High Grade Surface Osteosarcoma

A Clinicopathologic Study of 46 Cases

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BACKGROUND. High grade surface osteosarcoma is a rare subtype of osteosarcoma arising on the surface of bone, accounting for only 8.9% of surface osteosarcomas at the study institution.

METHODS. This study reviews 46 cases of high grade surface osteosarcoma, comprised of 13 cases from the Mayo Clinic files and 33 from the authors' files. Histologic features were reviewed in all cases, and radiographs were reviewed in 29 cases.

RESULTS. There was a definite male predominance, and 70% of the patients were in the second and third decades of life. Forty-four of the 46 patients had lesions involving the long bones, the most common site being the midportion of the femur. Radiographically, the majority of lesions showed dense to moderate mineralization with a fluffy, immature appearance. Radiating spicules of bone perpendicular to the long axis of the bone, characteristic of periosteal osteosarcoma, were sparse. Histologic findings were identical to those of conventional osteosarcoma. Overall, survival at 5 years was 46.1%. Statistical analysis revealed that marginal excision was associated with an increased risk of local recurrence and that the patients with Broders Grade 3 tumors had a better prognosis than those with Grade 4 tumors. A good response to chemotherapy was associated with better clinical outcome.

CONCLUSIONS. High grade surface osteosarcoma is a rare subtype of surface osteoscarcoma that has a prognosis similar to that of conventional osteosarcoma, in contrast to the more common type of osteosarcoma arising on the surface of bone. Wide excision and effective systemic chemotherapy are associated with better clinical results. ***Cancer* 1999;85:1044–54.** *© 1999 American Cancer Society.*

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Osteosarcomas arising on the surface of bone have distinct radiographic and histologic features. Three subtypes of this disease are known. Parosteal osteosarcoma, which has a good prognosis after adequate surgical treatment,[1] is the most common subtype. Periosteal osteosarcoma is the second most common subtype and is associated with a good prognosis, but not as good as that of parosteal osteosarcoma.[2] The third subtype, high grade surface osteosarcoma, is the most rare. It was described initially in 1964 by Francis et al.[3] They reported two cases that had essentially the same prognosis as any fully malignant osteosarcoma, regardless of location. Since the original report, several case reports and a few series have brought the total number of published cases to only 27,[4–13] and the clinicopathologic behavior of the disease is still obscure. This retrospective review of Mayo Clinic files was undertaken to describe the clinical and pathologic details of patients with high grade surface osteosarcoma

FIGURE 1. Age distribution and tumor location in high grade surface osteosarcomas.

and to determine the prognosis of these patients as a function of their primary therapy.

MATERIALS AND METHODS

We examined the records of 46 patients (13 were treated at the Mayo Clinic, and 33 were identified from our consultation files). Originally, we reviewed the records of 50 patients who had been diagnosed as having high grade surface osteosarcoma. The criteria for a diagnosis of high grade surface osteosarcoma were that the lesion had arisen on the surface of bone, that histologic findings of the tumor were identical to those of conventional osteosarcoma (Broders' Grade 3 or 4),[14] and that, even if medullary involvement was present, most of the tumor was on the surface of bone. Forty-six cases fulfilled the criteria. The four that were excluded were reclassified as dedifferentiated parosteal osteosarcoma (two cases), conventional osteosarcoma (one case), and extraskeletal osteosarcoma (one case). Nine patients in the previous report from our institution were included.[5] Four of the 46 cases were described previously in other case reports.[6,9,12,13]

Pertinent clinical information was gathered from the patients' charts and from the letters of the consulting pathologists. Preoperative radiographs were available for 29 patients. Gross specimens were available for review from 9 of the patients who were treated at the Mayo Clinic. Histologic sections stained with hematoxylin and eosin were available for all 46 patients. Follow-up information was obtained for all patients who were managed at the Mayo Clinic and for 70% (22 of 33) of the patients from the consultation files. The average duration of follow-up for the 13 patients who were treated at the Mayo Clinic was 5 years 8 months (range, 9 months to 21 years).

RESULTS

Clinical Features

Thirty of the 46 patients were males, and 16 were females. The ages of the 46 patients at diagnosis ranged from 8 years to 70 years (mean, 25 years). Seventy percent of the patients were in the second or third decade of life. The most frequent sites involved in our series were the midportion of the femur, the distal portion of the femur, and the midportion of the tibia (Fig. 1).

Information on symptoms and signs was available for 31 patients. The most common symptom, which was present in 22 patients (71%), was swelling. Nineteen patients complained of limb pain. Only 2 patients had limited range of motion of the joint adjacent to the tumor. Duration of the symptoms or signs before diagnosis was relatively short. Of the 27 patients for whom information about duration was available, 3 had symptoms or signs for less than 1 month, 11 had symptoms or signs for 1–3 months, 7 had symptoms or signs for 4–6 months, and 6 had symptoms or signs for 7–12 months. Only 2 patients had history of trauma.

Imaging Findings

Plain radiographs were analyzed for 29 patients. Eighteen patients had cross-sectional studies: 9 patients

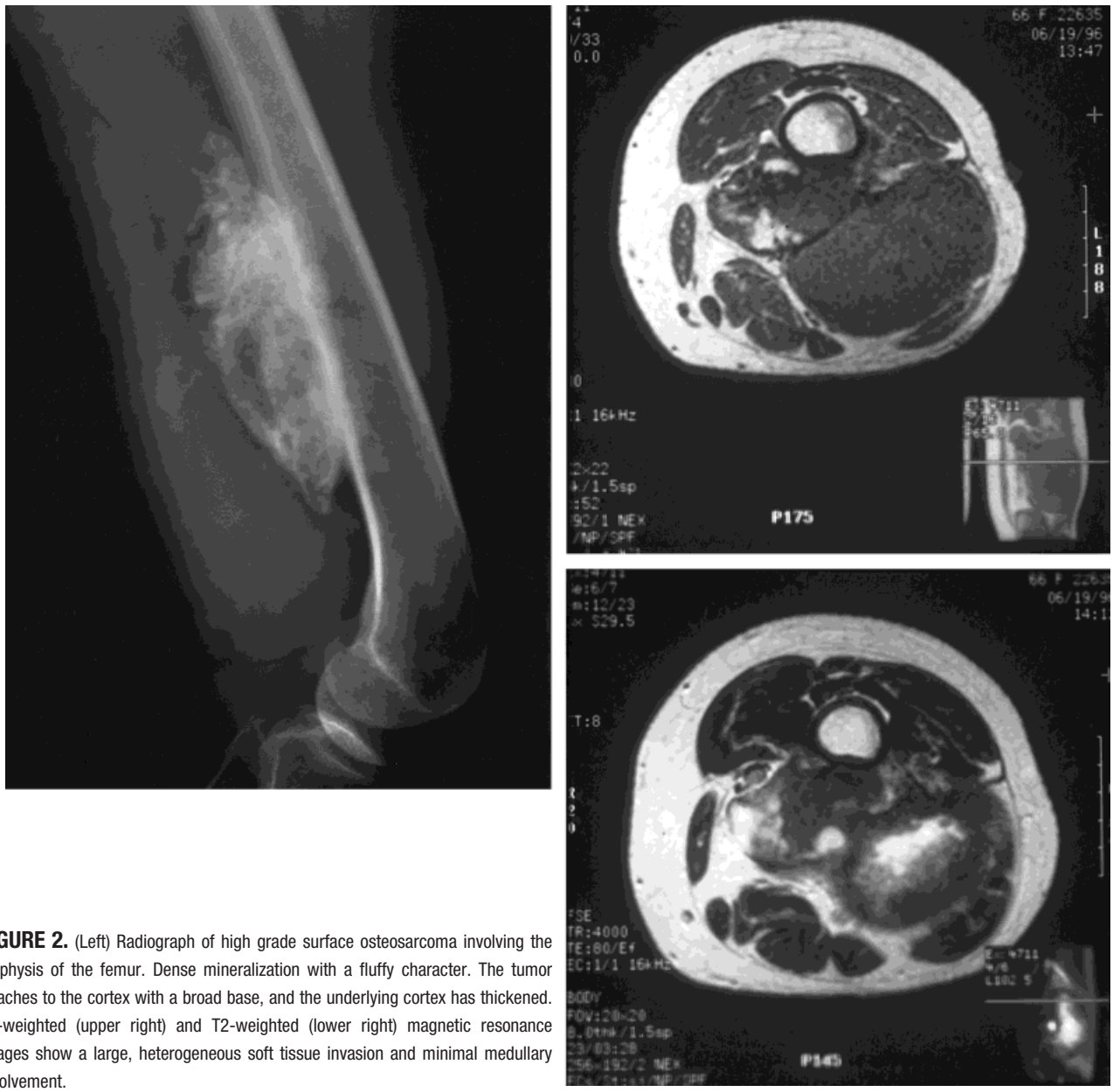

FIGURE 2. (Left) Radiograph of high grade surface osteosarcoma involving the diaphysis of the femur. Dense mineralization with a fluffy character. The tumor attaches to the cortex with a broad base, and the underlying cortex has thickened. T1-weighted (upper right) and T2-weighted (lower right) magnetic resonance images show a large, heterogeneous soft tissue invasion and minimal medullary involvement.

had computed tomography, 11 patients had magnetic resonance imaging, and 2 patients had both.

In all cases, the tumor arose from the surface of the bone. Eighteen of the 29 tumors (62%) involved the diaphysis of a long bone; 14 were limited to the diaphysis, and 4 were both metaphyseal and diaphyseal (Fig. 2). The remaining 11 tumors (38%) involved only the metaphysis (Fig. 2, upper right; Fig. 3, left). The tumors ranged in size from 3 cm to 18 cm (mean, 9.8 cm).

The amount of mineralization and distribution in the lesions varied, but a majority of tumors had dense to moderate mineralization with a fluffy, immature appearance. Nine lesions exhibited dense mineralization of the tumor. Twelve showed moderate mineralization, 6 had minimal mineralization, and 2 had none. In the 27 tumors in which mineral was observed, 26 (96%) showed fluffy, immature mineral. In 4 of these, the mineral had an aggressive, spiculated appearance. Only 1 tumor exhibited mineral that looked more mature. The distribution of mineralization within the tumor was predominantly at the base of the lesion in 17 of 27 cases (63%), centrally in 1 case, at the periphery in 3 cases, uniform in 3 cases, and scattered in 3 cases.

All 29 tumors exhibited a broad attachment to the

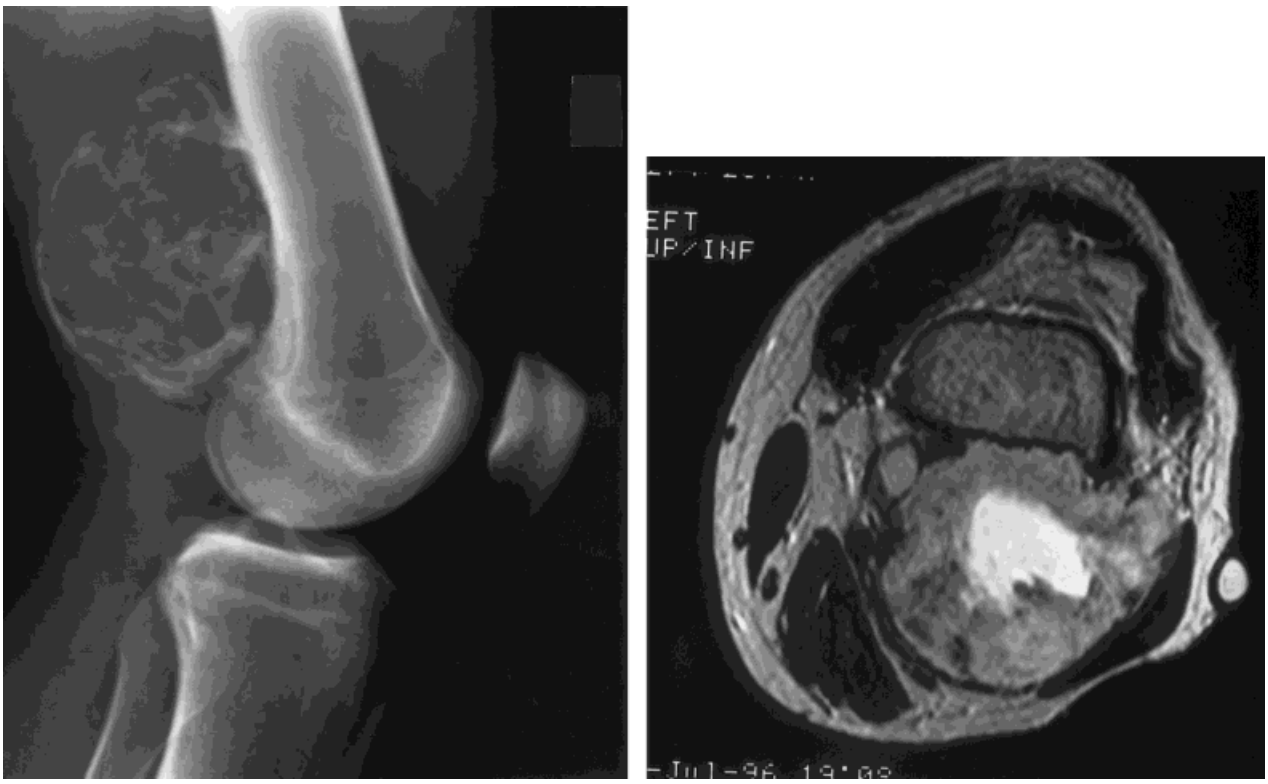

FIGURE 3. (Left) Radiograph of an uncommon appearance of high grade surface osteosarcoma with the lesion limited to the metaphysis. The location of the lesion resembles that of parosteal osteosarcoma. However, the pattern of mineralization (moderate amount, fluffy character, and peripheral distribution) is different from that of parosteal osteosarcoma. (Right) T2-weighted magnetic resonance image shows a heterogeneous soft tissue mass and a well preserved medullary space.

underlying cortex of the affected native bone. In contrast to parosteal osteosarcoma, a lucent zone between the mineralized tumor and the underlying cortex was rare (present in only 1 case). Circumferential involvement of the host bone was observed in 8 cases (28%). In 4 cases, circumferential involvement was greater than 50%, and, in 4 other cases, circumferential involvement was less than 50% (Fig. 4).

Alteration of the underlying cortex of the affected bone was seen commonly in high grade surface osteosarcoma. Cortical destruction was seen in 17 lesions, cortical thickening was present in 7 lesions, and both cortical destruction and thickening were observed in 4 lesions (Fig. 5). The cortex appeared normal in 9 tumors.

Periosteal reaction was associated with only three tumors. Two of the three tumors showed thick periosteal new bone, and one case had thin periosteal reaction. No tumor showed Codman's triangle or a spiculated periosteal reaction. Eight of the 29 tumors (28%) exhibited evidence of medullary involvement. Of the 18 patients who had cross-sectional studies, 6 (33%) had medullary involvement on imaging studies, but this can be difficult to detect.

Margination of the mineralized tumor was irregular and indistinct in 22 of the tumors (76%). Twenty-six of the 29 tumors (90%) had extension of a soft tissue mass beyond the mineralized portion. Of 17 tumors examined by cross-sectional study, 12 showed a heterogeneous soft tissue mass (Figs. 2, 3), and, in the remaining 5 tumors, the mass appeared homogeneous.

Retrospectively, the imaging findings of 27 of the 29 lesions were consistent with malignancy, and the remaining 2 lesions appeared benign. Differential diagnostic possibilities that arise when evaluating images of high grade surface osteosarcoma include conventional osteosarcoma, parosteal osteosarcoma, periosteal osteosarcoma, and myositis ossificans. In 4 lesions (14%), the radiographic features were similar to those of periosteal osteosarcoma, and, in 6 lesions, they resembled parosteal osteosarcoma.

Pathologic Findings

Grossly, the tumors frequently were multilobulated and bulky, with a mixture of hard and soft areas. They were attached to the underlying cortex with a broad base. The color of the tumors varied from region to

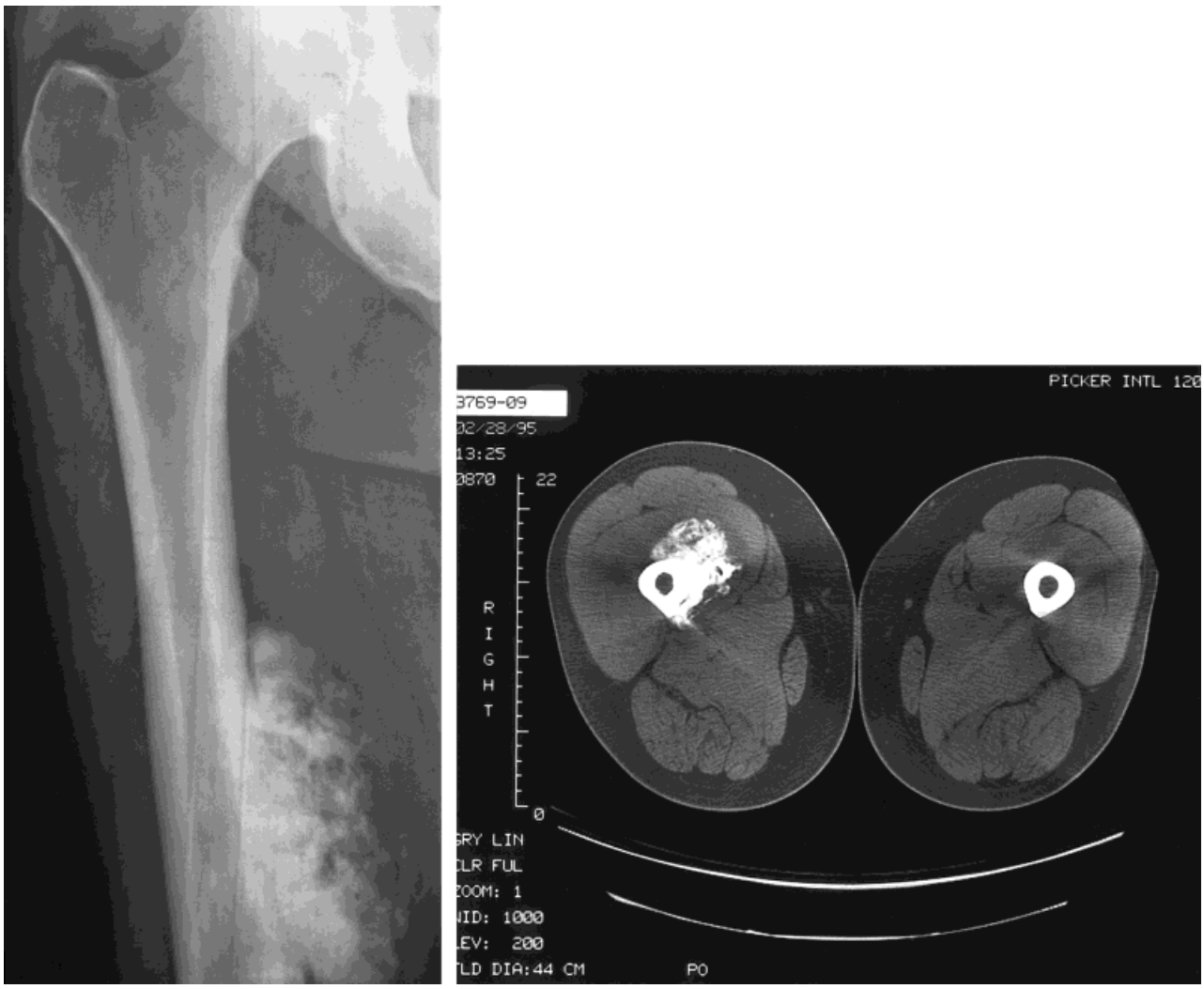

FIGURE 4. (Left) Radiograph of a high grade surface osteosarcoma involving the diaphysis of the femur of a 51-year-old man. (Right) Circumferential involvement of the femoral shaft is well illustrated on the computed tomographic image.

region, depending on the amount of osteoid, cartilage, hemorrhage, and necrosis. The outer margins adjacent to the surrounding tissue were irregular (Fig. 6).

Either grossly or microscopically, 19 of the 46 tumors (41%) showed infiltration into the cortex of the underlying bone (Fig. 7, top left). Medullary involvement was documented on gross or radiologic examination in 13 tumors and on microscopic examination in 6. All of the tumors showed soft tissue invasion surrounding the tumor.

Histologically, all of the tumors had areas of spindle cells with cellular atypia (Broders' Grade 3 or 4) and varied amounts of osteoid formation. Grade 3 osteoscarcoma was diagnosed when tumor cells were spindle shaped and closely packed together with hyprchromatic nuclei. Pleomorphism, that is, marked variation in size and shape of the nuclei, was not present. In Grade 4 osteosarcoma, the tumor cells also were spindle shaped and closely packed together. However, there was marked pleomorphism, with variation in size and shape of the nuclei. Many of the nuclei were plump and irregularly shaped and suggested giant cells under low power. Grading of chondroblastic osteosarcoma is based on the same principles. In Grade 3 sarcoma, lobules of malignant cartilate are surrounded by slender spindle cells. The tumor cells in the lacuna in the central chondroid lobules have the same cytologic features as the spindle cells. In Grade 4 osteosarcoma, sheets of spindle cells with very pleomorphic nuclei surrounded chrondroid islands. Basically, these features were identical to those of conventional osteosarcoma. Of the 46 tumors, 19 (14 Grade 4 and 5 Grade 3) were classified as osteoblastic osteosarcoma, 17 (12 Grade 4 and 5 Grade

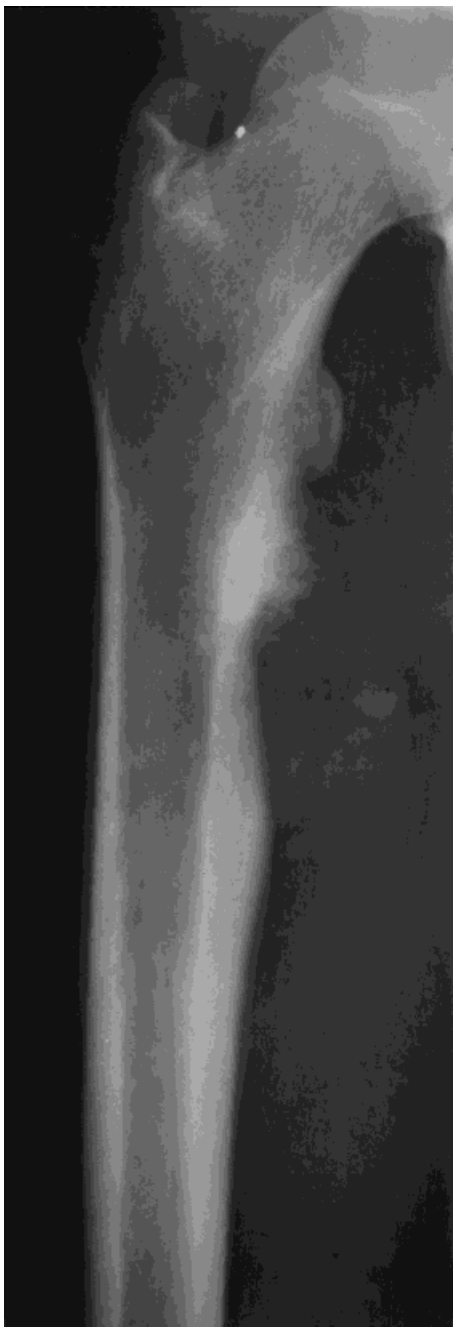

FIGURE 5. Radiograph of a lesion in the proximal femur of a 14-year-old boy. Mineralization of the tumor is fluffy and spiculated in character, and there is underlying cortical destruction.

3) were classified as fibroblastic osteoscaroma, and the remaining 10 (5 Grade 4 and 5 Grade 3) were classified as chondroblastic osteosarcoma (Fig. 7, top right, bottom left, and bottom right).

None of these tumors had classic areas of parosteal osteosarcoma, which consists of well differentiated bony trabeculae within fibrous stroma showing minimal cytologic atypia. The absence of well differentiated, low grade areas eliminated dedifferentiated parosteal osteosarcoma. The patients in the present study showed none of the characteristic histologic findings of periosteal osteosarcoma, such as chondroid lobules with peripheral hypercellularity and malignant appearing osteoid in the central portion.

Several histologic variations were observed. Six tumors showed giant cell-rich areas (Fig. 8, left). Two tumors showed aneurysmal bone cyst-like areas (Fig. 8, right).

Treatment and Clinical Outcome

Follow-up information on survival has been obtained in 35 patients (76%). Of these 35 patients, 18 died of disease, and 17 are still alive. Thirty-nine patients had information on the initial surgical margin. Six of the 39 patients had marginal excision as the initial treatment, and local recurrence developed in all of them from 1 month to 18 months later. Of these 6 patients, 5 patients died of pulmonary metastasis despite additional excision with wide margin, and 1 patient was lost to follow-up. Thirty-three patients had wide excision initially, and local recurrence developed in 2 of them. Of these 33 patients, 13 died of pulmonary metastasis, 17 are alive and well, and 3 were lost to follow-up. Pulmonary metastatic lesions were resected in 4 patients; 3 of those patients died of disease, and 1 patient was alive with disease 1 year and 7 months after the lung resection.

Systemic chemotherapy was administered to 24 patients, and follow-up information was available for 21 patients. Eight of the 21 patients died of disease, and the other 13 patients are alive and well. Information on the effectiveness of chemotherapy was available for 15 of these 21 patients. Among these 15 patients, 9 tumors showed no response to the chemotherapy, and 8 of the 9 patients died of disease; only 1 patient remains alive. All 6 patients with tumors that showed good response to chemotherapy are alive.

Information on medullary involvement and follow-up was available for 33 patients. Sixteen of the 33 patients had medullary involvement; 7 died as a result of their tumor, and the other 9 are alive. Seventeen of the 33 patients showed no medullary involvement. Nine of these patients died of disease, and the remaining 8 are alive.

Statistical Analysis of Survival

Survival was evaluated for 35 patients for whom follow-up information was available. The overall rate of survival was 57.5% at 3 years and 46.1% at 5 years.

The cumulative probability of local recurrence

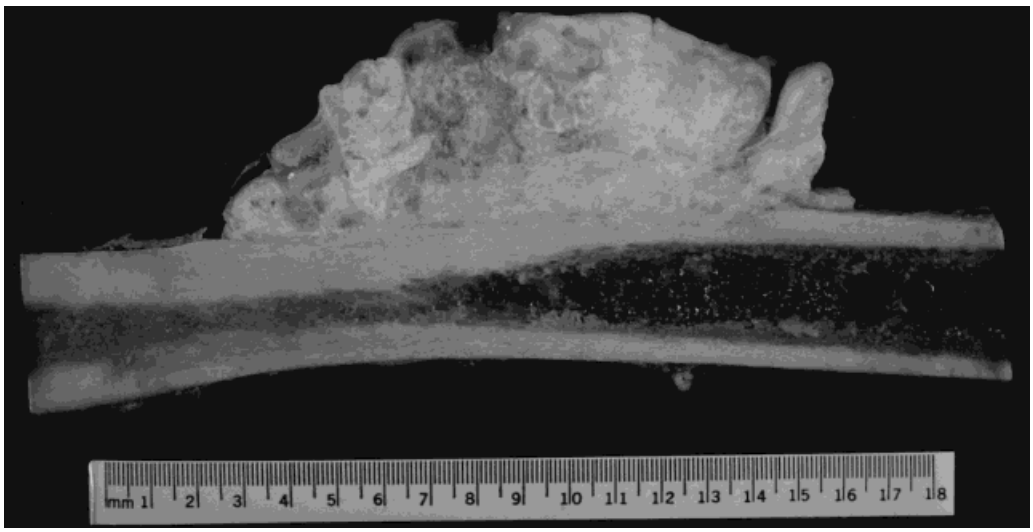

FIGURE 6. Grossly, the tumors presented as a bulky, multilobulated mass. The lesion on the distal femur shows a typical surface lesion without medullary involvement.

was 26% at 5 years. Marginal excision was associated significantly with an increased risk of recurrence (100% at 5 years compared with 8.8% in patients who underwent wide excision; $P < 0.01$; log-rank test). Factors that were not univariately related to local recurrence included age, sex, anatomic site, site in the long bone, size of the tumor, medullary involvement, and histologic type.

The patients with histologic Grade 3 tumors showed significantly better prognosis than those with Grade 4 sarcomas (85.7% disease free survival at 5 years compared with 29.3% for the patients with Grade 4; $P < 0.05$, log-rank test; Fig. 9, bottom left). All of the tumors were graded without knowledge of the outcome. Grading was done by using the criteria published previously.[14] A poor response to chemotherapy was associated significantly with an increased risk of death from disease (85.2% at 5 years compared with 0% in the patients who showed a good response to chemotherapy; $P < 0.01$, log-rank test; Fig. 9, bottom right). Prognosis after local recurrence was poor. Seven of the 8 patients in whom local recurrence developed died of disease 14–96 months after the initial surgical treatment, and the remaining 1 patient was lost to follow-up. However, these patients' survival rate was not significantly worse than that of the patients in whom local recurrence did not develop. Factors that were not associated univariately with an increased risk of death included age, sex, anatomic site, site in the long bone, size of the tumor, medullary involvement, and histologic type.

DISCUSSION

Osteosarcomas arising on the surface of the bone have been classified into three subgroups, two of which, parosteal osteosarcoma and periosteal osteosarcoma, tend to have a much better prognosis than conventional osteosarcoma.[1,2,15] Histologically, parosteal osteosarcoma is usually Grade 1 or 2 (Broders' grading system),[14] and periosteal osteosarcoma is Grade 2 or 3. Francis et al.[3] first reported two cases with high grade (Grade 3 or 4) osteosarcoma arising on the surface of the pubis and the humerus in 1964. In 1968, a case of high grade osteosarcoma arising on the surface of the skull was reported in the Japanese literature, along with a discussion on the classification of osteosarcoma.[4] In 1984, Wold et al.[5] described a series of nine cases in the Mayo Clinic files of high grade osteosarcoma arising on the surface of bone, which they referred to as high grade surface osteosarcoma. This is the third subtype of osteosarcoma arising on the surface of the bone.

High grade surface osteosarcomas are rare tumors. From 1926 to 1996, the number of conventional (intramedullary) osteosarcoma cases identified in the Mayo Clinic records was 4365; one in every 8.4 cases arose from the surface of bone. Among these 518 osteosarcomas, parosteal osteosarcoma accounted for 335 (64.7%), periosteal osteosarcoma accounted for 137 (26.4%), and high grade surface osteosarcoma accounted for only 46 (8.9%). We identified several clinical characteristics in the analysis of our 46 cases. Men are affected more frequently than women (male:female = 30:16). This is in contrast to parosteal osteo-

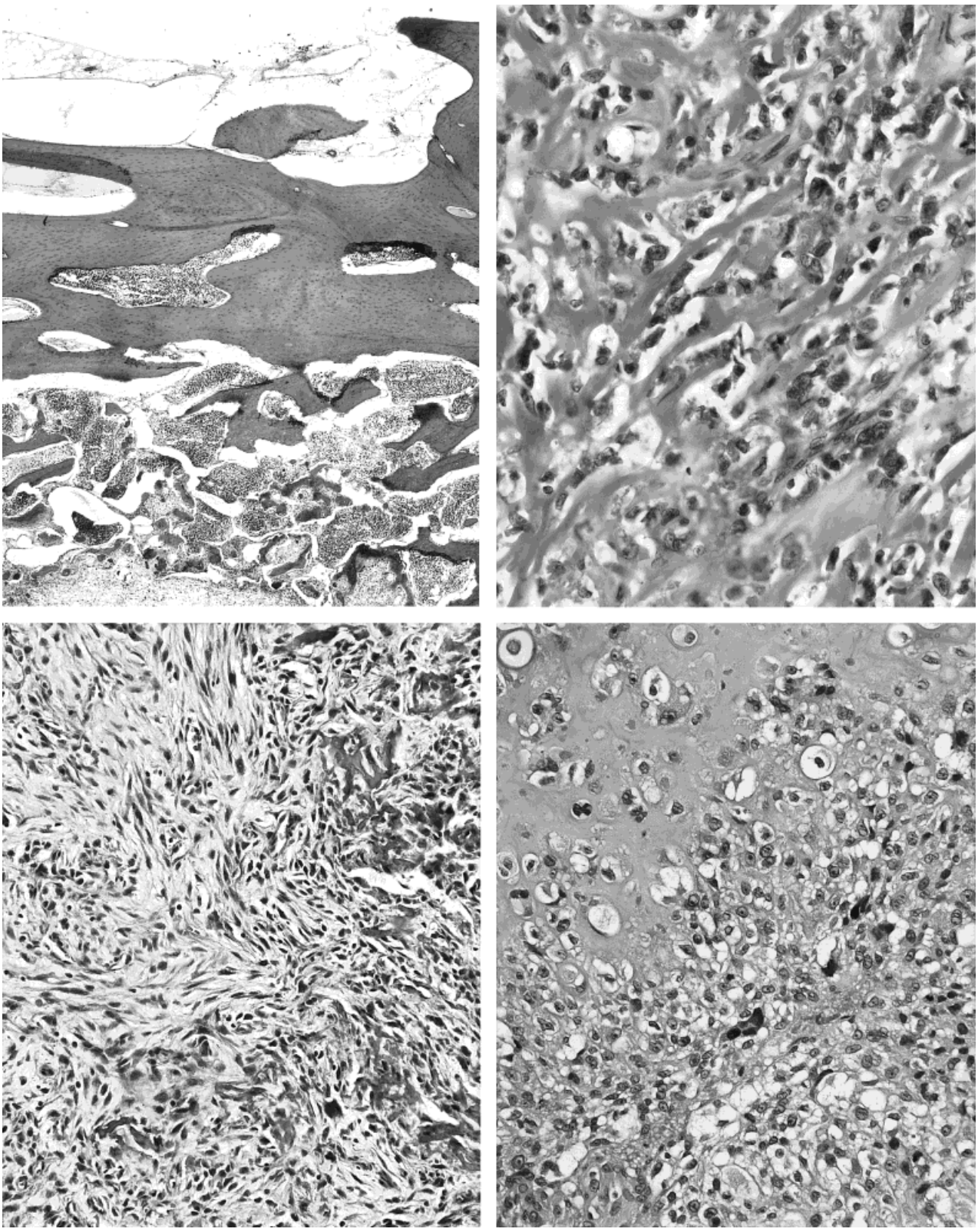

FIGURE 7. Typical histologic features of high grade surface osteosarcoma. (Top left) In a low power view, most of the tumor is situated on the surface of the bone, and the tumor partially shows medullary involvement. At high power, histologic features are identical to those of conventional osteosarcoma. Of the 46 tumors, 19 showed features identical to osteoblastic osteosarcoma (top right, ×400), 17 showed features identical to fibroblastic osteosarcoma (bottom left, ×200), and 10 showed features identical to chondroblastic osteosarcoma (bottom right, ×200; Hematoxylin and eosin [H&E]).

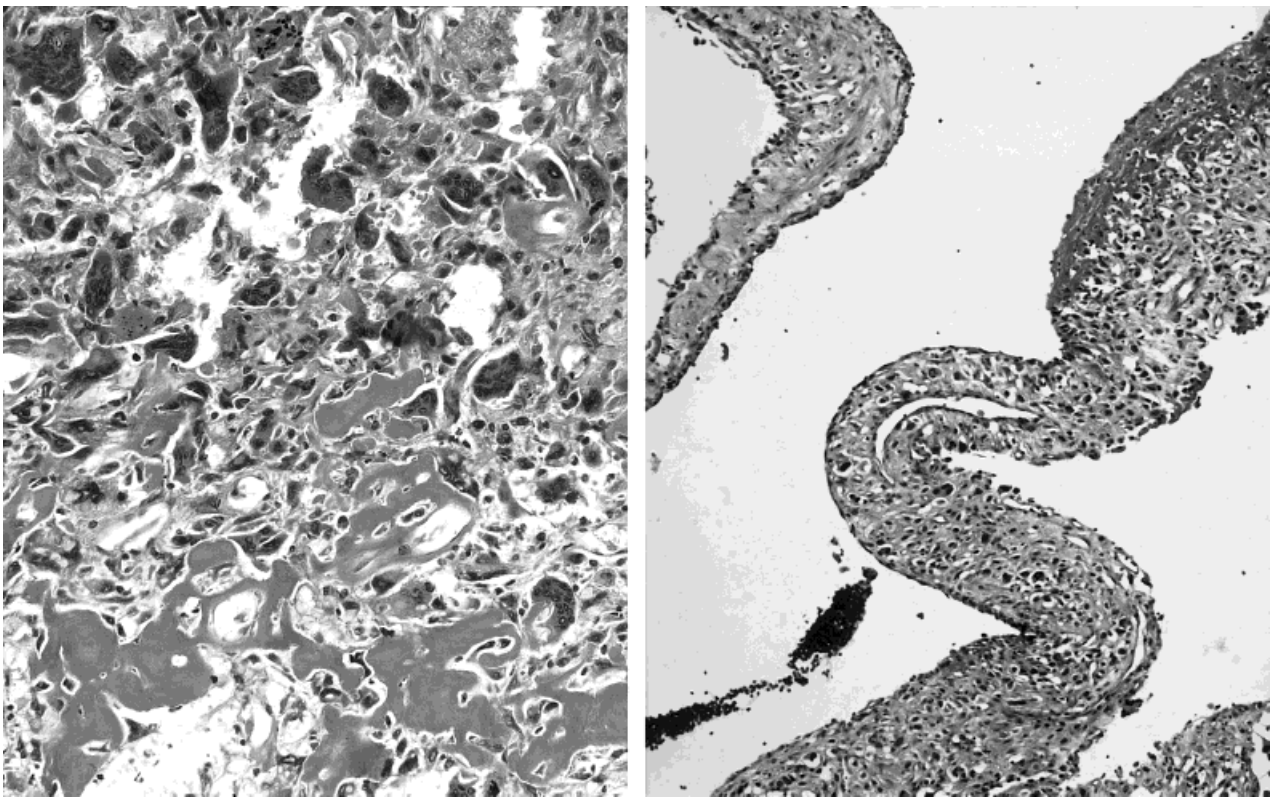

FIGURE 8. Histologic variations. (Left) Six tumors showed giant cell-rich areas (×200). (Right) Two tumors partially showed aneurysmal bone cyst-like areas (×100; H&E).

sarcoma, in which females outnumber males.[1] Thirty-two of the 46 patients (70%) were in the second or third decade of life. This is similar to the age grouping seen for patients with conventional osteosarcoma. In 44 of the 46 cases (96%), the lesion was located on a long bone. In contrast to periosteal osteosarcoma, for which the tibial shaft is the most common site, the most frequent site was the midfemur (30%), followed by the distal femur (24%) and the midtibia (17%). High grade surface osteosarcoma, in our series, infrequently involved the ileum[9] and the metacarpal.[12] The skull has been reported as a rare location of this tumor.[4] Clinical signs and symptoms of patients with high grade surface osteosarcoma resemble those of conventional osteosarcoma patients. Swelling and pain were the most common sign and symptom. In all patients, the duration of the signs and symptoms was less than 1 year. The stiffness and long duration of the symptoms that are observed occasionally in parosteal osteosarcoma are rare in high grade surface osteosarcoma.

Although previous reports described the similarity of radiologic features of high grade surface osteosarcoma to those of parosteal and periosteal osteosarcoma,[2,5,10] several differences were revealed in the present study. First, dense to moderate mineralization with a fluffy, immature appearance is characteristic of high grade surface osteosarcoma. In the present cases, this mineralization appeared predominantly at the base of the lesion, and the tumor was attached to the underlying bone with a broad base. In contrast to parosteal osteosarcoma, lucent zones between the tumor and the underlying cortex were quite rare (3%), and circumferential involvement was relatively rare (26%) in high grade surface osteosarcoma. In high grade surface osteosarcoma, periosteal reactions are sparse. In contrast, periosteal osteosarcoma typically showed a spiculated mineralization perpendicular to the long axis of the affected bone.[2,15] The most frequent location also differs among the three subtypes of osteosarcoma arising on the surface of bone: midfemur in high grade surface osteosarcoma, tibial proximal metaphysis in periosteal osteosarcoma, and distal femoral metaphysis in parosteal osteosarcoma. In addition, the size of the tumor varied from 3 cm to 18 cm in high grade surface osteosarcoma. This is in contrast to the size in periosteal osteosarcoma, which ranged from 2.5 cm to 3.5 cm.[15]

When a high grade surface osteosarcoma consists predominantly of chondroblastic elements, differen-

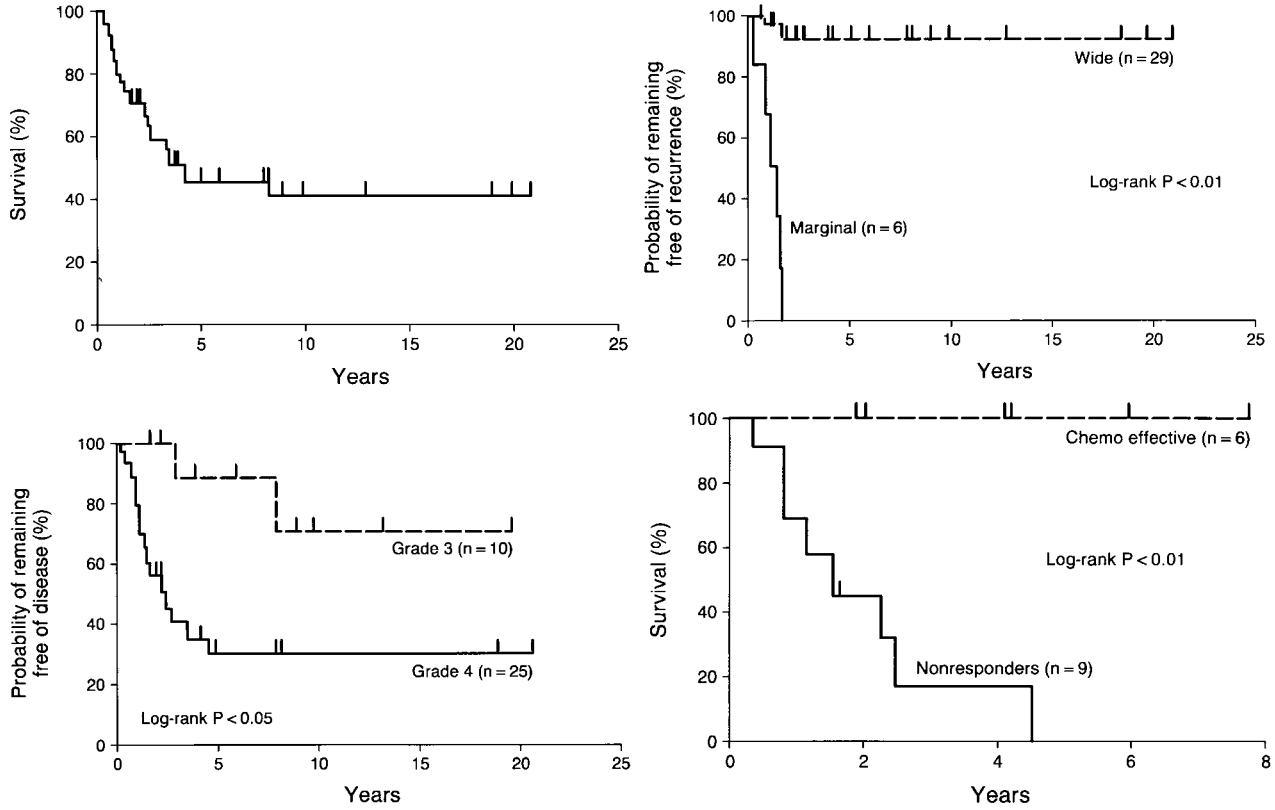

FIGURE 9. Statistical analysis of survival. (Top left) The overall rate of survival is 57.5% at 3 years and 46.1% at 5 years. (Top right) The correlation of recurrence free survival to the margin of tumor excision. Marginal excision is associated significantly with an increased risk of recurrence ($P < 0.01$, log-rank test). (Bottom left) The correlation of disease free survival to histologic grade. The patients with histologic Grade 3 tumors showed significantly better prognosis than those with Grade 4 tumors ($P < 0.05$, log-rank test). (Bottom right) Poor response to chemotherapy (Chemo) is associated significantly with increased risk of death ($P < 0.01$, log-rank test).

tial diagnosis with periosteal osteosarcoma can be a problem. However, in high grade surface osteosarcoma, perpendicular arrangement of chondral lobules and malignant appearing osteoid formation in the center of the lobules, which are characteristic features in periosteal osteosarcoma, are absent. In addition, soft tissue invasion was observed in all cases of high grade surface osteosarcoma, although the invasion is minimal in periosteal osteosarcoma.[15] To exclude dedifferentiated parosteal osteosarcoma, extensive examination of the surgical specimen is essential. If there is a coexistence of low grade, well differentiated osteosarcoma and high grade sarcoma, then dedifferentiated parosteal osteosarcoma should be considered. The differential diagnosis that includes conventional osteosarcoma also is important. Medullary involvement was found in the gross specimens or radiographs in 13 cases and on histologic examination in 6 cases. We are not aware of any strict criteria about how much medullary involvement is permissible in high grade surface osteosarcoma. We consider that minimal involvement is permissible, although how much is not clear. The numbers are so small that we do not believe that we will get reliable answers about prognosis if we separate tumors into those with less than 5% involvement, those with 5–10% involvement, and so on. The criterion used in this study was that the tumor presented as a surface lesion, and only rigorous examination showed medullary involvement.

Adequate surgical treatment is essential in the local control of high grade surface osteosarcoma. Six of 8 patients who had locally recurrent disease were treated initially by a marginal excision. Marginal excision is strongly associated with increased risk of local recurrence. In contrast, wide excision provided good results for local control. Also, in parosteal and periosteal osteosarcoma, marginal excision is associated with increased risk of local recurrence. Local management of osteosarcoma arising on the surface of the bone is best achieved with a wide surgical margin.

Follow-up information was available in 35 cases. The five-year survival rate was 46.1%. In contrast,

death was reported for only 15 of 226 patients (7%) with parosteal osteosarcoma and in only 4 of 22 patients (18.2%) with periosteal osteosarcoma in studies conducted at a large institution.[1,2] High grade surface osteosarcoma, therefore, should be differentiated from other osteosarcomas arising on the surface of the bone, because it is associated with a comparatively poor clinical outcome.

Twenty-four of the 46 patients had received systemic chemotherapy. The prognosis of the patients who had responded well to chemotherapy was better than that of the patients who responded poorly. In the treatment of osteosarcoma arising on the surface of bone, orthopedic surgeons tend to pay attention to surgical removal, because almost all cases of osteosarcoma arising on the surface of bone are low grade. In the treatment of high grade surface osteosarcoma, however, preoperative chemotherapy, adequate surgical treatment, and postoperative chemotherapy are probably essential. High grade surface osteosarcoma had biologic potential similar to that of conventional osteosarcoma. Effective chemotherapy improves the outcome of patients with high grade surface osteosarcoma.

It is unclear whether medullary involvement is associated with poorer outcome. Several reports of osteosarcomas arising on the surface of the bone mentioned the significance of medullary involvement. In parosteal osteosarcoma, medullary involvement has not been associated with poorer clinical outcome, although medullary involvement is observed more frequently in tumors with dedifferentiation.[1] The correlation between medullary involvement and clinical outcome in high grade surface osteosarcomas requires further investigation.

Recently, there has been controversy regarding the differentiation between dedifferentiated parosteal osteosarcoma and high grade surface osteosarcoma.[10] We believe that the term "dedifferentiated parosteal osteosarcoma" should be used when low grade, well-differentiated osteosarcoma and high grade sarcoma coexist or when the initial lesion is entirely low grade and the recurrent lesion contains any high grade areas, regardless of how small.[1]

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