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CLINICAL INVESTIGATION **Bone**

RADIATION THERAPY IN THE TREATMENT OF GIANT CELL TUMOR OF BONE

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Purpose: 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.

Methods and Materials: Twenty patients were irradiated for giant cell tumor of bone between 1983 and 1993. Fourteen patients received radiotherapy at the time of primary diagnosis (10 had biopsy and 4 partial surgery) and 6 patients at the time of local recurrence (following additional surgery in 2). Fourteen patients had tumors of the extremity and six of the vertebral column. The radiotherapy dose ranged from 40–60 Gy in 15–30 fractions over 3–6 weeks. The response to radiotherapy was assessed by clinical and radiological criteria and the probable factors influencing response were analyzed.

Results: The median follow-up period was 48 months (range, 4 months to 13 years). Local control was obtained in 18/20 patients. The two local failures were salvaged, one by reirradiation and the other by surgery. Only one patient died of giant cell tumor, following extensive bone marrow infiltration. There was no serious late toxicity or malignant transformation. The response to radiotherapy was not influenced by disease status at presentation, tumor site, radiotherapy schedule, or presence of soft tissue extension.

Conclusions: Radiotherapy is effective in producing local control in primary as well as recurrent giant cell tumor of bone. There are no major complications and no significant risk of malignant transformation. Radiotherapy could be considered as the primary treatment modality in patients where surgery would produce functional deficits. © **1999 Elsevier Science Inc.**

Bone neoplasm, Giant cell tumor, Radiotherapy.

INTRODUCTION

Giant cell tumor of bone (GCT) is a rare neoplasm, accounting for 4–8% of primary bone tumors (1, 2). A higher frequency of 15–25% has been reported in Asian countries (3–6). GCT is locally aggressive, with high local recurrence rate and low metastatic potential (1, 2, 7). Surgery is considered the primary treatment modality, although recurrence rates of 25–50% are reported after curettage (6–9). More radical surgical resections reduce recurrence rates to 0–7%, with significant loss of function (7, 10). Radiotherapy was considered to be less effective in producing local control, with significant local complications and risk of malignant transformation (2, 4, 7, 8, 11). However, recent reports suggest that megavoltage radiotherapy is an effective and well-tolerated alternative to surgery, without any risk of malignant change (3, 5, 12–15). This article reviews a series of patients treated at the Regional Cancer Center (RCC) with radiotherapy for primary as well as recurrent giant cell tumors of bone. The efficacy of radiotherapy in achieving local control and the probable factors influencing the response to radiotherapy are analyzed.

METHODS AND MATERIALS

Between 1983 and 1993, 20 patients with localized GCT were treated by megavoltage radiotherapy at the RCC. The age of the patients ranged from 15 to 65 years (mean 33 years) and the male to female ratio was 1.2:1. All patients had pathological confirmation of diagnosis. The histopathology specimens of all patients were reviewed prior to treatment. Tumors were graded based on the pleomorphism of the stromal cells. Eight patients had a grade 1 tumor, one grade 2, four grade 3, and in seven the numerical grade was not specified although the tumor was of benign appearance. Radiological evaluation included plain radiographs of the involved area and chest in all cases. Fourteen patients had involvement of extremity bones and six had vertebral tumors. Pain and swelling were the presenting symptoms in all patients with extremity tumors. Of the six patients with vertebral tumors, four presented with neurologic symptoms (paraparesis in two and cauda equina syndrome in two) and two with pain. Soft tissue extension of tumor was present in seven of the 20 patients.

Fourteen patients received radiotherapy at the time of initial diagnosis and six for local recurrence after previous

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surgery. Of the 14 previously untreated patients, 10 had biopsy only and four partial surgery. Of the six patients who underwent radiotherapy for local recurrence, two received additional surgery in the form of partial excision prior to irradiation.

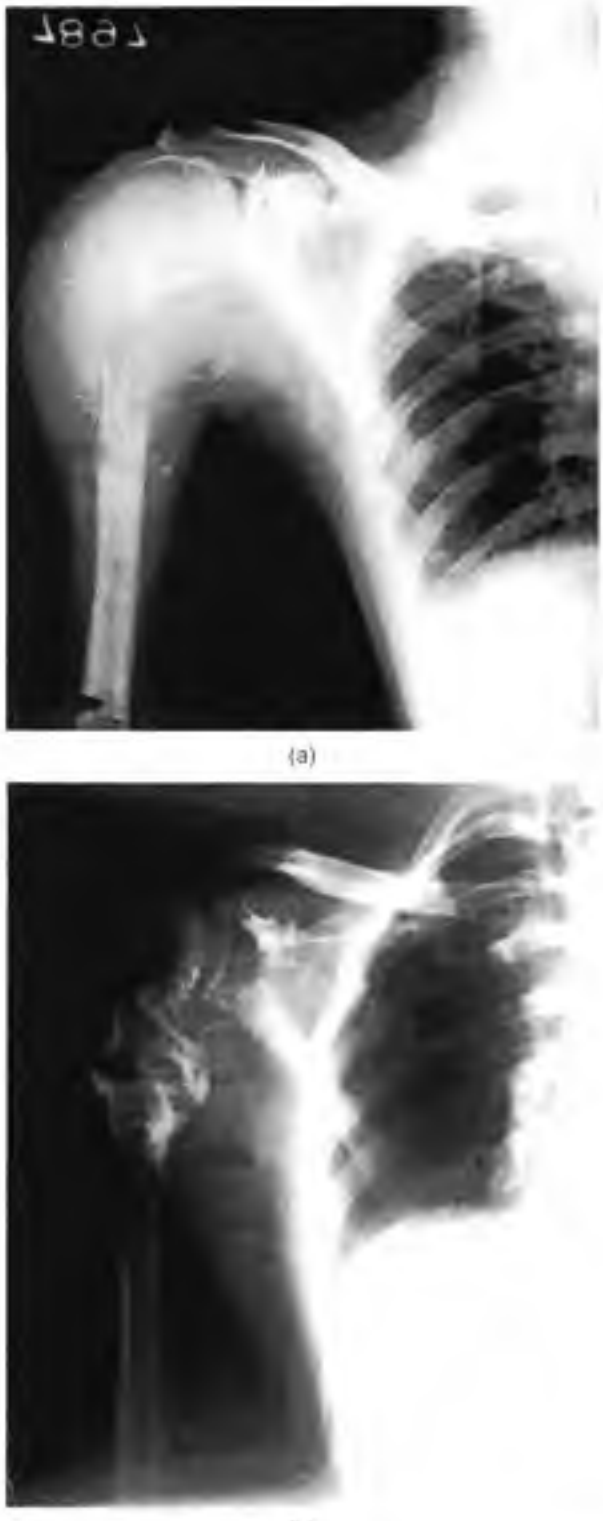
The technique of radiotherapy was anteroposterior or lateral parallel opposed portals for the extremities, and direct posterior onfield or oblique wedge pair for the spine. Treatment fields covered the gross primary tumor or tumor bed with a margin of 3–4 cm. Eleven patients were treated using a telecobalt machine and nine, a 4 MeV linear accelerator. The tumor dose ranged from 40 to 60 Gy over 3–6 weeks. The dosage schedule used was 40–45 Gy in 15–20 fractions over 3–4 weeks in seven patients, 50–55 Gy in 20–28 fractions over 4–5 weeks in seven, and 60 Gy in 30 fractions over 6 weeks in six patients.

The patients were reviewed at regular intervals after treatment, by clinical and radiological examination. The follow-up period was calculated from the start of radiotherapy. Response to radiotherapy was assessed by clinical and radiological criteria. Clinical response criteria included relief of pain, regression of swelling, and/or recovery of neurologic deficits, at the end of 6 months after radiotherapy. Radiologic response was scored by the presence or absence of bone sclerosis on plain radiographs at the end of 1 year (Fig. 1a, b). Local control was defined as absence of clinical and radiological evidence of tumor progression. Response to radiotherapy was compared with respect to disease- and treatment-related factors. The factors included disease status at presentation (primary/recurrent), site of tumor (vertebral/extremity), dosage schedule of radiotherapy, and presence of soft tissue involvement.

RESULTS

The clinical details and treatment outcome are summarized in Tables 1 and 2. The median follow-up was 48 months (range, 4 months to 13 years). Seventeen patients had local control after radiotherapy (85 %). Two patients recurred locally after irradiation, and the patient who died at 4 months was excluded from analysis of local control.

Seventeen patients (85%) had total relief of pain at 6 months, with complete or partial regression of swelling. Two patients had partial relief of pain. The response could not be assessed in one patient who died of unrelated causes at 4 months after treatment. Of the four patients presenting with neurologic deficit, complete neurologic recovery at 6 months was seen in two patients (one paraparesis and one cauda equina syndrome) and partial recovery in the other two (one each of paraparesis and cauda equina syndrome). Bone sclerosis was present in 13 patients (65%) at 1 year. Radiological response increased from 30% at 6 months to 65% at 1 year. The influence of disease- and treatment-related factors on clinical and radiological response is shown in Table 3. The disease status at presentation, tumor site, radiotherapy dosage schedule, and soft tissue involvement did not significantly influence the response to radiotherapy.



(a)

(b)

Fig. 1. (a, b) Plain AP radiograph of GCT of (R) humerus before and 1 year after irradiation. Note the radiologic response as evidenced by bone sclerosis in (b).

Table 1. Patient, disease, and treatment details of 14 patients with previously untreated GCT

Age and sex	Tumor site and grade	Present surgery	Radiotherapy schedule	Local failure	Distant metastasis	Present status
27 M	D7 Vertebra Grade 1	Laminectomy	40 Gy/15 fr/3 wk	Yes re-radiated	No	Alive NED 109 mth
55 F	Lower end of femur Benign nos	Biopsy	55 Gy/25 fr/5 wk	No	No	Alive NED 156 mth
65 F	Cervical spine Grade 1	Biopsy	45 Gy/20 fr/4 wk	No	No	Alive NED 156 mth
15 F	Lower end of radius Grade 1	Biopsy	60 Gy/30 fr/6 wk	No	Yes, lung	Alive diseased 145 mth
33 M	Lower end of radius Grade 1	Curettage	60 Gy/30 fr/6 wk	No	No	Alive NED 91 mth
37 M	Upper end of humerus Benign nos	Biopsy	55 Gy/28 fr/6 wk	No	No	Alive NED 66 mth
42 F	Lower end of tibia Benign	Biopsy	60 Gy/30 fr/6 wk	No	No	Alive NED 24 mth
40 M	L3 Vertebra Grade 2	Reexcision	60 Gy/30 fr/6 wk	No	No	Alive NED 69 mth
26 F	Upper end of fibula Grade 3	Excision	60 Gy/30 fr/6 wk	No	No	Alive NED 43 mth
21 F	S1 Vertebra Grade 1	Laminectomy and biopsy	60 Gy/30 fr/6 wk	No	Yes, marrow	Dead of disease 26 mth
28 M	Femoral condyle Grade 1	Biopsy	50 Gy/25 fr/5 wk	No	No	Dead NED 18 mth
33 M	D6 Spine Grade 1	Laminectomy	45 Gy/15 fr/5 wk	No	No	Dead NED 6 mth
18 M	Sacrum Benign nos	Biopsy	50 Gy/25 fr/5 wk	No	Yes, lung	Alive NED 36 mth
48 M	Lower end of femur Benign nos	Biopsy	45 Gy/15 fr/3 wk	No	No	Alive NED 26 mth

Abbreviations: NED = no evidence of disease progression; nos = numerical grade not specified.

Two patients developed local recurrence after radiotherapy, both within the initial target volume of radiotherapy. One, with a previously untreated primary tumor of the D7 spine, recurred 18 months after radiotherapy (40 Gy in 15 fractions over 3 weeks). This patient underwent reirradiation, and is alive with no neurologic deficit after 8 years. The other patient, who received 55 Gy in 25 fractions over 5 weeks for recurrent tumor of the lower end of radius, recurred 13 months later. A below elbow amputation was done, and the patient is alive and free of disease after 3 years.

Pulmonary metastases occurred in two patients during follow-up. Both had received radiotherapy for previously untreated primary tumor, and had local disease control. The interval from radiotherapy to the occurrence of lung metastasis was 19 months and 24 months. One patient had irra-

Table 2. Patient, disease, and treatment details of 6 patients with locally recurrent GCT

Age and sex	Tumor site and grade	Previous surgery	Present surgery	Radiotherapy schedule	Local failure	Metastasis	Present status
21 M	Lower end of fibula Grade 3	Excision 4 yr ago	Partial excision	50 Gy/25 fr/5 wk	No	No	Alive NED 58 mth
26 F	Lower end of radius Grade 3	Excision 4 yr ago	Reexcision	45 Gy/15 fr/3 wk	No	No	Alive NED 62 mth
28 F	Lower end of radius Grade 1	Curettage 6 mo ago	Biopsy	55 Gy/28 fr/6 wk	Yes amputated	No	Alive NED 53 mth
28 M	Lower end of femur Grade 1	Curettage 24 mo ago	Nil	50 Gy/25 fr/5 wk	No	No	Alive NED 48 mth
33 M	Upper end of tibia Benign nos	Curettage 7 mo ago	Nil	45 Gy/15 fr/3 wk	No	No	Alive NED 48 mth
29 F	Lower end of radius Benign nos	Excision 3 yr ago	Biopsy	45 Gy/20 fr/4 wk	No	No	Alive NED 26 mth

Abbreviations: NED = No evidence of disease progression; nos = numerical grade not specified.

Table 3. Factors influencing clinical and radiological response to radiotherapy

Factor	Symptom relief at 6 months				Bone sclerosis at 1 year			
	Complete response	Partial response	Not known	Total	Present	Absent	Not known	Total
Disease status								
Previously untreated	10	3	1	14	9	3	2	14
Locally recurrent	5	1	—	6	4	—	2	6
Site								
Vertebra	4	2	—	6	3	2	1	6
Extremity	11	2	1	14	10	1	3	14
Dosage schedule								
40–45 Gy/15–20 fr	5	1	1	7	3	2	2	7
50–55 Gy/20–28 fr	5	2	—	7	5	1	1	7
60 Gy/30 fr	5	1	—	6	5	—	1	6
Soft tissue involvement								
Yes	6	1	—	7	6	—	1	7
No	9	3	1	13	7	3	3	13

diation for metastasis and is surviving with stable disease at the end of 9 years. The other, who received no specific treatment, is alive with disease after 1 year.

Three patients died, two of unrelated causes 6 months and 18 months after radiotherapy. The only patient who died of GCT had an unusual clinical course, presenting with extensive bone marrow infiltration by GCT 20 months after irradiation of a sacral primary. The patient died 4 months later despite chemotherapy. The original histopathology specimen of this patient was reviewed in view of this extremely unusual presentation, and was confirmed to be a primary GCT of bone.

No severe acute or late complications of radiotherapy were observed, except for lymphedema in one patient irradiated for GCT of the femur. Malignant transformation of GCT or sarcomas in the irradiated field did not develop in any patient.

DISCUSSION

GCT is a locally aggressive tumor, with low metastatic potential (2, 7). Surgery has traditionally been the treatment of choice, often resulting in significant functional disability. Surgical recurrences are salvaged by amputation or other surgical techniques, resulting in loss of function (2, 4, 7, 10). Radiotherapy was formerly used only in inoperable GCT and for palliation of symptomatic local recurrences. However, recent reports have shown that radiotherapy is effective in achieving local control with minimal long-term effects (Table 4). In this series, 20 patients with GCT have been treated with primary radiotherapy after biopsy or limited surgery. The 14 previously untreated tumors were considered to be at high risk for surgery either by virtue of site or large size which would otherwise compromise functional outcome. In the other six patients, radiotherapy was used as salvage treatment for surgical recurrences. In spite of this being a high-risk group of patients, the local control rates compare favorably with those reported in the literature.

There are no standard criteria for assessment of response to radiotherapy in GCT. Schwartz *et al.* (15) scored response in terms of local control, i.e., absence of tumor regrowth as assessed clinically and radiologically. Chen *et al.* (3) defined response by a combination of pain relief, resolution of the mass, and improvement in Karnofsky's performance status. Bennet *et al.* (12) described the radiological changes after radiotherapy as disappearance of the sclerotic rim of the lesion, followed by reappearance, continued bone calcification, and resolution of the mass. In the

Table 4. Results of radiotherapy in GCT—review of literature

Author	Year	No. of patients	Local control	Distant metastasis	Malignant transformation
Harwood *et al.* (13)	1977	13	12/13	0	0
Bell *et al.* (17)	1983	15	14/15	0	1
Chen *et al.* (3)	1986	35	26/35	0	0
Seider *et al.* (18)	1986	10	7/10	3	0
Schwartz *et al.* (15)	1989	11	9/11	2	0
Sharma *et al.* (5)	1990	30	28/30	0	0
Bennet *et al.* (12)	1993	16	12/16	1	0
Malone *et al.* (14)	1995	21	19/21	0	0
Nair and Jyothirmayi	1998	20	18/20	3	0
Total		171	145/171 (85%)	9/171 (5.3%)	1/171 (0.6%)

series by Harwood *et al.* (13), healing with remineralization of bone was noted after an initial apparent deterioration. Sharma *et al.* (5) assessed response by a combination of bone recalcification, restitution of joint function, and tumor regression. In our series, response of GCT to radiotherapy was assessed by a combination of clinical and radiological criteria. Response to radiotherapy was comparable in primary and recurrent tumors, vertebral column, and extremities for various radiotherapy schedules and in the presence or absence of soft tissue involvement.

The factors affecting local control could not be analyzed in this series, as only two patients had local recurrence after radiotherapy. Radiotherapy is seen to produce equally good local control in primary GCT and postsurgical recurrence as previously reported (5, 12, 14, 15). Local control is especially important in vertebral tumors, since possibility of salvage therapy after local recurrence is remote (14). In this series, only one out of six patients with GCT of spine had local recurrence which was salvaged by reirradiation.

Histological grading of GCT has not been shown to correlate with clinical behavior (1). In this series too, three of the four patients with grade 3 tumors are alive and free of disease at last follow-up.

Recommendations regarding radiotherapy dose and fractionation schedules vary. Bennet *et al.* (12) and Chen *et al.* (3) recommend a total dose of at least 40 Gy for optimal local control. However, Harwood *et al.* (13) and Malone *et al.* (14) suggest a dose of 35 Gy in 15 fractions over 3 weeks as a safe and effective treatment regime. In this series, no difference in local control was observed at higher doses. A dose of 45 Gy in 15–20 fractions over 3–4 weeks appears well tolerated and effective in producing long-term local control.

There was a 10% incidence of pulmonary metastases in this series as compared to 5% reported in the literature (Table 4). The occurrence of pulmonary metastases is uncommon and does not necessarily indicate a fatal outcome. Hence treatment may be reserved for symptomatic patients.

A major concern regarding irradiation of GCT has been the risk of inducing malignant transformation. In the series by Campanacci *et al.* (7), 8/27 (29%) of patients developed sarcomatous change at the site of irradiation. McGrath *et al.* (9) reported malignant transformation in 5/21 (25%) patients following irradiation. Sarcomatous change was reported in 3/46 (7%) patients by Goldenberg *et al.* (8). In the series by Mnaymneh *et al.* (16), malignant transformation occurred in 2/16 patients (12.5%). Details regarding energy and radiation schedules are lacking in most of the earlier reports. However, recent series using megavoltage irradiation have reported no evidence of malignant transformation or sarcomatous change after long periods of follow-up (Table 4). In this series too, no patient developed malignant transformation.

Megavoltage radiotherapy using modern techniques appears a safe and effective option for the management of primary and recurrent GCT. Long-term local control is achieved after primary radiotherapy. The treatment carries little morbidity, and the risk of malignant transformation is probably overestimated. Radiotherapy could be considered as the first line of treatment for patients in whom surgery would produce functional disability.

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