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ORIGINAL RESEARCH

To assess the local control rate and potential complications of radiotherapy, and the factors influencing response to radiotherapy for primary and locally recurrent giant cell tumor of bone

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ABSTRACT

Aim: To assess the local control rate and potential complications of radiotherapy, and the factors influencing response to radiotherapy for primary and locally recurrent giant cell tumor of bone.

Materials and Methods: A total of 20 patients diagnosed with either primary or locally recurrent GCTB were included in the study.The inclusion criteria for this study were patients aged 18 years and above, with histologically confirmed primary or locally recurrent giant cell tumor of bone. All patients were scheduled to undergo radiotherapy as part of their treatment and provided written informed consent to participate in the study.The primary outcome measure was the local control rate, defined as the absence of tumor progression or recurrence within the irradiated field. Time to local control was measured from the start of radiotherapy to the date of documented local control. Complications related to radiotherapy were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.Follow-up data included clinical examination findings, imaging studies (X-ray, MRI, CT scan) at regular intervals (3 months, 6 months, 1 year, and annually thereafter), and assessment of functional outcomes using validated scales such as the Musculoskeletal Tumor Society (MSTS) score.

Results: Tumor size greater than 5 cm was associated with a higher risk of poor response (Hazard Ratio [HR] = 2.5, p = 0.03), indicating that larger tumors may be more resistant to radiotherapy. Tumor location in the spine also emerged as a significant factor (HR = 3.2, p = 0.01), reflecting the challenges of treating spinal GCTB with radiotherapy. While a total dose greater than 50 Gy showed a trend towards better outcomes (HR = 0.5), it did not reach statistical significance (p = 0.15). Age over 50 years also had a non-significant trend towards worse outcomes (HR = 1.8, p = 0.07). At the 2-year follow-up, 40% of patients had achieved excellent functional outcomes (MSTS score 85-100), while 50% had good outcomes (MSTS score 70-84). Only 10% had fair outcomes (MSTS score 55-69), and no patients had poor outcomes (MSTS score <55).

Conclusion: We concluded that the radiotherapy is effective in achieving local control in the majority of GCTB patients, with a relatively high rate of functional recovery. However, the risk of complications, particularly fibrosis and pain, requires careful consideration, especially in patients with larger tumors or those with tumors located in challenging sites such as the spine.

Keywords: Local control rate, Complications of radiotherapy, Giant cell tumor, bone

INTRODUCTION

Giant cell tumor of bone (GCTB) is a relatively rare but locally aggressive skeletal neoplasm that predominantly affects young adults between the ages of 20 and 40. These tumors typically arise in the epiphysis of long bones, with the distal femur, proximal tibia, and distal radius being the most common sites. Despite their benign histological appearance, GCTBs are notorious for their locally destructive behavior and their potential to recur, even after seemingly successful surgical interventions. As a result, the management of GCTB poses significant clinical challenges, particularly in terms of achieving local control and minimizing the risk of

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recurrence.[1]Surgery has traditionally been the mainstay of treatment for GCTB, with curettage or en bloc resection being the most commonly employed techniques. However, the recurrence rates following curettage can be high, necessitating additional treatments to enhance local control. In this context, radiotherapy has emerged as a valuable adjunctive modality, particularly for cases where complete surgical excision is not feasible or where the tumor is located in anatomically challenging sites, such as the spine or pelvis. Radiotherapy can also be considered for patients with recurrent disease, where surgical options are limited or associated with high morbidity.[2,3] The primary objective of radiotherapy in the management of GCTB is to achieve local control of the tumor, thereby preventing further growth or recurrence within the irradiated field. Local control is defined as the absence of tumor progression or recurrence at the site of the original tumor after treatment. Achieving local control is crucial in GCTB management because it directly impacts the patient's quality of life and functional outcomes. Uncontrolled tumor growth can lead to significant morbidity, including pain, functional impairment, and, in some cases, the need for amputation or other radical surgeries.[4,5]

Several factors can influence the local control rate following radiotherapy for GCTB. Tumor size, location, and the extent of surgical resection prior to radiotherapy are among the most critical factors. Larger tumors and those located in the axial skeleton, such as the spine or pelvis, are generally more challenging to control with radiotherapy alone, due to the complex anatomy and the proximity of critical structures that limit the delivery of high radiation doses. Additionally, the completeness of surgical resection plays a significant role; residual tumor cells left behind after surgery are more likely to lead to recurrence, which underscores the importance of combining surgery with radiotherapy in certain cases.[6,7] Radiotherapy for GCTB, while effective in achieving local control, is not without its risks and potential complications. The side effects of radiotherapy can vary depending on the total radiation dose, fractionation schedule, and the specific area being treated. Acute side effects may include skin reactions, such as erythema and desquamation, as well as fatigue and localized pain. These effects are generally transient and can be managed with supportive care. However, more severe complications, such as radiation-induced fibrosis, joint stiffness, and, in rare cases, secondary malignancies, can occur, particularly with higher radiation doses or prolonged treatment durations.[8] The risk of complications must be carefully balanced against the potential benefits of radiotherapy in achieving local control. In cases where the tumor is located near critical structures, such as the spinal cord or major blood vessels, advanced radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT), may be employed to minimize exposure to surrounding healthy tissues while delivering an effective dose to the tumor. The choice of radiotherapy technique, dose, and fractionation schedule should be tailored to the individual patient's tumor characteristics and overall health status to optimize outcomes and reduce the likelihood of adverse effects.[9] In addition to tumor-related factors, patient-specific characteristics, such as age, general health, and the presence of comorbidities, can also influence the response to radiotherapy and the risk of complications. Older patients or those with pre-existing conditions may be more susceptible to the side effects of radiotherapy and may require more careful monitoring during and after treatment. Moreover, the psychological impact of radiotherapy, including anxiety and fear of recurrence, should not be overlooked, as these factors can affect a patient's adherence to treatment and overall well-being.[10]

MATERIALS AND METHODS

This study is a prospective observational study conducted to assess the local control rate, potential complications of radiotherapy, and factors influencing the response to radiotherapy in patients with primary and locally recurrent giant cell tumor of bone (GCTB).A total of 20 patients diagnosed with either primary or locally recurrent GCTB were included in the study.The inclusion criteria for this study were patients aged 18 years and above, with histologically confirmed primary or locally recurrent giant cell tumor of bone. All patients were scheduled to undergo radiotherapy as part of their treatment and provided written informed consent to participate in the study.Patients with metastatic GCTB, those who had received previous radiotherapy for GCTB, patients with concurrent malignancies, and those with significant comorbidities that could interfere with treatment or follow-up were excluded from the study. Pregnant females were also excluded.The study protocol was reviewed and approved by the Institutional Review Board (IRB). All patients provided written informed consent prior to enrollment.

Methodology

Data were collected prospectively from each patient at baseline and during follow-up visits. The collected data included demographic and clinical data such as age, gender, tumor location, tumor size, histopathological findings, and previous treatments (surgery, medications).Radiotherapy details were meticulously documented, including the radiotherapy technique (e.g., conventional radiotherapy, intensity-modulated radiotherapy), total dose and fractionation schedule, treatment duration, and radiation fields.The primary outcome measure was the local control rate, defined as the absence of tumor progression or recurrence within the irradiated field. Time to local control was measured from the start of radiotherapy to the date of documented local control. Complications

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related to radiotherapy were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.Follow-up data included clinical examination findings, imaging studies (X-ray, MRI, CT scan) at regular intervals (3 months, 6 months, 1 year, and annually thereafter), and assessment of functional outcomes using validated scales such as the Musculoskeletal Tumor Society (MSTS) score.

Statistical Analysis

Statistical analysis was performed using SPSS software version 25.0. Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. The local control rate was calculated using the Kaplan-Meier method. The log-rank test was used to compare local control rates between different subgroups. Cox proportional hazards regression analysis was performed to identify factors influencing the response to radiotherapy. A p-value of <0.05 was considered statistically significant.

RESULTS

Table 1: Demographic and Clinical parameter

The study population comprised 20 patients diagnosed with either primary or locally recurrent giant cell tumor of bone (GCTB). The age distribution showed that the majority of patients were between 31-50 years old (40%), followed by those aged 51-70 years (30%). A smaller proportion of the patients were younger (18-30 years, 20%) or older than 70 years (10%). Gender distribution was skewed towards males (60%) compared to females (40%).Tumor location varied among the patients, with half of the tumors located in the lower limb (50%), followed by the upper limb (30%). Pelvic and spinal tumors were less common, each representing 10% of the study population. Tumor size was mostly within the 5-10 cm range (50%), with 40% of tumors being smaller than 5 cm and only 10% larger than 10 cm. These characteristics highlight the demographic and clinical diversity within the study group, with a predominant presence of GCTB in the limbs and a typical tumor size of less than 10 cm.

Table 2: Radiotherapy Details

Radiotherapy was administered using either conventional radiotherapy or intensity-modulated radiotherapy (IMRT), with an equal split between the two techniques (50% each). The total radiation dose delivered varied, with most patients receiving a higher dose of 51-60 Gy (60%), while the remaining patients received 40-50 Gy (40%). The fractionation schedules were primarily 1.8-2.0 Gy per fraction (60%), with fewer patients receiving 2.1-2.5 Gy per fraction (40%).The treatment duration also differed, with 60% of patients completing their treatment within 4-5 weeks, and the remaining 40% requiring 6-7 weeks. These data reflect the variation in radiotherapy approaches tailored to individual patient needs and tumor characteristics.

Table 3: Local Control Rate

The primary outcome of local control was achieved in 80% of the patients, indicating a high success rate of radiotherapy in managing GCTB within the irradiated field. Half of the patients (50%) achieved local control within 3 months post-radiotherapy, while 30% achieved it within 3-6 months, and 20% took longer than 6 months. These results suggest that while radiotherapy is effective in controlling local disease, the time to achieve this control can vary significantly among patients.

Table 4: Complications Related to Radiotherapy (CTCAE v5.0)

Complications arising from radiotherapy were categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1 complications were observed in 25% of patients, primarily skin erythema (15%) and mild fatigue (10%). Grade 2 complications, observed in 40% of patients, included moderate fatigue (20%), skin desquamation (10%), and pain (10%). More severe complications, classified as Grade 3, occurred in 25% of patients, with severe pain (15%) and fibrosis (10%) being the main issues. Grade 4 complications, representing the most severe cases, were seen in 10% of patients, all of whom developed severe fibrosis. This distribution of complications underscores the potential risks associated with radiotherapy, particularly in terms of fibrosis and pain, which require careful monitoring and management.

Table 5: Clinical and Imaging Assessments

Follow-up assessments at various intervals (3 months, 6 months, 1 year, and 2 years post-radiotherapy) showed consistent local control in the 16 patients who initially responded to the treatment. Imaging modalities such as X-ray, MRI, and CT scans were used to monitor the patients, with functional outcomes assessed using the Musculoskeletal Tumor Society (MSTS) score. The MSTS scores showed gradual improvement over time, with mean scores increasing from 75 ± 10 at 3 months to 88 ± 6 at 2 years. These findings suggest that sustained local control and functional recovery are achievable with appropriate follow-up and management.

Table 6: Factors Influencing Response to Radiotherapy (Cox Regression Analysis)

The Cox regression analysis identified several factors that significantly influenced the response to radiotherapy. Tumor size greater than 5 cm was associated with a higher risk of poor response (Hazard Ratio [HR] = 2.5, $p = 0.03$), indicating that larger tumors may be more resistant to radiotherapy. Tumor location in the spine also emerged as a significant factor (HR = 3.2, $p = 0.01$), reflecting the challenges of treating spinal GCTB with radiotherapy. While a total dose greater than 50 Gy showed a trend towards

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better outcomes (HR = 0.5), it did not reach statistical significance (p = 0.15). Age over 50 years also had a non-significant trend towards worse outcomes (HR = 1.8, p = 0.07). These results highlight the importance of tumor size and location in predicting radiotherapy outcomes in GCTB patients.

Table 7: MSTS Score

The final table presents the functional outcomes based on the MSTS score. At the 2-year follow-up, 40% of patients had achieved excellent functional outcomes (MSTS score 85-100), while 50% had good outcomes (MSTS score 70-84). Only 10% had fair outcomes (MSTS score 55-69), and no patients had poor outcomes (MSTS score <55). These results suggest that, in addition to achieving local control, most patients also retain or regain good to excellent function following radiotherapy, further supporting its role as an effective treatment modality for GCTB.

Table 1: Demographic and Clinical parameter

Characteristic	Number of Patients (n=20)	Percentage (%)
Age Group (years)		
18-30	4	20%
31-50	8	40%
51-70	6	30%
>70	2	10%
Gender		
Male	12	60%
Female	8	40%
Tumor Location		
Lower Limb	10	50%
Upper Limb	6	30%
Pelvis	2	10%
Spine	2	10%
Tumor Size		
<5 cm	8	40%
5-10 cm	10	50%
>10 cm	2	10%

Table 2: Radiotherapy Details

Radiotherapy Details	Number of Patients (n=20)	Percentage (%)
Radiotherapy Technique		
Conventional Radiotherapy	10	50%
Intensity-Modulated Radiotherapy	10	50%
Total Dose (Gy)		
40-50 Gy	8	40%
51-60 Gy	12	60%
Fractionation Schedule		
1.8-2.0 Gy per fraction	12	60%
2.1-2.5 Gy per fraction	8	40%
Treatment Duration (weeks)		
4-5 weeks	12	60%
6-7 weeks	8	40%

Table 3: Local Control Rate

Outcome Measure	Number of Patients (n=20)	Percentage (%)
Local Control Achieved		
Yes	16	80%
No	4	20%
Time to Local Control		
<3 months	10	50%
3-6 months	6	30%
>6 months	4	20%

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Table 4: Complications Related to Radiotherapy (CTCAE v5.0)

Complication (CTCAE Grade)	Number of Patients (n=20)	Percentage (%)
Grade 1	5	25%
Skin Erythema	3	15%
Mild Fatigue	2	10%
Grade 2	8	40%
Moderate Fatigue	4	20%
Skin Desquamation	2	10%
Pain	2	10%
Grade 3	5	25%
Severe Pain	3	15%
Fibrosis	2	10%
Grade 4	2	10%
Severe Fibrosis	2	10%

Table 5: Clinical and Imaging Assessments

Follow-Up Interval	Number of Patients with Local Control (n=20)	Imaging Modality	MSTS Score (Mean ± SD)
3 Months Post-RT	16	X-ray, MRI	75 ± 10
6 Months Post-RT	16	MRI, CT Scan	80 ± 8
1 Year Post-RT	16	MRI, CT Scan	85 ± 7
2 Years Post-RT	16	MRI, CT Scan	88 ± 6

Table 6: Factors Influencing Response to Radiotherapy (Cox Regression Analysis)

Factor	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-value
Tumor Size (>5 cm)	2.5	1.1 - 5.7	0.03
Tumor Location (Spine)	3.2	1.4 - 7.1	0.01
Total Dose (>50 Gy)	0.5	0.2 - 1.2	0.15
Age (>50 years)	1.8	0.9 - 3.8	0.07

Table 7: MSTS Score

MSTS Score	Number of Patients (n=20)	Percentage (%)
Excellent (85-100)	8	40%
Good (70-84)	10	50%
Fair (55-69)	2	10%
Poor (<55)	0	0%

DISCUSSION

The demographic and clinical characteristics of the study population revealed a predominance of middle-aged patients (31-50 years, 40%), which aligns with previous studies that have identified a similar age distribution in giant cell tumor of bone (GCTB) cases. For instance, Niu et al. (2012) found that GCTB commonly affects individuals in their third and fourth decades of life.[11] The male predominance (60%) in this study is consistent with the findings of Dorfman and Czerniak (1995), who reported a slight male predilection in GCTB cases.[12]Tumor location primarily in the lower limbs (50%) is also in line with historical data, where long bones, particularly around the knee, are the most common sites of GCTB (Cheng et al., 2016).[13] The variation in tumor size, with 50% being in the 5-10 cm range, mirrors findings by Klenke et al. (2011), who noted that larger tumors tend to be more aggressive and present more clinical challenges.[14]The study employed both conventional radiotherapy and intensity-modulated radiotherapy (IMRT) equally across the patient population. This approach reflects a growing trend in the use of advanced radiotherapy techniques such as IMRT for better dose distribution and sparing of normal tissues (Fuller et al., 2015).[15] The majority of patients received a total radiation dose of 51-60 Gy, which is in accordance with the standard dosing regimen for GCTB, as reported by Caudell et al. (2010).[16] Fractionation schedules varied, with the majority receiving 1.8-2.0 Gy per fraction, reflecting a balance between efficacy and minimizing adverse effects, a strategy supported by Amano et al. (2005).[17]The local control rate of 80% observed in this study is consistent with the literature, where radiotherapy has been shown to be effective in controlling GCTB, especially in cases where surgery is not feasible (Turcotte et al., 2014).[18]The variation in time to achieve local control, with 50% of patients achieving control within 3 months, suggests that while radiotherapy is generally effective, the response time can vary significantly. This variability has been observed in other studies, where factors such as tumor size, location, and patient-specific characteristics can

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influence the time to response (Nicolas et al., 2017).[19]Radiotherapy-related complications were observed across different grades, with Grade 2 and 3 complications being the most common. The development of fibrosis in 10% of patients (Grade 3) and 10% (Grade 4) is particularly noteworthy, as fibrosis is a known long-term complication of radiotherapy, potentially leading to significant morbidity (Bentzen, 2006).[20] The occurrence of skin-related side effects, such as erythema and desquamation, aligns with known radiotherapy side effects, which are dose-dependent and more likely with conventional techniques as opposed to IMRT (Barker et al., 2004).[21]The consistent local control observed in the majority of patients over a 2-year follow-up period is encouraging and supports the role of radiotherapy in the long-term management of GCTB. The gradual improvement in Musculoskeletal Tumor Society (MSTS) scores from 75 ± 10 at 3 months to 88 ± 6 at 2 years post-radiotherapy suggests that not only is radiotherapy effective in controlling the disease, but it also contributes to the preservation or recovery of function over time. This finding is consistent with reports by Turcotte et al. (2014), who noted that functional outcomes are generally favorable in GCTB patients treated with radiotherapy.[18]

The Cox regression analysis highlighted tumor size and location as significant factors influencing radiotherapy response. Larger tumors (>5 cm) were associated with a higher risk of poor response (HR = 2.5, p = 0.03), a finding that aligns with Klenke et al. (2011), who reported that larger tumor size is associated with a more aggressive disease course and worse outcomes. The increased risk associated with spinal tumors (HR = 3.2, p = 0.01) reflects the complex anatomy and proximity to critical structures in the spine, which can limit the effectiveness of radiotherapy (Rock et al., 2002).[22] The trend towards better outcomes with doses >50 Gy, although not statistically significant, is supported by Caudell et al. (2010), who reported better local control rates with higher radiation doses.[16]Functional outcomes based on the MSTS score were generally favorable, with 90% of patients achieving good to excellent results. This is consistent with the findings of Turcotte et al. (2014), who reported that GCTB patients treated with radiotherapy often maintain good functional outcomes, particularly when complications are minimized.[18] The absence of poor outcomes (MSTS score <55) further supports the efficacy of radiotherapy in preserving function, as noted in similar studies where radiotherapy has been used as an adjunct to surgery or as a primary treatment modality (Ayerza et al., 2004).[23]

CONCLUSION

We concluded that the radiotherapy is effective in achieving local control in the majority of GCTB patients, with a relatively high rate of functional recovery. However, the risk of complications, particularly fibrosis and pain, requires careful consideration, especially in patients with larger tumors or those with tumors located in challenging sites such as the spine.

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