Current Oncology Reports (2018) 20: 13
https://doi.org/10.1007/s11912-018-0658-1

SARCOMAS (SR PATEL, SECTION EDITOR)

Primary Osteosarcoma in the Elderly Revisited: Current Concepts in Diagnosis and Treatment

Rajendra Kumar[1] · Meena Kumar[2] · Kavin Malhotra[3] · Shreyaskumar Patel[3,4]

Published online: 28 February 2018

Abstract

Purpose of Review Osteosarcoma is mostly seen in bones of children and young adults. When it occurs in older persons, the tumor is considered secondary usually complicating Paget disease or irradiated bone. However, there is a second incidence peak of primary osteosarcoma later in life when these tumors occur de novo. This article describes the clinical, imaging, and treatment of POS in older patients, including demographic data of patients from our institution.

Findings We present our experience with 920 cases of osteosarcoma that were seen between 1984 and 2003 at the University of Texas MD Anderson Cancer Center in Houston, TX, USA. Among the 868 primary osteosarcoma of bones, there were 100 (11.52%), which comprised 69% of the tumors in patients over the age of 50 years. Older patients with primary osteosarcoma tend to have relatively more common axial skeleton involvement, have more distant disease, and are difficult to treat because of concomitant comorbidities. Despite that, most adult patients treated with chemotherapy have shown good results with longer disease-free survival.

Summary A lytic bone lesion seen in radiographs of elderly patients should include primary osteosarcoma among differential diagnoses. Radical surgery and chemotherapy seem to ensure long-term disease-free survival in most cases. The elderly patients with POS in pelvis, spine, and upper extremities and those with distant disease (metastases) have worse prognosis.

Keywords Osteosarcoma · Primary osteosarcoma · Primary osteosarcoma in older persons · Primary osteosarcoma in adults

This article is part of the Topical Collection on *Sarcomas*

✉ Rajendra Kumar
rajkumar@mdanderson.org

Meena Kumar
meena.kumar@va.gov

Kavin Malhotra
kavin_malhotra@hotmail.com

Shreyaskumar Patel
spatel@mdanderson.org

[1] Department of Diagnostic Imaging, UT MD Anderson Cancer Center, 1515 Holcombe Blvd., Unit 1475, Houston, TX 77030, USA

[2] Present address: Department of Diagnostic Imaging, Section of Nuclear Medicine, Veterans Administration Hospital, 1660 S. Columbian Way, Seattle, WA 98108, USA

[3] Present address: Victoria Radiology Associates, 2701 Hospital Drive, Victoria, TX 77901, USA

[4] Department of Sarcoma Medical Oncology, UT MD Anderson Cancer Center, 1400 – Holcombe Blvd., Unit # 450, Houston, TX 77030, USA

Introduction

Osteosarcoma (OS) is the most common primary malignant bone tumor in children and adolescents [1–4]. Although most OS in persons over 40 years is considered secondary, superimposed on Paget disease or irradiated bone, there is second age peak of primary OS (POS) in older population.

Epidemiology and Incidence

A world-wide incidence of 1.5–4 cases of POS/million/year population has been reported [1–5]. The tumor usually occurs in children and young adults, mostly in the first three decades of life [1–4]. Previously, it was thought that all cases of OS in older patients were secondary, superimposed on pre-existing benign bone lesions, such as Paget disease, irradiated bone, and bone infarct [3, 4]. Earlier reports suggested POS never occurred beyond the fifth decade [6]. However, it is now well documented that POS has bimodal age distribution with the second peak in the elderly, mostly in the seventh and eighth

decades of life, when the tumor occurs de novo, without pre-existing benign bone disease [1–4, 7–9].

Approximately 50% of osteosarcoma in the elderly tends to be primary tumors [3, 4, 7, 10]. This incidence is much higher in countries where Paget disease of bone is infrequent [3, 11]. Despite this, POS of bone in the elderly remains generally unrecognized by physicians resulting in misdiagnosis and unnecessary delay in treatment. Recent reports have pointed out that not only POS occurs in the elderly, but its incidence in patients over age 40 years may be increasing gradually [7, 8, 12]. Stark et al. reported the mean age for POS in Sweden increased from 19 to 40 years from 1972 to 1981; for those with POS at typical locations in long bones, it increased from 13 to 31 years [7]. The peak incidence of POS remained between ages 10 and 29 years, but was becoming smaller gradually due to growing fraction of the tumor in older patients [7]. Others also have reported increasing incidence of POS in older patients [11, 12]. However, some reports have also stated increasing incidence of POS in young patients while decreasing with age [3, 4].

Huvos reported 50 cases of POS in patients over 60 years of age between years 1973 and 1984 as compared with only 21 cases between years 1954–1973 from the same institution [8]. He reported 36 cases (36%) of POS among 101 patients with OS in the elderly. In a retrospective study of 920 cases of OS cases from 1984 to 2003 at our institution, we divided the patients into three age groups—< 35, > 35 to 50, and > 50 years. There were a total of 868 patients with POS of bone—641 (73.85%) in the first group, 127 (14.63%) in the second group, and 100 (11.52%) in the third age group [Table 1]. Additional 44 patients (31 patients were over age 50 years) had secondary OS—9 with Paget disease, 34 with previously irradiated bones, and 1 with fibrous dysplasia. Eight patients had extra-skeletal (soft tissue) POS—2 in chest wall, 5 in thigh, and 1 in retroperitoneum. Among the total of 868 bone POSs, 100 (11.5%) patients were over age 50 years, while among the total of 144 OSs in the same age group, there were 100 (69%) POSs. A previous report from our institution found only 24 (6%) patients with POS among 397 patients with OS between 1946 and 1975; 6 patients had secondary OS in that study [5]. Recent reports of decreasing incidence of Paget disease of bone in general population and improved therapeutic administration of radiation dose to bones may have some bearing on decreasing incidence of secondary OS in older patients [4, 13].

The usual explanation for increased incidence of POS in the young is thought to be related to rapid bone growth due to increased levels of growth hormone and other poorly understood nutritional, metabolic, and genetic factors in growing skeleton [3, 4]. Thus, bones with more rapid growth, such as distal femur and proximal tibia, tend to be the most affected sites for POS in the young. The increasing incidence of POS in the elderly population cannot be explained simply because of increase in aging population and increasing life span. It is possible that POS in the elderly is altogether a biologically different bone tumor [7, 11, 14].

Table 1 920 patients with primary and secondary osteosarcoma

		Total
Total patients with osteosarcoma		920
Primary osteosarcoma		876
Soft tissue osteosarcoma		8
	Chest wall	2
	Retroperitoneum	1
	Thigh	5
Bone osteosarcoma		868
	Conventional	821
	Parosteal	23
	Dedifferentiated	10
	Unusual cell type	6
	High-grade surface	8
Secondary bone osteosarcoma		44
	Paget's disease	9
	Irradiated bone	34
	Fibrous dysplasia	1

Age, Sex, and Race

Primary OS in older patients tends to be more common in men with male:female ratio of 1.7:1 [3, 4] [Table 2]; previously, a female:male ratio of 2.4:1 has been reported [5]. White men are more commonly affected in older age group in contrast to younger group in which POS more commonly occurs in black boys [3, 4]. Our own data of 868 patients with POS showed the majority in ages < 35 years were Hispanics (85.53%) [Table 3]. We attribute the preponderance of Hispanic patients in our younger age group to combination of changing demography reflecting growing Hispanic population in Texas and increased referrals from Mexico. The tumor affected 80% of whites over age > 50 years, and among the 186 cases of POS over age 40 years, 133 (71.5%) tumors occurred in the fifth and sixth decades [Tables 2 and 3].

Site

Similar to the younger age group, majority of primary osteosarcomas in older patients involve ends of long bones of extremities. However, in the elderly, axial skeleton is relatively more often affected by POS [3–5, 11, 15•]. Incidence of

Table 2. Age at Diagnosis by Gender in 868 Patients of Primary Osteosarcoma of Bone

Gender	Age at Diagnosis						Total	
	35 or Younger		35–50		Older than 50			
	N	(%)	N	(%)	N	(%)	N	(%)
Female	269	74.52	55	15.24	37	10.25	361	100.00
Male	372	73.37	72	14.20	63	12.43	507	100.00
Total	641	73.85	127	14.63	100	11.52	868	100.00

axial POS in elderly patients has been reported as 19–38.2% [15•]. Our own data show axial skeleton (non-extremity) involvement by POS was 42% in patients over age 50 years as compared with 18.4% in the younger age groups (< 35 years) [Table 4]. Pelvis (25%) and spine 15 (15%) were the most common sites of POS among our patients over 50 years of age.

Histopathology

Both in children and adults, POS tends to be osteoblastic [3, 4]. However, Huvos found fibrohistiocytoma variant to be the most frequent histopathologic OS in the older patients [8]. Despite these histologic variants, there is no difference in clinical behavior and management of POS in the elderly [16].

Clinical Presentation

Primary OS in the elderly has similar clinical presentation as in younger patients [5]. The tumor presents clinically as a rather rapidly growing localized soft tissue mass with variable pain and tenderness. Duration of symptoms may vary from weeks to months [5, 7]. At times, a patient may seek medical attention following trauma. Increased preoperative serum alkaline phosphatase and serum lactic acid dehydrogenase (LDH) levels usually indicate poor prognosis [17].

Table 3 Age at diagnosis by race

Race	Age at diagnosis						Total	
	35 or younger		35–50		Older than 50			
	N	(%)	*N*	(%)	*N*	(%)	*N*	(%)
Black	64	78.05	10	12.20	8	9.76	82	100.00
White	356	67.68	90	17.11	80	15.21	526	100.00
Hispanic	201	85.53	24	10.21	10	4.26	235	100.00
Others	20	80.00	3	12.00	2	8.00	25	100.00
Total	641	73.85	127	14.63	100	11.52	868	100.00

Imaging

Radiography Radiographs of a long bone with POS in an elderly patient show a mostly lytic meta-diaphyseal lesion of variable size, same as in younger patients [5]. Less often, a mixed lytic and blastic lesion may be present. The malignant tumor usually shows cortical breakthrough with extension into adjoining soft tissues and variable periosteal reaction. Often, the extra-osseous component of the tumor is much larger than the bone lesion itself. However, unlike POS in younger persons, POS in the elderly tends to be more lytic than blastic and often lacks periosteal reaction [5, 9]. At times, the tumor can extend into adjoining epiphysis, but rarely breaks through articular surface to extend directly into adjoining joint. Occasionally, a pathologic fracture may be present. Among differential diagnoses of lytic bone lesions in an elderly patient, metastasis, myeloma, chondrosarcoma, lymphoma, and giant cell tumor are frequently considered. However, POS is rarely mentioned a diagnostic possibility by radiologist in patients > age 30 years, thus delaying diagnosis [5, 9]. Chest radiographs routinely obtained tend to show more pulmonary metastases in elderly patients with POS than younger patients.

Radionuclide Bone Scan Bone radioscintigraphy is very sensitive in detecting bone and lung metastases, when calcified. Single photon emission computed tomography (SPECT) has additional advantage as combined bone scan (BS) with CT

Table 4 Site of primary osteosarcoma

Site	Age		
	Group I—≤ 35 years	Group II—> 35–50 years	Group III—> 50 years
Skull	15	13	8
Spine	7	2	15
Facial Bones	13	8	3
Sternum	22	3	1
Clavicle	1	1	0
Scapula	0	4	2
Ribs	11	11	6
Humerus	85	10	3
Radius	3	3	2
Ulna	2	1	0
Hand	0	1	1
Pelvis	56	19	22
Femur	381	43	25
Tibia	42	5	10
Fibula	3	2	1
Foot	0	1	1
Total	641	127	100

provides better localization and characterization of a bone lesion and can detect metastases in bone, lungs, and elsewhere.

Computed Tomography Computed tomography (CT) shows intra- and extra-osseous extents of POS and can detect even minimal mineralized osteoid production by tumor not visible on radiographs. CT is useful in evaluating pathologic fracture, when present. CT is the best imaging modality for assessment of POS occurring in complex bones, such as pelvis, spine, and craniofacial bones, which are more frequent sites in the elderly. Because of its multiplanar and 3-D imaging capabilities, CT also aids in presurgical planning. Chest CT detects pulmonary metastases not visible in chest radiographs. However, chest CT itself underestimates lung metastases by as much as 30% when compared with manual palpation of metastatic lung lesions during thoracotomy [18]. Biopsy of an indeterminate lung nodule detected on chest radiograph or CT should be obtained to confirm diagnosis.

Magnetic Resonance Imaging Magnetic resonance imaging (MRI), especially when combined with intravenous gadolinium, is the best imaging modality for tumor staging as it determines whether POS is uni-compartmental (confined to bone), or multi-compartmental by demonstrating cortical breakthrough and extra-osseous tumor extension into adjoining soft tissues, and regional lymphadenopathy. It also shows tumor relationship to adjoining neurovascular bundles and joint. MRI is used routinely to assess response of tumor to neoadjuvant and adjuvant chemotherapy and radiotherapy, and also postoperatively, to detect residual and recurrent tumor. MRI-guided biopsy of tumor can be performed for definitive diagnosis. When imaging with MRI of a long bone involved with POS, the entire length of the bone should be imaged to assess for skip metastases.

Positron Emission Tomography ^{F18}FDG positron emission tomography (PET) combined with CT is used to determine metabolic activity of POS, local and distant extent of disease, and in follow-up of patients after surgery, to assess tumor response to chemotherapy and radiation treatment, and also for detection of residual and recurrent tumor.

Irrespective of which image modality is selected, the same imaging modality should be used throughout the clinical course, and for surveillance after surgery. Routinely, BS for detection of bone metastases, and chest CT for detection of pulmonary metastases are recommended for preoperative staging and postoperative follow-up. For detection of soft tissue metastases, PET-CT and MRI are the best imaging modalities.

Tumor Staging

Tumor staging is required prior to definitive treatment of POS [19]. The tumor can be at stage I (low grade), stage II (high grade), or stage III (with distant metastases). Further substaging of the stages I and II determines whether the tumor is A (intra-compartmental—confined to involved bone), or B (extra-compartmental—with cortical breakthrough). Most POS of bone is high-grade extra-compartmental tumors (IIB). The current cancer staging classification from the combined American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) has a tumor, node, metastasis (TNM) staging system. The most recent AJCC Cancer Staging recommendation beginning January 1, 2018, requires separating T-stage classification for primary bone sarcomas into those tumors arising in the appendicular skeleton and most axial skeleton from those tumors arising in spine and pelvis [20].

Biopsy

Biopsy of a bone lesion under CT or MRI guidance should be performed by the same orthopedic surgeon who later will also perform the definitive surgery, including limb-salvage procedure. For core biopsy, close collaboration between orthopedic surgeon and interventional radiologist is essential to ensure accurate needle placement for obtaining tumor tissue.

Treatment

Once the diagnosis and staging of POS in an elderly patient is established, the treatment requires special considerations because of existing concomitant comorbidities, such as chronic respiratory, cardiac, renal, or other diseases, which may influence clinical course and prognosis [9]. A combination of neoadjuvant and adjuvant chemotherapy and radical surgery for long disease-free survival is advocated to treat all adult patients with POS irrespective of whether the tumor has metastasized or not. However, because of comorbidities with general poor health and greater involvement of axial skeleton, usually difficult areas to operate on, many elderly patients with POS may not be good candidates for chemotherapy and surgery [8]. Bacci et al. reported good response of POS of extremities to neoadjuvant chemotherapy, results similar to those seen with younger patients, in 24 of their 29 patients aged between 40 and 60 years of age, while 4 patients had no response, and in 1 patient, the disease had progressed [21•]. Histological response of the tumors to the chemotherapy was "good" in 8 patients and "poor" in 21. Twenty-five patients had limb-salvage surgery, while four had amputations. Chemotherapy not only improved the long-term survival rate but also obviated need for amputation in 80% of their patients. At median follow-up of 8 years (range 5–12 years), the disease-free survival was 57%, and the 8-year overall survival

was 62%. In contrast, in another group of 24 patients treated with surgery alone, the 8-year disease-free and overall survival was only 17%. Grimer and colleagues also advocated aggressive treatment of non-metastasizing POS in elderly patients with chemotherapy and surgical resection with good outcome and long survival [22]. Others have also reported similar good results with long survival with chemotherapy and surgery [3, 4, 15•, 21•, 23]. Combined neoadjuvant treatment with surgery gives a rate of healing of about 60–70% for patients with non-metastatic POS of the extremities, and of about 30% for tumors of the axial skeleton [12]. Similar good results also have been reported from our institution in treating POS in adult patients when neoadjuvant chemotherapy was used in those patients who showed positive results with preoperative chemotherapy and surgery [24•]. However, others have reported limited role of chemotherapy in treatment of POS in the elderly patients as they found no additional benefit of chemotherapy, especially in patients with non-metastatic POS [11, 14, 15•, 25]. Currently, chemotherapy for osteosarcoma is among the most exhausting for any solid tumors, and treatment of primary tumor may be associated with permanent disability of some degree [26]. As compared to the younger patients, the elderly with POS have greater incidence of distant metastases. Also, the patients with axial skeletal POS tend to have more distant metastases and worse prognosis [3, 4, 23]. Use of local conventional radiotherapy and carbon-ion radiation treatment are mostly reserved for the inoperable tumors involving craniofacial bones and spine [11]. Seer data in the USA from 1973 to 2004 showed the relative 5-year survival rate for young-onset OS was 61.6%; for middle-aged persons, 58.7%; and for the elderly patients over 60 years, 24.2%, respectively [3, 4]. Pulmonary metastasectomy should be considered in those patients with POS who have sufficient pulmonary reserve, when the lungs are the only site of metastatic disease, and when both the primary tumor and the pulmonary metastases can be completely resected [27]. At present, the prognostic role of angiogenesis in predicting outcome in elderly patients with POS treated with chemotherapy is controversial with conflicting results [23].

Conclusion

POS has bimodal incidence peaks in the first three decades and in older patients after 40 years of age. POS in the elderly, comprising of up to 30% of all POS, usually affects white men, involves relatively more axial bones, and tends to have more distant metastases, usually to lungs and bones. The survival depends upon anatomic site of tumor and tumor stage [11]. The elderly patients with POS in pelvis, spine, and upper extremities and those with distant disease (metastases) have worse prognosis [3, 4, 15•, 24•]. Despite controversy regarding chemotherapy at present, POS in the elderly requires aggressive treatment with neoadjuvant and adjuvant chemotherapy and radical surgery with limb-salvage procedure for long disease-free survival. However, the presence of comorbidities and poor general health may limit use of such treatment in the elderly. Palliative radiotherapy is used for inoperable tumors mostly affecting craniofacial bones and spine. It is predicted that with increasing life span and increase in the geriatric population, the incidence of POS in elderly persons will gradually increase and pose management challenge to the oncology team in future. Since the mid 1980s, there has been no real breakthrough in treating bone sarcomas [3, 4, 6, 21•]. Increased understanding of the biology of POS in the elderly will launch new therapeutic agents, such as biologic response modifiers, angiogenesis factors, and growth receptor modulation for prolonged disease-free survival [27].

Acknowledgments We are thankful to Mr. Wei Wei, Principal Biostatistician at UT MD Anderson Cancer Center, Houston, TX, for his valuable contribution in preparation of this manuscript.

Compliance with Ethical Standards

Conflict of Interest Rajendra Kumar declares that he has no conflict of interest.

Meena Kumar declares that she has no conflict of interest.

Kavin Malhotra declares that he has no conflict of interest.

Shreyaskumar Patel has received research funding through grants from Janssen, Eisai, and Morphotek, and has received compensation from Janssen, Eisai, Morphotek, EMD-Serono, CytRx, Bayer, Eli Lilly, Epizyme, and Novartis for service as a consultant.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Informed Consent In compliance with Institutional Review Board Guidelines that required IRB references # 15, 21 waiver for consent.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Meyers P, Gorlick R. Osteosarcoma. Pediatr Clin N Am. 1997;44(4):973–89. https://doi.org/10.1016/S0031-3955(05)70540-X.
2. Whelan JS. Osteosarcoma. Br J Cancer. 1997;33(10):1611–9.
3. Savage SA, Mirabello L. Using epidemiology and genomics to understand osteosarcoma etiology. Sarcoma. 2011. https://doi.org/10.1155/2011/548151.

4. Mirabello L, Troisi RJ, Savage SA. Osteosarcoma incidence and survival rates from 1973 to 2004; data from the surveillance, epidemiology, and end-results program. Cancer. 2009;115(7):1531–43. https://doi.org/10.1002/cncr.24121.
5. deSantos LA, Rosengren J-E, Wooten WB, Murray JA. Osteogenic sarcoma after the age 50: a radiographic evaluation. Am J Roentgenol. 1978;131(3):481–4. https://doi.org/10.2214/ajr.131.3.481.
6. Dahlin DC, Coventry MB. Osteogenic sarcoma. A study of six hundred cases. JBJS. 1967;49A:101–10.
7. Stark A, Kreicbergs A, Nilsonne ULF, Silfversward C. The age of osteosarcoma is increasing. JBJS (Br). 1990;72-B:89–93.
8. Huvos AG. Osteogenic sarcoma of bones and soft tissues in older persons. A clinicopathologic analysis of 117 patients older than 60 years. Cancer. 1986;57(7):1442–9. https://doi.org/10.1002/1097-0142(19860401)57:7<1442::AID-CNCR2820570734>3.0.CO;2-3.
9. Brooks S, Starkie CM, Clarke NMP. Ostosarcoma after the fourth decade. A clinic-pathologic review. Arch Orhtop Trauma Surg. 1985;104(2):100–5. https://doi.org/10.1007/BF00454247.
10. Weinfeld MS, Dudley HR Jr. Osteogenic sarcoma. A follow-up study of the ninety-four cases observed at the Massachusetts General Hospital from 1920 to 1960. JBJS. 1962;44-A:269–76.
11. Nashida Y, Isu K, Ueda T, Nishimoto Y, 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. https://doi.org/10.1002/jso.21287.
12. Longhi A, Errani C, Gonzales-Arabio D, Ferrari C, Mercuri M. Osteosarcoma in patients older than 65 years. J Clin Oncol. 2008;26(33):5368–73. https://doi.org/10.1200/JCO.2007.14.9104.
13. Basten S, Bird H, Gamble G, Cundy T. Paget's disease of bone—becoming a rarity? Rheumatology. 2009;48(10):1232–5. https://doi.org/10.1093/rheumatology/kep212.
14. Jeon DG, Lee SY, Cho WH, Song WS, Park JH. Primary osteosarcoma in patients older than 40 years of age. J Korean Med Sci. 2006;21(4):715–8. https://doi.org/10.3346/jkms.2006.21.4.715.
15.• Iwata S, Ishii T, Kawai A, Hiruma T, et al. Prognostic factors in elderly osteosarcoma patients: a multi-institutional retrospective study of 86 cases. Am Surg Oncol. 2014;21:263–8. https://doi.org/10.1245/s10434-013-3210-4. **This abstract outlined factors, such as axial skeleton involvement and more distant metastases that limit positive outcome in elderly patients with POS**.
16. Angelini A, Mavrogenis AF, Trovarelli G, Ferrari S, Picci P, Ruggieri P. Telangiectatic osteosarcoma21: a review of 87 cases. J Cancer Res Clin Oncol. 2016;142(10):2197–207. https://doi.org/10.1007/s00432-016-2210-8.
17. Chen J, Sun M, Hua Y, et al. Prognostic significance of serum lactate dehydrogenase in osteosarcoma: a meta-analysis. J Cancer Res Clin Oncol. 2014;140(7):1205–10. https://doi.org/10.1007/s00432-014-1644-0.
18. Kayton ML, Huvos AG, Casher J, Abramson SJ, Rosen NS, Wexler LH, et al. Computed tomographic scan of the chest underestimates the number of metastatic lesions in osteosarcoma. J Pediatr Surg. 2006;41(1):200–6. https://doi.org/10.1016/j.jpedsurg.2005.10.024.
19. Jawad MU, Scully SP. In brief: classification in brief: Enneking classification: benign and malignant tumors of the musculoskeltal system. Clin Orthop Relat Res. 2010;468(7):2000–2. https://doi.org/10.1007/s11999-010-1315-7.
20. Kneisl JS, Rosenberg AE, Anderson PM, et al. Bone. In: Amin MB, editor. AJCC cancer staging manual. 8th ed. Chicago: AJCC; 2016. p. 471.
21.• Bacci G, Ferrari S, Donati D, Longhi A, Bertonni F, et al. Neoadjuvant chemotherapy for osteosarcoma of the extremity in patients in the fourth and fifth decade of life. Oncol Rep. 1998;5:1259–1322. https://doi.org/10.3892/or.5.5.1259. **This abstract compared response of adult patients with osteosarcoma of extremities treated with adjuvant and neoadjuvant chemotherapy and surgery to those treated with surgery alone without chemotherapy, thus emphasizing role of chemotherapy in long-term disease-free survival**.
22. Grimer RJ, Cannon SR, Taminiau AM, Bielack, et al. Osteosarcoma over the age forty. Eur J Cancer. 2003;39(2):157–63. https://doi.org/10.1016/S0959-8049(02)00478-1.
23. Ek ETH, Ojaimi J, Kitagawa Y, Choong PFM. Outcome of patients with osteosarcoma over 40 years of age: is angiogenesis a marker for survival? Int Semin Surg Oncol. 2006;3:7. https://doi.org/10.1186/1477-7800-3-7.
24.• Wagner MJ, Livingston JA, Patel SR, Benjamin RS. Chemotherapy for bone sarcomas in adults. J Oncol Prac. 2016;12:208–16. **This abstract provided in detail the current treatment of POS in adult patients**.
25. Okada K, Hasegawa T, Nishida J, Ogose A, Tajino T, Osanai T, et al. Osteosarcomas after the age of 50: a clinicopathologic study of 64 cases—an experience in northern Japan. Ann Surg Oncol. 2004;11(11):998–1004. https://doi.org/10.1245/ASO.2004.03.004.
26. Sergi C, Zwerschke W. Osteogenic sarcoma (osteosarcoma) in the elderly: tumor delineation and predisposing conditions. Exp Gerontol. 2008;43(12):1039–43. https://doi.org/10.1016/j.exger.2008.09.009.
27. Todd R. The surgical treatment of pulmonary metastases. Chest. 1997;112(4):287–90(S). https://doi.org/10.1378/chest 112.4_Supplement.287S.
28. Ferguson WS, Goorin AM. Current treatment of osteosarcoma. Cancer Investig. 2001;19(3):292–315. https://doi.org/10.1081/CNV-100102557.