Title:

Clinical effectiveness of Enneking appropriate versus Enneking inappropriate procedure in patients with primary osteosarcoma of the spine: a systematic review with meta-analysis

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Abstract:

Purpose:

Primary osteosarcoma of the spine is a rare osseous tumour. En bloc resection, in contrast with intralesional resection, is the only procedure able to provide Enneking appropriate (EA) margins, which has improved local control and survival of patients with primary osteosarcoma of the spine. The objective of this study is to compare the risk of local recurrence, metastases development and survival in patients with primary osteosarcoma of the spine submitted to Enneking appropriate (EA) and Enneking inappropriate (EI) procedure.

Methods:

A systematic search was performed on EBSCO, PubMed and Web of Science, between 1966 and 2018, to identify studies evaluating patients submitted to resection of primary osteosarcoma of the spine. Two reviewers independently assessed all reports. The outcomes were local recurrence, metastases development and survival at 12, 24 and 60 months.

Results:

Five studies (108 patients) were included for systematic review. These studies support the conclusion that EA procedure has a lower local recurrence rate (RR: 0.33, 95% CI: 0.17-0.66), a lower metastases development rate (RR: 0.39, 95 % CI: 0.17-0.89), a higher survival rate at 24 months (RR: 1.78, 95 % CI: 1.24-2.55) and 60 months (RR: 1.97, 95 % CI: 1.14-3.42) of follow-up, however, at 12 months, there is a non-significant difference.

Conclusions:

EA procedure increases the ratio of remission and survival after 24 months of follow-up. Multidisciplinary oncologic groups should weigh the morbidity of an en bloc resection, knowing that in the first year the probability of survival is the same for EA and EI procedure.

Keywords:

Osteosarcoma; Primary spine tumours; Enneking margins; Local recurrence; Metastatic disease; Survival

Introduction:

Primary tumours of the spine are rare osseous tumours occurring in less than 10% of all spine tumours. Its incidence ranges between 2.5 and 8.5 cases per 100.000 persons per year accounting less than 5% of the malignant tumours of the spine [1,2].

The treatment, based on small case series [3-6], involves a multimodality therapy with neoadjuvant and/or adjuvant chemotherapy, radiation therapy, and surgical treatment [4,5,7-13]. They have reported a high local recurrence rate, metastatic disease and a variable survival [3,4,10,14-18].

As Enneking reported for osteosarcoma of the limbs[19], several studies proved the impact of surgical margins on the local recurrence and survival of patients with primary sarcomas of the spine[5,6,8,9,13,15,20-28]. They proposed a classification as Enneking appropriate (EA) margins - marginal or wide – or Enneking inappropriate (EI) margins – intralesional or contaminated [26,27]. For spine tumours there are few studies focusing on the margins of resection, but for spine this issue is even more relevant than for limbs because of the presence of the vertebral canal content.

To enhance negative margins, patients with primary osteosarcoma of the spine are usually treated first with neoadjuvant chemotherapy to reduce the tumour size, promoting local control, preventing systemic micrometastases and increasing survival[10,12,13].

En bloc resection - removal of the entire tumour's mass encased by a continuous shell of healthy tissue - is the only technique which could achieve negative margins providing the best chance of survival[2,27].

In addition, adjuvant chemotherapy has a proven survival benefit even in patients submitted to intralesional resection[12,13]. Radiation therapy does not have a proven survival benefit but promotes local control particularly in patients with positive margins or with intralesional resection[9,12,13].

The objective of this meta-analysis is to compare the overall local recurrence rates, metastases development rate and survival at 12, 24, and 60 months between EA and EI procedure in patients with primary osteosarcoma of the spine.

Methods:

This meta-analysis was designed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[29]. A comprehensive literature search was performed on EBSCO (1900-July 2018), PubMed (1966-July 2018), and Web of Science (1900-July 2018). The keywords searched were "osteosarcoma" or "osteogenic sarcoma", "spine", "primary", and "en bloc resection" or "intralesional resection". The research was done with different combinations of keywords. No limitations were applied for language or publication date. Reference lists of articles were scanned for selection of additional studies. The selection process is presented in Figure 1.

Inclusion and exclusion criteria:

Inclusion criteria were the following: studies published from 1900 to 2018 (July); clinical trial, case reports, case series, abstracts or oral communications. As exclusion criteria the following were defined: animal studies; studies not involving osteosarcoma of the spine or describing non-osteosarcoma lesions; studies without discrimination of tumour type; studies without en bloc resection or intralesional resection cases; studies without characterization of Enneking margins or survival; studies with less than four cases. Enneking margins were defined as appropriate (EA) - marginal or wide - or inappropriate (EI) – intralesional or contaminated. Surgeries followed the same denomination as the achieved margins - EA procedure or EI procedure. All studies were reviewed by two authors with respect to inclusion and exclusion criteria.

Data extraction:

One author extracted the data from included studies and a second author checked the extracted data. The GetData Graph Digitizer (Microsoft, Washington) software was used to extract data from diagrams when necessary. We developed a data extraction sheet where the data were registered. Any disagreement was resolved by discussion.

Extracted data were the following: author; publication year; location of the treated spine; sample size; sex; mean age; Enneking stage distribution; number of patients submitted to chemotherapy, radiotherapy and resection; number of patients with local recurrence; number of patients who survived; complications described; metastasis incidence; and main conclusions.

The outcomes were the local recurrence risk, metastases development risk and the survival at 12, 24 and 60 months.

Individual bias risk assessment:

To ascertain the validity of the included studies, two reviewers working independently determined the adequate definition of disease, clear baseline characteristics, inclusion of a representative cohort, valid method for diagnosis, standardized data collection and objective outcome measurement[30]. The risk was defined as low, unclear or high.

Quality assessment:

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach[31] was used for assessing the quality of evidence of the included studies at outcome level and was scored as high, moderate, low, or very low.

The judgement about quality was based on risk of bias, inconsistency, indirectness, imprecision, publication bias, magnitude of effect, dose response and the effect of all plausible confounding factors.

An overall GRADE quality rating across outcomes was defined from the lowest quality of evidence of the five outcomes.

Statistical analysis:

The Review Manager (Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) software was used for statistical analysis. We defined an error margin of .05.

The outcomes of each study were analysed according to risk ratio (RR) to assess the importance of margins appropriateness. The heterogeneity of the studies was assessed with I^2 statistic according PRISMA guidelines. When I^2 was inferior to 40 %[32], the studies were considered homogeneous, and the fixed-effects model[33] was used to determine the overall RR. If heterogeneity was verified, it was investigated by discarding studies from the analysis and seeing if that removed the heterogeneity[32]. Otherwise, the random-effects model was used.

Sensitivity analysis and publication bias assessment:

A sensitivity analysis was also used to explore the heterogeneity and robustness of the pooled results. We repeated the primary analysis with an altered dataset or statistical method to determine whether these changes have any effect on the pooled estimate. The choice of studies to discard was based on GRADE quality (low) and study size (< 30

patients). For each study we plotted the effect by the inverse of its standard error. The publication bias was visually assessed for the symmetry of funnel plot and with Egger's test[34,35].

Results:

The research performed on Ebsco, Pubmed and Web of Science provided a total of 1319 studies; 448 studies were reviewed after removal of duplicates. The number was reduced to 24 studies after applying the exclusion criteria. After qualitative evaluation, 19 studies were excluded for irrelevant content to perform the meta-analysis. No grey literature was included.

Five studies, published between 2002 and 2016, with relevant information with respect to local recurrence, metastases development and survival, were included and analysed [8,23-26]. All studies were retrospective case series and were developed in four countries (Germany, Italy, USA, and China) [8,23-25]. One study was a multicentre study developed in twelve different centres[26]. They were all published in English.

The aggregation of the five studies resulted in 123 patients (108 resections), treated between 1951 and 2012. The sample was composed of 56 male and 52 female patients with a weighted mean age of 34.4 ± 15.9 years. Eighty eight patients were staged in Enneking classification. Almost all the sample (88 %) was staged in high-grade extracompartmental IIb stage. The weighted mean of follow-up was 3.5 ± 2.6 years.

There is no statistically significant difference between patients submitted to EA procedure and EI procedure regarding age, sex, location, radiation therapy or chemotherapy ($p>0.05$).

Table 1 shows the general characteristics of the included studies in the meta-analysis. The risk of bias is presented in Graph 1.

Studies characterization:

The multicentre study reported by Dekutoski et al.[26] describes the experience of 58 patients (55 resections) with primary osteosarcoma of the mobile spine and sacrum across twelve international centres. The surgical techniques and treatment were centre and patient dependent.The study reported that 29 patients were submitted to EA procedure and 26 patients to EI procedure. In addition to surgical treatment, 45 patients received chemotherapy and 21 patients received radiation therapy. Local recurrence was significantly higher in EI procedures (42%) compared with EA procedures (1%) ($p=0.001$). In a similar way, EA procedure (69%) had a significant survival advantage over EI

procedure (50%) (p=0.048). Metastases were not analysed. The authors concluded that EA surgical procedures significantly reduce local recurrence and increase survival.

Feng et al.[24] in a retrospective review describe 16 patients which were treated for primary osteosarcoma of mobile spine. Two different protocols of surgical treatment (total en bloc spondylectomy and total piecemeal spondylectomy) were chosen. Ten patients were submitted to EI procedure and six patients to EA procedure. They were all followed by adjuvant chemotherapy (cisplatin, doxorubicin and methotrexate). The majority of the sample, 14 patients, also received adjuvant radiation therapy (35-65 Gy). Overall, six out of ten patients submitted to EI procedure (60%) experienced local recurrence of the tumour and only five patients (50%) survived. In contrast, the patients in the EA procedure group had no case of local recurrence and had survived during the follow-up period. This study is the only which reports the complications analysis: one patient developed anaphylactic shock, three patients were submitted to nerve root ligation and three patients had cerebrospinal fluid leak after the surgery. Although no statistical analysis was performed, the authors concluded that osteosarcoma in the cervical or thoracolumbar spine should be treated with a combination of en bloc resection, a wide or marginal margin, and chemotherapy.

Lim et al.[25] describe the experience of 10 patients with osteosarcoma of the mobile spine and sacrum. The treatment of choice was wide excision of the tumour. Seven patients underwent EA procedure and three patients EI procedure. Almost all sample received adjuvant chemotherapy or radiation therapy. The local recurrence was lower in patients submitted to EA procedure (57%) than in patients submitted to EI procedure (67%). On the other hand, the first group had lower survival (2.5 years) than the second group (3.5 years). The authors surmised that metastases, intralesional surgery or no surgery at all are poor prognostic factors.

The Cooperative Osteosarcoma Study Group (COSS) reported by Ozaki et al.[8] describes the outcome of 22 patients with primary osteosarcoma of the spine (mobile spine and sacrum). The surgical margins were described in only 12 patients. Five patients were submitted to EA procedure and seven patients to an EI procedure. All patients operated on received chemotherapy according to a COSS protocol modified in successive revisions and two patients received adjuvant radiation therapy (50-65 Gy). Local recurrence developed in one (20%) out of five patients who underwent EA procedure, and four (57%) out of seven patients who underwent EI procedure. There was a statistically significant benefit in overall survival for patients who underwent wide or marginal resection in

comparison to intralesional resection or no surgery (p=0.03). The authors concluded that patients should be treated with combination therapy, marginal excision and adjuvant radiation therapy.

The last study, by Schwab et al.[23], describes the results of 17 patients treated for primary osteosarcoma of the mobile spine. The surgical treatment involved en bloc spondylectomy or intralesional resection. Fifteen patients were operated on: four patients were submitted to EA procedure and 11 patients to EI procedure. All patients received neoadjuvant chemotherapy (adriamycin and methotrexate) and seven patients received adjuvant radiation therapy (40-45 Gy). Local recurrence occurred in one patient (25%) in the EA procedure group and in five patients (45%) in the EI procedure group. Median survival following en bloc resection was superior to that of subtotal resection (p=0.09). The authors concluded that en bloc resection of osteosarcoma in the mobile spine is associated with improved survival.

Meta-analysis of clinical outcomes

Local recurrence

The pooled results of five studies (108 patients) showed a statistically significant difference between EA and EI procedure groups (RR = 0.33, 95 % CI: 0.17-0.66; p = 0.002). The heterogeneity among these included studies was small, and a fixed-effect model was adopted (χ^2=4.36; df=4, I^2=8%; p=0.360; Graph 2). Funnel plot and Egger's test (p=0.746) were used to identify the potential publication bias of local recurrence, and results showed that the effect size was symmetrical and there was no publication bias. Sensitivity analysis was performed, and after removing each of the studies, the final outcome was not changed.

Metastases

Metastases analysis was performed in four studies (53 patients) and the pooled results indicated that there is a statistically significant difference between EA and EI procedure groups (RR = 0.39, 95 % CI: 0.17-0.89; p=0.03). The heterogeneity among these included studies was small, and a fixed-effect model was adopted (χ^2=0.20; df=3, I^2=0%; p=0.980; Graph 3). Funnel plot and Egger's test (p=0.954) showed that the effect size was symmetrical and there was no publication bias. Sensitivity analysis was performed and the final outcome was not changed.

Survival at 12 months

Survival at 12 months was reported in five studies (103 patients), and the pooled results indicated that there was no significant difference between EA and EI procedure groups (RR = 1.18, 95 % CI: 0.99-1.41; p=0.07). The heterogeneity among these included studies was small, and a fixed-effect model was adopted (χ^2=1.83; df=4, I^2=0%; p=0.770; Graph 4). Funnel plot and Egger's test (p=0.135) showed that the effect size was symmetrical and there was no publication bias. Sensitivity analysis was performed and the final outcome was not changed.

Survival at 24 months

Survival at 24 months was reported in five studies. The heterogeneity among these studies was high (χ^2=8.92; df=4, I^2=55%; p=0.06). After detailed investigation, the study of Feng et al[24] was the cause for the heterogeneity and was removed from the analysis. The pooled results of four studies (78 patients) indicated that there was a statistically significant difference between EA and EI procedure groups (RR = 1.78, 95 % CI: 1.24-2.55; p=0.002; Graph 5). Funnel plot and Egger's test (p=0.961) showed that the effect size was symmetrical and there was no publication bias. Sensitivity analysis was performed and the final outcome was not changed.

Survival at 60 months

Survival at 12 months was reported in five studies (73 patients), and the pooled results indicated that there is a statistically significant difference between EA and EI procedure groups (RR = 1.97, 95 % CI: 1.14-3.42; p=0.02). The heterogeneity among these included studies was small, and a fixed-effect model was adopted (χ^2=3.23; df=4, I^2=0%; p=0.520; Graph 6). Funnel plot and Egger's test (p=0.657) showed that the effect size was symmetrical and there was no publication bias. Sensitivity analysis was performed and the final outcome was not changed.

Discussion:

Our systematic review showed that, independently of age, sex, location, radiation therapy or chemotherapy, EA procedure has a potential benefit in primary osteosarcoma of the spine regarding local recurrence, metastases development and survival after 24 months post-operatively.

Five case series studies were included in our study and we considered one of them to be at low risk of bias[8]. The others are at unclear risk of bias for inclusion of representative cohort[23-25], standardized data collection[23-25]

and other bias[23,26]. The high number of patients operated on (108 patients) and the follow-up mean higher than 3 years provide sufficiently robust evidence to compare the Enneking margins appropriateness regarding the outcomes.

EA procedure was proven lower for local recurrence rate (0-57 %) than EI procedure (42-67 %)[8,23-26]. Our meta-analysis produced pooled results of 18 % for EA procedure and 48 % for EI procedure, a statistically significant three-fold lower recurrence rate.

Metastases development rate was lower for EA procedure (14-33 %) than for EI procedure (33-70 %) [8,23-25]. This meta-analysis identified a pooled metastases development rate of 23.7 % for EA procedure and 63.6 % for EI procedure, a statistically significant three-fold lower rate.

EA procedure was associated with higher survival rates at 12 months (88-100%; 67-100%), 24 months (57-100%; 47-90%) and 60 months (14-100%; 17-50%) than EI procedure [8,23-26].

At 12 months, the meta-analysis surmised a pooled survival rate of 92 % for EA procedure and 78 % for EI procedure, a non-statistically significant one-fold higher rate. The value almost reached a significant value.

At 24 months, the pooled survival rate decreased to 82 % for EA procedure and 45% for EI procedure. At 60 months, a great difference was detected with 52 % for EA procedure and 29 % for EI procedure. These values account to a statistically significant two-fold higher survival rate for EA procedure.

None of the studies identified a local recurrence rate and survival benefit between en bloc resection and intralesional excision [3,16]. Even when resecting the entire tumour in a single, intact piece, the surgical margins could be positive. Most likely, more than the technique used, the surgical margins are the key point to the overall benefit. However, the surgeons are inaccurate in their intraoperative assessment of clear margins achieved[36], biasing the conclusions of studies that investigate the benefit of en bloc resection.

Nevertheless, as other recent individual studies have reported [8-10,19,37-40], these pooled results suggest that the rate of local recurrence, metastases development and survival depends on the quality of the resection, even when neoadjuvant or adjuvant therapy is used.

In this study, the survival benefit is particularly inconsistent until 12 months of follow-up. We hypothesise that adjuvant chemotherapy could improve the survival of patients submitted to EI procedure in the first year. After that, local recurrence and metastases development have a negative impact on survival [20,27].

Multidisciplinary oncologic groups should carefully evaluate patients with primary osteosarcoma of the spine on a case-by-case basis, weighing the morbidity of an en bloc resection to achieve EA margins, knowing that in the first year the probability of survival is the same between EA and EI procedure.

The quality of the included studies demonstrated by GRADE classification of moderate or low is predictable for nonrandomized surgical studies. The individual bias risk assessment was defined as low or unclear. There are high heterogeneity between the different studies regarding surgical techniques, neoadjuvant and adjuvant chemotherapy and radiation therapy. The treatment was center and patient dependent making unavailable any comparison regarding these variables. The publication bias assessment demonstrated that all of the included studies fell within the funnel plot.

Limitations:

Firstly, the number of included studies was small, retrospective, and most of the studies included few patients. Secondly, there likely was a physician selection bias in choosing the type of operation regarding the clinical patients' characteristics. Thirdly, the studies are heterogeneous respective to the treatment as there are different adjuvant therapy protocols regarding neoadjuvant and/or adjuvant chemotherapy or radiation therapy. Fourthly, the two groups were not compared relative to timing of chemotherapy or radiation therapy delivery. There is the hypothesis that EA procedure group had been treated more frequently with neoadjuvant chemotherapy or adjuvant radiation therapy decreasing the metastases development or local recurrence rate. Finally, randomized controlled trials could not be conducted. This is explained by different issues: pathology rarity, lower surgical experience, ethical problems and tumour location. For this reasons we recommend a larger multi-center, high-quality, prospective cohort study, following the same protocol and controlling the bias, to verify the results of this meta-analysis.

Conclusion:

EA procedure for primary osteosarcoma of the spine - of the mobile and of the fixed spine - was associated with a significantly reduced risk for local recurrence, metastases development and survival after 24 months. The protocol treatment heterogeneity decreases the robustness of the conclusions. A larger multi-center, high-quality, prospective cohort study, following the same protocol, is needed to confirm these conclusions.

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Figure 1: Studies selection process

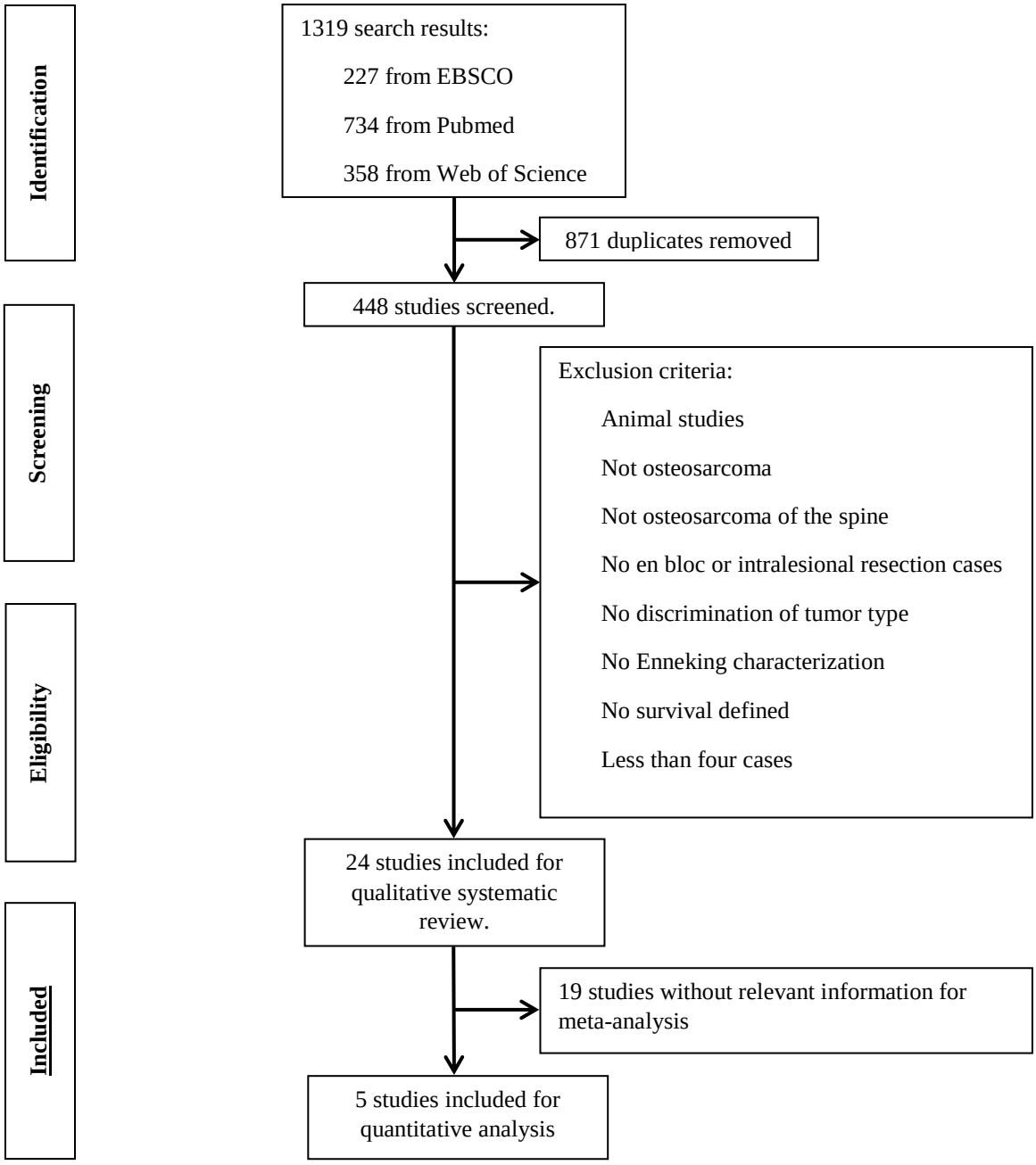


Table 1: Characterization of studies selected for meta-analysis

Study*	Dekutoski et al 2016	Feng et al 2013	Lim et al 2013	Ozaki et al 2002	Schwab et al 2012	Total	**p**
Design	Case series	Case series	Case series	Case series	Case series	-	-
N	55	16	10	12	15	108	-
Age, yrs[a]							
EA	36.6±15.5	43.7±13.1	41.7±16.6	24.4±10.2	37.9±18.4	37.0±16.0[b]	0.051[c]
EI	35.2±17.0	33.2±12.9	32.0±19.9	16.6±6.8	33.5±9.3	32.1±15.5[b]	
Sex, n[#]							
EA	14/15	4/2	4/3	3/2	2/2	27/24	0.084[d]
EI	12/14	6/4	3/0	2/5	6/5	29/28	
Location, n[∞]							
EA	18/11	6/0	6/1	2/3	4/0	36/15	0.330[e]
EI	20/6	10/0	2/1	4/3	11/0	47/10	
ES, n (%)	55	16	NA	NA	15	86	-
IA	-	-			-	-	
IB	2 (4)	-			-	2 (2)	
IIA	1 (2)	2 (13)			1 (7)	4 (5)	
IIB	52 (94)	13 (81)			11 (73)	76 (88)	
IIIA	-	1 (6)			-	1 (1)	
IIIB	-	-			3 (20)	3 (4)	
Margins, n (%)							
EA	29 (53)	6 (38)	7 (70)	5 (42)	4 (27)	51 (47)	-
EI	26 (47)	10 (62)	3 (30)	7 (58)	11 (73)	57 (53)	
RT, n (%[&])							
EA	10 (34)	6 (100)	6 (86)	1 (20)	1 (25)	24 (47)	0.590[f]
EI	11 (42)	8 (80)	3 (100)	1 (14)	6 (55)	29 (51)	
QT, n (%[&])							
EA	26 (90)	6 (100)	6 (86)	5 (100)	4 (100)	47 (92)	0.250[g]
EI	19 (73)	10 (100)	3 (100)	7 (100)	11 (100)	50 (88)	
Follow-up, yrs[a]	3.5 ± 3.5	3.5 ± 1.4	2.8 ± 1.9	3.3 ± 2.4	4.4 ± 3.7	3.5 ± 2.6[b]	-
Evidence Quality (GRADE)	Moderate	Low	Low	Low	Low	Low	-

EA: Enneking appropriate margins; EI: Enneking inappropriate margins; ES: Enneking Staging; RT: Radiation therapy; QT: Chemotherapy

NA: Not analysed

*Author, year

[#] Male/Female

[∞] Mobile Spine / Sacrum

[&] n/EA or n/EI

[a] Mean (STD)

[b] Weighted mean (STD)

[c] Mean difference: (IV, Fixed, 95% CI): 5.47 [-0.04, 10.97].

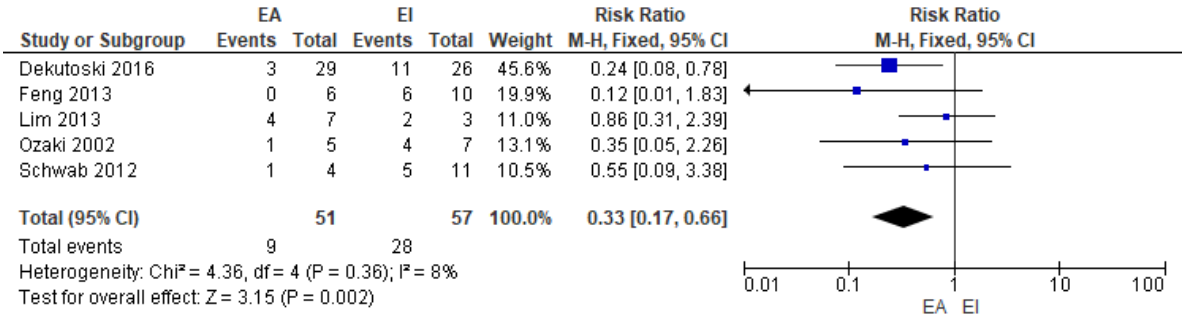
[d] Risk Ratio: (M-H, Fixed, 95% CI): 1.04 [0.72, 1.49]

[e] Risk Ratio: (M-H, Fixed, 95% CI): 0.90 [0.72, 1.11]

[f] Risk Ratio: (M-H, Fixed, 95% CI): 0.91 [0.63, 1.29]

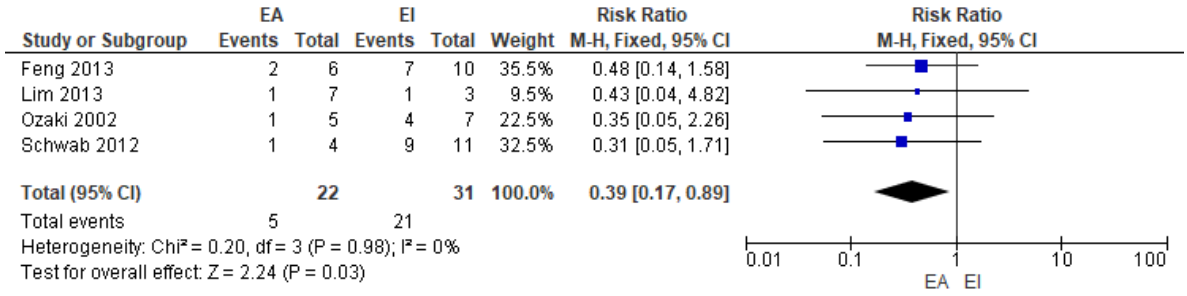
[g] Risk Ratio: (M-H, Fixed, 95% CI): 1.09 [0.94, 1.27]

Graph 2: Meta-analysis about the association between surgical margins and local recurrence



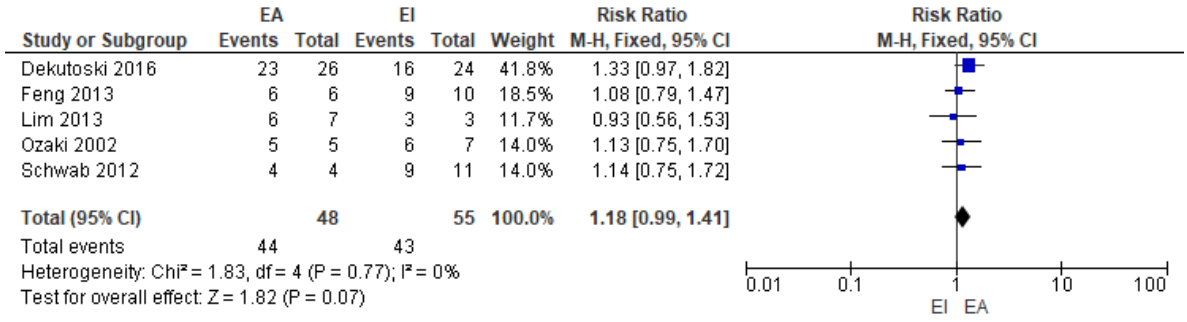
EA: Enneking appropriate margins; EI: Enneking inappropriate margins

Graph 3: Meta-analysis about the association between surgical margins and metastases



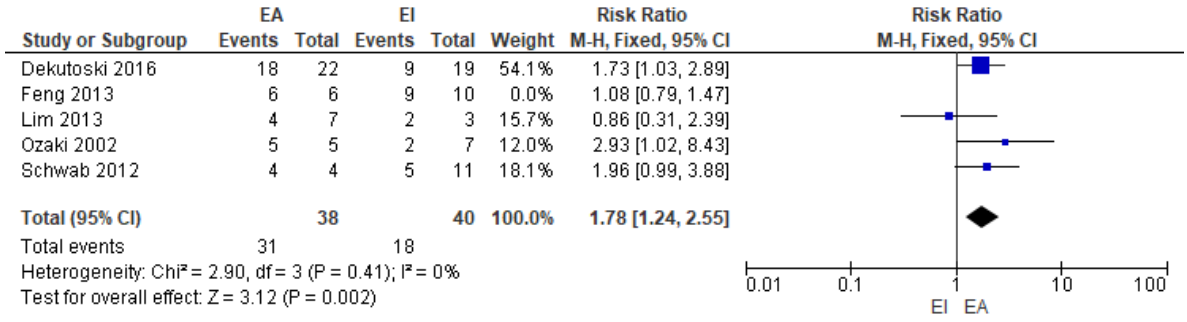
EA: Enneking appropriate margins; EI: Enneking inappropriate margins

Graph 4: Meta-analysis about the association between surgical margins and survival after 12 months



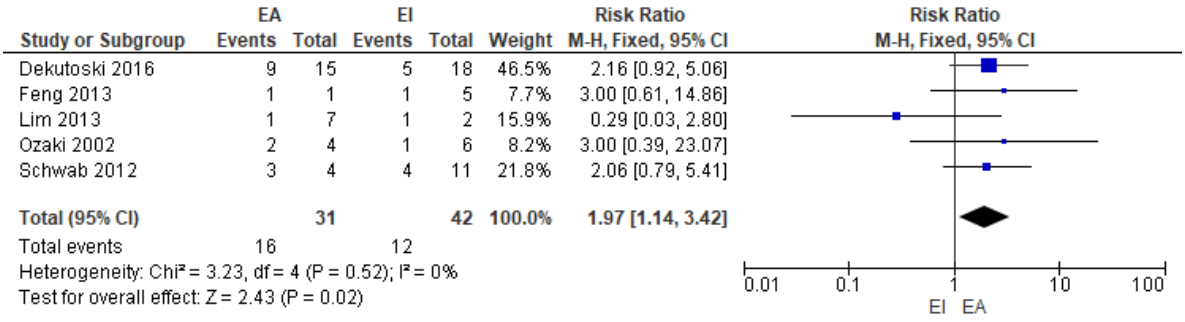
EA: Enneking appropriate margins; EI: Enneking inappropriate margins

Graph 5: Meta-analysis about the association between surgical margins and survival after 24 months



EA: Enneking appropriate margins; EI: Enneking inappropriate margins

Graph 6: Meta-analysis about the association between surgical margins and survival after 60 months



EA: Enneking appropriate margins; EI: Enneking inappropriate margins

Graph 1: Risk of bias