

Review Article

Periosteal osteosarcoma: a review of clinical evidence

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Abstract: Periosteal osteosarcoma (PO) is a rare primary malignant bone tumor and a variant of osteosarcoma. It is a surface lesion without evidence of medullary involvement. The radiologic appearance of periosteal osteosarcoma is a broad-based surface soft-tissue mass that causes extrinsic erosion of thickened underlying diaphyseal cortex and perpendicular periosteal reaction extending into the soft-tissue component. The tumour presents as non-homogeneous masses of speculated osteoid matrix progressively denser from the periphery to their cortical base. The average age is around 28 and the most common location is the proximal third of the femur; with all the lesions diaphyseal in location. The treatment usually indicated is amputation, but in selected cases, radical segmental resection is appropriate. Long-term disease-free survival is possible after resection of the local recurrence. Limb-salvage therapy seems to offer survival equivalent to amputation, and there does not seem to be a substantial risk of late recurrence, dedifferentiation, or disease progression. The current review also highlights on various rare occurrences of periosteal osteosarcoma including the one of calcaneum, fifth metatarsal, mandible cranium, jaws, clavicle, maxilla, sphenoid bone with extensive periosteal extension, metacarpal in a paediatric age group and bilateral metachronous periosteal osteosarcoma. Recent findings relating to genetic factors governing the pathogenesis of PO is also presented.

Keywords: Periosteal osteosarcoma

Introduction

Periosteal osteosarcoma (PO) is a rare primary malignant bone tumour and is a variant of osteosarcoma. It is a surface lesion without evidence of medullary involvement. It was first recognized by Ewing in 1939 and later described by various other authors. Lichtenstein in 1959 described periosteal osteosarcoma as a periosteal counterpart of central or inter-medullary osteosarcoma [1]. As high-grade osteosarcoma, PO affects young patients (i.e. those in 2nd and 3rd decades of life) and most frequent locations are tibia (40%) and femur (38%), followed by ulna and humerus (5-10%).

Diagnosis

The tumors in PO show variable imaging appearances at the site of the diaphyseal lesion of tibia and femur. Imaging appearances of periosteal sarcoma are done by various imaging techniques including radiography, computed

tomography, and magnetic resonance imaging. These techniques are used for detecting the location of tumor, size, cortical changes, medullary involvement and characteristics of tumor.

Radiography

The radiological appearance of periosteal osteosarcoma have been reported to present a broad based surface soft tissue mass, leading to extrinsic erosion of thickened diaphyseal cortex along with periosteal reaction, which invades into the soft tissue component. The periosteal reaction is predominantly perpendicular to the diaphyseal cortex. Radiography findings include thickening of the diaphyseal cortex with scalloping and perpendicular periosteal reaction extending into broad based soft tissue mass. The most commonly occurring periosteal reaction is non-aggressive, and solid in nature. Radiography also reveals the extent of mineralization in to soft tissue mass (mild, moderate, marked). The maturity and extent of mineraliza-

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Table 1. Differential diagnosis of Periosteal osteosarcoma from other carcinomas

Periosteal osteosarcoma	Parosteal osteosarcoma
Purely cortical lesion, thickened intact cortex is visible	No such observation
Spiculated matrix, which is osteoid in nature and radiates out from the cortex	No such observation
No such observation	Neoplasm often outgrows the base of origin and has a tendency to wrap around the cortex
2:1 Male preponderance	Female preponderance
The age group falls in between the medullary and parosteal types	Tumor incidence is high in 3 rd and 4 th decades of life
It is a cartilaginous osteosarcoma	It is fibrogenic osteosarcoma
Periosteal osteosarcoma	Central cancellous osteosarcoma
Significant male preponderance	Slight male preponderance
Periosteal osteosarcoma	Ewing's sarcoma
The amount of soft tissue component is in similar proportion to amount of ossified matrix	The soft tissue component is large in comparison to the bone involvement
Periosteal osteosarcoma	Myositis ossificans
No similar observations	A predictable biological pattern of maturation is evident from periphery to centre
Inner table is intact	Metastatic lesion involves the cortex from periosteum to the medullary cavity

tion in the soft tissue component is also examined by the radiography.

Computed tomography (CT)

Computed tomography (CT) technique is useful for detecting the presence of any soft tissue mass adhered to the cortex, any associated aberrations in medullary canal, cortex thickening, cortical scalloping, and any periosteal reaction perpendicular to diaphysis and extending into the soft tissue mass. CT is also used for the attenuation and homogeneity of the non-mineralized component of soft tissue mass. The CT can also evaluate calcification of the soft tissue mass.

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) is used for the presence of a soft tissue mass adhered to the cortex, any associated aberrations in medullary canal, cortex thickening, cortical scalloping, periosteal reaction perpendicular to diaphysis and extending into the soft tissue mass. It is also used to detect the presence and extent of mineralization in the soft tissue mass and percentage of the circumference of the cortex

surrounded by the soft tissue mass. The signal intensity and homogeneity of the non-mineralized component of the soft tissue mass is evaluated by this technique [2].

Differential diagnosis

Differential diagnosis of PO is important to elucidate the nature of osteosarcoma. Often histological and morphological findings mingle and may lead to misleading classification of osteosarcoma. PO may be confused with Ewing's, central cancellous, parosteal or central cancellous carcinomas due to closely resembling histological or radiological findings. Often small round tumors, particularly Ewing's sarcoma, may be present as a spiculated lesion in the cortical bone. In such cases, a permeative destructive lesion indicates Ewing's sarcoma whereas such observations are not reported in PO. Further, differential diagnosis of central osteosarcoma, parosteal osteosarcoma and PO is of immense clinical significance and is often guided by clinical radiographic diagnostic features. A central cancellous osteosarcoma is a central destructive lesion with varying amounts of osteoid matrix, is radiographically discernable. The tumor is aggressive with poor-

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Table 2. The major pathological features of PO

Sr. No.	Location	Author	Major findings
1	Cranium	Robertson and Newman, 2000 [29]	i. Reticular growth pattern of osteoblast with associated lace like strands of osteoid.
2	Bilateral metachronous periosteal osteosarcoma	Howat <i>et al.</i> , 1986 [10]	i. Destruction of outer cortex with an association of soft tissue matrix ii. Calcification in upper right femur iii. Lacy seams of osteoid present between tiny anaplastic cells
3	Mandible	Koyama <i>et al.</i> , 2002 [14]	i. An intact cortex and presence of medullary tumor
4	Calcaneum	Singh <i>et al.</i> , 2012 [31]	i. Atypical woven bone/ malignant osteoid ii. Nodular aggregates and osteoblast clusters indicating nuclear atypia at the periphery iii. Spindle shaped cells and chondroid cells with hyperchromatic nuclei and cartilagenous nodules along with new bone formation
5	Jaws	Piattelli and Favia 2000 [27]	i. Newly formed osteoid tissue with initial foci of calcification, osteoblast and spindle shaped cells ii. Presence of chondroblastic differentiation with moderately differentiated malignant bone, osteoid, and spindle cells
6	Fifth metatarsal of foot	Mohammadi <i>et al.</i> , 2011 [20]	i. Typical sunburst periosteal reaction in lateral surface of a signal fifth metatarsal bone
7	Metacarpal in paediatrics	Muir <i>et al.</i> , 2008 [21]	i. A primary chondroblastic lesion with cellular proliferation and atypia
8	Maxilla	Patterson <i>et al.</i> , 1990 [26]	i. The mass showed a glistening, granular, gritty, polypoid piece of soft tissue. ii. A richly cellular stroma composed of spindle shaped cells was visible. iii. Spindle shaped polyhedral cells with hyperchromatic nuclei consistent with malignant osteoblast were interspersed throughout stroma.
9	Sphenoid Bone	Hayashi <i>et al.</i> , 2000 [9]	i. Hypovascular lesion ii. Proliferation along the bone marrow spaces with negligible destruction of cranial bone. iii. Diffused proliferation of spindle shaped polygonal cells with nuclear atypia confirmed periosteal osteosarcoma
10	Clavicle	Lim <i>et al.</i> , 2012 [16]	i. Tumour composed of immature necrotic osteoids and necrotic chondroids. ii. Saucerisation accompanied by periosteal reaction and Codman's triangle iii. Atypical cells engrained in the chondroid matrix with hypercellular foci, bearing tiny hyperchromatic nuclei, unclear eosinophilic cytoplasm and cellular spindling
11	Tibia (Bilateral synchronous tibial periosteal osteosarcoma)	Maheshwari <i>et al.</i> , 2012 [17]	i. Bilateral synchronous tibial periosteal osteosarcoma ii. Cortical based sclerotic lesion on the antero-medial aspect of the proximal tibia with irregular erosion of the outer cortex iii. Osteogenic area of the tumor showed malignant osteoid production

ly defined matrix and damaged cortex. In parosteal osteosarcoma, a radiolucent zone between tumor and the bone of origin indicates a void between tumor mass, outgrowing its pedicle and cortex of the normal bone. The medullary cavity is violated and daughter mass is frequently observed. There is a mushrooming

mass attached with a thick pedicle, which circumvents the shaft of origin and often invades the medullary cavity. However, these findings are not mirrored in PO [3]. The primary differences between various types of osteosarcomas and periosteal osteosarcoma have been outlined in the **Table 1**.

Clinical symptoms

The prominent clinical symptomatology includes swelling accompanied by pain. Due to sluggish growth, tumor symptoms may be present years before the first surgical intervention. The duration of symptoms is modulated by the growth of neoplasm.

Risk factors

Various factors which have been identified defining the predilection of periosteal osteosarcoma encompass age, gender and site of tumor.

Gender: There is no clinical evidence advocating a significant predilection [4].

Age: This has been proven to be a significant factor affecting the incidence of periosteal osteosarcoma. The peak incidence of periosteal osteosarcomas been reported to 15-30 years.

Site of tumour: Periosteal osteosarcoma is primarily located in the long bones of limbs. The major areas involve femur, tibia, humerus, radius, fibula, ulna and phalanx.

Location of PO

PO is exclusively located in the long bones of limbs. The major areas involve femur, tibia, humerus, radius, fibula, ulna and phalanx. The lesion is primarily metaphyseal and rarely diaphyseal. Posterior aspect of distal femur, upper metaphysis in the tibia and humerus comprise the frequent location of periosteal osteosarcoma [5]. Bertoni *et al* [6] described mid uppermost and lowermost diaphysis of tibia, and femur to be the primary location of PO. Some of the rare occurrence sites of PO are described below and the major pathological features have been mentioned in **Table 2**.

Cranium

Robertson and Newman [7] demonstrated cranial PO in their pioneer investigation. They presented PO cases arising from the outer table of the skull in the vicinity of occiput. The morphology indicated a spiculated pattern of calcification [7].

Bilateral metachronous periosteal osteosarcoma

The pioneer investigation by Howat *et al.* [8] demonstrated bilateral metachronous PO. The biopsy indicated femoral soft tissue lesions showing lobular cartilaginous tumor invading into connective tissue. The femoral lesion also demonstrated a predominant cartilaginous tumor involving connective tissue and skeletal muscles.

Mandible

PO of mandible was demonstrated by Koyama *et al.* [9]. The findings indicated progression of tumor into bone marrow via periodontal ligament. The lesion extended within the body of mandible and buccal cavity. However, the lesions encompassed periodontal ligament space sparing the buccal cortex. A mass of poorly differentiated cartilaginous stroma accompanied by tumor invasion into the bone marrow along periodontal ligament was also shown. There was discernable involvement of intramedullary extensions which was reported for the first time differentiating it from the preceding reports [10, 11].

Calcaneum

Singh *et al.* [12] demonstrated PO of calcaneum. The morphological feature concluded a well-defined mass arising from calcaneum tuberosity. The features presented in this investigation were in concert with previous findings of Ritts *et al.* [13], where PO was shown to assess with strands of osteoid producing spindle shape cells radiating between lobules of cartilage.

Jaws

Piattelli and Favia [14] reported PO of jaws. The findings showed that the tumor were characterised by presence of moderately differentiated chondroblastic tumor with foci of osteoid and bone formation.

Fifth metatarsal of foot

Mohammadi *et al.* [15] described a rare case of PO localized to foot. The findings also demonstrated large hyperchromatic, pleomorphic cartilage cell. This was the pioneer report showing localisation of PO in foot.

Metacarpal in paediatrics

Muier *et al.* [16] reported a case of PO of the hand of a paediatric patient. A firm, fixed, and mildly tender mass on the dorsal aspect of first metacarpal was reported. The mass was sans fluctuance skin abnormality and was associated with lymph adenopathy. The lesion was located on the surface of metatarsal, close to proximal physis. Island of primitive osteoid formation with poorly differentiated spindle cells, reported in a previous study [17], demonstrated PO of hand. These studies provide evidence that PO can occur in the hands of paediatric population. This may be the immense value when patients present suspicious bone forming lesion in the hand.

Maxilla

PO of maxilla is primary juxtacortical in nature, which can be either parosteal or periosteal [18]. Patterson *et al.* [19] described PO of maxilla. The tumor was composed of well organised trabeculae of lamellar bone which invaded the cortical plate of maxilla. Malignant tumor osteoid was reported in between chondroid and cocious trabeculae. The histopathology revealed malignant tumor osteoid arising proximal to pleomorphic osteoblast. PO of maxilla seems to possess more favorable prognosis than in long bones due to more aggressive biologic behaviour of the osteosarcoma.

Sphenoid bone

Hayashi *et al.* [20] reported a PO of sphenoid bone. A ring enhanced mass in the right temporal lobe with perifocal brain edema was observed. An extra cranial mass including the temporalis muscle and an enhanced mass in the orbit was also reported. The sphenoid bone showed moderate hypertrophic changes but was devoid of bone destruction.

Clavicle

Lim *et al.* [21] reported a rare case of PO of clavicle. A focal evidence of cortical erosion with negligible medullary component was observed. PO was confirmed with 95% necrotic structures in the tumor. A negligible medullary invasion was recorded. This was the second case of PO of clavicle after Oda *et al.* [22] A soft tissue mass bearing a calcified matrix was also evident. The clavicle is a rare site for PO

because of its biology. The clavicle starts to ossify prior to any other bone in the human body hence, the chances of PO of clavicle are minimal in general population.

Bilateral synchronous tibial periosteal osteosarcoma with familial incidence

A recent report by Maheshwari *et al.* [23] revealed a rare case of bilateral synchronous tibial PO. The tissue fragments indicated a predominantly cartilaginous composition with malignant features equivalent to grade II/III chondrosarcoma. The chondroblastic regions were segregated by sarcomatous cells showing osteoid production and immature bone which led to a diagnosis of bilateral intermediate grade PO. A needle core biopsy demonstrated an osteosarcoma with chondroblastic and osteoblastic features consistent with an intermediate-grade periosteal osteosarcoma.

Prognosis

The prognosis of PO is governed by various factors. These encompass the anatomical location of tumors, degree of invasion into the cortex and medulla and histological grade of malignancy [5]. Similar prognosis rates were reported in patients suffering with tumor located proximally or distally. This trend was extrapolated periosteal osteosarcoma patients presenting femoral and non-femoral tumors [24].

Metastatic periosteal osteosarcoma

Metastasis is an inevitable phenomenon associated with all forms of oncogenic proliferations. PO has been associated with metastatic tumour formations. In a pioneer report of metastatic PO, by Dash *et al.* [25], a patient with periosteal osteogenic sarcoma with intravascular metastases died with cardiac and renal failure [25]. Multifocal periosteal osteosarcoma are very rare and have been reported only in metachronous mode. Howat *et al.* [8] reported a case of periosteal osteosarcoma of the femur with a metachronous periosteal lesion in the contralateral femur after 3 years. However, the patient suffered with multiple lung metastases over the next 6 months. Barakat *et al.* [26] reported a case of periosteal OS of the tibia that which was treated by wide excision and a fibular graft. Two years later, the patient developed a metachronous lesion just below the fib-

ular graft. In a study by Grimer *et al.* [27], the combined members of the European Musculoskeletal Oncology Society, 17 of the 119 patients with periosteal osteosarcoma developed metastasis. Of these, 16 had lung metastasis and only one had intramedullary metastasis to the bone in contralateral leg. Jaffe *et al.* [28] described a case of periosteal OS with a metachronous osteoblastic intramedullary lesion in the contralateral femur after 3 years. This patient died 12 months later with pulmonary and intracranial metastases. These studies suggest that osteosarcoma possesses a prominent metastatic component which is devoid of any preference for a particular organ system.

Treatment

Adequate surgical treatment is indispensable for tumor control. If surgical treatment is timely and adequate, the survival rate is increased and metastasis significantly reduced. The treatment of periosteal osteosarcoma consists primarily of surgical interventions, which may or may not be accompanied by chemotherapeutic interventions. Surgical treatment comprises amputation, limb salvation, and resection.

Amputation

The amputation of upper extremities or regions above/below the knee may be carried out to provide remission to the patient. Hemipelvectomy or disarticulation may also accompany such procedures. In case of large and recurrent tumor, where radiographic evidence demonstrates involvement of medullary spaces or histological indication of malignancy, amputation is treatment of choice. A secondary amputation may have to be carried out if recurrence were noticed in an amputation stump.

Resection

Resection may be classified into either localised excision or segmental resection. Segmental selection is generally advised if the tumor size is small, its nature non-recurrent, and it does not invade cortex and medullary spaces. A marginal excision may also be carried out along with a secondary wide excision, if a recurrence of PO occurs.

Salvation therapy

In case of inadequate tumor control, evident by frequent local recurrence at the marginal or intra lesion involvement, limb salvage technique may provide disease alleviation. Limb salvation techniques are appropriate in tumor remission when wide margins are available. The limb sacrificing surgery may be substituted with limb sparing procedures without imperative need of reoperation when limb salvage procedures are used to treat the tumor.

Chemotherapy

Adjuvant chemotherapy may be prescribed to provide pharmacological support to surgical procedures. An adjuvant cisplatin and doxorubicin regimen has been occasionally prescribed but the outcome remains inconclusive. The patients are prescribed chemotherapeutic regimens with the caveat of its uncertain benefits. The findings of Cesari *et al.* [29] recently demonstrated the inability of chemotherapeutic agents to halt reverse or alleviate PO and enhances probability of survival.

Pre operative investigations to establish the involvement of medullary cancer is indispensable before carrying out any surgical procedures, which may be determined using well-defined CT (computer tomography). Usually a conservative treatment is advocated to treat PO. Generally a marginal excision maybe insufficient, elucidating the need of wide surgical excision which may or may not involve amputation. The reason for such guidelines is insufficiency of marginal excision to elude recurrence. Primary wide excision is effective in inhibiting recurrence but suffers from contamination and uncontrolled spread of tumour in to surrounding tissues in case of previous biopsy.

Role of genetic factors

In a recent report, of bilateral synchronous tibial PO was described by Maheshwari *et al.* [30] where the pathogenesis of PO two patients belonging to same family was directed towards a TP53 mutation. Direct sequencing of exons 5 through 8 demonstrated missense mutation in at least one allele of the TP53 gene (exon 8). A connection with Li-Fraumeni Syndrome was suspected and both the cases are under follow

up currently. TP53 is one of the most commonly mutated genes in human cancer and mutations leading to inactivation of TP53 are common in osteosarcoma tumorigenesis [31]. TP53 plays a crucial role in a number of pathways related to cellular stress, DNA repair, and apoptosis [32]. TP53 is regulated by MDM2, a protein that blocks the activity of the TP53 protein by directing it to the ubiquitin-mediated degradation pathway which in turn is linked to Wnt signaling via a number of pathways punctuated with p14ARF, CHK2, Dkk1, LRP5 [33-35].

It is known that Wnt signaling plays an important role in aggravation of osteosarcoma tumorigenesis by downregulating repair of the surrounding bone and by enhancing the motility and invasiveness of the tumor cell signaling via Wnt pathway is decisive for differentiating progenitor cells into osteoblasts. When Wnt signaling is inhibited, mesenchymal stem cells enter the cell cycle and osteogenesis is halted. Dickkopf 1 (DKK1) disturbs the Wnt signaling cascade leading to inhibition of osteogenesis [36]. A similar genetic derangement may be implicated in precipitation and aggravation of PO. The recent findings of Maheshwari *et al* [23] depicting the genetic origin of periosteal osteosarcoma may be a new facet for further research in this domain and may open novel avenues of treatment regimens to assure complete remission of PO.

Conclusion

The clinical evidence suggests that PO needs to be treated using well defined surgical procedures instead of chemotherapeutic intervention to ensure complete remission and elude chances of relapse. Investigation of genetic factors contributing to the pathogenesis must be examined using the state of the art technology to unravel the underlying cause of PO during initial phases of diagnosis and care.

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Disclosure of conflict of interest

None.

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References

- [1] Lichtenstein L. Tumors of periosteal origin. *Cancer* 1955; 8: 1068-9.
- [2] Murphey MD, Jelinek JS, Temple HT, Flemming DJ and Gannon FH. Imaging of periosteal osteosarcoma: radiologic-pathologic comparison. *Radiology* 2004; 233: 129-38.
- [3] DeSantos LA, Murray JA, Finklestein JB, Spjut HJ and Ayala AG. The radiographic spectrum of periosteal osteosarcoma. *Radiology* 1978; 127: 123-9.
- [4] Dahlin DC and Coventy MB. Osteogenic sarcoma: a study of six hundred cases. *J Bone Joint Surg Am* 1967; 49: 101-10.
- [5] Comapanacci M and Giunti A. Periosteal osteosarcoma: Review of 41 cases, 22 with long-term follow-up. *Ital J Orthop Traumatol* 1976; 2: 23-35.
- [6] Bertoni F, Boriani S, Laus M and Campanacci M. Periosteal chondrosarcoma and periosteal osteosarcoma. Two distinct entities. *J Bone Joint Surg Br* 1982; 64: 370-6.
- [7] Robertson NJ and Newman PL. Periosteal osteosarcoma of the cranium. *Ann Diagn Pathol* 2000; 4: 300-2.
- [8] Howat AJ, Dickens DR, Boldt DW, Waters KD and Campbell PE. Bilateral metachronous periosteal osteosarcoma. *Cancer* 1986; 58: 1139-43.
- [9] Koyama J, Ito J and Hayashi T. Periosteal osteosarcoma of the mandible. *Dentomaxillofac Radiol* 2002; 31: 63-4.
- [10] Minic AJ. Periosteal osteosarcoma of the mandible. *Int J Oral Maxillofac Surg* 1995; 24: 226-8.
- [11] Zarbo JR and Baker RS. Periosteal osteogenic sarcoma of the mandible. *Oral Surg Oral Med Oral Pathol* 1984; 57: 643-7.
- [12] Singh D, Sen R, Chaudhary S and Tripathy SK. Periosteal osteosarcoma of the calcaneum: a case report. *Foot Ankle Spec* 2012; 5: 121-3.
- [13] Ritts GD, Pritchard DJ, Unni KK, Beabout JW and Eckardt JJ. Periosteal osteosarcoma. *Clin Orthop Relat Res* 1987; 219: 299-307.
- [14] Piattelli A and Favia GF. Periosteal osteosarcoma of the jaws: report of 2 cases. *J Periodontol* 2000; 71: 325-9.
- [15] Mohammadi A, Porghasem J, Noroozinia F, Ilkhanizadeh B, Ghasemi-Rad M and Khenari S. Periosteal osteosarcoma of the fifth meta-

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- tarsal: a rare pedal tumor. *J Foot Ankle Surg* 2011; 50: 620-2.
- [16] Muir TM, Lehman TP and Meyer WH. Periosteal osteosarcoma in the hand of a pediatric patient: a case report. *J Hand Surg Am* 2008; 33: 266-8.
- [17] Okada K, Wold LE, Beabout JW and Shives TC. Osteosarcoma of the hand. A clinicopathologic study of 12 cases. *Cancer* 1993; 72: 719-25.
- [18] Zarbo JR and Baker RS. Periosteal osteogenic sarcoma of the mandible. *Oral Surg Oral Med Oral Pathol* 1984; 57: 643-7.
- [19] Patterson A, Greer RO Jr and Howard D. Periosteal osteosarcoma of the maxilla: a case report and review of literature. *J Oral Maxillofac Surg* 1990; 48: 522-6.
- [20] Hayashi T, Kuroshima Y, Yoshida K, Kawase T, Ikeda E and Mukai M. Primary osteosarcoma of the sphenoid bone with extensive periosteal extension—case report. *Neurol Med Chir (Tokyo)* 2000; 40: 419-22.
- [21] Lim C, Lee H, Schatz J, Alvaro F, Boyle R and Bonar SF. Case report: periosteal osteosarcoma of the clavicle. *Skeletal Radiol* 2012; 41: 1011-5.
- [22] Oda Y, Hashimoto H, Tsuneyoshi M and Masuda S. Case report 793. Periosteal osteosarcoma of the clavicle. *Skeletal Radiol* 1993; 22: 375-7.
- [23] Maheshwari AV, Jelinek JS, Seibel NL, Meloni-Ehrig AM, Kumar D and Henshaw RM. Bilateral synchronous tibial periosteal osteosarcoma with familial incidence. *Skeletal Radiol* 2012; 41: 1005-9.
- [24] Rose PS, Dickey ID, Wenger DE, Unni KK and Sim FH. Periosteal osteosarcoma: long-term outcome and risk of late recurrence. *Clin Orthop Relat Res* 2006; 453: 314-7.
- [25] Dash H, Little JR, Zaino R, Colao DJ, Chaurushiya P, Schoolwerth AC, O'Neill MJ, Hart JC, Martin GB. Metastatic periosteal osteosarcoma causing cardiac and renal failure. *Am J Med* 1983; 75: 145-9.
- [26] Barakat MJ, Collins C, Dixon JH. Distal recurrence of periosteal osteosarcoma after complete excision of proximal primary tumour with good excision margins. *Sarcoma* 2003; 7: 79-80.
- [27] Grimer RJ, Bielack S, Flege S, Cannon SR, Foleas G, Andreeff I, Sokolov T, Taminiau A, Dominkus M, Julian MS, Kollender Y, Gosheger G. European Musculo Skeletal Oncology Society. Periosteal osteosarcoma—a European review of outcome. *Eur J Cancer* 2005; 41: 2806-11.
- [28] Jaffe N, Pearson P, Yasko AW, Lin P, Herzog C and Raymond K. Single and multiple metachronous osteosarcoma tumors after therapy. *Cancer* 2003; 98: 2457-66.
- [29] Cesari M, Alberghini M, Vanel D, Palmerini E, Staals E, Longhi A, Abate M, Ferrari C, Balladli A, Ferrari S. Periosteal osteosarcoma: a single-institution experience. *Cancer* 2011; 117: 1731-5.
- [30] Maheshwari AV, Jelinek JS, Seibel NL, Meloni-Ehrig AM, Kumar D and Henshaw RM. Bilateral synchronous tibial periosteal osteosarcoma with familial incidence. *Skeletal Radiol* 2012; 41: 1005-9.
- [31] Toledo F and Wahl GM. Regulating the p53 pathway: in vitro hypotheses, in vivo veritas. *Nat Rev Cancer* 2006; 6: 909-23.
- [32] Stiewe T. The p53 family in differentiation and tumorigenesis. *Nat Rev Cancer* 2007; 7: 165-8.
- [33] Kawaguchi K, Oda Y, Sakamoto A, Saito T, Tamiya S, Iwamoto Y, Tsuneyoshi M. Molecular analysis of p53, MDM2, and H-ras genes in osteosarcoma and malignant fibrous histiocytoma of bone in patients older than 40 years. *Mod Pathol* 2002; 15: 878-88.
- [34] Wei G, Lonardo F, Ueda T, Kim T, Huvos AG, Healey JH and Ladanyi M. CDK4 gene amplification in osteosarcoma: reciprocal relationship with INK4A gene alterations and mapping of 12q13 amplicons. *Int J Cancer* 1999; 80: 199-204.
- [35] Zhang Y and Xiong Y. Control of p53 ubiquitination and nuclear export by MDM2 and ARF. *Cell Growth Differ* 2001; 12: 175-86.
- [36] Niehrs C. Function and biological roles of the Dickkopf family of Wnt modulators. *Oncogene* 2000; 25: 7469-81.