RESEARCH

Gastrointestinal stromal tumours (GISTs): an insight into clinical practice with review of literature

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ABSTRACT

Background Gastrointestinal stromal tumours (GISTs) are rare mesenchymal tumours of the gastrointestinal tract. We retrospectively reviewed the clinical management of all patients with GIST presenting to a regional multidisciplinary upper gastrointestinal cancer group in the north of England.

Methods Clinical, pathological, immunohistochemical treatment strategies, follow-up and outcome data on all patients with GIST between 2007 and 2012 were reviewed. Tumours were categorised by risk according to the National Institutes of Health (NIH) and AFIP models.

Results 36 (85.7%) of 42 tumours were located in the stomach, 5 (11.9%) in the small intestine and 1 (2.4%) in the oesophagus. Median age of patients was 68 (range 43–91) years. 24 patients (57.1%) were female. Tumour size ranged from 1.0 to 12.7 cm with mean size of 5.46 cm. Metastasis was present in 19 (45.2%) patients at diagnosis with distant metastases in 12 patients. Liver was the most common site of metastases. Histology and immunohistochemical analysis was available in 32 (76.2%) patients. Most common histology was spindle cell morphology 17/32 (53.1%) followed by epithelioid 9/32 (28.1%) and mixed morphology 5/32 (15.6%). The positive rate for KIT protein (CD117) was 90.6%, while that for CD34 was 75.0%. 12/25 (48.0%) and 8/23 (34.8%) patients were categorised as high risk as per NIH and AFIP risk scores, respectively. 23/42 (54.8%) patients underwent surgical resection, after which 5/23 (21.7%) had adjuvant imatinib therapy. Imatinib was given as primary therapy in 14/42 (33.3%) patients.

Conclusions Surgery alone may not be a curative treatment for GISTs. Targeted therapy with imatinib may play an important role in the treatment of GISTs. Further risk categorisation models may be needed to evaluate GIST behaviour and prognosis.

INTRODUCTION

Gastrointestinal stromal tumours (GISTs) are rare mesenchymal tumours of the gastrointestinal (GI) tract, representing 0.1–3% of all GI neoplasms.^{1 2} The vast majority of GISTs (60–70%) arise in the stomach, with 20–30% originating in the small intestine and the remaining 5–10% occurring elsewhere in the GI tract (oesophagus, colon, rectum, omentum and peritoneum).³ GISTs usually affect males and females equally with peak incidence in the sixth decade.⁴ They rarely occur in children or young adults, unless in association with neurofibromatosis (specifically neurofibromatosis-1) or Carney's triad (gastric stromal tumour, extra-adrenal paraganglioma and pulmonary chordoma).⁵

The clinical presentation of GISTs is variable. Symptoms are relatively non-specific and depend on the size of the lesion and organ involvement. Many GIST tumours are small (<2 cm) and asymptomatic, with approximately a third discovered incidentally during endoscopic, imaging or surgical evaluation.⁶ Gastric GISTs usually present with vague abdominal pain, dyspepsia and vomiting. Less commonly, they may present with secondary complications such as upper GI bleeding and perforation.^{4 7} Occasionally, the lesion may be pedunculated and can obstruct the pylorus or duodenum.⁸ Spontaneous rupture of a large mass into gastric lumen has also been reported.⁷ Metastases at presentation are generally uncommon. However, metastatic sites may include liver, bone, lung, soft tissue or skin.⁹

Accurate diagnosis of GIST is fundamental given the unique criteria for predicting behaviour and the availability of

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targeted therapy. As such, knowledge of the macroscopic features, histological spectrum and immunocytochemistry profile of GIST is essential. In this case series, we review the clinical practice of GISTs in a regional multidisciplinary centre for several referring hospitals in the north of England and provide an overview of the current literature in terms of diagnostic procedures, assessment of malignant potential and available treatment modalities.

METHODS

A list of patients with a diagnosis of GIST discussed at the regional tertiary multidisciplinary meeting between 2007 and 2012 was obtained from the Regional Tumour Registry Database. We recorded the patients' age, gender, clinical symptoms, tumour site, maximal tumour diameter, surgical procedure, extent of surgical resection, local recurrence or distant metastasis, and clinical outcome until the last follow-up. A diagnosis of GIST was based on compatible radiological or histopathological appearance where available. The morphological characteristics of the tumours were evaluated according to the risk stratification criteria of the National Institutes of Health (NIH) consensus and AFIP (Armed Forces Institute of Pathology), which classifies GISTs into risk categories based on tumour size, mitotic activity and tumour site in the latter score. Immunohistochemical analysis was performed where specimens were available as per routine investigation.

Statistical analysis

Owing to the retrospective nature of the data, most of the results are mainly descriptive. Statistics were computed using SPSS V.17. Simple descriptive statistics including mean and SD were used for continuous parametric data, median and IQR for continuous non-parametric data, and frequencies and percentages for categorical data.

RESULTS

Clinical characteristics

From June 2007 to December 2012, 42 patients were diagnosed with GIST. The median age of these patients was 68 years (range 34–91). Of the 42 patients, 24 (57.1%) were female. The most frequent primary site of tumour was the stomach (36 patients; 85.7%), followed by the small intestine (5; 11.9%) with one case located in the oesophagus. Tumours varied in size from 1.0 to 12.7 cm. The mean size of primary tumours was 5.46 cm. Nine (21.4%) tumours were incidental findings. Eight (19.0%) patients had concurrent tumour diagnoses including colorectal adenocarcinoma, breast adenocarcinoma, endometrial carcinoma, melanoma, thymoma, lymphoma and carcinoid tumour. Two (4.8%) patients were identified with multiple primaries at time of diagnosis, and metastasis was present in 19 (45.2%) patients at diagnosis with local metastases in 7 and distant metastases

in 12 patients, respectively. The liver was the most common site of metastases in nine (21.4%) patients.

Histopathological features

In total, 32/42 (76.2%) patients had available histopathology. The majority of tumours were predominantly spindle-shaped (53.1%), epithelioid (28.1%) in morphology or a mixed type (15.6%). On immunohistochemical analysis, 90.6% were CD117 positive, 75.0% were CD34 positive, 15.6% were smooth muscle antibody positive, 3.1% were S-100 positive and none were desmin positive. DOG1 markers were measured in 18 patients and were positive in 100%.

Mitotic index was available in 23/32 (71.8%) patients where sampling or excision had been performed. Based on the size of the primary tumour and the mitotic index, 2 (8.0%), 7 (28.0%), 4 (16.0%) and 12 (48.0%) patients were classified into very low, low, intermediate and high-risk groups, respectively, according to the NIH risk categorisation. Two patients with a tumour size >10 cm were classified as high risk according to this model with an unknown mitotic rate. Likewise, two (8.7%), five (21.7%), four (17.4%), four (17.4%) and eight (34.8%) were classified into no risk, very low risk, low risk, moderate risk and high risk, respectively, according to the AFIP risk categorisation model.

Treatment and outcomes

In total, 23/42 (54.8%) patients underwent surgical resection, after which 5/23 (21.7%) had adjuvant imatinib therapy. Imatinib was given as primary therapy in 14/42 (33.3%) patients. In two patients, upfront imatinib converted the tumour from unresectable to removable. Up to the point of publication, 4/42 (9.5%) patients have died. One patient was already receiving chemotherapy for an underlying endometrial carcinoma. Two patients were given palliative chemotherapy, with palliative radiotherapy given to alleviate symptoms of bone metastases in one of these patients. The remaining patient was considered too frail for treatment and opted for conservative management. Recurrence occurred in four (9.5%) patients, two of whom had undergone extensive surgical resection and had been categorised as low risk of progression according to current risk categorisation models. One patient had been treated with surgery and adjuvant imatinib therapy and one had stopped imatinib therapy of their own accord.

DISCUSSION

This study examined the treatment outcomes of GISTs over a 5-year period in a regional referral centre in the northeast of England. The study highlights some of the diagnostic and therapeutic challenges gastroenterologists are faced with when they encounter GIST tumours.

GIST constitutes a distinct group of rare GI tract tumours that originate from the interstitial cells of Cajal.¹⁰ These cells are regulators of gut peristalsis and normally express CD117, a product of the c-kit proto-oncogene that encodes a tyrosine kinase receptor responsible for regulating cellular proliferation in GISTs.^{10–11} These tumours are recognised for their diversity in behaviour and difficulty in determining malignant potential and prognostic characteristics.

Accurate diagnosis relies on imaging and immunohistochemistry. The two main imaging modalities currently employed are CT scanning and endoscopic ultrasound (EUS). These are important in terms of initial diagnosis and staging, assessing operative suitability and postoperative follow-up.¹² CT scanning can show abnormalities in up to 87% of cases and can define the end luminal and exophytic extent of a tumour.¹³ Smaller GISTs usually appear as smooth, well-defined rounded intramural masses with homogeneous attenuation on contrast enhancement. Larger tumours appear as lobulated, hypervascular masses that may displace adjacent structures. These often enhance heterogeneously because of cystic degeneration and central liquefactive necrosis.¹⁴ Almost half of the patients in our study had reported necrosis on imaging. However, previous studies have reported a lack of correlation between radiological appearance and malignant potential.¹⁵ Approximately 20–30% of tumours are reported to have metastasised at diagnosis, with CT demonstrating good sensitivity in the detection of metastatic liver, peritoneal, lung and bone lesions. In our study, a much higher proportion of patients (45%) had confirmed metastases at presentation. This may be explained by the high number of patients with concurrent malignancies in this cohort in comparison to other similar studies. In terms of follow-up, a reduction in tumour size, extensive cystic changes and calcification in primary and metastatic GISTs on CT indicates disease response to therapy.¹⁶

EUS also plays a crucial role in the evaluation of GISTs, particularly in small submucosal lesions found incidentally at endoscopy. Characteristics associated with malignancy include tumour size >4 cm, an irregular extraluminal border, echogenic foci and cystic spaces.¹⁷ In one study, the sensitivity for detecting malignancy using these features ranged between 80% and 100%.¹⁸ However, malignancy cannot be excluded if these features are not present; therefore, EUS fine-needle aspiration may improve diagnostic accuracy, with studies demonstrating a sensitivity of 86% and 91%, respectively.^{18–19} In our study, 8/32 (25%) patients had samples taken using this technique, with confirmation of histology in 5 (15.6%) patients. Samples in the other three patients were too small to confidently determine cell type or mitotic index.

Other imaging modalities less frequently used in diagnosis and follow-up of GISTs include MRI and

functional positron emission tomography (PET-CT) scanning.²⁰ MRI is of particular benefit in cases of rectal primary GISTs and metastatic hepatic lesions whereby increased specificity can be gained by using hepatobiliary-specific contrast agents.²¹ PET-CT scanning using radioactive fluorine-18-labelled fluoro-deoxyglucose (18F-FDG) is highly sensitive and has contributed to early detection of treatment response and recurrence.^{22–24} Data suggest the detection of occult metastasis with PET-CT is better than CT alone. However, the major pitfall associated with this technique is that 20% of GISTs <5 cm size do not take up FDG and are therefore negative on PET scans.²⁵ PET-CT is increasingly used for follow-up of GISTs both post surgery and post oncotherapy compared with a baseline PET-CT scan to determine treatment efficacy.²⁴

Immunohistochemistry

Immunohistochemistry plays a critical role in the diagnosis and therapeutic potential of GISTs. Mutational status appears to influence GIST development and response to current therapies, and therefore accurate identification could potentially predict prognostic behaviour of the disease.

Over 90% of GISTs express KIT antibodies to CD117, and as such, immunopositivity for this marker is a key component in diagnosing GISTs.^{25–26} However, this marker is also expressed in a large number of other tumours including melanoma, dermatofibrosarcoma, rhabdomyosarcoma and large cell lymphoma.²⁷ Approximately 60–80% of GISTs are immunopositive for CD34, malignant tumours showing a slightly lower frequency than benign ones, and site specificity being increasingly recognised in terms of low expression in small bowel tumours and high expression in colorectal and oesophageal tumours.^{28–29} GISTs, therefore, appear to be the only Kit+CD34+vimentin+ cell in the gut.²⁸ Other markers include smooth muscle actin, which may be present in approximately 20–40% of GIST tumours, S-100 protein, which is positive in fewer than 5% of GISTs, and Desmin, positivity being rare, occurring principally in a focal fashion in only 1–2% of cases.^{3–28}

A subset of GISTs (5–10%) carry constitutively activating mutations in the gene encoding platelet-derived growth factor receptor- α (PDGFR- α), a tyrosine kinase receptor homologous to KIT.^{30–31} PDGFR- α -mutated GISTs are associated with a distinct clinical and pathological phenotype and represent <10% of GISTs. They are generally limited to the stomach, with a predominantly epithelioid or mixed-type morphology, a variable or absent KIT expression and a low mitotic count conferring a lower malignant potential.^{31–32}

The search for oncogenic mutations of KIT and PDGFR- α should identify the majority of GISTs. However, a subset of tumours lack mutations in both

KIT and PDGFR- α .³² This wild-type adult GIST shows no particular association with anatomical site. Consequently, standard GIST therapies are less efficacious in this group. Gene-profiling studies have recently facilitated identification of two novel antibodies that have a high sensitivity and specificity for KIT-negative GISTs, called DOG-1 and protein kinase C- θ .^{33 34} DOG-1 should definitely be considered as part of the investigative work-up in KIT-immunonegative GISTs.

Risk stratification systems to predict malignant behaviour of GISTs

Initial morphological risk stratification systems of GISTs emphasised the value of tumour size (<5 cm vs >5 cm) and mitotic count (<5 vs >5/50 high-power fields (HPFs)) to separate GISTs into low-risk and high-risk subgroups, respectively.³⁵ Fletcher's (NIH) criteria expanded on this using tumour size and mitotic activity as the sole parameters to define eight prognostic categories that were further subdivided into four risk groups.³⁶ Based on this system, benign GISTs do not exist and instead the most harmless tumours are deemed to have a 'very low malignant potential'. This system is the most popular among clinicians and pathologists given its limited number of risk groups and its simple application. Meitinen's (AFIP) criteria are distinguished from the NIH system by taking the anatomical site of the tumour into consideration, the prognostic significance of which has been confirmed in other studies.³⁷ However, it is thought that excessive subdivision of the different subgroups may reduce the prognostic sensitivity and specificity of recurrence. Joensuu used the NIH system as a base to include the presence of tumour rupture as a high-risk factor irrespective of size and mitotic count.³⁸ Tumour rupture was correlated with a high risk for recurrence in the study by Rutkowski *et al*³⁹ and was included as a high-risk criterion in the revised NIH system. Takahashi *et al*⁴⁰ suggested the inclusion of a 'clinically malignant group' to include patients with peritoneal dissemination, metastasis, invasion into adjacent organs and/or tumour rupture.

Gold *et al*⁴¹ proposed a nomogram for estimating the risk of tumour progression whereby each tumour was assigned points on a scale based on tumour site (gastric vs small intestine vs colorectal vs extra-gastrointestinal), size and mitotic index (<5 vs >5 per 50 HPFs) with a view to predict the 2-year and 5-year recurrence-free survival probabilities. Concordance probability of 0.78 was achieved. However, it remains to be further analysed whether the nomogram can predict the long-term disease-free survival in GISTs with an indolent course and late progression.

Woodall *et al*⁴² proposed a system for GIST staging based on tumour grade metastasis. A cut-off point of 70 mm for tumour size was used to separate clinical behaviour in GISTs. The presence of nodal and distant metastasis was considered advanced stage. The

newly proposed International Union Against Cancer tumour, node, metastases classification for GISTs represents the most recent hallmark on this topic; yet, its usefulness remains to be tested in clinical studies.

Treatment modalities

GISTs exhibit a highly variable behaviour after resection of the primary tumour. Patients need to be followed up on a long-term basis as local recurrence and metastases can occur many years after surgery. These tumours spread by the haematogenous route predominantly to the liver and peritoneum. Lymph node (LN) involvement is very rare, and therefore, LN resection is not routinely indicated.⁴³ In general, local recurrence or metastases develop in approximately 50% of patients who have had potentially curative surgery.⁴⁴ The median disease-specific survival for patients with primary GIST is approximately 5 years.⁴⁵ Endoscopic resection of small submucosal tumours is now possible using endoscopic submucosal dissection, but this is not widely available in Western countries.

Before imatinib, surgical resection was the only treatment option available as GISTs are highly resistant to standard chemoradiotherapy regimens. The 5-year survival rate was 35–80% following complete resection with a median survival of 10–20 months for patients with unresectable disease.^{4 45} The introduction of imatinib, a tyrosine kinase inhibitor, has dramatically improved treatment outcomes. Clinical trials have demonstrated a significant decrease in tumour size rendering initially inoperable tumours resectable, as demonstrated in a small number of patients in our study. Phase I and II trials have demonstrated a partial response with reduction of at least 50% of tumour burden in 79% of patients, stable disease in 28% and progressive disease in 13% with an overall survival rate after 1 year of 88%.^{46 47} Currently, imatinib is approved for the treatment of advanced disease and also recommended as an adjuvant treatment for up to 3 years for adults who are at high risk of relapse after surgery for KIT (CD-117)-positive GISTs, as defined by the Miettinen 2006 criteria.¹ This is also recommended by the National Institute for Health and Care Excellence (NICE) technology appraisal guidance (TA326) published in November 2014. It is well tolerated orally with minimal side effects such as rash, nausea, diarrhoea, muscle cramps, periorbital and peripheral oedema. Myelosuppression is rare. The recent NICE guidelines and National Comprehensive Cancer Network (NCCN) guidelines have recommended imatinib adjuvant treatment duration up to 3 years based on the Scandinavian sarcoma group study results showing improvement of both relapse-free survival and overall survival compared with 12-month imatinib treatment ([figure 1](#)).⁴⁸ While the standard recommended dose is 400 mg daily, the presence of specific exon 9 KIT mutation in advanced GIST has shown

Figure 1 Overall survival.

to benefit from a higher dose of imatinib (800 mg daily).⁴⁹

Sunitinib is approved as second-line therapy in imatinib-resistant or rare intolerant cases.⁵⁰ Patients who progress on sunitinib can be given a third agent, regorafenib—a prospective placebo-controlled randomised trial showed that regorafenib, at the dose of 160 mg daily for 3 weeks of every 4 week cycle, is able to significantly prolong progression-free survival.⁵¹ While it has US Food and Drug Administration and European Union approval as third-line therapy for GIST, it is available in England only through cancer drug funding application.

Guidelines following resection of GIST are yet to be defined. According to published NCCN practice guidelines, all completely resected GISTs should be followed up in clinic with interval CT scanning at 3–6 months for the first five years and then annually. For imatinib-treated patients, CT should be performed within 1–3 months of initiating therapy. FDG-PET should be considered if CT findings are inconclusive. Less surveillance is acceptable for low-risk patients.²⁵

CONCLUSION

Over the last decade, our understanding of GISTs has been transformed by the landmark discovery of the central role of molecular oncogenic mutations in the pathogenesis of these tumours and the recognition that these can be used as markers of disease, revolutionising our approach to the management of GISTs. The diagnosis of GIST should be considered whenever an intramural mass in a submucosal location is seen in the stomach or small intestine. Although GIST can be suggested histologically, the diagnosis must be confirmed immunochemically as mutational status may influence response to treatment. All GISTs have the potential for aggressive behaviour. Mutational status, mitotic index, size and location of the tumour are the most informative criteria for the choice of treatment strategy and prognosis. This study emphasises the need for a further validated, standardised, risk stratification and staging system for evaluating and treating

GIST tumours taking into account the great heterogeneity of the disease.

Key messages

What is already known on this topic?

- ▶ Gastrointestinal stromal tumours (GISTs) are rare tumours of the gastrointestinal system and are difficult to manage.
- ▶ Most GISTs are low risk, require endoscopic ultrasound for diagnosis and annual surveillance for follow-up.
- ▶ Excision is reserved for GISTs that grow in size to >2 cm or become symptomatic.
- ▶ Imatinib is the treatment of choice for metastatic GISTs.

What this study adds?

- ▶ This study details the clinical epidemiology of GISTs in the north of England.
- ▶ The mean size of primary tumours is larger than previously reported in other studies.
- ▶ The incidence of metastatic GISTs is higher in the north of England (45.2%).
- ▶ Just over half the patients underwent surgical excision.

How might it impact on clinical practice in the foreseeable future?

- ▶ Local areas should determine the clinical presentation of GISTs to raise awareness on the size and metastatic potential of these tumours.
- ▶ GISTs should be discussed in a multidisciplinary meeting to determine management.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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