Chapter 16
Radiation-Induced Sarcoma

One of the few known causes of sarcomas is therapeutic irradiation. Therapeutic radiation has also been associated with development of breast cancer, lung cancer, and accelerated coronary artery disease in patients receiving thoracic radiation [1–3]. With the increased recognition of second cancers as a long-term side effect of radiation therapy, attempts have been made to use radiation more sparingly. For example, there is a question as to whether surgery for ductal carcinoma in situ is necessary, whereas at least one present standard of care is lumpectomy and radiation therapy, despite the ability to obtain negative margins in at least 95 % of patients with surgery alone, and no difference in long-term breast cancer mortality with the addition of radiation therapy [4, 5]. The incidence of a sarcoma after radiation is not precisely known, and may vary from one part of the body to the next. In a series of patients treated for cancer of all sites in Finland, for example, the crude risk was of the order of 0.05 % [6].

In the prospectively collected series from MSKCC, consistent patterns have arisen regarding the types of diseases treated with radiation and the forms of sarcoma that arise after radiation. The most recent MSKCC update comes from Gladdy et al. from 2010 [7]. A total of 130 radiation-induced sarcomas (RIS) were examined in over 7600 patients treated surgically for sarcoma at MSKCC. A total of 34 % of patients with RIS were treated for breast cancer, 18 % for leukemia or lymphoma, and 17 % for genitourinary tumors. In this update, the median latency for development of the RIS was 10 years; however, the median latency varied based on the type of sarcoma involved, with the shortest median latency for liposarcomas (median 4.3 years) and longest for leiomyosarcoma (23 years).

Common RIS histologies included high grade undifferentiated pleomorphic sarcoma (26 %), angiosarcoma (21 %), leiomyosarcoma (12 %), and fibrosarcoma not otherwise specified (12 %). These data are somewhat different from other series, in which osteosarcomas were seen more frequently than in this series. Median age at presentation was 58.5 years (range 18–86). The trunk was the most common primary site (61 %) highlighting secondary sarcomas of the breast. Five-year

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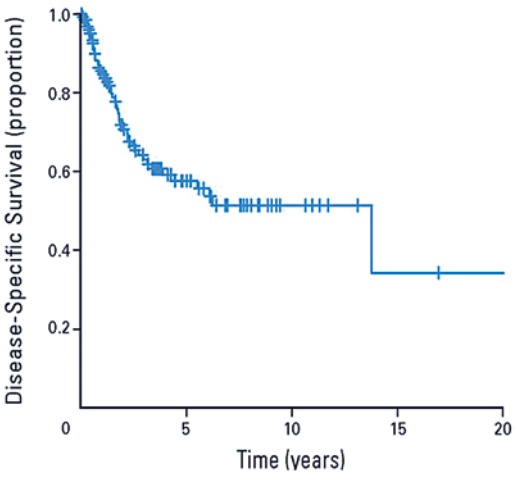

Fig. 16.1 Disease-specific survival (DSS) for resected primary radiation-associated sarcomas (RASs). *LMS* leiomyosarcoma, *AS* angiosarcoma, *MFH* malignant fibrous histiocytoma, *MPNST* malignant peripheral nerve sheath tumor, *FS/MYXF* fibrosarcoma or myxofibrosarcoma. With permission from: Gladdy RA, et al. J Clin Oncol 28:2064–2069, 2010

disease-specific survival was 58 % (Fig. 16.1), and independent predictors of poor outcome were large size >5 cm, margin status, and RIS histology.

Primary management of RIS remains surgical. Given the difficulty in administering radiation to control these tumors, and given the nature of the field to be operated upon, it is not surprising that there is a significant local–regional recurrence risk postoperatively, and survival appears inferior to patient with similar sarcomas that are not radiation induced (Fig. 16.2) [3, 7–10]. Radiation therapy, in particular the use of brachytherapy for resectable tumors and/or IMRT preoperatively to deliver highly localized radiation therapy, can be entertained in some patients, despite prior use of radiation as a treatment for the initial clinical problem, especially for patients who had a longtime interval from their initial radiation.

The development of RIS begs the question of whether less radiation therapy can be employed to decrease the risk of such malignancies developed. For example, can surgery without radiation therapy be employed for primary treatment of sarcomas? Given the low local recurrence risk of tumors under 5 cm in size in the MSKCC series, surgery alone is a good standard of care for sarcomas removed with negative margins, if there is a follow-up operation that can still be limb sparing. However, if there is a question of a margin, in particular in regions of the body such as the head and neck, where a second operation is less likely to achieve a good margin, then adjuvant or neoadjuvant radiation therapy should be considered.

An example of a radiation-induced sarcoma is shown in Figs. 16.3, 16.4, 16.5, 16.6, 16.7, and 16.8, a 48-year-old woman treated with radiation therapy following excision of ductal carcinoma in situ of the breast. Two years later she presented with a high grade undifferentiated pleomorphic sarcoma. She was treated by local resection and she then presented 2 years later (Fig. 16.3) with a fungating mass (Fig. 16.4) involving the chest wall with multiple foci. This was resected with the chest wall (Fig. 16.5) with reconstruction using methylmethacrylate for the rib cage (Fig. 16.6) and a rotational flap to cover the defect (Fig. 16.7). All margins were negative at the time. Within 2 years, she had further recurrence of a left anterior chest wall nodule

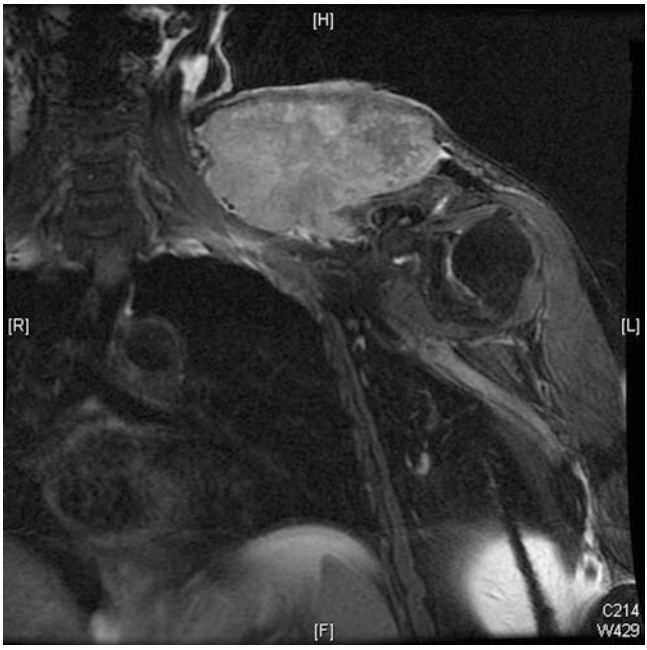

Fig. 16.2 Sagittal T2-weighted fat-saturated MRI image of a radiation-induced high grade myofibroblastic sarcoma of the left trapezius/supraspinatus

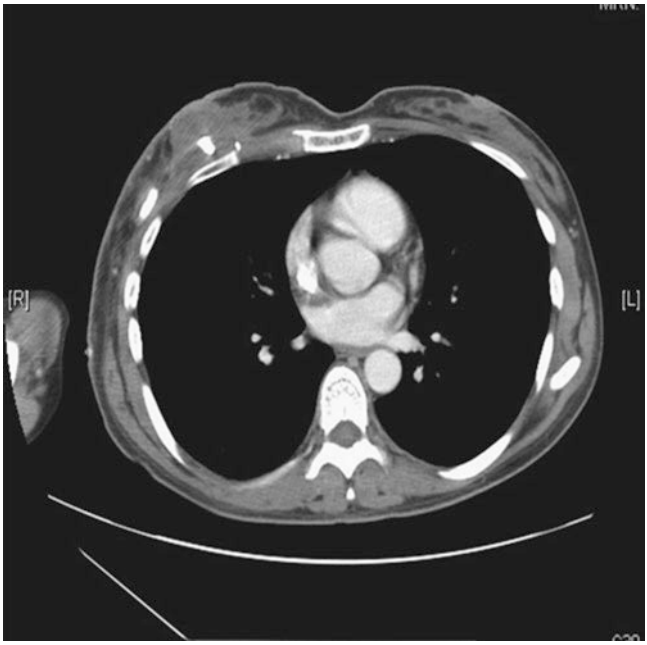

Fig. 16.3 Contrast-enhanced CT image of a radiation-induced sarcoma of the right chest wall after surgery and radiation therapy for ductal carcinoma in situ

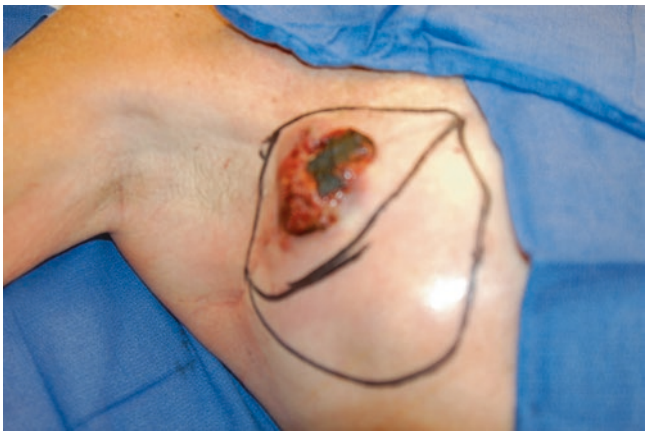

Fig. 16.4 Preoperative CT image of the right chest wall radiation-induced sarcoma from Fig. 16.3

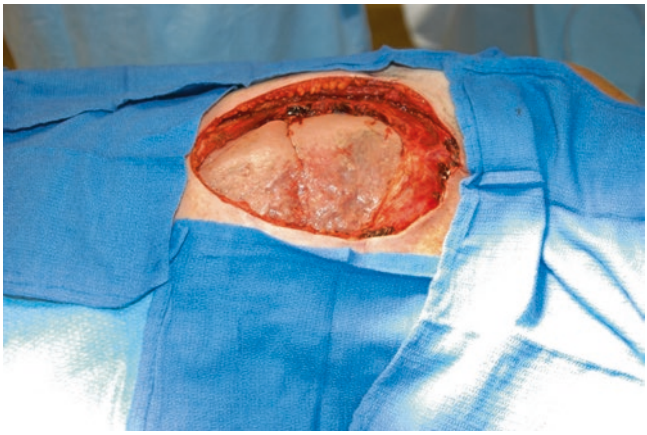

Fig. 16.5 Post-resection CT image of the chest wall resection of the patient in Figs. 16.3 and 16.4

and received chemotherapy. She progressed to demise within 1 year with extensive intrathoracic and chest wall recurrence (Fig. 16.8). A similar lesion in the right groin of a radiation-induced extraskeletal osteogenic sarcoma is demonstrated (Fig. 16.9), requiring a tissue flap for reconstruction of the defect.

Treatment for these lesions follows the principles used for the specific histological subtypes discussed elsewhere in this volume. There are few histology-specific data. In a large series of what was termed UPS at MD Anderson, those UPS associated with radiation had inferior outcomes both in terms of local recurrences and disease-specific survival [3]. As for chemotherapy for RIS, there are no specific guidelines, other than to use agents appropriate for the histology at hand. For exam-

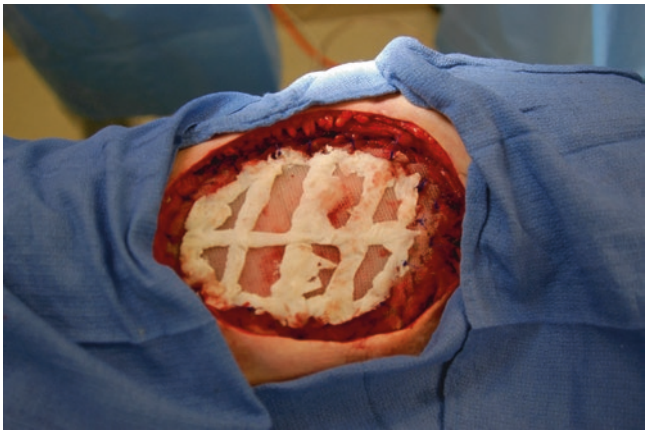

Fig. 16.6 Reconstruction of the chest wall after resection of the tumor from Figs. 16.3, 16.4, and 16.5

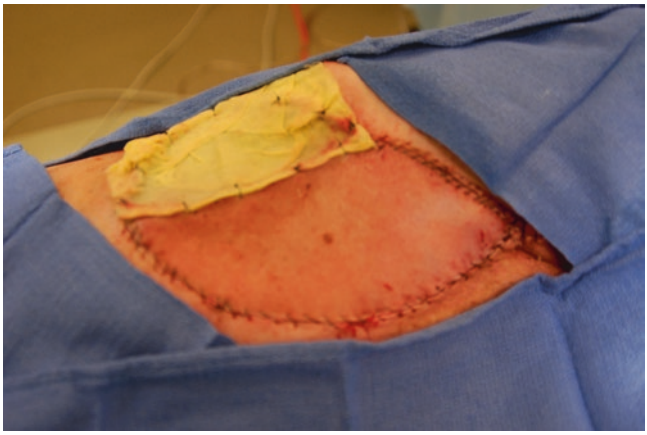

Fig. 16.7 Final surgical result for the patient from Figs. 16.3, 16.4, 16.5, and 16.6.

ple, angiosarcomas are responsive to anthracyclines and taxanes, and recent clinical data suggest that agents targeting VEGF (vascular endothelial growth factor) receptors can be active in radiation-induced angiosarcoma of the breast [11], although at present it is unclear if this is due to presence of KDR/VEGFR2 mutations in some breast angiosarcomas [12] or not. It should be noted that limb perfusion with tumor necrosis factor and chemotherapy such as melphalan is a possible option for patients with recurrent disease despite attempts at local control, if the tumor site can be isolated for such therapy [13]. It is also notable that RIS such as UPS are among the most highly mutated sarcomas. Given the responses noted in early studies of PD1 inhibitors of UPS and some osteosarcomas these may be good targets for immune checkpoint or related immunological approaches [14].

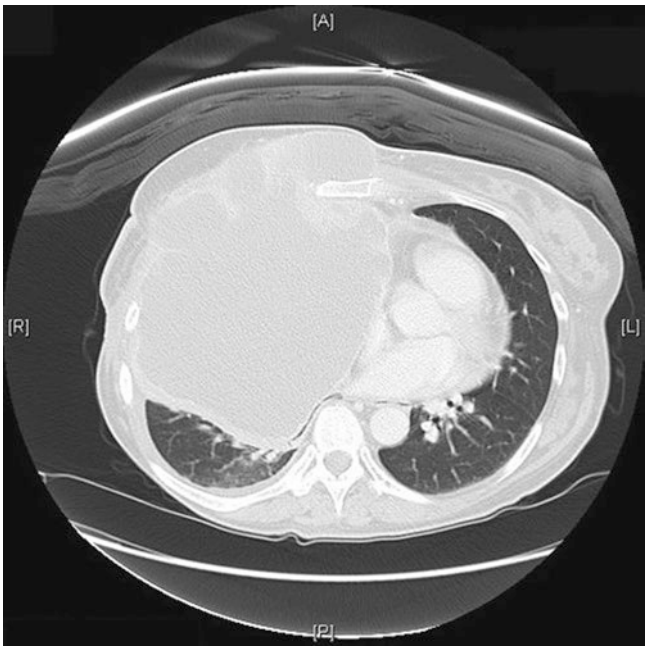

Fig. 16.8 Radiation-induced sarcoma after surgery and radiation for infiltrating ductal breast adenocarcinoma

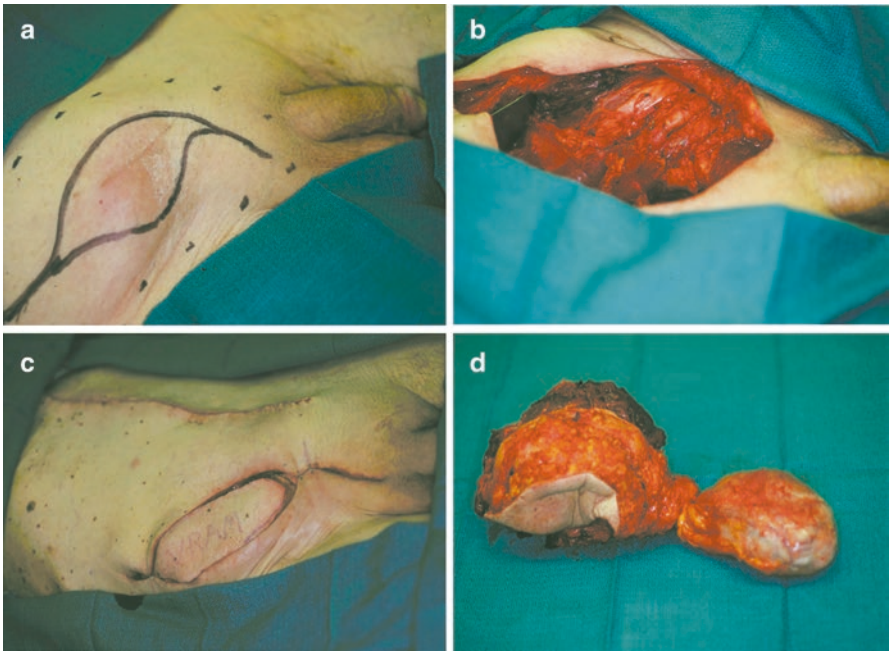

Fig. 16.9 Resection of a radiation-induced extraskeletal osteosarcoma of the right groin: (**a**) preoperative, (**b**) intraoperative, and (**c**) postoperative, and (**d**) an image of the resection specimen

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