Multicentric Osteosarcoma

Clinicopathologic and Radiographic Study of 56 Cases

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Abstract

Multicentric osteosarcoma (M-OGS) is characterized by multicentricity of osseous osteosarcomas, either synchronous or metachronous, without visceral involvement. The study’s purpose was to clinicopathologically and radiographically analyze 56 cases of M-OGS (22 synchronous and 34 metachronous). The distal femur was the most common site. Histologically, all tumors were high grade. Of 22 patients with synchronous M-OGS, 16 had 3 or more simultaneous tumors; the axial skeleton was involved in 14 (64%) of 22 cases. In metachronous M-OGS, the second malignancy occurred after a median of 22 months. Treatment was surgery, chemotherapy, radiotherapy, or a combination of these. Patients with metachronous osteosarcoma had a median survival longer than did patients with synchronous tumors. Overall, 8 long-term survivors were treated by aggressive surgery with wide margins (plus chemotherapy and/or radiotherapy). M-OGS combines multiple skeletal locations of high-grade conventional osteosarcomas and has a poor prognosis. Aggressive surgery may result in improved long-term survival, particularly in patients with metachronous disease.

Osteosarcoma is the most common primary sarcoma of bone, representing about 35% of cases and constituting approximately 0.07% of all neoplasms.1 Its biologic behavior is characterized by aggressive local growth and early metastatic dissemination.2 A small number of patients with osteosarcoma have involvement of multiple skeletal sites, either synchronous or metachronous, but without evidence of visceral metastases.3 Arbitrarily, the absence of visceral metastases at the time of diagnosis may be taken as evidence of multifocal rather than metastatic bone disease.4,5

Owing to the rarity of the disease, the clinicopathologic characteristics of multicentric osteosarcoma (M-OGS) have not been well defined: only a few cases have been reported in the English-language literature, and most of these reports are limited to single case reports or smaller case series.3-13 Moreover, sufficient information concerning the differences between synchronous and metachronous osteosarcoma is lacking.

The purpose of the present study was to examine the pathologic, radiologic, and clinical characteristics of a large series of consecutive patients affected by M-OGS treated at Mayo Clinic, Rochester, MN, and Rizzoli Orthopedic Institute, Bologna, Italy, concentrating particularly on the characteristics of synchronous and metachronous cases.

Materials and Methods

Patient Population

All bone tumors in patients seen at the Mayo Clinic and the Rizzoli Orthopedic Institute have been categorized and filed in each institution’s pathology department. With
approval of Mayo Clinic and Rizzoli Orthopedic Institute institutional review boards, a search for cases of M-OGS was made in these files. The criteria for inclusion in the study were as follows: (1) synchronous appearance (S group) or metachronous appearance (M group, with a minimum of 6 months between primary and secondary lesions) of 2 or more skeletal foci of osteosarcoma; (2) absence of any visceral metastasis at the time of diagnosis and, in the M group, up to the metachronous bone occurrence(s); and (3) no prior radiation therapy.

Among 2,028 and 1,804 patients with osteosarcoma evaluated at Mayo Clinic (between 1900 and 2005) and Rizzoli Orthopedic Institute (between 1975 and 2004), respectively, we identified 56 consecutive cases (1.5%) of M-OGS (35 males [63%] and 21 females [38%]). Of the 56 patients, 22 (39%) were included in the S group and 34 (61%) in the M group.

Pertinent clinical information (age at diagnosis, tumor locations and size, symptoms, treatments, outcome, and follow-up) was obtained from the clinical charts and letters from clinicians who had treated the patients. Long-term survivors were defined as patients affected by M-OGS who survived more than 10 years.14

**Histopathologic Review**

Histologic sections were reviewed in all cases to verify the diagnoses. The tumors were graded according to the Broders method (scale of 1 to 4). Grades 1 and 2 were considered low grade and grades 3 and 4 were high grade. Depending on the histopathologic characteristics of the neoplastic cell component and its predominance, tumors were subclassified as osteoblastic, chondroblastic, or fibroblastic.15,16

**Imaging Review**

Imaging studies were available for review for 26 of 34 patients in the M group. For these 26 patients, imaging studies of 50 lesions were reviewed, including radiographs of 43, computed tomographic (CT) images of 17, and magnetic resonance (MR) images of 13. Imaging studies were available for review for 13 of 22 patients in the S group. For these 13 patients, imaging studies of 63 lesions were reviewed, including radiographs of 62, CT images of 7, and MR images of 8.

The lesions were evaluated for their location in a long bone or flat bone and for their anatomic localization within the long bones as epiphyseal, metaphyseal, diaphyseal, or multiple locations. The imaging features of the lesions were analyzed with regard to their pattern of bone destruction (osteolytic, osteosclerotic, or both) and zone of transition (wide or narrow). The lesions were also evaluated for the presence or absence of cortical destruction, soft tissue mass, and benign or malignant periosteal new bone formation. The presence of osteoid matrix within the lesion was recorded, along with the presence or absence of an associated pathologic fracture. The lesions were divided into 2 groups according to whether they had imaging features that favored the diagnosis of a primary aggressive destructive bone tumor (destructive lesion with cortical destruction, wide zone of transition, soft tissue mass, matrix mineral production, and malignant periosteal new bone formation) or metastatic osteosarcoma (purely osteosclerotic medullary lesion with narrow zone of transition and no evidence of cortical destruction, soft tissue mass, or periosteal new bone formation).

For patients with a large number of lesions involving multiple bones, the exact number of lesions in each bone could not be accurately counted and assessed. Therefore, by convention, the number of lesions was recorded as 1 lesion per affected bone. For example, a patient with synchronous osteosarcoma with multiple lesions in both femurs, 1 tibia, 1 humerus, and 1 ilium was counted as having 4 lesions in long bones and 1 in a flat bone. An assessment of the symmetry of anatomic distribution of lesions in the skeleton could not be performed because of variations in the imaging studies available for review for each patient.

**Statistical Analysis**

The Mann-Whitney statistical test was used to compare ages and symptom durations between patients affected by synchronous and metachronous osteosarcomas. Survival after disease onset was calculated with use of a Kaplan-Meier analysis and compared between the 2 groups with the log-rank test. All tests were performed using SPSS 18.0 software (SPSS, Chicago, IL). *P* values less than .05 were considered statistically significant.

**Results**

**Patients With Synchronous M-OGS**

There were 14 males (64%) and 8 females (36%), ranging in age from 2 to 70 years (median, 16 years). At the time of diagnosis, 19 patients (86%) complained of pain, 12 (55%) had local swelling, 3 (14%) had difficulties in walking, and 1 (5%) each had hydrothorax, paresthesias, tinnitus, and vertigo. Constitutional symptoms such as weakness and weight loss were also present in 2 patients (9%). The duration of symptoms or signs before the diagnosis of synchronous M-OGS ranged from 1 to 24 months (median, 3 months). In addition to synchronous tumors, metachronous occurrences of osteosarcoma developed in 5 patients (median, 19 months; range, 12-206 months).

In 4 patients, other conditions were present that may have predisposed them to development of osteosarcoma. Paget disease of bone affected 1 patient (diagnosed 4 years...
among the 88 documented synchronous lesions in the S group, the most commonly involved anatomic sites were the distal femur (15 tumors [17%]), proximal tibia (14 tumors [16%]), proximal humerus (9 tumors [10%]), skull (9 tumors [10%]), pelvic bones (7 tumors [8%]), spine (7 tumors [8%]), and ribs (7 tumors [8%]). one patient had extensive diffuse metastases in the liver and kidney.

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Patients With Metachronous M-OGS

In the M group there were 21 males (62%) and 13 females (38%). their ages at diagnosis of the first localization ranged from 4 to 29 years (median, 16 years). the most common symptoms at the onset were pain in 31 patients (91%), local swelling in 18 (53%), limping in 4 (12%), joint effusion in 2 (6%), and inability to completely extend the leg in 2 (6%). weight loss was also present in 2 patients (6%). these symptoms had been present for a median of 3 months (range, 1-12 months).

The interval between the diagnosis of the primary osteosarcomas and the metachronous tumors ranged from 7 to 171 months (median, 21 months). In addition, further metachronous osteosarcomas developed in 8 patients (24%) after a median of 8 months (range, 3-24 months) from the second tumor. The second malignancies manifested clinically with symptoms and signs similar to those of the primary osteosarcomas.

Two patients had possible predisposing conditions. One patient had McCune-Albright syndrome characterized by short stature, hearing loss, galactorrhea, and macular lesions of the skin of the back, and another had Rothmund-Thomson syndrome, with short stature, skin pigmentation, and skeletal abnormalities.

Among the 105 documented lesions in the M group, the most commonly involved anatomic sites were the distal femur (19 tumors [18.1%]), spine (15 tumors [14.3%]), proximal humerus (11 tumors [10.5%]), pelvic bones (11 tumors [10.5%]), proximal tibia (11 tumors [10.5%]), sacrum (5 tumors [4.8%]), skull (5 tumors [4.8%]), and ribs (5 tumors [4.8%]). The first osteosarcoma affected the appendicular skeleton in all patients; throughout the course of the disease, the occurrences involved the appendicular skeleton in 18 patients (53%) and the axial and appendicular skeleton in the remaining 16 (47%). There were no noteworthy differences in these percentages between patients who died of the osteosarcoma and long-term survivors.

Pathologic Findings

All lesions identified in the M and S groups were high-grade medullary osteosarcomas [Image 1A and Image 2A]. The tumor sizes varied from 1 to 17 cm. In the S group, 24 (73%) of 33 osteosarcomas were osteoblastic, 8 (24%) were fibroblastic, and 1 (3%) was chondroblastic. Of 33 cases, 26 (79%) were classified as grade 4 and 7 (21%) as grade 3. In the M group, 46 (67%) of 69 lesions were osteoblastic, 16 (23%) were fibroblastic, and 7 (10%) were chondroblastic. Of 69 lesions, 60 (87%) were grade 4 and 9 (13%) were grade 3. There were no low-grade tumors.

In the S group, all but 1 patient showed the same histopathologic subtype in the multiple tumor locations. In contrast, in the M group, 11 patients had at least 1 skeletal lesion characterized by a different histopathologic subtype compared with the primary osteosarcoma.

Radiographic Findings

Metachronous Lesions

In the M group, imaging studies were available for review for 50 lesions in 26 patients. The majority of the lesions showed aggressive imaging features with a mixed lytic and sclerotic pattern of bone destruction, a wide zone of transition, osteoid matrix production, cortical destruction with an associated soft tissue mass, and malignant periosteal new bone formation [Table 1]. The majority (38/50 [76%]) of the lesions were located in the long bones compared with 12/50 (24%) in the flat bones. Of the 38 lesions in the long bones, the majority (29/38 [76%]) involved the metadiaphyseal region, with 12 of the 29 cases involving the epiphysis in addition to the metadiaphyseal region. Six involved the diaphysis only, and 3 involved both the epiphysis and metaphysis. Only 2 (4%) of the 50 lesions were associated with a pathologic fracture. The constellation of imaging features of the majority of the lesions in the M group favored the diagnosis of a primary osteosarcoma (Images 1A-1D).

Synchronous Lesions

In the S group, imaging studies were available for review for 63 lesions in 13 patients. In contrast with the M group, a minority (13/62 [21%]) of the lesions demonstrated imaging features suggestive of a primary osteosarcoma (Table 1). The majority of lesions had imaging features more suggestive of osteosclerotic metastases (Images 2E and 2F) manifesting....
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as purely sclerotic, heavily mineralized lesions with osteoid matrix in the medullary canal with a narrow zone of transition and no evidence of cortical destruction, associated soft tissue mass, or malignant periosteal new bone formation. Of the 63 lesions, 41 (65%) were located in the long bones, and 22 lesions (35%) involved the flat bones of the axial skeleton. Of the 41 lesions in the long bones, 40 (98%) involved the metaphyseal region, with 15 lesions involving the metaphysis only, 13 in the metadiaphysis, and 12 involving a combination of the epiphysis, metaphysis, and diaphysis. Only 1 lesion involved the diaphysis exclusively. The 5 purely osteolytic lesions all occurred in 1 patient with multifocal disease and showed no evidence of matrix mineralization. Only 1 patient had a pathologic fracture. Of the 13 patients with synchronous osteosarcomas, 10 had at least 1 lesion that had features typical of a primary osteosarcoma, with additional lesions more suggestive of osteosclerotic metastases. Two patients had 1 lesion each that looked like a primary osteosarcoma,
In 4 patients (7%) with synchronous osteosarcomas and 9 (17%) with metachronous osteosarcomas, treatment included surgery, radiotherapy, or both in the era before chemotherapy. Two patients, in view of their disseminated disease, had no antineoplastic treatment. Systemic chemotherapy (neoadjuvant, adjuvant, or both) was additionally administered to the but additional imaging studies were not available to assess the features of the additional lesions. In addition, 1 of the 13 patients in the S group had a total of 3 lesions, 2 of which had features typical of a primary osteosarcoma, and the third had features that could represent a primary or a metastatic lesion (Image 2). The latter patient was the only patient in the S group with long-term survival.

**Image 2** A case of synchronous multicentric osteosarcoma. An anteroposterior (AP) radiograph (A) and a coronal T1-weighted magnetic resonance image (MRI; B) of the tibia show a malignant, destructive, mixed lytic and sclerotic lesion in the proximal metadiaphysis with an associated cortical destruction medially. An AP radiograph (C) and a sagittal T1-weighted MRI (D) of the proximal humerus show an additional lesion that has imaging features typical of a primary osteosarcoma manifesting as a heavily mineralized destructive lesion in the metadiaphysis with malignant periosteal new bone formation and an associated soft tissue mass. Both of these lesions have imaging features typical of primary osteosarcoma. An additional AP radiograph (E) and coronal T1-weighted MRI (F) of a third lesion in the distal fibular metadiaphysis show a densely sclerotic lesion with no detectable cortical destruction, periosteal new bone formation, or soft tissue mass. The latter imaging features could be seen with an osteosclerotic metastasis or a primary osteosarcoma. **G.** A high-power histologic view of the fibroblastic osteosarcoma involving the proximal tibia shows highly atypical spindled elements in stroma with some osteoid deposition (H&E, ×40).

**Treatment and Outcome**

In 4 patients (7%) with synchronous osteosarcomas and 9 (17%) with metachronous osteosarcomas, treatment included surgery, radiotherapy, or both in the era before chemotherapy. Two patients, in view of their disseminated disease, had no antineoplastic treatment. Systemic chemotherapy (neoadjuvant, adjuvant, or both) was additionally administered to the
remaining patients; this consisted of various combinations of doxorubicin, cisplatin, high-dose methotrexate, cyclophosphamide, ifosfamide, and vincristine. As for the efficacy of preoperative chemotherapy, assessed by the Huvos grading system, this information was available for 5 cases in the S group and 16 cases in the M group. In the S group, it was grade 3 in 3 cases and grades 2 plus 4 (evaluated in 2 different tumor locations) in 2 patients. In the M group, 3 cases were grade 1, 3 cases were grade 2, 9 cases were grade 3, and 1 case was grade 4.

Follow-up of the patients in the S group ranged from 4 to 211 months (median, 15 months). All of the 22 patients died of disease after a median of 15 months from the diagnosis (range, 4-211 months). Pulmonary metastases were present in 8 (36%) of these patients.

Patients in the M group had a median follow-up of 43 months (range, 13-497 months). In 7 patients (21%), pulmonary metastases developed after onset of the metachronous lesion. Of the 34 patients, 29 (85%) died, 27 (79%) of disease. One patient died during surgery for a duodenal peptic ulcer (12 years after the metachronous osteosarcoma), and another patient died as a consequence of advanced-stage breast carcinoma 8 years after the second osteosarcoma. In the M group, patients died after a median of 38 months (range, 13-120 months) from the diagnosis of the first tumor.

Long-Term Survivors

Of all patients, 8 were long-term survivors, 7 in the M group and 1 in the S group. In the M group, 2 patients died as a consequence of other diseases, as stated. In the S group, 1 patient died of disease 211 months after the onset of initial disease. Long-term survivor characteristics are summarized in Table 2 and Table 3.

Statistical Analysis

Age and symptom duration were comparable between the S and M groups. There were no differences in the age of patients (see earlier text) at the first manifestation of symptoms. Of the 56 patients, 43 (77%) were in their second or third decade of life. Two patients affected by synchronous osteosarcoma were 60 and 70 years of age, the first one having Paget disease of bone, which explains the late manifestation of the malignancy. Local pain and swelling were the most frequent clinical signs and symptoms of patients affected by synchronous or metachronous M-OGS. Regardless of the type of manifestation, all M-OGS lesions were most commonly located in long bones of the knee region, particularly in the distal femur. Overall, the clinical findings were similar to those seen in patients with isolated conventional osteogenic sarcomas. In the long bones, the majority of the lesions in both patient groups showed a predilection for the metaphysis or metadiaphyseal region, as would be expected for primary osteosarcoma.16,19

Histologically, there were no differences between synchronous and metachronous tumors. Both groups contained tumors manifesting as high-grade (grade 3 or 4) conventional tumors.
osteosarcomas, mainly osteoblastic and fibroblastic subtypes. After excluding the cases from the prechemotherapeutic era, in the M group the median survival was significantly longer than in the S group (43.0 months [95% confidence interval (CI), 39.3-46.7 months] vs 14.0 months [95% CI, 11.2-16.8 months], respectively; \( P < .001 \)) if calculated from the onset of the disease in both groups. This difference was also detected when the M group median survival, calculated from the diagnosis of the second malignancy, was compared with the S group median survival, calculated from the beginning of the disease (34.0 months [95% CI, 21.1-46.9 months] vs 14.0 months [95% CI, 11.2-16.8 months], respectively; \( P = .003 \)). These survival results remained valid when patients treated without chemotherapy were considered as subgroups (\( P = .001 \)) and if the data for patients with genetic syndromes had been excluded from the comparison (\( P = .001 \)).

**Discussion**

First described in 1936, multicentricity is a rare presentation of osteosarcoma characterized by multiple skeletal lesions that may occur simultaneously (synchronous) or sequentially (metachronous). Because a large percentage of osteosarcomas harbor pulmonary micrometastases at the time of diagnosis and the lungs represent the most common site of metastatic disease in these cases, it is reasonable to consider as multicentric only the cases that manifest without visceral involvement at the time of diagnosis.

This study confirms the rarity of multicentric osteosarcoma. It represented only 1.5% of all osteosarcomas in the files of Mayo Clinic and Rizzoli Orthopedic Institute (0.6% synchronous and 0.9% metachronous). These values are similar to other large series of osteogenic sarcoma previously reported in the English-language literature.

Although the overall incidence of osteosarcoma in the general population is low, osteosarcoma is often associated with other types of malignant neoplasms that have a relative risk of 2.4 to 2.7 for developing a second malignancy. The association of 2 or more osteosarcomas could be considered an extreme example of this phenomenon. The question as to whether multiple foci of osteosarcoma represent independent tumors or metastases from a primary bone tumor has been debated for many years. Although the cause and pathogenesis of M-OGS are unknown, multiple theories have been proposed supporting the hypothesis of a true multiprimary pathologic entity or a mere metastatic disease.

Even though the imaging evaluation of tumors in this study has some limitations because of variability in the type and quality of examinations performed during the span of 10 decades, some distinguishing imaging features showed potential for differentiating synchronous and metachronous osteosarcoma. The majority of the lesions in patients with metachronous osteosarcoma demonstrated imaging features typical of a primary malignant sarcoma of bone. The imaging features typical of a primary osteosarcoma included an aggressive mixed lytic and sclerotic pattern of bone destruction with associated cortical destruction, soft tissue extension, a wide zone of transition, and malignant periosteal new bone formation. The majority also showed evidence of osteoid matrix, which further suggested the diagnosis of primary osteosarcoma. In contrast, the majority of lesions in patients with synchronous osteosarcoma had imaging features more suggestive of skeletal metastases. However, of interest, the majority of the patients with synchronous osteosarcoma had at least 1 lesion with features suggestive of a primary osteosarcoma, with the remaining lesions more suggestive of metastatic lesions. The latter lesions typically manifested as purely sclerotic and/or heavily mineralized lesions with a narrow transition zone and showed no evidence of cortical destruction, soft tissue mass, or malignant periosteal new bone formation. One of the patients with synchronous osteosarcoma had 2 lesions with imaging features suggestive of a primary osteosarcoma; however, the majority of the patients had additional lesions with imaging features suggestive of metastases.

The constellation of imaging findings in the 2 groups favors the hypothesis that many of the lesions in patients with synchronous osteosarcoma actually represent skeletal metastases from one of the lesions that likely represents a...
primary lesion. These findings agree with those of previous investigators. However, in our study, 1 patient in the S group with long-term survival had 3 lesions, 2 of which had imaging features more suggestive of primary osteosarcoma and 1 that had mixed features that could have represented a primary or secondary lesion. The lesions in this patient showed variable response to chemotherapy with 65% necrosis in 2 lesions and 100% necrosis in the third lesion. These findings mitigate against the hypothesis supported in previous series that synchronous osteosarcomas likely represent metastatic disease from an aggressive primary lesion because all lesions evaluated had a similar response to chemotherapy.

All of the tumors in this series were conventional osteosarcomas, a finding that coincides with previous reports on M-OGS. In this series, osteosarcomas with multifocal skeletal lesions had a poor prognosis, and patients with synchronous lesions had a worse outcome than patients whose secondary lesions developed at a later time. Kaplan-Meier analysis revealed that, after excluding the cases from the prechemotherapeutic era, survival was considerably shorter in patients with synchronous tumors than in patients with metachronous tumors (median, 14 vs 43 months; \( P = .001 \)). This result was still true when, in the M group, survival was calculated from the occurrence of the second malignancy (ie, when the process had become metachronous), in patients treated without chemotherapy, or after excluding from the comparison the 6 patients affected by genetic susceptibility (Huvos grading) were not available for all cases. In addition, 14 patients were first seen in the pre-CT and MR era and 42 after the advent of these diagnostic imaging modalities; thus, comparisons between these 2 groups should be interpreted cautiously since MR images and CT are more sensitive for the detection of osseous lesions and their visceral metastases. These modalities also provide superior lesion characterization and assessment of anatomic extent of disease. Moreover, this study was limited in its ability to accurately assess the anatomic distribution and extent of lesions in the 2 patient groups because of the variations in imaging studies available for each patient and each lesion.

In addition, owing to the known clinical dissemination of disease, some synchronous and metachronous occurrences were not biopsied and diagnosis was made only on the basis of the characteristic imaging features. Finally, the percentage of lesions with features more suggestive of metastatic lesions in the synchronous group was underestimated because of the inability to accurately count all lesions present in all bones. An accurate assessment of the symmetry and anatomic distribution would require a skeletal survey or whole-body bone scan in each patient.

In the present study, we analyzed the clinicopathologic and radiographic characteristics of a large series of patients affected by M-OGS that occurred simultaneously (synchronous cases) or sequentially (metachronous cases). The major findings of our investigation are as follows: (1) Multicentricity is a rare clinical manifestation of osteosarcoma. (2) Clinical findings and site of involvement between synchronous and metachronous osteosarcomas are not significantly different. (3) Histologically, synchronous and metachronous lesions are high-grade osteosarcomas. (4) Radiographically, the majority of patients with metachronous osteosarcoma have lesions with imaging features suggestive of primary osteosarcoma, whereas the majority of the lesions in patients with synchronous osteosarcoma show features more suggestive of metastatic disease. (5) In terms of overall survival, synchronous osteosarcomas behave more aggressively than do metachronous osteosarcomas. (6) Aggressive individualized treatment may result in long-term survival, particularly in patients with metachronous disease.

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