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Microscopically Positive Margins for Primary Gastrointestinal Stromal Tumors: Analysis of Risk Factors and Tumor Recurrence

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Abstract

BACKGROUND—Little is known about the outcome of patients with microscopically positive (R1) resections for primary gastro-intestinal stromal tumors (GISTs), because existing retrospective series are comprised of small numbers of patients. The objective of this study was to analyze factors associated with R1 resection and assess the risk of recurrence with and without imatinib.

STUDY DESIGN—Operative and pathology reports for 819 patients undergoing resection of primary GIST from North American ACOSOG Z9000 and Z9001 clinical trials at 230 institutions

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testing adjuvant imatinib after resection of primary GIST were reviewed. Patient, tumor, operative characteristics, factors associated with R1 resections, and disease status were analyzed.

RESULTS—Seventy two (8.8%) patients had an R1 resection and were followed for a median of 49 months. Factors associated with R1 resection included tumor size (≥ 10 cm), location (rectum) and tumor rupture. The risk of disease recurrence in R1 patients was driven largely by the presence of tumor rupture. There was no significant difference in recurrence free survival for patients undergoing an R1 vs. R0 resection of GIST with (HR=1.095, 95% CI: 0.66, 1.82, $p=0.73$) or without (HR=1.51, 95% CI: 0.76, 2.99, $p=0.24$) adjuvant imatinib.

CONCLUSIONS—Approximately 9% of 819 GIST patients had an R1 resection. Significant factors associated with R1 resection include tumor size ≥ 10 cm, location and rupture. The difference in recurrence free survival with or without imatinib therapy in those undergoing an R1 vs. R0 resection was not statistically significant at a median follow-up of 4 years.

INTRODUCTION

Achieving a histologically margin negative resection (R0) is a fundamental goal of oncologic resections done for curative intent. In theory, such a resection should be associated with lower rates of local and systemic recurrence and better overall outcome compared to patients left with microscopic or gross residual disease. While margin status is not part of the most common tumor staging system (AJCC 7th ed.) for GIST, it has been found to be an important prognostic marker in many tumors including breast¹, gastric², rectal³ and soft tissue sarcoma⁴.

In treating soft tissue sarcomas, an R0 resection is considered the standard recommendation yet the influence of an R1 (grossly negative but microscopically positive) resection on overall survival is variable. For extremity soft tissue sarcomas, some investigators have found that a positive microscopic margin is associated with both increased local recurrence and sarcoma related death,⁴ while others have found that an inadequate margin predicts recurrence risk but a local recurrence is not necessarily prognostic for risk of metastasis or survival.⁵ In a series of over two thousand patients with extremity and retroperitoneal sarcomas, resection margin was significantly associated with distant recurrence-free survival and disease-specific survival with overall 5-year disease-specific survival rates for negative and positive margins being 83% and 75%, respectively.⁶ Yet, these same authors also found that a positive microscopic margin for retroperitoneal sarcomas was not necessarily associated with local recurrence. This conundrum is undoubtedly related to multiple confounders such as indication for an operation, completeness of resection, histologic type and grade, use of adjuvant therapy, etc. present in such retrospective studies.

The ultimate significance of an R1 resection for GIST is controversial as some investigators have found it to be a significant prognostic indicator of overall outcome^{7,8,9} while others have failed to find any significance in terms of recurrence free or overall survival.^{10,11,12} Relatively little is known about the fate of patients with R1 resections because existing series are generally comprised of retrospective institutional analysis from relatively small numbers of patients with wide ranging tumor heterogeneity. We sought to utilize the experience from large prospective randomized trials in patients undergoing a resection of a primary GIST to better assess the effect of an R1 resection in a single tumor type. The aim of this study was to analyze variables associated with an R1 resection and assess the impact of an R1 resection on recurrence free survival with and without adjuvant imatinib therapy.

METHODS

The dataset from 819 patients undergoing resection of primary GIST from the American College Of Surgeons Oncology Group (ACOSOG) Z9000 and Z9001 clinical trials was analyzed for R0 versus R1 resections. These prospective clinical trials assessed the efficacy of adjuvant imatinib (Gleevec, Novartis) following complete gross resection (R0 or R1) of primary GIST. Resections with gross residual disease (R2) were excluded. ACOSOG Z9000 is a phase II trial for patients with resected high risk GIST all of whom were treated with imatinib for 12 months then followed for recurrence. ACOSOG Z9001 is a prospective double blinded phase III trial for patients with resected GIST ≤ 3 cm in size. Details about the trials have been published previously and are available at clinicaltrials.gov.¹³ All tumors underwent independent centralized pathologic review to ensure the diagnosis of GIST and KIT (CD117) staining. The designation of R0 versus R1 resection was made at the time of central pathologic review based on the original pathology report and slides submitted for analysis. Patient (age, gender, height, weight, performance status) and tumor (location, size, resection margin, mitotic rate) variables were collected prospectively. In addition, all operative and pathology reports were subsequently reviewed to collect additional data not originally captured in the primary dataset. Every effort was made to try and identify additional information regarding variables such as the indication for operation, presenting symptoms, pre-operative evaluation, and intra-operative variables such as emergent operations, blood loss, other organs removed, or tumor rupture. The tumor site was designated by the local principal investigator. Those sites listed as other included undesigned (n=12), colon (n=8), retroperitoneum (n=4), or some region of the abdomen (n=6). The site of first documented recurrence was recorded as local or distant by the local principal investigator. The free text sites of disease recorded were analyzed and when available were subsequently scored as local if the site of recurrence was listed as the same site as the primary, regional if the recurrence was anywhere in the abdomen (including peritoneum and lymph nodes but excluding liver), or distant if it recurred in the liver, lung or other remote sites. When more than one site was recorded at the time of first recurrence, the higher score (distant or regional) was used for analysis. Univariable and multivariable logistic regression analyses were used to assess factors associated with an R1 resection. Kaplan-Meier survival estimates used to assess recurrence free survival. The study was approved by the institutional review board of each participating institution, and written informed consent was obtained from all patients.

RESULTS

Data from a total of 819 patients (106 from ACOSOG Z9000 and 713 from ACOSOG Z9001) were available for analysis. The general patient demographics for the combined trials are shown in Table 1. Seventy two patients (8.8%) had a pathologically documented R1 resection. Tumor pathologic characteristics for the combined groups are shown in Table 2. Factors associated with an R1 resection by univariable analysis included tumor size (≥ 10 cm), location, and intraperitoneal tumor rupture or bleed. A higher incidence of R1 resection was recorded in the rectum (40%, 4/10) and in sites other than the stomach, small intestine, or rectum (17%, 5/30 with 2 from the abdomen, 1 retroperitoneal, 1 colon and 1 other). Age, gender, BMI, mitotic rate, operative status, removal of additional other organs and blood loss were not statistically associated with an R1 resection (Table 3). There appeared to be a slightly higher, but not statistically significant, increase in the incidence of R1 resections in patients undergoing an emergent operation, however the true urgency of the operation was difficult to determine or unknown in a significant number of patients. Of the 72 patients in the R1 group, 21 (27%) had a documented intraperitoneal tumor rupture or bleed.

The median follow-up time for the combined group was 49 months and the primary endpoint of the Z9001 study is recurrence free survival. Recurrence free survival data was available for all 819 patients. For patients in the Z9001 placebo group (Figure 1A), the difference in recurrence free survival for patients undergoing an R1 (n=23) versus an R0 (n=330) resection was not statistically significant (60% versus 76% at 3 years, HR=1.51, 95% CI: 0.76, 2.99, p=0.24). Similarly, for the Z9000 and Z9001 patients assigned to receive one year of imatinib (Figure 1B), the difference in recurrence free survival (RFS) for patients undergoing an R1 (n=49) versus an R0 (n=415) resection of GIST was not statistically significant (82% versus 79% at 3 years, HR=1.095, 95% CI: 0.66, 1.82, p=0.73).

The risk of recurrence based on resection margin status and treatment group is shown in Table 4. The overall risk of recurrence for the entire group was 28% (36% for R1 and 27% for R0 resection). Within the placebo group, the overall risk of recurrence following an R1 versus R0 resection was 39% versus 27%. Within the imatinib treated group, the overall risk of recurrence following an R1 versus R0 resection was 35% versus 27%. Regarding risk for recurrence, a test for interaction in a Cox model between the factors of surgical margin and treatment found no significant difference (p=0.64). The site of first documented recurrence is shown in Table 5. There are a relatively small number of documented local recurrences but the data indicates that an R1 resection is associated with a higher rate of local recurrence as the first site (Chi sq. 6.4, p=0.04).

The risk of recurrence within the R1 group appears to be driven largely by the presence of tumor rupture or intra-peritoneal bleeding. The 3 year RFS for the 21 R1 patients with tumor rupture is 60% versus 80% in the 51 patients R1 patients without rupture (HR 3.58, 95% CI: 1.65, 7.79, p=0.001). Excluding all patients with documented tumor rupture results in a 3 year RFS of 79% for R1 versus 80% for R0 patients (HR 0.84, 95% CI: 0.47, 1.52, p=0.57).

DISCUSSION

It is commonly held assumption that a margin negative resection is the primary goal of cancer surgery performed with curative intent. While the logic underlying this statement seems intuitive, there is an inherent lack of prospective randomized data lending support to this assumption. None-the-less, it is clear from multiple large retrospective series in sarcoma patients that leaving gross tumor behind (R2) following an attempted resection is universally associated with significantly worse outcomes compared to patients undergoing a complete gross resection (R0) or even a microscopically positive resection margin (R1).^{11,12,14}

Achieving, documenting and confirming an R0 resection for sarcomas involving the retroperitoneum and abdominal viscera is a challenge. First, the size and location of these tumors abutting significant vascular, nerve, bone and other structures often limit the extent of resection that is feasible. While some adjacent organs such as portions of small or large intestine, liver or kidney may be routinely removed en -bloc with the tumor to ensure a negative margin in some areas, other structures such as the aorta, vertebral column or major nerve roots are generally preserved accepting a close or microscopically positive margin. Second, the perpetual motion of the abdominal viscera virtually ensures at least ephemeral contact with tumors that reside within the abdominal cavity such that microscopic cells may be left behind on other surfaces not immediately apparent at the time of resection. In addition, microscopic cells may potentially be shed at any time during tumor development or during surgical manipulation of the tumor and surrounding structures at the time of resection. Third, assessment of a positive margin based on a tissue section placed on a pathology slide is subject to numerous specimen processing variables such as tissue contraction following resection and fixation that are difficult to quantify and control. Although there was a central pathologic review for this study, one significant limitation of

the findings is the lack of standard specimen processing and the inherent differences encountered in specimen orientation, marking, and number of slides submitted for margin assessment which was determined by each of the individual institutional standards. Fourth, many historic retrospective series are confounded by the lack of standard pathologic and surgical definitions for microscopic versus macroscopically positive margins.^{12,15} Despite some of these noted challenges in assessing the status of the resection margin, the R1 resection rate in this prospective study (8.8%) is within the range (5–27%) of that reported in previous retrospective GIST studies (5–27%).^{7,9,10,11,16,17,18} An inclusion criterion for the present study was complete gross resection of the tumor as noted by the surgeon and confirmed by lack of any demonstrable tumor on post-operative cross-sectional imaging. This would suggest that the microscopically positive margin rate reported here is comparable with the previously reported studies. Therefore this report provides an opportunity to verify some of the historic observations by analyzing and following patients closely for recurrence as part of a prospective study.

Previous reports from large sarcoma databases have provided somewhat mixed messages as to the ultimate importance of a microscopically positive margin. On the one hand across all sarcoma subtypes and locations, Stojadinovic et.al. found that microscopic resection margin was significantly associated with distant recurrence free survival and with 5 year disease specific survival of 83% versus 75% for a positive margin.⁶ Likewise, Pisters et.al. concluded that a microscopically positive margin for extremity sarcomas was associated with a similarly inferior disease specific survival of 78% versus 69% at 5 years.⁴

While those conclusions from large databases of over one thousand sarcoma patients appear robust, these findings should be interpreted in light of the challenges associated with confirming margin status and natural biologic variability. This is highlighted by the finding that across all classes and locations of sarcoma, a positive microscopic margin does not always equate with inevitable local recurrence as 72% of patients with a positive margin do not experience a recurrence.⁶ Likewise in the current study, at a median of 49 months follow-up, 64% of patients with an R1 resection (versus 73% for R0 resection) did not experience a recurrence. Even without adjuvant imatinib therapy, 61% of patients in the placebo group with an R1 resection did not experience a recurrence.

As with other types of sarcoma, previous authors have reported their experience with microscopically positive resection margins for GIST and the results are also mixed. Langer and Unlap in their separate reviews found that a positive margin status, including microscopic and macroscopically positive margins, significantly worsens overall survival.^{7,19} On the other hand, Trovik and Keun found that margin status was not an important predictor of overall recurrence and survival for GIST.^{5,20} In a report from the era just prior to imatinib being available, DeMatteo noted that a microscopically positive margin had no influence on disease specific survival.¹¹ While these studies in GIST patients may have relatively few patients compared to the larger sarcoma series, the mixed findings do suggest some overlap in biologic behavior. In fact, it has been hypothesized that microscopically positive margins tend to occur in high risk GIST, in larger tumors that shed cells directly into the peritoneum, in tumors that rupture, or in tumors that exhibit biologic factors that outweigh the margin status when it comes to survival.^{11,21}

The risk factors associated with an R1 resection are similar in many ways to the general risk factors associated with overall risk of recurrence. In this study, the three factors associated with the risk of an R1 resection are related to size, location and rupture. Each of these factors present technical challenges in obtaining a margin negative resection.

Management of the patient with a positive microscopic margin presents additional challenges. Although the data presented here showed no statistically significant difference in recurrence free survival, there is a trend towards a higher recurrence rate in patients recorded with an R1 resection. Furthermore, the recurrence free survival curves for those few R1 patients randomized to imatinib approximates the recurrence free survival curves for patients having an R0 resection. Longer follow-up may provide additional information though it will undoubtedly be confounded by treatment with imatinib or other kinase inhibitors in those who do recur. Whether a microscopically positive margin remains primarily a technical versus biological problem cannot be determined from this study. Therefore the decision making process should involve a multidisciplinary care team to carefully consider the important pathologic, surgical and biologic factors for each individual patient. The most recent NCCN GIST task force suggested that surgical re-excision should be considered for patients in whom the margin in question can be clearly identified and resected without significant morbidity. For others, the decision to observe versus initiate adjuvant imatinib should be based on an assessment of the overall risk of recurrence.²² The data from this study calls into question the utility of re-resection as, in the absence of tumor rupture, an R1 resection (without tumor rupture) based on pathology review is associated with a similar 3 year RFS to patients with an R0 resection.

In conclusion, the significant risk factors associated with a positive microscopic margin include tumor size greater than 10 cm, primary location other than stomach and small intestine, and tumor rupture or bleed. In the 9% of patients with a microscopically positive margin there was no statistically significant difference in recurrence free survival with or without imatinib therapy compared to those undergoing an R0 resection. In the absence of tumor rupture, the majority of patients with an R1 resection do not experience a recurrence. For those patients with a positive microscopic margin, the risks of re-operation or imatinib therapy need to be carefully weighed against the overall risk of the tumor's biologic behavior.

ABBREVIATIONS

GIST	gastrointestinal stromal tumor
R0 resection	a grossly and histologically negative margin
R1 resection	a grossly negative but histologically positive margin
R2 resection	a grossly positive margin
ACOSOG	American College Of Surgeons Oncology Group
BMI	Body Mass Index
HR	Hazard Rate
CI	Confidence Interval
AJCC	American Joint Commission on Cancer
RFS	Disease Free Survival

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1A

1B

Figure 1.

(A) Recurrence-free survival by margin status for patients in the placebo arm (n=330 for R0 and 23 for R1). HR=1.5 (95% CI: 0.76, 2.99) p=0.24. (B) Recurrence-free survival by margin status for patients in the imatinib arm (n=415 for R0 and 49 for R1). HR=1.1 (95% CI: 0.66, 1.83) p=0.73.

Table 1

Patient Demographics

Variable		
Age, y		
	Median	58
	Min	18
	Max	91
Age, n (%)		
	<65	551 (67)
	65	268 (33)
Sex, n (%)		
	Male	421 (51)
	Female	398 (49)
Weight, kg		
	Median	77.3
	Min	37.3
	Max	219.2
BMI		
	Median	26.7
	Min	15.3
	Max	64.3
Performance status, n (%)		
	0	621 (76)
	1	186 (23)
	2	12 (1)

Table 2

Tumor Pathologic Characteristics

Variable		n	%
Location *			
	Stomach	444	54.2
	Small intestine	227	27.7
	Colorectal	10	1.2
	Other	30	3.7
	Unknown	108	13.2
Tumor size, cm *			
	3 and <6	292	35.7
	6 and <10	242	29.6
	10	179	21.9
	Unknown	106	12.9
Mitotic rate *			
	<5/HPF	390	47.6
	5/HPF	230	28.1
	Unknown	199	24.3
Tumor margin at pathology			
	R0	745	91.0
	R1	72	8.8
	Unknown	2	0.2

* Data for Z9001 alone.

Table 3

Factors Associated with R1 Resection

Factor	Resection Margin		RR (CI)	p Value
	R0, n (%)	R1, n (%)		
Age, y				0.233
<65	497 (90.4)	53 (9.6)	1.35 (0.82 – 2.24)	
65	248 (92.9)	19 (7.1)		
Tumor size, cm				0.048*
3 and <6	273 (93.8)	18 (6.2)	---	
6 and <10	225 (93.0)	17 (7.0)	0.88 (0.46 – 1.67)	
10	157 (87.7)	22 (12.3)	0.50 (0.28 – 0.91)	
BMI				0.82
<26.7	368 (91.3)	35 (8.7)	0.95 (0.61 – 1.48)	
26.7	368 (90.9)	37 (9.1)		
Tumor location				0.004*
Stomach	412 (93.0)	31 (7.0)	---	
Small Intestine	210 (92.5)	17 (7.5)	0.93 (0.53 – 1.65)	
Rectum	6 (60.0)	4 (40.0)	0.17 (0.08 – 0.40)	
Other	25 (83.3)	5 (16.7)	0.42 (0.18 – 1.00)	
Mitoses				0.20
<5	360 (92.5)	29 (7.5)	0.71 (0.43 – 1.20)	
5	206 (89.6)	24 (10.4)		
Operative status				0.22
Elective	298 (92.8)	23 (7.2)	---	
Urgent	49 (94.2)	3 (5.8)	1.34 (0.39 – 3.99)	
Emergent	148 (87.6)	21 (12.4)	0.58 (0.33 – 1.01)	
Unknown	245 (90.7)	25 (9.3)	0.77 (0.45 – 1.33)	
Other organs removed				0.25
Yes	199 (89.2)	24 (10.8)	0.76 (0.48 – 1.21)	
No	540 (91.8)	48 (8.2)		
Estimated blood loss				0.90

Factor	Resection Margin		RR (CI)	p Value
	R0, n (%)	R1, n (%)		
<100	211 (92.5)	17 (7.5)	1.04 (0.54 – 2.01)	0.0003 [*]
100	208 (92.9)	16 (7.1)		
Tumor rupture/bleed				
Yes	98 (82.4)	21 (17.6)		
No	634 (92.6)	51 (7.4)	0.42 (0.26 – 0.67)	

Values do not add up to 819 patients as some data missing for some variables.

* p Values significant by multivariable logistic regression analysis.

Table 4

Recurrent Disease by Resection Margin Status and Treatment Group

Group	%	Recurred, n (%)
Entire group (n=817)		230 (28)
R0 (n=745)	91	204 (27)
R1 (n=72)	9	26 (36)
Placebo (n=353)		99 (28)
R0 (n=330)	93	90 (27)
R1 (n=23)	7	9 (39)
Imatinib (n=464)		131 (28)
R0 (n=415)	89	114 (27)
R1 (n=49)	11	17 (35)

Table 5

Sites of First Recorded Recurrence by Margin Status

Recurrence	Resection Margin	
	R0, n (%)	R1, n (%)
Local	8 (4)	4 (16)
Regional	86 (48)	13 (52)
Distant	87 (48)	8 (32)

Chi Square 6.4, p=0.04.