choose the needle and the randomization will take place.

In the EUS-FNB with ROSE arm, the material obtained with the first pass will be processed for ROSE using the TIC. In case of inadequate sample, ROSE with TIC will be repeated up to a maximum of 3 passes. In case of adequate ROSE at the first or the second pass, the additional passes (to reach a maximum of three passes) will be performed as EUS-FNB and the material obtained placed directly into formalin or other fixative for subsequent histopathological evaluation.

In the EUS-FNB without ROSE arm, 3 needle passes will be performed and the samples obtained will be placed directly in a vial containing formalin (or other fixative according to the local individual protocol). The endoscopist will then perform a MOSE of the acquired sample.

When technical success is not achieved, the procedure is recorded as a failure. This event terminates the study for that patient.

Histological evaluation and ROSE will be performed following the Papanicolaou classification [36].

2.3. Enrollment

Sixteen centers are involved. Enrollment is stratified among the centers (50 patients per center). Progress will be evaluated every 3 months from the first enrollment and if the enrollment in a center will be falling behind, the allocation for the other centers may be increased up to about 100 patients each, to guarantee the aimed sample size.

2.4. Randomization and blinding

Patients will be randomized in a 1:1 ratio, using random 10 patients block sizes for allocation concealment between groups. Randomization is generated online at the time of the EUS procedure if patient is found suitable for inclusion, after the lesion is visualized. The choice of the needle to be used will be at the discretion of each endosonographer and is done before the randomization to limit results bias. Nor the endoscopist, neither the pathologist will be blinded to which needle will be used.

Table 2
Study schedule for data collection.

Item	T_0 (day of EUS)	T_1 (3 days after EUS)	T_1 (15 days after EUS)	T_3 (6 months after EUS)	T_4 (end of the study
Informed consent	X				
Assessment of eligibility	X				
Randomization	X				
Clinical/procedural data	X				
ROSE data	X				
Adverse events	X	X	X	X	
EUS-FNB histology data			X		
Surgical pathology data			X	X	
Follow-up[a]			X	X	X
Data analysis					X

[a] Clinical/imaging examination of disease course (disease related death, appearance of metastasis, lesion growth, weight loss, cachexia, further tissue sampling, etc.). EUS, endoscopic ultrasound; ROSE, rapid on-site evaluation; EUS-FNB, endoscopic ultrasound fine-needle aspiration.

2.5. Data collection

Case record forms will be recorded online. Immediately after the EUS procedure, the endoscopist will provide data regarding the procedure and ROSE. After 3 days, EUS-related adverse events will be investigated with a telephone interview or outpatient visit. Within 2 weeks, the pathologist will provide outcome data of the histological analysis, and a second patient interview will be performed to assess onset of adverse events and collect follow-up data. After 6 months, data will be collected to establish the gold standard diagnosis: results of imaging studies, final clinical diagnosis, and outcome based on the surgical resection specimen. At study closure, the clinical follow-up will be assessed again, to verify the gold standard diagnosis (Table 2).

2.6. Sample size calculation

The sample size has been calculated in order to demonstrate the non-inferiority of EUS-FNB without ROSE compared to EUS-FNB with ROSE in terms of diagnostic accuracy, having established a clinically acceptable margin of non-inferiority of 5%. The reported diagnostic accuracy of EUS-FNA with ROSE is 92%.[44] With a type I error α of 5% and a power $1 - \beta$ of 80%, the total required sample size amounts to 730 patients (one-sided hypothesis testing of categorical data, comparing two binomial proportions of independent samples). Considering a 9.5% of patients to add in order to counteract the estimated rate of drop-out and lost to follow-up, overall 800 patients will be needed, 400 per each group.

2.7. Statistical analysis

2.7.1. Descriptive statistics

Depending on distributional properties, outcome measures will be expressed as mean ± standard deviation (SD) or as median with interquartile range (IQR). Statistical significance will be assessed with Student's t-test for normally distributed continuous data, providing Satterthwaite approximation when variances are not homogeneous; either the chi-square test (with Yates' correction when appropriate) or Fisher exact-test (if at least one of the values in the cells of the contingency table is less than 5) for categorical data; and non-parametric statistics for non-normally distributed continuous data. A p-value <0.05 will be considered statistically significant. Data will be analyzed with IBM SPSS Statistics Version 22.0, Armonk, NY (IBM Corporation).

2.7.2. Univariate analysis

2.7.2.1. Primary endpoint. Overall diagnostic accuracy will be compared between the two groups, using the Pearson's chi-squared test or the Fisher's exact-test. Sensitivity, specificity, positive and negative predictive values will be computed for the two groups too. The Z test for two independent proportions will be used to test the non-inferiority hypothesis of EUS-FNB without ROSE compared to EUS-FNB with ROSE. Non-inferiority will be assessed by computing the two-tailed 95% confidence interval (CI) of the difference between the two proportions with Pearson's Chi-Square formula. Non-inferiority is met if the 95% CI does not cross the predefined non-inferiority margin $\Delta = -0.05$ and lies entirely to the right of the margin (i.e. non-inferiority will be demonstrated if the lower bound of the two-sided 95% CI of the difference is ≥ 0.05). If the 95% CI of the difference lies completely to the right of 0, the test treatment can be considered more effective than the standard treatment at a 5% significance level.

2.7.2.2. Secondary endpoints. Procedures safety and the presence of tissue cores will be compared between the two arms, using the Pearson's chi-squared test or the Fisher's exact-test. The procedure time and the quality scores of acquired tissue (see Table 1) will be compared using the unpaired Student's t-test or the Mann–Whitney test if the assumptions of the t-test would be not respected. The concordance between MOSE and presence of core at histopathological evaluation will be evaluated using the Cohen's K coefficient and a Z test will be made in order to evaluate if this concordance is statistically different from 0.

2.7.3. Multivariate analysis

To study the effect of the two methods on the different outcome measures, additional multivariate analysis will applied. Logistic regression will be applied to assess differences of accuracy and safety between the two methods, adjusted for age, sex, lesion location within the pancreas, lesion size, distance between GI-lumen and target lesion, and needle type used.

2.7.4. Analysis population

All analyses will be performed on an intention-to-treat (ITT), modified ITT (mITT), and per protocol (PP) population. ITT analysis includes every subject who is randomized according to the randomized treatment assignment. The mITT population is defined as all randomized patients for whom technical success will be achieved. The PP population is defined as all mITT patients without any major protocol deviations.

3. Discussion

The need for ROSE remains one of the most debated issues in the field of EUS-tissue acquisition. However, this old but still important question may be finally answered. The possibility to provide, at the same time, material suitable for ROSE and histological evaluation could combine the benefits of cytology and histology allowing the centers with an established ROSE service to continue to use it, providing also additional material which is needed in difficult cases and to perform molecular analyses in order to drive personalized treatments [37]. On the other hand in centers without ROSE,

EUS-FNB needles with an accuracy not inferior to the one obtainable with ROSE will help overcome the limitations of cytology, thus facilitating the widespread utilization of EUS in the community and throughout the world.

To answer this important question, we designed an international multicenter randomized study with the aim of comparing EUS-FNB with ROSE versus EUS-FNB without ROSE using three novel needles (the 20 G ProCore™, the 22 G SharkCore™ and the 22 G Acquire™ needle) in patients with solid pancreatic masses. The non-inferiority design of the study will test our hypothesis that EUS-FNB, by providing adequate samples for histological examination, will perform at least as good as EUS-FNB with ROSE. The choice of the 20 G ProCore™, the 22 G SharkCore™ or 22 G Acquire™, instead of the 25 G or the 19 G, balances the need to use a needle that acquires enough tissue to perform all the studies needed to reach the definitive diagnosis, with its usability, i.e. a needle that can be used by most, if not all the endosonographers and not only by the experts. In this regards, the 25 G seems too small to gather enough tissue in a consistent number of patients [38], while the 19 G is less maneuverable and more difficult to be used thus preventing its utilization by non-expert endosonographers [39].

Some limitations exist in the present study design. First, the experience with the TIC is limited worldwide. Moreover, ROSE is not routinely available at all involved centers. For these reasons, to limit possible results bias toward EUS-FNB alone, we asked the participating investigators and their pathologists to become familiar with the TIC before starting enrollment. Second, three different needles will be used in this trial and we cannot be sure that needle-related significant differences will not be found. However, the histological rate of these needles is almost equal in the published literature [26,28], and TIC performed equally using the SharkCore and the ProCore needles in a recent study [29]. Moreover, needle availability at each center depends not only on endosonographer preference but also on institutional dispositions based on reimbursement issues, and it would be very difficult to gather our study population using only one needle type. This limitation will give us the possibility of testing the concept of EUS-FNB performed with any of the available needles on the market, instead of performing a study driven by the industry where a single needle is tested. Third, all involved centers are referral institutions, thus the results of this study might not be the same in a community hospital setting. Fourth, we will be able to establish the number of passes needed for ROSE adequacy, but we will not for EUS-FNB alone arm because specimens collected after each pass will not be separated in different vials.

Conflict of interest

None declared.

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References

[1] Vilmann P, Jacobsen GK, Henriksen FW, Hancke S. Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreatic disease. Gastrointest Endosc 1992;38:172–3.
[2] Dumonceau JM, Polkowski M, Larghi A, Vilmann P, Giovannini M, Frossard JL, 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.
[3] Erickson RA, Sayage-Rabie L, Beissner RS. Factors predicting the number of EUS-guided fine-needle passes for diagnosis of pancreatic malignancies. Gastrointest Endosc 2000;51:184–90.
[4] Bang JY, Navaneethan U, Hasan MK, Hawes R, Varadarajulu S. Endoscopic ultrasound-guided specimen collection and evaluation techniques affect diagnostic accuracy. Clin Gastroenterol Hepatol 2018;16(November (11)):1820–8.
[5] Ieni A, Todaro P, Crino SF, Barresi V, Tuccari G. Endoscopic ultrasound-guided fine-needle aspiration cytology in pancreaticobiliary carcinomas: diagnostic efficacy of cell-block immunocytochemistry. Hepatobiliary Pancreat Dis Int 2015;14(June (3)):305–12.
[6] Ribeiro A, Vazquez-Sequeiros E, Wiersema LM, Wang KK, Clain JE, Wiersema MJ. EUS-guided fine-needle aspiration combined with flow cytometry and immunocytochemistry in the diagnosis of lymphoma. Gastrointest Endosc 2001;53:485–91.
[7] Bang JY, Magee SH, Ramesh J, Trevino JM, Varadarajulu S. Randomized trial comparing fanning with standard technique for endoscopic ultrasound-guided fine-needle aspiration of solid pancreatic mass lesions. Endoscopy 2013;45(June (6)):445–50.
[8] Crinò SF, Conti Bellocchi MC, Bernardoni L, Manfrin E, Parisi A, Amodio A, et al. Diagnostic yield of EUS-FNA of small (ò15 mm) solid pancreatic lesions using a 25-gauge needle. Hepatobiliary Pancreat Dis Int 2018;17(February (1)):70–4.
[9] Klapman JB, Logrono R, Dye CE, Waxman I. Clinical impact of on-site cytopathology interpretation on endoscopic ultrasound-guided fine needle aspiration. Am J Gastroenterol 2003;98:1289–94.
[10] Iglesias-Garcia J, Dominguez-Munoz JE, Abdulkader I, Larino-Noia J, Eugenyeva E, Lozano-Leon A, 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.
[11] Hebert-Magee S, Bae S, Varadarajulu S, Ramesh J, Frost AR, Eloubeidi MA, 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.
[12] Logrono R, Waxman I. Interactive role of the cytopathologist in EUS-guided fine needle aspiration: an efficient approach. Gastrointest Endosc 2001;54:485–90.
[13] Jhala NC, Jhala DN, Chieng DC, Eloubeidi MA, Eltoum IA. Endoscopic ultrasound-guided fine-needle aspiration. A cytopathologist's perspective. Am J Clin Pathol 2003;120:351–67.
[14] Crinò SF, Bernardoni L, Manfrin E, Parisi A, Gabbrielli A. Endoscopic ultrasound features of pancreatic schwannoma. Endosc Ultrasound 2016;5(November–December (6)):396–8.
[15] Wani S, Muthusamy VR, Komanduri S. EUS-guided tissue acquisition: an evidence-based approach (with videos). Gastrointest Endosc 2014;80:939–59.
[16] Larghi A, Eguia V, Hassan C, Verna EC, Tarantino I, Gonda TA. Economic crisis: the right time to widen endoscopic ultrasound utilization. Endoscopy 2014;46:80–1.
[17] Kalaitzakis E, Panos M, Sadik R, Aabakken L, Koumi A, Meenan J. Clinicians' attitudes towards endoscopic ultrasound: a survey of four European countries. Scand J Gastroenterol 2009;44:100–7.
[18] Al-Hawary MM, Kaza RK, Azar SF, Ruma JA, Francis IR. Mimics of pancreatic ductal adenocarcinoma. Cancer Imaging 2013;13(3):342–9.
[19] Bhattacharya A, Cruise M, Chahal P. Endoscopic ultrasound guided 22 gauge core needle biopsy for the diagnosis of Autoimmune pancreatitis. Pancreatology 2018;18(March (2)):168–9.
[20] Manfrin E, Perini C, Di Stefano S, Bernardoni L, Parisi A, Frulloni L, et al. Pseudo solid-appearing pancreatic serous microcystic adenomas: histologic diagnosis with the fork-tip EUS-FNB needle. Endosc Ultrasound 2019 [Epub ahead of print] https://doi.org/10.4103/eus.eus_11_19.
[21] Bang JY, Hebert-Magee S, Hasan MK, Navaneethan U, Hawes R, Varadarajulu S. Endoscopic ultrasonography-guided biopsy using a Franseen needle design: initial assessment. Dig Endosc 2017;29(May (3)):338–46.
[22] Mitri RD, Rimbaş M, Attili F, Fabbri C, Carrara S, Di Maurizio L, et al. Performance of a new needle for endoscopic ultrasound-guided fine-needle biopsy in patients with pancreatic solid lesions: a retrospective multicenter study. Endosc Ultrasound 2018;7(September–October (5)):329–34.
[23] Kandel P, Tranesh G, Nassar A, Bingham R, Raimondo M, Woodward TA, et al. EUS-guided fine-needle biopsy using a novel fork-tip needle: a case-control study. Gastrointest Endosc 2016;84:1034–9.
[24] Attili F, Rimbaş M, Fantin A, Fabbri C, Carrara S, Di Maurizio L, et al. Performance of a new histology needle for EUS-guided fine needle biopsy: a retrospective multicenter study. Dig Liver Dis 2018;50(May (5)):469–74.
[25] van Riet PA, Larghi A, Attili F, Rindi G, Nguyen NQ, Ruszkiewicz A, et al. A multicenter randomized trial comparing a 25-gauge EUS fine-needle aspiration device with a 20-gauge EUS fine-needle biopsy device. Gastrointest Endosc 2019;89(February (2)):329–39.
[26] Armellini E, Manfrin E, Trisolini E, Andorno S, Ballarè M, Bernardoni L, et al. Histologic retrieval rate of a newly designed side-bevelled 20G needle for EUS-guided tissue acquisition of solid pancreatic lesions United European. Gastroenterol J 2019;7(1):96–104.
[27] Bang JY, Hebert-Magee S, Navaneethan U, Hasan MK, Hawes R, Varadarajulu S. EUS-guided fine needle biopsy of pancreatic masses can yield true histology. Gut 2018;67(December (12)):2081–4.
[28] Bang JY, Hebert-Magee S, Navaneethan U, Hasan MK, Hawes R, Varadarajulu S. Randomized trial comparing the Franseen and Fork-tip needles for EUS-guided fine-needle biopsy sampling of solid pancreatic mass lesions. Gastrointest Endosc 2018;87(June (6)):1432–8.
[29] Crinò SF, Larghi A, Bernardoni L, Parisi A, Frulloni L, Gabbrielli A, et al. Touch imprint cytology on endoscopic ultrasound fine-needle biopsy provides comparable sample quality and diagnostic yield to standard endoscopic ultrasound

fine-needle aspiration specimens in the evaluation of solid pancreatic lesions. Cytopathology 2019;30(March;(2)):179–86.
[30] Bang JY, Kirtane S, Krall K, Navaneethan U, Hasan M, Hawes R, et al. In memoriam: fine-needle aspiration, birth: fine-needle biopsy: the changing trend in endoscopic ultrasound-guided tissue acquisition. Dig Endosc 2019;31(March;(2)):197–202.
[31] Cotton PB, Eisen GM, Aabakken L, Baron TH, Hutter MM, Jacobson BC, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc 2010;71(March (3)):446–54.
[32] Gerke H, Rizk MK, Vanderheyden AD, Jensen CS. Randomized study comparing endoscopic ultrasound-guided Trucut biopsy and fine needle aspiration with high suction. Cytopathology 2010;21(February (1)):44–51.
[33] Alatawi A, Beuvon F, Grabar S, Leblanc S, Chaussade S, Terris B, et al. Comparison of 22G reverse-beveled versus standard needle for endoscopic ultrasound-guided sampling of solid pancreatic lesions. United Eur Gastroenterol J 2015;3:343–52.
[34] Iwashita T, Yasuda I, Mukai T, Doi S, Nakashima M, Uemura S, et al. Macroscopic on-site quality evaluation of biopsy specimens to improve the diagnostic accuracy during EUS-guided FNA using a 19-gauge needle for solid lesions: a single-center prospective pilot study (MOSE study). Gastrointest Endosc 2015;81(January (1)):177–85.
[35] Leung Ki EL, Lemaistre AI, Fumex F, Gincul R, Lefort C, Lepilliez V, et al. Macroscopic onsite evaluation using endoscopic ultrasound fine needle biopsy as an alternative to rapid onsite evaluation. Endosc Int Open 2019;7(February (2)):E189–94.
[36] Pitman MB, Centeno BA, Ali SZ, Genevay M, Stelow E, Mino-Kenudson M, et al. Standardized terminology and nomenclature for pancreatobiliary cytology: the Papanicolaou Society of Cytopathology guidelines. Diagn Cytopathol 2014;42(April (4)):338–50.
[37] Brais RJ, Davies SE, O'Donovan M, Simpson BW, Cook N, Darbonne WC, et al. Direct histological processing of EUS biopsies enables rapid molecular biomarker analysis for interventional pancreatic cancer trials. Pancreatology 2012;12:8–15.
[38] Iwashita T, Nakai Y, Samarasena JB, Park DH, Zhang Z, Gu M, 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;7:909–15.
[39] Iglesias-García J, Abdulkader I, Lariño-Noia J, Domínguez-Muñoz JE. Evaluation of the adequacy and diagnostic accuracy of the histology samples obtained with a newly designed 19-gauge EUS histology needle. Rev Esp Enferm Dig 2014;106:6–14.