Surgical Oncology 27 (2018) 603–610

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

Prognostic factors for survival in Ewing sarcoma: A systematic review

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ARTICLE INFO

Keywords:
Ewing sarcoma
Prognostic factors
Survival
Prediction models
Personalized medicine
Prognosis

ABSTRACT

Development of a prognostic model for survival can assist in stratifying treatment according to the individual patients' risk, leading to risk- and response adaptive treatment strategies which allow for early decision making. The aim of this systematic review is to provide an overview of prognostic factors for overall survival (OS) and event-free survival (EFS) in Ewing sarcoma to be used in the development of prediction models and clinical trial design. A literature search was performed using Pubmed, Embase, Web of Science, Academic search premier and Cochrane databases. Studies were eligible if: 1) Sample size ≥100; 2) Follow-up ≥2 years or dead within 2 years; 3) Recruitment after 1975; 4) Outcome measure OS or EFS; 5) Multivariate analysis to assess the effect of prognostic factors on survival outcomes; 6) Study published in English. In case studies were derived from the same database the most all-embracing was selected. Study selection and quality assessment was performed by two reviewers independently. For each risk factor a level of evidence synthesis was performed. Kappa-statistic was used to determine inter-observer agreement. A total of 149 full-text articles were found, 21 eligible for inclusion. 24 prognostic factors were investigated, 14 relevant for this review. Prognostic factors associated with survival include metastasis at diagnosis, large tumors (volume ≥ 200 ml or largest diameter ≥ 8 cm), primary tumors located in the axial skeleton, especially pelvic and a histological response of less than 100%. These factors should be included as risk factors in the development of prediction models for ES.

1. Introduction

Ewing sarcoma (ES), first described in 1921 by James Ewing [1], is a small, round cell sarcoma that shows pathognomonic molecular findings and varying degrees of neural differentiation [2]. It is the second most frequent primary malignant bone sarcoma in children and young adults, showing a peak incidence in the second decade of life. As seen in many pediatric tumors there is a slight male dominance [3–5]. Caucasians are affected more than Asians and the negroid race, among whom the disease is rare [6,7]. ES tends to arise from the diaphysis of long bones of the extremities (predominantly the femur) and the pelvic area with early involvement of the surrounding soft tissue. The soft tissue mass is usually large, circumferential about the involved bone and might even exceed the intraosseous component in size [2,8]. Treatment of Ewing's sarcoma is multimodal, consisting of chemotherapy, surgery and/or radiotherapy. Improvement in survival outcomes is the result of collaborating trials; overall survival (OS) improved from approximately 10% at 5 years with radiotherapy alone to 55–65% in patients with localized disease, probably due to a multimodality approach [6–11]. At the time of diagnosis about 20–25% patients present with metastatic disease. Metastasis usually occurs to the lungs (70–80%) and to the bone (40–45%). Despite current aggressive cytotoxic treatment regimens the 5-year OS of patients with metastatic ES ranges from 20 to 35% [6–11]. Even in primary non-metastatic disease 30–40% of patients experience recurrence, either local, distant or combined, during follow-up. Survival after recurrence is poor, with 5-year post-relapse survival varying from 15 to 25%, local recurrence doing better than distant recurrence [12–15].

Personalized medicine is becoming more and more important, especially in cancer treatment in order to avoid under-treatment of high-risk patients or over-treatment in low-risk patients or in patients for whom treatment is expected to have limited benefit. Many trials have been performed to study prognostic factors of Ewing sarcoma in order to define risk groups that need tailored treatment. Development of a prognostic model for survival can assist in stratifying treatment according to an individual patients' risk profile, so that risk- and response adaptive treatment strategies can be developed to allow early decision making and shared decision making. Until today such a prognostic model for Ewing sarcoma has not yet been developed and validated.

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https://doi.org/10.1016/j.suronc.2018.07.016
Received 7 May 2018; Received in revised form 16 July 2018; Accepted 29 July 2018

The aim of this systematic review is to provide an overview of prognostic factors for survival in Ewing sarcoma in order to develop prediction models for survival.

2. Methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [16]. The review protocol for this study was prospectively registered at PROSPERO[1] (registration number CRD42017080534). Due to the presence of heterogeneity in treatment modalities among studies only a systematic review is performed.

2.1. Search strategy

Search strategies were run in the following databases in October 2017: PubMed MEDLINE, Embase, Cochrane Library, Web of Science and Academic Search Premier. Search strategies for all databases were adapted from the PubMed MEDLINE strategy. The search strategy specified keywords related to "Ewing sarcoma", "survival", "prognostic factors" and abbreviations thereof. The complete search strategies for each database are available in an online supplementary file (supplementary file 1). The results of all searches were combined and duplicates were removed.

2.2. Eligibility criteria

Clinical trials (phase I, II and III), prospective and retrospective cohort studies were all considered for inclusion in this review. Case reports and other type of publications including reviews, viewpoints or conference reports were excluded. Studies were eligible for inclusion if the following criteria were met [1]: Sample size of at least 100 patients with Ewing sarcoma eligible for analysis [2]; Follow-up of at least 2 years or patient died within 2 years [3]; Recruitment period started after 1975 to assure appropriate imaging and diagnosis [4]; Outcome measure is overall survival or event-free survival [5]; A multivariate analysis was employed to assess the effect of prognostic factors on survival [6]; The study is published in the English language. If studies were derived from the same database the most all-embracing study was selected. Separately published subgroup analyses of the same trial or performed in the same dataset were not included in this systematic review. The eligibility of the studies was assessed by two independent review authors (SB and OA). Disagreements were solved during a consensus meeting. In case of persisting disagreements a third reviewer (PDSD) was consulted.

2.3. Risk of bias

The Quality In Prognosis Studies (QUIPS) tool developed by Hayden et al. (17) was used to assess the risk of bias. The QUIPS tool uses six domains to evaluate the validity and bias in studies of prognostic factors: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding and analysis. The six domains of bias were scored as "high" (3 points), "moderate" (2 points) or "low" (1 point). The total score for each study ranges from 6 to 18 points, to distinguish high risk of bias studies from low risk of bias studies the cut-off was set at a maximum of 50% ($\leq$9 points). Risk of bias was scored by two review authors (SB and OA) independently. Disagreements were resolved during a consensus meeting. If disagreements persisted a third reviewer (PDSD) made a final decision about the risk of bias. Methodological quality of the included studies was assessed according to the grading of recommendation, assessment, development and evaluation (GRADE) approach [18].

[1] http://www.crd.york.ac.uk/prospero.

2.4. Data extraction

The following data was extracted from the included studies: study design, database/trial, study population, sample size, treatment (chemotherapy regimen, local treatment modality), recruitment period (years), median follow-up (years), prognostic factors investigated, outcome measure and results. For the level of evidence synthesis the risk factors age, size, volume, serum LDH level and histological response were combined regardless of differences in the cut-off points used.

2.5. Data analysis

Due to the presence of heterogeneity among treatments a meta-analysis is not performed, instead a level of evidence synthesis was conducted for each prognostic factor. If the results of at least 75% of the studies analyzing the effect of a specific prognostic factor point in the same direction the findings were considered consistent. Level of evidence is defined as "strong" if there are consistent findings ($\geq$75%) in multiple high-quality cohorts. If the results in $\geq$67% multiple high-quality cohorts go in the same direction the level of evidence is defined as being "moderate". When a prognostic factor is only investigated in a single high-quality cohort or shows consistent findings ($\geq$75%) in one or more low-quality cohorts the level of evidence is considered "limited". If the results show inconsistent findings, meaning that the results point in different directions, the level of evidence is considered "inconclusive", irrespective of study quality. In case of multiple high-quality cohorts only the high-quality cohorts are used to define the level of evidence.

2.6. Statistical analysis

Inter-observer agreement for the risk of bias assessment was determined by the kappa-statistic [19]. All analyses were performed using SPSS 23.0, Armonk NY, IBM Corp.

3. Results

3.1. Study selection

The initial search strategy identified 3716 records (Pubmed n = 1543; Embase n = 1247; Web of Science n = 834; Cochrane library n = 62; Academic Search Premier n = 30). After removal of 1842 duplicates, 1874 records were available for screening (Fig. 1 flow-chart). After screening of titles and abstracts, 149 full-text articles were obtained, 128 did not meet the eligibility criteria: 45 studies were derived from the same database; 31 studies did not report a multivariate analysis; 20 studies investigated another outcome, 19 studies did not focus solely on Ewing sarcoma; 7 studies had missing information on the recruitment period and/or follow-up and of 6 studies the full-text article was not available. In total 21 studies [20–40] were included (Fig. 1). The reviewers initially disagreed on 21 inclusions during the selection process. Consensus was reached for all studies.

3.2. Study characteristics

The characteristics of the 21 included studies are presented in Table 1. In five studies the results were based on prospectively collected data, in the other 15 studies the results were based on retrospectively collected data. In all cohorts patients were treated with neo-adjuvant chemotherapy followed by local treatment, surgery and/or radiotherapy of the primary tumor and adjuvant chemotherapy. The chemotherapy regimens used vary among the studies, but in all cohorts a polychemotherapy regimen was used. The follow-up duration was reported in 16 studies and ranged from 2 to 12 years. All included studies reported the recruitment period, duration ranged from 3 to 37 years.

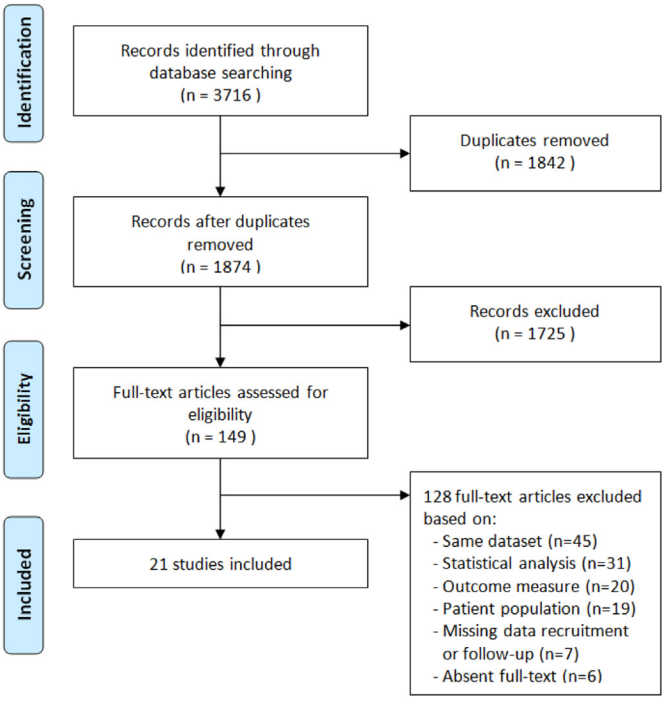

Fig. 1. Flowchart of the study selection process.

3.3. Risk of bias

Agreement on the risk of bias score was obtained for 17 out of the 21 included studies (81%). For the remaining 4 studies consensus was reached. A substantial inter-observer agreement was obtained for the overall risk of bias score (kappa 0.76). The domains prognostic factor measurement and statistical analysis showed the lowest level of agreement (kappa 0.46 and 0.31 respectively). The domains study attrition and study confounding showed the highest level of agreement (kappa 0.72 and 0.79 respectively). The complete results of the risk of bias score and inter-observer agreement are available in an online supplementary file (supplementary file 2).

3.4. Level of evidence for prognostic factors

24 prognostic factors were distinguished in the 21 included studies. Several studies investigated prognostic factors specific to the received treatment of the patients in the cohort, such as type of chemotherapy protocol (number of drugs, type of drugs, intensity, dose, etcetera) or treatment era. These prognostic factors were not considered relevant for the purpose of this study and are therefore excluded. Ten prognostic factors were only investigated once: socio-economic status (SES) [27], erythrocyte sedimentation rate (ESR) [22], white blood cell (WBC) count, hemoglobin level, albumin level, duration of symptoms, the presence of systemic symptoms [41], the presence of fever [28], hepatoma-derived growth factor (HDFG) and p53 expression [32]. Since these prognostic factors were only investigated in a single study, the level of evidence could by definition never exceed the level of "limited" and they are therefore excluded. Among the remaining 14 prognostic factors, 13 for overall survival and 13 for event-free survival are detailed in Tables 2 and 3 respectively.

3.5. Prognostic factors

The presence of metastasis at diagnosis, tumor size and site of the primary tumor were strongly associated with overall survival (OS). Prognostic factors that were commonly studied and did not have significant independent prognostic influence on OS include gender, serum LDH level, tumor origin and radiological response. The level of evidence for an association with OS for age, local treatment modality, race/ethnicity, site of metastatic lesions, histological response and surgical margins was inconclusive, meaning that the results from several high quality cohorts give contradictory results.

The presence of metastasis at diagnosis, tumor volume and histological response were strongly associated with EFS. Prognostic factors that were commonly studied and did not have significant association on EFS are gender, tumor origin, radiological response and the site of the metastatic lesions. The level of evidence for age, location of the primary tumor, tumor size, serum LDH level and local treatment modality in association with EFS was inconclusive.

3.5.1. Metastasis at diagnosis

The presence of metastasis at diagnosis was found to be independent and significantly associated with poorer OS in seven out of eight (88%) high-quality cohorts, hazard ratios (HR) varied from 2.4 to 4.4. All high-quality cohorts [25,26,30] and one low quality cohort [34] found a clear association with poorer EFS, HR 1.5 to 2.2.

3.5.2. Tumor size

Seven high-quality cohorts (100%) evaluated the effect of tumor size on OS. Six studies found that a diameter of 8 cm or more was associated with a poorer OS (HR 1.5 to 2.5), the other study found that a tumor size of 10 cm or more was associated with a worse OS (HR 1.84; 95%CI 1.22–2.78; $p = 0.04$). Two studies, using 5 cm and 8 cm as cut-off points found no clear association between tumor size and OS.

A tumor size of 8 cm or more was also associated with poorer EFS in four out of six (67%) high-quality cohorts [26,33,35,36], HR 1.8 to 2.9. One study using 10 cm as cut-off point could not find a clear association.

3.5.3. Tumor volume

Five studies measured tumor volume of which four (80%) found that larger volumes are associated with poorer EFS. One study [21] found that patients with a tumor volume of 100 ml or more have poorer EFS ($p = 0.001$, HR not given). Another study [24] found similar results, with a HR of 2.2 (95%CI 1.4–3.3; $p < 0.001$) for a tumor volume of 150 ml or more. Two other studies [28,37] found that patients with a tumor volume of 200 ml or more have a poorer EFS, RR 1.8 (95%CI 1.2–2.7; $p = 0.01$) and HR 1.8 (95%CI 1.1–3.0; $p < 0.001$) respectively.

3.5.4. Location of the primary tumor

Eight high-quality cohorts evaluated the effect of the primary tumor location on OS, six (75%) found significant results. Three compared extremity versus axial (including pelvic) location of which two [36,40] found that patients with a tumor in the axial skeleton have poorer OS, HR 1.98 ($p = 0.038$) and HR 1.3; 95% CI 1.0–1.5; $p = 0.021$, respectively. Two studies [33,39] compared tumors located in the pelvic or spine with all other locations and found similar results with a HR of 2.7 (95%CI 1.3–5.7; $p = 0.009$) and HR 1.1 (95%CI 0.9–1.4) for tumors located in the pelvic or spine. One study [20] comparing pelvic versus non-pelvic locations found that patients with pelvic tumors have a higher risk of death, RR 1.9 (95%CI 1.3–2.9; $p = 0.0025$). Another high-quality cohort [27] comparing a pelvic versus non-pelvic location could not confirm these results. The last study [23] compared tumors located in the proximal extremity or axial skeleton with all other locations and found that primary tumors in the proximal extremity or axial skeleton have poorer OS ($p = 0.02$; HR not given).

Eleven high-quality cohorts evaluated the effect of the location of the primary tumor on EFS, six studies found a positive association. Five studies compared an extremity versus axial location of the primary tumor. Two [25,36] found that patients with a tumor in the axial skeleton have a poorer EFS, RR 1.2 (95%CI 1.0–1.4; $p = 0.004$) and HR 1.9 ($p = 0.02$) respectively. Two studies [21,35] found that patients with a

Table 1
Characteristics of the 21 included studies.

ID	Author, year, country	Database/trial	Study design	n	Study population	Local treatment	Period of recruitment	FU[a] (years)	Outcome measure[b]	Risk of bias[c]
1	Fizazi, 1998, France [20]	Hospital database, multicenter	R	182	LOC + MET	S 47% RT 81%	1982–1992	5.5	OS	Low
2	Cotterill, 2000, United Kingdom [21]	MRC/UKCCSG: ET-1, ET-2 CESS-group: CESS-81. CESS-86	P	796	LOC	S 35% RT 40% S + RT 25%	1978–1993	6.6	EFS	Low
3	Oberlin, 2001, France [22]	EW88	P	141	LOC	S 37% RT 26% S + RT 37%	1988–1991	8.5	EFS	Low
4	Jenkin, 2002, Saudi Arabia [23]	Hospital database, single institution	R	163	LOC	S 18% RT 67% S + RT 12%	1975–1998	3.9	OS	Low
5	Bacci, 2006, Italy [24]	Hospital database, single institution	R	512	LOC + MET	S 38% RT 35% S + RT 27%	1979–1999	12	EFS	Low
6	Obata, 2007, Japan [25]	Hospital database, multicenter	R	243	LOC + MET	S 36% RT 24% S + RT 40%	1981–2003	5.5	EFS	Low
7	Rodriquez-Galindo, 2007, USA [26]	Hospital database, single institution	R	222	LOC + MET	S 20% RT 55% S + RT 25%	1979–2004	11.7	OS EFS	Low
8	Lee, 2010, USA [27]	California Cancer Registry (CCR)	R	725	LOC + MET	S 55% RT 53%	1989–2007	NR	OS	Low
9	Gaspar, 2012, France [28]	EW93	P	214	LOC	S 48% RT 14% S + RT 38%	1993–1999	8	EFS	Low
10	Drabko, 2012, Poland [29]	Hospital database, multicenter	R	119	LOC + MET	S ± RT 89% RT 11%	1999–2006	4.5	OS EFS	High
11	Arpaci, 2013, Turkey [30]	Hospital database, multicenter	R	114	LOC + MET	S 31% RT 18% S + RT 41%	2001–2010	2	OS EFS	Low
12	Koohbanani, 2013, USA [31]	Hospital database, single institution	R	135	LOC + MET	RT 42% S 50%	1987–2011	3.4	OS	Low
13	Yang, 2014, China [32]	Hospital database, single institution	R	108	LOC + MET	S 75%	1990–2010	NR	OS	High
14	Biswas, 2015, India [33]	Hospital database, single institution	R	224	LOC	S 27% RT 45% S + RT 28%	2003–2010	3.4	EFS OS	Low
15	Brunetto, 2015, Brazil [34]	SOBOPE – EWING1	P	175	LOC + MET	S 49% RT 28% S + RT 23%	2003–2010	4.4	OS EFS	High
16	Marina, 2015, USA [35]	Children's Oncology Group (INT-0091, INT-0154 and AEWS0031)	R	1444	LOC	NR	1988–2005	NR	EFS	Low
17	Albergo, 2016, UK [36]	Hospital database, single institution	R	293	LOC	S ± RT100%	1980–2012	9.1	OS EFS	Low
18	Foulon, 2016, France [37]	E.U.R.O-EWING 99	P	599	LOC	S 76% S + RT 24%	1999–2009	6.2	EFS	Low
19	Friedman, 2017, USA [38]	Hospital database, single institution	R	300	LOC + MET	S 42% RT 22% S + RT35%	1975–2012	7.8	OS	Low
20	Miller, 2017, USA [39]	National Cancer Data Base	R	1031	LOC + MET	S 46% RT 33% S + RT 21%	1998–2012	NR	OS	Low
21	Verma, 2017, USA [40]	Surveillance, Epidemiology and End Results (SEER)	R	1870	LOC + MET	S 52% RT 23% S + RT 25%	1983–2013	NR	OS	Low

FU = follow-up; NR = not reported; R = retrospective; P = prospective; LOC = localized Ewing Sarcoma; MET = metastatic Ewing Sarcoma; OS = overall survival; EFS = event-free survival; S = surgery; RT = radiotherapy.

[a] Median follow-up in years.

[b] Outcome measures overall survival (OS) and event-free survival (EFS) are computed from the date of diagnosis or first day of treatment.

[c] Risk of bias was assessed using the QUIPS tool [17]. Studies were scored based on six domains, if a study scored ≤9 points the risk of bias was considered low.

pelvic primary tumor have a poorer EFS, HR 1.4 (p = 0.003) and HR 1.3 (95%CI 1.1–1.7; p = 0.009) respectively. One [26] other high-quality cohort could not find the same association. One study [28] showed that patients with a primary tumor located in the trunk or proximal extremity have a poorer EFS, HR 1.7 (95%CI 1.0–2.9; p = 0.04). A study [37] found a HR of 2.1 (95%CI 1.1.-3.7) for a tumor in the axial skeleton, HR 2.3 (1.1–4.4) for a pelvic location and HR 3.5 (95%CI 1.3–9.5) for tumors in the sacrum or vertebrae compared to an extremity location.

3.5.5. Histological response

The effect of histological response on OS was evaluated in five studies of which 2 high-quality cohorts. One study [36] found that patients with 100% necrosis have the best OS, compared to patients with 0–50% necrosis, HR 6.9 (p < 0.001, 95%CI not given), and patients with 50–99% necrosis, HR 3.3 (p < 0.001, 95%CI not given).

Table 2
Level of evidence for investigated prognostic factors for overall survival.

Prognostic factor	Measure (good/poor survival)	Association	No association	Level of evidence
Metastasis at diagnosis	No/yes	**1, 7, 8, 11,** 13, 15**, 19, 20, 21**	10, **12**	S - 88%
Size	< 10 cm/≥10 cm	**1**		S – 100%
	< 8 cm/≥8 cm	**7, 8, 11, 14, 17, 20**	15	
	< 5 cm/≥5 cm		13	
Primary tumor site	Extremity/axial (incl. pelvis)	**17, 21**	10, **11**, 13	S - 75%
	Other/pelvic + spine	**14, 20**		
	Non-pelvic/pelvic	**1**	**8,** 15	
	Other	**4**		
Gender	Female/male	**20, 21**	**1, 4, 7, 8,** 10, **11, 12,** 13, **14,** 15**, 17, 19**	S - 82%
LDH	N/≥ 2× N		**11, 14**	S - 100%
	N/≥ 1,5× N		15	
Origin	Soft-tissue/bone		13, **14, 19**	S - 100%
Age	< 14y/≥14y	**4,** 10	**7**	I - 55%
	< 15y/≥15y		**14,** 15	
	< 16y/≥16y		**17**	
	< 18y/≥18y	**8, 20, 21**		
	Other	**12, 19**	**1, 11,** 13	
Local treatment modality	Surgery/no surgery	**8,** 10, 13, **21**	**11, 12,** 15	I - 50%
	Surgery ± RT/RT only	**14, 20**		
	RT/no RT	**8**	**19, 21**	
	Post-op RT/pre-op RT		**21**	
Race/ethnicity	White/non-white	**19**	**20, 21**	I - 60%
	White/Hispanic	**8, 12**		
Site of metastatic lesions	Lung only/other	**19**	**7,** 10	I - 50%
	Lung/lung combined/other		15	
Histological response (% necrosis)	100%/99-50%/0–50%	**17**		I - 50%
	≥95%/ < 95%		**1,** 15	
	≥90%/ < 90%		10, 13	
Surgical margin	Negative/positive	**20**	**11**	I - 50%
Radiological response	CR + PR/SD + PD		**11,** 15	L - 100%

Abbreviations: S = strong; M = moderate; I = inconclusive; L = limited; N = normal level; RT = radiotherapy; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.
The numbers refer to the study ID as presented in Table 1. Studies with a low risk of bias are presented in bold.

The other high quality cohort [20], using 95% necrosis as cut-off point, found no clear association between histological response and OS. Three low quality cohorts using 95% necrosis and 90% necrosis as cut-off point could also find no clear association.

Five high-quality studies investigated the effect of histological response on EFS of which four (80%) found a positive association. One study [22] found a HR of 5 (95%CI 2.5–10; p < 0.001) for patients with less than 95% necrosis. Another study [24] found a HR of 5.1 (95%CI 2.9–9) for patients with Picci grade I and a HR of 2.4 (95%CI 1.2–4.6) for patients with Picci grade II. A French study [28] found a RR of 2.3 (95%CI 1.4–3.8; p < 0.001) for patients with less than 90% necrosis and Albergo et al. [36] showed that patients with 100% necrosis have the best EFS, with a HR of 4.4 (p < 0.001, 95%CI not given) for patients with 0–50% necrosis and a HR of 2.4 (p < 0.001, 95%CI not given) for 50–99% necrosis.

3.5.6. Surgical margins

Two high-quality studies evaluated the effect of surgical margins on OS. In one study (39) patients with marginal or intralesional surgical margins have a HR of 1.6 (95%CI 1.1–2.5). The other study also evaluating marginal or intralesional margins versus radical margins did not find the same association. (30).

A significant association between intralesional or marginal (positive) surgical margins and poor EFS was found in two [24,30] out of three (67%) high-quality cohorts, HR 1.3 ((5%CI 1.0–1.7; p = 0.044) and p < 0.001 (HR not given), leading to a moderate level of evidence.

3.5.7. Local treatment modality

Eight high-quality studies investigated the effect of local treatment modality on OS. Two studies [27,40] found that patients who have surgery for local treatment have a better OS compared to patients who don't undergo surgery, HR 0.7 (95%CI 0.5–0.9; p = 0.002) and HR 0.6 (95%CI 0.5–0.7; p < 0.001) respectively. These results were however not confirmed in two other studies [30,31]. Two studies [33,39] found that patients only treated with radiotherapy (RT) for local treatment have poorer OS compared to patient treated with surgery with or without RT, HR 2.5 (95%CI 1.2–5.2; p = 0.01) and HR 2.1 (95%CI 1.6–2.8) respectively. One study [27] specifically evaluated the use of RT and found that patients who receive RT have a better OS compared to patients who don't receive RT, HR 0.8 (95%CI 0.6–0.99; p = 0.04). Two other studies [38,40] also investigating RT versus no RT could not identify a clear association between the use of RT and OS.

Eight studies investigated the effect of local treatment modality on EFS. 3 high-quality cohorts found an positive association. One [24] found a HR of 1.6 (95%CI 1.1–2.5; p = 0.015) for patients treated with radiotherapy (RT) only as local control. The other study [28] found that patients who did not undergo surgery for local control have a worse EFS, HR 2.2 (95%CI 1.4–3.6; p < 0.001). Three other high-quality cohorts [26,30,33] did not find that patients who have RT only as local control measure have poorer EFS. One study [37] showed a better EFS for patients who have post-operative RT, HR 0.4 (95%CI 0.2–0.9) compared to no post-operative RT.

3.5.8. Age

The effect of age on OS was evaluated in eleven high-quality cohorts; six (55%) studies found that older age is associated with poorer OS. Three studies [27,39,40] found that patients 18 years or older have poorer OS, HR 1.6 (95%CI 1.2–2.2; p < 0.001), HR 1.9 (95%CI 1.5–2.4) and HR 1.9 (95%CI 1.6–2.2; p < 0.001) respectively. Two studies used 14 years as a cut-off point of which one [23] found that patients 14 years or older have poorer OS (p = 0.02; HR not given). Two other studies [31,38] found that older patients have poorer OS, HR 1.03/years (p = 0.036) and HR 2.8 (95%CI 1.3–5.6; p = 0.005) for 10–18 years, HR 3.0 (95%CI 1.4–6.4; p = 0.004) for 20–29 years, HR 4.5 (95%CI 2.0–10.6; p < 0.001) for 30–39 years. The four remaining studies, using 15, 16, 26 and 30 years of age as cut-off points could not find an clear association between older age and OS.

Eleven high-quality cohorts evaluated the effect of age on EFS, in four cohorts a positive association between older age and EFS was found, HR 2.0 (95%CI 1.3–3.2; p = 0.003) for patients 14 years or older [24], HR 1.6 (p < 0.001) for patients 15 years or older [21], RR 1.2 (95%CI 1.0–1.5; p = 0.004) for patients 16 years or older and RR 1.2 (95%CI 1.0–1.6; p < 0.001) for patients 10–18 years and RR 2.1 (95%CI 1.6–2.9; p < 0.001) for age above 18 years [35]. Other high-quality cohorts, two investigating 14 years, three 15 years, one 16 years, one 20 years and one 26 years as cut-off point could not find a clear association between older age and EFS.

3.5.9. Race/ethnicity

Three out of the five high-quality cohorts that investigated the effect of ethnicity on OS found a positive association. Two [27,31] compared Hispanic to white and other ethnicities and found a HR of 1.3 (95%CI 1.0–1.8; p = 0.04) and HR 1.9 (p < 0.001, 95%CI not given) respectively for Hispanics. Three studies compared white to non-white race, one of these [38] found a HR of 2.1 (95%CI 1.3–3.3; p = 0.002) for

Table 3
Level of evidence for investigated prognostic factors for event-free survival.

Prognostic factor	Measure (good/poor survival)	Association	No association	Level of evidence
Metastasis at diagnosis	No/yes	**6, 7, 11, 15**	10	S – 100%
Volume	< 100 ml/≥100 ml	**2**		S – 80%
	< 150 ml/≥150 ml	**5**		
	< 200 ml/≥200 ml	**9, 18**	**3**	
Histological response (% necrosis)	100%/99-50%/0–50%	**17**		S – 80%
	100%/90–99%/ < 90%		**18**	
	≥95%/ < 95%	**3**	15	
	≥90%/ < 90%	**9**	10	
	Other	**5**		
Gender	Female/male		**2, 3, 5, 6, 7, 9,** 10 **11, 14,** 15**, 16, 17, 18**	S – 100%
Radiological response	CR/PR/SD/PD		**11, 18**	S – 100%
	CR + PR/SD +PD		**3, 9,** 15	
	CR/other		**6**	
Origin	Soft-tissue/bone		**14, 18**	S – 100%
Surgical margin	Negative/positive	**5, 11**	**18**	M – 67%
Site of metastatic lesions	Lung only/other		**7,** 10	M – 100%
	Lung only/lung combined/other		15	
Age	< 14y/≥14y	**5,** 10	**7, 18**	I – 64%
	< 15y/≥15y	**2**	**3, 9, 14,** 15	
	< 16y/≥16y	**6**	**17**	
	< 20y/≥20y		**3**	
	Other	**16**	**11**	
Location primary tumor	Extremity/axial	**6, 17**	**3, 5,** 10, **11,**	I – 55%
	Other/pelvic + spine		**14**	
	Non-pelvic/pelvic	**2, 16**	**7,** 15	
	Distal/proximal/other	**9**		
	Extremity/pelvic/sacrum + spine/other axial	**18**		
Size	< 8 cm/≥8 cm	**7, 14, 16, 17**	**3, 11,** 15	I – 57%
	< 10 cm/≥10 cm		**6**	
LDH	N/≥ 2× N	**2, 5**	**11, 14,**	I – 60%
	N/≥ 1,5× N		15	
	< 500 U/L/≥500 U/L		**3**	
Local treatment modality	Surgery/no surgery	**9**	10, **11,** 15	I – 50%
	Surgery/surgery + RT/RT	**5**	**7**	
	Surgery ± RT/RT only		**14**	
	No PORT/PORT	**18**		

Abbreviations: S = strong; M = moderate; I = inconclusive; L = limited; N = normal level; RT = radiotherapy; PORT = post-operative radiotherapy; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.
The numbers refer to the study ID as presented in Table 1. Studies with a low risk of bias are presented in bold.

non-white race, the other two could not find a clear association between ethnicity and OS [39,40].

3.5.10. Site of metastatic lesions

The site of metastatic lesions as a prognostic factor for OS was evaluated in two high-quality cohorts. One study [38] found a HR of 3.2 (95%CI 2.0–5.2; $p < 0.001$) for patients with only lung metastasis and a HR of 5.2 (95%CI 3.2–8.5; $p < 0.001$) for patients with extra-pulmonary metastasis. The other study and two low quality cohorts did not detect an association.

3.5.11. Serum LDH level

Two out of five high quality cohorts found that a serum LDH level two times the normal level is associated with poorer EFS, HR 4.2 (95%CI 2.7–6.5; $p < 0.001$) [24] and $p = 0.03$ (HR not given) [21]. Two other high-quality cohorts [30,33] did not find that serum LDH is associated with poorer EFS.

4. Discussion

The aim of this systematic review was to provide an overview of prognostic factors for survival in Ewing sarcoma in order to help guide development of prediction models and further studies.

The most significant prognostic factor influencing survival is the presence of metastasis at diagnosis. Other factors that consistently independent influence survival are: tumor size and volume, histological response and location of the primary tumor.

Large tumors were found to have an independent prognostic effect on survival. A tumor volume of 200 ml or more shows poorer EFS as well as a tumor diameter of 8 cm. Tumor dimensions can easily be recalculated into volume as shown by Göbel et al. [42]. Ewing sarcoma arises from the long and flat bones and presents with a varying degree of soft-tissue component [2,8]. Therefor volume is a more appropriate and accurate way of measuring tumor size, since the largest diameter could easily overestimate the size in the long bones and underestimate the size in case of an ellipse or round shaped tumor. With imaging modalities available nowadays, volume calculations can easily be made.

The prognostic significance of tumor location was commonly studied among the included studies, but evaluated by different means (extremity versus axial, pelvic versus non-pelvic etcetera). Overall tumors located in the axial skeleton, more specifically the pelvis were found to have poor overall survival and tumors located in the extremity, especially the distal extremity show better survival. A clear association with event-free survival (EFS) could not be found.

Histological response is used to tailor treatment in European trials for Ewing sarcoma [43] and considered of high prognostic value. The results from this systematic review show a tendency that necrosis of at least 90% improves EFS, evidence for a clear association with OS is however less consistent. Different cut-off points and different methods for evaluating and defining good histological response might explain this. Albergo et al. [36] found that patients with 100% necrosis of their tumor after neoadjuvant therapy have better survival over patients with viable tumor cells left, even if it is just 1%. The results from this review support this, with studies evaluating 90% and 95% cut-off points for

good responders showing inconsistent results.

Concerning the primary tumor resection, the data presented here show moderate evidence that obtaining negative, disease free tumor margins is of prognostic significance for EFS. There are 3 studies showing that achieving positive margins is not protective for survival and two studies not confirming this. Heterogeneity among centers in defining and evaluating surgical margins and the use of post-operative radiotherapy in case of inadequate margins might explain these somewhat inconsistent results.

Association between risk factors as age, race/ethnicity, LDH, site of the metastasis lesions, local treatment modality and survival are not consistent. Age was evaluated in almost all studies, showing that older age is associated with a poorer survival. The best cut-off point (14 or 18 years) needs to be further evaluated, since strong evidence for a specific cut-off point is lacking. Results suggest that white patients have better survival than other ethnicities. With only a few studies evaluating this, the evidence is limited. The same accounts for the serum LDH level and site of the metastatic lesions. Only two studies found that an elevated LDH leads to poorer EFS, no studies found any association with OS. Only a single study found that patients with only lung metastasis have a better OS compared to other metastatic sites.

Local treatment modality in relation with survival was evaluated by multiple studies which showed inconsistent results. The existing evidence available is based on retrospective, non-randomized trails. If surgery with or without radiotherapy is better than radiotherapy alone is still under debate. Many of these studies are affected by a selection bias, where radiotherapy is only indicated in specific groups of patients, for instance patients with less favorable prognostic factors. A recent systematic review by Werier et al. [44] on optimal local treatment strategies for localized Ewing sarcoma found that either surgery alone (if negative margins can be achieved) or RT alone are reasonable treatment options. The optimal local treatment should be decided by considering patient characteristics, side effects and patient preference. In order to assess the effect of local treatment on survival, randomized trials aimed at comparing surgery, radiotherapy and a combination of both or prospective comparative studies are needed.

Several limitations were observed despite the strict eligibility criteria for this study. Treatment of patients is heterogeneous among studies. Although all patients were treated with neo-adjuvant therapy, followed by local treatment of the primary tumor and adjuvant chemotherapy. The type of chemotherapy was not consistent among the studies. Chemotherapy agents, doses and combinations changed and differ among countries. There has been a major progress in improving chemotherapy protocols over the last decades and therefore improvement in survival. Presence of heterogeneity among treatment increases the risk of bias and therefor the quality of the results presented here. Also, several different cut-off points were used for the evaluation of age, size, volume, location of the primary tumor and histological response.

5. Conclusion

The presence of metastasis at diagnosis, large tumors (volume ≥ 200 ml or largest diameter ≥ 8 cm), primary tumors located in the axial skeleton, especially pelvic, and a histological response of less than 100% are strongly associated with poorer survival in Ewing sarcoma (ES). These factors should be included as risk factors in the development of prediction models for overall survival and event-free survival in ES. Insight about the effect of surgical margins and local treatment modality requires further investigation.

Declarations of interest

None.

Funding

This research was supported by the Team Westland Foundation.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.suronc.2018.07.016.

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