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# Endoscopic resection of Sub-mucosal tumours

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**Summary**

Submucosal gastrointestinal tumours represent a unique, diverse and challenging group of lesions found in modern medical practice. Whilst management has traditionally been surgical, the development of advanced endoscopic techniques is challenging this approach. This article aims to investigate the role of endotherapy in treatment pathways, with a focus on carcinoid and gastrointestinal stromal tumours (GIST). In particular, we will discuss which lesions can be safely treated endoscopically, the evidence base behind such approaches and the limitations of the current evidence. The article will consider how these techniques may change the management of submucosal tumours in the future.

**Key words**

EMR, ESD, submucosal tumour, Carcinoid, NET, GIST, gastroscopy

## Introduction

Submucosal gastrointestinal tumours represent a unique challenge to modern clinical practice. Whilst these tumours commonly arise within the submucosa (hence the term submucosal tumours) they are more appropriately termed as subepithelial tumours, as they can arise from layers other than the sub-mucosa, such as the muscularias mucosa (leiomyoma) or muscularias propria (GIST etc.). Whilst the exact incidence is unknown, currently such lesions occur with an incidence of 0.4% at diagnostic endoscopy [1]. This is very old data and we believe that they are actually much more common. With the advent of capsule endoscopy and improved access to endoscopic procedures this may increase as more subtle lesions are recognized and diagnosed.

A submucosal tumour is any neoplastic lesion originating beneath the epithelium. Clinically they can be divided as tumours without malignant potential, such as mesenchymal tumours, Lipoma, leiomyoma, schwanoma, desmoid tumors, Duplication cysts, Pancreatic rests, Inflammatory fibroid polyps, and giant cell tumour, and those with malignant potential, which includes glomus tumours, carcinoids, and gastrointestinal stromal tumours (GISTs). Finally malignant sarcomas can arise in this area. Frequency of each tumour type varies throughout the gastrointestinal tract and is summarized in table 1. The above classification illustrates the importance of a tissue diagnosis. However, a challenging aspect of obtaining histology on these lesions is directly related to their relationship to the mucosa. Traditional biopsies cannot sample beyond mucosa and due to the submucosal location of the tumour they fail to obtain diagnostic inflammation. It was suggested that tunneled biopsies could be

performed to obtain a tissue sample, but such techniques have poor sensitivity of 15-40%, with a high risk of bleeding (3%) [2] and therefore cannot be recommended in routine practice. If biopsies can be performed at the apex of the lesion then they will not interfere with subsequent resection of a submucosal lesion. However, if taken from near the edge of the lesion they can cause scarring. This is especially true for tunneled biopsies, which can cause severe fibrosis and difficulty if endoscopic resection is to be attempted later.

**Assessment of submucosal tumours and the role of endoscopic ultrasound**

There are essentially two key decisions to be made during assessment of submucosal tumours. The first issue is predicting the histological type of the lesion and the second issue is the layer from which the tumour arises. Both of these are important. There histology helps us decide the need for resection based on the malignant potential. The layer from which the lesion originates fundamentally helps decide the risk profile of endoscopic resection.

*Endoscopic assessment*

A key challenge with submucosal lesions is assessment. Due their origin beneath the epithelium this is not simple. Macroscopic examination is still important. GISTs generally have a characteristic appearance with depressed punctum in the centre whilst lipomas will usually demonstrate the 'pillow sign' when pressed. Further, whilst conventional surface pattern examination will not predict histology, it is of value in demonstrating that the observed abnormality does not arise from the epithelium.

*Endoscopic ultrasound*

Endoscopic ultrasound (EUS) is a minimally invasive method of evaluating submucosal lesions of the gastrointestinal tract. The examination has two distinct but complimentary roles; in establishing which part of the sub-mucosa a lesion originates from and in obtaining a tissue sample for histology.

Submucosal lesions can essentially originate from several areas; the muscularias mucosae, the sub-mucosa itself or the muscularias propria. The point of origin is important as it defines what treatment options are available. Lesions developing from the muscularias propria are best managed surgically, whereas endoscopic options exist for lesions arising from the muscularias mucosae or submucosa. It has often been questioned whether EUS can define which layer a lesion originates from. Unfortunately, whilst EUS is effective at confirming that a lesion is arising from the submucosa [3], it has not been successful in defining either lesion type or depth of invasion of sub-mucosal tumours. A small retrospective study from the United States examining 22 patients who underwent endoscopic resection of sub-mucosal gastric lesions found that EUS had an accuracy of 45% compared to the final histology [4]. A Japanese study has suggested that a better degree of accuracy can be achieved, with an accuracy in predicting depth of invasion of 88% being achieved [5]. Both of these studies were very small. A more recent, larger study has however shown a similar picture. Using a dedicated scoring system this single centre prospective series of 226 patients with gastric lesions found that EUS was able to achieve a sensitivity and specificity of 75.8% and 85.4% for GIST, 84.6% and 73.1% for ectopic pancreas, 75.9% and 99.5% for leiomyoma and 91.7% and 96.7% for lipoma [6].

Unfortunately there were no carcinoids in the series. A small study has suggested that when using the newest generation of EUS machines, contrast enhanced harmonic ultrasound (CEH-EUS) may enhance the diagnostic accuracy [7]. This study of 17 gastric or oesophageal lesions reported 100% accuracy in differentiating GISTs from benign lesions, with GISTs showing hyperenhancement. More work is required in this area.

EUS can be used to obtain a tissue diagnosis through either trucut biopsy or fine needle aspiration techniques. A small retrospective study has suggested that EUS guided tissue sampling can provide an accurate diagnosis in 91.7% EUS guided trucut biopsies and 84.6% of FNA biopsies. It should be noted that this study was very small with just 12 patients undergoing EUS guided biopsy and 13 undergoing EUS guided FNA [8]. A prospective uncontrolled study of 49 patients undergoing EUS guided trucut biopsy did not show such good results, with adequate samples to make a diagnosis only achieved in 63% of cases. Furthermore, whilst there was good agreement between the trucut biopsy diagnosis and the final histology from surgical resection, there was no correlation between the mitotic index estimated from the trucut specimen and that obtained on the final surgical histiology. This was attributed to the small size of the trucut biopsy specimens [9]. Biopsy is probably superior to FNA. However, it is not always possible to obtain a biopsy. A prospective multicenter study of 100 patients with gastric submucosal lesions found that tissue acquisition using EUS technique with a 19G FNA needle (i.e. tissue rather than cytology) was only possible in 46% of lesions. Furthermore, the diagnostic yield was only 52%. Furthermore, complications were not insignificant, with 22% of patients

developing self limiting haemorrhage but one patient suffering from a fatal abscess [10]. A larger study suggested the complication rate for endoscopic ultrasound-guided fine needle aspiration is lower. It looked at 1,135 cases, with just 5 cases of bleeding and one death from an unrelated cause [11]. EUS guided fine needle aspiration has been shown to be effective in diagnosing submucosal lesions in the upper gastrointestinal tract, with a prospective study of 50 cases suggesting that a sensitivity, specificity, positive and negative predictive values, and accuracy for diagnosing submucosal mesenchymal tumors of 82.9, 73.3, 87.9, 64.7, and 80%, respectively. Corresponding values for nonmesenchymal lesions of 100, 85.7, 80, 100, and 90.9% were achieved [12].

We believe that EUS is a potentially useful tool in characterizing the nature and origin of these tumours. The accuracy of EUS is likely to be high in expert hands at high volume centres and as the technology evolves it will get better. It is important to remember that a positive EUS can be helpful but a negative EUS is not very helpful and ultimate diagnosis may only be obtained by resection and removal of these tumours.

**Types of submucosal tumours and the challenges of management**

As referenced earlier, in treating submucosal tumours it is important to appreciate that this represents a broad range of lesion subtypes. To understand resection strategies it is helpful to appreciate some of the main categories of tumour and the challenges they represent.

Many of the submucosal tumours found during endoscopy are not causing the patient any symptoms, and are found as incidental findings. Asymptomatic lesions pose a significant challenge to the endoscopist. They often do not represent the reason for the patients presentation to endoscopy, and are essentially an 'incidenteloma'. Treatment of these lesions will often do little or nothing for the patients symptoms but might carry a risk of malignancy. Resection of these tumours is also fraught with dilemmas. Resection carries risk of complications, raises patient anxiety and the consequences of resection may even cause symptoms, dependent on location and area of bowel resected. This requires very careful thought process by weighing the risks and advantages of resecting these tumours.

**Neuroendocrine tumours (NETs)**

Neuroendocrine tumours arise from cells of the nervous and endocrine systems. Carcinoid tumours, arising from enterochromaffin cells, are the most common, accounting for 2/3 of all gastrointestinal NETs [13]. Such lesions have a prevalence of 35 per 100,000, although this may be higher if clinically silent tumours are included. Neuroendocrine tumours become symptomatic by production of hormones related to their cell type of origin, including flushing, diarrhea, palpitations and wheezing. However, many of the carcinoids found during endoscopic examination will not be hormone secreting and asymptomatic at time of discovery.

There are a number of ways of classifying neuroendocrine tumours, and consensus has been difficult to achieve. However, World Health Organisation (WHO) guidelines in 2010 were successful in producing a useful classification

system which divides NETs into two clinically distinct pathologic classes of well and poorly differentiated tumours [14]. The guideline makes the following definitions:

• Neuroendocrine neoplasms: the entire spectrum of neoplastic cell types with endocrine properties and phenotypes that express neural markers

• Neuroendocrine tumors (NETs): well-differentiated neuroendocrine neoplasms that can be divided into grade 1 (G1) and grade 2 (G2) depending on proliferation and histology

• Neuroendocrine carcinomas: poorly differentiated grade 3 (G3) neuroendocrine neoplasms

NETs may therefore be referred to using a variety of terms, such as "carcinoids," "carcinoid tumors," or "endocrine tumors." It was suggested that these terms can be used interchangeably with "NETs" as defined above and for the purposes of this article we will use the terms 'carcinoid' and 'NET' refer to the same pathology.

Carcinoids are most commonly found in the appendix. Other common sites include the stomach and rectum. Carcinoids have malignant potential. This has been thought to be related to size, with lesions greater than 2cm having greater malignant potential. Gastric carcinoids are of particular interest. They are broadly divided into four distinct sub-types [15]:

- Type I: Multiple Carcinoids on a background of Atrophic gastritis (Type A Chronic gastritis)

- Type II: Associated with Multiple endocrine neoplasia (MEN) or Zolllinger Ellison (ZE) syndrome
- Type III: Sporadic carcinoid without hypergastrinaemia
- Type IV: Poorly differentiated neuroendocrine carcinoma

*Type 1 gastric carcinoids* represent 70-80% of lesions. They are small (<2cm) and often multiple in nature, having a polypoid appearance. Associated with chronic atrophic gastritis, they are well differentiated. Often associated with elevated serum gastrin and elevated or normal pH, they have a low metastatic potential (2-5%).

*Type 2 gastric carcinoids* are much less common, representing 5-6% of lesions. Again small, multiple and polypoid in nature, they are associated with gastrinoma / MEN 1. Whilst serum gastrin levels are elevated, gastric pH levels are decreased. The risk of metastasis is higher (10-30%) although tumour related deaths are still low.

*Type 3 gastric carcinoids* are high risk. They represent 14-25% of gastric neuro-endocrine lesions. Unlike type 1 and 2 lesions, they are unique and often large (>2cm in size) with a polypoid, ulcerated appearance. Gastrin levels and pH are unchanged. Metastatic risk is very high (50-100% risk).

**Proposed management pathway for carcinoid tumours**

There are several key criteria which precludes safe endoscopic resection. For all submucosal tumours this includes invasion into muscularis propria and lympho-vascular invasion. G-2 and G-3 grade tumours, lesions >2cm in size for type 1 & II carcinoids and lesions >10mm if type III carcinoid lesions are not suitable for

endoscopic resection, due to an increased risk of lymph node metastasis in these types of tumour. Furthermore, in the case of multiple carcinoids in the presence of hypergastrinaemia (Type I and II lesions) a localized surgery, if possible, is likely to be more effective. There are a number of experts who recommend antrectomy for type 1 gastric carcinoids with greater than 5 lesions, lesions 1 cm or greater, or refractory anemia [16] [17]. The theory is that in multi-focal disease this can control local disease and lead to regression of the enterochromaffin-like cell hyperplasia. However, the American Society of Gastrointestinal Endoscopy guidelines have not been able to make an evidence-based position statement regarding this due to the lack of available evidence. The aim of endoscopic treatment is organ preservation. We believe that if a patient has multiple carcinoids, and an antrectomy is being considered, then endoscopic therapy is probably of little value as surgery largely defeats the purpose of endoscopic therapy. The exception may be in the case of junctional or fundic lesions where an antrectomy will leave the patient disease free if the more proximal pathology can be resected endoscopically, saving the patient from a total gastrectomy.

It is our contention that carcinoid tumours restricted to the submucosa and <20mm in size should be considered for endoscopic resection. The position with G2 carcinoids is more difficult to define. It is often difficult for pathologists to accurately determine Ki67 from biopsy and therefore true grading will only be possible post resection. In reality the Ki67 is a continuous variable and a tumour with a Ki67 of 19% will behave very differently to one with a Ki67 of 5%. In

reality there will be many G2 tumours which will be endoscopically resected which are subsequently found to be G2 tumours, and a proportion of these will not go to surgery for a wide range of reasons. It will be important for data to be collected on these cases and in the future it may be possible to refine guidelines to permit some G2 tumours to be resected endoscopically.

**Endoscopic resection of upper gastrointestinal carcinoid lesions**

There is a growing evidence base to support an endoscopic approach to the treatment of carcinoids. Many of the studies published have pooled results from the oesophagus, stomach and duodenum. One such study has examined the use of ESD in resecting neuroendocrine tumours from the upper GI tract [18]. In total 24 patients with 29 foregut NETs were treated, with lesions identified in the esophagus (1), cardia (1), stomach (23), and duodenal bulb (4). All of these lesions were found incidentally during routine upper gastrointestinal endoscopy and none had symptoms of carcinoid syndrome. Of the gastric lesions, 16 lesions were type I gastric neuro-endocrine tumours, whilst the other 8 solitary lesions were type III. All lesions were less than 30mm in size, with an average diameter of 9.4mm and were invading no deeper than submucosa. Complete resection was achieved in 96.6% of lesions, and no lymphovascular invasion was found. One patient had angiolymphatic and muscularis invasion and was referred for surgery. Delayed bleeding occurred in 1 case. There were no procedure-related perforations. Local recurrence occurred in one patient 7 months after ESD. A further larger study published the same year examined 42 carcinoid tumors, all

less than 10mm in size, located throughout the whole gastrointestinal tract (37 rectal, 2 gastric, and 3 duodenal) [19]. En bloc resection was achieved in all cases. Bleeding was uncommon, occurring in just two of the rectal cases, all managed endoscopically. There were two perforations, both in the duodenum, one managed endoscopically with clips. This led the authors to question whether ESD was an optimum technique for use in the duodenum. This position has been subsequently challenged, and will be discussed later. Critically there was no recurrence observed in any of the patients during the mean follow-up period of 37 months. Both of these studies have the limitation that they group together carcinoids from the eosophagus, stomach and duodenum. Furthermore, they are prospective series, and do not compare outcome to an alternative approach to management (including simple observation). Perforations are low in both of these studies, and recurrence is reassuringly low as well. They do however demonstrate feasibility and together provide evidence that endoscopic resection of carcinoids in the upper gastrointestinal tract is possible.

A Chinese study of 25 patients has reported high degrees of success using ESD to treat gastric carcinoids, with 100% clearance but with no perforations and just one delayed bleed [20]. It is less clear whether the same results can be achieved using EMR technique. There have however been comparisons of the effectiveness of different endoscopic techniques for the resection of gastric lesions. EMR carries the advantage over ESD of being simpler to learn and carries a reduced procedure time. However, it cannot go as deep as an ESD, does not provide the same fine degree of control as ESD and does not always produce a good en-bloc resection. A study of 13 gastric carcinoids resected with either EMR

or ESD compared effectiveness [21]. Whilst horizontal margins were clear in all cases, vertical deep resection margins were clear in only 67% of EMR specimens compared to 100% of ESD specimens. This would suggest that ESD is the superior technique for the resection of gastric tumours, at least in terms of achieving a clear deep resection margin. However, this is a very small series and we need to perform more comparative studies to reach this conclusion. A multicenter Japanese study looked 82 patients with type I gastric carcinoids, allocated to a range of management options [22]. This included endoscopic surveillance (25), endoscopic resection (41) or surgical resection (16). Of the lesions resected Intramucosal invasion was found in 19 patients, submucosal invasion in 44 patients and muscularis propria invasion in one patient. None of the patients showed rapidly growing tumors, local recurrence or metastasis. In the follow up period of median 7 years (0-20) recurrence free survival was 97.6% and disease free survival was 100% in all patients. The authors concluded that the prognosis is favorable regardless of the management strategy. It is important to appreciate however that once an incomplete resection has been performed endoscopic treatment options are effectively closed, and therefore it is our contention that ESD is the optimum technique for resecting these lesions.

**Endoscopic resection of duodenal carcinoid tumors**

Whilst it has been previously suggested that ESD should be avoided in the duodenum, there is evidence to support endoscopic resection of sub-mucosal lesions in the duodenum. A retrospective study examined the resection of 41 duodenal carcinoid tumours less than 10mm in size [23]. EMR was performed in 34 tumors, EMR after circumferential precutting in 3, and ESD in 4. En-bloc

resection was performed in 39 tumors (95%), and endoscopic complete resection was achieved in 98% of cases, but histological clearance of margins was only achieved in 41% of cases. The endoscopic complete resection rate did not differ according to the resection method, but histological clearance rate was higher for ESD. Intraprocedural bleeding was noted in five cases, with no perforations seen. No recurrences occurred during the follow up period of 17 months.

There have been case reports of resection of carcinoid tumours from the duodenal papilla [24] [25]. Both of the reports highlighted the advantages of avoiding pancreaticoduodenectomy. Whist data is limited in this area it should be considered an important area for further study. A difficulty in obtaining data about this sub-group of lesions is that they are a very uncommon finding. Whilst it is likely that they will behave in a similar fashion to other small bowel carcinoid lesions, from a therapeutic perspective resection poses unique challenges.

**Endoscopic resection of rectal carcinoid lesions**

Rectal carcinoids are a common finding, and there is a growing body of evidence for their endoscopic treatment. A large study of 107 rectal neuroendocrine tumours less than 10mm in size achieved a disappointing complete resection rate of 49.5% [26]. However, the authors were very precise on their description of complete resection and a further 34.6% of cases had indeterminate resection status with margins only definitely positive in 15.9% of cases. Recurrence or

metastasis was not seen during the follow-up period of 13 to 121 months. A recent study looked at the use of a novel technique for resection using a 'clutch cutter', which can grab and incise target tissue. This was used in 7 cases with 100% en-bloc resection and no complications [27]. Another study looked at conventional ESD technique in 35 patients with rectal carcinoids less than 1cm in size [28]. This again achieved very good results, with all lesions removed en-bloc without any immediate complications. One patient had evidence of perforation seen on computed tomography scan only, but had no clinical symptoms of perforation and was discharged home after 3 days. At histology complete resection was confirmed in 74% of cases. There was no lesion recurrence over a 25 month follow up period.

There has been debate as to whether ESD is the optimum technique for small rectal carcinoids, or whether EMR technique can achieve adequate results. Some papers which have suggested that ESD is superior [29] [30], citing improved outcomes and comparable safety. In contrast other studies have suggested that EMR can achieve comparable resection rates, is easier to learn and quicker to perform [31] [32] [33]. One study compared efficacy of endoscopic mucosal resection using a dual channel endoscope with ESD [34]. In this study 70 cases of neuroendocrine tumours of the rectum <16mm in size were resected, with 44 patients in the EMR group and 26 patients in the ESD group. The endoscopic complete resection rate did not differ between groups, with 100% clearance for both techniques. Histological complete resection rate also did not differ significantly between groups (86.3 vs. 88.4 %). Minor bleeding occurred in 1 EMR patient and in 3 ESD patients, with no perforations observed. The authors

concluded that EMR using a dual channel endoscope was, compared to ESD, technically simple, minimally invasive, and safe for treating small rectal neuroendocrine tumors contained within the submucosa.

A systematic review and meta-analysis concluded that ESD was the better treatment for rectal carcinoid as it was as safe as EMR and was more effective in achieving a complete resection [35]. However, a further systemic review and meta-analysis disputed this, and concluded that a modified EMR technique, using a ligation band device or suction cap, could achieve equivalent results to ESD [36]. However, the authors commented on the low level of available evidence. We suspect that for small rectal carcinoids the difference in outcome may be minimal and clinically insignificant. This would almost certainly not apply to lesions >10mm in size, but there is no evidence in this category to support endoscopic therapy. Indeed, in a study of 1914 submucosal carcinoids in the stomach and rectum lesions >10mm in size exhibited unexpectedly high aggressiveness in terms of metastasis, which would suggest that larger lesions may not be suitable for endoscopic resection. Smaller lesions 10mm or less in size had much lower rates of metastasis [37]. It should be noted however that there is insufficient evidence to confidently claim that a surgical resection of larger carcinoids results in better survival and further studies in this field are needed. In practice almost all rectal carcinoids are very small, so this is an academic point. It could well be argued whether there is any benefit to resection of these lesions at all. However, we feel the data does demonstrate that these lesions can be effectively and safely resected.

The above data demonstrated that endoscopic resection of carcinoid tumours is possible. This is summarized in table 2. Whilst the evidence is growing there are multiple factors which affect outcome, many of which are poorly defined, and assessment criteria for the prediction of successful resection are needed. It is our contention that for upper gastrointestinal lesions ESD is the optimum technique. The position is less clear in rectal carcinoids where EMR may be adequate. All such resections are challenging, and such cases should be handled in high volume referral centres by an endoscopist highly skilled in the endoscopic resection of neoplasia. It should be noted that the ESMO guidelines working group, who define standards for management of neuroendocrine tumours, have not yet commented on endoscopic therapy for gastric or small bowel carcinoids [38]. This reflects the rapidly changing nature of this field and we feel is likely to change when the guidelines are updated. They have stated that for localized disease surgery provides the only curative treatment, with 5 year survival of 80% to 100%. We would challenge this position based on the data presented in this article, but would acknowledge that long term follow up is lacking before this position becomes clear. In 2012 ENETS released an update to their consensus guidelines reflecting the changes in this field [39] [40]. These guidelines recognize the role of endoscopic therapy in this area, and suggests that for lesions over 1cm in size, endoscopic resection can be performed to resect type 1 gastric carcinoids providing there is no evidence of lymph node invasion on endoscopic ultrasound.

**Gastrointestinal stromal tumours (GISTs)**

GISTs are mesenchymal tumours originating from interstital cells of Cajal (Pacemaker cells) in the Gastrointestinal tract. They were traditionally described as a form of sarcoma without features of either smooth muscle or nerve cells. However, given the lack of completely clear differential in expression of muscle or nerve antigenic markers this is not completely true. It is now thought that 1/3 of GISTs differentiate along smooth muscle lineage, 1/3 are neurogenic in origin and 1/3 lack any detectable lineage-specific markers. Some tumours express both muscle and nerve sheath antigens. 95% of lesions exibit expression of CD117 (C-KIT) or PDGFRA. This is important as true leiomyosarcomas generally express two smooth muscle markers but fail to express CD117. CD34 expression is neither sensitive or specific for GIST as this is also present in desmoid tumours. The majority of GISTs originate in the stomach (60-70%) with the remainder being found in the small intestine or, rarely, oesophagus or colon. It is difficult to estimate the true incidence of GIST, but is currently placed at 15 cases per million [41]. The peak age of presentation is at 50years but can be seen at any age.

Like with carcinoids, the majority of GISTs are found as an incidental finding. Symptoms are usually only experienced when the tumour is larger than 5cm in size or causes a gastric outflow obstruction. Clinically silent tiny GISTs may be present in up to 35% of adult population. Symptoms will vary on location, but can cause vomiting, anorexia or early saiety. GISTs have the potential to bleed, and it has been suggested that up to 40% of GISTs present as acute haemorrhage.

The concept of whether a GIST is 'benign' or 'malignant' is challenging to define. The consensus opinion is that there are two key prognostic factors; size of primary tumour and the proliferative activity of the cells [42]. Recurrence rate is also dependent on location, with small bowel tumours showing a worse prognosis than gastric lesions. No GIST should be considered to be completely benign, and even small lesions have some risk to metastasize or recur. However, small GISTs <1cm in size are very low risk lesions, which can make the balance point between conservative management and resection challenging. The European Sarcoma Network Working group ESMO have produced clinical practice guidelines attempting to provide guidance in this area [43]. They recommend that lesions should be assessed and either resected or followed up as per patient's choice or co-morbidities permit. However, for rectal lesions it is advisable to obtain histological confirmation before resection. The reason cited for this is the perceived risk of a GIST at this site is higher and the local implications for surgery are more critical. A follow-up policy may still be an option, again a decision to be shared with the patient, in the case of small lesions and in specific clinical contexts.

**Treatment of gastrointestinal stromal tumours (GISTs)**

There is growing evidence that small submucosal tumours can be endoscopically resected safely and that, providing good endoscopic follow up is implemented, outcome can be excellent.

For Gastric GISTs lesions >2cm in size with >5 mitoses/50hpf carry significant risk of lymph node metastasis and recurrence and therefore should be referred for surgical resection. Current UK National comprehensive Cancer Network guidelines recommend that GIST >2cm should undergo surgical resection. In contrast, gastric GISTs <2cm with <5 mitoses/50hpf carry a negligible risk of LN mets & recurrence, and it is in this group that treatment options are more controversial. Lesions originating from the muscularis propria can sometimes be resected endoscopically, which will be examined in detail later in this article. See figures 1 and 2.

**Evidence for endoscopic resection of gastric GISTs**

There is growing evidence that endoscopic resection of GISTs is possible and, in expert centres, safe. Most of the research has concentrated on resection using ESD technique. There is probably the greatest experience of using ESD in the stomach, where the technique has been used to treat mucosal cancers for some time. The advantage of working in the stomach is that it is thick walled and there is greatest room to maneuver. Perhaps it is unsurprising therefore that the largest body of evidence supporting endoscopic resection of GISTs comes from the stomach. A large prospective series examined 144 gastric subepithelial tumours (SETs) [44]. This included 52 leiomyomas, 89 gastrointestinal stromal tumors, 3 neurogenic tumors and 1 lipoma. Some of these lesions were large, with a mean size of 15.14 ± 9.70 mm (range 3-50 mm). All were resected using endoscopic submucosal dissection (ESD) technique. En bloc resection was achieved in 134 of 145 tumors, a complete resection rate of 92%. There was a high perforation rate of 14.5%), all repaired with clips or nylon bands.

Intraoperative bleeding occurred in seven patients (4.83%) and was corrected with argon plasma coagulation (APC) or hot biopsy forceps. Critically there was no local recurrence or distant metastasis detected during the follow-up period of 19 months (range 3-51 months). It is important to note that the mixed histology of this dataset does make interpretation more challenging. However, most of the lesions were either leiomyomas or GISTs, and the data should be considered to represent this kind of lesion most accurately. A retrospective cohort study examined 20 cases of gastric lesions resected using ESD technique [45]. The size of the lesions was 29 mm (range 15-60 mm). The overall rate of R0 resection was 90%. There were two endoscopic failures, one for a submucosal tumor and one for a neoplasm deeply infiltrating the proper muscle layer. Perforation occurred in 3 patients, all managed conservatively. There were no cases of severe bleeding. The histology of this dataset was mixed, with the final histology confirming 6 cases of ectopic pancreas, 1 ectopic spleen, 3 leiomyoma, and 10 GIST. Among the 10 GIST cases treated by ESD there were no deaths with a 5-year disease-specific survival rate was 100 %. A Chinese study reported similar outcomes in a 20 patient case series of lesions 0.5-3.2cm in size [46]. A 95% success rate was achieved, with a 15% perforation rate, managed endoscopically. A further study of 20 GISTS, originating from the esophagogastric junction and resected using ESD technique, achieved a 100% success rate [47]. There was a 20% perforation rate, managed endoscopically. Post operative follow up was over 3-36 months, with no local recurrence or distant metastasis encountered. A problem with all of these studies is the relatively small number of cases, which probably explains the variance in perforation rates. However, the data suggests that although perforation rates for these tumours is high in experienced hands

these perforations can be managed endoscopically and surgery can be avoided. Whilst each study individually is small, together they suggest that the outcome post resection can be very good. Again, the studies are all case series, some being effectively a retrospective service evaluation. This carries inherent inaccuracies and this fact should be considered when interpreting the data.

A large, single centre study examined resection of 143 lesions from the gastric cardia or gastrooesophageal junction [48]. 87 of these were originating within the muscularis propria. The average maximum diameter of the lesions was 17.6 mm (range 5 - 50 mm). There was a 94% en-bloc resection rate achieved using ESD technique. Over a two year follow up period no recurrence occurred in any of the patients. Complications included pneumoperitonium in (4%), pneumothorax (1%) and surgical emphysema (0.7%). Similar results were obtained in a much smaller study of 18 patients [49]. In this study mean tumor size was 2.6 ± 1.2 cm (range 1.0-3.5 cm). Two patients developed perforation, which were both closed endoscopically with metallic clips. No severe complications occurred and there were no other immediate post-procedure complications. A second study of 31 lesions (14 esophageal, 7 cardial and 10 gastric) showed similar results, with a 96.8% complete resection rate [50]. Histological diagnosis was GIST in 16 lesions, 6 of which were classified as very low risk and 10 low risk according to the National Institutes of Health (NIH) risk classification. There were 15 leiomyoma. Perforation occurred in 12.9% cases, all managed by endoscopic clipping. There was no bleeding or recurrence seen (mean follow up 17.7 months). These resections are technically challenging.

However, one of these studies was large, and showed very good results. More studies will be useful in establishing more precise criteria for defining what pre-resection criteria predict success in this kind of tumour.

**Endoscopic resection of esophageal GISTs**

It is possible to remove gastrointestinal stromal tumours from the oesophagus. A recent paper has described a novel submucosal tunneling technique used in 33 patients with oesophageal sub-mucosal lesions [51]. This study did include mixed histology, with 30 leiomyomas tumors, 5 GIST and 1 lipoma tumor. Therefore caution should be taken in the interpretation of the findings in the context of the treatment of GISTs. Some of these lesions originated from deep layers, including the deep muscularis propria and serosa. A complete resection rate of 97% was achieved. Subcutaneous emphysema occurred in 3 patients (9.1%) suggestive of perforation, and pneumothorax developed in one case (3.0%). All of these complications were managed conservatively.

Submucosal tunneling has been attempted in a further, larger study where the technique was used in both the oesophagus (60 lesions), cardia (16 lesions) and stomach (9 lesions) [52]. Again, excellent success at initial resection was demonstrated with 100% of lesions successfully resected. During the procedure, eight patients developed pneumothorax, subcutaneous emphysema, and/or pneumoperitoneum suggestive of perforation. All of these patients recovered with conservative treatment. Again the histology was mixed, with a final pathological diagnosis of leiomyoma (77%), GIST (22%), and calcifying fibrous

tumor (1%). There were no recurrences over an 8 month follow up period. The studies are summarized in table 2.

In submucosal tumours with malignant potential it should be the intention to achieve an en-bloc resection without breeching the pseudocapsule surrounding the lesion. A breach to this capsule will lead to a high risk of recurrence and tumour dissemination. This applies to all modalities of resection, either endoscopic or laparoscopic. Endoscopists face an additional challenge, which is perforation of the deep muscle during resection of the tumour. These perforations can often be closed endoscopically if small but might require surgery if large. In the data presented in this article perforation rates varied between series, from as low as 0% to as high as 20%. If the tumour capsule is breached during the perforation then there will be an increased risk of dissemination. However, many of these perforations will not violate the pseudocapsule of the GIST or carcinoid and in most cases simply involve injury to the deeper muscle with no increased risk of recurrence or metastatic disease. Therefore this is not an issue unique to endoscopic resection, and the basic oncological principles of resection should be applied to any modality of treatment for any submucosal tumours with malignant potential (GISTs and carcinoids).

**Expert commentary**

There are considerable limitations in all of the studies published examining the endoscopic resection of sub-mucosal lesions. Much of the data comes from retrospective evaluation of case series. Almost all of the studies are single centre

experiences and there are no randomized controlled trials comparing endoscopic resection to surgery. Follow up is short in all of the studies. Given that many sub-mucosal tumours are slow growing it could be a long time before recurrence can be confidently excluded, yet in young patients this could be a significant issue. Many of the larger studies pool data from the oesophagus, stomach and duodenum, which in reality are very different places to perform ESD, and ideally such data should be handled separately. However, what these studies do demonstrate is that it is technically feasible to resect sub-mucosal lesions endoscopically with very few complications, most of which can be managed endoscopically. Unfortunately there are currently no studies which directly compare outcomes from endoscopic treatment to surveillance or surgery. Such studies would be challenging to construct, given the relatively low incidence of these lesions. We feel that such randomized trials would be of value but the ethical and practical dimensions of such work will probably render such work unrealistic.

The mortality and morbidity associated with surgery, particularly in the oesophagus, stomach or duodenum, should not be underestimated. Even in fit, healthy patients undergoing surgery in expert, high volume centres, there are complications associated with surgery, including death. Mortality does vary between series, with some data suggesting 0% with other studies as high as 32% [53] [54] [55]. With advances in surgical techniques and limited laparoscopic wedge techniques we feel that in fit patients a low mortality of 1-2% is probably realistic. This is consistent with recent ENETS consensus guidelines. Given the

encouraging data presented in this review it would be wrong not to consider the real benefits of endoscopic management of these tumors. The dilemma facing the clinician is to decide the nature of tumour, the best time to intervene or not to intervene, and the best intervention technique. Our review has thrown some light on the potential that endoscopic resection can offer in this field.

**Five year view**

Modern endoscopic techniques are challenging traditional management strategies for submucosal tumours. For small lesions less than 2cm in size there is now compelling evidence to suggest that endoscopic resection can be successfully performed with good outcomes. Whilst more research is needed, this offers a minimally invasive option with a rapid recovery and low complication rates. At present there is limited expertise in ESD outside of Japan, and this is currently a limiting factor in the endoscopic treatment of these lesions. However, this position is changing, and it is our contention that as experience grows endoscopic therapy of submucosal tumours will become a central part of treatment pathways in the future.

**Key issues**

- Sub-mucosal tumours are lesions originating beneath the epithelium, from the sub-mucosa, muscularias mucosa or muscularia propria
- They represent a wide variety of cell types, including mesenchymal tumours, Lipoma, leiomyoma, carcinoids, and gastrointestinal stromal

tumours (GISTs) and sarcomas can arise in this area. Malignant potential ranges from completely benign to malignant dependent on histology

- They are an increasingly common finding at endoscopy, with many lesions found as incidental findings
- Obtaining biopsy Samples can be challenging due to sup-epithelial location
- Endoscopic ultrasound can predict which layer the tumour originates from, but is not particularly effective in predicting histology. It can be used to obtain a targeted biopsy. A positive EUS is useful but a negative EUS may be under-staging the lesion.
- Resection may be the only reliable method to obtain histology in many lesions
- Type I and type II carcinoids <2cm in size can be effectively treated endoscopically
- Gastrointestinal GISTs <2cm in size with <5 mitoses per hpf can be effectively treated endoscopically
- Success rates of 90-100% have been found in most reported series, with perforation rates of 0-20% and bleeding rates of 0-5% reported
- Recurrence rates were reported as very low in all of the published series, although follow up was often short and long term follow up data is needed

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| | Carcinoid | GIST | Leiomyoma | Sarcoma |
|---|---|---|---|---|
| Oesophagus | 1% | 10% | 5% | 5% |
| Stomach | 3% | 70% | 67% | 50% |
| Small bowel | 20% | 20% | 19% | 30% |
| Ileum | 10% | 0% | | |
| Appendix | 38% | 0% | 9% | 15% |
| Colon | 9% | 0% | | |
| Rectum | 19% | 0% | | |
| Total | 100% | 100% | 100% | 100% |

**Table 1: Distribution of submucosal tumours throughout the gastrointestinal tract. Note how histology varies markedly by location**

| Author | Journal | Date | No. | Site | Histology | Initial resection | Perforation | Bleeding | Recurrence |
|---|---|---|---|---|---|---|---|---|---|
| Suzuki S et al [19] | Surg Endosc | 2012 | 42 | All | Carcinoid | 100% | 4.8% | 4.8% | 0% |
| Ye LP et al [52] | Surg Endosc | 2014 | 85 | Oesophagus (60) Cardia (16) Gastric (9) | Mixed | 100% | 9.4% | 0% | 0% |
| Jiao CH et al [51] | Zhonghua Wei Chang Wai Kw Za Zhi | 2013 | 33 | Oesophagus | Mixed | 97% | 9.1% | 0% | 0% |
| Li QL et al [18] | World J Gastroenterol | 2012 | 24 | Upper GI | carcinoid | 96.6% | 0% | 4.2% | 4.2% |
| He Z et al [44] | Scand J gastroenterol | 2013 | 144 | Gastric | Mixed | 92% | 14.5% | 4.83% | 0% |
| Catalano F et al [45] | Gastric Cancer | 2012 | 20 | Gastric | Mixed | 90% | 15% | 0% | 0% |
| Zhou PH et al [46] | Zhonghua Wei Chang Wai Kw Za Zhi | 2008 | 20 | Gastric | GIST | 95% | 15% | 0% | 0% |
| Li QL et al [47] | Zhonghua Wei Chang Wai Kw | 2012 | 20 | Gastric | GIST | 100% | 20% | 0% | 0% |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Za Zhi | | | | | | | | |
| Chen WF et al [20] | Scientific World Journal | 2012 | 25 | Gastric | Carcinoid | 100% | 0% | 4% | 0% |
| Sato Y et al [21] | Hepatogastrientero logy | 2013 | 13 | Gastric | Carcinoid | EMR 67% ESD 100% | 0% | 0% | 0% |
| Sato Y et al [22] | Dig Endosc | 2014 | 82 | Gastric | Carcinoid | Comparison of surgery ESD and surveillance | NA | NA | 2.4% |
| Kim GH et al [23] | J gastroenterol Hepatol | 2014 | 41 | Duodenum | Carcinoid | 98% | 0% | 12.2% | 0% |
| Kim GU et al [26] | Endoscopy | 2013 | 107 | Colon | Carcinoid | 49.5% | 0% | 0% | 0% |
| Komori K et al [27] | ANZ J Surg | 2014 | 7 | Colon | Carcinoid | 100% | 0% | 0% | 0% |
| Moon SH et al [28] | Endoscopic Adv Surg Tech A | 2011 | 35 | Colon | Carcinoid | 74% | 2.9% | 0% | 0% |
| IH et al [56] | J Laparoendosc Adv Surg Tech A | 2010 | 12 | Colon | carcinoid | 100% | 0% | 0% | 0% |

**Table 2: Success of endoscopic resection of submucosal tumours by location and histology. Data where available is reported for completion rates, tumour recurrence rates and complications. Where studies have pooled results from multiple locations or of mixed histology this has been indicated.**

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