

Analysis of Margin Classification Systems for Assessing the Risk of Local Recurrence After Soft Tissue Sarcoma Resection

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A B S T R A C T

Purpose

To compare the ability of margin classification systems to determine local recurrence (LR) risk after soft tissue sarcoma (STS) resection.

Methods

Two thousand two hundred seventeen patients with nonmetastatic extremity and truncal STS treated with surgical resection and multidisciplinary consideration of perioperative radiotherapy were retrospectively reviewed. Margins were coded by residual tumor (R) classification (in which microscopic tumor at inked margin defines R1), the R+1mm classification (in which microscopic tumor within 1 mm of ink defines R1), and the Toronto Margin Context Classification (TMCC; in which positive margins are separated into planned close but positive at critical structures, positive after whoops re-excision, and inadvertent positive margins). Multivariate competing risk regression models were created.

Results

By R classification, LR rates at 10-year follow-up were 8%, 21%, and 44% in R0, R1, and R2, respectively. R+1mm classification resulted in increased R1 margins (726 v 278, $P < .001$), but led to decreased LR for R1 margins without changing R0 LR; for R0, the 10-year LR rate was 8% (range, 7% to 10%); for R1, the 10-year LR rate was 12% (10% to 15%). The TMCC also showed various LR rates among its tiers ($P < .001$). LR rates for positive margins on critical structures were not different from R0 at 10 years (11% v 8%, $P = .18$), whereas inadvertent positive margins had high LR (5-year, 28% [95% CI, 19% to 37%]; 10-year, 35% [95% CI, 25% to 46%]; $P < .001$).

Conclusion

The R classification identified three distinct risk levels for LR in STS. An R+1mm classification reduced LR differences between R1 and R0, suggesting that a negative but < 1 -mm margin may be adequate with multidisciplinary treatment. The TMCC provides additional stratification of positive margins that may aid in surgical planning and patient education.

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INTRODUCTION

A positive surgical margin after resection of extremity soft tissue sarcoma (STS) is a well-established risk factor for local recurrence (LR).¹⁻³ When local control fails, subsequent treatments lead to additional morbidity and higher rates of amputation.^{4,5} Several large series, although not all, report that LR is also associated with decreased overall survival.⁵⁻⁷ Despite the importance of a negative surgical margin to maximize local control of STS, there is significant variability in how margins are reported.⁸

Various systems exist for the classification of surgical margins. Before modern multiplane

imaging and the widespread use of adjuvant radiation, a system by Enneking et al⁹ for describing STS resection margins described intralesional, marginal, wide, and radical margins, and noted improved local control through radical resections. Modern imaging and adjuvant radiotherapy facilitate successful functional limb salvage, often with margins that would be classified as marginal in the Enneking system.¹⁰⁻¹² Use of the American Joint Committee on Cancer (AJCC) residual tumor classification (R classification) is reported increasingly in sarcoma studies.⁸ The AJCC manual describes an R0 margin as free of malignancy, an R1 margin is defined as microscopic tumor cells present at the inked border of the

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specimen, and R2 refers to a grossly positive margin. Several studies of surgical margins in extremity STS have used this definition and found it prognostic for LR.^{3,13,14} Other authors have defined a surgical margin of < 1 mm from tumor as microscopically positive; this system has likewise been reported as prognostic for LR.^{4,15}

Separate from the distance-based R classification, two reports have determined that the context of a positive margin influences local control.^{13,16} With appropriate multidisciplinary discussion and adjuvant radiotherapy, planned close but ultimately positive margins around critical structures had LR rates similar to those when critical structures were resected.^{11,13,16} Unexpected positive margins after a tumor resection, referred to as inadvertent positive margins (IPMs), had the lowest rates of local control.¹⁷

Current guidelines recommend complete resection of STS with a negative surgical margin, without a specific recommendation for the width of that margin or a standard definition of a negative margin.¹⁸ Inconsistent reporting of outcomes impedes comparative research, particularly for rare diseases. An ideal margin classification system would be prognostic for LR and would be reproducible, to facilitate communication among clinicians and researchers. The question of which margin classification scheme best determines LR risk remains unanswered. Therefore, the purpose of this study was to compare three margin classification systems on the basis of their ability to discriminate the risk of LR among classification groups. The primary outcome was the cumulative probability of LR, with death as a competing risk.

METHODS

After research ethics board approval, we retrieved clinical and pathologic data from an institutional prospective STS database at a single tertiary center. Patients with STS treated surgically between 1989 and 2014 were eligible. Patients with dermatofibrosarcoma protuberans ($n = 35$), well-differentiated liposarcoma ($n = 109$), or metastatic disease at presentation ($n = 171$) were excluded. Patients with tumors located in the extremities, chest and abdominal wall, or paraspinal region were included; those with tumors in the abdominal cavity, retroperitoneum, or head and neck were excluded. The study group comprised 2,217 patients who were thus identified.

Margin status for each system was retrieved or determined from records. For the R classification, the margin was categorized either as grossly positive (R2), microscopically positive if tumor was at the inked surface (R1), or microscopically negative if there was no tumor at the inked surface (R0). For the R+1mm classification, the R2 category was unchanged; for specimens to be considered microscopically negative, there had to be at least 1 mm of normal tissue between the tumor and the inked border (R0), whereas specimens with tumor within 1 mm of the inked border were categorized as microscopically positive (R1). For the Toronto Margin Context Classification (TMCC), tumor resections were classified into four categories—negative margins (R0 according to the R classification); IPMs; planned close but with an ultimately positive microscopic margin along a critical structure; and positive margin after a tumor bed resection in patients treated initially with inadequate surgery elsewhere (the whoops procedure).^{13,16} IPMs were defined as an unexpected positive margin result during a primary resection, and the margin status was classified as planned close but ultimately positive only when it occurred along a major bone, blood vessel, or nerve as part of the planned multidisciplinary treatment.

Treatment decisions were reviewed and finalized at a weekly multidisciplinary sarcoma tumor board. Surgery alone was used when a wide

resection of at least 1 cm of circumferential normal tissue, or else intact fascia, could be obtained without removing critical structures. Otherwise, radiation therapy was used before or after surgery. Generally, critical neurovascular structures were not resected unless they were completely encased by tumor. Chemotherapy was administered in a minority of cases at the discretion of the multidisciplinary tumor board or as part of ongoing trials. Tumors were graded according to French Federation of Cancer Centers Sarcoma Group (FNCLCC)—criteria.

After surgery, follow-up for patients consisted of visits every 3 months for the first 2 years, every 6 months from year 2 to year 5, then annually until year 10. Surveillance consisted of chest imaging and examination of the wound and locoregional lymph nodes. Advanced imaging was not obtained routinely unless there was clinical concern for recurrence.

The primary end point of the analysis was LR. Analyses were completed with a competing risks framework. Death and metachronous distant metastases, whichever occurred first, were regarded as competing events. Crude cumulative incidence was estimated for LR. To obtain the estimated cumulative incidence of recurrence, we used a multivariate Fine and Gray model and calculated subdistribution hazard ratios (HRs) for the final predictor variables.¹⁹⁻²¹ This method accounts for the risk of metastasis or death when estimating the effects of covariates on LR, similar to a Cox proportional model for univariate analyses. Several predictor variables (patient age, tumor size, FNCLCC grade, tumor depth, and margin status with each system) were predefined and were applied in a backward procedure using the Akaike information criterion for variable selection. Statistical analyses were completed in R version 3.2.2, including the *cmprsk* package from the Comprehensive R Archive Network.²¹ This study was designed and reported using Strengthening the Reporting of Observation Studies in Epidemiology—criteria.²²

RESULTS

A total of 2,217 patients with STS who met the inclusion criteria were identified. Patient characteristics are listed in Table 1. The median age was 57 years (range, 13 to 97 years), and most tumors were high grade (54%) and deep (68%). Inadequate surgery before presentation occurred in 853 patients (38%). Use of radiotherapy was common (67%), with radiation administered preoperatively in 1,088 patients (49%), postoperatively in 330 patients (15%), and both before and after operative treatment in 74 patients (3%). Few patients received chemotherapy (18%). By the R classification, 1,908 tumors (86%) were resected with a microscopically negative margin. However, with the R+1mm system, the number of microscopically negative resections dropped to 1,459 (66%), with a corresponding increase in the number of microscopically positive resections (278 to 726, $P < .001$). Grossly positive margins were rare (26 for each system [1%]).

At a mean follow-up of 65 months (range, 0.3 to 309 months), the crude cumulative probability of LR at 5 years was 8% (95% CI, 7% to 9%) and the crude cumulative probability of LR at 10 years was 10% (95% CI, 9% to 12%). The three margin classification systems were all able to determine various levels of risk, as summarized in Table 2 ($P < .001$, Wald test). At 10 years, the probability of LR was 8% for R0, 21% for R1, and 44% for R2 resections using the R classification system. These values differed significantly from one another ($P < .001$). With the R+1mm classification, the probability of LR for R1 resections dropped to 12% without changing LR rates for those with the stricter definition of R0 (Table 2 and Fig 1). According to the TMCC, there were four distinct levels of risk on the basis of margin context. At 10 years the cumulative

Table 1. Clinicopathologic and Treatment Characteristics of Patients With Soft Tissue Sarcoma (N = 2,217)

Characteristic	No. (%)
Age, years	
Median	57
Range	13-97
Sex	
Female	979 (44)
Male	1,238 (56)
Tumor depth	
Deep	1,515 (68)
Superficial	697 (31)
Maximum tumor diameter, cm	
Median	6.7
Range	0.5-39.5
Surgical margins	
R classification	
R0	1,908 (86)
R1	278 (13)
R2	26 (1)
R+1mm classification	
R0	1,459 (66)
R1	726 (33)
R2	26 (1)
TMCC	
Negative	1,908 (86)
Planned close	103 (5)
Positive after whoops	116 (5)
IPM	90 (4)
FNCLCC grade	
1	282 (13)
2	709 (32)
3	1,193 (54)
Chemotherapy	
Administered	408 (18)
Not administered	1,804 (81)
Radiotherapy	
Administered	1,492 (67)
Not administered	706 (32)
Follow-up, months	
Mean	65
Range	0.3-309

NOTE. Data are presented as No. (%) unless indicated otherwise.
Abbreviations: FNCLCC, French Federation of Cancer Centers Sarcoma Group; IPM, inadvertent positive margin; TMCC, Toronto Margin Context Classification.

probably of LR was 8% for negative margins, 11% for planned close but ultimately positive margins at critical structures, 24% for positive margins after tumor bed re-excision after a whoops procedure, and 35% for IPMs ($P < .001$; Fig 2).

In Fine and Gray subdistribution hazards modeling, variables of age, sex, tumor location, and tumor size were eliminated, whereas grade, depth, and the use of radiotherapy were included with each margin system (Table 3). The effect of grade, depth, and use of radiotherapy was similar for each margin system's model and these effects are reported together. Grade 2 STS did not have a robust effect on LR ($P = .11$), but grade 3 tumors were more likely to recur ($P = .02$). Depth was also maintained as a predictor of LR (HR, 1.5; $P = .03$). The use of radiotherapy reduced the risk of LR by one half ($P < .001$).

With the R classification, both R1 (HR, 3.2) and R2 (HR, 7.6) were robustly significant hazards for LR. In the R+1mm classification, an R1 margin was less predictive of recurrence, with a hazard of 1.8 and a 95% CI ranging from 1 to 3.2 ($P < .001$).

In the 451 cases in which the margin changed from R0 to R1 in the R+1mm classification system, there was a cumulative LR probability of 6% (95% CI, 5% to 7%) at 5 years and 7% (95% CI, 6% to 8%) at 10 years. Grouped separately, these cases with < 1 mm of normal tissue from tumor on microscopic analysis had no significantly different risk of LR than did R0 cases (subdistribution hazard, 1.1 [95% CI, 0.9 to 1.3]; $P = .71$) and were significantly less likely than the remaining R1 cases to have LR (subdistribution hazard, 0.34 [95% CI, 0.1 to 0.58]; $P < .001$; Fig 3).

As in the cumulative probability plots, each margin context category in the TMCC was associated with particular hazards for LR. A planned close but ultimately positive margin at a critical structure did not significantly increase the risk of a LR when compared with a negative microscopic margin (subdistribution hazard, 1.6; $P = .18$). A positive margin after tumor bed re-excision after a whoops procedure raised the hazard for LR (HR, 3.9; $P < .001$), but the greatest hazard was associated with an IPM (HR, 5.7; $P < .001$).

Sensitivity analyses included testing with only those patients who received preoperative radiation. There were no substantial changes in the results.

DISCUSSION

In this study, we show that the R classification of surgical margins is able to identify three distinct levels of LR risk in patients after surgical treatment of STS. Patients with < 1 mm of normal tissue microscopically from margin to tumor did not have an elevated risk of LR. In addition, a margin context classification was able to determine low- and high-LR probability-positive margins in a competing risk analysis. If externally validated, more uniform collection and reporting of margins may aid in communication with patients as well as among clinicians and researchers.

Table 2. Cumulative Incidence of Soft Tissue Sarcoma Local Recurrence on the Basis of Margin System Categorizations

Characteristic	5-Year LR (%)	95% CI (%)	10-Year LR (%)	95% CI (%)	<i>P</i>
R classification					
R0	6	5 to 7	8	7 to 9	$< .001$
R1	17	12 to 21	21	16 to 26	
R2	38	20 to 57	44	23 to 64	
R+1mm classification					
R0	6	5 to 7	8	7 to 10	$< .001$
R1	10	8 to 13	12	10 to 15	
R2	38	20 to 57	44	23 to 64	
TMCC					
Negative	6	5 to 7	8	7 to 9	$< .001$
Planned close	10	5 to 17	11	6 to 19	
Positive after whoops	18	11 to 27	24	15 to 34	
IPM	28	19 to 37	35	25 to 46	

NOTE. Significant statistical comparisons within each classification system by Wald test are denoted by the *P* value.

Abbreviations: IPM, inadvertent positive margin; LR, local recurrence; TMCC, Toronto Margin Context Classification.

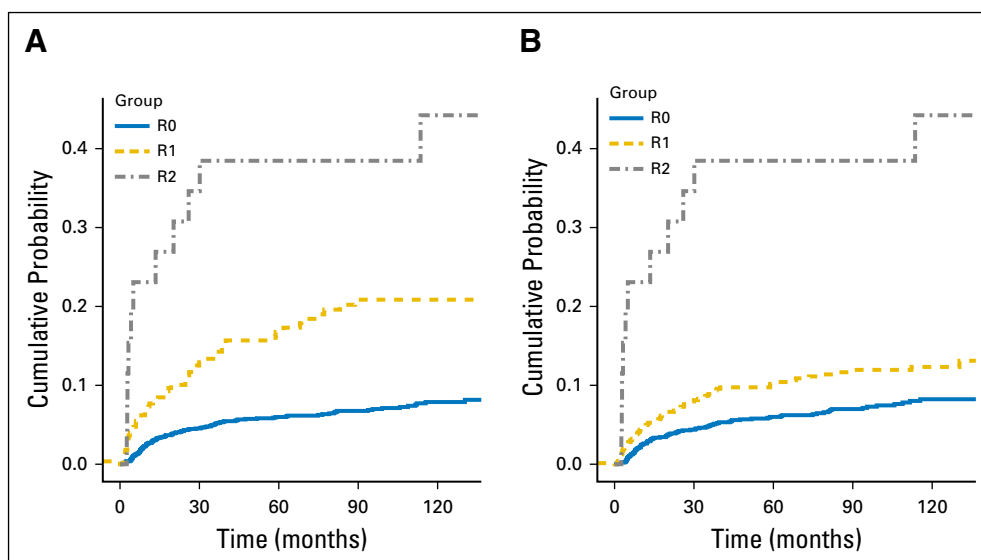


Fig 1. Cumulative probability of local recurrence by (A) R classification and (B) R+1mm classification.

Although the R classification designates a microscopically positive margin (R1) as the presence of tumor cells at the inked border, others have required 1 mm of normal tissue between tumor and margin to define a microscopically negative margin.^{4,13} This R+1mm classification is one of the varied, nonstandardized means of outcomes reporting in the sarcoma community.⁸ Requiring an additional 1 mm of normal tissue between the inked margin and the tumor results in more resections being considered microscopically positive. However, doing so did not lower the risk of LR among the remaining microscopically negative resections when compared with the standard R classification. Patients with a < 1-mm margin of normal tissue between the inked specimen and tumor have an LR rate lower than the R classification scheme's definition of R1 and similar to that of patients considered R0.

Finally, because the goal of margin classification is to help inform the risk of LR and perhaps guide surveillance, having three clear levels of risk within the R classification is more discriminative than the relatively similar cumulative incidence curves seen with the R+1mm classification (Fig 1). This contrasts with the results of Kainhofer et al,¹⁵ who in a study of 265 patients with STS and using a Kaplan-Meier analysis for LR, showed lower rates of LR by requiring an additional 1 mm of margin. This discrepancy may result from incorporating the competing risk of death³ in the current study, or other factors.

In a retrospective review of 111 patients after resection of STS, McKee et al²³ re-examined pathology slides and separated margin distance into microscopic positive, 1 to 9 mm, and > 10 mm. They demonstrated an overall 26% rate of LR; at 5 years, 84% (95% CI, 74% to 94%) of patients were free of LR with > 10-mm margins, compared with 58% with either 1- to 9-mm margins (95% CI, 40% to 74%) or a positive margin (95% CI, 30% to 86%). Although the authors concluded that a margin measuring < 10 mm was associated with an increased risk of LR, this may reflect the low rate of adjuvant radiotherapy of 38% (including 39% for patients with AJCC stage III STS) used in their sample, compared with 67% in this study. The importance of radiotherapy was clearly demonstrated in our study, with a HR of 0.5 for LR in those patients

receiving radiation. Biologically, this strong effect of radiotherapy may reflect the impact of sarcoma cells being found up to 4 cm away from the tumor mass in nonradiated specimens.²⁴

Measuring the closest distance from tumor to margin is at best an incomplete assessment of the three-dimensional boundary between tumor and normal or reactive tissue. This study also included a margin context classification system, which previously reported a prognostically significant difference in outcome and provides the rationale for close dissection to spare critical structures.^{13,16} In this competing risks model, with frequent perioperative radiotherapy, a planned close but ultimately positive margin along fixed critical structures such as bone or a major neurovascular bundle was not associated with an increased hazard for LR. In contrast, IPMs led to the highest risk of recurrence.¹⁷ Not all positive margins carry the same relative risk of LR. When

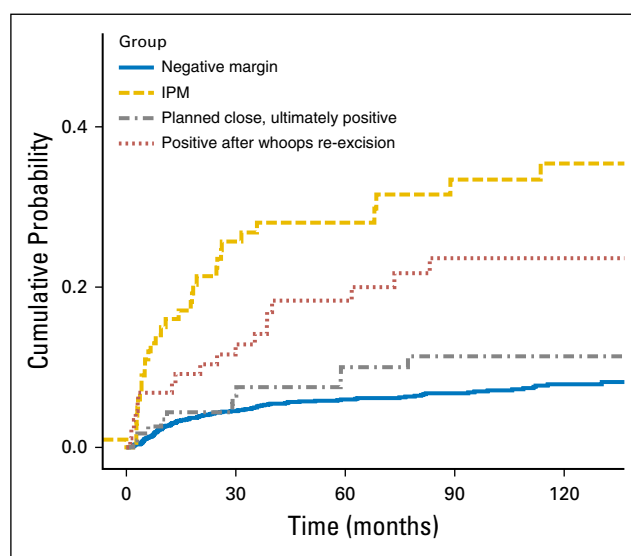


Fig 2. Cumulative probability of local recurrence by Toronto Margin Context Classification. IPM, inadvertent positive margin.

Table 3. Results of the Fine and Gray Subdistribution Hazards for Local Recurrence in Soft Tissue Sarcoma

Variable	HR	95% CI (%)	P
FNCLCC grade			
2 v 1	1.6	0.9 to 3	.110
3 v 1	2.0	1.1 to 3.6	.020
Depth			
Deep v superficial	1.5	1.1 to 2.2	.030
Radiotherapy			
Used v not used	0.5	0.3 to 0.6	< .001
R classification			
R1 v R0	3.2	2.3 to 4.6	< .001
R2 v R0	7.6	3.9 to 14.7	< .001
R+1mm classification			
R1 v R0	1.8	1 to 3.2	< .001
R2 v R0	7.6	3.9 to 14.9	< .001
TMCC			
Planned close v R0	1.6	0.8 to 2.9	.180
After whoops v R0	3.9	2.3 to 6.6	< .001
IPM v R0	5.7	3.7 to 8.6	< .001

NOTE. Significant statistical comparisons within each classification system are denoted by the P value.
Abbreviations: HR, hazard ratio; FNCLCC, French Federation of Cancer Centers Sarcoma Group; IPM, inadvertent positive margin; TMCC, Toronto Margin Context Classification.

the context of a positive margin is known, additional risk stratification is possible.

The R classification in either form does not take into account the tissue type in which a margin resides. The Japanese Orthopedic

Association published an alternative margin classification system, but it requires documentation of information that was not available for this study.^{2,25} It intuitively includes an assessment of the tissue context when calculating a margin's distance equivalent, to reflect the resistance to tumor spread through structures such as thick fascia and cartilage. Although rational and useful for operative planning, especially in practice settings keen to avoid the use of adjuvant radiotherapy,²⁶ this system is complex. Given the current lack of any consistent margin reporting system in more than one third of published sarcoma papers, a system that is simple and reproducible is more advisable.⁸

This study has a number of limitations. First, it is a retrospective analysis that is based on prospectively collected data from a single center, and its conclusions would be strengthened if validated by additional data samples. Second, margin determinations were recorded from pathology reports rather than readjudication, or prospective monitoring, and the possibility of tumor sampling error exists.²⁷ Local institutional practices regarding the use of neoadjuvant and adjuvant therapies and surgical techniques likely also influence outcomes, which limits the generalizability of these findings.

By direct comparison of three schemes for classifying the margin status in 2,217 patients with nonretroperitoneal STS at one center, we found that the R classification best determined the risk of LR via a competing risks framework. Defining an

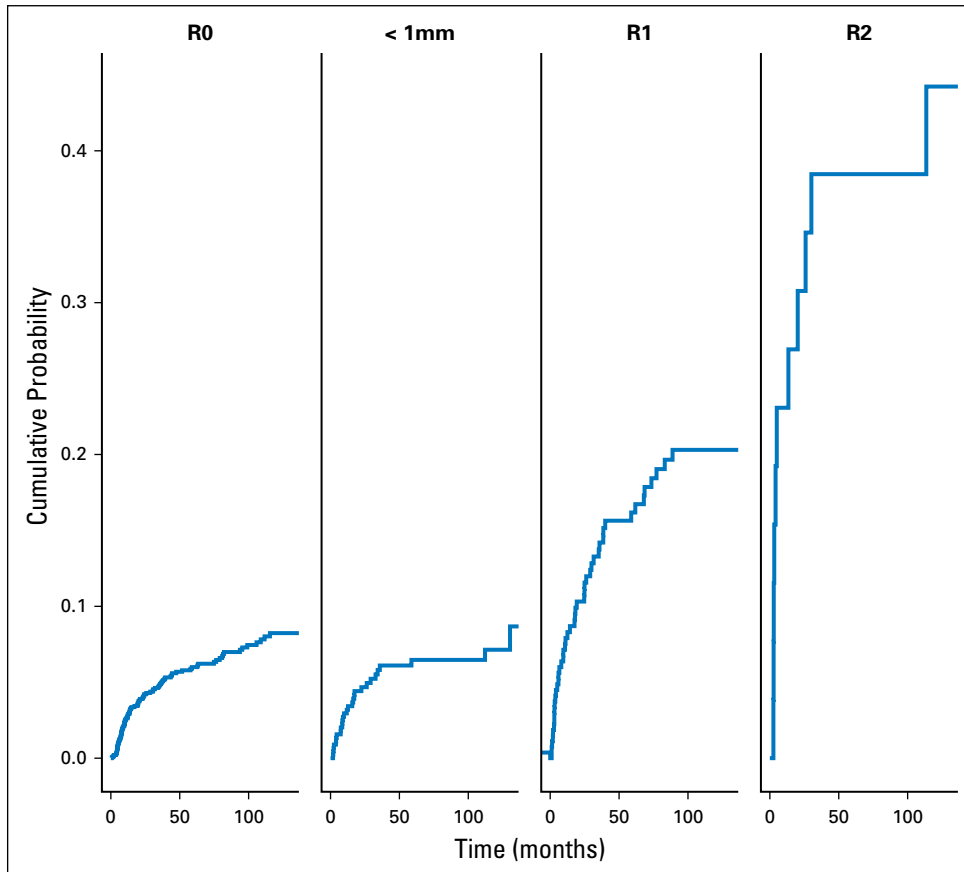


Fig 3. Cumulative probability of local recurrence by R classification, separating those with < 1-mm margins.

R1-positive microscopic margin as tumor at the inked border outperformed the concept of requiring at least 1 mm of normal tissue between the inked specimen and tumor. However, the margin context classification system (TMCC) further categorized high- and low-risk positive margins. More consistent margin status reporting could aid in collaboration, patient education, and directed surveillance.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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