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Original Article

Time to relapse predicts post-relapse survival in recurrent osteosarcoma: a meta-analysis

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Abstract: Background: Relapse in osteosarcoma is associated with very poor prognosis. The prognostic value of time to relapse in recurrent osteosarcomas remains controversial. Hence, a meta-analysis was conducted to investigate the effect of relapse-free interval (RFI) on post-relapse survival (PRS). Methods: From inception to November 2015, we searched for cohort studies using the following databases: PubMed, Cochrane Library, EBSCO and Science Direct. Eligible studies should provide the number of patients with a short and long RFI (24-months as a cutoff usually) and their corresponding 5-year PRS. The pooled relative risk (RR) with 95% confidence interval (95% CI) was used to assess the impact of RFI on PRS. Results: A total of 11 studies published between 2003 and 2014 were found to be in accordance with our inclusion criteria. 1692 cases of recurrent osteosarcomas were enrolled in this meta-analysis. Approximately 60% relapses occur early, usually within 24 months. The primary meta-analysis indicated that recurrent patients with a short RFI had a worse PRS (n=11, RR=2.63, 95% CI: 2.17 to 3.21, P<0.001). By subgroup analyses, we further found that 24-months was a common and alternative cutoff value (n=7, RR=2.37, 95% CI: 1.84 to 3.06, P<0.001). No significant differences were obtained after stratified by age range, sample size, and geographic region. And a complete surgical remission (CR) of primary tumor correlated with a higher probability of a long RFI (subgroup difference: P=0.01). Conclusion: The findings of our meta-analysis suggest that late relapses fares a better PRS in recurrent osteosarcomas. We recommend 24-months as a clinically alternative cutoff value and long-term follow-up. Complete surgical resection, if feasible, may be prerequisite for late relapse.

Keywords: Relapse-free interval, post-relapse survival, recurrent osteosarcoma, meta-analysis

Introduction

Osteosarcoma is the most common primary malignant bone tumor in children and adolescents [1]. Approximately 400 to 1000 new cases of pediatric osteosarcoma are diagnosed each year in the US and comparable incidence in Europe [2, 3]. Complete surgical resection (CR) of the primary tumor has been reliably linked to long-term survival in osteosarcoma [4-6]. Unfortunately, about 30-35% of these patients still had local or systemic relapse, in which the lung was the most common site [7, 8]. Disease relapses, local and/or distant, are difficult to treat and often will eventually lead to death [9]. Thus prognostic factors for post-relapse survival (PRS) are of great importance.

In fact the PRS rate for recurrent osteosarcoma ranges between 18% [8] and 40% [10], which were initially treated by combined modality therapy. There are several risk factors identified for PRS in recurrent osteosarcomas. The size of recurrence [7, 11] and complete surgical resection [12, 13] at the time of recurrence are two key prognostic factors, followed by site of relapse and chemotherapy response. Even so, prognostication in individual recurrent patients remains a problem.

It has been shown that most relapses occur early, usually within 2-3 years after the completion of initial treatment. And there are a number of studies which report the association of time to relapse and outcome of patients who relapse [6, 8, 14], but their definitions of early relapse are contrasting. Time to relapse was calculated either from the achievement of surgery resection or the initial diagnosis [13, 15]. Moreover, various intervals were identified as a cutoff to evaluate the influence on overall survival from time of relapse.

Some believe that relapse is not only an expression of tumor aggressiveness but also a prognostic factor. However, consensus has not been reached regarding whether time to relapse has a predictive effect on PRS in recurrent patients. Study by Crompton [16] showed that there was no difference in PRS when patients who recurred in less than 14 months from initial diagnosis were compared to those who recurred after 14 months. And Duffaud [17] reported that the difference in PRS for patients relapsing less than 20 months after diagnosis was not significant when compared to those who relapsing ≥20 months. Conversely, many other studies have demonstrated that an improved PRS was associated with a relapse-free interval (RFI) of more than 24 months [7, 8, 10, 13, 18, 19]. These discrepancies can be partly explained by the lack of homogeneity and the relatively small number of patients these individual studies based on. Therefore, there is no enough evidence to draw comprehensive and reliable conclusions.

As mentioned above, the aim of this study was to evaluate whether there is any difference in PRS between patients with early relapse and those with late relapse (local or systemic). To accomplish this goal, a comprehensive meta-analysis was conducted to assess the impact of RFI on PRS and to further explore the possible reasons.

Methods

Search strategy

Two of the authors (J M and T Z) simultaneously and independently searched eligible studies in the following databases: PubMed, Cochrane Library, EBSCO and ScienceDirect. The retrieval time was set as from inception to November 2015. The following keywords were used to identify possible articles: “post relapse”, “post recurrence”, “survival”, “osteosarcoma”, and “osteogenic sarcoma”. Studies that did not obviously conform to our criteria were excluded; examples of such included studies about patients with ewing’s sarcoma. The most recent or complete publication was included when the authors published several studies using data from overlapping samples. Studies about time to relapse in osteosarcomas were further evaluated, and any differences that arose were resolved by one of the other authors (T X). We reported the meta-analysis according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement [20].

Inclusion and exclusion criteria

In this meta-analysis, only published cohort studies on humans were included, and the language was without restriction. Studies were included if they fulfilled the following inclusion criteria: (1) patients with a definite diagnosis of osteosarcoma, and (2) who received (neo-adjuvant and/or adjuvant) chemotherapy and definitive surgery, (3) the studies should provide sufficient information about the number of recurrent patients with short and long RFI and their corresponding 5-year PRS.

Data extraction

The outcomes that we primarily focused on were RFI and 5-year PRS. The essential data were extracted from each study in a unified format that included the first author’s name, year of publication, country/group, age range, patient number (short/long RFI), cutoff value (months), follow-up (years) and the percentage of an achievement of first CR. The numbers of recurrent patients that experienced ashort/long RFI and the corresponding 5-year PRS were extracted directly from each study. We extracted the pooled relative risks (RRs) and 95% confidence intervals (95% CI) to evaluate survival effects.

Quality assessment

Two of the authors (HY and LS) independently completed quality assessments on the basis of the Newcastle-Ottawa Quality Assessment Scale (NOS) [21], which was validated for cohort studies in a meta-analysis. The NOS criteria included three aspects: (1) subject selection: 0-4; (2) comparability of subject: 0-2; (3) clinical outcome: 0-3. NOS scores ranged from 0 to 9. Studies with a score more than 7 indicated a good quality and were selected for further meta-analysis. Any differences were resolved by a third investigator (H G).

Statistical analysis

Statistical analyses were performed using STATA 12.0 (StataCorp, College Station, Texas)

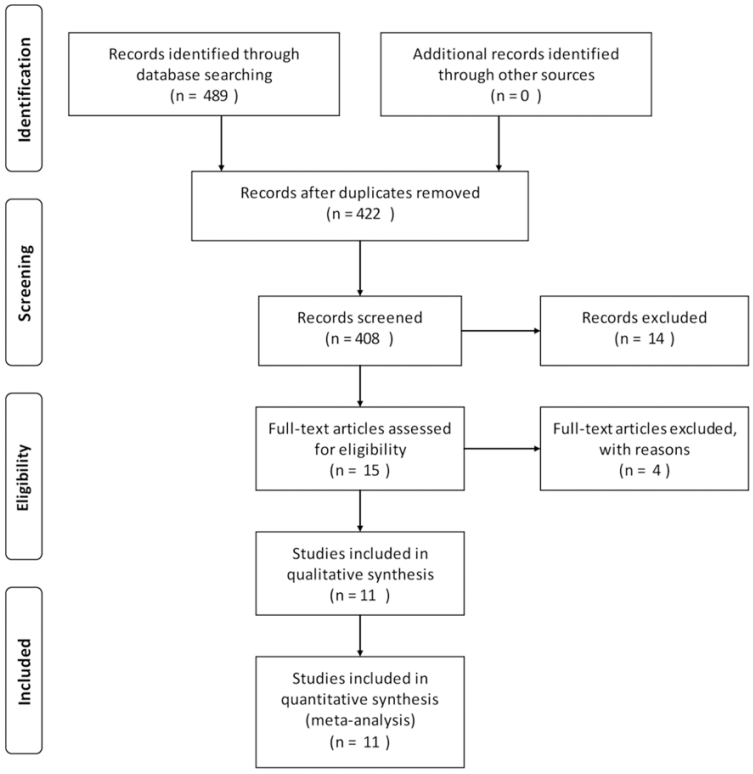

Figure 1. Flow diagram of study selection.

[22]. We calculated the pooled RRs and corresponding 95% CIs for dichotomous data. A fixed-effect model was utilized acquiescently. In cases where differences between groups ($P<0.05$ and $I^2>60\%$) existed simultaneously, we considered there was heterogeneity between studies and therefore used a random-effect model. When $I^2>75\%$, it indicated that there was an obvious statistical heterogeneity among the included studies. Then sensitivity analysis should be conducted to exclude studies at high risk of bias. To uncover the best cut-off value and further identify possible reasons, subgroup analyses were then undertaken whenever appropriate. The funnel plot and Egger's test [23] were used to reveal publication bias. For all analysis, *P*-value <0.05 was believed significant.

Results

Characteristics of the included studies

We identified 489 articles from the above discussed databases, and 15 [7, 8, 10-13, 15-19, 24-27] of these studies were included based on the search criteria and quality criteria. Upon further review, 4 studies were excluded: 2 were eliminated due to the duplicate population [12, 24]; 1 study [25] only focused on the influence of RFI on overall survival from first diagnosis instead of PRS; another one [26] was a study reported recurrent patients with the estimated 10-year PRS. Ultimately, a total of 11 cohort studies [7, 8, 10, 11, 13, 15-19, 27] were included in our meta-analysis. Except for the study by Lee [27], the language of all studies was English. Our search strategy and the steps applied to select eligible studies were summarized in the flow diagram showed in **Figure 1**.

Nearly all of the included studies calculated the5-year PRS as a measurement of long-term outcome after relapse. The exception included one study by Hawkins [19] that evaluated the 4-year PRS and another one by Chou [18] which reported the 3-year PRS. 7 studies defined RFI from initial diagnosis to relapse, and the others defined it from operation. Furthermore, a uniform cutoff value (months) differentiating between early relapse and late relapse did not exist. A majority of studies chose 24 months as a reference, while some others used 20 or 14 months, even still another one [27] adopted 12 months as a threshold value. We included all these studies because of their high quality and also to reduce heterogeneity as much as possible.

Among the included studies, 4 were multi-center studies [8, 10, 11, 19], and other 7 were single-center studies. When classifying the included studies based on the percentage of an achievement of a first CR, 6 studies [10, 11, 15, 17-19] were with patients all achieved a first CR, and other 5 studies included patients with inadequate surgical margins. The characteristics of the 11 included studies are summarized in **Table 1**.

A total of 1692 patients were included in our meta-analysis: 661 patients were with long RFI, and the remaining 1031 (60.9%) patients were

Table 1. Characteristics of included studies

Study	Year	Country/ Groups	Age (y)	Total	Long RFI	Short RFI	Definition (from)	Cutoff (mons)	Follow-up (y)	CR (%)	NOS
Bielack	2005	COSS	15 (2.2-68.2)	576	311	265	Diagnosis	18	5	100	9
Chou	2005	USA	15 (4.5-31.4)	43	17	26	Surgery	24	3	100	8
Crompton	2006	USA	17 (4.9-30.6)	37	18	19	Diagnosis	14	5	<81	7
Duffaud	2003	France	20 (12-55)	33	20	13	Diagnosis	20	5	100	8
Ferrari	2003	Italy	17 (5-47)	114	58	56	Surgery	24	5	100	9
Gelderblom	2011	EOI	<40	564	110	454	Diagnosis	24	5	<100	8
Hawkins	2003	USA	15 (4.5-23)	59	18	41	Diagnosis	24	4	100	8
Lee	2008	Korea	NA	180	78	102	Surgery	12	5	<70	7
Rodriguez	2004	USA	16 (5-24.6)	26	6	20	Diagnosis	24	5	46	8
Takeuchi	2014	USA	18 (6-71)	45	17	28	Surgery	24	5	96	8
Wong	2013	China	13 (3-18)	15	8	7	Diagnosis	24	5	100	8

Abbreviation: NA: Not available; COSS: Cooperative osteosarcoma study group; EOI: European organization for research and treatment of cancer; RFI: Relapse-free interval; CR: Complete surgical remission; NOS: Newcastle-ottawa quality assessment scale.

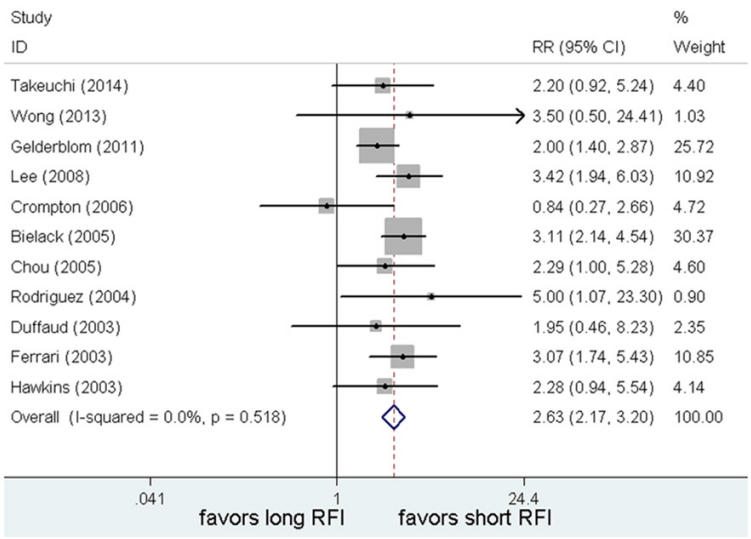

Figure 2. A long RFI was associated with significantly improved PRS when compared to early relapse. RR = Relative risk; CI = Confidence interval; RFI = Relapse-free interval.

with relatively shorter RFI. The sample size varied from 15 to 576 patients. It is additionally worth noting that out of all 6 studies that were included in our meta-analysis, only 50 recurrent patients were evaluated, which was a relatively small sample size.

Methodological quality of the studies

We presented the results of the assessment of the methodological quality in **Table 1**. Eleven included studies were all with high quality (score≥7) according to the NOS scores.

Post-relapse survival (PRS)

All of the 11 studies provided RR values about PRS. The 5-year PRS in recurrent osteosarcomas ranged from 18% [8] to 35% [18]. We chose a fixed-effect model because there was no significant differences between the above study groups (P=0.47 and I^2=0%). Time to relapse was found to be correlated with post-relapse outcome in recurrent osteosarcoma. An extended RFI was associated with significant improvements in PRS when compared to early relapse (n=11, RR=2.63, 95% CI: 2.17 to 3.21, P<0.001, see **Figure 2** and **Table 2**).

Subgroup analysis

Main results of subgroup analysis for PRS were listed in **Table 2**. Our included studies calculated time to relapse with the two possible definitions. The subgroup analysis indicated that there was no difference in PRS between the two definitions (from diagnosis: n=7, RR=2.49, 95% CI: 1.96 to 3.16, P<0.001; vs. from surgery: n=4, RR=2.95, 95% CI: 2.11 to 4.13, P< 0.001; subgroup difference: P=0.41). And our studies classified patients into early and late relapse, with various cutoff values. 7/11 of the

Table 2. A summary of RRs for the overall and subgroup analyses of time to relapse and PRS inrecurrent osteosarcomas

PRS	Studies	Total	RR	LL	UL	Heterogeneity			P
						Chi-squared	I^2	P	
Overall	11	1692	2.63	2.17	3.20	9.15	0	0.52	<0.001
Definition (from)									
Diagnosis	7	1310	2.49	1.96	3.16	7.23	17.0%	0.3	<0.001
Surgery	4	382	2.95	2.11	4.13	1.07	0.0%	0.78	<0.001
Cutoff									
24 months	7	866	2.37	1.84	3.06	2.74	0	0.84	<0.001
Other	4	826	2.91	2.17	3.90	5.21	42.4%	0.16	<0.001
First CR									
All	5	781	2.93	2.22	3.85	1.10	0	0.95	<0.001
Not all	6	911	2.29	1.75	3.01	6.37	37.2%	0.17	<0.001
Age									
<40 only	6	744	2.03	1.52	2.71	4.02	0	0.55	<0.001
All ages	4	768	2.96	2.21	3.97	0.86	0	0.83	<0.001
Sample size									
<50	6	199	2.05	1.3	3.22	3.98	0	0.55	0.002
>50	5	1492	2.76	2.22	3.42	4.31	7.1%	0.37	<0.001
Region									
Europe	4	1287	2.66	2.09	3.37	3.48	13.7%	0.32	<0.001
USA	5	210	2.03	1.32	3.12	3.75	0	0.44	0.001
Asia	2	195	3.43	1.99	5.91	0	0.0%	0.98	<0.001

Abbreviation: PRS: Post relapse survival; CR: Complete surgical remission; RR: Relative risk; LL: Lower limit; UL: Upper limit.

studies [7, 8, 10, 13, 15, 18, 19] chose 24-months as a cutoff value, while the others set various threshold values less than 24 months. There was no difference in PRS when a cutoff value of 24-months (n=7, RR=2.37, 95% CI: 1.84 to 3.06, P<0.001) compared with other values (n=4, RR=2.91, 95% CI: 2.17 to 3.90, P<0.001) (subgroup difference: P=0.22, see **Figure 3**). 24-months was a common and alternative cutoff value, since it preserved its significance and no better value was found.

Besides, no significantly different results were obtained after stratified by variables of percentage of an achievement of first CR, age range [28], sample size, and geographic region (details please see **Table 2**).

Another main question was that what kinds of recurrent patients favored late relapse? Two subgroups were also divided based on whether all patients achieved a first CR or not. Close to half (6/11) of the studies included patients all achieved an initial CR after chemotherapy and surgical excision. The subgroup analysis results indicated that there were significant differences among them (subgroup difference: P=0.01). The more patients achieved a first CR, the higher probability of late relapse (all CR: n=6, RR=2.02, 95% CI: 1.15 to 3.54, P=0.09; vs. not all CR: n=5, RR=0.93, 95% CI: 0.76 to 1.15, P<0.001, see **Figure 4**). In other words, complete resection of primary tumor was probably linked to late relapse in recurrent osteosarcomas. However, this result was cautious because of the high level of statistical heterogeneity among the included studies.

Publication bias

There was no evidence of asymmetry in the funnel plot (not shown). Simultaneously, formal evaluation using Egger's test failed to any reveal evidence for significant publication bias in the PRS (P=0.774).

Discussion

Time to relapse has been previously shown to be correlated with PRS for patients with recurrent malignancies such as breast cancer [29] and lymphoma [30]. To date, numerous

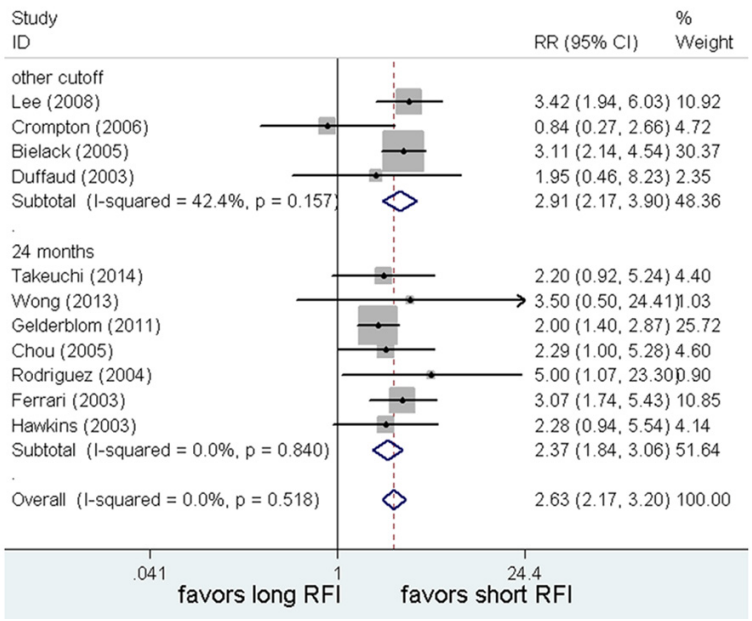

Figure 3. 24-months was an alternative cutoff value. RR = Relative risk; CI = Confidence interval; RFI = Relapse-free interval.

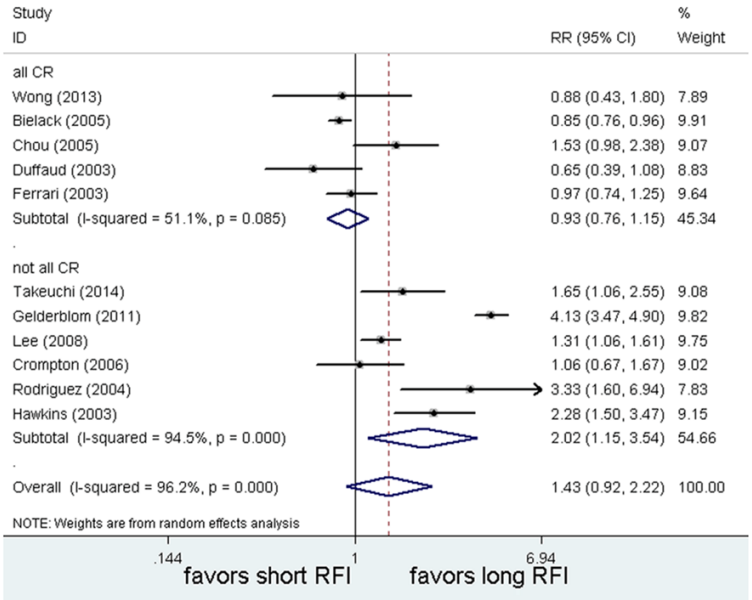

Figure 4. Complete resection was significantly linked to late relapse in recurrent osteosarcomas. CR = Complete resection; RR =Relative risk; CI = Confidence interval; RFI = Relapse-free interval.

authors have reported that the time to recurrence may be another prognostic factor for PRS in recurrent osteosarcomas. However, the results are still controversial in the literature. The convicting results might be partly attributed to the small patient numbers in prior studies. Furthermore, in the studies examining the prognostic role of RFI, there are differences in the definitions, cutoffs, follow-ups and first-line and second-line treatments. As inherent limitations and inconsistent conclusions were found among the previous studies, it was therefore necessary for us to synthesize as many studies as possible to summarize the most credible evidence.

Overall, approximately 40% relapses occur late, usually more than 24 months. In performing a comprehensive analysis of the 11 cohort studies that were focused on the effect of RFI on long-term PRS, we found that early relapse predicted a worse PRS in recurrent osteosarcomas. We confirmed the equivalent prognostic value of calculating time to relapse either from the initial diagnosisor the operation. Our study suggested that time to relapse might be used to recognize patients at higher risk for death after first relapse. Then by subgroup analysis, we found that 24-months was an alternative cutoff value for clinical consultation. No significantly different results were found after stratified by variables of percentage of a first CR, age range, sample size and geographic region. We further identified that the achievement of a first CR was a possible protective factor for late relapse. However, the underlying mechanism is still poorly understood.

Almost all the studies included in our meta-analysis were of high-quality. The majority of them were conducted in the United States [7, 13, 16, 18, 19], and the remaining were conducted in European countries and East Asia. The studies were published between 2003 and 2014; thus, they provided relatively new data. Many of the studies included in our analysis

were conducted by representative multicenter osteosarcoma groups, such as COSS/Cooperative Osteosarcoma Study Group [6], and EOI/European Organization for Research and Treatment of Cancer [8]. The first-line and second-line treatment did not substantially change over this period [31], and worldwide measures of 5-year PRS also were not significantly improved [32, 33]. Subgroup analyses showed that the conclusions were robust, regardless of percentage of a first CR, age range, sample size and geographic region. Both funnel plot and Egger's test were conducted to ensure that there was no obvious publication bias. All of the above made this meta-analysis more reliable.

There's no doubt that complete surgical resection at the time of recurrence is essential for PRS [15, 34]. Our results indicated that complete surgical resection of primary tumor might also be a protective factor for late relapse in recurrent patients. Therefore, every effort should be made to perform a complete surgical resection of primary tumor and all sites of tumor relapse. Long-term routine follow-up for detection of late relapse is warranted. Meanwhile, it must be noted that early relapse remains a negative prognostic factor even in patients achieved a first CR.

Similar to other meta-analyses, our meta-analysis also had several limitations. First, prognostic studies should be conducted in a large randomized design. However, osteosarcoma is a rare disease with a worldwide incidence rate of 3-4 cases per million per year. In rare tumors such as osteosarcoma, cohort studies are also sufficient enough to prove the prognostic role. Second, included studies classified patients into early and late relapse, with two possible definitions and various cutoff values. By subgroup analysis, our results indicated that both definitions had equivalent prognostic power and 24-months was an alternative cutoff value. However the best cutoff value still needs further investigation. Finally, as a lack of prospectively collected individual data, we were not able to evaluate the impact of other multiple response factors and treatment factors delivery on PRS.

In conclusion, the results of our meta-analysis suggest that a short time to relapseis a negative prognostic factor in recurrent osteosarcomas. 24-months is an alternative cutoff value for clinical consultation and adequate follow-up is warranted. The achievement of a first complete surgical resection, if feasible, may be essential for late relapse. The use of time to relapse as a criterion to stratify patients at first relapse might direct recurrent patients to innovative treatments in the future.

Disclosure of conflict of interest

None.

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