



Synopsis of Supraclavicular Sarcoma: Synthesis of Stratagem and Solutions



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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 $47 \times 75 \times 45$ 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 ifosfamide (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

Questions

1. What would be your initial therapy and sequencing of the overall regimen?
2. What are the optimal preoperative chemotherapy regimens given the unknown pathological subtype? What is the risk of radiation recall?
3. What are the treatment volumes, dose, and possible toxicities?
4. What are the data for combined preoperative chemoradiotherapy to maximize the chance of resectability?
5. What is the role for adjuvant chemotherapy?

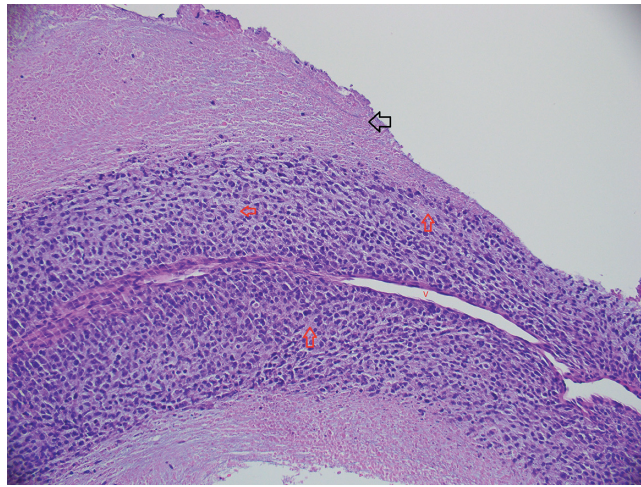


Fig. 1. Tumor sample HPF. Viable tumor surrounds central vessel, showing mild nuclear pleomorphism and a myxoid background, surrounded by tumor necrosis. Black arrow = necrosis; red arrows = myxoid stroma between viable tumor; V = vessel. Images credited to Daniel Griffin, MD (University of Kentucky,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

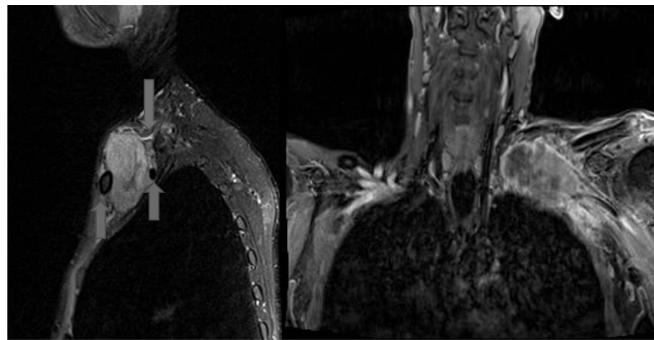


Fig. 2. Magnetic resonance imaging, sagittal STIR, and coronal postcontrast sequence, mass posterior to the clavicle (purple arrow) and abutting the left subclavian vessels (blue arrow) and enmeshed in the brachial plexus (red arrow). Images credited to Mark Murray, MD (University of Kentucky) (Department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

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GRAY ZONE EXPERT OPINION

Treating the Unknown: First Refine the Diagnosis



With over 100 subtypes of sarcoma with variable biology, further tests are needed to refine the diagnosis.¹ 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.² 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.³ The feasibility of concurrent adriamycin and ifosfamide with 25 Gy in 5 fractions was recently established.⁴ 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

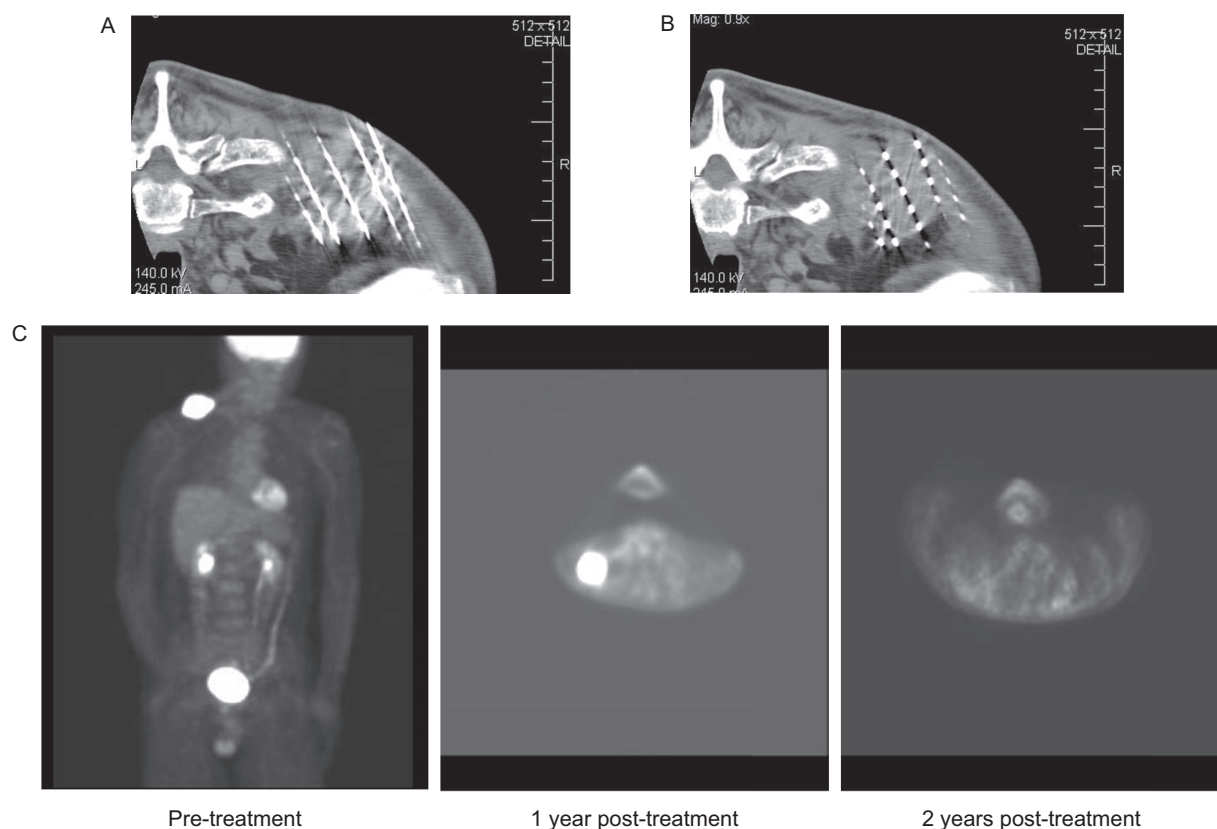


Fig. 1. After 50 Gy in 25 fractions to a radiation-associated sarcoma, (A) 12 needles were inserted under computed tomography guidance to (B) place 70 ¹²⁵I seeds within the sarcoma. An additional 55 Gy was given to 93% of the gross tumor volume. (C) Positron emission tomography/computed tomography before and after treatment.

carotid artery disease that precluded surgery. Because the patient was now inoperable, I used a permanent ^{125}I implant to achieve local control (Fig. 1). Unfortunately, the patient eventually developed brachial plexopathy.

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Recurrence Risk Related Rationale



There are competing risks associated with each treatment decision, so multidisciplinary collaboration is critical for complex sarcoma cases like this.¹ 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.² 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.³ Some patients may achieve durable local control with this nonoperative approach.

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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 case¹, 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.² 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.³

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.

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ChatGPT-4: Balancing Systemic and Local Control for Optimal Outcomes

User: You are an expert radiation oncologist from an academic center.

Please give your recommendation on the following case:

“ ... ”

Please give a specific recommendation of your most favored therapeutic approach in this patient case based on the available information and your reasoning for it.

ChatGPT-4: Based on the provided information, the patient has a locally advanced, likely metastatic soft tissue sarcoma with significant neurological symptoms and involvement of the brachial plexus. Given the worsening of the patient's lung metastases while on concurrent ifosfamide and radiation therapy, it is essential to focus on systemic treatment to control both local and metastatic disease.

My recommendation for this case would be as follows:

- 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.
- 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.
- 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.
- Consult with a pain management specialist and/or palliative care team to address the patient's neuropathic pain and ensure appropriate symptomatic relief.
- 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.
- 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.

- 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.

User: What would be your initial therapy and sequencing of the overall regimen?

ChatGPT-4: Given the patient's locally advanced and metastatic soft tissue sarcoma with significant neurological symptoms and brachial plexus involvement, the priority should be to control both local and systemic disease. My recommendation for the initial therapy and sequencing of the overall regimen would be as follows:

- Initiate systemic chemotherapy with the ifosfamide, doxorubicin, and mesna (AIM) regimen. The AIM regimen is a standard first-line treatment for metastatic soft tissue sarcomas and has shown efficacy in controlling the disease. The primary goal is to control the systemic metastatic disease and potentially reduce the tumor burden at the primary site.
- After a few cycles of AIM chemotherapy, reassess the patient's response 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.
- If local disease control is achieved with systemic therapy, consider consolidative radiation therapy to the primary site. This can help in reducing the risk of local recurrence and further improve symptom management. In this case, radiation therapy can be administered after completing the AIM chemotherapy cycles.
- 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.
- Throughout the treatment course, consult with a pain management specialist and/or palliative care team to address the patient's neuropathic pain and ensure appropriate symptomatic relief.
- 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 prioritize systemic control of the metastatic disease with chemotherapy, followed by consolidative radiation therapy to the primary site for local control if the systemic therapy is successful. This sequence aims to optimize the control of both local and metastatic disease while addressing the patient's symptoms and improving their quality of life.

User: What are the optimal preoperative chemotherapy regimens given the unknown pathological subtype? What is the risk of radiation recall?

ChatGPT-4: In the case of an unknown pathological subtype of soft tissue sarcoma, selecting the optimal preoperative chemotherapy regimen can be challenging. However, based on the available clinical and histological information, the most commonly used chemotherapy regimens for soft tissue sarcomas can still be considered. These regimens are generally based on anthracyclines and alkylating agents, as they have shown efficacy across a range of sarcoma subtypes.

The most common regimen for preoperative chemotherapy in soft tissue sarcomas is the combination of doxorubicin (an anthracycline) and ifosfamide (an alkylating agent). This regimen, as mentioned earlier, is known as AIM (ifosfamide, doxorubicin, and mesna). Mesna is included to protect the urinary tract from ifosfamide-induced toxicity. The AIM regimen has shown activity across a variety of sarcoma subtypes and can be used as a reasonable option in the setting of an unknown pathological subtype.

Another option could be the use of single-agent doxorubicin, which is a standard treatment for many soft tissue sarcoma subtypes. However, the combination of doxorubicin and ifosfamide has been reported to have a higher response rate compared to single-agent doxorubicin.

Regarding radiation recall, it is a rare but potentially severe inflammatory reaction in previously irradiated areas that can be triggered by certain chemotherapeutic agents, including doxorubicin. The risk of radiation recall is generally low, with the reported incidence varying between 2-23% depending on the chemotherapeutic agent used. The exact cause of radiation recall remains unclear, and the risk factors for its development are not well-established.

To minimize the risk of radiation recall, careful consideration should be given to the timing of chemotherapy and radiation therapy. In general, radiation recall is more likely to occur when the chemotherapeutic agent is administered shortly after the completion of radiation therapy. Therefore, allowing for a sufficient time interval between the completion of radiation therapy and the initiation of chemotherapy might help reduce the risk. However, the optimal timing should be individualized, considering the patient's clinical situation and the potential benefits and risks of the combined treatment approach.

It is essential to educate the patient about the potential risk of radiation recall and monitor for any signs of skin inflammation, pain, or other symptoms in the previously irradiated area during chemotherapy. In case radiation recall develops, appropriate management may include the

temporary discontinuation or dose modification of the chemotherapeutic agent, as well as the initiation of symptomatic treatment, such as corticosteroids, analgesics, and antibiotics if needed.

User: What are the treatment volumes, dose, and possible toxicities?

ChatGPT-4: In the case of radiation therapy for a soft tissue sarcoma involving the brachial plexus, the treatment volumes, dose, and possible toxicities are as follows:

Treatment Volumes:

- a) Gross Tumor Volume (GTV): The visible tumor on imaging studies (MRI or CT scan) and clinical examination.
- b) Clinical Target Volume (CTV): The GTV plus a margin to include potential microscopic disease extension. The margin size depends on the sarcoma subtype, location, and adjacent structures, typically ranging from 1-2 cm.
- c) Planning Target Volume (PTV): The CTV plus an additional margin to account for uncertainties in patient positioning and internal organ motion, usually ranging from 0.5-1 cm.

Dose:

- a) The recommended dose for preoperative or definitive radiation therapy in soft tissue sarcomas ranges from 50-66 Gy, typically given in daily fractions of 1.8-2 Gy. The specific dose depends on factors such as tumor size, location, histology, and the proximity of critical structures.
- b) For postoperative radiation therapy in cases of incomplete resection or positive margins, the dose can range from 60-66 Gy, while in cases of complete resection with negative margins, a dose of 50-60 Gy may be appropriate.

Possible Toxicities:

- Radiation therapy for a soft tissue sarcoma involving the brachial plexus can lead to various acute and late toxicities, including:
 - Acute toxicities (during or shortly after treatment):
 - a) Skin reactions: erythema, dry or moist desquamation
 - b) Fatigue
 - c) Pain or discomfort in the irradiated area
 - d) Edema or swelling in the treatment area
 - Late toxicities (months to years after treatment):
 - a) Fibrosis or scarring of the irradiated tissue, potentially affecting the range of motion and function

- b) Lymphedema: swelling due to impaired lymphatic drainage
- c) Brachial plexopathy: nerve damage leading to pain, numbness, tingling, and muscle weakness in the affected arm
- d) Radiation-induced malignancies: a rare but potential risk, particularly with high-dose radiation
- e) Damage to adjacent structures, such as blood vessels or lung tissue, depending on the tumor location and radiation dose

It is crucial to carefully plan the radiation therapy to minimize the dose to adjacent critical structures and reduce the risk of treatment-related toxicities. Regular monitoring and follow-up during and after radiation therapy are essential to identify and manage any treatment-related side effects promptly.

User: What are the data for combined preoperative chemoradiotherapy to maximize the chance of resectability?

ChatGPT-4: Combined preoperative chemoradiotherapy has been explored in soft tissue sarcomas as a means to improve resectability, increase the likelihood of negative surgical margins, and potentially improve local control and overall survival. The rationale behind preoperative chemoradiotherapy is that it may shrink the tumor, making it more amenable to surgical resection, and may also have a radiosensitizing effect, enhancing the efficacy of radiation therapy.

However, the available data on combined preoperative chemoradiotherapy in soft tissue sarcomas is limited and mostly comes from retrospective analyses, single-arm phase II trials, or small prospective randomized trials. There is no definitive evidence from large-scale, randomized, controlled trials to establish the superiority of combined preoperative chemoradiotherapy over single-modality neoadjuvant therapy (chemotherapy or radiotherapy alone) in terms of resectability, local control, or survival outcomes.

A few relevant studies on preoperative chemoradiotherapy in soft tissue sarcomas include:

The RTOG 9514 trial: This phase II trial evaluated the use of preoperative chemoradiotherapy with ifosfamide and etoposide in patients with high-grade, extremity soft tissue sarcomas. The trial reported a 5-year local control rate of 78% and overall survival of 56%. However, the trial included only 45 patients, and the results should be interpreted with caution.

The STRASS trial: This multicenter, randomized phase III trial compared preoperative radiotherapy alone with preoperative chemoradiotherapy using an anthracycline-based regimen in patients with high-risk, resectable, soft tissue sarcomas of the extremities or trunk wall. The trial showed no significant difference in overall survival, disease-free survival, or local recurrence rates between the two arms. However, the trial was underpowered due to low patient accrual.

Given the limited and inconclusive data, the use of combined preoperative chemoradiotherapy in soft tissue sarcomas should be individualized, taking into account the patient's performance status, tumor characteristics, and potential benefits and risks associated with the combined therapy.

In cases where maximizing the chance of resectability is a priority, neoadjuvant therapy (either chemotherapy, radiotherapy, or both) may be considered as part of a multidisciplinary approach. Close collaboration between medical oncologists, radiation oncologists, and surgical oncologists is essential to optimize the treatment plan and ensure the best possible outcomes for the patient.

User: What is the role for adjuvant chemotherapy?

ChatGPT-4: The role of adjuvant chemotherapy in soft tissue sarcomas remains a topic of debate and controversy. Adjuvant chemotherapy is given after surgery with the aim of eradicating any residual microscopic cancer cells, decreasing the risk of local and distant recurrence, and potentially improving overall survival. The most commonly used chemotherapy agents in adjuvant settings for soft tissue sarcomas are doxorubicin and ifosfamide, often in combination.

Several clinical trials and meta-analyses have been conducted to evaluate the role of adjuvant chemotherapy in soft tissue sarcomas, but the results have been inconsistent:

The Italian Sarcoma Group and the Spanish Sarcoma Group conducted a randomized trial comparing adjuvant chemotherapy with doxorubicin and ifosfamide versus observation alone in high-grade soft tissue sarcoma patients. The trial showed a significant improvement in disease-free survival with adjuvant chemotherapy but no significant difference in overall survival.

A meta-analysis by Pervaiz et al. (2008) found a statistically significant improvement in local recurrence-free survival, distant recurrence-free survival, and overall survival with adjuvant chemotherapy in soft tissue sarcoma patients. However, the absolute benefit in overall survival was small (about 5%).

Another meta-analysis by the Sarcoma Meta-Analysis Collaboration (1997) found a small but statistically significant improvement in overall survival with adjuvant chemotherapy. However, subsequent updates of this meta-analysis did not find any significant survival advantage.

Given the conflicting evidence, the role of adjuvant chemotherapy in soft tissue sarcomas remains uncertain. The potential benefits of adjuvant chemotherapy must be weighed against the potential side effects and the impact on the patient's quality of life.

Current guidelines recommend considering adjuvant chemotherapy for patients with high-grade, large, or deep-seated soft tissue sarcomas, particularly if the risk of local or distant recurrence is high. The decision to use adjuvant chemotherapy should be individualized, taking into account the patient's performance status, tumor characteristics, and the potential benefits and risks of the treatment. In any case, a multidisciplinary approach involving medical oncologists, radiation

oncologists, and surgical oncologists is essential for optimizing the treatment plan and ensuring the best possible outcomes for the patient.

User: Please summarize the other experts' recommendations in short sentences.

ChatGPT-4:

Expert 1: Recommends further testing to refine the diagnosis, considering concurrent ifosfamide and 50 Gy for MPNST if confirmed, and adjuvant chemotherapy with adriamycin and ifosfamide for lung metastases.

Expert 2: Advocates for a multidisciplinary approach, prioritizing local or systemic control based on primary concern, considering neoadjuvant AIM if downstaging is needed, and using ifosfamide-based chemoradiation for local control in non-candidates for curative resection.

Expert 3: Suggests neoadjuvant radiation therapy before surgery, stating that data for adding chemotherapy is inconclusive, and provides guidelines for treatment volumes and doses, while mentioning possible toxicities.

User: As an expert radiation oncologist, which of the above experts' recommendation do you think the most proper?

ChatGPT-4: As an expert radiation oncologist, I believe a combination of the recommendations from Experts 2 and 3 would be most appropriate for the patient described above. A multidisciplinary approach is essential in managing such a complex case.

First, I agree with Expert 2 that it is crucial to identify the most clinically significant risk for the patient, whether it is local or distant progression. This will help in determining whether to prioritize local or systemic control first.

Next, I would consider neoadjuvant radiotherapy as suggested by Expert 3, given the challenging tumor location and the potential benefit in improving the likelihood of an R0 resection. The treatment volumes and doses recommended by Expert 3 are also reasonable.

Regarding chemotherapy, I would consider the use of neoadjuvant AIM chemotherapy, as suggested by Expert 2, if the multidisciplinary team determines that downstaging would improve the likelihood of curative resection or meaningfully improve postoperative function. As Expert 2 mentioned, this allows an in vivo assessment of chemotherapy efficacy and time to assess the risk of metastasis before undertaking a potentially morbid local therapy.

Ultimately, 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 medical oncologists, radiation

oncologists, and surgical oncologists will help optimize the treatment plan and ensure the best possible outcomes for the patient.

User: At the beginning, you said that "My recommendation for this case would be as follows: 1. Continue the current systemic chemotherapy regimen with ifosfamide, doxorubicin, and mesna (AIM); 2. Reassess the patient's response to the AIM regimen after a few cycles, both clinically and radiographically; 3. 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. Consult with a pain management specialist and/or palliative care team to address the patient's neuropathic pain and ensure appropriate symptomatic relief. and so on." In this case, which expert's recommendation is your initial suggestion closest to?

ChatGPT-4: My initial suggestion is closest to Expert 2's recommendation. Both recommendations prioritize understanding the patient's primary concerns and risks (local or distant progression), emphasize the importance of a multidisciplinary approach, and consider neoadjuvant chemotherapy, specifically with AIM, to assess the in vivo efficacy of chemotherapy and the risk of metastasis before undertaking local therapy. Additionally, both recommendations address the need for a tailored approach that accounts for the patient's individual circumstances and tumor characteristics.

User: After seeing the other experts' recommendations, are you going to update your own recommendation of your most favored therapeutic approach in this patient case? If so, what is your updated recommendation and which expert/experts is your update based on?

ChatGPT-4: After reviewing the other three experts' recommendations, I would like to update my recommendation for the patient's therapeutic approach, incorporating aspects from Experts 2 and 3. My updated recommendation is as follows:

- Assess the most clinically significant risk for the patient, whether it is local or distant progression, in order to determine whether to prioritize local or systemic control first.
- Consider neoadjuvant radiotherapy, as suggested by Expert 3, due to the tumor's challenging location and potential benefit in improving the likelihood of an R0 resection.
- If the multidisciplinary team determines that downstaging is needed to improve the likelihood of curative resection or meaningfully improve postoperative function, consider neoadjuvant AIM chemotherapy, as suggested by Expert 2. This allows an in vivo assessment of chemotherapy efficacy and time to assess the risk of metastasis before undertaking a potentially morbid local therapy.
- Consult with a pain management specialist and/or palliative care team to address the patient's neuropathic pain and ensure appropriate symptomatic relief.

- Continuously reassess the patient's response to treatment, both clinically and radiographically, to guide further management decisions and adapt the treatment plan accordingly.

My updated recommendation combines the strengths of Experts 2 and 3's suggestions, emphasizing a multidisciplinary approach and tailoring the treatment plan to the individual patient's circumstances and tumor characteristics.