

Combined with Targeted Therapy Intensively Modulated Radiotherapy for Inoperable Giant Cell Sacral Tumor – Three - Year Follow-up of a Rare Borderline Tumor with Literature Review

Lena Marinova^{*1}, Radoslav Georgiev² and Kremena Petrova¹

¹Oncology Hospital, Department of Radiotherapy; Russe, Bulgaria

²Medical University, Department of Imaging, Radiation therapy and Nuclear medicine; Varna, Bulgaria

*Corresponding author

Lena Marinova, Oncology Hospital, Department of Radiotherapy; Russe, Bulgaria

Submitted: 29 Oct 2020; Accepted: 06 Nov 2020; Published: 16 Nov 2020

Abstract

Giant cell bone tumors are rare benign, locally aggressive neoplasms, involving predominantly young patients. In a 26-year-old patient with inoperable sacral giant cell tumor, definitive intensive-modulated radiotherapy (IMRT) up to total dose 64Gy with daily dose 2 Gy was performed. After 3 years of diagnosis and complex treatment (radiotherapy and targeted therapy) the patient is asymptomatic, with achieved local tumor control, without distant metastases and without dynamics in terms of bone recalcification. Radiotherapy is an alternative to surgery for axial bone localizations with a high risk of unacceptable postoperative deformities.

Keywords: Giant Cell Bone Tumors, Inoperable Sacral Giant Cell Tumor, Borderline Bone Tumor, Radiotherapy, Targeted Therapy, Local Tumor Control, Complex Treatment

Introduction

Giant cell bone tumors (GCTs) are rare benign borderline tumors, diagnosed mainly in 30 years old young women [1]. They make up 5% of primary bone neoplasms and 20% of all benign bone tumors [2, 3]. Although it is composed of mature tumor cells, distant metastases, most commonly lung (1% -5%), are found in 2% of clinical cases [4-6]. In the area of the tumor there is local pain with soft tissue edema, combined with reduced motor activity, and in large inoperable tumors - severe neurological pathology [7]. 50% of the GCTs are located near the knee - in the distal femur or proximal tibia, and 10% in the sacral region and vertebrae. Sacral GCTs are the third most common axially growing neoplasms [6, 8-14]. Due to the rare diagnosis of sacral GCTs and the relatively small number of clinical cases treated with different methods, the treatment of these tumors is controversial [15]. This article discusses a complex treatment approach for giant cell bone tumors, focusing on the indications for radiotherapy combined with targeted therapy.

Clinical Case: We present a 26-year-old patient with a giant sacral tumor. After trauma to the lumbar region, there is pain radiating to the lower extremities and swelling of the left leg. After CT and MRI, a large osteolytic lesion was found in the area of the sacrum and coccygeal axis.

From the examinations: CT of the small pelvis with intravenous contrast / 03.17 - Presence of a solid cystic formation with

dimensions 105/55 mm, with lobulated contours, infiltrating sacrum and presacral space with a density of about 35-40 HU. It has a soft tissue component with heterogeneous structure; MRI / 03.17 - The finding corresponds to a giant cell tumor with components of an aneurysmal bone cyst of the sacrum. There is an expansive osteolytic tumor mass with a heterogeneous signal characteristic - strong in STIR and low in T1 measurements of signal intensity. Existence of so-called “fluid-fluid” levels.

Biopsy with pathohistological and immunohistochemical (IHC) analysis /26.04.17: Giant cell tumor of the sacrum with destructive biological behavior of borderline malignancy. There is proliferation of osteoclast-like multinuclear giant cells and polygonal, oval and drained mononuclear stromal cells with sparse cytoplasm, cytological atypism and mitotic figures. There is stromal fibrosis, osteoid formation, necrosis and hemorrhage.

Immunohistochemistry: Mononuclear tumor cells express CD99 in 90% and multinucleated CD 68 / T2N0M0 (G1-2). PET / CT / 04.05.17 - Soft tissue lesion in the area of the sacral bone with axial dimensions 57/49 mm and SUV max 9.2. The corticalis is destroyed both dorsally and to the pelvis. Initiated treatment with targeted therapy X-Geva 120 mg s.c. monthly. CT of the pelvis/ 22.11.17 before radiotherapy (RT) - Osteolytic and osteosclerotic lesion of the sacrum and coccygeal axis with a heterogeneous structure. Presence of a soft tissue component (Figure 1). During

the month November and December 2017, a definitive intensive-modulated radiotherapy (IMRT) was performed up to total dose (TD) 64Gy with daily dose (DD) 2 Gy (Figure 2).

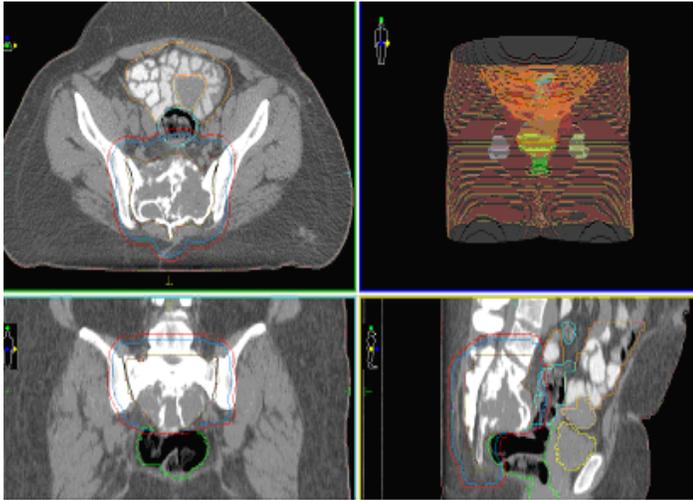


Figure 1: Localization CT of a sacral giant cell tumor with delineation of the radiotherapy volumes (CTV and PTV) before the radiotherapy.

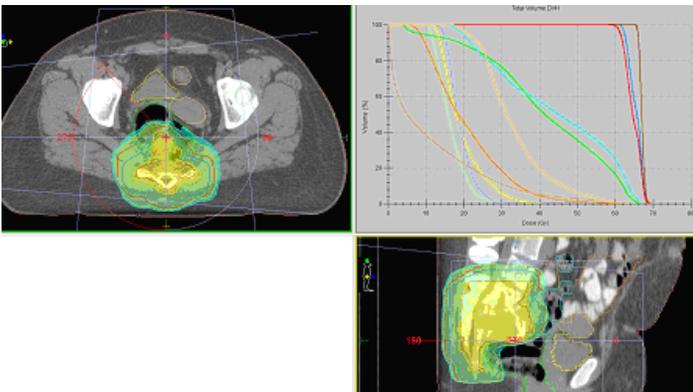


Figure 2: Intensive-modulated RT equipment for sacral giant cell tumor up to TD 64 Gy with DD 2 Gy

After completion of RT, the patient continued targeted therapy (X-Geva 120 mg s.c. monthly), which currently runs for 3 years.

Control CT of the pelvis after 6 months from RT /15.06.18- Osteolytic and osteosclerotic lesion of sacrum and coccygeal axis with heterogeneous structure. The soft tissue lesion associated with the coccyx axis has fibrous changes. There are no enlarged lymph nodes in the small pelvis (Figure 3). The pain syndrome has significantly decreased.

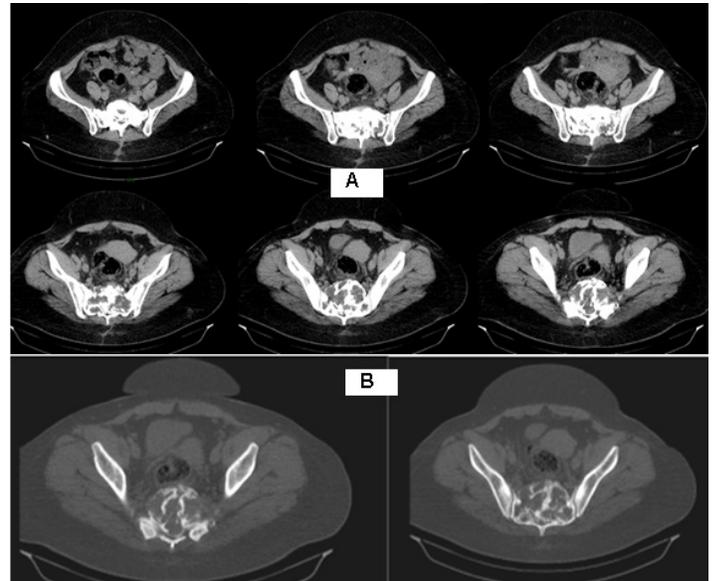


Figure 3: A/CT of the sacrum 6 months after definitive radiotherapy up to TD 64 Gy with DOD 2 Gy with a fibrous soft tissue component; B/ CT of a bone window

Control CT of the pelvis after 1 year from RT /04.01.19- Osteolytic and osteosclerotic lesion of the sacrum. There are no enlarged lymph nodes in the small pelvis (Figure 4). Control pelvic CT after 2 years from RT/ 03.02. 20g (Figure 5). The pain syndrome is completely absent.

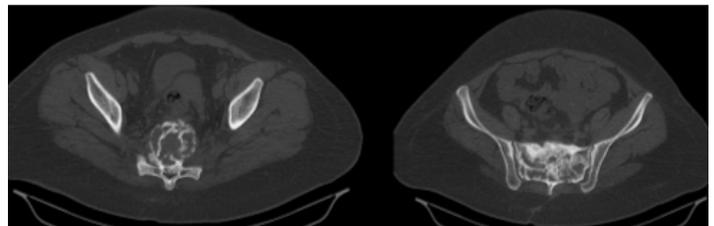


Figure 4: CT of a bone window after 1 year from definitive radiotherapy up to TD 64 Gy combined with targeted therapy.

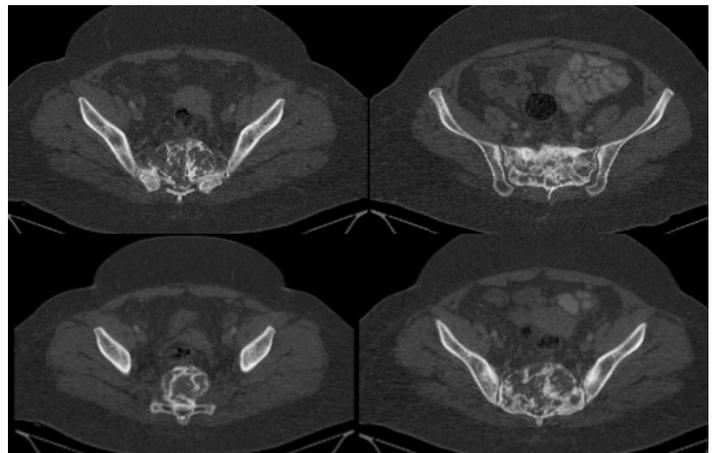


Figure 5: CT CT of a bone window after 2 years from definitive radiotherapy up to TD 64 Gy combined with targeted therapy.

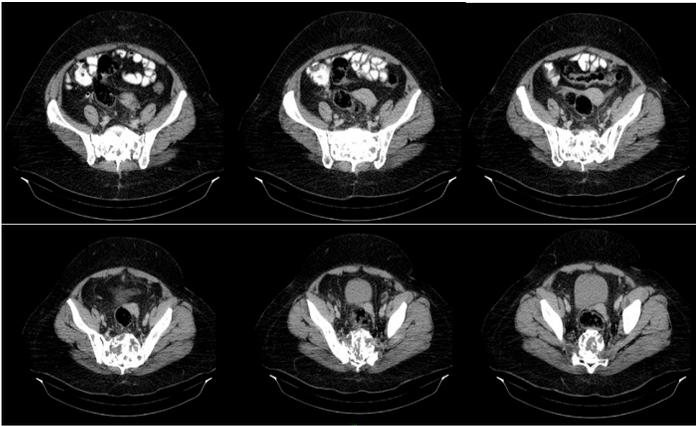


Figure 6: CT of the sacrum after 3 years from definitive radiotherapy up to TD 64 Gy combined with targeted therapy.

After 3 years of treatment and observation, the patient is in good general condition, without symptoms of the primary tumor and without the presence of distant metastasis.

Discussion

This is a rare borderline benign tumor with manifestations of malignancy (<2%) in adult patients (30-50 years) [16]. Due to the rare incidence of GCTs, there is no consensus on optimal complex treatment. To determine the optimal treatment approach, we need to consider several important characteristics of GCTs, determining its borderline malignancy, prognosis and individual complex approach. Pathohistological analysis establishes round or spindle-shaped mononuclear cells mixed with multinucleated giant cells resembling osteoclasts [8, 17]. The available giant cells, from which the name of this bone tumor comes, are not malignant. Primitive mononuclear mesenchymal stromal cells are malignant, resembling the previous state of osteoblasts [16].

On imaging (radiography, CT and MRI) lytic areas in the affected bone with or without soft tissue component are visualized (Figure 1) [17]. Single publications identified significant risk factors for local recurrence: lesions in the cervical spinal cord ($p = 0.049$), curettage ($p < 0.001$), reoperation ($p = 0.014$) and malignancy ($p < 0.001$) [18, 19]. Favorable prognostic factors have been determined on a large database of treatment results in GCTs after RT: lack of macroscopic tumor, tumor size below 10 cm and realized TD above 42 Gy [20].

Surgery: As it is a borderline benign locally aggressive tumor, the method of treatment is surgery. The volume of surgical resection depends on the tumor location. It is desirable to perform a radical volume operation - "en-bloc" resection with clean cells resection lines / without the presence of tumor cells or resection sufficiently tight [5, 21]. In smaller lesions in the cervical spine, spondylectomy is possible, followed by a bone graft (20). After radical surgery, 85-90% local tumor control (LTC) is achieved (3). After operations on axially localized GCTs, LTC is significantly lower, due to the difficulty of performing radical surgery, and in most cases the tumors are inoperable [22-27]. In the presented clinical case, the operation is not possible, as the entire sacrum, which is the main support of the entire pelvis, must be removed. Gentle surgery (curettage or subtotal tumor excision) is used in

large pelvic and spinal tumors with myelone infiltration, due to the need to preserve a number of organ functions and the stability of the pelvis and spine [28].

More than 50% of local recurrences are diagnosed after non-radical surgery, despite improved surgical techniques and the pursuit of complete tumor removal [29]. Optimal treatment for tumors of the pelvis and sacrum is controversial [14]. Local recurrences after radiotherapy alone reach 49%, after surgery with tumor-positive resection edges -47%, after surgery with positive resection edges and subsequent RT -46% and 0% after radical surgery [14]. Pelvic and sacral GCTs require more aggressive treatment due to the high level of local recurrence after non-radical tumor excision [14, 30]. Although sacral nerve damage is possible, extensive excision is the best surgical approach, despite the high probability of sacral nerve damage [31]. Extensive excision (total sacrectomy) is associated with high morbidity and pelvic / spinal instability [30].

Radiation Therapy: An important problem in the complex treatment of GCTs is the definition of indications for radiation therapy, radiotherapy volume and the required therapeutic radiation doses, as it is a borderline benign tumor in young individuals. Radiation therapy is not routinely used, due to an increased risk of secondary neoplasms in young people, as well as the risk of sarcoma cell transformation of this borderline tumor [24]. Indications for radiotherapy are tumors with pathohistologically undifferentiated, rapidly dividing tumor cells, tumor recurrences without RT performed, mainly tumors with pelvic and cranial localization and at risk of extended surgical interventions due to unacceptable postoperative deformities [2, 31-36]. Adjuvant RT in GCTs is required after non-radical surgery (in borderline and positive tumor cell resection lines), and as definitive RT in tumor localizations with a high risk of postoperative functional deficit [11, 13]. The radiotherapy response does not depend on the stage of the disease, the tumor location, the radiotherapy parameters or the presence of a soft tissue component [13]. In repeated, pre-treated patients, RT may worsen LTC, which requires consideration of other treatment alternatives [32].

In young patients, the risk of sarcoma cell transformation (SCT) after RT should be assessed. During the X-ray therapy era, SCT is observed up to 24%, as the dose absorbed into the bone is much higher compared to megavolt radiation therapy [2, 8, 22, 24, 34, 36-44]. After high-energy RT, the SCT is from 0 to 11% [14, 35, 36, 42]. After the application of high-tech RT, statistical meta-analysis reported a low risk of about 1% [35, 37]. Sarcoma transformation after single or adjuvant RT to a mean total dose of 45 Gy was diagnosed in 3% of patients [4].

Radiation doses and local tumor control: Due to the small number of patients who have undergone RT, the optimal radiation doses have not yet been determined. High carcinogenic doses do not reduce the rate of local recurrence [14]. GCTs offers a very large range of realized through conventionally fractionated RT up to 25-35-54-64Gy [11, 32, 33]. RT to TD 35-55 Gy at average TD 43 Gy with DD 1.67-2.33 Gy achieves 65% -77% -80% LTC [12, 33]. In GCTs less than 4 cm in diameter after single RT up to TD 40-45 Gy 90% LTC is reported, and in larger ones a combination of the operative and radiological methods is recommended [45, 46]. Definitive RT in locally advanced inoperable tumors with mean

TD 56 Gy with DD 1.8-2Gy achieves bone recalcification in 84% LTC, as well as 83% 5 years and 73% 10 years progression-free survival [11]. Definitely RT up to 40-60 Gy in 15-30 fractions in 3-6 weeks achieves 90% LTC [13]. 3D conformal RT and IMRT are possible to realize high radiation doses to increase LTC without significant late radiation changes in the adjacent healthy tissues. In the presented clinical case, we performed IMRT up to OOD 64 Gy (Figure 2). After 6 months on CT, fibrosis of the soft tissue tumor component was found in the presence of osteolytic foci in the sacrum (Figure 3A/B). The pain syndrome, which at the beginning of RT was suppressed with narcotic painkillers, has completely disappeared. After 1 year of RT, the condition of the tumor formation is the same with available osteolytic and osteosclerotic areas in the sacrum (Figure 4). CT of the lung does not show secondary lesions. The patient reported a mild pelvic pain syndrome. After 2 years of RT, the condition of the tumor formation is the same with available osteolytic and osteosclerotic areas in the sacrum (Figure 5). The pain syndrome has completely disappeared. The patient is in good general condition with a good quality of life. After 3 years of diagnosis and complex treatment (radiotherapy and targeted therapy) the patient is asymptomatic, with achieved LTC, without distant metastases and without dynamics in terms of bone recalcification (Figure 6).

Conclusion

Giant cell bone tumors are rare benign, locally aggressive neoplasms involving predominantly young patients. The main treatment method is surgery. Radiation therapy is an alternative to surgery for axial bone localizations with a high risk of unacceptable postoperative deformities. RT is a gentle and effective method for inoperable, recurrent or incompletely resected tumors. Large sacral tumors are often inoperable, which requires definitive intensive-modulated radiotherapy with a high radiation dose above 60 Gy. After complex treatment (radiotherapy and targeted therapy) in inoperable sacral giant cell tumor, we achieved 3 years of local tumor control without distant metastases and without dynamics in terms of bone recalcification.

References

1. Sigwalt L, Bourgeois E, Eid A, Chantal Durand, Jacques Grif-fet, et al. (2016) A thoracic spinal bone giant cell tumor in a skeletally immature girl. A case report and literature review. *Childs Nerv Syst* 32: 873-876.
2. Suit H, Spiro I (1999) Radiation treatment of benign mesenchymal disease. *Semin Radiat Oncol* 9: 171-178.
3. Kriz J, Eich HT, Mücke R, Jens Büntzel, Rolf-Peter Müller, et al. (2012) German Cooperative Group on Radiotherapy for Benign Diseases (GCG-BD). Radiotherapy for giant cell tumors of the bone: a safe and effective treatment modality. *Anticancer Res* 32: 2069-2073.
4. Shi W, Indelicato DJ, Reith J, Kristy B Smith, Christopher G Morris, et al. (2013) Radiotherapy in the management of giant cell tumor of bone. *Am J Clin Oncol* 36: 505-508.
5. Afsoun S, Saied SA, Amir N, Hamed J (2018) En-bloc Resection of a Giant Cell Tumor Causing Cervical Vertebral Collapse. *Asian J Neurosurg* 13: 150-153.
6. Randall RL (2003) Giant cell tumor of the sacrum. *Neurosurg Focus* 15: E13.
7. Malone S, O Sullivan B, Catton C, R Bell, V Fornasier, et al. (1995) Long-term follow up of efficiency and safety of megavoltage radiotherapy in high-risk giant cell tumors of bone. *Int J Radiat Oncol Biol Phys* 33: 689-694.
8. Malawer MM, Bickels J, Meller I, RG Buch, RM Henshaw, et al. (1999) Cryosurgery in the treatment of giant cell tumor: A long-term follow-up study. *Clin Orthop* 359: 176-188.
9. Niu X, Zhang Q, Hao L, Yi Ding, Yuan Li, et al. (2006) Giant cell tumor of the extremity: Retrospective analysis of 621 Chinese patients from one institution. *J Bone Joint Surg Am* 94: 461-467.
10. Turcotte RE (2006) Giant cell tumor of bone. *Orthop Clin North Am* 37: 35-51.
11. Ruka W, Rutkowski P, Morysiński T, Zbigniew Nowecki, Marcin Zdzienicki, et al. (2010) The megavoltage radiation therapy in treatment of patients with advanced or difficult giant cell tumors of bone. *Int J Radiat Oncol Biol Phys* 78: 494-498.
12. Feigenberg SJ, Marcus Jr RB, Zlotecki RA, Mark T Scarborough, B Hudson Berrey, et al. (2003) Radiation therapy for giant cell tumors of bone. *Clin Orthop Relat Res* 411: 207-216.
13. Nair MK, Jyothirmayi R (1999) Radiation therapy in the treatment of giant cell tumor of bone. *Int J Radiat Oncol Biol Phys* 43: 1065-1069.
14. Leggon RE, Zlotecki R, Reith J, Scarborough MT (2004) Giant cell tumor of the pelvis and sacrum: 17 cases and analysis of the literature. *Clin Orthop Relat Res* 423: 196-207.
15. Martin C, McCarthy EF (2010) Giant cell tumor of the sacrum and spine: series of 23 cases and a review of the literature. *Iowa Orthop J* 30: 69-75.
16. Hart J (2018) Giant cell tumor of bone. *Pathology Outlines*. <http://www.pathologyoutlines.com>
17. Moskovszky L, Idowu B, Taylor R, Fredrik Mertens, Nicholas Athanasou, et al. (2013) Analysis of giant cell tumour of bone cells for Noonan syndrome/cherubism-related mutations. *J Oral Pathol Med* 42: 95-98.
18. Shi LS, Li YQ, Wu WJ, Z K Zhang, F Gao, et al. (2015) Imaging appearance of giant cell tumour of the spine above the sacrum. *Br J Radiol* 88: 20140566.
19. Ouyang HQ, Jiang L, Liu XG, Feng Wei, Shao-Min Yang, et al. (2017) Recurrence Factors in Giant Cell Tumors of the Spine. *Chin Med J (Engl)* 130: 1557-1563.
20. Junming M, Cheng Y, Dong C, Xiao Jianru, Yang Xinghai, et al. (2008) Giant cell tumor of the cervical spine: a series of 22 cases and outcomes. *Spine (Phila Pa 1976)* 33: 280-288.
21. Pazonis TJ, Alradwan H, Deheshi BM, Robert Turcotte, Forough Farrokhyar, et al. (2013) A systematic review and meta-analysis of En-Bloc vs Intralesional resection for giant cell tumor of bone of the distal radius. *Open Orthop J* 7: 103-108.
22. Bini SA, Gill K, Johnson JO (1995) Giant cell tumor of bone. *Clin Orthop* 321: 245-250.
23. Turcotte RE, Sim FH, Unni KK (1993) Giant cell tumor of the sacrum. *Clin Orthop Rel Res* 291: 215-221.
24. Goldenberg RR, Campbell CJ, Bonfiglio M (1970) Giant cell tumor of bone: An analysis of two hundred and eighteen cases. *J Bone Joint Surg Am* 52: 619-664.
25. Turcotte RE, Wunder JS, Isler MH, Robert S Bell, Norman Schachar, et al. (2002) Giant cell tumor of long bone: A Canadian Sarcoma Group study. *Clin Orthop* 397: 248-258.
26. Ward WG Sr, Li G III (2002) Customized treatment algorithm

- for giant cell tumor of bone: Report of a series. *Clin Orthop* 397: 259-270.
27. Macrove RC, Weiss LD, Vaghaiwalla MR, Pearson R (1978) Cryosurgery in the treatment of giant cell tumor of the bone. *Cancer* 41: 957-969.
 28. Kriz J, Eich HT, Mücke R (2012) German Cooperative Group on Radiotherapy for Benign Diseases (GCG-BD). Radiotherapy for giant cell tumors of the bone: A safe and effective treatment modality. *Anticancer Res* 32: 2069-2073.
 29. Smitherman SM, Tatsui CE, Rao G, Garrett Walsh, Laurence D Rhines (2010) Image-guided multilevel vertebral osteotomies for en bloc resection of giant cell tumor of the thoracic spine: case report and description of operative technique. *Eur Spine J* 19: 1021-1028.
 30. Marcove RC, Sheth DS, Brien EW, Huvos AG, Healey JH (1994) Conservative surgery for giant cell tumors of the sacrum. The role of cryosurgery as a supplement to curettage and partial excision. *Cancer* 74: 1253-1260.
 31. Lin P, Lin N, Teng W (2018) Recurrence of Giant Cell Tumor of the Spine after Resection: A Report of 10 Cases. *Orthop Surg* 10: 107-114.
 32. Caudell JJ, Ballo MT, Zagars GK (2003) Radiotherapy in the management of giant cell tumor of bone. *Int J Radiat Oncol Biol Phys* 57: 158-165.
 33. Guo W, Tang XD, Li X, Ji T, Sun X (2008) The analysis of the treatment of giant cell tumor of the pelvis and sacrum. *Zhonghua Wai Ke Za Zhi* 46: 501-505.
 34. Caudell JJ, Ballo MT, Zagars GK (2003) Radiotherapy in the management of giant cell tumor of bone. *Int J Radiat Oncol Biol Phys* 57: 158-165.
 35. Feigenberg SJ, Marcus RB Jr, Zlotecki RA (2003) Radiation therapy for giant cell tumors of bone. *Clin Orthop Relat Res* 411: 207-216.
 36. Chakravarti A, Spiro IJ, Hug EB (1999) Megavoltage radiation therapy for axial and inoperable giant-cell tumor of bone. *J Bone Joint Surg Am* 81: 1566-1573.
 37. Roeder F, Timke C, Zwicker F (2010) Intensity modulated radiotherapy (IMRT) in benign giant cell tumors – a single institution case series and a short review of the literature. *Radiat Oncol* 5: 18-23.
 38. Cooper AS, Travers B (1999) *Surgical essays*. London: Cox, Longman & Co, 1818.
 39. Jaffe HL, Portis RB (1940) Giant cell tumor of Bone. Its pathologic appearance, grading. Supposed variants and treatment. *Arch Pathology* 30: 993.
 40. Mankin HJ, Doppelt SH, Sullivan TR, Tomford WW (1982) Osteoarticular and intercalary allograft transplantation in the management of malignant tumors of bone. *Cancer* 50: 613-630.
 41. Mendenhall WM, Zlotecki RA, Scarborough M (2006) Giant cell tumor of bone. *Am J Clin Oncol* 29: 96-99.
 42. Ruka W, Rutkowski P, Morysinski T, Nowecki Z, Zdzienicki M (2003) The megavoltage radiation therapy of patients with advanced or difficult giant cell tumor of the bone. *Int J Rad Oncol Biol Phys* 78: 494-498.
 43. Campanacci M, Baldini N, Boriani S, Sudanese A (1987) Giant cell tumor of bone. *J Bone Joint Surg Am* 69: 106-114.
 44. Dahlin DC, Cupps RE, Johnson EW (1970) Giant cell tumor: A study of 195 cases. *Cancer* 25: 1061-1070.
 45. Shi W, Indelicato DJ, Reith J, Smith KB (2013) Radiotherapy in the management of giant cell tumor of bone. *Am J Clin Oncol* 36: 505-508.
 46. Leszek Miszczyk, Jerzy Wydmański, Jerzy Spindel (2001) Efficacy of radiotherapy for giant cell tumor of bone: given either postoperatively or as sole treatment. *International Journal of Radiation Oncology, Biology, Physics* 49: 1239-1242.

Copyright: ©2020 Lena Marinova. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.