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Radiotherapy for osteoblastoma: the 25-year institutional experience

Bartłomiej Szostakowski[1], Tadeusz Morysiński[1], Piotr Rutkowski[1], Mateusz Jacek Spałek[1, 2]

[1]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[2]Department of Radiotherapy 1, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

ABSTRACT

Background: Osteoblastoma (OB) is a rare benign bone tumor, mainly affecting adolescents and young adults. It's commonly found in the spine and long bones, with a male-to-female ratio of 2:1. Surgery, primarily en bloc resection or curettage, is the main treatment. Radiotherapy (RT) or systemic treatment is considered in specific cases. However, optimal RT strategies remain unclear due to limited and outdated data. This study aims to evaluate RT role, efficacy, and safety in treating OB.

Matrials and methods: The study group was a cohort of consecutive patients with OB treated in our institute that received RT in years 1998–2023. We analyzed indication for RT, irradiated site, RT technique, total dose, dose per fraction, early and late tolerance, and survival.

Results: Thirteen patients meeting the criteria were analyzed. Most were males (10 out of 13) with a median age of 21. Most OBs were within the vertebral column. All patients received definitive RT for unresectable disease and underwent conventionally fractionated RT (1.8–2.0 Gy per fraction) to total doses 40–70.2 Gy. Only mild acute toxicity was observed. No late toxicity was reported. The median follow-up was 118 months. Local progression was observed in four patients, all of whom died.

Conclusions: RT is a valuable option for certain OB patients ineligible for surgery. Seeking treatment at specialized bone tumor centers with RT techniques is crucial due to OB's rarity and the lack of standardized guidelines. Recommended RT doses fall between 50–70 Gy using intensity-modulated techniques in conventional 1.8–2 Gy fractions.

Key words: osteoblastoma; bone tumor; radiotherapy; rare cancer; benign tumor

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Introduction

Osteoblastoma (OB) is a rare benign tumor that can be locally aggressive. It accounts for approximately 3% of all benign bone tumors and 1% of primary bone tumors [1]. The main differential diagnosis is osteosarcoma. OB has a reported male to female ratio of 2:1 and can occur in a wide age range, although it is most commonly observed in adolescents and young adults. It is rarely observed before the age of 10 or after the age of 30. OB is composed of osteoblasts that produce osteoid and bone. Its histology is usually similar to that of osteoid osteoma, from which it can be distinguished by symptoms and radiologic appearance. Osteoblastomas are also larger than 2 cm in diameter, whereas osteoid osteomas are usually less than 1.5 cm. The term 'benign OB' was first proposed by Jaffe and Lichtenstein in 1956 [2, 3] to describe a benign tumor characterized by the abundant presence of osteoblasts, as well as vascular and bone-forming features. OB commonly occurs in the vertebral col-

Address for correspondence: Mateusz Jacek Spałek, Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; e-mail: mateusz.spalek@nio.gov.pl

umn [3], followed by long tubular bones where it is usually observed in the metadiaphysis, hands, feet, and ribs [4]. Another common site is the mandible, where it is referred to as cementoblastoma.

According to Boriani et al., around 40% of OB occur in the spine, often leading to scoliosis, particularly in males [5]. Thoracic lesions are more prevalent than lumbar lesions, and neurological involvement is directly linked to erosion of the cortex. There is a tendency to form a soft tissue component that invades the spinal canal and affects the nerve roots. The pedicle and lamina are the areas more commonly affected than the body of the vertebra [6].

The main treatment for patients with OB is surgery. En bloc resection is the preferred approach, when possible, as it results in a lower risk of local recurrence or curettage, depending on the clinical situation, location within the bone, and suspicion of malignancy. In certain cases, local excision may be followed by adjuvant radiotherapy (RT) to complement surgical resection [7].

Systemic treatment should be reserved for cases where local treatment, including RT, is not possible or effective, or in rare situations where osteoblastoma has converted into osteosarcoma [7, 8] In the case of benign OB, promising results have been achieved with denosumab [9, 10]. Malignant variants are usually treated with regimens used in osteosarcoma [11].

Definitive RT, defined as treatment delivered to macroscopic disease, is a viable treatment option for residual, unresectable or recurrent osteoblastoma [12, 13]. However, the optimal indications, fractionation, total dose and RT technique remain unknown due to lack of data. The available publications are mostly case reports. Furthermore, most of the data are outdated and do not include recent developments in radiation oncology. The aim of this study is to evaluate the indications, efficacy and safety of RT in patients with OB treated at a tertiary sarcoma center.

Materials and methods

A retrospective review of a cohort of consecutive patients with a diagnosis of OB confirmed by central pathology review by experienced bone tumor pathologists. All patients received definitive RT at our institution between 1998 and 2023. Clinical data were obtained from medical records and the RT planning system (when available).

We performed a search of all available electronic medical records using MedStream Designer software from Transition Technologies. We analyzed the following parameters: indication for RT, irradiated site, total dose, dose per fraction, RT techniques, target volumes, organs at risk, early and late toxicity, local control, and survival. Toxicity was graded according to the Common Terminology Criteria for Adverse Events 5.0. All available records were independently reviewed by two coauthors. Missing data on date of death were obtained from the National Cancer Registry when available. Patients with missing data were excluded from the analysis.

Follow-up time was calculated using the reverse Kaplan-Meier method. Data analysis was performed using the R software environment, version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) and the jamovi project, version 2.3.28 (obtained from https://www.jamovi.org, Sydney, Australia).

Results

Patients' characteristics

We found 83 patients who were treated or consulted for osteoblastoma between 1998 and 2023. Of these, thirteen patients met the inclusion criteria (Fig. 1). Of these, ten were male and three were female. The median age was 21 years, with a minimum of 17 years and a maximum of 68 years. All but three of the OBs were located within the vertebral column. Patient characteristics are summarized in Table 1.

Radiotherapy parameters

All patients received definitive RT for unresectable disease, mostly in the thoracic and lumbar spine. All patients received conventionally fractionated RT (1.8–2.0 Gy per fraction) for total doses ranging from 40–70.2 Gy. Seven patients were treated with older RT techniques, namely two-dimensional and three-dimensional static RT, while six patients were treated with intensity-modulated techniques, which allow better sparing of organs at risk, especially the spinal cord (Fig. 2). All RT-related parameters are shown in Table 2.

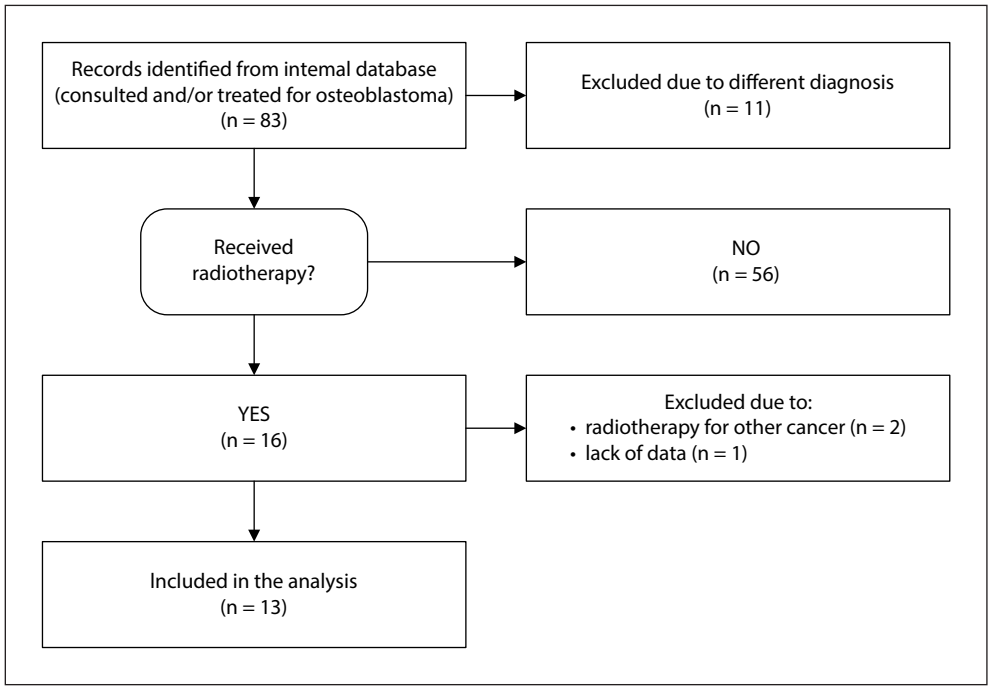

Figure 1. Data extraction flow chart

Table 1. Patients' characteristics

Patient number	Sex	Age at diagnosis	Date of diagnosis	Tumor site	Treatment before radiotherapy	Clinical situation	Start of radiotherapy
1	Male	31	09.1999	Thoracic spine	None	Unresectable primary	11.1999
2	Female	21	03.2000	Thoracic spine	Surgery	Unresectable recurrence	07.2003
3	Male	32	10.2008	Lumbar spine	Surgery	Unresectable recurrence	02.2010
4	Female	17	02.2009	Pelvis	Surgery	Unresectable recurrence	11.2011
5	Male	17	10.2009	Thoracic spine	Surgery	Unresectable recurrence	05.2010
6	Female	19	05.2010	Thoracic spine	None	Unresectable primary	12.2010
7	Male	27	02.2012	Lumbar spine	Surgery	Unresectable recurrence	08.2012
8	Male	68	02.2012	Phalanx	None	Unresectable primary (refused amputation)	07.2012
9	Male	19	10.2012	Pelvis	Macroscopically non-radical (R2) surgery	Remaining tumor	04.2013
10	Male	48	11.2012	Lumbar spine	Macroscopically non-radical (R2) surgery	Remaining tumor	08.2013
11	Male	19	01.2013	Tibia	Surgery	Unresectable recurrence	06.2013
12	Male	46	11.2014	Lumbar spine	None	Unresectable primary	06.2015
13	Male	19	06.2022	Thoracic spine	None	Unresectable primary	01.2023

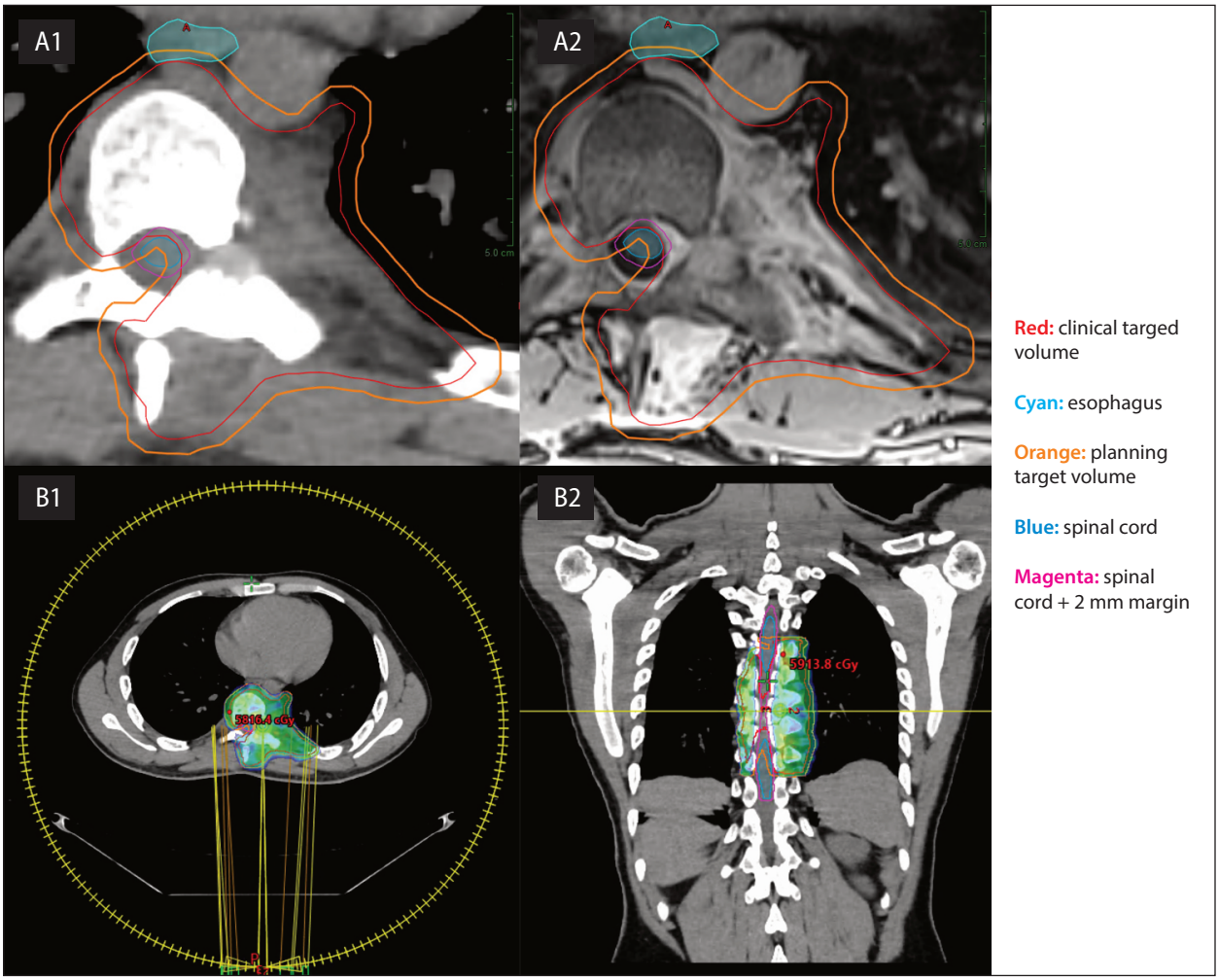

Figure 2. Radiotherapy planning in a patient with osteoblastoma; **A**. Tumor delineation based on planning computed tomography (**A1**) with planning magnetic resonance imaging (A2); **B**. Volumetric modulated arc therapy plan, the dose distribution of 56 Gy in 2 Gy fractions in transversal (**B1**) and coronal views (**B2**), 95% of the prescribed dose (53.2 Gy)

Toxicity and efficacy

RT appeared to be well tolerated. Only grade 1 and 2 skin and gastrointestinal toxicities were reported in the medical records (Tab. 2). No significant late toxicity was reported.

The median follow-up was 117 [93 — not reached, 95% confidence interval (CI)] months. The Kaplan-Meier plot for follow-up is shown in Figure 3. Four patients showed local progression and, unfortunately, all of them died. Two of these patients also developed distant metastases and were treated with chemotherapy. The remaining two patients underwent salvage surgery. The oldest patient in our cohort died of unknown causes at the age of 76 years. He died eight years after RT with no evidence of disease progression. Eight patients had no evidence of disease at the longest recurrence-free survival time of twelve years. All data are summarized in Table 3.

Discussion and conclusions

This study presents the largest cohort of patients with OB who underwent definitive RT. Our analysis shows that RT enables high local control with excellent treatment tolerance. Although a review of the available literature shows that RT is rarely used for definitive treatment of OB, some authors advocate the use of RT after intralesional curettage to aid surgical excision [7, 12–16]. In all of the aforementioned reports, the authors described a similar efficacy and favorable toxicity profile of RT. Recurrence-free survival of up to 25 years after adjuvant RT for

Table 2. Radiotherapy parameters and acute toxicity

Patient number	Technique	FD [Gy]	TD [Gy]	CTV [cm^3]	PTV [cm^3]	CTV-PTV margin [cm]	Number of fields or arcs	Imaging	Spinal cord with margin maximum in 0.035 cm^3 [Gy]	Volume of small bowel that received 45 Gy or more [cm^3]	Acute toxicity [grade]
1	Co-60 + electrons	2	56	ND	ND	ND	ND	ND	ND	ND	Nausea G2, vomiting G2
2	2D-RT	1.8	50.4	ND	ND	ND	3	MV	ND	ND	None
3	IMRT	1.8	70.2	ND	2171.78	ND	9	kV	40.2	516	Skin G1
4	3D-CRT	2	70	19.53	89.2	1	3	kV	ND	ND	Skin G1
5	IMRT	2	70	ND	627.96	ND	9	kV	41.2	ND	Skin G2, mucosal G1
6	IMRT	2	70	ND	173.54	ND	7	kV	32	ND	Skin G2
7	IMRT	1.8	50.4	1122	1307.99	0.3	7	MV	ND	6.7	Diarrhea G1
8	3D-CRT	2	50	40.79	74.39	0.5	2	MV	ND	ND	None
9	3D-CRT	2	50	563.51	976.24	1	5	kV	ND	152.3	Skin G2
10	3D-CRT	2	40*	739.31	977.04	0.5	4	kV	ND	ND	None
11	3D-CRT	2	50	344.8	514.2	0.5	2	kV	ND	ND	Skin G1
12	IMRT	1.8	50.4	527.89	728.42	0.7	9	kV	44.9	ND	Skin G2
13	VMAT	2	56	332.13	451.88	0.3	3	CBCT	44.2	ND	Skin G1

2D-RT — two-dimensional radiotherapy; 3D-CRT — three-dimensional conformal radiotherapy; CBCT — cone beam computed tomography; CTV — clinical target volume; FD — fraction dose; IMRT — intensity modulated radiotherapy; kV — kilovoltage portal imaging; MV — megavoltage portal imaging; ND — no data; PTV — planning target volume; TD — total dose; VMAT — volumetric modulated arc therapy; *The dose may be reduced by the treating radiation oncologist due to the length of the target volume (the entire lumbar spine) and the associated proximity of the bowel; however, this is only the authors' hypothesis

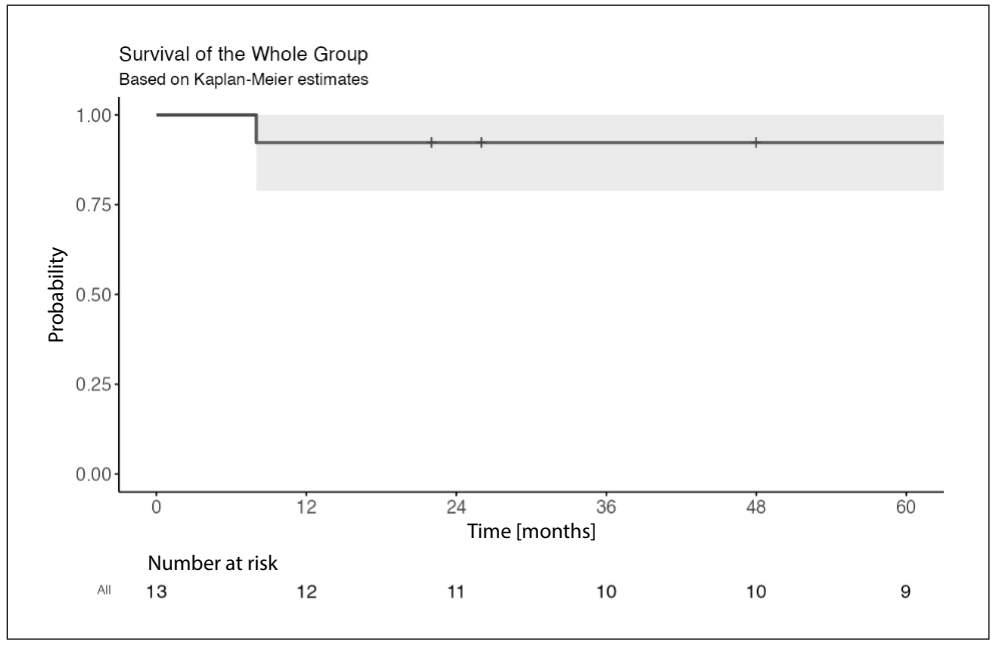

Figure 3. Reverse Kaplan-Meier plot for follow-up

Table 3. Efficacy and survival

Patient number	Local progression	Date of local progression	Distant metastases	Date of distant relapse	Salvage treatment	Survival at the last follow-up	Date of death or last follow-up
1	Yes	12.2000	Yes	12.2000	CHT*	DOD	02.2002
2	Yes	08.2013	No		Surgery	DOD	08.2021
3	Yes	05.2013	Yes	02.2014	CHT#	DOD	02.2014
4	No		No			NED	07.2022
5	Yes	02.2011	No		Surgery	DOD	03.2012
6	No		No			NED	03.2023
7	No		No			NED	08.2022
8	No		No			DOO	03.2020
9	No		No			NED	04.2023
10	No		No			NED	01.2021
11	No		No			NED	10.2021
12	No		No			NED	04.2023
13	No		No			NED	09.2023

CHT — chemotherapy; DOD — dead of disease; DOO — dead of other; NED — no evidence of disease; *First line: doxorubicin, cisplatin; second line: doxorubicin, ifosfamide; #First line: doxorubicin, cisplatin; second line: gemcitabine

osteoblastoma has been reported in the literature [14, 16].

One may wonder why two patients in our cohort developed distant metastases in the case of benign tumor. The first explanation could be the misdiagnosis of the primary tumor, which could have been misdiagnosed as osteosarcoma, especially osteoblastoma-like osteosarcoma. The differential diagnosis of osteoblastoma-like osteosarcoma from OB is challenging but crucial due to dramatically different clinical behavior and high risk of metastatic spread [17, 18]. Another scenario is related to the rare phenomenon of malignant transformation of OB to osteosarcoma that has been described in the literature [8]. However, we are unable to confirm any of these hypotheses due to the lack of secondary biopsies after disease progression and the lack of formalin-fixed paraffin-embedded blocks that were sent for consultation and returned to the primary pathology laboratory.

This study has limitations. The sample of patients obtained may not accurately represent the entire population of patients with OB due to selection bias resulting from the retrospective nature of the analysis. To mitigate this bias, two coauthors (BS, MJS) independently reviewed all data. However, due to the retrospective approach and events spanning decades, there is a significant risk of incomplete or misinterpreted data. This risk is compounded by changes in diagnostic tools, RT techniques, and treatment modalities over the past 25 years. As a result, our cohort may not be a true reflection of the current population. In addition, it was difficult to determine why some patients received a higher total dose than others, especially those who received only 40 Gy, which, interestingly, allowed for long-term local control. In addition, the retrospective assessment of toxicity is based solely on written physician observations, which may have been very brief, especially in the case of late toxicity. The recommended follow-up regimen for non-malignant tumors at our center is at least every six months for two years, followed by once a year for the next few years. Importantly, in the case of severe toxicity, physicians usually report it accurately. However, the results of the analysis should be interpreted with caution. Although the study has limitations, it provides valuable insights for multidisciplinary teams considering RT as a treatment for a patient with OB.

Future research on the role of RT for OB should focus on two unresolved aspects. First, we have no data on the role of innovative RT approaches in OB, namely stereotactic body RT (SBRT) and particle therapy [19]. SBRT has been shown to be an effective and safe way to treat metastases from radioresistant tumors, such as kidney cancer or bone sarcomas, as well as radioresistant benign tumors located near vital organs at risk [20–23]. Furthermore, SBRT seems to be a more cost-ef-

fective and convenient option than conventionally fractionated RT [24, 25]. Unfortunately, there are no published data on the role of SBRT in OB.

Other interesting options for patients with OB, especially when tumor is close to the critical nervous structures, could be protons and heavy ions. They show a phenomenon called a "Bragg peak" [26]. This means that these particles put most of their energy into the last part of their path as they slow down. Attiah et al. presented a case of a patient with OB of the temporal bone who underwent gross total resection followed by adjuvant proton therapy [27]. Heavy ions may be useful in the treatment of radioresistant and slow-growing tumors such as OB [28]. This is due to their higher linear energy transfer, less dependence on hypoxia, and ability to cause more double-strand breaks in DNA. Honda et al. reported a case of a lumbar multiple recurrent OB who underwent successful carbon ion therapy with ten years of follow-up without disease progression and significant late toxicity [29].

The second aforementioned area for further research is contouring. Currently, there is no consensus or established recommendations for contouring in RT for OB. This is due to the complexity of contouring caused by the different radiological presentations of OB. At a minimum, contouring should be based on planning computed tomography and planning magnetic resonance imaging. The question of whether to include an elective margin for subclinical disease spread that cannot be fully imaged remains unanswered.

In conclusion, RT is a valuable treatment option in selected patients with OB who are ineligible for definitive surgery or where the size or location of the tumor is not amenable to surgical resection. Due to the rarity of OB and the lack of recommendations, it is highly recommended that patients be treated at tertiary bone tumor centers with access to modern RT techniques. Total doses between 50–70 Gy in conventional 1.8–2 Gy fractions delivered with dose intensity modulation techniques should be considered as the recommended approach.

Author contributions

All authors contributed to the conception and design. Conceptualization, B.S., M.J.S.; methodology, B.S., M.J.S.; software, M.J.S.; validation, P.R., M.J.S.; formal analysis, B.S., T.M., M.J.S.; investigation, B.S., M.J.S.; funding acquisition, M.J.S.; resources, T.M., M.J.S.; data curation, B.S., M.J.S.; writing–original draft preparation, B.S., T.M., P.R., M.J.S.; writing–review and editing, B.S., T.M., P.R., M.J.S; visualization, M.J.S.; supervision, P.R., M.J.S.; project administration, B.S., M.J.S. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Data availability

All data generated or analyzed during this study are available in the manuscript.

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