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Prognostic factors and outcomes for osteosarcoma: An international collaboration

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ABSTRACT

We aimed to evaluate the prognostic significance of traditional clinical predictors in osteosarcoma through an international collaboration of 10 teams of investigators (2680 patients) who participated. In multivariate models the mortality risk increased with older age, presence of metastatic disease at diagnosis, development of local recurrence when the patient was first seen, use of amputation instead of limb salvage/wide resection, employment of unusual treatments, use of chemotherapeutic regimens other than anthracycline and platinum and use of methotrexate. It was also influenced by the site of the tumour. The risk of metastasis increased when metastatic disease was present at the time the patient was first seen and also increased with use of amputation or unusual treatment combinations or chemotherapy regimens not including anthracycline and platinum. Local recurrence risk was higher in older patients, in those who had local recurrence when first seen and when no anthracycline and platinum were used in chemotherapy. Results were

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similar when limited to patients seen after 1990 and treated with surgery plus combination chemotherapy. This large-scale international collaboration identifies strong predictors of major clinical outcomes in osteosarcoma.

1. Introduction

Osteosarcoma is the most common malignant bone tumour of childhood and adolescence,[1] and the second most common primary tumour involving bone in the general population. Males are affected slightly more frequently than females.[2–4] The pathogenesis remains unclear, although several causative factors have been proposed.[4–9] In recent studies the reported 5-year survival ranges from 50% to 75%,[10–14] but the disease has a variable course and the prognostic factors that affect this variability are not fully understood. Moreover, while the main treatment approach typically includes the combination of surgery with chemotherapy, there is limited knowledge on how different types of surgery (limb salvage versus amputation), chemotherapy (pre- and post-operatively), or other treatments (e.g. radiotherapy) influence the outcome. Understanding risk factors would be important in estimating and communicating risk to patients and in making appropriate therapeutic decisions.

Several prognostic factors have been reported to be associated with osteosarcoma outcomes. To clarify the impact of patient, tumour and management characteristics as prognostic factors in patients with osteosarcoma across diverse settings, we set up an international collaboration, where several teams of investigators contributed data on their patients according to a standardised protocol.

2. Materials and methods

2.1. Construction of the consortium

In April 2006, PubMed searches were performed on 'osteosarcoma', limited to studies with human subjects with a publication date from 1993 to 2006. This search identified 6128 items. The abstracts were screened to identify studies on prognostic factors of osteosarcoma with at least 20 patients. This procedure left 2224 potentially eligible articles from 153 distinct research groups that had published on various putative predictive factors for osteosarcoma. In October 2006, an invitation was sent to these groups to probe their interest in an international collaborative study of osteosarcoma outcomes and prognostic factors. As a prerequisite it was requested that a team should be able to contribute at least 40 patients with information on major clinical outcomes (death, metastasis and local recurrence) plus a minimum dataset of potential prognostic factors. A preliminary protocol was circulated and interested teams were asked to make amendments and improvements. Ten teams of investigators responded favourably, participated in finalising the protocol (with mutually agreed definitions of all variables of interest) and sent data. The participating teams were located in Birmingham, Vienna, Sao Paolo, Pamplona, Florence, Ankara, Paris, Valencia, Zagreb and Cincinnati. One team (Ankara) had enrolled only children or adolescents (<20 years old when seen), while others enrolled both children/adolescents and adults.

According to the protocol, investigators were encouraged to send data on all cases of osteosarcomas that they have seen in their centres, regardless of whether they have followed up these cases since the time of diagnosis or not, and regardless of whether they still follow these patients or not, so as to be able to judge the extent of missing information. The investigators were encouraged to communicate with the coordinators to clarify any unclear issues on how cases should be selected, minimise potential selection biases, and maximise standardisation across teams. Of note, the collaborative analysis utilises data from teams that have already published some information from their patients, but the information available for the collaborative project may be different from the published data due to various reasons: more patients included, extended coverage of variables, standardisation and harmonisation of definitions and data cleaning.

Data collection was completed on 30th October 2007. Clarification of data queries between the coordinating team and collaborators and further cleaning of databases were performed until April 2008.

2.2. Data: definitions and standardisations

Osteosarcoma cases were eligible regardless of age at diagnosis, site, diagnostic group or other characteristics. Follow-up started when a patient was first seen by the participating team of investigators with a diagnosis of osteosarcoma. This means that for some cases follow-up did not start at the time of the primary diagnosis, but later, e.g. this could be at a time when local recurrence or metastatic disease was detected. Incident cases were defined as those where follow-up started within 4 months of initial diagnosis. Follow-up was censored on 30th May 2006.

Each team contributed data on gender, age at the start of the follow-up, tumour size (largest diameter), bone location (including whether proximal or distal in long bones), clinical type (conventional, paraosteal, periosteal, others), histological type (osteoblastic, chondroblastic, fibroblastic, telangiectatic, small cell, others), presence of metastases and local recurrence at the start of the follow-up, initial treatment received at the time of initial diagnosis (surgery, chemotherapy, radiotherapy or others and combinations thereof), type of surgical treatment (classified as amputation versus limb salvage [including wide resection]), type of chemotherapy (based on whether it included anthracycline and/or platinum and whether methotrexate was used or not), timing of chemotherapy (preoperatively, postoperatively, both), histological response to preoperative chemotherapy (defining responders as those having 90% or higher necrosis, i.e. grade 3 or 4 re-

sponse as per the Huvos system[15] and class 1,2 or 3 response as per the Salzer-Kuntschik system[16]), date of diagnosis and date when first seen, development of local recurrence, time to local recurrence, development of metastasis, time to metastasis, location of metastasis, death and time to death or last follow-up.

2.3. Outcomes

The primary outcome was death from any cause. Secondary outcomes were the development of metastasis and local recurrence. For patients who already had a local recurrence when first seen by the team, we counted only the development of a new local recurrent lesion as a local recurrence outcome. Similarly, for patients who already had metastasis when first seen by the team, we counted only the development of metastasis at a different, new localisation as a metastatic event.

2.4. Statistical analysis

The analysis included all patients regardless of whether they were incident cases or not (prevalent cases). We initially intended to perform secondary analyses examining the incident and prevalent cases separately (because cases with prevalent diagnoses at the time first seen by a team may have survivorship bias), but the limited number of prevalent cases ($n = 108$) precluded their separate analysis. Most prevalent cases, moreover, had been diagnosed close to 4 months before first seen by a participating team. Analyses limited to incident cases did not materially change any of the estimates (not shown).

Descriptive tables were generated showing the distribution of candidate predictors and summary data on outcomes. We also examined by *t*-test and ANOVA, whether tumour size was associated with the initial treatment, timing of chemotherapy and choice of surgical procedure (amputation or not).

For each candidate predictor and for each outcome, we performed analyses in each team using proportional hazards models, after checking Kaplan–Meier plots and formal testing using time-dependent variables. Analyses per team are not presented, but are available from the authors upon request. Cox models estimated hazard ratios for gender, age, tumour size, tumour location, location in long bones, clinical type, histological type, metastasis at the start of the follow-up, local recurrence at the start of the follow-up, initial treatment received, type of surgery, timing of chemotherapy, type of chemotherapeutic regimen, histological response to preoperative chemotherapy and calendar year of diagnosis. We considered variables with $p < 0.05$ in univariate models for inclusion in a stepwise entry approach for building the multivariate model according to likelihood ratio criteria. We did not consider for the multivariate model variables with missing information on more than 20% of the patients (tumour size, histological type, grade and histological response to chemotherapy). We also estimated for the final multivariate model, the coefficient of determination, i.e. the proportion of the between-individual variance in outcome that is explained by the selected variables. This is given by 1 – exp([change in –2LL with the inclusion of variables]/n), where –2LL is the –2log likelihood and n is the number of patients included in the Cox model analysis. Finally, in order to focus also on more recently diagnosed cases who had received standard treatment, a set of sensitivity analyses were limited to cases diagnosed after 1990 who had been treated with surgery plus combination chemotherapy.

Analyses were conducted by using SPSS (version 14.0; SPSS, Inc., Chicago, IL). *P*-values were two tailed. All data and analyses were handled at the coordinating centre at the University of Ioannina. The corresponding author had full access to all the data in the study and had final responsibility to decide on the submission of the manuscript.

3. Results

3.1. Characteristics of eligible patients

Data from 2680 patients were assembled (Table 1 and Supplementary Table 1). Most (86%) had been first seen after 1980. Most patients were adolescents and there was a slight male predominance. The median tumour size in the 1216 patients who had accurate measurements was 10.0 cm. The tumour was located in the femur in approximately half of the patients, and in the tibia in a quarter. In the majority of osteosarcomas in long bones (56%) the tumour was located in distal part of the bone, but proximal locations were also common (38%). When location was noted, most femoral tumours (88%) had a distal location and most tibia tumours (80%) had a proximal location. Non-conventional osteosarcomas were very uncommon (3%). Among 1859 patients with available data on histological type, approximately half had osteoblastic tumours, but many other histological types were represented (Table 1 and Supplementary Table 1). One in seven patients presented with metastases and 1% of cases had local recurrences when first seen by the participating team.

Most patients (78%) had combined surgery and chemotherapy, 14% had surgery alone, 3% had chemotherapy alone and 5% had other combinations or treatments. In surgical management, about a fifth of the patients underwent amputation. Chemotherapy was most commonly given both pre- and post-operatively. An extreme heterogeneity was observed in chemotherapeutic schemes used by each team. The main regimens used in various combinations were doxorubicin, methotrexate, ifosfamide, etoposide, bleomycin, cyclophosphamide, dactinomycin and carboplatin. Most patients received combination chemotherapy, and in the large majority this included both anthracycline and platinum. Surgery plus combination chemotherapy was used in the large majority of patients. For patients with preoperative chemotherapy we had available data for the histological response in 1734 patients. The median (IQR) histological response was 65% (30–90%). Less than a third (29%) of the patients had histological response $\geqslant$90%. A total of 1409 patients had been seen after 1990 and had been treated with surgery plus combination chemotherapy.

Based on the available data, there was no clear association between tumour size and the type of initial treatment ($p = 0.08$), or timing of chemotherapy ($p = 0.24$), but patients who had amputation had modestly larger tumours than those who had limb salvage/wide resection procedures (mean [SD] 12.7 (6.0) cm versus 10.5 (5.4) cm, $p < 0.001$).

Table 1 – Characteristics of patients included in the study.

Date when seen by the team, N (%)	
⩽1970	286 (11)
1971–1980	112 (4)
1981–1990	537 (20)
1991–2000	1135 (42)
>2000	610 (23)
Males, N (%)	1527 (57)
Median size (IQR) in mm	100 (74–140)
Localisation, N (%)	
Femur	1400 (52)
Tibia	638 (24)
Humerus	266 (10)
Others	376 (14)
Site in long bones, N (%)	
Distal	946 (56)
Proximal	652 (38)
Diaphysis	72 (4)
Whole bone	26 (2)
Clinical type, N (%)	
Conventional	2284 (96)
Paraosteal	59 (2)
Periosteal	25 (1)
Others	9 (1)
Histological type, N (%)	
Osteoblastic	1041 (49)
Chondroblastic	309 (15)
Fibroblastic	175 (8)
Telangiectatic	95 (4)
Small cell	15 (1)
Others	479 (23)
Metastasis when first seen, N (%)	362 (13)
Recurrence when first seen, N (%)	36 (1)
Initial treatment, N (%)	
Surgery + chemotherapy	2091 (78)
Surgery	385 (14)
Chemotherapy	73 (3)
Surgery + chemotherapy + RT	86 (3)
Others	43 (2)
Type of surgery, N (%)	
Limb salvage/wide resection	1891 (77)
Amputation	572 (23)
Timing of Chemotherapy, N (%)	
Pre- and post-operatively	1982 (91)
Pre-operatively	35 (2)
Post-operatively	153 (7)
Type of chemotherapy	
Both anthracycline and platinum included	1665 (74)
Combination with anthracycline, but without platinum	52 (2)
Combination with platinum, but without anthracycline	14 (1)
Others – not specified	530 (23)
Use of methotrexate	
No	601 (27)
Yes	1278 (55)
Not specified	412 (18)
Histological response, N (%)	
⩾90	509 (29)
<90	1225 (71)

IQR: interquartile range, OS: osteosarcoma, NA: not available, S: surgery, C: chemotherapy, RT: radiotherapy.
Percentages were calculated from available data.

Complete information on dates of the start of the follow-up and date of event or last follow-up without an event was available for 2365 patients for mortality, 2286 patients for metastasis and 2285 patients for local recurrence analyses and these patients were included in the time-to-event analyses that encompassed 1083 deaths, 867 patients with metastasis events and 292 patients with local recurrence events. The large majority of missing data on outcomes pertain to patients diagnosed before 1970. When limited to patients first seen after 1990 and receiving surgery and combination chemotherapy, the analyses included 519 deaths, 481 patients with metastatic events and 174 patients with local recurrence events.

3.2. Mortality

Across the whole collaboration, 5-year mortality risk was 48%. The results of univariate analyses are given in Supplementary Table 2. In multivariate analyses (Table 2), survival was worse with older age (7% relative risk increase per decade) and the presence of metastases or local recurrence each tripled the mortality risk. Tumours that were located in the tibia had 26% decreased risk of death than those located in the femur. Besides these clinical characteristics, compared with patients treated with both surgery and chemotherapy, addition of radiotherapy was associated with 92% increased relative risk of death and amputation was associated with a 76% increased relative risk versus limb salvage/wide resection procedures. Patients who received only anthracycline and not platinum had 79% increased risk of death than those who received both regimens in their chemotherapy schema. Patients that received other chemotherapeutic regimens than those including anthracycline and platinum had 45% increased risk of death. Patients who received methotrexate had 32% increased risk of death than those in whom methotrexate was not used. The multivariate model explained 10.6% of the variance. In multivariate analyses limited to patients first seen after 1990 and receiving standard treatment, the results were similar, but the presence of local recurrence did not reach formal significance; moreover, data were available on response to chemotherapy and patients with poor response to preoperative chemotherapy had more than double mortality risk (Table 2).

3.3. Metastasis

The vast majority of documented metastases (74%) were located in lung, followed by bone metastases (10%). The 5-year risk of metastasis was 45% across the whole collaboration. The results of univariate analyses are given in Supplementary Table 3. In multivariate analysis (Table 3), the presence of metastases when seen by the team increased the risk for a new metastasis fivefold, but no other clinical or demographic characteristics were independently associated with metastasis risk. In addition, patients where radiotherapy was added to the combination of surgery and chemotherapy and patients who had received chemotherapy not including both anthracycline and platinum had worse prognosis. The multivariate model explained 10.3% of the variance. In multivariate analyses limited to patients first seen after 1990 and receiving standard treatment increased risk for metastasis was ob-

Table 2 – Multivariate analyses for predictors of death in patients with osteosarcoma.

	Main analysis[a]		Sensitivity analysis[b]	
	HR (95% confidence intervals)	*p* Value	HR (95% confidence intervals)	*p* Value
Calendar year (per decade)	NS		NS	
Age (per year)	1.008 (1.001–1.014)	0.03	NS	
Size (per cm)	NI		NI	
Site				
Femur	Reference		Reference	
Tibia	0.74 (0.62–0.89)	0.001	0.55 (0.43–0.71)	<0.001
Humerus	1.23 (0.97–1.55)	0.08	1.23 (0.90–1.67)	0.20
Others	1.03 (0.82–1.30)	0.80	1.02 (0.73–1.42)	0.91
Clinical type				
Conventional	Reference		Reference	
Paraosteal	NS		NS	
Periosteal	NS		NS	
Others	NS		NS	
Histological type				
Osteoblastic	Reference		Reference	
Chondroblastic	NI		NI	
Fibroblastic	NI		NI	
Telangiectatic	NI		NI	
Small cell	NI		NI	
Others	NI		NI	
Metastasis when first seen	2.89 (2.36–3.54)	<0.001	3.39 (2.62–4.39)	<0.001
Local Recurrence when first seen	3.04 (1.60–5.78)	0.001	NS	
Initial treatment[c]				
Surgery and chemotherapy	Reference		NA	
Surgery			NA	
Chemotherapy			NA	
Surgery + chemotherapy + RT	1.92 (1.35–2.72)	<0.001	NA	
Others			NA	
Type of surgery				
Limb salvage/wide resection	Reference		Reference	
Amputation	1.76 (1.49–2.07)	<0.001	1.85 (1.46–2.35)	<0.001
Time of chemotherapy				
Pre- and post-operatively	Reference		Reference	
Pre-operatively	NI		NS	
Post-operatively	NI		NS	
Type of chemotherapy				
Both anthracycline and platinum	Reference		Reference	
Only anthracycline	1.79 (1.03–3.10)	0.04	S	
Only platinum	0.82 (0.26–2.65)	0.74	S	
Others – not specified	1.45 (1.09–1.94)	0.01	S	
Use of methotrexate				
No	Reference		Reference	
Yes	1.32 (1.06–1.64)	0.01	NS	
Not specified	0.85 (0.60–1.19)	0.33	NS	
Histological response (Reference ⩾ 90%)				
<90%	NI	2.17 (1.63–2.88)	<0.001	

HR: hazard ratio, RT: radiotherapy, NI: not included (missing information on over 20% of the analysed sample), NS: non-significant, not selected, NA: non-applicable.

a For both the main and sensitivity analyses, variables are not shown in the table because they were not included in the multivariate model due to missing information on more than 20% of the patients were tumour size, particular site in long bones, histological type and grade.

b The sensitivity analysis considered patients treated after 1990 with the combination of surgery and chemotherapy of at least two combined regiments.

c In multivariate analysis patients who did not have surgery and chemotherapy were excluded.

served for patients with metastatic disease when seen by the team, amputation procedures and poor response to preoperative chemotherapy, while tumours located in the tibia had lower risk of metastasis (Table 3).

Table 3 – Multivariate analyses for predictors of metastasis in patients with osteosarcoma.

	Main analysis[a]		Sensitivity analysis[a,b]	
	HR (95% confidence intervals)	*p* Value	HR (95% confidence intervals)	*p* Value
Calendar year (per decade)	NS		NS	
Size (per cm)	NI		NI	
Site				
Femur	Reference		Reference	
Tibia	NS		0.66 (0.51–0.88)	0.004
Humerus	NS		1.04 (0.74–1.46)	0.81
Others	NS		0.97 (0.69–1.37)	0.88
Clinical type				
Conventional	Reference		Reference	
Paraosteal	NS		NS	
Periosteal	NS		NS	
Others	NS		NS	
Histological type				
Osteoblastic	Reference		Reference	
Chondroblastic	NI		NI	
Fibroblastic	NI		NI	
Telangiectatic	NI		NI	
Small cell	NI		NI	
Others	NI		NI	
Metastasis when first seen	5.07 (3.98–6.47)	<0.001	6.59 (4.77–9.09)	<0.001
Local Recurrence when first seen	NS		NS	
Initial treatment[c]				
Surgery and chemotherapy	Reference		Reference	
Surgery			NA	
Chemo therapy			NA	
Surgery + chemotherapy + RT	1.70 (1.18–2.46)	0.004	NA	
Others			NA	
Type of surgery				
Limb salvage/wide resection	Reference		Reference	
Amputation	1.64 (1.36–1.97)	<0.001	1.56 (1.20–2.03)	0.001
Time of chemotherapy				
Pre- and Post-operatively	Reference		Reference	
Pre-operatively	NS		NS	
Post-operatively	NS		NS	
Type of chemotherapy				
Both anthracycline and platinum	Reference		Reference	
Only anthracycline	1.21 (0.66–2.21)	0.53	NS	
Only platinum	2.10 (0.89–4.96)	0.09	NS	
Others – not specified	1.51 (1.26–1.82)	<0.001	NS	
Histological response				
⩾90%	Reference		Reference	
<90%	NI		1.67 (1.29–2.16)	<0.001

HR: hazard ratio, RT: radiotherapy, NI: not included (missing information on over 20% of the analysed sample), NS: non-significant, not selected, NA: non-applicable.

a For both the main and sensitivity analyses, variables are not shown in the table because they were not included in the multivariate model due to missing information on more than 20% of the patients were tumour size, particular site in long bones, histological type and grade.

b The sensitivity analysis considered patients treated after 1990 with the combination of surgery and chemotherapy of at least two combined regiments.

c In multivariate analysis patients who did not have surgery and chemotherapy were excluded.

3.4. *Local recurrence*

The 5-year risk of local recurrence was 16% across the whole collaboration. The results of univariate analyses are given in Supplementary Table 4. Multivariate analysis (Table 4) showed a worse prognosis with increasing age, in the presence of local recurrence when seen by the team and when chemotherapy regimens were used which included neither anthracycline nor platinum. The multivariate model explained 2.7% of the variance. In multivariate analyses limited

Table 4 – Multivariate analyses for predictors of local recurrence in patients with osteosarcoma.

	Main analysis[a]		Sensitivity analysis[a,b]	
	HR (95% confidence intervals)	*p* Value	HR (95% confidence intervals)	*p* Value
Calendar year (per decade)	NS		NS	
Age (per year)	1.016 (1.004–1.027)	0.006	NS	
Site				
Femur	Reference		Reference	
Tibia	NS		NS	
Humerus	NS		NS	
Other	NS		NS	
Clinical type				
Conventional	Reference		Reference	
Paraosteal	NS		NS	
Periosteal	NS		NS	
Other	NS		NS	
Histological type				
Osteoblastic	Reference		Reference	
Chondroblastic	NI		NI	
Fibroblastic	NI		NI	
Telangiectatic	NI		NI	
Small cell	NI		NI	
Other	NI		NI	
Local Recurrence when first seen	8.95 (4.79–16.71)	<0.001	9.77 (3.45–27.68)	<0.001
Type of chemotherapy				
Both anthracycline and platinum	Reference		Reference	
Only anthracycline	1.12 (0.38–3.25)	0.84	NS	
Only platinum	0.54 (0.07–4.00)	0.55	NS	
Other – not specified	1.66 (1.18–2.34)	0.004	NS	
Use of methotrexate				
No	Reference		Reference	
Yes	NS		NS	
Not specified	NS		NS	
Histological response (Reference ⩾90%)				
<90%	NI		2.96 (1.78–4.92)	<0.001

HR: hazard ratio, RT: radiotherapy, NI: not included (missing information on over 20% of the analysed sample), NS: non-significant, not selected, NA: non-applicable.

a For both the main and sensitivity analyses, variables not shown in the table because they were not included in the multivariate model due to missing information on more than 20% of the patients were tumour size, histological type and grade.

b The sensitivity analysis considered patients treated after 1990 with the combination of surgery and chemotherapy of at least 2 combined regiments.

to patients first seen after 1990 and receiving standard treatment, the presence of recurrent disease when seen by the team and poor response to chemotherapy were associated with increased risk for local recurrence (10 times and 3 times, respectively) (Table 4).

4. Discussion

This international collaboration has accumulated the largest database assembled to date on prognostic factors and clinical outcomes for patients with osteosarcoma. We have been able to obtain prognostic information for death, metastatic risk and risk of local recurrence on demographic, clinical and treatment management factors combining data from several centres around the world which treat osteosarcoma patients. This information may be useful for risk stratification and for informing the management of patients with osteosarcoma.

This collaborative analysis is not a discovery exercise, i.e. we did not set up to identify new prognostic factors, but to validate and appreciate the strength of previously proposed variables with large-scale evidence. Previous studies have drawn attention to several of the demographic and clinical predictors that we have found in our analyses,[10,17–21] including age,[10] tumour size,[10,17,18] location,[19,20] histological type[20,21] and site.[19] However, reporting of such associations across different studies has often been inconsistent (different variables and different definitions). Larger studies on prognostic factors of osteosarcoma [10,19,22,23], have been a welcome improvement, even if they have not all addressed the same prognostic factors. The currently available predictors seem to explain a

minority of the variability in outcomes of osteosarcoma. This means that large studies such as this one and others can be a useful starting point for assessing the incremental contribution of new proposed predictive markers beyond what is already known.

Our analysis also provides insights about the outcomes of different management options. There is an increasing number of well-conducted randomised trials in osteosarcoma,[11,14,24–28] but most report on different chemotherapeutic regimens used.[14,26,27] Many treatment decisions such as the type of initial intervention and the type of surgery are based largely on empirical observations. The prognostic associations that we observed are likely to reflect to some extent confounding by indication, therefore associations should not be interpreted as necessarily providing proof of differential clinical effectiveness. The worse prognosis for patients who did not have any surgery may reflect that these patients were perceived to have worse prognosis and/or were considered inoperable. Also patients to whom radiotherapy was added may have been felt to have been less than optimally treated and/or had soft tissue mass extension and thus an effort was made to add some adjunctive treatment. However, we saw no major difference in tumour size between groups of patients who had different initial treatments. Our data suggest that a combination of surgery and chemotherapy should be the standard of choice and similarly chemotherapy may best be used both pre- and post-operatively. However, we should keep in mind that at least one randomised trial of 100 patients has shown that pre-operative chemotherapy may not improve outcomes.[24]

We also observed that patients who had an amputation had increased risk of death and metastasis than patients who had limb sparing/wide resection procedures. Amputation only conferred a marginal benefit against local recurrence, but the absolute benefit, if real, would still be small. While amputation may have been selected for larger tumours and patients with perceived worse prognosis, the major difference in outcomes suggests that amputation may not be a procedure of choice and efforts to avoid it are warranted. Robust randomised trials would be needed to verify the benefit of these proposed therapeutic choices, but large-scale observational evidence may offer some useful information in the absence of randomised data.[28] We documented a clear improvement in survival in more recent years, but it is difficult to decipher whether this is a reflection of the improved management of patients or recruitment of more cases with good prognosis in more recent cohorts.

Even though our data were more limited for histological response, we observed that examination of tumour necrosis was a strong predictor for all major clinical outcomes. However, our data do not suffice to examine whether particular chemotherapy regimens are better than others. Besides the non-randomised nature of our data, chemotherapy regimens were also extremely variable. Toxicity risk based on experience from other malignancies where these regimens have been used may need to be also considered in management decisions. A trial of 407 patients has shown no survival benefit with multi-drug regimens versus two-drug regimens.[29] Another trial of 497 patients has shown that intensification of chemotherapy improves histological response without concomitant improvement in progression-free or overall survival.[14]

Some other limitations of our study should be acknowledged. First, we made an effort to contact all teams that have worked and published on osteosarcoma, even with small patient series, but only 10 teams responded to our invitation. Unavoidably, the study population is shaped under the selection forces of each participating centre. Still, this coalition led to the largest study ever conducted on this malignancy. Second, despite making several efforts to maximise harmonisation and completeness of the information, the extent of missing information was considerable. This led us to exclude several factors from the multivariate analyses. Third, correlation between some clinical and management characteristics may affect the magnitude of the estimated relative risks in the multivariate model. Fourth, we made no effort to build a model based on training and perform a separate validation procedure. We chose the strategy of analysing all data together with appropriate team stratification so as to maximise power. For associations with highly significant prognostic effects, their credibility is likely to be high, although we cannot exclude modest inflation of some prognostic effect sizes.[30] As in any observational analysis, residual confounding cannot be excluded, but we did consider practically all the major known postulated risk factors. Fifth, we did not have the ability to perform standardised pathology reviews on the included cases. Use of centralised pathology reviewing centre would be very difficult, and for most cases the histological material is not available to reappraise. Nevertheless, all the participating centres have considerable experience in osteosarcoma and thus errors in diagnosis are quite unlikely.

Acknowledging these caveats, our collaborative analysis helps understand the prognostic implications of osteosarcoma. This collaboration can also be a starting point for addressing also other candidate predictors such as molecular markers and for examining whether they can offer additional incremental information on the outcome of this lethal malignancy.

Contributions

The idea was generated by J.P.A.I. E.E.P., A.D.N., R.J.G., H.D.K. and J.P.A.I. wrote the protocol and this was revised by comments from all other co-authors. E.E.P., A.D.N., R.J.G. and J.P.A.I. collected and cleaned the data in communication with the contributing investigators. E.E.P., A.D.N. and J.P.A.I. performed the statistical analyses and wrote the first draft. All other authors also interpreted the results and were invited to comment on the draft of the manuscript. The final version was approved by all authors.

Conflict of interest statement

None declared.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2009.03.005.

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