Review of Osteosarcoma and Current Management

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ABSTRACT

Osteosarcoma is the most common primary malignancy of bone in children and young adults. This tumor has a very heterogeneous genetic profile and lacks any consistent unifying event that leads to the pathogenesis of osteosarcoma. In this review, some of the important genetic events involved in osteosarcoma will be highlighted. Additionally, the clinical diagnosis of osteosarcoma will be discussed, as well as contemporary chemotherapeutic and surgical management of this tumor. Finally, the review will discuss some of the novel approaches to treating this disease.

Keywords: Limb preservation surgery; Osteosarcoma; Review; Targeted therapy

OSTEOSARCOMA

Osteosarcoma (OS) is a high-grade primary skeletal malignancy characterized by spindle cells of mesenchymal origin depositing immature osteoid matrix [1, 2]. With an annual incidence rate of 3.1 cases per million in the US, OS accounts for less than 1% of all newly diagnosed cancers in adults and 3–5% of those in children, but it is the most common primary malignancy in adolescents outside of leukemia and lymphoma [3]. Although rare overall, OS is the most common primary malignancy of bone in children [3–5]. OS incidence is distributed bimodally across age. An initial peak is observed between the ages of 10 and 14 years during the pubertal growth spurt, and is followed by a smaller second peak after the age of 60 years [6]. OS develops in adolescents most often at the metaphysis of lower extremity long bones (~75% of cases), and these findings suggest a relationship between the hormonal changes of puberty and/or physiologic bone growth and the pathogenesis of OS [4, 6–8]. While long bones of the extremities continue to be the most common site for OS after the age of 60 years,
they no longer account for the majority of cases due to an increase in the diversity of primary tumor sites. Craniofacial and axial tumors increase in frequency with age, accounting for 40% of all OS cases after 60 years of age, compared to less than 12% before the age of 24 years [6]. Juxtacortical osteosarcomas that occur along the surface of bones are usually lower grade, although there are some exceptions [9].

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

PREDISPOISING CONDITIONS AND RISK FACTORS FOR OS

Genetics of OS

Phenotypic risk factors for OS are related to physiologic growth and include both a tall height and a high birth weight [10]. The vast majority of cases are the result of sporadic mutations, but loss of tumor suppressor function is commonly identified in OS and represents a critical step in its pathogenesis [11–13]. Overall, there is no unifying genetic event that leads to the development of OS. In addition to somatic mutations, there are a few well-identified syndromes that predispose to OS, and these are usually discussed to highlight some of the sentinel genetic events that are involved in pathogenesis.

Li–Fraumeni syndrome (LFS) is the most common syndrome predisposing to pediatric sarcomas and involves a germline mutation of the TP53 gene. TP53 encodes for p53, a master transcription factor regulating expression of DNA repair genes and initiating apoptosis when damage is irreparable [14]. Loss of this tumor suppressor function predisposes to a multitude of malignancies, and an estimated 30% of patients with LFS develop OS during their lives [15, 16]. Although LFS is rare, damage to the p53 pathway is not. Mutations at TP53 represent the most frequently identified genetic alterations in human cancers. Somatic loss of p53 has also been identified in 18–26.5% of sporadic cases of OS [8, 17].

Retinoblastoma is another condition commonly identified to predispose to OS. The retinoblastoma protein pRb (encoded by RB1) binds the E2F family of transcription factors and halts progression through the G1 phase of the cell cycle [18]. Loss of pRb induces unregulated cell cycle progression. Germline loss of RB1 in 13q14 microdeletion syndrome (hereditary retinoblastoma) is associated with an increased risk for retinoblastoma and, to a lesser degree, soft-tissue sarcomas, melanoma, and OS [19–21]. Sarcomas are the most common secondary tumors in retinoblastoma patients, representing 60% of cases, and may be due in part to the use of radiation in the treatment of retinoblastoma [21, 22]. Loss of pRb is common in sporadic cases of OS as well (>60% of cases in one series), and is predictive of unfavorable outcomes [23, 24]. Loss of other genes in this pathway are functionally equivalent to loss of RB1 and have been identified in OS tumors lacking RB1 alterations [25, 26].

RecQ helicases are members of a conserved family of proteins that unwind double-stranded DNA prior to replication. Loss of RecQ helicases is an inheritable risk factor for OS [27, 28]. Germline mutations in genes in the RecQ family give rise to the rare autosomal recessive cancer predisposition disorders (e.g., Bloom’s syndrome, Werner’s syndrome, and Rothmund–Thomson syndrome).
syndrome), which are all associated with increased incidence of OS [29].

In addition to genetic alterations due to chromosomal instability and loss of tumor suppressor genes, OS can also have disruptions in major signaling pathways, creating a bone microenvironment that promotes proliferation and metastasis. The TGF-β proteins are part of a superfamily of five isoforms (TGF-β1–5) and the bone morphogenic proteins (BMP1–15) [30]. Skeletal tissue harbors the largest reserve of TGF-β [31]. TGF-β has a broad range of activities, including stimulating mesenchymal cell growth, immunosuppression, and enhancing extracellular matrix production; TGF-β1 has a mitogenic effect on OS cell lines [32].

Alterations in the insulin-like growth factor-I (IGF-RI) receptor pathway have been identified in the development of OS [33–40]. Upon binding the IGF-RI, IGF-I/II activate downstream PI3K/Akt/mTOR and MAPK/ERK cascades promoting proliferation, migration, and survival. Burrow et al. found overexpression of IGF-IR, IGF-I, and IGF-II in a significant proportion of 48 OS primary tumors, with no difference in expression between primary and metastatic samples [38]. In preclinical studies, OS proliferation was enhanced by IGF-I/II and inhibited when IGF-IR was silenced by monoclonal antibodies, RNA interference, or microRNA [39, 40]. Increased IGF-1 expression leads to more aggressive phenotypes in vitro and is a negative prognosticator when found in primary tumors [36, 37]. mTOR, a downstream target in the IGF-I/II pathway, is an attractive target in many cancers, and recent efforts have attempted to target this area in OS [41].

Metastatic OS has its own set of identifiable genetic alterations that allow tumor cells to migrate into the bloodstream, avoid apoptosis and immune destruction, and adhere and proliferate in distant tissues. Promotion of the Wnt/B-catenin and src pathways have been implicated in the migration of tumor cells into the circulation, and upregulation of the Notch1 and Notch2 receptors has been identified in highly metastatic OS specimens. The Fas/Fas ligand pathway is a death receptor pathway that is often downregulated in OS [42, 43]. Besides triggering apoptosis, Fas receptors also function to target the cell for elimination by natural killer (NK) cells. Elimination of this pathway allows OS cells to both avoid apoptosis and evade the immune system, and it is not surprising that samples from pulmonary OS metastases have been shown to be Fas negative [44, 45]. Once in target cells, tumor growth and progression is assisted by growth factors and angiogenic enzymes such as PDGF-R, VEGF, EGFR, and IL-8. The src pathway is again active at this step and is responsible for hyperproliferation of tumor cells and induction of neovascularity [46, 47].

As the science of molecular genetics advances, so does our understanding of osteosarcoma. A recent genome-wide association study of 941 cases of OS and 3291 controls was able to identify 2 loci with genome-wide significance, one at 6p21.3 in the glutamate receptor metabotropic 4 (GRM4) gene, and another in a gene desert on 2p25.2 [48]. The GRM4 gene is involved in cyclic AMP signaling and may have important interactions in bone metabolism. Another multi-institution genome-wide scan in 935 patients with metastatic OS found significance in a mutation of the NF1B gene. The mutation decreased NF1B activity, leading to increased OS cell migration, proliferation, and colony formation [49].

**Risk Factors for Secondary OS**

Secondary OS can develop following malignant degeneration of benign bone lesions or
exposure to ionizing radiation [50–52]. It accounts for one-third of cases in patients >65 years old [6]. Geographic variation in the incidence of risk factors for secondary OS, namely radiation exposure and Paget’s disease, has been used to explain OS incidence rates in the elderly [10]. The etiology of secondary OS in the setting of radiation is likely due to DNA damage from the ionizing radiation. In Paget’s disease, the pathogenesis to OS development is not well understood.

CLINICAL PRESENTATION AND MANAGEMENT OF OSTEOSARCOMA

Conventional OS is the most common histologic type and accounts for approximately 75% of all cases [53]. These tumors represent the classic form of OS: a high-grade mass of malignant mesenchymal cells with osteoid production and local tissue invasion. Conventional osteosarcomas are further classified into osteoblastic, chondroblastic, or fibroblastic types, depending on which matrix-producing cells dominate, but generally behave similarly in regards to appearance and prognosis [54]. Other high-grade central osteosarcomas include telangiectatic, giant cell-rich, small cell, and epithelioid variants, each with characteristic histology and small differences in survival [55]. A low-grade intramedullary type termed low-grade central osteosarcoma (LCOS) has a much lower rate of metastasis and greater overall survival [54, 55].

OS can originate along the cortex or periosteum as well. The most common of these juxtacortical lesions is parosteal sarcoma, which constitutes about 1–6% of all OS cases [54]. These lesions are found on the metaphyseal regions of long bones, typically the distal femur, and have a “stuck on” appearance. They are slow-growing and low-grade in comparison to conventional OS, and histologic examination shows well-differentiated fibrous stroma with osseous components. They may have a cartilage cap and can be confused with osteochondromas, but will not have the characteristic cortical–medullary continuity characteristic of those benign lesions [56]. Periosteal sarcomas are another type of juxtacortical OS with a similar “stuck on” appearance, but they exhibit more aggressive characteristics on radiographs and histology. These tumors represent mid-grade lesions, but rarely metastasize when treated appropriately [57]. Finally, high-grade surface OS is the most aggressive type and has a course similar to conventional high-grade OS [9].

Presenting Signs and Evaluation

Patients with OS often present with nonspecific complaints, including pain in the affected area. Pain during sleep, enlarging mass, and worsening pain without clear signs of infection or injury are particularly worrisome signs. Physical exam findings may reveal a palpable mass, restricted joint motion, pain with weight bearing, or localized warmth/erythema. An estimated 5–10% of patients will present with a pathological fracture as their first sign of illness [58]. The traditional signs of cancer—weight loss, malaise and fever—are usually only present in advanced disease and are not sensitive signs in children [59].

Workup should begin with orthogonal X-ray imaging of the affected extremity. Radiographs will typically demonstrate a poorly margined or moth-eaten appearance of the bone with mixed amounts of cloudy mineralized matrix and areas of bone resorption. Alternatively, a
cartilage or fibrous matrix may be present, or there may be tremendous bone resorption, depending on the subtype [56]. If the lesion has an associated soft tissue mass, a discontinuous or broken periosteal reaction is usually present (Fig. 1). Lab work is nondiagnostic, but high levels of alkaline phosphatase (ALK-P) and lactate dehydrogenase (LDH) have been shown to predict a poorer prognosis [60–63]. Advanced imaging is best accomplished with magnetic resonance imaging (MRI) and should be performed for the entire bone. MRI will clearly demonstrate the extent of the bone marrow invasion, the presence and size of any soft-tissue mass, and the relationship to surrounding vital structures (Fig. 2). Tumors are hypointense on T1, hyperintense on T2 and STIR imaging, usually exhibit mixed heterogeneity and surrounding peritumoral edema, and show abundant enhancement with contrast administration. It is important to image the entire bone involved to detect potential skip metastases and accurately plan resection and reconstruction efforts. Generally speaking, computed tomography (CT) is inferior to MRI, unless further information is needed regarding cortical integrity or the presence of fracture [54].

When a diagnosis of malignancy is suspected, a biopsy is required for tissue confirmation. This can usually be accomplished with a core needle biopsy using either ultrasound or CT guidance. The specialist performing the biopsy should communicate with the treating physician to plan the incision such that the biopsy tract can be easily removed with the tumor. Multiple cores can be obtained from the same incision, which increases the accuracy of diagnosis [56]. If needle biopsy is insufficient, an open biopsy can be performed, but it should be done...
through a small incision, with meticulous hemostasis. It is best performed by the surgeon who will carry out the final resection [64]. There is some evidence that not all needle biopsy tracts need to be resected [65], but an open biopsy tract should always be removed along with the tumor. At our institution, needle biopsy tracts are removed along with the final resection to prevent any chance of recurrence from residual tumor cells.

**Histologic Findings**

Histologic examination of conventional OS demonstrates malignant spindle or polyhedral mesenchymal cells with pleomorphic nuclei, scattered mitotic figures, and varying levels of anaplasia (Fig. 3). Immature and disorganized osteoid production is a characteristic hallmark and must be present for diagnosis. Conventional osteosarcomas may have a matrix dominated by osseous, cartilaginous, or fibrous elements, and are further subtyped depending on which of these matrix cells dominate. Other types of OS will show similar high-grade morphology along with areas of abundant giant cells, small cells, or epithelioid morphology, but must also contain osteoid somewhere in the sample. Lower-grade central and surface OS will demonstrate woven microtrabeculae of bone within a bland to moderately cellular fibrous stroma [54, 55].

**Staging**

Staging is important for detecting metastasis, establishing prognosis, and determining appropriate medical therapy and surgery [53, 63, 66]. Since over 75% of metastases involve the lungs, all patients with bone sarcoma should receive a CT scan of the chest [67, 68]. At presentation, 20% of patients have metastatic disease detectable with current CT imaging. However, the majority of metastatic disease is microscopic, and it is estimated that another 60% of patients have micrometastatic disease [69–71]. A bone scan or positron emission tomography (PET) scan is recommended to detect metastatic bone and
soft-tissue disease (Fig. 4). Bone scan is more cost-effective and superior to PET for bony disease, but PET allows for better detection in soft tissue, and includes the chest and abdomen. Both are effective scanning techniques; the choice made usually varies by institution. An additional advantage of PET is that it may be able to identify tumors with higher metabolic activity and, therefore, higher-grade malignancies [72, 73]. Finally, if not already available, an MRI of the entire bone involved is important to rule out any skip metastases, which must be addressed with primary resection and predict a poor survival [74].

The two staging systems currently employed for staging OS are the Enneking system and the AJCC (Tables 1, 2). Enneking was the first to organize bone sarcoma into a comprehensive staging system, and the AJCC later used these principles to develop its own staging system with nomenclature similar to that used for other cancers. Both use histological grade and the presence/absence of metastases and differ in their evaluation of the size of the primary tumor. The Enneking system makes a distinction between whether the mass is intracompartmental or has become extracompartmental, while the AJCC system uses tumor size (<8 or >8 cm) to determine a T1 from a T2 tumor. Despite these differences, most tumors will be a similar stage in both systems, as the major driver of prognosis is the

![Fig. 4 X-ray (a) and MRI (b) of the distal femur of a 13-year-old girl, showing a large solitary lesion. However, staging with bone scan (c) and MRI (d) revealed additional skip metastasis in her ipsilateral femur diaphysis and peritrochanteric area that was not detected with initial imaging. The presence of the skip metastases changed the surgical plan from a distal femur resection to an entire femur resection and reconstruction (e)](image-url)
Treatment

Prior to the advent of chemotherapy, OS was almost a universally fatal disease. Patients with metastasis at diagnosis would typically survive only months, and those with localized disease would soon develop metastatic spread, despite radical and disabling surgical procedures. In the 1970s, Jaffe published the first significant success of chemotherapy, showing that methotrexate was a useful agent to manage metastases in advanced disease [76]. As new cytotoxic agents were discovered, the use of chemotherapy blossomed, but the practice remained controversial until a landmark study in 1985 which showed an increase in 6-year survival from 11 to 61% with the addition of multi-agent chemotherapy [69]. A study performed during the same time period at Memorial Sloan Kettering found similar increases in survival with chemotherapy that was given before surgery (neoadjuvant), showing that it was safe to delay surgery for treatment [77]. The authors preferred neoadjuvant chemotherapy because it allowed more time to fabricate endoprosthetic devices, decreased tumor size, and permitted an analysis of the surgical specimen for its response to chemotherapy [66].

Chemotherapy

Today, most OS patients receive neoadjuvant chemotherapy, followed by surgical resection of all detectable disease and a regimen of adjuvant chemotherapy postoperatively [78]. The current regimen of methotrexate, adriamycin, and
cisplatin (MAP) has become standard in North America and Europe [66, 79]. This is typically started after pathological diagnosis and staging studies have been completed, and continues for a period of 6–8 weeks depending on the institution [80]. Some centers will also add ifosfamide with or without etoposide, but this increases the toxicity of therapy, and recent randomized clinical trials have failed to show a survival advantage [81, 82]. Unfortunately, many agents are limited by their toxicity profile, and some side effects, such as adriamycin-induced cardiomyopathy, can be permanent [83]. There is a dose effect on treatment response, but recent research has shown that high-dose chemotherapy does not increase survival when compared to less toxic moderate doses [84]. Much research has been focused on changing chemotherapy to improve survival in patients with a poor histologic treatment response, but this has so far been unsuccessful [85, 86]. Resistance to chemotherapy is often multifactorial and an area of much recent research [87]. Chemotherapy has little effect on lower-grade types of OS, such as parosteal and periosteal sarcoma, and these tumors have good rates of survival without systemic therapy [9, 57, 88]. Radiation treatment is rarely included as an adjuvant, but has been used in unresectable cases [89–91].

Surgery

Regardless of the chemotherapy regimen, surgical removal of all evidence of disease remains critical to obtaining a remission and improving patient survival. Patients will undergo resection of the OS tumor by amputation or limb salvage surgery techniques as well as resection of any metastases if possible. All tumors should be removed with a wide margin to prevent residual disease; the adequacy of this margin is critical in preventing recurrences [92]. Recurrent disease is closely linked to a poor prognosis and the risk of metastatic disease. Following resection, pathological specimens are examined to see the effect that chemotherapy has had on the tumor. A necrosis rate of ≥90% is considered a “good response,” and these patients will have a better prognosis than those with less than 90% necrosis. Besides its prognostic value, histological response has been used to guide therapy. Patients with a good response are restarted on their preop chemo regimen, while patients with a poor response may be switched to a different combination of drugs. Despite some favorable results in smaller studies, no regimen has been shown to be superior in a poor responder, but this is an area of continued research [86]. Chemotherapy can usually be resumed 2–3 weeks after surgery, once the wound is healed [80, 93].

Historically, amputation was believed to be necessary to control local disease, but that has changed in recent decades, as advances in chemotherapy, imaging, and reconstruction techniques have made limb salvage surgeries more feasible [94, 95]. Today, about 85% of high-grade appendicular OS cases can be successfully resected and reconstructed with preservation of the affected limb and its function [94, 95]. In limb preservation surgery, the tumor is removed while maintaining a wide cuff of tissue around the tumor when possible, but allowing more narrow margins around vital neurovascular structures. Careful dissection preserves limb function but still removes all disease safely.

Theoretically, limb preservation increases the rate of local recurrence, but in experienced hands it can be performed with little or no increase in local recurrence compared to
In a report of 560 patients from the Rizzoli Institute, there was no difference in local recurrence between patients treated with amputation and those with limb preservation surgery [96]. In the Rizzoli study, recurrence correlated closely with margin status and tumor grade, showing that the quality of resection and underlying tumor biology are the most important factors in recurrence, not surgery type. The safety of limb preservation has been confirmed many times, with the most recent being a meta-analysis including over 1300 patients [96, 100–102]. Local recurrence was equal for amputation and limb salvage, and patients with limb salvage actually had a higher 5-year survival [100]. For these reasons, amputation is generally reserved only for those tumors in which a resection to disease-free margins is not possible without creating a nonfunctional limb [94].

Limb preservation surgery can be complex. There are a number of options for reconstruction. These include manufactured endoprosthetic devices, bulk allografts, biological constructs, or combinations of these elements. Endoprosthetic replacement of tumor defects has greatly increased over the past few decades and is now the surgery of choice in many centers (Fig. 5). Most are modular, allowing a degree of customization that can be adjusted intraoperatively to match the anatomic needs of each patient. They provide excellent reconstruction options for metaphyseal tumors, as the adjacent joint can be reconstructed, and are usually stable postoperatively for early mobilization and weight bearing. The main drawbacks of these devices are a lifelong infection risk, since the reconstruction is nonbiological, as well as complications from wear, hardware breakdown, and the risk of eventual mechanical failure. Implant survivorship is typically over 80% at 5 years and drops to 60% at 10 years. A recent British study with over 15 years of follow-up found that 42% of patients with endoprosthetic reconstruction required revision or amputation within 10 years, with 51% of these revisions being due to mechanical failure and 33% due to infection [103]. Given a long enough lifespan, most survivors of OS with endoprosthetic reconstruction will have to undergo one or more revision surgeries [104].

Bulk allograft reconstruction involves matching the resected specimen with a donor graft of comparable size and shape. Successful outcome is contingent on a biological union between the host and implanted bone; rigid fixation is paramount for this process to occur. Over time, these implants slowly undergo variable rates of osseous and vascular integration by the body and have a theoretical advantage of being a permanent replacement for the resected bone [105]. Other advantages include higher rates of soft-tissue integration and customizability for nonstandard resections. Unfortunately, failure rates can be as high as 17–20% due to infection, nonunion, or implant fracture. Additionally, union rates are decreased by radiotherapy, chemotherapy, and poor nutritional states, one or more of which is usually present in patients with OS. The risk of failure is highest in the first 3 years but plateaus thereafter. Approximately 75% of patients with a graft present for over 5 years report good or better outcomes as far out as 20 years after surgery [105].

When used for reconstructing joint surfaces, osteoarticular allografts develop subchondral collapse, with the resulting arthritis quickly leading to early failure. However, they can be combined with manufactured joint implants, resulting in an allograft–prosthetic composite. The outcome is an implant with the advantages (and disadvantages) of both an allograft and an
endoprosthesis. The allograft side allows for a stronger and more complete reconstruction of the periarticular soft-tissue envelope and incorporates into the patient’s host bone, while the prosthetic side creates a stable and predictable joint articulation. These implants represent a high degree of complexity for the surgeon, but have been shown by several centers to provide a stable reconstruction with similar failure rates to other methods [106, 107].

Most OS cases occur in younger patients, many of which have active growth plates at the time of diagnosis. Since most of these tumors originate in the metaphysis and expand circumferentially, the physis is often at risk. When the physis must be sacrificed along with the tumor mass, reconstruction must plan to resolve or prevent significant limb length discrepancy resulting from growth. In lower extremities, this is usually agreed to be a limb length discrepancy of greater than 2 cm at maturity, but is less defined in the upper extremity. A variety of options exist, and the appropriate choice is often a subject of controversy. Reconstruction strategies include leaving the operative extremity longer than the contralateral side to allow growth, slowing or halting the growth of the nonoperative limb, replacing the defect with an implant that can be expanded as the child grows, or choosing a functional amputation, such as Van Ness rotationplasty (Fig. 6).

In our institution, we have found success with a physeal sparing resection with allograft reconstruction when possible (Fig. 7). This technique has been recently reported in a series of 35 Argentinean patients with 95% survival of the limb at 5 and 10 years [108]. When the physis cannot be preserved, we prefer modulated growth for defects of less than 3 cm and an expandable prosthesis for larger defects. Several expandable implants exist on the market. Some require minimal surgery for mechanical expansion, while others rely on an electromagnet for noninvasive lengthening. The noninvasive implants have the advantage of avoiding further surgery, but the first generation has had an intolerable failure rate [109, 110]. Second-generation noninvasive implants have only been available for a short time, but may be more stable. Most expandable prostheses will eventually have to undergo revision, given the age and activity level of their patients. Rotationplasty remains a useful and lasting option in patients with distal femur OS, especially for patients who desire high-demand activity, but few patients and their parents are comfortable with this type of amputation [111].

OS in axial locations is rare, but often presents unique challenges. Pelvis OS accounts for only about 8% of all cases, but these tumors tend to be larger, more biologically active, and have metastatic disease more often compared to extremity OS [112, 113]. Resection is still necessary for cure, but is more complicated given the three-dimensional anatomy of the bony pelvis and surrounding vital structures. Reconstruction is also more difficult and should only be attempted in certain cases, as many reconstructions only increase the complication rate without improving postoperative function [114, 115]. In addition to surgery, radiotherapy can be used for added local control and may improve overall survival [116]. OS of the spine is rare as well but, when present, usually occurs in the vertebral body and requires en-bloc
resection for cure [117]. OS metastases, when present, should be removed in close chronology to the main tumor. Although lung metastasis predicts a poorer prognosis, resection of metastatic disease can still lead to remission in some cases and has been shown to improve survival [118, 119].

Following completion of treatment, patients with OS must be observed closely for signs of recurrence. The National Comprehensive Cancer Network (NCCN) recommends imaging of both the chest and the surgical site as often as every 3 months during the first 2 years, and continued surveillance at increasing intervals thereafter [67]. Recurrence, either local or distant, was found to occur in 20–30% of patients who presented with localized disease and 80% of patients who presented with metastasis within the first 3 years [120]. Recurrent OS is treated with second-line chemotherapy and surgery. If the recurrence can be completely surgically removed, the patient has a greatly increased chance of survival [121].

**Prognosis**

Survival rates for patients with OS increased dramatically with the introduction of chemotherapy, but have since plateaued. Today, 5-year survival for all patient groups with high-grade OS is 60–66% but remains highly dependent on stage at diagnosis. Patients with localized disease can expect 5-year survival rates as high as 60–78%, but survival drops to 20–30% for those with metastatic disease [66, 78, 92, 101, 122]. Other poor predictors of survival are increased tumor size, increased serum alkaline phosphatase, axial location, and secondary OS [102].

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**Fig. 6** An 11-year-old male patient with a large osteosarcoma of the distal femur that was reconstructed with an expandable endoprosthesis. Preop (a), immediate postop (b), and 2-year postoperative (c) X-ray images are shown. A lengthening of almost 5 cm was achieved with the expandable construct by age 13.
Advanced adult age is associated with increases in both higher-grade tumors and axial tumors, along with decreased response to and toleration of chemotherapy. Subsequently, older adults have a poorer prognosis [123]. Recurrent disease, either local or distant, decreases average 5-year survival to 20%, but can be as high as 45% for relapses greater than 2 years out that can be surgically resected. Lower-grade osteosarcomas, including parosteal and

Fig. 7 17-year-old male with periosteal osteosarcoma. MRI images (a, b) show the cortically based tumor is located in the metaphysis with some invasion of the marrow and a soft-tissue mass. A polyhedral, metaphysis-sparing bone cut was planned with navigation software (c), and intraoperative guidance was used to assist with the bone cuts according to the preoperative plan (d). A matching allograft was used to fill the defect and fixed to the patient’s remaining bone (e). Two-year follow-up shows robust union at the junction sites (f).
periosteal sarcomas, have a much better prognosis than the high-grade conventional type. The 5-year survival of periosteal sarcoma is around 83%, and parosteal sarcoma has a reported 5-year survival of 91%. This is primarily due to the low rate of metastasis.

**New Therapies**

A number of preclinical and clinical agents are currently being investigated for OS. One area of significant research involves using specific agents to target known processes important in OS pathogenesis. One attractive target is the mTOR pathway, a downstream pathway of IGF-1 that stimulates proliferation, survival, and angiogenesis. Sirolimus, an mTOR inhibitor, was found to inhibit metastasis and OS xenograft growth in mice [124, 125]. Everolimus, an oral mTOR inhibitor, also showed activity against human and mice OS cells, an effect that was enhanced by combination with zoledronic acid [126]. A recent phase I trial has shown that oral everolimus is safe in pediatric populations [127], and a phase II study is currently ongoing in refractory OS [128]. Disruption of angiogenesis is another strategy, and several targeted agents have been tested in OS. Pazopanib is an inhibitor of VEGFR, PDGFR, and c-kit that has shown some efficacy in metastatic OS [129]. The drug is well tolerated in children and currently under investigation in a phase II clinical trial among OS patients with lung metastases. Sorafenib is an oral anti-angiogenic agent with activity against VEGFR-2 and PDGFR-B that has shown good activity as a second- or third-line agent in refractory OS [130]. Surprisingly, a recent clinical study failed to show efficacy when sorafenib was combined with everolimus in inoperable high-grade progressive OS patients [131].

Immune modulation is another area of increased OS research. As discussed earlier, inhibition of the Fas pathway helps OS cells avoid apoptosis and immune-mediated destruction [43]. Targeting this pathway has successfully been accomplished in preclinical models with the use of interleukin 12 (IL-12). IL-12 functions to activate Fas on cell surfaces, leading to increased cell death and immune clearance [42, 44]. Unfortunately, IL-12 is toxic when administered systemically. Liposomal muramyl tripeptide phosphatidyl ethanolamine (liposomal MTP-PE) is a promising agent that functions to induce endogenous IL-12 and thus provides the effect of IL-12 without the toxicity. In a recent Children’s Oncology Group (COG) phase III trial, liposomal MTP-PE improved overall survival regardless of treatment regimen [45, 132].

Another class of drugs currently garnering attention in OS are bisphosphonates. Besides their effects on osteoclast activity, bisphosphonates also act to inhibit cell growth and proliferation, can induce apoptosis, and downregulate angiogenic growth factors [133]. In a preclinical study, zoledronate successfully suppressed tumor growth and lung metastasis in a mouse model and is now the subject of an ongoing trial with combination chemotherapy [126, 133]. In recent years, an international collaboration, the EURAMOS group, has been successful at overcoming the small numbers of patients at each institution by designing cooperative randomized trials across institutions, and even nations. The first phase, EURAMOS-1, tested the addition of pegylated interferon to chemotherapy as maintenance therapy in good responders, and, while the treatment was unsuccessful, the trial showed that international collaboration is possible in this rare tumor [86, 134].

The field of pharmacogenetics seeks to predict response to therapy and prognosis, and
is being used to personalize treatment across healthcare. Recently, Caronia et al. used single nucleotide polymorphisms (SNPs) to identify four variations in two genes responsible for chemotherapy resistance. Their work identified polymorphisms in the *ABCC3* gene, a member of the multi-drug resistance protein family, and *ABCB1*, which encodes for an ATP-mediated efflux pump. Patients with these polymorphisms had inferior estimated 5-year survival [135]. Other authors have used similar techniques to describe variations in different genes leading to changes in prognosis or resistance to chemotherapy [136, 137]. As this field evolves, new information about a patient’s genetic profile can be used to select the most efficacious therapy, minimize side effects, and better inform prognosis.

**CONCLUSION**

Advances in chemotherapy and surgery have taken OS from an almost universally fatal disease to one in which the majority of patients will survive with a meaningful quality of life. Despite this, a fair number of those affected will still develop fatal metastatic disease or serious complications of treatment, emphasizing the need for further clinical advancements. Accurate and efficient diagnosis, preoperative chemotherapy, surgical resection, postoperative chemotherapy, and lifelong surveillance are all vital in managing this complicated and potentially deadly disease.

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