Prognostic factors in patients with relapsed high-grade osteosarcoma: a systematic review

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Abstract

Background: Outcome of patients with osteosarcoma after relapse is very poor, with a 5-year overall survival (OS) below 30%. Prognostic factors in this setting remain poorly defined, limiting treatment decisions. This study identifies key clinical and biological prognostic factors to guide future trials.

Methods: A systematic review and meta-analysis included studies published between 1976 and 2022 with ≥35 patients. Searches were performed in MEDLINE/PUBMED, EMBASE, and Cochrane. Study quality was assessed using QUIPS tool. Studies reporting any clinical outcomes in the post-relapse setting were included.

Results: Nineteen studies involving 3,245 patients were analyzed. Nine prognostic factors were identified: relapse-free interval, site, number and size of lesions, resectability, sex, age, alkaline phosphatase levels and response to chemotherapy. Meta-analysis confirmed bilateral lung metastases worsened OS (HR 1.68, 95% CI 1.42–1.99). A relapse-free interval >24 months and complete surgical resection were consistently associated with better outcomes. Results on chemotherapy use were inconsistent. Substantial heterogeneity and low methodological quality were noted across studies.

Conclusions: Key prognostic factors should address clinical trial design. Stratification by resectability, number and site of lesions and relapse-free interval is essential to evaluate treatment efficacy. Standardized protocols are needed to improve outcomes and provide tailored strategies for relapsed osteosarcoma.

Background

Osteosarcoma is the most common malignant bone tumor, primarily affecting adolescents and young adults(1,2). Although treatment advances have improved outcomes, approximately 30-35% of patients experience a relapse or progression of disease. At relapse, the 5-year overall survival (OS) rate is under 30%(3). Achieving surgical complete remission is essential for survival, especially in patients with single and oligometastatic relapses(3). The benefit of additional systemic therapies is uncertain(4–6) and encouraging phase II trial results did not translate into phase III randomised trials(7,8). This severe outlook underlines the critical need for improved treatment strategies at relapse.

Systematic analysis of two decades of phase-II therapeutic trials including patients with relapsed and refractory osteosarcoma highlighted the heterogeneity in trial design and methodology(7–9). Despite the proposal for baseline event free survival (EFS) efficacy assumptions for measurable versus resected disease in single-arm trials, developed by the Children's Oncology Group (COG) in 2016, heterogeneity in phase-II trial design remains an important issue. Due to the variability in patient inclusion criteria, the different endpoints and statistical design results from single-arm trials are often not comparable or eligible for meta-analysis. Only in a limited number of trials patients were randomised(8). The phase I/II trials on multi-tyrosine kinase inhibitors (MTKI) are a clear example of this issue, where due to the incomparability it was not possible to collectively analyse results and define the most promising agent.

Furthermore, it is unknown whether evaluated drugs might be most effective in patients with or without measurable disease. As a result, trials may yield false-negative results, failing to identify therapeutic options that could benefit specific subsets of patients. Understanding of prognostic differences that may exist between patients at relapse is important to improve patients selection or understanding of results of the studies(8). In fact, while the presence of distant metastases, large tumor size, axial location, unresectable disease and poor histological response to neoadjuvant chemotherapy are recognized prognostic indicators at initial diagnosis, their relevance in the recurrent setting is not well-defined (6,10,11).

Therefore, the primary aim of this study is to systematically review the current evidence of clinical and biological prognostic factors for survival in relapsed or progressive high-grade osteosarcoma patients. The results of this study will be included in the development of a solid framework for development of new phase-II clinical trials, as part of the Fight Osteosarcoma Through European Research (FOSTER) consortium, to improve the management of this challenging stage of the disease.

Methods

Inclusion and exclusion criteria

Clinical trials and cohort studies investigating prognostic markers at the point of relapse in high-grade osteosarcoma were included. Preclinical research, non-prognostic marker studies, reviews and guidelines were excluded. The study population included children, adolescents and adults (no age restriction) with high-grade osteosarcoma.

Studies had to provide data separately for this group, evident in at least one survival curve, table or summary statistic. A minimal sample size of 35 or more patients with high-grade relapsed osteosarcoma was considered. Studies published in other languages than English were excluded.

Search

We searched MEDLINE/PUBMED, EMBASE and the Cochrane database, including publications from January 1, 1976, up to the December 31, 2022. The search terms used were: osteosarcoma* AND (prognos* OR surviv* OR mortal* OR outcome OR follow-up OR predict*) AND (marke* OR biomark* OR factor*) AND (relaps* OR recurren*).

Study selection and data extraction

Independent evaluation of all titles and abstracts were screened by two reviewers, excluding trials that did clearly not match the eligibility criteria, independently. Full-text papers were evaluated by two separate reviewers (ARS, RE), independently. Any discrepancies were resolved through group consensus (ARS, RE, WW, GS, MC). Data extraction was performed by two reviewers per paper (ARS, WW), independently. In case of discrepancy, extraction was discussed with a third reviewer (MC).

Data were collected and organized in a Microsoft Excel table. For each included study, details on study design (prospective versus retrospective, multicenter versus monocenter), study setting, number of patients, prognostic factors evaluated, outcome measure used, statistical method applied and results (hazard ratio, p-value) (Supplementary file 1).

Quality assessment

Risk of bias of the included studies was assessed by two reviewers (ARS, WW) using the Quality in Prognosis Studies (QUIPS) instrument, designed to assess the risk of bias for prognostic studies(12). If needed, a third reviewer was involved to achieve consensus (MC). The QUIPS instrument consists of six domains—study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting.

Outcome measures

We included studies reporting any form of survival outcome in the post-relapse setting, including but not limited to overall survival (OS), progression-free survival (PFS) and event-free survival (EFS). Definitions were applied as defined in the included studies.

Data analysis

We evaluated both univariate and multivariate results to identify prognostic markers in relapsed osteosarcoma. Markers were categorized based on their nature into demographic characteristics, tumor-related markers, laboratory markers, genomic markers (at the DNA level), expression biomarkers (at the mRNA or protein level), and therapy response, among others. A meta-analysis was planned for all markers demonstrating a statistically significant association with survival ($p < 0.05$) in two or more studies, provided the quality and consistency of the data allowed. The impact of study heterogeneity on meta-analysis was assessed using methods described by Higgins and Thompson(13).

Reporting

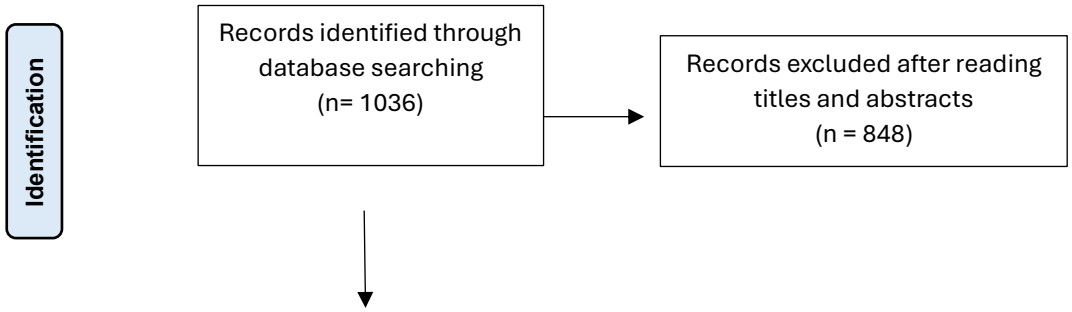
We reported this systematic review according to the PRISMA guidelines(14,15)

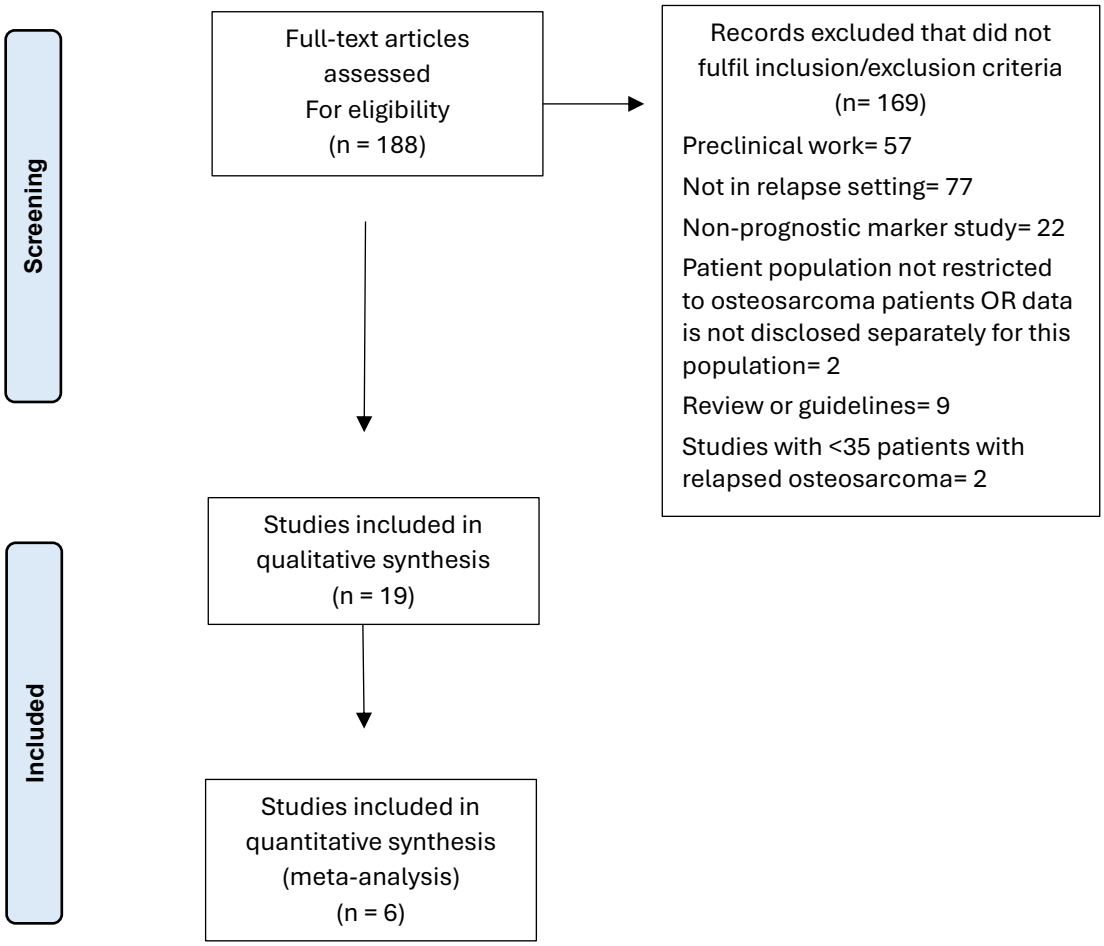
3. Results

3.1. Eligible studies

Our search retrieved 1036 hits in the initial search. After title and abstract screening 848 studies were excluded (Supplementary file 1). After full-text screening of 188 studies, 19 met all eligibility criteria and were included in this review (Figure 1). The 19 studies included a total population of 3245 relapsed osteosarcoma patients.

Figure 1. Flow-diagram of the study selection process




Screening
Full-text articles assessed For eligibility (n = 188)
Records excluded that did not fulfil inclusion/exclusion criteria (n= 169)
Preclinical work= 57
Not in relapse setting= 77
Non-prognostic marker study= 22
Patient population not restricted to osteosarcoma patients OR data is not disclosed separately for this population= 2
Review or guidelines= 9
Studies with <35 patients with relapsed osteosarcoma= 2
Included
Studies included in qualitative synthesis (n = 19)
Studies included in quantitative synthesis (meta-analysis) (n = 6)

3.2. Study characteristics

The studies were published between 1983 and 2022, with a global distribution point to Europe (57.89%), USA (26.32%) and Asia (15.79%) as the main contributors. Ten were multicenter and 9 were single center studies. Out of the 19 studies, 16 were retrospective and 3 prospective. Most (n = 13) articles included a study population consisting of relapsed osteosarcoma only, 6 articles included a relapsed osteosarcoma population as a subpopulation and performed separate outcome analysis on that population.

The mean study sample size of the articles was 159 patients (range: 37-576; standard deviation = 174). Twelve studies reported the time of follow-up of the population, with a median of 3.8 years (range 0-29.2 years).

All 19 studies reported post-relapse survival (PRS) as an outcome measure. 17/19 studies measured PRS from the date of recurrence/relapse. One study with a focus on pulmonary metastases measured PRS from the date of thoracotomy(16) and one study measured survival from the date of treatment for initial diagnosis but restricted analysis to those with metachronous metastases(17). Post-relapse event-free survival was reported in 5/19 studies, with events defined as subsequent relapse or death in 3 studies and inadequately described in the other 2. Post-relapse PFS, disease-free survival, local recurrence-free survival and time to relapse were also reported separately in 4 different studies.

As PRS was the most consistently reported outcome and is arguably the most clinically meaningful endpoint in this setting, this was the focus of our qualitative and quantitative analyses.

The main characteristics of the studies are shown in Table 1.

1 Table 1. Characteristics of the analyzed studies

First Author; year	Journal	Design	N	Centers	Age at relapse (years)	Site of relapse	Treatment period	Median follow up (years)
Ferrari S, 2003(6)	J Clin Oncol	Retrospective	162	Multicenter	5 to 47	Any	1986-1995	Unknown
Kempf-Bielack B, 2005(3)	J Clin Oncol	Retrospective	576	Multicenter	Unknown	Any	1979-1998	4,20
Ferrari S, 1997(18)	Ann Oncol	Retrospective	69	Single center	5 to 43	Any	1983-1986	12,00
Bielack SS, 2009(19)	J Clin Oncol	Prospective/ observational	249	Multicenter	5.7 to 54	Second relapse	Unknown	2,95
Grimer RJ, 2005(20)	Eur J Cancer	Retrospective	96	Single center	5 to 71	Local relapse	1976-2001	2,08
Crompton BD, 2006(21)	Pediatr Blood Cancer	Retrospective	37	Single center	< 30	Any	1974-1996	Unknown
Hawkins DS, 2003(22)	Cancer	Retrospective	59	Single center	4.5 to 23	Any	1990-2000	Unknown
Gelderblom H, 2011(23)	Eur J Cancer	Retrospective	564	Multicenter	≤40	Any	1983-2022	Unknown
Bacci G, 2006(24)	Cancer	Retrospective	44	Single center	≤40	Local relapse in the extremity	1983-1999	9,10
Saeter G, 1995(25)	Cancer	Retrospective	60	Single center	5 to 44	Metastatic first relapse	1975-1993	5,66
Putnam JB Jr, 1983(16)	Ann Thorac Surg	Prospective	38	Multicenter	6 to 49	Pulmonary first relapse	1975-1982	Unknown
Bao J, 2019(17)	J Cancer	Retrospective	59	Single center	7 to 29	Metastatic first relapse	2004-2013	Unknown
Takeuchi A, 2014(26)	Clin Orthop Relat Res	Retrospective	45	Single center	6 to 71	Local relapse in the extremity	1985-2007	3,25
Durnali A, 2013(27)	Med Oncol	Retrospective	145	Multicenter	13 to 74	Any	1995-2011	2,54
Daw NC, 2015(28)	Br J Cancer	Retrospective	39	Multicenter	Unknown	Single pulmonary metastasis	1977-2002	7,70

Tirtei E, 2018(29)	Tumori	Retrospective	58	Multicenter	Unknown	Second relapse	2003-2013	Unknown
Spraker-Perlman HL, 2019(30)	Pediatr Blood Cancer	Retrospective	431	Multicenter	Unknown	Any	1993-2005	3,50
Liu Z, 2022(31)	J Thorac Cardiovasc Surg	Retrospective	125	Single center	7.2 to 32	Pulmonary relapse	2004-2018	Unknown
Thebault E, 2021(32)	Cancers (Basel)	Prospective/ observational	157	Multicenter	7.7–52	Any	2007-2014	4,50

2 N: Number of patients, OS: Overall survival, EFS: Event free survival, UKN: Unknown

3

3.3. Quality assessment.

The quality of the included studies was assessed using the QUIPS (Quality In Prognosis Studies) tool(12). Each domain was rated for risk of bias as low, moderate, or high based on predetermined criteria. While study populations tended to be well-defined, prognostic factor measurements were often poorly described and methods for accounting for potential confounding factors were often limited or missing (Supplementary file 2 table 1).

3.4. Prognostic factors

A total of 9 factors were identified as prognostic markers, defined as factors that showed a significant association with one or more of the known clinical outcomes (OS, EFS, and PFS) in at least two identified studies. The markers were categorized in: Demographic characteristics (sex, age), tumor-related markers (relapse-free interval, site of relapse, number of lesions, and size of recurrence), laboratory markers (alkaline phosphatase level (ALP)-), and therapy response markers (treatment with surgery and treatment with chemotherapy).
From the 9 prognostic markers none were validated by using an independent cohort.
Table 2 summarizes the evidence across the included studies regarding prognostic factors and the highest hazard ratios observed in both univariable and multivariable analyses.

Table 2. Summary of evidence supporting prognostic factors across included studies

Prognostic factor	No. of Studies Reporting	No. of Studies with Significant Association	Largest significant effect size reported for PRS HR (95% CI), p-value	
			Univariable analysis	Multivariable analysis
Sex	6	3	(M vs F): 2.31 (1.20–4.44), p=0.012 (17)	(F vs M): 0.56 (0.33–0.94), p=0.031 (31)
Age	2	2	HRs for post-relapse PFS* (12-17y vs <12y): 1.43 (0.78–2.62) (18-25y vs <12y): 0.78 (0.41–1.48), (>25y vs <12y): 1.52 (0.73–3.17) Overall p=0.02 (32)	(<1y vs 10-17y): 0.65 (0.45–0.94), p= 0.0225 (≥18y vs 10-17y): 2.27 (1.44–3.59), p=0.0004 (30)
Relapse-free interval	17	10	(≥24mo vs <24 mo): 0.53 (0.41–0.69), p<0.001 (23)	(≤18mo vs >18mo): 1.86 (1.48–2.34), p<0.001 (3)
Site of relapse	15	10	Metastases at diagnosis of recurrence: 3.98 (95% CI 2.36-6.71), p<0.0001 (20)	(Lung only vs local only): 1.56 (1.02-2.39), p=0.039 (Other vs local only): 2.58 (1.64-4.07), p<0.001 (23)

Impact of number of lesions	9	6	(Solitary pulmonary vs multiple pulmonary or other organs): 0.20 (0.07–0.58), p=0.003 (17)	(Solitary pulmonary vs multiple pulmonary or other organs): 0.27 (0.09–0.80), p=0.018 (17)
Size of recurrence	6	4	(>5cm vs ≤5cm): 10.58 (95% CI 1.8-61.7), p=0.0089 (20)	(≥5cm vs <5cm): 13.4 (3.2-55.9), p<0.0001 (26)
Alkaline phosphatase level	2	2	(Elevation vs normal): 6.20 (2.56-15.05), p<0.001 (17)	(Elevation vs normal): 8.72, (3.08-24.67), p<0.001 (17)
Surgical treatment	13	9	No surgical excision of local recurrence: 6.36 (3.58-11.29), p<0.0001 (20)	(Pulmonary metastasectomy + chemotherapy vs chemotherapy only): 0.19 (0.10-0.33), p<0.001 (31)
Chemotherapy treatment	12	6	No chemotherapy: 1.62 (1.18-2.23), p=0.003 (19)	No chemotherapy: 14.96 (1.96-110.23), p=0.009 (27)

PRS: Post-relapse survival, HR: Hazard Ratio, M: Male, F: Female, ALP: Alkaline Phosphatase, CI: Confidence Interval, mo: Months, OS: Overall Survival, PFS: Progression-free survival

*No univariable HRs for associations between age and PRS reported

3.4.1 Prognostic impact of sex

Sex was evaluated in six studies (Supplementary file 2 table 2): four were multicenter (three retrospective and one prospective) and two single-center studies (both retrospective). The median number of patients was 75 (range 38-145 patients). Three studies found an increased risk of worse outcome for male patients, but it was statistically significant in multivariate analysis in only one study.

3.4.2 Prognostic impact of age

Only two studies evaluated impact of age as prognostic factor in relapsed osteosarcoma patients (Supplementary file 2 table 2): one study was retrospective while the other was prospective/observational; both were multicenter studies. The median number of patients included was 294 (range 157-431 patients). These studies showed a risk of an adverse outcome with increasing age, and it was statistically significant in multivariate analysis in one study (HR for ≥ 18y = 2.27).

3.4.3 Prognostic impact of relapse-free interval

Seventeen studies evaluated the impact of relapse-free interval/time to recurrence or metastases, or time to local recurrence (one study) (Supplementary file 2 table 2). Fourteen

were retrospective (six multicenter and eight single-center studies), while three were prospective/observational (all multicenter studies). The median number of patients included was 163 (range 37-576 patients). Eight studies used a cut-off value of 24 months, showing a significant better survival for those patients relapsed after 24 months.
There was a variability in the chosen cut-offs for analysis (commonly 12 months and 24 months), that hindered the possibility of conducting a meta-analysis for this factor.

3.4.4 Prognostic impact of site of relapse

Fifteen studies evaluated the prognostic impact of the site of relapse (Supplementary file 2 table 2): twelve were retrospective (six studies multicenter and six single-center studies) and three were prospective/observational (all multicenter studies). The median number of included patients was 183 (range 38-576 patients). Four studies observed a statistically significant better 5-y PRS for those patients relapsed only with lung involvement (especially with a single pulmonary nodule) and four studies showed a significant better 5-y PRS for those with unilateral lung involvement. Patients with multiple sites of metastases showed the worst prognosis. Moreover, two studies underlined a significant better 5-y PRS for those patients who have relapsed only locally.

3.4.5 Prognostic impact of number of lesions

Nine studies evaluated the impact of the number of metastases (Supplementary file 2 table 2). The median number of patients was 60 (range 38-557). Seven studies were retrospective (three were multicenter and four single-center studies), while two were prospective/observational (one was multicenter and one single-center study). Four studies pointed out a significant better survival for patients with solitary lung metastasis and two studies showed a significant better survival for those relapsed with ≤ 2 metastases.

3.4.6 Prognostic impact of size of recurrence

Six studies evaluated the size of metastases and osteosarcoma outcome (Supplementary file 2 table 2). The median number of patients was 77 (range 36-157). Five studies were retrospective (two were multicenter studies and three single-center studies), while one was a multicenter prospective/observational study. Different cut-off value (< or ≥ 1 cm; < or ≥ 5 cm; < or ≥ 8 cm) were used and two studies pointed out a significant better survival in multivariate analysis for patients with smaller size lesions.

3.4.7 Prognostic impact of alkaline phosphatase (ALP)

Only two studies evaluated the prognostic impact of ALP in relapsed osteosarcoma (Supplementary file 2 table 2). Both studies were retrospective and single-center studies, and both highlighted a worse outcome for those patients with pathological ALP level.

3.4.8 Prognostic impact of surgical treatment

Thirteen studies evaluated the impact of surgery in patients with relapsed osteosarcoma (Supplementary file 2 table 2). Eleven studies were retrospective (four multicenter and seven single-center studies) and two were prospective/observational (both multicenter studies). The median of included patients was 69 (range 38-576). Nine studies underlined the crucial role of surgery at relapse, showing a significant better outcome for those patients with complete surgical remission.

3.4.9 Prognostic impact of chemotherapy treatment

Twelve studies evaluated the impact of chemotherapy in patients with relapsed osteosarcoma (Supplementary file 2 table 2). Eleven studies were retrospective (five multicenter and six single-center studies) and one was prospective/observational (multicenter study). The median of included patients was 59 (range 21-576). Six studies indicated a potential benefit of chemotherapy in patients who did not achieve complete surgical remission. However, in other scenarios—such as local relapse with complete surgical remission or metastatic relapse—the evidence suggested only limited benefit.

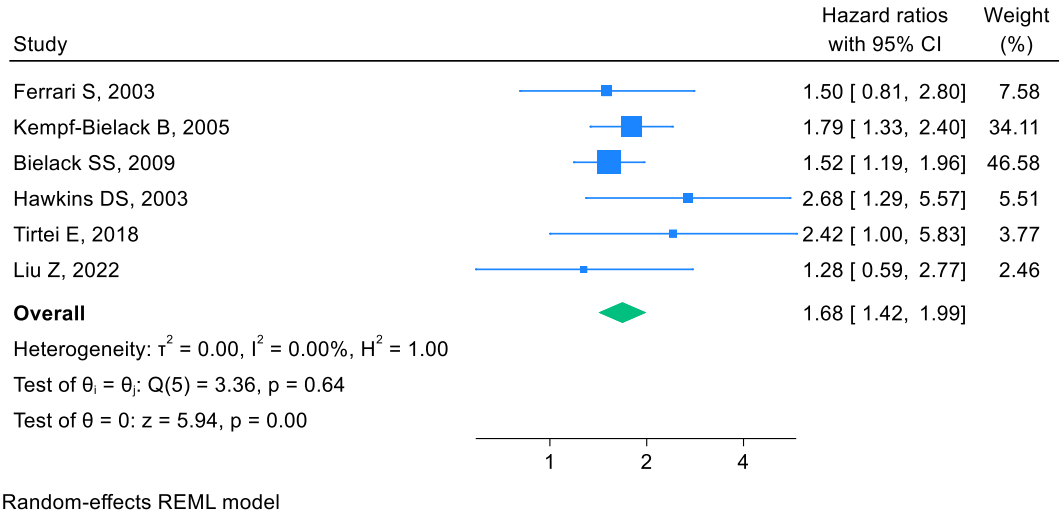
3.5 Meta-Analysis of the bilateral versus unilateral lung metastases at recurrence

Due to heterogeneity across the studies in terms of methodology, population characteristics, and definition of prognostic factors, it was not possible to conduct a meta-analysis of the outcome data in almost all cases. The exception to this is laterality of lung metastases covered under site of relapse. For the Bielack SS(19) study focusing on second and subsequent recurrences, only information related to the second recurrence has been used. Putnam JB Jr(16) study looked at laterality of lung metastases as a prognostic factor, however no estimates or survival curves were provided, and it simply stated that there was no significant difference. That study was therefore not included in this analysis.

The study by Liu Z(31) reported a hazard ratio and confidence interval for the effect of lung laterality which has been used in the analysis. For all others, we have used the methods described by Parmar et al(33) to estimate the hazard ratio and corresponding standard error.

Bilateral lung metastases were significantly associated with worse OS as compared to unilateral lung recurrence (HR 1.68 (95%CI 1.42–1.99)) (Figure 2). There was no evidence of an impact of study heterogeneity on meta-analysis outcomes (I^2<0.01%).

Figure 2. Meta-analysis forest plot comparing patients with bilateral lung metastases at recurrence to those with unilateral



4 Discussion

Our systematic review and meta-analysis provides a comprehensive overview of clinical and biological prognostic factors in patients with relapsed high-grade osteosarcoma. Nine prognostic significant factors were identified from 19 studies. Quality assessment revealed considerable risk of bias across studies. No markers were prospectively, externally, validated in a systematic study. After analysis, a long relapse-free interval, ≤ 2 lesions of lung metastases, small size of recurrence, and a complete surgical remission were the most consistent favorable prognostic factors.

Despite analyzing data spanning over four decades, there are still relatively few studies dedicated to examining prognostic factors in relapsed osteosarcoma. Most of these studies are retrospective, with small sample sizes and lacking external validation cohorts. The quality assessment revealed considerable variability in the risk of bias across the evaluated studies, with most exhibiting moderate to high risk in areas such as prognostic factor measurement and study confounding, indicating potential methodological limitations. This, combined with the previously reported significant heterogeneity and lack of consistency across therapeutic clinical trials in this population(9,34), makes it difficult to translate research findings into clinical results. These

issues underscore the need for stringent study design and analysis protocols in future research in recurrent/refractory osteosarcoma.

Our review identified nine significant prognostic factors, categorized into demographic characteristics, tumor-related markers, laboratory markers, and therapy markers. While demographic factors like sex and age were not consistently reported across studies, certain studies did emphasize the relapse-free interval importance. Importantly, our findings also reflect a key gap in the field: despite the growing interest in biological and molecular stratification, no biomarker has yet demonstrated consistent prognostic value in relapsed osteosarcoma.

Tumor-related markers, including relapse-free interval, site of relapse, number of lesions, and size of recurrence, demonstrated significant prognostic relevance. However, the inclusion criteria and patient cohorts varied, complicating also meta-analytic synthesis for most of these variables. Relapse-free interval was significantly associated with PRS in 10 out of 15 studies reporting this association. Additionally, studies by Tirtei et al.(29) and Liu et al.(31) suggested some evidence of this association ($p<0.1$), despite not reaching statistical significance. The variability in the chosen cut-offs for analysis, commonly 12 and 24 months, hindered the possibility of conducting a meta-analysis for this factor. Importantly, ESMO guidelines put 'timing of recurrences' among main factors in recurrence treatment decision making(5)

The analysis of laterality of lung metastases was consistent across studies and therefore suitable for meta-analysis, revealing a significant association between bilateral lung metastases and worse overall survival. The number and location of nodules in the lungs have been shown to predict prognosis, with patients having unilateral deposits and fewer metastases experiencing better outcomes, aligning with previous findings in first line setting(35,36). Additionally, it is worth noting that two studies in our review reported significantly better survival outcomes in patients with smaller recurrence lesions in multivariate analysis. However, while these findings suggest a potential link between smaller lesion size and improved survival, this association is not widely established in the broader osteosarcoma literature. Most research emphasizes complete surgery of disease as a more universally recognized prognostic factor(4,37), including repeated metastasectomies(38), with lesion size alone playing a less consistently role.

At diagnosis, elevated ALP levels had already been linked with worse overall survival and event-free survival in a previously published systematic review and meta-analysis(39). Additionally, high LDH levels have been recognized as a prognostic factor at diagnosis in this population(11). However, in our systematic review, we found that ALP levels were the only laboratory parameter

significantly associated with prognosis, and no correlation was observed between LDH levels and prognosis.

There is significant variability in the chemotherapy strategies used in relapsed osteosarcoma, reflecting the lack of a universally established regimen(5,40). Numerous trials have investigated the efficacy of different combination regimens, such as ifosfamide and etoposide, as well as gemcitabine and docetaxel and new agents(34). Results of these studies have been conflicting; for example, while the gemcitabine/docetaxel combination showed limited efficacy in phase-II trials(41,42), it exhibited some potential in retrospective studies(43). While ifosfamide +/- etoposide is often used in recurrent osteosarcoma, the lack of prospective, randomized trials as well as the variations in dosages and schedules, have further complicated the establishment of a possible second line treatment(44,45). Some studies in our review indicated that chemotherapy could improve post-relapse survival, particularly in patients who did not achieve complete surgical remission(19,29), but the diversity in chemotherapy regimens across studies prevented the possibility of a meta-analysis. In the context of surgery, complete resection has long been established as a critical prognostic factor in osteosarcoma at diagnosis(38,46,47). Studies such as those by Bielack et al.(19) and Saeter et al.(25) congruently underscored the importance of achieving complete surgical remission also at relapse setting. These findings have been consistently validated by numerous subsequent studies, establishing surgical resection as a cornerstone of osteosarcoma treatment, including patients with local only relapse (48,49). Trials should carefully evaluate not only which patients are deemed resectable but also how many actually proceed to surgery. For instance, in the OLIE study, although 20% of patients in both arms were initially classified as resectable, the actual surgery rate differed substantially (40% in the chemotherapy-alone arm vs. 20% in the chemotherapy-plus-lenvatinib arm), potentially biasing the study's results(50). Therefore, careful consideration of both surgical potential and the procedures ultimately carried out is crucial.

A limitation of our study is that we did not obtain individual patient data; instead, we extracted results from published studies. We recognize the drawbacks of pooling evidence from methodologically limited studies, as specific biases inherent to their design may affect the findings. Furthermore, we lack detailed information on the included subpopulation and the received therapy, including surgery characteristics, in some of the papers. These limitations have to been taken into consideration when meta-analysis for lung laterality is assessed. This analysis is heavily weighted by the two COSS studies(3,19). There appears to be an overlap between these studies as they seem to use the same data source, focusing on first and subsequent recurrences, respectively. This overlap might result in some patients being counted twice, which

was not accounted for in this analysis. Moreover, the Ferrari et al. study (51) only describes the effect of lung laterality in patients with complete surgical remission, a specification not consistently made in other studies. Furthermore, our review may not encompass all published articles, as some may be inaccessible or published in journals not covered by our search.

To conclude, our systematic review underscores essential prognostic factors—such as relapse-free interval, number and site of lesions, and resectability—that should guide the design of future phase III trials for relapsed osteosarcoma. While large single-cohort studies such as those from the COSS group have provided critical insights into relapsed osteosarcoma, our systematic review adds value by integrating evidence across multiple independent cohorts, thereby offering a broader and less population-specific synthesis of prognostic factors that can better inform stratification for future clinical trials. Stratifying patients by these factors, particularly by distinguishing those with resectable local relapses and late relapse, from those with early non-resectable or metastatic recurrences, would allow for a more accurate assessment of treatment efficacy within relevant subgroups. Given that complete surgical resection remains one of the strongest indicators of prognosis, trials should rigorously assess and report resectability. Certain subgroups, such as patients with a solitary lung lesion occurring more than 1–2 years post-therapy, may also require separate analysis or considered as a stratification factor, considering their relatively favorable outcomes. Additionally, addressing the variability in chemotherapy regimens is equally important, as inconsistent protocols have limited reliable outcome assessments; implementing a standardized chemotherapy protocol would enhance consistency in evaluating systemic therapy effects. In parallel, there is a need to integrate translational research into future studies, so that biological insights can progressively complement and enhance current risk stratification strategies based on clinical variables. By refining these design elements, future trials can yield clearer insights into therapeutic effectiveness and support more tailored approaches for managing recurrent high-grade osteosarcoma.

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Authors' contributions:

A.R.S.: Conceived and designed the study, led the systematic review process, performed data acquisition and analysis, interpreted results, and drafted the manuscript. Reviewed and approved the final manuscript version and agreed to be accountable for all aspects of the work. She has had full access to the data in the study and final responsibility for the decision to submit for publication.

W.W.: Contributed to the study design, performed data acquisition and analysis, interpreted results, and revised the manuscript critically for important intellectual content. Reviewed and approved the final manuscript version and agreed to be accountable for all aspects of the work.

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