Radiation-Induced Sarcoma Following Treatment of Breast Cancer

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The use of radiation therapy in the treatment of breast cancer also may be associated with the development of posttreatment sarcomas.

Background: Radiation therapy (XRT) is an important modality in the treatment of cancer, and XRT is now commonly utilized in the treatment of early-stage breast cancer. However, its use has occasionally resulted in the development of secondary malignancies. We present a critical review of radiation-induced sarcoma (RIS) that develops after irradiation for the treatment of breast cancer.

Methods: The case of a patient who developed sarcoma after radiation for breast cancer is presented, and current literature on RIS is reviewed. The role of XRT in the development of RIS is examined, and the evaluation and treatment of these malignancies are reviewed.

Results: RIS occurs in 0.2% of patients following treatment of breast cancer. The role of radiation in the development of RIS has been clearly demonstrated. Clinical presentation varies, and diagnosis is commonly delayed. Treatment consists of wide surgical excision. The role of chemotherapy is controversial.

Conclusions: The occurrence of RIS following treatment of breast cancer is rare. Its development has an average latency of over 10 years and likely correlates with the dose and technique of the radiation treatment. The prognosis of patients with RIS following treatment for breast cancer is poor predominantly due to a delay in diagnosis. However, the benefit derived by breast cancer patients from XRT far outweighs the risk of RIS and should not affect the decision to treat these patients with this modality.

Introduction

In 1895, Wilhelm Conrad Roentgen introduced the application of radiation energy for therapeutic purposes. Soon after, Frieben described the appearance of a squamous cell carcinoma on the hand of an x-ray technician. Although radiation therapy (XRT) was initially used for the treatment of benign conditions, its use quickly broadened to encompass malignant diseases as well. Today, a majority of cancer patients are treated with radiotherapy at some point in their treatment course, whether for curative or palliative intent.

In the 1920s, radiation-induced sarcoma (RIS) was described in patients following treatment with XRT for tuberculous arthritis and in workers painting radium watch dials.2 Since that time, numerous reports on the development of sarcomas following XRT for malignant diseases have been published. In 1948, Cahan et al3 first described the criteria for the diagnosis of RIS. These include a prior history of XRT, a latency period of several years (5 or more), the development of sarcoma within a previously irradiated field, and a histologic confirmation of sarcoma. These criteria, though later modified to include the tissues adjacent to the radiated field (not further defined) and a shorter latency period of 3 to 4 years,4 continue to define RIS. Published reports suggest an incidence of RIS of 0.03% to 0.2% in patients receiving XRT.5,7 According to a recent population-based, case-control study by Karlsson et al,8 the relative risk of developing a soft-tissue sarcoma after surgery and XRT for breast cancer was 2.2. In this study, the radiotherapy dose significantly correlated with the development of soft-tissue sarcoma, and this association remained significant after stratification for arm edema.

RIS occurs more frequently in women (female to male ratio of greater than 2 to 1), with the majority of these patients having previously been treated for cancers of the breast and female genital tract. The higher incidence of RIS in women reflects the frequency of these primary tumors, the use of XRT in their treatment, and the long survival of many of these patients. As the prognosis of patients treated for non-Hodgkin’s lymphomas and Hodgkin’s disease has improved, the frequency of RIS has increased in this group of patients as well. In addition, RIS has also been reported in patients treated for retinoblastoma,9,10 Ewing’s sarcoma, and Wilms’ tumor.11

Case Report

A 70-year-old woman was referred for evaluation of an anterior chest wall mass. Her history dates back to 1951, when at the age of 27, she underwent a left radical mastectomy followed by chest wall irradiation (case records are irretrievable) for an infiltrating ductal carcinoma of the left breast with multiple involved axillary lymph nodes. The cancer was diagnosed six weeks after her only child was born. She also received radioablation of her ovaries as adjuvant treatment. Ten years later, in 1961, she underwent a right radical mastectomy with right chest wall radiotherapy for a 1.9-cm infiltrating ductal carcinoma with involvement of multiple axillary nodes. She remained disease free for more than 30 years until 1995, when she presented with an asymptomatic enlarging left anterior chest wall mass.

As in other such cases with long latencies to the development of the sarcoma, information is lacking about the roentgen dose, radiation fields, or type of equipment.
used. In the time period in which the patient was treated, it was common practice to irradiate all the draining lymph-node-bearing regions including the supraclavicular area, axilla, and internal mammary region. This was usually accomplished with a single anterior field matched to tangential chest wall fields. Some older techniques would commonly result in overlap of the radiation fields at the junction between the chest wall fields and the lymph node fields.

On physical examination, a 13-cm firm mass involved the left infraclavicular fossa and extended superior and lateral to involve the supraclavicular fossa and the mid-axillary line (Fig 1). The chest wall had multiple telangiectasias, but there was no area suggestive of matchline fibrosis. The left radial pulse was strong, and the left shoulder joint maintained full range of motion. Magnetic resonance imaging (MRI) of the chest showed a solid soft-tissue tumor that was adherent to the pleural surface of the lung, with no evidence of neurovascular involvement (Fig 2). A venogram and an arteriogram revealed no obvious subclavian vessel encasement or thrombosis, and an extensive metastatic workup was negative.

![Preoperative photograph of a 13-cm radiation-associated sarcoma involving the left clavicular region. The patient is in the supine position, with the head at the top of the photograph, and the left arm abducted. Note the radical mastectomy scar.](image1)

![Axial proton-density-weighted MRI scan (TR = 2400 msec, TE = 15 msec) of the upper chest of the same patient, which demonstrates a well-defined mass in the left anterior chest wall, compressing the lung apex. Note that the signal intensity of this fibromyxoid sarcoma is higher than that of muscle.](image2)

The patient underwent an excisional biopsy of the chest wall mass that revealed a low-grade fibromyxoid sarcoma (Fig 3) measuring 19 x 14 x 8 cm, with surgical margins free of pathologic involvement and no vascular or lymphatic invasion. There was no evidence of breast cancer in the biopsy specimen. The patient subsequently completed a wide local excision with chest wall resection and reconstruction involving a latissimus dorsi flap with split-thickness skin graft coverage. Adjuvant therapy was not recommended. The patient did well and remains free of recurrent sarcoma at 3 years.

![Histologic section of this RIS demonstrating a typical low-grade fibromyxoid sarcoma (hematoxylin-eosin). Note the myxoid change with low mitotic activity.](image3)
Historical Perspective

The first cases of sarcoma arising after XRT for breast cancer were reported by Warren and Sommer in 1936. They retrospectively analyzed 163 cases of fibrosarcoma of the soft parts. Of these, five cases were associated with "irritative stimuli"; in two cases, the tumor developed following roentgen or radium treatment of pre-existing lesions. One case occurred in a 74-year-old woman who had undergone roentgen treatment of a breast cancer 24 years earlier and was diagnosed concurrently with an epidermoid carcinoma of the skin. She was treated with surgery alone and was alive and well 3.5 years after her diagnosis. In 1945, Hatcher reported on three cases of sarcomas developing in irradiated bone. Two patients had received roentgen therapy for benign bone tumors. The third patient developed a chondrosarcoma of the seventh rib 11 years after undergoing a radical mastectomy and receiving chest wall irradiation for breast carcinoma.

In 1948, Stewart and Treves were the first to describe six cases of angiosarcoma occurring in patients with lymphedematous extremities developing after radical mastectomy (Stewart-Treves syndrome). In their series, the average age of patients at the time of diagnosis of the initial breast tumor was 49 years. The average latency period to the development of angiosarcoma was 12.5 years. In all cases, postmastectomy edema of the arm developed immediately on the operated side. The treatment of the secondary tumor was by surgical amputation in four of the cases, local excision in one case, and XRT alone in another. The follow-up of these six patients was approximately 12 months, during which two patients died of pulmonary metastases, two were lost to follow-up, one was alive with pleural metastases, and one had no evidence of disease at six months.

The incidence of sarcomas in breast cancer patients following mastectomy and chest wall irradiation has been reported to be approximately 0.2% at 10 years. Computing incidence following radiotherapy is difficult and made more so by the occurrence of sarcomas following mastectomy alone for adenocarcinoma of the breast. In addition, the risk of developing a RIS is a function of the time of follow-up and survival rate.

The surgical treatment of breast cancer has evolved over many decades. Prior to the 1980s, radical mastectomies and, more recently, modified radical mastectomies were standard operations for early-stage breast cancer. In the 1980s, there was a trend toward breast-conservation therapy consisting of lumpectomy and breast radiotherapy. This has resulted in fewer women being treated by mastectomy alone and a concomitant increase in the number of irradiated patients. RIS was first described in the setting of radical mastectomies, and were later described in patients undergoing lumpectomy and radiation therapy. As breast-conserving therapy becomes more prevalent, it will be important to monitor the frequency of this complication.

Patient and Tumor Characteristics of RIS

An important distinction to be made is among (1) lymphangiosarcomas arising in lymphedematous extremities following mastectomy (Stewart-Treves syndrome), (2) angiosarcomas secondary to radiation therapy arising most commonly on the chest wall or axilla within the previously irradiated field and usually not associated with chronic lymphedema, and (3) other histologic types of RIS.

In general, de novo angiosarcoma, a malignant neoplasm of vascular origin, occurs equally in both sexes and predominantly at a young age. When angiosarcoma occurs after treatment for breast cancer, it affects older women with a mean age of 68 years. The relationship between radical mastectomy and lymphedema is thought to be central to the development of lymphangiosarcoma, although most patients have also received chest wall radiotherapy. Whether the association between radiotherapy and lymphangiosarcoma is due to the increased incidence of lymphedema associated with its use or is due to the fact that it serves as an additional risk factor for lymphangiosarcoma of the arm is controversial. In support of the latter, Valagussa et al. found no cases of lymphangiosarcoma in 845 patients with breast cancer treated with radical or modified radical mastectomy, though 21 other second solid tumors were identified. None of the patients received XRT.

The etiology of breast cancer-associated angiosarcomas is controversial. Some investigators believe that many reported cases are metaplastic variants of the original carcinoma. Immunohistochemical stains of tumor tissue such as factor VIII-related antigen and Ulex lectin stains are required to confirm the diagnosis of angiosarcoma and to differentiate it from metastatic recurrent breast carcinoma.

Non-lymphangiosarcoma RIS developing in patients following breast cancer therapy has received much less attention, although they occur more frequently than the Stewart-Treves syndrome. Interestingly, in a study by Brady et al., patients who developed RIS were young when diagnosed with breast cancer (range = 26 to 54 years, median = 43 years) compared to patients with lymphangiosarcoma (range = 39 to 69 years, median = 51 years; P < 0.001) and the general breast cancer population, in whom the average age is approximately 59 years. Radiation-associated sarcomas are usually high-grade tumors, as reflected by the advanced clinical stage at the time of diagnosis. RIS consists predominantly of malignant fibrous histiocytomas, with fibrosarcomas and osteosarcomas following in frequency. Chondrosarcoma, neurosarcoma, leiomyosarcoma, liposarcoma, and other mesenchymal tumors have also been described.

Clinically, radiation-associated sarcomas occur after treatment of breast cancer present as cutaneous lumps within the previously irradiated area of the chest wall (ie, parasternal area, supraclavicular fossa, shoulder girdle, and conserved breast). Mammography is typically negative. Of the sarcomas arising in bone, the most frequently involved site is the scapula, followed by the humerus, clavicle, rib, and sternum. The tumor size varies widely, but a median diameter of 8 cm (range: 1.0 to 18 cm) was reported by Brady et al. The latency period described by these authors is approximately 11 years (range: 4 to 44 years), which is similar to that recorded for secondary lymphangiosarcoma and RIS in general. Pathologic diagnosis is often delayed (8 to 12 months), due to both the lack of symptom specificity and the long latency period after diagnosis of the original tumor. Additional reasons cited for delayed diagnosis include difficulty in detecting the tumor in previously irradiated tissue (eg, due to fibrosis) and inadequate biopsies (not large enough or performed in the wrong place). Therefore, a high level of suspicion, careful patient evaluation, and adequate biopsy tissue for pathologic diagnosis are mandatory.

Pathogenesis

The role of XRT in the development of secondary sarcomas has been clearly described. Radiation-induced neoplastic transformation is thought to be related to irreversible DNA damage. Several years or decades following RT, dominant gene mutations and gene deletions accumulate in the genome, making carcinogenesis a multistage process. Redpath and Sun showed that cells in the G2 and M phases of the cell cycle are radiosensitive in terms of both cell killing and induction of neoplastic transformation compared with cells in the mid G1 phase. The molecular mechanisms of tumor promotion by ionizing radiation, however, are presently unknown. Proto-oncogene c-jun expression and inactivation of tumor suppressor genes p53 and Rb are two commonly discussed theories.

The retinoblastoma locus may be important in the pathogenesis of soft-tissue sarcomas. Retinoblastoma gene alterations have been detected in de novo leiomyosarcomas as well as RIS. Carcinogens associated with the development of sarcomas, such as radiation and phenoxycetic acids, may act by causing deletion or mutations of the normal retinoblastoma gene. Much has been written about ataxia telangiectasia (AT) or AT heterozygosity and the risk of secondary neoplasia.
Malignant lymphomas (including small-cell lymphosarcoma, histiocytic lymphoma, histiocytosarcoma, and Hodgkin’s disease) markedly predominate among the reported neoplasms. AT patients are uniquely sensitive to x-rays and gamma rays, and this hypersensitivity is assumed to result from an inability to recognize or respond to DNA damage. Despite this hypersensitivity to radiation, there has been no association with the subsequent development of sarcomas. Part of the problem in assessing such a relationship stems from the fact that these patients do not survive long enough to develop RIS.

It is difficult to analyze the relationship between the total irradiation dose, the individual fraction dose, and the incidence of RIS. This difficulty is due to inadequate data provided in the cases of RIS in the literature and the difficulty in retrieving information many years after the primary treatment, as is the case with our patient. Nevertheless, minimum total doses of 10 Gy in conventional doses per fraction appear necessary to result in RIS, and most cases of RIS occur in association with total radiation doses in the range of 40 to 50 Gy. No increase in sarcomas has been reported after low-dose irradiation in atomic bomb survivors or in patients who were irradiated for ankylosing spondylitis. Despite this postulated relationship between the radiation dose and the subsequent development of a sarcoma, there has been no supporting evidence of a relationship between the extent of acute radiation toxicity and the development of a subsequent neoplasm. Only one report of a subcutaneous leiomyosarcoma developing in an area of radiation dermatitis has been published. This sarcoma was thought to be induced by radiotherapy for a mediastinal tumor diagnosed 35 years earlier (“radiotherapy case records lost”).

The treatment of orthovoltage radiation to megavoltage radiation was thought to decrease the risk of subsequent sarcomas; however, recent reports do not support this expectation. No decrease in RIS has been observed, and although fewer cutaneous and subcutaneous radiation-associated sarcomas were seen with megavoltage radiation due to its skin-sparing effect, bone tumors were actually more frequent. Also, the threshold latency for the development of RIS is much longer for orthovoltage radiation (11.3 years) than for megavoltage radiation (3.4 years). Nevertheless, improvements in radiotherapy techniques over the last two decades have also consisted of improved dose distribution and limitation of lymphatic field irradiation. These techniques have reduced the risk of damage to normal tissues and will hopefully translate into a reduction of RIS risk in future decades.

Pierce et al. reported long-term radiation complications in 1,624 patients treated with conservative surgery and radiation at the Joint Center for Radiation Therapy between 1968 and 1985. Three of these patients developed an in-field sarcoma for a crude incidence of 0.18%. All three were treated with a three-field radiation technique, and two of the tumors were located in the region of the matchline. Although we have been unable to obtain exact radiation records for our patient, the clavicular location of the tumor would suggest an area of matching radiation fields. Pierce et al. suggest that there may be a relationship between radiation technique, ie, the potential overlapping of fields, and the development of secondary tumors. Thus, improvement in radiation technique in regard to matching of a third radiation field may also serve to limit the incidence of RIS.

The quantitative risk of RIS following breast-conserving treatment appears to be no greater than that following mastectomy, but with an apparent latency period of more than 10 years, it is still too early to draw firm conclusions regarding the incidence of RIS. The use of chemotherapy, especially with alkylating agents, has also been associated with an increased incidence of sarcomas, particularly osteogenic sarcomas. According to several reports, patients receiving both XRT and chemotherapy may be at highest risk for secondary malignancies, including sarcomas and leukemias.

### Diagnostic Evaluation

The diagnostic evaluation of a radiation-associated sarcoma is similar to that of a soft-tissue sarcoma occurring de novo. When a fixed undiagnosed mass is noted, plain radiographs will serve to determine whether the lesion is primarily in soft tissue or bone. While plain radiographs are the best initial method of assessing coexistent bone involvement in patients with soft-tissue sarcomas, they are not accurate in assessing the degree of aggressiveness of the tumor, and they do not provide information about the extent of the primary lesion.

MRI is the next step in imaging these lesions because of its superior soft-tissue contrast, multiplanar imaging capability, and absence of streak artifact. MRI is superior to CT in delineating tumor relationships to muscle, fat, fibrous tissue, and adjacent blood vessels. CT is superior to MRI only in the identification and evaluation of matrix/rim calcification and in the evaluation for pulmonary metastases. Neither modality can provide a definitive determination of whether a mass is benign or malignant. With the advent of magnetic resonance angiography, conventional angiography is seldom necessary in the preoperative evaluation except when preoperative embolization or regional perfusion chemotherapy is to be used.

Approximately 4% to 11% of patients presenting with a primary soft-tissue sarcoma will already have metastatic disease. Since the lungs are the most common site of metastases, a CT scan of the chest should be part of the preoperative evaluation of all patients with sarcoma. Regional lymph node metastases are uncommon. Weingrad and Rosenberg reviewed 2,500 patients in the literature and found that only 5% presented with nodal metastases. Bone metastases are also unusual as an isolated manifestation of metastatic disease. Consequently, routine nuclear scintigraphy in patients without other evidence of metastatic disease is not indicated.

One of the diagnostic criteria of RIS described by Cahan et al. was a histologic confirmation of sarcoma. The technique of biopsy and, more importantly, its location are important in the overall management of these patients. Incisional biopsies are the preferred method because they allow for ample tissue sampling with optimal hemostasis. With this technique, a histologic grade can be definitively assigned to the tumor. Excisional biopsies can be used for masses of less than 3 cm or for larger lesions (<5 cm) that are superficial to the deep fascia and can be removed with minimal dissection. The incision for any open biopsy of a soft-tissue tumor should be oriented to facilitate a subsequent wide excision, since the biopsy site must be excised with any definitive resection. The biopsy tissue should be analyzed both histologically and immunohistochemically.

### Treatment

The treatment of choice for sarcomas of any histologic type, occurring de novo or after exposure to radiation, is a wide margin surgical resection, a procedure that can become quite challenging in chest wall sarcomas because of its proximity to vital structures. Frequently, these centrally located sarcomas recur due to the inadequacy of the resection, despite obtaining negative surgical margins. In general, however, patients with advanced soft-tissue sarcomas are not cured with single-modality therapy, and attempts at combining surgical resection with chemotherapy and, at times, XRT are necessary. An extensive review of the treatment of advanced soft-tissue sarcomas with systemic therapy has recently been published by Okuno and Edmonson.

### Conclusions

To date, it is difficult to clearly define whether the prognosis of RIS is different from that of de novo sarcomas. Some investigators report survival times that vary between 10 and 48 months. This poor survival is thought to be due to delay in diagnosis, the aggressive local nature of these tumors, and their truncal location,
making radical extirpative surgery technically difficult. Prognostic determinants are similar in RIS and de novo sarcomas.

Experience with adjuvant chemotherapy in RIS is limited but disappointing. Some investigators believe that chemotherapy will prove to be less effective in RIS due to the fibrotic tissue changes in the previously irradiated field, thus preventing the chemotherapy from reaching adequate concentrations in the target organ.

The role of radiation therapy in inducing the development of sarcomas seems to be evident. However, the risk of RIS is no greater than the risks of anesthetic or operative death. In addition, this risk is not increasing with time, despite increased use of XRT. The benefit offered by irradiation in the treatment of breast cancer far outweighs the risk of secondary malignancies and should not affect the decision to treat a breast cancer patient with adjuvant XRT.

References


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