# Osteosarcoma. Review of Literature

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## Abstract

Osteosarcoma is the most common primary malignant bone tumor, predominantly occurring in long bones and occasionally in the maxillofacial region. In the maxillofacial region, approximately 5% of OS starts in maxillary bones while the mandible is the most involved site. OS of the maxilla usually involves adults with ages ranging between the third and fourth decades of life. In addition, metastasis are rare and the prognosis is significantly better when compared to its counterpart in long bones. However, the World Health Organization (WHO) listed several variants that differ in location, clinical behavior and level of cellular atypia. The conventional or classical osteosarcoma is the most frequent variant, which develops in the medullary region of the bone and can be subdivided in osteoblastic, chondroblastic and fibroblastic histological types, depending on the type of extra-cellular matrix produced by tumour cells. The aim of this literature review is to provide information about osteosarcoma for further education in this field

Key words: Osteosarcoma, WHO, Classification

**Introduction**

Osteosarcoma is a primary intramedullary high grade malignant tumour in which the neoplastic cells produce osteoid, even in only small amount and represent a heterogenous group of tumours with different histologic and clinical features, biologic behavior and therapy. Osteosarcomas are subclassified by WHO into many variants that differ in location, clinical presentation and histopathological features such as conventional osteosarcoma, (osteoblastic, chondroblastic and fibroblastic), telangiectatic osteosarcoma, small cell osteosarcoma, low grade osteosarcoma, secondary osteosarcoma, praosteal osteosarcoma, priosteal osteosarcoma, and high grade surface osteosarcoma (1,2,3).

**Epidemiology and aetiology .** Osteosarcoma is the most common primary malignant bone tumor (2) , by definition, an osteosarcoma is a neoplasm in which osteoid is synthesized by malignant cells. Conventional osteosarcoma accounts for 90 % of all osteosarcomas. It begins in the medullar canal and some times penetrates the cortex and invades the adjacent soft tissues (1,2). Osteosarcoma, usually affects children and young adults with estimated incidence of 4-5 per million population, and appears to be there is no significant association with ethnic group or race (1) . Moreover, the neoplasm is extremely rare in young children. It most frequently

The precise aetiology of OS remains unknown due to lack of understanding of the cell or origin, the absence of identifiable precursor lesions, its marked genetic complexity at the time of presentation and most of OS contain clonal chromosomal aberrations, that the aberrations are complex, comprising an abundance of numerical and structural alterations. The estimated incidence of OS is about 4-5 per million population and there dose not to be significant association with ethnic group or race. OS is largely a disease of young adults, where it most frequently occurs in the second decade with some 60% of patients under the age of 25 years. It appears that males are affected 1.5 to 2 times as frequently as females.(2,3,4).

occurs in the second decade of life with some 60% of patients under the age of 25 years, although 30% of osteosarcomas occur in patients over 40 years of age (2,3,4).

Although, many osteosarcomas have predisposing factors such as Paget's disease of bone, prior radiation therapy, osteoblastoma, osteochondroma, fibrous dysplasia, osteomyelitis, endoprosthesis implantation, Rothmund-Thomson syndrome and Li-Fraumeni syndrome , which all have been linked with osteosarcoma, but the precise aetiology remains unknown. Osteosarcoma affects males more frequently than females in a ratio of 3:2 especially in patients under the age of 20 years. However, about 91% of conventional osteosarcoma occurs in the metaphysis while about 9% occurs in diaphysis , although primary involvement of the epiphyses is extremely rare (5,6,7,8,9,10,11,12).

**Sites of involvement.** In younger patients conventional osteosarcoma most commonly occurs in the long bones, in particular, the distal femur, proximal tibia, proximal humerus and around the knee. By contrast, older patients tends to develop osteosarcoma more frequently in non-long bones such as jaws , pelvis, spine and skull, while osteosarcoma arising in bones distal to the wrists and ankles is extremely rare (13,14).

**Clinical and radiological features.** Pain with or without a palpable mass , tenderness, or swelling rarely occurring for more than a few months, are the usual presenting symptoms. Pain is usually deep, boring and severe, other findings may include limitation of normal function, oedema, localized warmth, tellangectasias and pathological fracture. In the jaws, osteosarcoma is slightly more common in the mandibular than maxilla. The tumours presents as rapidly enlarging swelling that may be accompanied by pain, numbness of the lip, trismus, and displacement and loosening of teeth. Nasal obstruction and symptoms referable to the eye may also be features of maxillary tumours (13,14,15,16).

The overall radiographic features of osteosarcoma is variable and depends on the amount of normal bone destroyed by the tumour and the amount of neoplastic bone formed within the lesion. However, the lesion may be purely osteoblastic, osteolytic or mixed lytic/blastic lesion. Moreover, The lesion may appear as as a poorly circumscribed medullary radiolucencey with mottled areas of radiodense and cortical bone destruction with a focally mineralized soft tissue mass, whereas, sclerosing types produce irregular areas of radiopacity.

When the cortical plates are perforated, the periosteum is raised and the tumour may extend into the surrounding soft tissue to produce the classical sun-ray appearance. CT scan and MRI may be helpful in delineating the extent of tumor into the surrounding tissue, but are not necessary to establish the diagnosis of osteosarcoma (14,15,16).

**Macroscopy and histopatholoyg.** Gross examination of osteosarcomas is often show a large tumor, usually over 5 cm, fleshy or hard in consistency which may contain osteoid, fibrous tissue or cartilage. It frequently perforated the cortex and associated with a soft tissue mass. Some osteoblastic variety may appear grey-tan or pumice-like in colour, while others become, sclerotic and more yellow-white . Chondroblastic variety tends to be white to tan in colour, and variably calcified with a fish-flesh or rope-like cut surface(13,14).

Osteosarcoma is frequently referred to as spindle cell tumor, it tends to be a highly anaplastic, pleomorphic tumor in which the tumor cells may be epitheloid, plasmacytoid fusiform, ovoid small round cells, clear

Microscopically, osteosarcomas show considerable variation in pattern, but by definition, the tumor is characterized by formation of osteoid or bone by the neoplastic cells (osteoblastic type) or production of abundant fibrous tissue (fibroblastic type) and/or a cartilage (chondroblastic type) (3).

cells, mono or multinucleated giant cells, or spindle cells. Most cases are complex mixtures of two or more of these cell types. In osteoblastic osteosarcoma, bone and/or osteoid are the predominant matrix, the pattern

and the distribution of osteoid is often variable, in some areas, osteoid is deposited in fine lace-like seams, in other areas broad sheets of osteoid may entrap single neoplastic osteoblasts. Histologically, osteoid is a dense, pink, amorphous intercellular material which must be distinguished from other eosinophilic extra-cellular material such as fibrin and amyloid. (3,12,13,14,15,16).

of differentiation that may be focally present resembles fibrosarcoma or malignant fibrous histiocytoma is the fibroblastic osteosarcoma, which is a high drade spindle cell malignancy, these atypical spindle cells are often arranged in a storiform pattern admixed with tumour giant cells with only minimal amounts of osteoid with or with out cartilage (13,16).

**Immunophenotype and genetics.** Osteosarcoma is immunoreactive with antibodies to smooth muscle actin and may be immunoreactive for cytokeratin. Osteosarcoma, usually has a diffuse moderate to strong intra-cytoplasmic staining for CD99. Osteocalcin and osteonectin have sometimes been used to highlight osteoid.

Cytogenetic studies of osteosarcomas, showed that the most, if not all, osteosarcomas have clonal chromosomal aberration either numerical or structural. Multiple clones are common and diploid ploidy pattern by DNA cytofluorometry has been reported to be a poor prognostic sign. Although, no specific translocation or other diagnostic structural aberration has been assigned to conventional osteosarcoma. However, there is recurrent involvement of certain chromosomal regions such as 1p11-13, 1q11-12, 1q21-22, 11p14-15, 14p11-13, 15p11-13, 17p and 19q13 are most frequently affected by chromosomal structural aberration and the most common imbalances are +1, -6q, -9, -10, -13 and -17 as well as cytogenetic manifestations of gene amplification are frequently seen. Furthermore, chromosome arms 3q, 13q, 17p, and 18q are most frequently involved in loss of heterozygosity (LOH), as the LOH incidence is high at 3q26.6-26.3 (17,18,19,20).

However, some patients may be genetically predisposed to develop osteosarcoma. For example, patients who

In addition to osteoblastic areas, other patterns such as chondroblastic differentiation are often present, in which chondroid matrix is predominant, which contain lobules or islands of cartilage with markedly atypical chondrocytes. Myxoid and other forms of cartilage are uncommon except in the jaws and pelvis. A third pattern

have hereditary retinoblastoma have a several hundred-folds increase in the incidence of osteosarcoma. Those patients have inactive retinoblastoma gene (RB1 tumour suppressor gene), located on chromosome 13, which renders them susceptibale to numerous malignancies, including osteosarcoma. In addition, patients with the Rothmund-Thomson syndrome and Li-Fraumeni syndrome with a TP 53 germ line mutation are also more prone to developing osteosarcoma. The frequency of RB1 mutation in sporadic osteosarcoma has been found to vary between 30-40% (5,6,7,11,12,20,21).

**Prognostic factors.** Untreated, conventional osteosarcoma is universilly fatal and the various histological patterns do not appear to affect the prognosis to any great extent. Age, gender, location, tumor size, stage and the result of various laboratory tests have been used in an effort to predict prognosis. Moreover, there is a concordance between intensive positive staining of vascular endothelial growth factor (VEGF) pathway which is the key regulator of angiogenesis and poor prognosis. The overall 5-year survival rate for osteosarcoma of the jaws is about 40 per cent, in contrast to other sites, jaw lesions metastasize infrequently but local recurrence rates are high, leading eventually to death from uncontrolled local disease(1,2).

**Parosteal osteosarcoma.** Parosteal osteosarcoma is a low-grade, slow-growing neoplasm that originate from the surface of the cortex and forms a bony mass in the soft tissue and account for about 5 % of all osteosarcoma. Clinically, the neoplasm presented with slow-growing painless mass with duration, usually of a year or more. Although about 75% of cases are between the ages 20 and 45 yeas and about 73% of cases are

seen in the posterior aspect of the distal femur. Radiographically paosteal osteosarcoma characteristically appears as radiodense lobulated mass of about 4-6 cm in diameter attached to the cortex with a broad base. Histologically, parosteal osteosarcomas are well-differentiated fibroosseous neoplasms that produce osteoid in a bland fibrous tissue stroma and show only minimal cellular atypia (22).

**Periosteal osteosarcoma.** Periosteal osteosarcoma is a rare variant of osteosarcoma which extends from the cortex like a bony knob and as with most

**Low grade central osteosarcoma.** Low grade central osteosarcoma, also known as intraosseous well-differentiated osteosarcoma, is a rare variant of osteosarcoma with an incidence of about 2% of osteosarcomas. Low grade central osteosarcoma is a slow-growing, low grade neoplasm, but, however, about 15% of cases dedifferntiate to high grade osteosarcoma. Low grade central osteosarcoma has a wide age range from 9 to 83 years but it occurs most frequently in second decade of life which presented with pain and a mass usually for over a year, range in size from 2 to 25 cm in maximum dimension. Although, low grade central osteosarcoma has a tendency to occur in the distal femur and proximal tibia where it is usually confined to the medullary canal which may mimic fibrous dysplasia(24).

Radiographically, most of the lesions are radiodense in either a diffuse or mottled pattern or in few cases the lesion may be entirely radiolucent. Histologically, the neoplasm is similar to the parosteal osteosarcoma and fibrous dysplasia, but there are two important distinguished features. First, the fibrous tissue stroma in fibrous dysplasia is very cellular without cytological atypia. Second, the lesional bone in fibrous dysplasia is woven bone and is deposited as thin isolated trabeculae arranged in curved shapes as Chinese letters(24,25).

**Telangiectatic osteosarcoma.** Telangiectatic osteosarcosma is a rare high grade intramedullary osteosarcoma characterized by large spaces filled with blood with or without septa and accounting for only 0.08 % of all primary osteosarcomas. Although, the osteosarcomas, patients are usually between 15 and 25 years of age. Periosteal osteosarcoma has tendency to involve the diaphysis, where the tibia and femur are the most frequently sites affected. Radiographically, peiosteal osteosarcoma appears as a dense circumscribed surface mass with usually a reactive bone radiating from the cortex and focal erosion. Histologically, periosteal osteosarcom a is a chondroblastic neoplasm consists almost entirely of lobules of cellular, atypical chondroid tissue separated by thin bands of fibrous tissue(23).

neoplasm has a wide age range but it most frequently occurs in the second decade of life. Pain, rapid swelling and pathological fracture are the most important features with a tendency to occur in distal femur and proximal tibia. Radiographically, the neoplasm appears as purely lytic lesion due to lack of osteoid production by tumor cells that may be identical to the radiological features of aneurysmal bone cyst.

Histologically, the tumor is characterized by many blood-filled or empty cystic -like spaces separated by thin septa resembling aneurysmal bone cyst. The neoplasm is difficult to distinguish from aneurysmal bone cyst especially if the aneurysmal bone cyst is highly destructive, therfore the diagnostic feature of telangiectatic osteosarcoma is the presence of focal areas of high-grade sarcoma with marked cellular atypia and mitotic figures (26,27).

**Secondary osteosarcoma.** Secondary osteosarcoma is an osteoid forming sarcoma that occurs in association with a variety of conditions affecting bone, such as Paget's disease of bone or radiation exposure, and rarely various other disorders such as osteoblastoma, osteochondroma, fibrous dysplasia, osteomyelitis, Rothmund-Thomson syndrome and endoprosthesis implantation. However, in Paget's disease the sarcomatous change are most frequently occur in the pelvic bones, femur, humerus and tibia, but any bone affected by Paget's disease has the potential to undergo osteosarcomatous change with an incidence of less than 1% of cases. Pain, swelling, and pathological fracture are usually the most common clinical

presentation , while, the radiological features are most frequently the lytic destructive pattren rather than the osteoblastic pattren, while those that cause cortical disruption and a soft tissue mass usually show radiological features of Paget's disease (5,6,7,8,12).

Histologically, the secondary osteosarcoma of Paget's disaese is a high grade sarcoma, most frequently of osteoblastic type. However, in postradiation osteosarcom any skeletal site may be affected, but most commonly they arose in bones of the pelvic and shoulder girdles or at the distal end of the femur. The mean and the median radiation doses were 6.040 cGY rad and 5.700 **cGY** rad, while the period of latency between irradiation and the appearance of the bone that distinguishe this neoplasm from osteoid osteoma. High-grade surface osteosarcoma is a very rare high-grade bone-forming malignant tumor which arise from the surface of the bone. The behavior and the histological features of this neoplasm is similar to the conventional sarcoma ranged from 3.5 to 4.7 years. However, radiographically the lesion may appear lytic or densely sclerotic, while histologically, the tumor is usually of high grade osteosarcoma (9,10,11)

**Intracortical and high-grade surface osteosarcoma.**

Intracortical osteosarcoma is a very rare high-grade osteoblastic osteosarcoma, in which most of the cases involve the tibia or femur of children. The tumor is usually small and localized with average size of 1.5 cm in dimension, while the radiological fetures are similar to osteoid osteoma which appears as well-defined intracortical radiolucency surrounded by a sclerotic rim. Histologically, the neoplastic tissue is associated with atypical sromal cells with a destructive growth pattren

osteosarcoma. The neoplasm has a wide age range between 9 and 62 years, while the radiographic features are similar to the periosteal and parosteal osteosarcoma. The typical radiological feature of this neoplasm is the partial mineralization of the tumor mass reflecting the amount of osseous or chondroid matrix produced by the tumor cells (28,29,30).

**Small cell osteosarcoma.** Small cell osteosarcoma, is a rare subtype of osteogenic osteosarcoma, consists of sheets of small round blue cells that produce an osteoid matrix. It may be confused with Ewing sarcoma if the osteoid is not included in the biopsy. The clinical presentation of this neoplasm is similar to those of conventional osteosarcoma while the incidence rate is approximately 1.3 % of all osteosarcomas. Small cell osteosarcoma most frequently involve the distal femur, proximal tibia, and proximal femur and has a wide age range but most frequently occurs in teens or 20s. Radiographically, small cell osteosarcoma generally have a very permeative feature, a feature similar to Ewing sarcoma. In addition, cortical destruction is common and unlike Ewing sarcoma, the mineralization of the matrix is (32,33).

usually extensive, which may highly suggestive of small cell osteosarcoma (31).

Histologically, the neoplasm is composed of small cells similar to those of other small round blue cell tumors associated with osteoid formation and few lesions are associated with chondroid areas as well as cytoplasmic glycogen. However, there are three histopathological features. First, the cells of small cell osteosarcoma resemble those of Ewing sarcoma, which consist of small round cell with round, densely hyperchromatic nuclei and coarsely clumped chromatin. Second, the pattren resemble large cell lymphoma, in which the cells have more abundant cytoplasm and a large, more vesicular nucleus. Third, is small short and densely packed spindle cells. However, small cell osteosarcoma must be distinguished from other small round blue cell tumors. The cells of small cell osteosarcoma do not stain for common leukocyte antigen or B-cell markers and can be thus distinguished from primary lymphoma of bone. Furthermore tumor cells may be positive for CD99, vimentin, osteocalcin, osteonectin, smooth musle specific stain, Leu-7 and KP1

## References

**1.Dorfman, H. D. & Czerniak, B.** (**1995**). *Bone cancers.*, Cancer 75 : 203-210.

**2. Gorlick, R. & Khanna, C.** (**2010**). *Osteosarcoma.*, J Bone Miner Res 25 : 683-691.

**3. Murphey, M. D.** (**2007**). *World Health Organization classification of bone and soft tissue tumors: modifications and implications for radiologists.*, Semin Musculoskelet Radiol 11 : 201-214.

**4. Sanerkin, N. G.** (**1980**). *Definitions of osteosarcoma, chondrosarcoma, and fibrosarcoma of bone.*, Cancer 46 : 178-185.

**5. Brien, W. W.; Salvati, E. A.; Healey, J. H.; Bansal, M.; Ghelman, B. & Betts, F.** (**1990**). *Osteogenic sarcoma arising in the area of a total hip replacement. A case report.*, J Bone Joint Surg Am 72 : 1097-1099.

**6. Kozlowski, K.; Scougall, J. S. & Oates, R. K.** (**1980**). *Osteosarcoma in a boy with Rothmund-Thomson syndrome.*, Pediatr Radiol 10 : 42-45.

**7. Ruggieri, P.; Sim, F. H.; Bond, J. R. & Unni, K. K.** (**1994**). *Malignancies in fibrous dysplasia.*, Cancer 73 : 1411-1424.

**8. Avigad, S.; Peleg, D.; Barel, D.; Benyaminy, H.; Ben-Baruch, N.; Taub, E.; Shohat, M.; Goshen, Y.; Cohen, I. J.; Yaniv, I. & Zaizov, R.** (**2004**). *Prenatal diagnosis in Li-Fraumeni syndrome.*, J Pediatr Hematol Oncol 26 : 541-545.

**9. Huvos, A. G.; Butler, A. & Bretsky, S. S.** (**1983**). *Osteogenic sarcoma associated with Paget's disease of bone. A clinicopathologic study of 65 patients.*, Cancer 52 : 1489-1495.

**10. Huvos, A. G. & Woodard, H. Q.** (**1988**). *Postradiation sarcomas of bone.*, Health Phys 55 : 631-636.

**11. Hansen, M. F.; Seton, M. & Merchant, A.** (**2006**). *Osteosarcoma in Paget's disease of bone.*, J Bone Miner Res 21 Suppl 2 : P58-P63.

**12. Hansen, M. R. & Moffat, J. C.** (**2003**). *Osteosarcoma of the Skull Base after Radiation Therapy in a Patient with McCune-Albright Syndrome: Case Report.*, Skull Base 13 : 79-83.

**13. Baena-Ocampo, L. D. C.; Ramirez-Perez, E.; Linares-Gonzalez, L. M. & Delgado-Chavez, R.** (**2009**). *Epidemiology of bone tumors in Mexico City: retrospective clinicopathologic study of 566 patients at a referral institution.*, Ann Diagn Pathol 13 : 16-21.

**14. Ajura, A. J. & Lau, S. H.** (**2010**). *A retrospective clinicopathological study of 59 osteogenic sarcoma of jaw bone archived in a stomatology unit.*, Malays J Pathol 32 : 27-34.

**15. Okada, K.; Hasegawa, T.; Nishida, J.; Ogose, A.; Tajino, T.; Osanai, T.; Yanagisawa, M. & Hatori, M.** (**2004**). *Osteosarcomas after the age of 50: a clinicopathologic study of 64 cases--an experience in northern Japan.*, Ann Surg Oncol 11 : 998-1004.

**16. Clark, J. L.; Unni, K. K.; Dahlin, D. C. & Devine, K. D.** (**1983**). *Osteosarcoma of the jaw.*, Cancer 51 : 2311-2316.

**17. Araki, N.; Uchida, A.; Kimura, T.; Yoshikawa, H.; Aoki, Y.; Ueda, T.; Takai, S.; Miki, T. & Ono, K.** (**1991**). *Involvement of the retinoblastoma gene in primary osteosarcomas and other bone and soft-tissue tumors.*, Clin Orthop Relat Res : 271-277.

**18. Benedict, W. F.; Fung, Y. K. & Murphree, A. L.** (**1988**). *The gene responsible for the development of retinoblastoma and osteosarcoma.*, Cancer 62 : 1691-1694.

**19. Bridge, J. A.; Nelson, M.; McComb, E.; McGuire, M. H.; Rosenthal, H.; Vergara, G.; Maale, G. E.; Spanier, S. & Neff, J. R.** (**1997**). *Cytogenetic findings in 73 osteosarcoma specimens and a review of the literature.*, Cancer Genet Cytogenet 95 : 74-87.

**20.Bajpai, J.; Sharma, M.; Sreenivas, V.; Kumar, R.; Gamnagatti, S.; Khan, S. A.; Rastogi, S.; Malhotra, A. & Bakhshi, S.** (**2009**). *VEGF expression as a prognostic marker in osteosarcoma.*, Pediatr Blood Cancer 53 : 1035-1039

**21. Atiye, J.; Wolf, M.; Kaur, S.; Monni, O.; Böhling, T.; Kivioja, A.; Tas, E.; Serra, M.; Tarkkanen, M. & Knuutila, S.** (**2005**). *Gene amplifications in osteosarcoma-CGH microarray analysis.*, Genes Chromosomes Cancer 42 : 158-163

**22. Unni, K. K.; Dahlin, D. C.; Beabout, J. W. & Ivins, J. C.** (**1976a**). *Parosteal osteogenic sarcoma.*, Cancer 37 : 2466-2475.

**23.Unni, K. K.; Dahlin, D. C.; Beabout, J. W. & Ivins, J. C.** (**1976a**). *Parosteal osteogenic sarcoma.*, Cancer 37 : 2466-2475.

**24. Bartalena, T.; Rimondi, E.; Rossi, G.; Bianchi, G. & Alberghini, M.** (**2007**). *Low grade central chondrosarcoma of the fifth costotransverse joint.*, Australas Radiol 51 Spec No. : B122-B125.

**25. Antonescu, C. R. & Huvos, A. G.** (**2000**). *Low-grade osteogenic sarcoma arising in medullary and surface osseous locations.*, Am J Clin Pathol 114 Suppl : S90-103.

**26. Liu, H. & Huang, X.** (**2002**). *Telangiectatic osteosarcoma: a clinicopathologic analysis of 14 cases.*, Zhonghua Bing Li Xue Za Zhi 31 : 213-216.

**27. Discepola, F.; Powell, T. I. & Nahal, A.** (**2009**). *Telangiectatic osteosarcoma: radiologic and pathologic findings.*, Radiographics 29 : 380-383.

**28. Unni, K. K.; Dahlin, D. C.; McLeod, R. A. & Pritchard, D. J.** (**1977**). *Intraosseous well-differentiated osteosarcoma.*, Cancer 40 : 1337-1347.

**29. Vigorita, V. J.; Jones, J. K.; Ghelman, B. & Marcove, R. C.** (**1984**). *Intracortical osteosarcoma.*, Am J Surg Pathol 8 : 65-71.

**30. Wold, L. E.; Unni, K. K.; Beabout, J. W. & Pritchard, D. J.** (**1984**). *High-grade surface osteosarcomas.*, Am J Surg Pathol 8 : 181-186

**31. Edeiken, J.; Raymond, A. K.; Ayala, A. G.; Benjamin, R. S.; Murray, J. A. & Carrasco, H. C.** (**1987**). *Small-cell osteosarcoma.*, Skeletal Radiol 16 : 621-628.

222 : 330-332.

**32. Devaney, K.; Vinh, T. N. & Sweet, D. E.** (**1993**). *Small cell osteosarcoma of bone: an immunohistochemical study with differential diagnostic considerations.*, Hum Pathol 24 : 1211-1225.

**33. Nakajima, H.; Sim, F. H.; Bond, J. R. & Unni, K. K.** (**1997**). *Small cell osteosarcoma of bone. Review of 72 cases.*, Cancer 79 : 2095-2106.