의학석사 학위논문

Impact of Surgical Margin on Survival in Extremity Soft Tissue Sarcoma: A Systematic Review and Meta-analysis

사지 연부조직 육종에서 생존율에 대한 수술적
절제연의 영향:
체계적 문헌 고찰 및 메타분석

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서울대학교 대학원
의학과 정형외과학 전공
장 우 영

Abstract

Introduction: A correct understanding of the prognostic effect of the surgical margin is essential in extremity soft tissue sarcoma (STS). If the status of surgical margin has by itself a significant impact on survival, wider surgical margins would be needed, and larger functional sequelae justified. However, if the status of surgical margin does not affect survival, closer surgical margins with a lower loss of function may be advantageous. The impact of surgical margin status on survival in extremity STS remains to be clearly defined. Therefore, a systematic review and meta-analysis were conducted to determine the impact of SM status on survival in extremity STS.

Methods: A literature search of the National Library of Medicine and National Institutes of Health (PubMed), EMBASE, and Cochrane Controlled Trials Register (CENTRAL) electronic database and by hand searching reference lists of original studies was performed. We searched the studies 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 quality of each study was assessed using the Newcastle–Ottawa Scale (NOS). A pooled HR was analyzed using an inverse variance weighting method and the random effects model or fixed effect model was selected according to heterogeneity. For identifying publication bias, Begg's test was used.

Results: A total of 6 studies were included in the meta-analysis. All six studies were conducted at a single institution and were of high quality (NOS $\geq$ 7). Meta-analysis of all 6 studies showed that a positive SM predicted poor 5-year survival compared to patients with negative surgical margin in a random-effects model with moderate heterogeneity among studies (SHRs = 1.56, 95 % CI 1.12–2.17; test for heterogeneity $p<0.002$, $I^2 = 64.18\%$). Formal evaluation using Begg's test revealed no evidence for significant publication bias in the 5-year survival ($p = 0.086$).

Conclusion: This meta-analysis supports the hypothesis that positive surgical margin is a poor prognostic factor for survival in extremity STS. Our study provides guidance for surgeons undertaking limb salvage surgery in deciding the extent of the SM and its effect in terms of survival.

Keywords : Extremity soft tissue sarcoma, Surgical margin, Survival, Systematic review, Meta-analysis
Student Number : 2011-23756

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List of Abbreviations

STS, soft tissue sarcoma

NOS, Newcastle–Ottawa Scale

SM, surgical margin

OS, overall survival

MeSH, Medical Subject Heading

HR, hazard ratio

CIs, confidence intervals

SHR, summarized hazard ratio

INTRODUCTION

Soft tissue sarcomas (STS) are relatively rare, but 50% to 70% of all tumors arise in the extremities(1). Multimodality treatment of soft tissue sarcomas of the extremitees has improved over the past decades(2). Consequently, limb-sparing surgery combined with adjuvant radiotherapy(3), chemotherapy or both has replaced amputation as the principal treatment(4). A correct understanding of the prognostic implications of the resection margin status is essential in extremity STS(5). If the status of the surgical margin(SM) has in itself, a significant impact on survival, a wider SM would be needed and larger functional sequelae justified. However, if the status of SM does not affect survival, closer surgical margins with a lower loss of function may be advantageous.

The impact of SM status on survival in extremity STS remains to be clearly defined(6-11). Although SM status is thought to be of prognostic importance for local recurrence, its effect on survival remains controversial in extremity STS. Relatively large, retrospective studies exploring the impact of SM status on survival have produced widely varying findings.

In our clinical practice, we have long been impressed by the association of positive SM and decreased overall survival (OS). We hypothesized that a large study size could possibly bypass the limitations of previous studies that were not sufficiently powered to determine differences. Therefore, in the present study, we conducted a systematic review and meta-analysis to determine the impact of SM status on survival in extremity STS.

MATERIALS AND METHODS

Search strategy

A literature search was conducted using PubMed MEDLINE (January 1950 to January 2016), EMBASE (January 1966 to January 2016), and the Cochrane Library databases (January 1960 to January 2016). Hand searching reference lists of original studies was performed. The research question was formulated using the 'PICO framework'- Population Intervention Comparator and Outcome, a process used to identify the clinical question. In this review the PICO framework was as follows: Population: adult patients, Intervention: negative surgical margin, Comparator: positive surgical margin, Outcome: survival. We searched the studies 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". Searched articles were restricted to English due to lack of accessibility and comprehension. Titles and abstracts of eligible citations were screened. Selected articles were evaluated independently and disagreements resolved in consensus.

Inclusion criteria and Exclusion criteria

Studies that met the inclusion criteria for the meta-analysis had the following characteristics: (1) detailed information of surgical margin status, (2) greater than 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 local recurrence, presence of distant metastasis, adjuvant therapy) for survival rate. Studies were excluded if they had the following characteristics: (1) soft tissue sarcoma of a truncal site and (2) p-value was not presented although multivariate analysis was performed.

Quality assessment

The quality of each study was assessed using the Newcastle–Ottawa Scale (NOS)(12). The NOS consists of three parameters of quality: selection, comparability, and outcome (cohort studies). The NOS assigns a maximum of four points for selection, two points for comparability and three points for exposure or outcome. Any discrepancies between reviewers were addressed by a joint reevaluation of the original article.

Extraction of data

Data from the selected studies included were extracted: number of patients, sex, age, tumor grade, definition of negative surgical margin, presence or absence of adjuvant therapy and HR of a positive margin on 5-year survival. We resolved disagreements in consensus.

Outcome Measures

Survival is a time-to-event outcome. Tierney et al.(13) advocated that time-to-event outcomes take account of whether an event takes place and also the time at which the event occurs, such that both the event and the timing of the event are important. In the analysis of survival, both the overall survival and disease specific survival were included. We considered the HR of each study as effect size.

Statistical analysis

We used Higgins I^2 statistics to determine the percentage of the total variation across studies that was due to heterogeneity. The value of I^2 ranges from 0% (no observed heterogeneity) to 100% (maximal heterogeneity). I^2 >50% may be considered to represent substantial heterogeneity. A pooled HR was analyzed using an inverse variance weighting method and the random effects model or fixed effect model was selected according to heterogeneity. A forest plot was used to displace meta-analysis data. The point estimate for the risk ratio was represented by a square and the confidence interval 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 given to studies with larger sample sizes or data of better quality or both. Sensitivity analysis was employed to determine the influence of each individual study on the summary results by repeating the random-effects meta-analysis after omitting one study at a time. For identifying publication bias, Begg's funnel plot was used. All of the statistical analyses used in this study were performed using R version 3.1.2 (metafor packages). A p-value < 0.05 was considered statistically significant.

RESULTS

Studies Identified

The literature search of 3 electronic databases using the aforementioned search terms identified 564 publications. All of the studies retrieved from the databases were independently evaluated. After a review of the abstracts and/or titles, 25 potentially relevant publications 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 due to potentially duplicate data of the same population 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 (Figure 1).

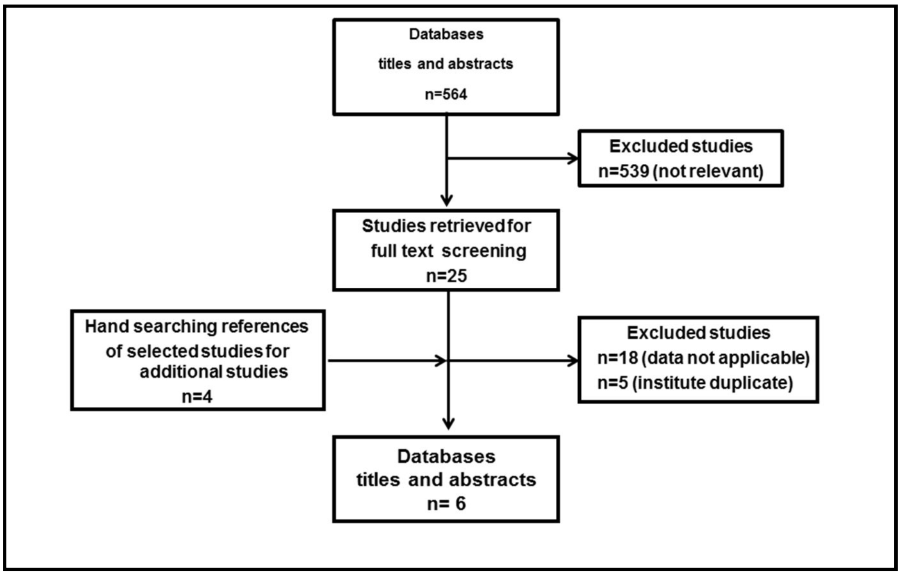

Figure 1. Flowchart of selection of studies included in the meta-analysis

Study Characteristics and Quality assessment

The selected studies were published between 1994 and 2013, with reports on a total of 2917 cases of soft tissue sarcomas of the extremities. All of the eligible studies were observational cohort studies. The sample size ranged from 48 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 positive SM and OS, while the other 3 studies reported a significant association between positive SM and OS. The definition of a positive surgical margin varied slightly among the studies. Tanabe et al.(14), Weitz et al.(1), Gronchi et al.(15), and Potter et al.(16) defined the SM as positive when there was microscopic evidence of tumor cells at the resection margin or within 2.5cm. Lui et al.(17) classified the distance between the tumor and resection margin into the following categories (0-1 mm, 1-4 mm, 5-9 mm, 10-19 mm, 20-29 mm, >30 mm) and considered a SM to be clinically positive when the distance from the margin was less than 10 mm. All six studies were conducted at a single institution and were of high quality (NOS ≥ 7, Table 1).

Table 1. Characteristics of 6 observational studies

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

*NOS: Newcastle–Ottawa Scale

Data synthesis and review

Meta-analysis of all 6 studies showed that a positive SM predicted poor 5-year OS compared to patients with negative surgical margin in a random-effects model with moderate heterogeneity among studies (SHRs = 1.56, 95 % CI 1.12–2.17; test for heterogeneity $p<0.002$, $I^2 = 64.18\%$, Figure 2).

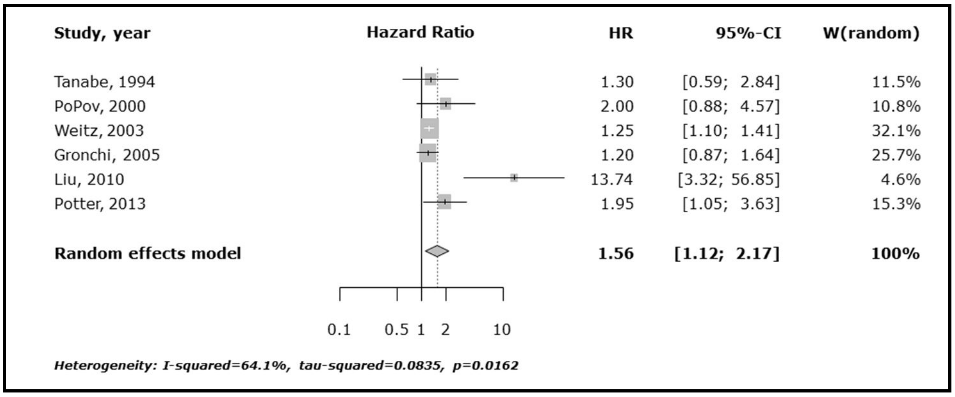

Figure 2. Forest plots of hazard risk of overall survival associated with positive surgical margin.

Due to differences in the definition of positive surgical margin by Lui et al.(17) and Popov et al.(18), which caused heterogeneity on the forest plot, subgroup analysis was done. In subgroup analysis, meta-analysis of these showed that a positive SM predicted poor 5-year OS compared to patients with a negative surgical margin in a fixed-effects model with low heterogeneity among studies (SHRs = 1.26, 95 % CI 1.13–1.41; test for heterogeneity $p<0.56$, $I^2 = 0\%$, Figure 3).

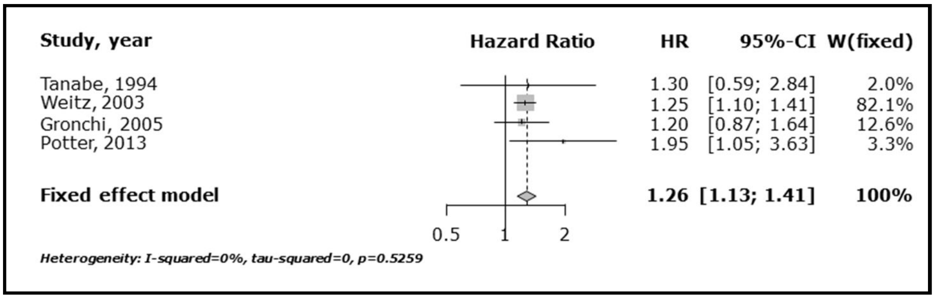

Figure 3. In subgroup analysis, forest plots showed that significant association between positive surgical margin and decreased overall survival.

Due to differences in the definition of a positive SM between the studies, sensitivity analysis of the studies was done, without a significant effect on the results of the meta-analysis (Figure 4).

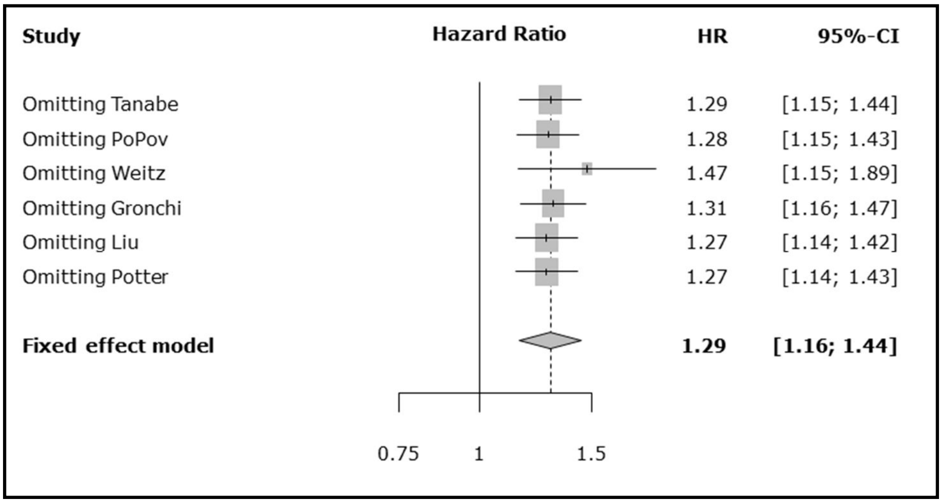

Figure 4. Sensitivity analysis showed no significant difference according to omit one study at a time.

Publication Bias

Funnel plots were performed to estimate the publication bias of the included literature. The shapes of the funnel plots revealed that the included studies had apparent asymmetry (Figure 5). However, formal evaluation using Begg's test failed to reveal evidence for significant publication bias in the 5-year OS (p = 0.086)

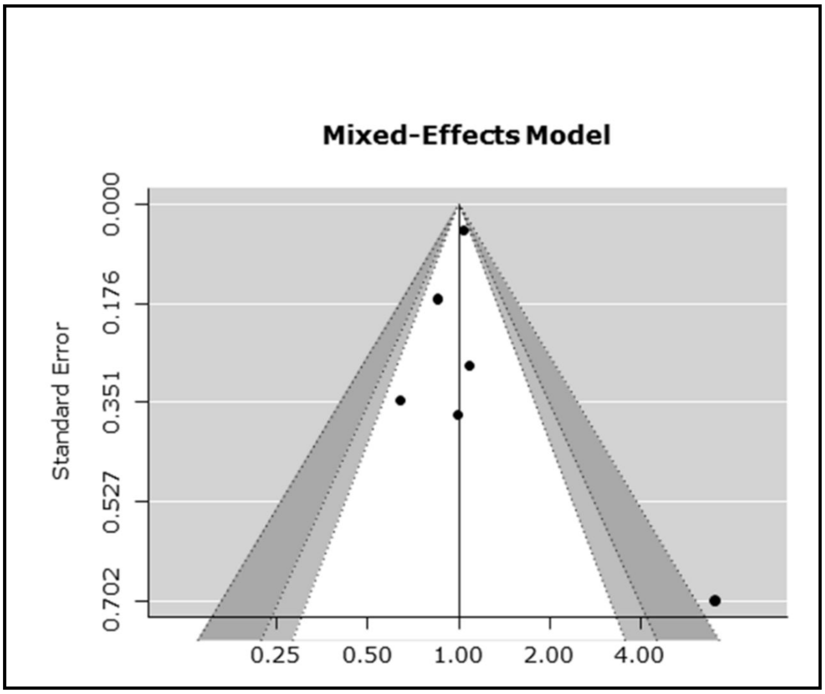

Figure 5. Funnel plot of studies evaluating the association between positive surgical margin and overall survival. Begg's test (p = 0.086)

DISCUSSION

Surgical excision of extremity STS is the fundamental treatment of choice(5, 11). Although the principle of surgical excision is to obtain a wide resection margin to prevent local recurrence, there is debate about the size of the resection margin and whether a wide surgical margin with ensuing severe functional disability is warranted. There are insufficient and conflicting reports of the impact of the surgical margin on survival. Extremity STS are rare and heterogeneous tumors that require specialized centers with a multidisciplinary team for treatment. The paucity of such centers and lack of large-scale patient studies makes evidence based treatment decisions difficult for this group of patients. For these reasons, we investigated the impact of positive SM on survival by meta-analysis of observational cohort studies and results suggest that a positive surgical margin leads to decreased survival.

Meta-analysis is a method of scientific and statistical integration of results from a series of individual researchers, which can provide important insights for application to patient care(19, 20). Since the systemic review and meta-analysis is 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 quality assessment according to the NOS tool for each article. All included articles were scored at 7 points, indicating high quality of the studies. Furthermore, because many factors including age, sex, and tumor size affect survival, only those studies that presented the HR by multivariate analysis were included for analysis(22, 23).

Surgical margin has been traditionally classified according to the staging proposed by Enneking(24), consisting of a system of 4 grades: intralesional, marginal, wide and radical margin. However, a qualitative system such as the Enneking classification is difficult to apply, thus most retrospective studies use a quantitative system for definitions of the surgical margin. Of the studies included in this meta-analysis, only one defined the SM by a qualitative system. Popov et al.(18) qualitatively classified the surgical margin as intracompartmental, extracompartmental (en bloc excision of the involved muscle compartment) or wide (having a 2.5 cm clear zone or intact fascia). When the intracompartmental margin was compared to the extracompartmental margin, there was no statistically significant difference in survival, and the study reported that surgical margin was not a prognostic factor of survival. Four of the other five studies used a quantitative classification system which defined a positive surgical margin as tumor cells within 1 mm of the margin(16, 25-30). The remaining study by Lui et al., classified the SM by the proximity of tumor cells to the margin into 6 grades: 0-1 mm, 1-4 mm, 5-9 mm, 10-19 mm, 20-29 mm, and >30 mm. It was reported that there was a tendency towards increased survival with greater clear surgical margins with a 10 mm margin being the most clinically significant to survival. Further subgroup analysis was undertaken without the 2 aforementioned studies due to discrepancies in definitions of the SM. However, most of patients with inadequate margin in his study received post-operative radiotherapy, which results in increased survival rate in patients with inadequate SM.

Some authors have reported that positive SM does not have an effect on survival(14, 15, 18, 31-33). However, there may have been insufficient power due to small numbers of patients in the studies If the number of subjects is small, only very significant factors on survival is demonstrated while factors with moderate influence such as surgical margin can be difficult to detect. Another reason for previous reports of a lack of association may be due to the fact that surgical margin has impact on survival after a certain time interval. In other words, the effects of positive SM is difficult to show within a short time period. High grade STS itself results in low five years survival rate making the detection of the influence of SM on 5 year survival more difficult. Gronchi et al.(15) also reported no significant association between positive SM and survival in a study of 911 patients, however, this may have been due to the increased proportion of high grade STS (44%). Another prospective randomized trial that assessed local control with survival concluded that a positive SM was not a statistically significant prognostic factor for survival(34, 35). However, the subjects of this study were high grade STS patients. Recently, Willeumier et al.(32) reported that it was difficult to know the effect of surgical margin on survival because the biologic aggressiveness of high grade STS decreased the five years survival rate. We believe the effect of positive SM on survival will show in longer follow up, as in the study by Lewis et al.(36) in which the effect of positive SM on survival was detected in the 10-years follow up and not in the 5-year follow up.

Our meta-analysis has limitations that affect interpretation of the true results. All studies in this meta-analysis were retrospective studies, which are more susceptible to selection biases than randomized control studies. However, randomized control studies of SM in extremity STS management are not ethically feasible Only studies of extremity STS were included for analysis with exclusion of many studies that included truncal STS. Also, in order adjust for other factors affecting survival, only those studies presenting HR with multivariate analysis were included, limiting the meta-analysis to six studies. The adjusted multivariate factors in each study were different and since only significant factors by univariate analysis are usually selected in multivariate analysis, bias resulting from unknown confounders may have affected our results.

In summary, margin status is an important predictor of outcome. This meta-analysis supports the hypothesis that positive surgical margin is a poor prognostic factor for survival in extremity STS. Our study provides guidance for surgeons undertaking limb salvage surgery in deciding the extent of the SM and its effect in terms of overall survival.

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국문 초록

서론: 사지의 연부조직 육종의 치료에 있어서, 수술적 절제연이 예후에 미치는 영향에 대하여 정확한 이해가 중요하다. 만약 수술적 절제연 상태 그 자체가 생존율에 유의한 영향을 미친다면, 큰 기능적 후유증을 일으킬 수 있는 광범위 수술적 절제연이 정당할 것이다. 수술적 절제연이 생존율에 유의한 영향을 미치지 않는다면, 기능적 손실을 적게 일으키는 경계적 수술적 절제연을 얻는 것이 더 이득이다. 하지만 사지의 연부조직 육종에서 수술적 절제연이 생존율에 미치는 영향에 대해서는 아직 불분명하게 남아있다. 따라서 수술적 절제연이 생존율에 미치는 영향을 규명하기 위해 체계적 문헌 고찰 및 메타분석을 시행하였다.

방법: 3개의 전자문헌 (Pubmed, EMBASE, Cochrane)과 원문의 참고문헌을 검색하였다. 검색어는 "neoplasm", "sarcoma", "connective tissue", "soft tissue" "extremity", "margin"의 텍스트나 MESH 단어를 사용하였다. 질적 평가는 Newcastle-Ottawa Scale (NOS)를 이용하여 시행되었다. 종합된 위험도는 역분산 방법에 따라서 가중치를 주었으며, 이질성의 정도에 따라서 임의 모형 효과나 고정 모형 방법으로 계산되었다. 출판 비뚤림은 베그 검정을 이용하여 확인하였다.

결과: 6개의 문헌이 이번 연구에 포함되었다. 6개 논문 모두 단일 기관연구이며, NOS 7 점 이상이었다. 임의 모형 효과를 이용한 메타분석에서 양성의 수술적 절제연은 수술 후 5년 생존율에 유의한 나쁜 예후인자로 나타났다(종합 위험도= 1.56, 95 % 신뢰도 범위: 1.12-2.17; 이질성(I^2) = 64.18%). 출판 비뚤림이 나타나지 않았다(p = 0.086).

결론: 이번 메타분석은 사지의 연부조직 육종에서 양성의 수술적 절제연이 생존에 나쁜 예후인자라는 가설을 뒷받침한다. 이번 연구는 사지 구제술시에, 수술적 절제연의 범위와 이에 따른 생존률에 미치는 영향을 결정하는데 지침을 제공한다.

Keywords : 사지 연부조직 육종, 수술적 절제연, 생존율, 체계적 문헌 고찰, 메타분석
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