


Impact of surgical margin on survival in extremity soft tissue sarcoma

A systematic review and meta-analysis

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Abstract

Background: The impact of surgical margin status on the survival of patients with extremity soft tissue sarcoma (STS) remains to be clearly defined. The evidence regarding the impact of surgical margins on survival is limited by retrospective single-institution cohort studies. We conducted a systematic review and meta-analysis to examine the impact of surgical margin status on patient survival in extremity STS.

Methods: A literature search in the PubMed, EMBASE, and Cochrane Controlled Trials Register electronic databases, and a manual search of reference lists of original studies was performed. The following text words and/or Medical Subject Heading terms were searched: (neoplasm) or/and (sarcoma) and/or (connective tissue) and/or (soft tissue) and/or (extremity) and/or (extremity) and/or (surgical margin).

Results: Six selected studies that reported a total of 2917 cases of extremity STS were published between 1994 and 2013. All the eligible studies were observational cohort studies, and the sample size ranged from 95 to 1261 patients. A meta-analysis of 6 studies showed that a positive surgical margin predicted poor 5-year OS in a random-effects model (summary hazard ratio, 1.56; 95% confidence interval, 1.12–2.17). Moderate heterogeneity was observed among the studies ($P < .075$; heterogeneity, 45.6%).

Conclusions: This meta-analysis supports the hypothesis that adequate surgical margins are associated with improved survival in extremity STS.

Abbreviations: CI = confidence interval, HR = hazard ratio, MeSH = Medical Subject Heading, NOS = Newcastle-Ottawa Scale, STS = soft tissue sarcoma.

Keywords: extremity soft tissue sarcoma, hazard ratio, surgical margin, survival

1. Introduction

Soft tissue sarcoma (STS) is relatively rare, but 50% to 70% of STS cases arise in the extremities.^[1] Limb-sparing surgery with adequate surgical margin combined with adjuvant radiotherapy or chemotherapy has replaced amputation as the principal treatment for extremity STS.^[2] Achieving adequate surgical

margins has been the holy grail of extremity STS surgery and a measure of successful surgery. Adequate surgical margins are generally regarded to translate directly into improved survival by reducing the rates of local recurrence and subsequent risk of metastases.^[3] However, attempts to achieve adequate surgical margins may result in increased morbidity and larger functional deficits. Moreover, in extremity STS, unlike most other cancers, by virtue of its location from vital structures, local recurrence per se does not directly influence survival.^[4]

The association of positive surgical margins with increased risk of local recurrence in extremity STS has been well documented.^[5] Meanwhile, the association between local recurrence and patient survival has also been reported; however, whether local recurrence is causally related to survival remains unclear.^[6] Moreover, whether surgical margins affect the survival of patients with extremity STS is unclear.

Evidence regarding the impact of surgical margins on survival is mostly provided by retrospective single-institution cohort studies. To provide a higher level of evidence on this critical issue, a prospective randomized study would be ideal. However, the rarity of extremity STS and the ethical issues regarding the exposure of patients to harmful risks make such studies in extremity STS unfeasible. Meta-analysis is a statistical method that combines the results of more than one study to find the average or common effect across studies.^[7] It can provide a higher level of evidence not only in randomized controlled trials, but also in observational studies.^[8] In this regard, we conducted a systematic review and meta-analysis of all available cohort

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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studies to provide the best available evidence regarding the impact of surgical margin on the survival of patients with extremity STS.

2. Methods

2.1. Search strategy

Institutional review board approval and patient consent were not required since this study was a meta-analysis. A literature search was conducted in the PubMed and MEDLINE (January 1950 to December 2019), EMBASE (January 1966 to December 2019), and Cochrane Library databases (January 1960 to December 2019). The reference lists of the original studies were searched independently by 2 authors (WYJ and IH). We searched for articles with the following text words and/or Medical Subject Heading (MeSH) terms: “neoplasm” or “sarcoma” or “connective tissue” or “soft tissue” and “extremity” and “margin.” The searched articles were restricted to English because of the lack of accessibility and comprehension. Two authors (WYJ and IH) independently screened the titles and abstracts of eligible citations and determined whether they met the inclusion criteria. The selected articles were evaluated independently, and disagreements were resolved in consensus.

2.2. Inclusion and exclusion criteria

Studies that met the inclusion criteria for the meta-analysis had the following characteristics:

1. detailed information on surgical margins,
2. >5 years of follow-up, and
3. calculation of hazard ratio (HR) with corresponding 95% confidence intervals (CIs) by multivariate analysis adjusting for confounding factors (age, sex, tumor grade, tumor size, presence of distant metastasis at diagnosis, and adjuvant therapy) for survival rate.

Studies were excluded if they reported

1. cases of STS in a truncal site and
2. no *P* values, although a multivariate analysis was performed.

2.3. Quality assessment

The quality of each study was assessed independently by 2 reviewers (WYJ and IH) using the Newcastle-Ottawa Scale (NOS).^[9] The NOS consists of 3 parameters: selection, comparability, and outcome. The NOS assigns a maximum of 4 points for selection, 2 points for comparability, and 3 points for exposure or outcome. Any discrepancies between the reviewers were addressed by a joint reevaluation of the original article.

2.4. Extraction of data

Two authors (WYJ and IH) independently extracted data from the selected studies, including the number of patients, sex, age, tumor grade, definition of surgical margin, administration of adjuvant therapy, and HR of a positive margin for 5-year survival. Consensus was reached for disagreements in assessments.

2.5. Outcome measures

Survival is a time-to-event outcome. Tierney et al^[10] advocated that time-to-event outcomes account for whether an event took

place and the time at which the event occurred, such that both the event and the timing of its occurrence are important. In the survival analysis, both overall and disease-specific survival was included. We considered the HR of each study as the effect size.

2.6. Statistical analyses

We used Higgins I^2 statistics to determine the percentage of the total variation across studies due to heterogeneity. The I^2 value ranges from 0% (no observed heterogeneity) to 100% (maximal heterogeneity). An I^2 value >50% may be considered to represent substantial heterogeneity.^[11] Pooled HRs were analyzed using an inverse variance weighting method, and either the random- or fixed-effect model was chosen according to heterogeneity. A forest plot was used to display the meta-analysis data. The point estimate for the HR was represented by a square, and the CI for each study was represented by a horizontal line. The size of the square corresponds to the weight of the study in the meta-analysis, with larger shapes assigned to studies with larger sample sizes or data of better quality. A sensitivity analysis was used to determine the influence of each individual study on the summary results by repeating the random-effects meta-analysis after omitting 1 study at a time. For identifying publication bias, the Begg funnel plot was used. All statistical analyses in this study were performed using R version 3.1.2 (meta for packages). A *P* value <.05 was considered statistically significant.

3. Results

3.1. Studies identified

The literature search in 3 electronic databases using the aforementioned search terms identified 564 studies. All the studies retrieved from the databases were independently evaluated. After reviewing the abstracts and/or titles, 25 potentially relevant articles were identified for further full-text examination. By searching the reference lists of the 25 relevant publications, an additional 4 reports were added for a total of 29 full-text examinations. Of these, 18 records did not have adequate data for meta-analysis and were excluded. Five records were removed because of potentially duplicate data from the same population, and from the same institute. In the case of duplicate data, the most recent publication that met the inclusion criteria was chosen. A total of 6 studies were included in the meta-analysis (Fig. 1).

3.2. Study characteristics and quality assessment

The selected studies were published between 1994 and 2013, with reports on a total of 2917 cases of extremity STS. All eligible studies were patient follow-up studies. The sample size ranged from 95 to 1261 patients. The mean age was 53 years, with 1612 male and 1305 female patients. Three of the 6 studies reported no significant association between surgical margin and patient survival, while the other 3 studies reported a significant association between surgical margin and patient survival. The definition of a positive surgical margin varied slightly among the studies. Tanabe et al,^[12] Weitz et al,^[1] Gronchi et al,^[13] and Potter et al^[14] defined the surgical margin as positive when microscopic evidence of tumor cells was found at the resection margin or within 1 mm. Lui et al^[15] classified the distance between the tumor and the resection margin into the categories 0–1, 2–4, 5–9, 10–19, 20–29, and >30 mm, and considered a

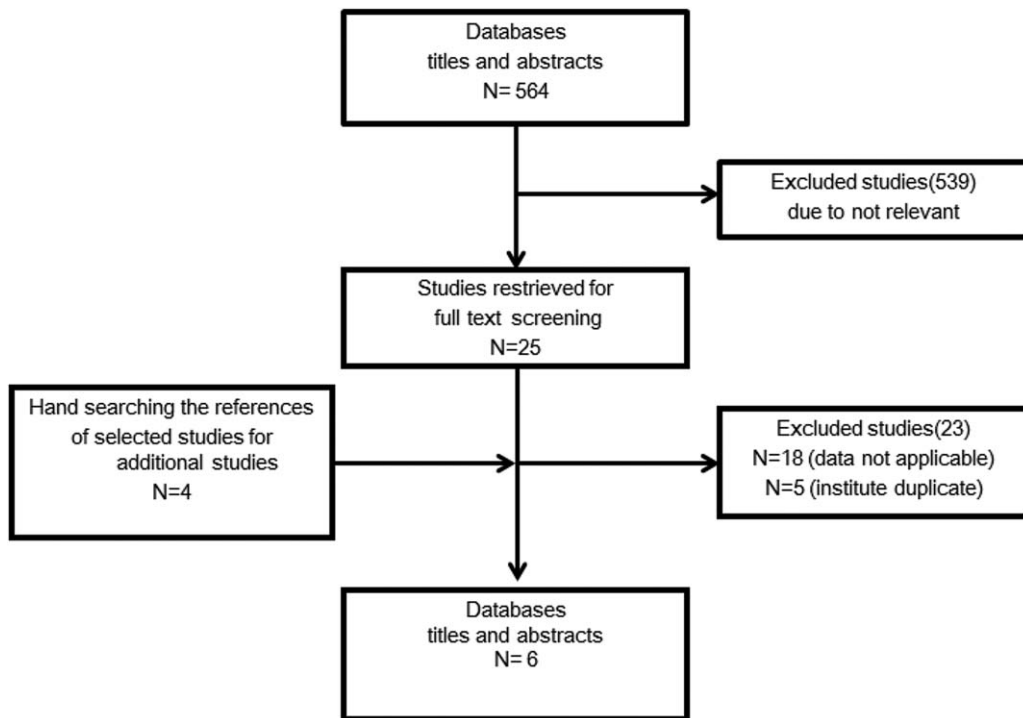


Figure 1. Flowchart of the selection of the studies included in the meta-analysis.

surgical margin positive when the distance from the margin was <10 mm. All six studies were conducted at a single institution and were of high quality (NOS score ≥7; Table 1).

3.3. Data synthesis and review

The meta-analysis of all the 6 studies revealed that a positive surgical margin predicted poor 5-year survival as compared with

a negative surgical margin in a random-effects model with moderate heterogeneity among studies (summary HR [sHR], 1.56; 95% CI, 1.12–2.17; test for heterogeneity: $P < .002$, $I^2 = 64.18\%$; Fig. 2). Owing to differences between the definitions of positive surgical margins by Lui et al^[15] and Popov et al,^[16] which might have caused the heterogeneity in the forest plot, a subgroup analysis without these studies was performed. The

Table 1 Characteristics of the 6 observational studies.

First author	Institute	Patient age (years)	Criterion of positive margin	Positive margin (n)	Negative margin (n)	Tumor grade	Tumor size (cm)	Median follow-up (years)	NOS*
Tanabe ^[12]	M.D. Anderson Cancer Center	≤51:46 >51:49	microscopically within	24	71	Low (n=0), Intermediate (n=46)	<10:43	5.5	7
Popov ^[16]	Helsinki University Central Hospital	≤50:45 >51:61	intralesional	44	62	High (n=54) Low (n=28)	>10:57 <10:65	4.6	7
Weitz ^[11]	Memorial Sloan-Kettering Cancer Center	53 (range: 16–95)	microscopically within	215	1046	High (n=77) Unclassified (n=1) Low (n=464)	>10:41 <10:133	4.6	7
Gronchi ^[13]	Istituto Nazionale	50 (range: 16–90)	<1 mm	163	748	High (n=797) Low (n=255) Intermediate (n=226)	>10:49 –	8.9	7
Liu ^[15]	Taiwan University	54 (range: 15–91)	<10 mm	70	111	High (n=430) Low (n=41) Intermediate (n=65)	<15:143 >15:38	3.6	7
Potter ^[14]	Walter Reed National Military Medical Center	46 (<50:200 ≥50:163)	<1 mm	123	240	High (n=75) Low (n=118) Intermediate (n=112) High (n=133)	<10:288 >10:75	6.8	7

* NOS = Newcastle-Ottawa Scale.

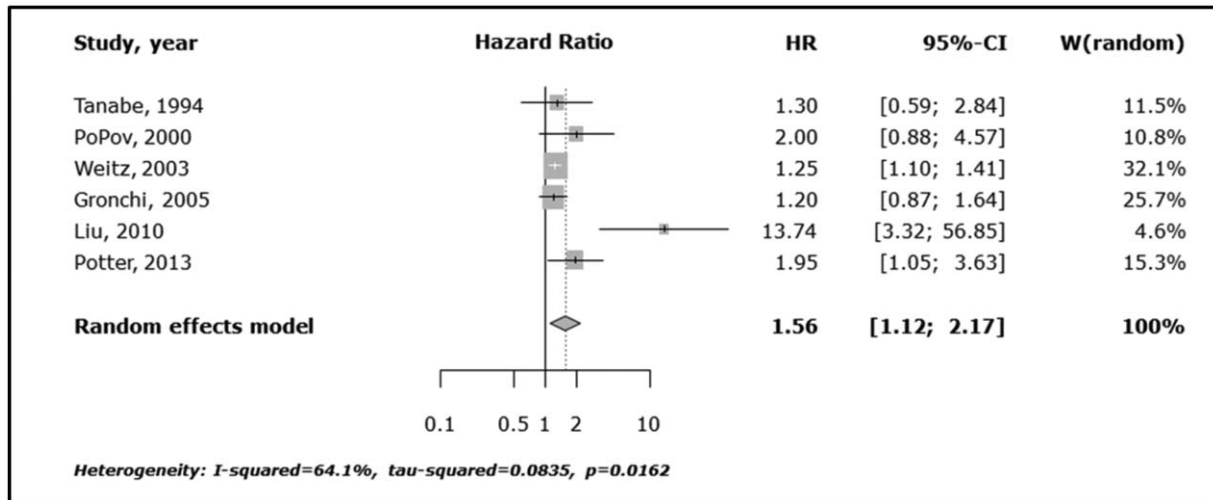


Figure 2. Forest plots of the hazard ratios of survival associated with positive surgical margin. W: weight.

subgroup analysis revealed that positive surgical margin predicted poor 5-year survival as compared with negative surgical margin in a fixed-effects model with low heterogeneity among studies (sHR, 1.26; 95% CI, 1.13–1.41; test for heterogeneity: $P < .56$, $I^2 = 0\%$; Fig. 3). Owing to differences in the definition of a positive surgical margin between the studies, a sensitivity analysis of the studies was performed, without a significant effect on the results of the meta-analysis (Fig. 4).

3.4. Publication bias

Funnel plots were used to estimate the publication bias of the included literature. No significant publication bias in 5-year OS was found ($P = .086$; Fig. 5).

4. Discussion

Surgical excision is the fundamental treatment of choice for extremity STS.^[17,18] Although the principle of surgical excision is to obtain a wide resection margin to prevent local recurrence, the size of the resection margin and whether a wide surgical margin with ensuing severe functional disability is warranted are

controversial. Reports on the impacts of surgical margins on patient survival are insufficient and conflicting. Extremity STS is a rare and heterogeneous tumor. Owing to the paucity of large-scale studies, evidence-based treatment decisions could not be made. For these reasons, we investigated the impacts of positive surgical margins on survival by a meta-analysis of observational cohort studies. Our results suggest that a positive surgical margin is associated with decreased survival.

Meta-analysis is a method of scientific and statistical integration of results from a series of individual studies to find the average or common effect, which can provide important insights for application to patient care.^[19,20] As systematic reviews and meta-analyses are affected by the quality of included articles, assessment of the quality of the primary studies is important to minimize the potential for biased estimates of intervention effects.^[21] We performed a quality assessment according to the NOS tool for each article. All the included articles were scored at 7 points, indicating the high quality of the studies. Furthermore, because many factors, including age, sex, and tumor size affect survival, only those studies that presented HRs obtained by multivariate analyses were included in the analysis.^[22,23]

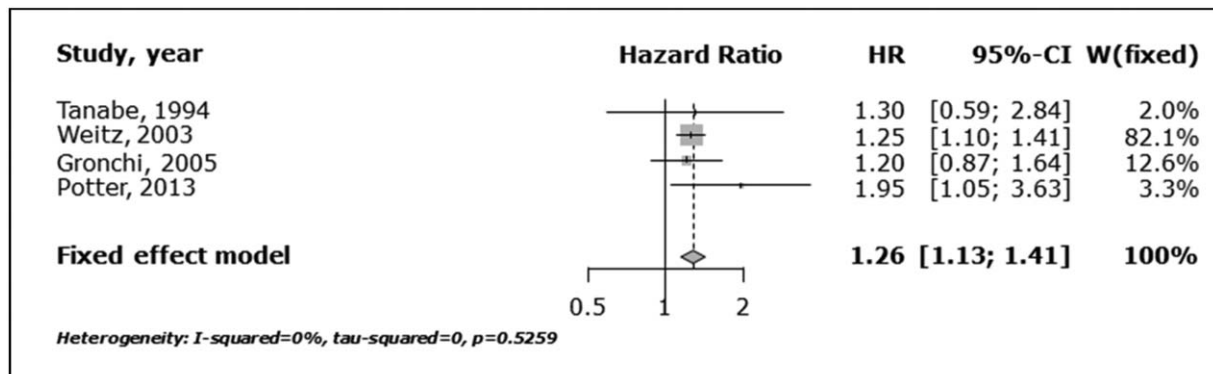


Figure 3. Subgroup forest plots of the hazard ratios of survival associated with positive surgical margin. W: weight.

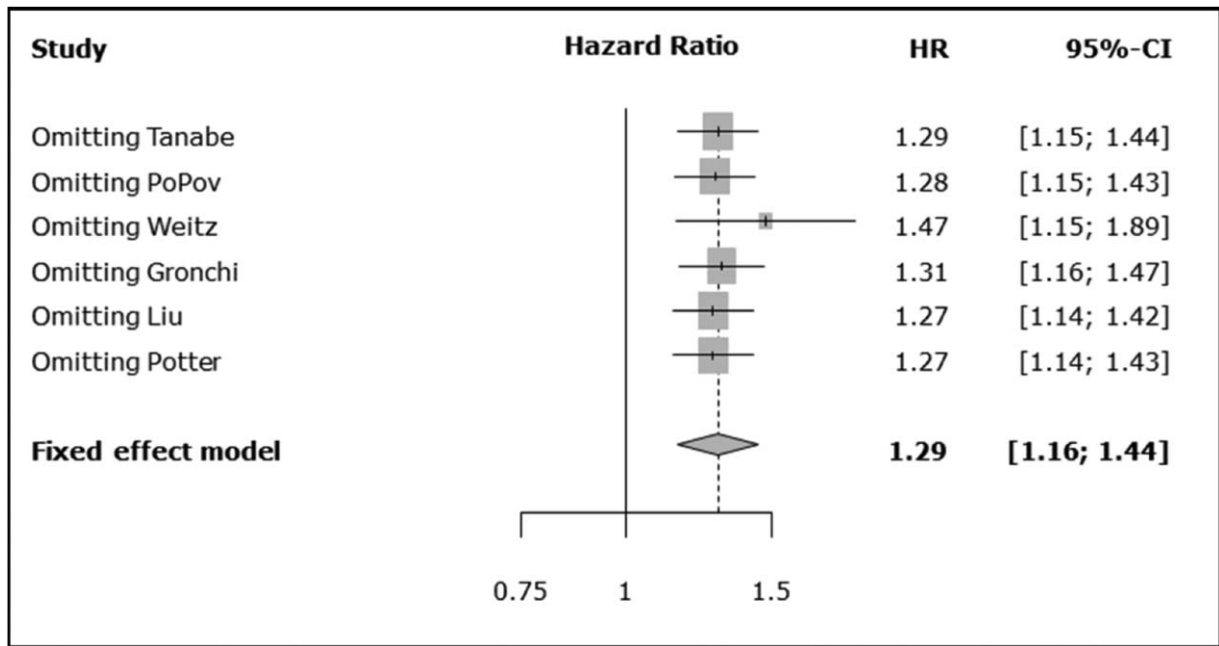


Figure 4. Sensitivity analysis results showing no significant difference according to the omission of one study at a time.

Surgical margins have been traditionally classified according to the staging proposed by Enneking,^[24] which consists of a system of 4 grades, namely intralesional, marginal, wide, and radical margins. However, a qualitative system such as the Enneking classification is difficult to apply; thus, most retrospective studies use a quantitative system for defining surgical margins. Of the studies included in this meta-analysis, only 1 study defined surgical margin using a qualitative system. Popov et al^[16]

qualitatively classified surgical margins as intracompartmental, extracompartmental (en bloc excision of the involved muscle compartment), or wide (with a 2.5-cm clear zone or intact fascia). When the intracompartmental margin was compared with the extracompartmental margin, no statistically significant difference in survival was found, and the study reported that surgical margin was not a prognostic factor of survival. Four of the other 5 studies used a quantitative classification system, which defined

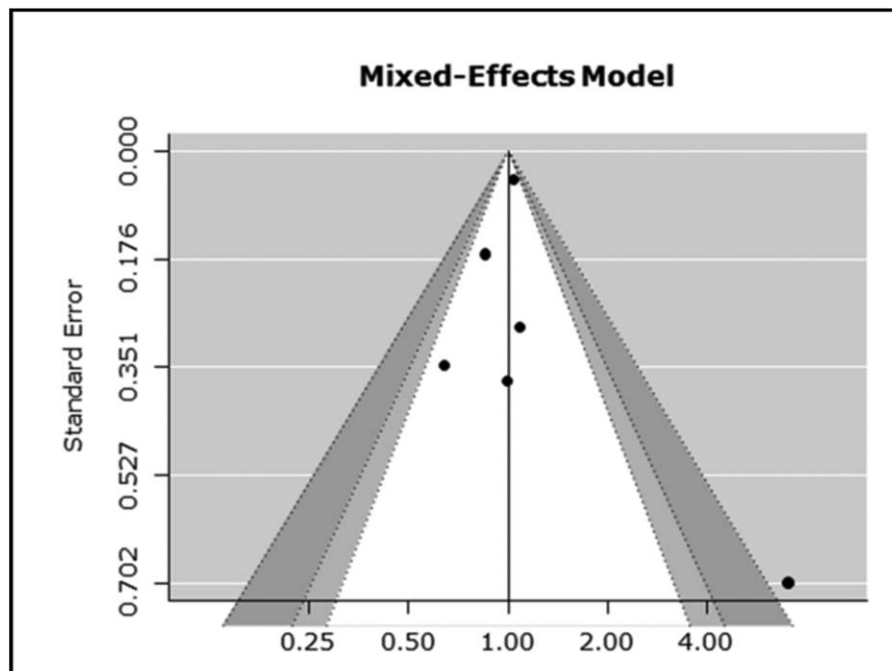


Figure 5. Funnel plot of studies that evaluated the association between positive surgical margin and overall survival.

a positive surgical margin as tumor cells within 1 mm of the margin.^[14,25–29] The remaining study by Lui et al^[14] classified surgical margins according to the proximity of tumor cells to the margin using 6 grades as follows: 0–1, 2–4, 5–9, 10–19, 20–29, and >30 mm. A tendency toward increased survival with greater clear surgical margins, with a 10-mm margin being the most clinically significant to survival, was reported. A further subgroup analysis was undertaken without the 2 aforementioned studies because of discrepancies in the definitions of the surgical margin. However, most of the patients with inadequate margins in this meta-analysis study received postoperative radiotherapy, which resulted in an increased survival rate in the patients with inadequate surgical margins.

Some authors have reported that positive surgical margins do not have an effect on survival.^[12,13,16,30–32] However, the power of these studies may have been insufficient owing to the small number of patients included in the studies. If the number of subjects is small, only significant factors of survival are demonstrated, while factors with moderate influence, such as surgical margin, can be difficult to detect. Another reason for the previous reports of the lack of association may be the fact that surgical margin has an impact on patient survival after a certain time interval. In other words, the effects of positive surgical margins are difficult to show within a short period. High-grade STS itself results in a low 5-year survival rate, making the detection of the influence of surgical margin on 5-year survival even more difficult. Gronchi et al^[13] also reported no significant association between positive surgical margin and survival in a study of 911 patients; however, this might have been due to the increased proportion of high-grade STS cases (44%). Another prospective randomized trial that assessed local control with survival concluded that a positive surgical margin was not a statistically significant prognostic factor of survival.^[33,34] However, the subjects of this study had high-grade STS. Recently, Willeumier et al^[31] reported the effect of surgical margin on survival was difficult to determine because the biological aggressiveness of high-grade STS decreased the 5-year survival rate. We believe that the effect of positive surgical margin on survival will manifest over a longer follow-up, as in the study by Lewis et al,^[35] in which the effect of positive surgical margin on survival was detected in a 10-year follow-up and not in a 5-year follow-up.

Our meta-analysis has limitations that affected the interpretation of the true results. First, all the studies included in this meta-analysis were patient follow-up studies, which are more susceptible to selection bias than randomized controlled studies. However, randomized controlled studies of surgical margins in extremity STS management are difficult to conduct. Second, only studies on extremity STS were included for the analysis, with the exclusion of many studies that included truncal STS cases. Third, to adjust for other factors that affect survival, only those studies that presented HRs obtained by multivariate analyses were included, limiting the meta-analysis to 6 studies. The adjusted multivariate factors in each study were different, and because only significant factors identified in a univariate analysis are usually selected for the multivariate analysis, bias resulting from unknown confounders may have affected our results.

5. Conclusion

This meta-analysis supports the hypothesis that a positive surgical margin is a poor prognostic factor of survival in patients

with extremity STS. This study provides the best available evidence regarding the impact of surgical margins on the survival of patients with extremity STS.

Author contributions

Conceptualization: Woo Young Jang, Han-Soo Kim, Ilkyu Han.

Data curation: Woo Young Jang.

Funding acquisition: Ilkyu Han.

Formal analysis: Woo Young Jang, Ilkyu Han.

Investigation: Han-Soo Kim.

Supervision: Han-Soo Kim, Ilkyu Han.

Validation: Ilkyu Han.

Writing – original draft: Woo Young Jang, Ilkyu Han.

Writing – review & editing: Woo Young Jang, Han-Soo Kim, Ilkyu Han.

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