Sarcoma: Bony Lesion

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Osteosarcoma of the Head and Neck in Children

Introduction and Epidemiology

Osteosarcoma is the most common malignant bone tumor in children. With an annual incidence of approximately 400/year in the United States, osteosarcoma represents 56% of all malignant pediatric bone tumors [18]. Osteosarcoma occurs most often in the metaphysis of the distal femur, proximal tibia, and the humerus in children, and, less often, in the pelvis. The peak incidence is in the second decade of life, correlating with the adolescent growth spurt. In many data sets, there is a slight increased incidence in boys [18].

The literature on head and neck osteosarcoma (HNOS), in adults and children, is confined largely to case reports and case series due to its low frequency. Approximately 8% of all osteosarcomas occur in the head and neck, and most of these are gnathic [9]. In pediatric patients the proportion of osteosarcoma occurring in the head and neck is even less. In a St. Jude Children's Research Hospital cohort of 812 pediatric bone tumors, only 18, or 4.8%, were HNOS [9]. Unlike osteosarcoma of the appendicular skeleton, which occurs typically in the second decade of life, HNOS seems to present approximately a decade later, pushing most of the HNOS diagnoses into the adult age range [13] (Fig. 40.1).

Clinical Presentation

When all HNOS, pediatric and adult, are considered together, tumors occur most commonly in the mandible (45–49%) with the maxilla closely following as the second most common site (47–40%) [17, 23]. In one of the only reports on pediatric HNOS, of 18 individuals the maxilla and mandible were equally involved (44.5% each) and other sites were involved 11% of the time [9]. The majority of patients with HNOS present with a mass lesion or swelling which can be accompanied by pain [12, 15]. Trismus is rarely described as an isolated symptom in HNOS, likely because it is almost always accompanied by pain. It is also important to recognize that symptoms of gnathic osteosarcoma may mimic dental infection. In fact, in one study, 44% of individuals with these tumors presented to their dentist first for presumed tooth etiology [15]. Other rarer signs and symptoms of HNOS can include cranial nerve palsies, proptosis, or increased intracranial pressure [31].

Etiology and Biology

Like with all osteosarcomas, the etiology for most primary osteosarcoma of the head and neck is unknown. The most significant risk factor for HNOS in children is hereditary retinoblastoma. Other risk factors include prior radiation therapy, and additional cancer predisposition syndromes. Li–Fraumeni and Rothmund–Thomson syndromes predispose individuals to osteosarcoma in general but not specifically HNOS. Paget's Disease of bone also results in predisposition to osteosarcoma; however, because it causes osteosarcoma in older individuals, Paget's disease will not be discussed here.

Li–Fraumeni syndrome is an autosomal dominant familial condition involving germline mutations of the *TP53* gene that manifests with a very high incidence of malignancies, including osteosarcoma. A study of a large database of *TP53* mutation carriers published in 2003 demonstrated that 13.4% of these individuals with tumors had osteosarcoma [32]. However, the literature does not suggest that anatomic distribution of osteosarcoma in Li–Fraumeni syndrome differs from sporadic osteosarcoma.

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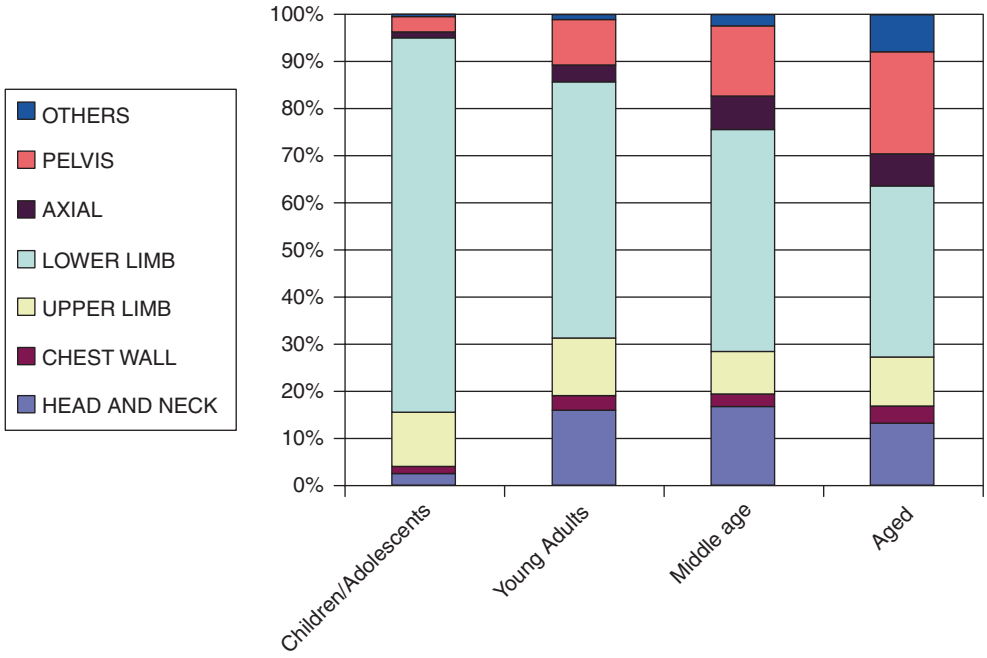

Fig. 40.1 Frequency of primary sites of osteosarcoma according to age. (Data obtained from SEER 17 database) [30]

Rothmund–Thomson syndrome is an autosomal recessive disorder associated with poikiloderma and other skin abnormalities, as well as bone developmental defects. An increased likelihood of osteosarcoma was first shown in 1990. There are no reported cases of Rothmund–Thomson-syndrome-associated HNOS; rather, these are appendicular skeleton tumors [24].

Hereditary retinoblastoma is caused by a heterozygous germline mutation in the *RB1* gene, on the long arm of chromosome 13 [1]. In children who suffer from hereditary retinoblastoma, about 50 % of secondary tumors (after occurrence of retinoblastoma) are osteosarcomas [20]. Originally, the increased risk of osteosarcoma in hereditary retinoblastoma was thought to be strictly secondary to DNA damage inflicted by radiation therapy delivered to the orbit to treat retinoblastoma. However, it is now known that the genetic defect in hereditary retinoblastoma contributes to increased osteosarcoma incidence independent of radiation therapy as demonstrated by an increased prevalence of osteosarcoma in patients with hereditary retinoblastoma at sites distant from radiation fields, such as the extremities. Radiation exposure does further increase HNOS risk in hereditary retinoblastoma. Children who have been irradiated for hereditary retinoblastoma therapy are 2,000 times more likely to get osteosarcoma of the skull than the average person, while they are 500 times more likely to develop osteosarcoma of the extremities [26]. Among children and adults with HNOS, a history of hereditary retinoblastoma is common. Four percent of 173 children and adults with HNOS [23] and 33 % of a group of 18 children with HNOS had a history of hereditary osteosarcoma [9]. While retinoblastoma is almost always diagnosed before the age of five, secondary osteosarcoma may not be diagnosed until adulthood.

Secondary osteosarcoma due to radiation from other pediatric tumors of the head and neck, such as leukemia, brain tumors, and other soft tissue tumors, such as rhabdomyosarcoma, does occur in very small numbers, and the latency period is often a decade or more [34]. It is notable that throughout the literature HNOS secondary to radiation is statistically linked to decreased survival compared to other non-radiation-associated primary HNOS, suggesting that this is a more aggressive tumor type [17, 15].

Diagnosis and Staging

Complete assessment of a newly identified head and neck bone tumor with imaging is required prior to biopsy in order to allow for appropriate planning of the best biopsy approach. Plain films are a good initial imaging modality to help identify the bone or region of interest for further evaluation and to define the extent of periosteal new bone formation or osteolysis present, but plain films are of limited utility because superimposed bony structures in the head and neck region permit only crude visualization of mass lesions. On cross-section imaging, osteosarcomas typically appear as a tumor arising from bone, causing cortical destruction and resulting in a soft tissue mass containing calcification. Computerized tomography (CT) shows more details of bony involvement and invasion into surrounding structures, and 3D modeling from CT can be helpful for presurgical mapping of the tumor (Fig. 40.2). Magnetic resonance imaging (MRI) provides the

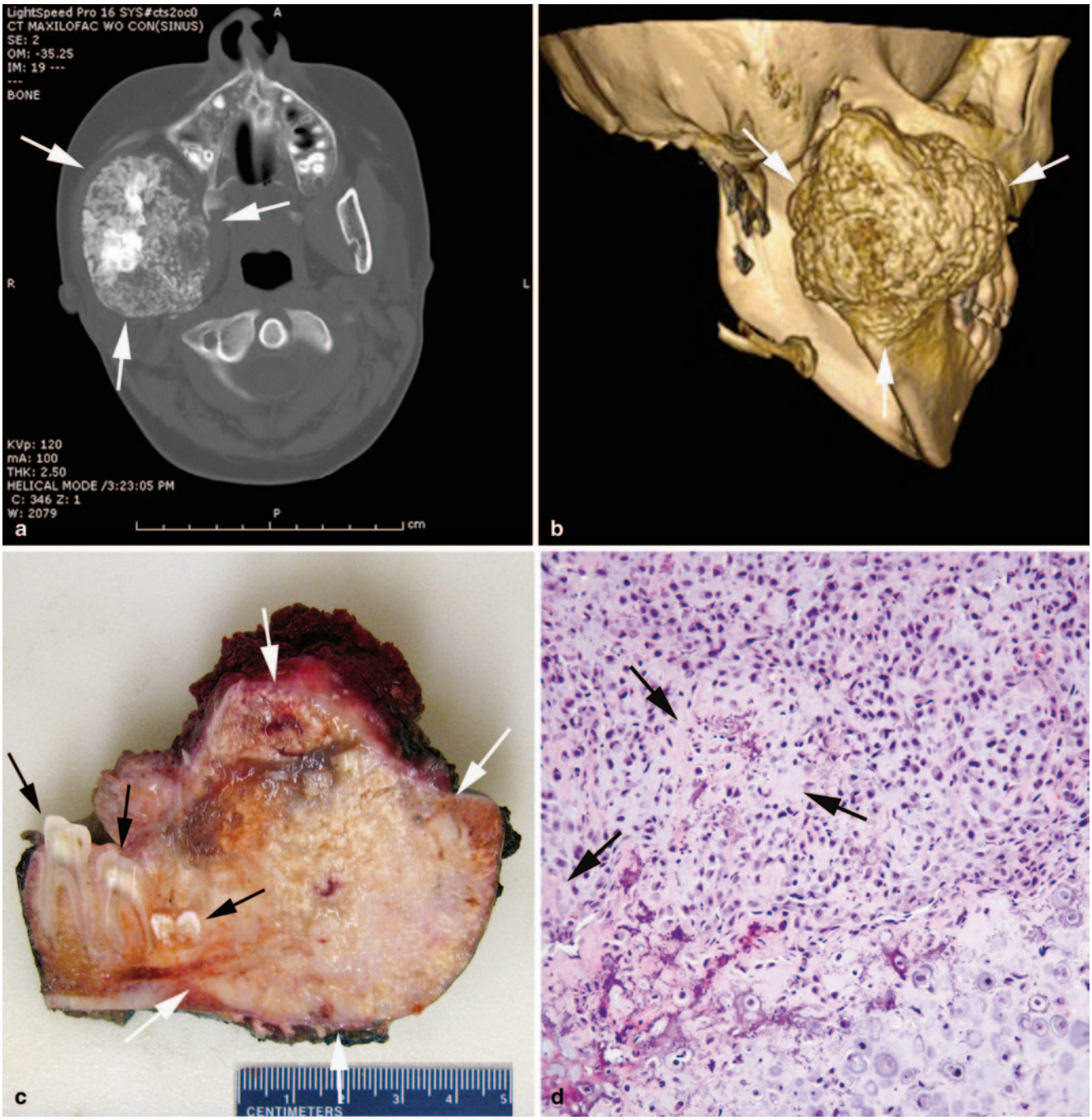

Fig. 40.2 Chondroblastic osteosarcoma of the mandible. **a** Bone-destructive, irregularly spherical mass centered in the right posterior mandible (between *arrows*). The mass reveals prominent spotty calcifications. **b** Three-dimensional reconstruction of the posterior mandibular mass (between *arrows*). **c** Cut section of the resected specimen showing the firm, destructive mass (between *white arrows*) with white-gray color, granular calcifications and areas of necrosis and hemorrhage. Cut section of the molars is indicated by *black arrows*. **d** Cellular tumor composed of large atypical cells with focal osteoid formation (*arrows*). Chondroid matrix is seen on the *right lower corner* of the photograph

most details of soft tissue involvement [9]. Up to 15–20% of patients with osteosarcoma have metastatic spread at the time of diagnosis; sites of distant metastases in osteosarcoma are, most commonly, the lungs followed by bones. Chest CT and bone scan are performed as part of staging work up to look for distant metastases [42].

Definitive diagnosis of HNOS requires a tissue biopsy. Surgical open biopsy is the traditional approach for obtaining a tissue biopsy. More recently, interventional radiology-guided, percutaneous, core needle biopsy has become a common approach, especially at tertiary care centers with interventional radiology specialists and large volumes of

Table 40.1 Differential diagnosis of HNOS

Other malignant primary bone tumors
Ewing sarcoma
Chondrosarcoma
Fibrosarcoma
Other malignancies presenting as bone tumor(s)
Lymphoma
Neuroblastoma
Metastatic rhabdomyosarcoma
Metastatic melanoma
Langerhans cell histiocytosis
Benign bone tumors
Aneurysmal bone cyst
Osteoblastoma
Osteoid osteoma
Giant cell tumor
Unicameral bone cyst
Hemangioma
Infectious/inflammatory
Osteomyelitis
Chronic recurrent multifocal osteomyelitis

pediatric solid tumor patients. The diagnostic yield of a core needle biopsy is operator dependent and ranges between 78 and 94% [4, 22, 41]. More recent studies that benefit from updated technology and user familiarity with the technique demonstrate diagnostic percentages on the higher end of this range. Regardless of the biopsy approach, it is important to sample the soft tissue component of the mass if possible, as this usually provides the greatest diagnostic yield. Surgical biopsy is most often incisional rather than excisional given that neo-adjuvant chemotherapy is often given prior to surgical resection. Osteosarcoma has been reported to recur into the tract left by the biopsy apparatus, so it is essential for the physician performing the biopsy, either percutaneously or surgically, to choose an entry point that will be removed en bloc with the tumor when it is surgically excised [8].

Differential diagnosis of HNOS includes other malignant primary bone tumors, other malignancies involving bone, benign bone tumors, and infectious and inflammatory conditions (Table 40.1). On pathologic examination osteosarcoma is a malignant tumor composed of pleomorphic cells associated with osteoid matrix production. Based on the degree of atypia, differentiation, and necrosis, the tumors can be classified as low, intermediate, or high grade. In children, low-grade tumors are very uncommon. In the head and neck, osteosarcomas are usually rich in chondroid matrix (Fig. 40.2).

Natural History

One interesting difference between HNOS and osteosarcoma of the long bones is the difference in propensity for metastases, both at time of diagnosis and following initial surgical and/or medical therapy for the primary tumor. The available case series on these tumors, in both adults and children, suggest that metastasis at time of diagnosis is very rare in primary HNOS, as opposed to in osteosarcoma in general, where 25% of initial diagnoses are made in the presence of distant metastases. In the St. Jude pediatric cohort, none of the 18 patients with HNOS had distant metastases at time of diagnosis [9]. A small case series of five pediatric patients of St. Louis, published in 1973 concluded that none of their cases had metastasized at time of diagnosis [10]. At M.D. Anderson, too, in a cohort of 12 patients between the ages of 12 and 21 years that were retrospectively examined none had evidence of distant metastases at time of diagnosis [21].

Management

In non-head and neck osteosarcoma the standard treatment approach is a combination of systemic chemotherapy and local control, most often accomplished by complete surgical resection with wide margins. The current and historical data show that with surgery alone, more than 80% of non-head and neck osteosarcoma will recur with distant metastases because of micro-metastatic disease [26]. Chemotherapy when added to surgical resection has been proven to improve overall survival [25]. However, in HNOS some controversy exists regarding whether to administer chemotherapy due to lack of data concerning the utility of chemotherapy in this disease.

Chemotherapy

Standard of care for chemotherapy treatment of osteosarcoma in sites other than the head and neck is four cycles of treatment with doxorubicin, cisplatin, and high-dose methotrexate and two cycles of treatment with doxorubicin and high-dose methotrexate (Fig. 40.3). This regimen is typically abbreviated as MAP. Some institutions, particularly in Europe, add ifosfamide to MAP and, in doing so, decrease the cumulative dose of doxorubicin given [3, 27]. Typically two cycles of MAP therapy are given prior to surgery in order to facilitate early initiation of chemotherapy and surgical planning, but upfront resection followed by chemotherapy is also an acceptable approach. Because of the differences in the natural history of HNOS compared to all other osteosarcomas, the role of chemotherapy is less certain.

As discussed above, HNOS differs in that it metastasizes infrequently. Retrospective studies to evaluate whether the use of chemotherapy impacts survival in HNOS are difficult to interpret due to the inevitable issue of confounding factors. In one study from Memorial Sloan–Kettering Cancer Center that included adults and children who were treated with radical surgery following neo-adjuvant chemotherapy, chemotherapy did not significantly improve event-free survival. However, only patients who were determined to

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Chemo	A			M	M	A			M	M	Surgery	A			M	M	A			M	M	A		M	M	A		M	M
	P					P						P					P												

A = Doxorubicin 75 mg/m^2 continuous infusion over 48 hours

P = Cisplatin 60 mg/m^2/day x 2 days

M = Methotrexate 12 gm/m^{2}x 1 dose, maximum dose 20 gm

Fig. 40.3 MAP chemotherapy regimen for the treatment of osteosarcoma

have high-grade tumors, unresectable tumors, or predisposing factors to HNOS such as retinoblastoma were offered chemotherapy in this study [33]. In patients who have positive surgical margins following resection or an unresectable HNOS, retrospective studies suggest that patients receiving chemotherapy have a better outcome; however, the study populations are small [31].

Two meta-analyses of combined adult and pediatric data published in 1997 assessed the role of chemotherapy in HNOS. These studies oppose one another. In the first, only adjuvant chemotherapy was addressed, and the authors concluded that there was no significant difference in 5-year survival between the groups that received chemotherapy (50%) versus surgery alone; however, the study did not address the question of surgical margins or resectability of the tumors—both important prognostic factors [23]. In the second study, the authors concluded that the addition of chemotherapy led to significantly prolonged survival and better outcomes in general for patients with HNOS, both for individuals who had complete surgical removal and who had incomplete resections. They recommended the same protocol for HNOS as for non-head and neck osteosarcoma [38].

In pediatrics, the practice is generally to offer chemotherapy for HNOS patients, and children with HNOS have been permitted to enroll on Children's Oncology Group studies of chemotherapeutic regimens in osteosarcoma [14, 27]. In order to determine the impact of chemotherapy in HNOS in children, randomized control trials would be needed but patient numbers are too small to permit studies of this type.

Local Control: Surgery

Because osteosarcoma is relatively resistant to radiotherapy, definitive local control of HNOS, like any osteosarcoma, requires complete surgical resection with negative surgical margins. In non-head and neck osteosarcomas, surgical resectability is an important prognostic factor. For this reason osteosarcoma of the pelvis has a significantly worse outcome than osteosarcoma involving other sites [19]. Similarly, retrospective studies have shown that complete surgical resection of HNOS with negative margins is the most significant prognostic factor influencing overall survival [17, 33, 42]. This includes a retrospective study in a pediatric cohort, where a Kaplan–Meier survival analysis of HNOS patients showed a 75% 5-year survival of individuals who underwent complete resection as compared to a 35% 5-year survival of those who underwent incomplete resection or biopsy, regardless of adjuvant therapy [9]. The surgical management of HNOS is complicated by anatomical challenges of resection of the gnathic, neck, and skull bones. Mandibular tumors have the highest rates of negative margins because of ease of surgical access, and therefore have the best outcome, followed by maxillary lesions and skull tumors, which are the most difficult to resect. Therefore, the goal should always be complete removal with negative margins, which, unfortunately, is not always achievable in the head and neck region.

The extent of surgical margin required in osteosarcoma in order to be considered adequate to decrease the risk of local recurrence is a topic of great debate. Marginal and intralesional margins are associated with a poor outcome and an increased risk of local recurrence [5]. In general, orthopedic surgeons treating osteosarcoma of the limb aim for margins of 2–5 mm for soft tissue and 2–3 cm for bone marrow. The pathological/surgical staging system utilized in osteosarcoma is the Enneking staging system (Table 40.2) [11]. Most osteosarcomas in children are high grade (G2) and extracompartmental, meaning that the tumor has broken through the cortex of the bone. Consequently, most osteosarcomas in children are Enneking stage IIB or III.

Local Control: Radiation

In the head and neck region, radiotherapy has not been well studied, particularly in pediatrics, where the number of patients in published retrospective studies who have received radiation is too small to come to definitive conclusions about its effects [9, 12]. The Smeele 1997 retrospective study of chemotherapy regimens in HNOS reported that 34% of the patients included in the study had received radiation, either in combination with chemotherapy and/or surgery, or as a single modality. In their analysis, they found that radiation therapy was insignificant as a modifier of disease outcome [38]. However, radiation may play a key role, especially in patients with positive surgical margins, as demonstrated in a retrospective 2009 study from M.D. Anderson where 5-year local control of tumors in patients with incomplete surgical resection or positive margins who received radiation therapy was 80% as opposed to 31% with surgery alone [17]. Therefore,

Table 40.2 Enneking staging system for osteosarcoma [11]

Stage	Grade	Site	Metastasis
IA	G1	T1	M0
IB	G1	T2	M0
IIA	G2	T1	M0
IIB	G2	T2	M0
III	G1,2	T1,2	M1

G1 Low grade, characterized by few mitoses and a relatively well-differentiated appearance
G2 High grade characterized by higher mitotic rate and a less differentiated appearance
T1 Tumor is intracompartmental or confined to the anatomic compartment of origin
T2 Tumor is extracompartmental or extends beyond the anatomic compartment of origin
M0 No distant metastases present
M1 Distant metastases present

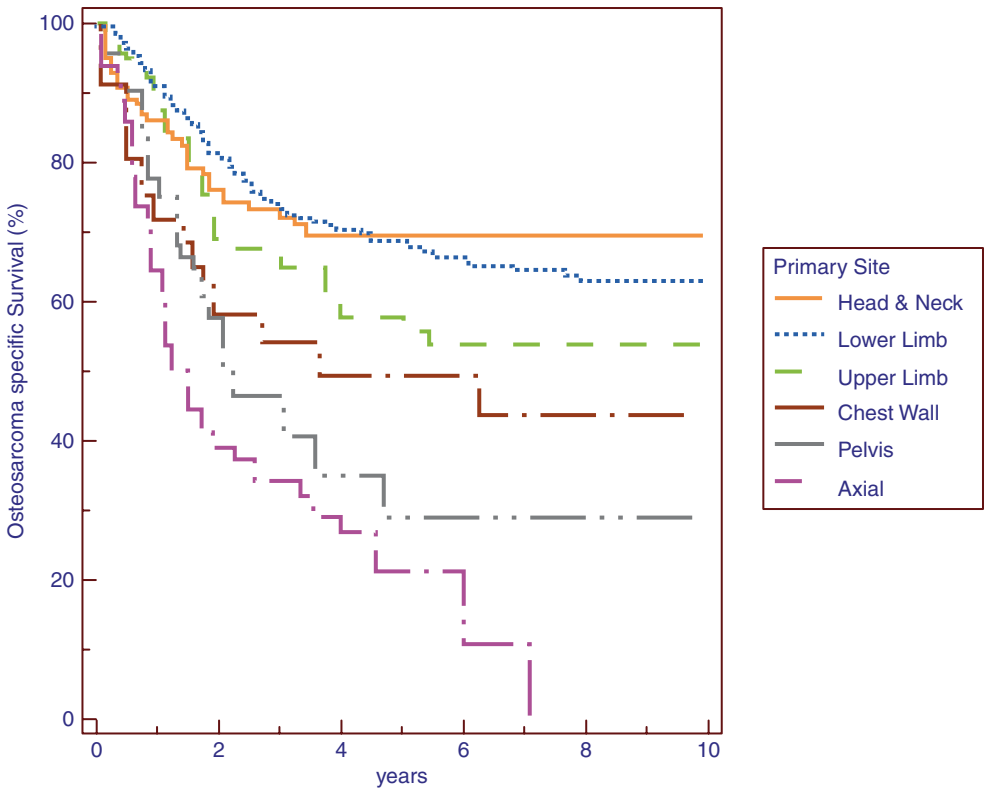

Fig. 40.4 Osteosarcoma-specific survival by site. (SEER 9 database, 1996–2005) [30]

the generally accepted role of radiation therapy in osteosarcoma is for treatment of positive surgical margins where re-resection to achieve negative margins is not feasible.

Outcome

Five-year overall survival in osteosarcoma ranges from 65 to 70%. Five-year overall survival in HNOS is slightly higher, ranging from 60 to 75% in individuals who underwent complete surgical resection [9, 39] (Fig. 40.4). There is evidence to support the fact that gnathic osteosarcomas have significantly higher 5-year survival rates than extra-gnathic HNOS [23].

Recurrences of non-head and neck osteosarcomas are almost always distant, usually affecting lung or bone, with <5% recurring locally. HNOS tumors, instead, usually recur locally; while only 7–17% have distant metastatic recurrence [42]. In one study of all pediatric patients, 32% had local recurrence following surgical intervention, with no differences in the recurrence rate between gnathic and skull lesions [12]. This is similar in more aggressive, radiation-related HNOS, where in one study of these individuals, 86% of the study population that recurred did so locally, instead of with distant metastases [31]. When HNOS does metastasize, it behaves like other osteosarcomas, occurring most commonly in the lung [15]. Also, it is important to point out that local recurrence is not a positive outcome, given that these tumors are oftentimes unresectable and lead to a large local tumor burden with eventual development of significant morbidity and mortality.

Ewing Sarcoma of the Head and Neck in Children

Introduction and Epidemiology

Ewing sarcoma is the second most common primary bone malignancy in children with approximately 200 cases occurring in children each year in the United States. As with osteosarcoma, incidence peaks in adolescence coincident with the peak in growth velocity. For girls peak incidence occurs at age 10–14 and in boys peak incidence occurs at age 15–19 years. One particularly interesting demographic feature of Ewing sarcoma is that the disease is extremely rare in people of African or Asian descent [29].

Only 4–9 % of Ewing sarcomas occur in the head and neck making this a rare entity [2, 37]. As with HNOS, published data regarding Ewing sarcoma of the head and neck are limited to case reports and case series. The most comprehensive manuscript, reporting on patients enrolled on four intergroup Ewing's Sarcoma Studies, describes 29 patients with head and neck Ewing sarcoma [37].

Clinical Presentation

As with Ewing sarcoma in other sites, Ewing sarcoma of the head and neck most often present as a painful mass lesion. The most common sites in the head and neck for Ewing sarcoma are the skull bones, mandible, and maxilla. Ewing sarcoma has also been reported to occur in the orbit, nasal cavity, and cervical vertebrae. Clinical presentation of Ewing sarcoma in these less common sites includes proptosis, oculomotor dysfunction, and symptoms of cord compression [2, 37]. Rare head and neck locations described in case reports include the larynx, sinuses, and thyroid [6, 7, 45].

Up to 15–20 % of patients with Ewing sarcoma have metastatic disease at the time of diagnosis; in those cases the most common sites of metastasis are lung, bone, and bone marrow. Patients with metastatic disease often have multiple sites involved. Loco-regional lymph nodes are rarely involved with metastatic disease at the time of diagnosis [28, 35]. Although data are limited, it appears as though a similar proportion of patients with head and neck Ewing sarcoma present with metastatic disease [2].

Etiology and Biology

As with most pediatric malignancies, the cause of Ewing Sarcoma is not known. Ninty-five percent of Ewing sarcomas have a translocation involving the *EWSR1* gene. In most cases the translocation partner is *FLI1,* an E-twenty-six (ETS) family transcription factor [36]. How this translocation leads to transformation is not known and this is an active area of ongoing research. Unlike osteosarcoma, Ewing sarcoma does not frequently occur in the setting of a cancer predisposition syndrome and it is not a common second malignancy following radiation therapy [40]. While Ewing sarcoma is classified as a primary bone tumor, the cell of origin is not known and 25 % of tumors arise in extra-skeletal locations. Most of the rare head and neck locations for Ewing sarcoma are extra-skeletal.

Diagnosis and Staging

While radiographic features of Ewing sarcoma differ from those in osteosarcoma, it is not possible to distinguish these two primary bone tumors on the basis of imaging alone. As with osteosarcoma, tissue biopsy is required for definitive diagnosis. The best imaging modality for evaluation of the primary tumor for the purposes of planning for biopsy and ultimate surgical resection is MRI. CT scan can be helpful in bone tumors in some cases. A complete staging evaluation in Ewing sarcoma consists of, at a minimum, a CT scan of the chest and a bone scan. Ewing sarcoma is positive on fluorodeoxyglucose positron emission tomography (FDG-PET), and this diagnostic modality is often performed in addition to bone scan. Bilateral bone marrow aspirates and biopsies are routinely performed for staging in pediatric patients.

Differential diagnosis of Ewing sarcoma of the head and neck includes those considerations listed for osteosarcoma (Table 40.1). When head and neck Ewing sarcoma occurs in rare extra-skeletal locations, the differential diagnosis is broader and includes soft tissue sarcomas such as rhabdomyosarcoma and other soft tissue sarcomas as well as malignant tumors occurring in the location from which the Ewing sarcoma is arising, such as nasopharyngeal carcinoma.

Considerations in the approach to biopsy of Ewing sarcoma are essentially the same as those in the approach to biopsy in osteosarcoma (see previous discussion). Acceptable methods of obtaining a tissue biopsy are open surgical incisional biopsy and interventional radiology-guided, core needle biopsy. Regardless of approach, biopsy should be performed at a center with experience in the diagnosis and treatment of pediatric sarcomas of the head and neck. With rare exceptions, upfront resection or excisional biopsy should not be performed for Ewing sarcoma. This is particularly true for Ewing sarcoma of the head and neck in which radiation therapy rather than surgery is often used for definitive local control (see local control: surgery and radiation below).

On histologic examination, Ewing sarcoma is a small, round, blue cell tumor (Fig. 40.5). Immunohistochemistry for CD99 can aid in the diagnosis as Ewing sarcoma has a membranous staining pattern for CD99. Fluorescence in situ hybridization (FISH) for a translocation involving *EWSR1*

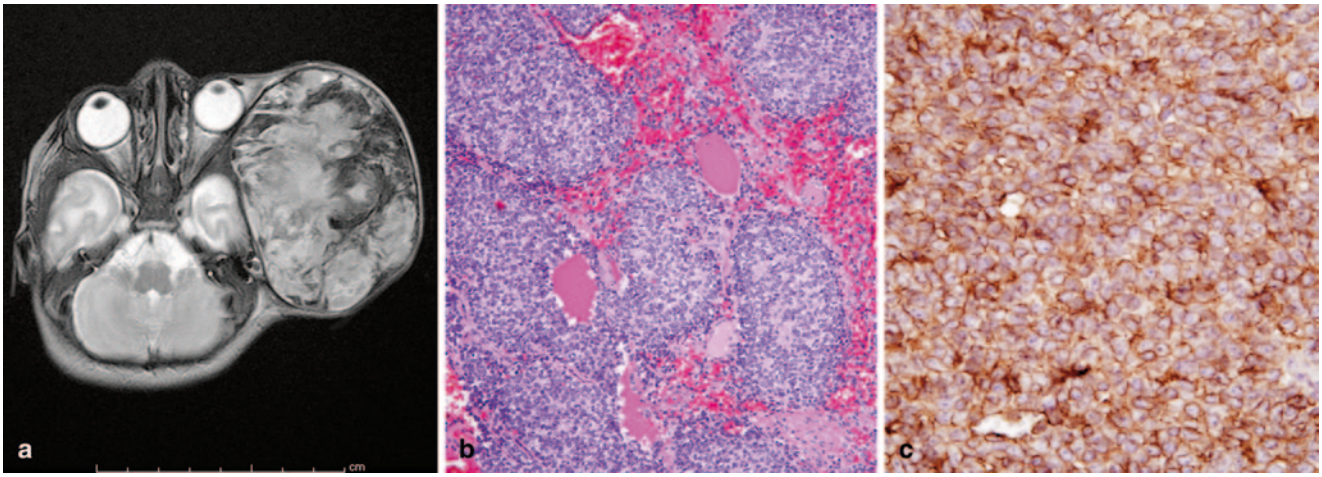

Fig. 40.5 Ewing sarcoma/malignant primitive neuroectodermal tumor. **a** Large heterogeneous destructive mass involving the skull. **b** Islands of undifferentiated small, round cells with focally poorly formed rosettes. **c** Diffuse, strong membranous immunoreactivity for CD99 in tumor cells

can also be informative as 95% of Ewing sarcomas contain translocations involving *EWSR1* [36].

Management

Because the natural history of head and neck Ewing sarcoma appears to be similar to that of non-head and neck Ewing sarcoma, the approach to treatment for head and neck Ewing sarcoma is the same as the approach to treatment of non-head and neck Ewing sarcoma. The standard approach to management of Ewing sarcoma is a multi-modality approach with chemotherapy administration and local control accomplished by either surgery or radiation therapy.

Chemotherapy

Prior to uniform use of modern multi-modality therapy for Ewing sarcoma overall survival was less than 45% [18]. With modern multi-modality therapy including chemotherapy overall survival is now 80% in those with localized disease [44]. Over the past 30 years, chemotherapy regimens have been studied in large prospective phase III trials. The current approach to standard of care is based on the results of these trials. The best reported outcomes in Ewing sarcoma are from chemotherapy regimens including five drugs: vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide with chemotherapy cycles administered in an interval-compressed manner of every 2 weeks [16, 44] (Fig. 40.6).

Local Control: Surgery and Radiation

In stark contrast to osteosarcoma, both radiation therapy and surgical resection with negative margins are effective methods of local control in Ewing sarcoma. Whether surgical resection with negative margins results in a decreased risk of local recurrence when compared to radiation therapy is a subject of considerable debate. As randomized controlled trials to answer this question are not feasible, data are limited to retrospective studies, which are subject to confounding by additional prognostic variables such as tumor size, tumor site, and the presence of metastatic disease. Retrospective studies, including a recently presented large study of patients treated on prospective Children's Oncology Group trials, suggest that there is a slightly increased risk of local recurrence when local control is performed with radiation alone as compared to surgery or surgery plus radiation therapy [35, 43]. However, because local recurrence is a rare event, this slight increased risk of local recurrence does not appear to translate into an increased risk of disease-related death [43]. Consequently, selection of the optimal approach to local control for patients with Ewing sarcoma is an individualized decision in which disease control, acute complications, late-effects, functional compromise, and cosmesis resulting from surgery and radiation are considered in a multi-disciplinary discussion. Patients being treated in centers without experience in local control for Ewing sarcoma should consider referral to a center with this expertise for consultation regarding the optimal approach to local control. In head and neck Ewing sarcoma, because of the challenges in achieving complete surgical resection with negative margins without significant functional compromise and impact on cosmesis, radiation therapy is the most common approach utilized for local control [2, 37].

When performed, local control surgery should occur after induction chemotherapy as Ewing sarcoma primary tumors often undergo considerable shrinkage in response to chemotherapy making surgical resection easier. In order for surgery alone to constitute adequate local control, resection margins must be free of involvement by tumor. As with osteosarcoma, the extent of normal tissue margin needed to reduce the

Induction (Before local control):

Week	1	3	5	7	9	11	13
Vincristine	*		*		*		Local Control[1]
Doxorubicin	*		*		*		
Cyclophosphamide	*		*		*		
Ifosfamide		*		*		*	
Etoposide		*		*		*	
Filgrastim	*	*	*	*	*	*	

Consolidation (After or during local control):

Week[2]	13	15	17	19	21	23	25	27
Vincristine	*		*		*		*	
Doxorubicin[3]	*		*					
Cyclophosphamide	*		*		*		*	
Ifosfamide		*		*		*		*
Etoposide		*		*		*		*
Filgrastim	*	*	*	*	*	*	*	*

[1] Local control is achieved with surgery, radiation or, on occasion, both.

[2] Chemotherapy continues during radiation therapy (if given).

[3] Two of the vincristine, doxorubicin and cyclophosphamide cycles include only vincristine and cyclophosphamide without doxorubicin. When chemotherapy is continued during radiation therapy doxorubicin is not administered concurrently with radiation and is held for several weeks following completion of radiation therapy to prevent radiation recall.

Fig. 40.6 Standard of care chemotherapy regimen for the treatment of Ewing sarcoma used in North America

risk of local recurrence is not known. The dose of radiation therapy utilized in treatment of Ewing sarcoma varies depending on the clinical scenario. For definitive local control of gross disease doses of 55.8 Gy are utilized.

Outcome

Overall survival at 5 years in localized Ewing sarcoma following treatment with modern multi-modality therapy is 80% [16, 44]. Outcomes are much worse in patients with metastatic Ewing sarcoma where overall survival at 5 years is approximately 30–40% [35]. In addition to metastatic disease, prognostic factors in Ewing sarcoma are age, size, and anatomic site with older patients and those with larger tumors having worse outcomes. Head and neck appears to be a good prognostic variable. Case series consistently demonstrate a better outcome for head and neck Ewing sarcoma when compared to other sites with the exception of cervical Ewing sarcoma which appears to have a similar outcome to non-head and neck sites [2, 37]. However, these case series include patients who did not receive modern therapy. Whether the improved outcomes in non-head and neck Ewing sarcoma with modern therapy have eliminated this difference in outcomes between non-head and neck and head and neck sites is not know.

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