Radiotherapy for marginally resected, unresectable or recurrent giant cell tumor of the bone: a rare cancer network study

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Abstract

The role of radiotherapy for local control of marginally resected, unresectable, and recurrent giant cell tumors of bone (GCToB) has not been well defined. The number of patients affected by this rare disease is low. We present a series of 58 patients with biopsy proven GCToB who were treated with radiation therapy. A retrospective review of the role of radiotherapy in the treatment of GCToB was conducted in participating institutions of the Rare Cancer Network. Eligibility criteria consisted of the use of radiotherapy for marginally resected, unresectable, and recurrent GCToB. Fifty-eight patients with biopsy proven GCToB were analyzed from 9 participating North American and European institutions. Forty-five patients had a primary tumor and 13 patients had a recurrent tumor. Median radiation dose was 50 Gy in a median of 25 fractions. Indication for radiation therapy was marginal resection in 33 patients, unresectable tumor in 13 patients, recurrence in 9 patients and palliation in 2 patients. Median tumor size was 7.0 cm. A significant proportion of the tumors involved critical structures. Median follow-up was 8.0 years. Five year local control was 85% . Of the 7 local failures, 3 were treated successfully with salvage surgery. All patients who received palliation achieved symptom relief. Five year overall survival was 94%. None of the patients experienced grade 3 or higher acute toxicity. This study reports a large published experience in the treatment of GCToB with radiotherapy. Radiotherapy can provide excellent local control for incompletely resected, unresectable or recurrent GCToB with acceptable morbidity.

Introduction

Giant cell tumors of the bone compose 5% of all bone tumors. They have a slight female predominance and are the most common during the third and fourth decade of life. Histologically these tumors exhibit mononuclear stromal cells and multinucleated giant cells. It is believed that these stromal cells promote the growth of multinucleated osteoclast-like cells.[1,2] Despite their histology, a small portion of these tumors develop hematogenous metastasis. These patients, however, can still have long survival due to the indolent nature of this disease. As these tumors can be locally aggressive, local control is very important. Surgery, typically consisting of en bloc resection with negative margins, remains the most important treatment modality. However, in many instances, these tumors occur in places not amenable to complete surgical resection. The role of radiotherapy remains to be defined.[3-5] We report the results of a large multi-institutional experience evaluating the role of radiotherapy for marginally resected, unresectable and recurrent GCToB.

Materials and Methods

A retrospective review of the role of radiotherapy in 58 consecutively treated patients with GCToB was conducted in 9 participating institutions of the Rare Cancer Network. Eligibility criteria consisted of the role of radiotherapy for marginally resected, unresectable or recurrent GCToB. Cancers that were deemed unresectable by the surgeon were due to location adjacent to critical structures that would compromise function. Primary study endpoints included local failure (LF) and overall survival (OS) rates. Secondary endpoints included toxicity, secondary malignancy occurrence, and prognostic factors. The Kaplan-Meier actuarial method was used to calculate survivals and tumor failures. Log-Rank testing was used to determine prognostic factors. This study was approved by the Mayo Foundation Institutional Review Board and at each participating site independently.

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Results

Patient and tumor characteristics

A total of 58 patients with biopsy proven GCToB of histology ICD-0-3-92501 and 92503 were analyzed from European and North American academic centers (Table 1). Forty-five patients had a newly diagnosed GCToB with a median number of tumors at presentation of 1 (range 1 to 2). Thirteen patients had a recurrent tumor with a median number of localizations at presentation of 1 (range 1 to 4).

Median age was 31 years (range 12 to 84). Median tumor size was 7 cm (range 2 to 15 cm). A significant portion of the tumors involved the long bones of the lower limb. In 55% of the cases, critical structures were involved, of which the sacral plexus was the most common one.

Treatment characteristics

Thirteen patients had an unresectable tumor and therefore did not have surgery as a component of their treatment (Table 2). Of the patients who had surgery, 30 patients had a R1 resection and 26 patients had a R2 resection. R1 resection was defined as microscopic disease left behind and R2 defined as gross disease left behind at the time of surgery. Out of the 26 patients who underwent a R2 resection, the largest diameter of the residual tumor was known for 14 patients. The median diameter of residual disease after R2 resection was 9.5 cm (range 2.0 to 14.0 cm).

All patients received radiation between 1976 to 2007. Indications for radiotherapy were recurrent GCToB after prior therapy, unresectable GCToB due to potential involvement of

adjacent critical structures, marginal resection of GCToB without critical structure involvement and other indications where the risk of recurrence was deemed high enough to warrant adjuvant or definitive radiotherapy. An additional two patients received treatment for palliation. The most common indication was marginal resection or residual tumor. Median radiation dose was 50Gy (range 20 to 64.8Gy). Median number of fractions was 25 (range 5 to 36 fractions). Median dose per fraction was 2Gy. Median energy used was 6MV photons (range 1.25 to 25). For purposes of analysis, a local RT field was defined as GTV plus a margin that was less than or equal to 4 cm to the geometric edge of the radiotherapy field.

Overall survival

Median follow up was 8 years (range 4 months to 28.2 years). Survival information was available on all 58 patients. Five-year overall survival was 94% (Figure 1). There were 5 deaths. Cause of death was GCToB in 2 patients, unknown in 1 patient.

Disease free survival

Data was available for 54 patients. Five-year disease free survival was 81% (Figure 2). Of the 10 patients with failures, 2 patients had distant failures, 7 patients had local failures and one patient had both local and distant failure.

Local control

Five year local control was 85% (Figure 3). Of the 7 local failures, 3 failures were salvaged successfully with surgery. All palliative patients achieved symptom relief with radiation. Eleven patients received chemotherapy.

Toxicity

Twenty-eight patients did not experience any acute toxicity. Of the patients who experienced toxicity, the most common acute toxicity consisted of grade 1-2 skin changes. None of the patients experienced grade 3 or higher acute toxicity. Forty-six patients did not suffer from any chronic toxicity. Of patients who experienced chronic toxicity, the most common chronic toxicity consisted of skin changes. Two patients experienced grade 3 toxicity. This consisted of grade 3 anovulatory toxicity in one patient and grade 3 irregular menses in the other patient.

One patient developed an adenocarcinoma of the uterine cervix as a possible secondary malignancy in the field of radiation.

Prognostic factors

Univariate analysis did not reveal an association between gender, histology, grade, tumor type, tumor location, tumor size, R1/R2 resection, radiation dose, or indication of radiation (Table 3). There was a trend for improved 5 year local control in patients less than 30.8 years when compared to the older group (96% compared to 73%). There was improved disease free survival and overall survival in the younger age group as well (96% compared to 65%) and (100% compared to 87%) respectively.

Table 1. Patient and tumor characteristics.

Characteristics	Number of patients (%)
Age	
Age > 30.8 years	27 (49)
Age ≤ 30.8 years	28 (51)
Gender	
Male	30 (55)
Female	25 (45)
Histology	
92501	54 (93)
92503	4 (7)
Grade	
Grade 1	9 (35)
Grade 2	13 (50)
Grade 3	4 (15)
Tumor Dimension	
≥ 4cm	35 (78)
< 4 cm	10 (22)
Tumor Type prior to treatment	
Primary	45 (78)
Recurrence	13 (22)
Primary bones involved	
Appendicular	28 (48)
Axial	30 (52)
Primary bones involved by site	
Lower limb long bone	23 (40)
Upper limb long bone	5 (9)
Lower limb small bone	0 (0)
Upper limb small bone	2 (3)
Craniofacial	2 (3)
Vertebral cervical	3 (5)
Vertebral thoracic/lumbar	8 (14)
Ribs/clavicle	1 (2)
Pelvic bones	10 (17)
Bones lumbar to pelvic	4 (7)
Most critical structures involved	
None	26 (45)
Craniofacial	2 (3)
Brain/Spinal Cord	7 (12)
Sacral Plexus	13 (22)
Genitourinary tract	0 (0)
Joint	4 (7)
Neurovascular structure	2 (3)
Other	4 (7)

Table 2. Treatment and radiation therapy characteristics.

Characteristic	Number of patients (%)
Extent of resection	
R0	2 (3)
R1	30 (52)
R2	26 (45)
Indication for radiation	
Marginal resection, residual tumor	33 (58)
Unresectable due to critical structures	13 (23)
Recurrence	9 (16)
Palliation	2 (4)
Radiation Dose	
>50Gy	25 (43)
≤50 Gy	33 (57)
Radiation fractions	
≥25 fractions	41 (71)
<25 fractions	17 (29)
Radiation delivery	
Co-60	24 (44)
Linear Accelerator	22 (40)
Co-60 and Linear Accelerator	3 (5)
Roentgen therapy (X-ray)	2 (4)
Other	4 (7)
Field description	
Local	48 (83)
Wide	10 (17)

Discussion

Giant cell tumors of bone are locally aggressive tumors with little tendency for metastasis.[1] The treatment of choice for these tumors, historically, has been surgical resection.[1] In some cases, surgical resection can result in

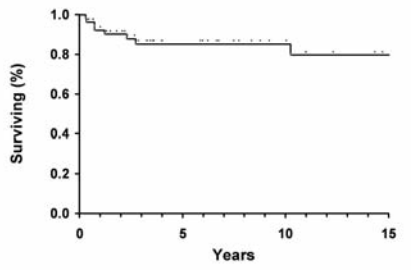

Figure 1. Overall survival.

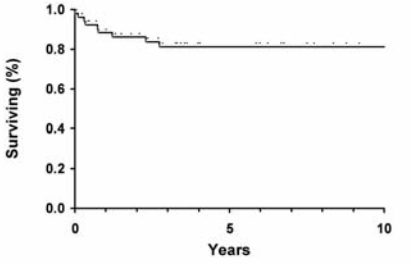

Figure 2. Disease free survival.

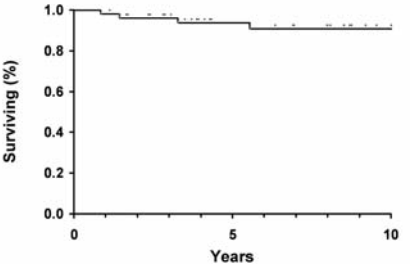

Figure 3. Local control.

Table 3. Prognostic factors assessed on univariate analysis.

Prognostic factor	Overall survival	Disease free survival	Local Control
Age	.03	.03	.09
Gender	.69	.42	.28
Grade	.14	.68	.29
Histology	.21	.33	.42
Tumor type (primary *vs.* recurrence)	.15	.45	.61
Tumor location (appendicular *vs.* axial)	.94	.15	.49
Tumor size	.76	.87	.45
Extent of resection	.90	.75	.89
Indication for radiation	.15	.76	.78
Radiation dose	.99	.44	.60

All numbers represent P values.

severe impairment. In other cases, the site of the tumor and the neighboring organs render them inoperable.[3] However, marginal resections result in a high rates of recurrence, mostly occurring within the first couple of years, justifying the use of adjuvant therapy.

GCToB are well responsive to radiation therapy. Local control following adjuvant or primary radiation therapy has ranged from 69% to 90% according to recent studies.[1,3,6,7,8,9]

Our study reports a large published experience in the treatment of GCToB with radiotherapy. The use of radiotherapy in this study resulted in an 85% local control rate. We were unable to identify any significant prognostic factors except for age. Possible explanations for this prognostic factor could be selection bias and the choice for more aggressive surgery in younger patients.

Other studies of GCToB have identified size and location as having a significant impact on local control. Miszczyk *et al.* identified tumor size >4 cm as a negative prognostic factor for local control.[8] Caudell *et al.* and Feignberg *et al.* identified recurrent tumors as a negative prognostic factor for local control.[3,10] Feignberg *et al.* also identified a dose-effect relationship with radiation, which revealed a correlation between doses of 40 Gy or less and a failure in local control.[3] Our analysis did not find any correlation with site, size or dose in terms of local control or outcome. This could possibly be explained by the high local control rate achieved in our study and the inability to identify a poor prognostic group. Additionally, the median radiation dose utilized was 50Gy. Another possible explanation could be the heterogeneity of the patient population.

This study confirms the safety and efficacy of radiation therapy as treatment for GCToB. The median follow up for patients within this study was 8 years (range 4 months to 28.2 years). To date, none of the patients in this study developed malignant transformation of the GCToB or a radiation induced sarcoma. It is important to note that one patient developed an adenocarcinoma of the uterine cervix after treatment of her GCToB. This can possibly be attributed to a secondary malignancy from use of radiation therapy.

This is a multi-institutional study that was retrospectively performed. The limitations include the retrospective nature, lack of uniform treatment and follow up as well as possible selection bias. However, despite these limitations, our results in a fairly large group of patients with this very uncommon disease confirm the findings of other studies in this rare disease site with the use of radiation therapy.

It should be noted that the use of radiation therapy for treatment of GCToB has significantly improved the local control rates for this rare tumor when compared to local control rates for GCToB in which the sole treatment is surgical resection. We suggest that the treatment decision is made at a multidisciplinary level to judge on an individual patient basis the most appropriate treatment based on age, the neighborhood of critical structures and surgical resectability. At our institution, we typically offer radiation therapy to marginally resected, unresectable or recurrent Giant Cell Tumors of the Bone to a dose of 50Gy in 25 fractions, although treatment may be customized based on the patient's age, volume of residual disease, and extent of unresected gross tumor. The clinical treatment volume consists of the preoperative gross tumor volume plus sites of known or potential residual disease and potential areas of local extension.

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