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Review

Prognostic factors in localized extremity osteosarcoma: A systematic review

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Abstract

Aim: Finding reliable prognostic factors for osteosarcoma remains problematic. A systematic review [Davis AM, Bell RS, Goodwin PJ. Prognostic factors in osteosarcoma: a critical review. *Journal of Clinical Oncology* 1994; **12**(2): 423–431.] showed chemotherapy response as only independent factor. We tried to identify evidence-based prognostic factors in the literature since 1992 and to establish pooled relative risks of factors.

Methods: MEDLINE and Embase search (1992–August 2006). Two reviewers independently selected papers addressing prognostic factors in localized extremity osteosarcoma, which were studied for methodological quality, and valuable new factors. An attempt was made to pool results.

Results: Of 1777 ''hits'', 93 papers were studied in depth. Several ''new'' prognostic factors were found. Only 7 papers were of sufficient quality to analyze. Chemotherapy response, tumor size and site, alkaline phosphatase level and p-glycoprotein expression seemed to be independent factors. Some new factors looked promising.

Conclusions: Although the literature is abundant, it is disappointing that only few papers are of sufficient quality to allow hard conclusions. Because of heterogeneity of the studies pooling results is hardly possible. There is a need for standardization of studies and reports.

Keywords: Humans; Osteosarcoma; Bone neoplasms; Prognosis; Survival analysis; Extremities

Introduction

Survival in osteosarcoma and the importance of prognostication

Since the 1970s, survival in patients with high-grade osteosarcoma has improved from around 15% to 60–70%,[2] and has even been reported to be 86% in one population.[3] This improvement is generally attributed to the development of adjuvant and neo-adjuvant chemotherapy.[4–8] The possibility of downgrading tumors before operation facilitated the evolution of reconstruction methods after tumor resection. Whereas up to the late seventies 80% of patients with an extremity osteosarcoma ended up with an amputation, nowadays limb saving surgery is possible in 90% of patients. Decision making has become multifactorial with this. Some (especially biological) reconstruction methods, have excellent long term results but require a long (up to 2 year) rehabilitation time, whereas others, such as endo-prosthetic replacements, allow early mobilization but have problems in the long term.[9] A reasonably accurate estimate of survival chance for patients early in treatment would be helpful in counseling patients and their parents and in therapeutic decision making. Choice and possible change of chemotherapy and of surgical approach could be tailored to the patient.

Prognostic factors

Chemotherapy response has always been the most important, and most consistently reported, predictor for

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survival.[1,2,5,6,8,10,11] Prognostication in individual patients remains a problem. Many prognostic factors in osteosarcoma have been reported. The studies however vary significantly in methodology and quality. Several reviews have been done addressing specific factors,[12–15] but their conclusions are cautious because of heterogeneity of the included studies. Attempts to review the complete range of relevant factors are sparse. In 1997 Saeter gave a narrative overview about most known factors. Stage at diagnose was considered to be the most important predictive factor, followed by chemotherapy response, tumor volume, old age, sex, and possibly p-glycoprotein expression.[16]

In 1994 Davis et al. published a systematic review giving an overview of the literature until 1992.[1] Studies were included concerning patients with non-metastatic, high grade, osteosarcoma of extremities, treated with chemotherapy and surgery. A critical appraisal was done on the methodological quality of included studies. Prognostic factors were analyzed only if they were at least considered in 4 of the included studies. Eventually 8 papers were included in this review. Analyzed factors were age, sex, tumor location, tumor size and necrosis after chemotherapy. Their conclusion was that chemotherapy response was the only proven independent factor predicting survival.

Aim of the study

The objective of our current systematic review was to elaborate on the work of Davis and colleagues, to try and identify new independent predictive factors, and to investigate whether meta-analysis of the results of different studies was possible, in order to establish pooled estimates of the effect of specific predictive factors.

Methods

Search strategy and study selection

MEDLINE and Embase were searched for eligible studies published in English, French or German between January 1992 and August 2006. We applied the following search strategy: [“osteosarcoma” OR “osteogenic sarcoma”] AND [“prognosis” OR “survival”]. Reports were selected, specifically addressing factors predicting survival in osteosarcoma patients. Inclusion was limited to patients with non-metastatic, high grade, primary osteosarcoma of an extremity.

Quality assessment and analysis

For all included studies we assessed methodological quality[17](Table 1) and abstracted data. Data were recorded on a standardized form. Information was collected on patient characteristics, prognostic factors, adjusted relative risks for death (event free survival or overall survival), and timing of follow-up measurements. Study selection, assessment of methodological quality and data extraction were done by two reviewers independently. Disagreements were resolved by discussion with a 3rd reviewer.

Studies fulfilling all these quality criteria were selected for further meta-analysis. Studies for which the participants, prognostic factors, outcome measures, timing of follow-up measurements and adjustments for confounders were considered to be sufficiently similar were combined. We pooled adjusted relative risks of each prognostic factor by the use of a random effects model. To assess statistical heterogeneity we used the Chi-square test (p-value <0.10) and heterogeneity was quantified by the I^2 statistic. In case of statistical heterogeneity, we explored sources of heterogeneity by meta-regression analysis. Meta-analysis was done by the use of Review Manager (RevMan [Computer program]. Version 4.2 for Windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003) and SPSS version 11.5 (SPSS, Chicago, IL). Studies that were clinically heterogeneous or did not present the data in sufficient detail to enable statistical pooling were qualitatively summarized. The level of evidence of studies was determined according to Harbour and Miller.[18]

Results

Search results and inclusion of papers

The search resulted in 1777 “hits”, of which 93 were included. Sufficient follow up (≥90% completeness, ≥3 years) was absent in 60% of these studies. No multivariate

Table 1
Methodological criteria for inclusion in the meta-analysis.[a]

1. Study participation	Clearly defined patient sample, assembled at common point in course of the disease
	Dates of researched period stated
2. Study attrition	Sufficiently long and complete follow up (≥3 years and ≥90%)
	Explaining reasons for patients being lost to follow up
3. Prognostic factor measurement	Clear definition and valid assessment of prognostic factors
4. Outcome measurement	Well defined outcome parameters (survival: overall, metastasic free, event free)
5. Confounding measurement and account	Clearly defined and comparable treatment for patients
	Confounding factors are accounted for in analysis
6. Analysis	Valid statistical analysis is done
	Multivariate analysis is done

[a] Adopted from Hayden et al.[28]