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EDITORIAL

Potential role of new technological innovations in nonvariceal hemorrhage

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Abstract

The present armamentarium of endoscopic hemostatic therapy for non-variceal upper gastrointestinal hemorrhage includes injection, electrocautery and clips. There are newer endoscopic options such as hemostatic sprays, endoscopic suturing and modifications of current options including coagulation forceps and over-the-scope clips. Peptic hemorrhage is the most prevalent type of nonvariceal upper gastrointestinal hemorrhage and traditional endoscopic interventions have demonstrated significant hemostasis success. However, the hemostatic success rate is less for other entities such as Dieulafoy's lesions and bleeding from malignant lesions. Novel innovations such as endoscopic submucosal dissection and peroral endoscopic myotomy has spawned a need for dependable hemostasis. Gastric antral vascular ectasias are associated with chronic gastrointestinal bleeding and usually treated by standard argon plasma coagulation (APC), but newer modalities such as radiofrequency ablation, banding, cryotherapy and hybrid APC have been utilized as well. We will opine on whether the newer hemostatic modalities have generated success when traditional modalities fail and should any of these modalities be routinely available in the endoscopic toolbox.

Key words: NoN-variceal upper gastrointestinal hemorrhage; Endoscopic hemostasis; Gastric antral vascular ectasias; Over-the-scope clips; Endoscopic suturing

Core tip: New devices are available for hemostasis of non-variceal upper gastrointestinal hemorrhage that may supplement or supplant traditional modalities. These devices however have a varying track record in hemostasis with different learning curves, costs and detriments.

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INTRODUCTION

Non-variceal upper gastrointestinal hemorrhage is prevalent and associated with significant morbidity and mortality. The most common cause of non-variceal upper gastrointestinal hemorrhage (NVUGIH) is peptic hemorrhage but there is a broad range of other pathologies including Dieulafoy lesions, Mallory-Weiss tears, malignant lesions, vascular ectasias and iatrogenic causes. Prompt endoscopy for diagnosis and potential hemostasis usually results in a favorable outcome. However, refractory or recurrent bleeding can occur with standard medical management and possible endoscopic intervention in up to 13% of patients, often necessitating other interventions such as interventional radiology or surgery[1]. Novel endoscopic interventions such as endoscopic submucosal dissection (ESD) and peroral endoscopic myotomy (POEM) have a particular penchant to potentially have a wide area for bleeding and impingement of adjacent vascular structures[2]. Gastric antral vascular ectasias (GAVE) can result in chronic and occasionally acute gastrointestinal blood loss and this entity is readily treated by argon plasma coagulation (APC) but newer modalities have also demonstrated efficacy[3]. We will discuss the experience to date with these new interventions and discuss whether they should be routinely available.

BACKGROUND

The over-the-scope clip (OTSC) (Ovesco Endoscopy, Tubingin Ger) has demonstrated efficacy in closing perforations and hemostasis[4]. This clip has proved itself capable in achieving hemostasis (> 90%) both as rescue and first line therapy for peptic and Dieulafoy's lesions[5,6]. It is particularly useful for lesions with a large visible, fibrotic base and bleeding sites not easily treated by devices passed through the accessory channel[7]. Validating series have included Dieulafoy's and Mallory-Weiss lesions but most are peptic lesions[5,6,8]. Though multiple clip placement has been described, good endoscopic visualization and precise placement of the clip is paramount as these clips are very difficult to remove. There is limited hemostatic experience for another OTSC-the Padlock Clip (Aponos Medical Kingston, NH)[9]. Overall, the experience of OTSC's for NVUGIH has been impressive (Figure 1).

A recent multicenter series of 10 patients with refractory peptic hemorrhage were all successfully treated with the Apollo endoscopic suturing system (Apollo Endosurgery Austin Tx) and no rebleeding was noted[10]. This device has been useful in mini-mizing chronic blood loss from marginal and anastomosis ulcers[11]. Endoscopic suturing after endoscopic mucosal resection and ESD is an attractive option, but studies to date have not specifically addressed hemostasis[12].

Hemospray (Cook Medical, Winston-Salem, NC) is a nonabsorbable powder that becomes adhesive and cohesive when hydrated. Unlike cautery and clips, it does not treat the underlying bleeding lesion. Sixty-three patients compiled from a registry with NVUGIH (half ulcer-related) were treated with Hemospray[13]. Fifty-five were only treated with Hemospray and 8 were treated as a salvage intervention when traditional therapy failed. The monotherapy group had 85% primary hemostasis with 15% rebleed at 7 d. The salvage therapy group had 100% primary hemostasis and 25% rebleed at 7 d[13]. This and other work supported use in NVUGIH including peptic lesions, Mallory-Weiss tears and anastomosis ulcers. A small randomized comparison study of NVUGIH demonstrated therapeutic equivalency between clips and Hemospray when each was combined with epinephrine[14]. The topical hemostasis niche is likely to become crowded as several new products are being evaluated[15].

The literature contains a plethora of miscellaneous interventions reflecting the innovative vision of endoscopists. Endoscopic banding for ulcers has largely been abandoned but occasionally banding can be used for other lesions such as a Dieulafoy's[16]. Detachable snares in concert with clips have been used for NVUGIH[17]. Metal stents have been used for esophageal NVUGIH and post-sphincterotomy bleeding[18,19]. Some centers tout the usefulness of EUS-guided therapy and vascular (doppler) probes to assess arteries[20,21].

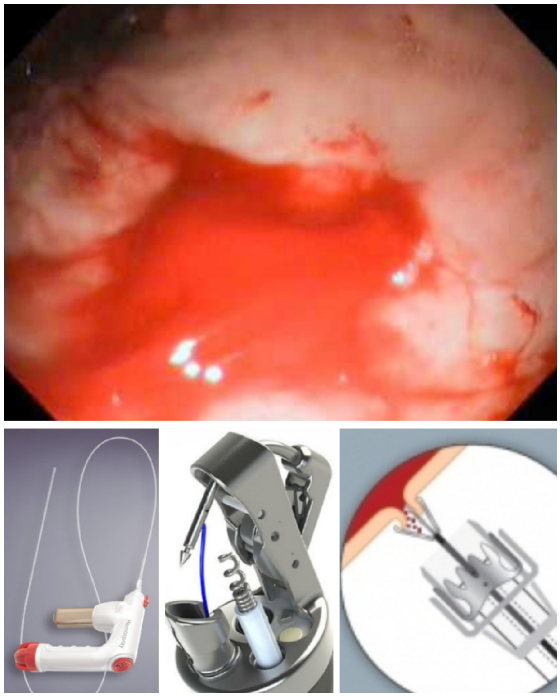

Figure 1 Three new modalities for gastrointestinal hemorrhage. Hemospray/Suturing Device/over-the-scope clip.

Most operators performing ESD and potentially extraluminal procedures such as POEM desire a monopolar device with precise clasping and coaptive ability such as the Coagrasper (Olympus Endoscopy, Center Valley Pa)[22]. ESD defects are often not practically closed by clips and Hemospray, suturing and fibrin glue have been employed though none is standard. Polyglycolic shields adhered by fibrin glue have been proposed as method to minimize post-ESD bleeding but results regarding this are mixed[23,24].

Endoscopic banding appears comparable to APC-the current standard- in treating GAVE[25]. It may be di-fficult to band after APC due to fibrosis however. Radiofrequency ablation (RFA) has also been well validated for GAVE hemostasis[26]. Cryotherapy and hybrid APC had been evaluated[27,28]. Multiple other modalities have also been utilized for GAVE (Table 1).

CONCLUSION

The decision of which of the newer modalities to have available for endoscopic hemostasis depends on track record of hemostatic success, respective ease-of-use (largely related to prior experience and/or training), cross- utilization and cost. The OTSC's fare quite well with these criteria in that the Ovesco clip has been well validated as a hemostatic instrument, only moderately challenging to use even with limited experience, utilized in high-volume units for perforation/fistula closure and relatively inexpensive. Hemospray also fares well in that it has a limited but positive record regarding hemostasis, and is exceptionally easy to use. It is moderately expensive and has no cross-utilization however. The Apollo suturing device is not expensive, but has a moderately steep learning curve and its use for ulcer hemostasis would likely be infrequent. RFA has a moderate record in GAVE treatment and easy to use but it is expensive and should only be available if it is also used for Barrett's ablation. Endoscopic banding is cheap and variceal experience can be extrapolated to NVUGIH hemostasis. However, it has a sparse record in hemostasis. Experienced ESD operators will likely have a monopolar device which would be compatible with their cautery unit. The issue of tissue shields after ESD is intriguing, but it will likely be years before a formal recommendation could be made.

Table 1 Novel modalities for non-variceal upper gastrointestinal hemorrhage

	Over-the-scope clips	Hemospray	Endoscopic suturing
Hemostatic efficacy	Very good	Moderate	Good
Ease of use	Good	Very Good	Fair
Cross utilization	Good	Poor	Very good
Cost	Moderate	High	Moderate

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REVIEW

Endoscopic ultrasound-guided sampling of solid pancreatic masses: the fine needle aspiration or fine needle biopsy dilemma. Is the best needle yet to come?

Clara Benedetta Conti, Fabrizio Cereatti, Roberto Grassia

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Abstract

Fine needle aspiration (FNA) is currently the standard of care for sampling pancreatic solid masses by using endoscopic ultrasound (EUS). The accuracy of the technique is reported to be high, especially if coupled with the rapid on site evaluation (ROSE), and it has a high safety profile. However, FNA presents some limitations, such as the small amount of tissue that can be collected and the inability of obtaining a core tissue with intact histological architecture, which is relevant to perform immunohistochemical analysis, molecular profiling and, therefore, targeted therapies. Moreover, the presence of the ROSE by an expert cytopathologist is very important to maximize the diagnostic yield of FNA technique; however, it is not widely available, especially in small centers. Hence, the introduction of EUS fine needle biopsy (FNB) with a new generation of needles, which show a high safety profile too and a satisfying diagnostic accuracy even in the absence of ROSE, could be the key to overcome the limitations of FNA. However, FNB has not yet shown diagnostic superiority over FNA. Considering all the technical aspects of FNA and FNB, the different types of needle currently available, comparisons in term of diagnostic yield, and the different techniques of sampling, a tailored approach should be used in order to determine the needle that is most appropriate for the different specific scenarios.

Key words: Fine needle aspiration; Fine needle biopsy; Endoscopic ultrasound; Needle performance; Diagnostic yield; Diagnostic accuracy; Pancreatic sampling

Core tip: Endoscopic ultrasound guided fine needle aspiration (FNA) is the gold standard for sampling solid pancreatic masses, but the small amount of tissue collected and the need of on site evaluation to maximize the diagnostic yield are some disadvantages. New

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fine needle biopsy (FNB) needles, with high safety profile and satisfying diagnostic accuracy even in absence of on site evaluation, could overcome FNA limitations. However, FNB has not yet shown a clear diagnostic superiority. Thus, in order to choose the better needle for a given scenario, it is important to know the technical aspects of FNA and FNB, the different sampling techniques, the types of needle available, and their diagnostic performance.

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INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer related fatalities in Western countries[1,2]. Ductal adenocarcinoma (ADK) is considered the main cause of pancreatic mass, but many other neoplasms and benign conditions can be detected in the pancreas. Distinguishing different types of pancreatic masses is an important clinical challenge because the pathological diagnostic confirmation is highly relevant for establishing the best treatment. Endoscopic ultrasound (EUS) guided-fine needle aspiration (EUS-FNA) is currently the standard of care for sampling pancreatic masses, with a diagnostic accuracy ranging in literature from 77% to 95%[3,4].

EUS-FNA is a safe technique, with related morbidity and mortality rates < 1% and complications such as pain (0.38%), bleeding (0.10%), and pancreatitis (0.4%; n = 8246)[5]. There were some concerns about the risk of seeding, but peritoneal carcinomatosis may occur more frequently in patients undergoing percutaneous FNA than those who have EUS-FNA for the diagnosis of pancreatic cancer. The reported risk of seeding during pancreatic tissue acquisition is significantly lower during EUS-guided procedure compared with percutaneous sampling (2.2% *vs* 16.3%; $P < 0.025$)[6].

A recent study has indicated that EUS-FNA could be carried out without consequence on efficacy of surgery[7]. Again, the European Society for Medical Oncology guidelines recommended EUS-FNA, especially in doubtful cases. Percutaneous biopsy of the pancreas is contra-indicated in potentially resectable cases[8]. When performing EUS tissue acquisition, the operator should consider several variables that may influence the outcome to maximize the accuracy and reduce adverse events. These include correct EUS assessment of target lesion and type, size of needle, and most suitable sampling technique[9]. Of note, considering strict cytological criteria, EUS-FNA sensitivity has been reported to be as low as 77%, even in expert hands, due to inadequate samples and the presence of extensive necrosis or fibrosis[10,11].

Therefore, rapid on site evaluation (ROSE) by a cytopathologist, firstly described by Hikichi *et al*[12], has been proposed to improve EUS-FNA diagnostic accuracy by evaluating samples adequacy/cellularity and thus, theoretically, increasing the overall accuracy and reducing needle passes. Unfortunately, ROSE is not widely available, and its real impact on diagnostic accuracy is not well established[13].

Although EUS-FNA is usually adequate for the final diagnosis of pancreatic ADK, it is not able to obtain a core tissue with a preserved architecture, essential for a definite diagnosis of other pancreatic solid tumors and benign conditions[14]. Moreover, cytological samples do not allow immunohistochemistry, phenotyping, and genetic analysis, which are fundamental factors for risk stratification and tailored oncological management. To overcome the aforementioned shortcomings, fine needle biopsy (FNB) was developed in order to guarantee the acquisition of a core tissue, ideally providing a sample with preserved architecture for both histological, immunohistochemical, and genetic profiling.

The aim of this review is to provide an overview about the diagnostic yield of EUS-FNA and FNB for pancreatic masses, to analyze the technical features of the different needles and the different techniques in sampling (*e.g.*, stylet/no stylet; different aspiration methods, needle sizes) in order to provide a small practical guide with reference to the different possible scenarios where EUS guided sampling is performed.

LITERATURE SEARCH

An extensive bibliographic search in PubMed *via* MeSH was performed using the following key words and free terms: Pancreatic mass, pancreatic cancer, FNA, FNB, endoscopic ultrasound, EUS sampling, EUS needle, comparisons between FNA and FNB, FNB *versus* FNA, FNB *versus* FNB, FNA *versus* FNA needle, AND pancreatic masses. The reference lists from the selected studies were manually examined to identify further relevant reports. Non-English-language papers were excluded.

EUS-FNA ACCURACY: THE ROLE OF ROSE ON THE WAY TO FNB

One recent study of 985 patients with pancreatic masses[15] found that pre-operative EUS-FNA led to "significantly fewer benign lesions resected" compared with the group that underwent surgery without EUS ($P = 0.024$). Hence, if "tissue is the issue", the main purpose of EUS is to collect material for pathological evaluation. EUS-guided tissue acquisition of solid pancreatic lesions can be performed using two different methods: FNA and FNB.

Historically, FNA needles were developed only to obtain an adequately representative cellularity of the lesion. Therefore, EUS-FNA does not necessarily retain the stroma and requires the presence of an expert pathologist both for the preparation of the collected specimens and for their interpretation. The ROSE process, done during the procedure in the endoscopy suite, involves the processing of a tissue smear and the evaluation under a light microscope by a trained cytopathologist. An on-site cytopathologist is fundamental to confirm adequate tissue sampling, which increases the diagnostic accuracy, when compared to EUS-FNA performed without ROSE[16]. ROSE reduces the number of needle passes necessary to obtain an adequate specimen and increases the diagnostic capability of the endosonographer through immediate feedback during the procedure[17-18]. Early data from three meta-analyses demonstrated that ROSE was associated with a statistically significant ($P < 0.001$) improvement in the adequacy rate (average 10%, 95%confidence interval (CI): 5%-24 %)[16,19-20].

Hence, EUS-FNA with ROSE has been considered the reference standard for obtaining high diagnostic accuracy in the biopsy sampling of the pancreas[21]. However, the main limitation of this approach is represented by the cost related to the presence of a dedicated and skilled cytopathologist in the endoscopic room; and although EUS-FNA with ROSE reduces the number of passes necessary to obtain a suitable sample, it seems to increase the overall procedure time, both for the need of specimen processing and for the time requested for the interpretation[22].

However, high quality studies reported conflicting conclusions[23]. Two randomized clinical trials (RCTs) conducted in 2015[23,24] showed no significant difference in the diagnostic yield of malignancy, proportion of inadequate specimens, and accuracy in patients with pancreatic mass undergoing EUS-FNA with or without ROSE. FNA without ROSE was performed using a fixed number of needle passes, which was significantly higher compared to the number of passes needed in the group with on-site pathologist. No difference was reported in terms of complications related to the number of passes in RCTs and meta-analyses

Moreover, high-volume centers had adequacy rates > 90% of the sample without ROSE, suggesting that ROSE should be considered in centers where the specimen adequacy rate is < 90%[25,26]. A meta-analysis published in 2016 compared EUS-FNA with and without ROSE, including RCTs, with a total of 1299 patients[27]. No statistically significant difference was found between the EUS-FNA with or without ROSE in term of diagnostic yield of malignancy or proportion of patients with adequate specimens. The diagnostic sensitivity and specificity between the two groups were also comparable.

Since ROSE is a time-consuming service with poor reimbursement and is not available in many centers, it should not be strongly recommended to provide a ROSE service throughout all centers performing EUS for pancreatic lesions[28].

In order to theoretically overcome these limitations, a new-generation of needles has been developed. FNB-needles were specially designed to obtain a core specimen with preserved tissue architecture. The specimen fragments are not lost or consumed during cell block centrifugation or specimen sectioning, and histological architecture and tissue integrity can be retained in most of the specimens. The FNB needles are the ideal sampling method for solid masses, like subepithelial lesions of the gastrointestinal (GI) tract, lymph nodes, and pancreatic and non-pancreatic lesions (such as liver parenchyma) as FNB allows immunohistochemical testing relevant in

many diseases.

The FNB needles procure large volumes of tumor cells and desmoplastic stroma, providing better histological samples with a diagnostic yield exceeding 90%. This observation is important for low volume centers without ROSE or a dedicated cytopathologist because a cell block specimen can be interpreted by any GI pathologist without special expertise in cytopathology. Indeed, a recent systematic review and meta-analysis compared the diagnostic yield of FNA with FNB on solid GI lesions, lymph nodes, and pancreatic lesions, specifically evaluating the diagnostic value of ROSE while comparing the two types of needles[29]. Fifteen studies (n = 1024) were included in the analysis. No significant difference in diagnostic adequacy [Relative risk (RR): 0.98, CI: 0.91-1.06, I^2 = 51%] was observed. Although not statistically significant (P = 0.06), FNB without ROSE showed a relatively better diagnostic adequacy. For solid pancreatic lesions only, there was no difference in diagnostic adequacy (RR: 0.96, CI: 0.86-1.09, I^2 = 66%), but, in the absence of ROSE, FNB was associated with better diagnostic adequacy (P = 0.02). In terms of both diagnostic accuracy (RR: 0.99, CI: 0.95-1.03, I^2 = 27%) and optimal quality core histological sample procurement (RR: 0.97, CI: 0.89-1.05, I^2 = 9.6%), there were no significant differences. However, FNB established the diagnosis with fewer passes (Standardized mean difference: 0.93, CI: 0.45-1.42), I^2 = 84%). In the presence of ROSE, FNA required relatively fewer passes to establish the diagnosis than in its absence. The authors concluded that FNB without ROSE can replace EUS-FNA with ROSE without loss of diagnostic accuracy[29]. In case of pancreatic mass, when ROSE is unavailable, current European Society of Gastrointestinal Endoscopy guidelines suggest (low quality evidence, weak recommendation) performance of three to four needle passes with an FNA needle or two to three passes with an FNB needle[30].

EUS-FNB NEEDLES: EVOLUTION AND TYPES

The evolution of FNB needles started from a Menghini-type 18G core needle, adapted to a prototype 2.8 mm channel convex array echoendoscope[31]. The technical limitation of this needle was the poor penetration into the pancreatic tissue and a consequent poor diagnostic yield. However, that was the first description of EUS-FNB, and it set the stage for all future development.

The first original FNB needle (QuickCore® Biopsy Needle; Cook Medical) was a Tru-Cut needle (Medline Industries) that could be used with echoendoscopes and was introduced in the early 2000s. The Quick-Core was composed of a cannula, a tissue penetrating stylet that can be disposed within the cannula, and a handle mechanism to advance the cannula over the stylet to maintain the cannula capability to move smoothly over the stylet, even when the scope is bent.

However, technical issues included challenges in deploying the spring-loaded tray when the needle was pulled back, especially within the duodenum or in case of not having the specimen be retained. Additionally, a certain track length within the pancreas was needed in order to deploy safely the needle and avoid injury of the pancreatic duct, which can increase the risk of pancreatitis[32].

The currently available core biopsy needles can be mainly classified as non-cutting or cutting type, including side-type and the most recently introduced end-type (Figure 1).

The Echo Tip® HD ProCore™ (Wilson-Cook Medical Inc., Winston-Salem, NC, United States) needle was introduced in 2011. It is a cutting, end-side needle. It has two distinct cutting surfaces: the tip and a reverse bevel, just distal to the tip that promotes collection of a core sample during the retrograde movement of the needle within a lesion. The reverse bevel has a potential advantage of increasing tissue acquisition amount while preserving histological architecture. The EchoTipProCore is available in 19 (4.8 French sheath), 22, and 25 gauge (G) (5.2 French sheath). Early published results on the performance of ProCore needles demonstrate high diagnostic accuracy rates (86%-89%)[33-35]. In 2015, a 20 G FNB needle (8 French sheath) was developed to increase the diagnostic accuracy; it was designed to combine a large lumen and enhanced flexibility to facilitate tissue acquisition, even from an angulated endoscope position. According to the manufacturer's design specifications, this was achieved by coating the sheet of the needle with a smooth and flexible material (polytetra-fluoroethylene). Also, the cutting edges of the needle were changed from a reverse- to a forward-facing bevel, and from a Lancet to a Menghini tip design, in order to decrease resistance when traversing the tissue (Figure 2).

The SharkCore™ (Medtronic Inc., Sunnyvale, CA, United States) is a fork-tip FNB needle with six distal cutting surfaces in an asymmetric design, specifically designed to obtain cohesive units of tissue with intact cell architecture. By minimizing tissue

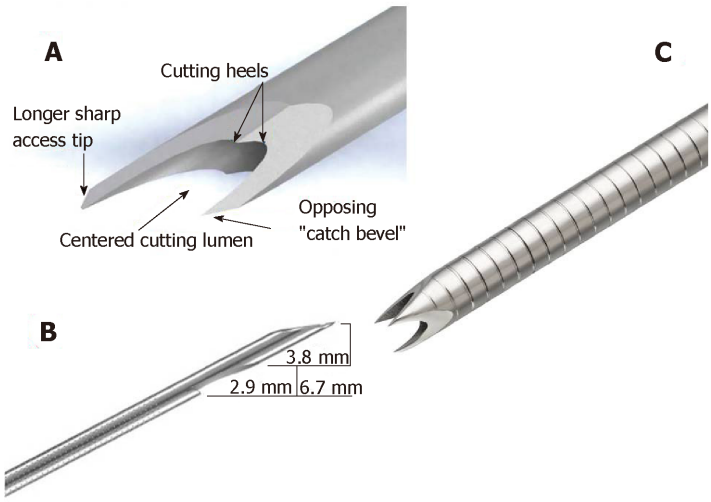

Figure 1 Fine needle biopsy needles types. A: Acquire (Boston Scientific, Marlborough, MA, United States) needle; B: SharkCore™ (Medtronic Inc., Sunnyvale, CA, United States) needle; C: ProCore™ (Wilson-Cook Medical Inc., Winston-Salem, NC, United States) needle.

stacking and fracturing, the needle can potentially provide better core samples. This needle is available in 19, 22, and 25 G (8 French sheath).

The SharkCore needle uses the Beacon™ EUS delivery system, which allows needle removal from the sheath, maintaining the position of the sheath in the endoscope and consequently its relation to the lesion. Theoretically, this system could allow the endoscopist to maintain the position or even to replace the needle with one of a different size.

A large and initial multicenter retrospective experience of EUS-guided fine needle biopsies obtained using the SharkCore FNB needle on different solid lesions (pancreas, subepithelial lesion, and lymph node) demonstrated an excellent 88% overall pathologic diagnostic yield with a median number of two passes only. Overall, histological diagnosability and thus pathologic yield for each lesion subtype were as follows: pancreatic lesions 86%, subepithelial lesions 87%, lymph nodes 93%. The needle size did not have an impact on pathologic diagnostic yield, as both 25 G needle and 22 G needle performed at a very high level, 86% and 89%, respectively[36].

The most recently introduced FNB-needle is the Acquire™ needle (Boston Scientific, Marlborough, MA, United States). This is a Franseen needle with a three-plane symmetric cutting surface. This structure of the electropolished tip improves control and stability of the needle and allows penetrating the tissue, minimizing sample tearing and fragmentation. Furthermore, the Acquire needle is made of cobalt-chromium, a material subject to less deformation than stainless steel alloys.

The Acquire core biopsy needle is available in 19 (5.2 French sheath; minimum working channel 2.8 mm), 22 (5 French sheath; minimum working channel 2.4 mm), and 25 G (4.8 French sheath; minimum working channel 2.4 mm).

A multicenter retrospective study of 200 patients undergoing EUS-FNB of solid lesions with Acquire needle showed a high rate of tissue adequacy and tissue core, with no adverse events. The tissue obtained by EUS-FNB was adequate for evaluation and diagnosis by ROSE in 98.5% of cases. In 90% of cases, a core of tissue was obtained[37].

TECHNIQUES IN SAMPLING

The use and type of suction

Emerging data suggest that needle aspiration techniques could have a direct effect on the yield of EUS-FNA or EUS-FNB.

Conventionally, when performing EUS-FNA, a negative pressure is applied using suction with a 10 or 20-mL syringe ("standard suction"). In the "high pressure suction", a negative pressure with a 50-mL syringe is applied during EUS-FNA. To avoid GI contamination of the sample, the stopcock of the syringe is usually closed before needle removal. However, a negative pressure persists in the syringe and can be neutralized by disconnecting the syringe stopcock from the needle port before

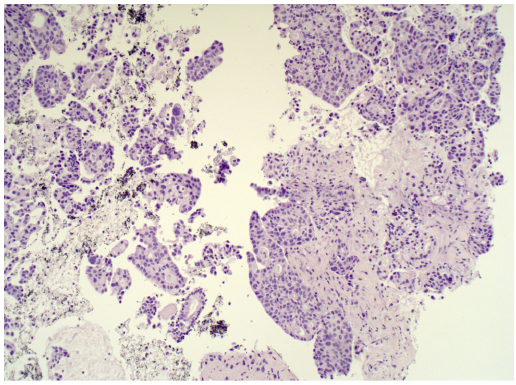

Figure 2 Fine needle biopsy sample of pancreatic adenocarcinoma, which clearly shows the preserved histological architecture of the malignant tissue (hematoxylin and eosin staining, 10 ×).

withdrawing the needle from the lesion.

In the "stylet slow-pull" technique, the stylet is slowly and continuously withdrawn as the needle moves to-and-from within the target lesion, creating minimal negative pressure (about 5% of the force generated with a standard suction technique). The suction and the no suction methods are similar in terms of diagnostic adequacy. However, the suction method applies a lot of pressure, causing more bleeding and more tissue damage, leading to reduced sample quality and an increase in the number of slides used, but it improves both the cellularity and the quality of the aspirate. The capillary action may improve specimen quality by reducing the amount of blood in the aspirated material.

Many trials compared the diagnostic yield of EUS-FNA samples obtained with slow-pull and with standard suction technique[38]. No differences in term of smear cellularity, diagnostic yield, and sufficient histological material obtained were found, but bleeding was significantly higher in the standard suction group ($P < 0.001$).

In the "wet suction" technique, the needle is preloaded with saline solution in order to replace the column of air with liquid, which is less compressible and transmits better to the needle tip the negative pressure applied to the proximal part of the needle. Therefore, the wet suction technique may be considered a modified standard suction technique. A blinded randomized trial by Attam *et al*[39] compared the wet technique with the dry technique. The results revealed that the wet technique yielded a significantly higher cellularity (1.82 *vs* 1.45; $P < 0.0003$) and a significantly better diagnostic yield (85.5% *vs* 75.2%; $P < 0.035$) compared to the dry technique.

The "hybrid technique" consists of preparing the needle as in the wet technique but applying the suction as the dry technique. It has the advantage of having a column of fluid in the needle that guarantees a continuous negative pressure with a 10 cc prevacuum syringe. This avoids the manual suction of the syringe, as performed in the wet technique, while sampling the lesion. A single-center underpowered pilot study compared wet, dry, and hybrid techniques. Considering diagnostic yield, there was no statistically significant difference between the three techniques (hybrid 100%, wet 92%, dry 90%)[39].

The role of the different aspiration techniques when performing FNB was assumed from previous studies on FNA needles. Lee *et al*[40] carried out a randomized trial enrolling patients ($n = 50$) with suspected pancreatic malignancy and undergoing EUS-FNB. A 22 G ProCore needle, used without ROSE, was randomized at the use of stylet slow-pull-back technique (group A), standard suction (group B), or non-suction after stylet removal (group C) method. The rate of good or excellent cellularity was highest in group A compared with groups B and C (72% *vs* 60% *vs* 50%; $P = 0.049$). A > 25% rate of blood contamination was prevalent in group B (30% *vs* 42% *vs* 10%; $P = 0.009$). The rate of adequate core-tissue acquisition was not different among the groups (52% *vs* 34% *vs* 50%; $P = 0.140$).

The use of stylet

The use of stylet theoretically reduces the sample contamination by the GI cells and clogging of the needle. It also allows an easier escape of the sample from the needle. Unfortunately, the use of the stylet extends the procedure time and reduces the needle flexibility, especially when the scope tip is bent (duodenal position) or if a large needle (19 G) is used.

A 2016 meta-analysis of these studies (five RCTs and two retrospective studies for a total of 5491 specimens) demonstrated no significant difference in the rate of sample

adequacy between the stylet group (2135/2504, 85.26 %) and no-stylet group (2609/2987, 87.35 %) (odds ratio: 0.94, 95%CI: 0.79-1.11, P = 0.45). Furthermore, the rate of cellularity > 50 % and the contamination rate and blood contamination rate were not significantly superior in the stylet group when compared with the no-stylet group[41].

FNA NEEDLES COMPARISON

22 G versus 25 G FNA-needles

Regarding the diagnostic performance (sample adequacy and quality) of FNA needles of different caliber, no significant differences between 22 G *versus* 25 G needles were found[42,43].

However, conflicting results can be derived from two recent meta-analyses, in terms of the diagnostic sensitivity, specificity, and safety of 22 G and 25 G FNA needles in sampling solid pancreatic lesions[44,45]. Facciorusso *et al*[44] included seven trials with a total of 732 lesions: 295 lesions were sampled with 22 G needle, 309 were sampled with 25 G needle, and 128 lesions with both needles. Regarding the pooled sensitivity, a non-significant superiority of 25 G needle over 22 G was found [RR: 0.93 (0.91-0.95) *vs* 0.89 (0.85-0.94) for 25 G and 22 G needle, respectively; P=0.13], and no difference was observed when considering specificity (P=0.85). No differences in safety and sample adequacy were found.

Xu *et al*[45], on the contrary, obtained a higher sensitivity for the 25 G needle in the diagnosis of solid pancreatic lesions. In detail, 11 prospective RCTs were analyzed, including 837 patients of which 412 were sampled with 22 G and 425 with 25 G FNA needle. The 25 G needle was superior in terms of sensitivity [92% (95%CI: 0.89-0.95)] compared to the 22-G needle [88% (95%CI: 0.84-0.91)] in sampling solid pancreatic masses (P = 0.046), whereas the specificity of the two needles were comparable. Importantly, the pooled positive and negative likelihood ratio for the 22 G needle were 12.61 (95%CI: 5.65-28.14) and 0.16 (95%CI: 0.12-0.21), respectively, whereas the pooled positive and negative likelihood ratio for the 25 G needle were 8.44 (95%CI: 3.87-18.42) and 0.13 (95%CI: 0.09-0.18), respectively, with area under the receiver operating curve of 0.97 for the 22 G needle and 0.96 for the 25 G needle.

Similarly, a meta-analysis in 2018 that included four RCTs, with a total of 462 patients (233 sampled by using 25 G needle and 229 by using 22 G needle) highlighted a slight not statistically significant superiority of 25 G needle over 22 G[46]. The diagnostic sensitivity was 93% and 91% for the 25 G and 22 G needle, respectively. The specificity was 87% and 83% for 25 G and 22 G needle, respectively. However, area under the receiver operating curve did not show any statistically significant difference between the two needles (P = 0.497).

Hence, no definitive recommendations over the use of one particular device can be made, as there was no strong superiority of one needle on the other. In addition, a RCT[47] comparing 22 G FNA needles with and without a side port did not find significant differences between them in terms of both diagnostic accuracy and sample adequacy.

19 G versus 22 G FNA needle

Some studies focused on the possibility of obtaining histological samples by using a large caliber needle, such as a 19 G FNA needle, which could preserve the architecture of the tissue. An RCT in 2010 compared the diagnostic accuracy of 19 G needle *versus* 22 G needle in a cohort of 117 patients with solid pancreatic/peripancreatic masses[48]. EUS-FNA was performed without ROSE. The accuracy of the samples obtained from the body/tail lesion was higher for the 19 G needle (95.0%) than the 22 G (76.7%) (P = 0.031), and the amount of cellular material obtained was significantly higher in the 19 G needle group (P = 0.033). However, the overall diagnostic accuracy was not significantly different (86.7% *vs* 78.9% for 19 G and 22 G, respectively; P = 0.268).

Moreover, using the 19 G needle could be difficult when sampling pancreatic masses with the scope in the duodenum because of its stiffness and caliber, which could affect the needle flexibility and its diagnostic yield. In a large multicenter prospective study from Attili *et al*[49], 246 patients with solid lesions (203 cases) or enlarged lymph nodes (43 cases) were examined. The procedure was technically feasible in 228 patients, with an overall procurement yield of 76.8%, which was very low. Considering malignant *versus* nonmalignant disease, the sensitivity, specificity, and positive/negative likelihood ratios were 70.7% [95%CI: 64.3-76.6, 100% (95%CI: 79.6-100), and 35.3 (95%CI: 2.3-549.8)/0.3 (95%CI: 0.2-0.4)], respectively, with a diagnostic accuracy of 73.6% (95%CI: 67.6-79.0).

FNA *VERSUS* FNB NEEDLES

The main outcomes considered in the studies that evaluated and compared the performance of FNA *versus* FNB needles were: safety, diagnostic accuracy, sample adequacy, sample quality, technical performance of the needle, and costs(Table 1). Importantly, no studies found a relevant difference in the safety between FNA and FNB. Therefore, the most important outcome considered in the comparison between the two methods was the diagnostic accuracy.

The technical aspects and the presence of ROSE, as already stressed, are important issues in the evaluation of the overall results when comparing FNA and FNB. Although the literature evidence did not support a strong superiority of FNB over FNA, most recent studies showed a trend in favor of FNB, especially without ROSE, in terms of specimen adequacy with fewer needle passes. A 2012 RCT compared 22 G FNA without suction (Expect; Boston Scientific, Natick, MA, United States) and 22 G FNB (Echotip ProCore; Cook Endoscopy, Bloomington, IN, United States) performance[4]. Both the procedures were performed with ROSE. This study examined a cohort of 28 FNA and 28 FNB procedures and found no significant difference in terms of median number of passes required to obtain a diagnosis, rate of diagnostic sufficiency reached, complication rates, and rate of obtaining histological core and its quality. The 22 G biopsy needle obtained a diagnostic cytological specimen in 89.3% of patients and histological specimen in 80% of patients; on-site cytological diagnosis was established with biopsy needle in nearly 90% of patients.

Accordingly, Alatawi *et al*[50] found a similar accuracy of 22 G FNA or 22 G Procore FNB needle in the diagnosis of malignancy, when biopsying pancreatic solid masses (sensitivity of 88.4% *vs* 97.8%, respectively, specificity of 100% for both methods). However, a lower number of passes was required with FNB needles *versus* FNA (two passes *vs* three passes). The use of FNB also improved the histopathological quality of the specimens, in term of slide cellularity and tissue microfragments. These results were obtained by the examination of 100 patients[50].

A large recent RCT conducted by Cheng *et al*[51] found EUS-FNB samples to be more accurate in diagnosing pancreatic masses than EUS-FNA samples. In detail, they examined 190 pts patients undergoing EUS-FNA (22 G EchoTip Ultra needles; Cook Medical) and 187 pts undergoing FNB (22G EchoTip ProCore needle; Cook Medical) for the sampling of solid masses: pancreatic (249 patients), abdominal (82 patients), and mediastinal (46 patients). For each procedure, four passes with the slow-pull technique were performed. ROSE was available in all cases. Diagnosis was accurate in 91.4% of cases for FNB, whereas it was 80% for FNA cases, based on the final patient diagnoses ($P = 0.0015$). In the subgroup of pancreatic masses, diagnosis with FNB was accurate in 92.7% of the cases, whereas it was 81.7% for FNA ($P = 0.0099$). Regarding the cytological analysis of the pancreatic masses, FNB samples accurately identified 88.6% of all pancreatic lesions, whereas FNA samples only accurately identified 79.4% ($P = 0.0046$).

No significant difference between FNA and FNB needle were found when comparing the performance of the technique without ROSE. An advantage in terms of passes needed to obtain a diagnosis was found with the 22 G FNB needle (Cook EchoTip ProCore) in comparison to 22 G FNA (Olympus, GF UCT 160) when using the suction method without ROSE[52]. This study found an overall diagnostic yield of 83.3% for both techniques (a total of 136 patients), with 1.11 passes *versus* 1.83 passes ($P < 0.05$) required when using FNA and FNB, respectively.

Data from a large meta-analysis including eight RCTs (921 cases) supported these results[53], as FNB gave higher specimen adequacy compared to FNA, despite the need of fewer needle passes.

A retrospective review of consecutive patients undergoing FNB sampling and FNA of the same single lesion with the same needle gauge and number of passes without ROSE and another retrospective cohort reviewed a total of 87 consecutive EUS-FNB specimens using either a 22 G Franseen needle (51 patients) or a 22 G FNA needle (36 patients) for sampling pancreatic diseases[54,55]. The diagnostic accuracy of the two methods was statistically comparable, but the median sample area was significantly larger in samples obtained from FNB than those obtained from FNA (4.07 *vs* 1.31 mm^2, $P < 0.0001$). ROSE was not available in this study. Furthermore, a recent systematic review and a meta-analysis already cited in the previous paragraph showed that FNB required fewer passes to establish the diagnosis than FNA sampling with ROSE[29].

In the studies conducted in centers where ROSE was not available, FNA and FNB seemed to perform similarly[54,55], but FNB allowed for obtaining larger samples with fewer needle passes. These observations open the possibility of using FNB instead of FNA when ROSE is not available, as it maintains the same diagnostic accuracy.

Most of the available studies that compared FNA and FNB investigated the

Table 1 Published comparative studies regarding fine needle aspiration *versus* fine needle biopsy needles performance in terms of diagnostic yields

Ref	Study design	N°Lesions,pancreatic	Rose	Needles (G),FNA *vs* FNB	Overall diagnostic yield	Sample adequacy	Comments
[4]	RCT	(56)	Yes	22 *vs* 22 Procore	Equivalent	Equivalent	
[29]	Meta-analysis (11 observational study and 4 RCTs)	1024 (mainly pancreatic and lymph nodes)	#6 NO #9 Yes	19 (only one study); 22 and 25 G *vs* 22	Equivalent	Equivalent	in the absence of ROSE, FNB was associated with better diagnostic adequacy (P = 0.02) and FNB required less passes
[50]	RCT	194 (100)	No	22 *vs* 22 Procore	84 *vs* 90	Equivalent	Lower n° of passes for FNB *vs* FNA needle (2 *vs* 3)
[51]	RCT	377 (249)	Yes	22 *vs* 22 Procore	Equivalent	81.7 *vs* 92.6	
[52]	RCT	(36)	No	22 *vs* 22 Procore	Equivalent	Equivalent	1.1 passes needed for FNB *vs* 1.83 passes for FNA (P < 0.05)
[53]	Meta-analysis (8 RCT)	921	No	22, 25, and 19 (only one study) G *vs* 22	Equivalent	Equivalent	Few passes for FNB
[54]	Retrospective	42 (12)	Yes	22 or 25	Equivalent	Equivalent	
[55]	Retrospective	(87)	No	22 *vs* 22 Franseen	Equivalent	Equivalent	
[56]	Retrospective	(76)	No	22 *vs* 25	32.4 *vs* 60	Equivalent	
[57]	RCT	(214)	No	25 *vs* 25 Procore	Equivalent	69.4 *vs* 81	
[58]	RCT	(116)	Yes	22, 25 *vs* 22, 25 Procore	Equivalent	Equivalent	Few passes for FNB
[59]	Meta-analysis (7 comparative studies and 4 single cohort studies)	896 (pancreatic and lymph nodes)	Only in 4 studies	22 and 25	Equivalent	Equivalent	
[60]	RCT	140 (73)	YES	19, 22, 25	67 *vs* 90	Equivalent	Diagnostic yield only for pancreatic masses was equivalent
[61]	Prospective comparative	145 (69)	No	22 *vs* 22 Procore	Equivalent	Equivalent	Few passes for FNB
[62]	RCT	58 (16)	No	22 *vs* 22 Procore	Equivalent	Equivalent	Few passes for FNB
[63]	RCT (13 centers)	608 (312)	In 7 centers	25 *vs* 20 Procore	44 *vs* 77	Equivalent	

RCT: Randomized clinical trial; FNB: Fine needle biopsy; FNA: Fine needle aspiration; ROSE: Rapid on site evaluation

performance of 22 G FNA *versus* 22 G FNB needles. However, beyond the 22 G needles comparisons, some evidence is available.

A retrospective study examined a cohort of patients sampled with 22 G FNA (Echotip Ultra; Cook Ireland Ltd., Limerick, Ireland) *versus* a cohort sampled with 25 G FNB needle (Echotip ProCore; Cook Ireland Ltd.) for EUS-guided sampling of solid pancreatic masses without ROSE[56]. Among a total of 76 patients, there were no significant differences in safety, technical success (100% for both), and mean number of passes between the two cohorts (38 patients each). However, interestingly, the 25 G FNB group had a higher amount of both diagnostic cellular material and preservation of tissue architecture than FNA (P = 0.030 and 0.010, respectively), with a better diagnostic yield for specific tumor discrimination compared with the 22 G FNA group (P = 0.018).

Moreover, four RCTs[4,50,57,58] and a meta-analysis including 11 studies and 896 patients[59] compared FNA and reverse bevel needles in patients with solid pancreatic masses. The RCTs evaluated mainly 22 G and 25 G needles. ROSE was available only in some of them[4,58], and they used stylet or suction method[50]. No difference was found in the accuracy of final diagnosis in all studies, but the sample histological

quality was higher for reverse bevel than for FNA needles[49,56]. Lee *et al*[58] found a higher accuracy for samples obtained with reverse bevel needles during the ROSE. A similar observation on the rate of diagnostic samples adequacy for ROSE was found by Aadam *et al*[60]. Moreover, based on the observations of three RCTs, it seems that reverse bevel needles required fewer passes to obtain adequate samples for histological diagnosis, offering potentially shorter procedure time[49,61,62].

Interestingly, in the recent ASPRO multicenter trial, the authors compared the performance of a commonly used 25 G FNA needle with the new 20 G FNB needle on 608 patients with solid lesion[63]. The 20 G FNB needle outperformed the 25 G FNA needle in terms of histological yield (77% *vs* 44%; $P < 0.001$) and diagnostic accuracy (87% *vs* 78%; $P = 0.002$), with a 99% technical success rate of the FNB needle.

FNB NEEDLES COMPARISON

With the increasing availability of new FNB needles, some studies have focused on comparing their performances, mainly in term of diagnostic yield comparison.

In detail, a cohort study compared the opposing bevel-tipped needles (22 and 25 G) and reverse-bevel needles (20, 22, and 25 G)[64]. The fanning technique was used for all procedures. Twenty-five gauge needles were used preferentially for transduodenal biopsy. A minimum of three needle passes were performed, and ROSE was not available. A higher diagnostic sensitivity and higher diagnostic overall accuracy for the opposing bevel needle was obtained in comparison with the reverse-bevel needle: 71.1% *vs* 90.1%; $P = 0.0006$ and 74% *vs* 92%; $P = 0.0006$, respectively. The percentage of samples adequate for histology was 87% for the reverse bevel needle *versus* 99% for the opposing bevel needle ($P = 0.002$). Therefore, this study concluded that the opposing bevel tip seems to be superior, in terms of diagnostic performance, compared with a reverse-bevel needle (Table 2).

Another recent study compared the diagnostic yield of the Franseen needle with the fork-tip needle[65]. A total of 194 solid lesions were sampled, 100 of them located in pancreas (52%). For solid pancreatic masses, the yield with the Franseen needle was lower [34/53 (64%) in comparison with the fork-tip needle 40/47 (85%), OR 3.4, 9.1-8.9; ($P = 0.017$)]. At the multivariate analysis the number of passes, the site, and lesion size did not affect the diagnostic yield. However, in this study, one of the endosonographer used the ROSE, and this affected the overall methodology.

An RCT also compared the 22 G Franseen and 22 G fork-tip needles in sampling of pancreatic masses[66]. Fifty patients were sampled using both 22 G Franseen and 22 G fork-tip needles, with randomization of the needle order. Two passes were performed using both needles for cell block, and dedicated passes were performed for ROSE, using both needles until the diagnosis was established. They observed that there was no significant difference in term of surface of total tissue ($P = 0.50$), retained architecture, diagnostic cell block, and diagnostic adequacy at ROSE (94.0% *vs* 98.0%; $P = 0.32$) between Franseen and fork-tip needles, respectively. The authors concluded also that, given their ability to yield diagnostic cell block in greater than 90% of patients, ROSE is not mandatory.

Lastly, in terms of needle performance, no significant difference was found between 22 and 25 G FNB needle in a prospective study[67].

In conclusion, the comparison among the different FNB models available seems to be an interesting topic in the perspective of identifying the perfect needle for histology, but larger comparative studies are needed.

PRACTICAL RECOMMENDATIONS

Multiple factors may contribute to the outcomes of pancreatic EUS-guided tissue acquisition, as above reported: Site selection for sampling, sampling technique, location, and nature of the lesion, size and type of needle, ROSE availability, experience of the endosonographer, cytopathologist expertise, and methods of handling and processing the sample.

In order to maximize the diagnostic yield of pancreatic masses sampling, we propose a practical guide that takes into account the aforementioned factors and groups them into three main categories. The choice of the needle could be therefore made by combining these factors and their categories (Figure 3).

The three categories we choose are: Lesion related factors; patient-related factors; and institute related factors.

Lesion related factors

Among the factors linked to the pancreatic lesions, its location is a key factor to consider, for the difficulty of using a needle of greater caliber for lesions located in the head, uncinate process, or on the most distal portion of the tail, where it is more

Table 2 Published comparative studies regarding fine needle biopsy needles performance in terms of diagnostic yield

Ref	Study design	N°Lesions,pan-creatic	Rose	Needles	Gauge	Diagnostic yield, %	Sample adequacy, %	Comments
[64]	Cohort	(201)	No	Opposing bevel *vs* reverse bevel	22-25 *vs* 20-22-25	71 *vs* 90	87 *vs* 99	Opposing bevel needle resulted superior
[65]	Cohort	194 (100)	Only in 12% of cases	Franseen *vs* fork tip	22	64 *vs* 85	The use of ROSE is a confounding factor	Fork tip seems superior, but the study lack of methodology
[66]	RCT	(50)	Yes	Franseen *vs* fork tip	22	> 90%, equivalent	94 *vs* 98	Equivalent
[67]	Cohort	(66)		Procore	22 *vs* 25	87.5 *vs* 82.1	98 *vs* 95	Equivalent

RCT: Randomized clinical trial; ROSE: Rapid on site evaluation.

difficult to move the needle from the working channel, with the scope torqued in the duodenum or in the gastric fundus. Even the stylet use is more difficult with larger caliber needles in the case of sampling performed through the duodenum[68,69].

Considering the size of the lesion, approximately 60% of small solid pancreatic lesions ≤ 15 mm are not reported as being histologically consistent with ADK and, therefore, do not require radical surgery[70]. Without preoperative diagnosis, an unacceptably large proportion of patients would be exposed to unnecessary radical surgery, with significant morbidity and mortality. Many studies have reported a correlation between EUS-FNA accuracy and lesion size[11,71-73]. Pancreatic tumors are frequently stiff, accompanied by inflammation and desmoplasia and are thus difficult to penetrate with a needle. Once the needle reaches the target lesion, some limitations may be found, such as the lack of space to perform the back-and forth movement and the displacement of the needle from the lesion during the maneuvers. The lower diagnostic yield of EUS–FNA in small pancreatic lesions may be related to the presence of inflammatory tissue and desmoplastic stroma, which surround and constitute the most of small carcinomas. Agarwal *et al*[71] reported an increasing sensitivity from 75% to 94% for lesions smaller or larger than 20 mm, respectively. Similarly, another retrospective study reported that EUS-FNA accuracy without ROSE was 71% and 90% for lesions smaller or larger than 30 mm, respectively, and these were significant *via* multivariate analysis[72]. Siddiqui *et al*[11] showed that the EUS–FNA sensitivity for pancreatic lesions with < 1 cm size and with 1-2 cm in diameter was 40% and 75.9%, respectively, and the sensitivity strongly correlated with tumor size (P = 0.001). Similarly, the accuracy of EUS-FNA increased directly with the lesion size, ranging from 47% for tumors less than 1 cm in size to 88% for tumors larger than 4 cm (P < 0.05). On the other hand, Fabbri *et al*[73] suggested that EUS-FNB of small pancreatic lesions (mean lesion size: 16.5 mm) using a 22 G ProCore needle was effective, with a diagnostic accuracy of 82%, and the presence of a tissue core was recorded in 52.9% of the samples. The authors explained the high needle performance on small lesion with the presence of the side fenestration, increasing the efficacy of tissue sampling: the tissue specimens could be collected not only *via* frontal orifice but also *via* side fenestration, which remains in the center of the small lesion during repeated needle passages[73].

Taking into account the nature of the lesions, obtaining a tissue histology has been recognized as important for the diagnosis of autoimmune pancreatitis, especially in focal form[74], or in case of Hodgkin lymphoma[75]. Hence, FNB needle should be considered when facing these diagnostic suspects.

Furthermore, although neuroendocrine tumor (NEN) diagnosis and the assessment of the degree of their differentiation with FNA needles are possible[76], the use of FNB needle may be helpful for their definitive diagnosis. In a recent retrospective study of patients with histologically confirmed pancreatic NENs (pan-NENs), Chen *et al*[77] found that a definitive diagnosis of pan-NENs was possible only in 13/21 (61.9%) of EUS-FNA specimens. Each of the 13 cases with definitive diagnosis showed adequate cell block material, used for ancillary testing, underpinning the need for robust cell block material to render a conclusive determination of pan-NENs. Conversely, in a recent 15-year retrospective study, 30% of false-positive EUS-FNA diagnoses of ADK were proved to be pan-NENs on the resected specimen[78]. The recent study by Witt *et al*[79] on patients with known or suspected pan-NENs compared EUS sampling with SharkCore® in patients receiving EUS-FNA using a standard needle. The authors confirmed that the FNB needle showed promising results in obtaining suitable tissue

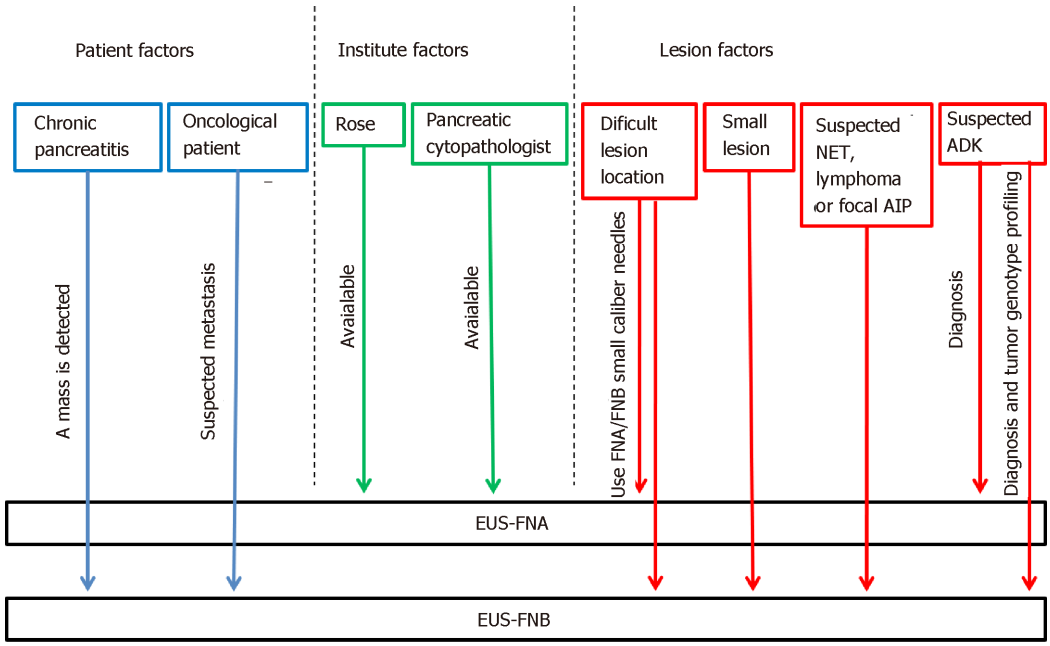

Figure 3 A practical flow chart for selecting among the available needles in each scenario (pancreatic neuroendocrine tumors, pancreatic neuroendocrine tumors; autoimmune pancreatitis, autoimmune pancreatitis; adenocarcinoma, adenocarcinoma). ROSE: Rapid on site evaluation; EUS-FNA: Endoscopic ultrasound guided-fine needle aspiration; EUS-FNB: Endoscopic ultrasound guided-fine needle biopsy; ADK: Adenocarcinoma; AIP: Autoimmune pancreatitis.

for ancillary tests, allowing for more definitive pathologic interpretations.

Moreover, pancreatic ADK genotyping will play an increasingly important role in cancer therapy in the next years. Therefore, tissue histology and the ability to obtain a cell block for additional studies will soon be included among the goals of EUS-sampling. Today, the role of "personalized medicine" in cancer therapy remains a process in evolution, and the amount of tissue needed for molecular profiling still remains to be defined. Although repeatedly smaller amounts of DNA are required to achieve "Next Generation Sequencing", a current benchmark of adequate tissue is considered as 1 mm of tissue, eight to 10 slides, or 5 × 5 mm surface area, with at least 20% tumor tissue[80]. These expectations could be easily fulfilled by FNB needles (Figure 4).

Patient related factors

One of the most relevant issues is the presence of an underlying chronic pancreatitis. Identifying a neoplasia in the setting of chronic pancreatitis can be challenging. This difficulty is compounded by the fact that patients with chronic pancreatitis are at increased risk of developing pancreatic ADK, whereas patients with pancreatic ADK often have focal areas of chronic pancreatitis too. The reported sensitivity of EUS-FNA when sampling solid pancreatic masses in the setting of chronic pancreatitis ranged from 54% to 74%, which is unacceptably low[81,82]. The presence of underlying chronic pancreatitis makes the morphological interpretation of neoplasms even more challenging because of their very similar imaging features. The pancreatitis-induced morphological changes (*e.g.*, lobulations) may mimic a pancreatic mass, while the presence of acoustic shadowing from a calcified stone may reduce the ultrasound's capability to detect a neoplasm. Again, the coexistence of collateral vascularization in patients with severe chronic pancreatitis makes the EUS sampling even more difficult. On the other hand, when EUS-guided sampling is possible, the pathological interpretation can be hard. Some of the cytological features that may mimic malignancy in chronic pancreatitis are occasional atypical cells, enlarged, single cells with large nuclei, degenerative vacuoles, and occasional mitosis. Diagnosing well-differentiated ADK can be particularly challenging as they tend to lack the typical hyperchromasia, display only minimal architectural disorders, and have only modestly increased nuclear-to-cytoplasmic ratios[83]. The use of contrast harmonic imaging and elastography, doing more FNA passes, repeating the procedure with ROSE, and consulting an experienced pancreatic cytologist may be helpful to improve the overall EUS accuracy. But above all, the use of the new EUS-FNB needles or FNA19 G needles may be considered[84]. Theoretically, a core biopsy yields tissue fragments with an intact histological architecture, which is sometimes required, particularly in patients with chronic pancreatitis and well-differentiated pancreatic

Figure 4 Endoscopic ultrasound guided-fine needle biopsy sample of a pancreatic lesion, obtained by using ProCore 22 G needle.

ADK when cytology is inconclusive. Currently, although it seems reasonable to use FNB needles in this setting, its role in discriminating pseudotumoral masses from pancreatic cancer in the setting of chronic pancreatitis has not yet been explored.

Again, FNB needle may be preferable in the context of an oncological patient with evidence of focal pancreatic lesion. In these cases, when a solid pancreatic mass is identified, even though it is a single lesion, the possibility of facing a secondary lesion should be considered. The collaboration of an experienced cytopathologist and the use of EUS-FNB needles may facilitate the diagnosis, increasing both the diagnostic accuracy and the quantity of material required; especially for patients requiring complementary immunohistochemical studies[83-87].

Institute related factors

Finally, among the institute setting factors, we remember the availability of ROSE and the availability of a pancreatic cytopathologist as key aspects in sampling a pancreatic solid mass (see EUS-FNA accuracy: the role of ROSE on the way to FNB). If both these elements are present in the hospital, the option of FNA needles may be preferable.

CONCLUSIONS: WHICH IS THE BEST NEEDLE?

EUS-FNA is currently still the standard of care for sampling pancreatic masses with high diagnostic accuracy, especially if coupled with ROSE, and high safety profile. However, FNA presents some intrinsic drawbacks that probably will reduce, in the near future, its use as first line method for tissue acquisition. These include the small amount of tissue with scant cellularity without the ability to guarantee a core tissue with intact histological architecture, which impairs immunohistochemical analysis and molecular profiling. Before long, these two features will become of paramount importance not only to aid definite diagnosis but even to guide tailored personalized oncological therapies. Secondly, FNA requires ROSE to maximize its diagnostic yield, which may prolong procedural time, and is unfortunately not widely available outside referral center.

Second generation FNB needles have shown satisfying diagnostic accuracy even in the absence of on-site pathology, reducing the number of passes required to establish the diagnosis. Nonetheless, FNB has not yet showed a clear undisputed diagnostic superiority over FNA, especially when considering pancreatic masses sampling. Indeed, the 2017 European Society of Gastrointestinal Endoscopy guidelines stated that for routine EUS-guided sampling of solid masses and lymph nodes, FNA and FNB needles are equally recommended (high quality evidence, strong recommendation)[30].

Theoretically the ideal needle should provide specimens with preserved cellular architecture and fulfill the attributes pin-pointed by Lachter[88]. Among them the most relevant should be needle safety, high accuracy (thus reducing false negatives), tip visibility, flexibility, and low cost.

In real practice, the aforementioned attributes are seldom fulfilled by a single kind of needle. The best needle is the one that better complies with the different factors (lesion related, patient related, and institute related), influencing the overall performance of tissue acquisition.

Currently, a "one size fits all" approach should be abandoned in favor of a tailored approach, selecting each time the needle better adaptive to the different specific

scenarios. According to our proposed flowchart on needle selection, FNB should be preferred in case of concomitant chronic pancreatitis, diagnosis of focal autoimmune pancreatitis and pan-NENs, pancreatic masses suspected for metastases, need for tumoral genotype profiling, and in cases where ROSE is not available, in order to reduce needle passes.

In the near future, with the development of newly designed core biopsy needles, it is expected that FNB will most probably replace FNA as the standard of care for tissue acquisition.

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MINIREVIEWS

Magnetic sphincter augmentation: Optimal patient selection and referral care pathways

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Abstract

Outcomes associated with magnetic sphincter augmentation (MSA) in patients with gastroesophageal reflux disease (GERD) have been reported, however the optimal population for MSA and the related patient care pathways have not been summarized. This Minireview presents evidence that describes the optimal patient population for MSA, delineates diagnostics to identify these patients, and outlines opportunities for improving GERD patient care pathways. Relevant publications from MEDLINE/EMBASE and guidelines were identified from 2000-2018. Clinical experts contextualized the evidence based on clinical experience. The optimal MSA population may be the 2.2-2.4% of GERD patients who, despite optimal medical management, continue experiencing symptoms of heartburn and/or uncontrolled regurgitation, have abnormal pH, and have intact esophageal function as determined by high resolution manometry. Diagnostic work-ups include ambulatory pH monitoring, high-resolution manometry, barium swallow, and esophagogastroduodenoscopy. GERD patients may present with a range of typical or atypical symptoms. In addition to primary care providers (PCPs) and gastroenterologists (GIs), other specialties involved may include otolaryngologists, allergists, pulmonologists, among others. Objective diagnostic testing is required to ascertain surgical necessity for GERD. Current referral pathways for GERD management are suboptimal. Opportunities exist for enabling patients, PCPs, GIs, and surgeons to act as a team in developing evidence-based optimal care plans.

Key words: Gastroesophageal reflux disease; Surgery; Magnetic sphincter augmentation; Referral pathways

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Core Tip: While the outcomes associated with magnetic sphincter augmentation (MSA) in patients with gastroesophageal reflux disease (GERD) have been previously reported, the optimal population for MSA and the related patient care pathways have not been summarized. This review presents evidence that describes the optimal patient population for MSA, delineates diagnostics to identify these patients, and outlines opportunities for improving GERD patient care pathways. Current referral pathways for GERD management are suboptimal. Opportunities exist for enabling patients, primary care providers, gastroenterologists, and surgeons to act as a team in developing evidence-based optimal care plans.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is an inherently mechanical disease whose primary etiology lies in a weakened lower esophageal sphincter (LES)[1-5] which opens abnormally and allows the reflux of gastric content into the esophagus. The opening of the LES and reflux result from changes in gastric fluid pressure relative to abdominal pressure regulated by adjustments in the anatomical conformation of the sphincteric muscles[6]. Additionally, it is contended that the crura contribute to the competence of the anatomic anti-reflux mechanism[7-11]. The presence of a hiatal hernia adversely affects LES pressure, relaxation, and esophageal acid clearance. Furthermore, the frequency and duration of acid exposure in the esophagus is significantly impacted by the incidence of transient LES relaxations (tLESRs), and patients need to be considered for treatment with these mechanical aspects in mind[12-14].

Based on disease severity and responsiveness to medical management, some patients with GERD may benefit from surgical intervention. However, effective treatment of patients with GERD requires an awareness of the clinical spectrum of GERD, its varied symptomatology and potential complications, the reasons for referral, and the many treatment options available[15,16]. Sub-optimal referral of patients may affect the process of patient evaluation, treatment, and continuity of care, and can affect clinical outcomes and costs[17]. Despite multiple treatment options, a considerable number of patients with GERD have inadequate disease management[18]. GERD is inherently a multi-specialty disease and in order to ensure that the appropriate interventions are delivered efficiently, a better understanding of GERD patient care pathways is needed[19].

Treatment options for GERD vary depending on the progression and symptoms of their disease, however, there are currently three primary means of treating GERD: lifestyle changes, medical therapy, and surgical intervention[20]. Lifestyle interventions should be included as part of the therapy for GERD[15]. Counseling is often helpful to provide information regarding weight loss, head of bed elevation, tobacco and alcohol cessation, avoidance of late-night meals, and cessation of foods that can potentially aggravate reflux symptoms including caffeine, coffee, chocolate, spicy foods, highly acidic foods such as oranges and tomatoes, and foods with high fat content[15]. While medical therapy with anti-acid medications such as proton pump inhibitors (PPIs) is the mainstay of treatment that can control heartburn in the majority of patients, other symptoms such as regurgitation and respiratory symptoms may not be controlled, particularly in patients with compromised LES and/or hiatal hernias[2,21-23]. Although external factors such as inadequate dosing or nonadherence to treatment may play a role in PPI failure, persistent GERD symptoms despite anti-secretory drugs may be indicative of an incompetent LES that allows abnormal reflux of gastric content into the esophagus[1-5]. Endoscopic therapies for GERD have been developed but evidence for their long-term efficacy is limited[15]. These include radiofrequency augmentation to the LES, silicone injection into the LES, and endoscopic suturing of the LES[15]. Recent alternative approaches have included transoral incisionless fundoplication, a

suturing device designed to create a full thickness gastroesophageal valve from inside the stomach[15]. Unfortunately, long-term data regarding efficacy of this device are limited to a small number of subjects and short duration of follow-up[15].

Anti-reflux surgery is an option to better control symptoms and avoid lifelong medical therapy[24]. Currently, the *de facto* treatment option for surgical treatment of GERD is the laparoscopic Nissen Fundoplication (LNF) procedure[25]. LNF involves wrapping a portion of the stomach around the esophagus to reinforce the weakened LES. While LNF has long been associated with effective reflux control, it has several limitations: (1) It results in anatomical and physiological alteration of the fundus; (2) Potential side effects including gas bloat and an inability to belch or vomit may occur[5,26]; and (3) The procedure is difficult to standardize and teach, resulting in variable efficacy[26,27]. Sixty-seven percent of patients undergoing LNF (54/87) reported new symptoms (*i.e.*, excessive gas, abdominal bloating, dysphagia) after surgery[28]. LNF is associated with up to 15% reoperation rates and a cumulative surgery failure rate of up to 27.1%[26,29].

An alternative to LNF is Magnetic Sphincter Augmentation (MSA). MSA with the LINX® Reflux Management System was FDA approved via the premarket approval (PMA) process and has shown beneficial effects in studies in diverse patient populations[27,30-44]. The LINX Reflux Management System is a laparoscopic, fundic-sparing anti-reflux procedure indicated for patients diagnosed with GERD as defined by abnormal pH testing, and who are seeking an alternative to continuous acid suppression therapy (*i.e.*, PPIs or equivalent) in the management of their GERD. LINX is contraindicated in patients with suspected or known allergies to titanium, stainless steel, nickel, or ferrous materials. LINX is an implantable device consisting of a series of titanium beads, each containing a magnetic core connected with independent titanium wires that allows dynamic augmentation of the LES without compression of the esophagus (Figure 1).

The magnetic attraction of the device is designed to close the LES immediately after swallowing, restoring the body's natural barrier to reflux. Warren *et al*[45] demonstrated how a manometrically defective LES can essentially be restored to a normal sphincter with MSA, thus reestablishing the mechanical barrier to reflux. Compared to baseline, studies of patient outcomes with MSA have reported excellent pH control with more than 50% of patients normalizing pH scores at 1 year, and significant improvements in symptom scores and PPI usage at the 5-year interval[31,33,42]. A randomized control trial (RCT) compared LINX to twice-daily (BID) 20 mg omeprazole PPI demonstrated significant relief from regurgitation with LINX therapy compared to patients in whom the PPI dosage was increased from single to double-dose[44]. Overall, MSA has been demonstrated to be potentially safe and efficacious, reversible and reproducible, and associated with fewer side effects compared to LNF[30-41]. Importantly, MSA patients experienced improvement in regurgitation, PPI dependence, heartburn, and patient satisfaction that persisted for 5 years[30,35,40,44]. More than 75% of MSA patients experienced complete cessation of PPI use at up to 5 years[30,32-34,40,44,46,47]. The 5-year reoperation rate with MSA has been shown to range from 6.8%-7.0%[30,33]. The most common side effects of MSA were gas/bloating (26.7% with MSA *vs* 53.4% with LNF; $P = 0.06$) and postoperative dysphagia (33.9% with LINX *vs* 47.1% with LNF; $P = 0.43$)[35]. When performed responsibly and on appropriately-selected patients, MSA can be an important treatment to optimally control these patients' reflux disease, thereby increasing their quality of life, and minimizing potential side effects.

In regards to the economic consequences associated with MSA, a meta-analysis by Chen *et al*[48] showed that MSA had a significantly shorter operative time (MSA and fundoplication: RR = -18.80 min, 95%CI: -24.57 to -13.04, and $P = 0.001$) and length of stay (RR = -14.21 h, 95%CI: -24.18 to -4.23, and $P = 0.005$) compared to fundoplication. A retrospective analysis of 1-year outcomes of patients undergoing MSA and LNF by Reynolds *et al*[36] showed that LNF and MSA were comparable in overall hospital charges ($48491 *vs* $50111, $P = 0.506$). The charge for the MSA device was offset by lower charges in pharmacy/drug use, laboratory/tests/radiology, OR services, anesthesia, and room and board. There were significant differences in OR time (66 min MSA *vs* 82 min LNF, $P < 0.01$) and LOS (17 h MSA *vs* 38 h LNF, $P < 0.01$).

While the outcomes associated with MSA have previously been evaluated, evidence describing the optimal population for MSA and the related GERD patient pathways have not yet been summarized. Proper patient selection is central to obtaining the best possible surgical outcomes in patients with GERD[5,15,19,49]. As such, the purpose of this review is to (1) Describe the optimal population for MSA; (2) Delineate the diagnostic evaluation necessary to identify those patients; and (3) Assess gaps in patient care pathway and identify opportunities to improve care coordination.

A narrative literature review was undertaken to obtain a comprehensive and critical analysis of the current knowledge on the topic.

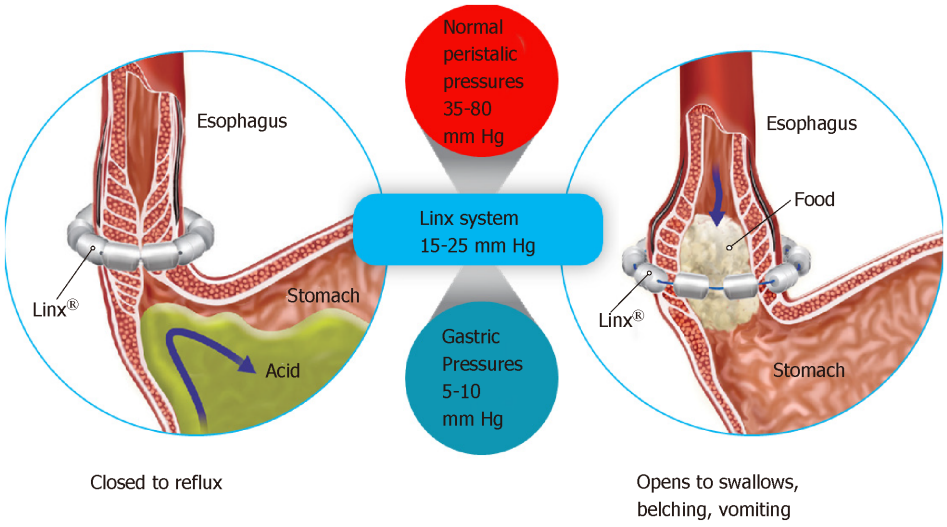

Figure 1 LINX magnetic sphincter augmentation implantable device.

Data sources and searches

Comprehensive searches of the literature were performed using the Medline (PubMed) and EMBASE databases with the timeframe of January 1, 2000 to December 16, 2018. A search for guidelines available from the National Guideline Clearinghouse (NGS) was also conducted. Search terms utilized in the literature search included: "gastroesophageal reflux disease", "GERD", "refractory", "surgery", "magnetic sphincter augmentation", "LINX", "fundoplication", "Nissen", "pH monitoring", "manometry", "lower esophageal sphincter", and "mechanical". Reference lists of selected studies were also reviewed for possible additional articles.

Study selection criteria

Study and guideline inclusion criteria were publications that presented evidence for current treatment pathways of patients with GERD. Exclusion criteria included publication of abstracts only, case reports, letters, or commentaries; animal studies; languages other than English; duplicate studies; and studies that did not evaluate the patient population of interest (*e.g.*, malignancy, any form of esophageal dysmotility, achalasia and scleroderma). After removing excluded abstracts, full articles were obtained, and studies were screened again more thoroughly using the same exclusion criteria. A total of 86 articles were identified for inclusion in this narrative review. Studies were assessed for quality; the study types (designs) used to address the research questions were: Level I – randomized controlled trials; Level II – prospective, non-randomized trials; Level III – retrospective comparative studies; Level IV – single-arm case series; and Level V – expert opinion.

FINDINGS-TARGET POPULATION AND REFERRAL PATHWAYS FOR MSA

Describing the target population potentially eligible for anti-reflux surgery

GERD can have significant potential complications such as erosive esophagitis, Barrett's esophagus, and esophageal adenocarcinoma[50]. Persistent reflux symptoms, despite PPI therapy, have been associated with debilitating comorbidities including mental health disorders, sleep disorders, and psychological distress to patients[51,52]. Additionally, GERD is known to negatively impact health related quality of life, work productivity, and overall healthcare resource utilization[53].

While there is evidence that acid-suppressive drugs reduce the acidic content of refluxate, abnormal reflux continues and associated symptoms such as regurgitation and respiratory symptoms are often not controlled with medical management[54]. Between 30%-40% of patients on PPI therapy (even those on double-dose therapy) continue to experience heartburn or regurgitation symptoms despite adequate healing of esophagitis[55]. Treatment in clinical practice has been primarily focused on increasing escalation of the PPI dose and/or frequency, or supplementing with additional anti-acid medications[56]. In patients who failed twice daily PPI, alternative

treatments range from lifestyle and diet modification, weight loss, medical treatment with a focus on controlling the frequency of tLESRs, attenuating esophageal pain perception using visceral analgesics, cognitive behavior therapy, and anti-reflux surgery[56]. As symptoms of GERD become increasingly severe and burdensome to the patient despite various treatment approaches, patients may be advised to seek, or may refer themselves for, surgical therapy[2,23,57].

A search of the Agency for Healthcare Research and Quality (AHRQ)'s National Guideline Clearinghouse[58] identified two clinical guidelines evaluating surgery for GERD: the American College of Gastroenterology (ACG) 2013 Guidelines[23] and the University of Michigan Health System (UMHS) 2012 Guidelines[59]. Both guidelines agree that: (1) Surgery is a treatment option for patients with chronic reflux and refractory symptoms; (2) Surgical therapy is generally not recommended for patients who do not have at least a partial response to acid reduction therapy; and (3) Surgery appears to be more effective in patients with typical symptoms of heartburn and/or regurgitation than in patients with extraesophageal or atypical symptoms[23,59].

Reasons to refer GERD patients for surgery, including MSA, may include persistent symptoms despite medical therapy, desire to discontinue medical therapy, or presence of a large hiatal hernia[2,23,42]. It is important that MSA candidates have normal esophageal motility documented by high resolution manometry. This is to ensure enough esophageal power to break the magnetic bonds and allow the device to open, allowing for normal swallowing[23]. Potential surgical candidates for MSA are those GERD patients (14-20%[57] of U.S. population[60]) who, despite optimal medical management, continue to experience symptoms of heartburn and/or uncontrolled regurgitation [medically managed and refractory to lifestyle and pharmacological interventions (6.0%-24.0%)[22,55,61,62]], have abnormal pH off PPI (61.0%-71.0%)[63-67], and do not have esophageal dysmotility (88.0%-96.0%)[68,69]. Overall, among patients with GERD, the total eligible population for MSA is estimated to be in the 2.2%-2.4% range (Figure 2).

Currently, it is estimated that only 0.1% of GERD patients[70] in fact undergo anti-reflux surgery. The reasons underlying the significant gap are multifactorial and would benefit from a more well-defined care pathway. Additional reasons to refer GERD patients for surgery include the desire to discontinue medical therapy, non-compliance, side-effects associated with medical therapy, and the presence of a large hiatal hernia[23,71]. In practice, patient identification and treatment are based on a combination of the guidelines[23,71], a robust preoperative work-up, and ultimately, physician assessment of patient symptoms and disease severity.

DIAGNOSTICS TO DETERMINE SURGICAL ELIGIBILITY OF GERD PATIENTS

In order to appropriately identify those patients who might benefit from anti-reflux surgery, it is important that thorough testing be performed. Objective testing is required to confirm the diagnosis of GERD in patients being considered for surgery. Diagnostic testing is recommended for patients with GERD who do not respond to prior treatments, have symptoms suggestive of complications or other conditions (*e.g.*, dysphagia, odynophagia, bleeding, anemia, weight loss), or are at risk for developing Barrett's esophagus[23]. Typical pre-operative diagnostic testing includes esophagogastroduodenoscopy (EGD), ambulatory pH monitoring, esophageal high-resolution manometry, and esophagram (Figure 3)[23,57]. Each testing modality has a specific role in the diagnosis and evaluation of GERD, and no single test alone can provide the entire clinical picture[72].

EGD

The American Society for Gastrointestinal Endoscopy (ASGE)[73] and the American Gastroenterological Association (AGA)[57] recommend that EGD be performed for patients who have symptoms suggesting complicated GERD or alarm symptoms. Repeat EGD should also be performed in patients with severe erosive esophagitis after at least an 8-wk course of PPI therapy to exclude underlying Barrett's esophagus and dysplasia[73,74].

pH monitoring

Ambulatory esophageal pH monitoring is critical to establish a diagnosis of GERD[75]. pH monitoring directly measures the extent and frequency with which acid refluxes into the esophagus and has been shown to be the most sensitive and specific test to objectively diagnose GERD[57,63]. pH-impedance monitoring also measures the proximal extent of reflux and can differentiate between acidic, weakly-acidic and non-

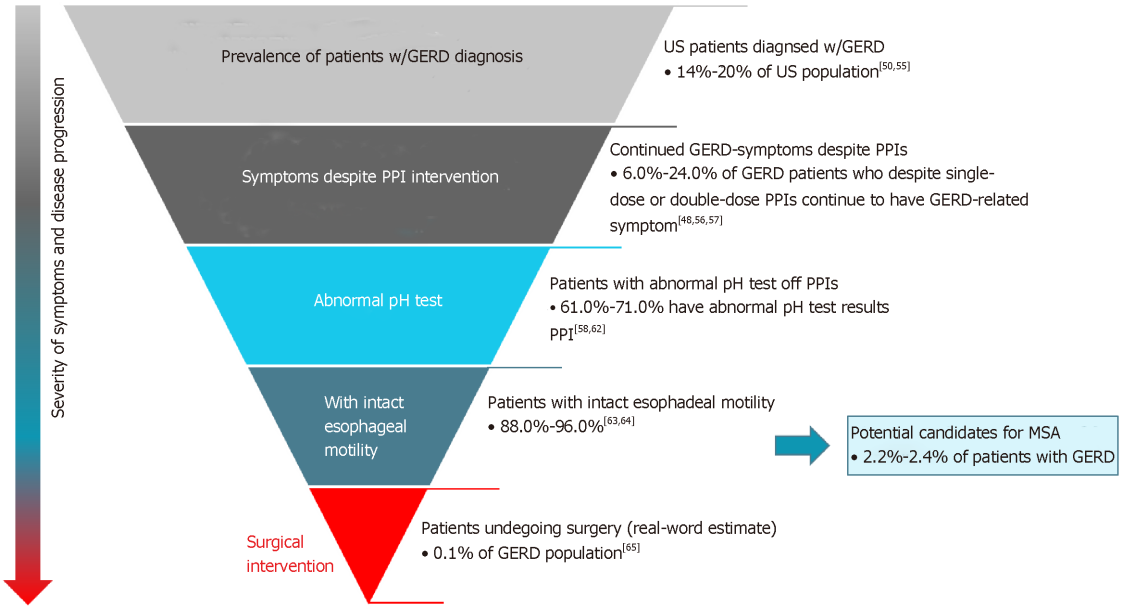

Figure 2 Typical eligibility criteria for anti-reflux surgery procedures as patients progress from medical management to surgery.

acid reflux.

Manometry

In addition to upper endoscopy and esophageal pH testing, a preoperative evaluation should include high resolution manometry to ensure normal esophageal motility[19,57]. Manometry measures the pressure in the upper and lower esophageal sphincters, determines the effectiveness and coordination of peristalsis, and detects abnormal contractions. Manometry can be used to diagnose esophageal motility disorders such as achalasia, esophageal spasm, and lower esophageal sphincter hypotension and hypertension[57].

TYPICAL CLINICAL PATHWAYS FOR GERD SYMPTOMS AND OPPORTUNITIES FOR IMPROVING CARE WITH MSA

The diversity of clinical presentations of GERD poses challenges for clinicians in primary and specialty care settings. As Figure 4 illustrates, GERD patients may present with a range of typical or atypical symptoms. Typical symptoms of GERD include heartburn, regurgitation, and dysphagia[2,23,76,77]. Although dysphagia can be associated with uncomplicated GERD, its presence warrants investigation for alternative etiologies, including underlying motility disorder, stricture, ring, or neoplasm[23,78]. Atypical GERD symptoms may include dyspepsia, epigastric pain, nausea, bloating, and belching[19,23]. Extraesophageal GERD symptoms include chronic cough, chronic laryngitis, and associated asthma symptoms[23,77,79,80]. Atypical symptoms may overlap with other conditions, complicating diagnosis and treatment. Distinguishing them from GERD with appropriate diagnosis is important[81].

There is significant room for improvement in GERD diagnosis and treatment, particularly among patients with atypical symptoms for optimal patient care and healthcare resource utilization[81-83]. A study from AHRQ demonstrated that hospitalizations for disorders caused by GERD rose 103 percent between 1998 and 2005[84]. As such, detailed investigations and objective measurements in patients with symptoms of GERD should be performed with the intent of making the correct diagnosis, thus enabling choice of appropriate therapy[85].

Clinical pathways

In addition to obtaining an accurate diagnosis of GERD and conducting a through evaluation of the esophagus, it is also important that algorithms for referral for diagnosis to treatment be defined. When the diagnosis is uncertain or when GERD symptoms do not resolve following self-treatment, patients often present to primary care providers (PCPs)[81]. Some research has shown that patients with chronic diseases may have better health outcomes when PCPs co-manage care with specialists[86]. Patients with GERD also often present to emergency rooms (ERs). In an AHRQ

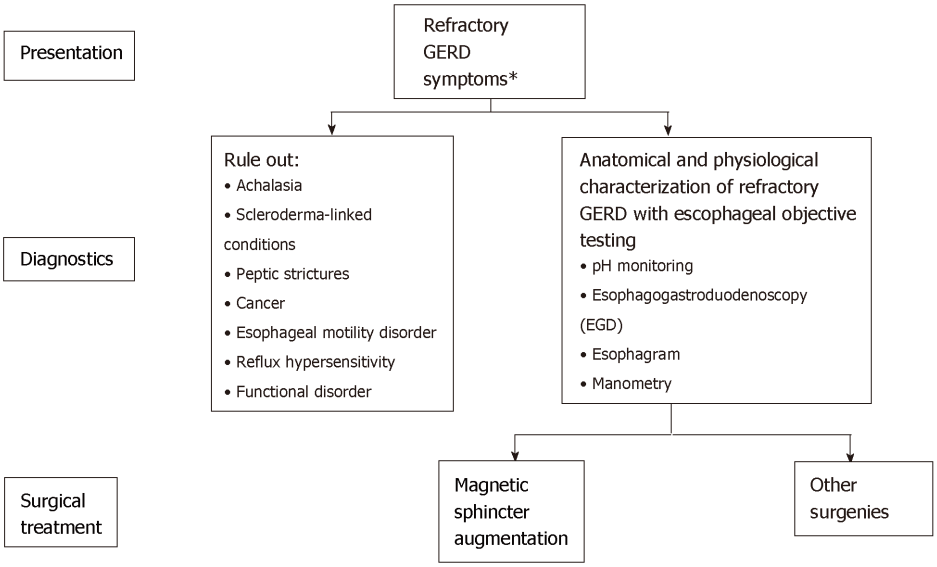

Figure 3 Patient diagnostics used in the evaluation of gastroesophageal reflux disease symptoms[23,61].

analysis of GERD hospitalizations, 69% of patients initially presented to the ER[84]. Patients with GERD may also seek care from otolaryngologists, allergists, immunologists, and pulmonologists, as it is estimated that 38%-51% of asthmatics have GERD[79], and approximately 60% of patients with obstructive sleep apnea may have GERD[52]. In some cases, referrals to anti-reflux surgery may be limited to only those patients with severe disease and large hiatal hernias[87]. Timely referral of patients to a specialist in GERD when empiric treatment is insufficient may lead to improved clinical management[88]. However, referral algorithms across the spectrum of medical and surgical options are not established. Those data indicate that improved education and disease state awareness are critical for recognizing symptoms suggestive of GERD, and for navigating patients through appropriate diagnostic pathways to ensure timely specialty referral[86]. As such, establishing an easily understood, evidence-based algorithmic approach to implement best practices would serve better inform patients and physicians alike[89,90].

CONCLUSION

Optimal GERD management requires an emphasis on care coordination, improving healthcare quality through a patient-centered and evidence-based approach. An individualized approach to the GERD patient with a thorough understanding of optimal patient selection and patient referral to appropriate specialists is important for achieving desirable outcomes[15,49]. While lifestyle modi-fications and pharmacological therapy control symptoms for most GERD patients, there is a significant subset of patients whose symptoms are not adequately controlled. Objective testing is required to confirm the diagnosis, and to anatomically and physiologically evaluate the nature and severity of GERD and to help reveal the optimal patient treatment. For MSA surgery, the optimal population may be described and identified as a sub-segment of patient population who experience GERD symptoms of heartburn and/or uncontrolled regurgitation despite optimal medical management, have abnormal pH, and have normal esophageal motility.

Management algorithms incorporating medical and surgical treatments of GERD are not established. Currently, only a small fraction of eligible patients benefit from anti-reflux surgery. Reasons underlying the gap between potential surgical candidates and real-world utilization of anti-reflux surgery have not been well studied. Further studies are needed to identify impediments to access to surgical options for eligible patients. Strategies that may narrow this treatment gap include: (1) Improving PCP and gastroenterologist awareness of surgical guidelines; (2) Improving physician training curricula with respect to the evolving anti-reflux surgery procedures (such as MSA); and (3) Importantly developing an evidence-based, multidisciplinary referral network that includes the patient, the PCP, the gastroenterologist, and the surgeon. Such a network will empower both patients and providers access to all treatment options to optimally control their reflux disease, thereby potentially increasing the

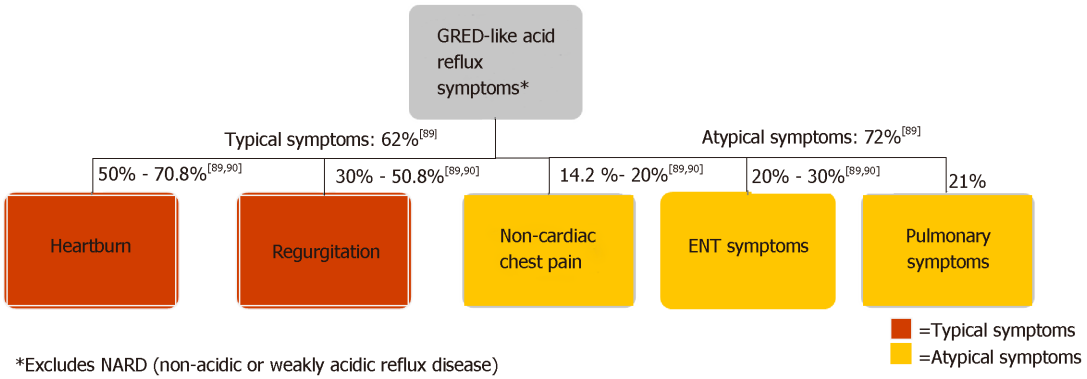

Figure 4 Typical patient presentation in gastroesophageal reflux disease[89,90].

quality of life of patients and decreasing overall healthcare resource utilization.

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