National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Bone Cancer

Version 2.2026 — December 19, 2025

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

NCCN Guidelines for Patients® available at www.nccn.org/patients

National Comprehensive Cancer Network®

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Þ Internal medicine
† Medical oncology
ᴛ Orthopedics
≠ Pathology
¥ Patient advocacy
€ Pediatric oncology
§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
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Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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Updates in Version 2.2026 of the NCCN Guidelines for Bone Cancer include:

BONE-B 1 of 7
- Footnote c added: Pembrolizumab and berahyaluronidase alfa-pmph subcutaneous injection may be substituted for IV pembrolizumab. Pembrolizumab and berahyaluronidase alfa-pmph has different dosing and administration instructions compared to IV pembrolizumab. (Also for BONE-B 2)

MS-1
- The discussion section has been updated to reflect the changes in the algorithm.

Updates in Version 1.2026 of the NCCN Guidelines for Bone Cancer include:

Global
- References updated throughout the guideline.

TEAM-1
- Footnote a added: Refer to the NCCN Distress Thermometer and Problem List, which includes social determinants of health. See NCCN Guidelines for Distress Management (DIS-A).

BONE-1
- Workup for potential bone metastasis as clinically indicated, imaging recommendations revised: Bone scan or FDG-PET/CT (category 2B) *and/or Skeletal survey, plain film, or CT (if multiple myeloma suspected)*

CHON-4
- Footnote k revised: Consider ~~comprehensive genomic profiling (CGP)~~*multigene panel testing (MGPT)* with a validated and/or FDA-approved assay to determine targeted therapy opportunities. (Also for CHOR-3 and EW-3)

CHOR-1
- Workup, 3rd bullet revised: Adequate cross-sectional imaging of primary site (eg, ~~x-ray,~~ MRI, CT) and screening MRI of spinal axis
- Histologic Subtype revised: Conventional ~~or~~ *(including* chondroid)

EW-1
- Workup
  - 6th bullet revised: Cytogenetics and/or ~~molecular studies~~ *biomarker testing*
  - 8th bullet revised: Fertility consultation should be ~~considered~~ *offered*
- Footnote d revised: Consider ~~CGP~~ *MGPT*... (Also for EW-3 and OSTEO-3)
- Footnote g revised: Ninety percent of Ewing sarcomas will have one of four specific ~~cytogenetic~~ *chromosome* translocations...For those who are negative, additional ~~molecular~~ *biomarker*...
- Footnote i added: For patients with mesenchymal chondrosarcoma, single-agent doxorubicin and doxorubicin/ifosfamide can be considered as primary systemic therapy treatment options. See BONE-B 1 of 7.
- Footnote j revised: Longer treatment prior to local control therapy can be considered in patients with metastatic disease based on response*; select patients with present, or impending, pathologic fracture or fungation may benefit from immediate surgery.*

Continued

Updates in Version 1.2026 of the NCCN Guidelines for Bone Cancer include:

GCTB-2
- Footnote removed and added to BONE-B: An FDA-approved biosimilar is an appropriate substitute for any systemic biologic therapy in the NCCN Guidelines. (Also for GCTB-3)

OSTEO-2
- Neoadjuvant Treatment revised: ~~Preoperative~~ *Perioperative* chemotherapy (category 1) *(preoperative preferred)*
- Footnote i added: There does not appear to be a survival benefit for individuals who have received neoadjuvant chemotherapy compared to adjuvant chemotherapy. Histologic response to neoadjuvant chemotherapy may provide prognostic information, but does not affect outcome. Bernthal NM, et al. Cancer 2012;118:5888-5893; Provisor AJ, et al. J Clin Oncol 1997;15:76-84.

OSTEO-4
- Relapse/Progression
  - Treatment option added: Excision, if possible or Clinical trial or RT *or Embolization/ablation* or Best supportive care

BONE-A
- Principles of Bone Cancer Management language updated throughout section: ~~molecular studies~~ *biomarker testing*

BONE-B 1 of 7
- Chondrosarcoma
  - Dedifferentiated
    - ◊ Preferred, 1st bullet revised: ~~Follow~~ *Consider* osteosarcoma regimens (category 2B)
    - ◊ Useful in Certain Circumstances, treatment options added as category 2A recommendations
      - – Pazopanib or Sunitinib
      - – Pembrolizumab or Nivolumab
      - – Sunitinib + Nivolumab
  - Mesenchymal, Preferred
    - ◊ 1st bullet revised: ~~Follow~~ Ewing sarcoma regimens (category 2B)
    - ◊ Treatment options added as category 2A recommendations
      - – Doxorubicin
      - – Doxorubicin/Ifosfamide
- Footnote b revised: Pembrolizumab is a systemic treatment option for adult and pediatric patients with unresectable or metastatic, MSI-high (MSI-H) or MMR deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. ~~Additional dosing recommendations are as follows: 200 mg IV Day 1, repeat every 3 weeks or 400 mg IV Day 1, repeat every 6 weeks until disease progression, unacceptable toxicity, or up to 24 months for treatment of patients with MSI-H bone cancer.~~ Not for giant cell tumor of bone.
- Footnote c revised: Consider ~~CGP~~ *MGPT* with a validated and/or FDA-approved assay to determine targeted therapy opportunities. TMB~~-high (TMB-H)~~ *testing is recommended* for patients with unresectable or metastatic tumors who have progressed following prior treatment and who have no satisfactory alternative treatment options. Not for giant cell tumor of bone.
- Footnote e added: Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

Continued
UPDATES

Updates in Version 1.2026 of the NCCN Guidelines for Bone Cancer include:

BONE-B 2 of 7
• Chordoma, Other Recommended: Pembrolizumab added as a category 2A recommendation

BONE-C 1 of 6
• Principles of Radiation Therapy language updated throughout section
- R0 replaced with: negative margins
- R1 replaced with: microscopically positive margins
- R2 replaced with: gross positive margins
- Footnote removed: R0 = No microscopic residual disease, R1 = Microscopic residual disease, R2 = Gross residual disease.

BONE-C 3 of 6
• Principles of Radiation Therapy
- Preoperative RT, 1st bullet, 1st sub-bullet revised: May be considered for marginally resectable tumors and is given concurrently with ~~consolidation~~ chemotherapy
- Postoperative RT, 1st bullet, 1st sub-bullet revised: Should begin within 60 days of surgery and is given concurrently with ~~consolidation~~ chemotherapy

BONE-D 1 of 2
• Principles of Pathology
- 4th bullet, 11th sub-bullet, Margin status
  - ◊ 1st diamond sub-bullet removed: R0, R1, or R2 (R classification system per AJCC)
  - ◊ 2nd diamond sub-bullet, 1st dash revised: Necrotic tumor at margin for Ewing sarcoma is considered a negative ~~(R0)~~ margin if there is a complete pathologic response.
- 4th bullet, 12th sub-bullet, Ancillary studies
  - ◊ 1st diamond sub-bullet revised: Decalcification *on a portion of the specimen* should optimally be performed with solutions that preserve RNA and DNA; *strong* acid-based decalcification (other than EDTA *or EDTA + formic acid solutions*) should therefore be avoided.

MULTIDISCIPLINARY TEAM[a]

Primary bone tumors and selected metastatic tumors should be evaluated and treated by a multidisciplinary team with expertise in the management of these tumors. The team should meet on a regular basis and should include:

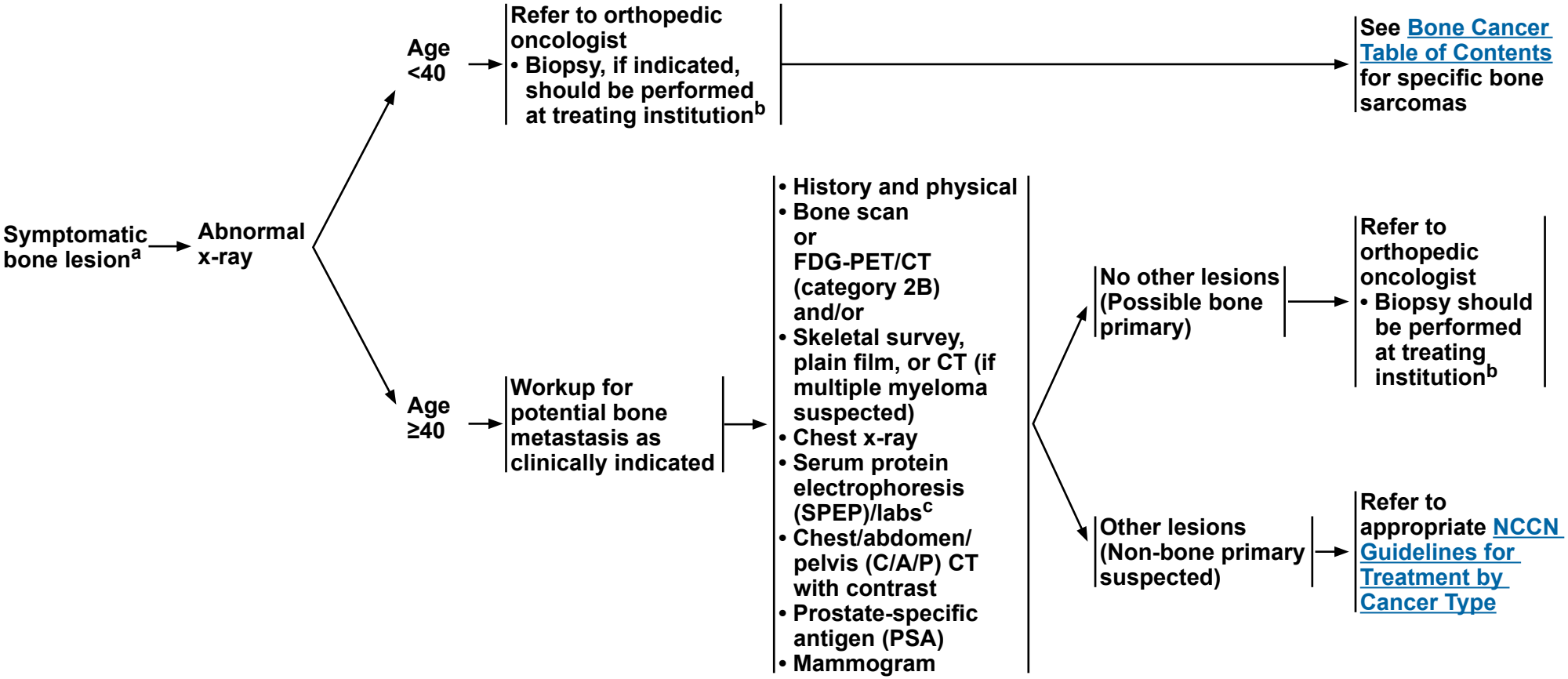
Core Group
- **Orthopedic oncologist**
- **Bone pathologist**
- **Medical/pediatric oncologist**
- **Radiation oncologist**
- **Musculoskeletal radiologist**

Specialists Critical in Certain Cases
- **Thoracic surgeon**
- **Plastic surgeon**
- **Interventional radiologist**
- **Physiatrist**
- **Vascular/general surgeon**
- **Neurosurgeon/orthopedic spine surgeon**
- **Palliative care physician**
- **Additional surgical subspecialties as clinically indicated**

[a] Refer to the NCCN Distress Thermometer and Problem List, which includes social determinants of health. See NCCN Guidelines for Distress Management (DIS-A).

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

WORKUP



[a] Multidisciplinary Team (TEAM-1).
[b] Principles of Bone Cancer Management (BONE-A).
[c] Labs include complete blood count (CBC) and comprehensive metabolic panel (CMP) with calcium to assess for hypercalcemia.

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

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Chondrosarcoma

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PRESENTATION[a,b,c]

Atypical cartilaginous tumors[d] → CHON-2

Low-grade extracompartmental appendicular tumors
or
Grade I axial tumors
or
High-grade (grade II, grade III)
or
Clear cell
or
Extracompartmental → CHON-3

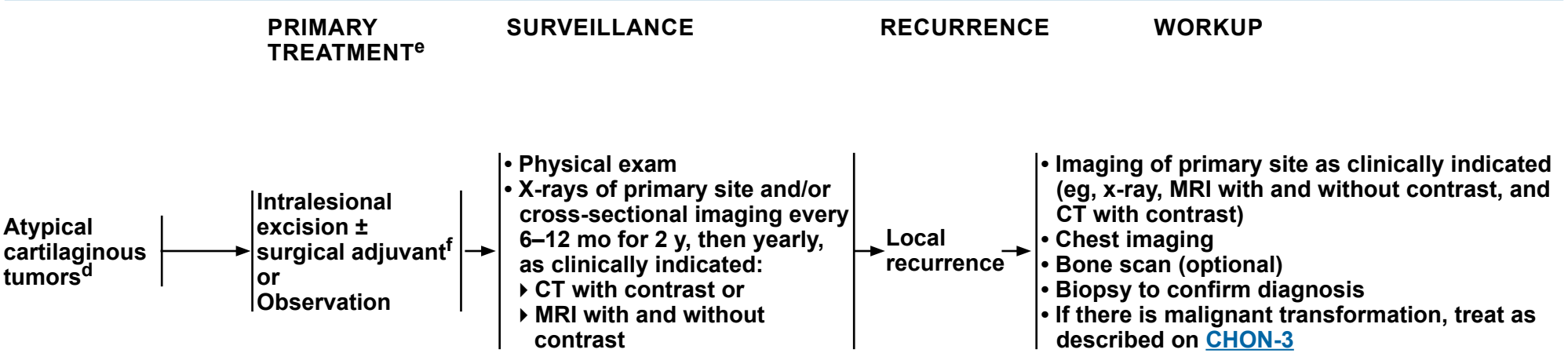
Metastatic disease at presentation → CHON-4

Dedifferentiated → CHON-3 and CHON-4

Mesenchymal → CHON-3 and CHON-4

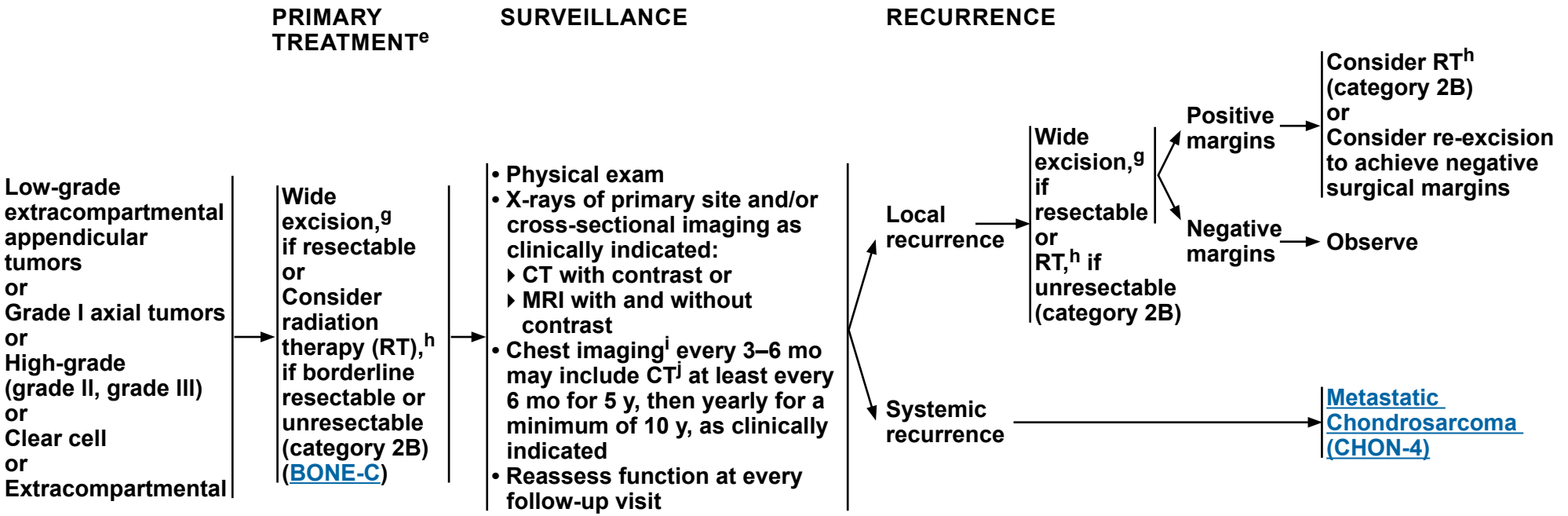
[a] Multidisciplinary Team (TEAM-1).
[b] Principles of Bone Cancer Management (BONE-A).
[c] There is considerable controversy regarding the grading of chondrosarcoma. In addition to histology, radiologic features, size, and location of tumors should also be considered in deciding local treatment.
[d] Defined as low-grade intracompartmental appendicular tumors. WHO Classification of Tumours Editorial Board. Soft Tissue and Bone Tumours. Lyon (France): International Agency for Research on Cancer; 2020. WHO Classification of Tumours Series, 5th Edition, Volume 3.

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



[d] Defined as low-grade intracompartmental appendicular tumors. WHO Classification of Tumours Editorial Board. Soft tissue and bone tumours. Lyon (France): International Agency for Research on Cancer; 2020. (WHO classification of tumours series, 5th ed.; vol. 3).
[e] There are no known standard chemotherapy options for conventional chondrosarcoma grades 1–3, but ivosidenib is an option for susceptible *IDH1* mutations. See Systemic Therapy Agents (BONE-B).
[f] Wide excision optional in expendable bones.

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



Dedifferentiated → May consider treating as osteosarcoma (category 2B) (OSTEO-1)

Mesenchymal → EW-1

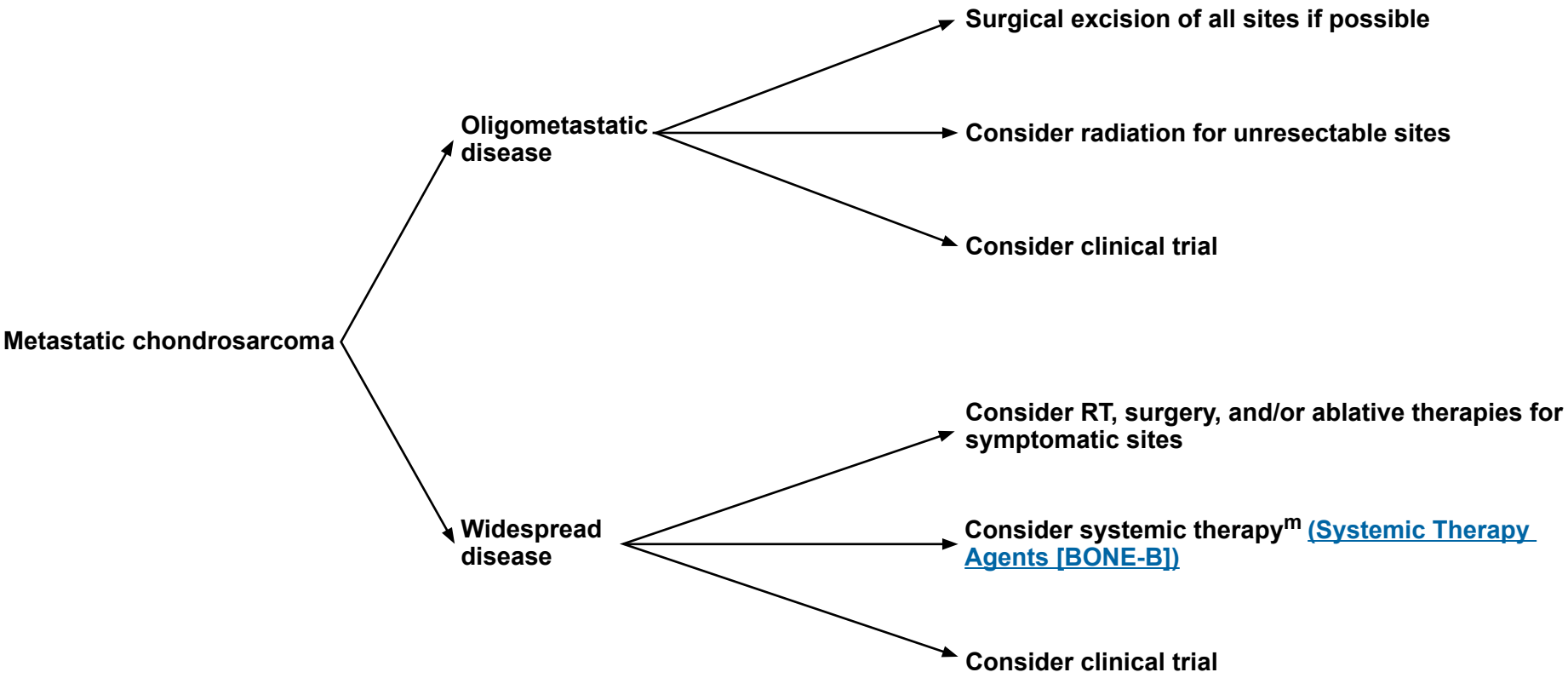
[e] There are no known standard chemotherapy options for conventional chondrosarcoma grades 1–3, but ivosidenib is an option for susceptible *IDH1* mutations. See Systemic Therapy Agents (BONE-B).
[g] Wide excision should provide histologically negative surgical margins. This may be achieved by either limb-sparing excision or limb amputation.
[h] Principles of Radiation Therapy (BONE-C).
[i] Based on physician's concern for risk of recurrence.
[j] Chest CT can be performed with or without contrast as clinically indicated. Low-dose, non-contrast CT is recommended for restaging.

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

METASTATIC CHONDROSARCOMA[k]

Dedifferentiated[l]

Mesenchymal (EW-1)



[k] Consider multigene panel testing (MGPT) with a validated and/or FDA-approved assay to determine targeted therapy opportunities.
[l] May consider treating as osteosarcoma (category 2B) (OSTEO-1).
[m] Consider testing for tumor mutational burden (TMB) and mismatch repair/microsatellite instability (MMR/MSI) as determined by a validated and/or FDA-approved assay to inform treatment options.

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

WORKUP[a]

- All patients should be evaluated and treated by a multidisciplinary team with expertise in the management of chordoma[a]
- History and physical
- Adequate cross-sectional imaging of primary site (eg, MRI, CT) and screening MRI of spinal axis
- C/A/P CT with contrast
- Consider FDG-PET/CT (skull base to mid-thigh)
- Consider bone scan if FDG-PET/CT is negative

HISTOLOGIC SUBTYPE

- Conventional (including chondroid) → Presentation and Primary Treatment (CHOR-2)
- Poorly differentiated or Dedifferentiated → NCCN Guidelines for Soft Tissue Sarcoma

[a] Multidisciplinary Team (TEAM-1).

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

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Chordoma

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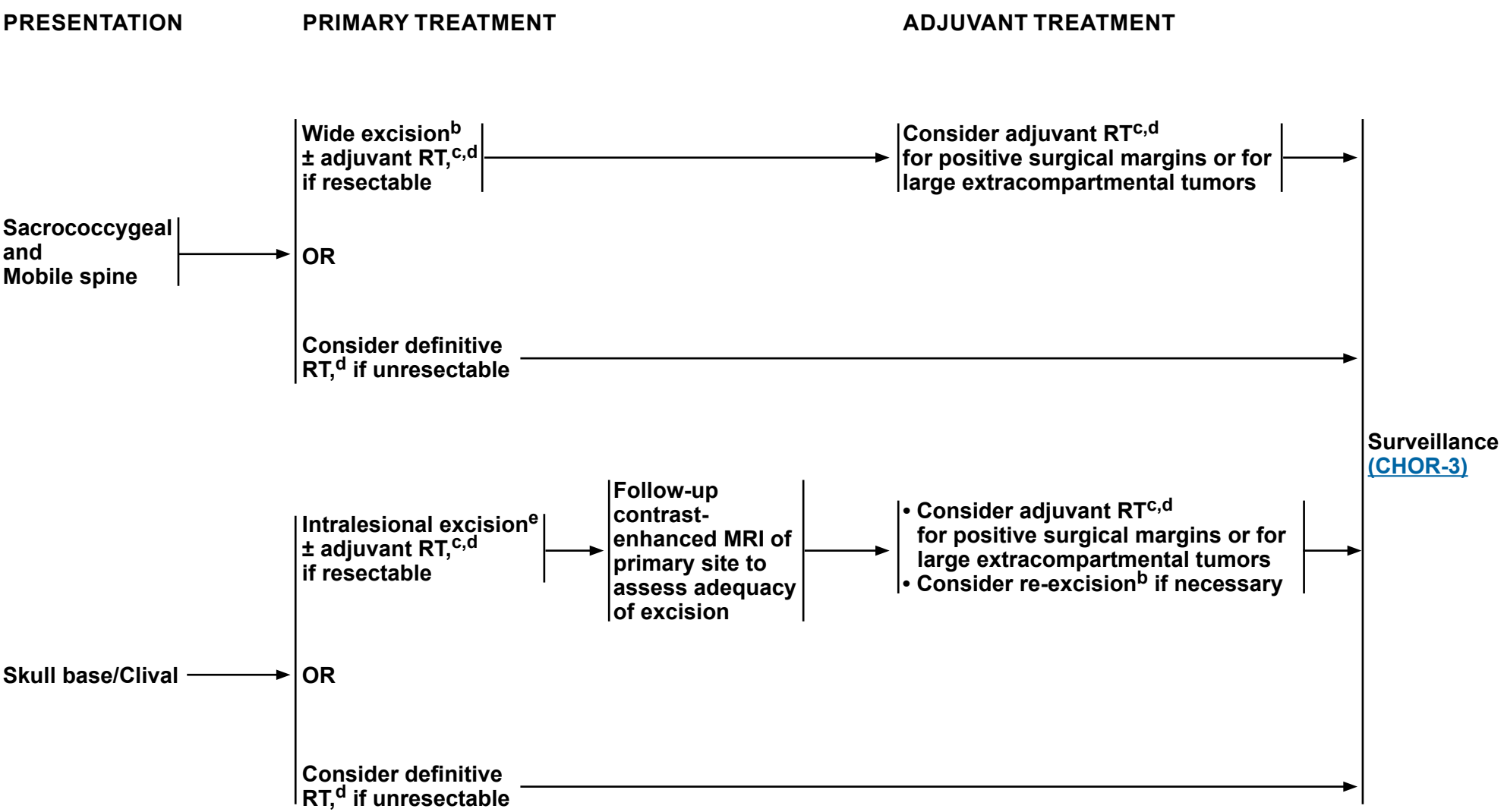
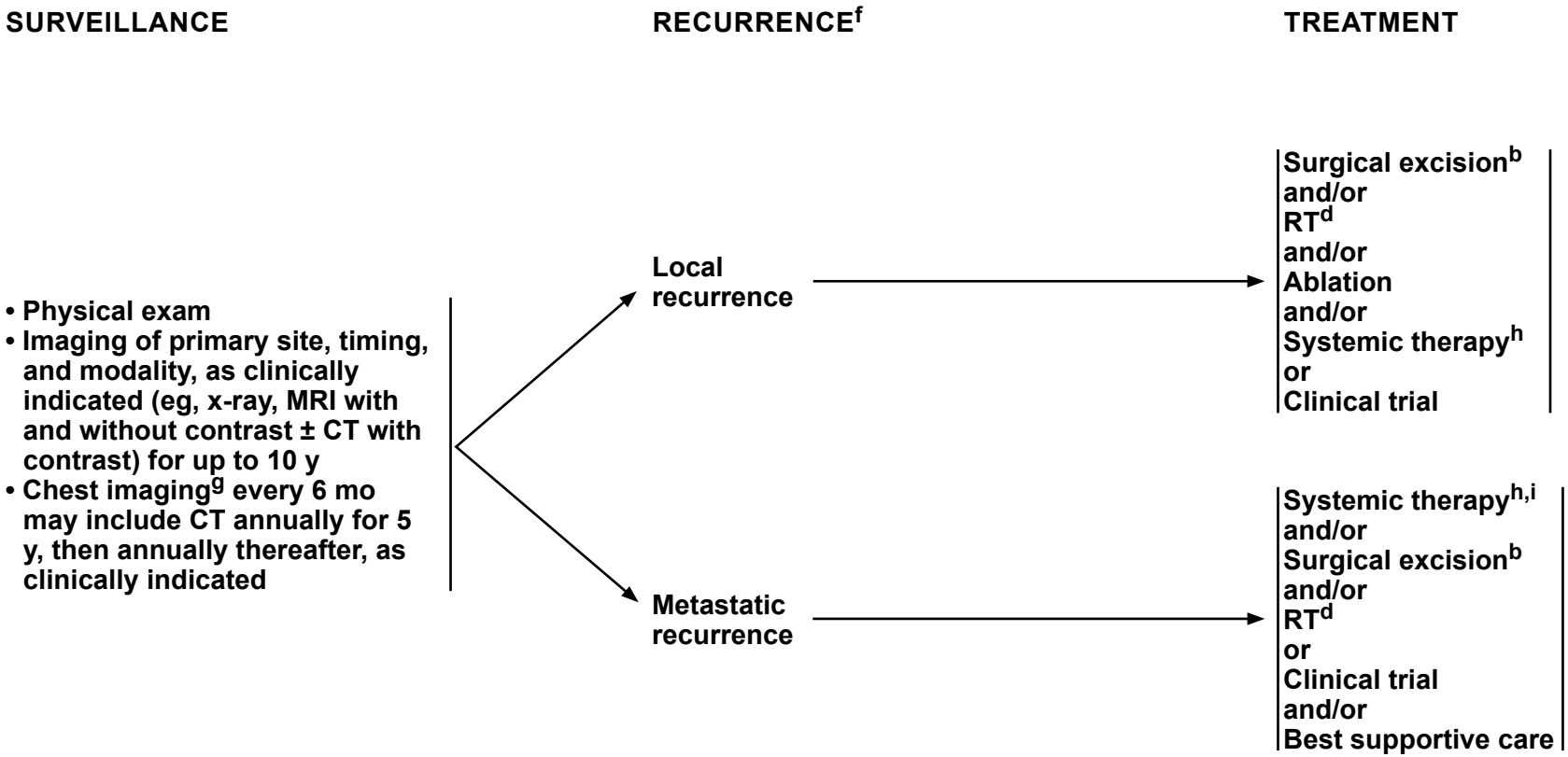


[b] Principles of Bone Cancer Management (BONE-A).
[c] RT may be given preoperatively, intraoperatively, and/or postoperatively.
[d] Principles of Radiation Therapy (BONE-C).
[e] Maximal safe excision. Maximal tumor removal is recommended when appropriate.

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



[b] Principles of Bone Cancer Management (BONE-A).
[d] Principles of Radiation Therapy (BONE-C).
[f] Consider MGPT with a validated and/or FDA-approved assay to determine targeted therapy opportunities.
[g] Chest CT can be performed with or without contrast as clinically indicated. Low-dose, non-contrast CT is recommended for restaging.
[h] Bone Cancer Systemic Therapy Agents (BONE-B).
[i] Consider testing for TMB and MMR/MSI as determined by a validated and/or FDA-approved assay to inform treatment options.

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

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Ewing Sarcoma

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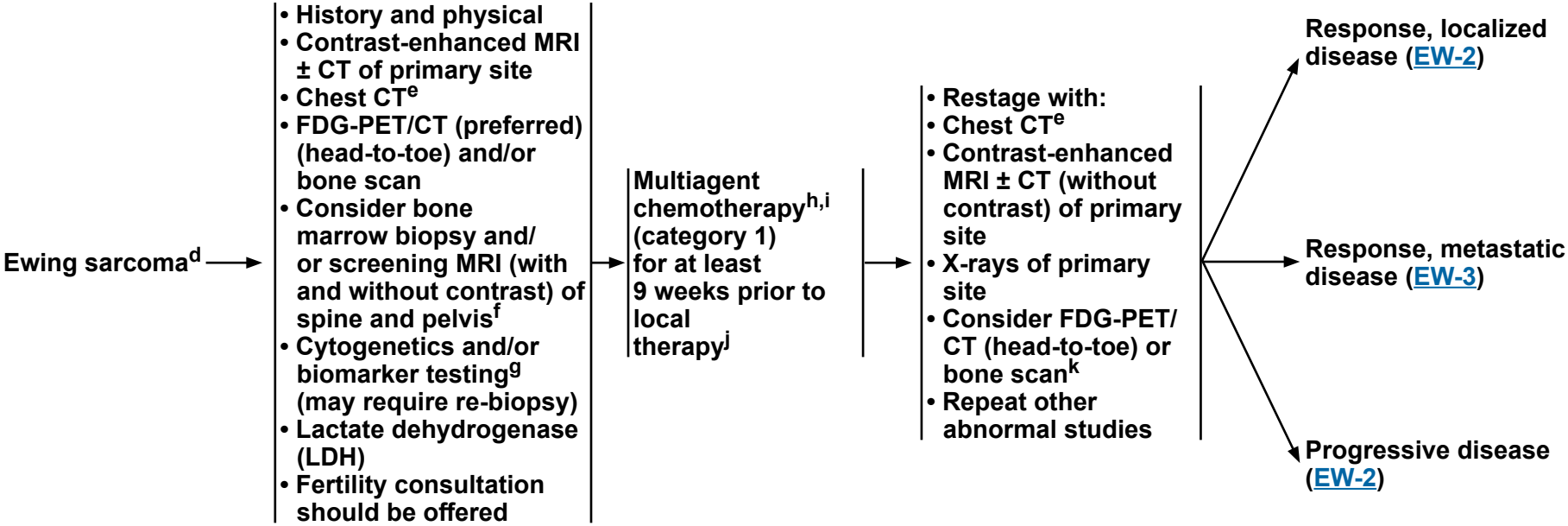

[a] Multidisciplinary Team (TEAM-1).
[b] Principles of Bone Cancer Management (BONE-A).
[c] Ewing sarcoma can be treated using this algorithm, including primitive neuroectodermal tumor of bone, Askin tumor, and extraosseous Ewing sarcoma.
[d] Consider MGPT or other fusion panel for Ewing sarcoma to identify translocations if pathologic workup of targeted polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH), or cytogenetics is negative.
[e] Chest CT can be performed with or without contrast as clinically indicated. Low-dose, non-contrast CT is recommended for restaging.
[f] Campbell KM, et al. Pediatr Blood Cancer 2021;68:e28807.
[g] Ninety percent of Ewing sarcomas will have one of four specific chromosome translocations. For patients with other primary round cell sarcomas of bone (eg, *CIC::DUX4, BCOR::CCNB3*), treating as Ewing sarcoma can be considered. For those who are negative, additional biomarker testing is recommended. Other primary round cell sarcoma of bone was previously referred to as Ewing-like sarcoma, which is terminology that is no longer included in the WHO classification.
[h] Bone Cancer Systemic Therapy Agents (BONE-B).
[i] For patients with mesenchymal chondrosarcoma, single-agent doxorubicin and doxorubicin/ifosfamide can be considered as primary systemic therapy treatment options. See BONE-B 1 of 7.
[j] Longer treatment prior to local control therapy can be considered in patients with metastatic disease based on response; select patients with present, or impending, pathologic fracture or fungation may benefit from immediate surgery.
[k] 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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Ewing Sarcoma

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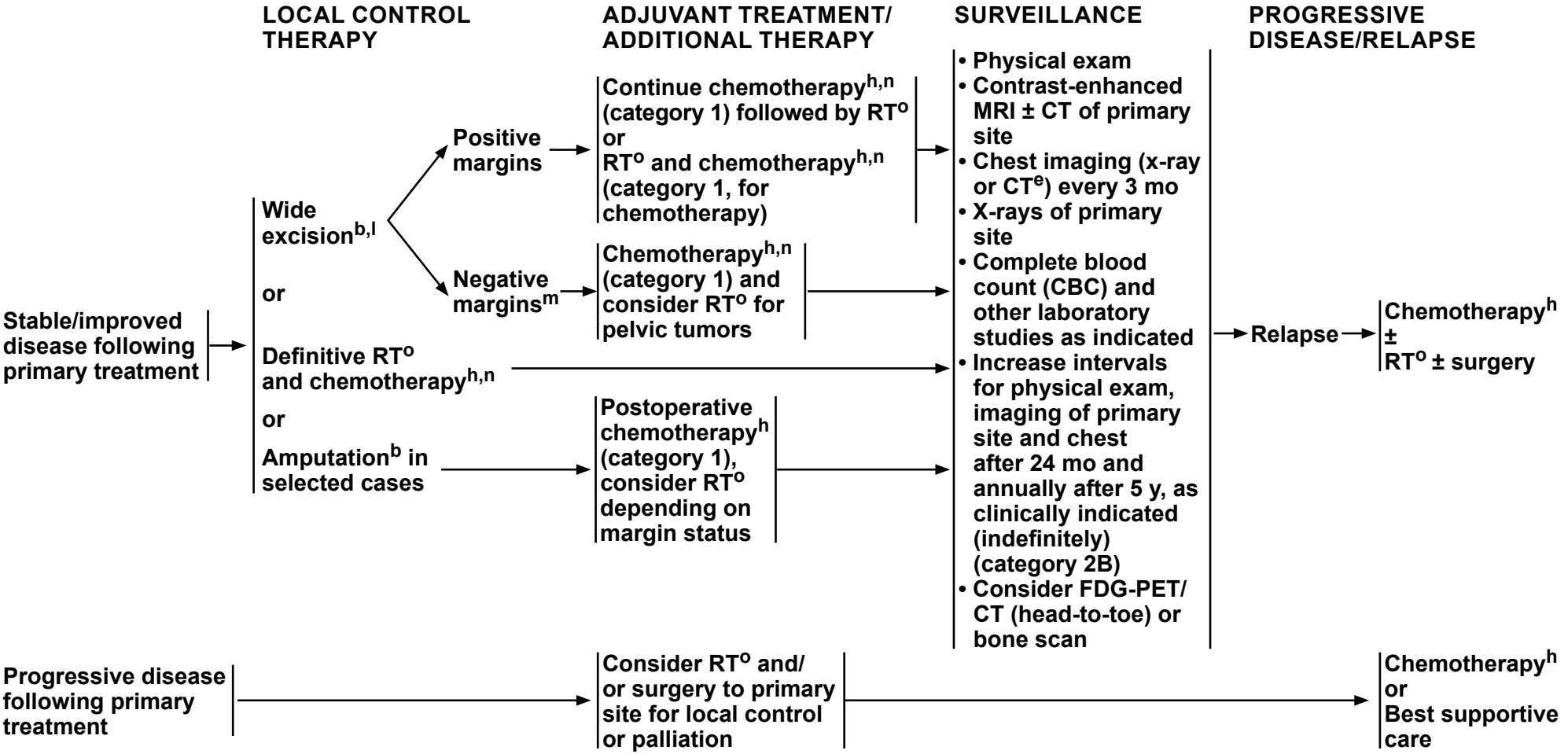
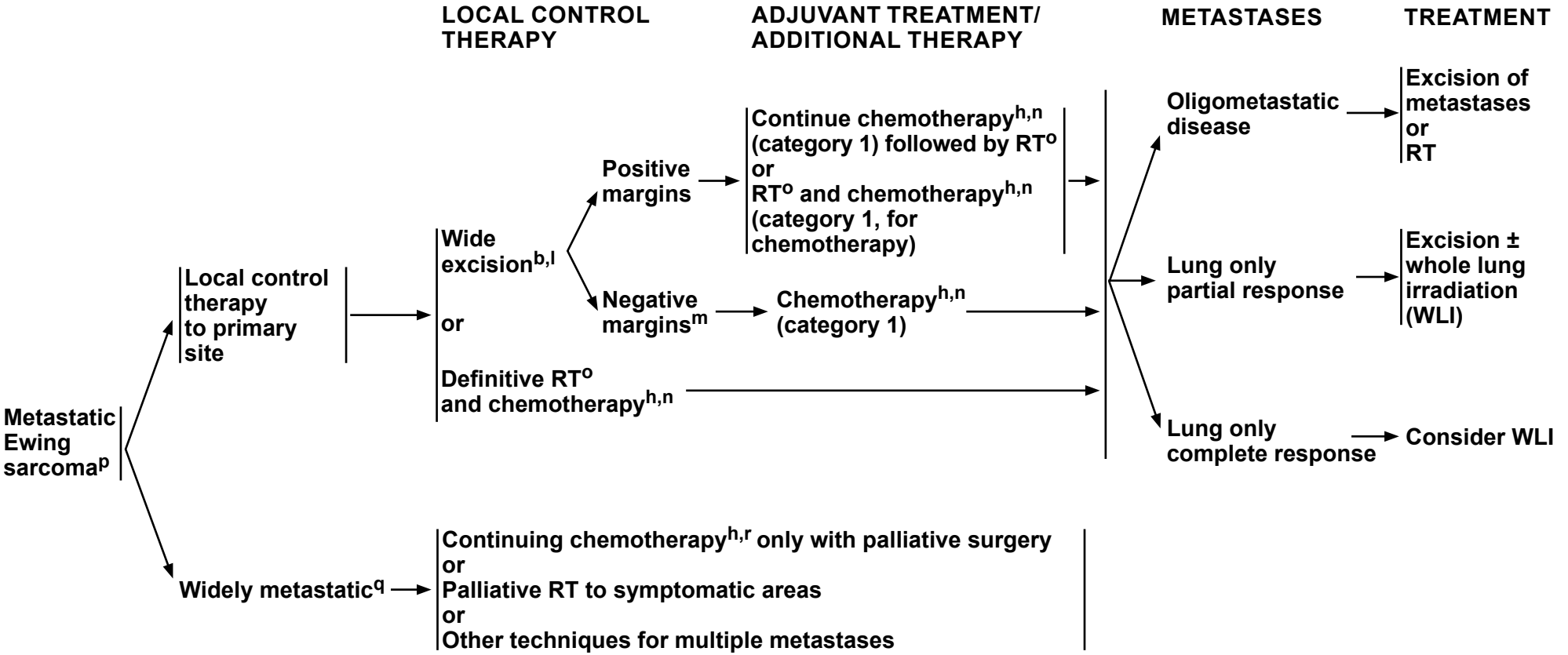


[b] Principles of Bone Cancer Management (BONE-A).
[e] Chest CT can be performed with or without contrast as clinically indicated. Low-dose, non-contrast CT is recommended for restaging.
[h] Bone Cancer Systemic Therapy Agents (BONE-B).
[l] Consider preoperative RT for marginally resectable lesions.
[m] RT may be considered for close margins.
[n] There is category 1 evidence for between 28 and 49 weeks of chemotherapy depending on the chemotherapy and dosing schedule used.
[o] Principles of Radiation Therapy (BONE-C).

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



[b] Principles of Bone Cancer Management (BONE-A).
[h] Bone Cancer Systemic Therapy Agents (BONE-B).
[l] Consider preoperative RT for marginally resectable lesions.
[m] RT may be considered for close margins.
[n] There is category 1 evidence for between 28 and 49 weeks of chemotherapy depending on the chemotherapy and dosing schedule used.
[o] Principles of Radiation Therapy (BONE-C).
[p] Consider MGPT with a validated and/or FDA-approved assay to determine targeted therapy opportunities.
[q] Local control cannot be delivered to all areas of disease.
[r] Consider testing for TMB (category 2B) and MMR/MSI as determined by a validated and/or FDA-approved assay to inform treatment options.

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

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Giant Cell Tumor of Bone

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WORKUP

- History and physical examination
- Imaging of primary site as clinically indicated (eg, x-ray and MRI with and without contrast ± CT)
- Chest imaging
- Bone scan (optional)
- Biopsy to confirm diagnosis[a,b]
- If there is malignant transformation, treat as described for osteosarcoma (OSTEO-1)

PRESENTATION

Localized disease → GCTB-2

Metastatic disease at presentation → GCTB-2

[a] Brown tumor of hyperparathyroidism should be considered as a differential diagnosis.
[b] Principles of Bone Cancer Management (BONE-A).

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

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Giant Cell Tumor of Bone

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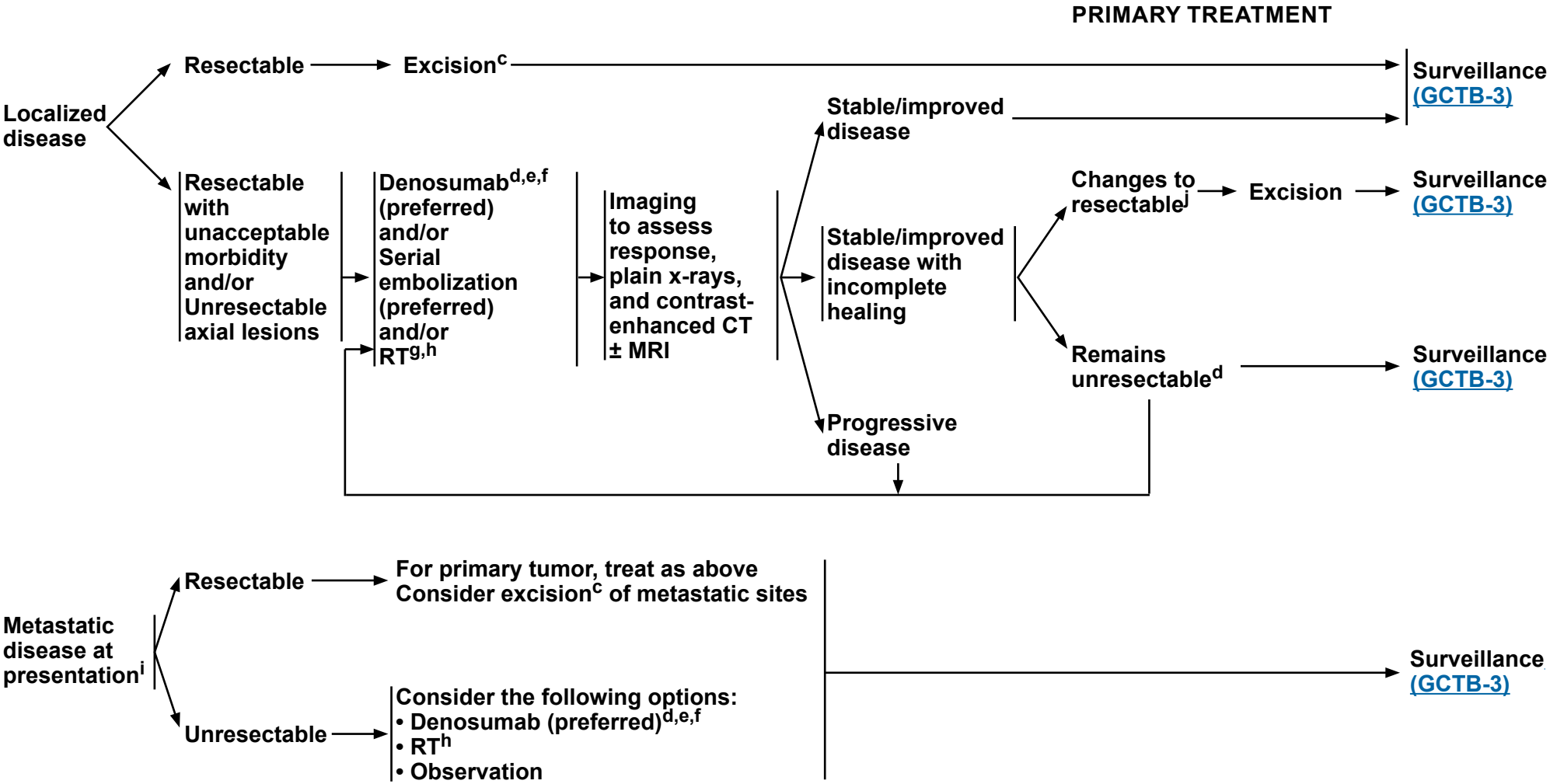

[c] Intralesional excision with an effective adjuvant may be adequate.
[d] Denosumab may be continued until disease progression, in responding disease.
[e] Bone Cancer Systemic Therapy Agents (BONE-B).
[f] Consider consultation with dentist prior to initial therapy.
[g] RT may be associated with increased risk of malignant transformation.
[h] Principles of Radiation Therapy (BONE-C).
[i] Treatment of primary tumor is as described for localized disease.
[j] Long-term denosumab use may be associated with increased risk of local recurrence.

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

SURVEILLANCE

- Physical exam
- Imaging of surgical site as clinically indicated (eg, x-ray, contrast-enhanced CT and/or MRI)
- Chest imaging every 6–12 mo for 4 y then annually thereafter, as clinically indicated

RECURRENCE

Local recurrence

- Resectable → Consider chest imaging → Consider denosumab prior to surgery[k] (GCTB-2)
- Resectable with unacceptable morbidity or unresectable axial lesions → GCTB-2

Metastatic recurrence → GCTB-2

[k] Risk of local recurrence is increased when denosumab is used prior to curettage. Denosumab may be beneficial to define peripheral tumor extent when planning wide excision.

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

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Osteosarcoma

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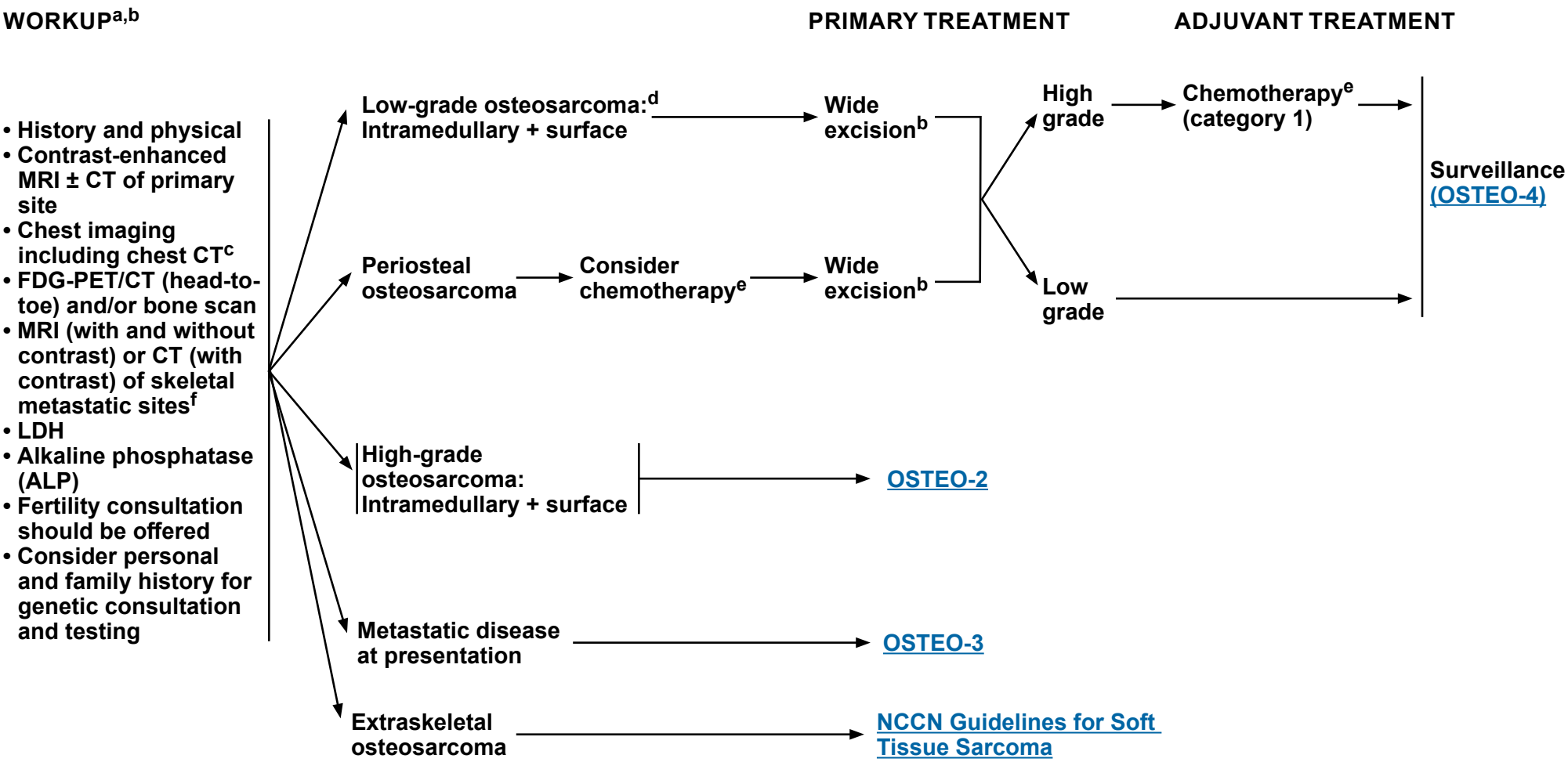

[a] Multidisciplinary Team (TEAM-1).
[b] Principles of Bone Cancer Management (BONE-A).
[c] Chest CT can be performed with or without contrast as clinically indicated. Low-dose, non-contrast CT is recommended for restaging.
[d] Dedifferentiated parosteal osteosarcomas are not considered to be low-grade tumors.
[e] Bone Cancer Systemic Therapy Agents (BONE-B).
[f] More detailed imaging (CT or MRI) of abnormalities identified on primary imaging is required for suspected metastatic disease.

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

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Osteosarcoma

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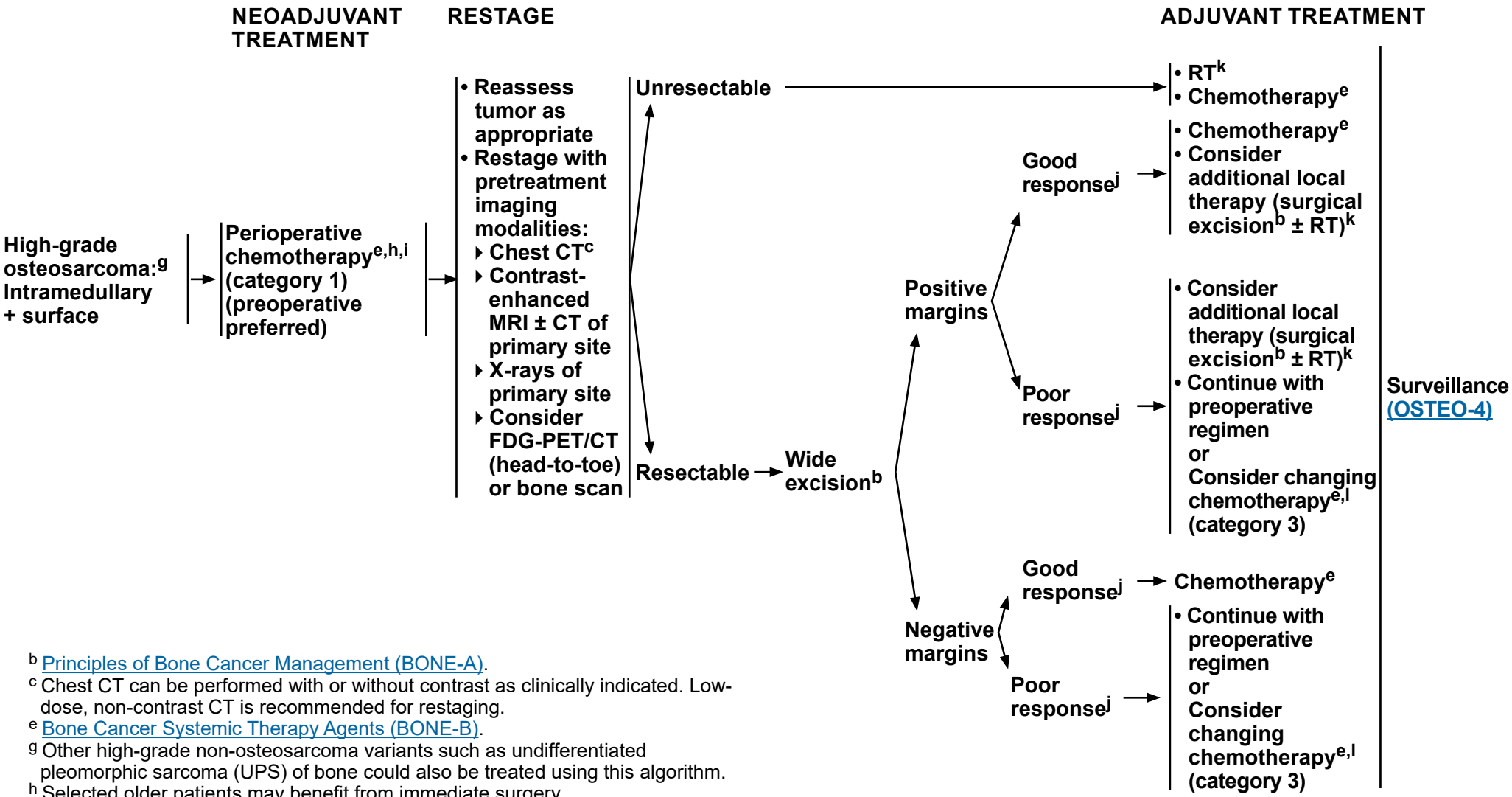
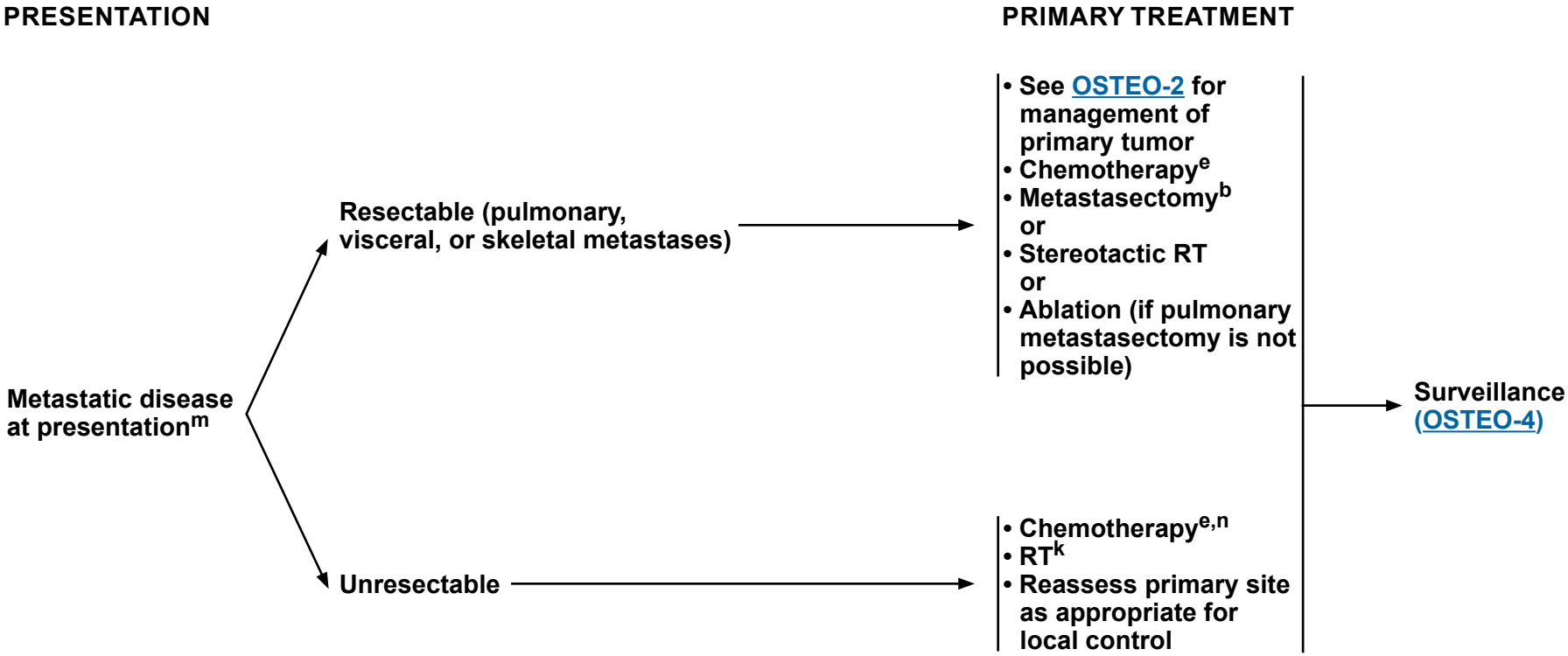


[b] Principles of Bone Cancer Management (BONE-A).
[c] Chest CT can be performed with or without contrast as clinically indicated. Low-dose, non-contrast CT is recommended for restaging.
[e] Bone Cancer Systemic Therapy Agents (BONE-B).
[g] Other high-grade non-osteosarcoma variants such as undifferentiated pleomorphic sarcoma (UPS) of bone could also be treated using this algorithm.
[h] Selected older patients may benefit from immediate surgery.
[i] There does not appear to be a survival benefit for individuals who have received neoadjuvant chemotherapy compared to adjuvant chemotherapy. Histologic response to neoadjuvant chemotherapy may provide prognostic information, but does not affect outcome. Bernthal NM, et al. Cancer 2012;118:5888-5893; Provisor AJ, et al. J Clin Oncol 1997;15:76-84.
[j] Response is defined by pathologic mapping per institutional guidelines; the amount of viable tumor is reported as <10% of the tumor area in cases showing a good response and ≥10% in cases showing a poor response.
[k] Principles of Radiation Therapy (BONE-C).
[l] See Discussion for further information.

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



[b] Principles of Bone Cancer Management (BONE-A).
[e] Bone Cancer Systemic Therapy Agents (BONE-B).
[k] Principles of Radiation Therapy (BONE-C).
[m] Consider MGPT with a validated and/or FDA-approved assay to determine targeted therapy opportunities.
[n] Consider testing for TMB and MMR/MSI as determined by a validated and/or FDA-approved assay to inform treatment options.

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

SURVEILLANCE

- Physical exam, imaging of primary site and chest[o]
- Follow-up schedule: (Orthopedic and oncologic)
  - 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, as clinically indicated
- CBC and other laboratory studies as clinically indicated
- Consider FDG-PET/CT (head-to-toe) and/or bone scan (category 2B)
- Reassess function every visit

→ **Relapse** → **Chemotherapy[e] and/or excision if possible** → **Imaging to assess response:**
- X-rays of primary site
- Contrast-enhanced CT ± MRI of local sites
- Chest CT[c]

→ **Response** → **Surveillance**

→ **Relapse/ Progression** → **Excision,[b] if possible**
or
Clinical trial
or
RT[k,p]
or
Embolization/ablation
or
Best supportive care

[b] Principles of Bone Cancer Management (BONE-A).
[c] Chest CT can be performed with or without contrast as clinically indicated. Low-dose, non-contrast CT is recommended for restaging.
[e] Bone Cancer Systemic Therapy Agents (BONE-B).
[k] Principles of Radiation Therapy (BONE-C).
[o] Use the same imaging technique that was performed in the initial workup.
[p] May include radiopharmaceuticals, including radium-223.

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

PRINCIPLES OF BONE CANCER MANAGEMENT

Biopsy
- Prior to biopsy, consultation should be obtained with an orthopedic oncologist regarding appropriate prebiopsy imaging.
- Preoperative biopsy consultation with a pediatric oncologist as appropriate is recommended for children.
- Biopsy diagnosis is necessary prior to any surgical procedure or fixation of primary site.
- Biopsy is optimally performed at a center that will do definitive management.
- Placement of biopsy is critical.
- Biopsy should be core needle or surgical biopsy.
- Technique: Apply same principles for core needle or open biopsy. Needle biopsy is not recommended for skull base tumors.
- Appropriate communication between the surgeon, musculoskeletal or interventional radiologist, and bone pathologist is critical.
- Fresh tissue may be needed for biomarker testing and tissue banking.
- In general, not following appropriate biopsy procedures may lead to adverse patient outcomes.

Surgery
- Wide excision should achieve histologically negative surgical margins.
- Negative surgical margins optimize local tumor control.
- Local tumor control may be achieved by either limb-sparing excision or limb amputation (individualized for a given patient).
- Limb-sparing excision is preferred to optimize function if reasonable functional expectations can be achieved.
- Final pathologic evaluation should include assessment of surgical margins, size/dimensions of tumor, and response to preoperative therapy.
- Fresh tissue may be needed for biomarker testing and tissue banking.

Laboratory Studies
- Laboratory studies such as CBC, LDH, and ALP may have relevance in the diagnosis, prognosis, and treatment of patients with bone sarcoma and should be done prior to definitive treatment and periodically during treatment and surveillance.
- Consider biomarker testing to delineate potential therapeutic options.

Treatment
- Fertility issues should be addressed with patients prior to commencing chemotherapy.
- See NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology.
- Select patients with osteosarcoma or chondrosarcoma may benefit from a referral for genetic consultation and testing based on family history with a genetic predisposition for bone sarcomas.
- Care for patients with bone cancer should be delivered directly by physicians on the multidisciplinary team (category 1). See TEAM-1.

Long-Term Follow-up and Surveillance/Survivorship
- Patients should have a survivorship prescription to schedule follow-up with a multidisciplinary team.
- Life-long follow-up is recommended for surveillance and treatment of late effects of surgery, radiation, and chemotherapy in long-term survivors.
- See NCCN Guidelines for Survivorship.

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

SYSTEMIC THERAPY AGENTS[a]

MSI-H/dMMR Tumors
Preferred • Pembrolizumab[1,2,b,c]
TMB-H (≥10 mutations/megabase) Tumors
Useful in Certain Circumstances • Pembrolizumab[3,4,c,d] • Ipilimumab + Nivolumab[5,d]

Chondrosarcoma	
Metastatic and widespread disease	**Other Recommended** • Dasatinib[6,7] • Pazopanib[8]
Conventional (Grades 1–3)	**Preferred** • No known standard chemotherapy options **Useful in Certain Circumstances** • Ivosidenib[9,e] (for susceptible *IDH1* mutations)
Dedifferentiated	**Preferred** • Consider osteosarcoma regimens (category 2B) **Useful in Certain Circumstances** • Ivosidenib[9,e] (for susceptible *IDH1* mutations) • Pazopanib[8] or Sunitinib[10] • Pembrolizumab[c,11] or Nivolumab[10,f] • Sunitinib + Nivolumab[10,f]
Mesenchymal	**Preferred** • Ewing sarcoma regimens (category 2B) • Doxorubicin[12-14,g] • Doxorubicin/Ifosfamide/Mesna[12-16,g]

[a] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[b] Pembrolizumab is a systemic treatment option for adult and pediatric patients with unresectable or metastatic, MSI-high (MSI-H) or MMR deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. Not for giant cell tumor of bone.
[c] Pembrolizumab and berahyaluronidase alfa-pmph subcutaneous injection may be substituted for IV pembrolizumab. Pembrolizumab and berahyaluronidase alfa-pmph has different dosing and administration instructions compared to IV pembrolizumab.
[d] Consider MGPT with a validated and/or FDA-approved assay to determine targeted therapy opportunities. TMB testing is recommended for patients with unresectable or metastatic tumors who have progressed following prior treatment and who have no satisfactory alternative treatment options. Not for giant cell tumor of bone.
[e] Testing for *IDH1* mutation can be performed by next-generation sequencing (NGS) or targeted exon sequencing.
[f] Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.
[g] Dactinomycin can be substituted for doxorubicin for concerns regarding cardiotoxicity.

References

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

SYSTEMIC THERAPY AGENTS[a]

Chordoma	
Other Recommended • Imatinib[17,18,19] • Dasatinib[6,7] • Pembrolizumab[20,c] • Sunitinib[21]	**Useful in Certain Circumstances** • Cisplatin/Imatinib[22] • Imatinib/Sirolimus[23] • Erlotinib[24] • Lapatinib for EGFR-positive chordomas[25] • Sorafenib[26,27]

[a] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[c] Pembrolizumab and berahyaluronidase alfa-pmph subcutaneous injection may be substituted for IV pembrolizumab. Pembrolizumab and berahyaluronidase alfa-pmph has different dosing and administration instructions compared to IV pembrolizumab.

References

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

SYSTEMIC THERAPY AGENTS[a]

Ewing Sarcoma[h]			
First-line therapy (primary/ neoadjuvant/adjuvant therapy)[g]	**Preferred** • VDC-IE (Vincristine/Doxorubicin/ Cyclophosphamide/ Mesna-Ifosfamide/Mesna/ Etoposide)[28,29,i] (category 1)	**Other Recommended** • VAIA (Vincristine/Doxorubicin/Ifosfamide/Mesna/ Dactinomycin)[30,31,33] • VIDE (Vincristine/Ifosfamide/Mesna/Doxorubicin/Etoposide)[32,33]	
Primary therapy for metastatic disease at initial presentation[g]	**Preferred** • VAIA[30,31] • VDC (Vincristine/Doxorubicin/Cyclophosphamide)[34] • VDC-IE[28] • VIDE[32]		
Second-line therapy (relapsed/ refractory or metastatic disease)	**Preferred** • Cyclophosphamide/ Topotecan[35-38,j] • Irinotecan/Temozolomide[39-44] • Irinotecan/Temozolomide/ Vincristine[39-44]	**Other Recommended** • Cabozantinib[45] • Docetaxel/Gemcitabine[46,j] • High-Dose Ifosfamide/Mesna[47] • Regorafenib[48]	**Useful in Certain Circumstances** • ICE (Ifosfamide/Mesna/ Carboplatin/Etoposide)[49,j] • Lurbinectedin[50,k] (category 2B)

[a] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[g] Dactinomycin can be substituted for doxorubicin for concerns regarding cardiotoxicity.
[h] Other primary round cell tumors of bone (eg, *CIC::DUX4, BCOR::CCNB3*) can be treated like Ewing sarcoma.
[i] In patients <18 years, evidence supports 2-week compressed treatment.
[j] Vincristine could be added to these regimens.
[k] Myelosuppression was reversible and primary granulocyte colony-stimulating factor (G-CSF) prophylaxis may be considered during lurbinectedin treatment (category 2B).

References

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

SYSTEMIC THERAPY AGENTS[a]

Giant Cell Tumor of Bone
Preferred • Denosumab[51-55]

Osteosarcoma			
First-line therapy (primary/ neoadjuvant/adjuvant therapy or metastatic disease)[g]	**Preferred** • Cisplatin/Doxorubicin[56-58] (category 1) • MAP (High-Dose Methotrexate/ Leucovorin/Doxorubicin/ Cisplatin)[58-61] (category 1)[l,m]	**Other Recommended** • Cisplatin/Doxorubicin/Ifosfamide/Mesna/High-Dose Methotrexate/ Leucovorin[66,l]	
Second-line therapy (relapsed/ refractory or metastatic disease)	**Preferred** • Etoposide/High-Dose Ifosfamide/Mesna[62,63] • High-Dose Ifosfamide/ Mesna[62,63] • Regorafenib[64] (category 1) • Sorafenib[65]	**Other Recommended** • Cabozantinib[45] • Cyclophosphamide/ Topotecan[37,38] • Docetaxel/Gemcitabine[46,67] • Gemcitabine[67] • Everolimus/Sorafenib (category 2B)[68]	**Useful in Certain Circumstances** • Cyclophosphamide/Mesna/ Etoposide[69] • ICE[49] • High-Dose Methotrexate/ Leucovorin - Etoposide/ Ifosfamide/Mesna[70,l] • High-Dose Methotrexate/ Leucovorin[l] • Radiopharmaceuticals including radium-223 for relapsed or refractory disease beyond second-line therapy[71]

High-Grade Undifferentiated Pleomorphic Sarcoma (UPS)
Follow osteosarcoma regimens (category 2B)

[a] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[g] Dactinomycin can be substituted for doxorubicin for concerns regarding cardiotoxicity.
[l] In the event a patient receiving high-dose methotrexate experiences delayed elimination due to renal impairment, glucarpidase is strongly recommended. See glucarpidase prescribing information for more information.
[m] MAP is preferred in patients <40 years with excellent performance status.

References

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

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

PRINCIPLES OF RADIATION THERAPY

General Principles

- Patients should be strongly encouraged to have RT at the same specialized center that is providing surgical and systemic interventions.
- Specialized techniques such as intensity-modulated RT (IMRT); particle beam RT with protons, carbon ions, or other heavy ions; or stereotactic radiosurgery (SRS) should be considered as indicated in order to allow high-dose therapy while maximizing normal tissue sparing.
- The RT doses listed below for chondrosarcoma and chordoma are for conventional fractionated regimens (1.8–2.0 Gy). Alternative total dose and fractionation schemes are necessary for specialized techniques such as SRS and stereotactic body RT (SBRT).

General Treatment and Dosing Information - Chondrosarcoma

Dosing Prescription Regimen

- Low-grade extracompartmental appendicular or grade I axial tumors
  - Unresectable:
    - ◊ Consider RT (70 Gy) with specialized techniques.

- High-grade, clear cell, or extracompartmental
  - Resectable:
    - ◊ Preoperative RT: Consider if positive margins are likely (19.8–50.4 Gy) followed by individualized postoperative RT with final target dose of 70 Gy for microscopically positive margins and 72–78 Gy for gross positive margins.
    - ◊ Postoperative RT: Consider, especially for high-grade/dedifferentiated subtype, 70 Gy for microscopically positive margins and >70 Gy for gross positive margins using specialized techniques.
    - ◊ Radiation is not needed for negative margins; there should be no pre- or postoperative considerations.
  - Unresectable:
    - ◊ Consider RT (>70 Gy) with specialized techniques.

Continued
References

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

PRINCIPLES OF RADIATION THERAPY

General Treatment and Dosing Information - Chordoma

Dosing Prescription Regimen

- **Extracranial (mobile spine/sacrum)**
  - **Resectable:**
    - ◊ **Preoperative RT: Consider if positive margins are likely (19.8–50.4 Gy) followed by individualized postoperative RT.**
- **Postoperative RT: Consider postoperative RT for microscopically positive margins/gross positive margins using specialized techniques with final target dose of 70 Gy for microscopically positive margins and 72–78 Gy for gross positive margins.**
  - **Unresectable:**
    - ◊ **Consider RT (>70 Gy) using specialized techniques.**

- **Cranial (base of skull)**
  - **Resectable:**
    - ◊ **Preoperative RT: Consider if positive margins are likely (19.8–50.4 Gy) followed by individualized postoperative RT.**
    - ◊ **Consider postoperative RT (>70 Gy) for microscopically positive margins/gross positive margins using specialized techniques.**
  - **Unresectable:**
    - ◊ **Consider RT (>70 Gy) using specialized techniques.**

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

Continued
References

PRINCIPLES OF RADIATION THERAPY

General Treatment and Dosing Information - Ewing Sarcoma

Treatment of Primary Tumor/Dosing Prescription Regimen

- **Definitive RT**
  - Should start by week 12 of VDC/IE chemotherapy or week 18 of VIDE and is given concurrently with chemotherapy, withholding anthracyclines during RT per the Womer Protocol
  - Treatment volumes and doses:
    - ◊ 45 Gy to initial gross tumor volume (GTV1) + 1–1.5 cm for clinical target volume 1 (CTV1) + 0.5–1 cm for planning target volume 1 (PTV1)
      - – GTV1 is defined as pre-treatment extent of bone and soft tissue disease. If the tumor has responded to chemotherapy and normal tissues have returned to their natural position, GTV1 should exclude pre-chemotherapy soft tissue volume that extended into a cavity (eg, tumors indenting lung, intestine, or bladder resume normal position following chemotherapy)
    - ◊ Cone-down (CD) to cover original bony extent to a total of 55.8 Gy to post-chemotherapy soft tissue volume (GTV2) + 1–1.5 cm for CTV2 + 0.5–1 cm for PTV2 (consider dose escalation for select patients)
- **Preoperative RT**
  - May be considered for marginally resectable tumors and is given concurrently with chemotherapy
  - Treatment volumes and doses:
    - ◊ 36–45 Gy for initial GTV + 2 cm
- **Postoperative RT**
  - Should begin within 60 days of surgery and is given concurrently with chemotherapy
  - Treatment volumes and doses:
    - ◊ Negative margins: Consider treatment for poor histologic response even if margins are adequate (45 Gy to GTV2 equivalent volume + 1–1.5 cm for CTV1 + 0.5–1 cm for PTV1)
    - ◊ Microscopically positive margins: 45 Gy GTV2 equivalent volume + 1–1.5 cm for CTV1 + 0.5–1 cm for PTV1
    - ◊ Gross positive margins: 45 Gy to GTV2 equivalent volume + 1–1.5 cm for CTV1 + 0.5–1 cm for PTV1 followed by CD to residual disease plus a total of 55.8 Gy to GTV2 + 1–1.5 cm for CTV2 + 0.5–1 cm for PTV2

Hemithorax Irradiation

- Should be considered for chest wall primaries with extensive ipsilateral pleural involvement
- 15–20 Gy (1.5 Gy/fraction) followed by CD to primary site (final dose based on resection margins)

Treatment of Metastatic Disease

- Consider WLI for pulmonary metastases following completion of chemotherapy/metastasectomy (category 3)
  - 15 Gy (1.5 Gy/fraction) for patients <14 years
  - 18 Gy (1.5 Gy/fraction) for patients >14 years
- Current Children's Oncology Group (COG) study stratifies age before or after 6 years (12 vs. 15 Gy)
- Consider use of SRS/SBRT, especially for oligometastases

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

Continued
References

PRINCIPLES OF RADIATION THERAPY

General Treatment and Dosing Information - Giant Cell Tumor of Bone

Treatment of Primary Site or Metastatic Disease/Dosing Prescription Regimen
- **Consider RT (50–60 Gy) for unresectable/progressive/recurrent disease that has not responded to denosumab, serial embolizations, or other treatments.**
- **An increased risk of malignant transformation following RT has been noted in some studies.**

General Treatment and Dosing Information - Osteosarcoma

Treatment of Primary Tumor/Dosing Prescription Regimen
- **Consider RT for microscopically positive margins or gross positive margins or unresectable disease.**
- **Postoperative RT (microscopically and gross positive margins):55 Gy with 9–13 Gy boost to microscopic or gross disease (total dose to high-risk sites 64–68 Gy)**
- **Unresectable disease: 60–70 Gy (total dose will depend on normal tissue tolerance)**

Treatment of Metastatic Disease
- **Consider use of radiopharmaceuticals, including radium-223.**
- **Consider use of SRS/SBRT, especially for oligometastases.**

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

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PRINCIPLES OF PATHOLOGY

- **Biopsy should provide a specific diagnosis and histologic grade, when appropriate and feasible.**
- **Pathologic evaluation should be performed by an experienced sarcoma pathologist.**
- **Microscopic examination is the gold standard for diagnosis of bone tumors, which should be performed in conjunction with review of radiologic studies. Ancillary techniques should be applied to support the diagnosis of selected sarcoma types, such as Ewing sarcoma (eg, immunohistochemistry, fluorescence in situ hybridization [FISH], and/or molecular genetic testing).**
- **The pathology report for resection specimens should include the following features[1] (synoptic reporting according to the College of American Pathologists protocol is required for accreditation purposes)[2]:**
  - **Neoadjuvant therapy (and type)**
  - **Operative procedure**
  - **Tumor anatomic site**
  - **Tumor size (greatest dimension)**
  - **Tumor location and extent of invasion**
    - ◊ **Add "surface" if tumor originates on periosteal surface (especially relevant for osteosarcoma subtypes)**
    - ◊ **Add "intracompartmental" or "extracompartmental" (especially relevant for defining atypical cartilaginous tumors)**
  - **Presence of skip metastases (discontinuous tumor)**
  - **Histologic tumor type (WHO Classification)[3]**
  - **Histologic tumor grade**
  - **Presence and extent of necrosis**
  - **Treatment effect and extent**
  - **Margin status**
    - ◊ **Distance to and localization of closest margin(s)**
      - – **Necrotic tumor at margin for Ewing sarcoma is considered a negative margin if there is a complete pathologic response.[4]**
  - **Ancillary studies**
    - ◊ **Decalcification on a portion of the specimen should optimally be performed with solutions that preserve RNA and DNA; strong acid-based decalcification (other than EDTA or EDTA + formic acid solutions) should therefore be avoided.[1]**
  - **Pathologic stage classification (AJCC 8th Edition)[5]**

References

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

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

American Joint Committee on Cancer (AJCC)
TNM Staging System for Bone *(Primary malignant lymphoma and multiple myeloma are not included)*

Table 1. **Definitions for T, N, M**

Appendicular Skeleton, Trunk, Skull, and Facial Bones

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤8 cm in greatest dimension
T2	Tumor >8 cm in greatest dimension
T3	Discontinuous tumors in the primary bone site

Spine

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor confined to one vertebral segment or two adjacent vertebral segments
T2	Tumor confined to three adjacent vertebral segments
T3	Tumor confined to four or more adjacent vertebral segments, or any nonadjacent vertebral segments
T4	Extension into the spinal canal or great vessels
T4a	Extension into the spinal canal
T4b	Evidence of gross vascular invasion or tumor thrombus in the great vessels

Pelvis

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor confined to one pelvic segment with no extraosseous extension
T1a	Tumor ≤8 cm in greatest dimension
T1b	Tumor >8 cm in greatest dimension
T2	Tumor confined to one pelvic segment with extraosseous extension or two segments without extraosseous extension
T2a	Tumor ≤8 cm in greatest dimension
T2b	Tumor >8 cm in greatest dimension
T3	Tumor spanning two pelvic segments with extraosseous extension
T3a	Tumor ≤8 cm in greatest dimension
T3b	Tumor >8 cm in greatest dimension
T4	Tumor spanning three pelvic segments or crossing the sacroiliac joint
T4a	Tumor involves sacroiliac joint and extends medial to the sacral neuroforamen
T4b	Tumor encasement of external iliac vessels or presence of gross tumor thrombus in major pelvic vessels

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed

Because of the rarity of lymph node involvement in bone sarcomas, the designation NX may not be appropriate and cases should be considered N0 unless clinical node involvement is clearly evident.

N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

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The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

Continued

American Joint Committee on Cancer (AJCC)
TNM Staging System for Bone *(continued)*

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis
M1a	Lung
M1b	Bone or other distant sites

G	Histologic Grade
GX	Grade cannot be assessed
G1	Well differentiated — Low Grade
G2	Moderately differentiated — High Grade
G3	Poorly differentiated — High Grade

Table 2. **AJCC Prognostic Groups**

There are no AJCC prognostic stage groupings for spine and pelvis.

	T	N	M	G
Stage IA	T1	N0	M0	G1, GX
Stage IB	T2	N0	M0	G1, GX
	T3	N0	M0	G1, GX
Stage IIA	T1	N0	M0	G2, G3
Stage IIB	T2	N0	M0	G2, G3
Stage III	T3	N0	M0	G2, G3
Stage IVA	Any T	N0	M1a	Any G
Stage IVB	Any T	N1	Any M	Any G
	Any T	Any N	M1b	Any G

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ABBREVIATIONS

ALP	alkaline phosphatase
C/A/P	chest/abdomen/pelvis
CBC	complete blood count
CD	cone-down
CMP	comprehensive metabolic panel
COG	Children's Oncology Group
CTV	clinical target volume
dMMR	mismatch repair deficient
FDG	fluorodeoxyglucose
FISH	fluorescence in situ hybridization
G-CSF	granulocyte colony-stimulating factor
GTV	gross tumor volume
IMRT	intensity-modulated radiation therapy
LDH	lactate dehydrogenase
MGPT	multigene panel testing
MMR	mismatch repair
MSI	microsatellite instability
MSI-H	microsatellite instability-high
NGS	next-generation sequencing
PCR	polymerase chain reaction
PSA	prostate-specific antigen
PTV	planning target volume
SBRT	stereotactic body radiation therapy
SPEP	serum protein electrophoresis
SRS	stereotactic radiosurgery
TMB	tumor mutational burden
TMB-H	tumor mutational burden-high
UPS	undifferentiated pleomorphic sarcoma
WLI	whole lung irradiation

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2026
Bone Cancer

Discussion

This discussion corresponds to the NCCN Guidelines for Bone Cancer. Last updated on December 19, 2025

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Overview

Primary bone cancers are extremely rare neoplasms accounting for ~0.2% of all cancers, although the true incidence is difficult to determine secondary to the rarity of these tumors.[1] In 2025 an estimated 3770 people will be diagnosed in the United States and 2190 people will die from these diseases.[2]

Primary bone cancers demonstrate wide clinical heterogeneity and may be curable with proper treatment. In adults, chondrosarcoma is the most common primary bone cancer, accounting for >40% of newly diagnosed bone cancers, followed by osteosarcoma (~25%), chordoma (10%), and Ewing sarcoma (8%).[3] Other less common primary bone tumors include giant cell tumor of bone (GCTB) and undifferentiated pleomorphic sarcoma (UPS). In children and adolescents, osteosarcoma and Ewing sarcoma are far more common than chondrosarcoma and chordoma.[3,4] High-grade UPS of bone and GCTB are relatively rare tumors, with each constituting <5% of primary bone tumors.[5] GCTB has both benign and exceptionally rare malignant forms. Various types of bone cancers are named based on their histologic line of differentiation. Chondrosarcomas differentiate toward cartilage, osteosarcomas toward bone, angiosarcoma and epithelioid hemangioendothelioma show endothelial (vascular) differentiation, and chordoma shows notochordal differentiation. Several primary bone cancers, including Ewing sarcoma, are of unknown lineage. Chondrosarcoma is more prevalent in individuals >50 years of age.[6] Osteosarcoma and Ewing sarcoma develop mainly in children and young adults. Chordoma is more common in males, with the peak incidence in the fifth to sixth decade of life.[7-9]

The pathogenesis and etiology of most bone cancers remain unclear. Some evidence suggests that up to 20% of sarcomas may be associated with variations in cancer predisposition genes.[10] Gene rearrangements between the FET (usually *EWSR1*) and ETS (usually *FLI1*) family of genes have been implicated in the pathogenesis of Ewing sarcoma.[11-15] Specific germline mutations have been linked to the development of osteosarcoma.[16] Li-Fraumeni syndrome, characterized by a germline mutation in the *TP53* gene, is associated with a high risk of developing cancer, including osteosarcoma.[17-19] Osteosarcoma is the most common second primary malignancy in patients with a history of retinoblastoma, characterized by a germline mutation in the retinoblastoma gene *RB1*.[20-22] Evidence suggests that the risk of developing osteosarcoma after having had retinoblastoma is 300 to 600 times more likely than the general population. [23] Increased incidences of osteosarcoma have also been associated with other genetic mutations and inherited genetic predisposition syndromes.[22] Osteosarcoma is also the most common radiation-induced bone sarcoma.[24,25]

The development of multiagent chemotherapy regimens for neoadjuvant and adjuvant treatment has markedly improved the prognosis for patients with osteosarcoma and Ewing sarcoma.[26,27] With current multimodality treatment, approximately 60% to 70% of patients diagnosed with osteosarcoma (without clinically evident metastases) are cured, and ~90% of patients diagnosed with osteosarcoma can be treated with limb-sparing approaches.[28-30] Five-year relative survival rates have improved to 82% in patients with localized Ewing sarcoma.[31] In patients with Ewing sarcoma and osteosarcoma, a cure is still achievable in selected patients diagnosed with metastatic disease at presentation.[32,33] The 5-year survival across all types of primary bone cancers is 68%.[1]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bone Cancer focus on chordoma, chondrosarcoma, Ewing sarcoma, and osteosarcoma. The guidelines also provide recommendations for treating GCTB. Although typically benign, GCTB is locally aggressive and can lead to significant bone destruction. Malignant transformation is also possible.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines® are available at www.NCCN.org.

Literature Search Criteria

Prior to the update of this version of the NCCN Guidelines for Bone Cancer, an electronic search of the PubMed database was performed to obtain key literature published in bone cancer since the previous Guidelines update, using the following search terms: chondrosarcoma OR chordoma OR Ewing sarcoma OR giant cell tumor of the bone OR osteosarcoma OR bone sarcoma OR primary bone cancer OR primary bone neoplasm OR primary bone tumor.

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines and discussed by the Panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[34] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Staging

The eighth edition of the AJCC staging classification (2018) is based on the assessment of histologic grade (G), tumor size (T), and presence of regional (N) and/or distant metastases (M).[35]

The NCCN Panel would like to clarify that although some studies interpret imaging before chemotherapy treatment based on the extent of tumor invasion relative to the periosteum (eg, extraperiosteal, intraperiosteal) for prognostic purposes, these terms do not specifically occur in any validated staging systems and the significance is unknown.

Principles of Bone Cancer Management

Multidisciplinary Team Involvement

Primary bone tumors and selected metastatic tumors should be evaluated and treated by a multidisciplinary team of physicians with demonstrated expertise in the management of these tumors. The core team should include, at minimum, the following: orthopedic oncologist, bone pathologist, medical/pediatric oncologist, radiation oncologist, and

musculoskeletal radiologist. Other specialists who may be critical in certain cases include the following: thoracic surgeon, plastic surgeon, interventional radiologist, physiatrist, vascular/general surgeon, neurosurgeon/orthopedic spine surgeon, and palliative care physician. Additional surgical subspecialties may be included as clinically indicated.

Long-term surveillance and follow-up are necessary when considering the risk of recurrence and comorbidities associated with systemic therapy and radiation therapy (RT). Life-long follow-up is recommended for surveillance and treatment of late effects of surgery, RT, and systemic therapy in long-term survivors. Patients should be given a survivorship prescription to schedule follow-up with a multidisciplinary team.

Fertility issues should be discussed with appropriate patients.[36] For further details and recommendations, including information on disease- and survivorship-related issues for adolescent and young adult (AYA) patients, please refer to the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology, available at www.NCCN.org.

Finally, select patients with a history of osteosarcoma or chondrosarcoma may benefit from genetic consultation and testing based on family history with a genetic predisposition to bone sarcomas.

Diagnostic Workup

Suspicion of a malignant bone tumor in a patient with a symptomatic lesion often begins when a poorly marginated lesion is seen on a plain radiograph.

In patients <40 years, an aggressive, symptomatic bone lesion has a significant risk of being a malignant primary bone tumor. Referral to an orthopedic oncologist should be considered prior to further workup.

In patients ≥40 years of age, workup for potential bone metastasis is recommended as indicated. This would include history and physical (H&P), bone scan, chest x-ray, and computed tomography (CT) of the chest/abdomen/pelvis (C/A/P) with intravenous contrast. Additional testing, such as serum protein electrophoresis (SPEP), complete blood count (CBC), comprehensive metabolic panel (CMP), prostate-specific antigen (PSA) test, or mammogram may also be included.[37] Other imaging studies such as 18F-fluorodeoxyglucose (FDG)-PET/CT (category 2B) and/or skeletal survey (if multiple myeloma is suspected) may be performed.[37-39]

Prior to biopsy, all patients with suspected bone sarcoma should undergo complete staging as well as consultation with an oncologist regarding pre-biopsy imaging.

Depending on the suspected type of primary bone cancer, the standard staging workup can include H&P, x-ray, cross-sectional imaging of the primary site (eg, contrast-enhanced MRI of the entire bone, and/or CT scan if MRI contraindicated), screening MRI of spinal axis, and CT C/A/P with contrast.[40] FDG-PET/CT and/or bone scan can be considered if clinically indicated.

Fertility consultation should be offered to individuals of child-bearing potential if cytotoxic chemotherapy will be given. The American Society for Reproductive Medicine (ASRM) recommends that conversations concerning fertility be undertaken by an interdisciplinary medical team comprised of oncologists, reproductive endocrinologists and urologists, and reproductive surgeons trained in fertility preservation methods and that fertility preservation programs be affiliated with an experienced assisted reproductive technology (ART) program.[41,42]

Laboratory studies, such as CBC, CMP with calcium to assess hypercalcemia, lactate dehydrogenase (LDH), and alkaline phosphatase

(ALP) should be done prior to definitive treatment and periodically during treatment and surveillance. Molecular studies can be considered to delineate potential therapeutic options.

Biopsy

Percutaneous biopsy (core needle) or incisional (open) biopsy are the two techniques historically used in the diagnosis of musculoskeletal lesions.[43,44]

Open biopsy is the most accurate method because of larger sample size, which is useful for performing additional studies such as immunohistochemistry or cytogenetics.[45] However, open biopsy requires general or regional anesthesia and operating room facilities; moreover, it can lead to contamination of surrounding tissues. Core biopsy can be performed under moderate sedation. Core needle biopsy is also highly diagnostic, with accuracy rates ranging from 88% to 96% when adequate samples are obtained.[46-49] Core biopsy is associated with a low complication rate and cost savings may be realized when needle biopsy is employed in selected patients.[46,49,50] Advances in imaging techniques have contributed to the increasing use of image-guided percutaneous biopsy for the diagnosis of primary and secondary bone tumors.[51] Furthermore, rates of complications, particularly altered treatment and outcomes, are considerably higher with open biopsy.[44,52] Although no randomized controlled trials have compared core needle biopsy with open biopsy, the higher complication rate and cost of open biopsy have resulted in a shift to the use of primarily core biopsy for diagnosis.

The guidelines recommend core needle or open biopsy to confirm the diagnosis of primary bone tumor prior to any surgical procedure or fixation of primary site. Biopsy is optimally performed at a center that will provide definitive treatment for patients with a suspected primary malignant bone tumor. At the time of biopsy, careful consideration should be given to appropriate measures to protect against impending pathologic fracture. The placement of biopsy is critical to the planning of limb-sparing surgery. A multidisciplinary approach including the radiologist and orthopedic oncologic surgeon should be taken to follow appropriate biopsy procedures and decrease risk of adverse patient outcomes.[53,54] In a multicenter review of 597 patients with musculoskeletal tumors, alteration of the treatment plan (complex resection or the use of adjunctive treatment) was encountered in 19% of patients and unnecessary amputation was performed in 18 patients.[52]

Both core needle and open biopsy techniques are associated with risk of local tumor recurrence, either by tumor spillage or tumor seeding along the biopsy tract, if the scar is not removed en bloc during the tumor resection. The risk of tumor seeding is less with core needle biopsy.[55-57] Nevertheless, the same principles should be applied for core needle and open biopsy. Appropriate communication between the surgeon, musculoskeletal or interventional radiologist, and bone pathologist is critical in planning the biopsy route. In the case of children, consultation with a pediatric oncologist is recommended. It is essential to select the biopsy route in collaboration with the surgeon to ensure that the biopsy tract lies within the planned resection bed so that it can be resected with the same wide margins as the primary tumor during surgery. Although the risk of tumor seeding is not significant with FNA biopsy, it is not suitable for the diagnosis of primary lesions since the diagnostic accuracy of FNA is less than that of core needle biopsy.[58]

Surgery

Surgical margins should be negative for most sarcomas, wide enough to minimize potential local recurrence, and narrow enough to maximize function. Wide excision implies histologically negative surgical margins, which are necessary to optimize local control. Local control may be achieved either by limb-sparing surgery or amputation. In selected

cases, amputation may be the most appropriate option to achieve this goal. However, limb-sparing surgery is preferred if reasonable functional outcomes can be achieved. Final pathologic evaluation should include assessment of surgical margins and size/dimensions of tumor. Fresh tissue may be needed for molecular studies and tissue banking. The response to preoperative therapy should be evaluated utilizing pathologic mapping. Consultation with a physiatrist may assist with mobility training and prescribing an appropriate rehabilitation program.

Radiation Therapy

RT is used either as an adjuvant to surgery for patients with resectable tumors or as definitive therapy in patients with tumors not amenable to surgery. Specialized techniques such as intensity-modulated RT (IMRT); particle beam RT with protons, carbon ions, or other heavy ions; or stereotactic radiosurgery (SRS)/stereotactic RT (SRT) should be considered as clinically indicated in order to deliver high radiation doses while maximizing normal tissue sparing.[59,60] RT should be administered at the same specialized center that is providing surgical and systemic interventions. See *Principles of Radiation Therapy* in the algorithm for treatment volumes and radiation doses specific to each subtype.

Chondrosarcoma

Chondrosarcomas characteristically produce cartilage matrices from neoplastic tissue devoid of osteoid and may occur at any age, but they are more common in older adults.[61,62] They may be classified according to the location from which they arise, with the pelvis and the proximal femur being the most common primary sites of origin. They may also be distinguished by their location along the bone as follows: 1) primary or central lesions (arising normally from the medullary cavity) originating from previously normal-appearing bone preformed from cartilage; or 2) secondary or peripheral tumors (arising from the periosteum) that develop from preexisting benign cartilage lesions, such as enchondromas, or from the cartilaginous portion of an osteochondroma.[61,63,64] Conventional chondrosarcoma (CCS) of the bone constitutes approximately nearly 90% of all chondrosarcomas, and, of these, 90% are low to intermediate grade.[65]

Low-grade (grade 1) tumors in the appendicular skeleton are currently classified by the World Health Organization (WHO) as atypical cartilaginous tumors, and are sometimes also referred to as low-grade intracompartmental appendicular tumors, while those that occur in the axial skeleton are considered grade 1 chondrosarcomas.[5]

Malignant transformation has been reported in patients with Ollier disease (enchondromatosis) and Maffucci syndrome (enchondromatosis associated with soft tissue hemangioma).[66] The peripheral or secondary tumors are usually low grade with infrequent metastasis.[67] Nearly 65% of chondrosarcoma cases and nearly all cases of Ollier disease and Maffucci syndrome are related to isocitrate dehydrogenase (*IDH1* or *IDH2*) mutations.[65,68-70] Other implicated genetic aberrations include inactivating mutations of *CDKN2A* and *COL2A1*.[64] In addition to CCS, there are several non-conventional subtypes constituting about 10% to 15% of all chondrosarcomas.[61] These include clear cell, juxtacortical, dedifferentiated, myxoid, and mesenchymal forms of chondrosarcoma.[61,71,72] Primary skeletal myxoid chondrosarcoma (myxoid chondrosarcoma of bone) is an extremely rare neoplasm that has not been fully characterized as a distinct clinicopathologic entity.[73,74] It is considered to be a myxoid variant of intermediate- or high-grade chondrosarcoma and is commonly located in the bones around the hip joint.[61,74] An epidemiologic study of mesenchymal chondrosarcomas using the SEER database found that 40% of these were skeletal and 60% were extraskeletal.[75] Research suggests that alterations in the retinoblastoma pathway are present in a significant majority of clear cell, dedifferentiated, and mesenchymal chondrosarcomas.[71]

Extraskeletal myxoid chondrosarcoma, on the other hand, is a rare soft tissue sarcoma that is characterized by chromosomal translocations t(9;22)(q22;q11-12) or t(9;17)(q22;q11), generating the fusion genes *EWS::CHN (EWSR1::NR4A3)* or *RBP56::CHN (TAF2N::NR4A3)*, respectively.[76,77] In addition, two other variant chromosomal translocations, t(9;15)(q22;q21) and t(3;9)(q12;q22), resulting in fusion genes *TCF12::NR4A3* and *TFG::NR4A3*, respectively, have also been identified in case reports.[78] A retrospective study demonstrated prolonged overall survival (OS) in patients with extraskeletal myxoid chondrosarcoma despite high rates of local and distant recurrence.[79] The data also revealed a significant pattern of decreased event-free survival (EFS) with increasing tumor size. For recommendations on the treatment of extraskeletal myxoid chondrosarcoma, see the NCCN Guidelines for Soft Tissue Sarcoma, available at www.NCCN.org.

Symptoms of chondrosarcoma are usually mild and depend on tumor size and location. Patients with pelvic or axial lesions typically present later in the disease course, as the associated pain has a more insidious onset and often occurs when the tumor has reached a significant size.[80-82] Central chondrosarcomas demonstrate cortical destruction and loss of medullary bone trabeculations on radiographs, as well as calcification and destruction.[81] MRI will show the intramedullary involvement as well as extraosseous extension of the tumor. Secondary lesions arise from preexisting lesions. Serial radiographs will demonstrate a slow increase in size of the osteochondroma or enchondroma. A cartilage “cap” measuring >2 cm on a pre-existing lesion or documented growth after skeletal maturity should raise the suspicion of sarcomatous transformation.[83]

Prognostic Factors

Whether the lesion is primary or secondary, central or peripheral, the anatomic location, histologic grade, and size of the lesion are essential prognostic features.[75,80,84-88] In an analysis of 2890 patients with chondrosarcoma from the SEER database, female sex, a low histologic grade, and local surgical stage were associated with a significant disease-specific survival benefit in the univariate analysis, whereas only grade and stage had significant association with disease-specific survival on multivariate analysis.[89] An epidemiologic study examined the impact of demographic and tumor characteristics on OS.[75] No differences in OS were observed between skeletal and extraskeletal mesenchymal chondrosarcoma, with a 5- and 10-year OS of 51% and 43%, respectively. Anatomic tumor location was a significant prognostic factor, with poorer OS observed among patients with axial versus cranial or appendicular tumor locations. Cranial tumors had different clinical behavior compared with axial and appendicular locations, with data suggesting better OS for younger patients. Prognostic factors were also examined in a retrospective, multi-institutional analysis of 225 patients with low-grade chondrosarcoma.[90] Metastasis-free survival (MFS) probability was 95% at 5 years and 92% at 10 years. A low histologic grade and no recurrence had a significant MFS benefit, but tumor size at diagnosis and surgical margin width had no effect on MFS. In a SEER database analysis, differences in the presence of metastasis were noted among the various chondrosarcoma subtypes.[72] Dedifferentiated (19.8%) followed by mesenchymal (10.6%) chondrosarcoma were most associated with the presence of metastasis on presentation, whereas juxtacortical chondrosarcoma was least associated (2.1%) with the presence of metastasis on presentation.[72] Similarly, median survival was found to be lowest with the dedifferentiated subtype (11 months) and highest with the juxtacortical subtype (97 months).[72]

Treatment

Surgery

Wide excision with negative margins is the preferred primary treatment for patients with large tumors and pelvic localization, irrespective of the grade.[86,91-93] Wide resection with adequate surgical margins is associated

with higher EFS and OS rates in patients with chondrosarcoma of axial skeleton and pelvic girdle. The 10-year OS and EFS rates were 61% and 44%, respectively, for patients who underwent resection with adequate surgical margins compared to the corresponding survival rates of 17% and 0% for those who underwent resection with inadequate surgical margins.[94] Intralesional curettage with adjuvant cryosurgery has been shown to be associated with low rates of recurrence in patients with atypical cartilaginous tumors (formerly known as grade I intracompartmental chondrosarcomas).[95-97] In selected patients with low-grade and less radiographically aggressive, non-pelvic chondrosarcomas, intralesional excision can be used as an alternative to wide excision without compromising outcomes.[98-101] This approach should be restricted to extremity tumors.[102] Intralesional excision is considered the standard treatment for extremity chondrosarcoma tumors. In a meta-analysis comparing outcome in patients with central, atypical cartilaginous tumor of the long bones following either intralesional excision or wide resection, there was little difference in the recurrence-free survival between both groups after 24 months. The rate of major complications was found to be higher following wide resection of the lesion (230 per 1000 vs. 40 per 1000 for intralesional curettage).[103]

Radiation Therapy

Clinical data demonstrate that RT also has a role in the treatment of chondrosarcoma.[61,62] A systematic review of the role of postoperative radiation in skull-base chondrosarcomas compared progression-free survival (PFS) after 3, 5, and 10 years in 1388 patients, of which 186 received surgery only.[104] At 5 years, PFS rates varied from 60% to 92.9% versus 57.1% to 100% for the surgery-only approach compared to the postoperative radiotherapy group, respectively. Recurrence rates ranged from 5.3% to 39.0% in the surgery-only group to 1.5% to 42.9% in the postoperative radiation group. A prospective outcomes study of patients with chondrosarcomas (n = 17) of the sacrum, cervical spine, and thoracolumbar spine found that high-dose external proton beam RT had a 4-year OS rate of 72% and more than half of patients (58%) had local control of disease. Treating patients with RT at the time of diagnosis is suggested to reduce the likelihood of local progression.[105]

Proton beam RT alone or in combination with photon beam RT has been associated with an excellent local tumor control and long-term survival in the treatment of patients with low-grade skull base and cervical spine chondrosarcomas.[106-114] In two separate studies, proton beam RT resulted in local control rates of 92% and 94% in patients with skull base chondrosarcoma.[106,110] Noel and colleagues reported a 3-year local control rate of 92% in 26 patients with chondrosarcoma of the skull base and upper cervical spine treated with surgical resection followed by a combination of proton and photon beam RT.[109] In a larger series involving 229 patients with skull base chondrosarcoma the combination of proton and photon beam RT resulted in 10-year local control rates of 94%.[107] Carbon ion RT has also been reported to result in high local control rates in patients with skull base chondrosarcoma[115,116] and patients with other unresectable chondrosarcomas.[117] SRS has also been evaluated for adjuvant treatment of skull base chondrosarcoma.[118]

Systemic Therapy

Chemotherapy is generally not effective in chondrosarcoma, particularly for the conventional and dedifferentiated subtypes.[119] Mitchell and colleagues reported that adjuvant chemotherapy with cisplatin and doxorubicin was associated with improved survival in patients with dedifferentiated chondrosarcoma.[120] However, this finding could not be confirmed in other studies.[121-124] For example, a SEER database analysis of 185 patients with dedifferentiated chondrosarcoma reported no OS benefit associated with perioperative chemotherapy.[124]

Furthermore, a review of outcomes for 113 patients with mesenchymal chondrosarcoma reported that the addition of chemotherapy was

associated with reduced risk of recurrence and death.[125] A retrospective review of 163 evaluable patients with chondrosarcoma showed the highest objective response rate from chemotherapy was in those with mesenchymal subtype.[126] A single-institution retrospective review of 12 patients with mesenchymal chondrosarcoma who received adjuvant chemotherapy (most commonly ifosfamide/doxorubicin) and/or radiation showed 5-year disease-free survival (DFS) and OS at 68.2% and 88.9%, respectively.[127] Another report from the German study group confirmed that the outcome was better in younger patients with mesenchymal chondrosarcoma who received chemotherapy.[128] However, in the absence of data from prospective randomized trials, the role of chemotherapy in the treatment of chondrosarcomas remains undefined.[129,130]

A multicenter, phase 2, single-arm study in patients with advanced sarcoma evaluated dasatinib, the small-molecule inhibitor of kinases (including SRC family, *BCR::ABL*, c-KIT, and platelet-derived growth factor receptors [PDGFRs] α and β). The Sarcoma Alliance for Research through Collaboration (SARC) coordinated this study, known as SARC009, which included three parallel trials focused on different rare sarcoma histologic types: aggressive sarcoma subtypes, indolent sarcoma subtypes, and gastrointestinal stromal tumors. The indolent substudy included patients with unresectable, recurrent, or metastatic soft tissue or bone sarcoma, which included 33 patients with grade 1 or 2 chondrosarcoma.[131] The primary endpoint was PFS at 6 months using the Choi criteria, which for patients with chondrosarcoma was 47%, just below the 50% cutoff for an active agent. Six patients had objective tumor response and four patients (12%) had stable disease for >1 year, suggesting some tumor control. An editorial published in the same issue of *Cancer* compared results of this and other trials using different chemotherapies for chondrosarcoma and found improved PFS at 6 months with dasatinib.[132]

Similarly, pazopanib is an oral, multikinase inhibitor with antiangiogenic activity. A single-arm, multicenter, phase 2 study evaluated the safety and efficacy of pazopanib in 42 patients with unresectable or metastatic CCS. The primary endpoint of the study was disease control rate (DCR) at week 16 and the secondary endpoints included PFS and OS. Overall, treatment with pazopanib resulted in a DCR of 43% at 16 weeks, a median PFS of 7.9 months, and a median OS of 17.6 months. Prior reports of the antitumor activity of pazopanib (including a case report and a small cohort study) in unresectable or metastatic chondrosarcoma are also favorable.[65]

A multicenter, open-label, dose-escalation and -expansion phase 1 trial in patients with *IDH1*-mutant advanced solid tumors, including 21 patients with advanced chondrosarcoma, evaluated the response to ivosidenib, a selective IDH1 inhibitor. Median PFS was 5.6 months (95% CI, 1.9–7.4 months), PFS at 6 months was 39.5%, and 52% of patients had stable disease. All patients demonstrated decreased plasma 2-hydroxyglutarate (2-HG) levels following treatment.[133]

The multicenter, single-arm, phase 2 IMMUNOSARC trial evaluated the efficacy of the tyrosine kinase inhibitor (TKI) sunitinib in combination with nivolumab in adult patients with advanced bone sarcomas.[134] The primary endpoint was PFS at 6 months and was evaluated based on radiologic review. Secondary endpoints included OS and overall response rate (ORR). Of the 38 evaluable patients, 14 (35%) had chondrosarcoma (10 CCS, four dedifferentiated [DDCS]). Median PFS was 9.5 months (95% CI, 0–19.3) for those with CCS and 1.8 months (95% CI, NA) for individuals with DDCS. Median OS and ORR by RECIST criteria (among all histologies) were 11.9 months and 5%, respectively. One individual with DDCS had a complete response (>4 years) and of the two individuals with partial responses, one had DDCS.

One study found that 41% of dedifferentiated chondrosarcomas were positive for programmed death ligand 1 (PD-L1) expression;[135] however,

the efficacy data supporting the use of programmed cell death protein 1 (PD-1)/PD-L1 inhibitors as monotherapy in the management of these tumors are limited. The activity and safety of pembrolizumab was evaluated in a two-cohort, single-arm, open-label, phase 2 study that included 40 patients with advanced bone sarcomas.[136] At median follow-up (17.8 months) one of the five patients with chondrosarcoma (dedifferentiated) had a partial response. Similarly, a retrospective review of patients with relapsed metastatic/unresectable soft tissue or bone sarcomas (n = 28) also showed a partial response to nivolumab in one patient with dedifferentiated chondrosarcoma.[137]

NCCN Recommendations

The histologic grade and tumor locations are the most important variables that determine the choice of primary treatment for chondrosarcoma. Radiologic features and size should also be considered when determining local treatment.

Intralesional excision with or without a surgical adjuvant is the primary treatment option for patients with atypical cartilaginous lesions; observation is also an option.[99,100]

High-grade (grade II, III), clear cell, extracompartmental, grade I axial tumors or low-grade extracompartmental appendicular lesions, if resectable, should be treated with wide excision obtaining negative surgical margins. Wide excision should provide negative surgical margins and may be achieved by either limb-sparing surgery or amputation.

Postoperative treatment with proton and/or photon beam RT may be useful for patients with tumors in an unfavorable location not amenable to resection, especially in chondrosarcomas of the skull base and axial skeleton.[61,62] RT can be considered for patients with borderline resectable or unresectable tumors as a primary treatment option. However, since there are not enough data to support the use of RT in patients with chondrosarcoma, the Panel has included this option as a category 2B recommendation.

Patients with mesenchymal chondrosarcomas may be treated with systemic therapy regimens used for Ewing sarcoma (category 2B), doxorubicin monotherapy, or doxorubicin/ifosfamide/mesna.

Providers may consider treating those with dedifferentiated chondrosarcomas as osteosarcoma (category 2B). Regimens used to treat osteosarcoma can be considered as preferred systemic therapy options. Single-agent pazopanib, sunitinib, pembrolizumab, or nivolumab have been included as options for dedifferentiated chondrosarcomas, in addition to sunitinib and nivolumab combination therapy.

There are no standard chemotherapy options for CCS grades 1–3 that are recommended by the NCCN Panel. However, ivosidenib can be considered as an option for certain patients with chondrosarcoma with *IDH1* mutations. Next-generation sequencing (NGS) or targeted exon sequencing can be used to detect *IDH1* mutations and other potential targeted therapy opportunities. See the *Biomarker Testing and Additional Treatment Options* section.

Metastatic Disease

Metastatic chondrosarcoma that is not dedifferentiated or mesenchymal either after recurrence or at presentation can be classified as oligometastatic or widespread disease. In general, patients with oligometastatic disease are amenable to local control (potentially rendering it disease free), such as with surgical excision or RT, or treated as part of a clinical trial (goal is disease free/cure; more likely to proceed with surgery or radiation).

For oligometastatic disease that is resectable, NCCN recommends surgical excision of all sites of disease, if possible. For oligometastatic

disease that is unresectable, consider RT that may include ablative therapy. For widespread disease, NCCN recommends considering RT, surgery, and/or ablative therapies for symptomatic sites, systemic therapy, or clinical trial. Dasatinib and pazopanib are included as category 2A treatment options for patients with metastatic or widespread chondrosarcoma. NCCN recommends that multigene panel testing (MGPT) with a validated and/or FDA-approved assay should be considered for patients with metastatic chondrosarcoma to identify potential targeted therapy opportunities. In addition, testing for tumor mutational burden (TMB) and mismatch repair (MMR)/microsatellite instability (MSI) as determined by a validated and/or FDA-approved assay should be considered. See *Biomarker Testing and Additional Treatment Options* below.

Surveillance

Surveillance for atypical cartilaginous tumors consists of a physical exam and imaging. Imaging with radiographs of the primary site, and/or cross-sectional imaging (CT with contrast or MRI with and without contrast) are recommended every 6 to 12 months for 2 years and then yearly as clinically indicated.

Surveillance for high-grade (grade II, III), clear cell, extracompartmental, grade I axial tumors or low-grade extracompartmental appendicular lesions consists of a physical exam, radiographs of the primary site, and/or cross-sectional imaging (CT with contrast or MRI with and without contrast) as clinically indicated as well as chest imaging based on physician's concern for risk of recurrence. Chest imaging should occur every 3 to 6 months (may include CT with or without contrast at least biannually) for the first 5 years and yearly thereafter for a minimum of 10 years as clinically indicated, as late metastases and recurrences after 5 years are more common with chondrosarcoma than with other sarcomas.[85] Functional assessment should be performed at every visit.

Relapsed Disease

For local recurrence of atypical cartilaginous tumors, workup including imaging of primary site, chest imaging, and biopsy to confirm diagnosis should be performed. Bone scans are optional. If there is malignant transformation, treat as described below.

For high-grade (grade II, III), clear cell, extracompartmental, grade I axial tumors or low-grade extracompartmental appendicular lesions, local recurrence should be treated with wide excision if the lesions are resectable. If there are positive margins, RT (category 2B) or re-excision to achieve negative surgical margins should be considered. If there are negative surgical margins, observation is recommended. Unresectable recurrences are treated with RT (category 2B). A study in 25 patients demonstrated effective local control and low acute toxicity with carbon ion RT in patients with recurrent skull base chordoma or chondrosarcoma.[138] Patients with systemic recurrence should follow the recommendations described above for *Metastatic Disease*.

Chordoma

Chordomas arise from the embryonic remnants of the notochord and are more commonly diagnosed in adults aged 40 to 75 years.[139] Chordomas predominantly arise in the axial skeleton, with the sacrum (50%–60%), skull base (25%–35%), and spine (15%) being the most common primary sites.[8,9,140] Chordomas are traditionally classified by the WHO into three histologic variants: conventional, chondroid, and dedifferentiated. Conventional chordomas are the most common histologic subtype characterized by the absence of cartilaginous or mesenchymal components. Chondroid chordomas present with histologic features of chordoma and cartilage elements, accounting for 5% to 15% of all chordomas. Dedifferentiated chordomas constitute about 2% to 8% of all chordomas and have features of high-grade pleomorphic spindle cell soft tissue sarcoma and an aggressive clinical course.[140] An additional subset

of chordoma has been identified in children. Poorly differentiated chordoma is characterized molecularly by the absence of *SMARCB1* expression. The protein encoded by *SMARCB1* is a chromatin remodeling agent and its absence is also implicated in the pathogenesis of some sarcomas, including but not limited to epithelioid sarcoma, malignant rhabdoid tumor, and epithelioid malignant peripheral nerve sheath tumor (MPNST). It is reported that poorly differentiated chordoma may be more common in the pediatric population and show a predilection for occurrence in the skull base and cervical spine. Although further research is warranted, poorly differentiated chordoma is considered to be more aggressive than either the conventional or chondroid variants with a poorer OS.[141,142] Chordomas of the spine and sacrum present with localized deep pain or radiculopathies, whereas cervical chordomas can cause airway obstruction or dysphagia and might present as an oropharyngeal mass. Neurologic deficit is more often associated with chordomas of the skull base and mobile spine than chordomas of sacrococcygeal region.[8,143] A review of 47 patients with skull base chordomas suggested that male sex was associated with worse PFS and OS.[144]

Workup

Initial workup should include H&P examination with adequate cross-sectional imaging of primary site (eg, MRI, CT), screening MRI of spinal axis, and C/A/P CT with contrast. Skull base to mid-thigh FDG-PET/CT or bone scan (if FDG-PET/CT is negative) can be considered for unusual cases. Benign notochordal cell tumors (BNCTs) are considered precursors to chordomas and do not require surgical management.[145-147] CT and MRI may be useful in distinguishing BNCTs from chordomas.[148,149]

For skull base chordomas, CT is useful to delineate bone destruction and the presence of calcifications, whereas MRI is the modality of choice to define the tumor margin from brain, characterize the position and extension of tumors into the adjacent soft tissue structures, and visualize blood vessels.[150-152] For sacrococcygeal chordomas, CT and MRI are useful to assess the soft tissue involvement, calcifications, and epidural extension.[153-155] MRI provides more precise and superior contrast with surrounding soft tissues compared with CT and is helpful to assess recurrent or metastatic lesions.[153,154] CT is also of particular importance to assess bony involvement, calcifications, and soft tissue and epidural extension of spinal chordomas, whereas MRI is the best imaging modality to detect tumor extension, cord compression, local recurrence, and residual tumor in the surgical scar tissue after surgical resection.[156,157] CT is also useful in planning the reconstruction of the resistant osseous defect in tumors of the proximal sacrum.

Treatment

Surgery

Wide excision with adequate margins is the preferred primary treatment for patients with resectable chordoma of the sacrococcygeal and mobile spine.[158,159] Data from two retrospective cohort studies suggest that surgery is associated with improved OS in patients with chordoma.[159,160] Several other reports have confirmed the prognostic significance of wide surgical margins, in terms of relapse-free survival (RFS) and OS, in patients with chordomas of the sacrum,[161-164] skull base,[165-171] and spine.[163,172,173] Among patients with chordoma of the mobile spine, only margin-free en bloc resection was associated with continuous DFS with a follow-up of >5 years; 12 of 18 patients were continuously disease-free at an average of 8 years after en bloc resection, whereas all patients who were treated with intralesional excision experienced recurrences in <2 years.[172] Following en-bloc resection a local recurrence rate of 14.8% and distant disease recurrence rate of 7.4% in 27 patients with chordomas of the sacrum were reported based on a single-center retrospective study.[174] Positive or <2 mm resection margins were associated with disease progression in 40.7% of patients. In a meta-analysis of 33 noncomparative studies evaluating the management of sacrococcygeal chordomas, the

overall mortality rate was found to be lowest with surgical resection followed by adjuvant RT (16%) when compared to either surgical resection (28%) or RT (43%) alone. Additionally, the PFS at 60-month follow-up was higher after surgical resection with adjuvant RT (74%) than when compared to only surgery (55%) or only RT (36%).[175]

For individuals with resectable skull base/clival chordomas, intralesional excision (with maximal safe excision) is recommended.[143] One study found that aggressive microsurgical resection is associated with long-term, tumor-free survival with good functional outcome in patients with cranial base chordomas; gross total removal was achieved in 72% of patients resulting in local control rates of 50%.[166] In a 10-year meta-analysis that included 802 patients with skull base chordoma, patients with incomplete resection were 3.83 times more likely to experience a recurrence at 5 years than patients with complete resection.[169,170]

Radiation Therapy

RT (preoperative, postoperative, or intraoperative) is used in combination with surgery to improve local control and DFS for patients with resectable chordomas. Various retrospective studies and case series have demonstrated improved local control and DFS with combined surgical/RT approaches for treating spinal/sacral[105,112,176-180] and clival/skull base chordomas.[165,178,181-185]

A retrospective review analyzed the role of RT following surgical resection in 1478 patients with skull base, sacral, and mobile spine chordomas.[186] In those with positive surgical margins, the 5-year survival rate was significantly higher among those who received adjuvant RT than the patients who received surgery alone (82.3% vs. 70.6%; $P = .03$). In contrast, adjuvant RT following surgery did not improve the survival rate among patients with negative surgical margins. A retrospective review evaluated outcomes in 37 patients with craniospinal chordoma who underwent subtotal resection (STR) (n = 23), gross total resection (GTR) (n = 12), or biopsy (n = 2) with or without adjuvant RT.[143] Results showed the best long-term survival outcomes among individuals who underwent GTR. Adjuvant RT following STR improved long-term survival; however, it had no effect on patients who underwent GTR.

Particle beam RT (either alone or in combination with photon beam RT) with high-energy protons[106-109,112,177,184,187-193] or carbon ions[115,116,193-198] resulted in local control rates ranging from 46% to 92% in patients with skull base as well as extracranial chordomas involving the spine and sacrum. Carbon ion RT also resulted in favorable outcomes for individuals with skull-base chordomas regarding local control, OS, and toxicity profile.[199] The 5- and 10-year local control rates were 80% and 56%, respectively.

A prospective trial of high-dose photon/proton RT in 50 patients with bone sarcomas of the spine (n = 29 chordoma, 14 chondrosarcoma, 7 other histologies) resulted in 5- and 8-year actuarial local control rates of 94% and 85% for primary tumors and 81% and 74% for primary and locally recurrent tumors. The 8-year actuarial risk of grades 3–4 RT toxicity was 13%.[112] A subsequent retrospective review of 126 patients with spinal/sacral chordoma who received high-dose proton therapy revealed 5-year OS and local control rates of 81% and 62%, respectively.[177] A retrospective analysis of 40 patients with unresected chordoma treated with photon/proton RT showed a 5-year local control rate and OS of 85.4% and 81.9%, respectively.[200] Similarly, a phase I/phase II trial with 20 patients confirmed to have non-metastatic chordoma or chondrosarcoma treated with proton RT also reported favorable results with a 3-year local control rate of 86% and a PFS of 81%.[201] A meta-analysis of 25 studies evaluating the 3-, 5-, and 10-year OS rates of conformal RT (CRT), SRT, proton therapy, and carbon ion therapy found that the OS rates were higher for SRT, proton therapy, and carbon ion therapy when compared to CRT.[202] Specialized techniques such as IMRT and SRS/SRT have also

been associated with good local control rates in cranial as well as extracranial chordomas.[113,203-207]

Systemic Therapy

Chordomas are typically not sensitive to conventional cytotoxic chemotherapy.[208] Several signal transduction pathways including PDGFR, epidermal growth factor receptor (EGFR), and mammalian target of rapamycin (mTOR) have been implicated in the pathogenesis of chordomas, leading to the development of targeted therapies.[209-211]

In a phase II trial of 56 patients with advanced chordoma treated with imatinib, a TKI, 70% of patients had stable disease. The clinical benefit rate (CBR) as determined by RECIST criteria (complete response + partial response and stable disease ≥6 months) was 64%, and the median PFS in the intention-to-treat population was 9 months.[212] Imatinib in combination with cisplatin or sirolimus has also been effective in a small series of patients with advanced chordoma resistant to prior imatinib therapy.[213,214] A retrospective study of imatinib in advanced, progressive, and inoperable chordoma achieved stable disease in 74% of patients, with a median PFS of 9.9 months.[215]

The efficacy of EGFR inhibitors such as erlotinib and lapatinib has also been demonstrated in patients with advanced chordoma resistant to imatinib.[216-218] In a phase II study of 18 patients with locally advanced and metastatic chordoma, lapatinib induced partial response in 33% of patients and 39% of patients had stable disease, based on Choi response criteria, whereas all patients had stable disease based on RECIST criteria.[218] The median PFS was 6 months and 8 months (with a CBR of 22%) based on Choi and RECIST criteria, respectively.

The multikinase inhibitor sorafenib is included as a systemic therapy option based on data from a phase II trial in 27 patients with advanced/metastatic chordoma. In this trial, the intent-to-treat best objective response was 1/27 (3.7%; 95% CI, 0.1%–19.0%), 9-month PFS was 73.0% (95% CI, 46.1–88.0), and 12-month OS was 86.5% (95% CI, 55.8–96.5).[219,220]

Dasatinib is also included as a systemic therapy option based on data from the SARC009 indolent substudy that included 32 patients with unresectable, recurrent, or metastatic chordoma.[131] The primary endpoint was PFS at 6 months using the Choi criteria, which for patients with chordoma was 54%. For patients with chordoma, the median PFS was 6.3 months, and the 5-year OS was 18%. The authors also compared reported patient outcomes in selected phase 2 studies in patients with chordomas and no substantial differences in ORR, median PFS, or 6-month PFS compared with imatinib or lapatinib treatment. The inclusion of sunitinib in the guidelines is based on data from a phase II study in which 44% (4/9) of patients with advanced chordoma treated with sunitinib achieved stable disease for at least 16 weeks.[221]

The Panel included pembrolizumab as a systemic therapy option based on data from the non-randomized, open-label, phase II basket trial that evaluated the efficacy of pembrolizumab in 97 patients with rare and ultra-rare sarcomas refractory or resistant to standard therapy.[222] Of the 34 patients with chordoma, an objective response was reported in 4 individuals at week 12 and the median PFS was 6.1 months (95% CI, 4.6–11.5).

NCCN Recommendations

Tumor location is the most important variable in determining the choice of primary treatment for patients with conventional (including chondroid) chordomas. Dedifferentiated and poorly differentiated chordomas are usually managed as described in the NCCN Guidelines for Soft Tissue Sarcoma, available at www.NCCN.org.

Wide excision with or without adjuvant RT is a primary treatment option for patients with resectable conventional (including chondroid) chordomas of the sacrum and mobile spine.[158,159] Intralesional excision with or without adjuvant RT (followed by contrast-enhanced MRI to assess the adequacy of resection) is the treatment of choice for patients with resectable skull base/clival tumors of conventional or chondroid histology.[143] Maximal safe excision is recommended when appropriate.[168] Adjuvant treatment with RT can be considered for large extracompartmental tumors or for positive surgical margins following resection. Postoperative RT has been associated with improved local control and DFS following surgery with macroscopic surgical margins or intralesional excision.[176,178,183,223,224] Re-excision, if necessary, can be considered for skull base tumors with positive surgical margins.

Definitive RT is the primary treatment option for patients with unresectable chordomas, irrespective of the location of the tumor.

Surveillance

Surveillance consists of a physical exam, imaging (ie, x-ray, MRI with or without contrast ± CT with contrast) of the primary site (timing and modality as clinically indicated) for up to 10 years, and chest imaging (every 6 months for 5 years and annually thereafter; may include CT annually; chest CT may be done with or without contrast as clinically indicated).

Relapsed Disease

Chordomas are characterized by a high rate of local recurrence, and distant metastases to lungs, bone, soft tissue, lymph nodes, liver, and skin have been reported in up to 40% of patients with local recurrence.[161,187,225-227] Among patients with recurrent chordomas of skull base and spine, Fagundes and colleagues reported a higher 2-year actuarial OS rate for patients treated with STR than those who received supportive care only (63% and 21%, respectively; $P = .001$).[187] However, some studies have reported that surgery and RT are associated with lower local control rates for recurrent tumors than for primary tumors in patients with sacral chordomas.[189,205] A study of 25 patients demonstrated effective local control and low acute toxicity with carbon ion RT in patients with recurrent skull base chordoma or chondrosarcoma.[138]

Patients with recurrent disease can be treated with surgery and/or RT[228] and/or systemic therapy and/or ablation (local recurrence only). The guidelines include imatinib (with or without cisplatin or sirolimus), dasatinib, pembrolizumab, sunitinib, erlotinib, lapatinib (for patients with EGFR-positive disease), and sorafenib as systemic therapy options for patients with recurrent tumors. Enrollment in a clinical trial is included as an option for recurrent (local or metastatic) disease and/or best supportive care for metastatic recurrence only. MGPT with a validated and/or FDA-approved assay should be considered for patients with recurrent chordoma to determine targeted therapy opportunities. See *Biomarker Testing and Additional Treatment Options* below.

Ewing Sarcoma

Ewing sarcoma is characterized by the fusion of the *EWS* gene (*EWSR1*) on chromosome 22q12 with various members of the ETS gene family (*FLI1*, *ERG*, *ETV1*, *ETV4,* and *FEV*).[12,13] The *EWSR1::FLI1* fusion transcript resulting from the fusion of *EWSR1* and *FLI1* on chromosome 11 and the corresponding chromosomal translocation, t(11;22)(q24;q12), is identified in about 85% of patients with Ewing sarcoma.[12,15] In 5% to 10% of cases, *EWSR1* is fused with other members of the ETS gene family. In rare cases, *FUS* can substitute for *EWSR1* resulting in fusion transcripts with no *EWSR1* rearrangement [*FUS*::*ERG* fusion transcript resulting from the translocation t(16;21)(p11;q24) or *FUS*::*FEV* fusion transcript resulting from the translocation t(2;16)(q35;p11)].[229,230] Overall, 90% of Ewing sarcomas will have one of four cytogenetic translocations.

Ewing sarcoma is also characterized by the strong expression of cell surface glycoprotein MIC2 (CD99).[231,232] The expression of CD99 may be useful in the differential diagnosis of Ewing sarcoma from other small round-cell neoplasms, although it is not exclusively specific to these tumors.[233] Similar in morphology with various molecular signatures, other primary round cell sarcomas of bone, previously referred to as Ewing-like sarcomas, are a heterogenous group of tumors that primarily affect the pediatric and adolescent population.[234] These tumors include: *CIC*-rearranged sarcomas (eg, *CIC::DUX4*), *BCOR*-rearranged sarcomas, and round cell sarcomas with *EWSR1* fusions with non-ETS genes.[235]

Typically, Ewing sarcoma occurs in AYAs, with an incidence of 1 case per 1.5 million.[236] The most common primary sites are the pelvic bones, femur, and the bones of the chest wall, although any bone may be affected.[26] However, in approximately 20% of cases, these tumors emerge from extraosseous tissue.[236] When arising in a long bone, the diaphysis is the most frequently affected site.[26] On imaging, the bone appears mottled. Periosteal reaction is classic and is referred to as “onion skin” by radiologists.

Patients with Ewing sarcoma, as with most patients with bone sarcomas, seek attention because of localized pain or swelling. Unlike other bone sarcomas, constitutional symptoms such as fever, weight loss, and fatigue are occasionally noted at presentation. Abnormal laboratory studies may include elevated serum LDH and leukocytosis.

Prognostic Factors

The important indicators of favorable prognosis include a distal/peripheral site of primary disease, tumor volume <100 mL, normal LDH level at presentation, and the absence of metastatic disease at the time of presentation.[237-244] Ewing sarcoma in the spine and sacrum is associated with significantly worse outcome and prognosis than primary Ewing sarcoma in other sites.[245] In a systematic review, Bosma and colleagues also reported tumor size (diameter >8 cm) and histologic response to initial systemic treatment (≥90% necrosis) to be important prognostic variables.[246] Nevertheless, metastatic disease at presentation is the most significant adverse prognostic factor observed in those with Ewing sarcoma, as it is for other bone sarcomas.[32,241,247] The lungs, bone, and bone marrow are the most common sites of metastasis. In a retrospective analysis of 975 patients from the EICESS Study Group, 5-year RFS was 22% for patients with metastatic disease at diagnosis compared with 55% for patients without metastases at diagnosis.[32] Among patients with metastases, there was a trend for better survival for those with lung metastases compared to those with bone metastases or a combination of lung and bone metastases.[32,248] Metastases to uncommon sites (ie, brain, liver, spleen) were associated with a worse prognosis in a retrospective study of 30 patients.[249] Poor histologic/radiologic response to chemotherapy has also been identified as an adverse prognostic factor in patients with localized non-metastatic disease,[240,244,250,251] even when chemotherapy was followed by complete resection.[252]

The results of the Intergroup Ewing’s Sarcoma Study (IESS) analyzing the clinicopathologic features of 303 cases of Ewing sarcoma showed that patients with primary tumors in pelvic bones have lower survival rates compared with patients with lesions in distal bones of the extremities.[253] In an analysis of 53 patients (24 adult and 29 pediatric) with Ewing sarcoma treated with chemotherapy, Gupta and colleagues identified pelvic disease and time to local therapy as significant prognostic factors associated with EFS in a multivariate analysis.[254] In another retrospective analysis of patients with Ewing sarcoma from a large population-based cancer registry, Lee and colleagues determined

that adult age, Hispanic ancestry, metastatic disease, large tumor size, and low socioeconomic status are poor prognostic factors for OS.[255]

Workup

If Ewing sarcoma is suspected as a diagnosis, the patient should undergo complete staging prior to biopsy. This should include CT of the chest with or without contrast as clinically indicated (non-contrast CT is recommended for restaging); contrast-enhanced; MRI with or without CT of the primary site; whole body FDG-PET/CT (preferred) and/or bone scan; and possibly bone marrow biopsy and/or screening MRI with or without contrast of the spine and pelvis. In a systematic review and meta-analysis, Treglia and colleagues reported that the combination of FDG-PET/CT with conventional imaging is a valuable tool for the staging and restaging of Ewing sarcoma, with 96% sensitivity and 92% specificity.[256] Another systematic review indicated that FDG-PET without bone marrow biopsy may be considered for staging in newly diagnosed Ewing sarcoma patients, as FDG-PET demonstrated 100% sensitivity and 96% specificity based on pooled patient data from four studies.[257] Results from ACRIN 6660, a multicenter prospective cohort study conducted by the American College of Radiology Imaging Network (ACRIN) comparing whole-body MRI and conventional imaging in pediatric patients with common malignant tumors (including Ewing sarcoma), found that the noninferior accuracy for diagnosis of distant metastasis was not established for the use of whole-body MRI compared with conventional imaging.[258] However, the accuracy of whole-body MRI was higher for patients with solid tumors compared to those with lymphomas (P = .006).

Cytogenetic and/or biomarker testing of the biopsy specimen should be performed to evaluate t(11;22) or other less common translocations. MGPT has also been used to identify potentially actionable translocations in patients with sarcoma.[259,260] In the case that pathologic workup of targeted polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH), or cytogenetics is negative, MGPT or other fusion panels for Ewing sarcoma should be considered to identify translocations, including atypical translocations.

Preliminary reports suggest that *EWSR1::FLI1* translocation is associated with a better prognosis than other variants.[261-263] However, reports from the EURO-EWING 99 study and the Children's Oncology Group study suggest that with currently available effective therapies, patients with Ewing sarcoma have similar outcomes, regardless of fusion subtype in contrast to previous reports.[264,265] In addition to *EWSR1, FUS* should be considered as a fusion gene partner in the molecular diagnosis to identify the rare cases of Ewing sarcoma with *FUS*::*ERG* or *FUS*::*FEV* fusion transcripts.[229,230] Since serum LDH has been shown to have prognostic value as a tumor marker, the guidelines have included this test as part of initial evaluation. Since serum LDH has been shown to have prognostic value as a tumor marker, the guidelines have included this test as part of initial evaluation.

Fertility consultation should be offered. See the *Diagnostic Workup* section above.

Treatment

Chemotherapy

Multiagent chemotherapy regimens including VDC (vincristine, doxorubicin, and cyclophosphamide) alternating with IE (ifosfamide and etoposide) have been shown to be effective in patients with localized Ewing sarcoma in single- as well as multi-institution collaborative trials in the United States and Europe. Multiagent chemotherapy for at least 9 weeks is recommended prior to surgery to downstage the tumor and increase the probability of achieving a complete resection with microscopically negative margins. Data support the use of adjuvant

chemotherapy following surgical resection, resulting in improved RFS and OS.[266-270] Surgical resection with or without RT is used for local control following chemotherapy.

The addition of ifosfamide, alone or in combination with etoposide to standard chemotherapy, was evaluated in patients with newly diagnosed, non-metastatic Ewing sarcoma.[268,271-275] In the Pediatric Oncology Group-Children's Cancer Group (POG-CCG) study (INT-0091), 398 patients with non-metastatic Ewing sarcoma were randomized to receive chemotherapy with VACD (vincristine, dactinomycin, cyclophosphamide, and doxorubicin) alone or VACD-IE (VACD alternating with ifosfamide and etoposide) for a total of 17 cycles.[268] The 5-year EFS rate was significantly higher in the VACD-IE group than in the VACD alone group (69% and 54%, respectively; P = .005). The 5-year OS rate was also significantly better among patients in the VACD-IE group (72% and 61%, respectively; P = .01). VACD-IE also was associated with lower incidences of local disease progression (11%) compared with VACD (30%) irrespective of the type of local control therapy; 5-year cumulative incidences of local disease progression were 30% in the VACD arm compared with 11% in the VACD-IE arm.[276]

While dose escalation of alkylating agents in the VDC-IE regimen did not improve the outcome for patients with localized disease,[277] chemotherapy intensification through interval compression improved outcome in patients with localized disease.[278] In a randomized trial for patients <50 years with localized Ewing sarcoma (n = 568), Womer and colleagues reported that VDC-IE given on an every-2-week schedule was found to be more effective than VDC-IE given on an every-3-week schedule, with no increase in toxicity; median 5-year EFS was 73% and 65%, respectively.[278]

The EURO EWING 2012 (EE2012) was a randomized analysis conducted to compare the induction and consolidation regimens for newly diagnosed Ewing sarcoma in both the United States and Europe.[279] Six hundred forty patients between the ages of 2 and 49 years were randomized to two treatment arms. Treatment arm A received the European regimen: VIDE (vincristine, ifosfamide, doxorubicin, and etoposide) induction therapy followed by vincristine, actinomycin D, with ifosfamide or cyclophosphamide, or busulfan and melphalan consolidation. Treatment arm B received the U.S. regimen: compressed VDC-IE induction followed by VC (vincristine and cyclophosphamide) or vincristine, actinomycin D, and ifosfamide, with busulfan and melphalan consolidation. The primary endpoint of the study was EFS while the secondary endpoints were OS and toxicity. EFS at 3 years was 61% and 67% for treatment arms A and B, respectively (adjusted hazard ratio [HR] 0.71 [95% credible interval 0.55–0.92 in favor of treatment arm A]). Grade 3–5 febrile neutropenia occurred in 74% of participants in treatment arm A and in 58% of participants in treatment arm B. More participants in treatment arm A required at least one platelet transfusion; however, more participants in treatment arm B required more blood transfusions. The VDC-IE regimen proved superior to the European regimen in terms of EFS and OS with similar toxicity profiles.

IESS-I and IESS-II showed that RT plus adjuvant chemotherapy with VACD was superior to VAC in patients with localized non-metastatic disease.[267] The 5-year RFS rates were 60% and 24% for VACD and VAC, respectively (P < .001). The corresponding OS rates were 65% and 28% (P < .001).

In the INT-0091 study, which included 120 patients with metastatic disease, there was no significant difference in the EFS and OS rates between the VACD-IE and VACD regimens.[268] The 5-year EFS rate was 22% for both regimens and the 5-year OS rate was 34% and 35% for the VACD-IE and VACD groups, respectively. In a study of 68 patients (44 patients with locoregional disease and 24 patients with distant

metastases), Kolb and colleagues reported 4-year EFS and OS rates of 82% and 89%, respectively, for patients with locoregional disease treated with intensive chemotherapy (doxorubicin and vincristine with or without high-dose cyclophosphamide) followed by ifosfamide and etoposide.[273] In patients with distant metastases the corresponding survival rates were 12% and 18%, respectively. Miser and colleagues also reported similar findings in patients with Ewing sarcoma with metastases at diagnosis.[280]

The EICESS-92 study investigated whether cyclophosphamide has efficacy similar to ifosfamide in patients with standard-risk Ewing sarcoma (small localized tumors) and whether the addition of etoposide to a regimen already containing ifosfamide improves survival in patients with high-risk disease (large tumors or metastatic disease at diagnosis).[281] Patients with standard-risk disease were randomly assigned to VAID (vincristine, dactinomycin, ifosfamide, and doxorubicin; n = 76) followed by either VAID or VACD (n = 79).[281] The 3-year EFS rates were 73% and 74%, respectively, for VACD and VAID, suggesting that cyclophosphamide has the same efficacy as ifosfamide in this group of patients. Patients with high-risk disease were randomly assigned to VAID or EVAID (VAID plus etoposide). The 3-year EFS rate was not significantly different between the two treatment groups (52% and 47%, respectively, for EVAID and VAID).[281]

As a follow-up to the EICESS-92 study, the Euro-EWING99-R1 trial evaluated cyclophosphamide as a replacement for ifosfamide as part of consolidation therapy that also included vincristine and dactinomycin (VAC vs. VAI) after VIDE induction chemotherapy in 856 patients with standard-risk Ewing sarcoma. VAC was statistically not inferior to VAI but was associated with a slight increase in events (2.8% decrease in 3-year EFS). The proportion of patients experiencing severe hematologic toxicity was slightly higher in the VAC arm, but renal tubular function impairment was more significant for patients receiving VAI.[282]

High-Dose Therapy Followed by Hematopoietic Cell Transplant

High-dose therapy followed by hematopoietic cell transplant (HDT/HCT) has been evaluated in patients with localized as well as metastatic disease. HDT/HCT has been associated with potential survival benefit in patients with non-metastatic disease.[283,284] However, studies that have evaluated HDT/HCT in patients with primary metastatic disease have shown conflicting results.[285-291]

The EURO-EWING 99 study was the first large randomized trial designed to evaluate the efficacy and safety of multiagent induction chemotherapy with six courses of VIDE, local treatment (surgery and/or RT), and HDT/HCT in 281 patients with Ewing sarcoma with primary disseminated disease.[286] After a median follow-up of 3.8 years, the EFS and OS rates at 3 years for the entire study cohort were 27% and 34%, respectively.[290] The EFS rates were 57% and 25%, respectively, for patients with complete and partial response after HDT/HCT. Patients' age, tumor volume, and extent of metastatic spread were identified as relevant risk factors. The outcome of patients with and without HDT/HCT was not performed because of the bias introduced early in the non-transplant group (82% of patients without HDT/HCT died after a median time of 1 year).

The EURO-EWING 99 and Ewing-2008 randomized trial asked whether consolidation high-dose chemotherapy improved survival in patients with localized Ewing sarcoma.[291] Two hundred forty patients at high risk were randomly assigned to receive seven VAI courses (n = 118) or one course of BuMel (busulfan and melphalan) HDT with autologous HCT (n = 122), after a VIDE six-course induction plus one VAI consolidation course. Patients were followed for 15 years; median follow-up time was 7.8 years. Patients treated with BuMel had greater improvement in 3-year

EFS (69.0% vs. 56.7%) and 8-year EFS (60.7% vs. 47.1%) compared to VAI-treated patients. There were three treatment-related deaths: two due to BuMel toxicity and one due to VAI toxicity. More patients experienced severe acute toxicities related to the BuMel versus the VAI course.

Local Control Therapy

Surgery and RT are the local control treatment modalities used for patients with localized disease, but no randomized trials have compared these approaches head-to-head.

In patients with localized Ewing sarcoma treated in cooperative intergroup studies there was no significant effect of local control modality (surgery, RT, or surgery plus RT) on OS or EFS rates.[276,292] In the CESS 86 trial, although radical surgery and resection plus RT resulted in better local control rates (100% and 95%, respectively) than definitive RT (86%), there was no improvement in RFS or OS because of higher frequency of metastases after surgery.[292] In the INT-0091 study, the incidences of local disease progression were similar for patients treated with surgery or RT alone (25%), but surgery plus RT resulted in lower incidences of local disease progression (10.5%).[276] The 5-year EFS rate was also not significantly different between the groups (42%, 52%, and 47% for patients treated with surgery, RT, and surgery plus RT, respectively).

Data from other retrospective analyses suggest that surgery (with or without postoperative RT) affords better local control than RT alone in patients with localized disease.[293,294] The combined analysis of 1058 patients treated in the CESS 81, CESS 86, and EICESS 92 trials showed that the rate of local progression was significantly lower after surgery (with or without postoperative RT) than after definitive RT (7.5% vs. 26.3%, respectively; P = .001), whereas the local control rate with preoperative RT was comparable to that of the surgery group (5.3%).[293] A retrospective analysis of sequential studies (INT-0091, INT-0154, or AEWS0031) performed by the Children's Oncology Group also demonstrated that definitive RT was associated with a higher risk of local disease progression than surgery plus RT at 25.0% and 6.3%, respectively, but there was no effect on distant disease progression. [295]

Definitive RT could be an effective treatment option for patients with tumors in anatomical locations not amenable to achieve surgery with wider resection margins.[296,297] In a retrospective analysis of patients with Ewing sarcoma of vertebrae treated in the CESS 81/86 and EICESS 92 studies, definitive RT resulted in a local control rate of 22.6%, which was comparable to those of other tumor sites treated with definitive RT; EFS and OS at 5 years were 47% and 58%, respectively.[296] Tumor size and RT dose have been shown to be predictive of local control rates in patients with non-metastatic Ewing sarcoma treated with chemotherapy and definitive RT.[298,299] Local control therapy has also been associated with improved outcomes in patients with primary metastatic disease.[300-302] In the EURO-EWING 99 trial, the 3-year EFS was significantly lower in patients with primary metastatic disease who did not receive any local control therapy compared to those treated with local therapy for primary tumor.[300] Retrospective analysis of 198 patients from EURO-EWING 99 showed no improvement of 5-year EFS associated with adjuvant RT in the setting of completely resected disease of the chest wall.[303]

NCCN Recommendations

All patients with Ewing sarcoma should be treated with the following protocol: primary treatment followed by local control therapy and adjuvant treatment. Primary treatment consists of multiagent chemotherapy along with appropriate growth factor support for at least 9 weeks (category 1). Longer duration could be considered for patients with metastatic disease based on response. VDC-IE is the preferred regimen for patients with localized disease and is a category 1 recommendation. See *Bone Cancer Systemic Therapy Agents* in the algorithm for a list of other chemotherapy

regimens that are recommended for patients with localized and metastatic disease. Of note, patients with other primary round cell sarcoma of bone can be treated like Ewing sarcoma.

Disease should be restaged with imaging following primary treatment. Chest imaging (specifically non-contrast CT) is recommended for restaging. Additionally, primary site imaging should include contrast-enhanced MRI with or without CT and plain radiograph. Head-to-toe FDG-PET/CT or bone scan can be used for restaging depending on the imaging technique that was used in the initial workup.

Patients with stable or improved disease after primary treatment should be treated with local control therapy. Local control options include wide excision, definitive RT with chemotherapy, or amputation in selected cases.[293,296,298,300] The choice of local control therapy should be individualized and is dependent on tumor location, size, response to chemotherapy, patient age, anticipated morbidity, and patient preference.[276]

Adjuvant chemotherapy following wide excision or amputation is recommended for all patients regardless of surgical margins. The Panel strongly recommends that the duration of chemotherapy following wide excision or amputation should be between 28 and 49 weeks depending on the type of regimen and the dosing schedule (category 1).[266-268] The addition of postoperative RT to chemotherapy is recommended for patients with positive or very close surgical margins.[293] Denbo and colleagues reported that in patients with smaller tumor size (<8 cm) and negative margins, postoperative RT can be omitted without any decrement in OS.[304] The 15-year estimated OS for patients who received adjuvant RT was 80% compared to 100% for those who did not. The guidelines have included adjuvant chemotherapy alone for patients treated with wide excision and negative margins.

In the setting of widely metastatic disease, palliative therapies may be considered. For metastatic disease that may be amenable to local therapy, local control modalities, in the form of wide excision or definitive RT with adjuvant chemotherapy, are recommended. Regardless of postoperative margin status, chemotherapy for at least 28 to 49 weeks is to be administered (category 1). RT, in addition to chemotherapy, may be considered for positive surgical margins. Following adjuvant treatment, metastases may be managed according to the location. In the case of oligometastatic disease, excision or RT is recommended. SRS/stereotactic body RT (SBRT) can be considered, especially for oligometastases.[305-307] For pulmonary metastases, dependent on the response, resection and/or whole lung irradiation (WLI) may be considered.[308] Based on the EORTC-SIOP phase III study published in 1988, which concluded there to be no survival benefit of WLI over adjuvant chemotherapy for patients with osteosarcoma, a systematic review of both prophylactic as well as curative WLI in patients with osteosarcoma and Ewing sarcoma was conducted.[309,310] Only two studies compared the results of chemotherapy alone and chemotherapy and curative WLI in patients with metastatic Ewing sarcoma. In both trials, patients experienced some benefit with WLI and chemotherapy when compared to chemotherapy alone. For instance, in the EICESS-92 trial, patients who also received WLI showed a 12% improvement in 5-year OS.[310,311] Ultimately, it was concluded that the decision to use WLI should be based on the patient's risk of pulmonary metastases and any coexisting respiratory diseases.[310] Progressive disease following primary treatment is best managed with RT and/or surgery to primary site followed by chemotherapy or best supportive care.

Surveillance

Surveillance of patients with Ewing sarcoma should include a physical exam, CBC and other laboratory studies (as indicated), contrast-enhanced MRI with or without CT, and plain radiographs of the primary

site. Chest imaging (x-ray or CT) is recommended every 3 months. Head-to-toe FDG-PET/CT or bone scan can be considered as appropriate. Surveillance intervals should be increased after 2 years. Long-term surveillance should be performed annually after 5 years, and as clinically indicated (indefinitely) (category 2B).[312]

Relapsed or Refractory Disease

Approximately 30% to 40% of patients with localized Ewing sarcoma at presentation and 60% to 80% with metastatic disease at presentation experience recurrence (local and/or distant) and have a very poor prognosis.[313] Patients with a longer time to first recurrence have a better chance of survival following recurrence. Late relapse (≥2 years 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 (<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 adverse prognostic factors.[314-317] In a retrospective analysis, site of first relapse and time to first relapse were significant prognostic factors for adult patients with localized Ewing sarcoma.[318] The probability of 5-year post-relapse survival was 55% and 22%, 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.[32,313,318] Overall, it is reported that close to 70% of relapses are early relapses, of which two-thirds occur at distant sites (in the lungs and/or bones). Patients who initially presented with widespread disease are more likely to relapse at distant sites, whereas those individuals who presented with localized disease are more likely to develop local relapse.[319]

Topoisomerase I inhibitors (topotecan and irinotecan) in combination with cyclophosphamide and temozolomide have been associated with favorable response rates in patients with relapsed or refractory bone sarcomas.[320-326] In a series of 54 patients with relapsed or refractory Ewing sarcoma, cyclophosphamide and topotecan induced responses in 44% of patients (35% of patients had a complete response and 9% had a partial response).[321] After a median follow-up of 23 months, 26% of patients were in continuous remission. In a retrospective analysis of patients with recurrent or progressive Ewing sarcoma, irinotecan and temozolomide resulted in an overall objective response rate of 63%. The median time to progression (TTP) for all the evaluable patients (n = 20) was 8.3 months (16.2 months for the subset of patients with recurrent disease).[324] Patients who were in a 2-year first remission and those with primary localized disease had better median TTP compared to those who relapsed within 2 years from diagnosis and patients with metastatic disease at diagnosis.

Combination therapy with vincristine, irinotecan, and temozolomide also appears to be active and well-tolerated in patients with relapsed or refractory Ewing sarcoma, with an ORR of 68%.[327] A review of 107 patients with relapsed or refractory Ewing sarcoma examined the combination of etoposide with a platinum agent (ie, cisplatin or carboplatin), suggesting that further study of etoposide and carboplatin may be warranted.[328] HDT/HCT has been associated with improved long-term survival in patients with relapsed or progressive Ewing sarcoma in small, single-institution studies.[329-331] The role of this approach is yet to be determined in prospective randomized studies.

The CABONE trial, a multicenter, single-arm phase 2 trial, evaluated the activity of cabozantinib in patients with advanced Ewing sarcoma and osteosarcoma.[332] Currently approved for renal carcinoma, hepatocellular carcinoma, and medullary thyroid cancer, cabozantinib is a vascular

endothelial growth factor receptor-2 (VEGFR2) TKI with inhibitory activity against the MET receptor. For Ewing sarcoma, the primary endpoint in this study was a 6-month objective response, while the secondary endpoints included safety, 6-month non-progression, best overall response, 1-year and 2-year PFS and OS, and metabolic response (evaluated by FDG-PET/CT 28 days after the first dose). The primary endpoint was achieved with a 6-month objective response of 26% (95% CI, 13–42) among 39 patients with Ewing sarcoma. Additionally, the median OS was reported to be 10.2 months with a median PFS of 4.4 months. OS was noted to be 84% at 6 months, 48% at 12 months, and finally 14% at 24 months. Forty-two percent (95% CI, 25–61) of patients exhibited a metabolic tumor response. Cabozantinib was well-tolerated among patients with the most common grade 3 or 4 adverse effects being hypophosphatemia, elevated aspartate aminotransferase (AST), palmar-plantar syndrome, pneumothorax, and neutropenia.[332]

The efficacy of regorafenib has been evaluated in the phase II SARC024 trial in 30 patients with metastatic Ewing sarcoma whose disease progressed following at least 1 line of therapy. The 8-week progression-free rate was 63% and the median OS was 53 weeks.[333]

The phase III rEECur trial compared the efficacy of IFOS (high-dose ifosfamide) (n = 73) against topotecan and cyclophosphamide (TC) (n = 73) in patients with relapsed or refractory Ewing sarcoma.[334] The median EFS was 3.7 months and 5.7 months for TC and IFOS, respectively, and the median OS was 10.4 months and 16.8 months for TC and IFOS, respectively. Greater survival for EFS and OS was also seen in individuals aged <14 years.

A retrospective study evaluated docetaxel in combination with gemcitabine in 22 children and young adults with refractory bone sarcomas.[335] The median duration of response was 4.8 months and the objective response rate was 29%.

The combination of ifosfamide, carboplatin, and etoposide has also been evaluated in three Children's Cancer Group phase I/II trials in 97 patients with relapsed or refractory bone sarcomas.[336] The ORR was 51%.

A single-arm phase II study evaluated the efficacy and safety of lurbinectedin in a cohort of 28 adult patients with relapsed Ewing sarcoma.[337] Treatment with lurbinectedin resulted in an ORR of 14.3% and a median duration of response of 4.2 months.

In a study evaluating 26 patients treated for local recurrence of Ewing sarcoma, surgical treatment was associated with better survival (P < .001).[338] In addition to chemotherapy, surgery may be a treatment option for some patients who experience relapsed disease.

NCCN Recommendations

Treatment options for patients with relapsed or refractory disease include participation in a clinical trial and chemotherapy (with or without RT or with or without surgery). See *Bone Cancer Systemic Therapy Agents* in the algorithm for a list of other systemic therapy regimens recommended for patients with relapsed or refractory Ewing sarcoma.

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

Giant Cell Tumor of Bone

GCTB is a rare benign primary tumor of the bone accounting for about 3% to 5% of all primary bone tumors, with a strong tendency for local recurrence and that may metastasize to the lungs.[339,340] GCTB usually occurs between 20 and 40 years of age. The meta-epiphyseal regions of the distal femur and proximal tibia are the most common primary sites.[341] Malignant transformation to high-grade osteosarcoma has been observed in rare cases and is associated with a poor prognosis.[342,343]

Workup

Initial workup should include H&P examination with imaging (eg, x-ray, MRI with and without contrast ± CT) of the primary site as clinically indicated, in addition to chest imaging. CT is useful to define the extent of cortical destruction, whereas MRI is the preferred imaging modality to assess the extension of tumors into the adjacent soft tissue and neurovascular structures.[344,345] Chest imaging is essential to identify the presence of metastatic disease. Bone scan can be considered for unusual cases. Biopsy is essential to confirm the diagnosis. Brown tumor of hyperparathyroidism should be considered as a differential diagnosis; routine evaluation of serum calcium, phosphate, and parathyroid hormone levels can help exclude this diagnosis.[346] If there is malignant transformation, treat as osteosarcoma.

Treatment

Surgery

Wide excision and intralesional curettage are the two surgical treatment options for patients with resectable tumors.[347-353] Wide excision is associated with a lower risk of local recurrence than intralesional curettage, with the local recurrence rates ranging from 0% to 12% for wide excision and 12% to 65% for intralesional curettage. In some studies, the extent of intralesional excision and the tumor stage have been identified as prognostic indicators for risk of recurrence.[354-356] Blackley and colleagues reported a local recurrence rate of 12% in 59 patients who were treated with curettage with high-speed burr and bone grafting, which was similar to that observed with the use of adjuvants; the majority of the patients had grade II or III tumors.[355] In another retrospective analysis of 137 patients, Prosser and colleagues reported local recurrences in 19% of patients following curettage as a primary treatment; local recurrence rate was only 7% for patients with grade I and II tumors confined to the bone compared with 29% for those with grade III tumors with extraosseous extension.[356]

Surgical adjuvants have been used in conjunction with intralesional curettage to improve local control rates. However, the findings from studies that have evaluated intralesional curettage, with and without adjuvant in the same cohort of patients with primary or recurrent GCTB, are inconsistent, with some reporting decreased local recurrence rates with the use of adjuvants.[351,357-360] Others, however, have reported no significant difference in local recurrence rates with and without adjuvants.[162,361,362]

Wide excision is also associated with poor functional outcome and greater surgical complications.[363-368] Therefore, intralesional curettage is considered the treatment of choice in a majority of patients with stage I or II tumors. Wide excision is usually reserved for more aggressive stage III tumors with extraosseous extension or otherwise unresectable tumors.[356,369-372]

Radiation Therapy

RT has been used either as a primary treatment or in combination with surgery to improve local control and DFS for patients with marginally resected, unresectable, progressive, or recurrent disease.[373-384] In a retrospective analysis of 58 patients with GCTB (45 patients with primary tumor and 13 patients with recurrent tumor) treated with RT, the 5-year local control and OS rates were 85% and 94%, respectively.[383] Median follow-up was 8 years. In this analysis, patient age was the only prognostic factor with local control rates (96% for patients ≤30.8 years vs. 73% for patients >30.8 years) as well as OS (100% vs. 87%) and DFS rates (96% vs. 65%). Other studies have identified tumor size >4 cm, recurrent tumors, and RT doses of ≤40 Gy as negative prognostic factors for local control.[379-381,384]

Specialized techniques such as 3D-CRT and IMRT have also been associated with good local control rates in patients with GCTB in locations that are not amenable to complete surgical resection.[385,386]

Adverse side effects have occurred as a result of RT. As GCTB is a benign growth, radiation use should be considered riskier than for malignant tumors. [387,388] Therefore, the Panel recommends that RT should be considered if no other treatment options are available, if possible.

Systemic Therapy

Denosumab (a fully humanized monoclonal antibody against the RANK ligand) has demonstrated activity in patients with unresectable or recurrent GCTB.[389-396] In June 2013, denosumab was approved by the FDA for the treatment of adults and skeletally mature adolescents with GCTB that is unresectable or where surgical resection is likely to result in severe morbidity. It is a preferred option in resectable localized disease with unacceptable morbidity and/or with unresectable axial lesions, or unresectable metastatic disease at presentation.

Several phase II trials have examined the efficacy of denosumab for treating primary and recurrent GCTB. In an open-label, phase II study (n = 37), denosumab induced tumor response (defined as the elimination of ≥90% of giant cells or no radiologic progression of the target lesion for ≤25 weeks) in 86% (30 of 35 evaluable patients) of patients with unresectable or recurrent GCTB.[389] An open-label, parallel-group, phase II study divided patients with GCTB into three cohorts: those with unresectable GCTB (cohort 1), those with resectable GCTB associated with severe surgical morbidity (cohort 2), and those transferred from a previous study of denosumab for GCTB (cohort 3).[391,397,398] After a median follow-up of 58.1 months, TTP or recurrence in 253 patients in cohort 1 had not been reached.[398] Clinically significant reductions in pain were reported by over half of the study patients within 2 months.[399] Final analysis of outcomes from cohort 2 (n = 222) showed that denosumab enabled 48% of patients to delay/avoid surgery and 38% to undergo less morbid resections.

The risk of local recurrence has been reported to be higher when denosumab is used prior to curettage. In a retrospective analysis of 408 patients treated for GCTB using either intralesional curettage or wide excision, the local recurrence rate for patients treated with curettage and denosumab was 60%, compared to 16% for those individuals treated with curettage alone.[400] Additionally, the joint preservation rate of patients treated with curettage and denosumab was 80% compared to 94% for those treated with curettage alone. Although denosumab usage was reported to be the only independent factor associated with increased recurrence, it is likely that such an association may also stem from selection bias.[400] Use of denosumab before surgery, however, may aid in defining a peripheral rim around the tumor.[401,402]

Phase II trial data have also suggested that sequential FDG-PET imaging appears to be a sensitive tool for early detection of tumor response to denosumab treatment.[403]

There have been reports of increased risk of developing osteosarcoma associated with denosumab therapy in recurrent GCTB.[404-406] The data are limited to determine the cause of the increased risk, but the NCCN Panel identifies some possibilities, such as spontaneous conversion to a secondary sarcoma, or a diagnostic and/or sampling error that erroneously categorizes a tumor as GCTB.

In prior versions of the guidelines, interferon (IFN) was recommended as a treatment option, based on case reports that reported the efficacy of IFN in the management of GCTB.[407-410] However, since IFN is no longer available in the United States, it is no longer included as a treatment option in the guidelines.

NCCN Recommendations

Localized Disease

Intralesional excision with an effective adjuvant may be an adequate primary treatment for resectable tumors.[162,361,362]

Serial arterial embolizations have been shown to be effective in the comprehensive care of patients with giant cell tumors of the extremities, especially for tumors with large cortical defects or joint involvement and for those with large giant cell tumors of the sacrum.[411-414]

For patients with lesions that are resectable with unacceptable morbidity and/or unresectable axial lesions, the guidelines have included denosumab and/or serial embolization as preferred options. Consultation with a dentist should be considered prior to initiating denosumab therapy.[415,416] RT is another recommended option, although it may be associated with an increased risk of malignant transformation. Imaging should be used to assess treatment response and should include plain radiographs as well as contrast-enhanced CT with or without MRI.

Following primary treatment, patients with stable/improved disease can be observed. For patients with stable/improved disease with incomplete healing following primary treatment, excision is recommended if the lesion has become resectable. Long-term denosumab use may be associated with increased risk of local recurrence.

Patients whose disease remains unresectable should be retreated with denosumab, serial embolization, and/or RT. Denosumab may be continued until disease progression, in responding disease.

Metastatic Disease

For patients presenting with resectable metastases, the guidelines recommend that the primary tumor be managed as described above for localized disease.[339,340,417,418] Intralesional excision may also be used for resectable metastatic sites. Denosumab (preferred), observation, and RT are options for patients with unresectable metastases.

Surveillance and Recurrence

Surveillance should include a physical exam, imaging (eg, x-ray, contrast-enhanced CT and/or MRI) of the surgical site as clinically indicated, and chest imaging. As the average time to metastasis ranges from approximately 2 to 4 years,[417-419] chest imaging should be performed every 6 to 12 months for 4 years, then annually thereafter, as clinically indicated.

Recurrent disease (local or metastatic) should be managed as per primary treatment for localized disease or metastatic disease at presentation. For patients with local recurrence and resectable disease, chest imaging and denosumab can be considered prior to surgery. However, the risk of local recurrence is increased when denosumab is used prior to curettage. Denosumab may be beneficial to define peripheral tumor extent when planning wide resection.

Osteosarcoma

Osteosarcoma is the most common primary malignant bone tumor in children and young adults. With bimodal age distribution, incidences first peak among patients aged 10 to 14 years, and again in patients >65 years.[420] In adults >65 years, osteosarcoma may develop as a secondary malignancy related to Paget disease of the bone.[20] Osteosarcoma is broadly classified into three histologic subtypes (intramedullary, surface, and extraskeletal).[421]

High-grade intramedullary osteosarcoma is the classic or conventional form, comprising nearly 80% of osteosarcomas.[421] It is a spindle cell or pleomorphic tumor that produces osteoid or immature bone. The most frequent sites include the metaphysis of the distal femur or proximal tibia, which correspond to the physes of maximum growth in normal skeletal development. Low-grade intramedullary osteosarcoma comprise <2% of all osteosarcomas; the most common sites are similar to that of conventional osteosarcoma.[422]

Parosteal and periosteal osteosarcomas are juxtacortical or surface variants. Parosteal osteosarcomas are low-grade lesions accounting for up to 5% of all osteosarcomas.[422] The most common site is the posterior distal femur. This variant is associated with very low metastatic potential. Transformation of low-grade parosteal osteosarcoma into high-grade osteosarcoma has been documented in 24% to 43% of cases.[423,424] Periosteal osteosarcomas are intermediate-grade lesions, showing partial cartilaginous differentiation, and most often involve the femur, followed by the tibia.[422] High-grade surface osteosarcomas are very rare, accounting for 10% of all juxtacortical osteosarcomas.[425,426]

Pain and swelling are the most frequent early symptoms. Pain is often intermittent in the beginning, and a thorough workup sometimes is delayed because symptoms may be confused with growing pains or confounded by musculoskeletal injury. Osteosarcoma spreads hematogenously, with the lung being the most common metastatic site, though “skip lesions” in the same bone can also occur.

For treating extraskeletal osteosarcomas, please see the NCCN Guidelines for Soft Tissue Sarcoma, available at www.NCCN.org.

Prognostic Factors

Tumor site and size, patient age, presence and location of metastases, histologic response to chemotherapy, and type of surgery and surgical margins are significant prognostic factors for patients with osteosarcoma of the extremities and trunk.[427-435] A meta-analysis and systematic review of 18,126 participants showed that patient sex, tumor site (extremity versus non-extremity), tumor size, response to chemotherapy, and surgery (amputation versus limb-sparing) were identified as prognostic factors in osteosarcoma.[436] In patients with extremity osteosarcomas, in addition to these variables, size and location within the limb at the time of diagnosis also had significant influence on outcome.[436] All factors except age were significant in multivariate testing, with surgical remission and histologic response to chemotherapy emerging as the key prognostic factors. In a meta-analysis of data from prospective neoadjuvant chemotherapy trials in 4838 patients with osteosarcoma, female sex was associated with increased chemotherapy-induced tumor necrosis and greater OS, and children had better outcomes than adolescents and adults.[437] In a report of the combined analysis of three European Osteosarcoma Intergroup randomized controlled trials, Whelan and colleagues reported that good histologic response to preoperative chemotherapy, distal location (other than proximal humerus/femur), and female gender were associated with improved survival.[432] However, high body mass index (BMI) in patients with osteosarcoma was associated with lower OS compared with patients with normal BMI.[438]

In patients with proven primary metastatic osteosarcoma, the number of metastases at diagnosis and the completeness of surgical resection of all clinically detected tumor sites are of independent prognostic value.[33] Patients with one or a few resectable pulmonary metastases have a survival rate that approaches that of patients without metastatic disease.[439,440]

Elevated serum ALP and LDH levels have also been identified as prognostic indicators in patients with osteosarcoma.[428,430,431,441,442] In a cohort of 1421 patients with osteosarcoma of the extremity, Bacci and colleagues reported significantly higher serum LDH levels in patients with metastatic disease at presentation than in patients with localized disease (36.6% vs. 18.8%; $P < .0001$).[430] The 5-year DFS correlated with serum LDH levels (39.5% for patients with high LDH levels and 60% for those with normal values). In another retrospective analysis of 789 patients with osteosarcoma of the extremity, it was reported that serum ALP level was a significant prognostic factor of EFS in patients with osteosarcoma of the extremity; the 5-year EFS rate was 24% for patients with a serum

ALP value of more than four times higher than the normal value and 46% for patients with high values below this limit ($P < .001$).[431] However, in multivariate analyses, these markers did not retain their prognostic significance when compared to tumor volume, age, and histologic response to chemotherapy.[428,430]

Workup

Osteosarcomas present both a local control problem and a concern for distant metastasis. Initial workup should include imaging of the primary site (contrast-enhanced MRI with or without CT), chest imaging including chest CT, and head-to-toe FDG-PET/CT and/or bone scan. More detailed imaging (MRI with and without contrast or CT) of skeletal metastatic sites to identify abnormalities identified on primary imaging is required for suspected metastatic disease.

Plain x-rays of osteosarcomas show cortical destruction and irregular reactive bone formation. Bone scan, while uniformly abnormal at the lesion, may be useful to identify additional synchronous lesions. MRI provides excellent soft tissue contrast and may be essential for operative planning. MRI is the best imaging modality to define the extent of the lesion within the bone as well as within the soft tissues, to detect “skip” metastases and to evaluate anatomic relationships with the surrounding structures. In addition, ALP and LDH are frequently elevated in patients with osteosarcoma. Serum LDH was significantly higher in patients with metastatic disease at presentation than in patients with localized disease.[430]

Given that osteosarcoma is most common among children and AYAs, the effect of cancer and its treatment on fertility must be discussed with patients. Fertility preservation methods and alternatives should be discussed with patients as appropriate. See the *Diagnostic Workup* section above.

Finally, a number of genetic aberrations may underly osteosarcoma.[443] For instance, it is reported that nearly 70% of patients with osteosarcoma may exhibit mutations in the tumor suppressor retinoblastoma gene, *RB1*.[443] Genetic cancer syndromes that exhibit a predisposition for osteosarcoma include: Li-Fraumeni syndrome, hereditary retinoblastoma, Rothmund-Thomson syndrome type 2, Bloom syndrome, Werner syndrome, RAPADILINO syndrome, and Diamond-Blackfan anemia. Thus, the NCCN Panel recommends that genetic consultation and testing be considered for patients diagnosed with chondrosarcoma or osteosarcoma who possess a family or personal history of bone sarcomas.[22]

Treatment

Surgery

Surgery (limb-sparing surgery or amputation) remains an essential part of comprehensive care for patients with osteosarcoma.[444] Studies that have compared limb-sparing surgery and amputation in patients with high-grade, non-metastatic osteosarcoma have not shown any significant difference in survival and local recurrence rates between these procedures.[445-447] However, limb-sparing surgery is associated with better functional outcomes.[448] In patients with high-grade osteosarcomas with good histologic response to neoadjuvant chemotherapy, limb-sparing surgery is considered the preferred surgical modality if wide surgical margins can be achieved.[445,449] Amputation is generally reserved for patients with tumors in unfavorable anatomical locations not amenable to limb-sparing surgery with adequate surgical margins and for management of local relapse when limb-sparing procedures are not practical.[444,449]

Chemotherapy

The addition of adjuvant and neoadjuvant chemotherapy regimens to surgery has revolutionized outcomes in patients with localized osteosarcoma.[450] Early trials used chemotherapy regimens including at least three or more of the following drugs: doxorubicin, cisplatin,

bleomycin, cyclophosphamide or ifosfamide, dactinomycin, and high-dose methotrexate.[451-456] Subsequent clinical trials have demonstrated that short, intensive chemotherapy regimens including cisplatin and doxorubicin with or without high-dose methotrexate and ifosfamide produce excellent long-term results, similar to those achieved with standard-dose multiagent chemotherapy.[457-466] Cisplatin and doxorubicin and MAP (high-dose methotrexate, cisplatin, and doxorubicin) are included as category 1 recommended regimens for first-line therapy. MAP is preferred in patients <40 years with excellent performance status. In the event a patient receiving high-dose methotrexate experiences delayed elimination due to renal impairment, glucarpidase is strongly recommended.

In a randomized trial conducted by the European Osteosarcoma Group, the combination of doxorubicin and cisplatin was better tolerated compared to a multi-drug regimen with no difference in survival between the groups in patients with operable, non-metastatic osteosarcoma.[458] The 3-year and 5-year OS rates were 65% and 55%, respectively, in both groups. The 5-year PFS rate was 44% in both groups. In the INT-0133 study, which compared the 3-drug regimen (cisplatin, doxorubicin, and methotrexate) with the 4-drug regimen (cisplatin, doxorubicin, methotrexate, and ifosfamide) for the treatment of patients with non-metastatic resectable osteosarcoma, there was no difference in the 6-year EFS (63% and 64%, respectively) and OS (74% and 70%, respectively) between the two groups.[464]

Chemotherapy regimens without doxorubicin or cisplatin have also been evaluated in patients with localized osteosarcoma with the aim of minimizing long-term cardiotoxicity and ototoxicity.[467,468] In a randomized multicenter trial (SFOP-OS94), the combination of ifosfamide and etoposide resulted in a higher histologic response rate than the regimen containing high-dose methotrexate and doxorubicin (56% and 39%, respectively). However, the 5-year OS was similar in both arms and there was no significant difference in 5-year EFS rates.[468]

Good histopathologic response (>90% necrosis) to neoadjuvant chemotherapy is associated with improved survival regardless of the type of chemotherapy administered after surgery.[312,469,470] In an analysis of 881 patients with non-metastatic osteosarcoma of the extremities treated with neoadjuvant chemotherapy and surgery at the Rizzoli Orthopaedic Institute, Bacci and colleagues showed that the 5-year DFS and OS correlated significantly with histologic response to chemotherapy.[471] The 5-year DFS and OS in patients with good and poor response to chemotherapy were 67.9% versus 51.3% ($P < .0001$) and 78.4% versus 63.7% ($P < .0001$), respectively. A report from the Children's Oncology Group also confirmed these findings; the 8-year postoperative EFS and OS rates were 81% and 87%, respectively, in patients with good response.[469] The corresponding survival rates were 46% and 52%, respectively, in patients with poorly responding disease. For individuals with poorly responding disease, completion of chemotherapy is still warranted, as outcomes are still better than for those who do not complete chemotherapy.

NCCN Recommendations

Localized Disease

The guidelines recommend wide excision as the primary treatment for patients with low-grade (intramedullary and surface) osteosarcomas and periosteal lesions. If pathologic high-grade disease is discovered after wide excision, adjuvant chemotherapy is a category 1 recommendation. Long-term results (>25 years of follow-up) from patients with high-grade, localized osteosarcoma reveal significant benefits of adjuvant chemotherapy on DFS and OS.[470] Chemotherapy prior to wide excision could be considered for patients with periosteal lesions. Although chemotherapy (neoadjuvant or adjuvant) has been used in the treatment

of patients with periosteal osteosarcoma, there are no data to support that the addition of chemotherapy to wide excision improves outcome in patients with periosteal osteosarcoma.[472-474] In a review of 119 patients with periosteal sarcoma published by the European Musculo-Skeletal Oncology Society, the use of neoadjuvant chemotherapy was not a prognostic factor, although it was used in the majority of the patients.[473] 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 for those who underwent surgery alone (P = .73).[472] A systematic review of 13 studies, including 291 patients with periosteal osteosarcoma, found no statistically significant improvement in mortality rates among those who received surgery and (neo-) adjuvant chemotherapy and those who received surgery alone. [474]

Neoadjuvant chemotherapy prior to wide excision is preferred for those with high-grade osteosarcoma (category 1).[439,457-459,462-464,467,468,475] Repeat imaging using pretreatment imaging modalities should be used to reassess the tumor for resectability. Selected older patients may benefit from immediate surgery.

Following wide excision, patients whose disease has a good histologic response (amount of viable tumor is <10% of the tumor area) should continue to receive several more cycles of the same chemotherapy. Surgical re-excision with or without RT can be considered for positive surgical margins. In a study of 119 patients with osteosarcoma of the head and neck, combined modality treatment with surgery and RT (vs. surgery alone) improved local control and OS for patients with positive or uncertain surgical margins.[476] Combined photon/proton or proton beam RT has been shown to be effective for local control in some patients with unresectable or incompletely resected osteosarcoma.[477,478]

Patients whose disease has a poor response (viable tumor is ≥10% of the tumor area) can continue with the preoperative regimen or be considered for chemotherapy with a different regimen (category 3). However, attempts to improve the outcome of those with poor response by modifying the adjuvant chemotherapy remain unsuccessful.[465,479-482]

In individuals whose sarcoma remains unresectable following preoperative chemotherapy, RT or adjuvant chemotherapy is recommended. A randomized phase III trial of the European and American Osteosarcoma Study (EURAMOS) Group evaluated treatment strategies for resectable osteosarcoma based on histologic response to preoperative chemotherapy.[479,483] The EURAMOS-1 trial included cohorts that received maintenance therapy with MAP; MAP with IFN-α-2b therapy; or MAPIE (MAP with ifosfamide and etoposide). The addition of maintenance IFN-α-2b therapy to MAP in the adjuvant setting did not improve outcomes for individuals whose disease had a good response to preoperative chemotherapy.[483] However, the authors note that a significant portion of patients assigned to the IFN arm (n = 357) did not receive the intended dose of IFN-α-2b due to patient declination to initiate therapy (n = 86; 24%) or premature termination of therapy (n = 105; 39%). Additionally, adding ifosfamide and etoposide to MAP (ie, MAPIE) did not improve outcomes for individuals whose disease responded poorly to preoperative chemotherapy.[479] Of the 307 EFS events reported, data showed that restricted mean survival time (RMST) was 43.3 months (95% CI, 40.1–46.4) for individuals who received MAP (n = 153) and 44.1 months (41.1–47.1) for individuals assigned to the MAPIE (n = 154) cohort. No difference in EFS between cohorts was reported.

Chemotherapy should include appropriate growth factor support. See the NCCN Guidelines for Hematopoietic Growth Factors (available at www.NCCN.org) for growth factor support. See *Bone Cancer Systemic Therapy Agents* in the algorithm for a list of specific chemotherapy regimens. Additional treatment options for patients whose disease has

positive margins and poor response may include additional local therapy such as re-excision with or without RT.

Metastatic Disease at Presentation

Approximately 10% to 20% of patients present with metastatic disease at diagnosis.[33,484,485] The number of metastases at diagnosis and complete surgical resection of all clinically detected tumor sites are of independent prognostic value in patients with primary metastatic disease at presentation.[33] Unilateral metastases and lower number of lung nodules were associated with improved outcomes with chemotherapy in patients with synchronous lung metastases.[439,440] The 2-year DFS rate was significantly higher for patients with only one or two metastatic lesions than for patients with three or more lesions (78% and 28%, respectively).[439]

Although chemotherapy is associated with improved outcomes in patients with non-metastatic, high-grade, localized osteosarcoma, the results were significantly poorer in patients with metastatic disease at presentation.[484,486-488] In a study of 57 patients with metastatic disease at presentation treated with cisplatin, doxorubicin, and a high dose of methotrexate and ifosfamide, the 2-year EFS and OS rates were 21% and 55%, respectively, compared to 75% and 94% in patients with non-metastatic disease at presentation, treated with the same chemotherapy protocol.[487] High-dose ifosfamide plus etoposide was examined in a phase II/III trial of 43 patients with newly diagnosed metastatic osteosarcoma, revealing an ORR of 59% ± 8%, but considerable toxicity.[489]

Among patients with primary metastases treated in cooperative osteosarcoma trials, long-term survival rates were higher for patients whose metastases were excised following chemotherapy and surgery of the primary tumor compared to those patients whose metastases could not be removed (48% and 5%, respectively).[490] The combination of aggressive chemotherapy with simultaneous resection of primary and metastatic lesions has also resulted in improved outcomes in patients with osteosarcoma of the extremity with lung metastases at presentation.[491]

For patients with resectable metastases (pulmonary, visceral, or skeletal) at presentation, the guidelines recommend preoperative chemotherapy followed by wide excision of the primary tumor. Chemotherapy, metastasectomy, and SRT are included as options for the management of resectable metastatic disease. In the event that pulmonary metastasectomy is not feasible, ablation procedures may be considered. A retrospective review of 83 patients with high-grade osteosarcoma and widespread metastases who underwent complete resection of the primary tumor and surgical removal of all detectable metastases followed by chemotherapy analyzed tumor characteristics, treatment regimens, and their impact on survival.[492] Nine (10.8%) patients had an initial complete remission, of which one patient remained 12.7 years later. Sixty-three of the remaining 74 patients died secondary to their disease, and 2 died from other causes. Actuarial EFS and OS after 5 years was 1.4 ± 1.4%, and 8.7 ± 3.3%, respectively. Data showed that complete microscopic resection of the primary tumor and macroscopic complete resection of metastases (and local treatment), in addition to good response to first-line chemotherapy, resulted in better outcomes when compared to individuals whose disease progressed during first-line treatment. Patients who presented with pleural effusion and metastasis at distant bones also had poorer outcomes.

In a study conducted by University of California, Los Angeles (UCLA), 16 patients (who had received either prior chemotherapy or surgery) with lung metastases from high-grade sarcomas were treated with SBRT.[306] In total, 25 lesions were identified and treated with a median SBRT dose of 54 Gy (range 36–54 Gy) in 3 to 4 fractions.[306] OS at 4 years was

reported to be 78%.[306] In another study, 30 patients with sarcoma with pulmonary metastases received SBRT at a median dose of 50 Gy in 4 to 5 fractions.[305] Patients had received prior chemotherapy, surgery, or thoracic RT. Local control at 12 and 24 months was reported to be 94% and 86%, respectively, while OS was 76% and 43%.[305] These reports suggest that SBRT may prove to be a promising alternative to surgery for oligometastatic disease. Unresectable metastatic disease should be managed with chemotherapy and/or RT followed by reassessment of the primary site for local control.

Surveillance

Once treatment is completed, surveillance should occur every 3 months for years 1 and 2, then every 4 months for year 3, then every 6 months for years 4 and 5, and annually thereafter, as clinically indicated. Surveillance should include a complete physical exam and imaging of the primary site and chest as performed during initial disease workup. Head-to-toe FDG-PET/CT and/or bone scan (category 2B) may also be considered. Functional reassessment should be performed at every visit. CBC and other laboratory studies can be performed as clinically indicated.

Relapsed or Refractory Disease

Approximately 30% to 40% of patients with localized disease and 80% of patients presenting with metastatic disease will relapse.[493,494] The presence of solitary metastases, time to first relapse, 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 third recurrence have a poor prognosis.[493-498] In patients with primary non-metastatic osteosarcoma, a longer relapse-free interval to pulmonary metastases was significantly associated with better survival.[497] The prognostic significance of surgical clearance among patients with second and subsequent recurrences was also confirmed in a report of survival estimates derived from large cohorts of unselected patients treated at the COSS group trials.[499]

The combination of etoposide with cyclophosphamide or ifosfamide has been evaluated in clinical trials.[500-502] In a phase II trial of the French Society of Pediatric Oncology, high-dose ifosfamide and etoposide resulted in a response rate of 48% in patients with relapsed or refractory osteosarcoma.[501] In another phase II trial, cyclophosphamide and etoposide resulted in a 19% response rate and 35% rate of stable disease in patients with relapsed high-risk osteosarcoma.[500] PFS at 4 months was 42%.

In a non-comparative, double-blind, placebo-controlled, phase II trial (REGOBONE), the efficacy and safety of regorafenib, a multikinase inhibitor, was evaluated among patients with progressive metastatic osteosarcoma (who underwent 1–2 previous lines of chemotherapy and had a performance status of ECOG 0–1).[503] It was found that 65% of patients in the regorafenib arm exhibited non-progressive disease at 8 weeks compared to no patients in the placebo arm. In view of confirmed disease progression, 10 patients in the placebo arm were permitted to cross over to the regorafenib arm to receive treatment. The most commonly noted adverse effects associated with regorafenib included hypertension and hand-foot skin reaction. It was concluded that regorafenib displayed antitumor activity in progressive metastatic osteosarcoma, delaying disease progression. Similarly, in another randomized, double-blind phase II study (SARC024), the activity of regorafenib was again evaluated in patients with progressive metastatic osteosarcoma.[504] The study met its primary endpoint with a median PFS of 3.6 months in the regorafenib arm versus 1.7 months in the placebo arm (CI, 0.21–0.85; P = .017; HR, 0.42). The NCCN Panel has included

regorafenib under second-line therapy for osteosarcoma (relapsed, refractory, or metastatic disease) with a category 1 recommendation.

Similar to its activity in patients with advanced Ewing sarcoma, cabozantinib, as aforementioned, also exhibited activity in patients with advanced osteosarcoma. In the CABONE trial, the primary endpoint for patients with osteosarcoma included 6-month objective response as well as 6-month non-progression.[332] Secondary endpoints included safety, best overall response, 1-year and 2-year PFS and OS, and metabolic response (evaluated by FDG-PET/CT 28 days after the first dose). Similar to that of Ewing sarcoma, the primary endpoints for patients with osteosarcoma were reached as 12% of patients showed an objective response and 33% were progression-free at 6 months. Seventeen percent of patients exhibited partial response and 62% of patients showed stable disease as their best overall response. Of those with stable disease, 33% of individuals displayed tumor shrinkage. Cabozantinib has thus been included in the guideline as a second-line treatment option for patients with relapsed, refractory, or metastatic osteosarcoma.

Single-agent gemcitabine and combination regimens such as docetaxel and gemcitabine; cyclophosphamide and topotecan; high-dose methotrexate with or without etoposide and ifosfamide; or ifosfamide, carboplatin, and etoposide have also been effective in the treatment of patients with relapsed or refractory bone sarcomas.[323,335,336,468,505-509]

Radium 223 dichloride is an alpha-emitting, bone-targeting radiopharmaceutical, and was studied in a phase I trial in 18 patients with recurrent or metastatic osteosarcoma. [510] A metabolic response was observed in 1 patient, while mixed responses were observed in 4 patients. A response in brain metastases was observed in 1 patient. The median OS time was 25 weeks.

Samarium-153 ethylene diamine tetramethylene phosphonate (Sm-153-EDTMP) is a beta-particle–emitting, bone-seeking radiopharmaceutical that was previously recommended as a second-line treatment option in the guidelines based on data in patients with locally recurrent or metastatic osteosarcoma or skeletal metastases.[511,512] However, NCCN no longer recommends Sm-153-EDTMP in the guidelines as it is no longer available in the United States.

Targeted inhibition of a variety of molecular pathways such as mTOR, SRC family of kinases, and VEGFRs are being evaluated in clinical trials to improve outcomes in patients with relapsed or refractory osteosarcoma. In a phase II trial of the Italian Sarcoma Group (n = 30), sorafenib (VEGFR inhibitor) demonstrated activity in patients with relapsed and unresectable high-grade osteosarcoma after progression of disease on standard multimodal therapy.[513] The PFS at 4 months (primary endpoint) was 46%. Median PFS and OS were 4 months and 7 months, respectively. The CBR (defined as no progression at 6 months) was 29%. Partial response and stable disease were seen in 8% and 34% of patients, respectively, and were durable for ≥6 months in 17% of patients. Sorafenib is a preferred second-line therapy option for osteosarcoma in the guidelines.

To extend the duration of activity, a study examined sorafenib combined with everolimus for patients with unresectable or relapsed high-grade osteosarcoma (n = 38).[514] Data suggested that this regimen is active in the second-line setting, but toxicity required dose reductions and/or treatment interruptions in 66% of patients. Therefore, under second-line options for patients with osteosarcoma, sorafenib in combination with everolimus is categorized under “Other Recommended” (category 2B recommendation).

The safety and efficacy of HDT/HCT in patients with locally advanced, metastatic, or relapsed osteosarcoma have also been evaluated.[515,516] In

the Italian Sarcoma Group study, treatment with carboplatin and etoposide was followed by stem cell rescue, combined with surgery-induced complete response in chemosensitive disease.[516] Transplant-related mortality was 3.1%. The 3-year OS and DFS rates were 20% and 12%, respectively. The efficacy of this approach in patients with high-risk disease is yet to be determined in prospective randomized studies.

The optimal treatment strategy for patients with relapsed or refractory disease has yet to be defined. If relapse occurs, the patient should receive second-line chemotherapy and/or surgical resection when feasible, followed by imaging to assess treatment response. See the *Bone Cancer Systemic Therapy Agents* in the algorithm for a complete list of second-line chemotherapy regimens. Surveillance is recommended for patients with disease that responds to second-line therapy.

Patients with disease progression or relapse after second-line therapy could be treated with resection, RT[517] (that may include radiopharmaceuticals, including radium-223), embolization/ablation, or best supportive care. Participation in a clinical trial is strongly encouraged.

High-Grade Undifferentiated Pleomorphic Sarcoma of Bone

High-grade UPS of the bone most frequently arises in the appendicular skeleton and is associated with both a high rate of local recurrence and local nodal and distal metastases.[518] The addition of chemotherapy to surgery has been shown to improve clinical outcomes in patients with non-metastatic malignant fibrous histiocytoma (MFH).[519-521] In the European Osteosarcoma Intergroup study, adjuvant or neoadjuvant chemotherapy with doxorubicin and cisplatin resulted in good pathologic response rates and survival (quite comparable with those for osteosarcoma) in patients with non-metastatic MFH.[521] Median survival time was 63 months, and the 5-year PFS and OS rates were 56% and 59%, respectively. The guidelines recommend that patients with high-grade UPS of bone should be treated with regimens listed for osteosarcoma (category 2B).

Biomarker Testing and Additional Treatment Options

NCCN defines MGPT as sequencing tests that assess mutations in multiple cancer-associated genes, such as NGS.[522,523] Due to the availability of new targeted therapies, patients with bone cancer may benefit from MGPT.

In a single-center chart review study of 102 patients with advanced sarcoma (including 11% with osteosarcoma, 4% with chondrosarcoma, 3% with chordoma, and 3% with Ewing sarcoma), 93% had at least one genomic alteration and 61% had a potentially actionable alteration based on CGP. Out of the 16% of patients who received targeted therapy based on the CGP results, 50% achieved at least stable disease.[524] A multicenter prospective study of 357 patients with bone tumors including 227 with osteosarcoma, 43 with chondrosarcoma, 14 with chordoma, and 25 with GCTB (including malignant GCTB) underwent NGS to identify genomic alterations.[525] One hundred forty-five actionable targeted mutations were detected in 122 patients. Just over 66% (n = 81) of the actionable targeted mutations were identified in the osteosarcoma subgroup. Actionable targeted mutations were also reported in 17 patients with chondrosarcomas and six patients with chordomas. MGPT or another fusion panel should be considered for Ewing sarcoma to identify translocations if pathologic workup of targeted PCR, FISH, or cytogenetics is negative. NCCN also recommends that MGPT with a validated and/or FDA-approved assay should be considered to determine targeted therapy opportunities for patients with metastatic chondrosarcoma, recurrent chordoma, metastatic Ewing sarcoma, and metastatic osteosarcoma.

Treatment Options Based on Biomarker Testing Results

Data have demonstrated that tumors with TMB-high (TMB-H) or MSI-high (MSI-H)/MMR deficiency (dMMR) may respond to certain immunotherapy agents (ie, checkpoint inhibitors).

The single-arm, open-label, phase II KEYNOTE-158 study evaluated 233 patients with advanced MSI-H/dMMR noncolorectal cancers whose disease progressed following prior therapy.[526] Twenty-seven tumor types (including sarcomas) were represented in this trial. The ORR was 30.8% and the median duration of response was 47.5 months.

KEYNOTE-158 also evaluated whether TMB status was associated with outcomes in patients with previously treated advanced solid tumors who were treated with pembrolizumab.[527] Patients were evaluated for tissue TMB (tTMB) status by NGS and those with TMB-H status (defined as ≥10 mutations/megabase) exhibited clinical improvement with an ORR of 29% compared to 6% among the non–tTMB-H group. [527]

The PD-1 inhibitor nivolumab in combination with the CTLA-4 inhibitor ipilimumab was evaluated in CheckMate 848, a randomized, open-label, phase II study in patients with advanced or metastatic solid TMB-H tumors.[528] The ORR rate with nivolumab/ipilimumab was 35.3% for those with tTMB-H in an interim analysis, and 22.5% in those with high blood TMB (bTMB-H) in a final analysis.

Based on these data, the Guidelines state that testing for TMB and MMR/MSI as determined by a validated and/or FDA-approved assay can be considered for select patients with metastatic chondrosarcoma, recurrent chordoma, metastatic Ewing sarcoma, or unresectable metastatic osteosarcoma.

Pembrolizumab and nivolumab/ipilimumab are recommended as options under Useful in Certain Circumstances for those with unresectable or metastatic TMB-H (≥10 mutations/megabase) tumors whose disease progressed following prior treatment and who have no satisfactory alternative treatment options. Pembrolizumab is also included as a preferred treatment option for patients with unresectable or metastatic TMB-H (≥10 mutations/megabase) whose disease progressed following prior treatment and who have no satisfactory alternative treatment options.

The Panel does not recommend pembrolizumab or nivolumab/ipilimumab as treatment options for GCTB, which is not technically a malignant tumor.

Other molecular-guided therapy options included in the guidelines are ivosidenib for chondrosarcoma with susceptible *IDH1* mutations [133] and lapatinib for *EGFR*-positive chordomas.[218,529]

Summary

The NCCN Guidelines for Bone Cancer provide recommendations for the treatment of chondrosarcoma, osteosarcoma, chordoma, Ewing sarcoma, and GCTB. Depending on the subtype, recommended treatment modalities for bone cancer may include surgery, RT, and systemic therapy. Evaluation by a multidisciplinary team with expertise in the management of bone cancer is highly recommended prior to initiation of therapy to ensure that patients receive the most appropriate treatments. The NCCN Guidelines for Bone Cancer will continue to be updated at least once a year by the NCCN Bone Cancer Panel based on consensus and clinical evidence.

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