Original Article

Second primary osteosarcomas in patients with retinoblastoma

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Abstract

Objective: Second primary malignancies have become the leading cause of death in retinoblastoma survivors. Although osteosarcoma is the most common second malignancy, little is known about its clinical and therapeutic features.

Methods: We retrospectively reviewed a database of patients with retinoblastoma and osteosarcoma occurring as a second malignancy between 1964 and 2010 at the National Cancer Center Hospital of Japan.

Results: Among 857 patients with retinoblastoma registered in the database, 10 (1.1%) developed osteosarcoma as a second malignancy. The median age at the onset of retinoblastoma was 3 months, being bilateral in nine patients and unilateral in one. Systemic chemoreduction was performed in three patients and intra-arterial chemotherapy in six; all patients received external beam radiotherapy. The median age at the onset of second primary osteosarcoma was 11.2 years; four were radiation-related and six were located in an extremity. Among five patients treated at our institute, four patients with tumors on an extremity were treated by wide resection with neoadjuvant and adjuvant chemotherapy. Three of these four patients (75%) were good responders to high-dose methotrexate-based multi-agent chemotherapy and survived with no evidence of disease (median follow-up period, 17.3 years). One patient whose temporal bone was affected underwent radiotherapy with chemotherapy but died after local recurrence.

Conclusions: The clinical outcomes of second primary osteosarcoma in an extremity occurring in retinoblastoma survivors may be more favorable than those of conventional osteosarcoma. Early diagnosis of radiation-related osteosarcoma arising in the craniofacial region should be made at a stage where complete resection is possible.

Key words: retinoblastoma, osteosarcoma, chemotherapy, radiotherapy, surgery
Introduction

Retinoblastoma is the most frequently occurring primary ocular malignancy in pediatric ages (1–3). The incidence of retinoblastoma is one per 15 000–20 000 live births worldwide, corresponding to ∼9000 new cases every year (1,2). Retinoblastoma can be hereditary (30–40%) or non-hereditary (60–70%) (3–5). Patients with a positive family history and/or bilateral retinoblastoma are carriers of a germ-line mutation of the RBP1 gene and are classified as having hereditary retinoblastoma (4,5), whereas those with unilateral retinoblastoma and no family history are generally classified as non-hereditary (4,5). Notably, patients with second primary osteosarcoma following unilateral retinoblastoma, whose age at the onset of retinoblastoma is much younger than that of patients with unilateral forms, are considered to be heterozygous carriers of an RBP1 mutation, even those without a family history (6).

A century ago, retinoblastoma was almost uniformly fatal. However, in recent years early diagnosis and treatment have greatly improved the survival rates and quality of vision of affected patients (7,8). In fact, cure rates of >90% have been achieved in developed countries (7). Consequently, second malignancies now represent the primary cause of death in retinoblastoma survivors (8,9). Bone sarcomas are among the most common second primary neoplasms occurring in retinoblastoma survivors, and their cumulative incidence following retinoblastoma has been estimated to be 7% at 20 years of age (3,10). The most common type of second bone malignancy is osteosarcoma, and both chondrosarcoma and Ewing sarcoma have also been reported in this context (3,5).

Osteosarcoma is the most common primary bone malignancy in children, adolescents and young adults (11). It has a bimodal age distribution, most cases developing between 10 and 14 years of age, with a second smaller peak in older adults (30% in individuals >40 years of age) (12). Primary osteosarcoma can arise from any bone, but it mostly affects the long bones of the extremities, particularly the distal femur (30%), followed by the proximal tibia (15%) and proximal humerus (15%) (12). In the present study, we reviewed the clinical and therapeutic features of second primary osteosarcoma after retinoblastoma in patients diagnosed or treated at the ophthalmologic or orthopedic division of the National Cancer Center Hospital (NCCH) of Japan.

Patients and methods

Enrollment

We conducted a retrospective review of the medical records of 857 patients with retinoblastoma diagnosed or treated at the NCCH between 1964 and 2010. The records of 10 patients who developed primary osteosarcoma as a second malignancy, five of whom were treated for osteosarcoma at the NCCH, were reviewed in detail. Data were collected on the basic diagnostic characteristics of retinoblastoma (age, sex, laterality, family history and metastasis at initial diagnosis) and second primary osteosarcoma (age, location and interval from retinoblastoma diagnosis) as well as on treatments and the clinical course for each (local treatments, focal chemotherapy, systemic chemotherapy, radiation therapy, surgery, chemotherapy response and oncologic outcomes).

Treatment for retinoblastoma

Enucleation was performed for high-risk eyes with tumor spread or symptomatic signs. Eye preservation by chemotherapy, focal therapy or radiation therapy was conducted for other cases. In the 1990s, external beam radiation therapy (EBRT) was performed as an initial treatment, followed by local consolidation, including laser or ophthalmic arterial injection therapy for any residual or recurrent tumors. Starting in 2001, the NCCH adopted systemic chemoreduction combined with aggressive local consolidation, and in cases resistant to these treatments, EBRT was added. Enucleation was eventually performed for resistant cases or those with severe symptoms. Histopathological examination of enucleated eyes was performed to determine whether adjuvant chemotherapy should be added. For recurrent cases, high-dose chemotherapy with autologous stem cell transplantation or EBRT was added.

Treatment for osteosarcoma

The basic treatment strategy used at the NCCH for osteosarcoma consists of wide excision of the tumor with pre-operative (neo-adjuvant) and post-operative (adjuvant) combination chemotherapy. Chemotherapy regimens were based on the Neo-adjuvant Chemotherapy for Osteosarcoma (NECO)-93/95J protocol between 1992 and 2002 (Case 7), the NCCH 2003 protocol between 2003 and 2007 (Case 8) and the Japan Clinical Oncology Group (JCOG) 0905 protocol since 2008 (Cases 9 and 10). According to each protocol (18), we administered neo-adjuvant and adjuvant chemotherapy consisting of adriamycin (ADM), cisplatin (CDDP) and high-dose methotrexate (HD-MTX) or ifosfamide. After neo-adjuvant chemotherapy, tumors were resected and assessed histologically for necrosis. We attempted wide resection of primary tumors to achieve a negative surgical margin whenever possible and used an endoprostheses or spacer prosthesis after tumor resection. For the case affecting the temporal bone (Case 1), we administered chemotherapy based on the MAP regimen (HD-MTX, ADM and CDDP), followed by radiation therapy at a dose of 60 Gy because the tumor could not be completely resected.

Assessment of tumor- and treatment-related variables

The clinical response of the primary tumor to chemotherapy based on magnetic resonance (MR) imaging, computed tomography (CT) and/or plain radiography findings was defined as follows: complete response, total disappearance of the tumor; partial response, a decrease in the diameter of the extramedullary lesion or induction of sclerotic change in the intramedullary lesion; no change, no change in the diameter of the extramedullary lesion and appearance of an intramedullary lesion; or progressive disease, an increase in the diameter of extramedullary and/or intramedullary lesions or appearance of a new lesion (18).

The pathological response was evaluated by the examination of resected tumors according to the Huvos grading system: Grade 4 (complete response), total necrosis of the tumor; Grade 3 (partial response), ≥90% necrosis of the tumor; Grade 2 (minor response), ≥50% but <90% necrosis of the tumor; Grade 1 (no response), <50% necrosis of the tumor (19).

Results

Clinical features at the onset of retinoblastoma and osteosarcoma

Among the 857 patients with retinoblastoma, 10 (1.1%) developed osteosarcoma as a second malignancy. The overall clinical features of each case are summarized in Table 1. The age at retinoblastoma diagn...
diagnosis ranged from 1 month to 1 year and 8 months (median, 3 months). Nine patients presented with bilateral retinoblastoma and one with unilateral retinoblastoma. A family history of retinoblastoma was present in two patients with bilateral retinoblastoma. The age at the onset of one unilateral patient without a family history was 3 months, considerably younger than other unilateral patients without second malignancies. No patients had metastatic spread at the time of initial diagnosis.

The age at which the primary osteosarcoma was diagnosed as a second malignancy ranged from 7 years and 2 months to 25 years and 1 month (median, 11 years and 2 months). The latent period from the diagnosis of retinoblastoma until the diagnosis of second primary osteosarcoma ranged from 7 years to 24 years and 1 month (median, 11 years 2 months and 3 months). The second primary osteosarcoma was located in the distal femur in three patients, the proximal tibia in three, the orbit in two, the temporal bone in one, and the skull base in one. Four patients developed second primary osteosarcoma within the radiation field.

**Retinoblastoma treatment and clinical course**

The overall treatments for retinoblastoma are summarized in Table 2. Chemotherapy for primary retinoblastoma was administered to seven patients. Systemic chemoreduction using multi-agent chemotherapy was administered to three patients, and arterial infusion chemotherapy using melphalan was administered to six patients. EBRT was administered to all patients at doses of 39–50 Gy. Plaque radiotherapy was combined with EBRT in two patients, and one patient underwent additional irradiation (total dose, 46 + 50 Gy) for local recurrence. Distant metastasis developed in the parietal lesion in one patient. None of the patients died from retinoblastoma.

**Osteosarcoma treatment and clinical course**

Among 10 patients diagnosed with second primary osteosarcoma, five were treated at our institution, whereas the other five were managed at other institutions (Table 3). Systemic chemotherapy was administered to all five patients treated at the NCCH. Surgical wide excision was performed for the four patients with affected extremities (Cases 7–10). The histological response of tumors to neoadjuvant chemotherapy according to the Huvos classification was Grade 4 (100% necrosis) in two patients (Cases 9 and 10; Fig. 1), Grade 3 in one (99% necrosis; Case 7) and Grade 1 in one (20% necrosis; Case 8). The tumor affecting the temporal bone in Case 1 was unresectable and was managed with regional radiation therapy (60 Gy). In this case, the response to systemic chemotherapy according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria was partial, and stable disease was maintained for 1.5 years until local recurrence developed (Fig. 2). However, the patient died of their disease because of rapid tumor growth after local recurrence. Three of the other four patients (75%) survived with no evidence of osteosarcoma (median follow-up period, 17.3 years).

**Discussion**

Improvements in diagnosis and treatment for retinoblastoma have allowed most patients to survive their ocular cancer (8). As a result, second malignant neoplasms have become the major cause of death in retinoblastoma survivors (8,9), with osteosarcoma being the most common second malignancy. Although the risk factors for second primary osteosarcoma have been well characterized (10,16,20), little is known about its clinical and therapeutic characteristics. Here, we reviewed the clinical features of osteosarcoma as a second malignant neoplasm of retinoblastoma. The review of patient records showed that HD-MTX-based multi-agent chemotherapy provided a good tumor response and, with wide tumor resection, it contributed to a good oncologic outcome. The clinical outcomes for second primary osteosarcoma of an extremity occurring in retinoblastoma survivors may be more favorable than those for conventional osteosarcoma.

In patients with hereditary retinoblastoma, a genetic predisposition is an important risk factor for the development of second malignancies (16,20). Previous reports have revealed that the incidence of osteosarcoma after heritable retinoblastoma is 300 times greater than that in the general population (24). In our series, all patients might be genetically predisposed and possess a risk for second primary osteosarcoma. In total, 9 of the 10 patients (90%) had bilateral retinoblastoma, and one had the unilateral form. Bilaterality has been shown to be a characteristic of retinoblastoma with a germline mutation, even in the absence of a family history (6,25). The age at the onset of our unilateral case (Case 10) was 3 months, which was considerably younger than that of unilateral forms in general (average, 24 months).
The age at the onset of unilateral retinoblastoma in our series was similar to that reported by Chauveinc et al. (6); they found that among 125 retinoblastoma survivors who subsequently developed osteosarcoma, the mean age at the onset of the unilateral form in 17 cases (14%) was at 12.3 months. Because the mean age at diagnosis of these patients was similar to that in published data on predisposed patients in general, although the mean age of non-predisposed patients was ∼24 months older (6,26), Chauveinc et al. (6) considered that a large proportion of unilateral retinoblastomas in their study appeared to have occurred in predisposed patients. Indeed, we have performed genetic counseling and gene testing for retinoblastoma (27). Germline mutations of the \( RB1 \) gene were detected in 100% (15/15) of patients with bilateral/familial retinoblastoma and in 98% (37/39) of patients with bilateral/nonfamilial retinoblastoma. On the other hand, these mutations were detected in 67% (4/6) of patients with unilateral/familial retinoblastoma and in 11% (3/28) of patients with unilateral/nonfamilial retinoblastoma. Interestingly, the disease onset of all patients with unilateral/nonfamilial retinoblastoma, whose germline \( RB1 \) mutations were detected, was younger than 12 months (27). These data also support the possibility of a genetic predisposition in unilateral retinoblastoma patients with early onset. According to these data, both our bilateral cases and our unilateral case are likely to be heterozygous carriers of an \( RB1 \) mutation (6,28,29).

Radiation therapy for retinoblastoma is another risk factor for the development of second malignancies (6,10,17,21,23,30). In this study, four patients who developed radiation-induced second primary osteosarcoma were bilateral retinoblastoma survivors, highly likely to be heterozygous carriers of an \( RB1 \) mutation (6,28,29).

Table 2. Treatment for retinoblastoma

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Enucleation</th>
<th>Chemotherapy</th>
<th>Arterial infusion chemotherapy</th>
<th>Radiation therapy</th>
<th>Metastasis</th>
<th>Onset of OS inside/outside RT field</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R, L</td>
<td></td>
<td></td>
<td>EBRT 49 Gy (R, L)</td>
<td>Inside</td>
<td>Inside</td>
</tr>
<tr>
<td>2</td>
<td>R</td>
<td>Melphalan (L)</td>
<td></td>
<td>EBRT (L)</td>
<td>Inside</td>
<td>Inside</td>
</tr>
<tr>
<td>3</td>
<td>R</td>
<td>Melphalan (L)</td>
<td>Plaque radiotherapy (L)</td>
<td>EBRT 50 Gy (R, L)</td>
<td>Inside</td>
<td>Inside</td>
</tr>
<tr>
<td>4</td>
<td>R</td>
<td>Melphalan (L)</td>
<td>EBRT 46 Gy (L)</td>
<td>EBRT 45 Gy (R)</td>
<td>Outside</td>
<td>Outside</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Melphalan (R, L)</td>
<td>Plaque radiotherapy (Co) (R)</td>
<td>EBRT 46 Gy (R, L)</td>
<td>Parietal region Outside</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>R, L</td>
<td>VCR, CY, THP, VP-16, CDDP, CPA, ADM</td>
<td>Melphalan (R, L)</td>
<td>EBRT 46 Gy (R, L)</td>
<td>Inside</td>
<td>Inside</td>
</tr>
<tr>
<td>7</td>
<td>R, L</td>
<td>VCR, CY, THP, IFM, VP16, CBDCA, VCA</td>
<td>Melphalan (R, L)</td>
<td>EBRT 39 Gy (R, L)</td>
<td>Outside</td>
<td>Outside</td>
</tr>
<tr>
<td>8</td>
<td>R, L</td>
<td>VCR, CY, THP, IFM, VP16, CBDCA, VCA</td>
<td>Melphalan (R, L)</td>
<td>EBRT 46 Gy + 50 Gy (R, L)</td>
<td>Outside</td>
<td>Outside</td>
</tr>
<tr>
<td>9</td>
<td>R</td>
<td>VCR, VP-16, CBDCA, CDDP, CY, THP, HiMEC (PBCST)</td>
<td>EBRT 50 Gy (R, L)</td>
<td>Outside</td>
<td>Outside</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>R</td>
<td>Melphalan (R)</td>
<td>EBRT 46 Gy (R)</td>
<td></td>
<td>Outside</td>
<td>Outside</td>
</tr>
</tbody>
</table>

VCR, vincristine; CY, cyclophosphamide; THP, tetrahydroxypyranyl adriamycin; IFM, ifosfamide; VP16, etoposide; CBDCA, carboplatin; ADM, adriamycin; HiMEC, melphalan + etoposide + carboplatin; PBST, peripheral blood stem cell transplantation; EBRT, extra beam radiation therapy; Co, cobalt; OS, osteosarcoma.

Table 3. Treatment for second primary osteosarcoma

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Site</th>
<th>Surgery</th>
<th>Chemotherapy</th>
<th>Radiation therapy</th>
<th>Response to chemotherapy</th>
<th>Local recurrence</th>
<th>Metastasis</th>
<th>Age at final follow-up (years/months)</th>
<th>Oncologic outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Temporal bone</td>
<td>MAP</td>
<td>AP</td>
<td>60 Gy</td>
<td>PR</td>
<td>+</td>
<td>–</td>
<td>27 years 6 months</td>
<td>DOD</td>
</tr>
<tr>
<td>7</td>
<td>Femur</td>
<td>Wide resection</td>
<td>MAP</td>
<td>MAP</td>
<td>Grade 3 (99% necrosis)</td>
<td>+</td>
<td>Humerus, pelvis</td>
<td>14 years 8 months</td>
<td>DOD</td>
</tr>
<tr>
<td>8</td>
<td>Tibia</td>
<td>Wide resection</td>
<td>I + AP</td>
<td>I + MA</td>
<td>Grade 1</td>
<td>–</td>
<td>–</td>
<td>19 years 5 months</td>
<td>NED</td>
</tr>
<tr>
<td>9</td>
<td>Tibia</td>
<td>Wide resection</td>
<td>MAP</td>
<td>MAP</td>
<td>Grade 4</td>
<td>–</td>
<td>–</td>
<td>16 years 10 months</td>
<td>NED</td>
</tr>
<tr>
<td>10</td>
<td>Femur</td>
<td>Wide resection</td>
<td>MAP</td>
<td>MAP</td>
<td>Grade 4</td>
<td>–</td>
<td>–</td>
<td>17 years 9 months</td>
<td>NED</td>
</tr>
</tbody>
</table>

M, methotrexate; A, adriamycin; P, cisplatin; I, ifosfamide; PR, partial response; DOD, dead of disease; NED, no evidence of disease.
registry data in Japan indicated the oncologic risks of radiation. Among 1252 osteosarcoma patients registered between 2006 and 2012, 991 patients (79.1%) had tumors on an extremity, whereas 23 patients (1.84%) had craniofacial tumors (31). Because 40% of the patients in this cohort developed craniofacial osteosarcoma after EBRT, this discrepancy in incidence rates supports the relevance of...
the onset of the second primary osteosarcoma and the genotoxicity of radiation. Indeed, the excess risk of radiotherapy-associated second bone malignancies in patients with bilateral retinoblastoma was estimated at 36.7 compared with 2.7 in patients without the congenital condition (23). This implies an interaction between a pre-existing genetic predisposition and the genotoxicity of radiation in the process of osteosarcoma development. In fact, genetic mapping in mice showed that multiple loci confer a genetic susceptibility to radiation-induced osteosarcoma (32), and RB1-heterozygous mice have an increased risk of radiation-induced osteosarcoma (33,34). Wong et al. (23) reported that the risk for the development of bone and soft tissue sarcoma was evident at radiation doses ≥5 Gy, the risk being 1.9-fold at 5–9.9 Gy, 3.7-fold at 10–29.9 Gy, 4.5-fold at 30–59.9 Gy and 10.7-fold at ≥60 Gy. Four patients with radiation-induced osteosarcoma in this study received EBRT at doses of ≥50 Gy as an initial therapy before 2000, which was considered to have increased the risk of second malignancies. Considering this risk associated with radiation therapy, the NCCH adopted our current treatment protocol in 2001: systemic chemoreduction as an initial therapy, additional local therapy (e.g., intra-arterial chemotherapy) as required, and EBRT limited to resistant or recurrent cases. In the cases treated with EBRT, a dose of 46 Gy was irradiated, which is considered to be within the ocular tolerance for radiation therapy (35). Subsequently, between 2001 and 2010, a total of 90 of 483 patients (18.6%) were treated by EBRT according to this protocol. To date, no patients have developed radiation-induced osteosarcomas, although further follow-up is needed.

Chemotherapy containing alkylating agents alone or in combination with radiotherapy might be another risk factor (10,16,21,22). In our series, six patients received selective ophthalmic arterial injection therapy with the alkylating agent melphalan, and all patients underwent EBRT. Indeed, our previous study showed that the incidence of second malignancies appeared to be largely associated with radiotherapy and that systemic chemotherapy or selective ophthalmic arterial injection therapy did not increase the incidence of second malignancies (36). Another investigation focusing on the risk factors for the development of second malignancies found that focal and systemic chemotherapy was not a significant risk factor (37).

Because the response of osteosarcoma to chemotherapy is one of the most important factors affecting prognosis (38), the chemosensitivity of second primary osteosarcoma is a clinically important issue. Biellack et al. (39) reported that, among 1320 conventional osteosarcomas resected after primary chemotherapy for which information on response was available, a good response was achieved in 734 (55.6%) tumors, and <10% were viable. Bacci et al. (38) investigated a group of 789 patients with conventional osteosarcoma treated at a single institution and stated that, among patients for whom information on histological response was available, 49% (63%) patients were good responders and 286 (37%) were poor responders. On the other hand, Aerts et al. (16) from the Institut Curie reported that the tumor response to pre-operative chemotherapy (including MTX, ADM, IFM and etoposide) was good in five of six patients (83%) with second primary osteosarcoma after retinoblastoma. Our current data revealed that HD-MTX-based multi-agent chemotherapy was effective for three (75%) of four patients who were evaluated for tumor response to chemotherapy. These data indicated that multi-agent chemotherapy, including HD-MTX, CDDP and ADM, may be more effective for second primary osteosarcoma after retinoblastoma than for conventional osteosarcoma.

In the present study, three of four patients with a second primary osteosarcoma in an extremity survived with no evidence of disease, which indicated that the 5-year overall survival rate for these patients was 75%. On the other hand, the 5-year overall survival rate for conventional osteosarcoma has been reported as 60–70% (40). Bacci et al. (38) reported that the 5-year overall survival rate for patients with conventional osteosarcoma in an extremity was 67.5%. Cho et al. (41) indicated that the 5-year and 10-year overall survival rates in patients with Stage IIB osteosarcoma were 60.2% and 44.8%, respectively. Therefore, the results of the present study indicated that clinical outcomes for second primary osteosarcoma in retinoblastoma survivors may be more favorable than those for conventional osteosarcoma. Notably, Case 1, the patient with temporal bone osteosarcoma, died of disease despite aggressive management with multi-agent chemotherapy and radiotherapy, suggesting that second primary osteosarcomas affecting sites other than the limbs have a poorer prognosis, largely because of the limitations to wide excision of these tumors. A recent report suggested that a better prognosis could be expected if complete surgical resection is possible. In a retrospective study of 44 second or third malignancies after hereditary retinoblastoma from the European Retinoblastoma Imaging Collaboration by Rodjan et al. (42), microscopically complete surgical resection of craniofacial malignancies, including 19 cases (43%) of osteosarcoma, was a major prognostic factor. They confirmed significantly better 5-year overall (83%) and event-free survival (80%) rates in patients who had undergone tumor resection with a microscopically negative margin, whereas the corresponding rates were 52 and 47% in patients with incomplete resection (42). Therefore, an early diagnosis of second primary osteosarcoma in the craniofacial region is important to ensure complete resection. Overall, our retrospective study demonstrates that a better prognosis can be expected with complete surgical resection in conjunction with multi-agent chemotherapy, even in patients with second primary osteosarcoma after retinoblastoma.

Conclusions
The clinical outcomes of second primary osteosarcoma of an extremity occurring in retinoblastoma survivors may be more favorable than those for conventional osteosarcoma. Careful and long-term follow-up is necessary for patients with retinoblastoma, and it is important to educate parents of children who need to rapidly seek medical advice for any pain or abnormalities in the head, face, or extremities to ensure an early diagnosis of second primary malignancies.

Author contributions
T.F., M.F. and K.N. collected the data, and T.F. drafted the manuscript. K.O., A.Y., T.Y., S.S. and A.K. helped to collect the data. All authors have read and approved the final manuscript.

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Conflict of interest statement
None declared.