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Daniel A. Erman, MD, Victoria V. Noble, Haliz M. Fazaeli, MD, Brittany Thomas, Peter T. Silverstein, MD

EDITORIAL
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Sarcoma Foundation of America

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WORLD SARCOMA
From the journals: sarcoma around the world

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Offer your patients with advanced liposarcoma a treatment that provides a **SIGNIFICANT OVERALL SURVIVAL BENEFIT**

HALAVEN® improved median overall survival vs dacarbazine (15.6 months vs 8.4 months)¹

**Indication**

Liposarcoma

HALAVEN (eribulin mesylate) Injection is indicated for the treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen.

**Selected Safety Information**

**Warnings and Precautions**

**Neutropenia:** Severe neutropenia (ANC <500/mm³) lasting >1 week occurred in 12% of patients with liposarcoma or leiomyosarcoma. Febrile neutropenia occurred in 0.9% of patients and fatal neutropenic sepsis occurred in 0.9% of patients. Monitor complete blood cell counts prior to each dose, and increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. Delay administration and reduce subsequent doses in patients who experience febrile neutropenia or Grade 4 neutropenia lasting >7 days.

Please see all Selected Safety Information throughout and adjacent brief summary of HALAVEN full Prescribing Information.
The first and only single agent to show a significant survival advantage in a Phase III study of patients with advanced liposarcoma.

The efficacy and safety of HALAVEN were evaluated in an open-label, randomized (1:1), multicenter, active-controlled trial. Eligible patients were required to have unresectable, locally advanced, or metastatic liposarcoma or leiomyosarcoma, at least 2 prior systemic chemotherapies (one of which must have included an anthracycline), and disease progression within 6 months of the most recent chemotherapy regimen. Patients were randomized to HALAVEN 1.4 mg/m² administered intravenously on Days 1 and 8 of a 21-day cycle or to dacarbazine at a dose of 650 mg/m², 1,000 mg/m², or 1,200 mg/m² administered intravenously every 21 days (dacarbazine dose was selected by the investigator prior to randomization). Treatment continued until disease progression or unacceptable toxicity. Randomization was stratified by histology (liposarcoma or leiomyosarcoma), number of prior therapies (2 vs ≥3), and geographic region. The most common (>40%) prior systemic chemotherapies were doxorubicin (96%), ifosfamide (62%), gemcitabine (59%), trabectedin (50%), and docetaxel (48%).

OS=overall survival; CI=confidence interval.

HALAVEN was studied in patients with dedifferentiated, myxoid/round cell, and pleomorphic liposarcoma subtypes.

Selected Safety Information

Peripheral Neuropathy: Grade 3 peripheral neuropathy occurred in 3.1% of patients with liposarcoma and leiomyosarcoma receiving HALAVEN and neuropathy lasting more than 60 days occurred in 58% (38/65) of patients who had neuropathy at the last treatment visit. Patients should be monitored for signs of peripheral motor and sensory neuropathy. Withhold HALAVEN in patients who experience Grade 3 or 4 peripheral neuropathy until resolution to Grade 2 or less.
Treatment effects of HALAVEN® were demonstrated in patients with advanced liposarcoma based on the preplanned, exploratory subgroup analysis of OS and PFS¹

**MEDIAN OS FOR HALAVEN AND DACARBAZINE:**

<table>
<thead>
<tr>
<th></th>
<th>LIPOSARCOMA STRATUM AND ALL PATIENTS¹,²,³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR=0.31 (95% CI: 2.35, 0.79)</td>
</tr>
<tr>
<td><strong>Halaven</strong></td>
<td>15.6 (10.2, 18.6) n=71</td>
</tr>
<tr>
<td><strong>DACARBAZINE</strong></td>
<td>8.4 (5.2, 10.1) n=72</td>
</tr>
<tr>
<td></td>
<td>HR=0.75 (95% CI: 2.51, 0.94), P=0.011</td>
</tr>
<tr>
<td></td>
<td>13.5 (11.1, 16.9) n=225</td>
</tr>
<tr>
<td></td>
<td>11.3 (8.5, 12.6) n=221</td>
</tr>
</tbody>
</table>

¹PFS=progression-free survival; HR=hazard ratio.
²Efficacy data from 1 study site enrolling 6 patients were excluded.
³All patients=liposarcoma and leiomyosarcoma.

There was no evidence of efficacy of HALAVEN in patients with advanced or metastatic leiomyosarcoma in this trial¹

**Secondary endpoint: PFS¹**

- Median PFS in the liposarcoma stratum was 2.9 months (95% CI: 2.6, 4.8) for patients receiving HALAVEN vs 1.7 months (95% CI: 1.4, 2.6) for patients receiving dacarbazine, HR=0.52 (95% CI: 0.35, 0.78)
- Median PFS in all patients was 2.6 months (95% CI: 2.0, 2.8) for patients receiving HALAVEN vs 2.6 months (95% CI: 1.7, 2.7) for patients receiving dacarbazine, HR=0.86 (95% CI: 0.69, 1.06)

**Selected Safety Information**

**Embryo-Fetal Toxicity:** HALAVEN can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with HALAVEN and for at least 2 weeks following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with HALAVEN and for 3.5 months following the final dose.

Please see all Selected Safety Information throughout and adjacent brief summary of HALAVEN full Prescribing Information.
Learn about the HALAVEN $0 Co-Pay Program and the Eisai Assistance Program by visiting www.eisaireimbursement.com/hcp/halaven or calling 1.866.611.EISAI (1.866.613.4724) Monday-Friday, 8 AM to 8 PM, ET

Learn more about the efficacy of HALAVEN at www.halaven.com/hcp/advanced-liposarcoma

Selected Safety Information

**QT Prolongation:** Monitor for prolonged QT intervals in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating HALAVEN and monitor these electrolytes periodically during therapy. Avoid in patients with congenital long QT syndrome.

**Adverse Reactions**

In patients with liposarcoma and leiomyosarcoma receiving HALAVEN, the most common adverse reactions (≥25%) reported in patients receiving HALAVEN were fatigue (62%), nausea (41%), alopecia (35%), constipation (32%), peripheral neuropathy (29%), abdominal pain (29%), and pyrexia (28%). The most common (≥25%) Grade 3-4 laboratory abnormalities reported in patients receiving HALAVEN were neutropenia (32%), hypokalemia (5.4%), and hypocalcemia (5%). Neutropenia (4.9%) and pyrexia (4.5%) were the most common serious adverse reactions. The most common adverse reactions resulting in discontinuation were fatigue and thrombocytopenia (0.9% each).

**Use in Specific Populations**

**Lactation:** Because of the potential for serious adverse reactions in breastfed infants from eribulin mesylate, advise women not to breastfeed during treatment with HALAVEN and for 2 weeks after the final dose.

**Hepatic and Renal Impairment:** A reduction in starting dose is recommended for patients with mild or moderate hepatic impairment and/or moderate or severe renal impairment.


Please see all Selected Safety Information throughout and adjacent brief summary of HALAVEN full Prescribing Information.
HALAVEN® (esulinib nesilatate) injection, for intravenous use

**BRIEF SUMMARY** – See package insert for full prescribing information.

**DOSE AND ADMINISTRATION**

**Recommended Dose:** The recommended dose of HALAVEN is 1.4 mg/m² administered intravenously on Days 1 and 8 of a 21-day cycle. The recommended dose of HALAVEN in patients with mild hepatic impairment Child-Pugh A is 1.1 mg/m² administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. The recommended dose of HALAVEN in patients with moderate hepatic impairment Child-Pugh B is 0.9 mg/m² administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. The recommended dose of HALAVEN in patients with severe hepatic impairment Child-Pugh C is 0.6 mg/m² administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.

**Dose Modification:** Assess for peripheral neuropathy and obtain complete blood cell counts prior to each dose.

**Recommended dose adjustments:**
- Do not administer HALAVEN on Day 1 or Day 8 if any of the following occurs:
  - ANC < 10,000/mm³
  - Platelets < 75,000/mm³
  - Grade 3 or 4 neutropenic toxicities
  - The Day 8 dose may be delayed for a maximum of 1 week.
  - If toxicities do not resolve or improve in Day 2 Grade 2 severity by Day 15, omit the dose.
  - If toxicities resolve or improve to ≤ Grade 1 severity by Day 15, restart HALAVEN at the reduced dose and initiate the next cycle no sooner than 2 weeks later.

**Recommended dose reductions:**
- If toxicities have occurred for toxicity and toxicities have occurred for Grade 2 severity or less, resume HALAVEN at a reduced dose as set out in Table 1. Do not discontinue HALAVEN after it has been reduced.

**Table 1: Recommended Dose Revisions**

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Recommended Dose Revisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanently reduce the 1.4 mg/m² dose of HALAVEN for any of the following:</td>
<td></td>
</tr>
<tr>
<td>ANC &lt; 50,000/mm³ for &gt; 7 days</td>
<td>1.1 mg/m²</td>
</tr>
<tr>
<td>ANC &lt; 10,000/mm³ with fever or infection</td>
<td>0.9 mg/m²</td>
</tr>
<tr>
<td>Platelets &lt; 50,000/mm³</td>
<td>0.7 mg/m²</td>
</tr>
<tr>
<td>Platelets &lt; 50,000/mm³ requiring transfusion</td>
<td>Discontinue HALAVEN</td>
</tr>
<tr>
<td>Neutropenia Grade 3 or 4 toxicities</td>
<td>Discontinue HALAVEN</td>
</tr>
<tr>
<td>Occurrence of any event requiring permanent dose reduction with escalation of 1.1 mg/m²</td>
<td>Discontinue HALAVEN</td>
</tr>
<tr>
<td>Occurrence of any event requiring permanent dose reduction with escalation of 0.7 mg/m²</td>
<td>Discontinue HALAVEN</td>
</tr>
</tbody>
</table>

**WARNINGS AND PRECAUTIONS**

**Neutropenia:** In Study 1, severe neutropenia (ANC < 500/mm³ lasting more than one week) occurred in 12% (22/183) of patients with metastatic breast cancer, leading to discontinuation in < 1% of patients. Neutropenic fever (fever > 38.5°C) occurred in 3% (5/183) of patients with Grade 3 or 4 neutropenia occurred in 5% (23/463) of patients; patients (0.04%) died from complications of febrile neutropenia. In Study 2, patients with a baseline neutrophil count < 1500/mm³ experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia than patients with normal or increased neutrophil levels. Patients with 

**Table 2: Adverse Reactions**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>N-500</th>
<th>N-247</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3</td>
<td>All Grades</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>62%</td>
<td>57%</td>
</tr>
<tr>
<td>Anemia</td>
<td>56%</td>
<td>2%</td>
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<tr>
<td>Neutropenia system</td>
<td>Neutropenia</td>
<td>35%</td>
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<tr>
<td>Neutropenia</td>
<td>Neutropenia</td>
<td>19%</td>
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<tr>
<td>Anemia</td>
<td>Anemia</td>
<td>5%</td>
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<tr>
<td>Neutropenia</td>
<td>Neutropenia</td>
<td>5%</td>
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<tr>
<td>Gastrointestinal</td>
<td>Diarrhea</td>
<td>20%</td>
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</table>
Liposarcoma: The safety of HALAVEN was evaluated in Study 2, an open-label, randomized, multicenter, active-control trial, in which patients were randomized (1:1) to receive either HALAVEN (1.5 mg/m² or Day 1 only) or 18-21 day cycle at doses of 1.8 mg/m² (84%), 1.5 mg/m² (6%), and 1.2 mg/m² (6%). In total, 223 patients received HALAVEN and 221 patients received dacarbazine. Patients were required to have received at least two prior chemotherapy regimens. The total enrolled patients with pre-existing Grade 3 or 4 peripheral neuropathy, chronic central nervous system metastasis, elevated serum bilirubin or significant chronic liver disease, history of myelosuppression within 2 weeks, history of New York Heart Association (NYHA) Class III or IV of heart failure, or cardiac interatrial block were excluded. The mean age of the safety population in study 2 was 68 years (range: 25 to 81 years); 33% female; 73% White, 3% Black or African American, 5% Asian/Pacific Islander, and 10% unknown. 93% received prior antitumor-resecting regimens, and 98% received prior 2 or 3 prior regimens. The median duration of exposure was 2.3 months (range: 2 to 12 months) for patients receiving HALAVEN.

The most common adverse reactions (>20%) reported in patients receiving HALAVEN were fatigue, vomiting, anorexia, constipation, peripheral neuropathy, and mucositis. The most common adverse reactions reported in patients receiving dacarbazine were nausea, vomiting, anorexia, and mucositis. The most common serious adverse reactions reported in patients receiving dacarbazine were nausea (4.5%) and pyrexia (4.5%). Common adverse reactions occurring in >8% of patients receiving HALAVEN were: nausea (81%), vomiting (42%), anorexia (25%), and constipation (15%).

Table 1 summarizes the incidence of adverse events occurring in at least 10% of patients in the HALAVEN treated arm in Study 2.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Neuropathy</td>
<td>12/14 (86%)</td>
<td>2/14 (14%)</td>
<td>0/14 (0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7/14 (50%)</td>
<td>2/14 (14%)</td>
<td>1/14 (7%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>8/14 (58%)</td>
<td>3/14 (21%)</td>
<td>2/14 (14%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>8/14 (58%)</td>
<td>3/14 (21%)</td>
<td>2/14 (14%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15/14 (105%)</td>
<td>4/14 (29%)</td>
<td>2/14 (14%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>14/14 (100%)</td>
<td>6/14 (43%)</td>
<td>3/14 (21%)</td>
</tr>
</tbody>
</table>

Table 2: Adverse Reactions Occurring in >20% of Patients Treated on the HALAVEN arm and at a Higher Incidence than in the Dacarbazine arm (Between Arm Difference ≥2% for All Grades or ≥2% for Grades 3 and 4) Study 2

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>53/14 (38%)</td>
<td>3/14 (21%)</td>
<td>1/14 (7%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>51/14 (36%)</td>
<td>3/14 (21%)</td>
<td>1/14 (7%)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased plasma amylase/creatine (ALT)</td>
<td>86/14 (61%)</td>
<td>2/14 (14%)</td>
<td>0/14 (0%)</td>
</tr>
<tr>
<td>Increased alkaline phosphatase (AST)</td>
<td>86/14 (61%)</td>
<td>2/14 (14%)</td>
<td>0/14 (0%)</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>50/14 (36%)</td>
<td>2/14 (14%)</td>
<td>1/14 (7%)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>50/14 (36%)</td>
<td>2/14 (14%)</td>
<td>1/14 (7%)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>47/14 (33%)</td>
<td>2/14 (14%)</td>
<td>1/14 (7%)</td>
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<tr>
<td>Gastrointestinal</td>
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<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>12/14 (86%)</td>
<td>2/14 (14%)</td>
<td>0/14 (0%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>5/14 (36%)</td>
<td>1/14 (7%)</td>
<td>0/14 (0%)</td>
</tr>
</tbody>
</table>

Table 3: Laboratory Abnormalities Occurring in >5% of Patients Treated on the HALAVEN arm and at a Higher Incidence than the Dacarbazine arm (Between Arm Difference ≥5% for All Grades or ≥2% for Grades 3 and 4) Study 2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>53/14 (38%)</td>
<td>3/14 (21%)</td>
<td>1/14 (7%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>51/14 (36%)</td>
<td>3/14 (21%)</td>
<td>1/14 (7%)</td>
</tr>
</tbody>
</table>

Hepatic: Administration of HALAVEN at a dose of 1.5 mg/m² to patients with mild hepatic impairment and 1.4 mg/m² to patients with moderate hepatic impairment resulted in increased exposure to eribulin as a dose of 1.4 mg/m² to patients with normal hepatic function. Therefore, a lower starting dose of 1.1 mg/m² is recommended for patients with mild hepatic impairment (Child-Pugh B). A dose of 1.1 mg/m² is recommended for patients with moderate hepatic impairment (Child-Pugh C). HALAVEN was not studied in patients with severe hepatic impairment (Child-Pugh D).

Renal: For patients with moderate or severe renal impairment (Ccr < 30 mL/min), reduce the starting dose to 1.1 mg/m².

OVERDOSE

Overdose of HALAVEN has been reported at approximately 4 times the recommended dose, which resulted in Grade 3 neuropathy lasting seven days and a Grade 3 hypersensitivity reaction lasting one day. There is no known antidote for HALAVEN overdose.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies have not been conducted with HALAVEN. Eribulin mesylate was positive in mouse lymphoma mutation assays, and it was clastogenic in an in vivo bone marrow micronucleus assay. In nonclinical studies, HALAVEN was treated with intravenous administration of 1.8 mg/m² in humans; however, no significant findings in repeat-dose dog and rat toxicology studies suggest that male fertility may be compromised by treatment with eribulin mesylate. Eribulin exhibited testicular toxicity in dogs but not in rats.

TREATMENT OF OVERDOSE

See OVERDOSE for appropriate treatment.

PATIENT COUNSELING

Advisers to the patient on the FDA-approved patient labeling (Patient Information).

Neuropathy: Advisers to patients to contact their healthcare provider for a week of 110°F or greater or other signs or symptoms of infections such as chills, cough, or burning or pain in extremities.

Emotional: Advisers to patients to report any allergic reactions or other side effects to the FDA or other regulatory agency.

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Sarcoma—rare, but not insignificant

This year, progress in treating rare cancers has been named the advance of the year by the American Society of Clinical Oncology (ASCO). Advancements in treating desmoid tumors, a subtype of sarcoma, was highlighted as one of the prominent breakthroughs for a rare cancer. While sarcoma is statistically rare, the impact of the disease is great, particularly on patients and families. ASCO’s recognition of rare cancer advancements demonstrates what the sarcoma community has long known: that “rare” shouldn’t mean unimportant or overlooked. In fact, the contributions of families, patients, caregivers, clinicians, researchers, foundations, organizations, and agencies in bringing sarcoma to the forefront and giving it prominence—spending time, effort, and energy in finding effective treatments—is of utmost importance, despite the disease’s rarity.

The Sarcoma Foundation of America (SFA) is leading the race to cure sarcoma, and it is doing so through research, advocacy, and education. Since its founding in 2001, donors to the foundation have funded over $9 million in research, with almost $2 million to be invested in research projects this year alone. The SFA supports research focused on discovering and developing new and effective therapies to treat and eradicate sarcoma—often high-risk, high-reward projects that would not likely be funded by the government or commercial interests. Driving the research agenda are members of its Medical Advisory Board—some of the brightest scientific minds in the world today, several of whom also serve on the Editorial Advisory Board of this, the SFA’s official journal. We are thankful for their dedication. Together, their efforts will continue to make a difference in the lives of those impacted by sarcoma. TSJ

The Sarcoma Foundation of America
Curesarcoma.org

ASCO’S RECOGNITION OF RARE CANCER ADVANCEMENTS DEMONSTRATES WHAT THE SARCOMA COMMUNITY HAS LONG KNOWN: THAT “RARE” SHOULDN’T MEAN UNIMPORTANT OR OVERLOOKED.

—The Sarcoma Foundation of America

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An unusual presentation of low-grade clavicle osteosarcoma: a case report and literature review

Osteosarcoma (OS) is a rare disease with approximately 800-900 newly diagnosed cases each year in the United States. Of those, the majority occur about the knee. The distal femur is the most common site, followed by the proximal tibia, with the proximal humerus being a distant third. OS of the clavicle has been reported, with the earliest case report dating from 1975. Since then, additional case reports of high-grade OS of the clavicle have been published. We describe the case of a 16-year-old female who presented with a mass on her right medial clavicle, which was confirmed to be a low-grade central OS.

CASE PRESENTATION
The patient is a 16-year-old female who presented to the Emergency Department (ED) for evaluation of a mass on her right clavicle, after being evaluated by her primary care physician (PCP). She noted an enlarging mass over the previous 2 months but stated that it had been asymptomatic until 4 days prior to presentation to her PCP, at which time she had developed tenderness to palpation and pain with range of motion of the right arm. X-rays were obtained at the PCP’s office and she was referred to the ED for further evaluation. She denied constitutional symptoms.

At the ED visit, she was noted to have an area of erythema and tenderness over the medial aspect of the right clavicle with increased bony prominence. A chest x-ray demonstrated medial clavicle enlargement with periosteal reaction and sclerosis (FIGURE 1).

MRI demonstrated a 6-cm x 3.8-cm x 4.1-cm mass arising from the right medial clavicle with cortical destruction and concomitant displacement of the right subclavian and brachiocephalic veins (FIGURE 2). A CT-guided biopsy was performed 1 week later and demonstrated low-grade OS. The pathologist was concerned about the possibility of sampling error and the presence of a higher-grade component, as low-grade OS of the clavicle had not been reported.

The patient was evaluated by a pediatric hematologist/oncologist 2 weeks later after having obtained the biopsy and a PET/CT scan. At that time, the PET/CT showed an FDC-avid mass at the clavicle without evidence of pulmonary metastatic disease (FIGURE 3). She was subsequently evaluated by orthopedic oncology, at which time a discussion was had regarding further treatment. There was essentially no literature to guide the surgical and medical teams, as low-grade clavicular OS is unknown. Based on the evidence of localized, low-grade disease, the determination was made to proceed...
with surgical resection. In the event that high-grade disease was identified at the time of final pathological evaluation, the pediatric hematology/oncology team felt that administering all of the patient's chemotherapy postoperatively would be acceptable and not affect her long-term prognosis. CT and CT angiogram were obtained for further operative planning (FIGURE 4).

Given the intimacy of the mass to the subclavian vessels, she was also seen preoperatively by pediatric general and cardiothoracic surgeons. The plan was formulated to have them in the operating room for mobilization of the subclavian vessels and in the event that a sternotomy was required for proximal control of the vessels. Following this visit, the case was discussed at the multidisciplinary pediatric tumor board and the consensus was to proceed with surgical resection.

**Surgical Technique**

General endotracheal anesthesia was administered without complication. The patient was positioned supine with a soft bump under her shoulders to place her neck in slight extension and thus facilitate access to the clavicle and great vessels. A 14-cm oblique incision was made over the subcutaneous clavicle extending to the contralateral sternoclavicular joint. Dissection was carried down to the fascia and the biopsy site was excised with the skin paddle. Dissection was carried through the sternocleidomastoid superiorly and the pectoralis major inferiorly, to 8 cm lateral from the right sternoclavicular joint. The clavicle was osteotomized well lateral of the palpable tumor and a narrow margin was sent for frozen section, which was found to be negative.

Dissection was continued circumferentially. Assistance from pediatric general and cardiothoracic surgery was required

**Figure 2.** MRI obtained in the ED. T1- and T2-weighted axial cuts (A), T1- and T2-weighted coronal cuts (B), and T2-weighted oblique imaging cut in the plane of the clavicle (C) are shown.

**Figure 3.** PET/CT obtained prior to medical oncology appointment. (A) FDG-avid mass at the medial aspect of the right clavicle. (B) Whole body topogram with no evidence of metastatic disease.
at the inferior aspect of the mass to assist with exposure and control of the subclavian vein (FIGURE 5A). A large branch of the subclavian vein near its junction with the internal jugular vein was found to be involved with the tumor and thus required suture ligation. The subclavian vein was noted to be intimate with the mass and somewhat friable. With the vein mobilized, a cuff of normal tissue was obtained inferiorly and superiorly to the mass. Medially, the sternoclavicular joint was disarticulated (FIGURE 5B). At this point, the specimen was delivered from the operative field and tagged in the usual fashion (FIGURE 5C). A medial soft tissue margin from the sternal side of the sternoclavicular joint was also sent and found to be negative for tumor. The wound was closed in layered fashion over a ¼" Penrose drain. A soft dressing was placed, and the patient was successfully extubated and transferred to the post-anesthesia care unit in stable condition.

Postoperative Course
The patient was found to be neurologically and vascularly intact on postoperative exam and was discharged on postoperative day 1.

She was seen 14 days postoperatively and was doing well at that time, with full range of motion of the shoulder, elbow, wrist, and hand. Final pathology confirmed a low-grade OS with extraskeletal extension. All margins were negative ex-

Figure 4. Chest CT and CT angiogram obtained prior to surgery. Representative axial (A), sagittal (B), and coronal (C) cuts are shown. Proximity of the mass to the subclavian vein is demonstrated on CT angiogram (D).
cept the medial (sternoclavicular joint) margin and the inferior margin adjacent to the subclavian vein. The intraoperative frozen section from the medial margin was negative for tumor.

The pediatric hematology/oncology team determined that, as no high-grade areas were identified, chemotherapy should be deferred. The positive margins were also discussed with the patient and her family specifically regarding further possible treatments. The findings from the pathology were discussed in a multidisciplinary tumor board and it was felt that, given the low-grade nature of the lesion as well as the high morbidity and risk of mortality with further surgery, additional surgery would be potentially more harmful than helpful. Additionally, low-grade OS is extremely resistant to radiotherapy. The plan remains to monitor her for local recurrence as well as metastases with serial imaging.

**DISCUSSION**

The clavicle is one of the first bones in the body to ossify but one of the last to have final physeal closure. Its unique characteristics have led to various descriptions, such as a "short tubular bone" versus a "flat bone." Of note are its paucity of a true intramedullary space and scanty red marrow, which make it an unlikely site for a primarily intramedullary-based neoplasm to arise. However, it has also been noted that malignant lesions are more common in the clavicle than benign lesions, and special attention should be paid to aggressive-appearing lesions in the clavicle.

Radiographs can be misleading as well. Prior studies have demonstrated that low-grade central OS can be readily misdiagnosed as fibrous dysplasia, desmoplastic fibroma, nonossifying fibroma, osteoblastoma, and aneurysmal bone cyst. Findings found in low-grade OS can include evidence of cortical interruption, local soft tissue mass development, intramedullary involvement, cortical destruction, and poor margination; however, low-grade OS is typically sclerotic and highly trabeculated. Cross-sectional imaging can help differentiate between

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**Figure 5. Intraoperative photographs. (A)** The lateral osteotomy of the clavicle has been performed and the clavicle is being retracted away from the vessels. There is a vessel loop around the subclavian vein and a large branch leading into the tumor is being dissected free. (B) The tumor bed once the specimen has been resected, subclavian vein at the base of the wound bed (marked with an asterisk). (C) The specimen once resected. Final measurements were 9.2 cm x 4.5 cm x 3.1 cm.

OS and other more benign pathologies and should be considered in the clavicle where biopsy may be perilous.
CASE REPORT

The difficulty of clavicular biopsy has been reported. Not only does clavicular anatomy make biopsy hazardous, but also the potential for sampling error does exist. In a case report of one patient with a high-grade lesion, fine needle aspiration biopsy was initially diagnosed as an aneurysmal bone cyst but was ultimately found to be osteosarcoma. Histology of low-grade lesions usually demonstrates minimal cytological atypia, rare mitotic activity, and variable osteoid production. Lower mitotic indices typically make wide resection curative for these patients, without the need for chemotherapy.

In this case, wide resection was carried out with the subclavian vein as the posterior-inferior margin and the sternoclavicular joint as the medial margin. Though the intra-operative medial margin was clear of disease, final pathology demonstrated focal (microscopic) involvement of the posterior and medial margins. A study of soft tissue sarcoma evaluated positive margins and concluded that the imperative of preservation of vital structures supersedes the need for negative margins. The rate of metastasis and overall survival was similar to surgical resections with positive margins. In the case of our patient, further resection would have carried significant morbidity and possibly mortality, including sacrifice of the major vessels to the arm below and entering into the sternum and thoracic cavity. The likely disability as well as the hazards of surgery were deemed to be too great to justify further excision. Frequent cross-sectional imaging will be necessary to evaluate the presence of recurrent or metastatic disease. To our knowledge, this is the first documented case of low-grade clavicle OS. This report demonstrates the need for multidisciplinary care at a center of excellence, particularly in instances of unusual diagnoses.

CORRESPONDENCE
Dr. Kurt R. Weiss, weissk.upmc.edu

REFERENCES

Wolf in sheep’s clothing: metatarsal osteosarcoma

Metatarsal bones are an unusual subsite for small bone involvement in osteosarcomas. This subgroup is often misdiagnosed and hence associated with significant treatment delays. The standard treatment of metatarsal osteosarcomas remains the same as for those treated at other sites, namely neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy. Limb salvage surgery or metatarsectomy in the foot is often a challenge owing to the poor compartmentalization of the disease. We hereby describe the case of a young girl with a metatarsal osteosarcoma who was managed with neoadjuvant chemotherapy and limb salvage surgery.

INTRODUCTION
Osteosarcomas are the most common primary malignant bone tumor in children and adolescents. Although predominantly occurring in pediatric and adolescent age groups, bimodal distribution (with a second incidence peak occurring in the sixth and seventh decades) is not uncommon. Osteosarcomas of the foot and small bones represent a rare and distinct clinical entity. This must have been a well-known observation for years that led to Watson-Jones stating, “Osteosarcoma of this [metatarsal] bone has not yet been reported in thousands of years in any country.” The incidence of osteosarcomas of the foot is estimated to be from 0.2% to 2%. These tumors, owing to their rarity, often lead to diagnostic dilemmas and hence treatment delays. They are usually mistaken for inflammatory conditions and often treated with—but not limited to—curettings and drainage procedures.
weight bearing on the fourth postoperative day and her sutures were removed on the twelfth postoperative day. She received adjuvant chemotherapy following surgery. The final histopathology report showed residual disease with Huvos grade III response (>90% necrosis) with all margins negative for malignancy (FIGURE 5). At present, the child is disease-free at 5 months of treatment completion and is undergoing regular follow-up visits.

DISCUSSION
Metatarsal involvement amongst small-bone osteosarcomas is uncommon.7 There are about 32 cases of osteosarcomas reported in the literature from 1940 to 2018 involving the metatarsal bones (TABLE 1). According to a review article from the Mayo Clinic, the most common bone of the foot involved is the calcaneum.8 While the incidence of osteosarcomas of the foot as a whole is around 0.2% to 2%,9 metatarsal involvement is documented in 0.5% of these patients.7 However, a recent study depicted metatarsal involvement in 33% of all osteosarcomas of the foot.8

Osteosarcomas at conventional sites tend to have a bimodal age distribution with respect to disease affliction.9 Metatarsal osteosarcomas, however, are more common in an older age group.8,10 Our patient is probably the second youngest reported case of metatarsal osteosarcoma in the literature.11
Biscaglia et al propounded that osteosarcomas of the metatarsal were a distinct subgroup due to the rarity of occurrence, anatomical location, and prognosis. This often led to misdiagnosis and subsequent inadequate or inappropriate surgery. In six out of the ten cases (60%) described in Table 1, an incorrect pretreatment diagnosis was made that led to treatment delay. None, except one patient, received neoadjuvant chemotherapy, which is currently the standard of care. The average duration from symptom onset to diagnosis was found to be 2 years. However, in our case, the duration of symptoms was approximately 2 months.

Surgery for metatarsal osteosarcomas can be challenging, as the compartments of the foot are narrow spaces with poor demarcation. Limb salvage surgery in the form of metatarsectomy needs proper preoperative planning and execution. Neoadjuvant chemotherapy will serve to downstage the tumor within the fascial barriers of the metatarsal compartment.


CASE REPORT

TABLE 1. Various studies on metatarsal osteosarcoma: treatment and outcomes

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Age/sex</th>
<th>Initial diagnosis</th>
<th>Initial treatment</th>
<th>Final treatment</th>
<th>Histology</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biscaglia R/1998</td>
<td>28 M</td>
<td>not known</td>
<td>NA</td>
<td>disarticulation</td>
<td>chondroblastic osteosarcoma</td>
<td>NED at 168 mo</td>
</tr>
<tr>
<td></td>
<td>20 M</td>
<td>not known</td>
<td>NA</td>
<td>resection</td>
<td>osteoblastic osteosarcoma</td>
<td>NED at 120 mo</td>
</tr>
<tr>
<td>Fukuda K/1999</td>
<td>18 F</td>
<td>not known</td>
<td>NA</td>
<td>NACT f/b BKA</td>
<td>osteoblastic osteosarcoma</td>
<td>NED at 55 mo</td>
</tr>
<tr>
<td>Lee EY/2000</td>
<td>25 F</td>
<td>enchondroma</td>
<td>curettage</td>
<td>ray resection</td>
<td>high-grade osteosarcoma</td>
<td>NED at 9 mo</td>
</tr>
<tr>
<td>Choong PFM/1999</td>
<td>27 M</td>
<td>osteosarcoma</td>
<td>NA</td>
<td>ray amputation radiotherapy</td>
<td>osteosarcoma grade II</td>
<td>DOD at 19 mo</td>
</tr>
<tr>
<td>Sneppen O/1978</td>
<td>22 M</td>
<td>benign osteochondroma</td>
<td>Non-radical excision</td>
<td>BKA</td>
<td>osteosarcoma</td>
<td>DOD at 13 mo</td>
</tr>
<tr>
<td>Padhy D/2010</td>
<td>17 M</td>
<td>osteosarcoma</td>
<td>NA</td>
<td>ray amputation f/b adjuvant chemotherapy</td>
<td>high-grade osteosarcoma</td>
<td>NED at 26 mo</td>
</tr>
<tr>
<td>Mohammadi A/2011</td>
<td>33 F</td>
<td>osteosarcoma</td>
<td>NA</td>
<td>radical excision</td>
<td>chondroblastic osteosarcoma</td>
<td>NED at 9 mo</td>
</tr>
<tr>
<td>Nishio J/2012</td>
<td>16 M</td>
<td>fibrous dysplasia/ giant cell reparative granuloma</td>
<td>curettage</td>
<td>wide excision + free vascularized flap graft</td>
<td>low-grade osteosarcoma</td>
<td>NED at 18 mo</td>
</tr>
<tr>
<td>Parsa R/2013</td>
<td>72 M</td>
<td>osteosarcoma</td>
<td>NA</td>
<td>metatarsectomy</td>
<td>low-grade osteosarcoma</td>
<td>NED at 48 mo</td>
</tr>
<tr>
<td>Aycan OE/2015</td>
<td>10 M</td>
<td>aneurysmal bone cyst/giant cell tumor</td>
<td>NA</td>
<td>resection</td>
<td>chondroblastoma-like osteosarcoma</td>
<td>NED at 6 mo</td>
</tr>
<tr>
<td>PRESENT CASE</td>
<td>10 F</td>
<td>chondroblastic</td>
<td>NA</td>
<td>NACT f/b metatarsectomy</td>
<td>chondroblastoma-like osteosarcoma</td>
<td>NED at 3 mo</td>
</tr>
</tbody>
</table>

BKA: below knee amputation; DOD: dead of disease; F: female; f/b: followed by; M: male; mo: months; NA: not available; NACT, neoadjuvant chemotherapy; NED, no evidence of disease

It has also been postulated that osteosarcoma of the foot may have a better prognosis and survival compared to other osteosarcoma subsites. This can be extrapolated from the fact that the majority are found to be low grade, and despite a long delay in treatment, there was no rapid increase in size and/or metastatic spread. However, tumor grade remains an important factor affecting survival—patients with higher grade tumors have worse survival.

A number of differentials, including benign tumors, are to be kept in mind when diagnosing and treating such patients (TABLE 2). The most common benign tumors affecting the metatarsal are giant cell tumors (GCT) followed by chondromyxoid fibroma. Osteosarcomas and Ewing sarcomas constitute the malignant tumors. Occasionally, infections like osteomyelitis of the small bones may mimic malignancy. The absence of an extensive soft tissue component and/or calcifications with the presence of bony changes (like sequestrum) favors a diagnosis of infection/osteomyelitis. In addition, clinical findings like fever, skin redness, and presence of a painful swelling (especially after onset of fever) point to an inflammatory pathology rather than malignancy. Stress fractures rarely simulate tumors. MRI showing marrow and soft tissue edema with a visible fracture line points to the diagnosis.

A plane radiograph showing corti-
TABLE 2. Important differential diagnosis of metatarsal swelling in a young patient

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Osteosarcoma</th>
<th>Chronic osteomyelitis</th>
<th>Ewing sarcoma</th>
<th>Eosinophilic granuloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td>10 – 30 years</td>
<td>2 – 12 years</td>
<td>10 – 20 years</td>
<td>Less than 10 years</td>
</tr>
<tr>
<td>Male:female</td>
<td>1.43:1</td>
<td>3:1</td>
<td>1.5:1</td>
<td>2:1</td>
</tr>
<tr>
<td>Most common site</td>
<td>Lower limb distal femur</td>
<td>Lower limb and lumbar vertebrae</td>
<td>Femur</td>
<td>Skull, mandible, spine, ribs</td>
</tr>
<tr>
<td>Imaging</td>
<td>MRI – On T1w – Bone marrow replaced by hypointense soft tissue mass. T2w – shows general hypointensity with thin marginal area of hyperintensity.</td>
<td>CT – best study to delineate sequestrum from another lesion (sequestrum does not enhance). MRI – sequestrum in cortical bone: hypointense and in cancellous bone sequestrum is hyperintense on T1, T2, and STIR sequences. Granulation tissue is hyperintense on T2.</td>
<td>CT – degree of bone destruction appreciated better. MRI – T1 – low signal. T2 – heterogeneously high signal. Shows high uptake on Ga67 and Tc99 bone scan.</td>
<td>CT – lytic lesion with periosteal reaction and cortical and medullary bone destruction. On spin-echo MRI, decreased SI on T1w and high on T2w. Lesion enhances on gadolinium.</td>
</tr>
</tbody>
</table>

CT, computed tomography; Ga, gadolinium; MRI, magnetic resonance imaging; SI, spin intensity; STIR, Short-T1 Inversion Recovery; T1, T2, longitudinal relaxation time; T2w, longitudinal relaxation time-weighted images; Tr, technetium

CONCLUSIONS

Osteosarcoma of the metatarsal is rare. Our case remains unique as it reports the second youngest patient in the literature. Erroneous or delayed diagnosis resulting in inadequate tumor excision and limb loss (amputation) often occurs in a majority of the cases. Proper pre-treatment radiological imaging becomes imperative, and when clinical suspicion is high, a needle biopsy must follow in those cases. Early diagnosis with administration of neoadjuvant chemotherapy may allow us to perform limb salvage surgery or wide excision in these cases. **TSJ**

CORRESPONDENCE
Dr. Abhay Kattepur, drabhay1985@gmail.com

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CONTINUED


Presentation of a rare malignancy: leiomyosarcoma of the prostate

Prostatic leiomyosarcoma is an aggressive malignancy with a high risk of metastasis and a poor prognosis that poses unique diagnostic and treatment challenges.

Prostatic leiomyosarcoma is a rare tumor. This neoplasm is composed of highly aggressive prostatic smooth muscle cells that present with nonspecific signs and symptoms mimicking other forms of prostatic pathology. Of the primary prostatic sarcomas, leiomyosarcoma represents the most common subtype in adults and is found in 38% to 52% of newly diagnosed prostate sarcoma. The prognosis is poor, and no clear guidelines exist regarding the optimal treatment approach. We report a case of prostatic leiomyosarcoma and describe the disease characteristics, diagnostic modalities, and treatment approach regarding these rare malignancies.

CASE PRESENTATION
A 72-year-old male presented with 6 months of progressive severe lower urinary tract symptoms (LUTS) secondary to bladder outlet obstruction. The patient was refractory to medical management with combination α-blocker and 5-α-reductase inhibitor therapy and continued to require multiple emergent bladder catheterizations. Workup with urinalysis, blood biochemistry, and prostate-specific antigen (PSA) levels were persistently normal. He reported no hematuria, weight loss, or perineal pain. The patient reported no history of tobacco use, exposure to hazardous chemicals, and had no family history of genitourinary cancers. On rectal exam, the prostate was firm and nodular, with induration noted along the right upper lobe of the prostate.

The patient was referred for a urology consultation and subsequently underwent transurethral resection of the prostate (TURP) for suspected severe benign prostatic hypertrophy (BPH). A histopathologic examination demonstrated atypical cytology consistent with high-grade leiomyosarcoma. Immunohistochemical analysis revealed positive staining for vimentin, smooth muscle actin, desmin (partial), cytokeratin, smooth muscle myosin, muscle-specific actin, and Ki-67 (50% to 60% expression).

Fluorodeoxyglucose positron emission tomography (FDG-PET) scan revealed a 5.7 x 5.9-cm tumor with a maximum standardized uptake value (SUVmax) of 12.6 in the right posterior prostate, without evidence of metastatic disease (FIGURES 1A AND 1B). The patient was referred to medical and radiation oncology. He was evaluated for radical prostatectomy and planned for surgery with neoadjuvant radiation. He received palliation of his symptoms with bilateral nephrostomy tubes; however, the patient had significant comorbidities and died prior to treatment.

DISCUSSION
Originating from prostatic interstitial cells, prostatic leiomyosarcoma is a rare tumor that accounts for <0.1% of all primary prostatic malignancies. Since its first description in 1950 by Riba and colleagues, <200 cases have been reported worldwide. Among the sarcomas of the prostate, it is the most common tumor, accounting for around 38% to 52% of prostate sarcoma presentations.
Patients typically present between the ages of 41 and 78 years (mean age 61 years). Signs and symptoms at presentation may vary; however, the most common symptoms are related to lower urinary tract obstruction (89.4% of patients). These symptoms include urinary frequency, urgency, nocturia, and may mimic the presentation of BPH.

Symptoms commonly associated with other malignancies, including constitutional symptoms such as weight loss, tend to occur less frequently or may be absent. Perineal or rectal pain may only be present in 25.6% of patients. Hematuria, burning on ejaculation, and constitutional symptoms are a less common presentation (<10% of patients). PSA levels typically do not rise and are found to be within normal limits. The lack of PSA elevation is related to the tumors' nonepithelial origin and may contribute to a delay in diagnosis.

**DIAGNOSIS**

Diagnosis may be further eluded, as digital rectal exam (DRE) findings tend to reveal nonspecific enlargement of the prostate, resembling that of BPH. DRE may show a hard and firm prostate with nodular induration at the base or over the lobes of the prostate. At this stage a urology consultation is useful, as diagnosis is most commonly achieved using transrectal ultrasound (TRUS) with ultrasound-guided needle biopsy or after a TURP procedure.

Prostate sarcoma is associated with markedly enlarged prostate volume, irregular margins with invasion, or heterogeneous hypoechoic lesions on TRUS. Transperineal biopsy, computed tomography (CT)-guided biopsy, or suprapubic prostatectomy have been less frequently employed for diagnosis in previously reported cases. Specialized imaging modalities, such as CT scan or bone scan, do not show any specific findings with regards to these tumors; their role is limited to evaluation of the local and distant metastasis and for follow-up assessments. Transabdominal ultrasound may assess hydronephrosis or enlarged prostate and its relation to nearby structures, although it has not been shown to be helpful in establishing a specific diagnosis.

Histologically, prostatic leiomyosarcoma is a distinct subtype of prostatic sarcoma. Other subtypes include stromal tumors such as rhabdomyosarcoma, fibrosarcoma, and spindle cell sarcoma. The majority of leiomyosarcomas are high-grade lesions demonstrating neoplastic spindle cells with nuclear atypia, multifocal necrosis, and cystic degeneration. Low-grade leiomyosarcomas are very rare. Immunohistochemistry is characteristically positive for vimentin, smooth muscle actin, and desmin expression. Cytokeratin may be positive in up to 25% of cases, whereas S-100, CD34, CD117, and PSA are negative. These histopathological findings help to
differentiate leiomyosarcoma from other prostatic tumors.

Tumor size may vary greatly, and measurements have been reported to range from 3 cm to 21 cm, frequently presenting with invasion of local structures. Advanced-stage disease is commonly found at initial diagnosis and is thought to be due to the lack of early specific symptoms. Metastatic disease at presentation may be found in up to one-third of patients, with the lungs being the most common site of metastasis, followed by the liver. Local extent and distant spread of disease may be determined by CT or magnetic resonance imaging (MRI) scans, which provide clear delineation of neoplastic and nonneoplastic tissues. These imaging techniques are important in assessing surgical resectability or potential for radiotherapy. Brain metastasis is a rare finding (3.6% of cases); therefore, imaging of the brain is not routinely performed unless high clinical suspicion of brain involvement is present. FDG-PET scans have become more readily available in clinical practice over recent years and have found use in staging prostatic sarcoma. Leiomyosarcomas, in particular, have been found to be FDG avid, and SUV$_{max}$ has been utilized as a likely predictor of tumor size and grade [FIGURE 2].

**TREATMENT**

Treatment regimens may include a multimodal approach of combination surgery, radiation, and chemotherapy. However, there are currently no standardized guidelines for treatment and the optimal therapy remains unknown. Surgery remains the mainstay of treatment, and patients with surgically resectable tumors are treated with curative intent. Surgeries performed include radical retropubic prostatectomy, radical cystoprostatectomy, suprapubic prostatectomy, and pelvic exenteration. These operations may be preceded or followed by radiation therapy and/or chemotherapy depending on extent of disease.

It has been reported that neoadjuvant chemotherapy and/or radiotherapy can aid in decreasing tumor burden to facilitate a complete resection. Patients who are determined to not be candidates for surgery or who have widespread disease may be offered systemic chemotherapy. Chemotherapy regimens vary, but common regimens include anthracyclines (doxorubicin or epirubicin), alkylating agents (cyclophosphamide, ifosfamide, dacarbazine), and/or vinca alkaloids (vinblastine or vincristine). Patients who do not receive surgical intervention rarely achieve a sustained remission.

The long-term prognosis of prostatic leiomyosarcoma is poor due to the aggressive nature of the neoplasm and the high chance of disease recurrence or metastasis. Median survival is estimated at 17 months, and 50% to 75% of patients die within 2 to 5 years of diagnosis.

**FIGURE 2.** Fluorodeoxyglucose positron emission tomography shows an enlarged prostate of 5.7 x 5.9 cm with increased fluorodeoxyglucose uptake.
Diagnosis may be improved in patients with localized disease at diagnosis who are candidates for complete surgical resection with negative margins. Adverse prognostic factors include metastatic disease at presentation and the presence of positive surgical margins after surgery. Overall survival is very poor, and it is estimated that the 1-, 3-, and 5-year survival rates are 68%, 34%, and 26%, respectively. However, some studies estimate the 5-year survival to be anywhere from 0% to 60%. Due to the substantially high risk of death, prostatic leiomyosarcoma may be one of the most aggressive and poorly prognostic malignancies involving the prostate.

CONCLUSION
Prostatic leiomyosarcoma poses a unique diagnostic challenge, as clinical presentation alone may not always be suggestive of underlying malignancy. This challenge is further exacerbated by its aggressive nature, high risk of metastasis, and difficulties with unclear treatment. Proper history and physical examination, differential diagnosis, and a multidisciplinary approach to patient care are the foundation for early detection and promoting improved survival.

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CORRESPONDENCE
Dr. Daniel Ermann, daniel.ermann@creighton.edu

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From the journals: sarcoma around the world

EWING SARCOMA IN NEPAL: Investigators reported what they believe to be the first prospective clinical trial providing state-of-the-art chemotherapy to patients with Ewing sarcoma in Nepal. They treated 20 newly diagnosed patients with combination chemotherapy, including a course of etoposide and ifosfamide during external-beam radiotherapy. Radiotherapy was the only available treatment modality for local tumor control because advanced tumor-orthopedic services are not available in Nepal.

The 11 females and 9 males enrolled ranged in age from 6 to 37 years.

The treatment protocol—based on the Nepali-Norwegian Ewing Sarcoma Study treatment initiative—consisted of:

- Cisplatin (1,200 mg/m² as a 30-minute intravenous [IV] infusion)
- Doxorubicin (40 mg/m²/d as a 4-hour IV infusion on days 1 and 2; total dose, 80 mg/m² in 2 days; total cumulative dose, 400 mg/m²)
- Etoposide (150 mg/m²/d as a 2-hour IV infusion; total dose, 450 mg/m² in 3 days)
- Ifosfamide (3,000 mg/m² over 21 to 24 hours as a 3-day continuous IV infusion; total dose, 9,000 mg/m² in 3 days)
- Vinorelbine (1.5 mg/m² IV push; maximum, 2 mg)

Patients received 5 courses of chemotherapy, then radiotherapy twice daily for 4 weeks for a total accumulated 54-Gy dose with a course of etoposide and ifosfamide, followed by 6 additional courses of chemotherapy.

Patients had primary tumors in the following sites: femur (n = 4), pubic bone (n = 1), fibula (n = 1), thoracic wall or costae (n = 4), clavicle (n = 1), craniofacial bone (n = 3), humerus (n = 3), forearm (n = 1), musculus sartorius with invasion into adjacent femur (n = 1), and uterine cervix (n = 1).

Eleven patients completed the entire treatment regimen, 6 of whom had no evidence of disease at a median follow-up of 2.3 years (range, 1.3 to 3.1 years). Four of them died of metastatic disease, and 1 experienced a recurrence 6 months later.

Three patients died due to chemotherapy-related toxicity, and 6 patients did not complete the treatment protocol, 4 of whom experienced progressive disease, were lost to follow-up, and presumed dead.

The investigators concluded that radiotherapy as the sole local treatment modality in combination with chemotherapy is feasible. They observed no fractures among the 15 patients who received radiotherapy.


RADIOTHERAPY WAS THE ONLY AVAILABLE TREATMENT MODALITY FOR LOCAL TUMOR CONTROL BECAUSE ADVANCED TUMOR-ORTHOPEDIC SERVICES ARE NOT AVAILABLE IN NEPAL.

PEDIATRIC SOFT TISSUE AND BONE SARCOMAS IN TANZANIA: In this retrospective review, investigators documented the epidemiologic and clinical features of pediatric sarcomas in the largest pediatric oncology center in Tanzania—Muhammad Ali National Hospital. Their objective in collecting the data was to compare the results with those of other countries and ultimately prioritize
treatment protocols and resources for the more common pediatric sarcomas in Tanzania. Prior to this study, no data existed on the frequency and types most commonly seen in the country.

Between 2011 and 2016, the investigators collected information on 135 pediatric cases seen at the hospital. Eighty-nine cases (66%) were soft tissue sarcomas (STS) and 46 (34%) were bone sarcomas. Most patients, they reported, presented with a painless swelling.

Investigators found that, as in other countries, embryonal rhabdomyosarcoma accounted for the majority (75%) of all sarcomas seen in this study and osteosarcoma accounted for most (87%) bone sarcomas. However, unlike pediatric sarcomas in other countries, few cases of Ewing sarcoma were diagnosed during the study period.

An important disparity between Tanzania and other countries is that most patients in Tanzania present with advanced-stage disease, when the possibility of curative therapy is vastly reduced. Investigators found the lung to be the most common site of distant metastasis.

Other clinical and tumor characteristics reported in this study included:

- Slight female predominance (51%)
- Mean age, 6.3 years
- 42% of STS patients were younger than 5 years (n = 37)
- 46% of bone sarcoma patients were 10 to 15 years old (n = 21)
- Head and neck were the most common sites for STS
- Extremities were the most common sites for bone sarcomas
- Most patients presented with large tumors (>5 cm for STS and >8 cm for bone sarcomas).

The investigators believe these findings and others they reported will help them adapt treatment protocols used in Europe and America so that they will be most appropriate for their patients.


**PEDIATRIC OSTEOSARCOMA IN LEBANON:** Investigators at a single institution in Lebanon reported a similar survival rate for newly diagnosed patients with pediatric osteosarcoma treated at their center as for those treated in more developed countries. In a retrospective review of the medical records of 38 patients treated at the American University of Beirut Medical Center between August 2001 and May 2012, they determined the 5-year overall survival (OS) for all patients to be 74% and the event-free survival (EFS), 62%. Patients with localized disease had a 5-year OS of 81% and an EFS of 68%. Patients with metastatic disease had OS and EFS rates of about 42%.

All patients with localized disease received chemotherapy according to the Pediatric Oncology Group 9351 protocol, which consisted of cisplatin, doxorubicin, and methotrexate. If patients had metastatic disease or tumor necrosis less than 90%, they also received ifosfamide and etoposide.

Patients were a mean age of 12.9 years at diagnosis and there were an equal number of male and female patients. Most patients (n=34) had a primary tumor site affecting the long bones around the knee.

Six patients had metastatic disease to the lungs, and 3 patients had multifocal bone disease with lung metastases.

Thirty-three patients (86.9%) underwent surgical resection after 2 courses of induction chemotherapy. Twenty-two (66.7%) of these patients had a delay in local tumor control of more than 4 weeks. And 12 patients (31.5%) had tumor necrosis of less than 90%.

The investigators analyzed the prognostic importance of age, sex, metastatic disease, tumor site, delay in local control, and degree of tumor necrosis. Bivariate analysis revealed that only the degree of tumor necrosis was a statistically significant adverse prognostic factor for EFS (P=.001) and OS (P=.002).

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