Outcome after Resection of One Hundred Gastrointestinal Stromal Tumors

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Key Words

Gastrointestinal stromal tumors • Complete tumor resection • Prognostic factors • Mitotic index

Abstract

Aims: To evaluate the outcome after surgical resection in patients with gastrointestinal stromal tumors and to determine the factors influencing local tumor recurrence or distant metastatic disease after locally complete tumor resection (R0). **Methods:** Outcomes of 100 patients with primary gastrointestinal stromal tumors (GIST) surgically managed between 1997 and 2006 at a single institution were reviewed. Univariate and bivariate analyses were used to determine factors affecting recurrence-free and tumor-free survival.

Results: All patients (n = 100) had c-kit-positive GIST. There were 17% (n = 17) very low risk, 41% (n = 41) low risk, 19% (n = 19) intermediate risk and 23% (n = 23) high risk GIST originating from the stomach, small bowel, colon and rectum. The median patient age was 68 years (range 39–92). Seventy-three percent of the patients had symptomatic local disease. Most (94%; n = 94) of them underwent R0 resections of their primary tumor. R0 resection was significantly associated with a lower tumor-related mortality rate (p = 0.0001). The patients with recurrence/metastases had significantly larger tumors (p = 0.0017) and a mitotic index higher

than 5/50 HPF (p = 0.0001). Seven of 20 patients from the high-risk group and 2 of 7 patients with metastatic disease developed local recurrence or further metastatic tumor spread following R0 resection. **Conclusion:** Surgical removal continues to be the mainstay of GIST treatment. R0 resection, tumor size and mitotic index are significant prognostic factors. Overall, more than 30% of the patients with high-risk GIST develop local recurrences and distant metastases despite R0 resection. Additional molecular pathological markers are needed to yield a more accurate tumor profile and to thus achieve a better predictability of the biological behavior of GIST.

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Introduction

Following the discovery of activating c-kit mutations and demonstration of c-kit (CD 117) immunoexpression on the surface of tumor cells in the majority of mesenchymal GI neoplasms formerly classified as smooth muscle or neurogenic neoplasms, gastrointestinal stromal tumors (GISTs) were redefined as an independent tumor entity. The incidence of GISTs is estimated to be 14.5 cases per million people per year [1]. The surgical R0 resection continues to be the treatment of choice for resectable

tumors. Diverse prognostic factors that would predict the development of recurrence and/or metastases after R0 resection of GIST have been evaluated by several research groups worldwide, in particular for the category of high-risk tumors. The question whether adjuvant treatment with imatinib is indicated in patients with R0-resected high-risk GISTs has not yet been conclusively settled. The objectives of this large single-center trial were to evaluate the outcome after surgical resection and determine the prognostic factors for tumor relapse and tumor-related death.

Materials and Methods

Patients

Follow-up data of patients who underwent surgery due to a GIST between January 1, 1997, and December 31, 2006, at the Department of Surgery of the Klinikum Nürnberg Nord were obtained and analyzed based on a questionnaire consisting of 36 questions regarding the patient's personal data, symptoms, macroscopic and histological features of the tumors, location and time until tumor recurrence or metastases, drug therapy, type and length of follow-up after primary resection and cause of death. These data were collected methodically in terms of personal interviews with the patients or their families and the attending primary care physicians. The risk group assessment was done by evaluating maximum tumor size and mitotic index according to the Fletcher risk assessment system [2] (table 1).

In all cases in which a safe R0 resection could be carried out while still preserving the organs, a limited organ-preserving resection was performed. Wedge resections of the stomach and intestinal segment resections were also counted as part of this group.

Patients who exhibited a locally progressive tumor with infiltration of neighboring organs received an en bloc multivisceral resection to ensure a safe R0 status. A systematic lymph node dissection was not performed.

We distinguished the type of tumor relapse into recurrence and metastases. Recurrence is defined as local recurrence in the already operated organ, and metastases are defined as tumor formation in other locations. Tumor relapse includes recurrence and metastases.

Statistical Methods

The frequency distribution of the two independent groups was calculated using Fisher's exact test to determine if significant differences exist. Comparison of the distribution of a metric variable of two independent groups was made using the Mann-Whitney U test. All tests were calculated two-sided with a significance level set at $p = 0.05$.

To test the simultaneous influence of several variables on a binary target variable, logistic regressions were carried out.

The Kaplan-Meier method was used to calculate survival time and/or recurrence-free and metastases-free time. This also includes times of censored observations. Censored values are the times of patients who are living and/or who have not developed

Table 1. Risk stratification of GISTs according to the Fletcher risk assessment system [2]

Malignancy risk	Tumor size cm	Mitotic index/ 50 HPF
Very low risk	<2	<5
Low risk	2–5	<5
Intermediate risk	<5	6–10
	5–10	<5
High risk	5–10	>5
	unrelated	>10
	>10	unrelated

any recurrence or metastases (then survival time corresponds to the observation time). All values are presented as mean with range.

The period from operation to detection of the first tumor recurrence or metastases was defined as the recurrence-free interval. Patients who were free of recurrence or metastasis at the last follow-up examination and patients who died and whose death was not due to GIST were captured in the analysis by the parameter tumor-free survival time.

Patients without indications of a localized recurrent tumor or metastases were included in the analysis of recurrence-free survival; here patients with persisting disease were excluded.

Patients in the metastasized stage were considered separately. All statistical analyses were conducted using SAS 9.1 for Windows.

Results

Patient and Tumor Characteristics

The analysis included 100 patients (54 female and 46 male) with an age range between 39 and 92 years (median age 67.8 years).

The average follow-up observation time was 4.9 years (range 3.6 months to 10.1 years). Seventy-three patients (73%) had tumor-related symptoms. Twenty patients (21.5%) had other synchronous malignancies. These patients with second malignancies have been included in a previous review [3].

The most common tumor site was the stomach ($n = 67$), followed by the jejunum/ileum ($n = 20$), duodenum ($n = 10$), colon ($n = 2$) and ($n = 1$) rectum.

The average (statistical mean) tumor size was 1.2 cm (range 0.6–2.0 cm) for tumors in the very-low-risk group versus a mean size of 9.1 cm (range 3.0–23.0 cm) in the high-risk group. Based on the risk stratification according to the NIH consensus criteria [2] (table 1), tumors

Table 2. Clinical data and tumor characteristics of 100 GIST patients

Tumor size	Mitotic index pro 50 HPF	Risk group	n	R0	R1	R2	Recurrence/metastases after R0 resection
<2 cm	<5	very low	16	16	0	0	0 of 16
2–5 cm	<5	low	38	38	0	0	0 of 38
<5 cm	6–10	intermediate	18	18	0	0	2 of 18
5–10 cm	<5	high risk	21	20	1	0	7 of 20
5–10 cm	>5						
Unrelated	>10						
>10 cm	unrelated						
Metastasized			7	2	0	5	2 of 2

Table 3. Descriptive characteristics of the tumor size (cm) of R0-resected patients¹

	n	Mean	STDDEV	Min.	25% percentile	Median	75% percentile	Max.	p value*
Without recurrence/metastases	84	4.62	4.18	0.60	2.00	3.45	6.00	23.0	0.017
Recurrence or metastases	8	7.10	4.25	4.00	4.40	6.00	7.50	17.0	

* p value of Mann-Whitney U test on differences of medians of the two groups.

¹ Without the patients with metastasizing GIST.

were classified as very low risk (n = 16), low risk (n = 38), intermediate risk (n = 18) and high risk (n = 2) (table 2). All patients in the very-low-risk and low-risk groups had a mitotic index of <5/50 HPF (table 1). In contrast, a mitotic index >5/50 HPF was noted in 4 (22.2%) of the patients of the intermediate-risk group and in 19 (90.5%) of the patients in the high-risk group.

Survival and Prognostic Factors

The tumor status at the time of therapy is represented with reference to the risk profile in table 2. The average follow-up was 4.9 years (range 3.6 months to 10.1 years). No recurrence was observed in any of the cases from the very-low-risk, low-risk and intermediate-risk groups following R0 resection. In the group with high-risk tumors (n = 21), there were 2 recurrences (9.5%) after R0 resection.

The average tumor size in cases with recurrent/metastatic disease after R0 resection was 7.0 cm (range 4.0–17.0 cm) and thus significantly larger compared to a mean size of 4.6 cm (range 4.18–23 cm) for those who remained disease-free at last follow-up (p = 0.017; table 3). The average time to recurrence or metastases following R0 resec-

tion was 14 months in the intermediate-risk group and 23 months in the high-risk group.

Another significant difference could be found between the patient groups with and without recurrence/metastases: the patients with recurrence/metastases had a mitotic index greater than 5 (p = 0.0001, table 4).

Four of the 21 patients (19.1%) in the high-risk group and 5 of the 7 patients (71.4%) in the subgroup with metastasized tumors died due to the tumor.

Within the high-risk group, the patients who were alive and tumor-free at the time of follow-up (n = 9) were compared with the patients who were not tumor-free or who died due to the tumor (n = 7). Concerning age (p = 0.490), gender (p = 0.615) and average size (p = 0.458) of the tumors, there were no significant differences between the groups.

We also could not find a statistically significant difference in the behavior of small bowel GIST compared to GIST of the stomach in our evaluation.

Furthermore, R1/R2-resected patients had a significantly higher (p = 0.0001; table 5) tumor-related mortality rate than R0-resected patients.

Table 4. Relationship between recurrence/metastasis and mitotic index in the group of R0-resected patients¹

Group	Mitotic index				p value*
	≤5		>5		
	index	% ²	index	% ²	
Without recurrence/metastasis	69	98.6	1	1.4	0.0001
Recurrence or metastases	15	68.2	7	31.8	

* p value of the Fisher exact test.

¹ Without the patients with metastasizing GIST.

² The percentages refer to the percentage of patients with a mitotic index ≤5/>5 within the groups (line total = 100%).

Table 5. Correlation between status of resection and tumor-related death

Resection status	Survivor		Death unrelated to tumor		Death due to tumor		p
	n	%	n	%	n	%	
R0	67	71.3	21	22.3	6	6.4	0.0001
R1/R2	1	16.7			5	83.3	

The percentages refer to the fraction of survivor/unrelated to tumor death and death due to tumor within the subgroups (line total = 100%).

Discussion

The objective of this study was to evaluate the outcome of GIST patients based on resection extent, tumor size and mitotic index. This large single-center study comprised 100 consecutive patients who underwent surgery for a GIST in our clinic between 1997 and 2006. We included those patients in the total study cohort who were admitted to our clinic for a primary GIST resection. In 7 cases, the patients had already had a primary resection in other hospitals and were also receiving imatinib drug therapy before presenting in our clinic for resection of metastases or a recurrent tumor. We studied these patients separately and did not include them in the overall analysis.

Our results show that the GIST prognosis is decisively influenced by the radicality of surgical resection, tumor size and the mitotic index. The rate of achieved complete resections was 94% in our study, similar to those of 86 and 90% in the studies of DeMatteo et al. [4] and Langer et al. [5], respectively. The R0 resection rates described in the reference literature varied between 50 and 90% [4, 6, 7].

This range of fluctuation of the R0 resection rate is due to the tumor characteristics of the studied patients. The rate of 94% in our study surely refers to the predominant fraction of patients committed to our institute with primary resectable tumors. In our patient groups, the R1/R2-resected patients had a significantly higher tumor-related mortality rate than the R0-resected patients (fig. 1).

These results agree with other studies showing better overall survival in the group of patients with a complete tumor removal compared to those who did not undergo a radical operation [8–10].

Beside the extent of surgical resection, the pathologic features tumor size and mitotic index are additional decisive predictors of outcome [4, 11]. In the subgroup of patients (n = 21) with tumors smaller than 2.5 cm, there was no case of tumor-related death, and the probability of a tumor-associated death increased with the growing size of the tumor (fig. 2).

We were able to show significant differences as to tumor size and mitotic index between the patient groups with and without recurrences/metastases. The patients

Fig. 1. Status of patients according to resection extent. * Without patients who died not tumor-associated or with metastasizing GIST [the group of patients (n = 21) with tumors <2.5 cm is not included in the table, in this group there was no tumor-related death].

with recurrences/metastases presented a significantly higher incidence of a mitotic index greater than 5 and, on average, their tumors were larger.

These findings are consistent with the results of other studies, which identify tumor size and mitotic index as the two most reliable prognostic factors of outcome for GISTs [8, 12–14].

In our study groups, none of the patients with very-low, low- and intermediate-risk tumors developed tumor relapse after R0 resection, but metastases appeared in 2 (11%) patients from the intermediate-risk group in the further course of the disease.

Thus, tumor size and low mitotic index cannot be equated in principle with a benign behavior of the tumor and correspondingly good prognosis [8, 14–17].

Despite complete resection, 7 (33.3%) of 21 patients from the high-risk group relapsed or developed metastases in the further course of the disease, and no patient from the subgroup of patients with metastasized tumor was cured.

Fig. 2. Kaplan-Meier survival estimation related to tumor size.

In the studies of De Matteo et al. [4], Mudan et al. [16] and Samiian et al. [18], comparable recurrence rates of 40–70% in the high-risk group were described. These high incidences of recurrent and metastatic disease after complete surgical resection is the rationale for using imatinib in the adjuvant setting [19, 20].

The analysis of recurrence-free survival shows that it is difficult to unambiguously define the subgroup that should be administered an adjuvant therapy following complete resection of a high-risk GIST. To select those patients who may benefit most from the adjuvant therapy is still a challenge [21].

Worldwide, several studies concerning these issues are ongoing at the present time to assess imatinib therapy in a neoadjuvant and adjuvant intent. It will certainly take a number of years before definite results can be expected [22–25]. As Joensuu et al. [9] report, most recurrences and metastases appear in the first 5 years after the primary operation. This corresponds to the observations made in our patient cohort, where 2.8 years was the longest period

it took for metastases to appear after the primary operation.

Most of the recurrences or metastases following R0 resection of a high-risk GIST appeared within 3 years following the primary operation. In other studies, disease recurrence or metastases were diagnosed within the first 2 years after initially complete surgical resection [16, 18]. This discrepancy is possibly due to the nonstandardized and inconsistent postoperative follow-up of the patients.

As in the studies of other research groups [8, 11, 14, 26], the tumor recurrence and metastases occurred intra-abdominally in all cases. Metastases outside of the abdomen, in particular bone and pulmonary metastases, are rare.

The average follow-up observation period in our study was 4.9 years. During this period we found no metastases or recurrences in patients in either of the two low-risk groups.

Accordingly, a standardized structured follow-up care in compliance with the recommendations of ESMO [27] should be carried out to possibly increase the detection rate of a resectable recurrent tumor mass or metastases at an early stage, thus facilitating a potentially curative surgical therapy.

Mudan et al. [16] report on single cases of late recurrences in the low-risk groups for up to 10 years after the primary operation.

The appearance of tumor relapse and metastases after R0 resection of GISTs [16] in these subgroups reveals a certain malignant tendency of all GISTs and, as a further consequence, demands the collection of data and structured long-term follow-up care of GIST patients regardless of their risk stratification.

Whether these individual observations justify lifelong follow-up examinations in all subgroups must still be determined within the framework of long-term studies of larger groups.

According to the latest data, the 3-year survival rate of patients with metastasized GIST under imatinib therapy was approximately 68% [28]. In the pre-imatinib era, the

average length of survival for these patients was between 6 and 18 months [4].

Given that imatinib is a more oncostatic than cytotoxic drug [29] and that patients with progressive or metastasized tumor [30–32] can develop imatinib resistances [33], surgical resection should be considered upon development of a metabolically active, resectable recurrent tumor or metastases, regardless of whether symptoms are present or not.

Andtbacka et al. [34] were able to show improvement in overall survival after surgical R0 resection of recurrent tumors or metastases under imatinib therapy, and Aparicio et al. [35] were able to achieve an R0 resection in 40% of the recurrences and metastases in their patient cohort, which was associated with a better outcome.

New mutations, despite otherwise good response to imatinib, can lead to isolated progressive metastases or tumor cells. Here the indication for surgical resection can be justified in individual cases [34, 36, 37].

Conclusion

Complete surgical removal remains the only possibility of treating gastrointestinal tumors in a curative intent. Nevertheless, in the group of high-risk GIST, we encounter a large number of patients with tumor relapse or metastases despite complete surgical resection of the primary tumor. Beside the already existing prognostic markers, the molecular pathological tumor characterization could in the future contribute decisively to an optimized patient selection by generating exact prognostic variables for the tumor risk profile. With these predictors and correspondingly adapted adjuvant and neoadjuvant drug-therapy concepts, a clear increase in the curative rate and prolongation of survival are to be expected. As long as recurrences appear in all subgroups, structured follow-up examination of all GIST patients is called for regardless of risk category.

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