Understanding Sex Differences in Musculoskeletal Oncology

Considerations for prognosis and treatment of primary bone tumors

JOHN H. HEALEY, MD, FACS

Sex-dependent differences in the incidence, etiology, and treatment of musculoskeletal tumors rarely receive adequate attention in clinical study protocols and have yet to be fully investigated. Due to their low incidence, primary bone tumors are infrequently encountered in a general orthopaedic surgical practice, so opportunities for firsthand observations of these differences are limited. However, cultivating a greater awareness of the sexual dimorphism in the genetics, metabolism, and epidemiology of these lesions can facilitate the use of more efficient diagnostic practices and more effective treatment strategies for patients who have these tumors.

Mechanisms that contribute to the sexual dimorphism of musculoskeletal tumors depend on both hormonal and genetic factors governing bone mineralization and remodeling. Differences in cellular response to estrogen and testosterone have been shown for male and female chondrocytes and osteoblasts. Several genes on the X chromosome influence bone mineralization, and patterns of age-related decreases in mineralization differ by sex, with a lower level of mineralization in postmenopausal women.

Hormonal differences in bone development at the cellular and molecular levels result in sexual dimorphism in the presentation of musculoskeletal neoplasms. For example, osteogenic sarcoma develops, on average, 2 years earlier in girls than in boys. New data suggest that relative levels of estrogen receptor (ER) variants ER-alpha and ER-beta have important clinical implications. Greater ER-alpha expression correlates with the absence of metastases at presentation and better event-free survival. ER-beta expression appears to be more frequent in males. Interestingly, ER-beta expression is also a feature of extra-abdominal fibromatoses (desmoid tumor), which is more prevalent in female patients and has been responsive to adjuvant anti-estrogen therapy.

Prevalence
Statistics from the Surveillance, Epidemiology, and End Results (SEER) cancer registry show that most common primary bone tumors are more prevalent in males than in females, with a male-to-female ratio of more than 2 to 1 for osteoid osteoma and osteoblastoma (Table 1). Giant cell tumors are exceptions, with a female-to-male ratio of almost 2 to 1.

Genetic factors play an important role. For example, ring chromosomes are almost universally found in surface osteosarcomas, suggesting that females are more disposed to the development of ring chromosomes. Additionally, environmental carcinogens may exert their effects on males and females in a differential fashion, as seen in data on radiation effects and the carcinogenic potential of fluoride exposure.

Efficacy and toxicity of chemotherapy
Sex-linked differences in musculoskeletal oncology are also evident in the response to chemotherapy treatment. An analysis of patients with high-grade osteoblastoma of the trunk or limbs who were treated with surgery and chemotherapy found that females responded better to chemotherapy than males. This translated into superior outcomes for females, as can be seen in the probability of 10-year event-free survival (51 percent for females compared with 48 percent for males). Similar results have been reported for soft-tissue sarcomas.

Unfortunately, the increased efficacy of certain chemotherapeutic agents in female patients may be accompanied by a simultaneous increase in complications or the severity of complications, such as those seen with methotrexate, doxorubicin, and fluoropyrimidines.

Drug metabolism and pharmacokinetics differ by sex and influence severity of adverse effects. For instance, there is greater toxicity in females who undergo isolated-limb perfusion for soft-tissue sarcoma than in males (22 percent compared with 7 percent). Increased rates of infertility have also been observed after chemotherapy, so clinicians should consider reproductive issues when selecting an appropriate agent for female patients.

Quality of life
Female sex can confer a distinct advantage in clinical outcomes after treatment for primary bone tumors. Five-year survival among patients with osteosarcoma, fibrosarcoma, and desmoid tumors was significantly higher in females. Females may have a better therapeutic regimens for female patients.

Putting sex in your orthopaedic practice

This quarterly column from the AAOS Women’s Health Issues Advisory Board and the Ruth Jackson Orthopaedic Society provides important information for your practice about issues related to sex (determined by our chromosomes) and gender (how we present ourselves as male or female, which can be influenced by environment, families and peers, and social institutions). It is our mission to promote the philosophy that male and female patients experience and react to musculoskeletal conditions differently; when it comes to patient care, surgeons should not have a one-size-fits-all mentality.

Top Line
- Giant cell tumor, parosteal/surface osteogenic sarcoma, and extra-abdominal fibromatoses (desmoid tumor) are more prevalent in females; most other primary musculoskeletal tumors are more prevalent in males.
- Females may have a better response to select chemotherapeutic agents (eg, doxorubicin, methotrexate), but this is accompanied by greater toxicity.
- Sex-linked biologic differences likely account for different chemotherapeutic responses between women and men, as survival rates for Ewing’s tumors and osteogenic sarcoma have been persistently higher for females.
- Adverse effects on the reproductive system should be taken into account when choosing chemotherapeutic regimens for female patients.
- Post-treatment QOL priorities may differ between female and male patients and should be considered in long-term management.

Table 1: Sex distribution of common bone tumors, number of cases (1973-1999)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Female</th>
<th>Male</th>
<th>Diagnosis</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteochondroma</td>
<td>325</td>
<td>547</td>
<td>Chondrosarcoma</td>
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<td>Osteoid osteoma</td>
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<td>245</td>
<td>Osteogenic sarcoma (OGS)</td>
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<td>Chondroblastoma</td>
<td>47</td>
<td>72</td>
<td>Ewing’s family tumor</td>
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<td>303</td>
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<tr>
<td>Osteoblastoma</td>
<td>24</td>
<td>63</td>
<td>Chordoma</td>
<td>128</td>
<td>228</td>
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<tr>
<td>Chondromyroid fibroma</td>
<td>17</td>
<td>28</td>
<td>Parosteal/perioskeletal OGS</td>
<td>60</td>
<td>35</td>
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<tr>
<td>Giant cell tumor</td>
<td>319</td>
<td>249</td>
<td>Paget’s sarcoma</td>
<td>21</td>
<td>44</td>
</tr>
</tbody>
</table>

Source: Surveillance, Epidemiology, and End Results (SEER) cancer registry, National Cancer Institute.

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