Acta Orthopaedica et Traumatologica Turcica 51 (2017) 123–127

Contents lists available at ScienceDirect

Acta Orthopaedica et Traumatologica Turcica

journal homepage: https://www.elsevier.com/locate/aott

Chemotherapy in primary osteogenic sarcoma in patients over the age of forty

Bulent Ozkurt [a], Kerem Basarir [b], Bulent Yalcin [c], Abdullah Merter [d, *], Yusuf Yildiz [b], Yener Saglik [b]

[a] Ankara Numune Education and Research Hospital, Ankara, Turkey
[b] Ankara University, School of Medicine, Ibn-i Sina Hospital, Department of Orthopedics, Oncology Section, Ankara, Turkey
[c] Ankara University, School of Medicine, Ibn-i Sina Hospital, Department of Oncology, Ankara, Turkey
[d] Afsin State Hospital, Kahramanmaraş, Turkey

ARTICLE INFO

Article history:
Received 24 January 2016
Accepted 30 April 2016
Available online 16 February 2017

Keywords:
Chemotherapy
Elderly
Osteogenic sarcoma
Survival rate

ABSTRACT

Objective: In this study, we sought to review the clinical and histopathological features and the chemotherapy regimens in osteogenic sarcoma in patients over 40 years of age, and we aimed at identifying the possible prognostic factors in this particular group of patients.
Methods: We reviewed 287 patients with osteosarcoma treated between the year 1986 and 2010. Patients from this group who met the following criteria were considered eligible for our study; presence of primary OS, had typical histological and radiographic features of OS, no prior history of cancer or any treatment elsewhere and no prior history of preexisting bone abnormalities.
Results: The Kaplan–Meier survival curve for the entire group, with a 95% confidence interval, at two and five years showed the survival rates as 76.2% and 72.8% respectively. The surgical margin was a significant factor affecting the survival. Presence of a pathological fracture also had a significant effect on the survival rate.
Conclusion: Osteogenic sarcoma remains a challenging disease to treat. Despite the expectation that elderly patients may not tolerate aggressive modern chemotherapy as the younger patients, we believe that patients with primary OS over the age of 40 should be treated aggressively with effective chemotherapy and complete surgical excision whenever possible.
Level of evidence: Level IV, therapeutic study

Osteogenic sarcoma (OS) has a well-recognized double peak of incidence. Besides being the most common childhood malignancy of the bone, there is a significant second peak in the seventh and eighth decades of life.[1–4]

The treatment of primary OS is well established and documented among younger patients, and the benefit of multimodality therapy, including chemotherapy, has been shown.[5–9] However, the low incidence of OS in the elderly and the fear of chemotherapy complications in these patients delayed the treatment trials for this particular group, and therefore much less are known about the treatment and its outcomes in the elderly. Some authors have reported no difference between surgery alone and surgery combined with chemotherapy, whereas others suggested that chemotherapy combined with surgery is more beneficial in patients older than 40 years.[2,5,7,10–13] In addition, in the majority of the reports, primary and secondary OS in the elderly group were included together, which rendered the evaluation of the results even more dismal.

In this study, we sought to review the clinical and histopathological features and the chemotherapy regimens in osteogenic sarcoma in patients over the age of 40 years, and aimed at identifying the possible prognostic factors in this particular group of patients.

Patients and methods

We reviewed 287 patients with osteosarcoma treated between the year 1986 and 2010. Of these, 40 patients (13.9%) were over 40

* Corresponding author.
E-mail address: dr.merter@gmail.com (A. Merter).
Peer review under responsibility of Turkish Association of Orthopaedics and Traumatology.

http://dx.doi.org/10.1016/j.aott.2016.04.005

years of age. Patients from this group who met the following criteria were considered eligible for our study; presence of primary OS, had typical histological and radiographic features of OS, no prior history of cancer or any treatment elsewhere and no prior history of preexisting bone abnormalities, such as Paget's disease and irradiated bones. Consequently, our study population comprised 36 patients (24 males [66.7%], 12 females [33.3%], mean age: 53.1 [range: 40–72] years) with biopsy-proven primary OS.

Clinical details including patient demographics, complete medical history and treatment information were collected. In all cases, histological diagnoses were confirmed on histological slides of the tumor tissue obtained by needle, tru-cut or open biopsy. The type of surgery was classified as marginal, wide and radical with particular attention to amputation or limb salvage and the type of reconstruction. Necessity for radiotherapy was decided according to tumor location and extension, patient's age, lifestyle and preferences. Patients were classified according to the margins of the surgery performed. Surgeries were classified according to the surgical margins and surgical staging for musculoskeletal tumors defined by Heare et al.[14]

Preoperative chemotherapy included weekly administration of methotrexate (12 g/m^2) for two weeks, followed by definitive surgery performed three weeks after completion of the neoadjuvant chemotherapy. These patients were treated by both neoadjuvant and adjuvant chemotherapy regimens in our center. The combination of ifosfamide (1.8 g/m^2 on Days 1–5) and doxorubicin (25 mg/m^2 on Days 1–3) with high-dose methotrexate (ranging doses from 750 mg/m^2 to 12 g/m^2 on Day 21 and 28), consisting of 4–6 cycles, was administered as adjuvant chemotherapy every five weeks. The histological responses were classified as poor (<90% necrosis) and good (>90% necrosis).

Actuarial survival was calculated from the date of diagnosis until the date of the last follow-up using the Kaplan-Meier method.[15] Other clinicopathologic variables were analyzed for prognostic value by the Kaplan-Meier method, and the differences were compared by the log-rank test or Cox's regression analysis, including age, gender, tumor site and size, preoperative duration of the symptoms, histological subtype, pathological fracture, surgery, surgical margin, local recurrence, preoperative chemotherapy, preoperative and postoperative chemotherapy and distant metastasis at presentation.

Results

The femur was the most commonly involved bone (n = 17) followed by the humerus (n = 9), tibia (n = 4), tarsal bones (n = 2), spine (n = 1), and ischium (n = 1) (Fig. 1). The main complaints were pain and/or swelling, followed by joint stiffness, limb deformity and pathological fracture. The mean duration of the symptoms was four months (range: 1–11 months) (Table 1).

The rate of histological subtypes of OS were osteoblastic (25%), chondroblastic (19.5%), fibroblastic (19.5%), telengiectatic (16.7%), parosteal (8.3%), small cell (8.3%) and jaw bone (2.8%).

Adjuvant chemotherapy was given to 31 patients. Complete chemotherapy was given to 29 patients out of 31.

Thirty-three patients underwent surgery (wide excision was performed on 27 patients [81.8%] while marginal excision was performed on six [18.2%]) and three patients were only treated with adjuvant chemotherapy. The median age of the patients in the wide excision group was 50 years (min: 40 years–max: 70 years) and the median follow-up period was 58 months (min: 4 months–max: 208 months). The median age of the patients in the marginal excision group was 62 years (min: 42 years–max: 72 years) and the median follow-up period was 7 months (min: 4 months–max: 27 months).

Surgical margins in six patients were concluded to be adequate and tumor cell-negative. There was only one patient with local recurrence (ischial OS) who had preoperative radiotherapy with the concern of inadequate margins. She had marginal excision of the lesion performed on her (Case 19). All of the patients in the marginal group who had undergone surgery (two cases who

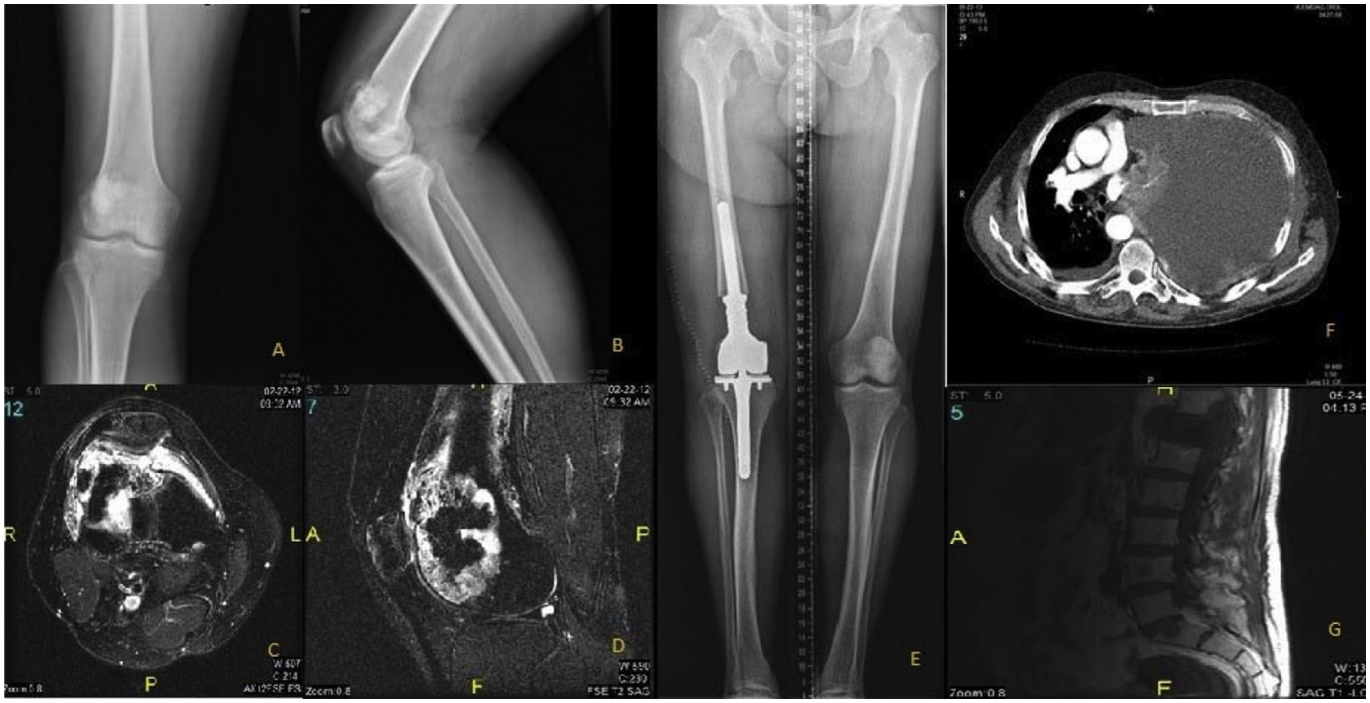

Fig. 1. Images of a 53-year-old male patient with osteosarcoma in the distal femur. **(A)** Coronal and **(B)** sagittal X-ray images. **(C)** Axial T2+C and **(D)** sagittal T2+C MRI views. **(E)** Postoperative X-ray image. **(F)** Metastasis in the left lung on the 18th month. **(G)** Metastasis in the T12 vertebra in the second year.

Table 1
Patient characteristics and treatment summary.

Case no.	Age	Sex	Pathology	Localization	Pathological fracture	Metastasis	Surgery	Surgical margin	Medical treatment	Follow-up (months)[a]	Notes
1	50	Male	Ob	Proximal tibia			Tumor resection prosthesis	Wide	Neo + Adj Chemo	46	
2	52	Male	Cb	Distal humerus			Amputation	Wide	Neo + Adj Chemo	32	Lost
3	54	Male	Cb	Distal femur		Lung	Tumor resection prosthesis	Marginal	Neo + Adj Chemo	8	DOD
4	55	Male	Ob	Distal femur	+		Amputation	Wide	Neo + Adj Chemo	58	
5	58	Male	Fb	Cuboid			Amputation	Wide	Neo + Adj Chemo	4	Lost
6	59	Male	TOS	Knee lateral soft tissue			Amputation	Wide	Neo + Adj Chemo	11	Lost
7	62	Male	Ob	Proximal humerus			Refused amputation		Adj Chemo	8	Lost
8	65	Female	TOS	Distal femur	+	Metastasis at diagnosis	No surgery		Adj Chemo	1	DOD
9	70	Male	Ob	L2 vertebra		Lung	Excision + Cement	Marginal	Neo + Adj Chemo	4	DOD
10	72	Male	Cb	Proximal femur		Metastasis at diagnosis	Amputation	Marginal	Ref Chemo	5	DOD
11	43	Male	Parosteal	Distal femur			Amputation	Wide		72	
12	48	Female	Fb	Distal femur			Amputation	Wide	Neo + Adj Chemo	66	
13	43	Male	Ob	Proximal femur			Amputation	Wide	Neo + Adj Chemo	73	
14	48	Female	Cb	Proximal femur			Amputation	Wide	Neo + Adj Chemo	65	
15	40	Male	TOS	Humerus		Lung	Plate + Cement	Wide	Neo + Adj Chemo	21	DOD
16	40	Female	Ob	Distal humerus			Amputation	Wide	Neo + Adj Chemo	105	
17	42	Male	TOS	Proximal humerus		Lung	Plate + Cement	Marginal	Adj Chemo	6	DOD
18	42	Male	Jawbone	Maxilla			Excision + Cement	Wide	Neo + Adj Chemo	60	Lost
19	42	Female	Ob	Ischium		Lung	Excision + Cement	Marginal	Neo+ Adj Chemo + Radiotherapy	21	DOD
20	42	Female	Fb	Distal femur			Tumor resection prosthesis	Wide	Neo + Adj Chemo	58	
21	43	Female	Parosteal	Distal femur			Tumor resection prosthesis	Wide		126	
22	45	Female	Fb	Proximal humerus			Tumor resection prosthesis	Wide	Neo + Adj Chemo	58	
23	46	Male	Ob	Proximal tibia		Lung	Refused amputation		Adj Chemo	5	DOD
24	47	Male	Cb	Proximal humerus			Amputation	Wide	Neo + Adj Chemo	208	
25	47	Male	TOS	Femur diaphysis	+		Diaphyseal prosthesis	Wide	Adj Chemo	5	Lost
26	49	Male	Parosteal	Proximal tibia			Plate + Cement	Wide		96	
27	51	Female	Small cell	Distal femur			Amputation	Wide	Neo + Adj Chemo	104	
28	53	Male	Ob	Distal humerus			Amputation	Wide	Neo + Adj Chemo	56	
29	56	Male	Fb	Distal femur			Amputation	Wide	Neo + Adj Chemo	62	
30	57	Male	Small cell	Proximal tibia		Lung	Amputation	Wide	Neo + Adj Chemo	50	
31	60	Female	Cb	Femur diaphysis			Autogenous bone grafting + Plate	Wide	Neo + Adj Chemo	18	Lost
32	61	Female	TOS	Cuneiform			Amputation	Wide	Ref Chemo	37	
33	61	Male	Fb	Distal humerus			Amputation	Wide	Neo + Adj Chemo	47	
34	71	Male	Small cell	Distal femur		Lung	Amputation	Marginal	Neo + Adj Chemo	27	DOD
35	70	Female	Fb	Femur diaphysis			Amputation	Wide	Neo + Adj Chemo	51	
36	69	Male	Cb	Distal femur			Amputation	Wide	Neo + Adj Chemo	49	

Adj Chemo: adjuvant chemotherapy, Cb: chondroblastic, DOD: died of disease, Fb: fibroblastic, Neo: neoadjuvant chemotherapy, Ob: osteoblastic, TOS: telengiectatic osteosarcoma.
[a] Time from the surgery or initial presentation to the latest follow-up.

underwent amputation and four cases who underwent limb salvage procedures) had metastases.

The follow-up period of the patients ranged from 1 to 208 (median: 48) months. Ten patients (27.8%) had metastases at the time of diagnosis or during the follow-up period. Nine patients died of disease (seven due to lung and the others due to multiple lung and liver metastases). Seven patients were lost to follow-up (four of them before completion of the minimum follow-up period of 12 months). The remaining 20 patients (55.6%) were alive at the final follow-up. The average follow-up period of the living patients was 74.4 (range: 37–208) months. Only one of the 20 living patients developed a known metastasis (lung) as of the latest follow-up.

The Kaplan–Meier survival curve for the entire group, with a 95% confidence interval, at two and five years showed the survival rates as 76.2% and 72.8%, respectively. The surgical margin was a significant factor affecting the survival. Patients with wide surgical margins had a two and five-year survival rate of 95.6% and 95.6% in comparison to the 16.7% and 0% rates for patients with marginal surgical margins. The difference was statistically significant ($p < 0.0001$). Presence of a pathological fracture was a significant factor affecting the survival. No patient with pathological fractures survived beyond five years. There was no significant difference in the survival rate between the patients who underwent surgery and adjuvant chemotherapy when compared to those who underwent neoadjuvant chemotherapy, surgery and adjuvant chemotherapy combined ($p > 0.05$).

Survival probability of the patients with no metastases was 100% at five years, whereas patients with metastases had one, two and five-year survival probabilities of 40%, 20% and 10% respectively. The relationship between the two groups was statistically significant ($p < 0.0001$). The overall survival probability of the patients who underwent limb salvage procedures was 56.6%, whereas overall survival probability of the patients who underwent amputation was 89.2% ($p < 0.03$).

Other potential prognostic factors, such as gender, age, histological subtype, histological findings and the preoperative duration of the symptoms were evaluated by Cox's regression analysis and were found to be insignificantly related to the disease-free survival rate ($p > 0.05$). The distribution of histopathological subtypes was not statistically different between the two genders ($p > 0.05$).

The surgical margin was a significant factor on metastases. All patients with surgical margins had metastases, whereas only two out of 25 patients with wide surgical margins had metastasis ($p < 0.001$) (Fig. 1). There was no statistically significant association between the histopathological subtypes and surgical margins due to inadequate number of patients in each subgroup. Wide surgical margins could be achieved in all patients with parosteal and fibroblastic osteosarcoma. In addition, there was no statistically significant association between the histopathological subtypes and metastases, once again due to inadequate number of patients in each subgroup. Metastases were more frequent in patients with telengiectatic osteosarcomas (three of six patients) and small cell osteosarcomas (two of three patients) when compared to the other subtypes.

Discussion

Osteogenic sarcoma is a rare, well-recognized, aggressive tumor and is predominantly a disease among children and adolescents.[2,5,11,16–19] The clinical and histopathological features and the treatment choices for OS in adolescents have been well described, with only a few reports available about OS in elderly patients.[1,2,5,11,16]

Reports about the elderly patients with OS indicated that most of the patients over the age of 40 present with secondary lesions and the condition has generally been attributed to sarcomatous transformation of Paget's disease and other benign bone lesions such as; preexisting bone infarction, giant cell tumor, myositis ossificans, previous trauma, total hip arthroplasty, fibrous dysplasia, preexisting solitary osteochondroma, dedifferentiated chondrosarcoma or previous radiotherapy.[1–5,11,12,16,20] OS has also been associated with myasthenia gravis and rickets.[21] In contrast to the literature, 36 of the 40 patients over the age of 40 years treated at our clinic had primary OS. Those 36 patients accounted for 6.6% of all primary malignant bone tumors at our clinic. Although there were 287 patients with OS, only 40 of them were older than 40 (13.9%). In four of them, OS was secondary to myositis ossificans, irradiation, giant cell tumor and Paget's disease.

In contrast to OS in adolescents, occurrence in the axial skeleton such as the pelvis and vertebrae is not uncommon.[2,3,5,12,16] Huvos found that only 15% of the OS in older patients occurred around the knee.[12] This site distribution indicates that the surgical treatment of OS in elderly patients is technically challenging. In many studies with large population, patients with axial lesions have had a poor prognosis when compared to the patients with lesions of the distal appendicular skeleton, presumably reflecting the higher likelihood of incomplete surgical resection.[19,22–24]

Although the treatment method of primary OS is well-established in younger patients, controversy still surrounds the treatment of this disease in the elderly. The efficacy of chemotherapy in patients older than 40 years and what role it should take in the treatment of this population is still a subject of discussion. The survival rates for OS in younger patients treated with chemotherapy have been reported several times, but there are only few reports on the survival rates in high-grade OS in elderly patients.[2,5,11,12,16,20] Moreover, in these few reports, there is no consensus on the effectiveness of chemotherapy in elderly patients. Different rates of survival and effectiveness of chemotherapy have been reported by several authors.[2,5,11,16]

Some investigations showed no difference in outcomes between surgery combined with systemic chemotherapy and surgery alone, whereas others have shown the evident benefits of systemic chemotherapy in OS patients older than 40 years.[2,5,7,10–12,16,19] In their study, Grimer et al[11] compared 481 elderly patients with OS to a younger age group treated similarly. The authors reported that patients with low-grade OS did well, and that the only long-term survivors in patients with high-grade tumors were those who received effective chemotherapy combined with surgery. In this study, patients treated by chemotherapy combined with surgery had a 5-year overall survival rate of 51% compared to the 39% of those treated with surgery alone. The report of Grimer et al demonstrated that elderly patients with OS should be treated similarly to younger patients with aggressive chemotherapy and complete surgical resection whenever possible, and with such treatment, the overall survival rate is a little bit different from the younger age group.[11] Bacci et al showed a considerable improvement in the rate of long-term survival among patients between 40 and 60 years, and reported a survival rate of 62% in their patients with OS older than forty and treated by chemotherapy combined with surgery.[10] Bielack et al reported overall and disease-free survival rates of 62% and 46% at 5-years among 340 patients in their 30s and above, and defended the similarity of prognosis and outcomes among adults when treated according to the same principles.[25] Okada et al[16] reported that systemic chemotherapy is not effective in the elderly patients with OS. The authors reported an overall survival rate of 55.5% in OS in patients over the age of fifty and found the effects of systemic chemotherapy poor in 82% of their 64 cases. However, in this study, the patients with secondary OS were not excluded, and this

should have been effective on the outcomes of the trial. As clearly known, most of the previous reports indicate that most of the OSs in elderly patients are secondary lesions. This considerable predominance of preexisting bone lesions is meaningful. The poor prognosis of OS associated with Paget's disease is well-known, the prognosis is dismal, and obtaining local control with surgery is difficult even following amputation.[3,4,11,16] As expected, the patients with secondary OS had worse prognosis and low rates of survival. Furthermore, administration of aggressive chemotherapy may not be always possible in these patients. We were not able to compare the survival rates of primary and secondary OSs in elderly patients due to the inadequate number of secondary OSs in our clinic. Studies state that prognosis worsens with age.[2,5,11,16] In our series, the 5-year overall survival probability for the patients over forty years of age was 72.8%, whereas it was 78% in our younger population. This relatively lower survival rate was probably related to the ages of our patients. In our series, the mean age was 53.1 years.

One of the major limitations of chemotherapy is the associated toxicities with the doses necessary to have an impact on disease-specific survival, especially in older patients and in patients with OS secondary to preexisting bone lesions.[2,5,11,16] The results of recent studies are not comparable to those of earlier reports, due to the addition of supportive agents such as hematopoietic growth factors that allow for higher doses, and hence, the trends in improved survival rates are being achieved. At our institution, the only two patients with high-grade OS who did not receive chemotherapy were those who refused the treatment. These patients did not survive as long as the patients who received chemotherapy. Adjuvant chemotherapy was used on 31 patients, while 26 patients were given both neoadjuvant and adjuvant chemotherapies with well chemotherapy tolerance. In our series, only the patients with primary lesions were included and this led to a higher chemotherapy tolerance for aggressive chemotherapy.

Osteogenic sarcoma remains a challenging disease to treat. The poor clinical outcome in elderly patients with primary OS previously reported is difficult to understand. High incidence of axial localization in elderly patients, inadequate surgical margins and high rates of metastatic diseases at presentation may cause lower survival rates. Under the light of the literature, we believe that patients with primary OS over the age of 40 should be treated aggressively with effective chemotherapy and complete surgical excision whenever possible just like the younger patients. Further studies are required to investigate the most beneficial chemotherapy regimen and other alternatives such as molecular-targeting chemotherapy to prevent metastatic diseases despite its life-threatening side effects in the elderly patients. However, radical surgical excision combined with systemic chemotherapy is still the mainstay of treatment in OS.

References

1. Stark A, Kreicbergs A, Nilsonne U, Silversward C. The age of osteosarcoma patients is increasing: an epidemiological study of osteosarcoma in Sweden. 1971 to 1984. *J Bone Jt Surg*. 1990;72-B:89–93.
2. Corsi B, Rock MG. Primary osteosarcoma in adults older than 40 years. *Clin Orthop Relat Res*. 2002;397:53–61.
3. Unni KK. General aspects and data on 11,087 cases. In: *Dahlin's Bone Tumors*. 5th ed. Philadelphia: Lippincott-Raven; 1996:143–196.
4. Campanacci M. In: Enneking FW, ed. *Bone and soft tissue tumors*. 2nd ed. Padova: Piccin Nuova Libraria; 1999:463–558.
5. Manos MW, Healey JH, Boland PJ, et al. De Novo osteogenic sarcoma in patients older than forty: benefits of multimodality therapy. *Clin Orthop Relat Res*. 2005;438:110–115.
6. Delephine N, Delephine G, Bacci G, Rosen G, Desbois J. Influence of Methotrexate dose intensity on outcome of patients with high grade osteogenic sarcoma: analysis of literature. *Cancer*. 1996;78:2127–2135.
7. Glasser D, Lane J, Huvos A, Marcove R, Rosen G. Survival, prognosis, and therapeutic response in osteogenic sarcoma. *Cancer*. 1992;69:698–708.
8. Kager L, Zoubek A, Pötschger U. Primary metastatic osteosarcoma: presentation and outcome of patients treated on neoadjuvant cooperative osteosarcoma study group protocols. *J Clin Oncol*. 2003;21:2011–2018.
9. Winkler K, Beron G, Delling G, et al. Neoadjuvant chemotherapy of osteosarcoma: results of a randomized cooperative trial (COSS-82) with salvage chemotherapy based on histological tumour response. *J Clin Oncol*. 1998;6:329–337.
10. Bacci G, Ferrari S, Donati D, et al. Neoadjuvant chemotherapy for osteosarcoma of the extremity in patients in the fourth and fifth decade of life. *Oncol Rep*. 1998;5:1259–1263.
11. Grimer RJ, Cannon SR, Taminiau AM, et al. Osteosarcoma over the age of forty. *Eur J Cancer*. 2003;39:157–163.
12. Huvos AG. Osteogenic sarcoma of bones and soft tissues in older persons: a clinicopathological analysis of 117 patients older than 60 years. *Cancer*. 1986;57:1442–1449.
13. Duffaud F, Digue L, Baciuchka-Palmaro M, et al. Osteosarcomas of flat bones in adolescents and adults. *Cancer*. 2000;88:324–332.
14. Heare TC, Enneking WF, Heare MM. Staging techniques and biopsy of bone tumours. *Orthop Clin North Am*. 1989;20:273–285.
15. Kaplan FL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;52:457–481.
16. Okada K, Hasegawa T, Nishida J, et al. Osteosarcomas after the age of 50: a clinicopathologic study of 64 cases- an experience in Northern Japan. *Ann Surg Oncol*. 2004;11:998–1004.
17. Mankin HJ, Hornicek FJ, Rosenberg AE, Harmon DC, Gebhardt MC. Survival data for 648 patients with osteosarcoma treated at one institution. *Clin Orthop Relat Res*. 2004;429:286–291.
18. Unni KK. Osteosarcoma of bone. *J Orthop Sci*. 1998;3:287–294.
19. Saeter G, Hoie J, Stenwig AE, Johansson AK, Hannisdal E, Solheim OP. Systemic relapse of the patients with osteogenic sarcoma. Prognostic factors for long term survival. *Cancer*. 1995;75:1084–1093.
20. Naka T, Fukada T, Shinohara N, Iwamoto Y, Sugioka Y, Tsuneyashi M. Osteosarcoma versus malignant fibrosus histiocytoma of bone in patients older than 40 years. *Cancer*. 1995;76:972–984.
21. Cheng CL, Ma J, Wu PC, Mason RS, Posen S. Osteomalacia secondary to osteosarcoma. A case report. *J Bone Jt Surg Am*. 1989;71:288–292.
22. Dorfman HD, Czerniak B. Bone cancers. *Cancer*. 1996;45:203–210.
23. Saeter G, Bruland OS, Folleras G, Boysen M, Hoie J. Extremity and non-extremity high-grade osteosarcoma: the Norwegian Radium Hospital experience during the modern chemotherapy era. *Acta Oncol*. 1996;35:129–134.
24. Saeter G, Wiebe T, Wiklund T, et al. Chemotherapy in osteosarcoma. The Scandanavian Sarcoma Group experience. *Acta Orthop Scand*. 1999;70:74–82.
25. Bielack SS, Flege S, Kempf-Bielack B, et al. Osteosarcoma in adults. An analysis of 340 patients presenting in the third decade of life or later. *Ann Oncol*. 2000;11:125–132.