Original article

Pattern of recurrence in patients with ruptured primary gastrointestinal stromal tumour

P. Hohenberger[1], U. Ronellenfitsch[2], O. Oladeji[1], D. Pink[3], P. Ströbel[4], E. Wardelmann[5] and P. Reichardt[3]

[1]Division of Surgical Oncology and Thoracic Surgery, [2]Department of Surgery and [3]Department of Haematology, Oncology and Palliative Care, Helios Medical Centre, Bad Saarow, [4]Department of Pathology, Medical Faculty Mannheim, University of Heidelberg and [5]Department of Pathology, University of Bonn Medical School, Bonn, Germany

Correspondence to: Professor P. Hohenberger, Division of Surgical Oncology and Thoracic Surgery, Mannheim University Medical Centre, University of Heidelberg, Theodor Kutzer Ufer 1-3, D-68167 Mannheim, Germany (e-mail: peter.hohenberger@umm.de)

Background: This study assessed the outcomes of patients with a gastrointestinal stromal tumour (GIST) that ruptured before or during resection.

Methods: The records of 23 patients (8 women, 15 men; median age 54 years) with ruptured primary non-metastatic GIST were retrieved from a database of 554 patients. The written surgical and pathology reports were analysed. Review pathology was performed in all 23 cases, and mutational analysis of *KIT* and platelet-derived growth factor α (*PDGFRA*) genes was performed in 21 patients. Median follow-up was 52 months.

Results: Tumour rupture was spontaneous in 16 patients, following abdominal trauma in two and occurred during resection in five. Primary tumour location was the stomach in six patients, duodenum in one and small bowel in 16. Mean tumour size was 10·2 (range 4–28) cm. According to the Miettinen and Lasota risk classification, the distribution of very low-, low-, intermediate- and high-risk cases was one, two, five and 15 respectively. One patient remained disease-free at 83 months. Fifteen of 16 patients who did not receive adjuvant therapy developed tumour recurrence after a median of 19 months. Median recurrence-free survival in patients with *KIT* mutations involving codons 557–558 was 11 months.

Conclusion: Patients with a rupture of GIST into the abdominal cavity have a risk of recurrence of nearly 100 per cent. In patients with deletion mutations involving codons 557–558, recurrence-free survival was less than 1 year. All patient groups are clear candidates for adjuvant drug therapy.

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Introduction

Gastrointestinal stromal tumours (GISTs) are thought to develop from the stroma of the wall of the intestinal tract, particularly from the interstitial cells of Cajal or their precursor cells. Tumours do not arise from epithelial layers and primary tumours usually do not metastasize to the regional lymph nodes. Tumour size, mitotic index and anatomical location are the classical characteristics used to predict the clinical course of patients who undergo complete tumour resection[1–3]. Two tyrosine kinase inhibitors (TKIs) have been approved for treatment of advanced GIST: imatinib and sunitinib. Imatinib has also received approval in the USA for the adjuvant treatment of GISTs larger than 3 cm, and in Europe for patients deemed to be at significant risk of relapse after complete resection.

Assessment of the risk of relapse is usually based on the characteristics indicated above. In addition, tumour rupture is thought to be associated with a substantially higher risk. GISTs are often highly vascular tumours which can be very soft and fragile and, if not handled gently, tend to erupt, particularly during laparoscopic procedures[4,5]. In ovarian and epithelial gastrointestinal tract cancer, tumour perforation is classified as R1, even when no visible metastases remain following tumour removal[6]. Likewise, children with preoperative or intraoperative rupture of a Wilms' tumour are upstaged[7]. In 2008 a refined classification system of GIST was advocated[8].

This risk stratification distinguished ruptured GIST and strongly recommended the use of adjuvant treatment with a TKI[8]. Tumour rupture has been classified together with incomplete (R1) resection in series analysing prognostic factors[1,9] because statistical analysis showed a less favourable outcome[9]. However, except for a historical series of patients with abdominal leiomyosarcoma with perforation[10], there are only sparse data on the risk and prognosis of patients with a ruptured GIST. The present study was undertaken to assess the outcome of patients with a GIST that ruptured before or during resection.

Methods

From a multi-institutional database (Mannheim–Berlin) containing 554 consecutively treated patients with a histologically confirmed GIST (patients who had surgery for the primary tumour or metastases in one of the departments, or patients referred for further treatment from other hospitals), records of patients with non-metastasized GIST at the time of operation and documented signs of tumour rupture were retrieved. Both surgical and pathology reports were reviewed to determine the extent of resection, lymphatic clearance, emergency resection, intraoperative findings, handling of the specimen, signs of rupture, margins of resection, and concordance between surgical and pathology documents. Results of review pathology to confirm the diagnosis and mutational analysis of the genes encoding KIT (*KIT*) and platelet-derived growth factor α (*PDGFRA*) were retrieved where available (21 of 23, 91 per cent). All patients were followed up routinely for tumour recurrence by means of abdominal cross-sectional imaging (computed tomography or magnetic resonance imaging) and vital status. Median follow-up was 52 (range 10–101) months.

Statistical analysis

SPSS® version 17·0 (SPSS, Cary, Illinois, USA) was used for data analysis. Data are given as median (range) or mean(s.d.) with 95 per cent confidence intervals (c.i.), and survival was determined.

Results

Twenty-three patients (8 women, 15 men) of median age 54 (range 26–69) years fulfilled the inclusion criteria. Pathology review to confirm the diagnosis was carried out in all cases, and mutational analysis of *KIT* and *PDGFRA* was performed for 21 specimens.

Primary tumour location

Six tumours were located in the stomach, one in the duodenum and 16 in the small bowel. Six of the small bowel tumours were in the jejunum, five in the ileum (of which 3 were described as arising in a Meckel's diverticulum) and five in an unspecified location.

Tumour characteristics

Mean(s.d.) tumour size was 10·2(5·8) (median 8, range 4–28) cm. No lymph node metastases were detected in resection specimens: pathological node (pN) 0, 17; pNx, six. Classification according to the consensus classification[1] of risk of malignant behaviour placed 18 of the 23 patients in the high-risk group. When classified according to Miettinen and Lasota[2], 15 patients were in the high-risk group and three were in the very low- and low-risk categories (*Table 1*).

Clinical presentation

Seventeen patients were operated on as emergency cases, 15 for an acute abdomen and two after abdominal trauma with intra-abdominal haemorrhage (*Table 2*). Six patients underwent elective operations. In two of these patients an unclear abdominal mass was found to be a

Table 1 Tumour characteristics

	No. of patients ($n = 23$)
Mean(s.d.) tumour size (cm)	10·2(5·8)
Tumour type	
Spindle cell	11
Epithelioid	1
Mixed	11
Risk classification	
Miettinen and Lasota[2]	
Very low	1
Low	2
Intermediate	5
High	15
Consensus[1]	
Intermediate	5
High	18
Mutational status ($n = 21$)	
KIT	
Exon 11	14
Exon 9	2
Exon 17	1
PDGFRA	
Exon 18	3
Wild type*	1
Not done	2

*No mutation found in exons 9, 11, 13 or 17 of *KIT* and exons 12 and 18 of *PDGFRA*.

Table 2 Clinical presentation of patients

	Suspected diagnosis/ indication	Intraoperative rupture
Emergency operations ($n = 17$*)		
Perforation, peritonitis	6	
Abscess formation	3	
Perforated Meckel's diverticulum	2	
Perforated appendicitis	2	
Torn ovarian cyst	2	1
Abscess formation	3	
Trauma, intra-abdominal haemorrhage	2	
Elective operations ($n = 6$)		
Abdominal mass	3	1
Ovarian cancer	1	1
Uterus myomatosus	1	1
Recurrent pain/laparoscopy	1	1

*Three patients had more than one indication.

GIST that had ruptured before surgery; in two other patients tumour rupture occurred during open resection, and in the final two patients grasping of the tumour with laparoscopic instruments before specimen retrieval resulted in tumour rupture.

Pattern of recurrence

Of 16 patients who received no adjuvant treatment, all but one developed tumour recurrence. Median recurrence-free survival was 19 (range 5–83, 95 per cent c.i. 8·5 to 35·4) months. Only one patient remained free from disease at 83 months. This patient was operated on for splenic rupture following a road traffic accident, and a ruptured GIST of the jejunum was detected incidentally at laparotomy and removed (within 6 h of perforation).

Seven patients were treated with adjuvant imatinib, 400 mg daily (3 patients for 1 year, 2 for 2 years, 1 for 3 years, and 1 for more than 15 months). Three of these patients developed tumour recurrence at 3, 15 and 29 months after stopping adjuvant therapy. The remaining four patients remained free from disease; two remained in treatment and the other two patients were followed up at 5 and 28 months after completion of adjuvant therapy. Eighteen patients developed metastases (peritoneum, 9; peritoneum and liver, 6; liver alone, 3).

Mutational analysis

Mutational analysis could be performed in 21 cases. Fourteen samples showed an exon 11 mutation (*Table 1*). The single most frequently detected mutation was deletion W557_558K, which was found in six cases. Three specimens showed involvement of these codons, two with point mutations in codon 557 and one with deletion of codons 557–559. When recurrence-free survival in patients with *KIT* mutations involving codons 557–558 was compared with that in patients with all other mutations or wild-type alleles, the difference was not significant (11 *versus* 26 months; $P = 0{\cdot}090$).

In three cases, a mutation of exon 18 of *PDGFRA* (D842V in 2 cases and V824V in combination with D842_H845del in the other) was detected.

In eight patients, biopsy material from recurrent tumour tissue was available before systemic therapy. This showed a mutation identical to that of the primary tumour in all cases.

Overall survival

The 5-year survival rate was 61 per cent (14 of 23 patients), with median survival not yet reached. Mean survival was 82 (95 per cent c.i. 68 to 96) months.

Discussion

In addition to tumour size, mitotic rate and tumour location, tumour rupture is thought to be a prognostic factor for the outcome of patients with GIST. The only data available thus far, however, stem exclusively from case reports[11–24]. Extraluminal bleeding to the abdominal cavity is reported less often, and results in haemoperitoneum or acute peritonitis requiring urgent treatment. The majority of patients have been treated as an emergency owing to haemoperitoneum and haemorrhagic shock[11,13,15,17,19,20,23,24]. The present series constitutes a larger study reporting clinical and tumour characteristics as well as the outcome of patients with ruptured GIST. In 1992, Ng and colleagues[10] analysed prognostic factors influencing survival of patients with gastrointestinal leiomyosarcoma in a series from MD Anderson Cancer Center in the USA. As GIST was not a recognized diagnosis at that time, it could be assumed that most of the cases would today be classified as GIST. The study included 201 patients diagnosed with leiomyosarcoma arising from the gastrointestinal tract, mesentery and omentum; tumours of the oesophagus and retroperitoneum were excluded. Tumour rupture was reported in 24 patients, either at the time of resection or just before surgery. In 22 of these patients, complete resection of the tumour was possible. Analysis showed that patients with complete resection without tumour rupture had a significantly better overall and disease-free survival. Patients with tumour rupture had a median survival of only 17 months, despite removal of all grossly visible disease[10].

Histological findings in ruptured GIST are inconsistent. All types of risk profile, according to the consensus classification[1], have been described[24]. Depending on the risk classification applied[1,2], 65 per cent (15 of 23) or 78 per cent (18 of 23) of patients in the present series belonged to the high-risk group. High mitotic count and rapid tumour growth could be features of GIST at increased risk of spontaneous perforation. However, six patients had fewer than five mitoses per 50 high-power fields. One of these patients presented with peritoneal metastases, two remained free from disease following adjuvant therapy, and the remaining three patients developed tumour relapse at 39, 47 and 60 months. The latter patient would have been classified as at very low risk according to the Miettinen and Lasota risk classification[2].

Tumour rupture occurred during surgery in five of the 23 patients. There is little guidance regarding appropriate surgical management options and their corresponding outcomes in patients with a ruptured GIST. The National Comprehensive Cancer Network's *NCCN Clinical Practice Guidelines in Oncology*™ – *Soft Tissue Sarcoma* V.2.2009 mention only that GISTs are soft and fragile and should be handled with care to avoid tumour rupture, and that the goal of surgery is 'to achieve complete gross resection with an intact pseudocapsule'[25]. In the Japanese guidelines[26], no recommendation is given on how to manage such patients. Furthermore, publications from sarcoma centres that address the surgical handling of primary GIST fail to mention this topic[27]. In the present authors' institutions, the recommendation strictly to avoid any handling that might put the tumour at risk of rupture was adopted. If feasible safely, laparoscopic resection is a permitted option. However, the threshold for conversion laparotomy must be much lower than for similar epithelial tumours, which are usually not as soft and fragile as GISTs.

According to guidelines published by the European Society for Medical Oncology[28], rupture should be recorded because it denotes a highly adverse prognosis as a result of peritoneal contamination. However, the guidelines also state that it is uncertain whether these patients should be considered to have metastatic disease, and mention that abdominal washing may be an option in case of tumour rupture. The present follow-up data show that nearly all patients develop abdominal metastases after rupture of GIST. The only patient in the present study who remained free from disease (out of 16 with no adjuvant treatment) had the tumour resected within 6 h after perforation and underwent abdominal lavage for haemoperitoneum due to splenic rupture. Dissemination of the disease might have been prevented by this measure, but this solitary finding would need confirmation in a larger series.

A recently published, randomized placebo-controlled trial conducted by the American College of Surgeons Oncology Group (ACOSOG Z9000)[29] demonstrated that adjuvant imatinib therapy led to prolonged recurrence-free survival after resection of GIST. The effect was most pronounced for larger tumours. Although early data for overall survival did not show any significant advantage for the treatment group, it should be noted that median follow-up was well below the median survival of patients with metastatic GIST in the era of TKIs. Based on these results, imatinib received registration for adjuvant treatment in the USA and Europe for patients with a resected primary GIST deemed to be at risk of recurrence.

Patients with tumour rupture in the present series were eligible to enter the ACOSOG study as well as the Scandinavian Sarcoma Group trial (SSGXVIII-AIO), the results of which are not yet available. Adjuvant treatment with imatinib was initiated in two of the patients reported[18,24] and in seven patients in the present series. Overall case numbers are too small to allow valid conclusions to be drawn regarding whether adjuvant treatment after resection of a ruptured GIST leads to a relapse-free survival comparable to that achieved with adjuvant treatment of a non-ruptured GIST with similar tumour characteristics (size, mitotic count and tumour location).

Patients with rupture are also considered in the recent proposal on risk stratification of GIST made by Joensuu[8]. This proposes that high-risk patients defined by the modified system[1] should have a greater than 15–20 per cent risk of disease recurrence[8]. This patient group clearly fulfils the European Medicines Agency criteria for adjuvant treatment with imatinib.

Two case reports have described late metastatic tumour growth[17]. In the present series, recurrence-free survival ranged widely, from 5 to 83 months, reflecting the biological behaviour of untreated disease. In patients with low-risk tumours, relapse is often detected after more than 3 years. Furthermore, there was no discrepancy between mutations in the primary tumour and those in subsequent metastases, supporting the assumption that secondary mutations are due mostly to selection pressure of drug treatment[30,31]. The overall survival of patients in the decade reported by Ng and colleagues[10] was worse than that of patients with tumour rupture in the era of imatinib and sunitinib, where the 5-year survival rate was 51 per cent in patients with metastatic disease[32]. Overall survival of the present cohort of patients was no worse, with a 61 per cent 5-year survival rate.

Patients with a primary GIST treated for spontaneous tumour rupture or with rupture occurring during resection

have a very high risk of tumour recurrence. These patients are clear candidates for adjuvant treatment with TKIs. From a surgical point of view, any intraoperative manipulation leading to a coarse laceration of the capsulated smooth serosal surface of a GIST must be avoided.

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