



Original Article

A Retrospective Cohort Study of 304 Patients with Gastrointestinal Stromal Tumors in Mackay Memorial Hospital

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Abstract

Background: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. GISTs often occur in middle-aged and older individuals. The main morphologic type of GISTs is the spindle cell type. Immunohistochemistry and genotyping can help to identify GISTs from other subgroups of sarcoma. **Materials and Methods:** This retrospective study collected 304 patients over a 10-year period (from January 2009 to June 2019) who were diagnosed with GISTs based on the pathological database of our hospital. We retrospectively analyzed the clinical manifestations and treatment strategies. **Results:** Anemia or gastrointestinal bleeding was the most common symptom (36.5%), followed by gastrointestinal discomfort (32.6%) and incidental findings (21.4%). Ruptured tumors with hollow organ perforation increased the mortality risk. Liver metastasis and peritoneal seeding were the most two common patterns of recurrence. GISTs arising in adults are characterized by the near-universal expression of CD117/KIT antigen. Early surgery with margin-free resection is the best strategy for GISTs without metastasis. Routine lymph node dissection is not recommended. Laparoscopic surgery is feasible and safe for GISTs in the gastrointestinal tract. Endoscopic submucosal dissection to treat GISTs is suitable for small tumors with very low-to-intermediate risk in the stomach. Postoperative treatment with tyrosine kinase inhibitors can prolong recurrence-free survival after surgery. **Conclusion:** Surgical resection is the preferred treatment for patients without metastasis. Administration of tyrosine kinase inhibitors such as imatinib is recommended for unresectable, metastatic, or recurrent GISTs. Postoperative follow-up by computed tomography to detect early recurrence is recommended.

Keywords: Endoscopic submucosal dissection, gastrointestinal stromal tumor, tyrosine kinase inhibitors

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common malignant subepithelial neoplasms of the gastrointestinal tract and are most often located in the stomach and proximal small intestine; however, they also can occur in any portion of the alimentary tract and occasionally in the omentum, mesentery,

and peritoneum.^[1-4] GISTs are submucosal tumors that can grow to a huge size before causing symptoms. The most common symptoms of GISTs are gastrointestinal bleeding, including acute melena and hematemesis with anemia, weakness, and

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abdominal pain, fullness and distension.^[5] Previous studies have shown that 15%–30% of patients with GISTs are asymptomatic, and that their GISTs are found incidentally during health examinations or surgery for treatment of other diseases.^[6]

The incidence of other primary neoplasms in GIST patients is relatively high. Previous studies over the past decade have reported annual incidence rates of 7–19 cases per million population. A study of 6142 cases between 2001 and 2011 reported an incidence of 0.68 per 100,000.^[2,7]

The main morphologic types of GISTs are the spindle cell type (70%), epithelial cell type (20%), and mixed type (10%) [Figure 1].^[8,9] Pathologically, the diagnosis of a GIST relies on morphology and immunohistochemistry. A diagnosis can also be made by the presence of KIT/CD117 or CD34 positivity. If the tumor is negative for CD117, CD34, desmin, and S-100, additional tests including discovered on GIST 1 (DOG1) staining or a mutation search of the CD117 or platelet-derived growth factor receptor- α genes are useful to diagnose GISTs.^[9,10] GISTs are considered to be a potentially malignant tumor and are classified as very low, low, intermediate, or high risk.^[6] The metastatic risk of GISTs has been reported to increase with the tumor size irrespective of the mitotic count.^[11]

The prognosis of this disease is associated with the tumor size and mitotic index. Surgical resection is the standard treatment for patients without metastasis.^[12–15] Tyrosine kinase inhibitors such as imatinib mesylate are the first-line standard therapy for unresectable, metastatic, or recurrent GISTs.^[9,16] When the patients have disease progression despite imatinib treatment or are unable to tolerate adverse events, sunitinib malate can serve as second-line treatment.^[17] Regorafenib can be used as third-line therapy.^[18]

METHODS

We searched medical records according to The International Statistical Classification of Diseases and Related Health

Problems 10th Revision, ICD-10 code and pathological database of our hospital to identify all patients with GISTs from January 2009 to June 2019. Data including the patient’s gender, age, time of first diagnosis, histological type, tumor size, mitotic figure <5 or $\geq$ 5 per 50 high-power fields, and immune histochemistry characteristics (CD117, CD34, DOG-01, smooth muscle actin, and S-100) were recorded. We also reviewed treatment strategies and patients with recurrence or metastasis to evaluate the interval to recurrence and location of the metastasis.

The institutional review board disclosure

This is a retrospective study of 304 patients in a single medical hospital in the past decade. The institutional review board approved this study (number: 20MMHIS068e) and waiver of informed consent was approved by MacKay Memorial Hospital Institutional Review Board.

RESULTS

A total of 304 patients were included in this retrospective cohort study (male-to-female ratio: 51%:49%). The patients’ characteristics are summarized in Table 1. GIST was the primary diagnosis in 250 patients (82.2%), 33 patients (10.9%) had recurrence or metastasis of GIST, and 21 patients (6.9%) were diagnosed accidentally when receiving other surgeries (3 for esophageal cancer, 6 for hemicolectomy, 8 for gynecology debulking surgery, 1 for prostate cancer, and 3 for sleeve gastrectomy). Anemia or gastrointestinal bleeding was the most common symptom (36.5%), followed by gastrointestinal discomfort (32.6%) and incidental findings (21.4%).

The anatomic distribution of GISTs in the primary diagnosis group was as follows: 177 in the stomach (58.2%), 83 in the small intestinal (27.3%), 17 in the colon (5.6%), and 3 (1.0%) in other unspecified sites [Table 2]. The mean tumor size was 5.7 cm (median: 4 cm and range: 0.2–29 cm) [Table 3].

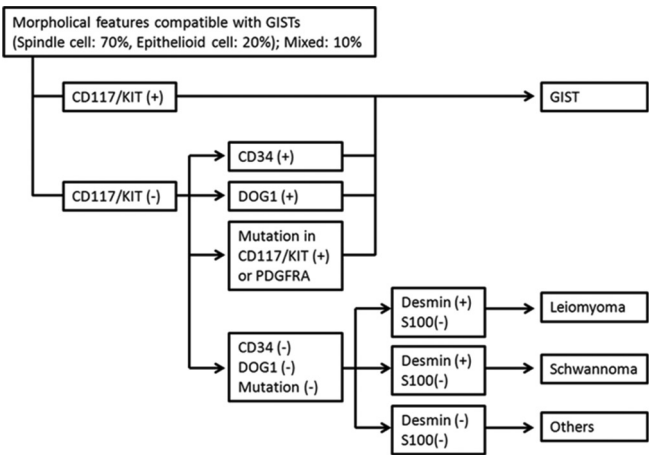


Figure 1: Pathological diagnosis of gastrointestinal stromal tumor by immunohistochemistry and genotyping^[9]

Table 1: Patient characteristics	
Characteristics	Patients No
Gender	
Male	155 (51%)
Female	149 (49%)
Age at GIST diagnoses	
Mean	62.9 y/o
Median	62 y/o
Range	23-92 y/o
Symptoms	
Overt or occult gastrointestinal bleeding	111 (36.5%)
Gastrointestinal pain or fullness sensation	99 (32.6%)
Incidental findings (asymptomatic)	65 (21.4%)
Palpable mass	17 (5.5%)
Acute abdomen	6 (2.0%)
Poor appetite	4 (1.3%)
GU symptoms	2 (0.7%)

A total of 275 patients (90%) received imatinib either before (neoadjuvant; 26 patients) or after (adjuvant; 262 patients) surgical resection. Thirty-three patients (10.9%) had recurrence or metastasis (18 males and 15 females). The mean interval to recurrence or metastasize was 4.14 years (range: 0.5–9 years and median: 2.1 years). Thirty-three patients had recurrent GISTs. Thirteen patients had metastasis to the liver only; 3 patients had metastasis to the liver, colon, and small intestine; 11 patients had seeding to intra-abdominal tissue or retroperitoneum; and 8 patients had recurrence to the gastrointestinal tract [Table 4].

During the study period, 6 patients died (2.0%). Five of them died within 3 months after surgery at our facility (mean: 21 days and range: 8–43 days). Among these 5 patients, 3 died of tumor rupture and hollow organ perforation and 2 had metastasis to the liver and colon and died of postoperative sepsis related to anastomosis leakage. One patient survived for over 10 years and died of pneumonia.

The endoscopic submucosal dissection (ESD) technique has been established in recent years [Figure 2]. It provides shorter postoperative hospital stay [Table 5]. In our experience, the ESD method (31 cases) was suitable for small tumors located in the stomach (mean: 1.45 cm, median: 1.2 cm, and range from 0.5 to 4.5 cm), with a very low-to-intermediate risk (22 very low risk, 3 low risk, and 6 intermediate risk).

Table 2: Antomic site of 1st diagnosis of GIST

Antomic site of 1 st diagnosis of GIST	Patients No
Stomach	177 (58.2%)
Small intestine	83 (27.3%)
Duodenum	25 (8.2%)
Other parts of small intestine	58 (19.1%)
Colon	17 (5.6%)
Other palce	
Esophagocardiac junction	2 (0.7%)
Pancreas	1 (0.3%)

Table 3: Tumor characteristics

Tumor sizes (exclude the tumors diagnosis via biopsy)	
<2cm	18.4%
2.1~5.0cm	44.2%
5.1~10cm	26.1%
>10cm	11.2%
Mitotic rate of GIST	
<5/50 HPF	53.0%
≥ 5/50 HPF	36.8%
Unknow	10.2%
Pathologically immunohistochemistry	
CD117/KIT	96.3%
CD34	68.8%
DOG1	96.0%
SMA	23.0%
S100	9%

DISCUSSION

GISTs are the most common sarcoma of the gastrointestinal tract. GISTs arising in adults are characterized by the near universal expression of CD117/KIT antigen. Early diagnosis (early GISTs without metastasis) with early surgical resection is the best chance to obtain a complete cure. The primary surgical goal is to achieve margin-free resection to the greatest extent possible. Routine lymph node dissection is not recommended. Partial resection or segmental resection with anastomosis to preserve organ function is recommended.^[19] With the introduction of surgical staplers and energy devices, laparoscopic surgery is feasible and safe for GISTs in the gastrointestinal tract. According to previous studies, it has similar outcomes when compared with traditional open surgery.^[20]

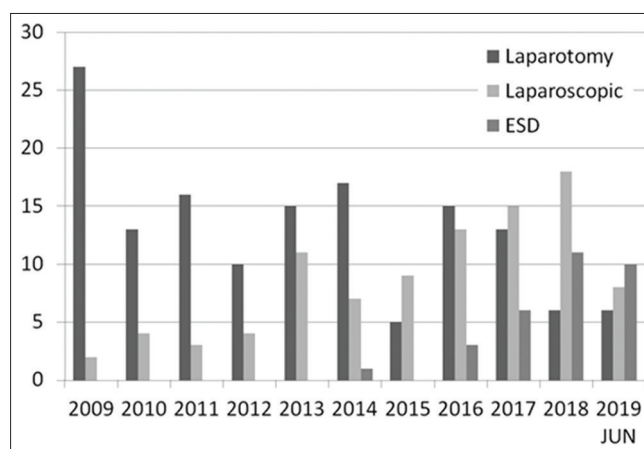


Figure 2: Shifting paradigm of approaches

Table 4: Metastatic antomic site of GIST

Characteristics	Patients No
Metastatic antomic site of GIST	33
Liver	16
GI tract	11
Intraabdominal tissue *	9
Retroperitoneal tissue	2

* Intraabdominal tissue including mesentery, peritoneum and omentum

Table 5: Clinical course characteristics

Clinical characteristics	
Operation methods	Patients No
Laparotomy	143 (47.0%)
Laparoscopic surgery	92 (30.2%)
ESD	31 (10.2%)
Biopsy	28 (9.2%)
Local excision (Rectum)	8 (2.6%)
ESD convert to Laparoscopic	2 (0.7%)
Post operation inpatient days	Days
Laparotomy	14.2
ESD convert to Laparoscopic	8.84
ESD	3.87

The use of ESD to treat GISTs is still under investigation, especially concerning the long-term safety.^[21] We found that ESD was associated with shorter hospital stay, better preservation of organ function, and better quality of life after surgery. However, it still has limitation when dealing with large GISTs.

Imatinib (a first-line tyrosine kinase inhibitor) can be given after surgery, as many studies have reported that it can prolong recurrence-free survival after surgery.^[22] In the present study, the omentum, peritoneal seeding, and liver were the most common GIST metastasis sites, which is compatible with the previous studies.^[4,23]

CONCLUSION

Tumor size, mitotic rate, and tumor location are the main prognostic determinants. Early surgical resection is the most reliable and curative treatment technique for patients without metastasis. Tumor recurrence tends to be intra-abdominal. The administration of tyrosine kinase inhibitors such as imatinib is recommended for unresectable, metastatic, or recurrent GISTs. Postoperative follow-up by computed tomography (CT) to detect recurrence is crucial. The Japanese clinical practice guidelines for GISTs recommend that GISTs with very low, low, and moderate risks are followed up by CT every 6–12 months, and that high risk and GISTs with metastasis should be followed up by CT every 4–6 months.^[9,23]

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Conflicts of interest

There are no conflicts of interest.

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