Secondary Osteosarcoma: Is There a Predilection for the Chondroblastic Subtype?

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abstract

Osteosarcoma is the most common form of primary bone cancer in the adolescent and young adult patient population. Outcomes in patients with secondary osteosarcoma are inferior compared with outcomes in patients with primary osteosarcoma. The goal of this study was to investigate whether there is a predilection for the chondroblastic histologic subtype in secondary osteosarcoma. A retrospective chart review was performed to identify cases of secondary osteosarcoma treated at 1 institution from 1991 to 2012. Histologic subtypes were evaluated by a pathologist, and a review of the literature was also performed to identify the histologic subclassification of additional series of secondary osteosarcomas. Of a total of 131 cases of osteosarcoma, 9 (6.9%) were identified as a secondary malignancy. Only 2 cases (22%) were identified as chondroblastic variants, although 6 (67%) showed some degree of chondroid differentiation. Of the 3 cases meeting the criteria for postradiation osteosarcoma, 2 (67%) were identified as chondroblastic variants and all 3 showed some degree of chondroid differentiation. Five other studies evaluating histologic subtypes in postradiation osteosarcoma showed a cumulative frequency of 20% for the chondroblastic variant. Although the study results did not support the hypothesis of an association between secondary osteosarcoma and the chondroblastic subtype, the high proportion of cases of postradiation osteosarcoma with the chondroblastic subtype and the even higher proportion showing some degree of chondroid differentiation are noteworthy features of this disease. [Orthopedics. 2015; 38(5):e359-e366.]
Osteosarcoma is the most common primary high-grade sarcoma of the bone.\textsuperscript{1,2} In approximately 10% of patients, osteosarcoma presents as a secondary malignancy, often in patients with cancer that was previously treated with radiation therapy or systemic chemotherapy, such as alkylating agents and/or anthracyclines.\textsuperscript{2-7} Secondary osteosarcoma is also associated with inheritable genetic disorders, such as retinoblastoma, Li-Fraumeni syndrome, and Rothmund-Thomson syndrome, and with benign bony lesions, including Paget disease, fibrous dysplasia, and giant cell tumor of bone.\textsuperscript{8-14}

Osteosarcoma is typically found in children and young adults, with more than 50% of cases occurring in patients 24 years and younger. Only 19% of cases of osteosarcoma are diagnosed in patients older than 60 years.\textsuperscript{2} Despite the large predilection of osteosarcoma for younger patients, secondary osteosarcoma is infrequent in this age group. Secondary osteosarcoma represents 46% of the cases seen in those older than 60 years, but only 20% of cases in children and young adults.\textsuperscript{2}

It is generally agreed that secondary osteosarcoma is associated with inferior outcomes compared with primary lesions.\textsuperscript{6} Proposed explanations for this observation include a greater histologic grade of malignancy; a higher incidence of secondary osteosarcoma arising in flat bones and the axial skeleton, leading to more difficult local control; older age at diagnosis; and the presence of pre-existing pathologic bone, such as Paget disease.\textsuperscript{5,15-20} Despite recent reports suggesting improved outcomes for secondary osteosarcoma in patients receiving intensive multimodal therapy combined with surgical resection with negative margins, the prognosis for secondary cases is inferior compared with that for de novo lesions.\textsuperscript{20-23} An additional explanation for the observed inferior outcomes associated with secondary osteosarcoma may be the histologic subtype of these tumors.

Various histologic variants of conventional osteosarcoma have been described. These include osteoblastic, chondroblastic, and fibroblastic, depending on the principal matrix. Other rare subtypes include telangiectatic and small cell osteosarcoma. Giant cell–rich, osteoblastoma-like, epithelioid, clear cell, and chondroblastoma-like osteosarcoma are rarer histologic patterns.\textsuperscript{24} The osteoblastic variant is the most common, representing 70% to 71% of cases of primary osteosarcoma, whereas chondroblastic, fibroblastic, and telangiectatic variants represent a smaller proportion of cases (10%-13%, 9%, and 6%, respectively).\textsuperscript{25,26} Although this finding is controversial, Bacci et al\textsuperscript{26} showed that overall survival in 718 patients with localized primary osteosarcoma was influenced by the histologic variant, with the lowest 5-year survival rate seen with the chondroblastic variant. Another study by Bacci et al\textsuperscript{27} of 789 patients with localized primary osteosarcoma showed that the rate of good response to chemotherapy was significantly lower in the chondroblastic variant compared with osteoblastic, fibroblastic, and telangiectatic tumors. A good histologic response to neoadjuvant chemotherapy (>90% tumor necrosis on microscopic examination) is a known predictor of survival in primary osteosarcoma.\textsuperscript{25,28} Because of the general rarity of secondary osteosarcoma, little analysis of histologic subtype has been done in these patients.\textsuperscript{5,20,29-31}

The goals of the current study were to query the authors’ local pediatric and adult pathology databases to identify all patients diagnosed with secondary osteosarcoma. The charts of all patients with a diagnosis of osteosarcoma between 1991 and 2012 were identified and reviewed. All patients identified with a diagnosis of osteosarcoma as a secondary malignancy were included. Secondary osteosarcoma was defined as occurring in the setting of a history of another malignancy, previous chemotherapy or radiation therapy, Paget disease of bone, fibrous dysplasia, and/or giant cell tumor of bone. In all identified cases of secondary osteosarcoma, histopathology was reviewed by a pediatric pathologist (A.R.P.) with a scholarly interest in pediatric sarcomas to confirm the diagnosis and assess the histologic subtype. Chi-square analysis was used to compare the proportion of chondroblastic histologic subtypes in primary vs secondary osteosarcoma.

A literature review was performed initially using the PubMed (MEDLINE) database with the MeSH search terms “osteosarcoma,” “radiation,” “radiation-induced,” and “secondary osteosarcoma.” Only English articles with human subjects were included. Additionally, the references of all articles identified in the PubMed search were further examined to ensure that all possible studies were identified. Only articles reporting the histologic subtype of secondary osteosarcoma were included in the final analysis. Case reports were not included.

**RESULTS**

In the authors’ local databases, a total of 131 cases of osteosarcoma were identified, 9 of which (6.9%) were identified as secondary osteosarcoma. Six patients were male, and 3 were female. Median age at diagnosis was 14 years. Of these 9 patients, 7 were 4 to 20 years and the remaining 2 were 65 to 71 years. Table 1 summarizes the cases of secondary osteosarcoma, including demographic data, oncologic details, and clinical outcomes.
The most common primary malignancy was bilateral retinoblastoma, which was seen in 5 of 9 patients (56%), all of whom received radiation therapy. Median latency time for these 5 patients (defined as the interval between treatment of primary malignancy and diagnosis of secondary osteosarcoma) was 10 years (range, 4–16 years). The histologic variants were osteoblastic in 4 cases (Figure 1) and telangiectatic in 1 case (Figure 2). Sites of secondary osteosarcoma included the humerus in 1 case, the lower extremity in 2 cases, and the periorbital region, within the field of irradiation, in 2 cases. Of the 4 patients who received neoadjuvant chemotherapy, 2 (50%) showed a good histologic response (defined as >90% tumor necrosis on microscopic examination). None of the 5 patients presented with lung metastases, but 4 of 5 (80%) had tumor recurrence at the last follow-up.

The remaining 4 cases of secondary osteosarcoma were observed in patients who did not have retinoblastoma, and all were treated with radiation therapy for other primary malignancies, including carcinoma of the breast, undifferentiated pleomorphic sarcoma (malignant fibrous histiocytoma) of the thigh, supratentorial neuroectodermal tumor of the thalamus, and neuroblastoma of the retroperitoneum. Median latency time was 11.5 years (range, 11–30 years). The histologic variant of osteosarcoma was chondroblastic in 2 cases (50%) (Figure 3) and osteoblastic in 2 cases (50%). Sites of secondary osteosarcoma included the sternocleidomas-roid muscle, distal femur, femur/tibia, and ilium. All but 1 of these cases of secondary osteosarcoma occurred in the radiation field. Chemotherapy was administered in 3 patients, and only 1 (33%) had a good histologic response. Of the 2 patients with the chondroblastic variant, 1 had greater than 95% necrosis and the other did not receive chemotherapy. Of these 4 patients, 2 (50%) presented with lung metastases.

Osteoblastic osteosarcoma was the most common histologic variant, representing 6 of 9 cases (67%); the chondroblastic variant was seen in 2 of 9 cases (22%), and the telangiectatic variant was seen in 1 of 9 cases (11%). No tumors in this study showed the fibroblastic variant. The proportion of cases of secondary osteosarcoma classifiable as the chondroblastic variant was not significantly different than that typically observed in primary osteosarcoma (P = .5). The chondroblastic variant was observed in 2 of 3 cases (67%) of true postradiation osteosarcoma (criteria initially defined by Cahan et al21) and was not seen in any secondary cases with a primary diagnosis of retinoblastoma. Additionally, of the 9 cases of secondary osteosarcoma, 6 (67%) showed some degree of chondroid differentiation on histologic analysis, although only 2 of these were classified as chondroblastic. All 3 cases of postradiation osteosarcoma showed varying degrees of chondroid differentiation, whereas only 2 of 5 cases (40%) of secondary osteosarcoma in patients with retinoblastoma showed chondroid differentiation.

Both patients with the chondroblastic variant of secondary osteosarcoma were alive at the last follow-up at 17 and 27 months. Of the 9 patients included in the study cohort, the overall survival rate was 44% at a median follow-up of 27 months. Unfortunately, because of the inadequate number of cases of secondary osteosarcoma, survival analysis correlating histologic subtype to event-free survival and overall survival was not feasible.

A review of the current literature on secondary osteosarcoma reporting histologic variants yielded 5 studies, including a total of 219 patients, as reported in Table 2.6,20,29,31 All 5 of these studies analyzed patients with postradiation osteosarcoma, excluding other types of secondary osteosarcoma and including those with a primary diagnosis of retinoblastoma. The fibroblastic variant was the most common in 3 reports,6,30,31 whereas the remaining 2 reports identified the osteoblastic variant as the most prevalent.20,29 The percent-

**DISCUSSION**

The primary goal of this study was to better gauge the role of chondroblastic histology in secondary osteosarcoma to further elucidate the poor outcomes associated with this disease. Only a small percentage of patients (22%) showed greater than 30% chondroid differentiation on histopathologic examination to be classified as having the chondroblastic variant,25 which was not supportive of the hypothesis. However, 4 additional patients (44%) showed 5% to 10% chondroid differentiation. Based on these observations, some degree of chondroid differentiation is a notable feature of secondary osteosarcoma. Furthermore, all 3 cases of postradiation osteosarcoma showed some degree of chondroid differentiation, including the 2 cases of bona fide chondroblastic osteosarcoma. To the authors’ knowledge, no study has reported the percentage of chondroid differentiation in secondary osteosarcoma, nullifying a thorough comparison of the current results and other reports.

The current study identified 9 patients with secondary osteosarcoma, including nearly 7% of the total local osteosarcoma registries. The demographic features observed in this study are similar to the finding that 10% of cases of osteosarcoma occurred as a secondary cancer as well as the finding of a 1.22:1 male-to-female ratio reported by Mirabello et al.2 Age distribution, however, is inversely represented compared with the current study, possibly because of the inclusion of patients with retinoblastoma.2 In studies of secondary osteosarcoma that included retinoblastoma as a primary lesion, the distribution of primary malignancies resembled the distribution in the current study.21,22
Table 1

<table>
<thead>
<tr>
<th>Case No./Age</th>
<th>Sex</th>
<th>Type</th>
<th>Site</th>
<th>Treatment</th>
<th>Latency</th>
<th>Age</th>
<th>Subtype</th>
<th>Histologic Necrosis</th>
<th>Neo-adjuvant</th>
<th>Adjuvant</th>
<th>Initial Surgery</th>
<th>Event-free Survival</th>
<th>Overall Survival</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/59 y</td>
<td>F</td>
<td>Carcinoma</td>
<td>Breast</td>
<td>RT, C, S</td>
<td>11 y</td>
<td>71 y</td>
<td>Chondroblastic, 70% chondroid differentiation</td>
<td>R neck</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>Incomplete resection</td>
<td>N/A</td>
<td>27 mo</td>
</tr>
<tr>
<td>2/M/35 y</td>
<td>M</td>
<td>Undifferentiated pleomorphic sarcoma (malignant fibrous histiocytoma)</td>
<td>R thigh</td>
<td>RT, S</td>
<td>30 y</td>
<td>65 y</td>
<td>Osteoblastic, 5% chondroid differentiation</td>
<td>R femur, tibia</td>
<td>Yes</td>
<td>Doxorubicin, cisplatin, methotrexate, ifosfamide, etoposide</td>
<td>Unknown</td>
<td>Resection</td>
<td>N/A</td>
<td>9 mo</td>
</tr>
<tr>
<td>3/M/3 mo</td>
<td>M</td>
<td>Neuroectodermal</td>
<td>Thalamus</td>
<td>RT, C</td>
<td>11 y</td>
<td>13 y</td>
<td>Osteoblastic, 10% chondroid differentiation</td>
<td>R femur</td>
<td>Yes</td>
<td>Doxorubicin, cisplatin, methotrexate</td>
<td>Doxorubicin, cisplatin, methotrexate, ifosfamide, etoposide</td>
<td>20%</td>
<td>Resection</td>
<td>N/A</td>
</tr>
<tr>
<td>4/F/22 mo</td>
<td>F</td>
<td>Neuroblastoma</td>
<td>R retroperitoneum</td>
<td>RT, C, S</td>
<td>12 y</td>
<td>14 y</td>
<td>Chondroblastic, 80% chondroid differentiation</td>
<td>R ilium</td>
<td>No</td>
<td>Doxorubicin, cisplatin, methotrexate</td>
<td>None</td>
<td>&gt;95%</td>
<td>Resection</td>
<td>9 mo</td>
</tr>
<tr>
<td>5/M/2 mo</td>
<td>M</td>
<td>Retinoblastoma</td>
<td>Bilateral eyes</td>
<td>RT, C, S</td>
<td>10 y</td>
<td>20 y</td>
<td>Osteoblastic, 0% chondroid differentiation</td>
<td>L femur</td>
<td>No</td>
<td>Doxorubicin, cisplatin, methotrexate</td>
<td>Doxorubicin, cisplatin, methotrexate</td>
<td>&gt;99%</td>
<td>Resection</td>
<td>13 mo</td>
</tr>
<tr>
<td>6/M/6 mo</td>
<td>M</td>
<td>Retinoblastoma</td>
<td>Bilateral eyes</td>
<td>RT, C, S</td>
<td>16 y</td>
<td>16 y</td>
<td>Telangiectatic, 0% chondroid differentiation</td>
<td>L humerus</td>
<td>No</td>
<td>Doxorubicin, cisplatin, methotrexate</td>
<td>Doxorubicin, cisplatin, methotrexate</td>
<td>97%</td>
<td>Resection</td>
<td>39 mo</td>
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Many recent studies of secondary osteosarcoma exclusively addressed postradiation osteosarcoma, excluding patients with retinoblastoma and other genetic conditions that independently increase the risk of secondary osteosarcoma.

Cahan et al originally proposed criteria for postradiation osteosarcoma that were subsequently modified by others: (1) the histologic features of the original lesion and the postradiation sarcoma should be completely different; (2) the postradiation sarcoma should be located within the field of irradiation; (3) patients with cancer syndromes, such as Li-Fraumeni syndrome or Rothmund-Thomson syndrome, should be excluded; and (4) the latent period should be greater than 3 to 5 years.

Only 3 of 9 (33%) of the patients in the current study met these criteria. In a review of the available literature, at least 5 authors commented on the histologic subtype of postradiation osteosarcoma. When the available 219 patients from these studies were pooled, the fibroblastic variant represented 37% of cases of postradiation osteosarcoma, the osteoblastic variant represented 33%, and the chondroblastic variant represented 20%.

In the current study population of 3 patients with postradiation osteosarcoma, 1 (33%) had the osteoblastic variant and 2 (67%) had the chondroblastic variant. Despite small study populations, these data may suggest a proportional difference of the chondroblastic variant.

Table 1 (cont'd)

<table>
<thead>
<tr>
<th>Case No./Sex/Age</th>
<th>Primary Malignancy</th>
<th>Secondary Osteosarcoma</th>
<th>Chemotherapy</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Treatment</td>
<td>Latency</td>
</tr>
<tr>
<td>7/M/9d</td>
<td>Retinoblastoma</td>
<td>Bilateral eyes</td>
<td>RT, C</td>
</tr>
<tr>
<td>8/F/4mo</td>
<td>Retinoblastoma</td>
<td>Bilateral eyes</td>
<td>RT</td>
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Abbreviations: AWD, alive with disease; C, chemotherapy; DOD, died of disease; L, left; N/A, not applicable; NED, no evidence of disease; R, right; RT, radiation therapy; S, surgery.

aOn presentation.
bFrom initial surgery to recurrence or death.
cFrom diagnosis to death or the last follow-up.

dCharacteristics and Outcomes of Patients With Secondary Osteosarcoma

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<td>RT</td>
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The chondroblastic variant of secondary osteosarcoma compared with primary osteosarcoma, in which the chondroblastic variant accounts for 10% to 13% of cases. Interestingly, some degree of chondroid differentiation was found in all 3 of the current patients with postradiation osteosarcoma, a variable not reported in any other study, to the authors’ knowledge. Multiple authors who specifically looked at postradiation osteosarcoma showed a 5-year event-free survival rate of 40% to 41% and a 5-year overall survival rate of 40% to 50%. In a study by Shaheen et al, patients with localized postradiation sarcoma of bone (including other bone sarcomas in addition to osteosarcoma) who were treated with chemotherapy and surgical resection showed a 5-year survival rate of 69%. The authors concluded that a combination of negative margins, complete surgical resection, and completion of multiagent chemotherapy can provide the outcomes associated with primary osteosarcoma in patients with secondary osteosarcoma. Of the 3 patients with postradiation osteosarcoma, the current study found an overall survival rate of 67% and an event-free survival rate of 0% at a median follow-up of 17 months. Koshy et al reported that the type of treatment had a significant effect on overall survival; those who had surgery and chemotherapy had a 5-year overall survival rate of 68.3% compared with those who had surgery alone (50.3%) or chemotherapy alone (17.3%). Of the 3 patients who had postradiation osteosarcoma, 2 (67%) underwent both surgery and chemotherapy, 1 of whom was alive with disease at 17 months, and 1 of 3 (33%) underwent only surgery and was alive with disease at 27 months.

Multiple authors showed the prognostic significance of a good histologic response to neoadjuvant chemotherapy (>90% tumor necrosis on microscopic examination) for survival in primary osteosarcoma. Patients with the chondroblastic variant showed a lower percentage of good response compared with other variants, although direct correlation between subtype and survival remains unclear. In contrast to primary lesions, Lewis et al found that the percentage of necrosis did not correlate with overall survival in postradiation osteosarcoma. Bacci et al reported a good response rate of 44% in postradiation osteosarcoma compared with 63% in primary osteosarcoma, although the finding was not statistically significant. Of the 2 patients in the current postradiation osteosarcoma cohort who received neoadjuvant chemotherapy, 1 (50%) had

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Secondary Osteosarcoma</th>
<th>No. of Patients</th>
<th>Osteoblastic</th>
<th>Fibroblastic</th>
<th>Chondroblastic</th>
<th>Telangiectatic</th>
<th>Other</th>
<th>Good Response to Chemotherapy</th>
<th>5-y Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huvos et al (1985)</td>
<td>Postradiation</td>
<td>6</td>
<td>66</td>
<td>18</td>
<td>45</td>
<td>3</td>
<td>21</td>
<td>17%</td>
<td>50%</td>
</tr>
<tr>
<td>Tabone et al (1999)</td>
<td>Postradiation</td>
<td>29</td>
<td>23</td>
<td>52</td>
<td>13</td>
<td>0</td>
<td>9</td>
<td>67%</td>
<td>50%</td>
</tr>
<tr>
<td>Inoue et al (2000)</td>
<td>Postradiation</td>
<td>30</td>
<td>83</td>
<td>34</td>
<td>52</td>
<td>0</td>
<td>0</td>
<td>31%</td>
<td>50%</td>
</tr>
<tr>
<td>Lewis et al (2006)</td>
<td>Postradiation</td>
<td>27</td>
<td>30</td>
<td>52</td>
<td>15</td>
<td>4</td>
<td>0</td>
<td>45%</td>
<td>26%</td>
</tr>
<tr>
<td>Bacci et al (2007)</td>
<td>Postradiation</td>
<td>20</td>
<td>65</td>
<td>10</td>
<td>10</td>
<td>15</td>
<td>0</td>
<td>15%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Figure 2: Pretreatment photomicrograph showing the classic histologic features of telangiectatic osteosarcoma. Thick septa surround empty cystic spaces. The septa are populated by pleomorphic cells with nuclear hyperchromasia. A rare osteoclast-type giant cell is present. Normal bone is seen in the lower right corner (Table 1, Case 6).

Figure 3: Photomicrograph of secondary chondroblastic osteosarcoma, with 80% of the matrix showing chondroblastic differentiation. Greater than 95% tumor necrosis is seen on this posttreatment resection. Scattered atypical, viable, and degenerating cells are seen within the lacunar spaces (Table 1, Case 4).
This study evaluated secondary osteosarcoma and its subtypes with a focus on the chondroblastic subtype. The authors found that secondary osteosarcoma, particularly the chondroblastic subtype, is associated with worse outcomes compared to primary osteosarcoma. The study also highlighted the importance of histologic analysis in determining the subtype of secondary osteosarcoma, as it can influence treatment decisions.

**Conclusion**

The results of this study suggest that histologic analysis is crucial in determining the subtype of secondary osteosarcoma, which can influence treatment outcomes. Further research is needed to validate these findings and to explore the potential benefits of targeted therapies for secondary osteosarcoma.

**References**


