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Review Article

Surgery as First Therapeutic Choice in Gastrointestinal Stromal Tumors (GIST). 10 Years of a Single Center Experience

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• GIST; Surgical treatment; Imatinib mesylate

Abstract

Gastrointestinal stromal tumor (GIST) is the term for a specific, immunohistochemically KIT-positive (90% of KIT mutations involve exon 11) mesenchymal neoplasm of the gastrointestinal tract and abdomen.

Neoadjuvant therapy can be effectively used for the treatment of metastatic and recurrent GIST or when the surgery can't be radical at the first time.

Symptoms of GIST are gastrointestinal bleeding, gastric pain, intestinal obstruction, hemoperitoneum because of tumor rupture. Most of GISTs are detected incidentally (CT scan, endoscopy for other reasons) and they are less than 5 cm in size.

As is known, surgical resection is always the first therapeutic option if R 0 can be achieved. Post-therapy surgery with Gleevec® (Novartis) is the choice in metastatic, recurrent GIST and in situations where due to the site or size, surgery may not prove radical or may jeopardise the patient's quality of life. Borderline cases should be discussed collectively in key centres with a radiologist, oncologist and surgeon.

ABBREVIATIONS

GIST: Gastro Intestinal Stromal Tumor; KIT: Kinase Tyrosinprotein; HPF: High Power Field; CT: Computed Tomography; GI: Gastro-Intestinal; ADK: Adenocarcinoma

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is the term for aspecific, immunohistochemically KIT-positive (90% of KIT mutations involve exon 11) mesenchymal neoplasm of the gastrointestinal tract and abdomen.

GISTs constitute a majority of GI mesenchymal tumors and they are 0.1-0.3% of all gastrointestinal neoplasms.

Pathologic activation of KIT signal transduction appears to be a central event in GIST pathogenesis.

The identification and proper definition of GIST has become more important after introduction of targeted treatment with KIT tyrosine kinase inhibitor Imatinib mesylate, STI571, commercially known as Gleevec®/Glivec® for metastatic and unresectable GISTs. The early results on isolated cases and clinical trials have shown tumor stabilization or regression in a great majority of metastatic and unresectable GISTs expanding the trials to large numbers of patients with malignant GISTs so management of GISTs has been transformed [1].

Neoadjuvant therapy can be effectively used for the treatment of metastatic and recurrent GIST or when the surgery can't be radical at the first time.

Symptoms of GIST are gastrointestinal bleeding, gastric pain, intestinal obstruction, haemoperitoneum because of tumor rupture. Most of GIST are detected incidentally (CT scan, endoscopy for other reasons) and they are less than 5 cm in size.

As is known, surgical resection is always the first therapeutic option if the disease can be removed completely. Post-therapy surgery with Gleevec® is the choice in metastatic, recurrent GIST and in situations where due to the site or size, surgery may not prove radical or may jeopardise the patient's quality of life. Borderline cases should be discussed collectively in key centres with a radiologist, oncologist and surgeon [2,3].

The surgical choice in resectable cases depends also on the site and size: in GISTs larger than 2 cm, gastric surgery involves an atypical segmental resection or a traditional gastric resection in prepyloric or precardial cases. Segmental resection is indicated in GIST of the jejunum-ileum, while traditional resection is the choice for colorectal tumours. In sites like the duodenum, the low rectum and oesophagus, in case of tumours of large dimensions, a neo-adjuvant therapy with Gleevec may be indicated, or another option that can be considered is enucleation of the mass, so as to avoid an extremely demolishing surgery [1,3].

GISTs smaller than 2 cm can be kept under control through careful follow-up, and may possibly be removed endoscopically in compromised or elderly patients.

With the exception of the above situations, enucleation should always be avoided and the most important oncological rule

requires gentle handling of the disease, so as to avoid capsular breakage and rupture of the mass. A successful surgery is one of the essential prognostic factors of the disease, next to the number of mitoses, the site and size [2].

The aims of the study are to demonstrate that appropriate surgery is an adequate therapy for GIST through a comparison of personal data with the available scientific literature.

MATERIAL AND METHODS

Our retrospective study has analysed the cases of a series of 52 patients (admitted for treatment at the Surgery Multi-Disciplinary Unit of the Piacenza, Fiorenzuola, Castel San Giovanni Hospitals) with histological diagnosis of a gastrointestinal stromal tumour (GIST), treated with surgical resection from January 2005 until December 2015.

The analysis took into consideration the following factors: site, size, mitotic index, appropriateness of surgical method, and other risk factors such as ulceration or necrosis. This data allowed us to stratify the disease's degree of aggressiveness (classification of Fletcher) [4-7] into low, medium and high grade. A modification to the standard Fletcher criteria has been proposed and used including tumor rupture as an important risk factor (Figure 1). Medium and high-risk patients have a higher risk of recurrence, metastasis and an increased mortality. The outcome evaluation was made considering the incidence of disease recurrence and mortality.

Kaplan-Meier analysis, a non-parametric statistic, was used to evaluate factors related to recurrence free survival.

RESULTS

Between January 2005 and December 2015, 52 patients underwent surgical resection for a primary neoplasm identifiable as a GIST of the gastrointestinal tract. Of these, 29 patients (56%) were men and 23 were women (44%).

The primary site was found to be the stomach in 33 patients (63%), the ileum in 15 patients (29%), the rectum in 3 patients (6%), and other sites (retro-peritoneum) in 1 patient (2%).

The size was <2 cm in 6 patients (11%), >2 and <5 cm in 29 patients (56%), and >5 cm in 17 patients (33%).

The number of mitoses was <1 /hpf in 12 patients (23%), >1 and <5/hpf in 29 patients (5%), and >5 /hpf in 11 patients (21%).

Based on this data, our patients were classified as followed: 25 low-risk patients (48%); 16 medium-risk patients (31%); and 11 high-risk patients (21%).

All patients were treated with surgery as first therapeutic choice, according to the NCCN guidelines.

The surgeries were elective in 45 cases (87%), and in emergency in 7 cases (13%). Patients were operated in emergency for severe bleeding in 3 cases (2 with gastric bleeding, 1 with ileal bleeding), occlusion and pain in 3 cases (all ileal), and for perforation resulting in rupture of the capsule (1 case, ileal GIST).

With regard to primary gastric tumours, the chosen surgical method was an anatomic gastro-resection or wedge resection

Proposed modification of consensus classification for selecting patients with GIST for adjuvant therapy

Risk category	Tumor size (cm)	Mitotic index (per 50 HPFs)	Primary tumor site
Very low risk	<2.0	≤5	Any
Low risk	2.1-5.0	≤5	Any
Intermediate risk	2.1-5.0	>5	Gastric
	<5.0	6-10	Any
	5.1-10.0	≤5	Gastric
High risk	Any	Any	Tumor rupture
	>10 cm	Any	Any
	Any	>10	Any
	>5.0	>5	Any
	2.1-5.0	>5	Nongastric
	5.1-10.0	≤5	Nongastric

Figure 1 Modified classification of Fletcher for patient's risk evaluation.

depending on the sites and size. In small bowel tumours, segmental ileal resection has always been the standard. GISTs in the rectum were treated with standard resection of the rectum, except in one case where old age (>80 years) and size (<1 cm) allowed for endoscopic removal [8-10].

The lymphadenectomy was not deemed necessary from an oncological point of view. In none of our patients was lymph node metastases described from the pathological analysis [11].

Laparoscopy was used in 12 cases (23%) (8 gastric resections, 4 ileal resections, all of which with size < 5 cm) [12,13].

Surgical adequacy was achieved in 94% of cases, i.e. in 49 patients. The three patients group for which a suboptimal surgery is described includes a rupture of the tumour's capsule in one case operated in emergency due to perforation, two patients with margins measuring < 1 mm in local-regional removals (disease of the rectum).

The follow-up was from 6 to 96 months.

The median disease-free survival rate was 43 months.

The overall median survival rate was 60 months.

Overall median survival for tumours with size <5 cm was 100% in 5 years; size between 5 and 10 cm 75% in 5 years; >10 cm 80% in 3 years and 70% in 5 years (Figure 2).

Survival based on the site was: in 33 patients with gastric site, 82% in 5 years, in 15 patients with ileal site, 75% in 5 years, and in 3 patients with rectal disease, the survival was 100% in 5 years, but two patients out of three developed recurrence of the disease, respectively one at a local-regional level and one at a hepatic level (Figure 3).

Survival based on the number of mitoses, if the number of mitoses is >5, was 75% in 3 years and 50% in 5 years. If the number of mitoses is >25, mortality in 5 years is 100% (Figure 4).

In total, considering all the risk factors combined, overall survival in 2 and 5 years in patients at LOW RISK is of 95% and

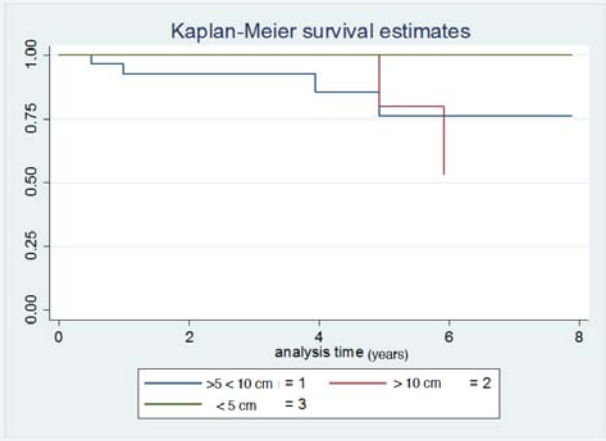

Figure 2 Kaplan-Meier estimates based on tumor size.

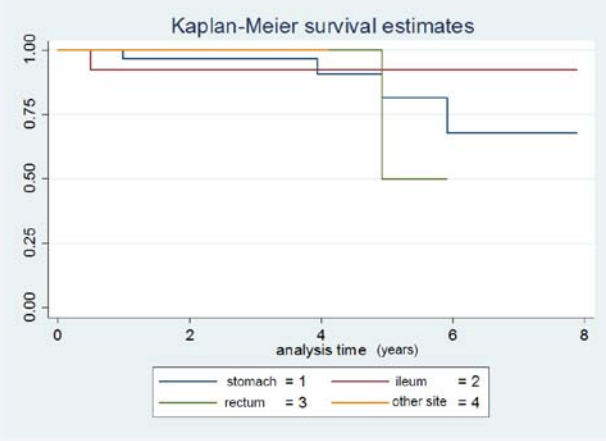

Figure 3 Overall survival based on site of presentation.

80% respectively, with disease-free patients in 100% of cases, in patients at MEDIUM RISK, 100% and 70% respectively, and in patients at HIGH RISK, 70 and 50% (Figure 5), with a disease free survival of 45% in 5 years (Figure 6).

Finally, 6 patients out of 52 (12%) developed the GIST synchronously to another tumour of the gastrointestinal tract (1 in the pancreas, 2 colorectal, 3 in the stomach). All synchronous GISTs had an overall low risk, and all synchronous GISTs of our case study were positive for CD117 and CD 34.

DISCUSSION & CONCLUSION

According to the international guidelines that identify the risk and degree of aggressiveness of the disease, patients were stratified into low, medium and high risk. The key factors examined were the site, the size, number of mitosis, right surgery.

More specifically, low-grade aggressiveness tumours are those with a size of less than 5 cm and a mitotic count of less than 5/50 high power field (HPF), those with medium-grade aggressiveness have a size of between 5 and 10 cm, with index below 5, or tumours with a diameter <5 cm, but a mitotic index of >50/50 HPF, but <10/50.

Finally, lesions with a high-grade malignity are those with a size of >10 cm, regardless of the mitotic count index, or with a size of <5 cm and mitotic index of >5 hpf.

The gastric site is associated with a better prognosis, while the colorectal site with a worse prognosis.

In our case study ileal presentation is associated most frequently with symptoms as occlusion or perforation and bleeding (5/7 patients operated in emergency).

Other characteristics taken into account were the degree of necrosis and ulceration encountered in 6 patients, all with lesions with a medium and high risk due to the high number of mitoses.

The female gender was not associated with any increased risk factor, unlike other studies reported in the scientific literature [4,14].

Surgery may be considered adequate in 95% of the cases, considering as parameters of appropriateness the resection margins and the non-rupture of the capsule.

The major risk factor for a disease recurrence related to surgery remains the rupture of the capsule [15] and the bleeding

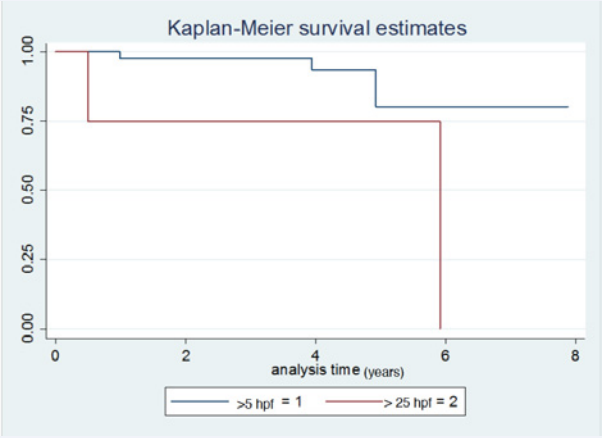

Figure 4 Overall survival based on number of mitosis (high power field).

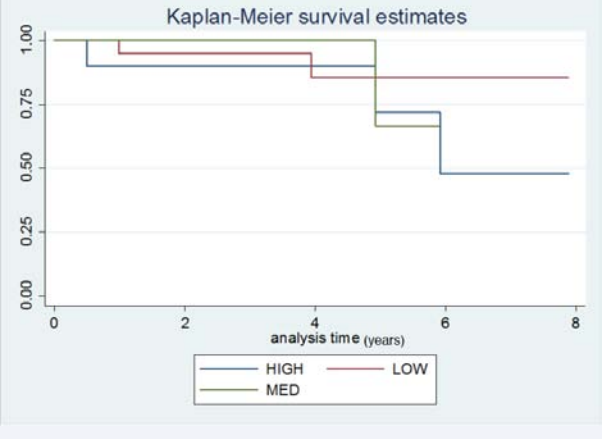

Figure 5 Kaplan-Meier estimates based on GIST risk classification.

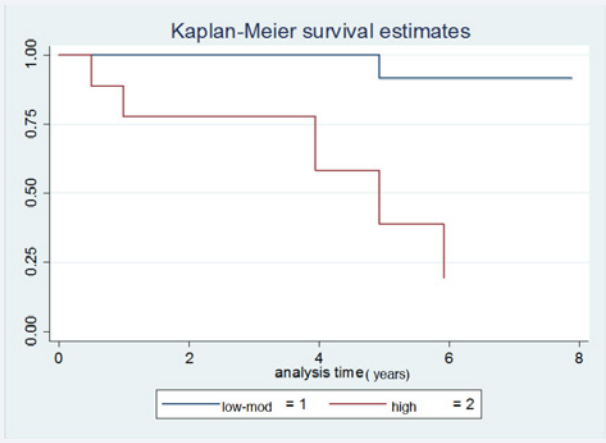

Figure 6 Disease-free survival based on GIST grade (low, medium and high).

of the lesion intra-operatively. Rupture of the tumour increases the risk of bleeding and contamination. As such, urgent surgery or improper handling can dramatically change the patient's prognosis [15,16].

In our specific case study, 13% of patients underwent emergency surgery. Clear breakage of the capsule was described in only one case. Even in patients with bleeding, proper resection was carried out of the entire disease, avoiding mass manipulation and proceeding with adequate peritoneal cavity washes.

The micro-invasion of the margins does not appear to be significant for the risk of recurrence; however the gold standard is the complete removal of the lesion with a negative margin. The margin <1 mm but without a clear micro-invasion of the margins does not necessarily represent indication for new surgery. There is no evidence that the patient with full macroscopic resection of the disease but with an R1 margin needs to undergo a re-excision. Moreover, new surgery is justified only by an acceptable morbidity tied to the surgery [13].

In both cases (inadequacy of margins, emergency surgery), the oncologist has to evaluate the need for adjuvant treatment with Gleevec® as the site, the size and number of mitoses are less important than the appropriateness of surgery in the definition of high risk [5].

The results of our case study were expressed using Kaplan-Meier curves.

The study focuses on the risk of disease recurrence and survival in relation to the single risk factor and evaluating the distribution of patients defined as low, medium and high risk according to the classification of Fletcher considering the site, number of mitoses and extent of disease as factors.

The overall survival rate is significantly dependent on the size of the tumour: patients with tumours of a size of less than 5% are all alive and free of disease in the time period studied, patients with a tumour with size between 5 and 10 cm and greater than 10 cm have a significant increase in recurrence rates and a lower survival rate over time (Figure 1).

With regard to the site of the tumour instead, in 33 patients with gastric disease, 18% died in 5 years, in 15 patients with ileal disease, 75% are alive after 5 years, 70% after 10 years, in 3 patients with rectal disease, 2 patients are alive but with hepatic disease treated with Gleevec®, and one patient presented local recurrence in 18 months (Figure 2).

The number of mitoses appears to be the most significant prognostic factor [1,7]with a net reduction of survival in patients with number of mitosis > 5 (75% in 3 years, 50% in 5 years), with a mortality of 100% in 3 years if the number of mitosis is greater than 25% (Figure 3).

Patients classified as Fletcher low risk had 2 and 5 years survival of 95% and 80% , all patients were disease free and death occurred for age or other co morbidities. Intermediate risk group had 2 and 5 years survival of 100% and 70% and recurrence free survival was 100% too. The high risk group had 2 and 5 years survival of 70% and 50% and recurrence free survival was about 45%. This confirms that tumors with low and intermediate risk had a significantly better prognosis and better recurrence free survival (p=0.0007 χ squared test) (Figure 4,5).

In our study GIST occurred synchronously with other neoplasm in 6 (12% of the total number of patients). The concomitant cases were primary tumors and during the planned treatment (CT scan or surgery) GIST were discovered. All the neoplasm was from GI tract (1 pancreas adk, 2 colon rectum, 3 gastric) and all were low risk gist [5].

These data are consistent with the current literature [8,10,17] which seems to associate an increased risk of developing tumours of the gastrointestinal tract in patients with GIST [6,9]. Our study confirms the major impact of GIST-associated malignancies on the prognosis of GIST [18].

In conclusion, knowing the management of gist is very important also in lower volume centers, because it's always possible a presentation in emergency [17], and also because most of GIST are detected incidentally (CT scan, endoscopy for other reasons) and, above all, because prognosis is closely linked to adequate surgery [6,14].

Results of our experience, in terms of overall survival, disease-free survival, stratification of risk, synchronous incidence with other gastrointestinal neoplasm, are superimposed on the results of larger volume centers and this underlines how right surgical treatment are decisive for best patient care even in an emergency setting due to an occasional diagnosis of GIST [13,15].

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