Survival in high-grade osteosarcoma: improvement over 21 years at a single institution

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Background: The purpose of this study was to analyze improvements in overall survival over 21 years (1982–2002), with a 5-year minimum follow-up, in the largest series from a single center ever reported.

Materials and methods: All diagnoses of high-grade osteosarcoma were included despite histological varieties, age, site and stage. Of the 1656 cases observed, 198 patients were excluded (41 consultation only, 129 low-grade varieties, and 28 lost to follow-up). Within 1458 included patients, 1032 had characteristics to be enrolled in conventional clinical trials (classic histology, age <41, localized, and extremity disease). Data are also analyzed in subgroups to define patients who benefited most.

Results: With a median follow-up of 12 years (5–25 years), 754 patients (51.7%) are alive, of whom 613 continuously disease free. Survival at 5, 10, and 15 years is 57%, 52%, and 51%, respectively. Patients candidates for clinical trials have a survival rate of 68%, 64%, and 61%, respectively. Survival for the other patients is 30%, 25%, and 24%, respectively. Trend (joingpoint statistical analysis at real 5-year follow-up) shows a yearly statistically significant improvement of 1.31% (95% confidence interval 0.5% to 2.1%) from 51% for patients treated in 1982 to 68% for those treated in 2002. Patients who statistically benefited were those who relapsed or presented with metastatic disease at diagnosis or had axial tumors.

Conclusions: Despite the lack of new drugs for osteosarcoma, survival has statistically improved, especially for those patients with the worst outcome. Aggressive treatments are recommended for all patients including those with poor prognosis.

Key words: bone neoplasms, osteosarcoma, survival

introduction

After the great improvement in survival for osteosarcoma in the 1970s, due to the adoption first of adjuvant [1–4] and then neoadjuvant chemotherapy [5–11], no major advancements have been reported in the last years [11–13]. The latest drug employed in this disease, ifosfamide, dates back to those years [11–14] but its role is still controversial [15]. Another difficulty in defining improvements in prognosis is the rarity of this tumor. The adoption of large multicentrical trials [4, 6, 8, 12–14] which are obviously important to increase recruitment of patients may cause bias due to different expertise in treatment among the different centers.

Another problem, also mainly due to the rarity of the tumor, is that reported data are generally dedicated to selected patients, those eligible for clinical trials, without considering the entire population of patients with osteosarcoma, independently from stage, location, age, and histological varieties.

Aim of this paper is to analyze overall survival in the largest series ever reported from a single institution, trying to evaluate possible improvement in prognosis and, if that is the case, to analyze which patients benefited most from this improvement.

This paper reports overall survival of all patients with high-grade osteosarcoma treated at a single institution over a 21-year period (1982–2002) including all high-grade histopathological varieties, sites of disease, stage, age, and treatment.

To make a comparison with other reported series possible, the same analysis is separately presented for those patients with characteristics to be enrolled in controlled clinical trials (primary high-grade osteosarcoma, no evidence of metastasis at diagnosis, extremity location, and age <41 years) and for those patients without these characteristics.

More detailed analyses are carried out on selected categories of patients, i.e. metastatic at diagnosis, axial location, patients >40 years, and with diagnostic varieties different from classic, high-grade surface, and telangiectatic osteosarcoma.

materials and methods

patients

From 1982 to 2002, 1656 new diagnoses of ‘osteosarcoma’ were made. Of these, 198 cases are not evaluable, being 41 in consultation only, 129 low-grade lesions, and 28 patients (mainly foreigners) lost to follow-up.
The remaining 1458 are included in this analysis. Of these patients, 1032 (70.8%) had the characteristics to enter controlled protocols (i.e. primary high-grade osteosarcoma, age <41 years, extremity site, and localized disease) and 426 (29.2%) did not have these characteristics. The institution ethical committee approved all clinical trials in this study.

Demographics and characteristics of patients and lesions are reported in Figure 1.

Recruitment varied from 43 to 83 cases per year for all patients (mean 69.5, median 71.5), from 29 to 68 cases for patients candidates to enter protocols (mean 48.5, median 48), and from 10 to 35 cases for patients without these characteristics (mean 20, median 19.5). No specific reasons could be detected for variability in recruitment.

**treatment chemotherapy.** Most patients were treated according to protocols active at the time of enrollment. These protocols have been accurately described in previous papers [10, 11, 14, 16].

All protocols included preoperative chemotherapy. In the first neoadjuvant study, primary treatment consisted of methotrexate (MTX) and cisplatin (CDP). Doxorubicin (DOX) was also added in the following studies. Postoperative therapy was based on histological response to primary chemotherapy. Good responder patients received the same drugs given preoperatively, whereas salvage chemotherapy was based on ifosfamide (Baxter Oncology-D, BAXTER ONKOLOGY GmbH, Halle, Germany) added to MTX, CDP, and DOX. In a more recent study protocol [14], ifosfamide was used at a high dose (15 g/m², 5-day continuous infusion) added to MTX, CDP, and DOX. The former study was a joint study carried out with the Scandinavian Sarcoma Group. Starting from 1999 protocols were national trials of the Italian Sarcoma Group.

surgery. Of the 1458 patients observed, 107 did not receive surgery. This was due to toxic death during preoperative chemotherapy (three cases), inoperable disease (33 cases), refusal (10 cases), diffused disease (60 cases), and in one case for other treatments given. None of these patients survived. Twenty-four more patients received surgery elsewhere and were treated at our institute only for chemotherapy. They are available for survival evaluation but not for surgical considerations.

Of the 1032 patients aged 40 years or under, with tumor in the extremities, classic histology, and without metastases at diagnosis, nine did not receive surgery: due to other treatments (one case), two toxic deaths previously mentioned, and six refusals. Ten more patients received surgery elsewhere.

Of the other 426 patients, 98 did not receive surgery: 33 cases were inoperable, four refused, one toxic death before surgery, and 60 had diffused disease. Fourteen more patients received surgery elsewhere.

follow-up. Routine follow-up consisted of outpatient control with imaging of both primary site and lungs every 2 months for the first 2 years, every 3 months the third year, every 4 months the fourth year, every 6 months the fifth year, and then yearly.

Date of death (or status of life, for patients who interrupted controls) was obtained through population registries (when available) or by request to registry offices where patients reside.

At March 2008, follow-up for surviving patients ranged from 58 to 303 months (mean 152 months, median 145 months) for the whole

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**Figure 1.** Characteristics of the 1458 patients with high-grade osteosarcoma considered in the study, diagnosed from 1982 to 2002. The figure is divided between cases with characteristics to be enrolled in prospective clinical trials (age <41 years, localized disease, extremity site, and conventional histology) and cases with characteristics usually leading to exclusion from clinical trials (metastatic at presentation, nonextremity site, age over 40 years, and histological varieties).
Survival analysis was carried out using the life table method with 1-year time intervals if the number of cases was large enough (100 cases for every survival curve); otherwise the Kaplan–Meier method was used.

To investigate the effect of the period of recruitment over survival, the 21 years of recruitment were divided into three cohorts of 7 years each. Then, the life table survival analysis with the Wilcoxon–Gehan test (large number of cases) or the Kaplan–Meier analysis with the log-rank test (small number of cases) was carried out to compare the three cohorts’ survival curves.

Cox regression survival analysis was used as multivariate analysis. This analysis included cases not accepted in protocols for specific reasons. These reasons were considered covariates to investigate their influence on survival.

Trends of the 5-year survival rates were analyzed by the joinpoint technique [17] which estimates the annual percentage change (APC) and the number and location of joinpoints (points at which trends change). The software enables pairwise comparisons of models differing by one joinpoint to ascertain the model with the optimum fit to the data series. We allowed a maximum of three joinpoints, and an overall significance level of 5% was used for the comparisons of models applied to each data series. For all tests, $P < 0.05$ was considered significant.

Statistical analysis was carried out by the Statistical Package for the Social Sciences (SPSS) software version 14.1 (SPSS Inc., Chicago, IL).

results

survival

entire series of patients. For the entire series of 1458 patients, at March 2008, 754 are alive (51.7%), of whom 613 (42.0%) continuously disease free, 137 without disease after one or more relapses, and four alive with disease. In all, 704 (48.3%) died between 1 week and 255 months (mean 31.5 months, median 23 months). Causes of death were as follows: disease in 685 cases, other causes unrelated to treatment in five cases (two suicides, two car accidents, and one hemorrhage in abortion), and causes related to treatment in 14 cases (five fatal cardiomyopathies at 11, 12, 13, 95, and 166 months, respectively, two veno-occlusive disease (VOD) at 9 and 38 months, one neurological complication at week 1, one respiratory complication at 76 months, one MTX delayed excretion at 2 months, one uncontrolled sepsis, one embolism after surgery, and two unknown causes at 2 and 4 months).

The survival curve shows a 5-year survival (true follow-up) of 57% and an expected survival at 10- and 15-years of 52% and 51%, respectively (Figure 2).

patients candidates to protocols. Of the 1032 patients eligible for protocols, 645 patients (62.5%) are alive, 532 continuously disease free (51.6%), 111 without disease after one or more relapses, and two with disease.

In all, 387 patients died (37.5%) between 2 and 255 months (mean 40 months, median 31 months), of whom 374 of disease, five already mentioned for unrelated causes, and eight due to treatment (four cardiomyopathies, one MTX toxicity, one VOD, one postoperative embolism, and one unknown cause).

The survival curve shows a 5-year survival (true follow-up) of 68% and an expected survival at 10- and 15-years of 64% and 61%, respectively (Figure 2).

patients non-candidates to protocols. Of the 426 patients not eligible for protocols, 109 survived (25.6%): 81 continuously disease free, 26 without disease after treatment for relapse, and two alive with disease. In all, 317 patients died (74.4%) between week 1 and 147 months (mean 21 months, median 14 months), 311 of disease, and six due to treatment complications.

The survival curve shows a 5-year survival (true follow-up) of 30% and an expected survival at 10- and 15-years of 25% and 24%, respectively (Figure 2).

surgery

entire series of patients. Surgery consisted of limb salvage procedures in 1022 cases (77.0%), rotationplasty in 43 (3.2%),...
and amputation in 262 (19.7%); patients not operated (107 patients) or treated elsewhere (24 patients) were omitted. A total number of 107 local recurrences were observed (8.1%). These occurred in 10 cases after demolitive surgery (3.8%), in one after rotationplasty (2.3%), and in 96 after limb salvage surgery (9.4%). Only 19 of the relapsed patients (17.8%) survived (all in the group initially treated by limb salvage procedures).

Patients candidates to protocols. Excluding the 19 ineligible patients, surgery consisted of limb salvage procedures in 811 cases (80.1%), rotationplasty in 40 (3.9%), and demolitive surgery in 162 (16.0%).

Local relapses were registered in 62 patients (6.1%), in two cases after demolitive surgery (1.2%), in one after rotationplasty (2.5%), and in 59 cases after limb salvage surgery (7.3%). Fifteen of these locally relapsed patients (24.2%) survived after further treatments.

Patients non-candidates to protocols. Surgery in these patients (excluding 112 cases not operated or operated elsewhere) consisted of 211 limb salvage procedures (67.2%), three rotationplasties (1.0%), and 100 demolitive procedures (31.8%).

A total number of 45 local relapses were observed (14.3%), eight after demolitive surgery (8.0%) and 37 after limb salvage surgery (7.3%). After local recurrence, only four patients (8.9%) survived.

Analysis of survival by year of recruitment

Figure 3 reports survival by year of recruitment for the whole series of patients, for candidates and non-candidates to protocols. Variability year by year can be explained by the small numbers when dividing patients in subgroups.

The three curves show an increase in survival, for patients treated from 1982 to 2002, ranging from 33% to 52% for the entire cohort, from 40% to 64% for patients candidates to protocols, and from 9% to 32% for non-candidates to protocols.

In the attempt to evaluate the statistically significant improvement over the years, patients were grouped into three cohorts by years of treatment: 1982–1988, 1989–1995, and 1996–2002.

Figure 4 shows these data: for the entire cohort and for patients non-candidates to protocols, the difference is statistically significant for patients treated in 1982–1988 compared with the other two groups. For patients candidates to protocols, besides the significance between the previously mentioned groups, there is also a trend between patients treated in 1989–1995 and 1996–2002 ($P = 0.07$).

Considering the fact that these data could be biased by a difference in follow-up, we analyzed survival by year of recruitment at the cut-off of 5-year follow-up. The method used is a joinpoint log regression analysis related to survival rates where a linear trend on a log scale implies a constant APC. The presence of joinpoints means that the APC is not constant.

The APC for all patients shows a yearly improvement (APC) in survival of 1.31% [95% confidence interval (CI) 0.5% to 2.1%] and a yearly improvement (APC) of 1.68% (95% CI 0.9% to 2.5%) for patients candidates to protocols; in both cases, these data are statistically significant at $P < 0.05$ (Figure 5).

Improvement in survival, especially for those patients candidates to enter protocols could be due to more aggressive treatment of relapses during the years. Totally, 47.5% of patients candidates to protocols presented local and/or distant relapses or second tumors (484 of 1019, excluding the 13 patients who died of other causes or toxicity). A total of 111 of these patients are alive (22.9%). A statistical analysis regarding the percentage of rescue of relapsed patients during the years was conducted, again, dividing the patients into three groups per year of recruitment: 1982–1988, 1989–1995, and 1996–2002: 31 of 189 (16.4%) survived in the years 1982–1988.
The analyses demonstrated a general improvement (APC) in survival during the period 1982–2002 of 1.31% (95% CI 0.5% to 2.1%) for all patients per year. The improvement (APC) for patients candidate to protocols was higher, with 1.68% (95% CI 0.9% to 2.5%) per year and an increase from 60% for patients treated in 1982 to 83% for those treated in 2002. In comparison, increase in survival for patients non-candidate to protocols moved from 19% to 35% for patients treated in 1982 and 2002, respectively.

Analysis of data demonstrated that the subgroups that most benefited from the increase were those patients with a worst initial survival: patients candidate to protocols who relapsed and were rescued (survival increased from 27% to 58%), patients metastatic at diagnosis (from 12% to 31%), and patients with tumor in axial sites (from 15% to 42%). Apart from a possible improvement due to a better use of conventional chemotherapy, it seems that these results are due to more aggressive multimodal treatments, including surgery for locations once considered inoperable or the use of iterative...
A recent paper from the American Surveillance, Epidemiology, and End Result (SEER) Program [18] reports data on 3482 patients with all types of osteosarcoma treated from 1973 to 2004. Although the aim of that paper was to verify differences in incidence and survival between three cohorts of patients based on the age of onset of the tumor (0–24, 25–59, and over 59 years), it confirms some of the data reported in this paper. The 5-year survival ranges from 61.6% for the younger group to 24.2% for the older one, similar to the survival here reported for patients candidate to protocols (68%) who are generally older and for patients non-candidate to protocols (30%) who are generally older. The SEER study demonstrated increased survival for those patients treated from 1983 in comparison with those treated before, but without further improvement for those treated from the 1990s. This is not in agreement with this paper, but we must keep in mind that the series here presented comes from a single institution, while the SEER data comes from population registries.

In conclusion, this paper demonstrated a small but constant improvement in survival for all patients presenting with osteosarcoma, in spite of the fact that very new treatment modalities or new drugs were not available. The evidence that patients who most benefited of the improvement in survival were those with a worst prognosis (relapsed, metastatic at

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**Figure 5.** Analyses of survival with the ‘joinpoint technique’ at the real follow-up of 5 years. (A) For all patients, the yearly improvement is 1.31% [95% confidence interval (CI) 0.5% to 2.1%], with survival increasing from 51% for patients treated in 1982 to 68% for those treated in 2002. (B) For patients candidate to protocols, the yearly improvement is 1.68% (95% CI 0.9% to 2.3%), increasing from 60% for patients treated in 1982 to 83% for those treated in 2002.
diagnosis, and unfavorable sites) justifies the use of aggressive treatments defined by multidisciplinary and harmonious teams to treat these patients not only at diagnosis but also in the following years to correctly approach the different aspects and phases of the disease.

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disclosure

The authors declare that they have no financial and personal relationships with other people or organizations that could bias their work. No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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Figure 6. Survival after relapse in patients candidate to protocols. (A) Kaplan–Meier curves, grouping the relapsed patients in three cohorts by year of first treatment, show a statistically significant improvement for those patients treated in the last two periods. (B) The same analysis carried out with the ‘joinpoint technique’ shows a yearly improvement of 3.9% (95% confidence interval (CI) 1.4% to 7.0%) increasing from 27% for patients treated in 1982 to 58% for patients treated in 2002. (C) Joinpoint analysis for event-free survival in patients candidate to protocols. The yearly improvement is 1.45% (95% CI 0.4% to 2.5%) with an increase from 50% for patients treated in 1982 to 60% for patients treated in 2002.


