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Lymphedema Secondary to Postmastectomy Radiation: Incidence and Risk Factors

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Background: Postmastectomy radiotherapy (PMRT) has proven benefits for certain patients with breast cancer; however, one of its complications is lymphedema. This study examines the incidence of and risk factors associated with lymphedema secondary to PMRT.

Methods: The charts of patients treated with mastectomy at Roswell Park Cancer Institute between January 1, 1995, and April 20, 2001, who received PMRT were reviewed. Univariate analysis of patient, disease, and treatment variables was conducted. Multivariate analysis was performed on variables found to be significant in univariate analysis.

Results: One hundred five patients received PMRT. The incidence of lymphedema was 27%. Patient age, body mass index, disease stage, positive lymph nodes, nodes resected, postoperative infection, duration of drainage, chemotherapy, and hormonal therapy were not associated with lymphedema. Total dose ($P = .032$), posterior axillary boost ($P = .047$), overlap technique ($P = .037$), radiotherapy before 1999 ($P = .028$), and radiotherapy at Roswell Park Cancer Institute ($P = .028$) were significantly associated with lymphedema. Increased lymphedema was noted with supraclavicular, internal mammary, mastectomy scar boost, and chest wall tangential photon beam radiation, but the associations were not statistically significant.

Conclusions: The high incidence and debilitating effects of lymphedema must be weighed against the benefits of PMRT. Efforts to prevent lymphedema should be emphasized.

Key Words: Lymphedema—Postmastectomy radiation—Risk factors—Complications—Breast neoplasms.

Postmastectomy radiotherapy (PMRT) reduces locoregional failure and prolongs disease-free survival and overall survival for certain patients with breast cancer.[1–5] However, PMRT carries a risk of lymphedema, brachial plexopathy, impaired shoulder mobility, chronic pain, skin fibrosis and telangiectasia, rib fractures, pulmonary fibrosis, and ischemic heart disease.[6–18]

Lymphedema is a chronic, incurable condition, the effects of which include limb swelling, heaviness, tightness, and pain.[19,20] In addition, it takes a psychological toll, causing anxiety, depression, and adjustment problems. Lymphedema affects the vocational, domestic, social, and sexual lives of those it afflicts, and it negatively affects quality of life.[21–27] It also places patients at increased risk for life-threatening soft tissue infections and malignancies.[28–32]

Despite its debilitating effects, the incidence of lymphedema secondary to PMRT, delivered with modern radiotherapy techniques, has not been widely reported. Furthermore, controversy exists as to which patient, disease, and treatment factors place individuals at higher risk for developing lymphedema. The intent of this study was to determine the incidence of lymphedema secondary to PMRT and to identify the risk factors associated with its occurrence.

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METHODS

The study protocol was approved by the Roswell Park Cancer Institute (RPCI) Institutional Review Board. The charts of 114 women treated with PMRT for breast cancer were reviewed. Nine patients developed lymphedema before radiotherapy was initiated and were excluded from the study. The remaining 105 patients underwent mastectomy at RPCI between January 1, 1995, and April 20, 2001. Subsequent radiotherapy was administered at either RPCI or referral centers.

Lymphedema was defined by the presence of ipsilateral arm edema noted by a treating physician. The date of onset and the severity were determined. Severity was classified as mild, moderate, or severe on the basis of the impression of the treating physician at the time of physical examination.

Patient demographic variables, disease factors, and treatment factors were determined. Patient age, body mass index, American Joint Committee on Cancer breast cancer stage, number of positive lymph nodes, number of lymph nodes resected, presence of wound infection, presence of intraoperatively placed drain for >10 days, treatment with chemotherapy, and treatment with tamoxifen were recorded. Radiation administration records were reviewed by a staff radiation oncologist (W.G.). Radiation doses, fields, techniques, use of computed tomography scanning in treatment planning, year of radiotherapy, and whether the patient received radiotherapy at RPCI or a referring center were determined. Radiation fields were classified as chest wall, supraclavicular, and internal mammary. Radiation techniques were classified as tangential field photon beam or en face electron beam. The use of mastectomy scar boosting or posterior axillary boosting was noted. The use of overlapping fields and compensation techniques was also noted.

Statistical analysis was performed with SPSS for Windows, version 10.0.5 (SPSS Inc., Chicago, IL). Descriptive analysis was performed, and crude percentages were calculated. Univariate and multivariate analyses were performed, and logistic regression was used to calculate odds ratios (OR), 95% confidence intervals (CI), and *P* values.

RESULTS

One-hundred five eligible patients were identified. Surgical treatment consisted of modified radical mastectomy in 96 patients, wide local excision with axillary lymph node dissection and subsequent simple mastectomy in 7 patients, and simple mastectomy in 2 patients. Radiotherapy was delivered to 56 patients at RPCI and to 49 patients at other facilities. Complete radiotherapy data were available on 87 patients. The remaining 18 patients had 1 or more incomplete radiotherapy data fields. Adjuvant systemic therapy included chemotherapy in 94 (90%) patients and tamoxifen in 75 (71%) patients.

Twenty-eight patients (27%) developed lymphedema. The severity was mild in 21 (20%), moderate in 6 (6%), and severe in 1 (1%). Median follow-up was 741 days (range, 31–2467 days). The median time to onset of lymphedema was 391 days (range, 33–1632 days), and the mean time to onset was 478 days (SD, 356 days). Median overall survival for the cohort of patients treated with PMRT has not yet been reached.

The results of univariate analysis of patient demographics and radiation variables, displaying the OR, CI, and *P* value for each variable, are listed in Tables 1 and 2, respectively. Nonradiation variables—including age, body mass index, American Joint Committee on Cancer stage, nodes positive, nodes resected, postoperative infection, intraoperatively placed drain present >10 days, adjuvant chemotherapy, and adjuvant tamoxifen—were not associated with lymphedema (Table 1). Analysis of radiation fields and techniques showed a statistically significant association with total dose ($P = .032$), posterior axillary boost ($P = .047$), overlapping technique ($P = .037$), radiotherapy before 1999 ($P = .028$), and radiotherapy at RPCI ($P = .028$; Table 2). We observed higher rates of lymphedema among women who received supraclavicular and internal mammary radiation and boost radiation to the mastectomy scar or posterior axillary field, but these findings were not significant. A higher dose to any given field and a higher boost dose were associated with higher rates of lymphedema, although these associations were not all statistically significant. Use of tangential photon beams to treat the chest wall was associated with higher rates of lymphedema than electrons, but the difference was not statistically significant (30% vs. 7%; $P = .088$). Overlapping radiation fields, used in 67% of cases, were associated with a significant increase in lymphedema ($P = .037$). The rate of lymphedema was higher for patients treated before 1999 (OR, 2.7; 95% CI, 1.1–6.6; $P = .028$) and for patients treated with radiotherapy at RPCI (OR, 2.8; 95% CI, 1.1–6.6; $P = .028$). On multivariate analysis of all factors found to be significant on univariate analysis, only treatment before 1999 was associated with a significant increase in lymphedema (OR, 3.1; 95% CI, 1.1–8.8; $P = .031$; Table 3).

Patients treated before 1999 more often received ≥60 Gy total dose ($P = .018$) and >10 Gy mastectomy scar boost radiation ($P = .020$). Some of the increased inci-

TABLE 1. *Univariate analysis of patient demographics*

Variable	n	Lymphedema (%)	OR	CI	*P* value
Age (y)					
≤50	56	18 (32.1)	1.000	.222–1.322	.178
>50	49	10 (20.4)	.541		
BMI (kg/m^2)					
<30	77	21 (27.3)	1.000	.330–2.396	.816
≥30	28	7 (25.0)	.889		
Stage					
I	3	1 (33.3)	1.000	NA	NA
II	63	18 (28.6)	.800	.068–9.382	.859
III	36	8 (22.2)	.571	.046–7.143	.571
IV	2	1 (50.0)	2.00	.051–78.250	.711
Nodes positive					
<5	55	16 (29.1)	1.000	.322–1.840	.556
≥5	50	12 (24.0)	.770		
Nodes resected					
<19	55	15 (27.3)	1.000	.394–2.229	.883
≥19	50	13 (26.0)	.937		
Postoperative infection					
−	89	22 (24.7)	1.000	.627–7.552	.221
+	12	5 (14.7)	2.175		
Drain present >10 d					
−	55	17 (30.9)	1.000	.127–1.168	.092
+	34	5 (14.7)	.386		
Chemotherapy					
−	11	3 (27.3)	1.000	.237–3.932	.962
+	94	25 (26.6)	.966		
Tamoxifen					
−	30	11 (36.7)	1.000	.202–1.268	.146
+	75	17 (22.7)	.506		

OR, odds ratio; CI, confidence interval; BMI, body mass index; NA, not available.

dence before 1999 may be due to the longer follow-up period for those treated earlier in the study. When the length of follow-up is restricted to the same length of time, the incidence of lymphedema is 28.2% for the early versus 18.3% for the later time period, but this difference is not statistically significant ($P = .251$).

Patients treated at RPCI had a higher incidence of lymphedema. Radiation treatment characteristics for RPCI and referring centers are compared in Table 4. Patients treated at RPCI received a significantly higher total radiation dose, more frequent treatment of additional fields, and more frequent and higher boost treatments.

DISCUSSION

PMRT reduces the risk of locoregional failure and improves overall survival for certain patients with invasive breast cancer. Numerous trials have shown a benefit in locoregional control.[2,4,33–38] Three prospective randomized trials showed improved overall survival for certain subsets of patients.[2–4] Treatment guidelines from the American Society of Clinical Oncology and the National Comprehensive Cancer Network recommend PMRT for patients with four or more positive axillary lymph nodes, tumors larger than 5 cm, and tumors invading the skin or chest wall.[1,39] PMRT for patients with one to three positive nodes remains controversial.

PMRT increases the risk of lymphedema over that with mastectomy with axillary dissection alone. Lymphedema is a chronic, debilitating condition that may result in severe consequences for those it affects. Symptoms include limb swelling, heaviness, tightness, and pain, and it may have harmful psychological effects.[21,22,24–26] In addition, arm morbidity from breast cancer treatment has been shown to have a significant detrimental effect on quality of life.[23,27] Relatively little attention is given to lymphedema in studies of PMRT. Several prominent studies do not even report the incidence of lymphedema as a consequence of treatment.[33,34,36,38,40,41]

The reported incidence of lymphedema secondary to PMRT ranges from 0% to 54%[13,14,35,37,42–48] (Table 5). These widely discrepant rates may be due to varying study designs, lymphedema definitions, and measurement techniques. Retrospective studies tend to underestimate incidence because of a lack of documentation in the medical record, transient signs and symptoms, de-

TABLE 2. *Univariate analysis of radiation variables*

Variable	n	Lymphedema (%)	OR	CI	*P* value
Total dose (Gy)					
<60	56	10 (17.9)	1.000	1.089–6.551	.032
≥60	49	18 (36.7)	2.670		
Supraclavicular radiation					
No	19	3 (15.8)	1.000	.585–8.163	.245
Yes	86	25 (29.1)	2.185		
Supraclavicular dose (Gy)					
<50.40	35	7 (20.0)	1.000	.796–5.977	.129
≥50.40	51	18 (35.3)	2.182		
Internal mammary radiation					
No	96	25 (26.0)	1.000	.330–6.108	.638
Yes	9	3 (33.3)	1.420		
Internal mammary dose (Gy)					
<50.40	3	0 (.0)	NA	NA	NA
≥50.40	6	3 (50.0)			
Mastectomy scar boost radiation					
No	42	10 (23.8)	1.000	.558–3.371	.491
Yes	60	18 (30.0)	1.371		
Mastectomy scar boost dose (Gy)					
≤10	43	11 (25.6)	1.000	.623–6.655	.239
>10	17	7 (41.2)	2.036		
Posterior axillary boost					
No	87	20 (23.0)	1.000	1.016–8.728	.047
Yes	17	8 (47.1)	2.978		
Chest wall tangents					
No	15	1 (6.7)	1.000	.763–48.703	.088
Yes	89	27 (30.3)	6.095		
Chest wall electron field					
No	89	27 (30.3)	1.000	.021–1.311	.088
Yes	15	1 (6.7)	.164		
Overlap technique					
No	30	4 (13.3)	1.000	1.076–11.363	.037
Yes	60	21 (35.0)	3.497		
Compensation					
No	16	1 (6.3)	1.000	.838–53.476	.073
Yes	81	25 (30.9)	6.694		
CT planning					
No	12	3 (25.0)	1.000	.272–4.370	.902
Yes	90	24 (26.7)	1.091		
Radiotherapy before 1999					
No	60	11 (18.3)	1.000	1.111–6.579	.028
Yes	45	17 (37.8)	2.703		
Radiotherapy at RPCI					
No	49	8 (16.3)	1.000	1.119–7.245	.028
Yes	56	20 (35.7)	2.847		

OR, odds ratio; CI, confidence interval; NA, not available; CT, computed tomography; RPCI, Roswell Park Cancer Institute.

layed onset, and failure to check for lymphedema. Prospective studies avoid many of these problems, but many of these are flawed by inconsistent lymphedema definitions and measures. Our study is retrospective and therefore may suffer from these limitations. However, even with these limitations, it showed that clinically evident lymphedema occurred in at least 27% of patients at a median follow-up of 741 days. Additional cases are likely to occur as follow-up continues.

A strength of this study is the systematic examination of the association of nonradiation and radiation variables with lymphedema. None of the nonradiation factors investigated was associated with lymphedema. Although this may be due, in part, to the small sample size, none of these factors was consistently associated with PMRT lymphedema in other studies. There are conflicting reports on the association of age, body habitus, breast cancer stage, number of positive nodes, and number of nodes resected with lymphedema secondary to breast cancer treatment.[49–54] Wound complications and prolonged postoperative drainage have not been reported to be associated with lymphedema. Systemic therapy has generally not been associated with lymphedema, although one report demonstrated an decreased risk with chemotherapy.[50,52–54]

TABLE 3. *Multivariate analysis*

Variable	OR	CI	*P* value
Radiotherapy at RPCI	1.352	.232–7.885	.73
Radiotherapy before 1999	3.135	1.109–8.850	.03
Total radiation dose ≥60 Gy	1.983	.516–7.622	.32
Overlap technique used	1.927	.405–9.165	.41
Posterior axillary boost given	1.433	.419–4.904	.57

OR, odds ratio; CI, confidence interval; RPCI, Roswell Park Cancer Institute.

This study revealed that total dose and posterior axillary boost were significantly associated with lymphedema. In addition, there was a trend toward increased lymphedema with the addition of any given treatment field and with higher doses to each field. This increased risk with increased volume and dose requires that we consider the relative risks and benefits when selecting treatment fields. The chest wall is the most common site of postmastectomy recurrence and may be involved in as many as 60% to 80% of patients with recurrence; it should be included with PMRT.[2,4,10,18,35,41,55–65]

TABLE 4. *Comparison of radiotherapy characteristics by treatment center*

Radiotherapy technique	RPCI (n = 56)	Referring center (n = 49)	*P* value
Total dose (Gy)			
<60	17 (30.4%)	39 (79.6%)	<.001
≥60	39 (69.6%)	10 (20.4%)	
Supraclavicular radiation			
No	4 (7.1%)	15 (30.6%)	.002
Yes	52 (92.9%)	34 (69.4%)	
Supraclavicular dose (Gy)			
<50.40	22 (42.3%)	13 (38.2%)	.707
≥50.40	30 (57.7%)	21 (61.8%)	
Internal mammary radiation			
No	48 (85.7%)	48 (98.0%)	.025
Yes	8 (14.3%)	1 (2.0%)	
Internal mammary dose (Gy)			
<50.40	3 (37.5%)	0 (.0%)	.453
≥50.40	5 (62.5%)	1 (100.0%)	
Mastectomy scar boost radiation			
No	8 (14.3%)	34 (73.9%)	<.001
Yes	48 (85.7%)	12 (26.1%)	
Mastectomy scar boost dose (Gy)			
<10.01	37 (77.1%)	6 (50.0%)	.063
≥10.01	11 (22.9%)	6 (50.0%)	
Posterior axillary boost			
No	43 (76.8%)	44 (91.7%)	.041
Yes	13 (23.2%)	4 (8.3%)	
Chest wall tangents			
No	1 (1.8%)	14 (29.2%)	<.001
Yes	55 (98.2%)	34 (70.8%)	
Chest wall electron field			
No	55 (98.2%)	34 (70.8%)	<.001
Yes	1 (1.8%)	14 (29.2%)	
Overlap technique			
No	5 (8.9%)	25 (73.5%)	<.001
Yes	51 (91.1%)	9 (26.5%)	
Compensation			
No	0 (.0%)	16 (39.0%)	<.001
Yes	56 (100.0%)	25 (61.0%)	
CT planning			
No	1 (1.8%)	11 (23.9%)	.001
Yes	55 (98.2%)	35 (76.1%)	

RPCI, Roswell Park Cancer Institute; CT, computed tomography.

TABLE 5. *Incidence of postmastectomy lymphedema in published series*

Study	Year	Patients	Incidence
Present study	2004	105	27%
Johansson[47]	2002	150	54%
Hojris[13]	2000	42	26%
Shikama[48]	1999	105	0%
Schunemann[42]	1998	579 (RM)	44%
		2148 (MRM)	29%
Ragaz[35]	1997	154	10%
Pezner[43]	1989	34	21%
Ryttov[14]	1988	13	46%
Brismar[44]	1983	58	26%
Ahmann[37]	1982	108	54%
Gregl[45]	1978	1203	45%
Gregl[46]	1967	1155	34%

RM, radical mastectomy; MRM, modified radical mastectomy.

The second most common site of locoregional failure is the supraclavicular fossa. The cumulative incidence of failure ranges from 10% to 35%.[10,55–62] The risk of supraclavicular recurrence is related to the number of positive nodes.[66–69] For patients with negative or one to three positive axillary nodes, the absolute risk of isolated regional nodal failure in the supraclavicular fossa is ≤2%.[62,70,71] Radiation to the supraclavicular field is probably not beneficial for patients with limited nodal involvement.

The risk of recurrence in the dissected, nonradiated axilla after mastectomy is low, and in the context of breast-conserving therapy with radiation, the risk of axillary recurrence after dissection is even lower.[55,59,61,72,73] Radiation to the chest wall and supraclavicular fossa, omitting the dissected axilla, provides high rates of locoregional control. Radiation to the dissected axilla incurs high rates of lymphedema (47% in this study). This high incidence of lymphedema must be weighed against the limited benefit of radiation to the dissected axilla.

The internal mammary lymph nodes are involved in 21% to 53% of patients with positive axillary nodes, and involvement is more common for inner quadrant and central tumors.[74–77] Internal mammary failure is uncommon. Fewer than 10% of patients with locoregional recurrence experience treatment failure in the internal mammary nodes.[10,55–62] Recent prospective, randomized studies showing a survival benefit for PMRT included the internal mammary field. The added risk of lymphedema with internal mammary radiation is unknown.[2–4]

The technique of radiation delivery may affect the incidence of lymphedema. Patients treated with chest wall electron beams had less lymphedema than those treated with tangential photon beams. Us of overlapping radiation fields was associated with increased incidence and may be a preventable factor that increases the risk of lymphedema. A monoisocentric technique that avoids overlap is now being used at RPCI.

Radiotherapy during the earlier years of the study (1995–1998) was associated with increased lymphedema risk compared with treatment after 1998. When follow-up of the early group was censured at the length of follow-up for the later group, the incidence of lymphedema remained higher for the group treated earlier (28% vs. 18%), although this difference was not statistically significant. With continued follow-up, the lymphedema rates in the two groups may be similar. Patients treated from 1995 to 1998 did receive higher total mastectomy scar boost doses of radiation, and this may have contributed to the higher incidence of lymphedema in this group.

A significantly higher incidence of lymphedema was noted among patients treated at RPCI. RPCI patients received higher radiation doses, additional treatment fields, and radiation boosting. This more aggressive radiation may account for the increased incidence of lymphedema. Whether higher radiation doses further reduce the rate of local failure cannot be determined from these data. The small sample sizes limit the power of such an analysis.

Our data indicate that lymphedema is a common complication of PMRT. It is significantly associated with an increased total radiotherapy dose, posterior axillary boost radiation, and overlapping technique. Multivariate analysis showed only the year of radiotherapy to be significantly associated with lymphedema incidence. However, the small size of this study limits the value of multivariate analysis. The risk of lymphedema must be considered when the benefits of PMRT are weighed. With advanced nodal disease, PMRT clearly reduces the risk of both locoregional failure and death. With more limited disease, the role of PMRT is less clear. When PMRT is used, a monoisocentric technique is preferred to prevent any increased risk of lymphedema from overlapping fields.

Because lymphedema is a chronic and debilitating condition, measures to prevent it are important. Beyond minimizing extended nodal therapy, there are limited data on specific measures to prevent lymphedema. Patients should be advised of the risk of lymphedema, instructed in skin care, and educated to detect its symptoms. Treatment should include referral to a multidisciplinary lymphedema treatment center that includes practitioners trained in comprehensive lymphedema management. Despite these treatments, lymphedema remains a prevalent and potentially incapacitating condition.

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