8 Osteosarcoma-Approach to Therapy

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8.1 Introduction

Osteosarcoma demonstrates that treatment success will only be achieved through close interdisciplinary collaboration. The most common subtype, high-grade central osteosarcoma, carries a very high risk of systemic dissemination, so that surgery alone will rarely lead to cure (Casali et al. 2018; Fletcher et al. 2013; Jaffe 1972; Link et al. 1986; Marcove et al. 1970). Chemotherapy without sufficient local therapy will also result in failure (Bielack et al. 2002; Jaffe et al. 2002). Combined uses of both approaches together, however, will often result in cure (Bielack et al. 2004, 2008; Ferrari and Serra 2015).

Rare low-grade central, parosteal, and periosteal osteosarcoma variants are of lower malignant potential and treated by surgery alone (Casali et al. 2018; Cesari et al. 2011; Fletcher et al. 2013; Grimer et al. 2005; Laitinen et al. 2015). Craniofacial osteosarcomas also carry a lower risk of metastatic spread, but a high risk of local failure, and recent guidelines favor a multidisciplinary approach (Casali et al. 2018). This chapter will focus on treatment of young patients with high-grade osteosarcoma.

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8.2 Clinical Presentation

The typical presentation of osteosarcoma is in a young mid-teenage male complaining of pain around the knee, gradually worsening over 2–3 months, and swelling, both impacting to an increasing degree on normal activities including broken sleep and reduced mobility. Systemic symptoms are unusual even if metastases are present. The male/female ratio of osteosarcoma patients aged <24 is 1.28, and median age at diagnosis is 15 years. Approximately 90% of primaries are located in the limbs (Mirabello et al. 2009; Whelan et al. 2012). Primary lung metastases are detected in 10–15% and metastases to other sites, most often bones, in a further 5% (Kager et al. 2003; Marko et al. 2016; Meyers et al. 1993). Osteosarcomas arising in non-extremity sites are uncommon in young persons. Both nonspecific symptoms and low levels of awareness of cancer among both professionals and public result in diagnostic delays (Brasme et al. 2012).

8.3 General Outline of Multidisciplinary Treatment

High-grade osteosarcoma is one of few pediatric tumors in which the value of systemic chemotherapy has been rigorously proven through a randomized clinical trial (Link et al. 1986). Even prior to this study, it was known that few patients with radiographically localized high-grade osteosarcoma would survive with surgery alone, suggesting microscopic metastatic disease was frequently present (Jaffe 1972; Marcove et al. 1970).

Local control of the primary tumor, typically by surgery, remains as critical as systemic chemotherapy. Until only a few decades ago, surgery usually meant amputation. This was subsequently replaced by limb-sparing resections followed by reconstruction, usually with an endoprosthesis. Initiating chemotherapy some months prior to surgery offers the advantages of allowing time for surgical planning, and the degree of necrosis of the resection specimen is prognostic (Bielack et al. 2002; Rosen et al. 1981), even if clinically exploiting that information has been challenging (Bielack et al. 2015; Marina et al. 2016; Whelan et al. 2015). The principles of managing metastatic high-grade osteosarcoma generally mirror those also used for localized disease with the addition of surgical clearance of all metastatic deposits.

8.4 Imaging at Diagnosis and During Systemic Treatment: Essentials

A plain radiograph is the first imaging study for a patient with suspected osteosarcoma. In cases of malignancy, the radiographic characteristics suggest an aggressive lesion (Meyer et al. 2008). Radiographs are followed by magnetic resonance imaging (MRI) to delineate the locoregional extent of disease as well as the tumor's relationship to neurovascular structures.

Computed tomography (CT) of the chest is the preferred method to detect metastatic lung disease (Bielack et al. 2002). It is now common to identify subcentimeter pulmonary lesions on chest CT (Ginsberg and Panicek 2000; Meyer et al. 2008). There is evidence that lesions >5 mm are more likely to be malignant (Ginsberg and Panicek 2000; Picci et al. 2001). The presence of at least one lung lesion >1 cm or more than three lesions at least 5 mm in diameter is often accepted as evidence of metastatic disease. The presence of lesions <5 mm raises the possibility of metastases, but in these instances tissue confirmation is recommended.

Extrapulmonary metastases are searched for by either technetium bone scintigraphy, whole body MRI, or positron emission tomography/computed tomography (PET/CT). Either modality provides information as long as the primary tumor is avid. The role of functional imaging remains controversial. In one study, PET/CT could not be consistently used to determine histological response of the tumor (Hawkins et al. 2009).

Imaging evaluation during systemic treatment should occur approximately every 3 months, its

purpose being to confirm the absence of local or distant progression. Patients are followed with chest X-ray and/or CT and MRI.

8.5 Biopsy: Procedure

Nearly all masses that require surgical resection will have biopsies performed prior to excision. It is essential that representative tissue be delivered to the pathologist. Heterogeneous sarcomas may require biopsy from multiple locations to ensure a representative sample. The biopsy tract should be placed as to be incorporated and excised en bloc with the definitive resection. Longitudinal incisions are used, and for extremity lesions, a direct approach with minimal extension into adjacent tissue planes is usually possible.

MRI can prove invaluable in deciding where to biopsy. Tumor margins can be distinguished from surrounding muscle, fat, and neurovascular bundles. Areas of necrosis, liquefaction, myxoid degeneration, hemorrhage, and fibrosis are typically avoided. Abrupt signal changes within a mass could indicate dedifferentiation and should be sampled. For many bone sarcomas the most viable portions are near the periphery or within a soft tissue component. Specimens are typically sent fresh to pathology, which allows use of specific fixatives for immunohistochemistry and molecular genetic studies. Newer sequencing technologies may also allow use of formalin-fixed paraffin-embedded samples in molecular testing (van de Rijn et al. 2014). Nearly all suspected osteosarcoma specimens require decalcification.

Core needle biopsies have been shown to be safe and less invasive than incisional biopsies and are accurate if adequate cores are obtained even in sclerotic bony lesions (Mitsuyoshi et al. 2006; Taupin et al. 2016). Core needle biopsies may not be as effective in telangiectatic osteosarcoma, misdiagnosing over one third of cases as aneurysmal bone cysts in one series (Gao et al. 2013). Frozen sections are often used to assess intramedullary marrow margins during definitive resection and should be interpreted in tandem with the gross specimen (Anderson et al. 2014).

8.6 What Can Be Learned from the Biopsy Specimen?

Osteosarcoma is defined as a malignant spindle cell tumor which produces osteoid (Fletcher et al. 2013). Despite being a genetically complex tumor, its diagnosis is not based on any molecular testing at present (Gorlick 2009), but on routine hematoxylin and eosin staining and conventional light microscopy. Beyond the histologic classification, all osteosarcomas can be categorized as low, intermediate, or high grade. Although most osteosarcomas in young patients are high grade, this distinction is of critical importance as it defines the need for systemic chemotherapy. Osteosarcoma can similarly be broken into histologic subtypes such as osteoblastic, chondroblastic, fibroblastic, and telangiectatic dependent on the predominant pattern of differentiation (Fletcher et al. 2013). Although these subtypes may be associated with characteristic radiographic appearances, they do not impact on treatment and in most studies have not been shown to influence prognosis.

Hampered by osteosarcoma's genetic complexity, defining biological risk factors and molecular alterations which can be targeted remains elusive. That said an explosion in the available knowledge with regard to osteosarcomas biology has occurred with efforts such as whole tumor genome sequencing (Bishop et al. 2016). One could be nihilistic and suggest that in the absence of clinical relevance of osteosarcoma biology studies, the only purpose of a biopsy is making the diagnosis. On the other hand, many remain hopeful that additional clinical progress can be made through enhanced biological understanding, provided that additional osteosarcoma specimens are available for analyses. In both North America and Europe, coordinated research efforts exist putting forward biology and banking studies for the collection of biomaterials from patients with osteosarcoma (Glover et al. 2015). Success of these efforts will require obtaining adequate samples to permit biological analyses from osteosarcoma patients, with the consent of the patients/guardians. These efforts are strongly supported by the authors of this chapter.

8.7 Systemic Treatment

8.7.1 Choice of Drugs

For over 30 years, systemic treatment of osteosarcoma has relied on the same few cytotoxic agents. High-dose methotrexate with folinic acid rescue (HD-MTX) (Jaffe et al. 1973, 1974), doxorubicin (DOX, adriamycin) (Cortes et al. 1974), and cisplatin (cis-diamminedichloridoplatinum(II), CDDP) thereafter (Freeman et al. 1979; Ochs et al. 1978) were introduced in the 1970s. Soon, combination regimens were employed (Pagani et al. 1975; Rosen et al. 1974, 1975; Winkler et al. 1977). Starting in the early 1980s, several protocols also included ifosfamide (IFOS) (Bielack et al. 2013; Ferrari and Serra 2015). A recent meta-analysis concluded that combining any three of those four drugs led to better results than using only two, but that adding the fourth was not associated with further improvements (Anninga et al. 2011). A combination of HD-MTX, DOX, and CDDP (MAP) (Meyers et al. 2005, 2008; Whelan et al. 2015) is considered a standard (Table 8.1), but other regimens which include several of the mentioned drugs may achieve similar results (Daw et al. 2011; Fuchs et al. 1998; Le Deley et al. 2007; Smeland et al. 2011). Outside of specific trials, patients with primary metastases generally receive the same systemic treatment as those with localized disease (Carrle and Bielack 2009; Kager et al. 2003; Meyers et al. 1993).

Table 8.1 Standard MAP regimen for osteosarcoma

Adriamycin (doxorubicin)	37.5 mg/m^2	i.v.	24 h infusion	Days 1, 2
Cisplatin	40 mg/m^2	i.v.	24 h infusion[a]	Days 1–3
Hyperhydration and forced mannitol diuresis required to reduce otherwise severe cisplatin nephrotoxicity				
Weeks 1; 6; 12; 17				
Adriamycin (doxorubicin)	37.5 mg/m^2	i.v.	24 h infusion[a]	Days 1, 2
Weeks 22; 26				
Methotrexate	12,000 mg/m^2	i.v.	4 h infusion	Day 1
Folinic acid (leucovorin)	15 mg/m^2	p.o./i.v.	Every 6 h, beginning 24 h from MTX Total of 12 doses	
Meticulous supportive care including hyperhydration, urinary alkalinization, repeated measurement of MTX serum levels, and folinic acid rescue obligatory to prevent life-threatening toxicity				
Weeks 4 + 5; 9 + 10; 15 + 16; 20 + 21; 24 + 25; 28 + 29				
Local therapy			Surgery of the primary tumor[b]	
Always strive for wide resection margins. Pathology must assess margins and grade histologic response to preoperative chemotherapy				
Week 11				

The MAP regimen as used for osteosarcoma (Ahmed et al. 2015; Marina 1997; Meyers et al. 1993, 2008; Wasilewski-Masker et al. 2009)

[a]Short infusion with dexrazoxane can be an alternative

[b]Primary metastases, if present, must also be resected. This is usually done during the months which follow surgery of the primary tumor

8.7.2 High-Dose Methotrexate

HD-MTX, commonly at 12 g/m^2, in combination with vigorous hydration and urinary alkalinization along with pharmacokinetically guided folinic acid "rescue" (FAR), is an essential component of osteosarcoma treatment (Jaffe et al. 1974). Methotrexate (MTX) is an analogue of folic acid which penetrates into cells via a specific membrane transport system used by physiological folates. Carrier-mediated transport limits the entry of MTX into cells until the extracellular concentration is as high as 20 μmol/L and passive diffusion occurs. Inside the cell MTX rapidly binds to and inhibits its target enzyme dihydrofolate reductase (DHFR), leading to an inhibition of purine and pyrimidine synthesis. In addition to direct inhibition of DHFR, the intracellular formation of MTX polyglutamyl metabolites is also thought to (a) increase intracellular drug accumulation, (b) increase intracellular drug retention, and (c) inhibit folate-dependent nucleotide synthesis, by effects at loci other than DHFR (Adamson et al. 2011).

High-dose methotrexate regimens are designed to circumvent MTX resistance.

Achieving and sustaining high plasma levels of the drug promotes passive diffusion of MTX, thus overcoming defective transmembrane transport systems (Guo et al. 1999). The doses of MTX required to achieve such high plasma concentrations must be followed by the antidote, folinic acid, to prevent excessive toxicity to normal tissues. Folinic acid replenishes the intracellular source of reduced active folates. Although this decreases the degree of MTX toxicity, patients will remain at risk as long as elevated MTX levels persist in their circulation. Moreover, if the extracellular MTX concentration is very high, folinic acid alone may prove inadequate.

Despite supportive measures, MTX-induced toxicity (myelosuppression, mucositis, hepatic and renal toxicity) still occurs and results in morbidity, patient discomfort, costs, and potentially reduced treatment efficacy, due to suboptimal chemotherapy doses and/or delays in chemotherapy administration (Widemann and Adamson 2006). Elevation of serum creatinine points out renal injury, which can result in delayed excretion of MTX, so close monitoring during administration is critical. In case of life-threatening MTX intoxication, administration of high-dose leucovorin or in selected cases glucarpidase may become necessary (Flombaum et al. 2018; Ramsey et al. 2018).

8.7.3 Doxorubicin

Doxorubicin in an anthracycline antibiotic isolated from cultures of *Streptomyces peucetius*. Doxorubicin intercalates to nucleotide base pairs and binds to the lipid membrane. Intercalation interferes with nucleotide replication and the action of DNA and RNA polymerases. Its interaction with topoisomerase II appears important for cytotoxic activity. Approximately 40% of the drug is excreted in the bile in 5 days. Only up to 12% of the drug is excreted in the urine (Adamson et al. 2011; Bedford Laboratories 2012).

The most common acute toxicities include nausea, vomiting, myelosuppression, and a pink or red color to the patient's secretions. It can also produce mucositis and liver toxicity. The most serious complication of doxorubicin administration is cardiotoxicity [Krischer et al. 1997; Lipshultz 2006; Nysom et al. 1998, see below]. Pediatric patients are usually treated with doses ranging from 25 to 90 mg/m^2 per dose. Cumulative doses >300 mg/m^2 are associated with higher long-term toxicity. As doxorubicin is one of the most effective agents against osteosarcoma, affected patients often receive such high cumulative doses (Smith et al. 1991). Strategies to decrease doxorubicin cardiotoxicity include the use of continuous infusions (Hortobagyi et al. 1989; Legha et al. 1982) and of cardioprotective agents (Huh et al. 2010; Sanchez-Medina et al. 2010; Wexler et al. 1996). Continuous infusion has successfully reduced cardiotoxicity in adults but is associated with increased mucositis (Bielack et al. 1996; Hortobagyi et al. 1989; Legha et al. 1982) and has been reported as unsuccessful in children (Lipshultz et al. 2013). Dexrazoxane has been successfully used in pediatric patients (Asselin et al. 2016; Huh et al. 2010; Lipshultz et al. 2013; Sanchez-Medina et al. 2010; Wexler et al. 1996). While it has been claimed that it may increase the risk of second malignancies (Tebbi et al. 2007), recent reports suggest this is not the case (Chow et al. 2015; Seif et al. 2015).

8.7.4 Cisplatin

Cisplatin is a platinum-containing DNA-damaging agent, the intracellular presence of which leads to DNA cross-linking and consequent apoptosis. Initially reported active as a single agent at a dose of 100 mg/m^2, it quickly came to be used in combination with doxorubicin (Gasparini et al. 1985; Pratt et al. 1985).

CDDP is highly emetogenic, a side effect which if uncontrolled can exacerbate renal impairment, the most challenging problem arising from its administration (Arany and Safirstein 2003). Acute glomerular toxicity can be ameliorated by hyperhydration, forced diuresis, and prolonged intravenous administration over 48–72 h rather than short infusions. Renal tubular damage may also occur, leading to electrolyte

imbalance and the need for replacement particularly of magnesium, calcium, and potassium. Ototoxicity and peripheral neuropathy are also limiting factors. CDDP causes tinnitus, often reversible, and irreversible hearing loss especially affecting high tones. Avoidance of other nephro- or neurotoxic agents such as aminoglycoside antibiotics and furosemide is advised. CDDP is also significantly myelosuppressive.

8.7.5 Ifosfamide

IFOS is a cyclophosphamide analogue which requires hepatic activation to the reactive 4-hydroxyifosfamide, which exists in equilibrium with aldoifosfamide. Aldoifosfamide is then converted to acrolein and ifosfamide mustard, the active bifunctional alkylating agent. Acrolein is presumed to be the cause of hemorrhagic cystitis, a side effect of both cyclophosphamide and ifosfamide. The metabolism of IFOS is autoinducible resulting in increased clearance and decreased toxicity over time (Kerbusch et al. 2001). The amount of IFOS excreted in the urine is directly proportional to the dose administered. There is more oxidation of chloroethyl groups by IFOS, which produces more chloroacetaldehyde (thought to be responsible for neurotoxicity and renal toxicity).

Evaluation of this drug in an upfront window approach revealed clinical responses in patients with recurrent and metastatic osteosarcoma (Goorin et al. 2002; Harris et al. 1995; Harris et al. 1998). The drug is usually administered by short infusions lasting 1–4 h depending on the total doses used, which range from 6–9 g/m^2 over 2–5 days (Fuchs et al. 1998; Meyers et al. 2005, 2008) to 14 g/m^2 over 5 days (Schwartz et al. 2016; Whelan et al. 2015). Fractionation reduces urotoxicity (Kerbusch et al. 2001), as does the use of mesna, which helps to prevent hemorrhagic cystitis. Patients receiving ifosfamide are monitored with urinalysis to make certain they do not develop hemorrhagic cystitis (Kerbusch et al. 2001) as well as with electrolyte measurements to evaluate for renal tubular dysfunction (Buttemer et al. 2011). Neurotoxicity can be managed by stopping the infusion and administration of methylene blue (Kerbusch et al. 2001). Other acute toxicities associated with IFOS include nausea, vomiting, hair loss, myelosuppression, and liver toxicity.

8.7.6 Other Agents

Addition of more cytotoxic chemotherapy to the standard treatment backbones has failed to further improve survival outcomes (Gatta et al. 2014; Mirabello et al. 2009; Stiller et al. 2018). This was most recently evident in the prospective, randomized European and American Osteosarcoma Study (EURAMOS)-1 which tested the addition of high-dose ifosfamide (14 g/m^2) plus etoposide to preoperative MAP in poor responders to preoperative MAP (Marina et al. 2016; Whelan et al. 2015). Early protocols had included the BCD combination of bleomycin with cyclophosphamide and actinomycin D (Mosende et al. 1977; Rosen et al. 1981; Winkler et al. 1977, 1988); however, this was largely abandoned when a phase 2 study failed to demonstrate activity (Pratt et al. 1987).

The macrophage activator mifamurtide (liposomal muramyl-tripeptide-diphosphatidyl-ethanolamine, MTP) was investigated in a randomized trial, INT0133, which also tested ifosfamide in a randomized 2 × 2 factorial design (Meyers et al. 2005, 2008). A first report concluded that interaction between the two randomizations precluded definitive statements regarding MTP (Meyers et al. 2005). With three additional years of follow-up, the authors performed a second analysis of event-free and overall survival in the localized disease cohort of the trial. They reported that the addition of MTP to chemotherapy resulted in a statistically significant improvement in overall survival and a trend toward better event-free survival (Meyers et al. 2008). Persisting statistical and interaction concerns, however, led others to caution that these results did not meet generally accepted standards for practice-changing conclusions and that confirmatory trials would be required before MTP should be considered for routine use (Bielack et al. 2008;

Hunsberger et al. 2008). The US-FDA denied a license stating that the applicants had failed to demonstrate substantial evidence of efficacy (U.S. Food and Drug Administration 2007). The European Medicines Agency approved mifamurtide for use in the treatment of newly diagnosed osteosarcoma, and the agent is now licensed for that indication in many countries.

Interferon alpha-2b (IFN-α-2b), which can act as an immune modulator as well as exerting anti-angiogenetic and direct antitumor effects (Whelan et al. 2010), was investigated in the good responder cohort of EURAMOS-1, where patients in the experimental arm received the agent as maintenance after concluding MAP chemotherapy (Bielack et al. 2015; Marina et al. 2009; Whelan et al. 2015). Compared to MAP alone, MAP plus IFN-α-2b was not statistically different. The interpretation of this finding is hampered by the fact that a considerable proportion of patients never started IFN-α-2b or stopped prematurely (Bielack et al. 2015).

In order to move things forward, effective drugs with novel mechanisms of action need to be identified. In the Children's Oncology Group, the decision has been made to await identification of a novel agent with efficacy in osteosarcoma prior to embarking upon a phase 3 trial testing the value of its addition to standard chemotherapy (Gorlick et al. 2013). Instead, the group is focused on performing a series of phase 2 trials in patients with recurrent osteosarcoma attempting to identify novel agents with efficacy. The rationale for each of these studies is varied but includes encouraging data obtained from the Pediatric Preclinical Testing Consortium, transgenic mouse models, and tumor profiling. A phase 2 trial of eribulin in unresectable recurrent osteosarcoma was rapidly completed but unfortunately did not demonstrate activity (Isakoff et al. 2018). Trials of denosumab in resectable and unresectable recurrent osteosarcoma, ch14.18 antibody in resectable recurrent osteosarcoma, and glembatumumab vedotin in unresectable recurrent osteosarcoma are ongoing. Other agents are being incorporated into additional phase 2 trials in development (Bishop et al. 2016).

Numerous other novel agents are being tested by different groups. The anti-PD-1 antibody pembrolizumab failed to show encouraging activity against osteosarcoma in the SARC028 phase 2 trial (Tawbi et al. 2017). Current European activities were most recently discussed in 2015 and 2017 during workshops of European Bone Sarcoma Research Networks (Kager et al. 2016; Strauss et al. 2018). Several trials are worth mentioning. While addition of zoledronate to standard osteosarcoma therapy was feasible, a French multicenter randomized trial failed to demonstrate it provided a survival advantage (Piperno-Neumann et al. 2016). The Italian Sarcoma Group has performed phase 2 trials of sorafenib and of sorafenib with everolimus (Grignani et al. 2012, 2015). Signals of activity were observed, as has been the case for regorafenib in a randomized French phase 2 trial (Duffaud et al. 2018). A group of investigators from Baylor have published results of CAR-T cells directed to HER-2 for the treatment of osteosarcoma (Ahmed et al. 2015). The US National Cancer Institute is investigating CAR-T cells directed to GD2 as a treatment for osteosarcoma (Bishop et al. 2016). It is hoped that some of the agents will prove to be effective driving phase 3 trials of these agents in the future.

8.8 Local Treatment of the Primary Tumor

Chemotherapy alone is insufficient to cure osteosarcoma (Bielack et al. 2002; Jaffe et al. 2002) and local therapy therefore remains an integral component of curative treatment. A successful osteosarcoma resection should have a wide surgical margin (DeLaney et al. 2005; Enneking 1986) while providing optimal functional status. Mutilating procedures are still indicated if this goal cannot be reached otherwise, but the role for amputation is dwindling (Fig. 8.1), and it does not confer significant survival benefit over limb salvage (Reddy et al. 2015; Schrager et al. 2011). Radiotherapy is reserved for situations where appropriate surgery cannot be performed (Schwarz et al. 2009).

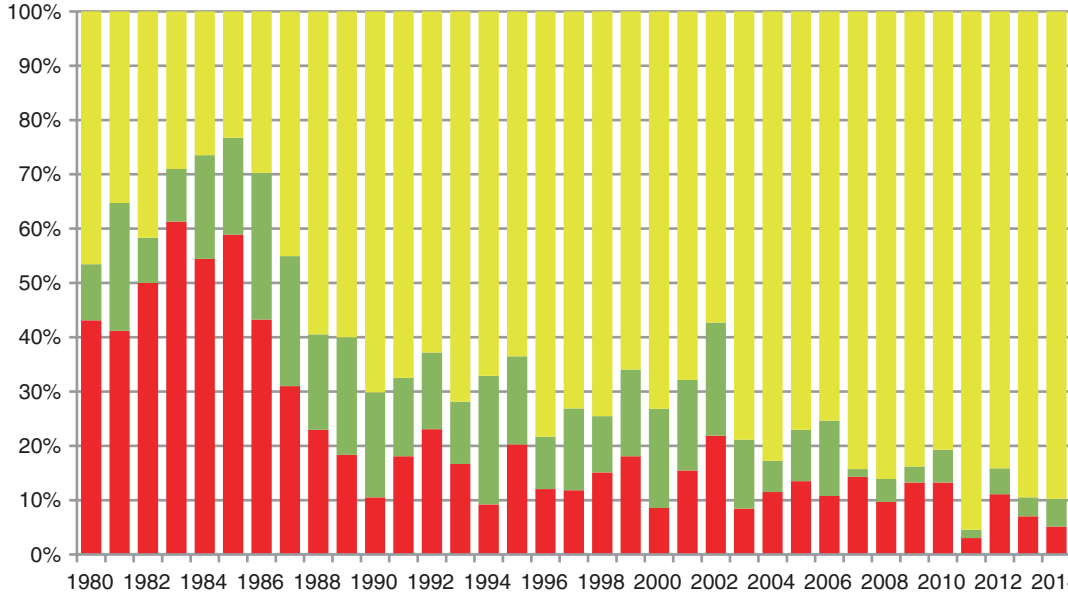

Fig. 8.1 Choice of definitive surgical procedures by year of osteosarcoma diagnosis. Data are from 2585 operated Cooperative Osteosarcoma Study Group COSS patients with previously untreated, localized high-grade central extremity osteosarcoma. Red, amputation; green, rotationplasty; yellow, limb salvage

Common limb salvage options include endoprosthetic reconstruction, allograft prosthetic composite (APC), massive bone allograft with soft tissue attachments, and rotationplasty. Reconstruction durability must be considered in children and adolescents, whose lifestyle expectations can vary tremendously.

In the pediatric or adolescent patient, endoprosthetic fixation is usually via a press-fit stem or a compress device. Screw and plate fixation is used with rotationplasty and massive bone allograft. Cement, while commonly used for prosthetic fixation in older patients, is used with caution in younger patients due to concerns of long-term aseptic loosening (Jeys et al. 2008).

General oncologic surgical principles should be adhered to during tumor resection, namely, meticulous hemostasis, careful identification and dissection of neurovascular structures, and maintenance of a soft tissue envelope around the osteosarcoma. Preoperative MRI is used for determining bony resection length (2 cm is recommended), and marrow margins should be sent as frozen sections after bone cuts are made and the canal plugged with bone wax (Loh et al. 2015). Once the tumor has been resected, gloves should be changed, fresh drapes placed over soiled portions of the surgical field, and separate instruments used during the reconstruction to avoid contamination. The tumor specimen should be oriented with a surgical pathologist, with mention of certain areas such as synovium or epineurium that may contain potentially close margins.

Proximal humerus tumors often necessitate resection of rotator cuff insertion(s). Unresected portions of anterior deltoid, supraspinatus, and subscapularis should be tagged as they are encountered to assist with reconstruction, and Gore-Tex or Alloderm can be used to reconstruct the joint capsule. In larger resections an APC with rotator cuff attachments may be favored over a traditional endoprosthesis. In younger children the biological alternative of clavicula pro humero should be considered (Calvert et al. 2015) as well as a vascularized free fibular transfer. In the proximal tibia, extensor mechanism involvement often dictates implant choice. The tibial insertion should be preserved when possible to promote bony ingrowth to the reconstruction. If the insertion is sacrificed with the articular

surface, then an APC with patellar tendon can be used. If the joint and epiphysis are spared, then massive intercalary allograft can be considered. The gastrocnemius may be included with the resection as a soft tissue margin or used as a rotational flap to cover the reconstructed extensor mechanism. If the tumor involves the tibial tubercle with extensive soft tissue involvement of the calf musculature, then rotationplasty may be the only alternative to through-knee amputation. In fact, rotationplasty, because of its predictable durability, may actually be preferred. Distal femur resections usually incorporate the vastus intermedius as a margin, and the reconstruction is covered with remaining musculature and a robust quadriceps tendon repair. In the proximal femur, although rare in children, critical soft tissue reconstruction involves reattachment of the abductors (preferably with a portion of the greater trochanter) and purse-string reapproximation of the joint capsule when possible.

The most common locations for osteosarcoma in the growing child are the distal femur, proximal tibia, and proximal humerus (Mirabello et al. 2009). Coincidentally this is where the most proliferative physes reside. If the physis can be spared, an intercalary reconstruction with allograft or fibula autograft may be considered, with graft incorporation and hypertrophy possible in skeletally immature patients (Aponte-Tinao et al. 2015). Remaining limb growth will aid with reconstruction choice if the physis is resected. A rotationplasty will continue to lengthen from the distal tibial physis (albeit half the rate of the distal femoral physis), and modular implant design can facilitate future lengthening procedures without sacrificing a well-incorporated base. Reconstruction can be intentionally long to accommodate for remaining growth or contralateral epiphysiodesis performed. Growing prostheses are still associated with poor implant survival rates and continued need for eventual surgical revision to adult-sized implants (Cipriano et al. 2015; Schinhan et al. 2015; Staals et al. 2015).

While surgery with wide margins remains the gold standard for local therapy, not all osteosarcomas are suitable candidates. This is particularly true for primaries located in the axial skeleton. It was demonstrated decades ago that radiotherapy can achieve temporary local remissions and that doses in excess of 60 Gy will lead to better control than lower doses (Cade 1952). The rate of permanent local control may increase if radiotherapy is administered within a multimodal context which also includes chemotherapy (DeLaney et al. 2005; Machak et al. 2003; Schwarz et al. 2009), when employed as part of first-line treatment rather than used against recurrences (DeLaney et al. 2005; Schwarz et al. 2009), and when it is used against osteosarcomas which show an imaging response to chemotherapy (Machak et al. 2003). Unless very high doses in excess of 70 Gy are used, it seems advisable to combine radiotherapy with subtotal resection (Ciernik et al. 2011; Schwarz et al. 2009). Innovative techniques such as proton (Ciernik et al. 2011) or carbon ion (Combs et al. 2012; Matsunobu et al. 2012; Sugahara et al. 2012; Zhang et al. 2016) radiotherapy have led to encouraging local control rates in some settings, but data on long-term effectiveness and side-effects are lacking (Leroy et al. 2016). A prospective trial of carbon ion radiotherapy in skeletally immature patients with unresectable osteosarcoma is currently ongoing (Blattmann et al. 2010).

8.9 Primary Metastases

Unless treated on specific trials, chemotherapy for patients with primary metastases usually reflects that used for those with localized disease. A good histological response to such therapy again confers a more favorable prognosis (Kager et al. 2003). All primary metastases should be resected if treatment is to be curative (Carrle and Bielack 2009; Kager et al. 2003). Owing to their matrix content, osteosarcoma metastases are often quite hard, and palpation may therefore detect more lesions than does CT (Kayton et al. 2006; Picci et al. 2001). Surgery for lung metastases is therefore generally performed by open thoracotomy (Carrle and Bielack 2009; Casali et al. 2018). Nonsurgical approaches such as per-

cutaneous computed tomography-guided thermal ablation (Yevich et al. 2016), radiofrequency ablation (Saumet et al. 2015), or stereotactic radiosurgery (Yu et al. 2014) may offer alternatives for lung metastases not eligible for surgery, their non-inferiority remaining to be established. Unresolved issues include the merit of contralateral exploration in seemingly unilateral pulmonary disease and how to proceed with small, nonspecific pulmonary nodules (Bhattasali et al. 2015; Carrle and Bielack 2009). Given the dismal outcome of patients in whom definitive metastases remain after surgery (Kager et al. 2003) and the inability to reliably distinguish small benign lung lesions from small lung metastases (Picci et al. 2001), many advocate an aggressive approach even for such "possible" metastases, but the benefit of this approach remains to be proven.

8.10 Prognosis After Multimodal Treatment

Despite chemotherapy and surgical resection, 30–40% of patients who initially present with localized disease will develop a recurrence. Recurrences most often affect the lungs but can also involve the former primary tumor site, distant bones or, less frequently, other sites including the brain, skin, and intraabdominal organs (Ferrari et al. 2003; Kempf-Bielack et al. 2005). At present the strongest prognostic factors for newly diagnosed osteosarcoma patients are the presence or absence of radiographically detectable metastatic disease and whether or not the primary tumor is resectable (Bielack et al. 2002). A large size of the primary tumor, a tumor site in the axial skeleton, or the proximal extremities and increased serum levels of alkaline phosphatase or lactate dehydrogenase have all been linked to inferior outcomes (Anderson 2016; Bielack et al. 2002). The presence of primary metastases is associated with an unfavorable prognosis particularly if these are multiple, involve both lungs, or involve several organ systems (Kager et al. 2003). Metastases which involve the pleura, chest wall, pericardium, or diaphragm are associated with very poor long-term survival expectancies. The prognosis of osteosarcoma patients with bone metastases, more than three lung nodules, or bilateral lung nodules is generally less than a 20% 5-year disease-free survival (Bielack et al. 2002; Kager et al. 2003).

Predictors of local recurrence include poor histologic response and narrow resection margins (Picci et al. 1994). Poor histologic response of the primary tumor is also a powerful predictive factor for distant recurrence and reduced overall-survival expectancies (Bielack et al. 2002) (Fig. 8.2).

8.11 Physical Rehabilitation and Surveillance for Late Effects

Complete surgical tumor resection is required for long-term survival (Bielack et al. 2002) but associated with functional impairments even years after treatment. Compared to other survivors bone tumor survivors are at higher risk of physical limitations (Ness et al. 2008, 2009) and chronic health conditions (Oeffinger et al. 2006). The degree of impairment appears related to the surgical procedure performed with greater functional impairment and activity limitations in patients treated with amputations (Marina et al. 2013).

Postoperative rehabilitation and physiotherapy can involve immediate passive range of motion, with partial weight-bearing recommended over the first 12 weeks for non-cemented implants to allow for bony ingrowth. Individual restrictions are made depending on the robustness of soft tissue reconstruction. Progressive weight-bearing as tolerated is possible with cemented components. It must be emphasized that function will likely not achieve preoperative levels, and activities of daily living are addressed and met first. Ensuring adequate time for rehabilitation before returning to sports and recreational activities can prove difficult with this age group.

Full-length standing films are taken for lower extremity resections to monitor for limb length

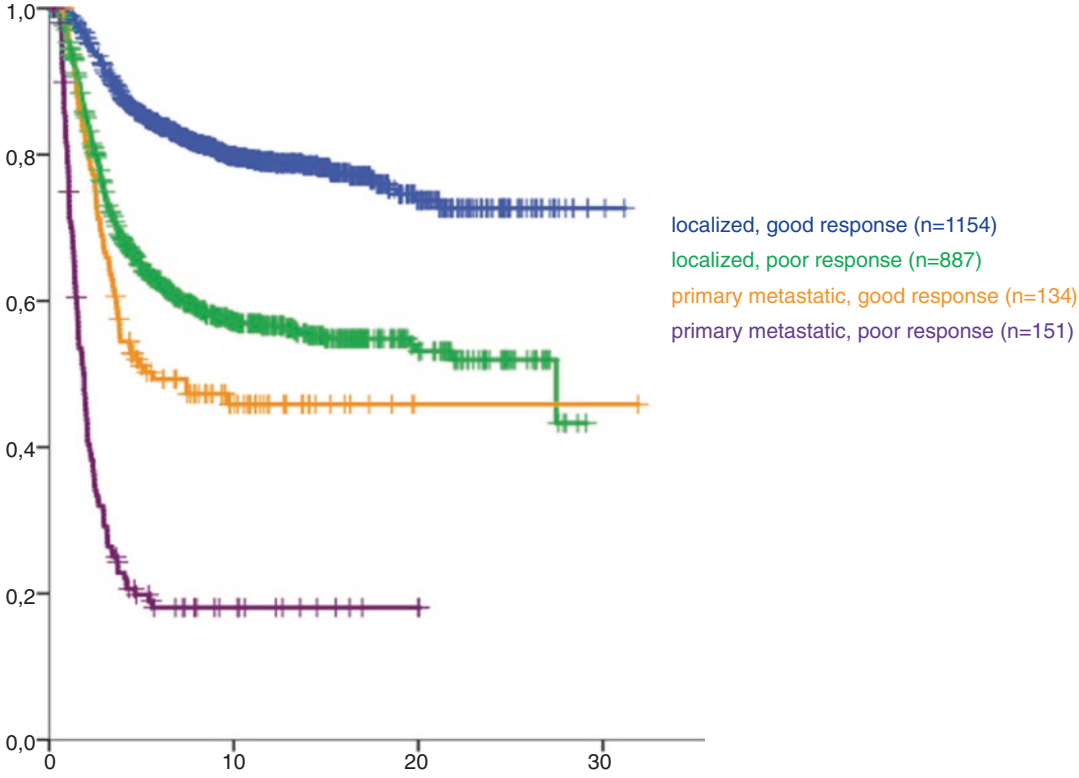

Fig. 8.2 Overall survival probability in correlation to primary metastatic status and response to preoperative chemotherapy. Data are from 2326 Cooperative Osteosarcoma Study Group COSS patients with previously untreated, high-grade central osteosarcomas of the extremities or axial skeleton. Good response: <10% viable tumor cells in the resection specimen

inequality. The need for eventual revision should be emphasized given the young age of these patients, with common transgressors including infection, aseptic loosening, limb length discrepancy, soft tissue instability, implant failure, and allograft nonunion (Jeys and Grimer 2009; Schinhan et al. 2015).

Treatment with multi-agent chemotherapy and surgery improves long-term survival expectancies (Link et al. 1991) but can also result in medical and psychosocial complications (Nagarajan et al. 2011). Medical consequences include the possibility of anthracycline-related cardiac dysfunction (Krischer et al. 1997; Lipshultz 2006; Nysom et al. 1998), gonadal dysfunction related to ifosfamide (Longhi et al. 2003; Williams et al. 2008), nephrotoxicity related to the use of cisplatin and/or ifosfamide (Buttemer et al. 2011; Rossi et al. 1999; Skinner 2003; Skinner et al. 1989), hearing loss related to treatment with cisplatin (Brock et al. 1991), and second malignant neoplasms most frequently associated with alkylating agents (Marina 1997; Smith et al. 2003; Tucker et al. 1987), etoposide (Le Deley et al. 2003; Stine et al. 1997), and anthracyclines (Le Deley et al. 2003).

Anthracycline cardiotoxicity ranges from subclinical to full-blown cardiomyopathy requiring chronic medical treatment (Lipshultz et al. 2008, 2013; Raj et al. 2014) and in some instances heart transplantation (Grande et al. 2003; Jenney and Jones 1992). The extent of cardiotoxicity is related to the total dose, cumulative dose, and the age at administration (Von Hoff et al. 1979). Since patients with osteosarcoma often receive high anthracycline doses, regular monitoring of

cardiac function by echocardiography is recommended (Armenian et al. 2015; Lipshultz et al. 2008, 2013).

Late toxicities can include gonadal dysfunction, particularly if treatment included the alkylator ifosfamide (Longhi et al. 2003; Williams et al. 2008). Patients should be offered the option of pretreatment fertility preservation so that they become knowledgeable about their options (Hug et al. 2012; Loren et al. 2013).

Patients treated with either cisplatin and/or ifosfamide should be monitored for renal dysfunction with electrolytes and creatinine once treatment is completed. Though renal failure is rare, tubular dysfunction leading to renal tubular acidosis and hypophosphatemic rickets can happen and continue for many years (Marina et al. 1995; Rossi et al. 1999; Skinner 2003; Skinner et al. 1989). Peripheral CDDP-associated neuropathy is especially problematic when treating older patients and, in contrast to vincristine-related neuropathy, most often presents after completion of CDDP and is irreversible (Avan et al. 2015).

Second malignant neoplasms are among the most feared complications (Nagarajan et al. 2011), and evaluation with complete blood count and radiograph for persistent pain and swelling are what is currently recommended.

8.12 Surveillance for Recurrence

Surveillance for recurrences focuses on the areas most likely to be affected, namely, the lungs and the former primary tumor site. Clinical surveillance usually involves at least 3-month intervals for 2 years, 3- to 6-month intervals for years 3–5, and semi-annual to annual visits thereafter (Meyer et al. 2008). Radiographs of the surgical site and particularly the chest are often performed at each visit. Rare recurrences may only arise during the second decade of follow-up (Wasilewski-Masker et al. 2009) or even later (Halldorsson et al. 2009), so that there is no unanimously agreed time point at which surveillance should end.

While recommended by some guidelines (Meyer et al. 2008), the use of chest CT rather than chest X-ray during routine follow-up has been challenged because of its high radiation burden (Dauer et al. 2008; McHugh and Roebuck 2014). Results from a recent randomized Indian study of sarcomas in general suggest that imaging during the first years should be every 3 rather than every 6 months, but that chest CT adds no survival benefit over chest X-ray (Puri et al. 2014).

8.13 Treatment Options in Case of Recurrence

Most patients with recurrent osteosarcoma will ultimately then die of their disease, but around 20–25% can be cured (Ferrari et al. 2003; Kempf-Bielack et al. 2005), and some may even survive multiple recurrences (Bielack et al. 2009). Factors favoring this are resectable disease and a first remission of 18 months or more. The mainstay of treatment is surgical resection (Daw et al. 2015). Repeated thoracotomies may be indicated. Surgical remission of disease at other sites can also be effective though repeated resection is associated with ever-shortening remission (Bacci et al. 2005; Bielack et al. 2009; Ferrari et al. 2003; Gelderblom et al. 2011; Kempf-Bielack et al. 2005).

The role of second-line chemotherapy is poorly defined by prospective evaluation. Its use correlates with limited prolongation of survival when used against unresectable recurrences but is more controversial in the setting of resectable recurrences (Ferrari et al. 2003; Kempf-Bielack et al. 2005). Responses are certainly seen to the most commonly applied regimen, ifosfamide and etoposide. These responses may reduce the risk of further recurrence when combined with surgical resection of all disease or provide palliative benefit. Responses have been increasingly reported to the combination of gemcitabine and docetaxel (Palmerini et al. 2016), but other effective new agents await to be identified. Radiotherapy can also improve symptoms and provide temporary disease control (Schwarz et al. 2009).

8.14 Conclusion

Successful treatment of osteosarcoma requires close collaboration between many diagnostic and therapeutic specialties. Multidisciplinary therapy consisting of surgery and chemotherapy leads to long-term, disease-free survival in 60–70% of patients. While the past decades have witnessed a major shift from amputation to limb-salvage surgery, chemotherapy still relies on the same few drugs as ever. Accordingly, despite dedicated multi-institutional and multinational efforts, survival expectancies stagnate. Efforts to better understand tumor biology are ongoing, and it is hoped that these will lead to the identification of suitable therapeutic targets for prospective trials and ultimately higher cure rates.

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