Management of radiation-induced sarcomas in a tertiary referral centre: A review of 25 cases

E. Erel*, E. Vlachou, M. Athanasiadou, S. Hassan, C.R. Chandrasekar, F. Peart

The Royal Orthopaedic Hospital NHS Foundation Trust, Birmingham, UK

Introduction

Radiotherapy has been implicated in the pathogenesis of sarcomas from as early as the early 1920s.\(^1\) Cahan et al. were the first to report 11 cases of radiation-induced osteosarcoma in English literature.\(^2\) With respect to sarcomas of the chest wall following radiotherapy treatment for breast carcinoma, the first four cases were described in the late seventies.\(^3\)–\(^6\) Since then there has been a wealth of publications on this matter, with more emphasis on the aetiology, incidence and epidemiology, rather than the surgical management.

It is now widely accepted that therapeutic radiation doses for the adjuvant treatment of breast carcinomas can induce sarcomas. The risk is small, but can be affected by numerous factors including the presence of chronic lymphoedema, as described in Stewart–Treves syndrome.\(^7\)–\(^8\) The aim of the present study is to document our experience of treating 25 patients with radiation-induced sarcoma (RIS) following breast cancer.

Patients and methods

Data contained in the Birmingham Royal Orthopaedic Hospital’s (ROH) prospective tumour database were retrospectively analysed.

All patients with a diagnosis of RIS between 1978 and 2009 with a history of previous breast cancer and radiotherapy were included. All the patients included in the study met the criteria for the diagnosis of RIS, proposed by Cahan in 1948.\(^2\)

Twenty-five patients were diagnosed and treated for RIS. All had appropriate staging studies with routine haematological and biochemical investigations, bone scan, MRI scan and CT of the chest. Tissue diagnoses were obtained in all the cases, usually by trucut biopsy. Patients under the age of 60 were offered neo-adjuvant chemotherapy and were then re-staged prior to a decision being made about surgery. Patients over the age of 60 underwent surgery (whenever possible) without prior chemotherapy. The decision to offer systemic therapy was made by the multi-disciplinary team. This was based on the view that the potential risks outweighed the potential benefits of systemic therapy for the patients over the age of 60.

The decision as to whether surgical intervention was suitable for local disease control was based on the local extent of the tumour on imaging, the response to pre-operative chemotherapy and patient preference. The surgical goal was wide local excision with or without plastic surgical reconstruction depending on the location of the tumour and the resulting defect.

We analysed patient, tumour and treatment factors in relation to overall survival, using Statview software. Differences between groups were assessed using Mann Whitney U-test. Survival was estimated using Kaplan–Meier survival curves with patients censored at the time of last follow-up. Significance was taken as \(p < 0.05\).
Results

Breast cancer was diagnosed at a mean age of 51 (range 33–79) years. Radiation-induced sarcomas following the diagnosis and treatment of breast cancer occurred after a mean period of 156 months (range 48–360) or 13 years. The anatomical distribution of sarcomas was: 12 breast and chest wall (Figs. 1, 2), 4 axilla, 6 scapular, 2 humeral and 1 clavicular. The histological diagnosis consisted of: 9 osteosarcomas, 5 angiosarcomas, 5 spindle cell sarcomas, 3 leiomyosarcomas and 3 other sarcomas.

Twenty one patients were treated surgically. Seventeen patients had wide local excision with plastic surgical reconstruction. Methods of chest wall reconstruction following wide local excision ranged from split thickness skin grafting to local flaps and free tissue transfer. Two patients required full thickness chest wall reconstruction using a polypropylene mesh and methyl methacrylate sandwich technique.9,10 Four patients underwent forequarter amputation. In four patients the sarcomas were deemed inoperable and they received palliative chemotherapy.

Surgical margins were available for 17 patients. Twelve patients had their margins described as “clear” and in five patients the margins were described as “marginal”. Clear surgical margins were defined as excisional margins through normal tissue, away from the reactive zone. Marginal margins were defined as those when the excisional margin was made through a reactive zone, but free of tumour. Local recurrence was documented in 11 (52%) of the patients who had surgery. Local recurrence occurred in all five patients who had marginal margins. Eight patients underwent further surgery to excise the local recurrence. The other three patients were however deemed inoperable and were therefore offered chemotherapy. Ten patients developed pulmonary metastaic disease.

Of the 25 patients eight patients are alive (as at January 2010). The estimated five year survival following the diagnosis of the RIS was 27% (Fig. 3). The estimated 10 year survival for this cohort of patients following the diagnosis and treatment of breast cancer was 77%; 20 years survival was 47% (Fig. 4).

Discussion

Radiation-induced sarcomas are uncommon. The most comprehensive study to date found the cumulative incidence of metachronous sarcoma to be 3.2 per 1000 at 15 years post-diagnosis.11

Management principally wishes the achieving of wide surgical margins but this can be difficult due to the location of the tumour.
Previous irradiation precludes the option of post-operative radiotherapy, and chemotherapy is often a palliative solution only. Radiation-induced sarcomas carry a poor prognosis and local recurrence and metastatic disease are both frequent.

In this study the following points were identified:

1. The median latency interval between the diagnosis of breast cancer and the development of sarcoma in the present series was 13 years. This is comparable to other published series in which the interval ranges from 11 to 14 years.\textsuperscript{11–14} The lengthy “lag period” means that patients may have already been discharged from follow-up by the time a RIS appears. Short of longer-term breast cancer follow-up, in order to identify these sarcomas early, an alternative is to warn patients of the specific potential danger and educate them in what to “look out for”.

2. The estimated five year survival in the current series is 27%. When excluding the patients with inoperable tumours this rose to 32%. Other units reported five year survival rates ranging from 29% to 48%.\textsuperscript{11–15}

3. According to three large patient series more than half the sarcomas found within a field of previous radiation are angiosarcomas.\textsuperscript{11–13} In the most recent study however from another UK tertiary referral centre, the histological type in half the cases was leiomyosarcoma or pleomorphic sarcoma.\textsuperscript{15} Osteosarcoma was the commonest tumour in our series (36%) followed by angiosarcoma (25%). Radiation-induced osteosarcoma has an even poorer prognosis than soft tissue RIS with 13% five year survival in the present series. The relatively low five year survival in our patient cohort may be attributable to this.

4. Local recurrence in the present series was 52%. Previous studies have also shown local disease recurrence to be high ranging from 50% to 68%.\textsuperscript{14–16} Local recurrence occurred in all five patients who had marginal excision margins which re-enforces the need for adequate excision margins. Our local practice is to carry out a wide local excision with a 3 cm skin/subcutaneous tissue margin, going down to one plane beyond the next anatomical plane for depth clearance. This may include pectoralis major on the chest wall, but if the ribs or clavicle is clinically involved, or too close, a chest wall excision may be required and will involve chest wall reconstruction (Fig. 5a and b).

We avoid total excision of the radiotherapy “field change” area in the first instance, as recurrence will still occur in deep tissues or at margins of generous excisions. We advise local flaps in the first instance, leaving larger regional flaps as options for potential reconstructions at a later date (Fig. 6). These sarcomas also have the documented ability to recur within flaps, a phenomenon which remains as yet unexplained, and can complicate their long-term management.

In summary, radiation-induced sarcomas are rare and carry a poor prognosis. They should be managed in a multi-disciplinary setting, with the goal of clinical management being wide surgical margins, wherever possible. Currently, chemotherapy remains a palliative option, but may become standard adjuvant treatment in the future with advances in chemotherapeutic agents. Plastic surgical reconstruction, and indeed chest wall reconstruction, may be necessary. The tendency to local recurrence within the radiation field, with the possible invasion of flap tissue, frequently results in repeated surgical episodes. Close patient follow-up is therefore mandatory to identify these areas early.

**Conflict of interest statement**

There are no conflicts of interest.

**References**


