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# Osteosarcoma over the age of forty☆

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**Abstract**

The European Musculo Skeletal Oncology Society (EMSOS) has carried out a retrospective review of patients over the age of 40 years with osteosarcoma. 481 patients from 12 centres or multicentric groups were included. 42 patients had osteosarcoma arising in Paget's disease, median survival was 9 months. Patients with axial or metastatic tumours also did badly whilst 41 patients with radiation-induced osteosarcoma had a prognosis paralleling conventional osteosarcoma matched for patient age and site of the tumour. 238 patients had high grade non-metastatic osteosarcoma and had a survival of 46% at 5 years. Older patients had less chemotherapy and fared worse. Osteosarcoma in the elderly is a curable condition and warrants intensive treatment with chemotherapy and surgical resection.


*Keywords:* Osteosarcoma; Paget's sarcoma; Radiation-induced sarcoma

## 1. Introduction

Osteosarcoma (OS) has a well recognised double peak of incidence. The majority arise in adolescence, but there is a significant second peak in the seventh and eighth decades of life. Osteosarcoma in the elderly can also be attributed to Paget's disease or previous radiotherapy.

The decreasing incidence of OS over the age of 40 years and the expectation that these elderly patients may not tolerate aggressive modern chemotherapy means that those patients who develop OS over the age of 40 years are excluded from current trials of treatment. As a result, remarkably little is known about the outcome for this age group [1–4].

Previous papers have predominantly concentrated on the clinico-pathological features of the disease although Bacci's paper commented that overall survival in their 29 patients did not seem to be much worse than for patients under the age of 40 years [1]. Naka reported a dismal 18% survival at 5 years for 12 patients with osteosarcoma in this age group and contrasted it with a

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survival of 67% in 7 patients with malignant fibrous histiocytoma (MFH) like osteosarcoma [4]. Recent publications on radiation-induced osteosarcoma [5] and Paget's osteosarcoma [6] have detailed outcomes for these two groups who are predominantly and exclusively over the age of 40 years, but no study has specifically looked at the management and prognosis for a heterogeneous group of patients with osteosarcoma over the age of 40 years.

Against this background, a retrospective analysis of patients taken from several centres was carried out by the European Musculo Skeletal Oncology Society (EMSOS).

## 2. Patients and methods

Invitations to contribute data were sent to members of EMSOS at all of the main musculo-skeletal tumour centres and multicentric groups in Europe. The entry criteria were: any patient with a newly diagnosed osteosarcoma of bone who was over the age of 40 years at the time of diagnosis and who had details on treatment and outcome. Patients treated after 1998 were excluded due to the short period of follow-up. Anonymised data regarding patient, tumour, treatment and outcome as regards local and systemic relapse was obtained. All duplicate entries were eliminated.

Information on diagnosis and age was available for all 481, sex in 478 and location of tumour in 477. The stage of tumour [7] at diagnosis was identified in 339 patients and details of treatment in 443. 452 patients had sufficient follow-up information to allow assessment of survival time. 357 patients underwent some sort of surgery for the primary tumour and details about surgical margins were available in 282.

The management of the patients varied greatly from centre to centre and by different age groups and for different diagnoses. As a result, the following categories were used for further analysis:

1. Paget's osteosarcoma
2. Radiation-induced osteosarcoma
3. Low-grade osteosarcoma
4. Axial and metastatic osteosarcoma
5. High-grade osteosarcoma not included in the above categories. This was split further into patients with and without metastases at diagnosis and by age groups above or below 60 years.

## 3. Statistical analysis

Demographic details including the distribution of age, site and type of osteosarcoma are described along with treatment variables. Differences between groups were assessed using the Chi-squared test. Overall survival was calculated using Kaplan–Meier survival curves and the impact of prognostic factors was assessed using the log-rank test [8,9]. Multivariate analysis was performed using Cox's proportional hazard method with variables being chosen using a forward conditional stepwise approach. Relative risks have been calculated using a proportional hazards model with only the noted covariate in the model. Significance was set at $P<0.05$ for two-sided tests. Survival time was calculated from the time of diagnosis when investigating the significance of tumour and patient characteristics. The end point was taken as the time of death or the last documented time the patient was known to be alive. Analyses were performed using Statview [10]. When factor analysis was undertaken the numbers involved have been highlighted.

## 4. Results

### 4.1. All patients

A total of 481 patients were included in the study. The mean age was 55 years (40–93 years) (Fig. 1). There were 272 males and 206 females (3 not classified). 26 patients had low grade osteosarcoma, 42 had osteosarcoma in association with Paget's disease and 41 after radiation. Of the remaining 372 patients, 270 were known to have high grade tumours, of whom 48 had metastases at diagnosis (i.e. Enneking, Stage III) [7].

The earliest patient to be registered was diagnosed in 1955 with increasing numbers ever since (Fig. 2). By the end of the study, an average of 40 patients a year were being registered at the 13 centres. The average size of the tumours was 11 cm (1–34 cm). The location of the tumours is shown in Table 1. Of the conventional high grade osteosarcomas, 29% involved the distal femur,

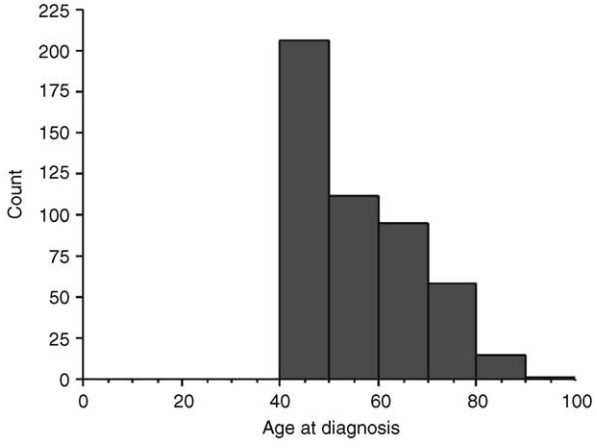


Fig. 1. The age distribution of the 481 patients.

14% the proximal tibia, 14% the pelvis, and 10% the humerus.

#### 4.1.1. Paget's osteosarcoma

There were 42 patients with Paget's osteosarcoma. Of those who had their stage documented, 7 already had metastases whilst 22 did not. The most commonly involved bones were the femur and the pelvis (12 each). Their mean age was 71 years (47–88 years). 28 were male and 14 female. Only 14 patients underwent surgical treatment in an attempt to surgically clear the disease and only 2 had chemotherapy. Of the 14 operations, five resulted in local recurrence (four of nine limb salvage procedures and one of five amputations). 22 patients had palliative radiotherapy. Median survival was 9 months although 1 patient survived 8 years following amputation for an osteosarcoma of the tibia (Fig. 3).

#### 4.1.2. Radiation induced osteosarcoma

There were 41 patients with radiation-induced osteosarcoma with a mean age of 58 years (40–82 years). There was a preponderance of females (29 females:12 males), probably reflecting the identified causes of the previous radiotherapy and the location of the tumours (pelvis ($n=12$) and scapula ($n=11$) being the most common sites following radiotherapy for ovarian/cervical cancer and breast cancer, respectively). Only 12 patients did not have axial tumours. There were 4 patients who had received previous radiotherapy for a lymphoma and 1 for a previous parosteal osteosarcoma. The time lag between radiotherapy and subsequent development of osteosarcoma ranged from 6 to 23 years in the patients with this information although further data about the dose of radiotherapy and time interval was not specifically requested for this study. Only 3 of the patients were known to have metastases at the time of diagnosis.

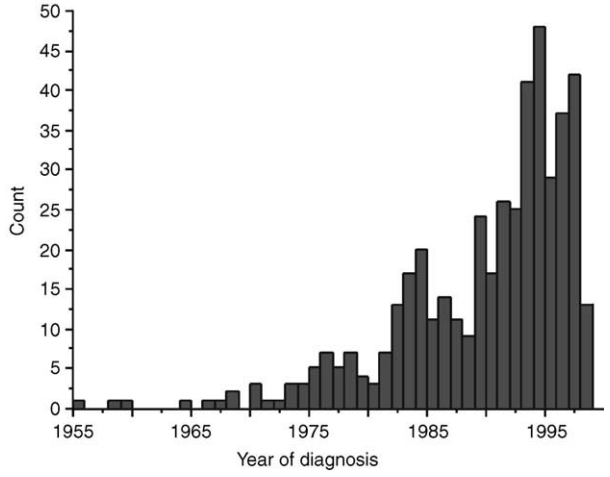


Fig. 2. Graph showing the number of patients registered per year in this study.

Table 1
Location of the tumours split by main sites/grades

| Site | Total | High grade | Paget's | Radiation-induced | Low grade |
|---|---|---|---|---|---|
| Femur | 189 | 159 | 12 | 4 | 14 |
| Pelvis | 72 | 45 | 12 | 12 | 3 |
| Tibia | 58 | 51 | 3 | 1 | 3 |
| Humerus | 50 | 33 | 9 | 6 | 2 |
| Scapula | 20 | 7 | 2 | 11 | 0 |
| Rib | 16 | 14 | 0 | 2 | 0 |
| Skull | 15 | 9 | 2 | 1 | 3 |
| Jaw | 11 | 10 | 0 | 0 | 1 |
| Others | 50 | 44 | 2 | 4 | 0 |
| Total | 481 | 372 | 42 | 41 | 26 |

22 patients received chemotherapy and 29 underwent surgery (15 having both chemotherapy and surgery). 8 patients had an amputation and 19 had limb salvage surgery. 11 patients developed local recurrence, two of the eight amputees (25%) and six of the 19 with limb salvage (32%). Only 3 patients received radiotherapy as part of their treatment.

All 3 patients with metastases at diagnosis died within 15 months of diagnosis, but in the remainder, the overall median survival was 33 months with a 35% overall survival rate at 5 years (Fig. 4). With the small numbers available for analysis, it was impossible to identify any good or bad prognostic groups, although patients treated with both chemotherapy and surgery did slightly better than those having chemotherapy alone, having a 40% survival at 5 years dropping to 27% at 10 years. Patients with axial tumours did worse than those with limb tumours (5-year survival 28% versus 55%, respectively). An age greater or less than 60 years did not appear to have an effect on survival. There were no survivors in patients not undergoing surgery.

#### 4.1.3. Low-grade osteosarcoma

There were 26 patients with low-grade osteosarcoma including parosteal and low-grade central osteosarcoma.

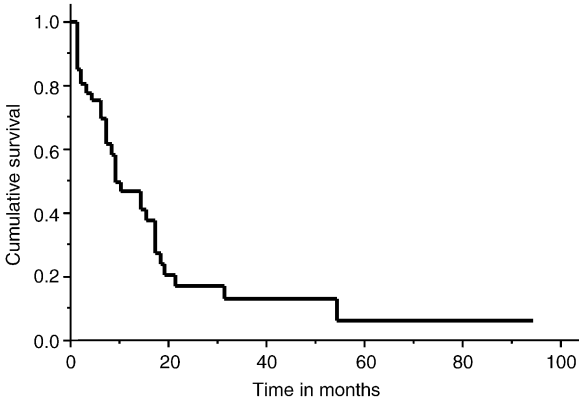


Fig. 3. Survivorship of patients with Paget's osteosarcoma.

A further 4 patients had low-grade tumours of the jaw or skull. The bone most commonly affected was the femur ($n=14$) followed by the tibia and pelvis. The mean age was 54 years and there were equal numbers of males and females. Only 2 patients had chemotherapy. 25 patients underwent surgical excision with only 1 requiring amputation. 4 patients developed local recurrence only 1 of whom subsequently died. 3 other patients developed metastatic disease and the 5-year survival was 88%.

#### 4.1.4. Axial and metastatic osteosarcoma

26 patients had osteosarcoma develop in the skull or jaw, with equal numbers of males and females affected and a mean age of 58 years. Of the 15 skull tumours, two arose in association with Paget's disease and one secondary to irradiation whilst three were low grade. Of the remaining 9 patients, 1 had metastases. One of the 11 jaw tumours was low grade whilst the rest were high grade and 1 patient presented with metastases. Treatment was surgical in 20 cases, but with a high local recurrence rate, six out of the 11 jaw excisions developed local recurrence whilst seven of the nine skull excisions developed local recurrence. Radiotherapy was used in 9 cases and 9 patients had chemotherapy. The skull tumours had a median survival of 15 months whilst the jaw tumours had a median survival of 57 months, but in both groups the long term survival was under 20% at 6 years (Fig. 5). Adequate surgery was essential for cure whilst grade had no significant impact on survival.

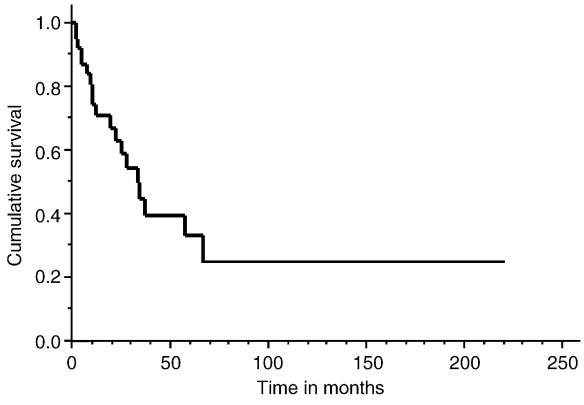


Fig. 4. Survivorship of patients with radiation-induced osteosarcoma.

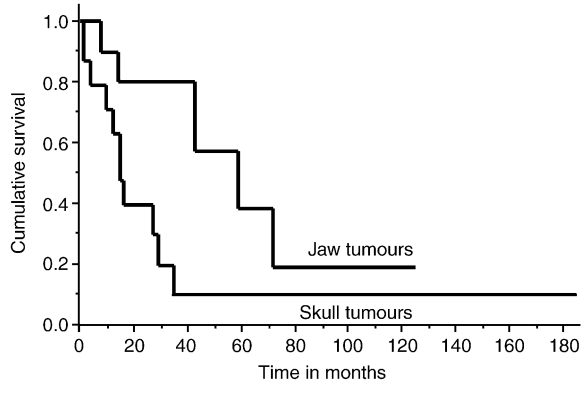


Fig. 5. Survival of patients with jaw and skull tumours.

3 patients had osteosarcoma of the spine and 5 osteosarcoma of the sacrum with an equal distribution of males and females and a mean age of 53 years. Two of the sacral tumours arose secondary to Paget's disease whilst one of the spinal tumours arose postirradiation. All three patients with spinal tumours survived without metastases following surgery and chemotherapy whilst all of the patients with sacral tumours died within 20 months of diagnosis.

72 patients had osteosarcoma of the pelvis (excluding the sacrum). Three had low-grade tumours and 11 had metastases at diagnosis. 12 tumours were associated with previous radiotherapy and 12 with Paget's disease, one arose in a patient with diaphyseal aclasia. 37 patients underwent surgery of whom 24 also had chemotherapy, whilst a further 17 had chemotherapy alone with or without radiotherapy. Median survival for the whole group was 14 months with only 14% long-term survivors. All the patients with low-grade tumours survived whilst all those with metastatic disease died. In the high-grade non-metastatic group, there was an improved survival (median 18 months) in patients who had surgical excision with or without chemotherapy. There were no survivors in patients over the age of 60 years nor in patients with Paget's disease (median survival 6 months). Patients with radiation-induced osteosarcoma had a median survival of 12 months whilst those with conventional osteosarcoma had a median survival of 15 months and a 23% survival rate at 5 years.

20 patients had high grade osteosarcoma of the axial skeleton not involving the spine or pelvis. 13 patients had osteosarcoma of the rib, 2 of the clavicle and 5 of the scapula. Despite surgery in 13 and chemotherapy in 8, the median survival was only 27 months and no patient survived 5 years.

41 patients with conventional osteosarcoma had metastases at the time of diagnosis. Although treated by a variety of methods median survival was 12 months. There was a 12% survival rate at 5 years in those who received chemotherapy and surgery.

#### 4.1.5. High-grade conventional osteosarcoma

There were 206 patients with definite non-metastatic high-grade osteosarcoma not secondary to Paget's or radiation and not involving the pelvis, skull or spine. There were a further 32 patients in whom the stage at diagnosis was not documented, but their results are virtually identical to the above 206 and hence they have been included in the final analysis which thus consists of 238 patients, although only 220 had follow-up data.

There were 91 women and 145 men (two not identified), with a mean age of 53 years (40–93 years). 168 were less than 60 years of age and 70 over the age of 60 years. 13 had intracompartmental tumours (Stage 2a) whilst 151 had documented stage 2b extracompartmental tumours. The most common site affected was the distal femur (104 cases) followed by the proximal tibia (48 cases), proximal femur (34 cases), proximal humerus (19 cases) and fibula (8 cases).

Surgical treatment was recorded as being by amputation in 86 cases and limb salvage surgery in 126 (of which 23 had excision alone, 7 had allografts and 78 had endoprostheses). 129 patients had adequate surgical margins (wide or radical) whilst 37 had marginal or intralesional surgery. Chemotherapy was used in 154 patients, only 29% of patients over the age of 60 years receiving chemotherapy whilst 80% under the age of 60 years received it. 63% had neoadjuvant chemotherapy and the rest had adjuvant treatment. The most common drugs used were doxorubicin, cisplatin, ifosfamide and methotrexate. Information on dosage and dose intensity was not collected, but in those given neoadjuvant treatment and who had the chemotherapy response assessed 19 out of 62 (31%) had greater than 90% necrosis. No patient over the age of 60 years was documented to have completed the full planned course of chemotherapy, but 73% of those under the age of 60 years did. There were four treatment-related deaths subsequent to the use of chemotherapy.

Radiotherapy was used in 22 patients, usually because of concerns about postoperative resection margins, but in some for palliative treatment.

Local recurrence arose in 25 patients, occurring in 5% of the amputees, 13% of those having limb salvage and 24% of those having simple surgical excision. Local recurrence was related to margins of excision with 6 out of 37 patients (16%) with marginal operations developing local recurrence compared with 11 of 129 (9%) with wide or radical operations.

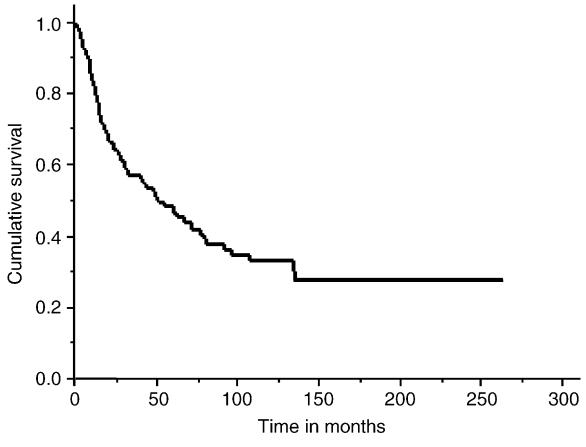


Fig. 6. Kaplan–Meier survivorship of patients with conventional, high grade non-metastatic osteosarcoma, excluding axial locations.

Overall survival was 46% at 5 years and 33% at 10 years. (Fig. 6). Factors found to be significant for overall survival at 5 years are shown in Table 2 and on multivariate testing in Table 3. This demonstrates that site (lower limb) and age (<60 years) (Fig. 7) are the two most important prognostic factors. Percentage necrosis was so rarely reported that it did not reach significance although interestingly those patients with documented percentage necrosis, be it good or bad, seemed to have a surprisingly good survival.

## 5. Discussion

This paper is by far the largest analysis of outcome in patients with osteosarcoma over the age of 40 years. The data has been supplied from 11 centres or multicentric groups and is by necessity retrospective. Not all the data is complete, but what is available appears reliable. No assumptions about survival beyond the last known date of follow-up have been made for any patient.

Osteosarcoma over the age of 40 years is not that uncommon—approximately 13% of patients with osteosarcoma will be over the age of 40 years. The data supplied has confirmed the wide variety of tumours in this population group and the large number of patients has allowed various subsets to be used to classify the results more meaningfully.

Only 8.7% of the total patients were recorded as having osteosarcoma in association with Paget's disease. The results of the analysis confirm other work on the same subject [6,11]. The prognosis for patients with Paget's osteosarcoma is dismal and obtaining local control with surgery is difficult, even following amputation. More effective treatment is clearly needed.

Radiation-induced osteosarcoma is, however, more amenable to treatment. The results of our 41 patients represent one of the largest cohort of patients with this type of osteosarcoma and confirm that cure can be achieved even in this older group of patients if treated aggressively with surgery and chemotherapy as has been shown in other recent publications [5,12].

Patients with low grade osteosarcomas do well and can usually be cured with adequate surgery. The role of chemotherapy remains unclear [13].

Osteosarcoma of the skull is very rare. Salvati reviewed 19 cases and reported that with chemotherapy there were 5 out of 9 patients surviving at 2 years [14], whilst Smeele and colleagues reviewed the cases of 201 patients with cranio-facial osteosarcoma from numerous centres and confirmed the value of chemotherapy [15]. Our results from an older age group are consistent with this.

Osteosarcoma of the pelvis has a bad reputation even in young patients and the results in this older age group

reflect this especially for those with Paget's or radiation-induced osteosarcoma [16–18]. The patients with low grade tumours do well, but the only long-term survivors in patients with high grade tumours were in those with effective chemotherapy and appropriate surgical excision. Patients with osteosarcoma of the pelvis over the age of 60 years had a poor outlook, but complete surgical excision may give these patients a possibility of cure.

Table 2
Overall survival at 5 years in the group of patients with primary, non-metastatic high-grade osteosarcoma of the extremities[a]

| Variable | Patients | Overall survival at 5 years (%) | *P* value (log rank) |
|---|---|---|---|
| All | 220 | 46 | |
| Age <60 years | 155 | 53 | <0.0001 |
| Age >60 years | 65 | 30 | |
| Age 40–49 years | 94 | 57 | 0.0004 |
| Age 50–59 years | 56 | 46 | 0.0151 |
| Age 60–69 years | 37 | 28 | 0.849 |
| Age 70+ years | 31 | 30 | |
| Upper limb | 23 | 23 | 0.0045 |
| Lower limb | 173 | 49 | |
| Chemotherapy | 142 | 50 | 0.020 |
| No chemotherapy | 69 | 42 | |
| Chemotherapy + surgery | 126 | 51 | 0.006 |
| Other treatment | 94 | 39 | |
| Limb salvage | 118 | 51 | 0.063 |
| Amputation | 77 | 43 | |
| Size <10 cm | 60 | 63 | 0.19 |
| Size >10 cm | 71 | 47 | |
| Necrosis ⩾90% | 15 | 69 | 0.48 |
| Necrosis <90% | 40 | 60 | |

[a] The numbers in the subgroups do not all add upto 220 due to missing data.

Table 3
Factors found to be significant on multivariate analysis for overall survival in the group of patients with primary, non-metastatic high grade osteosarcoma of the extremities

| Variable | RR | (95% CI) | *P* value |
|---|---|---|---|
| Age >60 years | 2.05 | (1.26–3.34) | 0.004 |
| Upper limb | 2.52 | (1.40–4.52) | 0.002 |
| Amputation | 1.42 | (0.92–2.19) | 0.112 |
| C/T + surgery | 0.74 | (0.46–1.19) | 0.208 |

(RR, relative risk; C/T, chemotherapy; 95% CI, 95% Confidence Interval. See Table 2 for contrasting factors.

Non-metastatic primary conventional osteosarcoma arising in the long bones affected almost half of the population group. Treatment was along similar lines to that for osteosarcoma in the younger age group but none of these patients was entered into published trials of treatment. The European Organization for Research and Treatment of Cancer (EORTC) and Cooperative Osteosarcoma Study Group (COSS) studies both excluded patients over the age of 40 years although patients were registered for the COSS study, but not randomised [19,20]. Thus, while patients may have had similar regimes of chemotherapy to younger patients, data about the toxicity and complications of this were not collected for this study. It is possible, however, to extrapolate the likely side-effects from papers detailing the use of similar chemotherapy regimes in patients up to the age of 60 years with MFH [5,21,22].

The surgical management of these patients has been similar to that used in the younger age group, with 60% of patients with documented surgical interventions having limb salvage surgery and 40% having amputation. The proportion having limb salvage was higher in the under 60 years age group (64%) compared with those over 60 years (49%). Interestingly, survival was found to be significantly better in patients having limb salvage surgery, an observation made in other studies and this is probably a reflection not only of the size and resectability of the tumour (prognostic factors notoriously difficult to quantify), but also of the response to neoadjuvant chemotherapy. As in most other studies of osteosarcoma, inadequate margins resulted in an increased risk of local recurrence although the prognostic significance of this in terms of survival remains unclear [23,24]. The high local recurrence rates following attempted surgery for Paget's and radiation-induced osteosarcoma as well as pelvic tumours all indicate the necessity for ultraspecialisation in the handling of these complex tumours to maximise surgical skills and the prospects of survival.

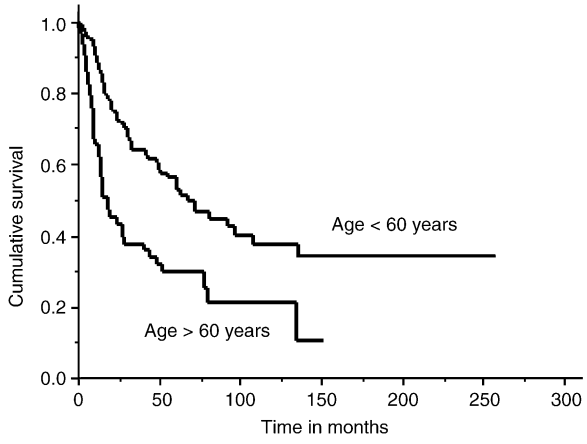


Fig. 7. Survivorship of conventional high grade osteosarcoma split by patients age above and below 60 years ($P < 0.0001$).

This paper represents the largest study ever carried out on patients with osteosarcoma over the age of 40 years. It has demonstrated that patients in this age group should be treated similarly to those in the younger age group with aggressive chemotherapy and complete surgical resection whenever possible. If this can be achieved then overall survival is little different to that for younger patients. Age as such is not a bad prognostic factor—it is more likely to be the difficulty in giving effective chemotherapy.

Osteosarcoma remains a challenging disease to treat. We would strongly urge clinicians to treat it aggressively and to use effective chemotherapy whenever possible. Surgical excision, if necessary by amputation, is essential for cure. Prospective studies of treatment for patients in this age group are required to identify the most effective, tolerable chemotherapy.

## Appendix

Data was obtained from the following organisations: Royal Orthopaedic Hospital, Birmingham, UK (R.J.G.); The Royal National Orthopaedic Hospital, Stanmore, UK (S.R.C.); Leiden University Medical Centre, Netherlands (A.M.T.); Cooperative Osteosarcoma Study Group (COSS) (S.B. and B.K-B.); Orthopaedic Krankenhaus Gersthof, Vienna, Austria (P.R.); University of Graz, Austria (R.W.); University of Vienna, Austria (M.D.); Norwegian Radium Hospital, Oslo (G.S.); Karolinska Hospital, Sweden (H.B.); Tel Aviv Sorasky Medical Centre, Israel (I.M.); Semmelweiss University, Budapest, Hungary (M.S.); University of Oslo, Norway (G.F.); University of Navarra, Pamplona, Spain (M.S-J.); Academisch Medisch Centrum, Amsterdam, Netherlands. (J.vdE.); Institut Gustav Ruissy, France.

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