J Gastrointest Surg (2009) 13:1220–1225
DOI 10.1007/s11605-009-0885-8

ORIGINAL ARTICLE

Surgical Therapy for Gastrointestinal Stromal Tumours of the Upper Gastrointestinal Tract

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Received: 2 December 2008 / Accepted: 24 March 2009 / Published online: 16 April 2009

Abstract
Aim This study aimed to examine clinicopathological features and outcomes after primary resection of gastrointestinal stromal tumours (GIST) of the upper gastrointestinal tract
Method Fifty consecutive patients were identified as having a mesenchymal tumour of the upper gastrointestinal tract resected at our institution, of which 47 were GISTs. The influence of clinicopathological variables on disease-free survival was evaluated using Kaplan–Meier estimates and Cox hazard model.
Results The median age was 62.8 (21.3–94.7). The commonest presenting symptoms were anaemia (43%) and pain (34%). Tumours were located in the stomach (64%), small bowel (34%) and oesophagus (2%). Median follow-up was 20.4 (2–106) months. Fletcher low/intermediate-risk tumours had a significantly better (p=0.0008) 2- and 5-year actuarial survival of 100% compared with 88% and 58% for high-risk group. Recurrence-free survival at 2 and 5 years was 100% for low/intermediate-risk group compared with 68% and 45% for the high-risk group (p=0.0008). Univariate analysis of predictors of recurrence identified male sex, high mitotic rate and tumour size as significant. Multivariate analysis showed high mitotic rate as the only poor prognosticator (Hazard ratio=16.7, p=0.02).
Conclusion Surgical excision of low- and intermediate-grade GIST has an excellent prognosis. Surgery remains the mainstay of treatments, and high-grade tumours carry a significantly worse prognosis. High mitotic rates are an independent poor prognosticator.

Keywords Gastrointestinal stromal tumours · Surgery · Outcomes · Prognostic factors

Presentation: This work has not been presented
Disclaimers: The authors indicated no potential conflicts of interest
Grant Support: None
Note all graphs produced using StatView statistical software and further edited with Adobe Photoshop.

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Introduction

Gastrointestinal stromal tumour (GIST) is the commonest mesenchymal tumour of the gastrointestinal tract. GISTs have only relatively recently been recognised as a distinct entity and in the past were often classified variously as leiomyoma, leiomyosarcoma, leiomyoblastoma or schwannoma.[1,2] GISTs are thought to arise from the interstitial cell of cajal.[3] A key mutation in the development of GIST involves a tyrosine kinase receptor function gain, which becomes constitutionally active resulting in proliferation of cells. The Ckit or CD117 is the commonest mutated protein involved, followed by PDGFRA mutations.[4] Improved understanding of these mutations has enabled the development and application of targeted therapy using tyrosine kinase inhibitors.[5] Targeted therapy has demonstrated efficacy in the treatment of metastatic or inoperable GIST, but currently definitive surgical resection offers the only possibility of cure. This study's aim was to evaluate the outcome and determine prognostic factors after surgical treatment of a primary GIST in our series of patients.

Material and Methods

A retrospective review of a prospectively collected database was searched for the last 50 consecutive patients at our institution to have undergone primary resection of upper gastrointestinal mesenchymal tumours. Of the 50 patients, 47 had excision of a GIST. The resections were performed between Dec 1999 and July 2008.

Patient demographics, symptoms at presentation, site of tumour and operation performed were recorded. The histological features of the tumour recorded included size, mitotic rate, presence of ckit or CD34 marker and necrosis or ulceration of the tumour. Tumour recurrence and mortality were used to evaluate outcome. The Fletcher[6] classification was used to stratify patients into low, intermediate and high risk for disease progression. Kaplan–Meier analysis with log rank test for significance was used to evaluate, in a univariate model, factors that affected recurrence-free survival. A multivariate Cox proportional hazard model was used to further examine prognostic factors identified in the univariate model.

Data analysis was performed using StatView v4.5 (Abacus Concepts Inc., Berkeley, CA, USA) for PC.

Results

Between Dec 1999 and July 2008, 47 patients had a primary excision for GIST. There were 26 males (55%) and 21 females (45%). Median age was 63 (see Table 1).

Table 1 Patient Characteristics

Number of patients	47
Male:female	26:21
Median age (range)	62.8 (21.3–94.7)
Presentation (%)	
Haematemesis/melaena	10 (21.3)
Anaemia	20 (42.6)
Obstruction	6 (12.7)
Pain	16 (34.0)

The commonest symptom at presentation was pain (34%), then haematemesis or melaena (21%), followed by obstructive symptoms (13%). Anaemia was present in 42% of patients.

The commonest site for GIST was the stomach, followed by duodenum, jejunum, ileum and oesophagus (see Table 2).

Resections performed included gastro-oesophagectomy for lower oesophageal and cardio-oesophageal tumours and total gastrectomy for large and/or proximal gastric tumours. Distal gastrectomy was performed for larger tumours of the antrum. For smaller body or fundal lesions, a laparoscopic wedge excision was carried out. Lesions in the second part of the duodenum were treated with a pancreaticoduodenectomy. Small bowel tumours were treated by segmental excision (Table 3).

The Fletcher[6] classification was used to stratify tumours as low, intermediate or high grade. Briefly, low-grade tumours are those with size <5 cm, mitotic count <5/50 high-power field (HPF). Intermediate grade are those with size between 5 and 10 cm with mitotic count <5 or size <5 cm and mitotic count of 6–10. High-grade lesions are those with size >10 cm or mitotic count >10 or size >5 cm with mitotic count>5.

Table 2 Tumour Location

Location of tumour	Number (% total)
Stomach	30 (64%)
Gastro-oesophageal jct	1 (2%)
Cardia	4 (9%)
Fundus	8 (17%)
Body	10 (21%)
Antrum	7 (15%)
Duodenum	7 (15%)
D2	4 (9%)
D4	3 (6%)
Jejunum	6 (13%)
Ileum	3 (6%)
Oesophagus, distal	1 (2%)

Table 3 Operations Performed

Surgical procedure	Number (% total)
Distal/partial gastrectomy	21 (45%)
Small bowel resection	12 (26)
Laparoscopic wedge excision	5 (11%)
Whipple's operation	4 (9%)
Total gastrectomy	3 (6%)
Oesophagectomy	2 (4%)

There were 20 low-risk tumours, 13 intermediate and 14 high-grade tumours (see Table 4). The overall median follow-up was 20.4 months (2–106 months). No deaths or recurrences occurred in the low-risk group. One distant recurrence but no deaths occurred in the intermediate group. Four patients in the high-risk group had distant recurrence and one other patient had metastatic disease at initial presentation. There were four deaths in this group. Tyrosine kinase inhibitors were not used in an adjuvant setting, with therapy only being instituted in the presence of proven recurrence. Imatinib was the preferred agent used in this setting. Sunitinib was used in two patients who developed resistance to imatinib.

Tumours classified as Fletcher low or intermediate risk had a significantly better (p=0.0008 chi-squared test) 2- and 5-year actuarial survival of 100% compared with 88% and 58% for the high-risk group. Recurrence-free survival at 2 and 5 years was 100% for the low- and intermediate-risk group compared with 68% and 45% for the high-risk group (p=0.0008 log rank test). The median time to death following recurrence was 32 months, ranging from 20 to 49 months. The Kaplan–Meier plot for recurrence-free survival according to tumour risk is shown in Fig. 1a.

Clinicopathological variables were further examined using a univariate model to determine significant predictors of recurrence (Table 5). Kaplan–Meier estimates with a log rank test for significance was used. Clinical variables examined included age >62.8 (median age of the group), gender, presence of anaemia or symptoms of pain. Pathological variables examined included presence of necrosis, ulceration, ckit or CD34 expression, tumour size >10 cm, a mitosis count >10 per 50 HPF. A p value <0.2 was considered significant in the univariate model. Female sex, a mitotic count >10 and tumour size >10 cm were found to be significant (see Fig. 1b–d). When these three variables were analysed in a Cox proportional hazard model, the only independent predictor of risk found was the mitotic count of the tumour (p=0.02).

Discussion

GISTs were once thought to be rare, but it is now appreciated that, while these tumours are not common, the incidence is several fold higher[7] than initially thought, possibly due to increased use of upper gastrointestinal endoscopy.[8]

The nearly even sex distribution of tumours and median age of 63 in our series of patients is consistent with published reports. We however found a broader age range (21–94 years) to that reported (40–80 years).[9–11]

Bleeding and anaemia are a common presentation (42%) and the development of symptoms is related to the size of the tumour. Larger tumours may also present with pain and obstruction.[6,12,13] Asymptomatic GISTs are usually found incidentally at endoscopy or laparotomy.

Surgery is the mainstay of treatment for primary localised GIST, its aim being to remove the tumour with clear margins

Table 4 Clinicopathological Features vs Fletcher Risk of Tumours

	Low	Intermediate	High
Number of patients (Male:female)	20 (9:11)	13 (6:7)	14 (11:3)
Median age (years)	65.1	65.7	60.9
Mean size tumour in millimeter (range)	33.5 (5–50)	72.2 (56–100)	97.6 (35–220)
Ckit positive (%)	95	92	100
CD34 positive (%)	50	69	57
Necrosis (%)	5	38	71
Ulceration (%)	20	62	93
Necrosis and ulceration (%)	0	23	71
Lymph node metastasis	0	0	0
Pain (%)	35	38	35
Anaemia (%)	55	54	79
Tumour recurrence (n, %)	0	1 (7.7%)	4 (28.6%)
Death (n, %)	0	0	4 (28.6%)

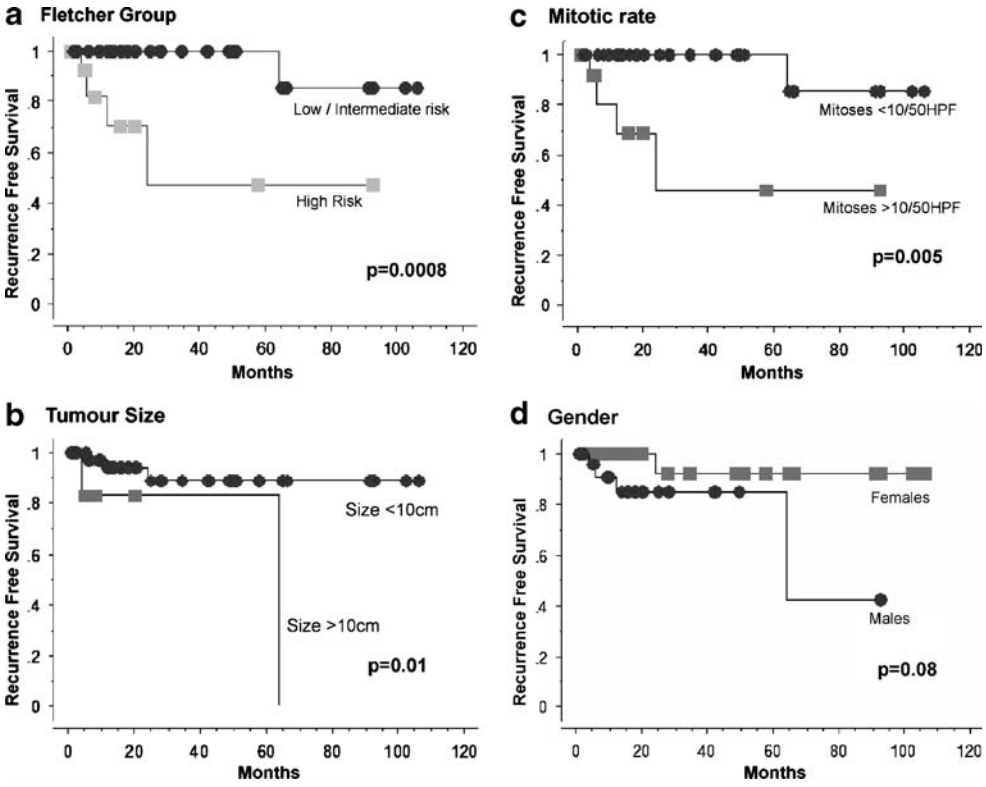

Figure 1 Kaplan–Meier plots according to **a** Fletcher risk, **b** tumour size, **c** mitotic rate and **d** gender.

(R0). This may necessitate removal of the entire organ afflicted such as the stomach for larger lesions, though more limited resections can be used with smaller lesions if the principle of a R0 resection is not compromised.

Minimally invasive approaches are being increasingly utilised, especially for tumours requiring limited resections.[14] Tumours most amenable to a laparoscopic approach are those located in the gastric body or fundus. In our series, 17% of patients with gastric GISTs had a minimally invasive resection. None of these patients had compromise of the resection margins. Endoscopic tattooing of the tumour margins either pre- or intra-operatively is a useful technique to help safeguard the resection margins in laparoscopic resections.

Tumour seeding from rupture of a GIST[15] is a potential complication which would render the patient incurable and is a risk at open and particularly during minimally invasive surgical approaches. Careful tumour handling is imperative at all times, and minimal manipulation of the tumour by graspers during laparoscopic surgery is advisable and the tumour should be enclosed in a bag in removal through the skin incision.

Table 5 Univariate and Multivariate Analysis of Predictors for Recurrence

	Number at risk	Univariate analysis	Multivariate analysis hazard ratio (95% CI)	*P* value
Age>62.8	23	p=0.81		
Female sex	21	p=0.08*	0.617 (0.046–8.20)	0.71
Ulceration	25	p=0.21		
Necrosis	16	p=NS		
CD34 positive	27	p=0.99		
Ckit positive	45	p=NS		
Mitosis >10/50	13	p=0.005*	16.7 (1.49–186.7)	0.02*
Size >10 cm	6	p=0.015*	5.76 (0.661–50.1)	0.11
Location in Stomach	30	p=0.68		
Presence of anaemia	29	p=0.26		
Pain symptoms	17	p=0.58		

Asterisks refer to p value reaching statistical significance

Lymphadenectomy is not usually required when a pre-operative diagnosis of a GIST has been made unless there is evidence of nodal spread either by pre-operative staging with computed tomography scanning, positron emission tomography scan or endoscopic ultrasound or if nodes appear to be involved at the time of surgery.[16] Lymph node involvement is a late event in the evolutionary progression of the tumour and is often preceded by haematogenous spread with a described risk of less than 2%.[17,18] Nodal disease was not identified in any of the cases in our series either with pre-operative investigations or at final histology, even in the high-risk group.

The biological behaviour of GISTs is uncertain, and it is difficult to classify a tumour into a definite benign or malignant category. Instead, risk stratification is used to predict risk of recurrence. The Fletcher[6] classification is one such approach; it is widely used and is based on tumour size and mitotic rate. Various other risk factors have been assessed in the literature, including age, sex, location of tumour and ckit and CD34 markers. In general, consensus for variables other than size and mitotic rate is lacking. While males have been reported[19] to have a worse outcome and higher rates of high-risk tumours,[20] this has not been supported by other studies[21,22] including ours ($p=0.08$)

Small bowel GISTs have been reported as having a worse prognosis compared to gastric tumours[20,22,23,24] but this has been challenged by other studies.[1,19,25]. Our series found no worse outcome being associated with small bowel tumours.

We confirmed the significance of tumour size and mitotic rate for predicting recurrence. However, on multivariate analysis, the only independent variable was mitotic rate ($p=0.02$).

Tumour size was not an independent predictor ($p=0.11$). Wu in a series of 100 GIST resections[26] and Singers' series of 48 patients[27] similarly found mitotic rate but not size to be an independent prognosticator. Larger series, however, have found both size and mitotic rate to be independent predictors.[19,28] This discrepancy may be explained by review of the hazard ratio as the hazard ratio for mitotic count >10/50HPF is high (HR 14.6–45.9) and is typically several fold larger than that for size >10 cm (HR 2.5–20.9).[19,29]

Achieving R0 resection is vital as recurrent disease fails to be indefinitely controlled with tyrosine kinase inhibitors. However, negative margins may not be sufficient to prevent recurrence particularly in high-risk patients. The 5-year recurrence rate of 45% for high-risk tumours underlines the need to better manage this group of patients to reduce their risk of future disease.[29] The ACOSOG Z9001[30] of imatinib versus placebo for intermediate- and high-risk tumours in the adjuvant setting was stopped early when preliminary analysis showed an improved survival-free advantage for imatinib. To further refine those patients who will benefit from adjuvant therapy, studies to investigate the promise shown by mutational analysis[25,29] are needed.

Down-staging therapy with imatinib for locally advanced GIST, where surgery alone is unlikely to achieve negative resection margin or do so with high morbidity, has been explored. In a series with 11 cases[31] of locally advanced tumours treated pre-operatively with imatinib for a median duration of 11.9 months, complete resection was possible in all cases. However, the pre-operative length of treatment and long-term outcomes have yet to be determined. Complete resection of recurrent or metastatic disease after imatinib therapy is associated with significantly improved outcome compared with an incomplete resection.[31,32] Similarly, the place of debulking surgery in patients with distant metastatic disease at the time of presentation compared to the use of targeted therapy alone has yet to be determined but it is possible that debulking of tumour may benefit patients with tyrosine-kinase-responsive disease as reduced tumour volume may translate into a delay in the development of resistance to chemotherapy.

Conclusion

GISTs of the upper GI tract commonly present with bleeding and anaemia, with the stomach being the most frequent site of involvement. Complete surgical excision of the primary tumour is necessary without the need for routine lymphadenectomy. The laparoscopic approach is feasible for tumours of the gastric body or fundus. Fletcher low/intermediate-risk tumours carry an excellent prognosis after resection. High-grade tumours are more likely to recur, and a high mitotic count is an independent predictor of recurrence.

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