

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

5,300

Open access books available

130,000

International authors and editors

155M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Osteosarcoma

*Gottardo Bianchi, Leticia Gaiero, Nicolas Casales,
Claudio Silveri and Ana C. Belzarena*

Abstract

Osteogenic sarcoma is the most common primary bone cancer frequently affecting children and teenagers. Despite many years of research, little have the survival rates changed in the last fifty years. Early diagnosis, a complete systemic treatment program with a good tumor response and adequate margins continue to be the main determinants of patients' prognosis in this disease. Neoadjuvant chemotherapy followed by surgery and subsequent adjuvant systemic treatment remain the standard of care. Numerous reconstruction options available provide these patients better function and improved quality of life.

Keywords: osteosarcoma, bone primary malignant tumor, osteogenic sarcoma

1. Introduction

Osteosarcoma, also known as osteogenic sarcoma, is a primary bone malignancy characterized for the production of osteoid, the mineralized portion of bone matrix [1]. Different from what its name suggests the origin of the tumor is not bone itself, but mesenchymal stem cells and osteosarcomas can also be found in soft tissues unrelated to any bone [2]. The incidence is approximately 1000 new cases each year in the United States [3]. Osteosarcoma is the third most common cancer in adolescents and is the most frequent primary bone malignant tumor in this age group. The peak incidence is between the second and third decade of life, although there is a second peak of patients aged older than 60 years of age [4, 5]. This tumor can be subclassified according to histologic grade, location within the bone and the histologic characteristics of the matrix, more than 90% are of high grade, intra-medullary location conventional ones [6]. The most common histologic subtypes are osteoblastic, chondroblastic, fibroblastic and telangiectatic. Additionally, these tumors can be classified as primary or secondary, depending on if the origin is in normal bone or altered bone due to prior pathology, for example Paget's disease, or radiation [7]. From a genetic perspective, osteosarcomas are characterized by highly disorganized genomic aberrations rather than a constant genetic alteration commonly found in other tumors [8]. Despite this, it has been linked to alterations in some specific genetic pathways expressed as syndromes. Such as Li-Fraumeni syndrome or Rothmund-Thomson syndrome or an alteration of the Rb protein causing retinoblastoma early in life as well as osteogenic sarcomas [9].

2. Clinical presentation

Osteosarcomas most commonly occur in the metaphysis of long bones, for the most part around the knee in the distal femur (43%) or proximal tibia (23%), followed in frequency by the humerus (10%) (**Figure 1**) [10]. One in ten patients has a tumor of axial location, most commonly in the pelvis. Tumors of axial location tend to have a worse prognosis with higher recurrence rates and more advanced stages at presentation [10–12]. Patients complaint about intermittent pain and swelling, the pain is known to be severe enough to awake the patient during sleep hours [13]. Pain of a high intensity can potentially be an indication of an impending pathological fracture, fact that occurs in up to 10% of these patients [14]. A pathological fracture may represent a more aggressive tumor and the microRNA profile of tumors that fractured have been shown to be different that those without a break. Additionally, tumors that presented with a fracture were associated with a higher risk of metastatic spread as well as a worse prognosis overall [14].

About 20% of osteosarcoma patients have metastatic disease at presentation. Most of those secondary lesions are in the lung, bone being the second most common spread location [10]. Tumor size has been implicated as a risk factor for lung spread [15]. When osteogenic sarcoma presents in older population, there is a more frequent axial location compared to younger patients, being almost 40% of the elderly patients versus 10% in children and teenagers [16]. Additionally, the older patients tend to have larger tumors, more frequency of metastatic disease at presentation and a worse general prognosis with less opportunity for limb salvage procedures and inability to receive the full systemic treatment protocol as compared to younger patients [17]. Moreover, when the chemotherapy response seems to

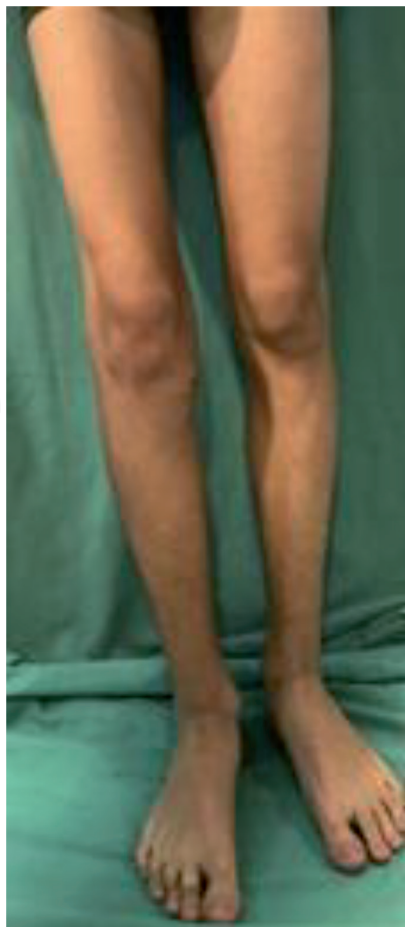


Figure 1.
Fifteen-year-old patient with a left proximal tibia osteosarcoma, presented with local pain and swelling.

be poorer in these patients with a lower percentage of necrosis noted on the post-chemotherapy tumor resection piece [10]. The 5-year overall survival is 50% for the elderly when surgical treatment is feasible, when surgery is not an option that rate drops to 8% [18].

3. Staging

The assessment of osteosarcoma patients usually begins with orthogonal plain radiographs of the site of pain or mass. Plain films usually reveal an aggressive appearing lesion that prompts more advanced imaging studies such as a CT scan or ideally an MRI with and without contrast of the entire affected bone. On radiographic imaging the lesions may be more blastic, lytic or mixed pattern depending on the osteosarcoma subtype. In more advanced cases, there will be cortical permeation and an associated soft tissue component, although this is a more common finding in Ewing's sarcomas [19]. For purely lytic lesions, radiographic evidence is only present when a substantial percentage of the bone has been affected (30–50%), thus the recommendation in cases of persistent symptoms is to proceed with an MRI even with a negative plain film [20]. Additional findings on radiographs include a wide area of transition, cortical destruction and a periosteal reaction such as Codman's triangle or a sunburnt pattern (**Figure 2**) [21].

The next imaging study should be a full bone length MRI with and without contrast of the affected area, this will serve diagnostic and staging purposes as well, since it has the ability of detecting skip lesions. MRI studies provide information regarding the complete extent of the tumor within the bone, and its closeness to surrounding structures such as vessels and nerves. Additionally, it provides information regarding joint invasion, and, extremely important in the pediatric population, physis involvement by the tumor [22]. This information will dictate the proposed surgical intervention (**Figure 3**). After neoadjuvant chemotherapy and prior to the definitive surgical treatment a new MRI with and without contrast of the affected bone must be obtained for tumor re-assessment.

Following the initial images, usually proceeds a close or open biopsy of the lesion for pathology confirmation of the diagnosis and grading of the tumor. It is

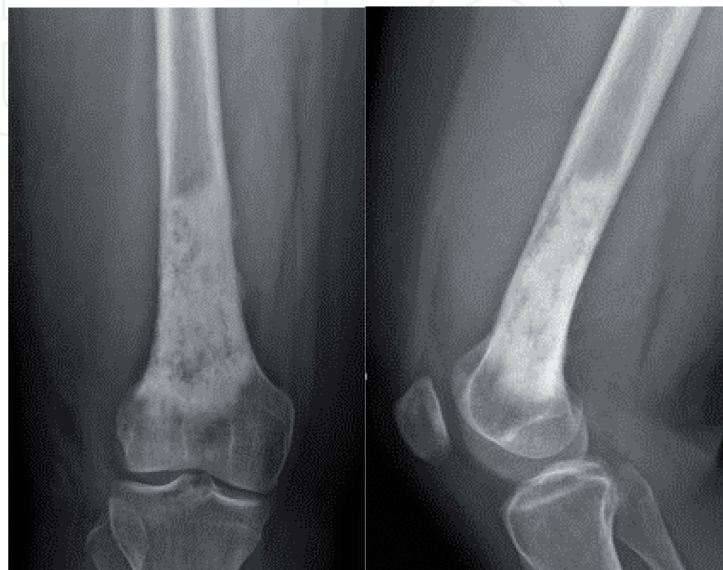


Figure 2.
Radiographic images of a patient with a distal femur conventional, central, osteoblastic, high grade osteosarcoma. The tumor presents a mixed, blastic and lytic, moth-eaten pattern.



Figure 3. MRI of the tibia of a 15-year-old patient with an osteoblastic osteosarcoma of the proximal tibia respecting the physis (D, E). T1-weighted sequence (A), stir sequence (B) and T1-fat suppressed post contrast sequence (C).

paramount that the biopsy is performed by a surgeon specialized and with experience in bone tumors, so that it can be done following important principles inherent to the specialty and have those not be respected it can potentially hinder the possibility of a limb salvage procedure for the patient [23].

Once the diagnosis of osteosarcoma has been confirmed, the next step is to proceed with staging of the patient. Approximately, 20% of patients debut with stage IV cancer [24]. Osteosarcomas are known to spread most commonly to lungs, 80% of the metastases, followed by bones (10%) [25, 26]. Therefore, the next imaging studies will be directed to assess the most common sites of spread. The lung assessment is performed with a non-contrasted chest CT and the bone staging can be performed by a bone scan or, more recently, with a PET-CT scan (**Figures 4 and 5**).

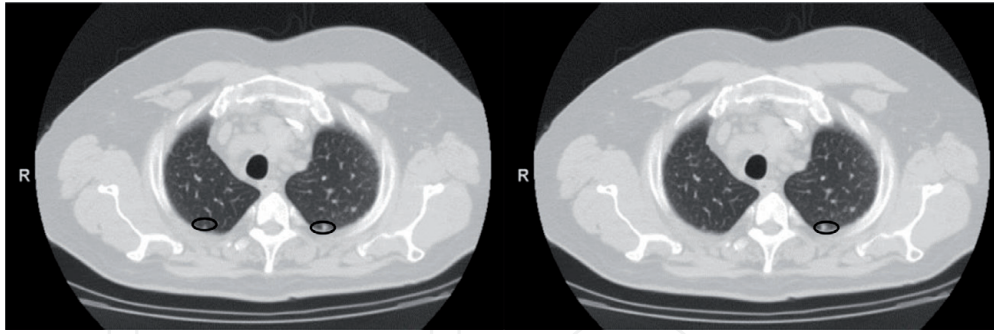


Figure 4.
Non-contrasted chest CT depicting peripheral lung nodules (circled) consistent with metastatic osteosarcoma.

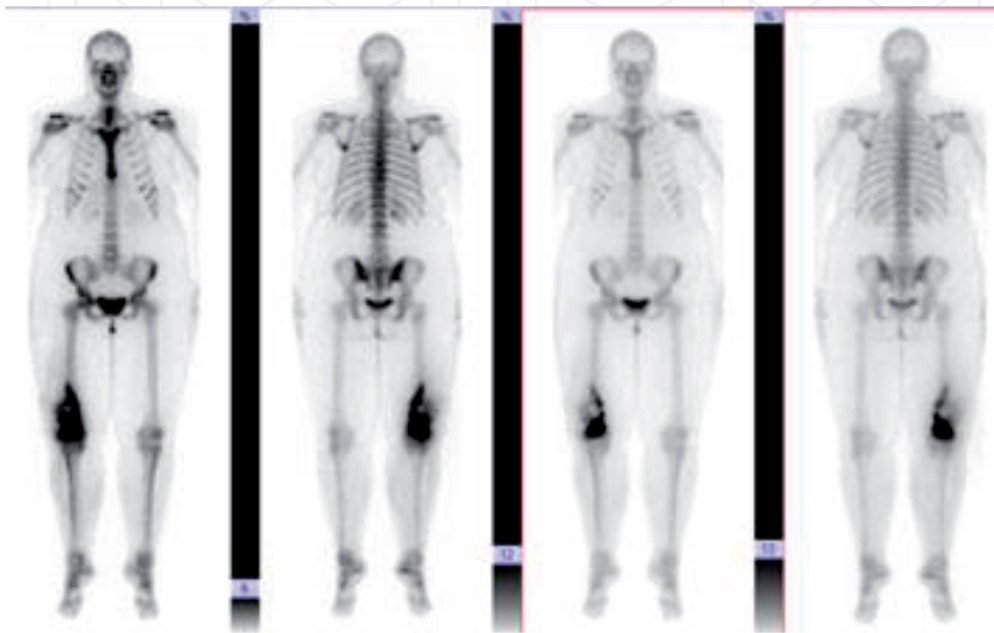


Figure 5.
Tecnetium-99 bone scan of a patient with a distal femur osteosarcoma. No other bone lesions were present.

Patients with metastatic disease at presentation have a worse prognosis than those with localized disease having an overall survival at 5 years of 40% or less [27]. Bone metastases have a particularly worse prognosis with higher rates of local recurrences and an overall survival of 13% [26].

Additional studies prior to the start of treatment, will be oriented at making a basal assessment of organs potentially affected by chemotherapy. Consequently, the patient will obtain an echocardiogram, kidney function studies, hemogram and complete metabolic panel as well as an audiology test [13]. Additionally, patients should be referred for fertility counseling since the systemic treatment is known to decrease the chances of conceiving even many years after the finalization of chemotherapy. Male patients present with particularly worse chances of conceiving than females and the cumulative dose of the drugs used seem to be the most important determinant factor to predict the ability to conceive after treatment [28].

4. Treatment

Currently, the treatment of localized osteogenic sarcoma is the same, independent of subtype and despite its different behaviors and genetic profiles, and includes a plan of neoadjuvant chemotherapy, followed by local treatment with

surgical resection with a subsequent round of adjuvant chemotherapy [29]. This plan was first implemented in the 1970's and improved long-term survival rates from its original 20% to the current 70%, which has remained unchanged for the past five decades [30]. The three main reasons for treatment failure are local recurrences, distant disease spread and the development of drug resistance [31].

Systemic treatment for young patients includes two cycles of 5 weeks with high dose methotrexate, doxorubicin and cisplatin (MAP) [32]. Once the neoadjuvant cycle has finalized new imaging studies are obtained and the surgical procedure is planned. The resection piece is afterwards analyzed by the pathologist who must inform the percentage of necrosis, a key factor of prognostic significance and a proxy for the tumor chemotherapy response [33]. Following local treatment, 3 to 6 cycles of the same drug regimen (MAP) are given to the patient.

Before the implementation of chemotherapy as part of the treatment plan of these patients, even the ones with localized disease, most patients underwent a limb amputation, and despite this aggressive procedure still had poor survival rates. Nowadays, the standard of care for most patients is a limb salvage procedure which has shown similar survival rates to an amputation when systemic treatment was added with a much-improved function and quality of life [34, 35]. The main goal of limb salvage procedures is to completely resect the tumor while preserving important structures for the limb survival as well as the patient's function. Several studies have addressed the importance of achieving adequate margins in a resection as a determinant factor for the feasibility of the limb salvage option [33, 36, 37]. Local recurrences, which occur in 10–15% of these patients, has been linked to the margin adequacy as a predicting factor [38].

Once a decision has been made regarding the limb salvage procedure, several options present in terms of reconstruction alternatives, all with their specific advantages and disadvantages. Resection and reconstruction with an endoprosthetic device, a non-biologic option, is the main trend worldwide currently (**Figure 6**). While the biologic alternatives include allografts, vascularized fibula, distraction osteogenesis or recycled and sterilized bone autograft [39–43]. The latter can be achieved through several different techniques such as pasteurization, irradiation, autoclave or most recently the use of liquid nitrogen [44].

Endoprosthetic reconstructions have shown good results in terms of function at short and medium-term. Among its disadvantages it is its high cost, low accessibility in some countries and limited survival (50–76% at 10 years) with a high rate of

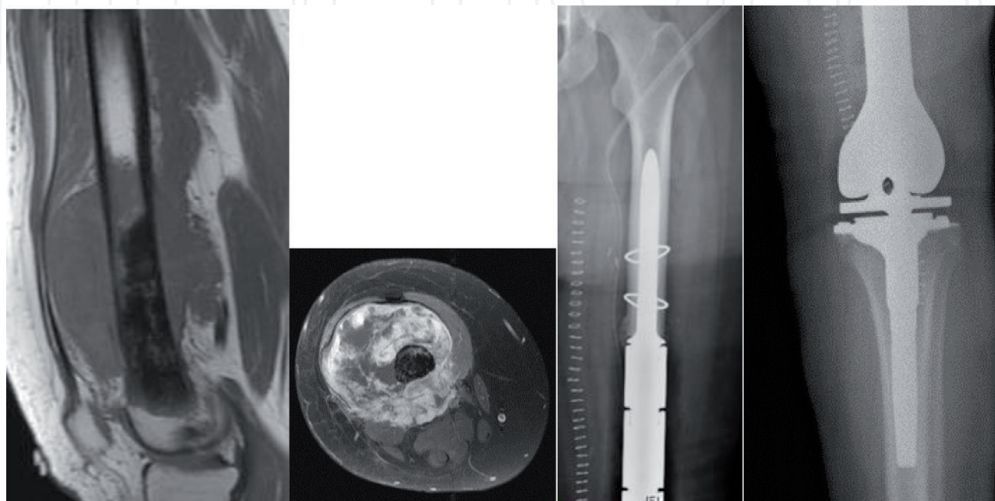


Figure 6. Distal femur osteogenic sarcoma resection and reconstruction with a distal femur endoprosthetic device non-cemented.

reoperation specially in pediatric patients, an age where primary bone malignant tumors are most frequent [45]. Allografts require a bone bank with matching bone pieces. Furthermore, allografts have the potential to transmit diseases and, in some cases, patient acceptance may be an added obstacle [46]. Bone transport is a lengthy complex treatment with multiple surgical procedures usually involved [43].



Figure 7. Case of a 15-year-old male with an osteoblastic osteosarcoma abutting the proximal tibial physis, treated with limb salvage surgery with liquid nitrogen pretreated bone tumor autograft. Careful surgical planning allowed the proximal physis to be preserved.

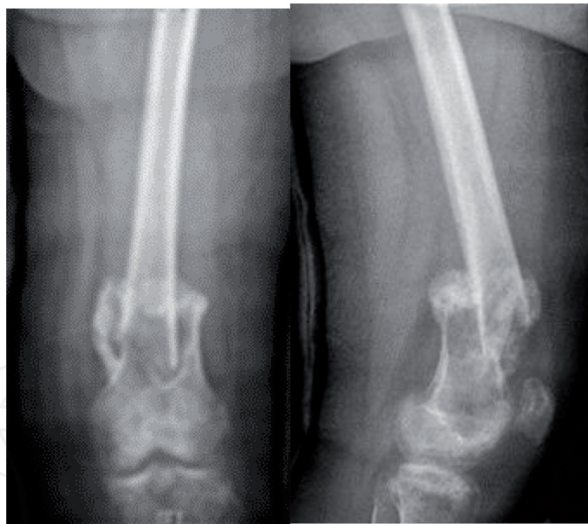


Figure 8.

Radiographic image depicting a pathological fracture through a distal femur osteosarcoma with displacement and shortening of the distal fragment.

Frozen autografts recycled in liquid nitrogen are a biologic solution with the advantages of low cost, easy access, complete removal of viable tumor, bone morphogenic protein preservation, osteoconduction and osteoinduction properties maintained, perfect matching at the osteotomy site, does not require a bone bank, allows reattachment of tendons and ligaments, no disease transmission and no graft rejection (**Figure 7**) [47]. Among its disadvantages, the bone piece cannot be sent for full pathology analysis and thus provide the information about the percentage of necrosis obtained after systemic treatment in the indicated cases. Nonetheless, the surrounding soft tissues which are resected prior to submerging the piece in LN are sent to pathology. This technique accomplishes full necrosis of the tumoral cells and prior studies have shown that the soft tissue resection prior to the sterilization in LN is representative of the tumor response to chemotherapy [48]. Additionally, this procedure has shown no difference in terms of bone resistance to compression when compared to unfrozen bone. This allows for the initial resistance of the reconstruction, being comparable or even superior to allografts [48].

One particular scenario, the treating orthopedic oncologist should be aware of is the case of an osteosarcoma with a pathological fracture at presentation. Fractures through an osteogenic sarcoma can occur in up to 10% of the cases (**Figure 8**) [14]. In the past, this circumstance used to be a contraindication for a limb salvage procedure and patients were indisputably recommended for an amputation. Nowadays, even though those patients tend to present a worse prognosis, a limb salvage procedure is considered an option with similar recurrence rates when compared to amputations [49]. Prior studies presented the hypothesis that these patients may have a worse outcome due to a hematoma formation at the fracture site, with tumor cell dissemination [50]. Although the ideal treatment is controversial, some authors recommend stabilization of the fracture, which could be achieved by casting, external fixation or limited internal fixation followed by neoadjuvant chemotherapy, subsequent definite surgical treatment and adjuvant systemic treatment [51, 52].

Radiotherapy has a role for unresectable tumors or in cases of positive margins to help with local control. The Cooperative Osteosarcoma Study Group (COSS) has presented promising results for the case of unresectable osteosarcomas of the spine and pelvis where the treatment with radiation with a curative intent improved the 5-year survival from 0 to 29% [53, 54]. Additional studies have shown radiation is well tolerated by the patients and can achieve up to 76% local control rates [55]. These findings seem to indicate osteosarcomas do have at least a moderate response

to radiotherapy, when in the past it used to be considered a radiotherapy resistant tumor. Supplementary indications for radiotherapy include symptom palliation and this treatment modality has shown to improve patients' symptoms such as pain in case of unresectable tumors [56].

Current investigation trials are in place to uncover targetable mutations that could also have prognostic implications as well studies to assess a potential role for immunotherapy in osteosarcoma patients [57]. Specifically, Cabozantinib, a tyrosine kinase inhibitor used for thyroid and renal cell cancers, has shown anti-tumor activity as well as a good tolerance and is currently under investigation through multicentre trials [58].

5. Conclusion

Osteosarcoma, the most common primary bone malignancy in children and adolescents, has come a long way since its initial approach where all patients underwent an amputation prior to the 1970's. Current systemic treatment options along the myriad of reconstruction alternatives, have allowed these patients to benefit from better survival rates and improved function and quality of life. Nonetheless, the overall survival rates have remained stable for the past 50 years, a disappointing number when compared to other malignancies' statistics, suggesting more resources and research are needed to continue enhancing the outcomes of patients suffering from this cancer.

Conflict of interest

The authors state no conflict of interest related to the writing of this chapter.

Author details

Gottardo Bianchi¹, Leticia Gaiero¹, Nicolas Casales¹, Claudio Silveri¹ and Ana C. Belzarena^{2*}

¹ Oncology Orthopedic Department, University of the Republic, Montevideo, Uruguay

² Oncology Orthopedic Service, Miami Cancer Institute, Baptist Health South Florida, Miami, Florida, United States

*Address all correspondence to: ceciliabel@baptisthealth.net

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Anderson ME. Update on survival in osteosarcoma, *Orthop. Clin. North Am.* 47 (1) (2016) 283e292.S.
- [2] Mutsaers AJ, Walkley CR. Cells of origin in osteosarcoma: mesenchymal stem cells or osteoblast committed cells?. *Bone.* 2014;62:56-63. doi:10.1016/j.bone.2014.02.003.
- [3] Key Statistics for Osteosarcoma. (n.d.). Retrieved February 01, 2021, from <https://www.cancer.org/cancer/osteosarcoma/about/key-statistics.html>
- [4] Cotterill SJ, Wright CM, Pearce MS, Craft AW. Stature of young people with malignant bone tumors. *Pediatr Blood Cancer.* 2004;42:59-63. doi: 10.1002/pbc.10437.
- [5] Pan Y, Chen D, Hu T, Lv G, Dai Z. Characteristics and Prognostic Factors of Patients With Osteosarcoma Older Than 60 Years From the SEER Database. *Cancer Control.* 2019;26(1):1073274819888893. doi:10.1177/1073274819888893.
- [6] Toki S, Kobayashi E, Yoshida A, et al. A clinical comparison between dedifferentiated low-grade osteosarcoma and conventional osteosarcoma. *Bone Joint J.* 2019;101-B(6):745-752. doi:10.1302/0301-620X.101B6.BJJ-2018-1207.R1.
- [7] Shimatani A, Aono M, Hoshi M, et al. Secondary osteosarcoma in patients previously treated for childhood cancer: Three case reports. *Mol Clin Oncol.* 2019;10(1):153-158. doi:10.3892/mco.2018.1752.
- [8] Martin JW, Squire JA, Zielenska M. The genetics of osteosarcoma. *Sarcoma.* 2012;2012:627254.
- [9] Morrow JJ, Khanna C. Osteosarcoma Genetics and Epigenetics: Emerging Biology and Candidate Therapies. *Crit Rev Oncog.* 2015;20(3-4):173-197. doi:10.1615/critrevoncog.2015013713.
- [10] Bielack SS, Kempf-Bielack B, Delling G, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: An analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. *J Clin Oncol.* 2002;20:776-790.
- [11] Kawai A, Huvos AG, Meyers PA, Healey JH. Osteosarcoma of the pelvis. Oncologic results of 40 patients, *Clin. Orthop. Relat. Res.* 348 (1998)196e207.
- [12] Han I, Lee YM, Cho HS, Oh JH, Lee SH, Kim HS. Outcome after surgical treatment of pelvic sarcomas, *Clin. Orthop. Surg.* 2 (3) (2010) 160e166.
- [13] Reed DR, Hayashi M, Wagner L, et al. Treatment pathway of bone sarcoma in children, adolescents, and young adults. *Cancer.* 2017;123(12):2206-2218. doi:10.1002/cncr.30589.
- [14] Lozano Calderón SA, Garbutt C, Kim J, et al. Clinical and Molecular Analysis of Pathologic Fracture-associated Osteosarcoma: MicroRNA profile Is Different and Correlates with Prognosis. *Clin Orthop Relat Res.* 2019;477(9):2114-2126. doi:10.1097/CORR.0000000000000867.
- [15] Zhang C, Guo X, Xu Y, et al. Lung metastases at the initial diagnosis of high-grade osteosarcoma: prevalence, risk factors and prognostic factors. A large population-based cohort study. *Sao Paulo Med J.* 2019;137(5):423-429. doi:10.1590/1516-3180.2018.0381120619.
- [16] Kumar R, Kumar M, Malhotra K, Patel S. Primary osteosarcoma in the elderly revisited: current concepts in

diagnosis and treatment. *Curr Oncol Rep.* 2018;20(2):13.

[17] Longhi A, Errani C, Gonzales-Arabo D, Ferrari C, Mercuri M. Osteosarcoma in patients older than 65 years. *J Clin Oncol.* 2008;26(33):5368-5373.

[18] Nishida Y, Isu K, Ueda T, et al. Osteosarcoma in the elderly over 60 years: a multicenter study by the Japanese Musculoskeletal Oncology Group. *J Surg Oncol.* 2009;100(1):48-54.

[19] Kundu ZS. Classification, imaging, biopsy and staging of osteosarcoma. *Indian J Orthop.* 2014;48(3):238-246. doi:10.4103/0019-5413.132491.

[20] Morrison WB, Dalinka MK, Daffner RH, et al. Bone tumors. In: ACR appropriateness criteria. Reston, VA: American College of Radiology, 2005:1-5.

[21] Resnick D. Tumors and tumor-like lesions of bone: radiographic principles. In: Resnick D, ed. *Diagnosis of bone and joint disorders.* Philadelphia, PA: Saunders, 2002:3745-3762.

[22] Rubin DA. Magnetic resonance imaging: Practical considerations. In: Resnick D, Kransdorf MJ, editors. *Bone and joint imaging.* 3rd ed. Philadelphia Pennsylvania: Elsevier Saunders; 2005. pp. 118-32.

[23] Mankin HJ, Mankin CJ, Simon MA. The hazards of biopsy, revisited: Members of Musculoskeletal Society. *J Bone Joint Surg.* 1996;64:656-63.

[24] Meyers PA, Heller G, Healey JH, et al. Osteogenic sarcoma with clinically detectable metastasis at initial presentation. *J Clin Oncol.* 1993;11(3):449-53. PMID: 8445419; doi: 10.1200/JCO.1993.11.3.449.

[25] Kager L, Zoubek A, Pötschger U, et al. Primary metastatic osteosarcoma:

presentation and outcome of patients treated on neoadjuvant Cooperative Osteosarcoma Study Group protocols. *J Clin Oncol.* 2003;21(10):2011-8. PMID: 12743156; doi: 10.1200/JCO.2003.08.132.

[26] Bacci G, Longhi A, Bertoni F, et al. Bone metastases in osteosarcoma patients treated with neoadjuvant or adjuvant chemotherapy: the Rizzoli experience in 52 patients. *Acta Orthop.* 2006;77(6):938-943. doi:10.1080/17453670610013268.

[27] Isakoff MS, Bielack SS, Meltzer P, Gorlick R. Osteosarcoma: Current Treatment and a Collaborative Pathway to Success. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2015; 33:3029-35.

[28] Hoshi M, Takami M, Ieguchi M, et al. Fertility following treatment of high-grade malignant bone and soft tissue tumors in young adults. *Mol Clin Oncol.* 2015;3(2):367-374. doi:10.3892/mco.2014.474.

[29] Gorlick R, Khanna C. Osteosarcoma. *J Bone Miner Res.* 2010; 25:683-91.

[30] Marina N, Gebhardt M, Teot L, Gorlick R. Biology and therapeutic advances for pediatric osteosarcoma. *Oncologist.* 2004;9(4):422-441.

[31] Chen R, Wang G, Zheng Y, Hua Y, Cai Z. Drug resistance-related microRNAs in osteosarcoma: Translating basic evidence into therapeutic strategies. *J Cell Mol Med.* 2019;23(4):2280-2292. doi:10.1111/jcmm.14064.

[32] Goorin AM, Schwartzentruber DJ, Devidas M, et al. Presurgical chemotherapy compared with immediate surgery and adjuvant chemotherapy for nonmetastatic osteosarcoma: Pediatric Oncology Group Study POG-8651. *J Clin Oncol.* 2003;21:1574-1580.

- [33] Picci P, Sangiorgi L, Rougraff BT, Neff JR, Casadei R, Campanacci M. Relationship of chemotherapy-induced necrosis and surgical margins to local recurrence in osteosarcoma. *J Clin Oncol.* 1994;12(12):2699-2705. doi:10.1200/JCO.1994.12.12.2699.
- [34] Marulanda GA, Henderson ER, Johnson DA, Letson GD, Cheong D. Orthopedic surgery options for the treatment of primary osteosarcoma. *Cancer Control.* 2008;15(1):13-20. doi:10.1177/107327480801500103.
- [35] Aksnes LH, Bauer HC, Jebsen NL, et al. Limb-sparing surgery preserves more function than amputation: a Scandinavian sarcoma group study of 118 patients. *J Bone Joint Surg Br.* 2008;90(6):786-794. doi:10.1302/0301-620X.90B6.19805.
- [36] Jeys LM, Thorne CJ, Parry M, Gaston CL, Sumathi VP, Grimer JR. A Novel System for the Surgical Staging of Primary High-grade Osteosarcoma: The Birmingham Classification. *Clin Orthop Relat Res.* 2017;475(3):842-850. doi:10.1007/s11999-016-4851-y.
- [37] Cates JM. Reporting Surgical Resection Margin Status for Osteosarcoma: Comparison of the AJCC, MSTS, and Margin Distance Methods. *Am J Surg Pathol.* 2017;41(5):633-642. doi:10.1097/PAS.0000000000000815.
- [38] Takeuchi A, Lewis VO, Satcher RL, Moon BS, Lin PP. What are the factors that affect survival and relapse after local recurrence of osteosarcoma?. *Clin Orthop Relat Res.* 2014;472(10):3188-3195. doi:10.1007/s11999-014-3759-7.
- [39] Frisoni T, Cevolani L, Giorgini A, et al. Factors affecting outcome of massive intercalary bone allografts in the treatment of tumours of the femur. *J Bone Joint Surg.* 2012; 94:836-41.
- [40] Mankin HJ, Gebhardt MC, Jennings LC, et al. Long-term results of allograft replacement in the management of bone tumors. *Clin Orthop Relat Res.* 1996; 324: 86-97.
- [41] Donati D, Colangeli M, Colangeli S, et al. Allograft-prosthetic composite in the proximal tibia after bone tumor resection. *Clin Orthop Relat Res.* 2008; 466:459-65.
- [42] Yajima, H, Tamai S, Mizumoto S et al. Vascularized fibular grafts for reconstruction of the femur. *J Bone Joint Surg.* 1993; 75: 123-28.
- [43] Watanabe K, Tsuchiya H, Yamamoto N, et al. Over 10-year follow-up of functional outcome in patients with bone tumors reconstructed using distraction osteogenesis. *J Orthop Sci.* 2013; 18:101-09.
- [44] Tsuchiya H, Tomita K. Reconstruction using an autograft containing tumour treated by liquid nitrogen. *J Bone Joint Surg Br.* 2005; 87:218-25.
- [45] Torbert JT, Fox EJ, Hosalkar HS, et al. Endoprosthetic reconstructions: results of long-term follow up of 139 patients. *Clin Orthop Relat Res.* 2005; 438:51-9.
- [46] Tomford WW. Transmission of disease through transplantation of musculoskeletal allografts. *J Bone Joint Surg Am.* 1995; 77(11): 1742-54.
- [47] Takata M, Sugimoto N, Yamamoto N, et al. Activity of bone morphogenetic protein-7 after treatment at various temperatures: freezing vs. pasteurization vs. allograft. *Cryobiology.* 2011; 63:235-39.
- [48] Yamamoto N, Tsuchiya H, Tomita K. Effects of liquid nitrogen treatment on the proliferation of osteosarcoma and the biomechanical properties of normal bone. *J Orthop Sci.* 2003; 8:374-80.

- [49] Bacci G, Ferrari S, Longhi A, Donati D, Manfrini M, Giacomini S, Briccoli A, Forni C, Galletti S. Nonmetastatic osteosarcoma of the extremity with pathologic fracture at presentation: local and systemic control by amputation or limb salvage after preoperative chemotherapy. *Acta Orthop Scand*. 2003;74:449-454.
- [50] Abudu A, Sferopoulos NK, Tillman RM, Carter SR, Grimer RJ. The surgical treatment and outcome of pathological fractures in localised osteosarcoma. *J Bone Joint Surg Br*. 1996;78(5):694-698.
- [51] Scully SP, Ghert MA, Zurakowski D, Thompson RC, Gebhardt MC. Pathologic fracture in osteosarcoma : prognostic importance and treatment implications [published correction appears in *J Bone Joint Surg Am* 2002 Apr;84-A(4):622]. *J Bone Joint Surg Am*. 2002;84(1):49-57.
- [52] Scully SP, Temple HT, O'Keefe RJ, Mankin HJ, Gebhardt M. The surgical treatment of patients with osteosarcoma who sustain a pathologic fracture. *Clin Orthop Relat Res*. 1996;(324):227-232. doi:10.1097/00003086-199603000-00028.
- [53] Ozaki T, Flege S, Kevric M, et al. Osteosarcoma of the pelvis: experience of the Cooperative Osteosarcoma Study Group. *J Clin Oncol* 2003;21(2):334-341.
- [54] Ozaki T, Flege S, Liljenqvist U, et al. Osteosarcoma of the spine: experience of the Cooperative Osteosarcoma Study Group. *Cancer* 2002;94(4):1069-1077.
- [55] Tinkle CL, Lu J, Han Y, et al. Curative-intent radiotherapy for pediatric osteosarcoma: The St. Jude experience. *Pediatr Blood Cancer*. 2019;66(8):e27763. doi:10.1002/pbc.27763.
- [56] Mahajan A, Woo SY, Kornguth DG, et al. Multimodality treatment of osteosarcoma: radiation in a high-risk cohort. *Pediatr. Blood Cancer* 2008;50(5):976-982.
- [57] Bishop MW, Janeway KA, Gorlick R. Future directions in the treatment of osteosarcoma. *Curr Opin Pediatr*. 2016;28(1):26-33. doi:10.1097/MOP.0000000000000298.
- [58] Italiano A, Mir O, Mathoulin-Pelissier S, et al. Cabozantinib in patients with advanced Ewing sarcoma or osteosarcoma (CABONE): a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2020;21(3):446-455. doi:10.1016/S1470-2045(19)30825-3.