Bone- and Cartilage-Forming Tumors and Ewing Sarcoma: An Update with a Gnathic Emphasis

Brian D. Stewart · John D. Reith ·
Jacquelyn A. Knapik · Angela C. Chi

Received: 30 September 2014 / Accepted: 3 November 2014 / Published online: 20 November 2014
© Springer Science+Business Media New York 2014

Abstract Over the past decade, there have been remarkable advances in bone tumor pathology. Insights into the genetic basis and pathobiology of many tumor types have impacted diagnosis, classification, and treatment. However, because gnathic lesions may comprise only a small proportion of cases overall for many tumors, clinicopathologic features and management considerations specific to this subset may be overlooked. Here we provide a summary of recent developments in the following tumor types: osteosarcoma (OS), chondrosarcoma (CS), osteoid osteoma (OO), osteoblastoma (OB), and Ewing sarcoma (ES). In particular, we will give special consideration to cases arising in the jaws.

Keywords Osteosarcoma · Chondrosarcoma · Osteoid osteoma · Osteoblastoma · Ewing sarcoma · Jaws

Osteosarcoma

The jaws represent the 4th most common site for osteosarcoma (OS), with about 6 % of all cases arising in this location. The most common gnathic sites of involvement are the mandibular body and the canine-premolar area of the maxilla. Most patients present with swelling and pain; tooth displacement and overlying ulceration are also possible [1, 2].

Gnathic OS recently has garnered attention as an entity distinct from extragnathic OS for several reasons [2–4]. First, extragnathic OS exhibits a bimodal age distribution, with a peak in the 1st and 2nd decades and a lesser peak among individuals older than 60 years. In contrast, jaw lesions exhibit a peak in the 4th decade, with a mean age of 36.9 years (approximately 1–2 decades older than the mean age for extragnathic lesions) [1, 2]. Secondly, extragnathic OS is highly aggressive and often presents with metastasis. Five-year survival with surgery alone is <50 % but has improved to about 70 % with current combined treatment protocols [e.g., for high-grade, resectable OS: neoadjuvant chemotherapy, primary tumor resection, metastectomy (if appropriate), and adjuvant chemotherapy]. OS of the jaws, however, metastasizes infrequently, with local progression accounting for most morbidity and mortality. Surgery is the mainstay of therapy, with approximately 70 % overall 5-year survival [3]. Reported outcomes for combined treatment of jaw tumors are variable; further studies are needed to determine whether there is a significant survival advantage for patients receiving chemotherapy and surgery versus surgery alone [2, 5]. In the largest series (n = 214) of gnathic OS reported to date, Baumhoer et al. [4] found that patients receiving chemotherapy did not exhibit significantly better outcomes compared to those not receiving chemotherapy. In this study, the only independent

B. D. Stewart · J. D. Reith · J. A. Knapik
Department of Pathology, Immunology, and Laboratory
Medicine, University of Florida College of Medicine,
Gainesville, FL, USA
e-mail: bstewart@ufl.edu

J. D. Reith
e-mail: reith@pathology.ufl.edu

J. A. Knapik
e-mail: knapik@pathology.ufl.edu

A. C. Chi (✉)
Division of Oral Pathology, College of Dental Medicine,
Medical University of South Carolina, 173 Ashley Ave.,
MSC 507, Charleston, SC 29425, USA
e-mail: chi@muscc.edu

Table 1 Osteosarcoma classification scheme

Type	Variants	Grade
Central (intramedullary)	Conventional variants	High
	Osteoblastic	
	Chondroblastic	
	Fibroblastic	
	Rare variants	High
	Telangiectatic	
	Small cell	
	Epithelioid	
	Giant cell-rich	
	Osteoblastoma-like	
Surface (juxtacortical)	Chondroblastoma-like	Low
	Low-grade central	
	Parosteal	
	Periosteal	
Extraskelatal	High-grade surface	Intermediate
		High
		Low to high

Source: Klein MJ, Siegal GP. Osteosarcoma: anatomic and histologic variants. Am J Clin Pathol. 2006;125:555–581

prognostic factors were resection margin status and metastasis. In particular, due to anatomic complexity, it is often more difficult to achieve complete surgical removal for maxillary compared to mandibular lesions. One small study noted greater Ki-67 proliferation indices and vascular endothelial growth factor (VEGF) expression in long bone tumors compared to jaw lesions, thereby giving support to the more aggressive nature of extragnathic OS [6]. However, more research is needed to elucidate the biology underlying differences in behavior.

A classification scheme for OS is provided in Table 1. Among conventional tumors, the osteoblastic variant is most common in the appendicular bones, whereas the chondroblastic variant is most common in the jaws (Fig. 1a, b).

Some gnathic tumors are very low grade, with radiographic and microscopic features that mimic a benign fibro-osseous lesion. Genetically, most low-grade central and parosteal OS exhibit supernumerary ring and giant marker chromosomes with amplification of 12q13–15—a feature typically not found in benign fibro-osseous lesions [7]. Within this region are the cell cycle-related genes *MDM2* and *CDK4*. Recent studies have found immunohistochemical expression of *MDM2* and/or *CDK4* to be present in 89–100 % of low-grade OS but absent in most benign mimics, including fibro-osseous lesions; these findings were confirmed by comparative genomic hybridization and quantitative real-time polymerase chain reaction (qRT-PCR) [7, 8]. However, Tabareau-Dalanlande et al. [9] noted discordant results, with 33 % of ossifying fibromas and 12 % of fibrous dysplasias exhibiting *MDM2*

Fig. 1 **a** Gross photograph of a large osteosarcoma involving the ramus (left) and body (right) of the mandible. This osteosarcoma, which contains a prominent chondroblastic component, extends out of the mandible into adjacent soft tissues circumferentially. **b** Classic chondroblastic osteosarcoma of the jaw, containing areas of cartilaginous differentiation and abundant osteoid matrix. (hematoxylin and eosin, original magnification $\times 200$)

amplification by qRT-PCR but no cases exhibiting *MDM2* overexpression by immunohistochemistry. These investigators also showed amplification of an *MDM2* neighbor, *RASAL1*, in all the fibro-osseous lesions with *MDM2* amplification but in none of the low-grade OS studied. Interestingly, there are a few reported cases of low-grade OS undergoing dedifferentiation with retained immunoppression of *MDM2* and *CDK4* [7, 8].

Chondrosarcoma

Compared to OS, chondrosarcoma (CS) is much rarer in the jaws. In the Mayo Clinic series, about 4 % of all

conventional CS originated from the jaw and facial bones, with about 30 % of this subset involving the mandible or maxilla [10]. Gnathic CS tends to arise in the mandibular symphysis, coronoid process, and condyle; these sites correspond to regions of endochondral bone formation. The peak age at presentation is in the 4th decade.

Conventional CS of the jaws and extragnathic sites exhibit similar histopathologic features (e.g., lobulated growth pattern, varying degrees of cellularity and atypia). Secondary features may include spindling of tumor cells, ossification, calcification, and myxoid matrix. The primary differential diagnosis for gnathic CS is chondroblastic OS. Chondroblastic OS arises more commonly in the jaws and is more responsive to chemotherapy compared to CS. Conventional CS produces hyaline or myxoid cartilage only; in contrast, chondroblastic OS produces both cartilage and osteoid matrix, although very careful histologic evaluation may be needed to identify only focal osteoid in some cases.

Immunohistochemical studies have noted more frequent expression of ezrin and galectin-1 in chondroblastic OS compared to CS [11, 12]. More recently, *IDH1* and *IDH2* mutations have emerged as the most useful markers for distinguishing cartilaginous lesions from their mimics. In an analysis of approximately 1,200 mesenchymal tumors by Sequenom[®] spectrometry, Amary et al. detected *IDH1* (codon R132) mutations or *IDH2* (codon R172 or R140) mutations in the majority of central and periosteal cartilaginous tumors (ranging from chondroma to high-grade CS) but not in OS, peripheral CS, or osteochondroma [13]. Similarly, Kerr et al. [14] found somatic mutations in *IDH1* (codon 132) or *IDH2* (exon 4) in 61 % of CS versus 0 % of OS.

Mesenchymal Chondrosarcoma

This CS variant is unusual in that it most often (22–27 % of cases) arises in the jaws. There is an even distribution between the mandible and maxilla. The tumor exhibits a distinctive biphasic microscopic pattern, characterized by cellular hyaline cartilage and small, undifferentiated round to spindled cells, often with staghorn-shaped vessels (Fig. 2a, b). Immunohistochemically, the chondrocytes are reactive for S-100 protein, and the small cells express CD99. Immunoreactivity for Sox9 (a master regulator of chondrogenesis) may help to distinguish mesenchymal chondrosarcoma (MC) from other small round cell tumors [15].

In 2012, Wang et al. [16] identified a novel, recurrent fusion involving two genes on chromosome 8: *HEY1* and *NCOA2*. *HEY1* is a downstream effector of Notch signaling, interacts with Runx2 in mice, and plays an important role in osteoblastic differentiation. *NCOA2* is a member of the p160 nuclear hormone receptor transcriptional co-

Fig. 2 **a** Gross photograph of a large mesenchymal chondrosarcoma arising within the ramus of the mandible. The biphasic nature of this tumor is evident, with the heavily calcified chondroid component centrally and the peripheral, fleshy-appearing areas which correspond to the round cell component. (Courtesy of Dr. Thomas W. Bauer, Cleveland Clinic Foundation). **b** Mesenchymal chondrosarcomas have a biphasic microscopic appearance, with a chondroid component as well as an undifferentiated component composed of small, round cells and prominent staghorn-shaped vessels. (hematoxylin and eosin, original magnification $\times 200$)

activator family; it facilitates chromatin remodeling and the transcription of nuclear receptor target genes. Wang et al. hypothesize that the pathogenesis of MC may be due in part to aberrant activation of Notch target genes by the *HEY1-NCOA2* fusion protein. Subsequent small-scale studies have identified *HEY1-NCOA2* fusion in 75–80 % of cases by FISH, alone or combined with whole genome sequencing [17, 18]. Furthermore, a novel *IRF2BP2-CDX1* fusion due to t(1;5) (q42;q32) has been noted in one case of extra-osseous MC [18]. Thus, although the *HEY1-NCOA2* fusion appears to be a sensitive marker for MC, there may be some genetic heterogeneity.

MC generally is aggressive. Some studies suggest that the prognosis is more favorable for lesions arising in the

jaws compared to other sites. Nevertheless, one recent study noted no significant difference in prognosis for maxillary versus extragnathic tumors [19].

Osteoid Osteoma

Combined analysis of recent reviews shows a total of 26 well-documented gnathic osteoid osteomas (OO) [20, 21]. Similar to extragnathic lesions, jaw lesions typically arise in young individuals (average age: 27 years, peak: 2nd and 3rd decades), albeit with a broad reported age range (4–77 years). There is an approximately even gender distribution, in contrast to a male predilection for OO overall. The mandible is affected more often than the maxilla (81 vs. 19 %). Most patients exhibit painful swelling. Lesions involving the mandibular condyle may cause limited mouth opening [22].

Classically, plain radiography shows either a radiolucent nidus with surrounding dense cortical sclerosis or, less commonly, a targetoid appearance (central sclerosis within a circumscribed radiolucency). However, among reported gnathic lesions, the nidus more often appears radiopaque or mixed than radiolucent. Interestingly, a jaw tumor recently described by An et al. [20] exhibited more than one nidus; this feature also has been noted in a few extragnathic lesions. A periosteal reaction also may be evident. CT is the best imaging method for OO but has been performed in only a few reported gnathic cases.

Because OO and osteoblastoma (OB) share similar microscopic features, diagnosis requires correlation with clinical and radiographic features, such as OO's tendency for cortical origin and limited growth potential (nidus <1–2 cm). However, some authors question whether size conventions based on extragnathic tumors apply to gnathic lesions [23]. Also, although nocturnally exacerbated pain relieved by nonsteroidal anti-inflammatory drugs (NSAIDs) is considered highly characteristic of OO, this feature has been described in only a few gnathic cases [22, 24–27].

A recent immunohistochemical study by Dancer et al. [28] showed strong nuclear expression of Osterix and Runx2 in OO and OB; these transcription factors play important roles in skeletal development and osteoblastic differentiation. Furthermore, Barlow et al. [29] demonstrated that OO and OB are similar with respect to the following: innervation (as evidenced by immunoreactivity pattern for S-100 protein, PGP9.5, and neurofilament and lack of reactivity for GFAP); stromal immunophenotype (positive for EMA and NSE, negative for SMA); and the presence of large, desmin-positive “smudge” (degenerating) cells. These authors propose that OO and OB should be regarded as a single entity.

OO of the jaws typically is treated by conservative surgical removal, although condylar lesions may require

resection. Biopsies obtained by traditional open surgery facilitate identification of characteristic microscopic features (i.e., abrupt interface between the nidus and surrounding reactive, sclerotic bone; central nidus with osteoid, bone, and differentiated osteoblasts within a vascularized fibrous stroma).

For extragnathic lesions, the trend toward minimally invasive treatment (e.g., image-guided percutaneous radiofrequency ablation, laser ablation, cryoablation, or trephine resection) can present challenges for the pathologist, such as limited samples with prominent artifact. Furthermore, successful treatment by noninvasive MR-guided focused ultrasound recently has been reported in a few patients [30]. The most conservative option is monitoring for spontaneous regression (typically over a period of months to years); NSAID administration might accelerate healing [31].

The prognosis is excellent. Recurrence or persistence after incomplete removal has been reported in only one gnathic case [20]. Sporadic reports suggest progression of OO to OB, although a recent critical appraisal by Chotel et al. [32] questions this concept.

Osteoblastoma

A review of the literature reveals at least 135 well-documented cases of gnathic OB [23, 33–52]. The average age is 23 years (range 3–78 years), with a 1.1:1 female-to-male ratio and 72 % involving the mandible. Most patients present with swelling accompanied by pain, tenderness, or discomfort, although some are asymptomatic. Radiographic findings are variable, ranging from radiolucent to mixed or radiopaque, with ill- to well-defined borders (Fig. 3a). Most gnathic lesions are treated by curettage or resection. For extragnathic lesions, percutaneous image-guided radiofrequency ablation has emerged as an alternative treatment. Persistence (following incomplete removal) or recurrence has been reported in 11 gnathic cases (6 mandibular, 5 maxillary) [35, 45, 48, 52]. Notably, Woźniak et al. [40] recently reported a mandibular OB that recurred twice, transformed into OS, and resulted in death.

There are several recent reports of “aggressive osteoblastoma” or “osteoblastoma with aggressive features” involving the jaws [43–45, 52]. Unfortunately, there is confusion regarding such terminology, with some authors describing lesions with truly aggressive clinical behavior and others describing lesions with merely epithelioid histomorphology. Nevertheless, there is no evidence that microscopic features alone are indicative of increased recurrence potential [53]. Instead, size >4 cm and an anatomic location that makes complete removal difficult may be of greater importance than histomorphology in

Fig. 3 **a:** Computed tomography (CT) image of a maxillary osteoblastoma shows a well-defined, expansile radiolucency with scattered opacification. (Courtesy of Dr. Michael Zetz). **b** Biopsy of the lesion depicted in **a** showed conventional osteoblastoma, with plump osteoblasts lining the bony trabeculae. (hematoxylin and eosin, original magnification $\times 400$). **c** Epithelioid osteoblastoma with numerous enlarged, epithelioid osteoblasts. (hematoxylin and eosin, original magnification $\times 200$). Current evidence suggests that epithelioid histomorphology alone is not indicative of aggressive clinical behavior

predicting aggressive behavior [43]. Microscopic features characteristic of the epithelioid variant include the following: large epithelioid osteoblasts that rim the bony trabeculae or form solid sheets (Fig. 3c); wide, irregular bony trabeculae with solid to lacelike osteoid deposition; occasional typical mitotic figures; lack of stromal pleomorphism and necrosis; and peripheral maturation of lesional bone without entrapment or permeation of normal host bone [43]. The latter features aid in distinction from OS.

Recent cytogenetic findings include $t(4;14;17)(q23 \sim 25; q31; q31)$ in an aggressive femoral OB and $t(1;2;14)(q42; q13; q24)$ in a conventional femoral tumor; similar abnormalities in chromosomes 1 and 14 have been described previously [54, 55]. Nord et al. [56] found more heavily rearranged genomes in 2 aggressive OBs compared to 9 conventional lesions. Furthermore, these authors found recurrent 22q deletions in one conventional and 2 aggressive OBs; the affected genes included *MNI* and *NF2* (both implicated in leukemia and solid tumor development) and *ZNRF3* and *KREMEN1* (inhibitors of the Wnt/beta-catenin signaling pathway). Aberrations in the Wnt/beta-catenin pathway have been described in osteoarthritis, osteoma, and OS as well.

Ewing Sarcoma

In the current WHO classification, the term “Ewing sarcoma” (ES) encompasses the following entities: classical ES, Askin tumor (small round cell tumor of the chest wall), primitive neuroectodermal tumor (PNET), atypical ES, and extraskeletal ES [57]. This recent simplification of terminology is based on genetic and clinicopathologic similarities. The histogenesis remains uncertain and controversial, although many authorities favor an origin from mesenchymal or neural crest-derived stem cells.

ES mainly affects pediatric patients; however, increased availability of molecular diagnosis has led to increased detection among adults [58]. Greater ES susceptibility among individuals of European compared to African descent correlates with the ethnic distribution of recently identified single nucleotide polymorphisms in the vicinity of *TARDBP* and *EGR2* [59]. Additional risk polymorphisms have been identified in *NROB1* microsatellites and *CTLA-4* [60, 61].

Recent sporadic reports demonstrate the potential for gnathic ES to mimic odontogenic or periodontal infection [62–66]. Clinical findings may include painful swelling, nonvital teeth, dental percussion tenderness, tooth mobility, increased periodontal probing depths, and/or fever. Radiographs may show nonspecific, ill-defined radiolucency. However, lack of improvement after endodontic therapy,

Table 2 Chromosomal abnormalities in Ewing sarcoma

Chromosomal abnormality	TET-ETS family fusion product	Approximate percentage of Ewing sarcoma cases (%)
t(11;22) (q24;q12)	EWS-FLI1	85
t(21;22) (q22;q12)	EWS-ERG	10
t(7;22) (p22;q12)	EWS-ETV1	<1
t(17;22) (q21;q12)	EWS-ETV4	<1
t(2;22) (q35;q12)	EWS-FEV	<1
t(16;21) (p11;q22)	FUS(TLS)-ERG	<1
t(2;16) (q35;p11)	FUS(TLS)-FEV	<1

Source: de Alava et al. [57]

antibiotics, and/or tooth extraction should prompt further evaluation. In some cases, paresthesia may portend malignancy.

Review of the English-language literature reveals only 11 cases of primary gnathic ES with genetic confirmation [65–70]. Most lesions exhibited conventional microscopic features and *EWSR1* or, more specifically, *EWSR1-FLI1* rearrangement. However, the case described by Makary et al. [69] exhibited spindle cell features. Also, Steyn et al. [71] described an unusual tumor with osteoid production, for which they considered classification as either atypical ES with osteoid production or small cell OS with *EWSR1* translocation. There is little data regarding uncommon chromosomal translocations (Table 2) in gnathic ES, although at least 2 cases with *EWSR1-ERG* translocation have been described [70, 72]. For extragnathic ES, studies with genetic confirmation have demonstrated remarkable histopathologic diversity—including not only enlarged pleomorphic cells in atypical ES but also lesser-known variants (e.g., sclerosing, adamantinoma-like, spindle cell, clear cell, and vascular-like types) [73, 74].

As for immunophenotype, CD99 and FLI1 remain the most widely recognized markers for ES, albeit with low specificity. Recent investigations also have demonstrated NKX2.2 immunoreactivity in 80–93 % of ES but only 11–16 % of other small round cell tumors studied; frequent galectin-1 expression in small cell OS but not ES; ERG expression in not only *ERG*-rearranged ES but also *EWSR1-FLI1*-associated ES and other tumor types; and variable ERG reactivity influenced by clone and antibody selection [75–78].

Importantly, detection of *EWSR1* rearrangement by FISH is not specific for ES. Indeed, other small round cell tumors—such as desmoplastic round cell tumor—may exhibit *EWSR1* rearrangement. Furthermore, because of variability in fusion partners and breakpoints (Table 2), a negative RT-PCR result does not entirely exclude ES [79].

Advances in molecular diagnosis have enabled the discovery of various rare fusions in so-called “Ewing-like

Table 3 Chromosomal abnormalities in Ewing-like sarcoma

Chromosomal abnormality	Corresponding fusion gene	Year first described [citation]
t(20;22) (q13;q12)	<i>EWSR1-NFATc2</i>	2009 [88]
t(6;22) (p21;q12)	<i>EWSR1-POU5F1</i>	2005 [89]
t(4;22) (p31;q12)	<i>EWSR1-SMARCA5</i>	2011 [90]
Paracentric inv(22) in t(1;22) (p36.1;q12)	<i>EWSR1-PATZ1</i>	2000 [91]
t(2;22) (q31;q12)	<i>EWSR1-SP3</i>	2007 [92]
t(4;19) (q35;q13)	<i>CIC-DUX4</i>	1996 [93]
t(X;19) (q13;q13.3)	<i>CIC-FOXO4</i>	2014 [94]
t(18;19) (q23;q13.2)	(<i>CIC</i> ?-unknown partner)	2010 [95]
inv(X) (p11.4p11.22)	<i>BCOR-CCNB3</i>	2012 [96]
t(16;20)	<i>FUS-NFATc2</i>	2014 [97]
t(12;15)	<i>ETV6-NTRK3</i>	2014 [97]

sarcomas” (i.e., undifferentiated small round cell sarcomas with histologic and immunophenotypic similarities to ES) (Table 3). It is uncertain whether Ewing-like sarcomas represent ES variants or distinct entities. There is an increased tendency among Ewing-like sarcomas (and also ES with rare translocation types) to arise within soft tissue and to exhibit atypical histopathologic features. To the best of our knowledge, no well-documented cases of gnathic Ewing-like sarcoma have been reported, although a recent abstract by Flaitz et al. [80] describes an infant with a congenital mandibular lesion exhibiting *EWSR1-NFATc2* translocation. Currently, patients with Ewing-like sarcomas and rare ES variants are treated in a manner similar to those with typical *EWSR1-FLI1*-associated ES. However, improved understanding of tumor biology may lead to tailored treatment in the future.

Although multimodal treatment protocols have been instrumental in improving patient outcomes, ES cure rates have plateaued for more than a decade [81]. The Children’s Oncology Group (COG) recently reported that multimodal therapy with intensified chemotherapy achieved 73 % event-free 5-year survival for patients with apparently localized disease [82]. In contrast, despite aggressive chemotherapy, patients with detectable metastatic disease at diagnosis continue to exhibit poor outcomes (5-year survival <35 %) [58, 83]. Likewise, the prognosis is poor for patients with refractory or recurrent disease. Hence, there is intense interest in developing novel treatment strategies.

Current ES translational research trends are reviewed in detail elsewhere [84, 85]. In brief, using gene expression-based, high-throughput screening methods, investigators have identified candidate compounds that may inhibit the aberrant transcription factor EWS-FLI1 directly or may modulate the expression of downstream targets of EWS-

FLI1. Other experimental strategies for developing novel therapies include disrupting epigenetic mechanisms of EWS-FLI1-mediated gene repression, PARP1 inhibition, p53 activation, overcoming tumor resistance to IGF-1R inhibition, and immunotherapy.

Evidence of metastasis at diagnosis is the most important prognostic factor. Additional adverse factors include large tumor size, poor histologic response to neoadjuvant chemotherapy, and axial location. The prognosis may be more favorable for ES of the jaws compared to the long bones and pelvis, although further study is needed [63].

Recent European-E.W.I.N.G. 99 and COG trials found no significant relationship between *EWSR1* fusion type and outcome [58, 86]. Apparently, the survival advantage previously reported for patients with fusion between exon 7 of *EWSR1* and exon 6 of *FLI1* no longer holds true with modern intensified treatment regimens [86]. Several retrospective studies suggest that *CDKN2A* (*INK4A/ARF*) and *TP53* abnormalities correlate with poor prognosis, and further evaluation of these cell cycle gene alterations is underway in a large-scale analysis by COG and the ES Biology Committee [87]. Also of potential prognostic significance but requiring validation are various chromosomal copy number alterations and subclinical disease detection by RT-PCR or flow cytometry. The search for early markers of treatment response has become especially urgent with the growing number of clinical trials for metastatic and/or refractory ES [87].

References

1. Padilla RJ, Murrah VA. The spectrum of gnathic osteosarcoma: caveats for the clinician and the pathologist. *Head Neck Pathol*. 2011;5:92–9.
2. Yildiz FR, Avci A, Dereci O, Erol B, Celasun B, Gunhan O. Gnathic osteosarcomas, experience of four institutions from Turkey. *Int J Clin Exp Pathol*. 2014;7:2800–8.
3. Thariat J, Julieron M, Bouchet A, Italiano A, Schouman T, Marcy PY, et al. Osteosarcomas of the mandible: are they different from other tumor sites? *Crit Rev Oncol Hematol*. 2012;82:280–95.
4. Baumhoer D, Brunner P, Eppenberger-Castori S, Smida J, Nathrath M, Jundt G. Osteosarcomas of the jaws differ from their peripheral counterparts and require a distinct treatment approach. Experiences from the DOESAK registry. *Oral Oncol*. 2014;50:147–53.
5. Guadagnolo BA, Zagars GK, Raymond AK, Benjamin RS, Sturgis EM. Osteosarcoma of the jaw/craniofacial region: outcomes after multimodality treatment. *Cancer*. 2009;115:3262–70.
6. Jawad SN, Abdullah BH. Proliferative, apoptotic and angiogenic potentials in jaws and long bones osteosarcomas: a comparative immunohistochemical study. *J Oral Pathol Med*. 2010;39:681–6.
7. Dujardin F, Binh MB, Bouvier C, Gomez-Bouchet A, Larousserie F, Muret A, et al. MDM2 and CDK4 immunohistochemistry is a valuable tool in the differential diagnosis of low-grade osteosarcomas and other primary fibro-osseous lesions of the bone. *Mod Pathol*. 2011;24:624–37.
8. Yoshida A, Ushiku T, Motoi T, Beppu Y, Fukayama M, Tsuda H, et al. MDM2 and CDK4 immunohistochemical coexpression in high-grade osteosarcoma: correlation with a dedifferentiated subtype. *Am J Surg Pathol*. 2012;36:423–31.
9. Tabareau-Delalande F, Collin C, Gomez-Bouchet A, Bouvier C, Decouvelaere AV, de Muret A, et al. Chromosome 12 long arm rearrangement covering MDM2 and *RASAL1* is associated with aggressive craniofacial juvenile ossifying fibroma and extracranial psammomatoid fibro-osseous lesions. *Mod Pathol*. 2014. doi:10.1038/modpathol.2014.80.
10. Inwards CY. Update on cartilage forming tumors of the head and neck. *Head Neck Pathol*. 2007;1:67–74.
11. Salas S, de Pinieux G, Gomez-Bouchet A, Larrousserie F, Leroy X, Aubert S, et al. Ezrin immunohistochemical expression in cartilaginous tumours: a useful tool for differential diagnosis between chondroblastic osteosarcoma and chondrosarcoma. *Virchows Arch*. 2009;454:81–7.
12. Gomez-Bouchet A, Mourcin F, Gourraud PA, Bouvier C, De Pinieux G, Le Guelec S, et al. Galectin-1 is a powerful marker to distinguish chondroblastic osteosarcoma and conventional chondrosarcoma. *Hum Pathol*. 2010;41:1220–30.
13. Amary MF, Bacsi K, Maggiani F, Damato S, Halai D, Berisha F, et al. IDH1 and IDH2 mutations are frequent events in central chondrosarcoma and central and periosteal chondromas but not in other mesenchymal tumours. *J Pathol*. 2011;224:334–43.
14. Kerr DA, Lopez HU, Deshpande V, Hornicek FJ, Duan Z, Zhang Y, et al. Molecular distinction of chondrosarcoma from chondroblastic osteosarcoma through IDH1/2 mutations. *Am J Surg Pathol*. 2013;37:787–95.
15. Wehrli BM, Huang W, De Crombrughe B, Ayala AG, Czerniak B. Sox9, a master regulator of chondrogenesis, distinguishes mesenchymal chondrosarcoma from other small blue round cell tumors. *Hum Pathol*. 2003;34:263–9.
16. Wang L, Motoi T, Khanin R, Olshen A, Mertens F, Bridge J, et al. Identification of a novel, recurrent HEY1-NCOA2 fusion in mesenchymal chondrosarcoma based on a genome-wide screen of exon-level expression data. *Genes Chromosom Cancer*. 2012;51:127–39.
17. Nakayama R, Miura Y, Ogino J, Susa M, Watanabe I, Horiuchi K, et al. Detection of HEY1-NCOA2 fusion by fluorescence in situ hybridization in formalin-fixed paraffin-embedded tissues as a possible diagnostic tool for mesenchymal chondrosarcoma. *Pathol Int*. 2012;62:823–6.
18. Nyquist KB, Panagopoulos I, Thorsen J, Haugom L, Gorunova L, Bjerkehaugen B, et al. Whole-transcriptome sequencing identifies novel IRF2BP2-CDX1 fusion gene brought about by translocation t(1;5)(q42;q32) in mesenchymal chondrosarcoma. *PLoS ONE*. 2012;7:e49705.
19. Tien N, Chaisuparat R, Fernandes R, Sarlani E, Papadimitriou JC, Ord RA, et al. Mesenchymal chondrosarcoma of the maxilla: case report and literature review. *J Oral Maxillofac Surg*. 2007;65:1260–6.
20. An SY, Shin HI, Choi KS, Park JW, Kim YG, Benavides E, et al. Unusual osteoid osteoma of the mandible: report of case and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2013;116:e134–40.
21. Singh A, Solomon MC. Osteoid osteoma of the mandible: a case report with review of the literature. *J Dent Sci*. 2012. doi:10.1016/j.jds.2012.10.002.
22. do Egito Vasconcelos BC, Porto GG, Bessa-Nogueira RV. Rare benign tumors of the mandibular condyle: report of 2 cases and literature review. *J Oral Maxillofac Surg*. 2007;65:1830–5.
23. Jones AC, Prihoda TJ, Kacher JE, Odingo NA, Freedman PD. Osteoblastoma of the maxilla and mandible: a report of 24 cases, review of the literature, and discussion of its relationship to osteoid osteoma of the jaws. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2006;102:639–50.

24. Festa L, Barbieri F. The mandibular location of an osteoid osteoma. A case report. *Radiol Med*. 1992;83:471–2.
25. Badauy C, Carrard V, Rados P, Sant'ana Filho M. Radiopaque mass of the posterior mandible with lingual expansion. *J Oral Maxillofac Surg*. 2007;65:2498–502.
26. Manjunatha BS, Nagarajappa D. Osteoid osteoma. *Indian J Dent Res*. 2009;20:514–5.
27. Lolli R, Venezia A, Bellardini M, Iori E. Osteoid osteomas of the jaws. Clinical and histopathological aspects. *Minerva Stomatol*. 1987;36:619–25.
28. Dancer JY, Henry SP, Bondaruk J, Lee S, Ayala AG, de Crombrughe B, et al. Expression of master regulatory genes controlling skeletal development in benign cartilage and bone forming tumors. *Hum Pathol*. 2010;41:1788–93.
29. Barlow E, Davies AM, Cool WP, Barlow D, Mangham DC. Osteoid osteoma and osteoblastoma: novel histological and immunohistochemical observations as evidence for a single entity. *J Clin Pathol*. 2013;66:768–74.
30. Geiger D, Napoli A, Conchiglia A, Gregori LM, Arrigoni F, Bazzocchi A, et al. MR-guided focused ultrasound (MRgFUS) ablation for the treatment of nonspinal osteoid osteoma: a prospective multicenter evaluation. *J Bone Joint Surg Am*. 2014;96:743–51.
31. Goto T, Shinoda Y, Okuma T, Ogura K, Tsuda Y, Yamakawa K, et al. Administration of nonsteroidal anti-inflammatory drugs accelerates spontaneous healing of osteoid osteoma. *Arch Orthop Trauma Surg*. 2011;131:619–25.
32. Chotel F, Franck F, Solla F, Dijoud F, Kohler R, Berard J, et al. Osteoid osteoma transformation into osteoblastoma: fact or fiction? *Orthop Traumatol Surg Res*. 2012;98:S98–104.
33. Ahmed MS, Nwoku AL. Benign osteoblastoma of the mandibular ramus: review of the literature and report of a case. *J Oral Maxillofac Surg*. 2000;58:1310–7.
34. Alvares Capelozza AL, Gião Dezotti MS, Casati Alvares L, Negrão Fleury R, Sant'Ana E. Osteoblastoma of the mandible: systematic review of the literature and report of a case. *Dento-maxillofac Radiol*. 2005;34:1–8.
35. Mahajan S, Srikant N, Boaz K, George T. Osteoblastoma of maxilla with cartilaginous matrix: review of literature and report of a case. *Singap Dent J*. 2007;29:12–8.
36. Rawal YB, Angiero F, Allen CM, Kalmar JR, Sedghizadeh PP, Steinhilber AM. Gnathic osteoblastoma: clinicopathologic review of seven cases with long-term follow-up. *Oral Oncol*. 2006;42:123–30.
37. Angiero F, Mellone P, Baldi A, Stefani M. Osteoblastoma of the jaw: report of two cases and review of the literature. *In Vivo*. 2006;20:665–70.
38. Dabholkar JP, Vora K, Vaidya A, Sharma A. Benign jaw tumors. *Indian J Otolaryngol Head Neck Surg*. 2009;61:240–4.
39. Yamada S, Kawasaki G, Shiraishi N, Kawano T, Rokutanda S, Baba N, et al. Osteoblastoma in the maxilla: report of a case. *Oral Med Pathol*. 2009;14:37–40.
40. Woźniak AW, Nowaczyk MT, Osmola K, Golusinski W. Malignant transformation of an osteoblastoma of the mandible: case report and review of the literature. *Eur Arch Otorhinolaryngol*. 2010;267:845–9.
41. Callejo Pérez P, Segura JJ. Osteoblastoma of mandible. *Int J Surg Pathol*. 2012;20:375–6.
42. Bokhari K, Hameed MS, Ajmal M, Togoo RA. Benign osteoblastoma involving maxilla: a case report and review of the literature. *Case Rep Dent*. 2012;2012:351241.
43. Harrington C, Accurso BT, Kalmar JR, Iwenofu OH, Agrawal A, Allen CM, et al. Aggressive osteoblastoma of the maxilla: a case report and review of the literature. *Head Neck Pathol*. 2011;5:165–70.
44. Kaur H, Verma S, Jawanda MK, Sharma A. Aggressive osteoblastoma of the mandible: a diagnostic dilemma. *Dent Res J*. 2012;9:334–7.
45. Lin B, Cai ZG, Yu GY, Jia LF. Osteoblastoma of the maxilla and mandible: a report of 2 cases and literature review. *Chin J Dent Res*. 2012;15:153–8.
46. More CB, Das SK, Bhavsar KS, Tailor MN. Benign osteoblastoma—an unusual rare clinical presentation. *J Adv Oral Res*. 2012;3:35–7.
47. Mahajan A, Kumar P, Desai K, Kaul RP. Osteoblastoma in the retromolar region—report of an unusual case and review of literature. *J Maxillofac Oral Surg*. 2013;12:338–40.
48. Shah S, Kim JE, Huh KH, Yi WJ, Heo MS, Lee SS. Recurrent osteoblastoma of the maxilla. *Dento-maxillofac Radiol*. 2013;42:20100263.
49. Sheikh S, Pallagatti S, Singla I, Kaur S, Aggarwal A. Osteoblastoma of mandible—a case report. *J Pioneer Med Sci*. 2014;4:60–3.
50. Theodorou DJ, Theodorou SJ, Sartoris DJ. Primary non-odontogenic tumors of the jawbones: an overview of essential radiographic findings. *Clin Imaging*. 2003;27:59–70.
51. Chrysomali E, Schoinohoriti O, Theologie-Lygidakis N, Goutzani L, Iatrou I. Malignant transformation of an osteoblastoma of the mandible: case report and review of the literature. *Open J Stomatol*. 2001;1:207–11.
52. Vinuth DP, Agarwal P, Gadewar D, Dube G, Dhirawani R. A large multifocal aggressive osteoblastoma of mandible: an immunohistochemistry case study report. *J Dent Res Dent Clin Dent Prospects*. 2014;8:51–5.
53. de Andrea CE, Bridge JA, Schiller A. Osteoblastoma. In: Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, editors. WHO classification of tumours of soft tissue and bone. 4th ed. Lyon: International Agency for Research on Cancer; 2013. p. 279–80.
54. Giannico G, Holt GE, Homlar KC, Johnson J, Pinnt J, Bridge JA. Osteoblastoma characterized by a three-way translocation: report of a case and review of the literature. *Cancer Genet Cytogenet*. 2009;195:168–71.
55. Baker AC, Rezeanu L, Klein MJ, Pitt MJ, Buecker P, Hersch JH, et al. Aggressive osteoblastoma: a case report involving a unique chromosomal aberration. *Int J Surg Pathol*. 2010;18:219–24.
56. Nord KH, Nilsson J, Arbajian E, von Steyern FV, Brosjö O, Cleton-Jansen AM, et al. Recurrent chromosome 22 deletions in osteoblastoma affect inhibitors of the Wnt/beta-catenin signaling pathway. *PLoS ONE*. 2013;8:e080725.
57. de Alava E, Lessnick SL, Sorenson PH. Ewing Sarcoma. In: Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, editors. WHO classification of tumours of soft tissue and bone. 4th ed. Lyon: International Agency for Research on Cancer; 2013. p. 306–9.
58. Potratz J, Dirksen U, Jurgens H, Craft A. Ewing sarcoma: clinical state-of-the-art. *Pediatr Hematol Oncol*. 2012;29:1–11.
59. Postel-Vinay S, Veron AS, Tirode F, Pierron G, Reynaud S, Kovar H, et al. Common variants near TARDBP and EGR2 are associated with susceptibility to Ewing sarcoma. *Nat Genet*. 2012;44:323–7.
60. Monument MJ, Johnson KM, McIlvaine E, Abegglen L, Watkins WS, Jorde LB, et al. Clinical and biochemical function of polymorphic NR0B1 GGAA-microsatellites in Ewing sarcoma: a report from the Children's Oncology Group. *PLoS ONE*. 2014;9:e104378.
61. Yu F, Miao J. Significant association between cytotoxic T lymphocyte antigen 4 +49G > A polymorphism and risk of malignant bone tumors. *Tumour Biol*. 2013;34:3371–5.
62. Keshani F, Jahanshahi G, Attar BM, Kalantari M, Razavi SM, Hashemzade Z, et al. Ewing's sarcoma in mandibular similar to dental abscess. *Adv Biomed Res*. 2014;3:62.
63. Davido N, Rigolet A, Kerner S, Gruffaz F, Boucher Y. Case of Ewing's sarcoma misdiagnosed as a periapical lesion of maxillary incisor. *J Endod*. 2011;37:259–64.

64. Brazão-Silva MT, Fernandes AV, Faria PR, Cardoso SV, Loyola AM. Ewing's sarcoma of the mandible in a young child. *Braz Dent J*. 2010;21:74–9.
65. Demetriades N, Prabhudev RK, Solomon LW, Shastri KA, Pa-pageorge MB. A clinico-pathologic correlation: primary Ewing's sarcoma of the mandibular body-ramus. *J Mass Dent Soc*. 2009;58:38–41.
66. Bornstein MM, von Arx T, Altermatt HJ. Loss of pulp sensitivity and pain as the first symptoms of a Ewing's sarcoma in the right maxillary sinus and alveolar process: report of a case. *J Endod*. 2008;34:1549–53.
67. Wexler LH, Kacker A, Piro JD, Haddad J Jr, Close LG. Combined modality treatment of Ewing's sarcoma of the maxilla. *Head Neck*. 2003;25:168–72.
68. Kanaya H, Hirabayashi H, Tanigaito Y, Baba K. Ewing's sarcoma/primitive neuroectodermal tumour of the mandible: report of a rare case and review of the literature. *J Otolaryngol*. 2007;36:E15–8.
69. Makary R, Tucker M, Fernandes RP, Shuja S. Unusual histological variant of Ewing's sarcoma of mandible. *Int J Oral Maxillofac Surg*. 2009;38:891–4.
70. Shibasaki M, Iwai T, Maegawa J, Inayama Y, Yokosuka T, Yokota S, et al. Mandibular Ewing sarcoma with chromosomal translocation t(21;22)(q22;q12). *J Craniofac Surg*. 2013;24:1469–72.
71. Steyn N, Heggie A, MacGregor D, Aldred MJ, Talacko AA, Coleman H, et al. Clinical pathologic conference case 4: a 15-year-old boy with radiographic changes in the left mandible. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2013;116:e71–5.
72. Yamaoka M, Akiyama M, Yokokawa Y, Terao Y, Yokoi K, Kato T, et al. Multidisciplinary therapy including proton beam radiotherapy for a Ewing sarcoma family tumor of maxillary sinus in a 4-year-old girl. *Head Neck*. 2013;35:E386–90.
73. Machado I, Noguera R, Mateos EA, Calabuig-Farinas S, Lopez FI, Martinez A, et al. The many faces of atypical Ewing's sarcoma. A true entity mimicking sarcomas, carcinomas and lymphomas. *Virchows Arch*. 2011;458:281–90.
74. Llombart-Bosch A, Machado I, Navarro S, Bertoni F, Bacchini P, Alberghini M, et al. Histological heterogeneity of Ewing's sarcoma/PNET: an immunohistochemical analysis of 415 genetically confirmed cases with clinical support. *Virchows Arch*. 2009;455:397–411.
75. Shibuya R, Matsuyama A, Nakamoto M, Shiba E, Kasai T, Hisaoka M. The combination of CD99 and NKX2.2, a transcriptional target of EWSR1-FLI1, is highly specific for the diagnosis of Ewing sarcoma. *Virchows Arch*. 2014;465:599–605.
76. Yoshida A, Sekine S, Tsuta K, Fukayama M, Furuta K, Tsuda H. NKX2.2 is a useful immunohistochemical marker for Ewing sarcoma. *Am J Surg Pathol*. 2012;36:993–9.
77. Machado I, Guerrero JAL, Navarro S, Mayordomo E, Scotlandi K, Picci P, et al. Galectin-1 (GAL-1) expression is a useful tool to differentiate between small cell osteosarcoma and Ewing sarcoma. *Virchows Arch*. 2013;462:665–71.
78. Machado I, Mayordomo-Aranda E, Scotlandi K, Picci P, Llombart-Bosch A. Immunoreactivity using anti-ERG monoclonal antibodies in sarcomas is influenced by clone selection. *Pathol Res Pract*. 2014;210:508–13.
79. Choi EY, Gardner JM, Lucas DR, McHugh JB, Patel RM. Ewing sarcoma. *Semin Diagn Pathol*. 2014;31:39–47.
80. Flaitz C, Hicks J. Genital Ewing sarcoma of the head and neck with novel EWS-NFATc2. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2011;111:e50–1.
81. Kovar H. Blocking the road, stopping the engine or killing the driver? Advances in targeting EWS/FLI-1 fusion in Ewing sarcoma as novel therapy. *Expert Opin Ther Targets*. 2014;18:1315–28.
82. Womer RB, West DC, Krailo MD, Dickman PS, Pawel BR, Grier HE, et al. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. *J Clin Oncol*. 2012;30:4148–54.
83. Miller BJ, Lynch CF, Buckwalter JA. Conditional survival is greater than overall survival at diagnosis in patients with osteosarcoma and Ewing's sarcoma. *Clin Orthop Relat Res*. 2013;471:3398–404.
84. Amaral AT, Ordonez JL, Otero-Motta AP, Garcia-Dominguez DJ, Sevillano MV, de Alava E. Innovative therapies in Ewing sarcoma. *Adv Anat Pathol*. 2014;21:44–62.
85. Kovar H, Alonso J, Aman P, Aryee DN, Ban J, Burchill SA, et al. The first European interdisciplinary Ewing sarcoma research summit. *Front Oncol*. 2012;2:54.
86. van Doorninck JA, Ji L, Schaub B, Shimada H, Wing MR, Krailo MD, et al. Current treatment protocols have eliminated the prognostic advantage of type 1 fusions in Ewing sarcoma: a report from the Children's Oncology Group. *J Clin Oncol*. 2010;28:1989–94.
87. Shukla N, Schiffman J, Reed D, Davis IJ, Womer RB, Lessnick SL, et al. Biomarkers in Ewing sarcoma: the promise and challenge of personalized medicine. A report from the Children's Oncology Group. *Front Oncol*. 2013;3:141.
88. Szuhai K, Ijszenga M, de Jong D, Karseladze A, Tanke HJ, Hogendoorn PC. The NFATc2 gene is involved in a novel cloned translocation in a Ewing sarcoma variant that couples its function in immunology to oncology. *Clin Cancer Res*. 2009;15:2259–68.
89. Yamaguchi S, Yamazaki Y, Ishikawa Y, Kawaguchi N, Mukai H, Nakamura T. EWSR1 is fused to POU5F1 in a bone tumor with translocation t(6;22)(p21;q12). *Genes Chromosom Cancer*. 2005;43:217–22.
90. Sumegi J, Nishio J, Nelson M, Frayer RW, Perry D, Bridge JA. A novel t(4;22)(q31;q12) produces an EWSR1-SMARCA5 fusion in extraskeletal Ewing sarcoma/primitive neuroectodermal tumor. *Mod Pathol*. 2011;24:333–42.
91. Mastrangelo T, Modena P, Tornelli S, Bullrich F, Testi MA, Mezzelani A, et al. A novel zinc finger gene is fused to EWS in small round cell tumor. *Oncogene*. 2000;19:3799–804.
92. Wang L, Bhargava R, Zheng T, Wexler L, Collins MH, Roulston D, et al. Undifferentiated small round cell sarcomas with rare EWS gene fusions: identification of a novel EWS-SP3 fusion and of additional cases with the EWS-ETV1 and EWS-FEV fusions. *J Mol Diagn*. 2007;9:498–509.
93. Richkind KE, Romansky SG, Finklestein JZ. t(4;19)(q35;q13.1): a recurrent change in primitive mesenchymal tumors? *Cancer Genet Cytogenet*. 1996;87:71–4.
94. Sugita S, Arai Y, Tonooka A, Hama N, Totoki Y, Fujii T, et al. A novel CIC-FOXO4 gene fusion in undifferentiated small round cell sarcoma: a genetically distinct variant of Ewing-like sarcoma. *Am J Surg Pathol*. 2014;38:1571–6.
95. Riccardi GF, Stein C, de la Roza G, Damron TA. Newly described translocation (18;19)(q23;q13.2) in abdominal wall soft-tissue tumor resembling Ewing sarcoma/primitive neuroectodermal tumor. *Cancer Genet Cytogenet*. 2010;201:1–5.
96. Pierron G, Tirode F, Lucchesi C, Reynaud S, Ballet S, Cohen-Gogo S, et al. A new subtype of bone sarcoma defined by BCOR-CCNB3 gene fusion. *Nat Genet*. 2012;44:461–6.
97. Brohl AS, Solomon DA, Chang W, Wang J, Song Y, Sindiri S, et al. The genomic landscape of the Ewing sarcoma family of tumors reveals recurrent STAG2 mutation. *PLoS Genet*. 2014;10:e1004475.