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STUDY TITLE:

WET-SUCTION VERSUS SLOW-PULL TECHNIQUE FOR ENDOSCOPIC ULTRA-SOUND-GUIDED FINE-NEEDLE BIOPSY OF SOLID LESIONS: A MULTICENTRIC RANDOMIZED CONTROLLED TRIAL

SHORT TITLE: WET SUCTION VERSUS SLOW-PULL FOR EUS-FNB OF SOLID LESIONS
CODICE: WEST-FNB

PROMOTER: University of Verona Hospital Trust – Gastroenterology and Digestive Endoscopy Unit

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LIST OF ABBREVIATIONS

EUS: endoscopic ultrasonography
TA: tissue acquiring
FNA: fine needle aspiration
FNB: fine needle biopsy
SPT: slow-pull technique
DST: dry suction technique
WST: wet suction technique

1. INTRODUCTION

Endoscopic ultrasound (EUS) with fine-needle aspiration (EUS-FNA) has become an essential tool for the diagnosis of solid pancreatic lesions (SPLs) and extrapancreatic lesions with 85% sensitivity and 98% specificity [1].

Several factors have been studied to optimize outcomes of EUS-FNA [1], such as the use of rapid on-site evaluation (ROSE) for immediate cytopathologic assessment [2], needles calibres and types [3], number of needle passes [4], and sampling techniques [5]. Currently, sampling techniques include standard suction (SS), slow-pull (SP) and wet-suction (WS).

The SS was the first technique used during EUS-FNA. It is performed applying a negative pressure suction at the proximal end of the needle after the stylet is removed with an air-filled pre-vacuum 10/20 ml syringe [6].

Differently, in the SP technique, after advancing the needle inside the lesion, the stylet is slowly removed, thus applying a capillary suction, while the operator performs some needle back and forth movements inside the lesion [7].

The WS relies on pre-flushing the needle with saline to replace the column of air with fluid, followed by aspiration at the proximal end of the needle, using a pre-vacuum 10/20 ml syringe [8,9]

A recent meta-analysis including seven randomized controlled trials compared the outcomes of SS versus SP for sampling of SPLs with EUS-FNA has been published [10]. The SP technique demonstrated similar adequacy and accuracy when compared to SS, with a non-significant trend in favour of SP (OR = 0.82; 95 % CI 0.36–1.85; P = 0.63) and moderate heterogeneity that was not explained by the sensitivity analyses. However, a significant improvement in bloodiness of the samples using the SP has been demonstrated [10].

In a single-blinded randomized trial on 117 patients comparing the WS with the SS for FNA, the WS yielded in significantly higher cellularity (1.82± 0.76 vs. 1.45±0.768, P<0.0003) and better specimen adequacy (85.5% vs. 75.2%, P<0.035) [9]. Recently, Wang et al. compared diagnostic accuracy in SS and WS for FNA of solid lesions (intrabdominal and mediastinal) in a multicentre randomized controlled trial. Among the 269 patients with pancreatic (n=161) and non-pancreatic (n=108) lesions analysed, the WS had a significantly better histological diagnostic accuracy (84.9% [95% confidence interval (CI) 79.9%–89.0%] vs. 73.2% [95%CI 67.1%–78.7%]; P= 0.001), higher specimen adequacy (94.8% vs. 78.8%; P< 0.001), and less blood contamination (P<0.001) than the SS technique [11].

All the aforementioned studies investigated the performance of the different sampling techniques in the setting of EUS-FNA. In the last decade, however, new EUS needles for the acquisition

of histological specimens have been developed with the purpose to overcome the limitations of cytology and obviate the need for ROSE.

In particular, end-cutting forward-acquiring needles (SharkCore™, Covidien/Medtronic, Boston, Massachusetts, and Acquire™, Boston Scientific, Marlborough, Massachusetts) have shown excellent histological yield [12,13], and several randomized trials have demonstrated their superiority compared with standard [14,15] and side-fenestrated needles [16], while they performed equally when compared each other in two randomized trials and one metanalysis [17-19]. Because of the high diagnostic accuracy of fine-needle biopsy (FNB) needles, current practice in moving from EUS-FNA to EUS-FNB [20].

The histological yield of newest generation histological needles is changing the role of EUS-FNB from diagnostic to prognostic and theranostic tool to drive precision medicine [21]. Development of next-generation sequencing (NGS) technologies has increased the speed and reduced the cost of sequencing the nucleic acids of cancer cells. The feasibility of NGS on EUS-FNB samples has been demonstrated [22] and requires a tumour fraction≥20% either for pancreatic duct adenocarcinoma (PDAC) [23] and pancreatic neuroendocrine tumors (pNETs) [24]. Therefore, EUS-FNB should guarantee a sample of adequate size and quality to perform molecular diagnostics.

Up to now, no studies investigating the impact of different suction techniques on histological yield and sample quality of specimens from solid lesions using EUS-FNB needles have been published.

2. STUDY AIMS AND ENDPOINTS

The primary aim of this study is to compare **the histologic yield** of EUS-FNB using the SP and the WS techniques. The primary endpoint is the rate of samples containing a tissue "core" (yes/no) for histological evaluation, defined as an intact piece of tissue of at least 550 μ [i.e., specimens scored 3 using the tissue integrity score (see **Table 1**)]. The length of intact histological fragments will be measured by using dedicated software at each participating center.

Secondary aims include:

1) Sample quality in terms of tissue integrity and the blood contamination. A score will be applied according to **Table 1** and outcomes using the two technique will be compared.

Table 1 *Sample quality scores (tissue integrity and blood contamination)*

SCORE	TISSUE INTEGRITY
0	No cells/tissue
1	Cytological specimen (disaggregated cells representative of the target lesion not allowing for tissue architectural assessment)
2	Histologic microfragments (sample adequate for histological evaluation, namely an architecturally intact piece of tissue but without a "core")
3	Histologic "core" (defined as an architecturally intact piece of tissue measuring at least 550 μ)
SCORE	**BLOOD CONTAMINATION**
0	Only blood
1	High blood contamination (>50% of the surface)
2	Moderate blood contamination (25-50% of the surface)
3	Low blood contamination (<25% of the surface)

2) Evaluation of tumor fraction with both techniques. The rate of samples collected with the two techniques containing an adequate tumor fraction ≥20% (i.e., ≥ 20% tumor cells in a background of benign nucleated cells) will be compared. Only PDAC and pNETs will be included for this aim.

3) Diagnostic accuracy using two sampling technique, measured against the final diagnosis. The finals diagnosis will be assessed on surgical whenever available, and in non-resected patients will be based on the diagnostic work-up (combined outcomes of imaging studies and any additional biopsy sample result) and clinical course of the disease of at least 6 months. The Papanicolaou classification (**Table 2**, simplified) [25] will be used either for EUS-FNB samples and surgical pathology for pancreaticobiliary masses. Lymph nodes will be classified as benign or malignant. For the evaluation of submucosal lesions, GIST and neuroendocrine tumors will be considered as malignant. Immunohistochemistry investigations will be performed, if required for diagnosis, as in normal clinical practice.

Table 2 *Diagnostic category and diagnoses according to the Papanicolaou classification*

Diagnostic Category	Sampling Features
1	Not adequate
2	Benign/neoplastic benign - chronic pancreatitis - autoimmune pancreatitis - intrapancreatic spleen - serous cystadenoma (solid type) - schwannoma
3	Atypical cells - Scant population of atypical cells of unclear origin
4	Neoplastic other - NET - solid pseudopapillary neoplasm - GIST
5	Suspicion for malignancy - Atypical cells suspicious for adenocarcinoma
6	Malignant - PDAC - neuroendocrine carcinoma - metastasis - other (specify)

3. PLAN OF INVESTIGATION

Design of the study

This is a multicenter, single-blind, randomized, controlled trial. All adult (≥ 18 years old) patients referred for EUS-FNB of solid lesions of the GI tract or adjacent to it will be assessed for eligibility. Patients with the following conditions will be included:

- Solid pancreatic lesions ≥ 1cm
- Peri-GI tract lymph nodes ≥ 1cm
- Peri-GI tract masses
- Lesions of the GI wall
- Signed informed consent

Patients with the following conditions will be excluded:

- Pancreatic cystic lesions (more than 50% of the volume)
- Diameter of lesion ≤ 1 cm
- Lesion not seen at EUS
- Pregnancy
- Coagulopathy (platelet count <50.000/mm3 and/or international normalized ratio >1.5);
- Severe cardiorespiratory dysfunction precluding endoscopy;
- Failure to provide informed consent

EUS-FNB procedures and samples processing

All the procedures will be performed by experienced endosonographers at each center and using a linear echoendoscope. A 22G end-cutting needle (SharkCore™ or Acquire™) will be used in all cases. The choice between the SharkCore and the Acquire needle will be left to the endosonographer's discretion or based on institutional disposition.

Four passes will be performed [27] using the same needle alternating the sampling techniques (SP and WS). The sequence of will be assessed in a randomized fashion.

For WS the stylet will be removed, and the needle will be pre-flushed with 1–2mL of saline. The lesion will then be punctured, and suction will be applied using a 10-mL pre-vacuum syringe [11]. The sample collected will be pushed into a formalin vial with saline.

For SP, after puncturing the lesion, the stylet will be slowly and gradually withdrawn for at least 40cm. The sample will be pushed into formalin using the stylet.

Each pass, regardless of the sampling procedure, the fanning technique [28] will be used. It consists of approximately 5-10 back-and-forth movements of the needle, positioned in different areas within the mass, by using the "up-down" dial of the echoendoscope and with minimal use of the elevator.. Afterwards, the needle will be withdrawn from the lesion.

The sample taken during 1st/3rd passes and 2nd/4th passes will be placed in two separate vials containing formalin and processed as standard histology. The flowchart in **Figure 1** illustrates the recruitment process. ROSE will be not used in any case.

Drop out

Patients will be not be considered included in the study in the following situations:

- Impossibility to perform EUS-FNB (e.g., for the interposition of vessels or technical failures).
- Impossibility to complete the procedure according to the protocol (e.g., it was not be possible to perform four needle passes).

Randomization and blinding

Once verified the eligibility to the trial, patients will be prospectively randomized in a 1:1 ratio in a cross-over design within each center into one of two study groups based on a computer-generated randomized blocks sequence (block size of 10) just before the procedure. Randomization will be stratified by type of lesion sampled (pancreatic versus other).

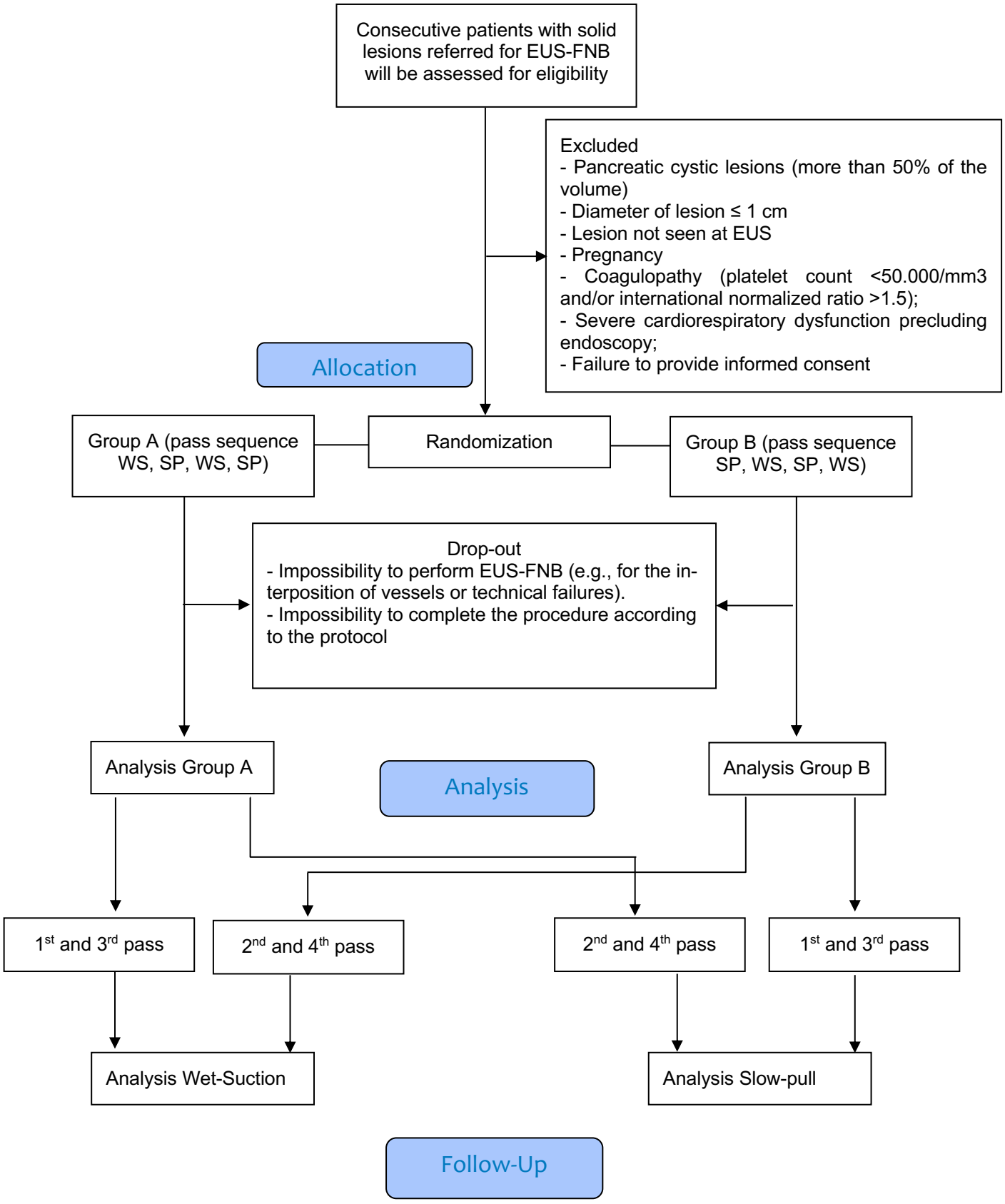
A data manager not involved in the data analysis or patient enrollment will generate the randomization lists and will prepare numerated sealed envelopes, containing the group assignment, that will be opened after study consent and EUS baseline assessment, just prior EUS-FNB. Patients will be randomly assigned into Group A and Group B in a 1:1 ratio. For Group A, the pass sequence is WS, SP, WS, SP. For Group B, the pass sequence is SP, WS, SP, WS.

The pathologist designated for the evaluation of the samples will be blinded on the type of TA technique performed and randomization during the entire study.

Follow-up

Patients will be followed for at least 6 months, in order to assess the outcome of surgical resection or clinical course of the disease.

Figure 1. *CONSORT flow-chart of the study*



Collected data and data management

The following data will be collected and included in a case record form (CRF) (see **CRF attached**):

- Sex
- Age
- Technical success (Y/N)
- Type of lesions (pancreatic/extrapancreatic/lymphnode)
- Lesion location
- EUS findings [site (e.g., head and size or the lesion), size (mm)]
- Needle type used (SharkCore 22G or Acquire 22G)
- Randomization (group A or B)
- Number of passes performed
- Fanning (Y/N)
- Histological findings (Tissue Integrity score, Blood Contamination score, tumor fraction >20% for pancreatic cancer and NET)
- Adverse events [29]
- Diagnostic category on EUS-FNB for pancreatic lesions
- Diagnosis for lymphnode (malignant/benign)
- Diagnosis on EUS-FNB for submucosal lesions (specify)
- Length (days) of the follow-up
- Patient/lesion's outcome at follow-up (death, weight loss/cachexia, surgery, lesion growth/infiltration/metastases appearance, lesion's stable or disappearance with patient well)
- Further sampling of the lesion (Y/N).
- Final Diagnosis (specify; e.g.; PDAC, NET, GIST, Leiomyoma, Malignant Lymphnode)

Enrollment and duration of study

Enrollment will be competitive between centers and will extend for a maximum period of 9 months after local Ethic Committee/IRB approval. It is plausible that Ethic Committee/IRB approval will be obtained at different time periods among the participating centers, thus requiring a total enrollment period of 18 months. A 6-month follow-up period is foreseen in order to evaluate the possible surgical treatment or other biopsy samplings or the evolution of the disease. We foresee a period of 3 months to complete the data analysis. The total duration of the study will be 27 months.

4. SAMPLE SIZE AND STATISTICAL ANALYSES

Sample size calculation

The sample size is calculated in the context of the primary binary outcome and considering the crossover design of the study with each lesion sampled with the two techniques. Assuming an expected pooled histological yield of 95% with WS [11] and 85% with SP [30,31] with α=0.05, power=0.9 and calculating the proportion of discordant pairs (equal to 0.18) with the approximation of Machin, Campbell, Fayers, and Pinol (1997) due to the lack of the data in the current literature, the total required sample size should be of 185 patients. Assuming approximately 8% dropout rate, we calculated a final sample size of 200 patients.

Statistical analyses

The characteristics of the sample will be summarized by descriptive statistics (mean with standard deviation or median with interquartile range for continuous variables and frequency distributions for categorical variables).

For the analysis of the primary end-point, the percentage of cases in which a histological sample was obtained will be calculated in each study arm. In particular, it will be possible to evaluate, for each group, through the McNemar test, if there is a statistically significant difference between the histological capacity of the two sampling techniques.

Sample quality scores and rate of samples containing an adequate tumor fraction will be compared using the McNemar test. Furthermore, the accuracy of the two techniques will be estimated by calculating sensitivity, specificity, positive predictive value, negative predictive value, and Area Under the ROC Curve respect to the the final diagnosis.

All analyses will be performed using the SPSS software with a statistical level of significance of 5% and respective 95% confidence intervals. A two-tailed distribution will be used and statistically significance will be considered for $P<0.05$.

5. ETHICAL CONSIDERATIONS

Regulation statement

The latest revision of the Helsinki declaration and the Declaration of Oviedo will be the basis for the ethical conduct of the study. This protocol will be designed and conducted to ensure adherence to the principles and procedures of the good clinical practice and comply with participants' Country legislations:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.

2. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
3. Directive 2001/20/EC
4. Directive 2005/28/EC
5. D. L.vo n.211 del 24 giugno 2003.
6. D. L.vo n.200 6 Novembre 2007.
7. D.M. 21 Dicembre 2007.

Essential documents will be preserved to demonstrate the validity and integrity of the data collected.

The Promoter of this study in accordance with the responsibilities provided for by the rules of good clinical practice (Legislative Decree 211/2003) and in compliance with the laws and regulations in force on data protection including the relevant European Regulation of personal data protection 2016/679, will process the personal data collected, exclusively for the purpose of carrying out the study.

Treatment and storage of biological samples

Biological samples taken during EUS-FNB will be treated in each center as normal clinical practice, so for the study will not be performed any study-specific processing techniques or immunohistochemistry or samples'conservation.
In particular, for the center of AOUI Verona, after FNB procedure, the sample will be transferred at the Pathology Division at the Department of diagnostic and Public Health, processed and analyzed according the current procedures normally used. The sample taken during the EUS-FNB, will be stored as usual.

Recruitment and consent

The treating physician will inform eligible patients about the study and will explain the aims, methods, anticipated benefits, and potential hazards at least 24 hours before. Also, this information will be provided in print. If patients have any further questions, they can also consult an independent physician.

Data management and procedures to guarantee the confidentiality of the data

The promoter will undertake to observe the Privacy Laws (as following defined), included the parts relevant security procedures and privacy. The promoter guarantee, for himself and for the investigator, to be completely informed on all the obligations following any applicable regulation regards the professional secret in medical field and the protection of the patient's personal data, included in exemplificative but not complete degree the guidelines UE 2016/679, the Privacy Code (D.Lgs 196/03, s.m.i.), the provisions, the guidelines and the current general authorizations of the Autorità Garante Italiana for the protection of personal data (collectively "Privacy Laws").

The promoter will undertake in order that its staff involved in the scientific study will respect the Privacy Laws and the Promoter's instructions on the protection of personal data, included security aspects and data confidentiality. This obligations includes, for example: (i) provide to the patient involved in the study a privacy informative according to law (UE guidelines 2016/679, D.Lgs. 196/2003 s.m.i, nonetheless the above-mentioned guidelines delle 24 July 2008); (ii) obtain a written informed consent by the patient, before his involvement in the study; (iii) respect the privacy of every involved person as regulated by the Privacy Laws; (iv) adopt all the adequate physical, logical, organizational, technical and informatic measures to follow the appliable Privacy Laws.

Due to the particular sensitivity of the data processed in the study, specific technical measures have been adopted to increase the level of data security, without prejudice to any other minimum measure. This, with particular reference to the registration operations with electronic and / or paper instruments of the data of the persons involved in the study at the testing centers, their transfer via e-mail to a single database at the subjects who perform, validation and processing data statistics and the management of the same database. The promoter has adopted secure communication protocols based on the use of cryptographic standards for the electronic transmission of the data collected by the testing centers to the centralized database at the promoter or other subjects who carry out the subsequent validation and statistical processing of the data. In relation to these processing operations, the promoter has taken appropriate measures to ensure the protection of data recorded by the risks of unauthorized access, theft or loss, partial or complete, of paper documents, storage media or portable or fixed processing systems (indicate, for example, through the partial or full application of cryptographic technologies to file systems or databases, or through the adoption of other IT protection measures that make unintelligible data to uninformed subjects: "It is necessary to insert a username and a password to access the computers where the data are entered in. Furthermore, access to the database in order to start a data entry session is protected by a username and password.

The following precautionary measures are taken to ensure data privacy and to prevent data manipulation and loss:

i) Access to data is restricted to authorized members only. The authorized members are the researchers directly involved in the study (Stefano Francesco Crinò and Maria Cristina Conti Bellocchi) that will collect, analyse and interpret the data.
ii) The network is protected by a firewall
iii) Internet connection is encrypted with a digital certificate (SSL technology)
iv) The database is on a server, password protected, which is changed periodically.
v) Access to the database is password protected and is accessible only to those responsible for the center.
vi) Periodic backups are performed.
vii) places of conservation are protected (e.g., "The paper materials related to clinical evaluations will be stored in wardrobes, whose keys will be in possession only of the persons authorized by the persons in charge of the study).
Finally, about the database, we will adopt a specific system for the authentication and authorization of the people involved in the study with different roles and the needs of access and suitable treatment and procedures for the periodic verification of the quality and consistency of the credential for the authentication of the profiles authorized assigned to the expert involved in the treatment.
The experimenter will adequately separate the patients' identification data from the results of the experiments (i.e., making anonymous those data by means of the individualization of the results with an alphanumeric code randomly generated) to allow the Promoter to analyze only pseudo-anonymous data.
The promoter will allow access to the clinic data (including clinic files) and all the other information that can be relevant for the study, always observing the Privacy Law and respecting all the security measures and data confidence.
Personal data of the subjects will be exclusively accessible for investigators and collaborators/co-investigators, monitors and auditors of the Promoter, and/or for the competent authority encharged, in agreement with what is included in the Informed consent.
The Promoter and the Investigator will make sure to inform the patients in a clear and thorough way about the modalities of personal data treatment before their participation to the experiment, as established by the applicable Privacy Laws.
Before data acquisition, the investigator will make sure to inform every patient about the nature, objectives, results, consequences and risks of the study before their participation in the study. Before recruitment, the investigator or an authorized delegate, will collect from the patient the written informed consent to: a) participate in the study; b) communicate their own confidential information; c) the treatment of personal data; d) transfer the documents containing personal data of the patient, including sensitive health data, to the Promoter and/or the authorities in charge and/or other institutions

including ones outside the European Union, in conformity to what is required by law and by the applicable Privacy Laws.

The Promoter will make sure to keep the original paper documents (ex. informed consent) for at least 7 years, in conformity with the dl200/2007.

6. AUTHORSHIP RULES

First and last authors will come from the centers of Verona and Roma. The number of Co-Authors from collaborating centers will be assessed according to the number of patients included: less than 15 patients: one co-author; 15-30 patients: two co-authors; more than 30 patients: 3 co-authors.

The research manager undertakes to protect the privacy of the participants in the study by processing the data exclusively for statistical and scientific research purposes and also undertakes not to communicate or spread them except in anonymous form.

7. REFERENCES

1. Dumonceau JM, Polkowski M, Larghi A, et al. European Society of Gastrointestinal Endoscopy. 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.
2. Iglesias-Garcia J, Lariño-Noia J, Abdulkader I, Domínguez-Muñoz JE. Rapid on-site evaluation of endoscopic-ultrasound-guided fine-needle aspiration diagnosis of pancreatic masses. World J Gastroenterol. 2014 Jul 28;20(28):9451-7.
3. 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(11):1820-1828.e4. doi:10.1016/j.cgh.2018.03.004
4. 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: 184–190.
5. Wani S. Basic techniques in endoscopic ultrasound-guided fine needle aspiration: Role of a stylet and suction. Endosc Ultrasound 2014;3:17-21.
6. Chen JY, Ding QY, Lv Y, et al. Slow-pull and different conventional suction techniques in endoscopic ultrasound-guided fine-needle aspiration of pancreatic solid lesions using 22-gauge needles. World J Gastroenterol. 2016;22(39):8790-8797
7. Bor R, Vasas B, Fábián A et al. Prospective comparison of slow-pull and standard suction techniques of endoscopic ultrasound-guided fine needle aspiration in the diagnosis of solid pancreatic cancer. BMC Gastroenterol 2019; 19: 6
8. Villa NA, Berzosa M, Wallace MB, Raijman I. Endoscopic ultrasound-guided fine needle aspiration: The wet suction technique. Endosc Ultrasound. 2016;5(1):17-20.
9. Attam R, Arain MA, Bloechl SJ, Trikudanathan G, Munigala S, Bakman Y, Singh M, Wallace T, Henderson JB, Catalano MF, et al. "Wet suction technique (WEST)": A novel way to enhance the quality of EUS-FNA aspirate. Results of a prospective, single-blind, randomized, controlled trial using a 22-gauge needle for EUS-FNA of solid lesions. Gastrointest Endosc. 2015; 81(6):1401–7.
10. Capurso G, Archibugi L, Petrone MC, Arcidiacono PG. Slow-pull compared to suction technique for EUS-guided sampling of pancreatic solid lesions: a meta-analysis of randomized controlled trials. Endosc Int Open. 2020;8(5):E636-E643
11. Wang Y, Wang RH, Ding Z, et al. Wet- versus dry-suction techniques for endoscopic ultrasound-guided fine-needle aspiration of solid lesions: a multicenter randomized controlled trial [published online ahead of print, 2020 May 15]. Endoscopy. 2020;10.1055/a-1167-2214.
12. Nayar MK, Paranandi B, Dawwas MF, Leeds JS, Darne A, Haugk B, Majumdar D, Ahmed MM, Oppong KW. Comparison of the diagnostic performance of 2 core biopsy needles for EUS-guided tissue acquisition from solid pancreatic lesions. Gastrointest Endosc. 2017 May;85(5):1017-1024
13. Bang JY, Kirtane S, Krall K, et al. In memoriam: Fine-needle aspiration, birth: Fine-needle biopsy: The changing trend in endoscopic ultrasound-guided tissue acquisition. Dig Endosc. 2019;31(2):197-202
14. Oppong KW, Bekkali NLH, Leeds JS, et al. Fork-tip needle biopsy versus fine-needle aspiration in endoscopic ultrasound-guided sampling of solid pancreatic masses: a randomized crossover study. Endoscopy. 2020;52(6):454-461

15. 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(12):2081-2084
16. Crinò SF, Le Grazie M, Manfrin E, et al. Randomized trial comparing the fork-tip and the side-fenestrated needles for EUS-guided fine-needle biopsy of solid pancreatic lesions [published online ahead of print, 2020 May 17]. Gastrointest Endosc. 2020;S0016-5107(20)34308-X. doi:10.1016/j.gie.2020.05.016
17. 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(6):1432-1438. doi:10.1016/j.gie.2017.11.036
18. Ashat M, Klair JS, Rooney SL, et al. Randomized controlled trial comparing the Franseen needle with the Fork-tip needle for EUS-guided fine-needle biopsy [published online ahead of print, 2020 Jun 9]. Gastrointest Endosc. 2020;S0016-5107(20)34407-2. doi:10.1016/j.gie.2020.05.057
19. Facciorusso A, Del Prete V, Buccino VR, Purohit P, Setia P, Muscatiello N. Diagnostic yield of Franseen and Fork-Tip biopsy needles for endoscopic ultrasound-guided tissue acquisition: a meta-analysis. Endosc Int Open. 2019;7(10):E1221-E1230.
20. Rimbaş M, Crino SF, Gasbarrini A, Costamagna G, Scarpa A, Larghi A. EUS-guided fine-needle tissue acquisition for solid pancreatic lesions: Finally moving from fine-needle aspiration to fine-needle biopsy?. Endosc Ultrasound. 2018;7(3):137-140.
21. Wani S, Muthusamy VR, McGrath CM, et al. AGA White Paper: Optimizing Endoscopic Ultrasound-Guided Tissue Acquisition and Future Directions. Clin Gastroenterol Hepatol. 2018;16(3):318-327
22. Dreyer SB, Jamieson NB, Evers L, et al. Feasibility and clinical utility of endoscopic ultrasound guided biopsy of pancreatic cancer for next-generation molecular profiling. Chin Clin Oncol. 2019;8(2):16
23. Gleeson, F.C.; Kerr, S.E.; Kipp, B.R.; Voss, J.S.; Minot, D.M.; Tu, Z.J.; Henry, M.R.; Graham, R.P.; Vasmatzis, G.; Cheville, J.C.; et al. Targeted next generation sequencing of endoscopic ultrasound acquired cytology from ampullary and pancreatic adenocarcinoma has the potential to aid patient stratification for optimal therapy selection. Oncotarget 2016, 7, 54526–54536.
24. Gleeson, F.C.; Voss, J.S.; Kipp, B.R.; Kerr, S.E.; Van Arnam, J.S.; Mills, J.R.; Marcou, C.A.; Schneider, A.R.; Tu, Z.J.; Henry, M.R.; et al. Assessment of pancreatic neuroendocrine tumor cytologic genotype diversity to guide personalized medicine using a custom gastroenteropancreatic next-generation sequencing panel. Oncotarget 2017, 8, 93464–93475.
25. Pitman MB, Layfield L. The Papanicolaou Society of Cytopathology System for Reporting Pancreaticobiliary Cytology. Switzerland: Springer International Publishing; 2015:6
26. Iwashita T, Yasuda I, Mukai T, 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;81:177–185
27. Polkowski M, Jenssen C, Kaye P, et al. Technical aspects of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Technical Guideline - March 2017. Endoscopy. 2017;49(10):989-1006. doi:10.1055/s-0043-119219
28. 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(6):445-450

29. Cotton PB, Eisen GM, Aabakken L, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc. 2010;71(3):446–454

30. Facciorusso A, Bajwa HS, Menon K, Buccino VR, Muscatiello N. Comparison between 22G aspiration and 22G biopsy needles for EUS-guided sampling of pancreatic lesions: A meta-analysis. Endosc Ultrasound. 2020;9(3):167-174. doi:10.4103/eus.eus_4_19

31. Facciorusso A, Sunny SP, Del Prete V, Antonino M, Muscatiello N. Comparison between fine-needle biopsy and fine-needle aspiration for EUS-guided sampling of subepithelial lesions: a meta-analysis. Gastrointest Endosc. 2020;91(1):14-22.e2. doi:10.1016/j.gie.2019.07.018

32. Cicchetti DV, Feinstein AR. High agreement but low kappa: II. Resolving the paradoxes. J Clin Epidemiol 1990;43:551-8.