SYSTAMATIC REVIEW

Efficacy of Local Control Strategies for Ewing Sarcoma After Neoadjuvant Chemotherapy: *A Network Meta-analysis*

Haixia Zhu[1], Yumei Li[1], Xiaoliang Xie[1], Shichao Zhang[2], Yuntao Xue[3] and Tianyou Fan[1]

From [1]Department of Orthopaedics, Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China; [2]Department of Orthopaedics, Jinshan Hospital of Fudan University, Shanghai, China; and [3]Department of Orthopaedics, Wuxi People's Hospital, Nanjing Medical University, Wuxi, China.

Correspondence to: Dr Tianyou Fan, Department of Orthopaedics, Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, No.274, Zhijiang Middle Road, Jing'an District, Shanghai 200071, China. fee1838794@163.com

Received: November 07, 2018; Initial review: April 29, 2019; Accepted: January 20, 2020.

Objective: This network meta-analysis aimed at comparing the efficacy of local control strategies after neoadjuvant chemotherapy in patients with Ewing sarcoma.

Design: Network meta-analysis was used to synthesize direct and indirect evidence in a network of trials that compare multiple interventions and has the potential to rank the competing treatments according to the studied outcome.

Setting: There are three treatment options for local Ewing's sarcoma after neoadjuvant chemotherapy, namely surgery, radiotherapy and surgery plus radiotherapy (SR).

Participants: Records of 2540 patients from 11 studies were analyzed.

Main outcome measures: Potentially relevant studies were retrieved from PubMed and Embase, and screened according to inclusion and exclusion criteria. Hazard ratios and the associated 95% confidence intervals were used to describe the efficacy of different interventions on 5-year local recurrence rate and 5-year event-free survival rate. Surface under the cumulative ranking curve (SUCRA) was calculated for ranking probabilities of different treatment.

Results: Compared with radiotherapy, surgery had better efficacy [local recurrence, OR (95% CI) 0.48 (0.33 - 0.87)] and SR had a similar effect as surgery [local recurrence, OR (95% CI) 0.50 (0.29 - 0.82)]. There were no statistically significant differences between three different local control strategies in 5-year local recurrence rate. SUCRA values suggested that surgery was better than SR for 5-year local recurrence rate (0.79 *vs* 0.70) and 5-year event free survival rate (0.67 *vs* 0.50), respectively.

Conclusions: Both surgery and SR were superior to radiotherapy in reducing 5-yer local recurrence of patients with Ewing sarcoma after neoadjuvant chemotherapy. Surgery had higher efficacy than SR on improving the prognosis of patients.

Keywords: *Management, Metastasis, Outcome, Prognosis, Relapse*.

Published online: **March 12, 2020;** ***PII:*** **S097475591600148**

Ewing sarcoma is the second most common primary bone cancer affecting mainly adolescents in the second decade of their life [1]. It has a predilection for long bones (47%), pelvis (26%), chest wall (16%) and spine (6%) [2]. Pain is the most common initial symptom as with other bone sarcomas [3]. Ewing sarcoma is highly metastatic; although, it can be locally controlled by radiotherapy or surgery, historically, 85%-90% of patients die within a few months from a metastasis without systematic treatment neither before nor after local treatment [4]. After the addition of doxorubicin to vincristine, actinomycin D, and cyclophosphamide (VACD regimen), the 5-year overall survival rate of local disease increased from 28% to 65% in the 1970s [5]. Chemotherapy was initially used as systematic treatment to control metastasis, and later in a neoadjuvant setting to enhance local control with confirmed efficacy [6].

Accompanying Editorial: Pages 503-04.

Local control is an important method to improve the overall survival rate and local control rate of Ewing sarcoma patients. Local treatment is recommended after chemotherapy for all patients. Current local control strategies include isolated radiotherapy, isolated surgery, or combined surgery and radiotherapy [7]. The debate over whether surgery and radiotherapy are comparable in terms of local control continues [8]. The optimal local control strategy for Ewing sarcoma remains unclear. The French association for pediatric research suggested that surgery or surgery combined with radiotherapy is the best local treatment for pelvic tumors, while radiotherapy is only available to patients who cannot undergo surgery or patients who are resistant to chemotherapy, or surgery involves amputation [10,11]. Zogopoulos, *et al*. [12] suggested that surgery is the most

effective method for local treatment, while radiotherapy should be used sparingly. Moreover, with the neoadjuvant application of chemotherapy, we are still looking for a conclusive analysis concerning whether surgery and radiotherapy are comparable in terms of local control. This network meta-analysis aimed at comparing the efficacy of local control strategies, including surgery, radiotherapy and combined treatment with radiotherapy and surgery after neoadjuvant chemotherapy in Ewing sarcoma patients.

METHODS

PubMed and Embase database were searched from inception through July 30, 2018, using controlled vocabulary supplemented with keywords describing Ewing sarcoma and neoadjuvant chemotherapy. Possible related studies were also manually identified by screening a reference list of retrieved articles. Two reviewers independently primarily evaluated the eligibility of retrieved articles by screening their titles and abstracts. Disagreement was resolved by discussion. Subsequently, full text of eligible articles was reviewed according to inclusion criteria. The included documents fulfilling the following criteria were eligible for our analysis: (*i*) patients were diagnosed with Ewing sarcoma, and tumors were clinically diagnosed as operable and non-metastatic; (*ii*) all the patients were treated with neoadjuvant chemotherapy; (*iii*) efficacy of at least two of three investigated local control strategies, *i.e.* surgery, radiotherapy, and surgery combined with radiotherapy, should be compared in the clinical trial, and all treatments for local control were performed after neoadjuvant chemotherapy; and (*iv*) available data was sufficient for further analysis. Furthermore, trials were excluded for duplicates, articles based on the same clinical trials, and those not reported in English. We applied Cochrane collaboration's tool for assessing risk of bias [13] to evaluate the quality of enrolled randomized clinical trials, and Methodological index for non-randomized studies (MINORS) for the quality of randomized trials [14].

In our analysis, we used 5-year local recurrence rate (5-LR) and 5-year event-free survival rate (5-EFSR) as outcomes of investigated treatment. Considering that the main evaluation method of Ewing sarcoma is local recurrence rate, and the survival data is relatively lacking, we used the local recurrence rate as the main outcome index and the survival data as the secondary outcome index.

Relevant data were extracted by two authors independently and discrepancies were dealt by discussion. General information including first author, year of publication, nationality of subjects, study design, sample size and treatment were documented. Odd ratios (ORs) for OS and EFS were either extracted from original articles as the summary statistics or estimated indirectly from survival curve or using other available information.

Statistical analyses: This meta-analysis was performed according to the guidelines of PRISMA with Bayesian

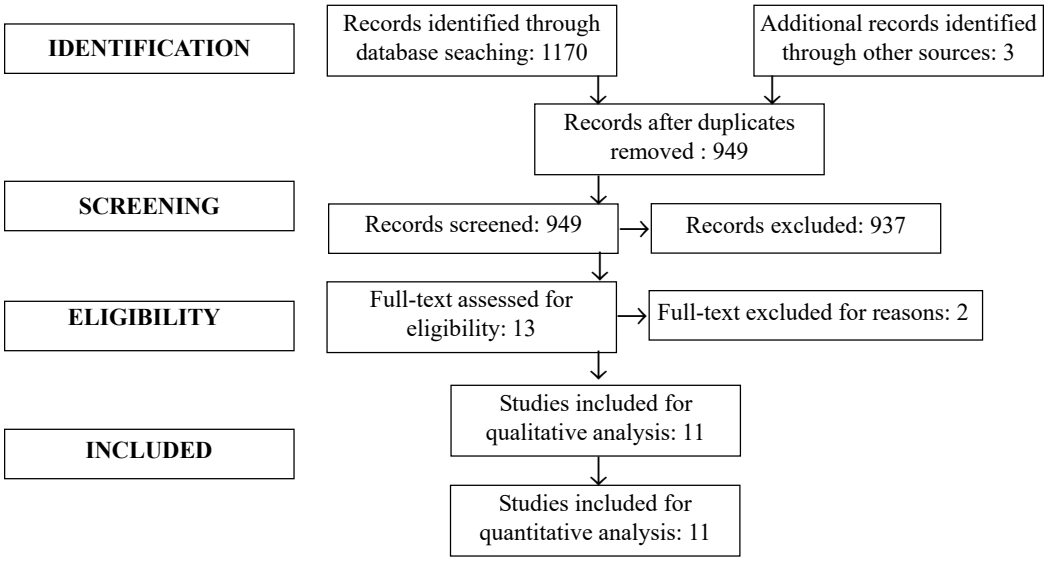


Fig. 1 *Flow diagram summarizing results of study identification and selection.*

Table I Details of Studies Included in the Meta-analysis

Author, year	*Country*	*Design*	*Follow-up (y)*	*Male*	*Age*	*N*	*Neo-CT*	*Intervention*
Reporting only LR recurrence rate								
Ahmed [9], 2017	US	Retrospective	8.3	69.0%	20 (6.6-64.9)	23	VDC/IE 41/Other 7	Surgery *vs.* RT *vs.* SR
Ahmed [15], 2017	US	Cohort	NR	55.0%	13 (0.5-45)	956	IE based	Surgery *vs.* RT *vs.* SR
Laitinen [16], 2016	UK	Retrospective	5.2	51.1%	12.4(2-16)	88	NR	Surgery *vs.* RT *vs.* SR
Shankar [21], 1999	UK	Retrospective	5.5	55.8%	12 (1-27)	190	IVAD	Surgery *vs.* RT *vs.* SR
Carrie [10], 1999	France	Retrospective	6.5	50.7%	12.9	53	EW-85/88/9	Surgery *vs.* RT *vs.* SR
Reporting only EFSR								
Grevener [17], 2016	Germany	Retrospective	10	54.0	11.5 (3-66)	43	VIDE	Surgery *vs.* RT *vs.* SR
Reporting both LR and EFSR								
Donati [8], 2007	Italy	Retrospective	7.3	47.1 %	18.4 (6-46)	66	CNR/ISG	RT *vs.* SR
Dubois [7], 2014	US	Cohort	NR	54.4%	12.4 (0.7-33)	465	VDC/IE	RT *vs.* SR
Bacci [18], 2009	Italy	Retrospective	15	62.0%	17.9 (3-40)	55	IOR	Surgery *vs.* RT *vs.* SR
Yock [19], 2006	US	Retrospective	4.4	52.0%	NR	75	VACA/VACA-IE	Surgery *vs.* RT *vs.* SR
Bacci [20], 2006	Italy	Retrospective	12	64.1%	NR	512	REN	RT *vs.* SR

CT: Chemotherapy; RT: radiotherapy; SR: Surgery combined with Radiotherapy; VDC/IE, Vincristine, Doxorubicin, Cyclophosphamide, and Ifosfamide, Etoposide; LR: Local recurrence rate; EFSR: Event-free survival rate.

model in WinBUGS (MRC Bio-statistics Unit, Cambridge, UK) for network meta-analysis and STATA 12.0 (Stata Corp, College Station, TX) for other analyses. For survival analysis, ORs and the associated 95% credible intervals (CrI) were used to describe the efficacy of different intervention on 5-LR and 5-EFSR. Surface under the cumulative ranking curve (SUCRA) was calculated in order to compare the relative ranking of different therapies. Publication bias was assessed using Begg and Egger tests. A *P* value less than 0.05 indicated the presence of publication bias. A two-side *P* value less than 0.05 was considered as significant.

RESULTS

As illustrated in the flow diagram **(*Fig.* 1)**, a total of 1170 articles were retrieved from the databases, and three more records were obtained from other sources. Finally, 11 studies [7-10, 15-21] from 1999 to 2017 were included in our analysis (***Table* I**). The quality of included studies was evaluated and they were all well-designed and reported reliable results. A total of 2540 patients were enrolled in the meta-analysis in total.

In the included studies, all patients received neoadjuvant chemotherapy prior to the investigated local control strategies. Three different strategies, surgery, radiotherapy and surgery combined with radiotherapy (SR), were evaluated in the included studies (***Table* I**). ***Web Fig.* 1** shows the net plot of the qualified comparison enrolled in our analysis. The width of the line represents the cumulative number of trials per comparison; the circled area represents the cumulative number of patients per intervention. For the outcomes 5-LR and 5-EFSR, the comparison between radiotherapy and SR was the most commonly reported one.

Local recurrence rate: The efficacy of different interventions was obtained by the use of a network meta-analysis. A total of 2474 patients from 9 clinical trials were involved in our analysis. As illustrated in ***Fig.* 2** and ***Table* II**, surgery and SR showed no statistical difference in 5-LR. However, both surgery and SR had statistically significant differences with radiotherapy. Compared with radiotherapy, surgery had better efficacy [OR (95% CI) 0.48 (0.33 -0.87)] and SR had a similar effect with surgery [OR (95% CI) 0.50 (0.29 -0.82)]. Surgery and SR could significantly reduce 5-LR of patients who received neoadjuvant chemotherapy.

The SUCRA values show the relative efficacy of different strategies (***Fig.* 3**). Surgery and SR ranked the highest for 5-LR (SUCRA value 0.79 and 0.70, respectively).

Survival analysis: 749 patients from seven clinical trials

Table II Network Meta-analysis Results for 5-LR and 5-EFSR in Ewing Sarcoma

	Trials	*OR (95% CrI)*
5 LR: No. of arms=28, Patients=2474		
*SG *vs*. RD	9	0.49 (0.30-0.82)
SG *vs*. SR	9	0.94 (0.56-1.72)
*RD *vs*. SG	9	2.05 (1.22-3.32)
*RD *vs*. SR	10	1.95 (1.17-3.32)
SR *vs*. SG	9	1.06 (0.58-1.79)
*SR *vs*. RD	10	0.51 (0.30-0.85)
SG *vs*. RD	6	1.25 (0.41-3.82)
5-EFSR: No. of arms=19, Patients=749		
SG *vs*. SR	6	1.28 (0.39-3.86)
RD *vs*. SG	6	0.8 (0.26-2.46)
RD *vs*. SR	7	1.03 (0.35-2.86)
SR *vs*. SG	6	0.78 (0.26-2.53)
SR *vs*. RD	7	0.97 (0.35-2.89)

*5-LR: 5 year local recurrence rate; 5-EFSR: 5 year event-free survival rate; OR (95% CrI) odds ratio (95% Credible interval); SG: surgery; RD, radiation therapy; SR, surgery combined with radiation; *P<0.03.*

were included in the analysis. There were no statistically significant differences between the three local control strategies in 5-EFSR (***Fig.* 2** and ***Table* 2**). As per SUCRA values, surgery ranked the highest for 5-EFSR. Radiotherapy and SR had lower SUCRA values for improving 5-EFSR (0.32 and 0.50, respectively). The publication bias of various studies for 5-LR and 5-EFSR is shown in ***Web Fig.* 2**.

DISCUSSION

In the present meta-analysis, radiotherapy was the least favorable for improving the prognosis of Ewing sarcoma patients, with significantly higher 5-LR when compared with SR and surgery. No significant difference was observed between surgery and SR, yet the SUCRA value indicated that surgery had higher ranking probability on decreasing 5-LR. Surgery, radiotherapy and SR showed no significant difference of 5-EFSR, while surgery ranked the highest as per ranking probabilities by SUCRA value.

DuBois, *et al*. [7] reported that radiation had a higher risk of local failure, when compared with that of localized ES patients treated with surgery. A study conducted by Bacci, *et al*. [20] showed that the recurrence rate after radiation therapy was high in patients with ES family tumors. In addition, the risk of second malignancies was another significant consideration for patients receiving radiation therapy [23]. Surgery was suggested to be better than radiotherapy in cases of extremity ES family tumors with achievable adequate surgical margins, and thus surgery was the optimal treatment for sites like extremities, which brought a better prognosis to patients [20].

Out results show that surgery is superior to SR. Our results are consistent with those of several previous researchers [7,18-20], which also indicated that additional radiotherapy did not show better outcomes when compared with surgery alone. However, the location of tumor may influence the efficacy of surgery. As reported previously, surgery was the best treatment for small tumors at humerus, yet surgery was only recommended for large tumors when good functional results and quality of life can be expected, and adequate surgical margins are achievable. The best treatment is uncertain for long bones that need to be rebuilt after large segmental resection (femur, tibia, and humerus) [18]. Moreover, the use of surgery for pelvic tumors in Ewing sarcoma is controversial [24,25].

Surgery combined with radiotherapy is the standard of care in the majority of high-risk extremity soft-tissue

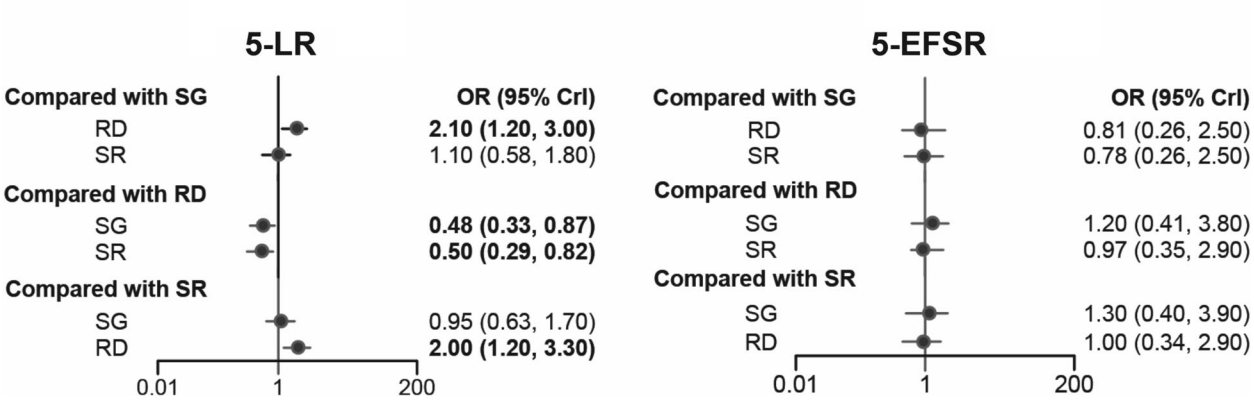


Fig. 2 *Five-year local recurrence rate and 5-year event-free survival rate in Ewing Sarcoma.*

WHAT THIS STUDY ADDS?

Surgery is the optimal option for improving 5-year local recurrence and 5-year event free survival in Ewing sarcoma patients, following neoadjuvant chemotherapy.

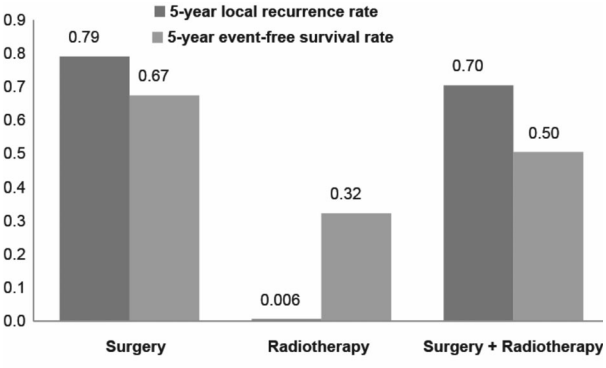


Fig. 3 *Surface under the cumulative ranking curve (SUCRA) of all treatments. Each column shows the probability of that treatment being ranked at the top.*

sarcomas [26]. Several retrospective studies reported that combined therapy had a local tumor control advantage over surgery alone, especially when tumor was larger than 200 mL at diagnosis or the removal of tissues were incomplete during surgery [23,27,28]. However, we did not find any survival benefit when combined intervention was compared with surgery alone. Moreover, combined radiotherapy after surgery resulted in increased risk of long-term treatment-associated toxicities [7]. Due to the lack of sufficient direct data, the adverse effects of SR and surgery were not compared in our network meta-analysis.

A previous meta-analysis enrolled eight retrospective clinical trials and reported inconsistent results in the efficacy of radiotherapy compared with surgery in localized Ewing sarcoma [1]. Whereas in our analysis, five newer studies were included, and one article was excluded due to lack of sufficient data [22]. Moreover, in the present analysis, we focused on the efficacy of local control strategies after neoadjuvant chemotherapy. Neoadjuvant chemotherapy helps to treat the disease early, reducing the chance of metastatic dissemination and also reduces tumor volume, making it resectable.

Some limitation of this study need to be highlighted. Firstly, the number of studies enrolled for our analysis were very limited. We were unable to investigate the effect of different local control strategies on overall survival, disease-free survival and survival rate with a shorter follow-up time due to the lack of sufficient data. Although the network meta-analysis enlarges source of evidence for different comparisons, we still need direct evidence for a robust conclusion. Secondly, since all local control strategies for Ewing sarcoma were performed after neoadjuvant chemotherapy, we did not specify different regimens and protocols for chemotherapy. This might confound the efficacy of local control strategies. Yet all the regimens and protocols used in enrolled RCTs were standard first-line treatments, the efficacy of which have been proven in previous studies. Thirdly, the used local treatment was the clinicians'choice based on patient and tumor characteristics. Radiation therapy is often used in cases of narrow or intralesional surgical margins or poor histological response to chemotherapy or when surgery would be too mutilating. Additionally, results of survival analysis were reported by odds ratios with extracted binary data from original articles. Hence, we were not able to compare the survival curves of different local control strategies. Moreover, since no reliable RCTs have been performed regarding to the efficacy of local control strategies on Ewing sarcoma patients, we enrolled only retrospective cohort studies in our analysis. The quality and reliability of involved data may thus limit the interpretation of our results.

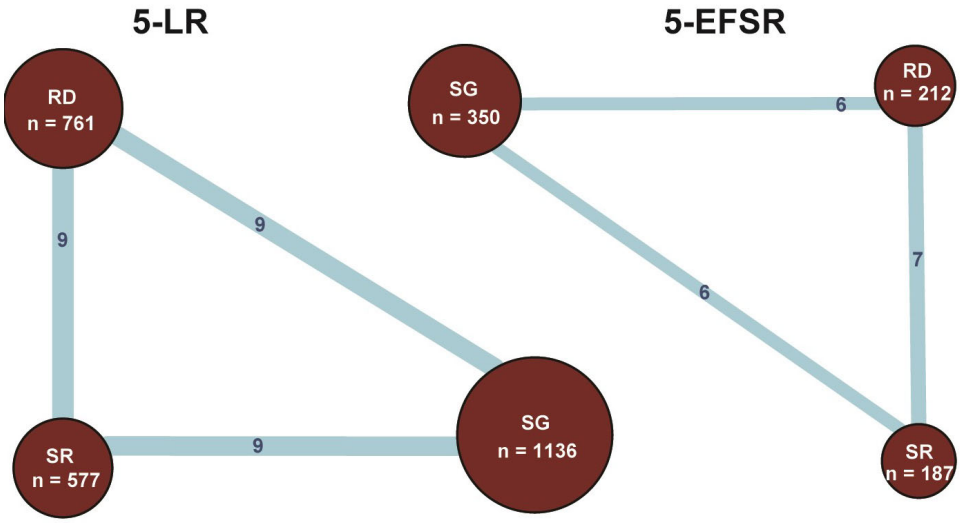
In conclusion, this network meta-analysis suggested that surgery might be the optimal option for improving 5-LR and 5-EFSR of Ewing sarcoma patients. However, due to the lack of high-quality data, the results should be interpreted with caution. The choice of local control strategy should be decided through consideration of patient characteristics, potential adverse effects, and patient preference. Further research and well-designed randomized clinical trials are warranted to clarify the optimal local control strategy for Ewing sarcoma.

Contributors: HZ,YL,XX: substantial contribution to the conception and design of the work; HZ,SZ,YX: acquisition, analysis, and interpretation of the data; HZ: drafting of the manuscript; TF: revising the manuscript critically. All authors have read and approved the final article.
Funding: None; *Competing interests*: None stated.

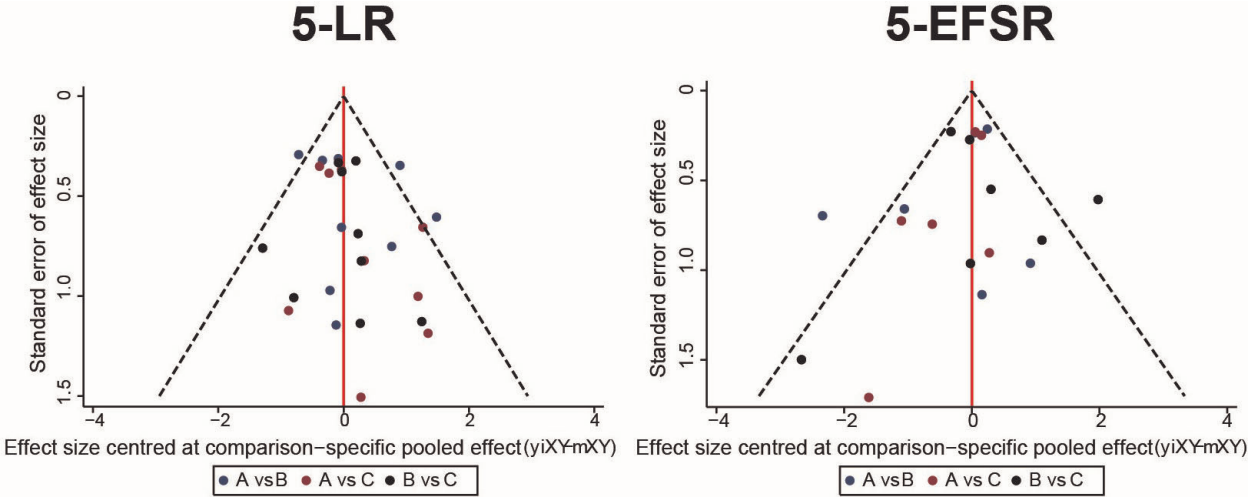
REFERENCES

1. Werier J, Yao X, Caudrelier JM, Di Primio G, Ghert M, Gupta AA, *et al*. A systematic review of optimal treatment

strategies for localized Ewing's sarcoma of bone after neo-adjuvant chemotherapy. Surg Oncol. 2016;25:16-23
2. Bolling T, Hardes J, Dirksen U. Management of bone tumours in paediatric oncology. Clin Oncol (R Coll Radiol). 2013;25:19-26.
3. Moore DD, Haydon RC. Ewing's sarcoma of bone. Cancer Treat Res. 2014;162:93-115.
4. Falk S, Alpert M. Five-year survival of patients with Ewing's sarcoma. Surg Gynecol Obstet. 1967;124:319-24.
5. Pretz JL, Barysauskas CM, George S, Hornick JL, Raut CP, Chen YE, *et al*. Localized adult ewing sarcoma: Favorable outcomes with alternating vincristine, doxorubicin, cyclophosphamide, and ifosfamide, etoposide (VDC/IE)-based multimodality therapy. Oncologist. 2017;22:1265-70.
6. Wardelmann E, Haas R, Bovée J, Terrier P, Lazar A, Messiou C, *et al*. Evaluation of Response After Neoadjuvant Treatment in Soft Tissue Sarcomas; the European Organization for Research and Treatment of Cancer–Soft Tissue and Bone Sarcoma Group (EORTC–STBSG) Recommendations for Pathological Examination and Reporting. Eur J Cancer. 2016;53:84-95.
7. DuBois SG, Krailo MD, Gebhardt MC, Donaldson SS, Marcus KJ, Dormans J, *et al*. Comparative evaluation of local control strategies in localized Ewing sarcoma of bone: A report from the Children's Oncology Group. Cancer. 2015;121:467-75.
8. Donati D, Yin J, Di Bella C, Colangeli M, Bacci G, Ferrari S, *et al*. Local and distant control in non-metastatic pelvic Ewing's sarcoma patients. J Surg Oncol. 2007;96:19-25.
9. Ahmed SK, Randall RL, DuBois SG, Harmsen WS, Krailo M, Marcus KJ, *et al*. Identification of patients with localized Ewing sarcoma at higher risk for local failure: A report from the Children's oncology group. Int J Radiat Oncol Biol Phys. 2017;99:1286-94.
10. Carrie C. Nonmetastatic Pelvic Ewing Sarcoma: Report of the French Society of Pediatric Oncology. Med Pediatr Oncol. 1999; 33:444-9;
11. De Marco S, Pollera CF, Cognetti F. Nephroblastoma in the adult. Med Pediatr Oncol. 1999;33:497-9.
12. Zogopoulos G, Teskey L, Sung L, Dix D, Grant R, Greenberg ML, *et al*. Ewing sarcoma: Favourable results with combined modality therapy and conservative use of radiotherapy. Pediatr Blood Cancer. 2004;43:35-9.
13. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. British Med J. 2011;343:d5928.
14. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): Development and validation of a new instrument. ANZ J Surg. 2003;73:712-6.
15. Ahmed SK, Robinson SI, Arndt CAS, Petersen IA, Haddock MG, Rose PS, *et al*. Pelvis Ewing sarcoma: Local control and survival in the modern era. Pediatr Blood Cancer. 2017;64:e26504.
16. Laitinen M, Parry M, Albergo JI, Jeys L, Sumathi V, Grimer R. Outcome of pelvic bone sarcomas in children. J Pediatr Orthop. 2016;38:537-42.
17. Grevener K, Haveman LM, Ranft A, van den Berg H, Jung S, Ladenstein R, *et al*. Management and outcome of Ewing sarcoma of the head and neck. Pediatr Blood Cancer. 2016;63:604-10.
18. Bacci G, Palmerini E, Staals EL, Longhi A, Barbieri E, Alberghini M, *et al*. Ewing's sarcoma family tumors of the humerus: Outcome of patients treated with radiotherapy, surgery or surgery and adjuvant radiotherapy. Radiother Oncol. 2009;93:383-7.
19. Yock TI, Krailo M, Fryer CJ, Donaldson SS, Miser JS, Chen Z, *et al*. Local control in pelvic Ewing sarcoma: analysis from INT-0091–A report from the Children's Oncology Group. J Clin Oncol. 2006;24:3838-43.
20. Bacci G, Longhi A, Briccoli A, Bertoni F, Versari M, Picci P. The role of surgical margins in treatment of Ewing's sarcoma family tumors: Experience of a single institution with 512 patients treated with adjuvant and neoadjuvant chemotherapy. Int J Radiat Oncol Biol Phys. 2006;65: 766-72.
21. Shankar AG. Local therapy and other factors Infuencing site of relapse in patients with localised Ewing's sarcoma. Eue J Cancer. 1999;35:1698-1704.
22. Sokolov T, Stoyanova A, Mumdjiev I, Mihova A. Comparison of two treatment approaches to localized Ewing's sarcoma. Ortopediya i Travmatologiya. 2000;36: 509-15.
23. Shankar AG, Pinkerton CR, Atra A, Ashley S, Lewis I, Spooner D, *et al*. Local therapy and other factors influencing site of relapse in patients with localised Ewing's sarcoma. United Kingdom Children's Cancer Study Group (UKCCSG). Eur J Cancer. 1999;35:1698-704.
24. Kawai A, Healey JH, Boland PJ, Lin PP, Huvos AG, Meyers PA. Prognostic factors for patients with sarcomas of the pelvic bones. Cancer. 1998;82:851-9.
25. Laitinen M, Parry M, Albergo JI, Jeys L, Sumathi V, Grimer R. Outcome of pelvic bone sarcomas in children. J Pediatr Orthop. 2018;38:537-42.
26. O'Sullivan B, Davis AM, Turcotte R, Bell R, Catton C, Chabot P, *et al*. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: A randomised trial. Lancet. 2002;359:2235-41
27. Foulon S, Brennan B, Gaspar N, Dirksen U, Jeys L, Cassoni A, *et al*. Can postoperative radiotherapy be omitted in localised standard-risk Ewing sarcoma? An observational study of the Euro-EWING group. Eur J Cancer. 2016;61:128-36.
28. Bacci G, Forni C, Longhi A, Ferrari S, Donati D, De Paolis M, *et al*. Long-term outcome for patients with non-metastatic Ewing's sarcoma treated with adjuvant and neoadjuvant chemotherapies. 402 patients treated at Rizzoli between 1972 and 1992. Eur J Cancer. 2004; 40:73-83.



Web Fig. 1 *Evidence net plots for local control strategies for Ewing sarcoma. The node size represents the sample size and the width of the lines represents the cumulative number of trials.*



Web Fig. 2 *Funnel plot for local control strategies for Ewing sarcoma.*