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Review Article

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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

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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).

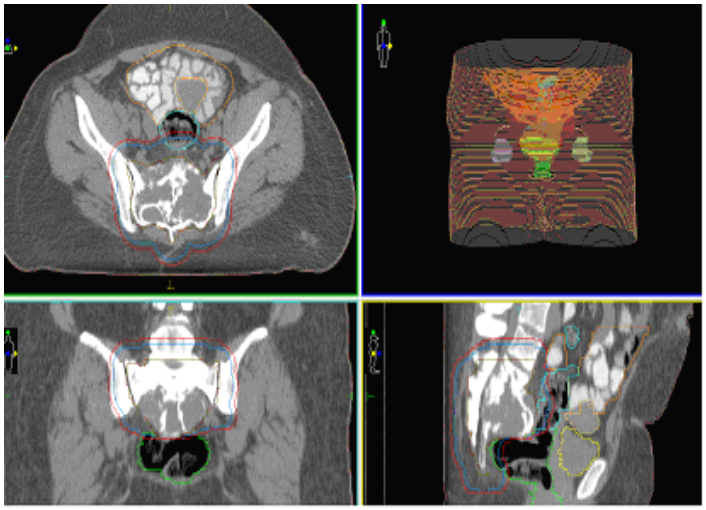

Figure 1: Localization CT of a sacral giant cell tumor with delineation of the radiotherapy volumes (CTV and PTV) before the radiotherapy.

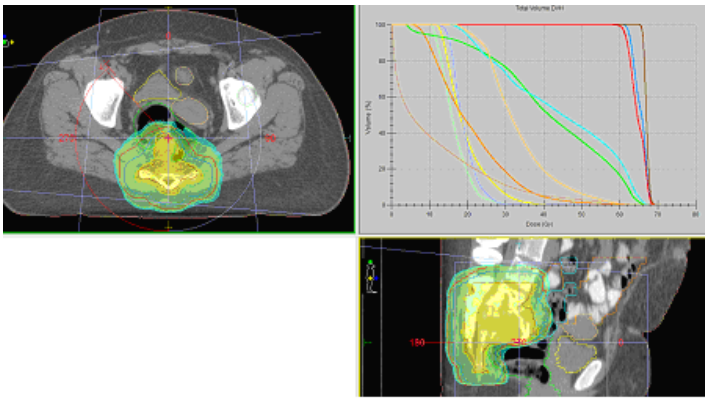

Figure 2: Intensive-modulated RT equipment for sacral giant cell tumor up to TD 64 Gy with DD 2 Gy

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.

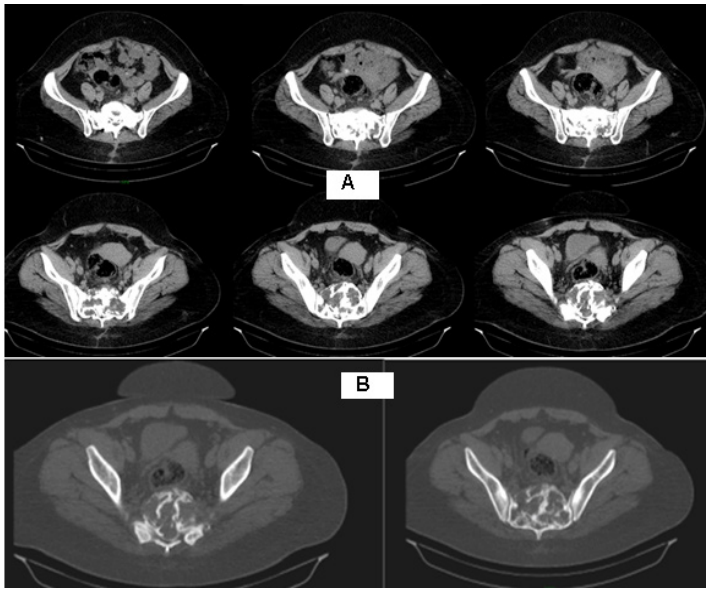

Figure 3: A/CT of the sacrum 6 months after definitive radiotherapy up to TD 64 Gy with DOD 2 Gy with a fibrous soft tissue component; B/ CT of a bone window

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.

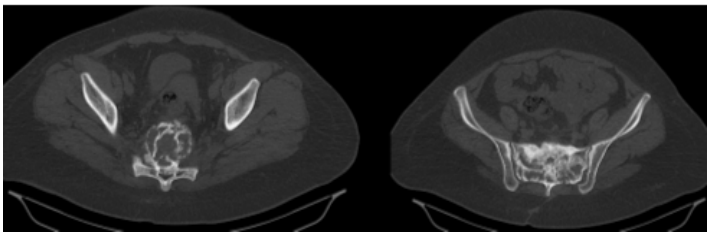

Figure 4: CT of a bone window after 1 year from definitive radiotherapy up to TD 64 Gy combined with targeted therapy.

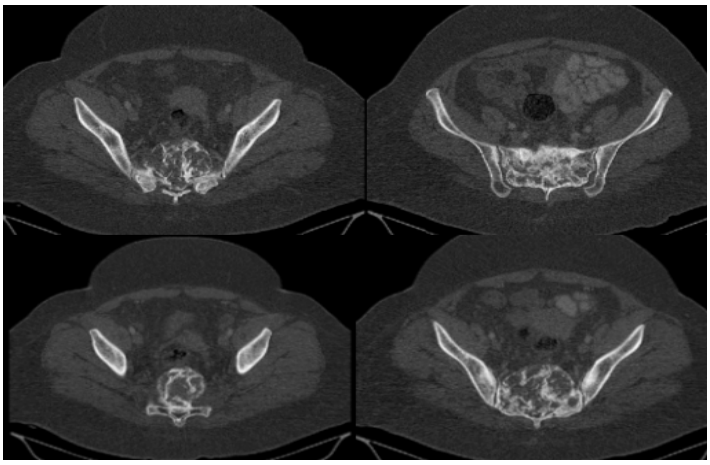

Figure 5: CT CT of a bone window after 2 years from definitive radiotherapy up to TD 64 Gy combined with targeted therapy.

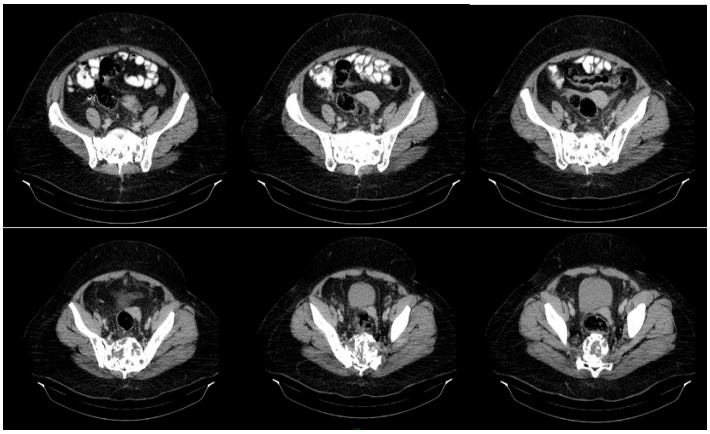

Figure 6: CT of the sacrum after 3 years from definitive radiotherapy up to TD 64 Gy combined with targeted therapy.

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.

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