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Impact of Radiation Therapy on Scleroderma and Cancer Outcomes in Scleroderma Patients with Breast Cancer

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Abstract

Objectives—We examined SSc patients with breast cancer to 1) identify the prevalence of radiation complications and 2) examine SSc outcomes in SSc patients who received radiation therapy (RT) as part of their cancer treatment.

Methods—Patients with SSc and breast cancer were identified from the Johns Hopkins and University of Pittsburgh Scleroderma Center databases. We examined whether erythema, blistering, ulceration, or thickening of the skin developed in the RT port. Changes in modified Rodnan skin score (mRSS) and forced vital capacity (FVC) 12 and 24 months post cancer diagnosis were compared between patients who did and did not receive RT.

Results—Forty three of 116 breast cancer patients at Johns Hopkins and 26 of 37 patients at Pittsburgh received breast RT. At Johns Hopkins, 4/30 (13.3%) with available data developed erythema, 0/30 had blistering, 1/30 (3.3%) developed ulceration, and 15/31 (48.4%) had skin thickening in the radiation port. At Pittsburgh, 7/11 (63.6%) patients with available data developed erythema, 2/11 (18.2%) had blistering, none developed ulceration, and 6/11 (54.6%) had skin thickening in the radiation port. In a limited sample, there were no significant changes in mRSS or FVC between patients who did or did not receive RT.

Conclusion—These data suggest that radiation injury causing local tissue fibrosis is not inevitable in SSc patients with breast cancer, occurring in ~50% of cases without evidence of lung

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or generalized skin disease flare. Therefore, the use of RT for breast cancer is considered an option based on the informed patient's preference.

Keywords

scleroderma; breast cancer; radiation therapy; outcomes

Introduction

Systemic sclerosis (scleroderma) is a heterogeneous, complex autoimmune disease characterized by widespread tissue fibrosis, a prominent vasculopathy, and immune system abnormalities. Patients with scleroderma have an increased risk of malignancy compared to the general population (1), and often cancers manifest around the time of rheumatic disease onset (2, 3). Breast cancers in particular may be detected within a short interval of the first scleroderma symptom and represent the most common cancer seen in scleroderma (4, 5). As a result, clinicians are commonly confronted with the dilemma of how best to treat breast cancer in this patient population.

While lumpectomy with radiation therapy is first line therapy for many patients with breast cancer, scleroderma is often considered to be a relative, if not absolute contraindication, for radiation therapy given the risk of radiation-induced fibrosis in the skin, lung and other organ systems (6). With respect to breast cancer, case reports and case series suggest that patients with scleroderma may develop exaggerated fibrosis of the irradiated breast (7–13), as illustrated in Figure 1. Pulmonary fibrosis in the radiation port has also been a concern. In addition to localized toxicity from radiation therapy, there is often concern that radiation therapy could trigger the systemic rheumatic disease to flare, yet rheumatic disease outcomes have not been studied to date. A major limitation of the existing literature on use of radiation therapy in scleroderma patients with breast cancer is small sample sizes of 4 or fewer patients where publication bias is likely.

In the present investigation, we examined all scleroderma patients with breast cancer seen at 2 large Scleroderma Centers. We sought to determine the prevalence of localized, radiation-induced cutaneous and pulmonary fibrosis in scleroderma patients with breast cancer. We also examined whether scleroderma systemically flared after radiation therapy, and whether cancer outcomes differed between scleroderma patients who did or did not receive radiation therapy for their breast cancer.

Patients and Methods

Study population

Patients with a history of scleroderma and breast cancer were identified from the Johns Hopkins University (1982–2013) and University of Pittsburgh Medical Center (1990–2014) Scleroderma Center databases. All consecutive, consenting patients who met either 1980 or 2013 American College of Rheumatology criteria for scleroderma (14, 15), had at least 3 of 5 CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly or telangiectasia) criteria, or had definite Raynaud's phenomenon, abnormal

naifold capillaries and a scleroderma specific autoantibody have been enrolled in both Centers' dynamic entry cohorts at their first visit. Eligible participants in this study consisted of the subset of scleroderma patients with a history of breast cancer. Demographic data, disease onset dates, scleroderma characteristics (16, 17), use of prior immunosuppressive therapies, and autoantibody data were abstracted from the Center databases, and where necessary, medical record review. Data collection methods pertaining to exposure and outcome assessment have differed historically at the 2 scleroderma centers (detailed below), and as a result, all results have been presented separately for the 2 centers.

Exposure assessment

Our primary exposure of interest was radiation therapy. At the Johns Hopkins Scleroderma Center, information about cancer diagnosis dates and radiation exposure has been collected prospectively over time in the Center's database. For the University of Pittsburgh, data on radiation exposure was obtained by medical record review and supplemented by questionnaires mailed to the 37 living patients for this study. Data regarding radiation dose, extent of field, and duration were not available for most participants in this retrospective study at either site, and these data are not reported.

Outcomes assessment

Three main categories of outcomes were specified a priori. These included localized cutaneous and pulmonary radiation complications; systemic worsening of scleroderma-associated fibrosis affecting the skin and lung; and cancer outcomes including cancer free survival.

Local/regional radiation toxicity—Our primary outcome of interest was development of skin thickening localized to the radiation port, a late radiation toxicity. Secondary outcomes included localized cutaneous erythema, blistering and ulceration, which are generally acute radiation toxicities. At both sites, medical records were extensively reviewed to identify whether patients developed skin changes localized to the radiation port. At the University of Pittsburgh, living patients were also mailed a questionnaire inquiring if they developed these specific radiation complications, as permitted by their IRB protocol. Pulmonary fibrosis localized to lung fields within the radiation port was identified by review of imaging study reports (chest computed tomography or radiography), and these data were only available for Johns Hopkins patients.

Systemic/scleroderma outcomes (JHU data only)—We focused our investigation on 2 scleroderma outcomes that may worsen due to exaggerated fibrosis, specifically the modified Rodnan skin score (mRSS) (18), which is a measure of the extent and severity of cutaneous fibrosis in scleroderma, and the forced vital capacity (FVC % predicted). Baseline data closest to initiation of radiation therapy, and data 12 and 24 months post-cancer diagnosis were abstracted from the Center database. Changes in mRSS and FVC at 12 and 24 months were calculated relative to baseline. These data were only available for the Johns Hopkins cohort.

Cancer outcomes—Medical records were reviewed to determine whether patients were cancer free 1, 2 and 5 years post cancer diagnosis.

Statistical analysis

Instead of combining two different centers' data, we present our results separately as data collection was not uniform between the two institutions. Differences in continuous variables and dichotomous/categorical variables were assessed by the Student's t test and the chi square or Fisher's exact test where appropriate. Statistical significance was defined as a 2-sided p value < 0.05. All statistical analyses were performed using Stata 13.1 (Stata Corp., College Station, TX, USA).

Results

One hundred sixteen patients with scleroderma and breast cancer were identified from the Johns Hopkins Scleroderma Center database, 43 of whom (37.1%) were exposed to radiation therapy. At the University of Pittsburgh, 67 patients with breast cancer were identified, of whom 30 had missing data for radiation exposure. Therefore, the remaining 37 patients, 26 of whom were treated with radiation therapy, were analyzed in this study.

The baseline characteristics of the study participants stratified by radiation exposure are presented for each site in Table 1. There were no differences in age at scleroderma onset, age at cancer diagnosis, cutaneous subtype, baseline modified Rodnan skin scores, baseline forced vital capacity or diffusing capacity, baseline right ventricular systolic pressure, or autoantibody status between those who received radiation therapy and those who did not. At Johns Hopkins, patients who received radiation therapy had a shorter cancer-scleroderma interval (3.2 ± 11.1 years versus 8.1 ± 14.1 years, $p=0.06$), whereas this was not different in the University of Pittsburgh cohort. At the University of Pittsburgh, patients who were not treated with radiation therapy were more likely to self-identify as black race (27.3%) than patients who were treated with radiation therapy (0%; $p=0.021$); there were no racial differences in the Hopkins cohort. At both sites, patients treated with radiation were more likely to have had breast conserving surgery than those who were not treated with radiation.

Radiation outcomes

Radiation outcomes for both cohorts are summarized in Table 2. In the Johns Hopkins cohort, 43 women received radiation therapy as part of their cancer treatment regimen. Of these 43 women, 4/30 (13.3%) patients with available data developed erythema, 0/30 had blistering, 1/30 (3.3%) developed ulceration, and 15/31 (48.4%) had skin thickening in the radiation port. Three out of 30 (10%) patients with available data developed pulmonary fibrosis that was restricted to the lung fields in the radiation port on imaging.

In the University of Pittsburgh cohort, 26 women received radiation therapy for their breast cancer. Seven of 11 (63.6%) patients with available data developed erythema, 2/11 patients (18.2%) had blistering, none developed ulceration, and 6/11 (54.6%) had skin thickening in the radiation port. No information about pulmonary fibrosis that was restricted to the radiation field was available.

It is important to note that many reports have demonstrated a close temporal relationship between breast cancer diagnosis and scleroderma onset, often with cancer shortly preceding the first clinical signs of scleroderma. In the Johns Hopkins cohort, among the 43 women who received radiation therapy for their breast cancer, 22 (51.2%) patients had scleroderma precede their cancer diagnosis whereas 21 (48.8%) patients had cancer develop before scleroderma. There was no difference in the prevalence of radiation induced thickening between patients who had cancer before scleroderma (6/15 or 40%) or those who had scleroderma before their cancer (9/16 or 56.3%; $p=0.366$). In the University of Pittsburgh cohort, 25 of the 26 women who were treated with radiation had available data on the date of cancer diagnosis. Of these 25 women, 18 (72%) had scleroderma precede cancer and 7 (28%) had cancer first. For the Pittsburgh cohort, data on radiation induced skin thickening were available primarily for patients who had scleroderma precede cancer (N=10 with scleroderma first vs. N=1 for cancer first).

We were specifically interested in whether patients who develop radiation-induced skin thickening were more likely to have new onset scleroderma or diffuse cutaneous disease. When restricting our analyses to patients who had scleroderma before their cancer at Johns Hopkins, the prevalence of radiation port cutaneous fibrosis was 56.25%. The mean scleroderma disease duration was similar between those who developed radiation induced skin thickening (8.9 ± 8.0) and those who did not (11.8 ± 10.6 ; $p=0.537$) at Johns Hopkins. The data were similar for the University of Pittsburgh cohort: 50% (5/10) had radiation port fibrosis. The mean disease duration was 10.3 ± 15.1 years in radiation induced skin thickening group compared to 7.1 ± 3.3 years in the no radiation fibrosis group ($p=0.647$). There were also no differences in cutaneous subtype or autoantibody status between the two groups in each cohort (data not shown).

Scleroderma outcomes

We were specifically interested in whether systemic fibrotic complications of scleroderma worsened after radiation therapy for breast cancer, and we focused our evaluations on cutaneous and pulmonary disease as measured by changes in modified Rodnan skin score (mRSS) and forced vital capacity (FVC) at 12 and 24 month post cancer diagnosis. In a limited sample of Johns Hopkins patients with longitudinal data, there were no significant changes in the modified Rodnan skin score or the forced vital capacity between patients who received radiation therapy versus those who did not (Table 3).

Cancer outcomes

In both cohorts, there were no statistically significant differences in the proportion of patients who were cancer free 1, 2, and 5 years post breast cancer diagnosis in patients who received radiation therapy versus those who did not (Table 4).

Discussion

In this two center, retrospective study of scleroderma patients with breast cancer, significant acute skin toxicity (blistering, ulceration) from radiation was uncommon, while approximately 50% developed long term radiation-induced cutaneous fibrosis that was

localized to the field of radiation. Interestingly, scleroderma cutaneous subtype, autoantibody status, and disease duration did not associate with a higher risk of radiation-induced skin thickening. Localized pulmonary fibrosis was a less common complication, noted in ~10% of patients. In a limited sample size, fibrotic complications of scleroderma did not appear to flare after radiation exposure, as measured by the modified Rodnan skin score and forced vital capacity.

Table 5 gives us a glimpse of prior literature describing radiation outcomes in scleroderma patients with breast cancer (7–13, 19–22). It is important to note that the majority of reports describe only one to four patients with scleroderma and breast cancer. In addition, the existing guidelines that suggest scleroderma should represent a strong contraindication to radiation are based primarily on early reports of severe toxicity in such patients. Prior to the year 2000, most patients were exposed to external beam radiation therapy using 2-dimensional techniques, which are often associated with a higher risk of toxicity (23), and these patients developed significant fibrotic reactions post radiation therapy. After the year 2000, there are more cases treated with modern radiotherapy techniques, and brachytherapy is more commonly utilized as a radiation modality for scleroderma patients with breast cancer. Interestingly, the patients treated with brachytherapy developed less fibrotic reactions and had better cosmetic outcomes, likely due to the more limited tissue exposure using this technique, suggesting that further study of this approach may be warranted in patients with scleroderma. Of note, with all of these reports, there is significant risk of publication bias, as patients with more severe adverse outcomes are the only ones likely to be discussed in case reports.

While this series lacks a comparison group, historical controls suggest that the rate of acute and late radiation toxicity in this series is not markedly higher than non-scleroderma patients treated with radiation therapy. Blistering, which is most commonly reported as moist desquamation in the radiation oncology literature, may occur in up to 50% of patients treated with breast conservation (23, 24), and nearly 75% in patients treated with post-mastectomy radiation (25). While this retrospective review may under-represent the actual incidence of acute skin toxicity, the rate does not appear to be higher than historical controls. With respect to late skin toxicity, radiation oncology series generally report breast fibrosis or induration rather than skin thickening. A large randomized trial comparing different fractionation approaches for radiation after breast conserving surgery reported a rate of 23% with moderate or marked breast induration at 10 year followup using conventionally fractionated approaches, which would almost always be the regimen used in scleroderma patients (26). The severity of skin thickening is not available in the current series, and may also include more mild cases. However it is possible that the rate of this late radiation toxicity is higher than historical controls, an important consideration for some patients.

Pulmonary fibrosis is a very rare toxicity from breast radiation, and is not commonly reported. Acute or sub-acute pneumonitis is also rare, ranging from 1-3% in most series (27, 28). Thus, the incidence of pulmonary fibrosis may also be higher than non-scleroderma patients, but is nonetheless quite low and appears not to translate to long-term changes in pulmonary function.

Our study represents the largest sample size of scleroderma patients with breast cancer treated with radiation therapy to date. Prior reports have been quite heterogeneous, mixing in scleroderma patients with those who have other collagen vascular diseases. These reports have lacked information on scleroderma outcomes that are of interest to rheumatologists, radiation oncologists, and patients alike, and it is important to have such data that may inform and guide shared medical decision making. While our sample size with available data was small, our study suggests that scleroderma skin disease itself does not flare with radiation therapy for breast cancer. It is important to note that our study has several important limitations, however. We were not able to examine the type of radiation therapy, the extent of the radiation field, and whether there were any dose related effects in these patients. Skin toxicities were not differentiated between breast conservation and mastectomy patients. In patients with scleroderma, the desire to avoid radiation is likely an additional consideration in determining breast surgery type. Mastectomy may have been chosen in some cases to avoid radiation therapy, but later required radiation therapy due to the presence of adverse risk factors. Given that both acute and late radiation toxicities are often more severe in patients treated with post-mastectomy radiation therapy, this is an important limitation of the study. Telangiectasias in the radiation field, which have been commonly reported as a late radiation toxicity in scleroderma patients, was not captured in this series. Cutaneous and pulmonary outcomes were ascertained by retrospective chart review rather than Radiation Therapy Oncology Group scoring criteria for acute and late toxicities. High resolution chest CT images after radiation exposure were not available in many patients; as a result, the frequency of radiation induced pulmonary fibrosis in our study may be an underestimate. While we were able to determine whether radiation induced skin thickening was present or absent, we could not grade the severity of fibrosis in this retrospective review. As our data were derived from tertiary care centers, we may overestimate the risk of radiation-induced fibrosis in scleroderma patients with breast cancer. We also could not investigate cosmetic surgical outcomes in scleroderma patients who required mastectomy, yet this may play an important role in evaluating the risks and benefits of whether or not to pursue radiation therapy for breast cancer in this patient population. Lastly, we lacked a contemporary local control population without scleroderma to ascertain whether and to what extent the risk of radiation-induced fibrosis is greater in patients with scleroderma than the general population.

In our clinical experience, many scleroderma patients are denied breast conserving surgery and radiation as a treatment option. From the findings of our study and the existing literature, we recommend counseling scleroderma patients with breast cancer about the estimates of risks of localized radiation induced fibrosis. These data suggest to us that the decision about whether to proceed with radiation therapy should involve a multidisciplinary discussion between the treating rheumatologist, medical and radiation oncologists, breast surgeon and patient factoring in each patient's preferences and tolerance for risk. Investigation of cosmetic surgical outcomes in scleroderma patients who are treated with mastectomy should be considered, and further study is required to examine the risk of fibrotic reactions, now that newer radiation therapy modalities such as 3D conformal approaches with improved dose homogeneity and brachytherapy are being instituted.

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Significance and Innovations

- In the largest study of scleroderma patients with breast cancer treated with radiation therapy to date, significant acute skin toxicity (blistering, ulceration) from radiation was uncommon, while approximately 50% developed long term radiation-induced cutaneous fibrosis that was localized to the field of radiation.
- Scleroderma cutaneous subtype, autoantibody status, and disease duration did not associate with a higher risk of radiation-induced skin thickening.
- Fibrotic complications of scleroderma did not appear to flare systemically after radiation exposure, as measured by the modified Rodnan skin score and forced vital capacity.
- These data suggest that the decision about whether to proceed with radiation therapy should involve a multidisciplinary discussion between the treating rheumatologist, medical and radiation oncologists, breast surgeon and patient factoring in each patient's preferences and tolerance for risk.

Figure 1. Radiation induced cutaneous fibrosis in a patient with scleroderma and breast cancer
The irradiated left breast demonstrates shiny skin, dermal fibrosis and retraction compared to the contralateral breast.

Table 1

Baseline characteristics of study participants

Variable	Johns Hopkins N=116		University of Pittsburgh N=37	
	Radiation N=43	No Radiation N=73	Radiation N=26	No Radiation N=11
Age at SSc onset (years), mean (SD)	50.4 (13.5)	48.7 (14.4)	50.8 (12.5)	51.0 (12.3)
Age at cancer diagnosis (years), mean (SD)	53.7 (9.2)	56.8 (11.5)	57.1 (9.7), N=25	57.6 (11.5)
Cancer-SSc interval (years), mean (SD)	3.2 (11.1)	8.1 (14.1)	7.3 (12.1), N=25	6.6 (13.0)
Disease duration at first visit to scleroderma center (years), mean (SD)	9.3 (11.1)	10.9 (11.4)	9.6 (12.8)	11.3 (7.3)
Self-identified race, no. (%)	N=42			
White	40 (95.2)	65 (89.0)	26 (100.0)	8 (72.7)**
Black	2 (4.8)	5 (6.9)	0 (0)	3 (27.3)
Other	0 (0)	3 (4.1)	0 (0)	0 (0)
Cutaneous subtype, no. (%)				
Diffuse	17 (39.5)	23 (31.5)	7 (26.9)	3 (27.3)
Limited	26 (60.5)	50 (68.5)	19 (73.1)	8 (72.7)
Baseline mRSS, mean (SD)	10 (10.7), N=38	8.5 (10.6), N=69	8.2 (12.0)	5.5 (5.2)
Baseline FVC (% predicted), mean (SD)	77.6 (20), N=35	81.3 (16.3), N=66	N/A	N/A
Baseline DLCO (% predicted), mean (SD)	74.9 (29.8), N=30	77.4 (27.0), N=59	N/A	N/A
Baseline RVSP (mmHg), mean (SD)	35.2 (9.8), N=21	38.0 (13.4), N=45	N/A	N/A
Use of immunosuppressive therapy prior to cancer diagnosis*, no. (%)	8 (36.4), N=22	25 (61.0), N=41	N/A	N/A
Autoantibodies, no. positive/no. tested (%)				
Centromere	12/41 (29.3)	22/67 (32.9)	6/21 (28.6)	0/7 (0)
Topoisomerase I	8/40 (20)	13/66 (19.7)	5/21 (23.8)	2/7 (28.6)
RNA polymerase III	9/31 (29.0)	17/61 (27.9)	5/21 (23.8)	2/7 (28.6)
Extent of surgery ultimately required, no. (%)^	N=39	N=58	N=26	N=10
Lumpectomy	25 (64.1)	13 (22.4)	18 (69.2)	1 (10)
Mastectomy	14 (35.9)	45 (77.6)	8 (30.8)	9 (90)

* Immunosuppressive drugs evaluated include methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, TNF inhibitors, and IVIG.

** p=0.021

^ p<0.001 for Johns Hopkins and p=0.002 for Pittsburgh

N/A = data not available

Table 2

Radiation outcomes

Radiation outcomes	Johns Hopkins (N=43)	Pittsburgh (N=26)
Erythema	4/30 (13.3%)	7/11 (63.6%)
Blistering	0/30 (0)	2/11 (18.2%)
Ulceration	1/30 (3.3%)	0/11 (0%)
Localized skin thickening	15/31 (48.4%)	6/11 (54.6%)
Localized pulmonary fibrosis	3/30 (10%)	No data

Table 3

Scleroderma outcomes at 12 and 24 month intervals compared to baseline

	Time after cancer	Radiation	No Radiation	P-value
Change in mRSS	12 months	−0.6 (0.9) N=5	0.5 (3.8) N=20	0.5376
	24 months	0.6 (4.6) N=5	0.3 (2.0) N=19	0.8017
Change in FVC (% predicted)	12 months	−3.9 (11.3) N=7	−1.3 (9.2) N=21	0.5387
	24 months	5.7 (6.8) N=6	−1.8 (11.9) N=24	0.1532

Table 4

Cancer outcomes (Years cancer free)

Year cancer free	Johns Hopkins		University of Pittsburgh	
	Radiation N=39 (%)	No Radiation N=58 (%)	Radiation N=26 (%)	No Radiation N=11 (%)
Year 1	21/26 (80.8)	41/45 (91)	9/10 (90)	5/5 (100)
Year 2	20/24 (83.3)	39/41 (95.1)	8/10 (80)*	4/5 (80)
Year 5	20/22 (90)	32/35 (91.4)	9/10 (90)	3/5 (60)

* One patient was reported to be cancer free at year 1, have a recurrence by year 2, and was again cancer free at year 5.

Table 5

Literature review of patients with scleroderma and breast cancer who received radiation therapy to the breast/ chest wall

First Author	Year	Number with SSc, breast cancer and local irradiation	Type of radiation therapy	Complications
Ransom (7)	1987	1	External beam; conventional fractionation	Marked late fibrosis, breast shrinkage
Fleck (8)	1989	1	External beam; conventional fractionation	Acute moist desquamation; late fibrosis, telangiectasias, and necrosis requiring surgical intervention; late pulmonary fibrosis
Matthews (9)	1989	1	External beam; conventional fractionation	Late fibrosis and telangiectasias
Robertson (10)	1991	1	External beam; conventional fractionation	Edema, with marked retraction and fibrosis of the breast; rib fractures; late development of limitation in left arm range of motion due to pectoralis muscle fibrosis
Varga (11)	1991	2	External beam; conventional fractionation to breast and hypofractionation to hip for metastatic lesion	New onset SSc developed 2 months after completion of radiation therapy in 1 st patient. Edema, induration and thickening on ipsilateral arm and trunk in 2 nd patient.
Morris (12)	1997	1	External beam; conventional fractionation	No acute toxicity; Painful fibrosis, cool arm as late effects
Chen (13)	2001	4	External beam; conventional fractionation	1 st patient: moist desquamation and pitting edema initially; later fibrosis, ulceration and progressive flap necrosis after mastectomy done 2 nd patient: minimal erythema and grade II moist desquamation; later decrease in left shoulder and arm range of motion associated with marked fibrosis, small ulceration and subsequent necrosis 3 rd patient: mild dry desquamation; later transient left vocal cord paralysis; progressive fibrosis and telangiectasia of breast over 5 year period followed by stabilization 4 th patient: none
Gold (19)	2007	1	External beam; conventional fractionation	Acute grade 2 skin toxicity (brisk erythema with or without limited moist desquamation); Late toxicity - telangiectasia and hyperpigmentation of skin in radiation field and incidentally noted pulmonary fibrosis
Kounalakis (20)	2011	1 (bilateral breast cancers)	Accelerated (PBI) partial breast irradiation brachytherapy	Transient erythema; mild induration and telangiectasias along incisions on both breasts
Dragun (21)	2011	1	Accelerated (PBI) partial breast irradiation brachytherapy	Outcomes specific to SSc unclear but no severe outcomes noted in CVD patients
Kyrgias (22)	2012	4	External beam; conventional fractionation	Acute skin toxicity grade 1 (mild erythema): 2 pts, grade 2 (brisk erythema with or without limited moist desquamation): 1 pt, grade 3 (extensive moist desquamation beyond skin folds): 1 pt. Late toxicity: grade 1 (slight atrophy) – two patients (after a follow-up of 12 and 127 months); grade 2 (moderate atrophy) – in one patient (after a follow-up of 155 months). One patient developed grade 1 lung toxicity (radiographic changes without symptoms).