# High-grade Surface Osteosarcoma

## *A Review of 25 Cases From the Rizzoli Institute*

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**BACKGROUND.** High-grade surface osteosarcoma is a rare variant of surface osteosarcoma and is associated with a poor prognosis.

**METHODS.** This retrospective study includes all cases of high-grade surface osteosarcoma filed at the Rizzoli Institute. A complete clinical, histologic, and radiologic review was performed of 25 cases.

**RESULTS.** There were 19 males and 6 females with an average age of 21 years. All tumors were localized at the lower limb and the most frequently involved segments were the femoral and the tibial diaphysis. All lesions demonstrated the histologic aspect of a high-grade osteosarcoma, 20 were osteoblastic, and 5 were chondroblastic. The circumferential involvement was on average 53% and in approximately half of the cases medullary canal involvement was detected. Nineteen patients underwent a combination of surgery and chemotherapy for treatment of their initial lesion, whereas 5 patients were managed with surgery alone. The average follow-up was 9 years and the overall 5-year survival rate was 82%.

**CONCLUSIONS.** High-grade surface osteosarcoma is an extremely rare subtype of osteosarcoma. The current series demonstrates good overall survival for patients with this tumor. Metastatic disease and limb-sacrificing surgery were associated with a worse prognosis. Wide surgical excision and chemotherapy might improve the outcome. ***Cancer* 2008;112:1592–9.** © *2008 American Cancer Society.*

**KEYWORDS: high-grade surface osteosarcoma, osteosarcoma, bone surface, treatment, outcome, survival.**

Osteosarcomas that arise from the surface of the bone are relatively rare tumors and account for approximately 12% of all osteosarcomas.[1,2] They can be divided into 4 main groups according to their histologic characteristics. Parosteal osteosarcoma, the most frequent type, is a low-grade tumor with a good prognosis after wide surgical resection. Periosteal osteosarcoma is an intermediate-grade tumor, more aggressive than parosteal osteosarcoma, but usually well controllable with wide surgical resection. Dedifferentiated parosteal osteosarcoma and high-grade surface osteosarcoma, the third and fourth types, are very rare and highly malignant tumors, associated with a poor prognosis.[3,4] These lesions frequently cause metastatic disease and death, and therefore these patients are usually managed with a combination of surgery and chemotherapy. High-grade surface osteosarcoma was first described by Francis et al. in 1964.[5] Since then, several case reports and a few series have described the clinicopathologic aspects of this lesion,[6–13] but many questions still remain regarding the treatment and outcome, especially in the modern era of musculoskeletal oncology with sophisticated radiologic imaging studies and new chemotherapeutic agents and protocols. The purpose of this retrospective study was to

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describe the clinical and pathologic aspects of this very rare tumor and to determine the outcome according to several treatment protocols.

## MATERIALS AND METHODS

We examined the records of all cases filed as high-grade surface osteosarcomas in the bone tumor archives of the Rizzoli Institute. A clinical, radiologic, and histologic review was performed of 28 cases, recorded between 1979 and 2006. We included all cases in which the lesion had arisen on the surface of the bone, in which the histologic aspects were identical to those of a conventional osteosarcoma, and in which there was no association with a low-grade osteosarcomatous component (as in dedifferentiated parosteal osteosarcoma). Although minimal medullary involvement was accepted, the majority of the lesion had to be located on the bone surface. Twenty-five cases fulfilled these criteria and were included in the study. Two of the 3 excluded cases were reclassified as central osteosarcomas. The other case was excluded because the histologic slides and radiologic studies were not available for review. Of the 25 cases, 21 were treated at the Rizzoli Institute, whereas 4 were consultation cases.

Clinical information was obtained from the medical charts. Radiologic studies and histologic slides were available for review in all 25 cases. Follow-up information was obtained for all patients.

## RESULTS

### Clinical Features

There were 19 males and 6 females. The age of the patients at diagnosis ranged from 10 years to 66 years (mean, 21 years) and 72% of the patients were in the second or third decade of life. All lesions originated at the lower limb. The femoral diaphysis was the most frequently involved bone segment (9 patients), followed by the tibial diaphysis (6 patients), distal femur (3 patients), proximal tibia (3 patients), proximal femur (2 patients), and fibular diaphysis (2 patients). The age and sex distribution and anatomic localizations are shown in Figure 1. Information regarding symptoms and signs was available for 24 patients. The most common symptoms were swelling and pain, present in, respectively, 92% and 67% of the cases. One patient was completely asymptomatic. The average duration of symptoms was 11 months (range, 0–120 months; median, 5 months).

### Radiologic Findings

Radiographic imaging studies were available for all 25 patients. Twenty-one patients had cross-sectional studies: 20 had computed tomography (CT) scans, 12 had magnetic resonance imaging (MRI) scans, and 11 had both. In all cases, the tumor arose from the surface of the bone. The average size was 11 cm × 5 cm × 5 cm (range, 4.5 cm × 2.5 cm × 1.5 cm to 22 cm × 14 cm × 13 cm). In 17 cases, the lesion involved the diaphysis, whereas in 8 cases it was localized at the metaphysis. The majority of the tumors demonstrated dense to moderate mineralization with a fluffy immature appearance (Fig. 2). The circumferential involvement was on average 53% (range, 20–100%). Of the 21 patients who had cross-sectional studies, medullary canal involvement was detected on evaluation of the radiologic imaging in 10 patients (48%). In all cases, the radiologic imaging studies demonstrated signs of a malignant lesion. In 6 cases the radiologic appearance was similar to that of a parosteal osteosarcoma, demonstrating a metaphyseal lesion that was relatively well-defined with intensely radiopaque bone production. In 3 cases the lesion radiographically simulated a periosteal osteosarcoma, demonstrating a diaphyseal, mainly radiolucent with thin and faded ossification within the tumor mass.

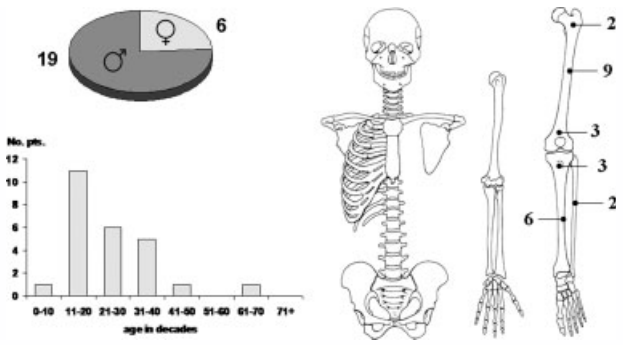


**FIGURE 1.** Distribution by sex, age, and anatomic localizations of the 25 cases of high-grade surface osteosarcoma in the current study.

### Pathologic Aspects

All tumors were classified as grade 4 osteosarcomas according to Broders' grading system. Twenty lesions were considered osteoblastic and 5 as chondroblastic osteosarcoma. Grade 4 osteoblastic surface osteosarcomas were characterized by highly malignant hyperchromatic, occasionally pleomorphic, large nuclei surrounded by a small amount of cytoplasm. The cells had a spindle cell or oval-spindle shape and were packed together or arranged in ribbons, nests, or filigree embedded in pink osteoid with a prominent lace-like architecture (Fig. 3). Grade 4 chondroblastic surface osteosarcoma were highly malignant lesions in which, along with bone production, there

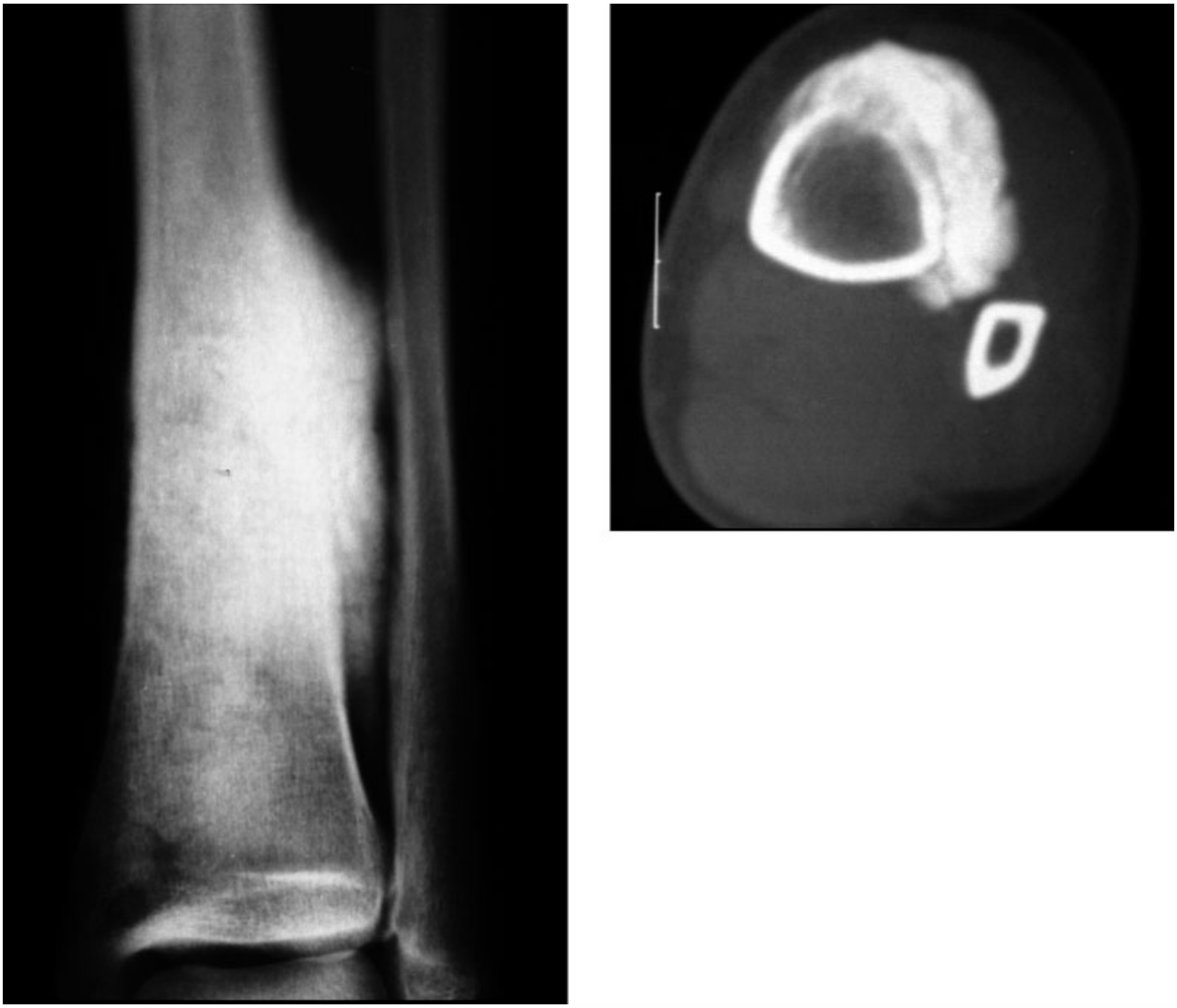

**FIGURE 2.** (Left) Anteroposterior radiograph showing a densely mineralized tumor at the distal metadiaphysis of the tibia. (Right) A computed tomography scan showing the lesion on the bone surface with minimal breakthrough of the anterolateral cortex and >50% of circumferential involvement.

were extensive areas (>50%) of cartilage production by the malignant cells (Fig. 4). No chondroid lobules with peripheral hypercellularity and a feather-like osteoid in the center of the lobuli (reminiscent of periosteal osteosarcoma) were present. Furthermore, no areas with streaming of low-grade spindle cells embedded between 'normalized trabeculae' (reminiscent of parosteal osteosarcoma) were appreciated. The morphology of our 25 cases was indistinguishable from classic high-grade central osteosarcoma. The radiographic features and the macroscopic appearance were indicative of lesions located on the bone surface. With regard to the histologic aspect, there was a complete overlapping between central and surface osteosarcoma.

On both macroscopic and microscopic examination, medullary involvement was present in 14 of 25 cases (56%) (Fig. 5).

The response to neoadjuvant chemotherapy was evaluated by 2 pathologists experienced in musculoskeletal oncology who estimated the percentage of tumor necrosis in the surgical specimen. The average percentage of tumor necrosis for the 15 patients who underwent neoadjuvant chemotherapy was 74% (range, 20–100%).

### Treatment and Outcome

Follow-up information regarding treatment and outcome was obtained for all cases (Table 1). The average duration of follow-up was 9 years (range, 6 months to

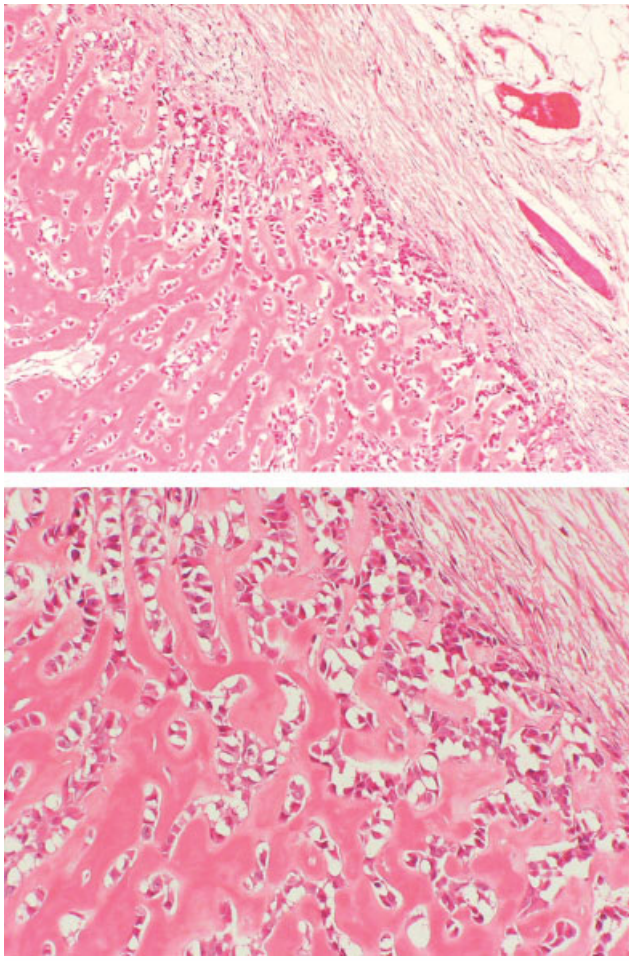

**FIGURE 3.** (Top) Low-power and (bottom) high-power histologic view of a osteoblastic high-grade surface osteosarcoma showing the highly malignant cells in ribbons, producing a lace-like osteoid.

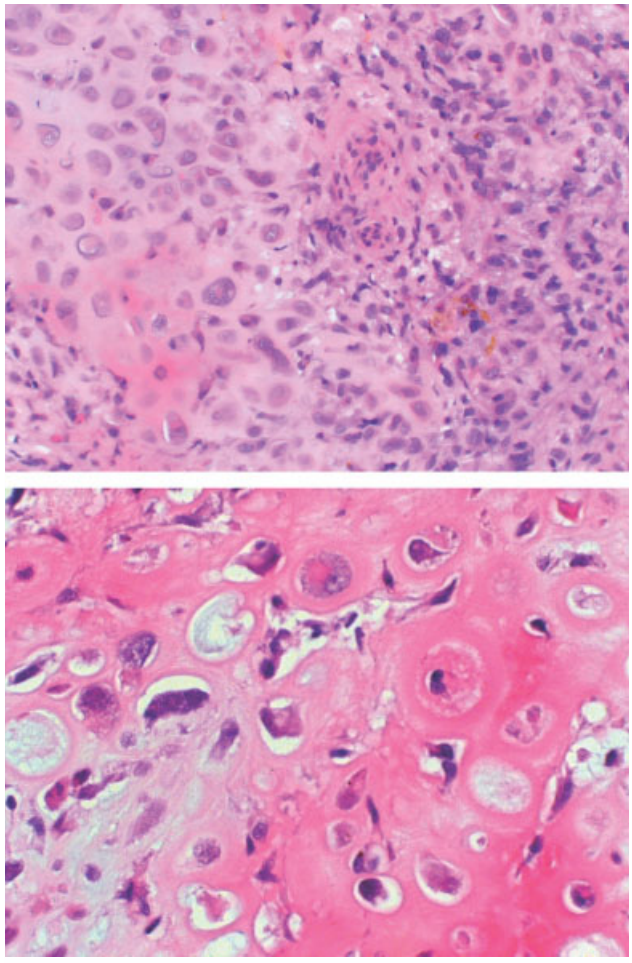

**FIGURE 4.** (Top) Low-power and (bottom) high-power histologic view of a chondroblastic high-grade osteosarcoma showing the hyperchromatic, pleomorphic, and large nuclei. In addition to areas of osteoid formation, there are areas with a cartilaginous aura.

26 years). Of the 25 patients, 4 died of disease, 1 died of unrelated causes after nearly 14 years, and 20 patients were alive at the time of last follow-up.

In 24 patients, surgery was a component of the initial treatment. Three patients underwent amputation, whereas in the remaining 21 patients (88%) a limb-sparing surgery was performed. One patient (Patient 15), with lung metastasis at the time of presentation, refused surgical treatment of the primary lesion and was managed with chemotherapy only.

Surgical margins were inadequate in 3 patients (intralesional in 2 patients and marginal in 1 patient). All 3 patients developed a local recurrence after 5 months, 7 months, and 22 months, respectively. One of these patients (Patient 22) developed lung metastasis after wide surgical excision and chemotherapy and died of disease after 60 months. The other 2 patients were long-term survivors after wide surgical excision and chemotherapy for their local recurrences. One died of unrelated causes after 165 months (Patient 3); the other had no evidence of disease at 156 months (Patient 2).

Five patients were treated with surgery alone for their primary lesion, whereas 19 patients were managed with a combination of surgery and systemic chemotherapy. Of these, 5 patients underwent postoperative chemotherapy only, whereas 14 patients received both preoperative and postoperative chemotherapy. The specifics of the chemotherapy regimen were determined by the medical oncologist consultant in each case. The choice of drugs and doses was based on the general health status of the patients and their tolerance to side effects. Chemotherapy regimens consisted of a combination of doxorubicin, cisplatin, methotrexate, and ifosfamide. Of the patients who were treated with surgery alone, 1 died of disease at 36 months after wide resection (Patient 11) and 1

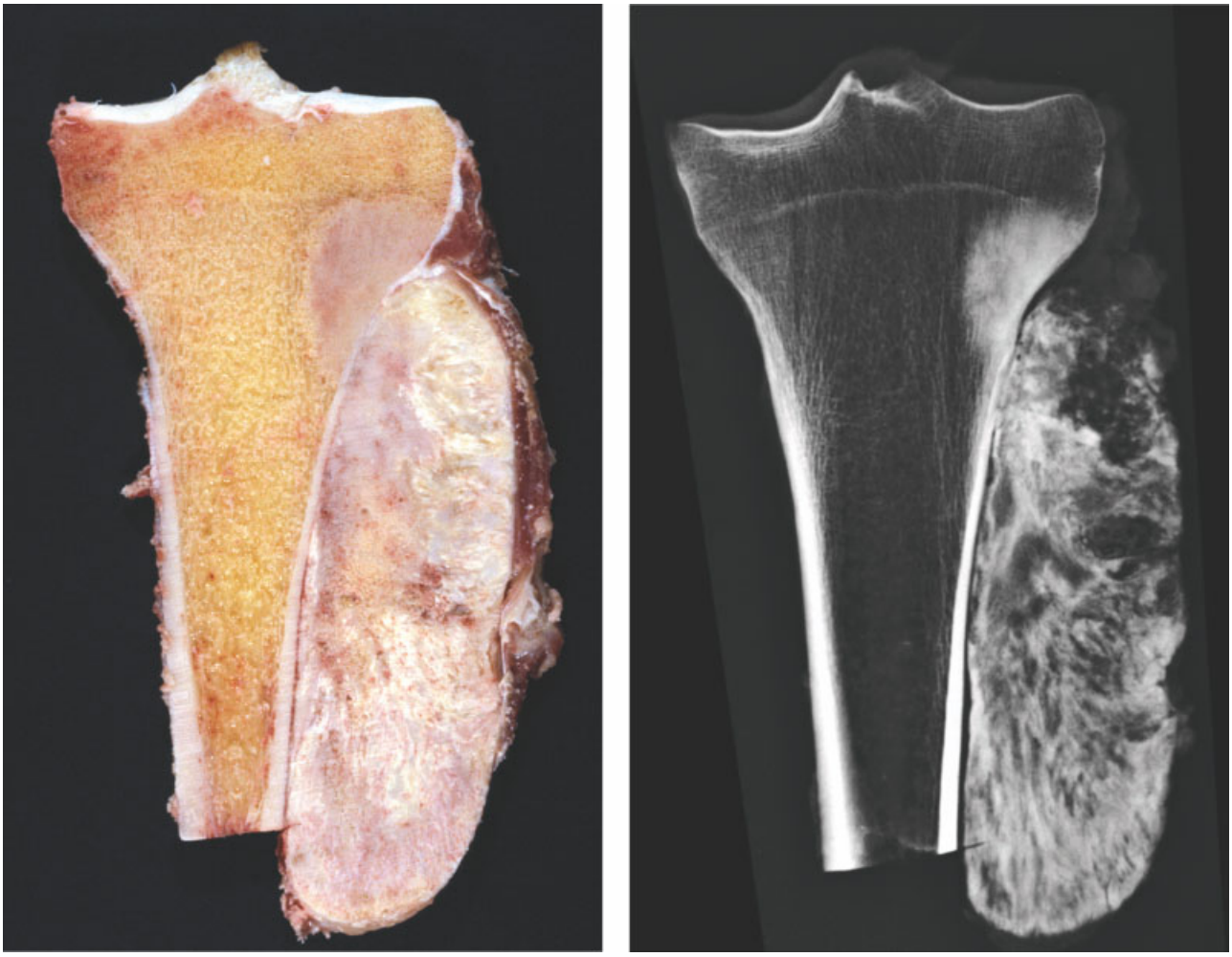

**FIGURE 5.** (Left) Macroscopic pathology photo and (right) radiograph of a frontal-cut surgical specimen after a proximal tibia resection. The lesion was located mainly on the bone surface, but there was medullary involvement within the proximal part of the heterogeneous tumor.

patient died after intralesional resection at 60 months of follow-up (Patient 22). Of the patients treated with a combination of surgery and chemotherapy, 1 died at 26 months of follow-up after wide amputation and neoadjuvant chemotherapy (Patient 19).

Two patients had lung metastasis at the time of presentation. One underwent wide resection of the primary lesion combined with surgical excision of the lung metastases and neoadjuvant chemotherapy. After 54 months of follow-up, new lung metastases were detected and the patient underwent surgical excision of these lesions. At the time of last follow-up, the patient was free of disease at 118 months (Patient 14). The other patient with lung metastasis at the time of presentation refused surgery and underwent only chemotherapy. He died of disease at 44 months of follow-up (Patient 15). Four other patients developed metastasis during follow-up. One patient (Patient 4) had a bone metastasis after 67 months and was free of disease at 5 months after surgical resection of the metastasis and chemotherapy. Three patients developed lung metastases, on average 12 months (range, 10–14 months) after diagnosis. Two patients (Patients 14 and 25) were free of disease after surgery and chemotherapy at 5 years and 7 years, respectively, from the surgical excision of the metastases. Two patients (Patients 11 and 19) died of disease at 16 months and 22 months, respectively, from the diagnosis of the metastases (1 after chemotherapy only, and 1 after surgery and chemotherapy).

### Survival Analysis

The 5-year overall survival rate was 82% (Fig. 6), with a mean survival time of 240 months (95% confidence interval [95% CI], 182–297 months). The 5-year dis-

**TABLE 1**
**Twenty-Five Cases of High-Grade Surface Osteosarcoma**

| No. | Date of patient accrual | Age, years/gender | Localization | Surgery | Surgical margins | Chemotherapy | Outcome | Follow-up, months | Recurrence, months |
|---|---|---|---|---|---|---|---|---|---|
| 1 | March 1999 | 33/F | Femur diaphysis | Resection | Wide | Neoadjuvant | NED | 85 | |
| 2 | May 1987 | 18/M | Tibia diaphysis | Resection | Marginal | — | NED2 | 156 | LR, 7 |
| 3 | October 1990 | 66/F | Tibia proximal | Resection | Intralesional | — | DOUC | 165 | LR, 22 |
| 4 | May 2000 | 12/M | Tibia diaphysis | Resection | Wide | Adjuvant | NED2 | 72 | Bone, 67 |
| 5 | February 1988 | 10/F | Tibia diaphysis | Resection | Wide | Neoadjuvant | NED | 128 | |
| 6 | March 2002 | 27/M | Tibia proximal | Resection | Wide | Neoadjuvant | NED | 30 | |
| 7 | October 1998 | 17/M | Tibia proximal | Resection | Wide | Neoadjuvant | NED | 95 | |
| 8 | May 1990 | 22/F | Femur diaphysis | Resection | Wide | Adjuvant | NED | 200 | |
| 9 | July 2006 | 47/M | Tibia diaphysis | Amputation | Wide | Neoadjuvant | NED | 6 | |
| 10 | October 1979 | 23/M | Femur distal | Resection | Wide | — | NED | 313 | |
| 11 | July 1991 | 17/M | Femur diaphysis | Resection | Wide | — | DOD | 36 | Lung, 14 |
| 12 | September 1998 | 18/M | Femur diaphysis | Resection | Wide | Neoadjuvant | NED | 90 | |
| 13 | October 2003 | 17/M | Femur diaphysis | Resection | Wide | Neoadjuvant | NED | 37 | |
| 14 | January 1997 | 17/M | Femur diaphysis | Resection | Wide | Neoadjuvant | NED2 | 118 | Lung, 54 |
| 15 | July 2003 | 21/M | Femur proximal | No* | — | Neoadjuvant | DOD | 44 | Progressive disease, 31 |
| 16 | June 1992 | 24/M | Fibula diaphysis | Resection | Wide | Adjuvant | NED | 171 | |
| 17 | August 1994 | 25/M | Femur diaphysis | Resection | Wide | Neoadjuvant | NED | 140 | |
| 18 | October 2000 | 13/M | Tibia diaphysis | Resection | Wide | Neoadjuvant | NED | 74 | |
| 19 | April 1995 | 34/M | Femur distal | Amputation | Wide | Neoadjuvant | DOD | 26 | Lung, 10 |
| 20 | March 1999 | 34/F | Fibula diaphysis | Resection | Wide | Neoadjuvant | NED | 92 | |
| 21 | December 2002 | 16/F | Femur proximal | Resection | Wide | Neoadjuvant | NED | 43 | |
| 22 | January 1979 | 33/M | Tibia diaphysis | Resection | Intralesional | — | DOD | 60 | LR, 5 |
| 23 | September 1982 | 15/M | Femur diaphysis | Amputation | Wide | Adjuvant | NED | 292 | |
| 24 | April 1993 | 35/M | Femur distal | Resection | Wide | Adjuvant | NED | 161 | |
| 25 | September 1997 | 18/M | Femur diaphysis | Resection | Wide | Neoadjuvant | NED2 | 100 | Lung, 12 |

F indicates female; NED, no evidence of disease; M, male; NED2, no evidence of disease after treatment for recurrence; LR, local recurrence; DOUC, dead of unrelated cause; Bone, bone metastasis; DOD, dead of disease; Lung, lung metastasis.

* This patient underwent only chemotherapy but no surgery for the femoral lesion.

ease-free survival rate was 70% (Fig. 7), with a mean survival time of 212 months (95% CI, 155–269 months). With the numbers available, no significant difference in overall and disease-free survival was found when sex, age of the patient, duration of symptoms, size of the lesion, anatomic location (proximal or distal to the knee), circumferential involvement of the lesion, and response to preoperative chemotherapy were evaluated as independent variables. Inadequate surgical margins always led to local recurrence, but local recurrence was not found to be significantly associated with a worse overall survival ($P > .32$). Metastatic disease and limb-sacrificing surgery were associated with a worse overall survival ($P = .04$ and $P = .05$, respectively) if confronted with localized disease and limb-sparing surgery. Both overall and disease-free survival tended to be better in those patients treated with chemotherapy compared with those managed with only surgery, although this difference was not found to be statistically significant ($P = .06$ and $P = .08$, respectively).

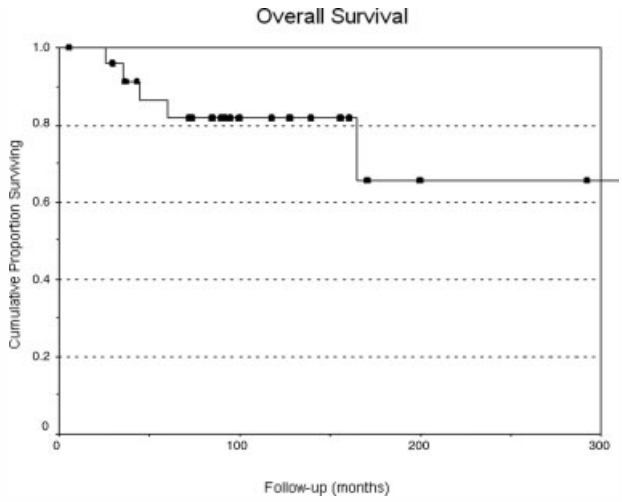


**FIGURE 6.** Kaplan-Meier overall survival curve of the group of 25 patients with high-grade osteosarcoma. The 5-year overall survival rate was 82%. All patients died of disease within the first 5 years of follow-up. One patient died of unrelated causes after 165 months.

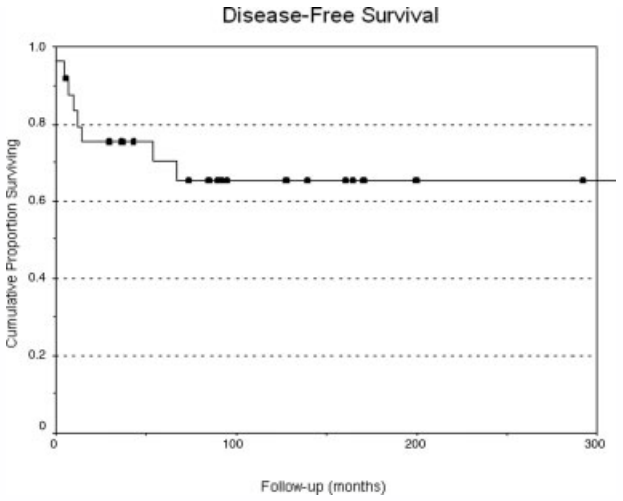


**FIGURE 7.** Kaplan-Meier disease-free survival curve. The 5-year disease-free survival rate was 70%.

## DISCUSSION

The majority of osteosarcomas that arise on the surface of the bone are either low-grade or intermediate grade tumors and have a relatively good prognosis after wide surgical resection.[1] High-grade surface osteosarcomas, conversely, demonstrate histologic characteristics identical to those of a conventional high-grade central osteosarcoma and have been associated with a poor prognosis.[1–3] This lesion was first described by Francis et al.[5] in 1964 but it was not until 1984 that Wold et al.[6] report what to our knowledge was the first series of this extremely rare tumor. Over the years, other authors, in several case reports and a few series, have described the clinicopathologic aspects of this lesion,[2,7–13] but many questions still remain regarding the treatment and outcome, especially in the modern era of musculoskeletal oncology with sophisticated radiologic imaging studies and new chemotherapeutic agents and protocols. To our knowledge, the largest series to date on high-grade surface osteosarcomas was reported in 1999 by Okada et al.[2] It included 46 cases from the files of the Mayo Clinic and approximately half of the patients were managed with a combination of surgery and systemic chemotherapy. Follow-up information was available for 35 patients and the 5-year overall survival rate was 46%. According to the authors, wide surgical margins were essential for local control and chemotherapy improved the outcome of patients with high-grade surface osteosarcoma.

The results of the current series confirm the clinicopathologic aspects of high-grade surface osteosarcomas as reported by others. There were more male than female patients and the vast majority of patients were in the second or third decade of their lives. The femoral and tibial diaphysis were the most frequent localizations. In this series, all lesions arose in the lower limb. Radiographically, the majority of lesions demonstrated specific characteristics of high-grade surface osteosarcomas, although more than a third of the lesions mimicked a lower-grade osteosarcoma. The histologic findings were identical to those of conventional central osteosarcomas.

The overall 5-year survival rate in the current series was 82%, which is significantly higher than in previous series of high-grade osteosarcoma.[2,6] It is also higher than the overall survival reported for both conventional central osteosarcoma (67.5%)[14] and dedifferentiated parosteal osteosarcoma (72%)[4] in our institution. We have no explanation for this surprisingly high survival rate, but we believe it is more likely because of the small group number, rather than a different behavior of surface tumors compared with central lesions.

The current series demonstrated excellent outcomes for patients after treatment with (neo-)adjuvant chemotherapy. Of the 19 patients who were managed with surgery and chemotherapy, only 1 died. Of the 5 patients treated with surgery only, 2 died of disease. However, with the numbers available, no statistically significant difference in overall survival was found between these 2 groups.

Surgical excision with wide margins is essential for local control. All 3 cases in which the margins were initially inadequate developed a local recurrence. After wide surgery and chemotherapy for their local recurrences, 1 patient died of lung metastasis, whereas the other 2 patients were free of disease after 13 years and 14 years, respectively. Thus, there is a strong correlation between inadequate surgical margins and local recurrence, but local recurrence is not necessarily associated with a bad outcome.

Metastatic disease was relatively frequent in this series but did not always lead to death. Of 6 patients who developed metastatic disease at some stage, 2 were free of disease at more than 5 years of follow-up after treatment for their metastases. Both patients were treated with a combination of surgery and chemotherapy. Of the other 4 patients with metastasis, 1 was free of disease at 5 months and 3 died of disease within 2 years after their recurrence.

It is difficult to draw conclusions from this series with relatively small group numbers, but it appears that early treatment with adequate surgery and chemotherapy can improve outcome for patients with high-grade surface osteosarcomas. The combination of aggressive surgical excision and systemic

chemotherapy also appears to be beneficial in cases of local recurrences or metastatic disease.

## REFERENCES


1. Unni KK. Dahlin's Bone Tumors: General Aspects and Data on 11,087 Cases. 5th ed. Philadelphia: Lippincott-Raven; 1996:143–183.
2. Okada K, Unni KK, Swee RG, Sim FH. High grade surface osteosarcoma. A clinicopathologic study of 46 cases. *Cancer*. 1999;85:1044–1054.
3. Raymond AK. Surface osteosarcoma. *Clin Orthop*. 1991; 270:140–148.
4. Bertoni F, Bacchini P, Staals EL, Davidovitz P. Dedifferentiated parosteal osteosarcoma: the experience of the Rizzoli Institute. *Cancer*. 2005;103:2373–2382.
5. Francis KC, Hutter RVP, Coley BL. Treatment of osteogenic sarcoma. In: Pack GT, Ariel IM, editors.Treatment of Cancer and Allied Diseases. Vol. 8, 2nd ed. New York: Harper & Row; 1964:374–399.
6. Wold LE, Unni KK, Beabout JW, Pritchard DJ. High-grade surface osteosarcomas. *Am J Surg Pathol*. 1984;8:181–186.
7. Sonneland PR, Unni KK. Case report 258. High-grade "surface" osteosarcoma arising from the femoral shaft. *Skeletal Radiol*. 1984;11:77–80.
8. Levine E, De Smet AA, Huntrakoon M. Juxtacortical osteosarcoma: a radiologic and histologic spectrum. *Skeletal Radiol*. 1985;14:38–46.
9. Schajowicz F, McGuire MH, Santini Araujo E, Muscolo DL, Gitelis S. Osteosarcomas arising on the surface of long bones. *J Bone Joint Surg Am*. 1988;70:555–564.
10. Yamaguchi H, Nojima T, Yagi T, Masuda T, Sasaki T. High-grade surface osteosarcoma of the left ileum. A case report and review of the litereature. *Acta Pathol Jpn*. 1988;38:235–240.
11. Hermann G, Abdelwahad IF, Kenan S, Lewis MM, Klein MJ. Case report 795. High-grade surface osteosarcoma of the radius. *Skeletal Radiol*. 1993;22:383–385.
12. Okada K, Kubota H, Ebina T, Kobayashi T, Abe E, Sato K. High-grade surface osteosarcoma of the humerus. *Skeletal Radiol*. 1995;24:531–534.
13. Hoshi M, Matsumoto S, Manabe J, et al. Report of 4 cases with high-grade surface osteosarcoma. *Jpn J Clin Oncol*. 2006;36:180–184.
14. Bacci G, Longhi A, Versari M, Mercuri M, Briccoli A, Picci P. Prognostic factors for osteosarcoma of the extremity treated with neoadjuvant chemotherapy: 15-year experience in 789 patients treated at a single institution. *Cancer*. 2006;106:1154–1161.