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Prognostic factors for survival in Ewing sarcoma: A systematic review

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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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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.