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GRUPUGE RECOMMENDATIONS

EUS-FNA & therapeutic procedures

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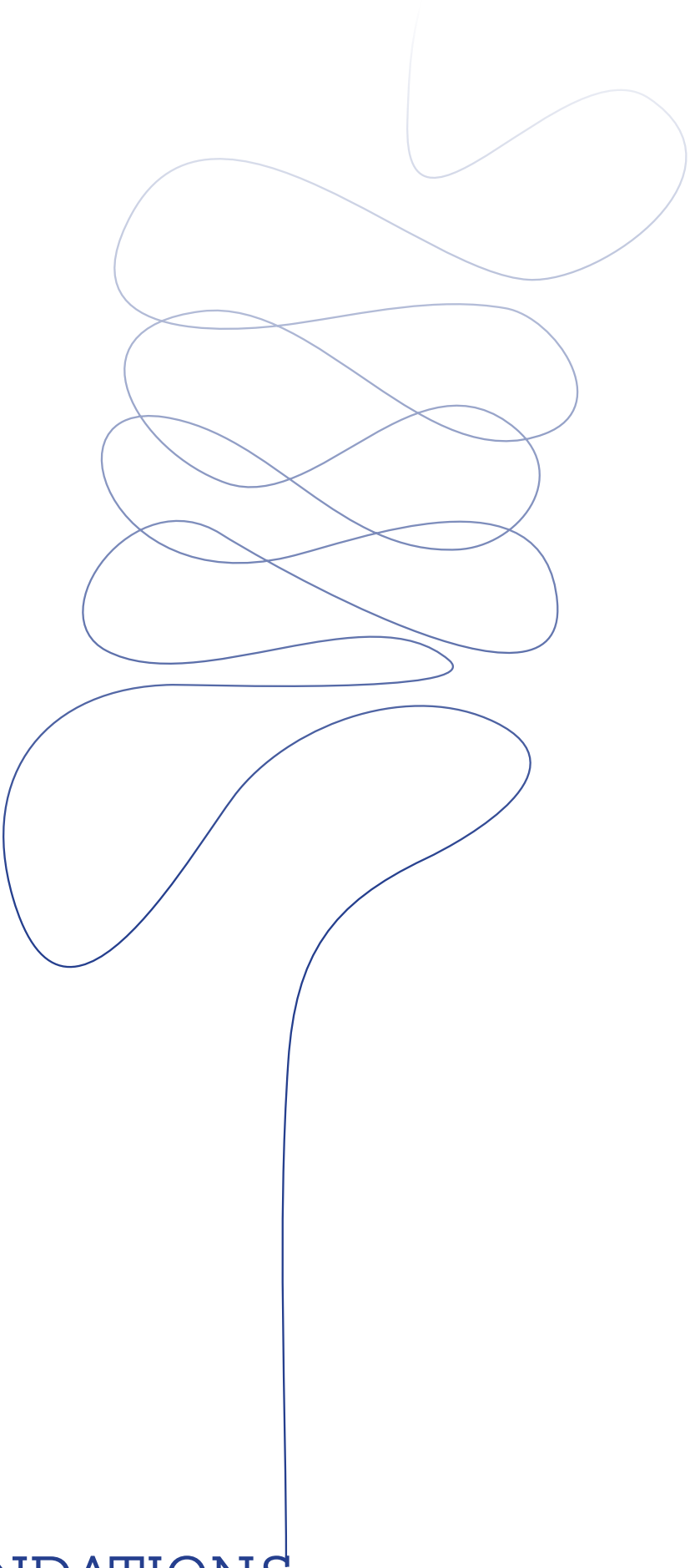

GRUPUGE RECOMMENDATIONS

EUS-FNA & therapeutic procedures

SUMMARY

I. THE BASICS IN EUS-FNA

Techniques, accessories; when to use specific needles?

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Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is a safe procedure and an accurate technique for establishing tissue diagnosis in patients with tumors or lesions in or adjacent to the gastrointestinal tract (1).

1. EUS-FNA Technique

After identifying the lesion to puncture and placing it in the center of the screen, adjacent to the transducer (1-2 cm), a scan of the FNA path should be performed to exclude any significant blood vessels between the lesion and the scope. The rubber cap covering the operating channel must be removed before inserting the needle system. The needle should be inserted into the working channel with the scope in a straight position. This makes needle movements easier and reduces the risks of damage to the channel (2, 3).

Once the needle is fully inserted into the scope, the system should be luer-locked to the operating channel. In some cases, the lesion to target may be less visible once the needle is in position, due to artifact created by the needle/sheath or to poor apposition between the transducer and the gut wall. Reducing the length of the sheath and applying suction to reduce air interposition may help to correct the problem (4).

When the scope is in position, fine movements must be performed to correctly position the lesion. Ideally, the lesion should be within the natural path of the needle, so that minimal tip and/or elevator deflection is needed. The needle sheath should be exteriorized 1-1,5 cm beyond the tip of the scope (2, 3).

Before puncturing the lesion, the safety ring must be unscrewed to allow needle deployment. The distance between the scope and the desired area to sample should be measured and the safety ring device adjusted accordingly.

The needle should first be advanced approximately 1 cm out of the sheath to allow real-time ultrasound guidance during tissue sampling, avoiding damage to other structures. Once the tip has been identified, the elevator can be used to adjust the trajectory if needed. The goal is to insert the needle into the lesion, and once this is confirmed to make repetitive back-and-forth thrusting movements to shear off cells and collect them within the needle lumen (3, 4). Constant suctioning can also be used to reduce any air seepage risk between the probe and gut wall.

Some studies favor a “multi-pass” technique,

which involves sampling widely through the lesion many times, before removing the needle from the scope. The needle is moved through the entire diameter of the lesion for 5 to 10 strokes, and the needle is withdrawn from the lesion and moved to a different region of the lesion. The multi-pass technique differs from the "fanning" technique since the latter involves sampling different regions without removing the needle completely from the lesion. "Fanning technique" has shown to be associated with fewer passes for same diagnostic yield compared to "one direction" puncture (3, 5).

After completing a pass, the needle should be completely withdrawn into the sheath. The locking device should be returned to its original upmost position and secured with the screw. To avoid clotting in the needle, the aspirate should be expressed from the needle as quickly as possible (3).

2. Technical factors

The role of a stylet and suction

All commercially available EUS-FNA needle systems include a removable stylet. For years the standard approach has been to reinsert the stylet into the needle before every pass to prevent sample contamination by cells from the digestive wall as well as blockage of the needle that would hinder sample aspiration. Data from randomized controlled trials demonstrates that the use of a stylet during EUS-FNA has no impact on the diagnostic yield of malignancy or the quality of specimens (cytologic characteristics). There is insufficient evidence to recommend for or against using the stylet and the decision in this regard should be left to the discretion of the endosonographer performing the procedure (6, 7).

Traditionally, suction is applied during EUS-FNA using a syringe. Applying continuous suction with a syringe during EUS-FNA improves the sensitivity for the diagnosis of malignancy in patients with solid masses. Data from a randomized controlled trial suggest that suction should not be used during EUS-FNA of lymph nodes as it increases bloodiness of specimens obtained and has no impact on the overall diagnostic yield (6, 7).

Sampling methods

Diagnostic yield of EUS-FNA and accuracy are also dependent on the way the material is processed after the extraction of the needle up to the microscope. Procured material after FNA can be processed in different ways. The samples are typically extracted from the needle either by flushing air or by using the more controlled method of stylet reinsertion. The material is then put on glass slides, which are air-dried or fixed with alcohol (8).

Methods described for collecting tissue fragments for histopathological examination from specimens obtained with standard EUS-FNA needles include injection of 2mL saline through the needle to expel the specimen directly into a fixative or expelling the specimen with the needle stylet onto a glass slide or into saline and picking up tissue fragments to immerse them into a fixative (6).

No adequate study has compared direct smear cytology vs. liquid-based cytology for processing specimens collected with EUS-FNA. Similarly, no study has evaluated which of the methods described for collecting tissue

fragments for histopathological examination is better. If infection is suspected, namely tuberculosis, the material from one needle pass should be reserved for specific analysis including polymerase chain reaction. If lymphoma is suspected, then flow cytometry should be used. If needed, a part of the material, from the same pass or from following ones, may be preserved for cell block. Cell block is a preparation in which the specimen is centrifuged into a pellet, formalin-fixed, paraffin-embedded, and sectioned for standard staining or ancillary test such as immunocytochemistry and genetic analysis. Cell blocks are used as a complement to rather than a replacement for smears (6, 8).

Several studies have demonstrated an advantage of combining cytological and histological methods for better accuracy (6, 8).

The role of rapid on-site cytopatological examination (ROSE)

ROSE provides a highly reliable diagnosis with an excellent agreement with the final cytopathological diagnosis. Intra procedural feedback on the adequacy of sampling may reduce procedure time and risk by minimizing needle passes. There is limited evidence to suggest that ROSE increases the diagnostic yield of EUS-FNA and accuracy for malignancy detection. The improvement in adequacy was most convincing when ROSE was performed by pathologists and at centers where the initial adequacy rates (without ROSE) were low and especially during the learning phase of EUS-FNA. Data on cost-effectiveness of ROSE are very limited (6, 8).

The needle pass

Factors that influence the number of fine needle passes made during EUS-FNA include type, location and sonography characteristics of the lesion but the main factor seems to be the presence of a cytopathologist during the EUS procedure and level of cytologic expertise available. When ROSE is not available, it is recommended performing three needle passes for lymph nodes and liver lesions, at least five needle passes for solid pancreatic masses and a single pass for pancreatic cysts (6, 8).

3. Accessories

Most EUS accessories are needles designed for tissue acquisition. All EUS accessories are designed for use with linear echoendoscopes, which allow continuous US visualization of the devices throughout their path once they are advanced beyond the gastrointestinal lumen and into the target structures (4).

A variety of partially reusable and single-use EUS-FNA needle devices are available in 19, 20, 22 and 25-gauge configurations. They are composed of a hollow needle with a solid removable stylet, a semi rigid protective sheath, and a handle with a port for stylet insertion or withdrawal, as well as an attachment of a vacuum syringe (4).

Needle size receives the most attention as an independent factor that could increase the diagnostic yield of EUS-FNA. Most studies showed no difference in quality of a specimen or diagnostic accuracy obtained by different needle sizes once the target lesion was successfully accessed. However, the 25-gauge needle demonstrated a higher success rate in

sampling lesion in the pancreatic head or its uncinated process, that may require a transduodenal access, compared with 22 or 19-gauge needles (6, 9, 10).

Certain conditions such as lymphoma, mesenchymal tumors, well-differentiated tumors and auto-immune pancreatitis may be difficult to diagnose by cytology alone. In an attempt to overcome some of the limitations of EUS-FNA, dedicated needles to obtain core tissue biopsy specimens for histologic examination under EUS guidance have been developed and tested. EUS Tru-Cut biopsy does not offer any clear advantage compared with EUS-FNA and is technically demanding, with a low transduodenal yield. Standard 19-G and 22-G FNA needles with or without high negative pressure have proved to be reliable in obtaining high-quality histologic samples in various indications. The novel 19-G and 22-G ProCore needles (Cook Medical, Bloomington, IN, US) have shown a high yield in obtaining histologic samples, whereas 25-G ProCore seems unsuitable for histology (6, 9, 10).

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HIGHLIGHTS

- EUS-FNA is a safe procedure and an accurate technique for establishing tissue diagnosis in patients with tumors or lesions in or adjacent to the gastrointestinal tract.
- Sampling various parts of the target lesion using the fanning technique has been shown to be associated with fewer passes for same diagnostic yield compared to standard technique.
- Applying continuous suction with a syringe during EUS-FNA improves the sensitivity for the diagnosis of malignancy in patients with solid masses but not in patients with lymphadenopathy.
- There is insufficient evidence to recommend for or against using the stylet.
- ROSE provides a highly reliable diagnosis with an excellent agreement with the final cytopathological diagnosis and may reduce procedure time and risk by minimizing needle passes.
- When ROSE is not available, it is recommended performing three needle passes for lymph nodes and liver lesions, at least five needle passes for solid pancreatic masses and a single pass for pancreatic cysts.
- Most studies showed no difference in quality of a specimen or diagnostic accuracy obtained by different needle sizes; however, the 25-gauge needle demonstrated a higher success rate in sampling lesion in the pancreatic head or its uncinated process compared with 22 or 19-gauge needles.
- Certain lesions or conditions require a histologic specimen in addition to or in lieu of a cytologic one for an accurate diagnosis and in those conditions the novel ProCore needles (Cook Medical, Bloomington, IN, US) may have advantages.

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II. DIAGNOSTIC EUS-FNA

A. Punctures in the mediastinum

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1. Mediastinal stations accessible by EUS

EUS can easily identify and sample lymph nodes in the posterior and inferior mediastinum, a common site of lung metastases, inaccessible to most alternative staging modalities [1]. Figure 1 represents mediastinal lymph node stations according to the Mountain-Dresler classification [2]. Lymph node stations 4L, 7, 8 and 9 are readily approachable by EUS and eventually stations 2, 4R and 5 (2, 4R and 5 access is variable) [1]. EUS-FNA of station 6 has been described, but requires transaortic passage of the needle [3].

Anterior upper mediastinal nodes and intrapulmonary nodes are inaccessible to EUS-FNA and in both situations endobronchial ultrasound-guided fine needle aspiration (EBUS-FNA) is the adequate sampling technique [1].

2. Indications

The primary roles for EUS-FNA in the mediastinum are diagnostic sampling of mediastinal disease [1] and staging of non-small cell lung cancer (NSCLC) [4] and esophageal cancer [5].

2.1. Diagnosis of mediastinal disease

EUS-FNA is safe and accurate in diagnosing mediastinal solid lesions, such as lymphadenopathies of unknown origin and masses, and it changes patients' management in more than 70% of cases [6]. However, EUS-FNA of mediastinal cysts is discouraged as it carries a risk of severe infection even if prophylactic antibiotics are administered [6].

2.1.1. Benign mediastinal disease

Several benign diseases, such as sarcoidosis and tuberculosis, can manifest as mediastinal lymphadenopathies, which can be accessed by EUS-FNA to confirm the diagnosis. Despite sarcoidosis diagnosis is usually based on clinical grounds supported by radiologic and laboratory findings, EUS-FNA of mediastinal lymph nodes may be needed to exclude malignancy. Because noncaseating granulomas are difficult to identify from cytopathology taken by FNA, a cellblock or a core biopsy may be useful [7]. If tuberculosis is suspected, specimens obtained by EUS-FNA should be sent for acid-fast stain and culture as well as for fungal culture. Polymerase chain reaction significantly increases the diagnostic yield and needle core

biopsy may be superior in identifying caseating granulomas from mediastinal lymph node tissue with tuberculosis [8].

If a granulomatous disease is suspected, consider obtain histologic specimen by EUS-core biopsy. If tuberculosis is suspected, samples should be sent for polymerase chain reaction, acid-fast stain and culture and fungal culture [1,6].

2.1.2. Malignant mediastinal disease

Malignant mediastinal lymph nodes are a common feature of metastatic cancer and lymphoma. Although FNA specimens can have a high diagnostic yield for metastasis, FNA is generally not ideal for lymphoproliferative disorders, as they often require histologic specimens to best delineate architecture and allow for performance of immunophenotyping by flow cytometry. Needle core biopsy may be more adequate for diagnosis and subtyping of lymphoma and may provide also prognostic information for certain types of lymphoma [9,10]. Given the limited diagnostic sensitivity of EUS-FNA for mediastinal lymphoma (73-80%) [11-14], excisional biopsy should be considered when FNA is negative [15].

If lymphoma is suspected, consider obtain histologic specimen by EUS-core biopsy and sample should be sent for flow cytometry [1,6].

2.2. Staging of non-small cell lung cancer and esophageal cancer

2.2.1. Non-small cell lung cancer (NSCLC)

Lung cancer is the most frequent cause of malignant mediastinal disease. NSCLC is staged according to the TNM system [4]. EUS can be useful to assess each component of the TMN staging system. It can identify tumor invasion of mediastinal structures (T4), such as the left atrium, aorta, pulmonary vessels, vertebra and esophagus, which precludes curative surgery [16]. EUS can also detect and sample suspicious mediastinal lymph nodes found by computed tomography (CT) or by positron emission tomography (PET). Lymph nodes with round shape, sharp margins and a short axis greater than 8.3 mm are more likely to be malignant and therefore EUS-FNA is recommended [17]. Even in the absence of suspicious lymph nodes on TC and/or PET, EUS-FNA may identify mediastinal lymph nodes metastasis in up to 20% of patients [18-20]. This technique is often complemented with EBUS-FNA to access the entire mediastinum, because EUS-FNA is better to approach the posterior and inferior lymph nodes, while EBUS-FNA is better to approach the anterior and superior lymph nodes. EUS-FNA accuracy to identify metastases to mediastinal lymph nodes is high (83-97%) with a sensitivity of approximately 90% and specificity near 100% (false-positive rate of 2%) [21,22]. In addiction, EUS-FNA aspirates of lymph nodes can be submitted for EGFR and K-ras mutation analysis to help tailor chemotherapy [23]. EUS is also useful to identify and sample distant metastases to the celiac lymph nodes, left lobe of the liver, left adrenal gland and occasionally right adrenal gland (M1), which precludes curative surgery. In a prospective study, EUS-FNA impacted the management of 25% of patients and detected advanced disease in 12% that precluded surgery (for example T4, N3 or M1) [24].

Restaging after neoadjuvant therapy can also

be assessed by EUS-FNA to detect residual NSCLC [25].

In patients with known or suspected potentially resectable lung cancer whose imaging reveals mediastinal adenopathy, EUS-FNA should be performed in patients with paraesophageal, posterior and inferior mediastinal adenopathy. In patients with paratracheal mediastinal adenopathy EBUS-FNA should be performed if it adds information to the staging [6].
In patients with known or suspected potentially resectable lung cancer whose imaging shows no evidence of adenopathy, combined EUS-FNA and EBUS-TBNA should be performed for staging [6].

2.2.2. Esophageal cancer

EUS is the most accurate imaging method for initial locoregional staging in esophageal cancer, superior to CT and PET [26]. The addiction of CT and PET do not change patient management if a complete EUS examination has been performed. Because of its higher sensitivity, EUS is recommended for patients who have no distant metastases on CT and/or PET [27,28]. In patients who are considered for surgical resection, EUS-FNA may impact treatment decisions in one third of cases by correcting the tumor stage determined by CT [29,30]. EUS-FNA change patient management by providing cytopathologic confirmation of metastasis to regional lymph nodes, to nonregional lymph nodes (mostly celiac) or to distant sites and therefore allocating a patient to a specific treatment option (primary surgical resection, definitive or neoadjuvant chemoradiation).
For restaging after neoadjuvant therapy, integrated CT and PET is recommended as it has it superior to EUS-FNA and to CT alone [31].

For initial stating of esophageal cancer, EUS-FNA should be performed whenever the cytological result is likely to affect the decision on what treatment option to choose to a given patient [6].

3. Technical Aspects

Very few studies have assessed the performance characteristics between 19G, 22G and 25G needles to perform EUS-FNA of lymph nodes, so there are no recommendations regarding the best needle to be used [32].
Diagnostic accuracy of EUS-FNA does not differ depending on whether the sampling is performed from the edge of a lymph node or from its centre [33].
There is evidence that applying continuous suction with a syringe during EUS-FNA improves the sensitivity for the diagnosis of malignancy in a patient with solid masses but not with lymphadenopathy. In fact, EUS-FNA of lymphadenopathy showed that the use of suction has no impact on specimen quality and diagnostic yield and is associated with excessive bloodiness [32,33]. The wet suction EUS-FNA technique is a new modality for sampling shown to be superior to the standard EUS-FNA technique with suction in terms of specimen quality and diagnostic yield. However, more studies are needed to validate these results [33].
Using the needle stylet does not seem to impact EUS-FNA sample quality and overall accuracy and is in fact associated with more bloodiness and increased procedure time and

risk of accidental needle stick injuries [32].
The diagnostic yield of EUS-FNA with rapid on-site cytopathologist evaluation (ROSE) exceeds 90% [32,33]. For EUS-core biopsy ROSE has no significant impact on the overall accuracy [33].

All parts of lymph nodes should be sampled (centre and edge) and at least 3 needle passes should be performed. Suction should be used for EUS-FNA of solid masses but not for EUS-FNA of lymph nodes. The routine use of a stylet during EUS-FNA is not mandatory. ROSE should be considered for EUS-FNA in centers in which specimen adequacy rates are below 90% [32,33].

4. Complications

Complications of EUS-FNA in the mediastinum (excluding cystic leions) are very uncommon and are similar to those in other locations of EUS-FNA. Reported complications include infection, hemorrhage, pharyngeal perforation, fistula and mediastinitis. Complication rate depend greatly on the type of the lesion to be sampled, as they are extremely rare in solid lesions (0,5%) comparing to cystic lesions (14%) [34]. Needle tract seeding is extremely rare [6].

The indication of EUS-FNA in mediastinal cysts should be carefully evaluated and if EUS-FNA is performed, prophylactic antibiotics should be administered [6].

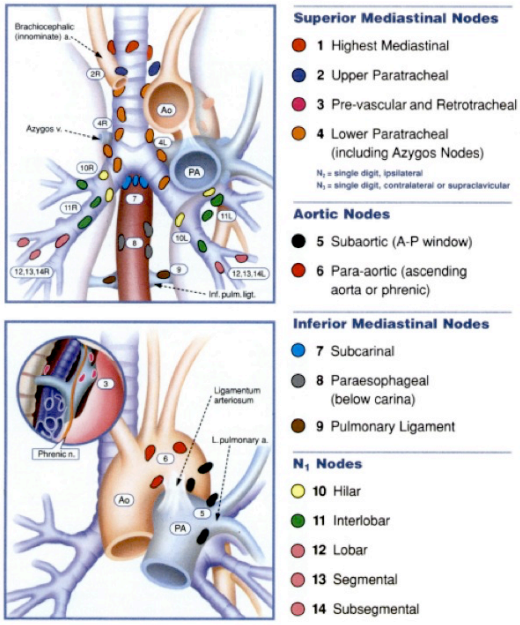

Figure 1. Mediastinal lymph node stations classification.

EUS-FNA can access stations 2, 4, 5, 7, 8, and 9 (2, 4R and 5 access is variable). EBUS-FNA can access stations 1, 2, 4, 7, 10, 11, and 12. *Ao, aorta; PA, pulmonary artery.*
Reprinted from Mountain and Dresler [2], with permission.

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II. DIAGNOSTIC EUS-FNA

B. Punctures of subepithelial lesions

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INTRODUCTION

Subepithelial lesions (SL) of the gastrointestinal (GI) are frequently encountered (gastric SL are found in about 0.36% of upper gastrointestinal endoscopies) and most often appear as asymptomatic protuberances in the GI tract with normal overlying mucosa. They represent an important source of referral for endosonographic evaluation and still remain a diagnostic challenge.

Some of these lesions can be benign and require no additional evaluation or intervention, whereas others can be premalignant or malignant requiring medical or surgical interventions (**Table 1**).

Imaging of SL using endoscopic ultrasound (EUS) has become a primary modality and can be helpful in narrowing the differential diagnosis, however, in many cases definitive diagnosis typically requires tissue acquisition. In fact, EUS shows typical findings for lipoma, duplication cyst and pancreatic rest, but in the majority of hypoechoic lesions, such as leiomyomas, gastrointestinal stromal tumors (GISTs) and schwannomas, EUS findings are not enough for definite diagnosis.

Table 1. **Subepithelial lesios of GI tract.**

Benign	Potentially malignant or Malignant
leiomyoma, schwannoma	gastrointestinal stromal tumor
lipoma, pancreatic rest	lymphoma
fibrovascular polyp,	carcinoid
lymphangioma, duplication cyst	glomus tumor
fibroma, neurofiboma, osteochondroma	granular cells tumor
hemangiomas, varices	metastasis

EUS findings can diagnose malignant SL with a sensitivity of only 64% and a specificity of 80%. Some EUS findings indicate increased risk of malignancy: tumors with more than 3 or 4 cm in size and irregular borders are the most important features. Other findings such as echogenic foci, cystic spaces, ulcerated mucosa, and lymph nodes with malignant pattern are not completely decided yet. Gastric tumors larger than 3cm, with irregular borders, mucosal ulceration, and non-

oval shape on EUS suggest high risk GISTs.
The current role of imaging studies for predicting malignant potential is being considered of less importance, so we should accept that all GISTs have certain malignant potential.
When there is a need to obtain a sample of the mass for diagnosis, many methods for acquiring tissue exist including EUS-guided fine needle aspiration (FNA), trucut biopsy (TCB), and fine needle biopsy (FNB).

MANAGEMENT OF SUBEPITHELIAL LESIONS

Management of SL depends on the etiology, location, size, symptoms and patients' characteristics such as age, comorbidities and need and frequency of follow-up examinations:
1) Asymptomatic benign lesions do not require follow-up or intervention. Such include most pancreas rests, leiomyomas, schwannomas, lipomas, duplication cysts, hemangiomas and inflammatory fibroid polyps;
2) Lesions with malignant or invasive risk should be resected or undergo endoscopic or EUS surveillance. These include carcinoids, granular cell tumors, lymphomas, glomus tumours and GISTs.
Endoscopic resection is indicated for all carcinoids of less than 1 cm in size as well as most type 1 and type 2 gastric carcinoids. Most granular cell tumors may be resected endoscopically, as can small GISTs arising from the 3rd layer (submucosa or muscularis mucosa).
Controversy exists as to the management of small incidentally found GISTs, especially gastric lesions less than 2 cm in size. These tumors appear to have a low risk of malignant behavior and may be considered for EUS surveillance. Factors to be considered in selecting patients for surveillance include patient's age, comorbidities and life expectancy. Although the optimal timing and number of surveillance examinations and duration are unknown, a study reported that 70% would survey annually. Any significant change in size or echo appearance should prompt its resection.
Nevertheless, guidelines on EUS surveillance of non-resected SL are still required.

TISSUE SAMPLING OF SUBEPITHELIAL LESIONS – WHEN IS IT INDICATED?

In the recent technical guidelines published in 2012 by the European Society of Gastrointestinal Endoscopy (ESGE), it is stated that:
There are some cases that EUS-guided sampling is not likely to impact management, so it **is not indicated** in patients with the followings: 1) plan of surgery for SL related symptoms, 2) typical echo features of a lipoma, and 3) small (<2 cm) SL of the esophagus and the stomach.

EUS-guided sampling **is indicated** in the following situations: 1) SL with a presumptive diagnosis of unresectable GIST for which treatment with tyrosine kinase inhibitors is contemplated, 2) patient with previous history of malignancy with a SL that may be consistent with a metastasis, 3) suspected diagnosis of lymphoma, neuroendocrine tumor or extrinsic tumor based on EUS, biological or clinical criteria.
The clinical benefit of EUS-guided sampling in patients with hypoechoic esophageal or gastric SL>2 cm is usually limited and should not be overstated.
For duodenal and colorectal SMTs, there are not sufficient data to suggest any recommendation.
When the decision is made to perform EUS-

guided FNA, obtaining adequate tissue is important for cytologic and histologic exams including immunohistochemical (IHC) stains, thus a great deal of effort has been made to increase tissue acquisition in order to improve diagnostic yield in SL.

Pathologists have long preferred as much tissue as possible since the diagnosis typically requires immunohistochemical staining for increased diagnostic yield.

Several technical factors must be considered.

TYPE AND SIZE of NEEDLES

EUS-FNA needles

EUS-FNA needles are commonly used to obtain tissue from suspicious lesions identified on EUS imaging. IHC staining of various cell proteins can be performed on FNA samples if a sufficient quantity of cells is obtained to provide additional diagnostic information; however, critical architecture remains absent and a major drawback to FNA as a sole diagnostic procedure. In this settings, the average diagnostic accuracy rate of EUS-FNA is 60% to 80%.

The currently available needle sizes for FNA are 19, 22 and 25 gauge needles. There are many factors to be considered when deciding which size needle to choose for FNA, such as the type of lesion, the location of the lesion and the degree of angulation en route to the target. A 19 gauge needle with its larger bore has the ability to obtain a larger sample size. Whether this leads to a higher diagnostic yield and better cellularity is controversial as the specimen may also be more blood dilute. In addition, the mechanical factors of a larger needle such as its stiffness may make it more difficult to maneuver into an area of the GI tract that is sharply angulated.

The standard 22 gauge needle is the one most commonly employed in published series. A recent meta-analysis and systematic review found that although there was a paucity of randomized controlled trials comparing needle sizes, there was a slight trend of the available data favoring the smaller 25 gauge needle, by causing less trauma and having as good if not slightly better yield due to less blood dilution of the specimen. However, there was no significant difference in accuracy, complication rates, or number of needle passes. In order to allow for a more detailed comparison between needle sizes, larger series prospective randomized trials are needed.

Although the standard cytologic sample obtained by EUS-guided FNA of SL has a high sensitivity and specificity, there are certain lesions in which obtaining a histologic rather than cytologic is desirable. In fact, in large or well-differentiated tumors and when conventional FNA needles fail to obtain a diagnosis, a core histopathology sample may be useful in establishing a definitive diagnosis.

EUS-TCB needles

To overcome the limitations of FNA, a 19-gauge Trucut core biopsy needle (QuickCore; Wilson-Cook Inc., Winston-Salem, NC, USA) has been proposed. This needle provides a core of tissue that can not only be used for individual cell morphology, but can be histologically examined for architectural change. However, the use of this needle is cumbersome in areas of the GI tract such as the antrum, fundus and duodenum. In areas where there is a high degree of endoscope angulation there is a

higher rate of technical failure and the use of this needle beyond the duodenal apex is not recommended. In practice, the diagnostic yield of EUS-TCB is modest relative to other techniques. Furthermore, although it had been hoped that EUS-TCB of GIST would allow determination of the mitotic index, in practice, the specimen is rarely large enough to supply 50 high-powered fields.

Combining EUS-FNA and EUS-TCB

EUS-FNA and EUS-TCB have limitation in diagnostic accuracy. Combining these two methods can increase the overall diagnostic accuracy up to 95% (76% for EUS-FNA only and 76% for EUS-TCB only) even without an immediate on-site cytopathologist. This finding is hard to apply in practice, however, due to more needle passes and higher costs of EUS-FNA and EUS-TCB. Instead, one method might be used as a rescue strategy when another one is failing

EUS-FNB needles

Due to limitations of the Trucut needle, a new histological needle with a core trap, a 19-gauge EUS-FNB device (ProCore; Cook Endoscopy, Winston-Salem, NC, USA), has been developed. This needle is uniquely designed to obtain both cytology and histology using reverse bevel technology, aiming for diagnosis on decreased number of passes. Core tissue samples can often be obtained using the ProCore needle making it possible to perform histology as well as IHC staining to help characterize SL. In a recent European study, the diagnostic accuracy was greater than 90% using this new 19-gauge EUS-FNB needle. The ProCore needle is now available in 19, 22 and 25 gauge sizes and a new 20 gauge is being introduced. The smaller caliber core biopsy needle may provide an advantage in terms of maneuverability and allow for a higher success when obtaining a sample from areas of the more angulated portions of the GI tract.
Further studies are needed to validate this approach in subepithelial lesions.

USE OF A STYLET and ASPIRATION

The use of the stylet has not been shown to increase the diagnostic yield or improve the quality of the cytology sample that is obtained. The use of suction during aspiration is also controversial. One common technique is to slowly withdraw the stylet during the FNA providing a capillary aspiration suction or microsuction. Many authors favor this technique as it appears to provide a good tissue specimen while minimizing blood dilution.

FANNING TECHNIQUE

If the center of the mass is more necrotic than the periphery, sampling multiple areas within it may increase the diagnostic yield during each individual pass, which may in turn lead to fewer overall passes in order to obtain a diagnosis. Nevertheless, more studies are needed to validate this strategy in SL.

NEEDLE PASSES AND ON-SITE CYTOPATHOLOGY EVALUATION

Some studies were performed to determine how many passes are needed for accurate diagnosis. In an European study, the accuracy of EUS-FNA increased gradually with each

consequent pass to reach a plateau after the 4th pass. In a Japanese study, sample adequacy was 83% with 2.5±0.7 passes, which was significantly better for lesions greater than 2 cm.

Having the cytopathology in the room can then allow the endosonographer to perform additional FNA passes or adjust their FNA technique in order to increase the likelihood of obtaining a diagnostic sample. However studies evaluating the efficacy of on-site cytopathology in the case of subepithelial lesions are limited and further studies are needed before its use in the standard practice of EUS-guided FNA can be recommended.

IMMUNOHISOCHEMICAL STAINS

Important differential diagnoses of the GISTs include epithelial neoplasms or malignant lymphomas. Differential diagnosis of GISTs with other mesenchymal tumors, such as leiomyomas, leiomyosarcomas, or schwannomas, is not possible on routine cytologic examinations, but adding immunocytochemical staining for C-KIT and/or CD34 is helpful for correct diagnosis. About 95% of GISTs have a positive reaction for C-KIT on immunohistochemistry, and 78% to 88% have mutations of the ***c-kit*** gene. Molecular analysis for ***c-kit*** mutation can be done on cell block materials from EUS-FNA. Ki67 (MIB-1) is a marker of proliferation and can be assessed in resected GISTs and EUS-guided FNA specimens but its ability to predict GIST behavior remains unclear and in need of further study. cKIT negative GISTs may be diagnosed through mutational analyses of c-kit and PDGFRA genes or staining for DOG-1.

ALTERNATIVES TO EUS TISSUE SAMPLING

1) Although rarely diagnostic, it is reasonable to perform biopsies of the mucosa overlying the subepithelial lesions. Stacked biopsies can be attempted; however, the yield remains low. **Bite on bite** technique using conventional sized forceps ranging from two to eight bites had a 38% diagnostic rate (54% in the esophagus, 28% in the stomach and duodenum) in a recent study.

2) endoscopic submucosal resection (ESMR) has adapted the techniques used for endoscopic mucosal resection to the removal of submucosal tumors (3rd layer). This technique has the advantage of simultaneously providing a definitive diagnosis and therapy of smaller lesions (up to 20 mm in size) with the main complications being bleeding (4-13%) and perforation (up to 5%).

3) endoscopic submucosal dissection (ESD) is an advanced therapeutic technique that has registered a crescent use in SL, especially the ones in the 4th layer. The main risk of perforation, which has been reported to be as high as 28%, so it should be reserved for very experienced and trained endoscopy centers.

COMPLICATIONS OF EUS-GUIDED FNA

The overall rate of EUS FNA-specific **morbidity** is low, estimated to be 0-2%.Complications after FNA of SLs are very rare and mostly consist of post-procedural abdominal pain. Infection following FNA is also rare and seen mainly when FNA is used to aspirate fluid from a cystic lesion. Antibiotic prophylaxis is now recommended as part of routine practice in cases when FNA of cystic lesions are performed. Neverthless, in

the particular case of mediastinal localization, it is recommended to avoid FNA if the cyst has typical EUS appearance of duplication or bronchogenic cyst. This is due to several reported case of infection from the FNA of duplication cysts in the mediastinum despite the use of prophylactic antibiotics

There have been no reports of **cancer seeding** after EUS-FNA for malignant subepithelial tumors, but peritoneal seeding can be developed if FNA needle penetrates the whole gastric wall and reach the peritoneal side.

• • •

HIGHLIGHTS

- Subepithelial lesions in the GI tract are frequently encountered endoscopic findings and encompass a heterogeneous group of lesions that range from benign to malignant.
- EUS is highly useful in their evaluation and tissue sampling when needed via EUS-guidance has become the standard first-line sampling modality.
- Management of these lesions depends on many factors. EUS characteristics of these lesions can help deciding whether or not tissue sampling is needed.
- A variety of factors such as the size and type of needle, whether or not to use a stylet or suction, use of the fanning technique or biopsy needles may affect the efficiency of sample acquisition as well as the diagnostic yield.
- Cytological evaluation of the specimen should include immunohistochemical stains to differentiate GIST (cKIT, CD117, DOG1) from leiomyomas (actin, desmin), schwannomas (S100) or other lesions.
- EUS-guided tissue acquisition, either by FNA, TCB or FNB, is a safe procedure with low complication rates.
- There is still controversy regarding the optimal strategy for EUS guided tissue acquisition, so larger prospective studies are needed.

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II. DIAGNOSTIC EUS-FNA

C. Punctures of solid pancreatic lesions

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Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) was first described in 1992 by Vilmann et al and since then it has been widely used as a valuable tool for obtaining histological diagnosis in several intramural and extramural gastrointestinal lesions including the pancreas.

Multiple published studies assessed the accuracy of EUS-FNA for the diagnosis of solid pancreatic masses; an adequate cytological specimen can be obtained in 82-91% of cases, with a diagnostic sensitivity for malignancy ranging from 64 to 96%. A recent meta-analysis evaluated 41 studies with a total of 4766 patients who have been submitted to EUS-FNA for pancreatic lesions reported an accuracy of 86,8% and a specificity of 95,8% (Puli 2013). In this analysis it was found that the accuracy of EUS-FNA improves over time since in a subgroup analysis, EUS-FNA accuracy was higher during 2001 to 2009 than between 1995 and 2000. This was confirmed by another systematic review including studies from the past 10 years which reported a pooled sensitivity and specificity rates of 92 and 96% (Chen 2012).
When compared to percutaneous CT-guided biopsy and endoscopic retrograde cholangiopancreatography (ERCP) brush citology, EUS-FNA is more sensitive and less invasive. The sensitivity of ERCP brush citology is quite low ranging from 30% to 85% (Athanassiadou, 2008). When compared to CT-guided biopsy, EUS-FNA has an increased sensitivity as reported in comparative studies and has a significant lower risk of peritoneal seeding, which has been shown in retrospective studies to be as high as 16,3% for CT-guided biopsy compared with a 2,2% risk for EUS-FNA (DeWitt 2007).

New diagnostic modalities namely elastography, the use of contrast agents and molecular studies such as microRNA and fluorescent ***in situ*** hybridization (FISH) can improve the accuracy of EUS-FNA in the diagnosis of solid pancreatic lesions. Elastography measures tissue stiffness which can differentiate benign from malignant tissue; the strain ratio which measures the relative stiffness of the lesion has been shown to have a sensitivity and specificity of 100% and 92,9% in the diagnosis of malignant pancreatic lesions (Iglesias-Garcia 2010). By using intravenous contrast lesion microvascularization is enhanced which may improve the diagnosis of

malignant lesions (Fusaroli, 2010).

Molecular imaging involves the use of special techniques such as FISH and micro-RNAs. FISH can detect several chromosomal abnormalities such as polisomy and trisomy which have been shown to be independent predictors of malignancy.

The use of microRNAs may also improve the accuracy of EUS-FNA in the diagnosis of pancreatic cancer; in one study recently published the sensitivity was increased from 78,8% with citology alone to 90,8% when combined with microRNA analysis. New studies definitely will assess the importance of these new technologies in the diagnosis of malignant pancreatic lesions.

EUS-FNA sampling:

Techniques and accessories

Positioning and technique

The endoscope should be in a stable position with a straight tip which allows an easy passage of the FNA needle. This position is more often achieved with a transesophageal ou transgastric position as opposed to the transduodenal route in which the tip of the endoscope is usually flexed making needle passage more difficult; in this instance a smaller gauge needle can be used (25 G) or the access should be obtained with the endoscope in a long position. Pancreatic neoplastic lesions are usually heterogeneous and in such cases cellular yeld can improve if the lesion is targeted in multiple areas. By using the dials and the elevator one can sample multiple areas of the lesion rather than on singular angle successively sampling several tracts of tissue and limiting the amount of blood and artifacts from previous tracts. This so-called “fanning-technique” was demonstrated to improve first pass diagnostic rates by 30%.

Type of needle. Onsite cytopathologist. Preparation of samples

There are a variety of needles which can be used and the choice should be made by each endoscopist according to their experience in order to optimize cellular yield, minimize complications and specimen contamination, as well as the need for needle flexibility mainly when a transduodenal route is used which may demand for a more pliable needle due to the flexed tip of the echoendoscope. There are three needle G (19, 22 and 25G) available for EUS-FNA. Although one prospective study (Sakamoto 2009 showed a clear benefit of the 25 G over the 22 G with diagnostic accuracies of 100% vs 33%, other posterior randomized-controlled trials (Camellini 2011, Fabbri 2011) found no statistically significant differences in diagnostic accuracy, although there was a trend towards significance in pancreatic head/uncinate tumors when using the 25G needle (Camellini 2011, Fabri 2011). A recent meta-analysis showed a slight benefit for 25 G needles when compared to 22G in terms of specimen adequacy; however this was not associated with significant diagnostic accuracy or fewer complications (Affolter 2013).

One of the drawbacks of EUS-FNA is the small amount of tissue obtained with the available needles. A 19G tru-cut needle is available but the diagnostic accuracy obtained was not impressive and the difficulty in its use in the head of the pancreas and the risks and complications described have limited

its use. With the recent pro-core needles by Cook Endoscopy a small core biopsy can be obtained but one randomized controlled study comparing 22G EUS-FNA with 22G pro-core needles for pancreatic lesions failed to demonstrate a significant difference both in diagnostic yield/adequacy, technical success and complications.

The use of suction on the FNA needle was considered to be the standard since it was thought that it could increase cellular yield; however it usually decreases the quality of the specimen due to the increased amount of blood which was shown in two randomized clinical trials (Wallace, 2001; Kundu 2009); recently a slow pull technique was shown to increase the diagnostic yield when compared to suction particularly when 25G needles are used (Nakai 2014). There is still no consensus on this matter but most of the authors advise to use suction in lesions where the cellular yield is low such as fibrotic lesions in chronic pancreatitis; on the other hand in softer lesions which may contain necrosis and blood, the use of suction is not advisable in order to minimize the distortion of the cellular sample.

The presence of a cytopathologist during the procedure is recommended by most authors since it was proved that a significantly lower number of needle passes is needed as well as a significantly lower number of inadequate samples are obtained. According to some studies a lower number of complications was also associated with the presence of an on-site cytopathologist. Furthermore the cost- benefit of onsite cytopathology was estimated to be over $400,00 annually for a single institution.

Specimens obtained by EUS-FNA can be either dried on air and stained with Diff-Quick or fixed in an alcohol solution and stained with hematoxilin-eosin or Papanicolau. A liquid medium (Thin prep) can also be used in order to obtain a cell block which can be used for several immunochemistry stains.

Complications

EUS guided FNA has a high diagnostic accuracy but a low incidence of complications such as pancreatitis, bleeding and perforation has been reported. However their severity has not been classified and risk factors for those events are not entirely clear. In a retrospective study from one institution an incidence of post-procedure complications was found in 3.4% of 327 procedures including mild to moderate pancreatitis, mild abdominal pain and mild bleeding. Univariate analysis found that adverse events were significantly increased in patients with tumors < 20 mm in diameter, those with neuroendocrine tumors and in patients in which normal pancreas had to be punctured to assess the lesion; multivariate analysis identified as risk factors tumors < 20 mm in diameter and neuroendocrine tumors (Katanuma et al 2013).

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II. DIAGNOSTIC EUS-FNA

D. Punctures of cystic pancreatic lesions

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If a cystic lesion is detected incidentally- and they are increasingly being recognized by imaging studies (19,9% by MRI vs 1.2-2.6 % by CT scan) – there is the need to establish the diagnosis, to decide on either the need for intervention, or to follow-up the lesion.

CLASSIFICATION OF PANCREATIC CYSTS		
No or Very Low Malignant Potential	**Malignant Potential**	**Malignant**
Pseudocyst	Intraductal papillary mucinous neoplasm	Pancreatic ductal adenocarcinoma
Lymphoepithelial cyst	Mucinous cystis neoplasm	Neuroendocrine tumos
Retention cyst		Solid pseudopapillary neoplasm
Congenital		Pancreatoblastoma
Lymphangioma		Acinar cystadenocarcinoma
Serous cystadenoma		

When is EUS recommended?

Sensitivity of EUS with or without citology, CEA and amylase, was superior at 76% compared with 48% for CT and MRI.

Despite not everyone with incidental pancreatic cyst needs EUS-EUS/FNA the 2012 international Consensus guidelines recommendations suggests EUS for patients who present with pancreatitis, or with the following “worrisome features” on imaging: cyst size > 3 cm; thick enhancing cyst wall; non enhancing nodule; main pancreatic duct 5-9 mm; abrupt change in MPD caliber with distal pancreatic atrophy and lymphadenopathy.

The primary rationale for EUS in these cases is to confirm the presence of a nodule, or main duct involvement, and eventually to obtain an aspirate to diagnose cytological atypia.

If any of these is confirmed then resection is indicated.

The potential power of EUS relies on the ability to safely perform EUS-FNA of pancreatic cysts to obtain cyst fluid for analysis.

When is EUS-FNA recommended?

From a practical point of view, it should be emphasized that when the imaging features of the cystic lesion are virtually diagnostic, FNA can be omitted, and the lesion should then be managed appropriately. FNA should also be omitted when the cystic lesion is symptomatic, because in this case, resection is clearly indicated. FNA should probably be entertained only when its results may change the therapeutic plan, e.g., when high-quality, cross-sectional imaging reveals non-diagnostic findings or when the clinical and morphologic characters of the cystic lesion have changed during follow-up.

Another potential indication for FNA is when a non–operative approach is considered for a presumed serous cystadenoma (SCA) not diagnosed confidentially on cross–sectional imaging. In this case, if the results of FNA analysis of the cystic fluid are compatible with a mucinous cystic neoplasm (MCN), the conservative approach should be reevaluated.

EUS-FNA: How do we do it ? and what to analyse?

Precautions

Antibiotherapy before and for 3 to 5 days after.
Observe guidelines for antiplatelets and anticoagulants.

How?

Size of the cystic lesion must be at least 1,5 cm.
No specific type or size of needle is prescribed; the choice is determined by the size of the cyst, its location, and the presence of vessels around the cyst.

The needle is introduced to the center of the cystic lesion.

The stylet is then removed and vacuum is then applied.

Cyst fluid is aspirated until the lesion is completely emptied in a single pass with the goal of completely collapsing the cyst.

Doing cyst wall cytology, which involves the simple technique of passing the needle back and forth, through the collapsed cyst wall following fluid aspiration, increases diagnostic yield by 29%.

What to analyse?

On the aspirated content we should verify:

// Viscosity

Aspirated fluid of SCAs is typically thin, clear and without mucin, but on occasion may be bloody. In contrast, the aspirated fluid in mucinous neoplasms is thick, viscid, and of a mucinous nature; the mucinous nature of the fluid can often be appreciated grossly.

Evaluate string sign: a long string sign, is highly predictive of a mucinous lesion.

// Cytology

Cytology is one of the most accurate methods of cyst diagnosis, however, cyst fluid aspirate is acellular or with minimal cellularity in up to 72% of aspirated cysts, so the low cellularity is a major limitation of FNA cytology for the differentiation between the different types of PCNs.

Brushing the cyst wall during FNA increases the diagnostic yield of EUS-guided FNA by 29%.

Glicogen rich cuboidal cells without cellular

atypia are highly specific to SCA.
Tall columnar that stain for mucin are specific for MCN.
Also cytology may diagnose malignant cystic lesions (e.g., cystadenocarcinoma) by demonstrating malignant cells or cells with high-grade atypia (dysplasia) in the aspirated cystic fluid.
Intraductal papillary mucinous neoplasms (IPMNs) have papillary clusters lined by columnar mucin-containing cells, usually with some degree of atypia.
FNA of pseudocysts yields a "dirty" material with macrophages and other inflamammatory cells, proteinaceous precipitates, and calcified debris.

Laboratory test

// Tumor markers

The quantification of various tumor marker concentrations in pancreatic cyst fluid has been shown to differentiate mucinous from non mucinous cyst.
Intracystic CEA level of > 192 ng/ml could predict the presence of mucinous cysts with a diagnosis accuracy of 79% which was superior to either EUS morfology alone (51%) or citology (59%), when CEA levels were > 800ng/ml the specificity for diferenciating mucinous cysts was 98%.
By contrast a CEA level < 6 ng/ml has been shown to be highly specific for serous/ non mucinous cysts.
Hence, we can only conclusively determine the nature of the cyst when the intracystic fluid CEA is < 6 ng/ ml or > 800ng/ml.

// Amylase

Amylase in cyst fluid can be used to identify communication with the PD.
Cystic fluid amylase is usefull in the differentiation of pseudocysts from cystic neoplasms.
Cysts with amylase < 250 IU/L were SCA, MCN or MCAC (sensitivity 44%, specificity, 98%, accuracy 65%).
An amylase level of < 250 U/L essentially excludes pseudocysts.

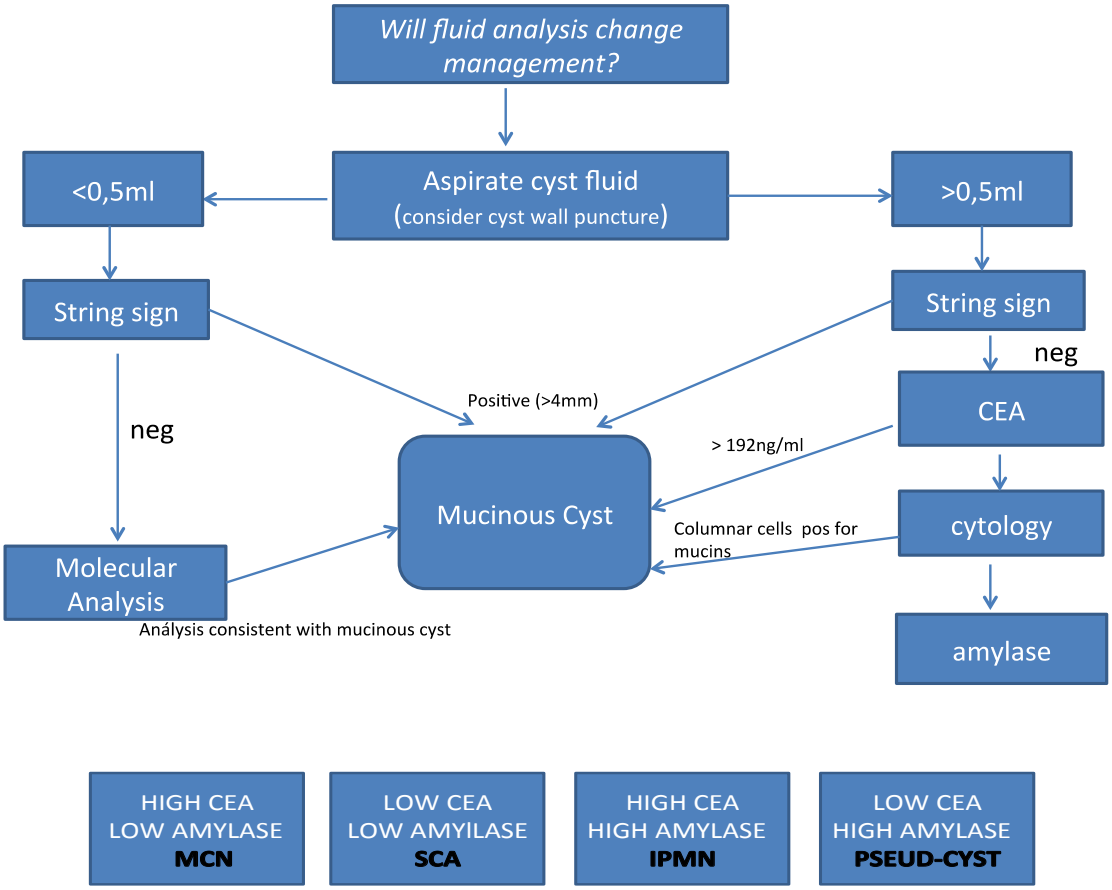
// Genetic Markers

The presence of K-ras mutation is highly specific (96%) but has a low sensitivity (45%) for MCNs. (Requires further confirmation in prospective trial).
DNA quantity > 40 ng/ ul has 90% specificity for MCN.
GNAS mutations are prevalent in IPMNs especially in the intestinal form and in invasive IPMN.
Micro(mi)RNAs: Four miRNA panels accurately differentiated SCAs from MCN and IPMN as well as MCN from branch duct-IPMN (BD-IPMN) with 85-100% sensitivity and 100% specificity.
A logistic regression model using nine miRNA allowed prediction of high-grade IPMNs, pancreatic neuroendocrine tumors and solid pseudopapilary neoplasms versus low-grade IPMNs and SCA with a sensitivity of 89%, and a specificity of 100% .

// Metabolomics

Two metabolites (glucose and kynunerine) in fluid from 45 resected cysts were significantly lower in mucinous compared with nonmucinous cysts.
Those novel biomarkers require large-scale validation in EUS-FNA cyst fluid.

Algotithm / EUS-FNA



Gastrointest Endoscopy Clin N Am 22 (2012); 169-185

Endoscopic innovations

Direct endoscopic visualization

Needle confocal endomicroscopy produces real time microscopic images of the cyst wall using a mini probe advanced through a 19G needle into a cyst .

Endomicroscopy was 59% sensitive and 100% specific for mucinous cysts

Brush cytology

The value of cyst wall brushing of pancreatic cystic lesions in addition to FNA appears to be modest.

A randomised controlled trial comparing the yield for EUS-guided FNA only with FNA and cyst wall brushing is warranted.

Treatment strategy

Surgery remains the mainstay treatment for pancreatic cystic neoplasms, either to relieve symptoms in nonmucinous benign lesions, or to prevent or eliminate malignant neoplasms.

Early resection of premalignant lesions is associated with survival benefit.

For example, the prognosis of a resected benign IPMN is excelent with a 10-year survival rate of > 95%.

This survival rate drops dramatically to 60% or lower when invasive IPMN-carcinoma is resected.

Surgery is recommended in patients with cystic lesions in association with obstructive jaundice, all surgically fit patients with main-duct-IPMN or MCN and BD-IPMN patients with high-risk stigmata such as an enhanced solid component (Mural Nodule) or when FNA obtains cytology suspicious or positive for malignancy.

Currently BD-IPMN without high-risk stigmata is usually monitored closely without immediate surgery.

SCA is rarely associated with malignancy. Surgery is not indicated unless SCA causes mechanical complications due to a large size (usually > 4 cm) or it shows a significant growth tendency of > 2-10 mm/year.

Other possible treatment approaches

Cyst ablation

In very selected patients, and with all the caution, cystic ablation can be discussed as an alternative to surgery, namely:

1) A 2-5 cm benign uni/oligo-loculated MCN or BD-IPMN (without high-risk stigmata) located in the head or body of the pancreas.
2) A 2-5 cm benign uni/oligo-loculated MCN or BD-IPMN (without high-risk stigmata) located in the tail of the pâncreas in a patient unfit for surgery.
3) MCN or IPMN with high-risk stigmata in a patient who refuses surgery.
4) Macrocystic benign SCA with tendency to develop mechanical complications.

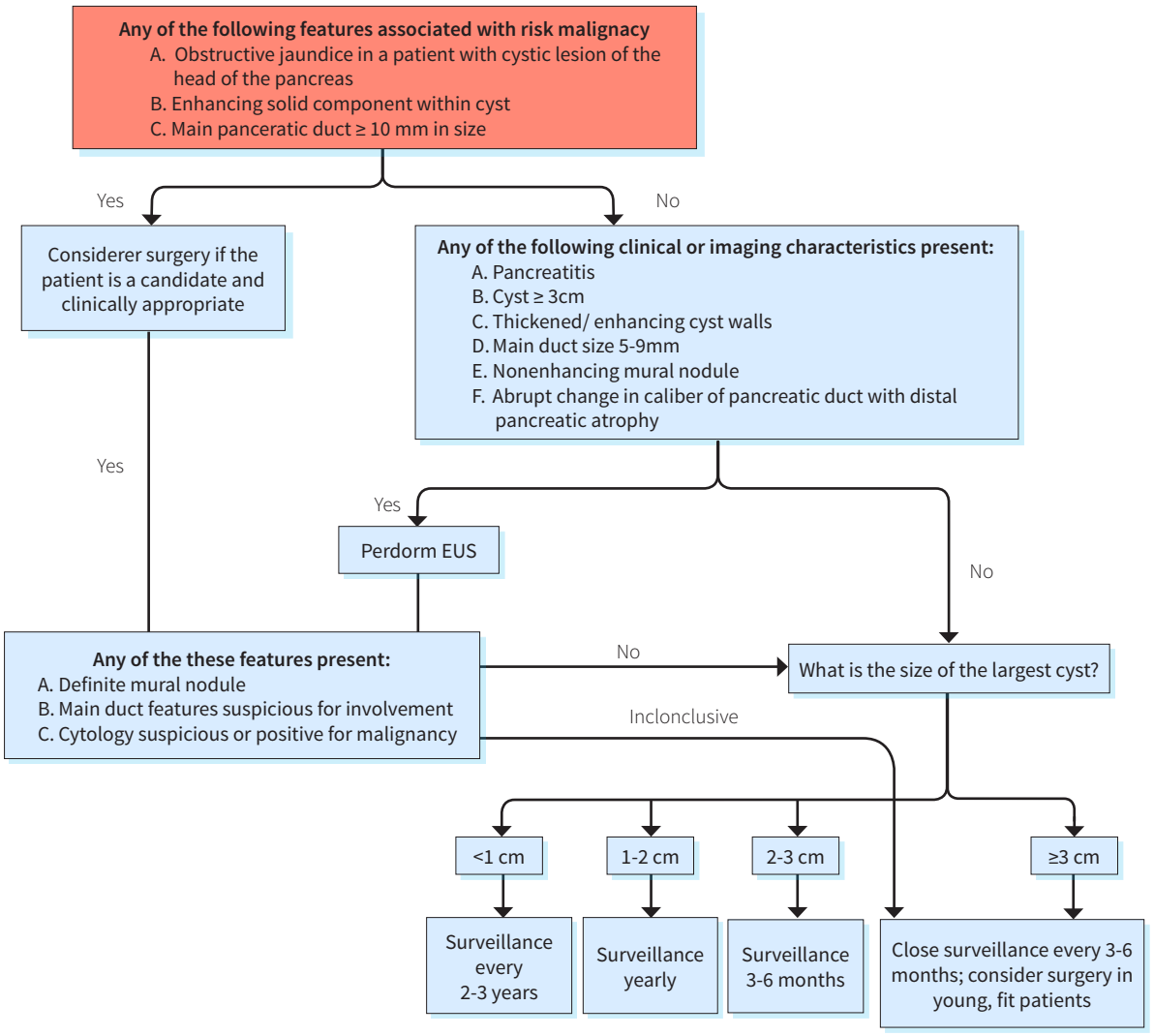
The decision to proceed to cystic ablation RELIES ON A PRECISE DIAGNOSIS.

Follow-Up

After a decision of not to treat surgically or by ablation most of the cysts needs follow-up, unless diagnosed definitively with a non-neoplastic cyst.

Invasive carcinoma is uncommon in patients with an asymptomatic cyst of 1 cm. Thus follow up without further investigation is generally acceptable.

ALGORITHMS FOR MANAGEMENT



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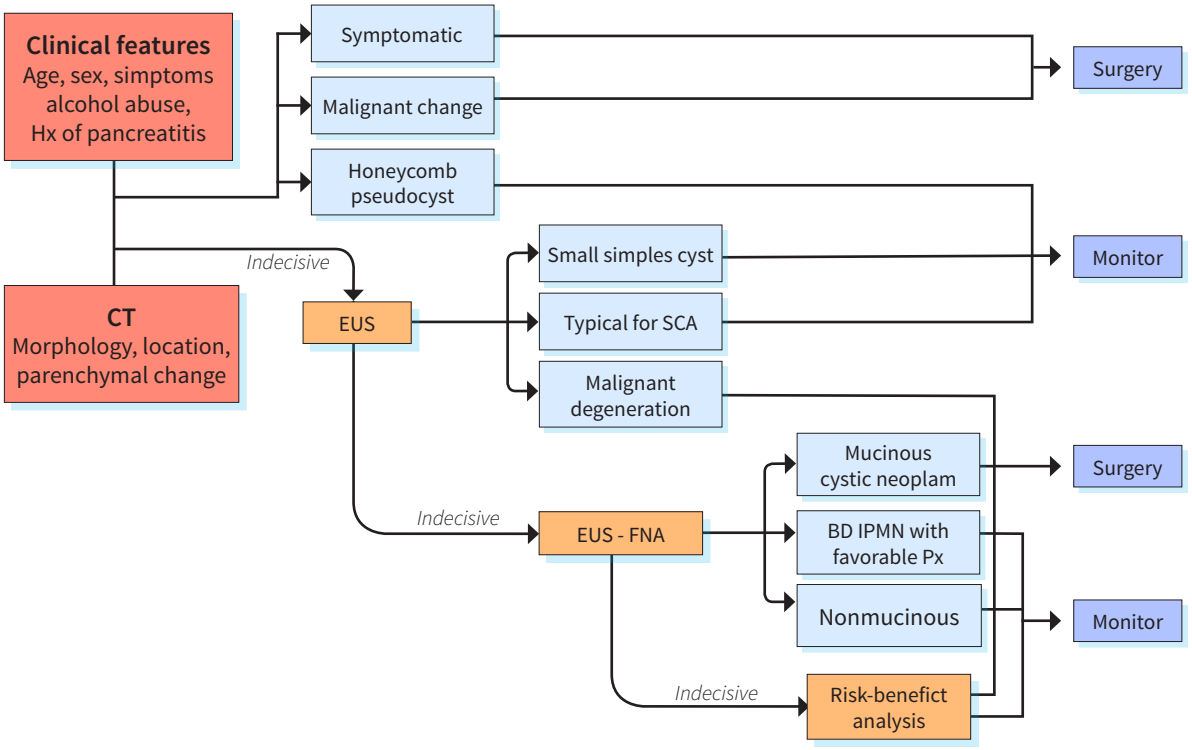

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III. THERAPEUTIC EUS-FNA

A. Drainage of pancreatic pseudocysts & peripancreatic collections

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HIGHLIGHTS

- Pancreatic Fluid Collections (PFC) may develop in the context of acute or chronic pancreatitis, surgery, trauma or neoplasia
- EUS-guided drainage is the preferred method for PFC treatment
- Requirements for EUS-drainage: well-defined mature wall of the collection; accessibility by endoscopy (distance from the gut wall < 1cm); coagulopathy (if present) correction; prophylactic antibiotics
- Equipment needed for the procedure include a therapeutic linear echoendoscope with a 3.7-3.8 mm working channel, a 19 G FNA needle, 8.5-10Fr cystotome, balloon dilator, 0.035" guidewire, stents (plastic or metallic), +/- nasocystic catheter.
- Technical success rate ranging from 94-100%, with clinical success rate over 90%
- Indications for pseudocyst drainage: symptoms, infection, obstruction of gastric outlet or biliary system, and disconnected pancreatic duct syndrome
- Acute PFC usually do not require drainage
- Size is no longer an indication for pseudocyst drainage
- Indications for Walled-off necrosis (WON) drainage: infection
- Sterile WON may be drained if refractory abdominal pain, clinical or radiologic evidence of gastric outlet, biliary or intestinal obstruction, and new onset or persistent organ failure.

Discussion

The revised Atlanta Classification of Acute Pancreatitis provided more objective terms to describe the local complications of acute pancreatitis, in order to allow a consistent terminology across all studies. **Pancreatic pseudocyst (PP)** is defined as an encapsulated collection of fluid with a well defined inflammatory/ fibrosous wall usually outside the pancreas with minimal or no necrosis. This entity usually occurs more than 4 weeks after onset of interstitial oedematous pancreatitis. An **acute necrotic collection (ANC)** is a collection containing variable amounts of both fluid and necrosis associated with necrotising pancreatitis with no definable wall encapsulating the collection. By contrast, **Walled-off necrosis (WON)** is defined as a mature, encapsulated collection of pancreatic and/or peri-pancreatic necrosis that has developed a well defined inflammatory wall and usually occurs >4 weeks after onset of necrotising pancreatitis.

Technical Considerations

EUS allows drainage of PP that do not cause luminal compression, located around the stomach and duodenum, and has the possibility of distinguishing a PP from a cystic neoplasm or a necrotic collection. The technical success rate is greater than 90%, and the complication rate is less than 5%. The drainage is one-step procedure, requiring fluoroscopic guidance and expertise in therapeutic maneuvers. After assessing the ideal place to puncture de collection under EUS guidance (avoiding interposed vessels, and choosing the best apposed site), a 19-G FNA needle is usually used to gain access. Contrast is injected under fluoroscopic guidance, to confirm position, and a 0.035" guidewire is introduced through the needle, and coiled within the cavity. To dilate the transmural tract two approaches may be used: a noncautery or a cautery technique. In the noncautery technique, a ERCP cannula or a Schoendra biliary dilator is used over the guide-wire, followed by a biliary balloon dilator. In the cautery technique, the transmural tract is dilated using a needle-knife catheter or cystotome. One alternative approach to puncture the cavity is to use a cystotome, that contains an integrated needle-knife inner catheter that can be used instead of the 19-G needle. The metal part of the inner catheter is withdrawn, and the guidewire is passed into the cavity. Then the outer sheath is advanced through the puncture site using cautery, after which is removed and the wire is left inside the cavity. When using the cystotome, 2 guidewires may be inserted simultaneously, allowing sequential stent placement without loosing access to the cavity and the need to recannulate. Independent of the technique used to create the fistulous tract, a biliary balloon dilator of 6-15mm is used afterwards to dilate the tract and allow deployment of 2 or more double-pigtails stents (7-10 Fr) under fluoroscopic control. Alternative, fully covered metal stents, specifically designed for drainage purpose, have been developed (AXIOS, Xlumena and NAGI, Taewoong-Medical Co). Both these stents are lumen apposing stents, developed to diminish the risk of migration. Their major advantage is a larger drainage orifice, particularly useful in the context of WON, and the possibility of repeated entry into the cavity for necrosectomy. In this case

scenario a nasocystic catheter is left in place to irrigation and drainage until sepsis resolution. Conventional endoscopic accessories (snares, baskets) can be used to carefully extract the necrotic material (debridement) into the stomach or duodenum. Usually, many repeated endoscopic sessions are necessary to mobilize the necrotic tissue completely.

Recently, the so-called multiple transluminal gateway technique has been reported by Varadarajulu for treatment of walled-off necrosis. This method requires the EUS-guided creation of two or more transmural tracts between the necrotic cavity and the gastrointestinal lumen. While one tract is used to flush saline solution via a nasocystic catheter, multiple stents are deployed in the other tracts to facilitate drainage of necrotic contents. This method was superior compared to the conventional single tract technique and might avoid the need for endoscopic debridement.

Technical and Clinical Outcomes

When considering technical success, EUS drainage of PFC is effective in more than 90% of cases. In terms of clinical outcomes, the EUS-guided drainage of PP achieves a success rate of more than 90%. By comparison, the success rate of drainage alone of WON is very low, but can be substantially improved if endoscopic necrosectomy is performed (75-90%). In a recent meta analysis from 14 studies, more than 80% of patients with WON could be successfully treated by endoscopic necrosectomy alone.

Complications

The major complications of these procedures are bleeding and perforation. EUS-guided drainage has the lower complication rate (1,5%) compared to surgical (28-34%), percutaneous (18%) and non—EUS guided drainage (15%). In terms of mortality, there are no deaths reported. In order to avoid or minimize complications, only collections with a mature wall and within 1 cm of the gastric/duonenal wall should be punctured. Coagulopathy should be corrected before the procedure and antiplatelets agents should be stopped. In order to prevent infection of a sterile collection, prophylactic antibiotics should be given to every patients urdergoing drainage. Minor complications are stent migrations and infection. When necrosectomy is the issue, the complication rate may be as high as 36%, with a mortality of 6%. Bleeding is the main complication (18%), and may be severe because often large vessels transverse the necrotic cavity. Air embolism as also been reported but may be avoided using carbon dioxide insufflation.

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III. THERAPEUTIC EUS-FNA

B. Drainage of bilio-pancreatic ducts

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I. INTRODUCTION

Endoscopic ultrasound (EUS) was developed as a diagnostic modality but rapidly gained a role for a variety of therapeutic applications. The continued need to develop less invasive alternatives to surgical and radiological interventions has driven the development of EUS-guided interventions. These include EUS-guided biliary drainage (EUS-BD) and EUS-guided pancreatic duct drainage (EUS-PD).

Although EUS-guided interventions have become increasingly popular it is of outmost importance to keep in mind that the level of evidence is still limited to small series/case reports and scarce prospective randomized trials. There is also no consensus among experts in the field regarding indications and optimal techniques.

Concerning ERCP, this is still the first line procedure for most biliary and pancreatic drainage cases. In a small subset of cases, due to altered anatomy, peri-ampullary pathology or malignant obstruction, other modalities, including EUS-guided interventions have an evolving role. Percutaneous biliary drainage or surgical intervention are alternatives but with considerable associated morbidity and mortality

II. BILIARY DRAINAGE

Three different EUS-guided BD approaches have been described:

a) Direct access with transluminal drainage (Choledocoduodenostomy, EUS-CDS, Hepaticogastrostomy, EUS-HGS); b) Rendezvous technique (RV); c) Antegrade approach (AG).

Direct access

EUS-HGS usually involves access through segment III (left liver lobe). The bulb is the usual window for EUS-CDS. Both procedures show similar technical and clinical success rate. Controversy remains regarding which is the safest route. Although early reports described decrease risk for

bile leak associated with EUS-HGS, extrahepatic biliary access may be safer, namely if ascites is present, since the CBD lies in the retroperitoneal space. Major complications are infection, bile leakage, bleeding, perforation and stent migration. Technical success rate is between 87-94% and the complication rate between 19-27%. There is a trend to use covered SEMS.

Rendezvous technique

If there is an endoscopically accessible ampulla this should probably be the first goal for a EUS-BD procedure. The intra-hepatic access is easier for antegrade purpose but implies biliary tree dilation and the long distance to the ampulla translates in lack of wire support/ability to steer. One station that should be considered although not frequently noted is the gastric lesser curve which could allow access to the extra-hepatic biliary tree. The extra-hepatic route usually uses the duodenum in a short unstable position to avoid the retrograde orientation from the bulb. This position also implies available "room" in the distal biliary tree which may not exist for instance in large pancreatic head cancer. The overall success rate is around 81%, with a longer procedure time and the complication rate is 10%. Thus, although a more laborious technique, it's safer.

Antegrade approach

This procedure results from placing a biliary stent with EUS-guided access from the gastric wall, in an antegrade fashion. Overall success rate is 77% with a complication rate of 5%. A word of note: If an antegrade stent is place into a trans or supra-papillary position one should understand that is case of stent occlusion, re-intervention is extremely difficult if not impossible.

Considering all forms of biliary drainage, these procedures have been described in just above 1000 patients. Although it's still early to draw final conclusions it appears that for the current knowledge, clinical success rate is similar to PTC but with less complications and cost. Based on historical data regarding surgical bilio-pancreatic drainage, this option is associated with higher complication rates.

III. PANCREATIC DRAINAGE

EUS-PD has been reported in less than 300 patients and is usually indicated after failed ERCP in patients with benign conditions such as ductal stones, strictures or post-surgical stenosis. Again, the current main indication are stenosis of pancreatico-jejunal or pancreatico-gastric anastomosis after a Whipple resection.

EUS-PD is technically more demanding than EUS-BD which translates in an overall technical success rate of 78%. Major drawbacks result from inability to place de instrument along the MPD axis, inability to dilate (fibrosis) or inability for endotherapy secondary from the acute access angulation. The rendezvous technique, if feasible, is usually attempted first since is associated with

less complications. If failure, stenting requires dilation and placement of plastic stent (covered or uncovered metallic stents are associated with adverse outcomes). One should keep in mind that, as for the helpful role of a EUS-guided cholangiography as a roadmap, EUS-guided pancreatography, with or without methylene blue, may assist ERCP-guided pancreatic endotherapy. The most important complications are pancreatitis (4%), leakage (3%), bleeding (3%), and perforation (3%). In the long term follow-up stent dysfunction is estimated to occur in over 50% of patients.

IV. CONCLUSIONS

EUS-BD / EUS-PD are technically feasible and relatively safe in the hands of experienced interventional endoscopists skilled in both therapeutic endoscopy and EUS. This technique offers a potential alternative to surgery in patients in whom conventional ERCP is unsuccessful or not possible. However, the risk of complications is not negligible and mortality has been described. Rendezvous procedures, biliary or pancreatic, have the lowest complication rates and if feasible should be the first option.

Currently, this procedure should be reserved for tertiary centers with highly skilled endoscopists using a multidisciplinary approach (i.e., bilio-pancreatic surgeons and interventional radiologists must be available if needed). Of note, the nurse role is also critical because these are long procedures with several medical devices used in different endoscopic techniques and with long wires not infrequently in unstable positions. Except for very specific clinical scenarios like symptomatic stenosis of a pancreatico-jejunal anastomosis, where EUS-guided therapy may be considered the first option, other clinical scenarios have different methods available that should be discuss with the patient. It is of uttermost importance that the centers implementing these procedures carefully monitor the results in order to either implement them in clinical practice or abandon them.

In conclusion, after two decades from the first case reports, EUS-BD / EUS-PD interventions still need well-design RCTs to assess which is the best method, defining the standard technique, safety and clinical benefits. New single step devices and better wire support/steering are also very welcome and external validation will allow us to know whether these procedures can really expand outside referral centers. In this field, ***primum non nocere*** is an ethical must.

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