

Presentation and Management of Gastrointestinal Stromal Tumours

Abstract :

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Abstract

Gastrointestinal stromal tumour (GIST) is the most common mesenchymal tumour of the gastrointestinal tract. The aim of this study was to present the experience of a single centre. A prospective GIST database from 1997 to 2011 in a tertiary referral centre was reviewed. 78 patients (36 male/42 female) with a median age of 66 (range 10-93) were diagnosed with GIST during this period. Surgery was the primary treatment for 70 patients (90%); 19 (24%) resections were laparoscopic. Nineteen patients (24%) received Imatinib therapy. At a median follow up of 3 years, 10 patients (15%) had recurrence. Five-year survival was 89%. Surgery remains the mainstay of treatment. Minimally invasive approaches may be carried out with high cure rates. This study highlights the changing presentation and treatment approach, as well as the excellent outcomes achievable for GIST tumours.

Introduction

Gastrointestinal stromal tumours (GISTs) represent the most common mesenchymal neoplasm of the digestive tract. Previously thought to arise from smooth muscle, GISTs were classified as leiomyomas, leiomyosarcomas or schwannomas. Mesenchymal neoplasms of the gastrointestinal tract with a phenotype ranging from indeterminate to minimally or incompletely myogenic or neural, are now termed GISTs. GISTs are associated with the interstitial cell of Cajal (ICC), and may originate from multipotential mesenchymal stem cells. Most (>90%) express the proto-oncogene CD117 (KIT), a growth factor receptor with tyrosine kinase activity. Immunophenotypic markers such as CD34, DOG-1, SMA, Desmin, S-100 and h-caldesmon demonstrate more variable expression. Morphologically, GISTs may be subdivided into spindle, epithelioid or mixed type.

Clinically significant GISTs are relatively rare (incidence 1.5/100,000/year), but microscopic undiagnosed GISTs are far more common. Peak age of diagnosis is 60 years. GISTs may develop anywhere along the GI tract, but most arise in the stomach (70%). Surgery represents the only chance for cure. Five-year survival after surgical resection ranges from 19%-75%. Minimally invasive approaches are increasingly employed, particularly for small(<5cm) lesions. Prognosis is determined by the US National Institutes of Health (NIH) consensus criteria based on tumour size and mitotic index. The emergence of tyrosine kinase inhibitors(TKI) has revolutionized the treatment of advanced and recurrent GIST. This study aims to review the changing presentation, management and outcomes associated with GIST in a single institution.

Methods

A retrospective analysis of all patients diagnosed with GIST in a high volume, upper gastrointestinal tertiary referral centre from 1997-2011 was performed. Tumours were reviewed by pathologists for confirmation of GIST nature. Clinical and histological data were retrieved from a prospectively maintained GIST database. The study included patients presenting with primary GIST and those diagnosed with an incidental GIST while undergoing investigation or treatment for a synchronous tumour. Both primary and incidental GISTs were included in all subsequent analysis except survival analysis. Survival analysis was conducted on primary GISTs only. Univariate analysis was performed using Mann-Whitney U test (nonparametric continuous data) and Fisher test (categorical variables). All statistical tests were two-sided, with the threshold of significance set at p<0.05. Kaplan-Meier survival curves were plotted. Survival differences were determined using the log-rank test.

Results

Patient Characteristics

78 consecutive patients (36 male/42 female) with a median age of 66 (range 10-93) were diagnosed with GIST at this unit between 1997 and 2011. Gastrointestinal bleeding was the most common presenting complaint (28%) (Table 1). GIST was an incidental diagnosis in 17 patients (22%) undergoing investigation and treatment for synchronous gastrointestinal cancers, most being oesophageal adenocarcinoma (82%). One patient was diagnosed with gastric adenocarcinoma and two with colorectal cancer. Endoscopy was the most frequently used method to diagnose GIST in the 61 patients with primary GIST (100% gastric GIST, 45% non-gastric GIST). Staging CT scans were performed in 60 patients (98%), PET in 18 patients (26%). Endoscopic ultrasound (EUS) was performed in 18 of the 50 patients with primary gastric GIST, of whom eight underwent FNA. FNA revealed malignant cells in five of these cases (63%).

Tumour Characteristics

Most GISTs were located in the stomach (n=60, 77%), the fundus being the most frequent gastric site (Table 1). Tumour size ranged from 0.1-20 cm (median 5.0cm). Mucosal ulceration was noted in 12 specimens (15%) and tumour necrosis in 22 samples (28%). Median (range) mitotic rate was 2 (0-100) per 50 High Power Field (HPF). Most specimens (92%) were CD117 positive by immunohistochemistry, CD34 was positive in 72% of cases. Infrequent mutations included DOG-1 (28%), SMA (6%), Vimentin (8%), S-100 (5%), Desmin(3%) and Actin (4%). The most common histological subtype was spindle cell carcinoma (65%), followed by mixed epithelioid/spindle cell, (15%) and epithelioid cell (13%).

Treatment

Most patients (n=70, 90%) were treated with curative intent, with surgical resection (table 2). Of these, two patients were deemed to have inoperable disease at laparotomy: 68 patients underwent surgical resection with curative intent. A laparoscopic approach was used in 19 cases (24%), all gastric, representing 43% of gastric resections. In the laparoscopic resection cohort there were no post-operative complications and no mortalities. Of the 51 patients undergoing open resection, 34 resections were for primary GISTs, while 17 resections related to an incidental GIST removed as part of surgery for another tumour. In total, 21 patients (14 for GIST surgery; 7 for incidental GISTs) suffered postoperative complications giving an overall complication rate of 30%. There was one death (1% mortality rate) in a patient with a colonic GIST, from multi-organ failure following an anastomotic leak after an anterior resection. Seven patients with intermediate or high risk lesions were commenced on adjuvant TKI therapy. Of the eight patients deemed unsuitable for curative therapy, three had distant metastases at diagnosis, two had inoperable primary disease and three were unfit for curative resection. TKI therapy was administered to three of these patients.

Risk Assessment & Outcomes

Classification according to the NIH criteria placed 20 patients (26%) in the high-risk group, 10 (13%) in the intermediate risk group, 21 (27%) in the low risk group and 15 (19%) in the very low risk group. NIH-classified high risk lesions had a significantly higher incidence of disease recurrence (p<0.0001). Complete negative margin resection was performed in 93% (n=64) of patients who underwent resection with curative intent (89% of those undergoing laparoscopic resection, 95% of those undergoing open resection). Recurrence was noted in 10 of the 68 (15%) patients who underwent curative surgical resection. Nine of these patients were commenced on TKI. Recurrence occurred significantly more often in patients with large tumours (p=0.0001), high mitotic index (p=0.0001), presence of tumour ulceration (p=0.01), tumour necrosis (p=0.005) and non-gastric versus gastric location (p=0.03). Resection margin and immunohistochemical marker positivity were not associated with recurrence. Overall survival at 1 year was 90% (Table 3). Patients with gastric GIST had significantly improved cumulative survival rates compared to non-gastric GISTs (p=0.003).

Discussion

This is the largest experience published from an Irish centre, and our goal is to highlight the pattern of presentation and treatment approach, in particular the increasing use of laparoscopic approaches, adjuvant TKI, and generally favourable outcomes. GISTs were an incidental diagnosis in 17 cases; all of these were low risk lesions detected during evaluation for a known cancer, usually oesophageal, either during staging or intra-operatively. GISTs are usually isolated lesions, but may rarely occur as part of a syndrome such as Carney’s triad. A review of 14 studies of 4777 patients reported 444 patients with second tumours, most occurring in the gastrointestinal tract and incidental at surgery. Kalmar demonstrated a higher rate of metachronous and synchronous gastrointestinal tumours in patients with GIST compared to the general population. Kowanowa examined 100 whole stomachs resected from patients with gastric adenocarcinoma where 50 microscopic GISTs were found in 35 of 100 stomachs. Given the relatively low annual incidence of clinical GISTs, it seems few of these microscopic lesions develop into clinically apparent GISTs with malignant potential. This centre treats a high volume of upper gastrointestinal cancers so coincidence alone may account for the high number of patients with synchronous neoplasia. However, the possibility of a common genetic mechanism or carcinogenic event resulting in two primary malignancies cannot be excluded.

Pre-operative diagnosis and risk stratification of GIST is based on histological, cytological and immunohistochemical examination, typically from endoscopic biopsy. GIST appears as a submucosal mass at endoscopy and a definitive diagnosis based solely on endoscopic biopsy may be difficult to establish. Thus, an increasing role for EUS in identifying GISTs has emerged, and FNA under EUS guidance is used to provide a tissue diagnosis. However, EUS-FNA is unsuitable for sites where it is difficult to puncture the tumour (gastric cardia or small intestine). In addition, GISTs may contain areas with different cellularity and necrosis and an accurate assessment of mitotic activity cannot be determined. EUS-FNA has significant limitations but remains a useful investigation, particularly in patients for whom previous endoscopic biopsy was unsuccessful in establishing a diagnosis. Gastric GISTs tend to have a more favourable clinical course than non-gastric GISTs of comparable size. This is reflected in the newer risk classification systems of Miettinen and Lasota which include tumour site as a prognostic variable. Our cohort of gastric GISTs of size 2-10cm had lower rates of recurrence compared to non-gastric GISTs of the same size (3% versus 38%, p=0.02).

Most patients were treated with curative intent (90%), perhaps reflecting referral bias to this specialist centre. Surgery remains the only curative treatment for primary localized GIST. Organ-preserving wedge excision was the most frequently performed operation. The aim of surgery is to achieve complete resection with gross negative margins,

consistent with standard surgical oncological principles although a consensus conference on GIST stated that positive microscopic margins or R1 do not compromise survival.^{16,17} This is refuted in other studies. We advocate a goal of negative margins, but there is no data to justify extensive margins, and a microscopically involved margin does not demand further surgery.

Lymph involvement is rare, and lymphadenectomy unwarranted.⁷ Most GISTs are located in the stomach with an exophytic growth pattern, making them technically very accessible. Given these features, a laparoscopic approach to GIST resection appears appealing. However, the role of laparoscopy is not completely clear. The 2007 National Comprehensive Cancer Network (NCCN) task force recommended that laparoscopic techniques may be used for tumours up to 5cm in size. Novitsky et al studied long-term outcomes of resected gastric GISTs up to 8.5cm in size, demonstrating three-year disease-free survival of 92% in their series of 50 laparoscopic resections.¹⁸ Similarly, our cohort of 19 laparoscopic resections had excellent results with no post-operative complications, deaths or recurrences after a median follow-up of two years. Median tumour size in this cohort was 3.0 cm (range 1.9-6.0 cm). All laparoscopic resections were performed in the latter half of the study period.

Most recurrences occur within two years but late (>5 years) recurrences have been described, so long term follow-up is important.¹⁹ Median time to recurrence in our cohort was 29 months (range 1-45 months). Five-year survival may be as high as 92% for low risk GISTs, while for high risk GISTs the 5-year survival rate is less than 30%. 5-year survival in our series was 89%. Most patients who developed recurrent disease in our cohort were treated with TKI (90%). At a median follow-up of 54 months seven of these nine patients are still alive. The phase III, double-blind, placebo-controlled, multicenter ACOSOG Z9001 study showed that adjuvant therapy is safe, and significantly improves recurrence-free survival compared to placebo when given postoperatively.^{20,21} The overall treatment has changed the treatment paradigm for GIST and TKIs are increasingly prescribed in this centre. Adjuvant TKI was administered to 7 patients with intermediate and high risk lesions in our series, six of these in the latter half of the study period. Median follow-up of these patients is 21 months, with no recurrences to date.²² The success of TKI

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