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The Role of Endoscopy in Diagnosis and Treatment of Gastrointestinal Subepithelial Lesions

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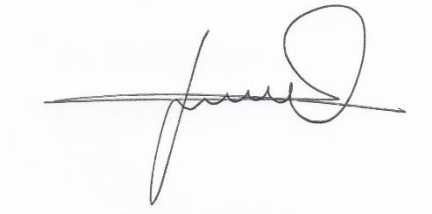
Assinatura do Estudante



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Resumo

Introdução e Objetivos: Lesões subepiteliais, definidas como uma massa ou protuberância que surge sob mucosa de aparência normal, são achados incidentais encontrados com alguma frequência ao longo do trato gastrointestinal, com origem intra ou extramural e uma incidência reportada de 0,36%, mais frequentemente no estômago. Podem ser assintomáticas ou apresentar-se com sintomas como dor abdominal, hemorragia ou obstrução, podendo ter comportamento benigno ou maligno. Para uma caracterização mais detalhada de lesões subepiteliais, exames imagiológicos transabdominais são bastante limitados. A Ecoendoscopia é um exame diagnóstico de elevada importância, capaz de identificar lesões subepiteliais através de algumas das suas características, tal como camada de origem na parede gastrointestinal, localização ou ecogenicidade. No entanto, quando usada isoladamente, demonstra uma precisão apenas razoável. Técnicas de obtenção de amostras de tecido, guiadas por ecoendoscopia, permitem uma análise histopatológica do tecido, aumentando a precisão diagnóstica, permitindo uma melhor abordagem e tratamento da lesão. Técnicas endoscópicas de tratamento, como modalidades minimamente invasivas quando comparadas a abordagens cirúrgicas laparoscópicas ou laparotómicas têm ganho uma importância significativa, com novas técnicas emergindo nos últimos anos. Este artigo tem como objetivo a revisão da abordagem de lesões subepiteliais gastrointestinais, focando-se nas técnicas endoscópicas emergentes utilizadas no diagnóstico e tratamento das mesmas.

Metodologia: Uma pesquisa foi efetuada no Pubmed, utilizando as palavras-chave: “subepithelial lesion”, “subepithelial tumor”, “submucosal lesion”, “submucosal tumor”, e “gastrointestinal stromal tumor”. Foram excluídos estudos não realizados em humanos e em língua não inglesa, encontrando-se as datas de publicação no período de 01/01/2009 até 01/09/2019. Após seleção por título e abstract e aplicação de critérios de exclusão e inclusão, foram selecionados sessenta e dois artigos e cuidadosamente analisados, permitindo a identificação e inclusão de outros catorze artigos oportunos, obtendo-se um total de setenta e seis artigos.

Conclusões: A ecoendoscopia e técnicas de aquisição de tecido guiadas por ecoendoscopia assumem um papel importante na obtenção de um diagnóstico fiável. A Aspiração por agulha fina e Biópsia por agulha fina são as mais utilizadas, sendo que alguns estudos demosntraram vantagem desta última na obtenção de amostras adequadas para análise histopatológica. Várias técnicas de resseção endoscópica são possiveis para a ressecção de lesões subepiteliais intramurais de menores dimensões, mas ainda não existe um consenso global relativamente à técnica a aplicar a cada caso. É crucial o desenvolvimento destas técnicas para permitir alternativas menos invasivas à ressecção

cirúrgica tradicional. Adicionalmente, são necessários avanços nas políticas de follow-up antes e após ressecção, para evitar abordagens erradas, cirurgias desnecessárias e a recorrência das lesões.

Palavras-chave: “lesão subepitelial”, “tumor subepitelial”, “lesão submucosa”, “tumor submucoso”, “tumor do estroma gastrointestinal”

Abstract

Introduction and Aims: Subepithelial lesions, defined as a mass or bulge arising beneath mucosa of normal appearance, are often an incidental finding along the Gastrointestinal tract, with intra or extramural source and a reported incidence of 0,36%, more frequently in the stomach. They can be asymptomatic or present with symptoms such as abdominal pain, hemorrhage or obstruction and may go from benign to malignant lesions. For a more detailed characterization of subepithelial lesions, transabdominal imaging procedures are very limited. Endoscopic ultrasonography is a very important diagnostic exam, able to identify a subepithelial lesion through some of its characteristics such as layer of origin, location or echogenicity. However, when used as an isolated diagnostic exam, it only shows an average precision. Tissue sampling techniques guided by endoscopic ultrasound, are important to adequately obtain tissue samples for further histopathological evaluation, in order to achieve a reliable diagnosis, allowing better management and treatment approaches. Endoscopic treatment techniques, as minimally invasive treatment modalities, associated with less adverse events and shorter hospitalization times when compared to traditional or laparoscopic surgical treatment, are gaining a significant importance, with new techniques emerging during the last few years. This article aims to review the management of subepithelial lesions of the Gastrointestinal tract, focusing on the emergent endoscopic techniques used to achieve a reliable diagnosis and apply effective treatment.

Methods: A search was performed on Pubmed, using the following key words: “subepithelial lesions”, “subepithelial tumor”, “submucosal lesions”, “submucosal tumor” and “gastrointestinal stromal tumor”, applying the filters “Human”, “English” and publication date from 2009/01/01 to 2019/09/01. After selection by title and abstract, and applying exclusion and inclusion criteria, a total of sixty-two articles were selected and thoroughly analyzed, enabling the identification and inclusion of fourteen other opportune articles, obtaining a total of seventy-six articles cited in this review.

Conclusions: Endoscopic ultrasound and Endoscopic ultrasound-guided tissue acquisition have an important role in achieving reliable diagnosis, with Fine-needle aspiration and Fine-needle Biopsy being the more frequently used globally, with some studies presenting some advantage for the latter, when obtaining more adequate tissue samples for histopathological evaluation. Endoscopic resection techniques have already been proved feasible for the resection of smaller intramural subepithelial lesions, but global consensus on which technique to use for each case has not yet been achieved. Further development of these techniques is crucial to provide minimally invasive

alternatives to traditional surgical approaches. Also, advancement in pre and post-resection follow-up policies is needed, in order to avoid wrong management, unnecessary surgeries and recurrence.

Keywords: “subepithelial lesion”, “subepithelial tumor”, “submucosal lesion”, “submucosal tumor”, “gastrointestinal stromal tumor”

List of Abbreviations

ASGE - American Society for Gastrointestinal Endoscopy
AFIP - Armed Forces Institute of Pathology
CEH-EUS – Contrast-enhanced harmonic endoscopic ultrasonography
GI - Gastrointestinal
EFTR - Endoscopic full-thickness resection
EMD - Endoscopic muscularis dissection
EMR - Endoscopic mucosal resection
ESD - Endoscopic submucosal dissection
ESMO - European Society for Medical Oncology
EUS - Endoscopic ultrasound
EUS - FNA - Endoscopic ultrasound - guided fine-needle aspiration
EUS - FNB Endoscopic ultrasound - guided fine-needle biopsy
EUS - TCB - Endoscopic ultrasound - guided Tru-cut biopsy
GIST - Gastrointestinal stromal tumor
HPF - High-power field
NCCN - National Comprehensive Cancer Network
NET - Neuroendocrine tumor
ROSE – Rapid-on-site cytopathological evaluation
SEL - Subepithelial lesion
STER - Submucosal tunneling endoscopic resection

Table of Contents

Table List

Figure List

Introduction

During gastrointestinal (GI) endoscopic procedures, subepithelial lesions (SEL) are frequently an incidental finding in the GI tract. These lesions consist in a mass, bulge, or lump appearing beneath mucosa of normal appearance. Traditionally referred as submucosal tumors, SELs are divided into intramural (arising from within the GI wall layers), and extramural (originating from beyond the limits of the GI wall) and may compress the GI tract and narrow its lumen. The incidence of GI SELs has been repeatedly reported to be around 0,36%, more frequently found in the stomach, 1 in every 300 endoscopies, and they can go from benign to dangerous malignant ones (15% at time of diagnosis) that need a careful management. [1,2] Usually asymptomatic (hence the incidental finding), they may cause symptoms like abdominal pain, GI hemorrhage, obstruction or dysphagia and even jaundice or pancreatitis if they are too close to the duodenal ampulla. [1–3]

Transabdominal imaging procedures, like ultrasonography, magnetic resonance imaging and computerized tomography can sometimes distinguish between intramural and extramural SELs. Even so, for a more detailed characterization of the SEL's layer of origin, these studies are very limited. Endoscopic ultrasonography (EUS) is a very important diagnostic exam, based on cross-sectional imaging and able to identify the five GI wall layers, which revolutionized the approach to the management of SELs allowing the diagnosis of SELs by its originating layer, location along the GI tract, echogenicity and internal echo pattern, size, morphology, mobility, hardness, pulsation, color, surface appearance, extent, surrounding structures and presence of lymphadenopathy. [2,4] The histological layers, which represent the normal structure of the GI wall, can be seen during EUS. However, different echo frequencies can give a different number of layers.[5] Using lower (7.5 – 12 MHz) EUS frequencies, the GI wall appears with a median of 5 layers: the mucosa, including the muscularis mucosa (first and second), submucosa (third), muscularis propria (fourth) and the subserosa and serosa (fifth). With higher frequencies (20MHz), the GI wall is detected with a maximum of 9 layers. [3–5] For this review, the GI wall will have a 5-layer approach.

Even if EUS's diagnostic accuracy for GI SELs is superior compared to the other imaging tests, principally when approaching small (<2cm) lesions, isolated precision of EUS evaluation, for the differential diagnosis of SELs, is average, even though it narrows downs the number of possibilities. [3,6] When EUS results aren't unequivocal, it's important to obtain tissue samples from the lesion to reach a more illative diagnosis.[7]

Histopathological evaluation of GI SELs, allowed by the acquisition of samples obtained by techniques, like Fine-needle aspiration (FNA), Fine-needle biopsy (FNB) and others, can increase the chances of a correct diagnosis, allowing the best management and treatment approach.[2,8]

Patients, during follow-up period, may be more vulnerable to emotional stress caused by the concern for possible malignancy. Also, costs are bigger if this period is too long. Lately, minimally invasive endoscopic modalities are gaining a significant importance in the management of SELs, pushing the boundaries of diagnostic and therapeutic resection approaches, turning them possible in the same session [9–11] Also, comparing to treatment through laparoscopic or traditional surgery, these endoscopic procedures are less invasive, decreasing the need for larger resections, hence reducing the occurrence of adverse events and patient morbidity. [10,11]

This article aims to review the management of SELs of the GI tract, focusing on the emergent endoscopic techniques used to achieve a reliable diagnosis and apply effective treatment.

Methods

A search was performed on Pubmed during September of 2019, using the following formula of words: “subepithelial lesion”, “subepithelial tumor”, “submucosal lesion”, “submucosal tumor” and “gastrointestinal stromal tumor”. The filters “Human”, “English” and publication date from 2009/01/01 to 2019/09/01 were used. Articles that did not meet the overstated criteria were automatically excluded, and duplicates removed. One hundred and eighty-seven articles were then selected by title and abstract.

Inclusion criteria were articles written in English, studies and reviews about diagnostic and treatment techniques, studies about management of subepithelial lesions, and comparative studies relevant to this review. Exclusion criteria were case-reports, studies with a sample below 10, surveys, individual opinion articles, articles about diagnostic and treatment techniques other than endoscopic ones. A total of sixty-two articles were selected by the author of this review, under the co-advisor’s supervision, and thoroughly analyzed to identify and include other opportune publications in this review, resulting in the addition of fourteen articles, obtaining a total of seventy-six articles (Figure 1).

Types of Subepithelial Lesions

Extramural compression may be caused by the spleen and its vessels, hepatic left lobe, gallbladder, colon, abscesses, cysts of the pancreas or kidneys, mass from the uterus, enlarged lymph nodes or even aneurysms. [2] The intramural lesions include gastrointestinal stromal tumors (GIST), schwannomas, leiomyomas, ectopic pancreas, duplication cysts, glomus tumors, lipomas, neuroendocrine tumors (NET), lymphangiomas, brunnerioma, granular cell tumor, or metastasis (table I).[2–4,12]

Gastrointestinal Stromal Tumor

GISTs are the most frequently identified mesenchymal tumor in the gastrointestinal tract, originating from the interstitial cells of Cajal in myenteric plexus.[4,13] The annual incidence varies, with reported values of 4.3 per million in Canada, USA, Czech Republic and Slovakia, and 22 per million in Norway, China and Korea, being this differences possibly explained by variations in the process of identification and reporting of data. The true incidence is unknown due to a historical shortage of diagnostic criteria. The gender distribution is similar, being the 60's the predominant age.[14] They more often result from oncogenic mutations in c-KIT (CD117) and platelet-derived growth factor receptor alpha (PDGFRA).[13,14] GISTs can occur anywhere in the GI tract but are more frequently found in the stomach (50-70%), followed by small intestine (20-30%), colon (5-10%), rectum (5%), esophagus (2-5%) and omentum/mesentery (7%).[2,3,13,15,16] These tumors, with a size range from a few millimeters to 35 cm or more, can be asymptomatic (mostly when < 2cm) or present symptoms like early satiety, fatigue, intraperitoneal or intraluminal GI bleeding, abdominal pain or obstruction. An enlarging GIST may grow towards the mucosa (increasing the risk of bleeding) or the serosa (less usual).[17] Most of them present as a single, well-circumscribed nodule, and some may show areas with necrosis, cystic degeneration or bleeding. Also lymph node metastases are rare.[13] Histologically, they may present as 1 of 3 histologic patterns: the most common, spindle cell type (70%), a low malignancy risk GIST with KIT mutation; epithelioid type (20%), an intermediate-high malignancy risk GIST with KIT mutation, where epithelioid cells prevail; and finally, the mixture of both spindle cell and epithelioid types (10%).[13,15]

With a spherical or fusiform shape, these tumors arise mostly from the fourth, and less frequently, second or third layers of the GI wall. On endoscopy they present as a smooth bulge covered by normal mucosa. During EUS, there is hypoechoic homogeneous lesion.[2,3,16] However, they also show up as heterogeneous with anechoic areas, or shadowing foci (calcification). It is important to assess the eventual presence of enlarged peritumoral adenopathy or the eventual proliferation to other layers of the GI wall.[2,3,16]

There are some discordant results from retrospective studies that report malignant characteristics on EUS. Kida *et al*.[4] proposed that malignancy is to be suspected if three or more of the following findings are present: 1) more than 3 cm; 2) nodular characteristics; 3) heterogeneity; 4) anechoic area and/or ulceration.[4] Still, there is no strong consensus on the features with best correlation to malignancy.[3,4] The National Comprehensive Cancer Network (NCCN) task force report together with the Armed Forces Institute of Pathology (AFIP) suggested that size, mitotic index, and location along the GI tract are the most important prognostic features. (table II). This NCCN-AFIP criteria suggests that GISTs ≤ 2 cm with a mitotic rate of ≤ 5 per 50 high-power field (HPF) have no malignancy risk whatever the location. GISTs > 2 cm already carry some risk, which may be increased depending on the mitotic rate (> or ≤ 5) and location. Also rectal or jejunum/ileum GISTs have higher risk of malignancy when compared to gastric ones.[13,18] The European Society for Medical Oncology (ESMO) also corroborated this information.[19] Additionally, tumor rupture during biopsy or excision is another factor of bad prognosis as it increases risk for tumor dissemination.[13,19]

It's difficult to differentiate GIST from leiomyoma or schwannoma through imaging examination, and because of the significant malignancy potential of the first it is of big importance to obtain the correct diagnosis.[4] Pathologic assessment of GIST malignancy risk involves the description of tumor size, location and mitotic rate, and to accurately obtain these information, tissue samples are needed. Also, the obtention of adequate specimens is of big importance to perform immunohistochemical analysis which is able to detect expressed markers like the KIT (CD117) (95% of GIST are positive), CD34, PDGFRA, BRAF, Protein kinase C theta or DOG1 helping to achieve correct diagnosis and management of the lesion.[3,13,16] Obtaining tissue samples or resecting GISTs, as a fourth layer lesion, can be challenging because the deep location of the tumor makes it less accessible to biopsy, with a risk of perforation to be considered.[2–4,13]

Leiomyoma

Leiomyoma is a benign tumor of the smooth muscle, presenting as a hypoechoic lesion on EUS, arising from either the muscularis mucosa or the muscularis propria.[2–4] They involve 60-80% of all SELs that have its origin in the fourth layer of the GI wall in esophagus. Of all esophageal leiomyomas, 90% are found in the middle and lower thirds of the esophagus, correlating with the esophageal muscular composition, where smooth muscle predominates in the lower third and a mixture of smooth and skeletal muscle is found in the middle third. In the stomach they appear mostly near the esophagogastric junction and in the body, and on EUS, as a hypoechoic lesion, it may be difficult to distinguish from GIST, emphasizing the importance of immunohistochemical analysis, where leiomyomas stain negative for CD117 and CD34 unlike most GISTs.[3] The appearance of symptoms is also related to size, location and direction of growth.[2,4]

Schwannoma

Schwannomas are tumors of spindle cells, with very low malignancy potential, and consequently with favorable outcome. They originate from the Auerbach's and Meissner's plexuses (the latter is less frequent), from any nerve with a Schwann cell sheath.[2,4] In a series of 33 cases, most of them originated in the stomach (70%) followed by the colon and rectum (15%), esophagus and none from the small intestine. On EUS, it's seen as a hypoechoic lesion arising from the third or fourth layers similar to GIST and Leiomyoma. [2–4]

Glomus Tumor

Glomus tumor are potentially malignant mesenchymal masses that originating from modified smooth muscle cells, acting like perivascular glomus bodies. They are more frequently found in the antrum of stomach, in the fourth layer of the GI wall, as an ulcerated mass. Despite that, they can also arise from the third layer and, even though unusually, extend to the second. On EUS they're either isoechoic and homogeneous or hypoechoic and heterogenous. [2,4]

Ectopic Pancreas

Ectopic pancreas, or aberrant pancreas consists in pancreatic tissue found outside the pancreas without any connection, anatomic or vascular, to the pancreas itself. Frequently asymptomatic, they can cause mucosal ulcer, bleeding, intussusception, intestinal or bile duct obstruction. Endoscopically they show up mostly in the gastric antrum, duodenum, and jejunum as an umbilicated lesion, a mass or ulcer. On EUS, two types of ectopic pancreas can be identified: the shallow type, small, limited to the third layer in the gastric antral area, and the deep type, larger, extending to the third and fourth layers, mostly in the middle and upper area of the stomach. Characteristic features can be seen on EUS, such as hypo-isoechoic echogenicity, badly demarcated contour, heterogeneous echo structure, ductal structure and/or cystic components. [2,4]

Duplication Cyst

GI duplications cysts are rare congenital anomalies. Normally asymptomatic in adults, their potential to malignancy is significatively low. On EUS, this cystic lesion show's up as an anechoic, homogeneous structure, with regular margins, originating from the third layer or in an extramural position, and may be found in the foregut and small bowel.[2,3]

Lipoma

Lipomas are benign tumors, more frequently found in the right side of the colon but can also appear in any location along the GI tract (gastric antrum and body, and duodenum). Generally asymptomatic, they can cause some symptoms, if large enough. Their malignant potential is

extremely low. Pillow and tent signs are specific but not sensitive features found on endoscopy, where they are also seen as plane SELs. On EUS, one can identify them as homogeneous hyperechoic masses in the third layer.[2–4]

Neuroendocrine Tumor

NETs, previously called carcinoid, are more often found in men with 40-50 years in the stomach, rectum and duodenum. Gastric NETs can be divided into 3 subtypes: Type I (well-differentiated, multifocal), with low potential to metastasize, associated to chronic atrophic gastritis and hypergastrinemia, with 5-year survival similar to that of general population; Type II (well differentiated, multifocal), with intermediate potential for metastasis, associated to Zollinger-Ellison syndrome, with 5-year survival rate between 60% and 75%; and finally Type III (well-differentiated, unifocal), often sporadic, and often metastatic at time of diagnosis, with 5-year survival below 50%.[3,20] Endoscopically NETs show up as red or yellow, small, round, sessile and polypoid lesions, sometimes presenting central depression or ulceration and dilated blood vessel. During EUS, they present as hypoechoic homogeneous oval to round tumor, with smooth border and clear margin, arising from the second layer and sometimes penetrating the third. Appropriate classification of NET at the moment of diagnosis is very important to perform adequate management of this SEL.[2–4,20]

Lymphangioma

Lymphangiomas are uncommon benign SELs. Children are more affected than adults, and the GI tract is rarely involved (when present, they appear in the small bowel). On endoscopy lymphangiomas present as soft, solitary, not so elevated SELs with pillow sign. On EUS, one can detect a lymphangioma in the third layer of the GI wall, with anechoic pattern, including a septum[4]

Brunnerioma

Brunnerioma are tumors of the Brunner gland, being considered the most frequent SEL found in the duodenum. On EUS, they appear as a hypoechoic tumor, although they can have, sometimes, cystic components.[4]

Granular Cell Tumor

Granular cell tumors are considered benign, though there are reported cases of malignancy, usually found in the esophagus and less frequently in the colon and stomach. During endoscopy they're seen small (<20mm), sessile, with yellowish-white color and "molar teeth appearance". On EUS they appear arising from the second layer (sometimes third) as homogeneous, hypoechoic lesions, with well demarcated contours.[3,4]

Metastasis

In the stomach, more than 50% of metastases present as SELs with a central depression, mostly in the upper and middle third of the organ. They more frequently originate from the lung, esophagus, breast and melanoma. On EUS metastases may show up in any layer of the GI wall, or extramural, as a hypoechoic and/ or heterogeneous mass.[2–4]

Diagnostic Methods

Knowing the more typical characteristics of the cited types of SELs and addressing all the EUS's features, like layer of origin and location in the GI tract, can help to narrow the differential diagnosis. For instance, it's less likely to be a GIST if one finds a fourth-layer SELs in the esophagus, but if it's found in the same layer in the stomach, the probability of being a GIST increases.[2,13]

Hwang et al.[21] showed, that EUS alone could only predict 43% of SELs. All the misdiagnosed lesions consisted in hypoechoic lesions, found in the submucosa and muscularis propria, respectively.[21] Many reasons could explain these results such as: a broad spectrum of SELs arising from the third and fourth layers of GI wall; also, several lesions present hypoechoic features, like GISTs, NETs or leiomyomas. Furthermore, GISTs are difficult to distinguish from schwannoma or leiomyomas on EUS; Interpretation of EUS images, is operator dependent and can also affect the diagnostic accuracy of EUS.[21,22]

This exposes the importance of obtaining tissue samples from SELs, allowing histopathological analysis, providing a more reliable diagnosis to take the best treatment decisions.[22,23] Tissue samples may be obtained through EUS – guided-tissue sampling. [2,4,22,24]

The isolate visualization of EUS appearances can be diagnostic for SELs like duplication cysts, lipomas and ectopic pancreas, without tissue sampling for further analysis. Nevertheless, for some hypoechoic and heterogeneous lesions like GISTs, leiomyomas, NETs and schwannomas, arising from the second, third and fourth layers, EUS alone may be insufficient. Consequently, obtention of tissue samples or even full removal may be required to achieve a reliable diagnosis, through immunohistochemistry, and ascertain the lesion's malignant potential.[3,7,25] SELs more often arise from the submucosa and muscularis propria layers, and that can be a challenge if tissue acquisition is necessary. Therefore, there are various described techniques to reach a correct diagnosis.[3]

Standard and Bite-on-bite Biopsy

During standard biopsy, an open biopsy forceps can be used to assess the size of a SEL. When using a closed biopsy forceps one can assess if the lesion is soft (lipoma) or firm (GIST). A standard biopsy forceps (jaw volume 5-6 mm^3), when used alone, is almost always insufficient for diagnosing SELs arising from the third and fourth layers. Bite-on-bite biopsy technique may be used for further tissue acquisition, creating a defect in the mucosa over the SEL, using a standard biopsy forceps or a large capacity biopsy forceps (jaw volume 9-10mm^3), obtaining deeper tissue samples.[3,26] However, this method presents a diagnostic yield of only 17-38% and there is risk for complications.[26]

Jumbo Biopsy

Allied to poor performance of bite-on-bite biopsy when using standard or large capacity biopsy forceps, Jumbo biopsy forceps (jaw volume 12-13 mm^3) have been used to obtain a wider or deeper field of tissue samples. However, bleeding is an often complication when using these forceps. Jumbo biopsy forceps improve the diagnostic yield when SELs arise from the submucosa, but when they originate from a deeper layer like muscularis propria, the diagnostic yield decreases.[3,26] Buscaglia et al.[26] reported diagnostic rates of 65% and 40% for lesions arising from submucosa and muscularis propria, respectively.[26]

Unroofing

The unroofing of a SEL consists in removing the overlying mucosa, enabling the obtention of tissue samples from deeper layers. Compared to a standard biopsy, these technique presents higher diagnostic yields. Unroofing can be performed by the single-incision needle-knife (SINK) technique, in which a linear incision (6-12mm) is created, by a needle-knife, over the highest convexity of the lesion, allowing tissue samples to be obtained from deeper layers, using biopsy forceps, with less adverse events. Ligation of a SEL before unroofing may reduce the risk of bleeding, alter the morphology of the lesion increasing its protrusion into the lumen aiding further manipulation, and strangulate the lesion, leading to ischemic ablation and sloughing of the lesion.[3,27,28]

Endoscopic Ultrasound – guided Fine-Needle Aspiration

EUS-FNA, first described by Vilmann et al. in 1992, is an accurate method to obtain tissue sample for the diagnosis of a wide spectrum of lesions.[29] When available, is globally the most used tissue obtaining technique for SELs originating from the third and fourth layers. Still, the values of this technique's diagnostic accuracy are between 46% and 93%.[30] Lesion size, type and size of the

used needle, biopsy technique, availability of on-site cytologic review and use of stylet or suction are some of the reported factors that may affect EUS-FNA's diagnostic yield.[3,30,31]

EUS-FNA needle systems include a removable stylet because it was hypothesized that its use may prevent clogging of the needle lumen by tissue when traversing the GI wall to reach the SEL, affecting the obtention of aspirate cells. Several trials concluded that there is no difference in the diagnostic yield of malignancy and specimen quality when using or not a stylet.[30] Concerning the use of suction during EUS-FNA, there are contradictory results in several studies evaluating the possible improvement of the diagnostic yield when using this technique, and so future trials are needed to understand the additional utility of suction to obtain better samples during EUS-FNA.[3,30,32] Accuracy of EUS-FNA when approaching SELs increases gradually with the number of passes, reaching the maximum at the fourth pass.[33] Rapid on-site cytopathological evaluation (ROSE) is performed by cytopathologist in a team-effort with the endosonographer providing real-time feedback regarding the adequacy and content of the obtained specimen, in order to make an accurate diagnosis, reducing the number of passes and improving the procedure's effectiveness. Also, ROSE may help to increase the quality of the specimen preparation so that it can be used in ancillary test like immunohistochemistry. However, there is conflicting data regarding the clinical impact of performing EUS-FNA with ROSE, and the existing data is currently insufficient to recommend the performance of ROSE in a routine basis.[3,30,32]

EUS-FNA it's a low-risk technique, and rarely provokes complications (mostly abdominal pain). Also, in case of cystic lesions, antibiotic prophylaxis should be considered.[2,24,25] For the maximizations of tissue acquisition for immunohistochemical staining it is important to choose the best needle and needle gauge. There are 3 standard needle gauges: 19-gauge, 22-gauge and 25-gauge. The last two (22G and 25G) may be used to obtain small aspirates of small mobile lesions, whilst 19G (a needle with larger caliber) may be used to acquire a larger amount of tissue. However, in some locations (proximal stomach or duodenum), it may be difficult to use 19G needle because of its size and the device's hardness, obtaining a higher percentage of bloody and contaminated samples, compared to smaller needles. Still, there is lack of studies comparing the different needle sizes. [3,32] Zhang et al.[25] reported that as larger needles are harder to use and smaller ones obtain smaller tissue samples, there is no significative difference between their diagnostic yield. Also, Imazu et al.[34] detected, in a prospective study, no significative difference between the diagnostic yields of 22G and 25G needles. However, differences in ease of puncture (25G easier than 22G), and quantity of obtained tissue (22G more quantity than 25G) were noticed, reinforcing that the decision of which needle to use should be based on the features of the SEL.[34] Aspirates generally consist mostly of cellular material and that is a limitation for this technique because acquisition of

histologically optimal core samples is necessary to evaluate architectural details, obtain mitotic rate and perform immunohistochemical staining required to differentiate GIST from other muscularis propria lesions like leiomyoma and schwannoma.[35–37]

Endoscopic Ultrasound – guided Fine-Needle Biopsy

To obtain core biopsies, new needles were specifically designed to perform EUS-FNB like: Cook's EchoTip® and ProCore® – 19G, 20G, 22G and 25G; Boston's Acquire® and Medtronic´s SharkCore® - 19G, 22G and 25G. [3,32,38] Kim et al.[36] reported rates of 92% and 75% for EUS-FNB and 30% and 20% for EUS-FNA in acquiring macroscopically and histologically optimal core samples, respectively, from hypoechoic SELs, located along all the GI tract, arising from the submucosa and/or muscularis propria. Also, the reported diagnostic yields of EUS-FNB and EUS-FNA when using 22G needles were 75% and 20%, respectively, when approaching SELs. Additionally, EUS-FNB had a lower median number of needle passes required to obtain optimal core specimens compared to EUS-FNA, 2 versus 4, respectively.[36] Iwai et al.[23] reported diagnostic rates of 73.1% and 91.3% from immunohistochemical analysis of tissue samples obtained through EUS-FNA and EUS-FNB, respectively.[23] Han et al.[33] found no significant differences in diagnostic yield from immunohistochemical assessment of gastric SELs and GIST, when comparing EUS-FNA (68,2% and 75.0%) with EUS-FNB (81.8% and 93.8%), respectively. Nevertheless, the number of needle passes required to obtain adequate samples was higher in EUS-FNA. EUS-FNB, like EUS-FNA, has some technical difficulties associated with the needle's gauge. Puncture from the duodenum may be difficult when using 19G needle, but this difficulty may be overcome by using a 22G needle, achieving similar macroscopically optimal core sample and diagnostic sufficiency rates, comparing the two needles gauges.[36] The complication rates of EUS-FNA are similar to EUS-FNB, 1-2,5% and 2-4% respectively, and the safety of both of both techniques is well established. ESGE guidelines report that EUS-FNA and EUS-FNB are equally recommended, though some evidence suggests that FNB may be more adequate for histologic diagnosis, with fewer needle passes required, but with higher monetary costs. Also 22G and 25G needles are equally recommended when approaching solid masses.[32] A meta-analysis, compared Boston's Franseen-tip and Medtronic's Fork-tip needles (end-type cutting needles), and reported no difference, when performing EUS-FNB, regarding diagnostic yield (with or without ROSE), number of needle passes (≤ 2 or > 2), and adverse event rates.[38] EUS-FNB is a feasible and safe technique, able to obtain histological core samples, and may be used as an alternative when EUS-FNA does not acquire an adequate sample for immunohistochemical analysis or is insufficient to achieve a correct diagnosis.[3,23,31]

To overcome the difficulty of diagnosing SELs arising from the muscularis propria without a tissue sample adequate for histologic diagnosis, EUS - Trucut biopsy (EUS-TCB), with a 19-gauge needle (Quick Core; Cook Medical®) was developed to obtain larger specimens without disruption of architecture that would affect histologic evaluation.[30,39] However, EUS-TCB is significantly limited by some factors: only 19G needle available, failure of the spring-loading charging mechanism and high stiffness which complicates the obtention of tissue samples across the duodenum (where scope flexion is required), with high failure rates (40%). Consequently, EUS-TCB does not improve over EUS-FNA's diagnostic yield.[23,30,39,40] One meta-analysis has not found significative difference between diagnostic rates of FNA, FNB and TCB.[25]

Contrast-Enhanced Harmonic - Endoscopic Ultrasonography

During the past few years, CEH-EUS was specifically developed for contrast-enhanced harmonic imaging. It allows the viewing of microvascularity and parenchymal perfusion in tumors, without artifacts related to Doppler, although the pattern analysis is operator dependent. The accuracy and diagnostic yield of CEH-EUS is still unknown. This method can classify lesions through the amount of blood flow (hypo or hyper-enhancement) and in terms of enhancement's pattern (homogeneous or inhomogeneous enhancement).[41–43] Kamata et al.[41] reported that in almost every case of GIST, hyper-enhancement, with homogeneous and inhomogeneous patterns for small and larger lesions respectively, was shown during CEH-EUS. In this study, hyper-enhancement showed good sensitivity for GISTs. Also, hypo-enhancement was noticed in most of benign SELs.[41] Additionally, Kannengiesser el al.[42] corroborated this, and reported that all found GISTs presented with hyper-enhancement, being CEH-EUS able to discriminate this potentially malignant lesions, from truly benign ones like leiomyoma and lipoma. This technique carries some advantages as it can be easily applied without consuming significative extra time during routine EUS and ultrasound contrast agents, like SonoVue or Sonazoid, are generally well tolerated.[41,42] Sakamoto et al.[44] however reported that the CEH-EUS was not able to distinguish between GISTs and other lesions. Also, this study reported that CEH-EUS may be used to see the intratumoral vascularity, an important factor in determining the malignancy potential with better results comparing to this technique's transabdominal version.[44] Lee el al.[43] reported that the operator dependent limitation can be avoided through the use of a perfusion analysis software, which is able to detect a different pattern with higher blood flow in GISTs comparing to leiomyomas, and so, could be a quantitative and independent method able to predict malignancy risk in GI SELs.

Endoscopic Ultrasound – guided Elastography

EUS-guided elastography, once more focused in the evaluation of solid pancreatic lesions and enlarged lymph nodes, has arisen as a very promising technique in the attempt of finding a more accurate, noninvasive diagnostic test for SELs. This exam is a real-time method to evaluate tissue stiffness, using the strain technique, based on lower strain presented by more stiff tissues so that they deform less then soft tissues, when under compression.[45] This tissue stiffness may be altered by some pathologic processes like inflammation, fibrosis or cancer.[45,46] Today, EUS-guided elastography allows qualitative and quantitative (through strain ration and strain histogram) evaluation of tissue stiffness., without any formal contraindications against its performance. Based on this technique, while benign SELs often present with soft-intermediate homogeneous stiffness, malignant ones show a heterogeneous stiff pattern, with GISTs being difficult cases to evaluate and distinguish from others like leiomyomas, and so EUS-guided elastography might not be efficient for the differential diagnosis of GIST .[45,47,48] EUS-guided elastography may help to increase the diagnostic confidence and staging of potentially malignant SELs. Although, only few reports exist regarding the use of EUS-guided elastography for subepithelial masses.[45]

Endoscopic Treatment Methods

Traditionally, removal of GI SELs was done through surgical approaches such as laparotomy and laparoscopy or thoracoscopy. Laparoscopic surgery is effective for the removal of SELs, but sometimes the precise identification of the resection area without additional need of an endoscope, the excessive excision of normal tissue, and the approach of lesions near the esophagogastric junction and pyloric ring pose a huge challenge for its successful performance. It was also common belief, that SELs arising from deeper layers, like muscularis propria, could not be endoscopically removed due to high risk of perforation. However, with the rapid advances in the development of minimally invasive technology and endoscopic skill, endoscopic resection became an important choice for the treatment of SELs, even the ones arising from the fourth layer. Also most SELs present intraluminal growth pattern, facilitating endoscopic treatment, and rarely metastasize so there is no need for lymphadenectomy.[9,10,49,50]

Endoscopic resection techniques, when compared to surgical resection, includes many advantages: prevents large scale resection of GI organs, with less intraoperative blood loss; shorter operation and postoperative hospitalization time; lower postoperative pain intensity and shorter time to first flatus and defecation, lower cost of hospitalization, requires fewer human resources. Also, endoscopic resection offers a treatment alternative for patients, such as the elderly, who were not able to tolerate surgical approaches.[10,51]

These endoscopic techniques include endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), submucosal tunneling with endoscopic resection (STER) and endoscopic full-thickness resection (EFTR).[3,52,53]

Endoscopic Mucosal Resection

EMR is used for removal of lesions from the mucosa and superficial part of the submucosa layer of the GI tract. It can be performed with the intention of treatment, but also with the goal of aiding diagnosis, by acquiring samples adequate for immunohistochemical assessment. EMR can be assisted by injection, cap, ligation or underwater techniques, and the removal can be by single resection, or in a piecemeal fashion (usually if > 20 mm), allowing also multiple sequential resections.[49,52–55]

During injection-assisted EMR, a saline solution is firstly injected into the submucosal space, beneath the lesion, thus creating a pillow which lifts the lesion allowing its capture using a snare. Broad areas of tissue can be resected through this technique, being the risk of perforation reduced by the cushion which protects the muscularis propria.[3,52,55]

In cap-assisted EMR, after a mandatory submucosal injection lifting the overlying lesion, a cap is positioned over it and suction is applied, retracting and capturing the lesion which is subsequently snare resected with electrocautery. There are available caps with an outer diameter of 18 mm, that can resect a lesion up to 2 cm of size.[53,55]

Ligation-assisted EMR employs a band ligation device attached to the endoscope, centered over the lesion, which can be or not lifted by submucosal injection. After suction of the lesion into the banding cap, the band is implanted, capturing the lesion and creating a neo-polyp, which is then resected using snare electrocautery above, below or through the band. The applied band extrudes the muscularis propria, and only the mucosa and superficial parts of the submucosa are captured, enabling the resection of lesions only from these layers.[3,50,52,55] The ligation devices diameters are usually between 9 and 11 mm, and through this technique, SELs up to 13 mm were removed from within or superficial to the submucosa layer of the esophagus, with no major adverse events.[50] Kim et al[56] reported the successful use of ligation-assisted EMR for the resection of < 10 mm NETs, if there is no involvement of the muscularis propria or lymph node metastasis. One study reported ligation-assisted EMR with apical mucosal incision as a feasible and effective method for tissue sampling and resection of <2 cm SELs from the muscularis propria of the stomach, but associated with high perforation rates, without cure assurance.[57]

Underwater EMR consists in filling the GI lumen, after suction of luminal air, immersing the bulge created by the SEL, allowing the visualization of the lesion without stretching the GI wall, keeping the superficial layers (mucosa and submucosa) “away” from the muscularis propria. This avoids the need for submucosal injection used in other EMR techniques, reducing the risk of perforating the lesion, and facilitating its resection. This technique also allows piecemeal resection of larger lesions.[52,53]

In general, injection-assisted EMR, as it does not require special equipment, is easily available. Cap-assisted EMR may be challenging because of the positioning of the snare, if the endoscopist is not familiar with the technique. Also, performing ligation-assisted EMR is relatively easy, as it uses routinely used endoscopic techniques and does not need special positioning of the snare.[3,52,55]

If a lesion is suspected to arise from the deep submucosa or beyond, the American Society for Gastrointestinal Endoscopy (ASGE) suggests that EMR should not be attempted, because of risk or perforation, tumor spillage and incomplete resection.[52] If after submucosal injection, the lesion does not lift, it may indicate that its origin is deeper in the GI wall, and consequently its removal by EMR has higher risk.[3,52,55]

Endoscopic Submucosal Dissection

Similar to EMR, during ESD there is submucosal injection lifting the lesion, which is within the mucosa and/or submucosa layers, followed by a circumferential incision, made around the lesion, by an ESD electrosurgical knife that creates a mucosal flap and allows the dissection of the lesion, strand-by-strand, through the submucosa plane, until the lesion is detached from the surrounding tissue, fulfilling the resection of the lesion. The most challenging step is usually the submucosal dissection, because there are frequently exposed submucosal blood vessels to manage and is difficult to maintain the endoscope within the submucosa plane, in order to prevent the incision of the lesion or the muscularis propria layer. Comparing to EMR, ESD offers better rates of successful curative resection of SELs, and facilitates complete histological resection, but with longer operation time and higher perforation risk. Also ESD is associated with bleeding and incomplete resection, particularly if the lesion is strongly attached to the muscularis propria, and shows extraluminal growth pattern[3,10,53,58,59] One prospective study reported that deep biopsy via ESD provided a 90% yield of diagnosis for SELs, since it obtained sufficiently large tissue samples for histopathological analysis.[60] With the development of endoscopic skills, performance of ESD has turned into a feasible technique for resecting SELs not only from the most superficial layers, but also deeply into the muscularis propria, although with lower success rates when compared to

mucosal and submucosal lesions.[61–63] However, 92.41% resection rate was reported in a prospective study with 144 patients with gastric subepithelial tumors.[63] ESD may be applied for the resection of esophageal, gastric and colorectal SELs like GIST, NETs and granular cell tumors.[62–64] Also, the diameter of the lesion should not exceed 5 cm, and lesions arising from the muscularis propria are associated with higher risk of perforation.[3,10,59,63]

Endoscopic muscularis dissection (EMD) is an ESD based method developed specially for the resection of SELs arising from the muscularis propria layer, being able to remove the whole lesion. However, EMD is different in some aspects, like using endoscopic blunt dissection to completely dissect the lesion from the outer muscle layer of the muscularis propria, minimizing the number of broken muscle fibers (reducing the risk of perforation) and performing a longitudinal incision instead of a circumferential reducing operation time. Liu et al.[10] reported complete resection rate of 96.8% for upper-GI SELs using EMD technique. Still, dissection of lesions found in the muscularis propria of esophagus has higher rates of perforation, comparing to gastric lesions, due to a narrower lumen and thinner wall of the esophagus. In general, EMD has a higher risk of perforation associated, when compared to ESD.[10]

Submucosal Tunneling Endoscopic Resection

STER involves incision in the mucosa, up to 5 cm proximally to the SEL, through which an endoscope is inserted into the submucosa through a tunnel between the submucosa and the muscularis propria, being the submucosal dissection performed until the lesion is seen in the created tunnel. Following this, using ESD techniques, the lesion is resected, without rupturing the overlying tissue, and then retrieved through the tunnel, being the mucosal incision closed afterwards. The fact that the mucosa maintains its integrity is one advantage of this technique, when compared to ESD, promoting a faster wound healing and reducing risk of infection. Nevertheless, it's a difficult procedure and one should be experienced enough to perform it, and deal with possible complications[3,58,65–67]

STER may be a feasible and safe technique for effective treatment of small upper GI SELs. However, it's not so typically applied in the duodenum as in the esophagus and stomach because of naturally difficult anatomical features.[3,9,58,65,66] SELs found in the rectum also pose a challenge.[9] Ye et al.[54] reported a complete resection rate of 97.1% for SELs arising from the muscularis propria, using STER (192 resected out of 197) and EMR (520 resected out of 536). Additionally to the most common complications of this type of procedure, like bleeding and perforation, some major complications like subcutaneous emphysema, pneumothorax and pneumoperitoneum have been reported.[65,68] Muscularis propria lesions with diameter < 3.5 cm can usually be reliably resected,

being esophageal and gastric ones the most suitable targets for this technique.[9,68] ASGE guidelines suggest that STER should be performed to resect SELs up to 4 cm of diameter.[67] One meta-analysis of 28 studies reported complete resection and en bloc resection rates of 97.5% and 94.6%, respectively.[68] Also, STER may be a useful strategy for treatment and obtention of adequate tissue samples (for histopathological analysis) from SELs arising from the muscularis propria in the esophagogastric junction, although carrying some challenges associated with the differences in the anatomic structure of the esophagus and stomach.[9,66]

Endoscopic Full – Thickness Resection

Endoscopic full-thickness resection (EFTR) was developed with the intention to completely remove a lesion arising from any layer of the GI wall, not only from the deeper layers but also the ones originating from the mucosa and submucosa. EFTR also allows the obtention of large tissue specimens, adequate for immunohistochemical analysis. This technique uses the same equipment as the one used for ESD and STER. EFTR may be executed through different techniques: clip-assisted EFTR and EFTR followed by endoscopic closure of the created defect. The key for this procedure's techniques is the successful closure of the created wall defect during the procedure, preventing peritonitis and the need for further surgical intervention.[3,9,67]

EFTR followed by endoscopic closure of the wall defect, considered standard EFTR, is not an advised procedure for SELs found in the esophagus and duodenum, mostly because of limited working space and limited maneuverability to close the created defect, and some reported complications such as mediastinitis and formation of fistulas. In the colon, due to less reliable defect closure and higher risk of perforation and peritonitis, this technique has also some limitations. However, it is indicated for resection of < 3 cm gastric lesions arising from the muscularis propria, being resection of lesions > 3 cm from the same locations, although possible, presented with some challenges associated with its extraction through the esophagus, and the larger size of the created defect in the mucosa.[3,9,67] Zhou et al.[49] reported an 100% resection en bloc rate of 26 gastric lesions located in the muscularis propria using this technique with no major adverse events.

Clip-assisted EFTR, a non-exposed EFTR technique, uses an over the scope cap with a clip, that is advanced to the target lesion, retracting the wall segment containing the lesions and suctioning it into the cap, followed by clip deployment, creating a full-thickness pseudopolyp with the apposition of the serosa layers, that is then resected with and electrosurgical snare above the clip. The cap may have different diameters and the clip different shapes, which can limit the size of the lesions that can be resected. To surpass this limitation, a dedicated full thickness resection device was developed to perform EFTR technique in only 1 step, for larger SELs, but its use for upper

GI EFTR still presents some risks of iatrogenic tear and perforation in anatomical locations like the cricopharyngeus muscle and pyloric ring. However, for SELs located in the lower GI tract, this technique is better employed with less risk for adverse events. [3,9,67,69,70] A prospective showed resection rates of 87% of SELs when performing lower GI EFTR with an over the scope dedicated device.[71] In general, clip assisted EFTR is adequate for resection of < 1cm lesions from the upper GI tract, and < 2 cm from the colorrectum.[3,9,69,70]

Potential adverse events reported are bleeding, perforation or infection, like the previous endoscopic resection techniques. Close-then-cut EFTR techniques may be able to obtain less rates of adverse events, due to the securing of patency of the GI wall before the resection of the target lesion.[3,9,69,70]

Management of Subepithelial Lesions

Up to now, there is no consensus regarding the management of GI SELs, which is influenced by many factors such as: etiology, location, size, symptoms and patient-related factors like age, life expectancy, comorbidities, personal preference, compliance with follow-up, necessity for vigilance exams and also the cost-effectiveness of the approach. Decision whether to follow-up or resect the lesion must be balanced with all these factors. One of the main concerns is the malignancy potential evidenced by some of these lesions, so the detection of the type of SEL may be of great importance. However, all diagnostic modalities, including EUS and tissue acquisition techniques stated above have their limitations.[3,7,16] Any extramural lesion, should be approached based on clinical indication.[3]

Subepithelial Lesions < 2 cm

SEL < 2 cm may be divided into lesions ≤ 1 cm, frequently identified during postoperative pathologic evaluation of other malignancies, or lesions between 1-2 cm. When a SEL ≤ 1 cm is found, the risk of malignancy is considered insignificant even if they consist in a GIST (micro-GIST). In fact, gastric micro-GISTs present no mitotic activity and do not progress in a clinically significant way and so, periodic endoscopic follow-up may be the best approach.[72] Also, in types I and II of gastric NETs ≤ 1 cm, endoscopic or EUS monitorization may be the best approach.[20] In incidentally detected SEL between 1-2 cm, assessment by endoscopy or EUS and further follow up is the standard approach. If during EUS, these are SELs identified as lipomas, duplications cysts, ectopic pancreas or leiomyomas, as benign lesions unlikely to grow, they may require no further vigilance, investigation or intervention, or may be followed up by endoscopy or EUS one or two times per year to assess changes in size or other high-risk features (irregular border, cystic spaces, ulceration, echogenic foci and heterogeneity), even if found originating from the muscularis propria.[2,3,12,19,73–75] Although there is no optimal vigilance policy, a short-term period until the first evaluation may be appropriate (3 months), and if there are no changes, further follow-up may have a more flexible schedule (6 to 12-month intervals). [3,13,19,73,75,76] In a retrospective study of 954 participants, there was no increase in size of 96.4% of GI SELs < 2 cm.[73]

Excision is reserved for patients whose tumors become symptomatic, show high-risk findings on EUS or increase size during surveillance period. A patient, depending on age, comorbidities and life expectancy, can optionally ask for an immunohistochemical analysis of the lesion, which may be performed after tissue sampling by EUS-FNA or EUS-FNB techniques, probably being the latter able to obtain better histologic samples.[19,32,37] Also EUS-FNA is not recommended for benign SELs < 2 cm, or symptomatic ones because they are planned for surgical excision.[37] ESD

and STER may be useful in obtaining adequate tissue samples for assessment of mitotic rate, although one should pay attention to possible complications.[9,60,66]

These lesions, if located in the esophagus, stomach or duodenum and proven to be GISTs, will be either low risk, or of unclear clinical significance, depending on mitotic rate. NCCN clinical practice guidelines suggest that asymptomatic < 2 cm GISTs without high-risk features should undergo annual or biannual EUS surveillance.[13] However, ESMO and Japanese clinical practice guidelines recommend excision with adequate margin and without rupture of any GIST < 2 cm as standard treatment, although ESMO may admit close follow-up of the lesion if it shows histological low risk.[19,75]

If these lesions are in the small bowel or rectum, they may require a different approach due to higher malignancy risk if proven to be GIST. In this locations the GIST's behavior is more aggressive, being its prognosis worst, and surgery risks more significant, with higher rates of recurrence after excision. Consequently, in the case of a small lesion, follow-up may be an option and patient's preference should be considered.[13,19]

Subepithelial Lesions ≥ 2 cm

GI SELs, when ≥ 2 cm, are associated with higher risk of malignancy if proven to be GIST, and so the standard approach is biopsy or excision: A) If the lesion is propitious to EUS or EUS-guided tissue acquisition (FNA or FNB)[19] or if its diameter is between 2-5 cm[75] it should undergo EUS evaluation and/or biopsy – if proven to be GIST or presents malignant findings, there is indication for surgery (laparoscopic or endoscopic); B) If the lesion is symptomatic, or is not amenable for EUS or tissue acquisition, or if it is > 5 cm, laparoscopic/laparotomic excision is the standard approach, being laparoscopy unadvised if lesion > 5 cm.[19,75] NCCN guidelines suggest resection of GIST ≥ 2 cm, via laparoscopic resection if they arise from sites amenable for this procedure, like gastric anterior wall, jejunum or ileum.[13] Also, ESMO recommends that if the mass demands a multivisceral resection, the standard approach is performing multiple core needle biopsies guided by EUS, allowing the obtention of histological diagnosis with low risk of peritoneal contamination and avoiding unnecessary surgery.[19] Another approach to a GIST requiring large scale resection could be neoadjuvant use of imatinib therapy in order to shrink the tumor before its resection. After resection of intermediate to high-risk GISTs, imatinib therapy is adequate. [13,16,19,75]

The fact that lymph node metastasis are rare for GISTs, may open doors for endoscopic resection by ESD, STER and EFTR techniques, capable of resecting SELs (benign or malignant) arising

not only from the most superficial layers but also deeply from the muscularis propria, if the size is amenable for this approach (< 3.5 – 4 cm).[9,49,59,63,67,68]

NETs as mucosal and submucosal based lesions may be resected by EMR depending on location, size and histological type: 1) Gastric Type I and II NETs may be monitored by endoscopy of EUS if < 1 cm or may require EMR. If larger, ESD or surgical resection. Type III should undergo surgery due to high risk of lymph node metastasis. 2) Rectal NETs, if ≤ 2 cm, may undergo EMR or transanal excision, without further surveillance (< 1 cm) or EUS follow-up (1 – 2 cm) in 6 to 12 months period. Surgical management is recommended if rectal NETs > 2 cm.[3,20] 3) Duodenal NETs may also be endoscopically resected if < 1 cm and loco regional or may undergo surgical resection, similarly to Jejunal/Ileal/Colonic NETs.[3,20,56]

A management algorithm for incidental gastric SELs, based on NCCN, ESMO and Japanese guidelines can be seen on Figures 2 and 3.

Follow – Up

There is lack of published data regarding the best follow-up policy to maintain before and after a SEL is resected. If benign SET is resected, first follow-up assessment should happen 3 months after, and if there is no recurrence there is no need for further evaluation. If there is recurrence, annual evaluation should be made.[70] In case the resected lesion was a proven GIST, high-intermediate risk patients should undergo follow-up with tight intervals, every 4 – 6 months, and low-risk patients in more relaxed periods, every 6 – 12 months.[13,19,70,75] The same should happen with other malignant SETs, like a NETs.[13,20,70]

Conclusions

SELs are an important entity in the GI tract, since some may have malignant potential, or present with significative symptoms. EUS and EUS-guided tissue acquisition have an important role in achieving reliable diagnosis, facilitating the management of these lesions, with EUS-FNA and EUS-FNB being the more frequently used globally, with some studies presenting some advantage for EUS-FNB, when obtaining more adequate tissue samples for immunohistochemical evaluation. In the future, emerging techniques like CEH-EUS and EUS-guided elastography may also play an important part in diagnosing SELs.

Endoscopic resection techniques have already been proved feasible for the resection of many intramural SELs, but global consensus on which technique to use for each case has not yet been achieved. Further development of these techniques is crucial to provide minimally invasive alternatives to traditional surgical approaches that may be inadequate/impossible to perform for some part of the affected population. Also, advancement in pre and post-resection follow-up policies is needed, in order to avoid wrong management, unnecessary surgeries and recurrence of SELs.

Attachments

Tables

Table I: Subepithelial lesion types, layers of origin, Appearance on endoscopic ultrasound, and most frequent location.[2–4,12]

Type of Lesion	EUS Layer	EUS appearance	Frequent Location (most to least frequent)
Gastrointestinal Stromal Tumor	4th (rarely 2nd or 3rd)	Hypo-Isoechoic; homogeneous lesion, some as heterogeneous lesion with anechoic areas, or shadowing foci (calcification)	Stomach, small intestine, colon, rectum, esophagus, omentum, mesentery.
Leiomyoma	2nd and 4th	Hypo-Isoechoic; Well-circumscribed	Esophagus and stomach.
Schwannoma	3rd and 4th	Hypo-Isoechoic	Stomach, colon, rectum, and esophagus
Glomus Tumor	3rd and 4th	Hypo-Isoechoic; With some hyperechoic spots, correspondent to calcifications	Stomach
Ectopic Pancreas	3rd and 4th	Hypo-Isoechoic; Indistinct margin, with anechoic cystic or tubular structures.	Stomach, duodenum and jejunum
Duplication Cyst	3rd and extramural	Anechoic; Round or oval	Esophagus, stomach, duodenum and small bowel
Lipoma	3rd	Hyperechoic; Homogeneous, with smooth margin, maybe polypoid.	Colon, stomach and duodenum
Neuroendocrine tumor	2nd and 3rd	Hypoechoic; Homogeneous, oval or round, with smooth margin	Stomach, rectum and duodenum
Lymphangioma	3rd	Anechoic; Presence of internal septs	Small bowel.
Brunnerioma	3rd	Hypo-Isoechoic; Smooth margin.	Duodenum
Granular Cell tumor	2nd and 3rd	Hypoechoic; Heterogeneous; Yellowish-white color and molar teeth appearance	Mostly esophagus
Metastasis	Any or extramural	Hypoechoic; Heterogeneous	All GI tract

Table II: Risk stratification of primary Gastrointestinal stromal tumor, by mitotic rate, size and site.

Tumor		**Risk for Progressive Disease (%)**			
Mitotic Rate	Size	Stomach	Jejunum/Ileum	Duodenum	Rectum
≤ 5 per 50 HPF	≤ 2 cm	None (0%)	None (0%)	None (0%)	None (0%)
	>2, ≤ 5 cm	Very low (1.9%)	Low (4.3%)	Low (8.3%)	Low (8.5%)
	>10 cm	Moderate (10%)	High (52%)	High (34%)	High (57%)
>5 per 50 HPF	≤ 2 cm	None	High	Insufficient data	High (54%)
	>2, ≤ 5 cm	Moderate (15%)	High (73%)	High (50%)	High (52%)
	>10 cm	High (86%)	High (90%)	High (86%)	High (71%)

Adapted from NCCN Task Force Report: Update on the Management of Patients with Gastrointestinal Stromal Tumors[13]

Figures

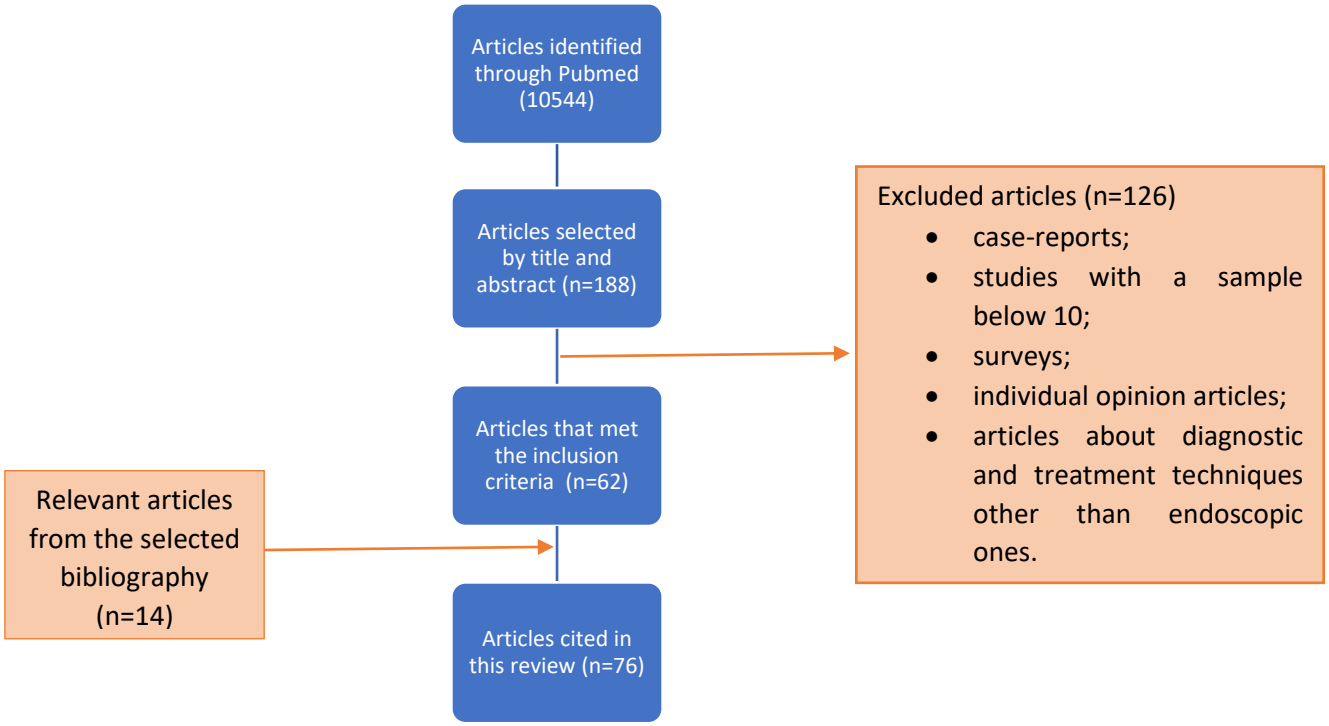
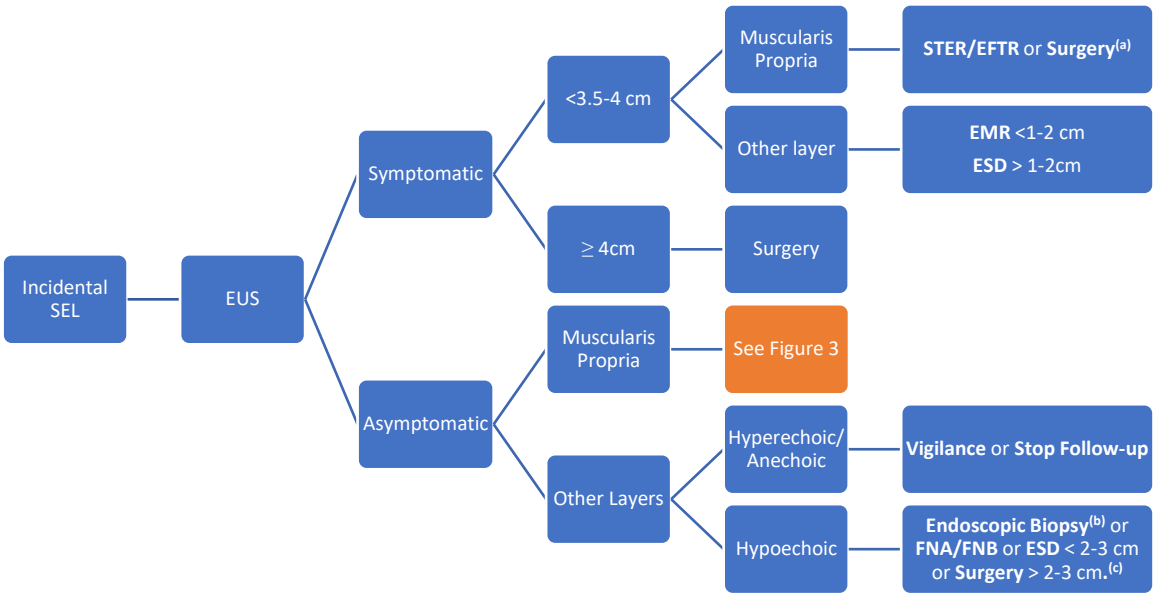
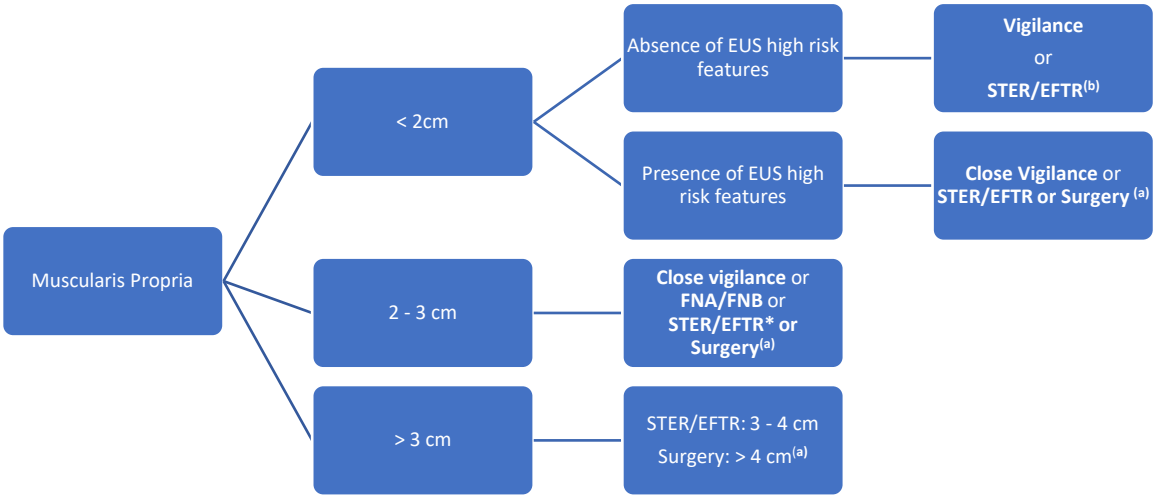


Figure 1 - Article selection flowchart



(a) - Depending on patient and local expertise; (b) - Endoscopic Biopsy: Bite-on-bite, Jumbo, Unroofing; (c) – If GIST or NET and/or > 2-3 cm, prefer surgery; EFTR – endoscopic full-thickness resection; ESD – endoscopic submucosal dissection EUS – endoscopic ultrasound; FNA – Fine-needle aspiration; FNB – Fine-needle biopsy; SEL – subepithelial lesion; STER – submucosal tunneling endoscopic resection;

Figure 2 – Management algorithm of incidental gastric SELs. [13,19,75]



(a) - Depending on patient and local expertise; (b) - NCCN guidelines recommend vigilance whereas ESMO and Japanese guidelines recommend endoscopic resection. EFTR – endoscopic full-thickness resection; EUS – endoscopic ultrasound; FNA – Fine-needle aspiration; FNB – Fine-needle biopsy; STER – submucosal tunneling endoscopic resection;

Figure 3 – Management algorithm of incidental gastric SELs (continuation of Figure 2). [13,19,75]

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