**Case 15: Synopsis of Supraclavicular Sarcoma: Synthesis of Stratagem and Solutions**

A 42-year-old left-handed man presented with unilateral plexopathy, was diagnosed as having a herniated disc, and was prescribed conservative treatment and physiotherapy. In the coming weeks, a left-sided supraclavicular mass and severe left upper extremity neuropathy worsened. Magnetic resonance imaging revealed a “large mass measuring 47 × 75 × 45 mm infiltrating the left infraclavicular/supraclavicular soft tissues, inseparable from the left brachial plexus; the left subclavian artery was also encased with flow void maintained.” A computed tomography (CT) scan of the neck/chest showed subcentimeter lung lesions.

Orthopedic oncology completed a CT-guided biopsy of the left supraclavicular mass, which revealed sarcoma (at least intermediate grade). SS18 (SYT) FISH studies were negative for translocation (18q11.2) gene locus, excluding synovial sarcoma. The biopsies demonstrated a malignant spindle cell neoplasm with abundant necrosis, moderate pleomorphism, myxoid background, and rare mitoses, consistent with sarcoma of at least intermediate grade. The differential diagnosis included myxofibrosarcoma, undifferentiated sarcoma, and CIC-rearranged sarcoma.

Immunohistochemical stains, CD99 and vimentin were positive. WT-1 had strong cytoplasmic but no nuclear staining. CK AE1/AE3, CAM5.2, SMA, desmin, MyoD1, CD34, S100, melan-A, CK7, and calretinin were negative.

Radiation oncology was emergently consulted, and the patient was started on high-dose dexamethasone owing to significant compressive neurologic symptoms. The patient clinically improved rapidly on this regimen. A multidisciplinary management decision was made to start concurrent ifosfasmide (weeks 1 and 5) concurrently with radiation. Photon radiation was administered in daily 2 Gy/day in a 3-dimensional conformal arrangement, continued to 50 Gy, at which point the patient developed unequivocal enlarging lung metastases. Therapy was then switched to ifosfamide, doxorubicin, and mesna (AIM) and radiation was stopped. Figs. 1 and 2

Fig. 1. Tumor sample HPF. Viable tumor surrounds central vessel, showing mild nuclear pleomorphism and a myxoid background, surrounded by tumor necrosis. Black arrow = necrosis; red arrows = myxoid stroma between viable tumor; V = vessel. Images credited to Daniel Griffin, MD (University of Kentucky, Department of Pathology).

Fig. 2. Magnetic resonance imaging, sagittal STIR, and coronal postcontrast sequence, mass posterior to the clavicle (purple arrow) and abutting the left subclavian vessels (blue arrow) and enmeshed in the brachial plexus (red arrow). Images credited to Mark Murray, MD (University of Kentucky) (Department of Radiology).

**Expert 1: Treating the Unknown: First Refine the Diagnosis**

With over 100 subtypes of sarcoma with variable biology, further tests are needed to refine the diagnosis. Imaging suggests a malignant peripheral nerve sheath tumor (MPNST), which is not ruled out by negative S100 staining. With improvement on dexamethasone, I recommend additional immunohistochemical testing. Loss of immunostaining for trimethylation at lysine 27 of histone 3 (H3K27me3) is a sensitive marker for MPNST.

In MPNST, concurrent ifosfamide and 50 Gy can lead to pathologic complete response. In high-grade sarcomas ≥8 cm, 3 cycles of neoadjuvant mesna, adriamycin, ifosfamide, and dacarbazine interdigitated with 2 cycles of 22 Gy in 11 fractions of radiation therapy has more toxicity but achieves excellent outcomes. The feasibility of concurrent adriamycin and ifosfamide with 25 Gy in 5 fractions was recently established. Radiation therapy volumes should follow RTOG-06305 with 3 cm of the brachial plexus in the clinical target volume. For patients with lung metastases, I recommend adjuvant chemotherapy with adriamycin and ifosfamide.

This sarcoma reminds me of a 68-year-old man with a pleomorphic sarcoma in the trapezius whom I treated with definitive radiation therapy. He developed an in-field sarcoma 16 years after chemoradiation therapy for nasopharyngeal cancer. Soon after 50 Gy preoperative radiation therapy, the patient had transient ischemic attacks due to bilateral internal carotid artery disease that precluded surgery. Because the patient was now inoperable, I used a permanent 125I implant to achieve local control. Unfortunately, the patient eventually developed brachial plexopathy.

**Expert 2: Recurrence Risk Related Rationale**

There are competing risks associated with each treatment decision, so multidisciplinary collaboration is critical for complex sarcoma cases like this. What is the most clinically significant risk for the patient? Identifying local or distant progression as the primary concern will help determine whether to prioritize local or systemic control first.

When developing a local therapy plan, it is important to consider whether the patient is a candidate for curative resection. Imaging suggests resection would be morbid. If our multidisciplinary team determines that downstaging would improve the likelihood of curative resection or meaningfully improve postoperative function, then we would recommend neoadjuvant adriamycin, ifosfamide, and mesna (AIM). This allows an in vivo assessment of chemotherapy efficacy and time to assess the risk of metastasis before undertaking a potentially morbid local therapy (typically preoperative radiation therapy followed by resection). AIM has shown improved disease-free survival compared with other histology-specific neoadjuvant chemotherapy regimens. Therefore, the lack of clear subtype in this case would not affect the choice of neoadjuvant chemotherapy regimen. The risk of progression during neoadjuvant chemotherapy is <10%. If a patient’s tumor shows response but the patient does not complete 6 cycles of AIM upfront, the remaining cycles may be delivered after local therapy.

If the patient is thought to be unlikely to become a candidate for a curative resection, then ifosfamide-based chemoradiation could be delivered to a definitive dose for local control (66-70 Gy) using standard target volumes and accounting for brachial plexus tolerance limits. Some patients may achieve durable local control with this nonoperative approach.

**Expert 3: Don't Panic and Rely on Data**

The standard treatment for intermediate- and high-grade soft tissue sarcomas remains excision and either pre- or postoperative radiation therapy. The treatment of soft tissue sarcoma in the supraclavicular fossa or axilla is difficult due to the proximity to neurovascular structures. Although arteries and veins can be resected and replaced with grafts, resection of branches of the brachial plexus leaves the patient with major motor and sensory deficits.

In this patient’s case, the tumor involves the vasculature and brachial plexus. At our center our multidisciplinary team would recommend neoadjuvant radiation therapy before any attempt at surgery. An analysis of the National Cancer Database showed that the use of preoperative radiation therapy was associated with an improved rate of R0 resection compared with postoperative radiation therapy. For large sarcomas or those in unfavorable locations like this, it is tempting to add neoadjuvant or concurrent chemotherapy to improve the response, but the data have not been conclusive. The National Comprehensive Cancer Network guidelines state that the use of neoadjuvant, concurrent, or adjuvant systemic therapy should be considered on an individual basis.

In our center, the treatment volumes would consist of a preoperative magnetic resonance imaging−defined gross tumor volume followed by a 1- to 1.5-cm clinical target volume expansion. The final planning target volume would include an additional 0.5-cm expansion. We would recommend a standard preoperative dose of 50 Gy in 25 fractions. Possible toxicities include wound healing difficulties, low risk of brachial plexus injury, and long-term soft tissue fibrosis.

ChatGPT’s initial recommendation

**Expert 4: Balancing Systemic and Local Control for Optimal Outcomes**

In this complex case involving a locally advanced, likely metastatic soft tissue sarcoma with significant neurological symptoms and involvement of the brachial plexus, a comprehensive approach that combines both systemic and local treatment modalities is essential to optimize the patient's outcomes.

1. Systemic treatment: Continue the current systemic chemotherapy regimen with ifosfamide, doxorubicin, and mesna (AIM). The AIM regimen is a standard first-line treatment for metastatic soft tissue sarcomas and has shown efficacy in controlling the disease.
2. Treatment reassessment: Reassess the patient's response to the AIM regimen after a few cycles, both clinically and radiographically. If there is a partial or complete response to the treatment, consider continuing the AIM chemotherapy for a total of 6 cycles, depending on the patient's tolerance to the treatment.
3. Second-line systemic treatment: If there is a lack of response or progression of disease while on AIM, consider switching to alternative second-line systemic treatment options, such as trabectedin, pazopanib, or eribulin, depending on the availability and the patient's performance status.
4. Pain management and palliative care: Consult with a pain management specialist and/or palliative care team to address the patient's neuropathic pain and ensure appropriate symptomatic relief.
5. Consolidative radiation therapy: If the patient shows a significant response to systemic treatment and local disease control is achieved, consider consolidative radiation therapy to the primary site. This can help in reducing the risk of local recurrence and further improve symptom management.
6. Monitoring and intervention: Regularly monitor the patient's clinical status and assess for any new neurological symptoms or worsening of existing symptoms, which might indicate the need for urgent intervention.
7. Multidisciplinary approach: Maintain a close multidisciplinary approach involving medical oncology, radiation oncology, and orthopedic oncology, to tailor the treatment plan based on the patient's response to therapy and individual needs.

The rationale for this approach is to provide effective systemic treatment to control both local and metastatic disease while addressing the patient's symptoms and improving their quality of life. The patient's response to treatment should be closely monitored, and treatment should be adjusted based on their individual needs and tolerance to therapy.

ChatGPT’s revised recommendation after seeing other human experts’ recommendations

**Expert 5: A Multidisciplinary, Tailored Approach for Optimal Management**

In this complex case involving a sarcoma of unknown subtype and challenging location, a multidisciplinary approach that includes medical oncologists, radiation oncologists, and surgical oncologists is essential to optimize the treatment plan and ensure the best possible outcomes for the patient.

First, assess the most clinically significant risk for the patient (local or distant progression) to determine whether to prioritize local or systemic control. Based on this assessment, the following steps should be considered:

1. Neoadjuvant radiotherapy: Given the tumor's challenging location, the potential benefits of neoadjuvant radiotherapy in improving the likelihood of an R0 resection should be considered. Standard preoperative doses of 50 Gy in 25 fractions, with treatment volumes and doses can be used.
2. Neoadjuvant AIM chemotherapy: If the multidisciplinary team determines that downstaging is needed to improve the likelihood of curative resection or meaningfully improve postoperative function, consider neoadjuvant AIM (adriamycin, ifosfamide, and mesna) chemotherapy. This approach allows an in vivo assessment of chemotherapy efficacy and time to assess the risk of metastasis before undertaking a potentially morbid local therapy.
3. Pain management and palliative care: Consult with a pain management specialist and/or palliative care team to address the patient's neuropathic pain and ensure appropriate symptomatic relief.
4. Continuous reassessment: Regularly reassess the patient's response to treatment, both clinically and radiographically, to guide further management decisions and adapt the treatment plan accordingly.

In conclusion, the management plan should be tailored to the individual patient, taking into account their performance status, tumor characteristics, and the potential benefits and risks associated with each treatment modality. A collaborative approach involving all relevant specialists will help optimize the treatment plan and maximize the patient's chances of a favorable outcome.