

REVIEW ARTICLE

GISTs of the large intestine: review of the literature

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Summary

Gastrointestinal stromal tumors (GISTs) of the large intestine are extremely rare entities that constitute approximately 5% of the reported GISTs and approximately 0.1% of all cancers of colon and rectum. Almost 85-95% of GISTs contain a mutation in the *c-kit* tyrosine kinase and positive expression of the CD117 antigen (*c-KIT*). About 5% of GISTs appear to be *c-kit*-negative and usually have a mutation on the platelet-derived growth factor receptor- α (*PDGFR- α*). Compared to other GISTs, GISTs of the colon demonstrate

different prevalence, incidence between various population subgroups, clinical appearance, molecular biology, treatment and prognosis. These parameters differ further depending on the GISTs primary site (colon, rectum or anus).

The aim of this article was to review the current literature of those rare tumors.

Key words: gastrointestinal stromal tumors, GIST, colorectal, anus, colon, mesenchymal tumors, cancer

Introduction

Gastrointestinal stromal tumors (GISTs) are of mesenchymal origin. They represent the majority of mesenchymal tumors of the gastrointestinal tract (GI), developing from the intermediate cells of Cajal (ICCs) or from multipotent stem cells. ICCs are cells of the autonomic nervous system, that regulate body processes such as food digestion. ICCs are sometimes called the “pacemakers” of the GI tract because they signal the muscles in the GI tract to contract to move food and liquid along. GISTs are rather rare tumors representing less than 1% of all gastrointestinal malignancies. They are even less frequent among different types of tumors of the lower GI, representing a mere 0.1% of all colorectal tumors [1].

In 1962, Stout described GISTs for the first time. He believed that GISTs originated from smooth muscle cells. Intermediate cells of Cajal have been incriminated as the cause of GISTs with

a tyrosine kinase protein, or CD117, playing a key role in the pathogenesis of GIST. CD117 expression is the main index in GISTs diagnosis as it confirms the presence of a specific tyrosine kinase. Molecular paths in the creation of GISTs have been studied extensively and continue to be a field of research as targeted molecular therapy, for example imatinib, contributes effectively in the therapy of GISTs [1-3].

GISTs can occur throughout the entire length of the GI tract, but they most commonly appear in the stomach (60-70%). Other locations are the small intestine (20-35%), duodenum (4-5%) esophagus (<1%), mesentery, omentum and peritoneum (rarely), gallbladder, pancreas, liver and bladder [4,5]. Lower GI tract GISTs constitute approximately 5% of the reported GISTs. The incidence of rectal GISTs is close to 4%, while colonic and appendiceal GISTs range from 1 to 2% of all cases [4].

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Although GISTs of the colon and rectum might be small in size and usually randomly detected, in their great majority they tend to be of high risk and show increased possibility of relapse and metastases. Surgery remains the therapy of choice for primary tumors. At present, targeted molecular therapies (especially tyrosine kinase inhibitors) attract increased research interest and when combined with surgery can provide rather good survival rates and extended disease-free and recurrence-free periods. A multidisciplinary team (MDT) composed by surgeons, oncologists, pathologists, and radiologists is necessary for the initial complete evaluation, treatment and follow-up of these patients [6-8].

Genetics

GISTs appear to originate from a mutation in the c-KIT of tyrosine kinase of the intermediate cells of Cajal which has leads to the continuous activation of c-KIT.

Stromal tumors are characterized from the expression of c-KIT (CD117) in 85-95% of the cases. A 5% of the cases of the stromal tumors do not express CD117 and have a mutation in PDGFR-a (platelet derived growth factor receptor). The KIT is a transmembranic receptor of tyrosine kinase that uses as a connector SCF (stem cell factor). It is coded by the protooncogene KIT and is structurally related to PDGFR-a and Bcr-Abl triggering the activation of a protein that transmits a signal for cellular proliferation and survivability [6].

The majority of KIT mutations in the gene occur at the exon 11. Other mutations in this gene according to frequency include exons 9, 13, and 17. The prognostic value of exon 11 mutations is controversial [2]. Some studies have shown that they are related to large tumors, high mitotic rate and high grade of malignancy. Other studies report that these mutations can be found in both malignant or benign tumors [9,10]. Mutations in exon 11 are heterogenic and the type of mutation might be related with the clinical result [6].

Most GISTs demonstrating a KIT mutation are sensitive to imatinib, an inhibitor of tyrosine kinase that can achieve high remission rates in CD117 positive GISTs. Mutations in exon 9 occur mainly in stromal tumors of the small intestine and are less sensitive to imatinib [2]. GISTs with PDGFR-a mutation in the exon 18- are usually resistant to imatinib. This type of mutation is mostly found in gastric GISTs. It seems that it is important to know the presence of mutations and the specific exon for the prognosis and planning of the molecular therapy. Mutation analysis is recommended mainly in locally infiltrating and metastatic GIST [6].

In lower GI tract GISTs, 17% appear to have detectable KIT expression. On the contrary, rectal GISTs present with a positive KIT expression in 9% of the cases [3]. Zhou et al reported that 93% of colorectal GISTs are CD117-positive, but only 9% appear to have a mutation in PDGFR-a [7]. Feng et al concluded that CD 117-positive GISTs are 82.8% of all cases [8].

Epidemiology

The incidence of GISTs ranges from 6.8 to 14.5 cases per million of the general population. Patients are mainly Caucasians (71%), less frequently Afroamericans (14%) while there are no data on 15% of the cases [6,11].

Lower GI tract GISTs constitute approximately 5% of the reported GISTs. The incidence of rectal GISTs is close to 4%, while colonic and appendiceal GISTs range from 1 to 2% of all cases [4]. Anal GISTs represent only 0.1-0.4% of all GISTs and therefore they are grouped and studied with rectal GISTs [12]. The most common location for colonic GISTs is the sigmoid colon (45.8%), followed by the tranverse colon (19.5%), descending colon (12.5%), ascending colon (11.1%) and cecum (11.1%) [8].

Age of first presentation ranges between 16 to 94 years with a median age of 60 years. Rectal GISTs are more common between the ages of 17 to 94 with a median of 59 years. Slightly increased is the median age of occurrence for colonic GISTs being at 62 with a range from 28 to 82 years of age [6,11]. Anal GISTs are more common in patients from 50.7 to 77 years of age [12].

Both genders are affected equally, with some studies exhibiting a minor predominance of men reaching a male to female ratio of 2:1 [1]. On the contrary, Feng et al reported that colonic GISTs show a predominance of women to men with percentages being 57 and 43%, respectively [8]. Rectal GISTs have a male predominance with a percentage of 62.1% [13]. GISTs of the anus have a male predominance, too [12].

Clinical presentation

GISTs of the lower gastrointestinal tract can present with a variety of clinical symptoms, including easily acquired fatigue, anemia, abdominal pain or discomfort, abdominal bloating, tumor rupture, GI or intraperitoneal hemorrhage, intestinal obstruction, appendicitis-like pain. GISTs can also be asymptomatic and detected in random controls [1,14].

Rectal GISTs are mainly intraluminal, and they present either as small sized asymptomatic intraluminal tumors, or as big masses occupying the pel-

vis causing pain, rectal hemorrhage, bowel obstruction and symptoms similar to those of prostatitis [15]. GISTs of the colon are mostly intramural, but they often exhibit both intramural and extramural symptoms, caused by the tumor size and the expansion of the colon. Smaller tumors of the colon are often randomly detected, while larger tumors present with lower GI hemorrhage, abdominal pain, perforation and bowel obstruction [16]. Abdominal pain is the first clinical symptom in 34% of the cases, obstruction in 23%, hemorrhage in 11%, GI tract perforation in 13.9% and presence of a large abdominal mass during palpation in 12.8% [8]. Approximately half of anorectal GISTs cases are asymptomatic. Symptomatic patients display anal hemorrhage, perianal pain, change of intestinal habits and obstruction. Cases of painless perianal mass in perianal GIST patients have been reported in bibliography [12].

GISTs size may vary widely and two extensive studies of lower GI tract GISTs have shown that they can be from 0.5 to 29 cm, with an average diameter from 5.7 to 6.5 cm [7,8]. Rectal GISTs rarely grow to more than 10cm in contrast to stomach and colon GISTs (12.2 vs. 20.6 vs. 20.4%, respectively) [13].

Diagnosis

Radiology

The most common modalities for diagnosis of GIST of the lower GI tract are computed tomography (CT), magnetic resonance imaging (MRI), colonoscopy and endoscopic ultrasound (EUS). CT is considered the method of choice for diagnosis, staging and determination of the surgical plan, as it reports on the tumor size and shape, local infiltration and the presence of distant metastases. Smaller tumors (<6cm) are usually homogeneous, but larger tumors tend to be heterogeneous with central areas of necrosis. Typically GISTs of the lower GI tract appear in CT and MRI scans as compact signal amplifying masses. Multiphase CT scan is needed for the diagnosis of rich-in-blood-supply hepatic metastases that might not be detected in the classic CT portal protocol. Tumors can expand along the circumference of the GI wall and this might lead to dilatation of the proximal colon. GISTs of the rectum are usually well circumscribed heterogeneous masses with heterogeneous areas of hemorrhage and necrosis. Anorectal lesions appear well defined and usually do not have any lymphadenopathy [17,18].

MRI is used in a similar way for the diagnosis of these tumors. MRI is most commonly used for rectal GISTs and possible liver metastasis detection. In T1 sequence rectal GISTs exhibit low to

medium signal intensity, while in T2 sequences they are depicted with high intensity signal [6].

Colonoscopy might be used when the tumor is small and polypoid, allowing endoscopic excision, but this is not possible in larger tumors as the risks of hemorrhage and tumor cells dissemination during biopsy are considered high [1]. Endoscopic-endorectal ultrasound (EUS-ERUS) and fine needle aspiration (FNA), or, EUS-guided Tru-cut biopsy (TCB) can solve the diagnostic problem ensuring safety and diagnostic capability. GISTs can be evaluated by EUS which can demonstrate the origin of a tumor from the muscle layer. There is debate concerning the preoperative biopsy of a potential GIST, because these tumors tend to be soft and fragile. Biopsy might not be necessary if the tumor is operable, but if there is a plan for preoperative therapy then a biopsy should be performed [1,6,19,20]. In the modern age, endoscopic capsule is also a tool that can be used to diagnose a GIST of the lower GI tract even when colonoscopy or other methods have failed [21]. PET scan, finally, is a useful tool for evaluating therapy response or for detection of a possible liver metastasis or a local/distal GIST recurrence [14,20].

Pathology (Histochemistry and immunohistochemistry)

Histologically, stromal tumors are divided into three categories: tumors from spindle cells (70%) and epithelioid tumors (20%) or polymorphous tumors. The majority of lower GI tract GISTs are also tumors originating from spindle cells [15].

Definitive GIST diagnosis is confirmed by the positive expression of tyrosine kinase c-KIT or CD117. CD34 can also indicate a diagnosis of GISTs, but its expression varies depending on the affected organ. As a result, gastric GISTs are CD34-positive in 46% of the cases, but in rectal GISTs this rate can reach 100% [22]. CD117 is expressed in approximately 85% of GISTs, making it a more useful marker in GIST diagnosis. CD117 is not positive in other mesenchymal tumors, which is useful for differential diagnosis [23]. Desmin, S-100 and b-catenin might be used in the differential diagnosis of GISTs and solid fibrous tumors, schwannomas and fibromas respectively, as these three markers have very weak expression in GISTs.

In terms of histological origin, GISTs are similar to tumors with smooth muscle differentiation, inflammatory polyps, fibromas, schwannomas and inflammatory myofibroelastic tumors [24]. Approximately 5% of the cases of stromal tumors that don't express CD117 have a mutation in PDGFR- α . Other immunohistochemical markers are nestin, vimentin, S-100 and ACAT2. DOG1 is another protein

with strong expression in GIST cell membrane and it is rarely expressed in other soft tissue tumors. Therefore, DOG1 is useful in the diagnosis of c-KIT-negative GISTs [25]. Grade is also determined by mitotic activity, with low-grade GISTs having a mitotic rate up to 5 per 50 HPF and high-grade GISTs presenting a mitotic rate higher than 5 per 50 HPF [26].

Zhou et al studied lower GI tract GISTs and reported that 93% of them expressed positivity for CD117, 79% for CD34, 9% for PDGFR- α , 22% for SMA, 8% for S-100 and 58% for vimentin [7]. Miettinen et al reported that anorectal GISTs are always positive for CD117, in 94% for CD34, in 8% for SMA, and in 1% for desmin [15]. Colonic GISTs are positive for CD117 in 76%, for CD34 in 59%, and for SMA in 23% of the cases. Desmin was found to be negative in all cases [16]. Anal GISTs almost always express CD34 and CD117, but less often SMA, desmin, S-100 and keratin 18 [12]. Tsai et al reported that rectal GISTs are positive in 83.6% for CD34, 28.5% for SMA, 4.1% for S-100, 16.3% for desmin, 30.6% for Ki67 and 34.5% for p53 [27]. Feng et al reported that colonic GISTs are 82.8% positive for CD117, 68.2% for CD34 and 66.7% for DOG-1 [8]. Positive SMA expression is <10% in rectal GISTs [22]. Desmin and S-100 are also rarely positive, nestine on the other hand has been reported to express positivity in up to 90-100% of GISTs [28].

Staging

The TNM classification for staging of GISTs of the large intestine is according to AJCC criteria implemented in 2018 [29]. It is worth to mention that lymph node metastasis is considered as stage IVA and mitotic rate seems to have a major role in staging of GISTs of the large intestine.

Therapy

Surgical therapy

The primary therapy of non-metastatic GISTs of the lower GI tract is surgical excision. R0 resection is the optimal surgical goal [1]. When the tumor infiltrates into adjacent organs, then surgical excision to healthy margins should be attempted. It is recommended that all stromal tumors of the large intestine should be surgically excised regardless of their size or level of suspicion for malignancy.

A typical resection without lymphadenectomy is recommended. Local tumor excision has a similar postoperative morbidity compared to a typical colectomy. Treatment of choice in stromal tumors

of the appendix is surgical excision, whereas local excision is an effective therapeutic method for rectal stromal tumors. Total mesorectal excision is not necessary. When a wider excision is required (e.g. abdominoperineal resection), preoperative administration of imatinib is recommended in order to reduce tumor's size and to provide a chance for a sphincter-preserving technique [6,20,30,31].

In rectal GISTs, positive surgical margin is a significant factor of poor prognosis. Imatinib may be administered preoperatively to patients with tumors >5cm [6,20,30,31]. A study by Zhu et al reported that rectal GISTs may be less likely treated with primary resection compared to gastric and colon GISTs (71.8 vs. 82.1 vs. 83.7%, $p < 0.001$, respectively). Local surgical excision is more common in rectal GISTs than in colonic (51.1 vs. 8.4%, $p < 0.0001$) [13]. This might be explained by the introduction of new transanal endoscopic surgical methods that allow a thorough, safe and effective excision of rectal GISTs with minimally invasive operative techniques like transanal minimal invasive surgery (TAMIS) and endoscopic full-thickness resection [32-34]. On the other hand, the possibility of a R0 excision is smaller in rectal GISTs than in gastric and colonic GISTs (77.7 vs. 90.5 vs. 83.5%, $p = 0.018$, respectively) [13]. Regarding GISTs of the lower anorectal region, local excision can be an adequate surgical treatment, although local recurrence is a serious complication in a significant percentage of patients. Finally, a more aggressive and wider surgical excision might be helpful in some cases, e.g. an abdominoperineal tumor resection to healthy margins. Pre- and post-operative administration of adjuvant therapy with tyrosine kinase inhibitors might be beneficial in these cases, because of the high risk of recurrence despite achieving total excision of the tumor [12].

Tyrosine kinase inhibitors (TKIs) therapy

The objective of using tyrosine kinase inhibitors (TKIs) is to convert a non-resectable or marginally resectable tumor to a resectable one. In this way, more limited excisions and preservation of the function of the affected organ are implemented. A non-resectable tumor or a locally advanced one, a potentially resectable tumor which has to be removed with complex excision of adjacent organs or very large tumors of the distal rectum are all indications for preoperative administration of imatinib (a TKI) aiming in radical (R0) resection. The suggested therapeutic scheme for the administration of imatinib is a period of 6-12 months with frequent diagnostic imaging and reevaluation of resectability at fixed intervals [6,20,30,35].

According to the new guidelines of ESMO, imatinib is the treatment of choice for locally advanced non-resectable tumors and metastatic disease. Surgery is not the first choice in metastatic disease. Imatinib is also recommended for patients with metastatic disease who have been subjected to extensive resection of all malignant foci. In cases of non-tolerance to imatinib, second line medication is sunitinib. Regorafenib is third line therapy, suitable for patients with disease progression or non responders to imatinib or sunitinib therapy [36].

According to Zhu’s et al study, rectal GISTs are more likely to receive preoperative therapy with TKIs compared to gastric and colon GISTs (55.2 vs. 34.0 vs. 34.2%, $p < 0.0001$, respectively). Regardless the tumor size, it is also more likely to receive systemic therapy in combination with surgical treatment (34.4 vs. 24.6 vs. 25.1%, $p < 0.0001$, respectively). The addition of a second line systemic therapy after surgery seems to improve overall survival rates only in rectal GISTs. The addition of second line systemic therapy in colonic GISTs <5 cm in size does not offer any increase in overall survival, but on the contrary it worsens the outcomes. Additional second line medication to colonic GISTs larger than 10cm leads to increased overall survival. Standard systemic therapy appears not to be effective in colonic GISTs, suggesting that GISTs of the large intestine may have biological differences related to the primary site of disease [13].

Suggested treatment algorithms

Our suggested treatment algorithms for different clinical situations are as follows:

Emergency setting

a) Colonic GISTs

In the emergency setting, resectable colonic GISTs causing obstruction can be managed by colectomy or local excision. Temporary stoma followed by TKI treatment and surgical excision or primary surgical excision followed by TKI treatment are both effective treatment options in locally advanced or metastatic colonic GISTs. In cases of hemorrhage treatment options depend on the stability of the patient (primary surgical excision can be performed in unstable patients or conservative management followed by elective surgery in stable patients). Intraperitoneal or intraluminal site of the tumor plays a key role on the feasibility of endoscopic hemostasis. In perforated GISTs emergency laparotomy and surgical excision followed by TKI treatment is the suggested management [1,6,12,13,20,30-36]. Suggested algorithms are shown on Figure 1.

b) Rectal GISTs

In the emergency setting the same management could be adopted (anterior resection instead of colectomy). In low rectal locally advanced GISTs with perforation, diverting stoma may be preferred as a treatment option for performing sphincter-preserving techniques after TKI treatment [1,6,12,13,20,30-36].

Elective setting

Resectability is crucial on whether TKI treatment comes before surgical excision or not. Mini-

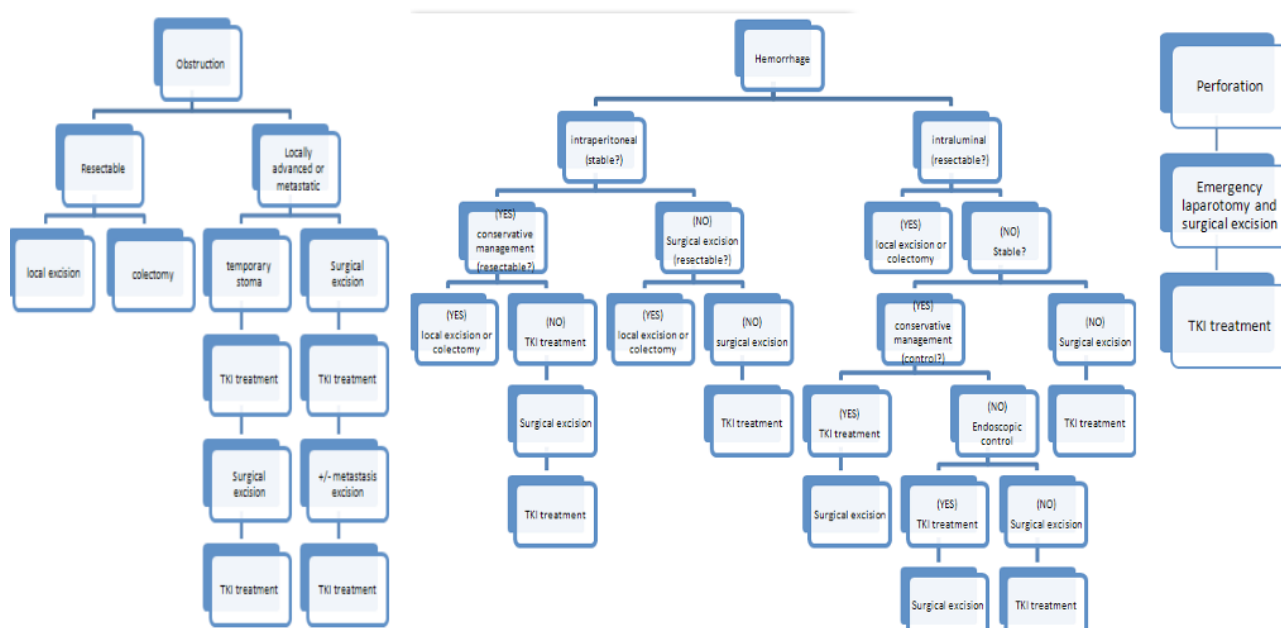


Figure 1. Treatment options in the emergency setting for colonic GISTs [1,6,12,13,20,30-36].

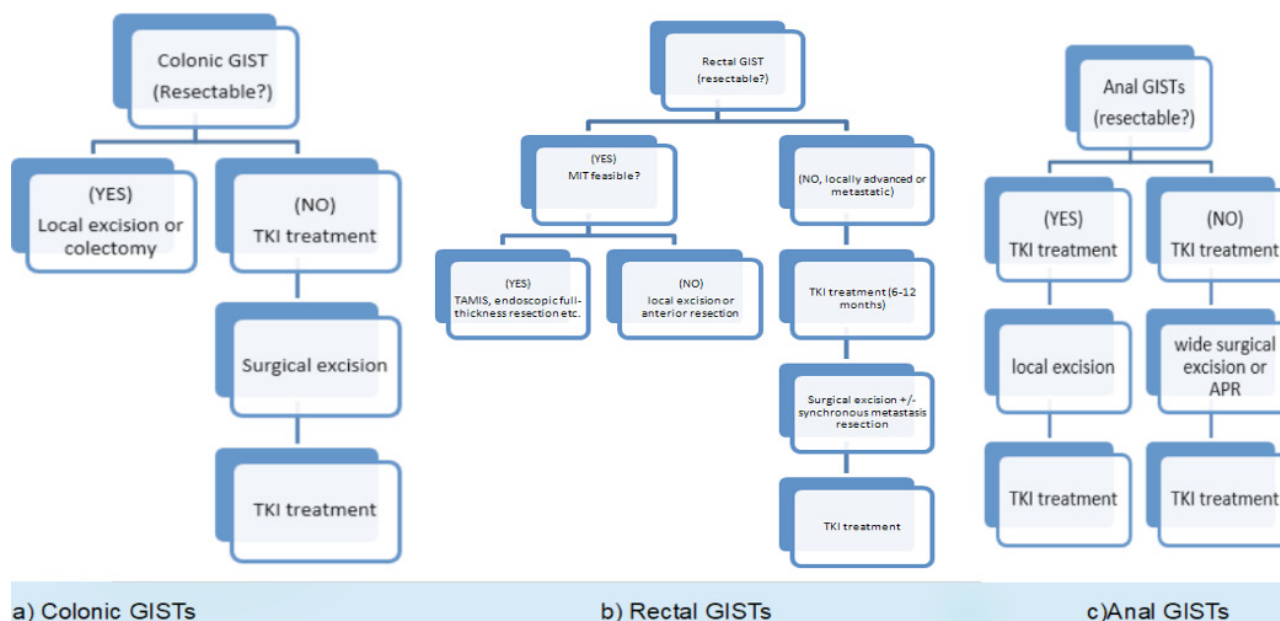


Figure 2. Elective management of large intestinal GISTs [1,6,12,13,20,30-36].

mally invasive techniques (MIT) such as TAMIS, endoscopic full thickness resection etc. may be feasible in rectal GISTs. Pre-operative TKI treatment is suggested in anal GISTs regardless of tumor resectability, as local recurrence is high and wide surgical excision or abdominoperineal resection (APR) for achieving R0 resection may be needed (Figure 2) [1,6,12,13,20,30-36].

Prognosis

A number of characteristics for the evaluation of the malignant potential of a stromal tumor were studied [36]. These characteristics include mitotic frequency of more than 5 per 50 HPF; size (tumors larger than 5cm are considered to be malignant, while tumors smaller than 5cm are considered to be benign); tumor localization (gastric GISTs have better prognosis than small intestine and rectal GISTs); resection radicality, histological type, degree of tumor infiltration, grade, presence of c-KIT mutation, age, recurrence and positive TP53 and Ki-67 markers [36,37].

Stromal tumors rarely give lymphatic metastases. Usually they spread through circulation to the liver, peritoneum, omentum and lungs. Bones and lymph nodes are rarely sites of metastases.

In general, gastric GISTs are less likely to metastasize than colonic and rectal GISTs (4.6, 8.3 and 6.1%, respectively) [13,28]. A study, including 20 cases of colonic GISTs with a follow-up of 30 to 240 months, concluded that metastases occurred in at least half of the cases [38]. The majority of the tumors that finally metastasized were located

in the ascending colon, while the descending colon gave metastases less frequently. From a total of 10 patients diagnosed with metastases, in 4 cases these were detected in the first follow-up examination, 2 more were reported in an interval of 1-4 months after surgical tumor resection, and the rest were detected in an interval of 17-80 postoperative months. Metastases were located mainly in liver (n=6), peritoneum (n=4), lymph nodes (n=4), spleen (n=2), pancreas (n=1) and lungs (n=1). The majority of patients (60%) presented with multiorgan metastases [38].

Zhu et al reported that rectal GISTs have better median survival rate than colonic (85.7 vs. 71.3 months, respectively, $p < 0.0001$) [13]. Overall survival was found to be approximately equal to gastric GISTs. Additionally, the incidence of metastatic rectal GISTs is smaller than metastatic colonic ones (6.1 vs. 8.3%, $p = 0.0012$) [13]. In the study of Kukar et al disease specific survival of colonic GISTs patients was 60 months and survival after surgical excision reached 78 months. Survival rate in patients diagnosed with rectal GIST less than 2cm in size and mitotic rate less than 5/50 was 100%. This rate decreases to 29% for patients with tumors larger than 10cm and mitotic rate higher than 5/50. Colonic location was an independent prognostic factor for poor prognosis [39]. A study by Tworek et al on anorectal GISTs concluded that a potential long interval for recurrence (up to over 4 years after the initial resection) may exist, suggesting that a long-term follow-up period of more than 5 years is necessary for patients with lower GI tract GISTs [40].

Conclusions

Lower GI tract GISTs are a small subgroup of tumors of the lower GI tract, that should be distinguished from other tumors of the lower GI tract as they exhibit different incidence, biologic behavior, malignant potential, prognosis and demand specific treatment management. Furthermore, there are differences in their biologic behavior and prognosis compared to the rest of GISTs, as well as inbetween

their own group depending on their primary site. That fact proves the imperative need for further research in molecular level, as well as more studies aiming in defining the biology and in finding even more effective treatment strategies for the most appropriate management of those rare tumors.

Conflict of interests

The authors declare no conflict of interests.

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