Bodine Journal

Volume 1 | Issue 1 Article 2

2008

Toxicity of Radiotherapy in Patients With Collagen Vascular Disease

Alexander Lin, MD
Department of Radiation Oncology, University of Michigan, Ann Arbor

Eyad Abu-Isa, MD
Department of Radiation Oncology, University of Michigan, Ann Arbor

Kent A. Griffith, MPH, MS
University of Michigan Cancer Center Biostatistics Core, Ann Arbor, Michigan

Edgar Ben-Josef, MD
Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan

Toxicity of Radiotherapy in Patients With Collagen Vascular Disease

Alexander Lin, MD,[1] Eyad Abu-Isa, MD,[1] Kent A. Griffith, MPH, MS[2]
Edgar Ben-Josef, MD[1]

[1]Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan.
[2]University of Michigan Cancer Center Biostatistics Core, Ann Arbor, Michigan.

The following article is reprinted with permission from John Wiley & Sons, Inc. It was originally published in CANCER, Volume 113, No. 3, pages 648-653, August 1, 2008.

Background
A diagnosis of collagen vascular disease (CVD) may predispose to radiotherapy (RT) toxicity. The objective of the current study was to identify factors that influence RT toxicity in the setting of CVD.

Methods
A total of 86 RT courses for 73 patients with CVD were delivered between 1985 and 2005. CVD subtypes include rheumatoid arthritis (RA; 33 patients), systemic lupus erythematosus (SLE; 13 patients), scleroderma (9 patients), dermatomyositis/polymyositis (5 patients), ankylosing spondylitis (4 patients), polymyalgia rheumatica/temporal arteritis (4 patients), Wegener granulomatosis (3 patients), and mixed connective tissue disorders (MCTD)/other (2 patients). Each patient with CVD was matched to 1 to 3 controls with respect to sex, race, site irradiated, RT dose (±2 Gray), and age (±5 years).

Results
There was no significant difference between CVD patients (65.1%) and controls (72.5%) experiencing any acute toxicity. CVD patients had a higher incidence of any late toxicity (29.1% vs 14%; $P = .001$), and a trend toward an increased rate of severe late toxicity (9.3% vs 3.7%; $P = .079$). RT delivered to the breast had increased risk of severe acute toxicity, whereas RT to the pelvis had increased risk of severe acute and late toxicity. RT administered in the setting of scleroderma carried a higher risk of severe late toxicity, whereas RT to SLE patients carried a higher risk of severe acute and late toxicity.

Conclusions
Although generally well tolerated, RT in the setting of CVD appears to carry a higher risk of late toxicity. RT to the pelvis or in the setting of SLE or scleroderma may predispose to an even greater risk of severe toxicity. These issues should be considered when deciding whether to offer RT for these patients. ***Cancer* 2008;113:648–53.** *©2008 American Cancer Society.*

Key Words: radiotherapy, collagen diseases, complications, adverse effects.

The decision of whether to offer therapeutic radiotherapy (RT) to patients with collagen vascular disease (CVD) continues to be a challenging one. It is believed that CVD may predispose patients to increased toxicity, and many practicing oncologists believe that a diagnosis of CVD is a relative contraindication to RT. However, to our knowledge, the available literature on this issue has been mixed. Early publications were largely case reports of CVD patients with increased toxicity from RT.[1-8] However, 2 separate matched control studies failed to observe any increased risk of acute or late complications in patients with CVD versus patients without CVD.[9,10] Other publications suggested that patients with nonrheumatoid arthritis CVD,[11,12] or patients with specific subtypes of CVD, may be at increased toxicity risk.[13-15] Further complicating the issue is the finding that some commonly prescribed medications, many of which are used in patients with CVD, may alter the radiation toxicity profile.[16–18] The goals of this matched control study were to determine whether patients with CVD were at a higher risk of RT-associated toxicity compared with patients without CVD and to identify factors that influence radiation toxicity in the setting of CVD, with particular emphasis on medications (antirheumatic drugs, nonsteroidal antiinflammatory drugs [NSAIDs], statins, and calcium channel blockers [CCBs]) that when taken concurrently may alter radiation toxicity.

Materials and Methods
After Institutional Review Board approval, 101 patients with a diagnosis of CVD treated in the Department of Radiation Oncology at the University of Michigan between 1985 and 2005 were identified. A total of 116 unique RT courses were delivered to these patients. A majority of these courses were delivered with 3-dimensional (3D) conformal techniques. Twenty-two cases were excluded because the diagnosis of CVD was made after the completion of RT. Of the remaining 94 RT courses, 8 courses could not be matched with a control. This left an analyzable sample of 86 CVD RT courses for 73 unique patients. Thirty-three patients had rheumatoid arthritis (RA), 13 had systemic lupus erythematosus (SLE), 9 had scleroderma, 5 had dermatomyositis/polymyositis, 4 had ankylosing spondylitis, 4 had polymyalgia rheumatica/temporal arteritis, 3 had Wegener granulomatosis, and 2 had mixed connective tissue disorders (MCTD)/other. Neither polymyalgia rheumatica/temporal arteritis nor Wegener granulomatosis are defined as a CVD; however, their inclusion was based on the systemic vasculitis noted with these diseases and its potential impact on RT toxicity. The mean age of the patients at time of RT was 58.2 years (range, 23-84 years) and the majority of patients were women (73.3%). Sixty patients received only a single RT course, with 13 patients receiving 2 RT courses in this dataset. Their medical records were reviewed for the following characteristics: age, sex, race, CVD type and activity, date of CVD diagnosis, concurrent medications, cancer diagnosis, chemotherapy treatment details, site and dose schedule of RT, acute and late toxicity, pattern of failure, and survival.

Of the total 86 RT courses, 15 were delivered to the thorax, 14 to the skin, 12 to the head and neck, 11 to bone, 11 to the pelvis, 8 to the breast, 6 to total body, 4 to the central nervous system, 4 to the abdomen, and 1 to an extremity.

Each CVD patient was then matched with a control patient without CVD for sex, race, site of disease treated by RT, dose delivered (±2 Gray [Gy]), and age at time of RT delivery (±5 years). For CVD patients with many matching controls, the controls with the smallest difference with regard to RT dose and age at

RT were chosen, with importance placed on minimizing the difference in RT dose over the difference in age at RT. An attempt was made to find 3 matching controls for each CVD RT course. Fifty-nine courses were matched to 3 controls, 18 courses were matched to 2 controls, and 9 courses were matched to a single control.

Acute toxicity was defined as toxicity from the time of commencement of RT through Day 90 after treatment and was scored using the Radiation Therapy Oncology Group (RTOG) common toxicity criteria.[19] Late toxicity was defined as occurring after Day 90 posttreatment, and was scored according to the RTOG/European Organization for Research and Treatment of Cancer (EORTC) late radiation morbidity scoring schema.[20] Severe acute or late toxicity was defined as ≥grade 3.

Because this is a match-pairs, case-control analysis, conditional logistic regression techniques were used. Because sex, age at RT, anatomic site treated, and RT dose were matched for by the design, these covariates were not adjusted for in the modeling process because their impact has been adjusted for by the study design. The remaining covariates of interest were as follows: concurrent infusional chemotherapy administration, and the use of steroids, NSAIDS, statins, CCBs, antimalarial antirheumatic drugs, and oral cytotoxic antirheumatics. Many of the medications apply only to the CVD cases and could not be adjusted for in the overall model. The medication list is therefore most appropriately used to help predict toxicity in the CVD group separately.

Overall crude rates for toxicity are reported by the anatomic site of RT delivery and by CVD subtype of the cases. Although these rates are instructive, formal comparison at the matched case-control level has not been attempted because of the small sample size. Formal comparisons were limited to the entire population. *P* values ≤.05 are considered statistically significant.

There were 4 endpoints of interest: any acute toxicity, severe acute toxicity, any late toxicity, and severe late toxicity.

Results

Acute Toxicity

With a median follow-up time of 1.3 years for each group, overall, there was no significant difference noted with regard to the incidence of acute toxicity between CVD and control cases, with 65.1% of CVD patients experiencing any acute toxicity, compared with 72.5% of control patients (Table 1). The incidence of severe acute toxicity was similar in both groups (10.5% vs 10.4%).

Table 1. Acute and Late Toxicity by CVD Status

	Toxicity Grade						Any	Severe
Frequency (percent)	**0**	**1**	**2**	**3**	**4**	**5**	***P*†**	***P*†**
Acute Toxicity*								
CVD cases	30 (34.9)	19 (22.1)	28 (32.6)	9 (10.5)	0	0	—	—
Control Cases	61 (27.5)	63 (28.4)	75 (33.8)	23 (10.4)	0	0	.97	.075
Late Toxicity‡								
CVD cases	61 (70.9)	10 (11.6)	7 (8.1)	4 (4.7)	2 (2.3)	2 (2.3)	—	—
Control Cases	191 (86.0)	14 (6.3)	9 (4.1)	7 (3.2)	1 (0.5)	0	.0010	.079

CVD indicates collagen vascular disease.

* Acute toxicity was defined as toxicity from the commencement of radiotherapy through Day 90 after treatment, and was scored using the Radiation Therapy Oncology Group (RTOG) common toxicity criteria.[19]

† Exact P value was derived from conditional logistic regression analysis.

‡ Late toxicity was defined as that occurring after Day 90 after treatment, and was scored according to the RTOG/European Organization for Research and Treatment of Cancer (EORTC) late radiation morbidity scoring schema.[20]

Late Toxicity

Overall, patients with a CVD diagnosis had a significantly higher incidence of any late toxicity (29.1% vs 14%; *P* =.001), with a trend toward increased severe late toxicity (9.3% vs 3.7%; *P* =.079) (Table 1).

Table 2. Acute and Late Toxicity by Anatomic Site of Radiotherapy Delivery

Frequency (Percent)	Acute toxicity grade*					
	0	**1**	**2**	**3**	**4**	**5**
Bone						
Cases (n = 11)	11 (100.0)	0	0	0	0	0
Controls (n = 28)	20 (71.4)	4 (14.3)	4 (14.3)	0	0	0
Breast						
Cases (n = 8)	1 (12.5)	1 (12.5)	4 (50.0)	2 (25.0)	0	0
Controls (n = 20)	0	6 (30.0)	14 (70.0)	0	0	0
Head and neck						
Cases (n = 12)	0	4 (33.3)	6 (50.0)	2 (16.7)	0	0
Controls (n = 32)	5 (15.6)	8 (25.0)	12 (37.5)	7 (21.9)	0	0
Pelvis						
Cases (n = 11)	0	1 (9.1)	6 (54.6)	4 (36.4)	0	0
Controls (n = 28)	2 (7.1)	7 (25.0)	16 (57.1)	3 (10.7)	0	0
Skin						
Cases (n = 14)	0	10 (71.4)	4 (28.6)	0	0	0
Controls (n = 35)	1 (2.9)	17 (48.6)	14 (40.0)	3 (8.6)	0	0
Thorax						
Cases (n = 15)	6 (40.0)	3 (20.0)	6 (40.0)	0	0	0
Controls (n = 41)	14 (34.2)	12 (29.3)	8 (19.5)	7 (17.1)	0	0
Other Sites†						
Cases (n = 15)	12 (80.0)	0	3 (20.0)	0	0	0
Controls (n = 38)	19 (50.0)	9 (23.7)	6 (15.8)	4 (10.5)	0	0

	Late toxicity grade‡					
	0	**1**	**2**	**3**	**4**	**5**
Bone						
Cases (n = 11)	11 (100.0)	0	0	0	0	0
Controls (n = 28)	27 (96.4)	1 (3.6)	0	0	0	0
Breast						
Cases (n = 8)	5 (62.5)	1 (12.5)	2 (25.0)	0	0	0
Controls (n = 20)	13 (65.0)	4 (20.0)	3 (15.0)	0	0	0
Head and neck						
Cases (n = 12)	6 (50.0)	2 (16.7)	2 (16.7)	2 (16.7)	0	0
Controls (n = 32)	24 (75.0)	2 (6.3)	2 (6.3)	3 (9.4)	1 (3.1)	0
Pelvis						
Cases (n = 11)	4 (36.4)	2 (18.2)	1 (9.1)	1 (9.1)	2 (18.2)	1 (9.1)
Controls (n = 28)	21 (75.0)	2 (7.1)	3 (10.7)	2 (7.1)	0	0
Skin						
Cases (n = 14)	10 (71.4)	4 (28.6)	0	0	0	0
Controls (n = 35)	35 (100.0)	0	0	0	0	0
Thorax						
Cases (n = 15)	11 (73.3)	1 (6.7)	2 (13.3)	1 (6.7)	0	0
Controls (n = 41)	36 (87.8)	4 (9.8)	1 (2.4)	0	0	0
Other Sites†						
Cases (n = 15)	14 (93.3)	0	0	0	0	1 (6.7)
Controls (n = 38)	36 (94.7)	0	0	2 (5.3)	0	0

CVD indicates collagen vascular disease.

* Acute toxicity was defined as toxicity from the commencement of radiotherapy through Day 90 after treatment, and was scored using the Radiation Therapy Oncology Group (RTOG) common toxicity criteria.[19]

† Other sites included the abdomen, central nervous system, extremities, and total body.

‡ Late toxicity was defined as that occurring after Day 90 after treatment, and was scored according to the RTOG/European Organization for Research and Treatment of Cancer (EORTC) late radiation morbidity scoring schema.[20]

Table 3. Distribution of Toxicity (Percent) by CVD Case/Control Status, by CVD Subtype

	Acute*				Late†			
	Any		Severe		Any		Severe	
CVD Subtype	CVD	Control	CVD	Control	CVD	Control	CVD	Control
Rheumatoid arthritis	64.9	76.2	10.8	9.9	29.7	13.9	2.7	4.0
Systemic lupus erythematosus	88.2	76.2	29.4	11.9	41.2	19.1	35.3	4.8
Dermatomyositis/polymyositis	66.7	91.7	0	8.3	16.7	8.3	0	0
Ankylosing spondylitis	0	0	0	0	0	0	0	0
Wegener granulomatosis	100	100	0	16.7	33.3	33.3	0	0
Scleroderma	30.0	53.9	0	11.5	20.0	15.4	10.0	3.9
Polymyalgia rheumatica/temporal arteritis	85.7	80.0	0	10.0	28.6	5.0	0	5.0
Mixed connective tissue disorder/other	50.0	83.3	0	16.7	50.0	16.7	0	0

CVD indicates collagen vascular disease.

* Acute toxicity was defined as toxicity from the commencement of radiotherapy through Day 90 after treatment, and was scored using the Radiation Therapy Oncology Group (RTOG) common toxicity criteria.[19]

† Late toxicity was defined as that occurring after Day 90 after treatment, and was scored according to the RTOG/European Organization for Research and Treatment of Cancer (EORTC) late radiation morbidity scoring schema.[20]

Toxicity by Irradiated Site

Although overall there was no significant difference noted with regard to the incidence of acute toxicity, CVD patients treated with RT to some anatomic sites were found to have a higher rate of severe acute toxicity (Table 2). RT to CVD patients produced higher crude rates of grade 3 acute toxicity when delivered to the breast (2 patients [25%] vs 0 patients [0%]) or pelvis (4 patients [36%] vs 3 patients [11%]). For the 2 CVD patients with severe breast acute toxicity, toxicity consisted of grade 3 skin desquamation. For the 4 CVD patients with severe pelvic acute toxicity, 3 had grade 3 skin desquamation alone, whereas the fourth patient had grade 3 skin desquamation, cystitis, and diarrhea/dehydration. However, given the small sample sizes per group and the matched case-control design of the study, formal statistical comparisons were not attempted.

RT to several anatomic sites produced a higher crude rate of any late toxicity in CVD patients (Table 2), including the head and neck (6 patients [50%] vs 8 patients [25%]), pelvis (7 patients [64%] vs 7 patients [25%]), skin (4 patients [29%] vs 0 patients [0%]), and thorax (4 patients [27%] vs 5 patients [12%]). The incidence of severe toxicity was greater mainly only in the pelvis subgroup, with 4 CVD patients (36%) experiencing grade 3+ toxicity (consisting of small bowel ulceration and dysuria), including 1 grade 5 event (intestinal perforation), versus 2 in the control group with severe toxicity (7%). RT to the other anatomic sites was found to be equally well tolerated by both CVD and control patients.

Toxicity by CVD Subtype

Table 3 summarizes the toxicity information when separated by CVD subtype. The only patients who had an appreciably higher crude incidence of any acute toxicity when compared with controls were patients with SLE (88.2% vs 76.2%). Patients with SLE were also the only CVD subset found to have a higher crude risk of severe acute toxicity (29.4% vs 11.9%), which was the highest rate of severe acute toxicity noted among all CVD subtypes. Otherwise, severe acute toxicity was uncommon.

Compared with controls, the incidence of any late toxicity was observed to be higher in several CVD subtypes: RA (29.7% vs 13.9%), SLE (41.2% vs 19.1%), dermatomyositis/polymyositis (16.7% vs 8.3%), polymyalgia rheumatica/temporal arteritis (28.6% vs 5.0%), and MCTD/other (50.0% vs 16.7%). The incidence of severe late toxicity was generally low among both CVD and control patients; however, patients with SLE (35.3% vs 4.8%) and scleroderma (10.0% vs 3.9%) had a higher risk of severe late toxicity versus controls.

Table 4. Medications and Frequency of Use for CVD Patients

	Cases (n = 86)	
Medication	Frequency	Percentage
NSAIDs	34	39.5
Corticosteroids	32	37.2
Antimalarials	25	29.1
CCB	20	23.2
Chemotherapy*	18	20.9
Oral cytotoxic, antirheumatic drugs	17	19.8
Statins	13	15.1

CVD indicates collagen vascular disease; NSAIDs, nonsteroidal antiinflammatory drugs; CCB, calcium-channel blocker.

* Concurrent with radiotherapy.

Concomitant Medication Use by CVD Patients

Table 4 lists several types of medications and their frequencies of use by CVD patients. Tables 5 and 6 list the distribution of acute and late toxicities for CVD cases, respectively. None of the following medications was found to be significantly associated with a risk of any acute or late toxicity: corticosteroids, NSAIDs, statins, CCBs, and antimalarials. The use of oral cytotoxic, rheumatologic agents was found to be significantly associated with a decreased risk of any acute toxicity (P = .0263), and concurrent infusional chemotherapy was found to be significantly associated with an increased risk of severe acute toxicity (P = .0022). Chemotherapy was the only concomitant medication that was found to be associated with increased risk of any (P = .009) or severe (P = .009) late toxicity.

Discussion

Delivering RT to patients with CVD continues to be a challenging clinical dilemma for radiation oncologists. The existing literature is difficult to interpret because of the heterogeneity in CVD subtype and activity, the variations in RT dose and site of treatment, as well as the potential role of concomitant medications in altering toxicity. Morris and Powell[11] reported that severe late effects were associated with CVD other than

Table 5.
Medications and Treatments by Acute Toxicity*: CVD Cases Only

	Toxicity Grade				Any	Severe
Frequency (percent)	0	1	2	3	P†	P†
Corticosteroids						
No	22 (40.7)	11 (20.4)	14 (25.9)	7 (13.0)		
Yes	8 (25.0)	8 (25.0)	14 (43.8)	2 (6.3)	.17	.47
NSAIDS						
No	17 (32.7)	11 (21.2)	18 (34.6)	6 (11.5)		
Yes	13 (38.2)	8 (23.5)	10 (29.4)	3 (8.8)	.65	~1
Statins						
No	28 (38.4)	13 (17.8)	23 (31.5)	9 (12.3)		
Yes	2 (6.7)	6 (46.2)	5 (38.5)	0	.13	.34
CCB						
No	23 (34.9)	15 (22.7)	21 (31.8)	7 (10.6)		
Yes	7 (35.0)	4 (20.0)	7 (35.0)	2 (10.0)	~1	~1
Antimalarials						
No	24 (39.3)	13 (21.3)	19 (31.2)	5 (8.2)		
Yes	6 (24.0)	6 (24.0)	9 (36.0)	4 (16.0)	.22	.44
Oral cytotoxics						
No	20 (29.0)	16 (23.2)	25 (36.2)	8 (11.6)		
Yes	10 (58.8)	3 (17.7)	3 (17.7)	1 (5.9)	.026	.68
Infusional chemotherapy						
No	23 (33.8)	19 (27.9)	23 (33.8)	3 (4.4)		
Yes	7 (38.9)	0	5 (27.8)	6 (33.3)	.78	.0022

CVD indicates collagen vascular disease; NSAID, nonsteroidal anti-inflammatory drug; CCB, calcium-channel blocker.
* Acute toxicity was defined as toxicity from the commencement of radiotherapy through Day 90 after treatment, and was scored using the Radiation Therapy Oncology Group (RTOG) common toxicity criteria.[19]
† *P* value was derived using the Fisher exact test.

Table 6.
Medications and Treatments by Late Toxicity*: CVD Cases Only

	Toxicity Grade						Any	Severe
Frequency (percent)	0	1	2	3	4	5	P†	P†
Corticosteroids								
No	37 (68.5)	6 (11.1)	5 (9.3)	3 (5.6)	2 (3.7)	1 (1.9)		
Yes	24 (75.0)	4 (12.5)	2 (6.3)	1 (3.1)	0	1 (3.1)	.63	.70
NSAIDS								
No	37 (71.2)	5 (9.6)	6 (11.5)	3 (5.8)	0	1 (1.9)		
Yes	24 (70.6)	5 (14.7)	1 (2.9)	1 (2.9)	2 (5.9)	1 (2.9)	~1	.71
Statins								
No	52 (71.2)	8 (11.0)	6 (8.2)	3 (4.1)	2 (2.7)	2 (2.7)		
Yes	9 (69.2)	2 (15.4)	1 (7.7)	1 (7.7)	0	0	~1	~1
CCB								
No	47 (71.2)	7 (10.6)	6 (9.1)	4 (6.1)	0	2 (3.0)		
Yes	14 (70.0)	3 (15.0)	1 (5.0)	0	2 (10.0)	0	~1	~1
Antimalarials								
No	45 (73.8)	6 (9.8)	6 (9.8)	3 (4.9)	0	1 (1.6)		
Yes	16 (64.0)	4 (16.0)	1 (4.0)	1 (4.0)	2 (8.0)	1 (1.0)	.44	.22
Oral cytotoxics								
No	48 (69.6)	7 (10.1)	7 (10.1)	4 (5.8)	2 (2.9)	1 (1.5)		
Yes	13 (76.5)	3 (17.6)	0	0	0	1 (5.9)	.77	~1
Infusional chemotherapy								
No	53 (77.9)	8 (11.8)	4 (5.9)	2 (2.9)	0	1 (1.5)		
Yes	8 (44.4)	2 (11.1)	3 (16.7)	2 (11.1)	2 (11.1)	1 (5.6)	.0087	.0089

CVD indicates collagen vascular disease; NSAIDs, nonsteroidal anti-inflammatory drugs; CCB, calcium-channel blocker.
* Late toxicity was defined as that occurring after Day 90 after treatment, and was scored according to the RTOG/European Organization for Research and Treatment of Cancer (EORTC) late radiation morbidity scoring schema.[20]
† *P* value was derived using the Fisher exact test.

RA, a finding that was also supported by a meta-analysis by Chon and Loeffler.[12] Other studies suggest that a diagnosis of scleroderma[13,14] or lupus[15] may increase the risk of RT associated toxicity. However, 2 separate matched control studies failed to observe any increased risk of acute or late complications in patients with CVD versus patients without CVD.[9,10]

To our knowledge, the current study is the largest matched-control analysis of acute and late complications in patients with CVDs receiving RT. Unlike the other matched control studies,[9,10] we did find that a diagnosis of a CVD increased the risk of having any late toxicity, with a trend toward increased severe late toxicity. We also examined a variety of factors that can potentially influence the toxicity profile. We found that there was little difference in toxicity profile for most irradiated sites. However, RT to the breast and pelvis were possible exceptions. Greater than one-third of all patients with RT to the pelvis experienced severe acute and late toxicity. Similar to previous studies,[11–15] we also found that patients with scleroderma or SLE were at the highest risk of experiencing severe acute or late complications. Morris and Powell[11] previously examined the impact of various medications on RT toxicity and found that patients undergoing NSAID therapy at the time of RT had a lower risk of late effects. Our findings demonstrated that most commonly used medications did not influence RT toxicity, but that concurrent chemotherapy was associated with increased severe acute and late toxicity.

There are strengths and limitations to the current study. Similar to previous publications on the subject, we were limited by the heterogeneity of CVD subtype, which thereby limited the number of patients analyzed for each subtype. Toxicity data was collected retrospectively, and there was no reliable method with which to assess CVD activity status at the time of RT. We were unable to analyze dose independently as a variable. Because dose was dependent on treatment site, it would require a range of RT doses at a given site and a reasonable sample size to make dose-specific comments. This was beyond the scope of our institutional patient experience. The strengths of this study lie in the total number of patients analyzed and the use of a 3:1 control:case match by age, sex, RT dose, and anatomic site. This approach allows for a more robust analysis of the risk profile, allowing us to determine that patients with scleroderma and SLE are at increased risk of severe toxicity. Although other CVD subtypes may also predispose to toxicity, the same conclusions cannot be made because of the limited sample size of patients with these subtypes in our study. It is also important to note that with a median follow-up of 1.3 years, the toxicity rates reported in our study may be underestimating the true rate of late toxicity. Another unique aspect of this study is the comprehensive analysis of concomitant medication use and its impact on the RT toxicity profile. Given the heterogeneity observed in CVD subtype and disease activity, and other variables such as RT dose and site, it is not likely that we will ever have prospective controlled data for these questions.

In summary, although a diagnosis of a CVD appears to predispose patients to a greater risk of late RT toxicity, treatment is generally well tolerated, with a relatively low incidence of severe acute or late toxicity. Other factors can impact the risk of toxicity, including CVD subtype, site of irradiation, RT dose, and the use of concurrent chemotherapy. In patients who may be at particularly high risk because of CVD subtype or RT site, careful attention to issues of toxicity is required. Treatment modifications such as reduction of fraction size, twice-daily treatment, or reduction of total dose for these patients may be considered. These factors should be taken into consideration in the risk-benefit analysis at the time of consultation.

References

1. Fleck R, McNeese MD, Ellerbroek NA, et al. Consequences of breast irradiation in patients with pre-existing collagen vascular disease. *Int J Radiat Oncol Biol Phys.* 1989;17:829–833.
2. Olivotto IA, Fairey RN, Gillies JH, et al. Fatal outcome of pelvic radiotherapy for carcinoma of the cervix in a patient with systemic lupus erythematosus. *Clin Oncol.* 1989;40: 83–84.
3. Ransom DT, Cameron FG. Scleroderma: a possible contraindication to lumpectomy and radiotherapy in breast carcinoma. *Australas Radiol.* 1987;31:317–318.
4. Robertson JM, Clarke DH, Pevzner MM, et al. Breast conservation therapy: severe breast fibrosis after radiation therapy in patients with collagen vascular disease. *Cancer.* 1991;68:502–508.
5. Teo P, Tai TH, Choy D. Nasopharyngeal carcinoma with dermatomyositis. *Int J Radiat Oncol Biol Phys.* 1989;16:471–474.
6. Varga J, Haustein UF, Creech RH, et al. Exaggerated radiation-induced fibrosis in patients with systemic sclerosis. *JAMA.* 1991;265:3292–3295.
7. Abu-Shakra M, Lee P. Exaggerated fibrosis in patients with systemic sclerosis (scleroderma) following radiation therapy. *J Rheumatol.* 1993;20:1601–1603.
8. Hareyama M, Nagakura H, Tamakawa M, et al. Severe reaction after chemoradiotherapy of nasopharyngeal carcinoma with collagen disease. *Int J Radiat Oncol Biol Phys.* 1995; 33:971.
9. Ross JG, Hussey DH, Mayr NA, et al. Acute and late reactions to radiation therapy in patients with collagen vascular diseases. *Cancer.* 1993;71:3744–3752.
10. Phan C, Mindrum M, Silverman C, et al. Matched-control retrospective study of the acute and late complications in patients with collagen vascular diseases treated with radiation therapy. *Cancer J.* 2003;9:461–466.
11. Morris MM, Powell SN. Irradiation in the setting of collagen vascular disease: acute and late complications. J Clin Oncol. 1997;15:2728–2735.
12. Chon BH, Loeffler JS. The effect of nonmalignant systemic disease on tolerance to radiation therapy. *Oncologist.* 2002;7:136–143.
13. Chen AM, Obedian E, Haffty BG. Breast-conserving therapy in the setting of collagen vascular disease. *Cancer J.* 2001;7:480–491.
14. Gold DG, Miller RC, Petersen IA, et al. Radiotherapy for malignancy in patients with scleroderma: the Mayo clinic experience. *Int J Radiat Oncol Biol Phys.* 2007;67:559–567.
15. Pinn ME, Gold DG, Petersen IA, et al. Systemic lupus erythematosus, radiotherapy, and the risk of acute and chronic toxicity: the Mayo Clinic experience. *Int J Radiat Oncol Biol Phys.* 2007 Dec 28 [Epub ahead of print].
16. Irwin B, Ben-Josef E, Tobi M. Calcium channel blockers may radiosensitize, statins and NSAIDs may radioprotect patients from radiation proctitis: a case control study. Presented at the American Gastroenterology Associations' Digestive Disease Week, Los Angeles, California, May 20–25, 2006.
17. Fuks Z, Smith KC. Effect of quinacrine on x-ray sensitivity and the repair of damaged DNA in Escherichia coli K-12. *Radiat Res.* 1971;48:63–73.
18. Voiculetz N, Smith KC, Kaplan HS. Effect of quinacrine on survival and DNA repair in x-irradiated Chinese hamster cells. *Cancer Res.* 1974;34:1038–1044.
19. Trotti A, Byhardt R, Stetz J, et al. Common toxicity criteria: version 2.0 an improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. *Int J Radiat Oncol Biol Phys.* 2000;47:13–47.
20. LENT SOMA scales for all anatomic sites. *Int J Radiat Oncol Biol Phys.* 1995;31:1049–1091