Radiation-induced sarcomas of bone

FACTORS THAT AFFECT OUTCOME

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We identified 42 patients who presented to our unit over a 27-year period with a secondary radiation-induced sarcoma of bone. We reviewed patient, tumour and treatment factors to identify those that affected outcome. The mean age of the patients at presentation was 45.6 years (10 to 84) and the mean latent interval between radiotherapy and diagnosis of the sarcoma was 17 years (4 to 50). The median dose of radiotherapy given was estimated at 50 Gy (mean 49; 20 to 66). There was no correlation between radiation dose and the time to development of a sarcoma. The pelvis was the most commonly affected site (14 patients (33%)). Breast cancer was the most common primary tumour (eight patients; 19%). Metastases were present at diagnosis of the sarcoma in nine patients (21.4%). Osteosarcoma was the most common diagnosis and occurred in 30 cases (71.4%). Treatment was by surgery and chemotherapy when indicated: 30 patients (71.4%) were treated with the intention to cure. The survival rate was 41% at five years for those treated with the intention to cure but in those treated palliatively the mean survival was only 8.8 months (2 to 22), and all had died by two years. The only factor found to be significant for survival was the ability to completely resect the tumour. Limb sarcomas had a better prognosis (66% survival at five years) than central ones (12% survival at five years) ($p = 0.009$).

Radiation-induced sarcoma is a rare complication of radiotherapy. Both surgical and oncological treatment is likely to be compromised by the treatment received previously by the patient.

The induction of a bone sarcoma by ionising radiation was first reported in 1922 by Beck,¹ who described the development of a sarcoma in bone irradiated for tuberculous arthritis. It was not known at the time if radiation was a direct causative agent. The causal link between radiation and bone sarcoma was established in 1929 when Martland and Humphries² reported a series of 42 bone sarcomas in 1468 female radium-dial painters, an incidence of 2.8%. The ingestion of radioactive paint was shown to cause osteitis, bone necrosis, anaemia and osteogenic sarcoma.³ The estimated dose of radiation to bone was approximately 500 Gy and the absolute risk was estimated as 0.1 cases/105 persons/rad/year.

In 1948 Cahan et al⁴ strengthened the aetiological link between radiation and bone sarcoma by reporting 11 patients with sarcoma arising in irradiated bone. Huvos et al⁵ reported 66 patients with radiation-induced sarcoma of bone and soft tissue in 1985 and more recently, the incidence of bone sarcoma has been reported to be high among Russians

who have worked in plutonium production facilities.⁶

Cahan et al⁴ proposed a series of diagnostic criteria for radiation-induced sarcoma of bone which were later modified by Arlen et al.⁷ These include:

1. Microscopic or radiological evidence of non-malignancy or a malignancy of different histological type before irradiation.
2. Radiation therapy administered to the patient and a sarcoma subsequently developing in the path of the radiation beam.
3. A relatively long asymptomatic period between irradiation of the primary tumour and the diagnosis of the secondary sarcoma (this period has been reported in various series to range from 3 to 33 years with means of 8 to 12 years).^{5, 8-11}
4. The diagnosis of the secondary sarcoma has been proven histologically.

Patients and Methods

Over a 27-year period between 1978 and 2005, 42 patients with a post-irradiation bone sarcoma

Fig. 1

Age distribution at presentation of radiation-induced bone sarcoma (n = 44).

Fig. 2

Age at first malignancy. There were 15 patients aged < 16 years at the time of their first malignancy (n = 41).

Table I. Primary malignancy for which radiation therapy was given

Type of primary malignancy	Frequency distribution of patients
Breast carcinoma	8
Ewing's sarcoma	7
Cancer of the cervix	5
Rhabdomyosarcoma	4
Hodgkin's	3
Non-Hodgkin's	3
Osteosarcoma	2
Giant cell tumour	2
Chondrosarcoma	1
Malignant fibrous histiocytoma	1
Leiomyosarcoma	1
Ovarian teratoma	1
Metastatic pinealblastoma	1
Bladder carcinoma	1
Neuroblastoma	1
Wilm's tumour	1

Fig. 3

Latent period for the development of secondary bone tumour after irradiation of bone (n = 41).

were treated at our hospital. There were 28 female and 14 male patients with a mean age of 45.6 years (10 to 84) (Fig. 1). Each tumour fulfilled the diagnostic criteria for post-irradiation bone sarcoma as modified by Arlen et al.⁷

Tumours were staged according to the system of the Musculoskeletal Tumour Society (MSTS) as proposed by Enneking, Spanier and Goodman.¹² The patients' mean age was 29.4 years (1 to 64) when their primary malignancy was treated with radiotherapy (Fig. 2). Their diagnoses are listed in Table I.

Follow-up was calculated from the time of diagnosis of the radiation-induced sarcoma to the time of last clinical follow-up. Survival curves were plotted using the Kaplan-Meier method.¹³

Prognostic factors were investigated using Cox proportional-hazards regression.

Results

The mean latent period between irradiation and the development of the sarcoma for all patients was 17 years (4 to 50) (Fig. 3); in children irradiated under the age of 16 years (mean age 12 years; 2 to 16), it was 15 years (4 to 32) and for adults (mean age 40 years; 19 to 64) it was 17 years (5 to 50). Thus there was no correlation between the patient's age at the time of the primary malignancy and the latent period for the development of a sarcoma.

Fig. 4a

Fig. 4b

Fig. 4c

Figure 4a – Anteroposterior radiograph of the pelvis showing a mixed lytic and sclerotic lesion around the left hip of a 46-year-old woman six years after receiving radiotherapy for carcinoma of the cervix. Figure 4b – CT scan of the pelvis confirmed a destructive lesion of the posterior column of the hip with extension into the hip joint. Biopsy confirmed a radiation-induced osteosarcoma. Figure 4c – After treatment with a hemipelvic endoprosthesis and neoadjuvant chemotherapy. The patient remains disease-free three years later.

The radiation dose was unknown in most patients. The likely total dose was therefore estimated by a senior radiation oncologist (DS) based on the age and diagnosis of the patient at the time of their primary malignancy. This was a mean of 49 Gy (20 to 66). There was no correlation between the estimated radiation dose and latent period for the development of a bone sarcoma.

There were 16 patients who had undergone chemotherapy for their primary malignancy who had a mean latent period of 12.7 years (4 to 35) compared with 19 years (5 to 50) for those who had not ($p = 0.06$).

Chemotherapy was combined with radiation therapy in 11 of 15 children (73%) and 8 of 27 adults (29.6%). The addition of chemotherapy to the radiotherapy did not affect the latent period between primary malignancy and secondary bone sarcoma.

The radiation-induced sarcomas were classified as either central (spine, pelvis and pectoral girdle) or peripheral (limbs). There were 22 central tumours and 20 peripheral tumours. The most commonly affected anatomical site was the pelvis, where there were 14 cases. There were nine tumours of the femur, seven of the scapula, six of the humerus, five of the tibia and one of the rib.

Osteosarcoma was the most common radiation-induced bone tumour, occurring in 30 cases (71.4%). All except one were of high grade. There was one low-grade periosteal osteosarcoma. The other 12 cases (28.6%) were spindle-cell sarcoma in seven (16.7%), malignant fibrous histiocytoma in two (4.8%), leiomyosarcoma in two (4.8%) and one chondrosarcoma (2.4%).

The tumour size was known in 22 patients and unknown in 20. The mean tumour size was 10.5 cm (3 to 20).

When diagnosed with a secondary bone sarcoma, four patients were staged IIA, 29 IIB and nine stage III.

Treatment. Overall, 30 tumours (71.4%) were treated with an intention to cure (Fig. 4) and 12 (28.6%) with an intention to palliate either because of metastases, size and loca-

tion of the tumour, or age of the patient at the time of diagnosis of the secondary sarcoma.

Chemotherapy was used in 24 patients (57.1%), with an intention to cure in 17 (40.5%) and to palliate in seven (16.7%). In many cases, the chemotherapy used for the treatment of the radiation-induced bone sarcoma had to be modified because of previous exposure to active agents when treating the primary malignancy. Palliative radiotherapy was used as well as chemotherapy in two patients (4.8%). Both died of their disease within a year. Surgery was used in 28 patients (66.6%) with an intention to cure. This took the form of excision in six (14.3%), excision and endoprosthetic replacement in 11 (26.2%) or amputation in 11 (26.2%).

Follow-up and outcome. *Survival.* Nine patients (21.4%) presented with metastases. Their mean survival time was 38 months (6 to 120). Two patients who presented with metastases were treated with neoadjuvant chemotherapy and primary amputation and remained disease-free beyond five years.

The 33 patients (78.6%) who presented with non-metastatic disease had a mean survival of 43 months (2 to 269).

At follow-up, seven patients (16.7%) were alive with no evidence of disease and a mean follow-up of 102 months (13 to 269) from diagnosis. Another five patients (11.9%) were alive with disease after a mean follow-up of 78.4 months (20 to 132).

Local recurrence. Eight patients (19%) developed a local recurrence after a mean of 18 months (10 to 48) from diagnosis. Seven of the 17 patients (41%) treated with limb salvage developed a local recurrence. Only one patient of the 11 treated by amputation as a primary procedure developed local recurrence ($p = 0.06$). This difference was not significant.

Local recurrence occurred in two of the 13 wide resections (15%), four of the seven marginal resections (57%) and two of the four intralesional resections (50%). The

Fig. 5a

Fig. 5b

Survival curves for a) all patients (five-year survival was 35%), and b) patients treated with curative or palliative intent (five-year survival was 41% for those treated with a curative intent).

patients with adequate margins (wide or radical) had a statistically lower risk of local recurrence than those with inadequate margins (intralesional or marginal) ($p = 0.048$). **Disease progression.** Metastases developed in 15 patients (35.7%) after a mean of 13 months (1 to 47). Disease progression resulted in death in 20 patients (47.6%) after a mean time of 17.4 months (2 to 50). Two patients died of other causes (bacterial peritonitis and haemorrhage).

Kaplan-Meier cumulative survival estimates. The overall survival rate, using Kaplan-Meier estimates, was 35% at five years (Fig. 5a).

The survival rate was 41% at five years for those treated with intention to cure but in those treated palliatively the mean survival was only 8.8 months (2 to 22) and all had died within two years (Fig. 5b).

Prognostic factors. Of those with non-metastatic disease at presentation 14 of 33 (42%) were alive at follow-up while only 3 of 9 (33%) of those with metastases at presentation had survived ($p = 0.13$). This difference was not significant.

The resectability of the tumour was a significant factor for survival. Limb sarcomas had a better prognosis (55% survival at five years) than central ones (12% survival at 5 years) ($p = 0.009$).

Radical surgical margins were obtained in two patients who had above-knee amputation. The resection margins were wide in 13 patients, marginal in seven and intralesional in three. Margins were not known in three patients.

Of these patients with adequate wide or radical surgical margins, 80% (12 of 15) were alive after a mean 83 months (13 to 269) while only 30% (3 of 10) of those with inadequate (intralesional or marginal) surgical margins survived after a mean 24.8 months (12 to 50) ($p = 0.02$).

The estimated survival for patients aged less than 40 years who had been treated with the intention to cure ($n = 14$) was

43% at five years. For those over the age of 40 years ($n = 16$) it was 37%. The difference was not significant.

The overall five-year survival in patients aged less than 40 years with a central tumour was 20% while none who were over the age of 40 with a central tumour were alive at five years.

The overall five-year survival of patients aged less than 40 years with a peripheral tumour was 56%. It was 85% for those over the age of 40 although the latter group only contained seven patients. The difference was not statistically significant.

Survival was not affected by the patient's age at the time of their first malignancy, the total dose of radiation given and the latent period between radiotherapy and the development of the secondary sarcoma.

Complications. There were two superficial wound infections, both in patients with major limb amputation following previous radiotherapy. Both infections settled with antibiotics.

As all patients who underwent surgery had previous radiation exposure to soft-tissues, the rate of wound complications was expected to be higher.

There were two deep infections, one occurred in a 73-year-old woman three months after endoprosthetic replacement of the proximal femur. She underwent a disarticulation of the hip after developing a local recurrence seven months later. The other was in a 20-year-old woman three years after a distal tibial endoprosthetic replacement. The infection was successfully treated by debridement but the patient died from disease progression a year later.

In one patient, a proximal humeral endoprosthetic replacement became loose 22 years after the original operation. The prosthesis was successfully revised.

One hip dislocated three times after a hemipelvectomy and endoprosthetic replacement of a secondary osteosarcoma of the acetabulum. The dislocation was reduced by closed manipulation on each occasion. The prosthesis remained stable at follow-up three years later.

Discussion

Although radiation exposure can occur from occupational and environmental sources, therapeutic radiation is currently the most common cause of radiation-induced bone sarcomas. Ionising radiation directly damages DNA by the generation of free radicals.

The pathophysiology of radiation-induced bone sarcomas is not fully understood. Secondary sarcomas occur more commonly in those with hereditary retinoblastoma suggesting a genetic role in their aetiology. The 'p53 gene' is involved in the maintenance of genomic integrity in its role as a tumour suppressor and either allows DNA repair to take place or induces apoptosis when the damage is beyond repair. In a study by Nakanishi et al,¹⁴ mutations of the p53 gene were found in every case of radiation-induced soft-tissue sarcoma: the mutation rate in sporadic soft-tissue sarcomas is 20%. Radiation-induced sarcomas are also characterised by complex karyotypes with frequent loss of material from chromosome arm 3p.¹⁵

Between 50% and 60% of radiation-induced sarcomas are osteosarcomas. It is estimated that the risk of developing osteosarcoma in irradiated bone is 0.03% to 0.8%.^{5-8,12-15} The prevalence of secondary osteosarcoma following radiation therapy for childhood malignant lesions is increasing as the survival of these patients increases.⁹ In a study by Bechler et al,⁹ 76 of 3768 children treated for a malignant lesion over a 20-year period developed a second malignancy, an incidence of 2%. Meadows et al¹⁰ reported an incidence of 1.8% for any kind of secondary bone sarcoma after radiation exposure. In our study 71.4% of all secondary bone sarcomas following exposure to radiation therapy were osteosarcomas.

There appears to be a minimum threshold dose of radiation required to induce bone sarcoma. In a cohort of 2383 female radium-dial workers, no worker who accumulated less than 10 Gy developed a sarcoma. All 64 bone sarcomas occurred in the 264 cases with more than 10 Gy of radiation exposure. A dose-response function was calculated for this cohort.¹⁶ In the present study the median dose of radiation was estimated to be 50 Gy, the minimum being 20 Gy. Tabone et al¹⁷ reported a median dose of 47 Gy.

The latent period for the development of radiation-induced bone sarcoma has been estimated to be a minimum of four years¹¹ and a mean of between 8.3 years¹⁸ and 21.3 years.¹¹ In the present study the mean latent period was 17 years (4 to 50).

The issue of whether the latent period for the development of post-irradiation bone sarcoma is significantly different in children, adolescents and adults is largely

unresolved. In our study, the mean latent period was 15 years in children under the age of 16 and 17 years in adults.

It was significantly greater in children (mean 21.3 years) than in adults (mean 11.7 years) in the 78 post-irradiation osteosarcomas reported by Weatherby, Dahlin and Ivins.¹⁹ On the other hand, Huvos and Woodward in 1988¹⁸ reported a lower mean latent period in adolescents (8.3 years) than adults (9.6 years). Two other studies have reported more consistent mean latent periods of 9.6 years¹⁰ and 10.1 years.⁹ Furthermore, Bechler et al⁹ did not find a difference in the latent period for children under the age of eight compared with those who were older.

In our study, it was difficult to establish whether the difference in latent periods for children and adults was significant, as 73% of children received chemotherapy with their radiation whereas 70.3% of adults did not. Chemotherapy administered for a first malignancy can accelerate the development of a second malignancy.²⁰ We found that the mean latent period was shorter by nine years in patients who had received chemotherapy for the treatment of their first malignancy than for those who did not. Newton et al²¹ reported that the mean latent period was shortened by four years in children who received anthracyclines as chemotherapy.

Radiation-induced sarcoma of bone is allegedly much more aggressive than its naturally occurring counterpart.^{22,23} In the past survival after radiation-induced sarcoma was poor. Adverse prognostic factors include a patient over 40 years of age, metastases at presentation, and central location of the tumour.²⁴ Sim et al²³ reported in 1972 that the mean survival after the diagnosis of post-irradiation bone sarcoma was 1.1 years.

Overall survival has improved in recent years. Tabone et al¹⁷ reported in 1999 that after surgery and chemotherapy for 23 radiation-induced osteosarcomas the overall survival at 7.5 years was 50%. In our study the survival rate was 41% at five years for those treated with a curative intent. Those who were under 40 years of age had a slightly better survival (43% at five years). The five-year survival for those over 40 years of age treated with a curative intent was 37%. These results are slightly worse than those reported by Souhami et al²⁵ in a randomised controlled trial of operable osteosarcoma in the United Kingdom. They reported a five-year survival of 55% for patients under 40 with a non-metastatic operable conventional osteosarcoma.

Most studies have reported a worse survival for conventional osteosarcoma in patients over 40 years of age. Grimer et al²⁴ reported a five-year survival of 46% at five years.

In our series the survival was better (66% at five years) for those with a peripheral lesion. Inoue et al²⁶ reported a similarly better survival of 68% for stage II-B resectable peripheral lesions. Survival for central lesions in our study was poor (12%) as these are often not completely resectable. Incomplete resection was found to be an adverse prognostic factor by Brady, Gaynor and Brennan.²⁷

The survival was better for those who presented with non-metastatic disease (mean survival: 43 months; 2 to 269) compared with those who presented with metastatic disease (mean survival: 17 months; 6 to 120). Metastatic disease at presentation was also found to be a poor prognostic factor in the study by Brady et al.²⁷

The adequacy of the surgical margin is an important factor in patient survival. In our study, 80% of patients with adequate surgical margins were alive at follow-up compared with only 27% of those with inadequate surgical margins. Buis and Spiro²⁸ also found that adequate resection margins are a predictor of disease-free survival.

Although tumour size was only known in 22 of the 42 patients (52.3%), it appeared to have no effect on disease free survival. However, tumour size of over 5 cm was considered to be an adverse prognostic factor by Brady et al.²⁷

Although amputation achieved better surgical margins and therefore better local control of the disease, 45% of the patients still developed metastases. This was higher than the metastasis rate of 27% in those who had limb salvage. This can be explained by the fact that amputation is carried out for particularly aggressive tumours which are more likely to metastasise. The higher rate of metastasis after amputation may therefore be a result of selection bias.

Even though many cancers are declared cured and the disease is considered 'spent' after a long disease-free interval, the possibility of a radiation-induced sarcoma should always be borne in mind and a high index of suspicion aids prompt diagnosis. Radiation-induced bone sarcomas are more aggressive than their conventional counterparts and a more aggressive approach to their management is needed. Their prognosis is reasonable using modern adjuvant chemotherapy and surgery if the tumour is widely resectable and presents without metastases.

Supplementary Material

Scatter diagrams showing poor correlation between age at first malignancy and radiation dose and latent period for the development of sarcoma are available with the electronic version of this article on our website at www.jbjs.org.uk

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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