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REVIEW

Therapeutic procedures for submucosal tumors in the gastrointestinal tract

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Abstract

This review is part three of three and will present an update on the therapeutic options and procedures concerning gastrointestinal (GI) submucosal tumors (SMTs). The aim of this paper is to investigate the treatments of GI SMTs and to present a case of a gastrointestinal stromal tumor (GIST). Literature searches were performed to find information on therapy for GI SMTs. Based on these searches, the optimal therapeutic procedures could be outlined. The choice of treatment of localized tumors is endoscopic resection if possible or, alternatively, laparoscopic resection or surgical resection by an open procedure. However, benign SMTs should only be excised if symptoms are present, and GISTs should be treated with particular precautions. Irresectable or recurrent GISTs may be successfully treated with the tyrosine kinase inhibitor, imatinib.

Key words: Submucosal tumor; Treatment; Case story; Endoscopic mucosal resection; Imatinib

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INTRODUCTION

Surgical resection is the golden standard for treatment of gastrointestinal (GI) submucosal tumors (SMTs). However, new surgical and medical therapeutic options for SMTs have emerged recently. These include, primarily, endoscopic resection and usage of the tyrosine kinase inhibitor, imatinib.

The choice of treatment is based on whether the SMT is thought to be: benign, malignant, exophytic, endophytic, its size, extent and the presence of symptoms. Treatment is mostly not indicated in an asymptomatic, benign SMT, found incidentally. These SMTs are instead controlled by follow-up examinations[1]. On the contrary, malignant SMTs should be excised surgically as a rule[2,3].

Gastrointestinal stromal tumors (GISTs), the most common mesenchymal tumors in the gastrointestinal tract, form a specific problem as they have the ability to metastasize, even though they may appear to be fully benign[4,5]. In recent years it has become clear that the tyrosine kinase inhibitor, imatinib, has a place in the treatment of inoperable, recurrent and metastatic GISTs[2,6-8].

Recent validation of these new treatment options has created a need for a review of the therapeutic options when dealing with SMTs. The aim of the present paper is to update the reader on the different therapeutic possibilities, mostly surgical, regarding various types of SMTs. A case story of a GIST is presented in this context.

ENDOSCOPIC SURGERY

For SMT resection, endoscopic surgical procedures represent an alternative to laparoscopic and conventional open surgical bowel resection procedures in selective cases. Endoscopic ultrasonography (EUS) and multi-slice CT are helpful tools for deciding on which type of surgical procedure should be performed[1]. A comparison between the different methods can be viewed in Table 1.

Standard snare polypectomy is performed with either a one- or a two-channel endoscope. With the one-channel endoscope, the cauterizing snare is placed around the SMT base and pulled as the resection is performed. With the two-channel endoscope, the oral part of the SMT is grasped with a forceps and held, while the snare is placed around the SMT[1].

Strip biopsy is initiated with a submucosal injection of physiologic saline, which may be EUS-guided. This separates the muscularis propria from the luminal layers. After placing a snare around the SMT base, excision is done with electrocoagulation while tightening the snare[1,9,10].

Resection can also be performed with a ligation

Table 1 Various endoscopic therapeutic procedures for the treatment of SMTs

	Indication	Contraindications[1]	Complications	Advantages	Disadvantages
SSP[1,56]	SMT < 2 cm; polypoid/ pedunculated; sessile with a base < 1-2 cm; intraluminal and originating in muscularis mucosa or submucosa	SMT > 2 cm; originating from the muscularis propria; intramural SMT; extraluminal SMT; located on the lesser curvature, posterior aspect of the stomach body or the cardia	Incomplete resection, hemorrhage, perforation (when the SMT is > 2.5 cm)	High success rate, few complications	See "Complications"
SB[1,9,10,57,58]	Same as for SSP	Same as for SSP	Minor bleeding treated with saline inj., metal clips or liquid thrombin	The saline injection prevents full-thickness burning and perforation; high success rate; safe, quick and easy method	If the saline is injected in the surrounding tissue, the SMT will become sessile and therefore more difficult to remove
ESMR-L[1]	SMT < 1 cm	SMT > 1 cm; originating from the muscularis propria	No serious complications have been reported	Not restricted by the location of the SMT; achieves deeper resection than SB and conventional EMR and thus a higher rate of curative resection	This technique can only be applied to small SMTs
ESMR-C[1]	SMT < 2 cm	SMT > 2 cm; SMTs in the muscularis propria	Minor hemorrhage, though rare.	Simpler and easier version of EMR; high success rate; saline inj., see SB	See "Complications"
UT[1,58]	Simple and multicystic SMTs (e.g. lipomas and cystic lymphangiomas)	Vascular tumors	Hemorrhage	Reduced risk of perforation, due to the fact that only the upper half is removed; can be applied to larger tumors	Only applicable in cases of lipomas and cystic lymphangiomas
EE-M[1]	Easiest if well capsulated; large SMTs and SMTs in the muscularis propria can be removed by this technique	SMTs with wide bases, severe adhesions or not well capsulated	Minor hemorrhage	Can be used to resect leiomyomas originating from the muscularis propria; sessile or large SMTs > 2 cm can be resected	Very difficult to perform
EE-I[1]	Large SMTs and SMTs in the muscularis propria can be removed by this technique	Unknown since this is a new technique	Perforation, minor hemorrhage	Like EE-M this technique is not limited by the size, sessile form or association with the muscularis propria	New method, which means that the efficacy and safety is not known for sure

[1]These are not absolute contraindications, but should rather be seen as circumstances, where resection is complicated. SSP: standard snare polypectomy; SB: strip biopsy; ESMR-L: resection performed with a ligation device; ESMR-C: endoscopic submucosal tumor resection with a transparent cap; UT: unroofing technique; EE-M: endoscopic enucleation performed with an initial mucosectomy; EE-I: endoscopic enucleation performed with an insulated-tip electrosurgical knife.

device. After a submucosal saline injection the SMT is aspirated into the ligation device and the elastic band is released around it. Snare resection is performed with electrocoagulation below the elastic band. Endoscopic SMT resection with a transparent cap is a simpler and easier method[1].

With the unroofing technique, the upper half of the SMT is resected with a snare, creating an opening in the overlying mucosa. In most cases, the remnant SMT resolves spontaneously[1].

Endoscopic enucleation can be performed with an initial mucosectomy. The superficial part of the tumor is removed employing a snare or a cutting knife. Then a biopsy forceps is used to separate the SMT from the surrounding tissue, and the tumor can be removed with a snare[1].

Endoscopic enucleation can also be performed with an insulated-tip electrosurgical knife. Epinephrine injected in the proximal aspect of the SMT detaches it from the overlying tissue. Using a needle-knife, a 3-5 mm diameter hole is made. With the insulated-tip electrosurgical knife introduced though the hole, a longitudinal incision is made in the overlying mucosa and the surrounding tissue is dissected away. The tumor can now be removed en bloc[1].

Some therapeutic interventions can also be performed with push-and-pull enteroscopy in selected cases, which is typically a symptomatic, benign, small intestinal SMT[11].

TREATMENT OF BENIGN SUBMUCOSAL TUMORS

Benign SMTs should generally only be treated if they are symptomatic. In case of asymptomatic SMTs, follow-up examinations seems to be the best approach[1]. Exceptions from this rule (e.g. heterotopic pancreatic tissue) will be dealt with in the following.

Leimyomas

Small, symptomatic, duodenal leiomyomas with benign features can be safely treated with local excision *via* a longitudinal duodenotomy[12]. If the leiomyoma is located in the esophagus it will often result in progressive dysphagia, in which case enucleation or resection is required[13]. Endoscopic excision is also an option, and even leiomyomas larger than 2cm can be removed by enucleation using a snare, cutting knife or an insulated-tip electrosurgical knife, see above[1]. A case report has shown a successful resection of an esophageal leiomyoma by

means of thoracoscopic enucleation[13]. In asymptomatic leiomyomas, follow-up may be preferred[1].

Schwannomas

Since GI Schwannomas are always benign, removal is only indicated in case of severe symptoms[14].

Granular cell tumors

In case of symptoms, endoscopic tumor excision is a good alternative, when the tumor is restricted to the inner layers, as recurrence or metastasis has never been documented in any patients[15,16]. When the tumor also invades the outer layers, EUS can contribute to planning the surgical resection[15].

An investigation of laser therapy for esophageal granular cell tumors included four patients. The method was successful in achieving complete necrosis of the esophageal changes, necessitating four sessions per patient. A mean follow-up period of 66 mo showed no evidence of tumor recurrence. No complications were observed leaving laser therapy as a putative new therapy in selected cases[17].

Heterotopic pancreatic tissue

Malignancy in heterotopic pancreas must be considered, although it is relatively rare[18-21]. If symptoms occur, surgery may be a necessity[18]. Endoscopic resection may be performed either by standard snare polypectomy, strip biopsy, resection performed with a ligation device or by endoscopic submucosal tumor resection with a transparent cap[1]. If heterotopic pancreatic tissue is found incidentally during operation for other reasons, prophylactic resection of the tissue is advisable for prevention of later complications[22].

Lipomas

Large lipomas may cause massive bleeding or intussusception[1]. If symptoms occur, the treatment of choice is surgical removal[23-26]. If the tumor is small, endoscopic polypectomy or enucleation may be preferred[23]. Large lipomas can be removed with the unroofing technique[1]. Asymptomatic lipomas should be followed without surgery[24,26] and some of them may in fact resolve spontaneously[1].

Neurofibromas

Neurofibromas are not easy to treat, as they may seem well defined macroscopically, but microscopy often reveals local infiltration. Therefore, these tumors commonly recur after excision[27]. Accordingly surgical resection has to be recommended due to high frequency of recurrence.

VASCULAR TUMORS

Hemangiomas

The therapeutic strategy depends on the size, number, location and symptoms[28]. Endoscopic coagulation or removal of a recurrently bleeding hemangioma may be performed either as an exploratory laparotomy with excision of the hemangioma or as laparoscopic excision with preceding push-and-pull enteroscopy, where the hemangioma is marked with ink[29]. However, in blue rubber-bleb nevi syndrome where multiple hemangiomas may be present, complete eradication may be impossible[28]. Alternatively, endoscopic laser photocoagulation or plasma argon coagulation may be performed[28].

Lymphangiomas

Large, symptomatic lymphangiomas can be removed endoscopically with the unroofing technique[1].

TREATMENT OF MALIGNANT SUBMUCOSAL TUMORS

Leiomyosarcomas

As leiomyosarcomas are considered radio- and chemoresistant[30], surgical resection remains the only effective treatment and involves both the tumor and adjacent mesentery in small-intestinal leiomyosarcomas[3].

Kaposi's sarcoma

Kaposi's sarcoma typically occurs in the coexistence of human herpes virus 8 and HIV[31,32]. The classical Kaposi's sarcoma is rarely fatal contrary to the much more frequent HIV-associated variant[31]. The treatment is usually dictated by the presence of symptoms[33], and should initially include highly active antiretroviral therapy against HIV with or without specific anti-Kaposi's sarcoma therapy. This has been shown to halt progression or induce regression. Kaposi's sarcoma is moderately responsive to radiation and chemotherapy[32].

Metastases

Treatment of metastases is angiographic embolization to control active tumor bleeding, endoscopic removal of the metastases, surgical exploration or medical treatment. If multiple organ involvement is present, and there is no active bleeding, the indication for treatment is questionable[34].

Treatment of gastrointestinal stromal tumors

GISTs stand out as especially complicated to treat compared to other SMTs. Therefore the treatment of these tumors will be described in more detail.

Surgical approaches: laparotomy or laparoscopy?

The first choice of treatment of localized GISTs is complete surgical resection, which seems to be the most important prognostic criterion[2,8,35,36]. The tumor should be removed en-bloc respecting a possible pseudocapsule to avoid intraperitoneal dissemination[6,36-38], and therefore adjacent organs adherent to the GIST should be resected en-bloc with the tumor[2,36]. GISTs should be resected aggressively with a tumor-free margin[2,6,37,39], and determining this is mostly not much of a problem, since GISTs tend to be exophytic[36]. Re-excision should be considered in case of intramural GISTs that have been excised intra-lesionally and do not infiltrate the serosal surface[2]. A consensus meeting in 2005 concluded that

laparoscopic surgery should be avoided, especially in GISTs larger than 2 cm, due to the risk of rupture[2]. Yet recent studies of even very large (up to 15 cm)GISTs showed successful and safe resection in nearly all of the patients employing laparoscopic resection. The reason for unsuccessful laparoscopic treatment (1 patient out of 64) was conversion to laparotomy due to suspected bowel injury when establishing pneumoperitoneum[37,40]. Lymphadenectomy is not a routine procedure owing to the route of malignant spread in GISTs, which is mainly hematological metastasis to the liver[2,6,39]. Hepatectomy for liver metastasis is not recommended as it does not seem to increase survival rates[41]. If the GIST is large or involves large vessels embolization should be considered.

Tyrosine kinase inhibitors-imatinib

GISTs are chemo- and radioresistant[42,43]. Immediate medical treatment with the tyrosine kinase inhibitor, imatinib, is indicated in case of metastatic, recurrent or irresectable GISTs[2,6-8]. Imatinib should also be considered in case of equivocal images[2]. The effect can be monitored with combined positron emission tomography (PET) and CT, PET-CT[44]. Imatinib is given as an oral treatment, with a recommended daily dose of 400 mg[2,7]. For lack of response, 600-800 mg/d may be attempted[2]. Treatment with imatinib should be continued until progression, intolerance or patient refusal[2].

Imatinib specifically inhibits a mutated tyrosine kinase receptor (kit-receptor; CD117) that normally regulates cell growth and survival, but a gain-of-function mutation has made it continuously active. However, imatinib has also shown to inhibit platelet derived growth factor receptor alpha mutations (a CD117-related tyrosine kinase receptor) and tumors without mutations[2,7,8,44-47] (e.g. neurofibromatosis type 1-associated GISTs)[48]. A reason for the dramatic effect of imatinib is probably that it inhibits the kit-receptor signaling, which secondarily inhibits the glucose uptake and metabolism and thus cell proliferation[44,49].

The effect of imatinib on GISTs often results in increased tumor size due to hemorrhage, edema and myxoid degeneration and therefore do not correlate to the response criteria of the World Health Organization or of Response Evaluation Criteria in Solid Tumors[2,50]. Decreased metabolism in fluorodeoxyglucose marked PET (FDG-PET), reduction in tumor density (Hounsfield units) in CT and symptomatic improvement all indicate tumor response to imatinib[2]. Long-term studies are still not available. However, patients did not survive for more than 1 year earlier, but with imatinib therapy they now live for more years[51]. High and intermediate risk GISTs should be followed with a CT scan every 3-4 mo for 3 years, then every 6 mo until 5 years and yearly thereafter. Low and very low risk GISTs can be followed every 6 mo for 5 years[2].

The side effects from imatinib tend to be mild and occur rather infrequently[44,50,52]. However, lethal complications such as bleeding may occur[50].

CASE STORY

A 61-year-old woman was hospitalized due to black stools for three days, fainting fits and hematemesis during the past week. The patient suffered from mild epigastric pain and had also experienced nausea.

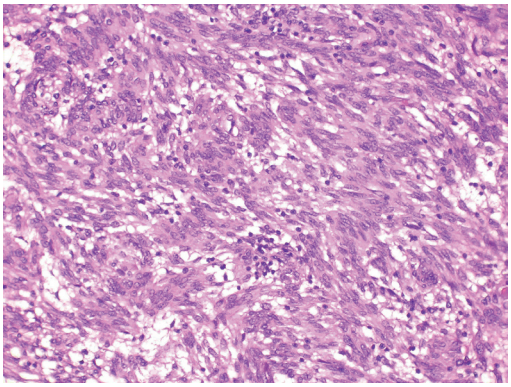

Figure 1 Histological findings of the gastrointestinal stromal tumor described in the case are presented showing spindle shaped cells with mild, nuclear atypia, few mitoses and slight, diffuse lymphocyte infiltration is seen (HE, x 100). Courtesy of B. Vainer.

On examination, the patient was found to be slightly tender corresponding to the epigastrium. Black feces were found at rectal exploration and fresh blood appeared from the stomach tube. Hemoglobin was only 4.5 mmol/L (reference interval: 7-10) at admission.

At standard upper endoscopy a 4 cm × 4 cm SMT was revealed in the anterior wall of the stomach, close to the cardia. It had a fibrin-coated ulceration showing stigmata of hemorrhage. The biopsies were inconclusive, due to lack of submucosal representation.

A CT scan confirmed the gastric mass, but also revealed a mass in the left adrenal gland. It was not possible to take a biopsy from the latter by ultrasound due to lack of visualization. Neither was it possible by CT owing to the fact that there was no free window to reach the tumor without serious risk of lung damage.

The patient was referred for resection of both tumors by an open surgical procedure. Postoperatively, an explorative laparotomy was performed due to non-specific hemorrhage. Furthermore, bilateral, moderate pleura exudates were found, however not requiring drainage. Apart from this, the postoperative course was uneventful.

Macroscopic examination showed a tumor size of 45 mm × 40 mm × 36 mm with a cystic lumen of 37 mm containing blood and mucus. The consistency of the tumor tissue was firm, it had a capsule-like structure with fibrous septa and the color was mixed gray-yellow and brown. Microscopically, the tumor tissue was whirled with distinct palisading nuclei (Figure 1). The cells were spindle shaped with mild nuclear atypia and few mitoses (1-2/50 high power fields). There was significant edema and mild, diffuse lymphocyte infiltration. Furthermore, central degeneration with sequelae from hemorrhage, fibrosis and coagulation necrosis surrounding vascular structures was seen. Additionally, multiple small, thin-walled cysts looking like dilated lymph vessels and invaginated serosal surface was found. No tumor necrosis was seen.

Immunohistochemically, the tumor tissue was strongly reactive for CD117 and CD34 (Figures 2 and 3) with smaller areas being positive for smooth muscle actin, and

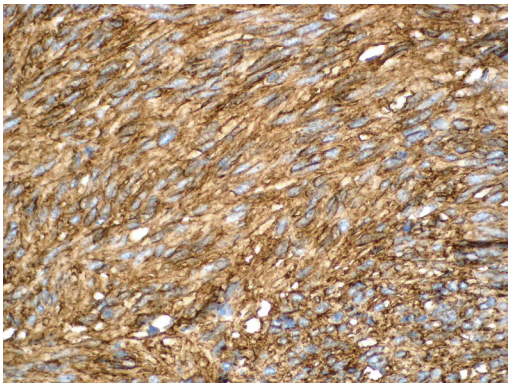

Figure 2 Histological findings of the gastrointestinal tumor described in the case are presented showing a positive CD34 immunoreaction (x 100). Courtesy of B. Vainer.

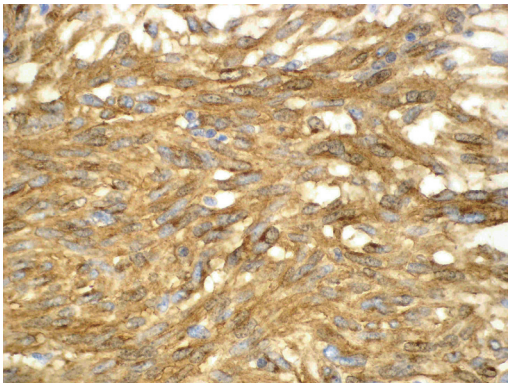

Figure 3 Histological findings of the gastrointestinal stromal tumor described in the case are presented showing a positive CD117 immunoreaction (x 200). Courtesy of B. Vainer.

negative for desmin, S-100 and cytokeratin. MIB-1 (Ki-67, proliferation marker) was reactive in 1%-2% of the cells.

In conclusion, the tumor was found to be a low-risk GIST with microscopically confirmed free resection margins. The adrenal tumor was a cortical adenoma and was not related to the GIST.

DISCUSSION

The choice of surgical procedure is dictated by the clinical condition of the patient, the type, size, shape, location and extent of the GI SMT. In general, benign appearing, asymptomatic SMTs should be evaluated by follow-up examinations, whereas surgical resection should be reserved for symptomatic SMTs or those suspicious of malignancy, including all GISTs[53,54].

The surgical procedure can either be performed endoscopically for intraluminal growing SMTs, laparoscopically for SMTs with extraluminal growth or through laparotomy for SMTs suspected to be malignant[39,55]. Employing endoscopic resection, there is an increased risk of perforation and hemorrhage, if the SMT is located near the serosa, but this may be prevented by the application of metal clips[1]. The availability for expertise in endoscopic and laparoscopic procedures will be a limiting factor until these techniques have been implemented. Referral to expert centers is therefore a necessity.

GISTs should always be removed, since all of these tumors can potentially metastasize. The laparoscopic and open surgical resection procedure with a "gentle-touch technique" is recommended in order to reduce the risk of hemorrhage and intra-peritoneal dissemination, as GISTs tend to have a friable consistency. Medical treatment with a tyrosine kinase inhibitor (i.e. imatinib) is indicated for recurrent or irresectable GISTs as this treatment has proven very effective, safe and tolerable. Follow-up with CT in patients with GISTs is recommended.

In the presented case, the GIST was excised *in toto* and adrenectomy was performed in the same intervention. Hemostasis was achieved. The following night, acute operation was performed due to hemorrhage, which arose from the adrenectomy area. The recommended follow-up interval for patients with low-risk GISTs like the present case is CT scans every 6 mo.

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