Original article

Prognostic factors influencing surgical management and outcome of gastrointestinal stromal tumours

C. Langer[1], B. Gunawan[2], P. Schüler[1], W. Huber[3], L. Füzesi[2] and H. Becker[1]

Departments of [1]General Surgery and [2]Pathology, Georg-August-University Göttingen and [3]Division of Molecular Genome Analysis, German Cancer Research Centre, Heidelberg, Germany

Correspondence to: Dr. C. Langer, Department of General Surgery, Georg-August-University Göttingen, Robert-Koch-Strasse 40, D-37075 Göttingen, Germany (e-mail: langer@med.uni-goettingen.de)

Background: The purpose of this study was to review surgical experience with gastrointestinal stromal tumours (GISTs) at a single tertiary university hospital, and to identify morphological and genetic prognostic markers of tumour progression.

Methods: Forty-eight GISTs from 39 patients were reviewed retrospectively. The prognostic significance of DNA copy number changes, measured by comparative genomic hybridization (CGH), and morphological markers in low-risk and high-risk tumours were investigated.

Results: Significantly more patients died from disease after incomplete tumour resection than after complete primary resection ($P = 0{\cdot}020$). Tumour size of 5 cm or greater, mitotic count of 2 or more, and proliferative activity greater than 10 per cent were significantly associated with a shorter recurrence-free survival ($P = 0{\cdot}020$, $P = 0{\cdot}001$ and $P = 0{\cdot}002$ respectively). Patients with low-risk tumours had a significantly better outcome than those with high-risk GISTs, both in terms of overall and recurrence-free survival ($P \leq 0{\cdot}001$). CGH performed on 16 tumours revealed fewer DNA sequence copy number changes in low-risk than in high-risk GISTs. Non-progressive GISTs contained significantly fewer genetic alterations than recurrent or metastatic tumours ($P < 0{\cdot}001$). Only tumours with more than five changes showed disease progression.

Conclusion: Complete surgical resection is the most important means of cure for GISTs. DNA copy number changes are related to the behaviour of these tumours and may serve as additional prognostic markers.

Paper accepted 30 August 2002

Published online 6 February 2003 in Wiley InterScience (www.bjs.co.uk). **DOI:** 10.1002/bjs.4046

Introduction

Gastrointestinal stromal tumours (GISTs) constitute the most important group of primary mesenchymal tumours of the gastrointestinal tract[1–4]. There has been considerable debate regarding diagnosis, prognosis and surgical management. GISTs are known for their diversity in clinical behaviour, and the difficulties in determining malignancy and prognosis[5–7]. Patients generally lack specific symptoms or typical diagnostic features[5,8–10]. To date, there have been no randomized studies comparing different treatments for GISTs. A review of the literature shows that surgery is the only real primary treatment modality, but the extent of the resection remains unclear[4,11–16]. Diversity in the management of these tumours contributes to the wide range in reported 5-year survival rates (from 20 to 78 per cent) after potentially curative resection[4,8,11,12,17,18]. To predict the biological potential and the risk of malignancy, several prognostic factors have been suggested[4,7,17,19–21]. Cytogenetic and comparative genomic hybridization (CGH) studies have indicated characteristic chromosomal patterns in GISTs, distinct from other mesenchymal tumours of the gastrointestinal tract[22–25]. Recent CGH studies of GISTs found that several DNA copy number changes were correlated with clinical behaviour[1,2], indicating that genetic changes might be used as complementary tools in determining prognosis, and in the differentiation between benign and malignant tumours.

The main objective of this study was to review experience with GISTs at a single surgical centre. DNA copy number

changes in low-risk and high-risk tumours were examined for their prognostic significance.

Patients and methods

Patients and tumour samples

There were 48 GISTs in 39 patients who underwent surgical treatment from 1990 to 2001. The tumours consisted of 39 primary GISTs, seven local recurrences and two metastases from eight of the primary GISTs. The tumours were reviewed by two pathologists (L.F., B.G.) to establish the diagnosis of GIST and to assess their risk for aggressive clinical behaviour as suggested by Franquemont[21]. On the basis of tumour size, mitotic rate and/or proliferation index, primary tumours were classified as low risk (size smaller than 5 cm and mitotic rate less than 2 per ten high-power fields (HPFs); or either size 5 cm or larger, or mitotic rate 2 or more per ten HPFs, and proliferation index 10 per cent or less) or high risk (size 5 cm or more and mitotic rate 2 or more per ten HPFs; or either size smaller than 5 cm, or mitotic rate less than 2 per ten HPFs, and proliferation index greater than 10 per cent). Mitotic count and proliferative activity were not available for one tumour, which was considered to be a low-risk tumour on the basis of size alone. Resection was classified as R0 (no residual tumour), R1 (microscopic residual tumour), or R2 (macroscopic residual tumour) according to the Union Internacional Contra la Cancrum system[26].

Comparative genomic hybridization

For comparative genomic hybridization, fresh tumour material was available from 13 primary tumours, two local recurrences and one simultaneous liver metastasis. Briefly, tumour DNA was extracted from snap-frozen tumour samples following standard protocols. For direct labelling, tumour DNA was nick-translated using biotin-16-2′-deoxyuridine 5′-triphosphates (dUTPs) (Roche, Mannheim, Germany). Digoxigenin-11-dUTP-labelled normal reference DNA (Roche) was used for co-hybridization. Hybridization, washings, digital image acquisition and image analysis (Applied Imaging, Newcastle upon Tyne, UK) were performed as described elsewhere. In each analysis, the average green-to-red ratio was calculated for each chromosome, including at least 16 observations per autosome and eight observations per sex chromosome. A gain of DNA sequences was assumed at chromosomal regions where the tumour : normal ratio was 1·25 or more, while loss of DNA sequences was assumed where the tumour : normal ratio was 0·75 or less. Exceptionally, in cases with too few tumour cells in the sample to allow detection of imbalances with the aforementioned thresholds, cut-off levels were set at 1·20 and 0·80 respectively. Over-representations were considered to be high-level amplifications when the ratio values exceeded 2·0. Chromosomal regions 1p32-pter, 13p, 14p, 15p, 19, 21p, 22p, telomeres, and constitutive heterochromatic regions at 1q, 9q, 16q and Yq, which are known to produce false results by CGH, were excluded from all analyses.

Immunohistochemical analysis

Immunohistochemical analysis was performed, applying a panel of antibodies against c-Kit (1 : 50) (Santa Cruz Biotechnology, Santa Cruz, California, USA) and CD34 (1 : 20) (Immunotech, Marseilles, France). Blood vessels and peripheral nerves served as internal immunohistochemical controls for smooth muscle and neural elements. The proliferative activity was determined using the immunohistochemical proliferation marker Ki-67 (1 : 10; Dianova, Hamburg, Germany). Computer-assisted analysis of Ki-67 staining was performed as described previously[27].

Statistical analysis

Clinicopathological variables (primary tumour site, tumour size, mitotic count, proliferative activity and risk index) were studied for their association with overall recurrence-free survival and tested with the Mantel–Haenszel test (log rank test) for censored data. Survival rates were plotted using the Kaplan–Meier method. The associations between clinicopathological variables and DNA copy number changes were evaluated using the two-sample Wilcoxon test and Fisher's exact test for contingency tables.

Results

Patients and preoperative diagnosis

There were 20 women and 19 men with a mean age at diagnosis of 60·1 (range 33–78) years (*Table 1*). There were 21 tumours in the upper digestive tract (20 gastric, one oesophageal) and 18 in the lower digestive tract (nine small intestinal, seven colorectal, two intra-abdominal). Ten patients were asymptomatic at first presentation; others had non-specific symptoms such as epigastric pain (12 patients), gastrointestinal bleeding (nine patients) or nausea (two patients). A variety of diagnostic and staging modalities was used (endoscopy, contrast radiology,

Table 1 Clinical and pathological findings for 48 gastrointestinal stromal tumours obtained from 39 patients

No.	Sex	Age (years)	Site	Size (cm)	Risk	Operation	R status	Follow-up (months)
4	M	33	Rectum	0·9	Low	Transanal local resection	R0	NED (10)
31	M	75	Stomach	1·5	Low	Gastric resection	R0	NED (1)
35	F	69	Stomach	1·7	Low	Gastrectomy	R0	NED (12)
2	M	53	Sigmoid	2	Low	Anterior resection	R0	NED (8)
16	F	41	Rectum	2	Low	Transanal local resection	R0	DFC (15)
20	M	54	Stomach	2·5	Low	Gastric resection	R0	NED (22)
34	F	72	Stomach	2·7	Low	Gastric resection	R0	NED (63)
5	M	35	Stomach	3	Low	Local resection	R0	NED (20)
21	M	33	Rectum	3	Low	Transanal local resection	R0	NED (120)
29	M	43	Oesophagus	3	Low	Local resection	R0	NED (22)
25	M	73	Stomach	3·5	Low	Gastric resection	R0	NED (26)
8	F	77	Stomach	4	Low	Gastric resection	R0	DFC (27)
28	F	57	Stomach	4·5	Low	Gastric resection	R0	NED (57)
17	F	58	Stomach	4·5	Low	Gastrectomy	R0	DFTD (98)
17r	F	62	Abdomen	3		Resection, splenectomy	R0	
15	F	77	Stomach	5	Low	Gastric resection	R0	DFC (9)
24	F	64	Stomach	5·5	Low	Gastric resection	R0	NED (16)
18	M	65	Stomach	6·5	Low	Gastric resection	R0	NED (4)
27	F	70	Stomach	7	Low	Local resection	R0	NED (61)
22	F	59	Stomach	7·5	Low	Gastric resection	R0	NED (1)
39	F	39	Stomach	10	Low	Gastric resection	R0	NED (14)
26	M	71	Duodenum	12·5	Low	Local resection, adrenalectomy	R0	NED (8)
19	M	57	Duodenum	15	Low	Local resection	R0	NED (29)
14	F	70	Jejunum	19	Low	Partial resection	R0	Alive (49)
14r	F	73	Jejunum	3·5		Partial jejunal and colonic segmental resection	R0	
33	F	58	Jejunum	4·5	High	Partial jejunal and right hemicolectomy	R0	DFTD (24)
33r1	F	59	Jejunum	13·5		Partial resection	R0	
33r2	F	59	Abdomen	10·5		Resection	R0	
6	F	71	Abdomen	5	High	Resection	R2	DFTD (4)
12	M	68	Jejunum	5·3	High	Partial resection	R0	NED (17)
32	F	70	Abdomen	6	High	Perineal resection	R0	DFTD (26)
32r	F	70	Abdomen	3·8		Exenteration	R0	
36	F	35	Stomach	6	High	Gastric resection	R0	NED (18)
1	M	56	Rectum	6·5	High	Abdominoperineal resection	R1	Alive (1)
1m	M	56	Liver	0·6		Biopsy		
30	M	53	Stomach	7	High	Wedge resection	R0	NED (24)
9	M	44	Rectum	8	High	Abdominoperineal resection	R0	NED (13)
38	M	77	Stomach	8	High	Gastrectomy	R0	DFTD (15)
7	M	61	Duodenum	10	High	Pylorus-preserving pancreaticoduodenectomy	R0	Alive (37)
7m	M	65	Liver	1·5		Resection	R2	
10	F	74	Duodenum	10	High	Local resection	R1	DFTD (41)
11	M	75	Rectum	10	High	Abdominoperineal resection	R2	DFTD (12)
13	F	73	Jejunum	12	High	Partial resection	R0	NED (18)
23	F	78	Stomach	13	High	Gastric and colonic transversum resection	R0	NED (1)
3	M	45	Jejunum	18	High	Partial jejunal and colonic segmental resection	R0	DFTD (59)
3r	M	45	Abdomen	5		Resection	R2	
37	F	61	Stomach	30	High	Gastric resection, splenectomy	R0	Alive (23)
37r	F	63	Abdomen			Gastrectomy, segmental colonic and local pancreatic resection	R0	

r, Local recurrence; m, metastasis; NED, no evidence of disease; DFC, died from other cause; DFTD, died from tumour disease.

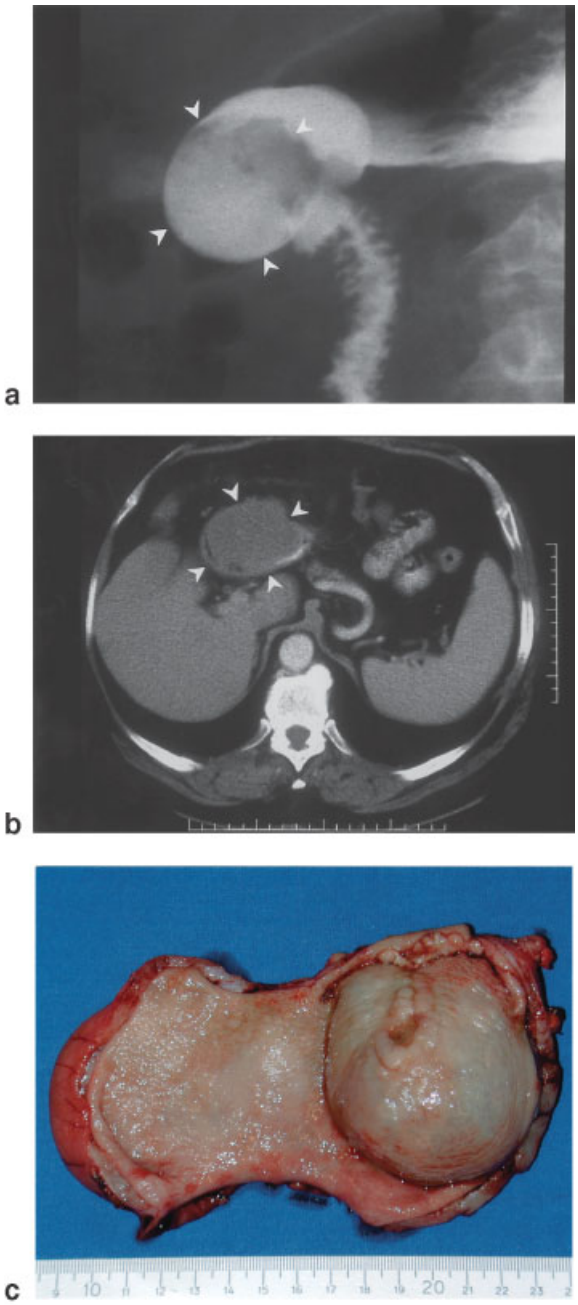

Fig. 1 Representative morphological findings in a gastric gastrointestinal stromal tumour. **a** Typical preoperative contrast radiographic image. **b** Preoperative computed tomographic scan of the same patient detecting tumour next to the liver. **c** The same tumour after partial gastric resection, typically covered by intact mucosa and a central ulceration

computed tomography (CT), magnetic resonance imaging and endosonography). Figure 1 gives an example of the characteristic radiographic and macroscopic aspects of a gastric GIST. Preoperative diagnostic measures suggested the diagnosis of a mesenchymal tumour in 17 patients, but no single test consistently identified the nature of the lesion. Two patients underwent emergency laparotomy without any specific preoperative staging.

Surgical treatment

All patients were treated surgically either by complete resection of the primary tumour with wide margins (R0) in 35 cases, R1 resection in two or R2 resection in another two cases (*Table 1*). The types of operation performed are also shown in *Table 1*. There was no operative death.

Pathology

The mean size of the 39 primary tumours was 6·8 (range 0·9–30) cm (*Table 1*). Tumour size greater than 5 cm was associated with worse recurrence-free survival ($P = 0{\cdot}020$), but not overall survival. In 36 tumours with available mitotic counts, 18 had fewer than 2 per ten HPFs. There was a significant association between mitotic count and survival. Patients with fewer than 2 mitotic counts per ten HPFs had a significantly better outcome than those with higher counts, for both overall and recurrence-free survival (both $P = 0{\cdot}001$). Similarly, in 34 patients with available proliferation index measurements, proliferative activity of 10 per cent or more was also significantly associated with worse overall and recurrence-free survival ($P = 0{\cdot}01$ and $P = 0{\cdot}002$ respectively). Overall, 23 primary GISTs were classified as low-risk and 16 as high-risk tumours. Patients with low-risk tumours had a far better outcome than those with high-risk tumours. The differences for both overall and recurrence-free survival were highly significant ($P < 0{\cdot}001$ and $P = 0{\cdot}001$ respectively) (*Fig. 2*).

Immunohistochemical analysis

All tumour samples revealed strong diffuse reactivity for c-Kit, whereas diffuse or focal CD34 expression was observed in 28 of 40 tumour samples for which CD34 reactivity was informative.

Comparative genomic hybridization analysis

CGH was performed on 13 primary tumours (seven low risk), two local recurrences and one liver metastasis. In all but one low-risk tumour, DNA copy number changes were detected (*Table 2*). The seven low-risk GISTs had a mean of 2·7 DNA copy number changes (range 0–5), including 0·6 gains (range 0–2) and 2·1 losses (range 0–5). The six high-risk tumours had a mean of 10·0 chromosomal imbalances

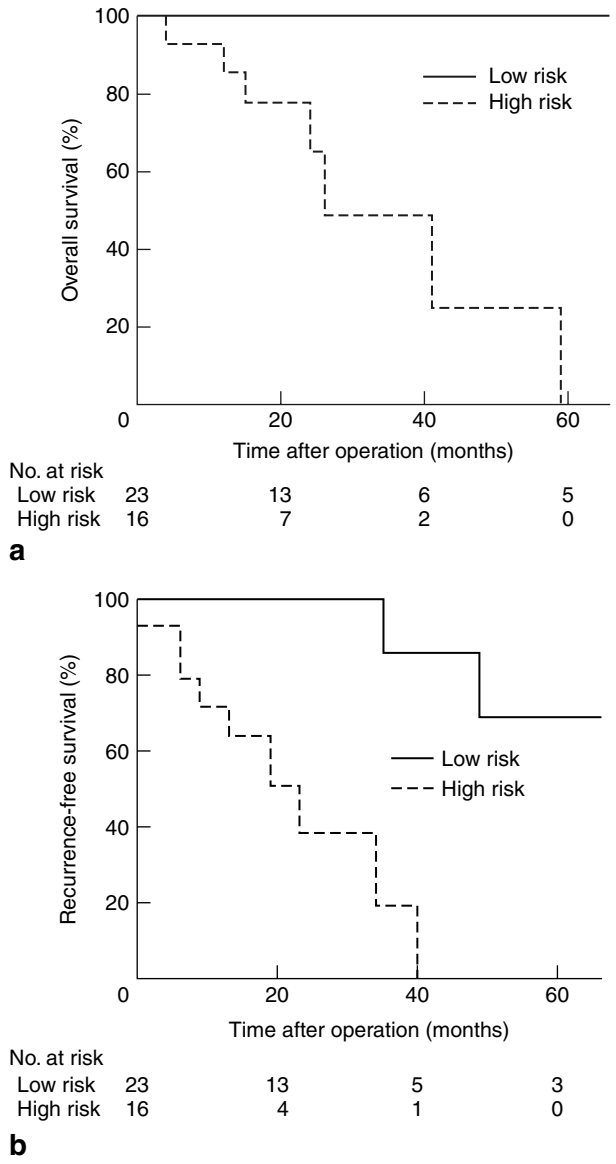

Fig. 2 Kaplan–Meier plot of **a** overall and **b** recurrence-free survival of 39 patients with low-risk (23 patients; one death and two with disease progression) and high-risk (16 patients; seven deaths and eight with disease progression) gastrointestinal stromal tumours. $P < 0{\cdot}001$ for overall and $P = 0{\cdot}001$ for recurrence-free survival (log rank test)

(range 2–24), including 4·8 gains (range 0–16) and 5·2 losses (range 2–9). With respect to disease progression (including the two recurrences and one case of metastasis) these differences were even more distinct: the nine non-progressive GISTs contained significantly fewer DNA copy number changes (mean 2·7; gains 0·4, losses 2·2) than the seven recurrent or metastatic tumours (mean 14·4; gains 6·6, losses 7·9) ($P < 0{\cdot}001$), and only tumours with more than five copy number changes were associated with disease progression.

Table 2 Comparative genomic hybridization karyotype findings for 16 gastrointestinal stromal tumours from 15 patients

		CGH karyotype	
No.	Risk	Gains	Losses
29	Low		
8	Low		14q
18	Low		14q
24	Low	8p, 8q	14q, 22q
19	Low	8q	1p, 15q, 22q
39	Low	5q	1p, 10q, 14q
25	Low		1p, 3p, 3q, 14q, 21q
23	High		14q, 22q
30	High		1p, 3p, 14q
7*	High	4p, 4q, 5p, 5q, 7q	1p, 15q, 22q
37*	High	8q	3q, 8p, 13q, 14q, 22q
37r*	Recurrence		3p, 3q, 6q, 9p, 9q, 13q, 14q, 22q
14r*	Recurrence	5p13–p15	1p, 5q, 8p, 9p, 10p, 13q, 14q, 15q, 22q
6*	High	5q, 6q, 8p, 8q, 12q, 13q, 18q	1p, 9q, 10p, 10q, 11p, 11q, 14q, 15q, 22q
1*	High	1q, 5p, 5q, 6p, 7p, 7q, 8p, 8q, 12p, 12q, 13q, 18p, 18q, 20p, Xp, Xq	1p, 2q, 4p, 6q, 9q, 10q, 14q, 22q
1m*	Metastasis	1q, 5p, 5q, 7p, 7q, 8p, 8q, 11p, 11q, 12p, 12q, 13q, 18q, 20p, Xp, Xq	1p, 3p, 3q, 4p, 4q, 6q, 9p, 9q, 10p, 10q, 14q, 22q

CGH, comparative genomic hybridization; r, local recurrence; m, metastasis. *Patients with progressive tumours.

The most common alterations detected in all GISTs ($n = 16$) were losses of chromosome 14q ($n = 13$) and 22q ($n = 10$). Further changes included (in decreasing order of frequency) 1p ($n = 9$), +8q ($n = 6$), +5q ($n = 5$), +5p ($n = 4$), −10q ($n = 4$), −15q ($n = 4$), −3p ($n = 4$), −3q ($n = 4$), −9p ($n = 3$) and +8p ($n = 1$). Of these, +5p, +8p, −15q and −9p were only observed in progressive tumours, including the two local recurrences and one metastasis. Loss of 9p was observed exclusively in the two recurrences and one metastasis.

Follow-up

Follow-up data were available for all 39 patients. The median duration of follow-up was 2·2 years (range 3 months to 10 years). The overall 2-year survival rate was 87 per cent, 100 per cent in the low-risk group and 75 per cent in the high-risk group (*Fig. 2a*). Only

five of 35 patients with complete tumour resection died from recurrent disease in contrast to three of four patients following incomplete resection ($P = 0{\cdot}020$). The overall recurrence rate was 26 per cent ($n = 10$), two of 23 in the low-risk group and eight of 16 in the high-risk group ($P = 0{\cdot}008$). Recurrences occurred after a mean interval of 23 (range 6–49) months. Two patients with low-risk tumours developed local recurrences and one additionally developed metachronous peritoneal metastases. Eight patients who had high-risk tumours developed progressive disease. Two had one or repeated local recurrences, three had synchronous local recurrences and liver metastases, one developed a recurrent tumour and a metachronous liver metastasis, one a solitary liver metastasis, and another developed metachronous lymph-node and peritoneal metastases.

In five of eight operations for recurrent or metastatic tumour, complete resection (R0) was performed. Two patients are alive following R0 resection of the recurrent tumours at 3 and 26 months, as is one patient after R2 resection of recurrent tumour and palliative chemotherapy of synchronous liver metastasis at 13 months. Another patient with an untreated liver metastasis is still alive 7 months after diagnosis of the metastasis. The remaining six patients all died from tumour disease with a mean survival time after detection of the first recurrence of 11 (range 1–24) months.

Discussion

In contrast to that of DeMatteo *et al.*[11], the present study indicates that resection status strongly influences outcome. Complete primary resection of the tumour was achieved in 35 of 39 patients; of these, only five died as a result of recurrent disease compared with three of four patients following R1 or R2 resection.

Primary tumour sites and clinical features were similar to those described in other series[3,5,8,13,14,17]. Preoperative diagnosis is not always easy[5,8,17,19,20], and precise determination of the organ of origin may be difficult, especially in large tumours. A radiological distinction between benign and malignant GISTs is not possible[9,10,14]. Accordingly, clues to the correct preoperative diagnosis of a mesenchymal tumour were obtained in only 17 of the 39 patients studied. The fact that the surgeon did not know the diagnosis before surgery in more than half of the cases makes it important to have an understanding of the special behaviour of GISTs and an R0 resection if possible, with the resection of adjacent structures[4,8,13,17,20]. Poor responses to radiation or chemotherapy[4,11,17,19,20,28] make surgery the only realistic prospect for cure of the primary lesion. Eight of ten patients with recurrence underwent further surgery with R0 resection in five. Similar to other studies[4,11] these recurrences occurred after a mean follow-up of 23 (range 6–49) months. Since most of the recurrent tumours were asymptomatic at the time of detection, close long-term surveillance is necessary. For asymptomatic patients who have undergone R0 resection, a yearly re-examination by ultrasonography and contrast-enhanced CT is therefore recommended. In the case of gastric or duodenal GIST, or localization within the colon or rectum, an endoscopy should also be performed.

Attempts have been made to differentiate benign from malignant tumours and to identify factors that might predict outcome. In agreement with Pierie *et al.*[20], classification into low- and high-risk tumours correlated well with both survival and recurrence rates. Recurrence rates were two of 23 for low-risk tumours and eight of 16 for high-risk tumours, supporting the view that all GISTs should be considered as potentially malignant tumours and referred to as low-risk or high-risk GISTs to indicate their estimated potential for aggressive clinical behaviour; the confusing terminology of 'benign' and 'malignant' GISTs should be discontinued.

It has been suggested that genetic changes in GISTs identified by conventional cytogenetics[23,25,29] and by CGH[1,2] can correlate with clinical behaviour. The finding that low-risk tumours contained significantly fewer DNA sequence copy number changes than high-risk tumours is in accordance with previous studies[2] and reflects increasing genetic instability during tumour progression. Even more important is the observation that DNA copy number changes appeared to be related to the behaviour of GISTs; recurrent or metastatic GISTs not only contained significantly more imbalances than non-progressive tumours, but also appeared to be characterized by a specific subset of additional genetic markers. Progressive tumours had more than five changes and almost exclusively exhibited gains at 5p and 8p, and losses in 10q, 15q and 9p. Loss of 9p was observed exclusively in the two recurrences and one metastasis, as well as in a high-risk GIST that had simultaneous lymph node metastases at the time of surgery, suggesting that loss of 9p is important in the malignant transformation and progression of GISTs. CGH may be a complementary tool with which to predict the potential for aggressive clinical behaviour of GISTs. The increased number of changes correlates not only with high-risk tumours, but also with unfavourable biological behaviour. Furthermore, additional genetic changes, such as +5p, +8p, −10q, −15q and −9p, may mark a characteristic pattern of potentially aggressive GISTs.

As the overall risk for recurrence in GISTs is high, even for low-risk and R0-resected tumours, there is a need to develop adjuvant therapies. The identification of genetic changes may identify those patients likely to benefit from this approach. Early reports indicate that inhibition of the constitutively active mutant c-kit tyrosine kinase in GISTs might represent an effective systemic therapy[30–32]. The first phase I study using imatinib in metastatic GISTs showed an objective response in 25 of 36 patients with GIST[33]; this clearly merits a randomized trial. The potential role of imatinib not only in metastatic GISTs but also for adjuvant or neoadjuvant therapy remains to be determined. In this context, the results of the first phase III trials should be awaited.

References

1 Knuutila S, Björkqvist A-M, Autio K, Tarkkanen M, Wolf M, Monni O *et al*. DNA copy number amplifications in human neoplasms. Review of comparative genomic hybridization studies. *Am J Pathol* 1998; **152**: 1107–1123.

2 El-Rifai W, Sarlomo-Rikala M, Andersson LC, Knuutila S, Miettinen M. DNA sequence copy number changes in gastrointestinal stromal tumors: tumor progression and prognostic significance. *Cancer Res* 2000; **60**: 3899–3903.

3 Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. *Hum Pathol* 1999; **30**: 1213–1220.

4 Ng E-H, Pollock RE, Munsell MF, Atkinson EN, Romsdahl MM. Prognostic factors influencing survival in gastrointestinal leiomyosarcomas. Implications for surgical management and staging. *Ann Surg* 1992; **215**: 68–77.

5 Sanders L, Silverman M, Rossi R, Braasch J, Munson L. Gastric smooth muscle tumors: diagnostic dilemmas and factors affecting outcome. *World J Surg* 1996; **20**: 992–995.

6 Evans H. Smooth muscle tumors of the gastrointestinal tract. A study of 56 cases followed up for a minimum of 10 years. *Cancer* 1985; **56**: 2242–2250.

7 Emory TS, Sobin LH, Lukes L, Lee DH, O'Leary TJ. Prognosis of gastrointestinal smooth-muscle (stromal) tumors: dependence on anatomic site. *Am J Surg Pathol* 1999; **23**: 82–87.

8 Peiper M, Schröder S, Zornig C. Stromal sarcoma of the stomach – a report of 20 surgically treated patients. *Langenbecks Arch Surg* 1998; **383**: 442–446.

9 Tervahartiala P, Halavaara J. Radiology of GIST. *Ann Chir Gynaecol* 1998; **87**: 291–292.

10 Levine MS. *Textbook of Gastrointestinal Radiology*. WB Saunders: Philadelphia, 1994; 628–683.

11 DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF *et al*. Two hundred gastrointestinal stromal tumours: recurrence patterns and prognostic factors for survival. *Ann Surg* 2000; **231**: 51–58.

12 Clary BM, DeMatteo RP, Lewis JJ, Leung D, Brennan MF. Gastrointestinal stromal tumors and leiomyosarcoma of the abdomen and retroperitoneum: a clinical comparison. *Ann Surg Oncol* 2001; **8**: 290–299.

13 Ludwig DJ, Traverso LW. Gut stromal tumors and their clinical behavior. *Am J Surg* 1997; **173**: 390–394.

14 Langer C, Bergmann F, Funke C, Füzesi L. Gastrointestinal stromal tumour (GIST) – problems of surgical treatment. *Viszeralchirurgie* 1999; **34**: 208–211.

15 Yoshida M, Otani Y, Ohgami M, Kubota T, Kumai K, Mukai M *et al*. Surgical management of gastric leiomyosarcoma: evaluation of the propriety of laparoscopic wedge resection. *World J Surg* 1997; **21**: 440–443.

16 Bandoh T, Isoyama T, Toyoshima H. Submucosal tumors of the stomach: a study of 100 operative cases. *Surgery* 1993; **113**: 498–506.

17 Lehnert T. Gastrointestinal sarcoma (GIST) – a review of surgical management. *Ann Chir Gynaecol* 1998; **87**: 297–305.

18 Ueyama T, Guo K-J, Hashimoto H, Daimaru Y, Enjoji M. A clinicopathologic and immunohistochemical study of gastrointestinal stromal tumors. *Cancer* 1992; **69**: 947–955.

19 Hoos A, Lewis JJ, Brennan MF. Weichgewebssarkome – prognostische Faktoren und multimodale Therapie. *Chirurg* 2000; **71**: 787–794.

20 Pierie JP, Choudry U, Muzikansky A, Yeap BY, Souba WW, Ott MJ *et al*. The effect of surgery and grade on outcome of gastrointestinal stromal tumors. *Arch Surg* 2001; **136**: 383–389.

21 Franquemont DW. Differentiation and risk assessment of gastrointestinal stromal tumors. *Am J Clin Pathol* 1995; **103**: 41–47.

22 Sarlomo-Rikala M, El-Rifai W, Lahtinen T, Andersson LC, Miettinen M, Knuutila S *et al*. Different patterns of DNA copy number changes in gastrointestinal stromal tumors, leiomyomas, and schwannomas. *Hum Pathol* 1998; **29**: 476–481.

23 Gunawan B, Bergmann F, Höer J, Langer C, Schumpelick V, Becker H *et al*. Biological and clinical significance of cytogenetic abnormalities in low-risk and high-risk gastrointestinal stromal tumors. *Hum Pathol* 2002; **33**: 316–321.

24 Bergmann F, Gunawan B, Hermanns B, Höer J, Schumpelick V, Füzesi L *et al*. Cytogenetic and morphologic characteristics of gastrointestinal stromal tumors. Recurrent rearrangement of chromosome 1 and losses of chromosomes 14 and 22 as common anomalies. *Verh Dtsch Ges Pathol* 1998; **82**: 275–278.

25 Breiner JA, Meis-Kindblom J, Kindblom L-G, McComb E, Liu J, Nelson M *et al*. Loss of 14q and 22q in gastrointestinal stromal tumors (pacemaker cell tumors). *Cancer Genet Cytogenet* 2000; **120**: 111–116.

26 Sobin LH, Wittekind C. *International Union Against Cancer: TNM Classification of Malignant Tumours* (5th edn). J Wiley and Sons: New York, 1997.

27 Biesterfeld S, Kluppel D, Koch R, Schneider S, Steinhagen G, Mihalcea AM *et al*. Rapid and prognostically valid quantification of immunohistochemical reactions by immunohistometry of the most positive tumour focus. A

prospective follow-up study on breast cancer using antibodies against MIB-1, PCNA, ER, and PR. *J Pathol* 1998; **185**: 25–31.

28 Plaat BEC, Hollema H, Molenaar WM, Torn Broers GH, Pijpe J, Mastik MF *et al*. Soft tissue leiomyosarcomas and malignant gastrointestinal stromal tumors: differences in clinical outcome and expression of multidrug resistance proteins. *J Clin Oncol* 2000; **18**: 3211–3220.

29 Marci V, Casorzo L, Sarotto I, Dogliani N, Milazzo MG, Risio M *et al*. Gastrointestinal stromal tumor, uncommitted type, with monosomies 14 and 22 as the only chromosomal abnormalities. *Cancer Genet Cytogenet* 1998; **102**: 135–138.

30 Joensuu H, Roberts PJ, Sarlomo-Rikala M, Andersson LC, Tervahatiala P, Tuveson D *et al*. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 2001; **344**: 1052–1056.

31 Taniguchi M, Nishida T, Hirota S, Isozaki K, Ito T, Nomura T *et al*. Effect of c-*kit* mutation on prognosis of gastrointestinal stromal tumors. *Cancer Res* 1999; **59**: 4297–4300.

32 Fukuda R, Hamamoto N, Uchida Y, Furuta K, Katsube T, Kazumori H *et al*. Gastrointestinal stromal tumor with a novel mutation of *KIT* proto-oncogene. *Intern Med* 2001; **40**: 301–303.

33 Van Oosterom AT, Judson I, Verweij J, Stroobants S, di Paola ED, Dimitrijevic S *et al*. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. *Lancet* 2001; **358**: 1421–1423.