Pediatric Congenital Hematologic Disorders Research Center
مرکزتحقیقات بیماری های خونی مادرزادی کودکان

Bone sarcoma

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NCCN Guidelines Version 2.2012
Ewing's Sarcoma

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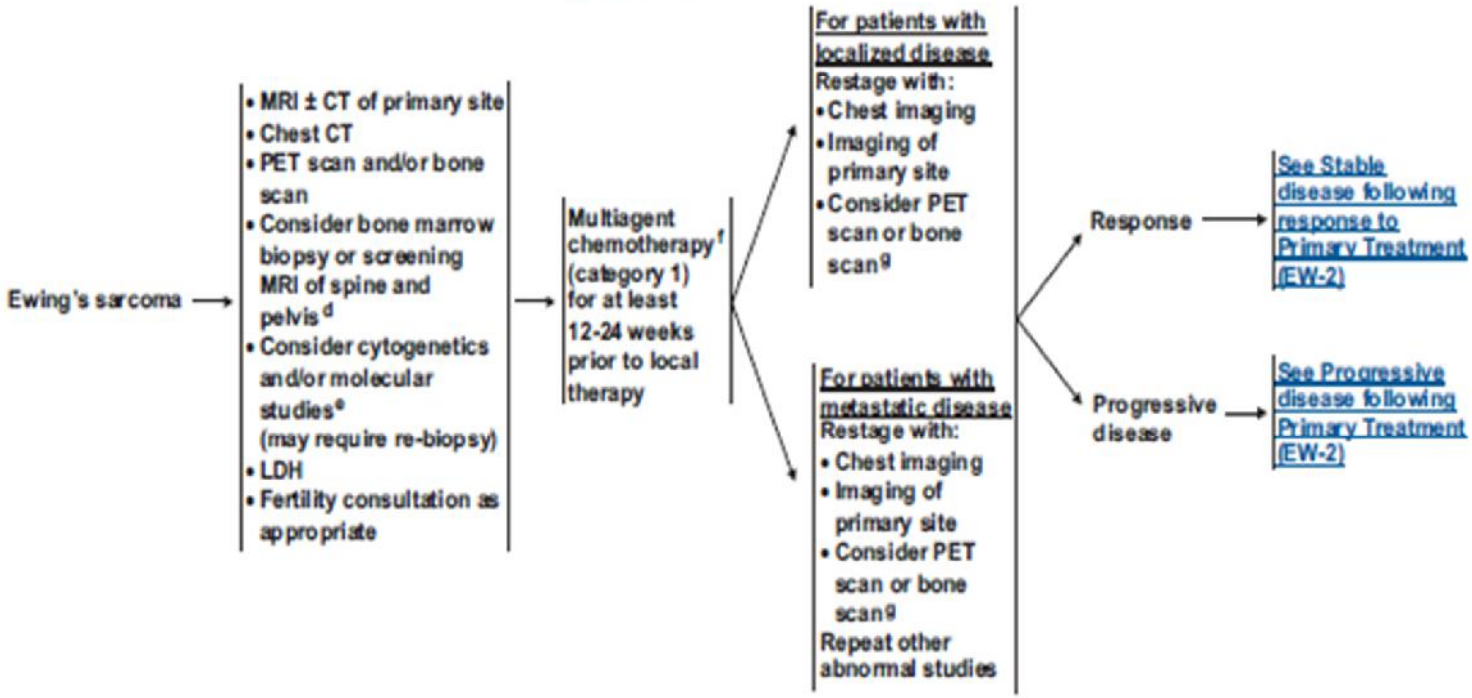
Discussion



[a] See Multidisciplinary Team (BONE-A)

[b] See Principles of Bone Cancer Management (BONE-B)

[c] Any member of the Ewing's family of tumors can be treated using this algorithm including primitive neuroectodermal tumor, Askin's tumor, PNET of bone and extraosseous Ewing's sarcoma.

[d] Kumar J, Seith A, Kumar A, et al. Whole-body MR imaging with the use of parallel imaging for detection of skeletal metastases in pediatric patients with small cell neoplasms: comparison with skeletal scintigraphy and FDG PET/CT. Pediatr Radiol 2008;38:953-962. Epub 2008 Jul 18.

[e] 90% of Ewing's family tumors will have one of four specific cytogenetic translocations.

[f] See Bone Cancer Systemic Therapy Agents (BONE-C)

[g] Use the same imaging technique that was performed in the initial workup.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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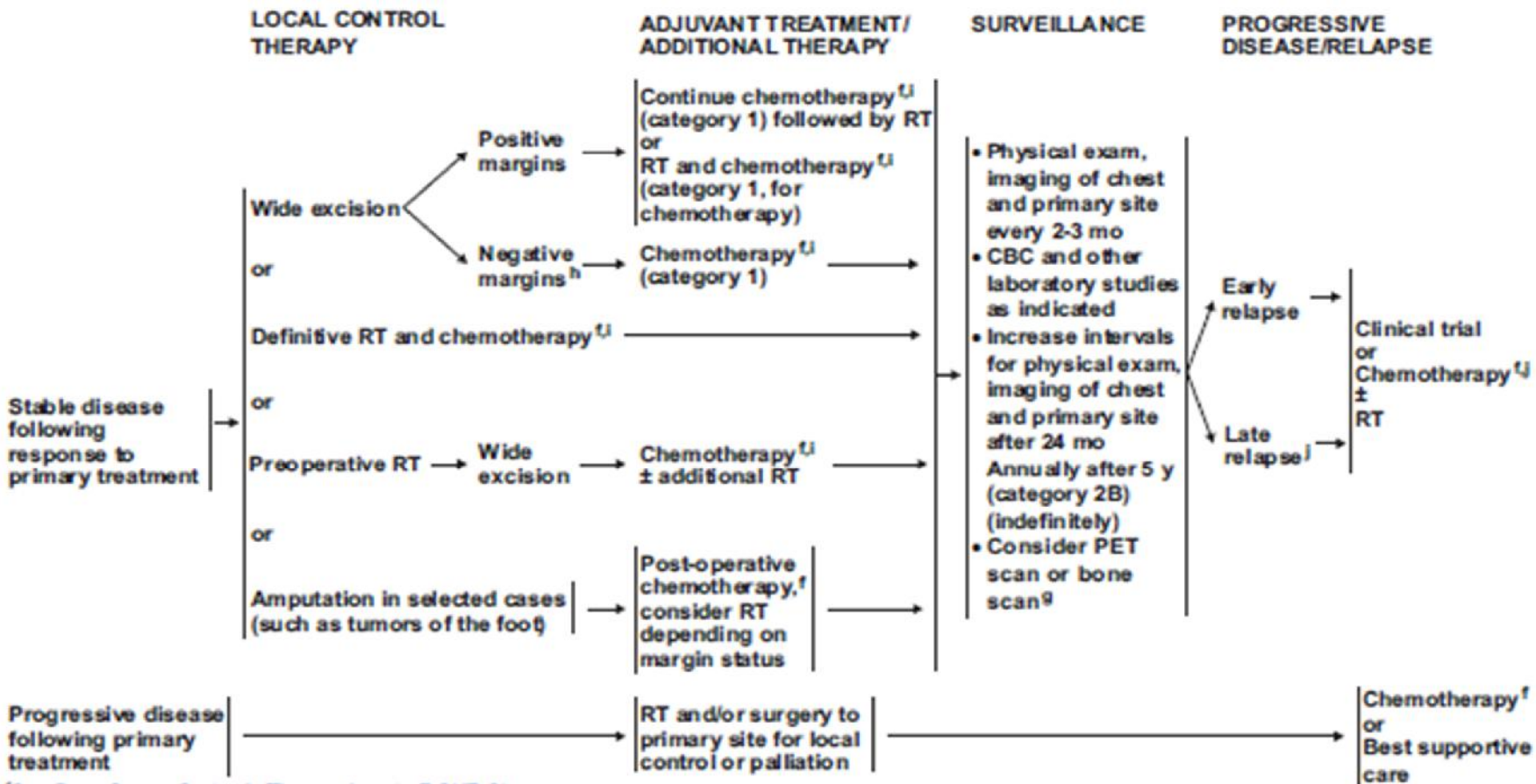

[f] See Bone Cancer Systemic Therapy Agents (BONE-C).
[g] Use the same imaging technique that was performed in the initial workup.
[h] RT may be considered for close margins.
[i] There is category 1 evidence for between 28 and 49 weeks of chemotherapy depending on the chemotherapy and dosing schedule used.
[j] For late relapse, consider re-treatment with previously effective regimen.

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Osteosarcoma

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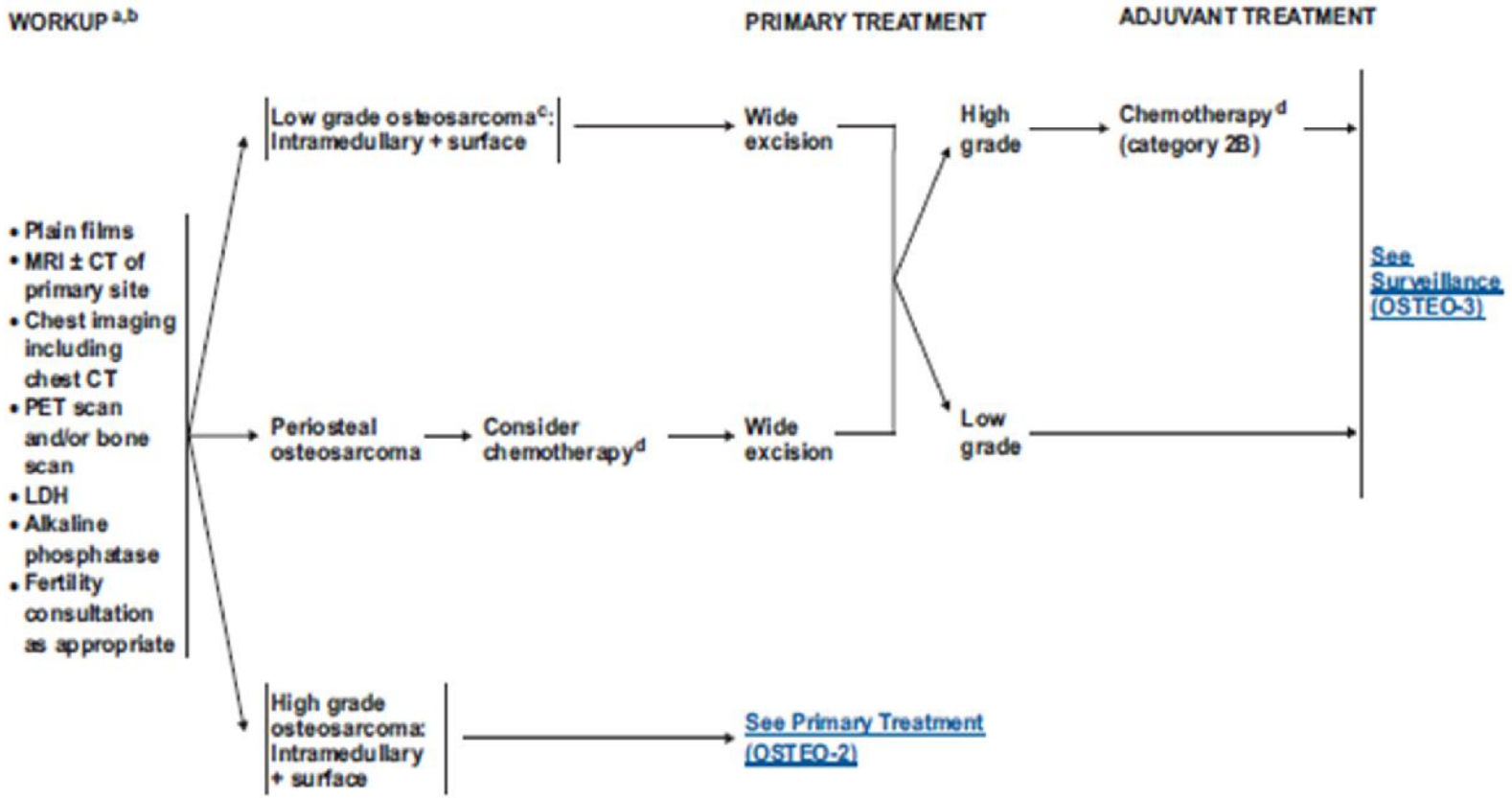

[a] See Multidisciplinary Team (BONE-A).
[b] See Principles of Bone Cancer Management (BONE-B).
[c] Dedifferentiated parosteal osteosarcomas are not considered to be low grade tumors.
[d] See Bone Cancer Systemic Therapy Agents (BONE-C).

Note: All recommendations are category 2A unless otherwise indicated.
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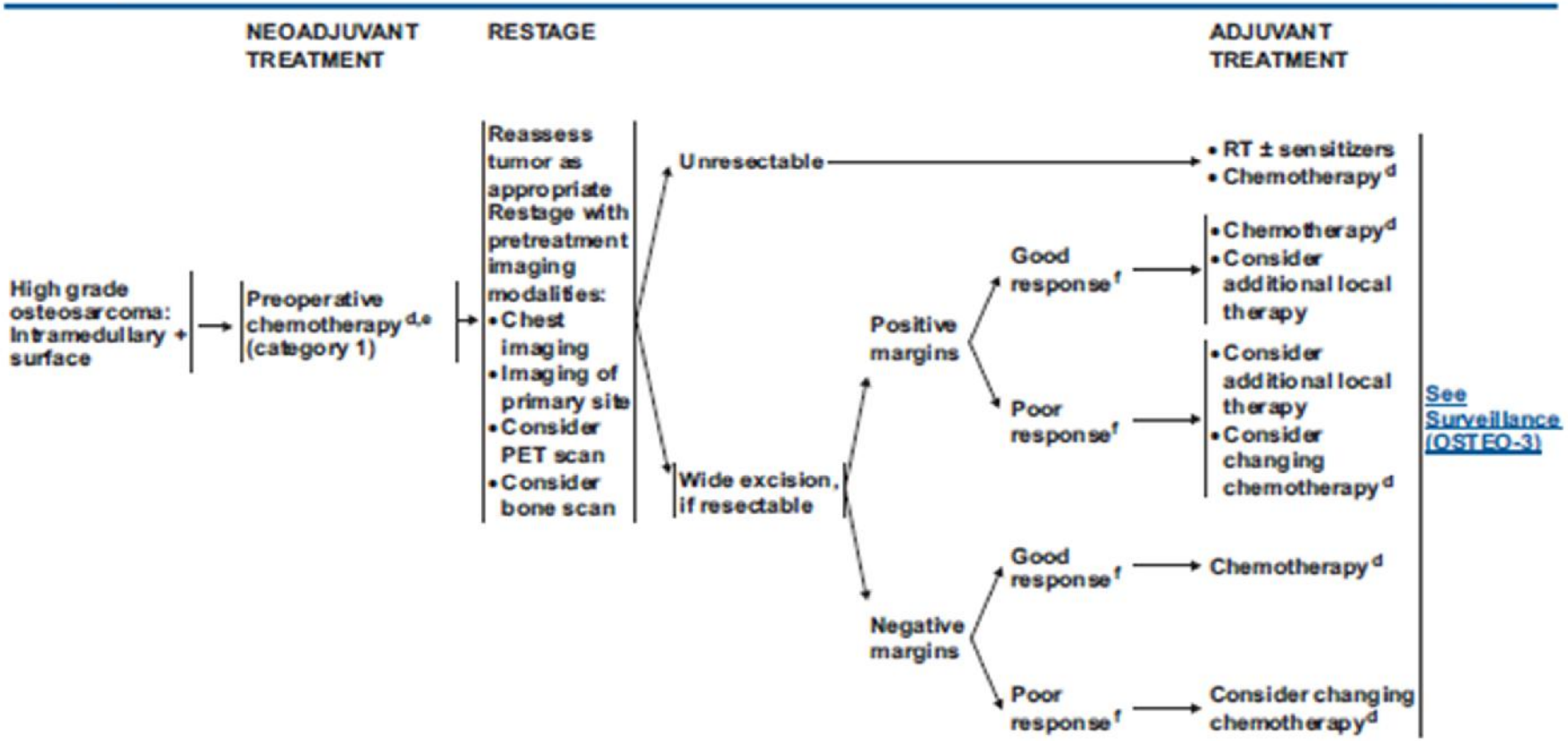

[d] See Bone Cancer Systemic Therapy Agents (BONE-C)
[e] Selected elderly patients may benefit from immediate surgery.
[f] Response defined by pathologic mapping.

Note: All recommendations are category 2A unless otherwise indicated.
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SURVEILLANCE

- Physical exam
- Chest imaging
- CBC and other laboratory studies as indicated
- Imaging of primary site[g]: Consider PET scan and/or bone scan (category 2B)
- Reassess function every visit

Follow-up schedule:

- Every 3 mo for y 1 and 2
- Every 4 mo for y 3
- Every 6 mo for y 4 and 5 and yearly thereafter

→ **Relapse** → Chemotherapy[d] and/or resection if possible

- Response → Surveillance
- Relapse → Resect or Best supportive care or Clinical trial or Samarium or Palliative RT

[d] See Bone Cancer Systemic Therapy Agents (BONE-C)

[g] Use the same imaging technique that was performed in the initial workup.

Note: All recommendations are category 2A unless otherwise indicated.
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The guidelines recommend the combination of cyclophosphamide, vincristine and doxorubicin (without the alternating cycle of ifosfamide and etoposide) as the preferred option for the treatment for primary metastatic disease at presentation.[102, 103] VAC/IE, VIDE and VIA regimens are included as alternative treatment options.

Patients should be restaged following primary treatment with an MRI of the lesion and chest imaging. PET scan and/or bone scan can be used for restaging depending on the imaging technique that was used in the initial workup. Patients responding to primary treatment should be treated with local control therapy. Local control options include wide excision with or without preoperative RT, definitive RT with chemotherapy or amputation in selected cases.[109-112]

Adjuvant chemotherapy with or without RT is recommended (regardless of surgical margins) following local control treatment (surgery or RT). The panel strongly recommends that the duration of chemotherapy should be between 28 and 49 weeks depending on the type of regimen and the dosing schedule (category 1).

Progressive disease following primary treatment is best managed with RT with or without surgery followed by chemotherapy or best supportive care.

Surveillance

Surveillance of patients with Ewing's sarcoma consists of a physical exam, CBC and other laboratory studies, imaging of the chest and primary site every 2-3 months.[113, 114] Surveillance intervals should be increased after 2 years. Long-term surveillance should be performed annually after 5 years (category 2B).

Treatment for Relapsed or Refractory Disease

About 30%-40% of patients with Ewing's sarcoma experience recurrence (local and/or distant) and have a very poor prognosis. The timing and type of recurrence are the important prognostic factors. Patients with a longer time to first recurrence have a better chance of survival following recurrence. Late relapse (2 years or more from the time of original diagnosis), lung only metastases, local recurrence that can be treated with radical surgery and intensive chemotherapy are the most favorable prognostic factors, whereas early relapse (less than 2 years from the time of original diagnosis) with metastases in lungs and/or other sites, recurrence at local and distant sites, elevated LDH at initial diagnosis and initial recurrence are considered as adverse prognostic factors.[115-117] In a recent retrospective analysis, site of first relapse and time to first relapse were significant prognostic factors for adult patients with localized Ewing's sarcoma.[118] The probability of 5-year post-relapse survival was 50% and 13% respectively for patients with local and distant relapse. The probability of 5-year post-relapse survival was also significantly higher for patients with late relapse than for those with early relapse (50% and 8% respectively; $p < 0.0001$).[118]

Ifosfamide in combination with etoposide with or without carboplatin has been evaluated in clinical trials for the treatment of patients with relapsed or refractory sarcoma.[119, 120] In phase II study, the combination of ifosfamide with mesna and etoposide was highly active with acceptable toxicity in the treatment of recurrent sarcomas in children and young adults.[119] In phase I/II studies conducted by the Children's Cancer Group, the overall response rate in patients with recurrent or refractory sarcoma was 51%; OS at 1 and 2 years was 49% and 28%, respectively. OS appeared significantly improved in patients who had complete or partial response.[120]

Docetaxel in combination with gemcitabine was found to be well tolerated and demonstrated antitumor activity in the treatment of children and young adults with refractory bone sarcoma.[121] Topoisomerase I inhibitors, topotecan[122-125] and irinotecan[126-128] in combination with cyclophosphamide and temozolomide respectively have shown promising response rates in patients with relapsed or refractory solid tumors. Cyclophosphamide and topotecan produced 44% response rate (35% of patients had complete response and 9% had partial response) in patients with recurrent or refractory Ewing's sarcoma.[123] After a median follow-up of 23.1 months, 25.9% of patients were in continuous remission. In retrospective analysis of patients with recurrent or progressive Ewing's sarcoma treated with irinotecan and temozolomide, the median time-to-progression (TTP) was 8.3 months.[126] In the subset of patients with recurrent disease, it was 16.2 months. Median TTP was better for patients who were in a 2-year first remission and for those with primary localized disease than for those who relapsed within 2 years from diagnosis and for patients with metastatic disease at diagnosis.

Inhibition of insulin-like growth factor-1 receptor (IGF-1R) may be an interesting approach in the treatment of some subtypes of sarcomas. Monoclonal antibodies such as figitumumab and R1507 have demonstrated safety and suggested possible efficacy in early phase trials in patients with relapsed or refractory sarcomas including Ewing's sarcoma.

HDT/SCT has been evaluated in patients with relapsed or progressive Ewing's sarcoma in several small studies.[129-135] The role of this approach in high-risk patients is yet to be determined in prospective randomized studies.

NCCN Recommendations

Treatment options for patients with relapsed or refractory disease include participation in a clinical trial, chemotherapy with or without RT. If a relapse is delayed, as sometimes occurs with this sarcoma, re-treating with previously effective regimen may be useful. The guidelines have included the following regimens as options for patients with relapsed or refractory disease:

- Cyclophosphamide and topotecan
- Temozolomide and irinotecan
- Ifosfamide and etoposide
- Ifosfamide, carboplatin and etoposide
- Docetaxel and gemcitabine

All patients with recurrent and metastatic disease should be considered for clinical trials investigating new treatment approaches.

Osteosarcoma

Osteosarcoma is the most common primary malignant bone tumor in children and young adults.[2] The median age for all osteosarcoma patients is 20 years. Osteosarcoma comprises a family of lesions with a variety of histological features and natural histories. Osteosarcomas are broadly classified into intramedullary, surface and extraskeletal.[136]

High-grade intramedullary osteosarcoma is the classic or conventional form comprising nearly 80% of osteosarcoma.[136] It is a spindle cell tumor that produces osteoid or immature bone. The most frequent sites are the metaphyseal areas of the distal femur or proximal tibia, which are the sites of maximum growth. Low-grade intramedullary osteosarcoma comprises of less than 2% of all osteosarcomas and the most common sites are similar to that of conventional osteosarcoma.[137]

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NCCN Recommendations

Wide excision is the primary treatment for patients with low-grade (intramedullary and surface) osteosarcomas and periosteal lesions. Although chemotherapy (neoadjuvant or adjuvant) has been used in the treatment of patients with periosteal osteosarcoma, there is no data to support that the addition of chemotherapy to wide excision improves outcome in patients with periosteal osteosarcoma.[164, 165] In a review of 119 patients with periosteal sarcoma published by the European Musculoskeletal Oncology Society (EMSOS), the use of neoadjuvant chemotherapy was not a prognostic factor, although it was used in the majority of the patients.[165] More recently Cesari and colleagues also reported similar findings; the 10-year OS rate was 86% and 83% respectively for patients who received adjuvant chemotherapy with surgery and those who were treated with underwent surgery alone ($p = 0.73$).[164] The guidelines recommend consideration of chemotherapy prior to wide excision for patients with periosteal lesions. Following wide excision (for resectable lesions), postoperative chemotherapy is recommended for patients with low-grade (intramedullary and surface) or periosteal sarcomas with pathologic findings of high grade disease.

Preoperative chemotherapy is preferred for those with high-grade osteosarcoma (category 1), prior to wide excision. Selected elderly patients may benefit from immediate surgery. Following wide excision, patients with a good histological response should continue to receive several more cycles of the same chemotherapy, whereas patients with a poor response should be considered for chemotherapy with a different regimen. An ongoing randomised trial of the European and American Osteosarcoma Study Group (EURAMOS1) is evaluating treatment strategies for resectable osteosarcoma based on histological response to pre-operative chemotherapy (www.euramos.org).

RT with or without sensitizers or adjuvant chemotherapy is recommended if the sarcoma remains unresectable following preoperative chemotherapy. Proton beam RT has been shown to be effective for local control in some patients with unresectable or incompletely resected osteosarcoma.[166]

Chemotherapy should include appropriate growth factor support. See the NCCN Guidelines for Myeloid Growth Factors in Cancer Treatment for growth factor support. The guidelines have included the following regimens for first-line therapy (primary/neoadjuvant/adjuvant) in patients with localized disease or primary therapy for metastatic disease:

- Cisplatin and doxorubicin
- MAP (High-dose methotrexate, cisplatin and doxorubicin)
- Doxorubicin, cisplatin, ifosfamide and high-dose methotrexate
- Ifosfamide, cisplatin and epirubicin

Surveillance

Once treatment is completed, surveillance should occur every 3 months for 2 years, then every 4 months for year 3, and then every 6 months for years 4 and 5 and yearly thereafter. Examination should include a complete physical, chest imaging, and imaging of the primary site. PET scan and/or bone scan (category 2B) may also be considered. Functional reassessment should be performed at every visit.

Treatment for Relapsed or Refractory Disease

About 30% of patients with localized disease and 80% of the patients presenting with metastatic disease will relapse. The presence of solitary metastases and complete resectability of the disease at first recurrence have been reported to be the most important prognostic indicators for improved survival, whereas patients not amenable to surgery and those

with a second or a third recurrence have a poor prognosis.[167-169] The prognostic significance of surgical clearance among patients with second and subsequent recurrences was also confirmed in a recent report of survival estimates derived from large cohorts of unselected patients treated at the COSS group trials.[170]

The combination of etoposide with cyclophosphamide or ifosfamide has been evaluated in clinical trials.[171, 172] In a phase II trial of French Society of Pediatric Oncology, ifosfamide and etoposide resulted in a response rate of 48% in patients with relapsed or refractory osteosarcoma.[172] In another phase II trial, cyclophosphamide and etoposide resulted in 19% response rate and 35% of stable disease in patients with relapsed high-risk osteosarcoma.[171] PFS at 4 months was 42%. Single agent gemcitabine and combination regimens such as docetaxel and gemcitabine, cyclophosphamide and topotecan, ifosfamide, carboplatin and etoposide have also been effective in the treatment of patients with relapsed or refractory bone sarcomas.[120, 121, 125, 173]

Samarium-153 ethylene diamine tetramethylene phosphonate (^{153}Sm-EDTMP), a bone seeking radiopharmaceutical has been evaluated in patients with locally recurrent or metastatic osteosarcoma or skeletal metastases.[174, 175] Andersen et al. have reported that ^{153}Sm-EDTMP with peripheral blood progenitor cell support had low non-hematologic toxicity and provided pain palliation for patients with osteosarcoma local recurrences or osteoblastic bone metastases.[174] Results of a recent dose finding study also demonstrated that ^{153}Sm-EDTMP can be effective in the treatment of patients with high-risk osteosarcoma.[175]

NCCN Recommendations

The optimal treatment strategy for patients with relapsed or metastatic disease has yet to be defined. If relapse occurs, the patient should receive second-line chemotherapy and/or surgical resection. Surveillance is recommended for patients who responded to second-line therapy. The guidelines have included the following regimens as options for patients with relapsed or refractory disease:

- Docetaxel and gemcitabine
- Cyclophosphamide and etoposide
- Cyclophosphamide and topotecan
- Gemcitabine
- Ifosfamide and etoposide
- Ifosfamide, carboplatin and etoposide
- High-dose methotrexate, etoposide and ifosfamide

Patients with progressive disease following second-line therapy should be treated with resection, RT for palliation or best supportive care. Participation in a clinical trial should be strongly encouraged. The guidelines have also included ^{153}Sm-EDTMP as one of the treatment options for patients with disease relapse following second-line therapy.

Malignant fibrous histiocytoma

MFH of the bone most frequently arises in the appendicular skeleton and is associated with both a high rate of local recurrence, local nodal and distal metastases.[176] The addition of chemotherapy to surgery has been shown to improve clinical outcomes in patients with nonmetastatic MFH.[177-179] In a European Osteosarcoma Intergroup study, adjuvant or neoadjuvant chemotherapy with doxorubicin and cisplatin resulted in good pathological response rates and survivals (quite comparable with those for osteosarcoma) in patients with nonmetastatic MFH.[179] Median