

Overview on Gastric Cancer

Chapter 4

The Surgical Management of Gastric GISTs

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Abstract

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract originating from the pacemaker cells of the intestinal tract called interstitial cells of Cajal. The majority of the GISTs are located in the stomach and the most common type is spindle cell subtype. The estimated annual incidence of GISTs is 1–2 cases per 100,000 people. The median age of GISTs diagnosis is 60–65 years old. Gastric GISTs are frequently located in the fundus and cardia, which is in accordance with the distribution of interstitial cells of Cajal throughout the stomach.

Patients with gastric GISTs commonly presents as abdominal pain, gastrointestinal bleeding such as hematemesis or melena and less commonly as a palpable mass in larger tumors. The work up tests include an upper gastrointestinal endoscopy and a computed tomography (CT) scan of the thorax-abdomen and pelvis. Endoscopic ultrasound scan (EUS) may be useful in confirming the particular intestinal layers and depth of involvement of the gastric GISTs before planning for surgery. Pre-operative EUS guided fine needle aspiration (FNA) biopsy can be used to confirm histological diagnosis and recommended in metastatic or unresectable disease and in those with borderline resectability planning neoadjuvant therapy.

Complete surgical resection of the gastric GISTs remains the standard treatment. Minimally invasive surgery is becoming more common in

order to achieve curative resection of gastric GISTs. Laparoscopic wedge resection (LWR) is the preferred choice of treatment, although partial gastrectomy or total gastrectomy may be necessary in some cases which have unusual tumor locations such as lesser curvature and near to gastroesophageal junction (GE). Lymphadenectomy is not required since gastric GISTs rarely metastasize via lymphatic vessels. Tumor rupture is associated with very poor outcomes so a gentle dissection should be made to prevent tumor rupture as well to prevent peritoneal dissemination during surgery.

The discovery of tyrosine kinase inhibitors (CD117) has changed the surgical management of advanced and metastatic GISTs. Although it is still under debate, neoadjuvant imatinib is suggested to reduce the extent of surgery and the chance of incomplete resection when unresectable or multiorgan resection is planned.

Keywords: GIST; Gastric GIST; Surgery; Laparoscopy; Tyrosine Kinase Inhibitors; Imatinib

1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common non-epithelial mesenchymal tumors of the gastrointestinal tract (GIT) [1]. GISTs are thought to originate from the pacemaker cells of the gastrointestinal tract called interstitial cells of Cajal. The majority of the GISTs (60%) are located in the stomach. Another common sites are jejunum and ileum (30%), duodenum (5%), rectum (2–3%), colon (1–2%), and esophagus (<1%) [2,3]. The incidence of GIST's has not been well established since they were usually misdiagnosed as leiomyomas, leiomyosarcomas, and leiomyoblastomas in the past [4].

The annual incidence of GISTs has increased from 0.028 per 100,000 in 1992 to 0.688 per 100,000 in 2002 (5). This increase is because of the apparent diagnosis of many smooth-muscle tumors as GISTs especially after the year 2000 [5,6,7]. In 1983, Mazur and Clark, firstly determined the GISTs as a separate group of tumors from gastrointestinal smooth muscle tumors [8]. In 1995, in a study published by Miettinen et al. revealed that 70 % of GISTs are positive for CD34 antigen [9]. In 1998, Hirota et al. found that GISTs expresses KIT (CD117), a receptor tyrosine kinase encoded by the proto-oncogene c-kit [10]. Several studies showed that 85–100 % of GISTs have mutations in c-KIT, but not in other smooth-muscle tumors such as leiomyomas or leiomyosarcomas. All these findings show that GISTs were poorly identified and were underdiagnosed until last 2 decades.

2. Demographics of GISTs

It has been reported that the majority of patients with GISTs are between 40 and 80 years old, with a median age of 60 years at the time of diagnosis and has a slight male predominance [6,7]. Although it is rare, GISTs also can be seen in the pediatric patients. Several studies reported that GISTs in pediatric patients are mostly of epithelioid type, tend to occur

morely in females, and also have a higher incidence of multifocal presentation and lymph node metastasis [11,12].

The risk factors for GISTs are not well known. Although the vast majority of GISTs are sporadic, a few group of hereditary syndromes with GISTs has been reported. Familial GIST syndrome represents with several family members with hereditary mutations in either the KIT or PDGFRA genes [13,14,15]. Multiple gastric and small intestine GISTs has been described in the members of these families. Carney-Stratakis syndrome is a disease which is characterized by multifocal GISTs and paragangliomas [16]. Another very rare syndromes associated with gastric GISTs are Carney's triad (Gastric GIST, paraganglioma and pulmonary chondromas) and Neurofibromatosis type 1 [16,17].

GISTs can be classified according to the mutations in KIT and PDGFRA genes that encode tyrosine kinase receptor type III [18].

2.1) KIT-mutant GISTs: In this type of GISTs, mutations of exon 11 (juxtamembrane domain) are determined nearly in 70-80 % of GISTs (3). In 9–20% of GISTs, mutations of exon 9 (extracellular domain) are detected and it is mostly seen in small bowel GISTs and expected to have greater malignancy potential (3).

2.2) PDGFRA-mutant GIST: PDGFRA mutations are found nearly in 5–10 % of GISTs. The majority of these tumors are epithelioid type and mostly located in the stomach (3). The most common type of mutation is the PDGFRA exon 18 mutation D842V. This type of GISTs is associated with imatinib resistance and has a lower malignant potential [19].

2.3) Wild-type GIST: Wild-type consists of GISTs which do not have KIT and PDGFRA mutations [20]. BRAF V600E mutations has been reported in several studies in this type of GISTs [21] and is associated with several hereditary syndromes such as Carney triad, NF1 and Carney-Stratakis syndrome (3).

3. Histopathology

There are three histopathologic subtypes of GIST, depending on the cytomorphology; spindle cell, epithelioid, and mixed types. Spindle cell subtype is the most common type and constitutes about 70 % of all GISTs, while epithelioid and mixed subtypes, are less common, accounting for 20 and 10 % of all GISTs, respectively (4). CD117(c-KIT) is positive in about 95 % of GISTs (3) (**Figure 1** and **2**). KIT positivity is more common in spindle cell type than epithelioid type [22]. CD34 which is a hematopoietic progenitor cell antigen, is expressed in 60-70 % of tumors localized in GIT.

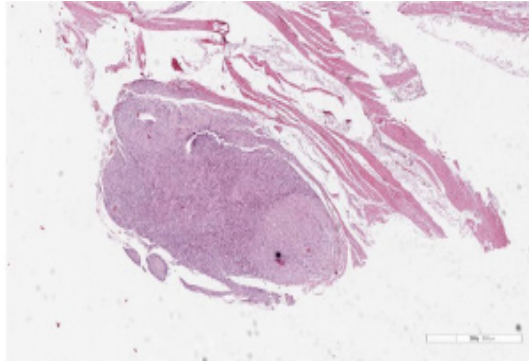


Figure 1: The hematoxylin and eosin (H&E) stained image demonstrating spindle-shaped cells on histopathology

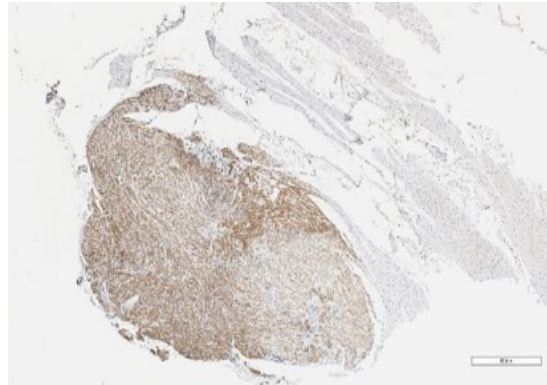


Figure 2: CD117(c-KIT) positivity on microscopic examination

Approximately 20-30 % of GISTs are positive for actin, 8–10 % for S-100, and 2–4 % for desmin [23]. DOG1 marker, also known as anoctamin I (ANO1), is now considered as a new marker that has more sensitivity than CD117 for GIST and is expressed in more than 35% of GISTs negative for c-kit [24,25].

3.1 Gastric GISTs: There are four main types of gastric GISTs: benign and malignant spindle cell tumors and benign and malignant epithelioid tumors. The histologic demographics of gastric GISTs are given in **Table 1** and **2**. The most common type of gastric GIST is epithelioid type (4).

Table 1: Histopathologic features of benign and malignant spindle gastric GISTs

Parameters	Benign	Malign
Cellularity	high	high
Mitotic figures	<2/50 HPF	Usually >5/50 HPF
Perinuclear vacuoles	present	usually absent
Nuclear atypia	often absent	present

*HPF, high power field

Table 2: Histopathologic features of benign and malignant epithelioid gastric GISTs

Parameters	Benign	Malign
Cellularity	low	high
Mitotic figures	<2/50 HPF	Usually >5/50 HPF
Necrosis	often absent	usually present
Nuclear atypia	often absent	usually Present

*HPF, high power field

4. Clinical Presentation of Gastric GISTs

The most common site of GISTs is the stomach (2,3). Gastric GISTs are frequently located in the fundus and cardia, which is in accordance with the distribution of interstitial cells of Cajal throughout the stomach [26]. The symptoms are non-specific and depend on tumor size as well as location [27].

In general, about 70 % of GISTs are associated with clinical symptoms, 20 % are not, and 10 % are detected at autopsy (6). Small gastric GISTs are usually asymptomatic and found incidentally during radiological investigations or surgical procedures especially during bariatric operations [28]. Gastric GISTs usually represents with gastrointestinal bleeding which is related with mucosal erosion. The other symptoms are dysphagia, satiety and abdominal pain (7,8).

Nearly half of patients with GISTs may present with metastatic disease and the most common site of metastasis is liver at about 65 % of patients. Other common metastatic sites are omentum and peritoneum. Extra-abdominal metastasis, lung, bone, and lymph node metastasis are not common [29].

5. Prognostic Factors and Risk Stratification in Gastric GISTs

Different risk stratification systems for assessing behavior of gastric GISTs has been proposed based on tumor size, mitotic activity, tumor rupture and tumor location (4). However an optimal staging system has not been established and validated yet. In general, gastric GISTs are known to have better prognosis than other gastrointestinal GISTs [30]. The most common used staging systems for prognosis of GISTs are shown in **Table 3,4,5**.

Table 3: NIH-Fletcher staging system for GISTs

NIH-Fletcher ⁴	
Risk	Features
Very low	< 2 cm and < 5 mitotic index
Low	2–5 cm and < 5 mitotic index
Intermediate	5–10 cm and <5 mitotic index or <5 cm and 6–10 mitotic index
High	>5 cm and >5 mitotic index or >10 cm and any mitotic index or any size and >10 mitotic index

Mitotic index = number of mitoses per 50 high power fields

Table 4: NIH-Miettinen staging system for gastric GISTs

NIH-Miettinen ³⁴	
Group	Features
Probably benign	≤5 cm and ≤5 mitotic index
Uncertain or low malignant potential	>5 cm, ≤10 cm, and ≤5 mitotic index
Probably malignant	>10 cm or >5 mitotic index

Mitotic index = number of mitoses per 50 high power fields

Table 5: AFIP-Miettinen staging system for gastric GISTs

AFIP-Miettinen ³⁰	
Risk	Features
Very low, if any malignant potential	≤2 cm and ≤5 mitotic index
Low malignant potential	>2≤10 cm and ≤5 mitotic index, ≤2 cm and >5 mitotic index
Intermediate malignant potential	>10 cm and ≤5 mitotic index, >2/ ≤5 cm and >5 mitotic index
High malignant potential	>5 cm and >5 mitotic index

Mitotic index = number of mitoses per 50 high power fields

American Joint Committee on Cancer (AJCC) has established TNM staging system for GISTs [31]. However it is not specific enough for gastric GISTs and therefore has not been commonly used. Recently, alternative risk classification systems such as nomograms have been developed to predict the prognosis of primary GISTs [32,33]. Nomograms have been used to predict the risk of recurrence following the complete resection of localized primary GISTs. Other risk factors for gastric GISTs recurrence are deletion type of mutations affecting codons 557 and 558 in KIT gene (3), lack of Pftin expression [35].

6. Diagnosis of Gastric GISTs

The majority of small gastric GISTs (≤2 cm) usually show no symptoms and found incidentally during endoscopic imaging or surgical procedures mostly during bariatric operations [28]. In suspicious of gastric GISTs, a detailed medical history and physical examination should be done. The latest NCCN guidelines suggests a CT (computed tomography) scan of the abdomen/pelvis as an initial imaging study for the extent of the primary tumor and evaluate the presence of metastatic disease. CT of gastric GISTs appearances vary with size and location. On a contrast-enhanced CT scan, GISTs typically shows a homogenous well-defined soft tissue of relatively low density (**Figure 3**). Enhancement of tumor is typically peripheral because of central necrosis and calcification is rare. Although MRI study has not been used routinely in clinical practice, a typically well-defined mass that is low to intermediate signal intensity on T1-weighted images and high signal intensity on T2-weighted images is highly suspicious of a gastric GIST. Fluorodeoxyglucose-positron emission tomography (FDG-PET) may be useful to asses response to tyrosine kinase inhibitors [36].



Figure 3: A 9x7x6 cm mass located in the pyloric antrum of the stomach. IV contrast-enhanced axial computed tomography shows a submucosal and exophytic tumor containing solid and necrotic area.

Gastric GISTs are detected as a submucosal tumor with normal mucosa in upper GI endoscopy (**Figure 4**). Mucosal ulceration may be seen in larger tumors. Endoscopic ultrasound (EUS) has led to the early detection of many small gastric GISTs and many studies revealed that EUS is the most appropriate method for submucosal gastric tumors [37]. Gastric GISTs appear as a hypoechoic, inhomogeneous, anechoic, or having a high echo (when tumors are malignant) on EUS imaging, and it is commonly located in the third and fourth layer, and rarely in the second layer [38]. In their study, Palazzo et al. revealed that the presence of enlarged lymph nodes, size greater than 4 cm, irregular margins and the presence of cystic spaces within the mass are suggestive of malignancy on EUS study [39].



Figure 4: A submucosal tumor with normal mucosa in upper GI endoscopy diagnosed as a gastric GISTs after surgical resection.

EUS-guided fine-needle aspiration (EUS-FNA) biopsy may be useful to achieve histological diagnosis or whether the patient should undergo further treatment such as neoadjuvant therapy for borderline resectable GISTs. EUS-FNA biopsy is not required for tumors less than 2 cm, high benign potential and the tumors for which surgical resection has already been planned [40].

7. Principles of Surgery for Gastric GISTs

Surgical resection remains the main treatment modality for the primary gastric GISTs with negative margins [41]. Although most guidelines suggest that tumors smaller than 2 cm may be observed because of the low potential for malignancy, NCCN guidelines recommends surgical resection of smaller GISTs less than 2 cm if they are suspicious with high risk EUS

features such as an irregular border, cystic spaces, ulceration, echogenic foci, or heterogeneity [42].

The main principles of surgery for gastric GISTs are complete resection to achieve negative microscopic margins. Unlike adenocarcinomas of the stomach wide normal mucosal margin is not needed since GISTs do not infiltrate the gastric wall. Lymphadenectomy is not required since gastric GISTs as well as other gastrointestinal GISTs rarely metastasize via lymphatic vessels [43]. However enlarged nodes should be considered during surgery.

Since gastric GISTs are soft and fragile tumors, a gentle dissection should be made to prevent tumor rupture as well to prevent peritoneal dissemination. It has been documented that tumor rupture is associated with very poor outcomes [44]. Because of these concerns enucleation procedures, either by an endoscopic or laparoscopic approach, should not be considered a standard treatment when GIST is suspected [45].

Although the indications of laparoscopic surgery for gastric GISTs is still under debate, safe laparoscopic resection of gastric GISTs has been well demonstrated in several studies [45, 46,47]. Currently, due to advances in laparoscopic surgery, the size of the tumor should not be the specific indicator for laparoscopic procedure because laparoscopic gastrectomy can be performed with minimal manipulation of the tumor. In a study, Karakousis et al reported that laparoscopic resection of gastric GISTs ≤ 8 cm resulted with similar oncological outcomes compared to an open resection with a median follow-up of 34 months [48]. After resection of tumor, the specimen should be removed from the abdomen with a plastic bag to prevent spillage or seeding to the port sites. Laparoscopic procedures are associated with less morbidity, length of hospital stay, less blood loss and low recurrence rates [49]. In this chapter we separately discussed the laparoscopic surgical procedure for gastric GISTs below.

8. Laparoscopic Approach for Gastric GISTs

The placement of trocars in to the abdomen differs due to the location of the gastric tumors and also surgeons preference. In general, the location of trocars in laparoscopic surgeries for gastric GISTs is as other gastric surgeries such as gastric cancer, sleeve gastrectomy or Nissen fundoplication. Preoperative or intraoperative endoscopy may help to confirm the adequacy of margins of gastric GISTs [50]. The choice of resection procedure depends on the size and the location of the tumor in the stomach [50]. The most common laparoscopic technique described is a simple gastric wedge resection with laparoscopic linear staplers.

Distal gastrectomy with gastrojejunostomy and/or vagotomy may be needed for GISTs located in the antrum or in the pre-pyloric part of the stomach. For tumors located in the fundus or greater curvature, laparoscopic partial gastrectomy (wedge resection) with laparoscopic endogia stapler is often adequate procedure. The tumors located in the lesser curvature and/or

gastro- esophageal junction (GEJ) are surgical challenge for surgeons. In general, for smaller tumors less than 3 cm, a gastrotomy is often performed to remove the tumor. Larger tumors near to the GEJ or in lesser curvature might require a proximal gastrectomy or an esophago-gastrectomy which can cause morbidities following postgastrectomy. In such cases the decision for the type of surgical procedure should be discussed in a multidisciplinary manner.

Laparoscopic endoscopic cooperative surgery (LECS) is a new technique which is used to manage gastric GISTs in Japan [51]. LECS has been reported to be safe and feasible for smaller gastric GISTs less than 5 cm with the outcomes similar to conventional laparoscopic wedge resections. The main advantage of this technique is the reduction in the resected area of the gastric wall compared to conventional laparoscopic wedge resection using a endogia stapler. LECS is may be used as an alternative technique to a difficult or failed endoscopic submucosal dissection (ESD) for gastric GISTs that fits the criteria for endoscopic resection.

9. Adjuvant Therapy for Primary Gastric GISTs

The discovery of KIT(CD117) (receptor tyrosine kinase) in GISTs has altered the management of GISTs. Imatinib mesylate is a selective tyrosine kinase inhibitor that inhibits KIT and had a significant impact on the prognosis of GISTs. Several trials and also guidelines recommends 3 years of adjuvant treatment with imatinib in high-risk patients (3). Adjuvant therapy with imatinib is not required for low-risk patients, and the data to support adjuvant imatinib therapy in intermediate-risk patients is insufficient (3). Neoadjuvant imatinib therapy might be considered for advanced or borderline resectable GISTs. Many studies have revealed that neoadjuvant imatinib therapy (with a dose of 400 mg/day) in patients with advanced GIST may reduce the tumor size and achieve an R0 resection with an increased chance of organ preservation. Sunitinib and regorafenib may be considered a second-line therapy for patients with advanced GIST resistant to imatinib therapy (3).

10. Follow-up

Most gastric GISTs recurrences occur within the first 5 years after surgery. Follow-up periods after surgery are based on the risk of aggressiveness and recurrence of gastric GISTs (3). Usually very low-risk tumors do not require a follow-up after surgical resection. Patients with low-risk tumors can be followed with CT annually. Follow-up for localized resectable gastric GISTs with intermediate- and high-risk features require CT every 4-6 months after the first 5 years following surgery. Patients with unresectable or metastatic GISTs should be followed based on clinical findings case by cases.

11. Conclusion

GISTs are rare tumors of the gastrointestinal tract with most common location in the

stomach. The initial diagnostic tests include an upper gastrointestinal endoscopy and a CT scan of the abdomen and pelvis. EUS with FNA biopsy is recommended for borderline resectable tumors if neoadjuvant therapy is planned. The aim of surgical treatment should be complete resection of the primary gastric GISTs, while avoiding tumor rupture and achieving negative microscopic margins. Laparoscopic approach should be the preferred choice of treatment for most gastric GISTs without limiting the indications by location and size. Tyrosine kinase inhibitors (CD117) is suggested to reduce the extent of surgery and the chance of incomplete resection when unresectable or multiorgan resection is planned.

12. References

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