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Postmastectomy Radiation Improves Local-Regional Control and Survival for Selected Patients With Locally Advanced Breast Cancer Treated With Neoadjuvant Chemotherapy and Mastectomy

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ABSTRACT

Purpose
To evaluate the efficacy of radiation in patients treated with neoadjuvant chemotherapy and mastectomy.

Patients and Methods
We retrospectively analyzed the outcomes of 542 patients treated on six consecutive institutional prospective trials with neoadjuvant chemotherapy, mastectomy, and radiation. These data were compared to those of 134 patients who received similar treatment in these same trials but without radiation.

Results
Irradiated patients had a lower rate of local-regional recurrence (LRR) (10-year rates: 11% *v* 22%, $P = .0001$). Radiation reduced LRR for patients with clinical T3 or T4 tumors, stage ≥ IIB disease (AJCC 1988), pathological tumor size >2 cm, or four or more positive nodes ($P \leq .002$ for all comparisons). Patients who presented with clinically advanced stage III or IV disease but subsequently achieved a pathological complete response to neoadjuvant chemotherapy still had a high rate of LRR, which was significantly reduced with radiation (10-year rates: 33% *v* 3%, $P = .006$). Radiation improved cause-specific survival (CSS) in the following subsets: stage ≥ IIIB disease, clinical T4 tumors, and four or more positive nodes ($P \leq .007$ for all comparisons). On multivariate analyses of LRR and CSS, the hazard ratios for lack of radiation were 4.7 (95% CI, 2.7 to 8.1; $P < .0001$) and 2.0 (95% CI, 1.4 to 2.9; $P < .0001$), respectively.

Conclusion
After neoadjuvant chemotherapy and mastectomy, comprehensive radiation was found to benefit both local control and survival for patients presenting with clinical T3 tumors or stage III-IV (ipsilateral supraclavicular nodal) disease and for patients with four or more positive nodes. Radiation should be considered for these patients regardless of their response to initial chemotherapy.

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INTRODUCTION

Treatment recommendations for radiation therapy in the setting of neoadjuvant chemotherapy and mastectomy are under considerable debate. A consensus was not established in the current guidelines of the American Society of Clinical Oncology regarding postmastectomy radiation because there were not enough data concerning the efficacy of radiation in this setting to adequately provide answers.[1] In fact, currently

there are no large retrospective or prospective studies addressing this issue. This question has become increasingly important because the use of neoadjuvant chemotherapy is rapidly becoming standard treatment for many subsets of patients with breast cancer.[2]

The value of postmastectomy radiation in conjunction with adjuvant chemotherapy has been established by three randomized trials and two recent meta-analyses.[3-7] These data have shown that, for properly selected populations, radiation can improve local-regional control rates by approximately 20% and survival rates by 10%. In general, the selection of patients for postmastectomy radiation is made on the basis of the pathological information concerning the extent of local-regional disease. For patients treated with surgery before chemotherapy, postmastectomy radiation is indicated for those with four or more positive axillary nodes and for those with clinical stage III disease or T3 tumors.[1,8]

The role of postmastectomy radiation after neoadjuvant chemotherapy, however, remains unclear. Most patients treated with neoadjuvant chemotherapy have significant treatment-related changes in the pathological extent of disease. For patients who receive this treatment sequencing, additional data are needed to determine which subsets of patients can benefit from radiation.

To address these questions, we recently reported our institutional experience on 150 patients treated with neoadjuvant chemotherapy and mastectomy without radiation therapy and identified factors predictive of local-regional recurrence (LRR).[9] To build on those findings, in this report, we retrospectively compared the outcomes of 542 patients who received radiation after neoadjuvant chemotherapy and mastectomy versus the outcomes of the patients from the previously published cohort who were treated on the same prospective clinical trials. Our purpose was to evaluate the efficacy of postmastectomy radiation in terms of local-regional control and survival in the setting of neoadjuvant chemotherapy and determine which subsets of these patients benefited from radiation treatment.

PATIENTS AND METHODS

Patient Population

We retrospectively analyzed the data from six consecutive prospective clinical trials conducted at The University of Texas M.D. Anderson Cancer Center (Houston, TX) that investigated the role of doxorubicin-based neoadjuvant chemotherapy for patients with nonmetastatic, noninflammatory breast cancer. The institutional review board approved each protocol, and participating patients gave written informed consent. The review board also approved this retrospective analysis.

From 1974 to 2000, 744 of the patients enrolled in these trials were treated with neoadjuvant chemotherapy and mastectomy. We compared the data from the 557 of these patients who received postmastectomy radiation treatment (37 received preoperative radiation because of refractory disease) to the data from the 150 patients who did not receive radiation. The initial outcomes of the cohort who did not receive radiation were previously reported,[9] but these data were updated for the purpose of the current study. Some patients did not receive radiation because of disease progression. To minimize this potential bias between comparative groups, all patients with disease recurrence within 2 months after mastectomy or completion of adjuvant chemotherapy were excluded: 15 (3%) in the irradiated group and 16 (11%) in the nonirradiated group. The remaining 676 patients formed the study population for this review.

All patients were prospectively clinically staged according to the 1988 American Joint Committee on Cancer Staging and End Results Reporting guidelines. Only patients without systemic metastases were eligible for these trials. The patients designated as having stage IV disease represent patients with ipsilateral supraclavicular lymph node involvement without systemic metastases.

Treatment Details

Table 1 presents the neoadjuvant chemotherapy regimens that the patients received. All patients received doxorubicin as part of a combination chemotherapy regimen, with 15% also receiving

Table 1. Neoadjuvant Chemotherapy Regimens

Protocol	Years of the Study	Neoadjuvant Chemotherapy Regimen	No. of Cycles	No. of Patients		
				CT + M	CT + M + RT	Total Study Population*
Advanced Primary	1974-1985	FAC	3	33	91	191
85-01	1985-1989	VACP	3	19	141	200
89-007	1989-1991	FAC	4	11	104	203
91-015	1991-1994	FAC or dose-escalated FAC	4	11	101	202
94-002	1994-1998	FAC or paclitaxel	4	60	41	174
97-099	1998-2000	AT	6	0	64	88
Total	1974-2000			134	542	1,058

Abbreviations: FAC, 5-fluorouracil, doxorubicin, cyclophosphamide; VACP, vincristine, doxorubicin, cyclophosphamide, and prednisone; AT, doxorubicin, docetaxel; CT, chemotherapy; M, mastectomy; RT, radiation.

*The total study population includes other patients who were not analyzed in this report, such as those receiving breast-conserving surgery with or without radiation.

a taxane. The details regarding these regimens have been published in earlier reports.[10-12] In summary, FAC chemotherapy consisted of 500 mg/m^2 fluorouracil given on days 1 and 4 or 8, 50 mg/m^2 doxorubicin given as a day 1 bolus or as a 48- to 72-hour continuous infusion, and 500 mg/m^2 cyclophosphamide given on day 1. For those patients receiving dose-escalated FAC, the doses of these drugs were increased to 600, 60, and 1,000 mg/m^2, respectively. The VACP regimen consisted of 1.5 mg/m^2 vincristine, 60 to 75 mg/m^2 doxorubicin, 600 to 750 mg/m^2 cyclophosphamide, and 40 mg prednisone. Lastly, the AT regimen consisted of 60 mg/m^2 doxorubicin and 60 mg/m^2 docetaxel given as IV boluses.

We limited our study to the patients in these trials who were treated with mastectomy. The median number of recovered axillary lymph nodes after mastectomy was 15. For the 542 patients treated with postmastectomy radiation, treatment volumes typically included the chest wall and draining lymphatics (median dose, 50 Gy), followed by a chest wall boost (median dose, 10 Gy). Radiation treatment was delivered at an outside institution for 94 patients.

Radiation treatment was not a randomized variable in the trials studied. The decisions to undergo radiation and/or mastectomy (rather than breast-conserving surgery) were determined by the patient and her physicians, and thus are subject to selection biases.

After neoadjuvant chemotherapy and mastectomy, 640 patients (95%) received adjuvant chemotherapy. These regimens changed over the period of time of the clinical trials and initially began with FAC (similar to the preoperative regimen). The historical strategy was to use cyclophosphamide, methotrexate, fluorouracil (CMF). Thereafter, either vinblastine and methotrexate, or vinblastine, methotrexate, fluorouracil was used. Finally, the most recent approach adopted for this cohort investigated the use of taxanes. Additionally, 233 patients (34%) also received adjuvant tamoxifen.

Statistical Analysis

The distributions of clinical and pathological factors between the two groups of patients were compared using the χ^2 test for dichotomized variables and the Mann-Whitney test for continuous variables. LRR was defined as disease recurrence on the ipsilateral chest wall or in the ipsilateral axillary, supraclavicular, infraclavicular, or internal mammary lymph nodes. Any other site of recurrence was considered distant metastasis. All LRR were considered as events, irrespective of their timing relative to distant metastases. The 5- and 10-year actuarial rates of LRR, isolated LRR (the first site of failure), overall survival (OS), and cause-specific survival (CSS) were calculated according to the Kaplan-Meier method, and comparisons between the two patient groups were made using the log-rank test.[13] Multivariate analysis was performed using the Cox proportional hazards model.[13] This model tested only those factors that were found to be significant on univariate analysis. All survival statistics were measured from the date of diagnosis. All P values were two-sided, and P values $\leq .05$ were considered significant.

RESULTS

Patient Characteristics

The median follow-up times of all irradiated and nonirradiated patients were 73 and 66 months, respectively (median time for all patients was 69 months). Table 2 presents the comparisons of clinical, pathological, and treatment characteristics between these two cohorts. When compared with patients who did not receive radiation, a greater percentage of irradiated patients had more advanced clinical T-stage, clinical N-stage, combined clinical stage (1988 AJCC), poorer clinical response to neoadjuvant chemotherapy, higher numbers of pathologically positive nodes, and close or positive surgical margins ($P \leq .01$ for all comparisons). There were no differences between the two groups with respect to age, use of tamoxifen, use of adjuvant chemotherapy, pathological tumor size, number of dissected axillary nodes, or percentage of estrogen receptor–negative tumors.

LRR Rates According to Use of Radiation and Disease Extent

Despite the imbalance in prognostic features between the two groups, the 10-year actuarial rate of LRR was higher in the patients not treated with postmastectomy radiation (22% *v* 11%, $P = .0001$; Fig 1). The 10-year rate of isolated LRR (the first site of failure) was also significantly reduced with radiation (20% *v* 8%, $P = .0002$). Table 3 presents data concerning the use of radiation and LRR for various subsets of patients. Radiation reduced LRR for patients with clinical T3 or T4 tumors and clinical N2 to N3 stage disease ($P \leq .002$ for all comparisons). For combined clinical stage, patients with stage IIB or greater disease had lower rates of LRR if treated with radiation (10-year rates, 26% *v* 11%; $P < .0001$). With respect to pathological features, radiation reduced LRR rates for patients with residual tumors larger than 2 cm and for patients with four or more positive nodes ($P \leq .001$ for both comparisons).

Radiation also significantly reduced LRR rates for patients who initially presented with clinical stage III or IV advanced disease but subsequently achieved a pathological complete response to neoadjuvant chemotherapy (10-year rates, 3% *v* 33%; $P = .006$; Fig 2). For patients presenting with early stage I to stage II disease who achieved a pathological complete response, no difference in LRR rates was observed ($P = .22$). In addition, in the subset of patients with clinical stage II disease with one to three positive lymph nodes after chemotherapy, no difference in LRR rates was observed ($P = .79$, n = 55).

On multivariate Cox regression analysis of factors associated with LRR (Table 4), radiation use was the most significant variable, with a hazard ratio for no radiation of 4.7 (95% CI, 2.7 to 8.1; $P < .0001$). Other factors found to be significant for developing LRR included: 20% or more positive axillary nodes, clinical stage IIIB to stage IV disease, no tamoxifen use, estrogen receptor–negative disease, and minimal or worse clinical response to neoadjuvant chemotherapy ($P \leq .033$ for all comparisons). Both forward and backward stepwise analysis confirmed that these same six

Table 2. Patient, Tumor, and Treatment Characteristics

Characteristic	No Radiation (n = 134) No.	%	Radiation (n = 542) No.	%	*P**
Age, years					NS
Median	48		49		
Interquartile range	41-59		41-57		
≤ 40	31	23	133	25	
41-50	46	34	151	28	
51-60	29	22	177	33	
> 60	28	21	81	15	
Clinical T-stage†					< .001
T1	5	4	13	2	
T2	54	40	73	13	
T3	41	31	195	36	
T4	34	25	261	48	
Clinical N-stage†					< .001
N0	42	31	97	18	
N1	65	49	213	39	
N2	26	19	217	40	
N3	1	1	15	3	
Clinical stage†					< .001
I	1	1	0	0	
IIA	21	16	8	1	
IIB	45	34	83	15	
IIIA	29	22	164	30	
IIIB	32	24	233	43	
IV	6	4	54	10	
Response to neoadjuvant chemotherapy					.001
CR	8	6	78	14	
PR	111	83	354	65	
MR	9	7	88	16	
NC	3	2	16	3	
PD	3	2	6	1	
Pathological size, cm					NS
Median	2.0		2.3		
Interquartile range	0.7-3.4		0.5-4.0		
≤ 1.0	38	28	176	32	
1.1-2.0	31	23	79	15	
2.1-3.0	24	18	95	18	
3.1-4.0	16	12	70	13	
4.1-5.0	9	7	44	8	
> 5.0	10	7	75	14	
Unknown	6	4	3	1	
No. positive nodes					< .001
Median	1		2		
Interquartile range	0-3		0-6		
0	60	45	141	26	
1-3	40	30	185	34	
4-9	22	16	138	25	
≥ 10	8	6	73	13	
Unknown	4	3	5	1	
No. nodes sampled					NS
Median	15		15		
Interquartile range	11-19		11-19		
< 10	14	10	99	18	
≥ 10	115	86	442	82	
Unknown	5	4	1	1	
Positive nodes, %					< .001
< 20	91	68	279	51	
≥ 20	37	28	257	47	
Unknown	6	4	6	1	

(continued on following page)

Table 2. Patient, Tumor, and Treatment Characteristics (continued)

Characteristic	No Radiation (n = 134) No.	%	Radiation (n = 542) No.	%	P*
Margin status					.010
Free/negative	127	95	477	88	
Involved/positive	1	1	19	4	
Close	3	2	41	8	
Unknown	3	2	5	1	
Estrogen-receptor status					NS
Positive	69	51	240	44	
Negative	43	32	213	39	
Unknown	22	16	89	16	
Hormonal treatment					NS
Yes	44	33	189	35	
No	87	65	353	65	
Unknown	3	2	0	0	
Adjuvant chemotherapy					NS
Yes	124	93	516	95	
No	10	7	26	5	

NOTE. Because of small differences in rounding numbers, percentages do not always equal 100%.
Abbreviations: NS, not significant; CR, complete response; PR, partial response; MR, minimal response; NC, no change; PD, progressive disease.
*The Mann-Whitney test was used for continuous variables (age, pathological size, number of positive nodes, and number of nodes sampled). All other *P* values were derived using the χ^2 test for equality of distributions.
†The multidisciplinary team prospectively assigned the clinical stages according to the 1988 American Joint Committee on Cancer Staging and End Results Reporting guidelines. Stage IV disease reflects patients with supraclavicular lymph node involvement without systemic metastases.

risk factors were significantly associated with developing LRR. On univariate analyses of the entire study population, achievement of a clinical complete response (6% *v* 14%, $P = .050$) or a pathological complete response (2% *v* 12%, $P = .088$) were associated with lower LRR. However, neither clinical nor pathological complete response to neoadjuvant chemotherapy was independently associated with LRR in the multivariate model.

Survival Rates According to Use of Radiation and Disease Extent

The 10-year actuarial rates of OS in the two groups were not significantly different (54% for radiation *v* 47% for

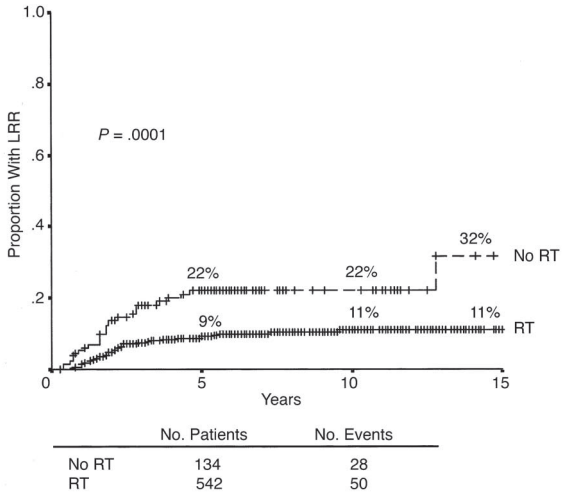

Fig 1. Rate of local-regional recurrence (LRR) for patients treated with radiation (RT; 542 patients, 50 events) and without RT (134 patients, 28 events).

Table 3. Ten-Year Actuarial Rates of LRR According to Clinical and Pathological Disease Status

Factor	10-year LRR Rate No Radiation (%)	Radiation (%)	P
Clinical T-stage			
T1	0	8	.535
T2	10	7	.408
T3	22	8	.002
T4	46	15	< .0001
Clinical N-stage			
N0	23	10	.014
N1	14	9	.062
N2-3	40	12	< .0001
Pathological tumor size, cm			
0-2	13	8	.051
2.1-5.0	31	14	.002
≥ 5.1	52	13	.001
No. of positive nodes			
0	11	4	.010
1-3	13	11	.636
≥ 4	59	16	< .0001

Abbreviation: LRR, local regional recurrence.

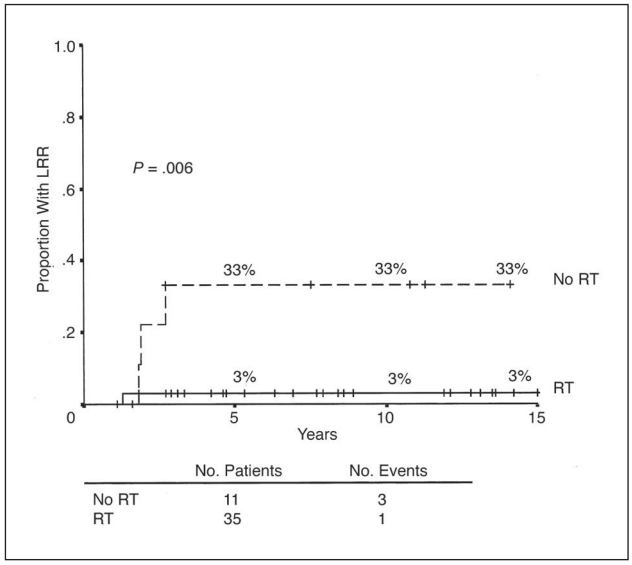

Fig 2. Rate of local-regional recurrence (LRR) for patients who initially had clinical stage III or IV advanced disease but subsequently achieved a pathological complete response to neoadjuvant chemotherapy. RT, with radiation; No RT, without radiation.

Table 5. Ten-Year Actuarial Rates of CSS According to Clinical and Pathological Disease Status

Factor	10-Year CSS Rate		*P*
	No Radiation (%)	Radiation (%)	
Combined clinical stage			
I-II	73	71	.482
IIIA	64	70	.742
≥ IIIB	22	44	.002
Clinical T-stage			
T1	80	92	.550
T2	56	66	.977
T3	71	69	.878
T4	24	45	.007
Clinical N-stage			
N0	65	62	.749
N1	66	64	.818
N2-3	27	49	.024
Pathological tumor size, cm			
0-2	64	69	.168
2.1-5.0	49	53	.887
≥ 5.1	25	37	.577
No. of positive nodes			
0	67	81	.271
1-3	70	56	.179
≥ 4	18	44	.005

Abbreviation: CSS, cause-specific survival.

no radiation, $P = .063$). Because a greater percentage of patients who did not receive radiation died of intercurrent disease, we focused our analyses on CSS. The 10-year actuarial rates of CSS were nearly identical in the two groups (58% for radiation *v* 55% for no radiation, $P = .85$). Table 5 presents the associations between radiation treatment and CSS for various subgroups. On univariate analysis, radiation improved CSS rates in patients with clinical stage IIIB to stage IV disease, clinical T4 tumors, or four or more positive nodes ($P \leq .007$ for all comparisons; Figs 3A to C). For these three subgroups, the benefit of radiation with respect to OS was also highly significant (42% *v* 20%, 42% *v* 20%, and 38% *v* 15%; $P \leq .0002$ for all comparisons).

Multivariate Cox regression analysis of factors associated with CSS for all 676 patients (Table 6) revealed that the hazard ratio for lack of radiation treatment was 2.0 (95% CI, 1.4 to 2.9; $P < .0001$). Other factors found to be significant for worse CSS included: clinical stage IIIB to stage IV disease, residual pathological tumor involvement after chemotherapy, four or more positive nodes, minimal or worse clinical response to neoadjuvant chemotherapy, fewer than 10 axillary nodes sampled, no tamoxifen, and estrogen receptor–negative disease ($P \leq .03$ for all comparisons). On univariate analyses of the entire study population, achievement of a clinical complete response (79% *v* 54%, $P < .001$) or a pathological complete response (95% *v* 55%, $P < .001$) were associated with higher CSS. However, neither clinical nor pathological complete response to neoadjuvant chemotherapy was independently associated with CSS in the multivariate model.

A separate analysis was completed (n = 713), which included the 37 patients who were treated with preoperative radiation. The results of this analysis continued to show significant differences with the irradiated cohort and its subgroups having lower rates of LRR and higher rates of CSS.

Table 4. Multivariate Analysis of LRR

Factor	Hazard Ratio	95% CI	*P*
No radiation	4.68	2.70 to 8.13	< .0001
≥ 20% sampled nodes positive	3.58	2.11 to 6.08	< .0001
Stage ≥ IIIB	2.38	1.42 to 4.02	.001
No tamoxifen	2.19	1.19 to 4.06	.012
Minimal or worse clinical response to neoadjuvant chemotherapy	1.88	1.10 to 3.23	.021
Estrogen receptor–negative	1.69	1.04 to 2.76	.033

Abbreviation: LRR, local-regional recurrence.

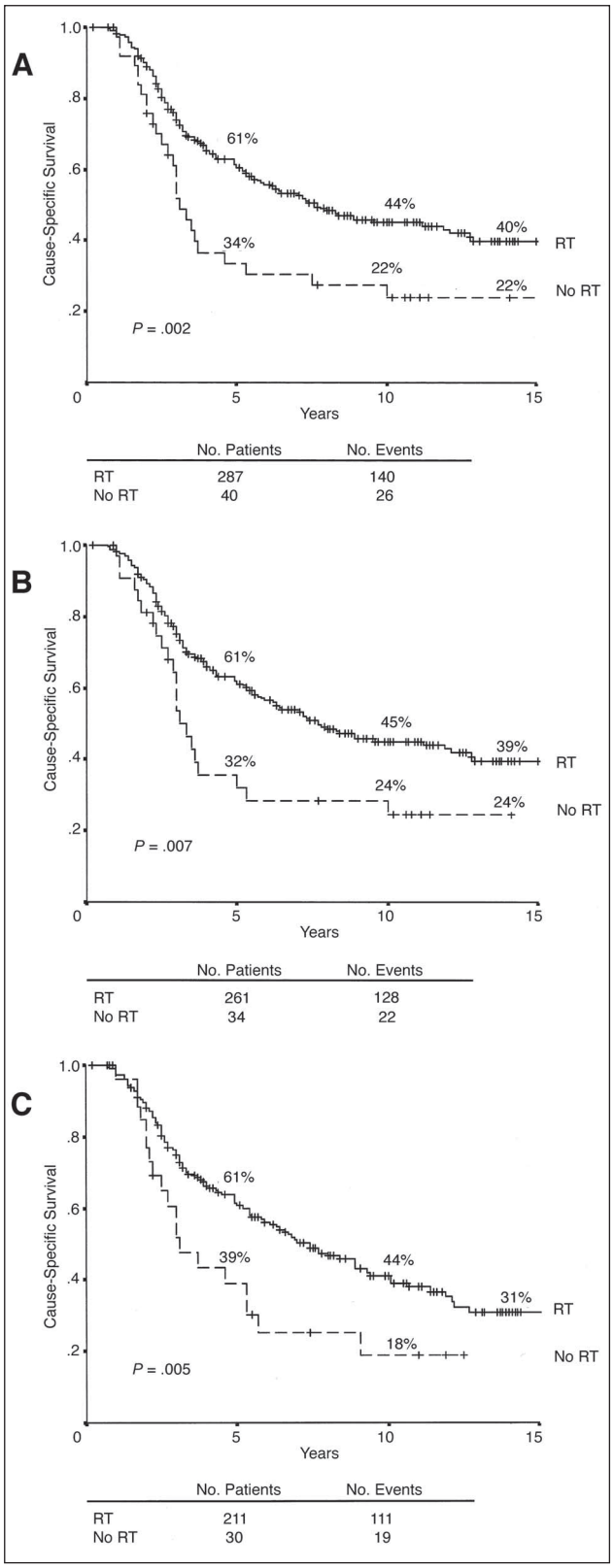

Fig 3. (A) Rate of cause-specific survival for patients with clinical stage IIIB to stage IV disease treated with radiation (RT) and without radiation (No RT). (B) Rate of cause-specific survival for patients with clinical T4 tumors treated with RT and without. (C) Rate of cause-specific survival for patients with four or more positive nodes treated with and without RT.

DISCUSSION

This report is the first large series investigating the efficacy of postmastectomy radiation for patients treated with neoadjuvant chemotherapy. The results represent a single institution's experience with all patients treated on prospective clinical trials with doxorubicin–based chemotherapy, mastectomy including a level I and II axillary dissection (median number of nodes recovered = 15), and radiation techniques comparable to modern standards of care. The results of this study suggest that the addition of radiation to neoadjuvant chemotherapy and mastectomy reduces the rate of LRR and may improve CSS for selected patients with locally advanced disease at presentation or with four or more positive lymph nodes after neoadjuvant treatment.

Multivariate analysis revealed that lack of radiation treatment was the greatest hazard associated with developing LRR (hazard ratio, 4.7). Radiation therapy reduced the relative risk for LRR two-fold for patients who presented with clinical stage IIB or greater disease, clinical T3 or T4 tumors, or clinical N2 to N3 disease (10-year rates, 11% *v* 26%, 8% *v* 22%, and 12% *v* 40%, respectively). In addition, patients who presented with clinically advanced stage III to stage IV disease but subsequently achieved a pathological complete response to neoadjuvant chemotherapy still had a high rate of LRR, which was significantly reduced with radiation (33% *v* 3%). Analyzing pathological factors from mastectomy, we found that radiation significantly reduced the risk of developing LRR for patients with four or more positive nodes or with tumor sizes greater than 2 cm (10-year rates, 16% *v* 59%, 14% *v* 31%, respectively).

The reduction in LRR rates in this study with radiation is similar in magnitude to data regarding the efficacy of postmastectomy radiation after mastectomy and adjuvant chemotherapy. We recently reported the LRR outcome of 1,500 patients treated with mastectomy and adjuvant chemotherapy and found that radiation reduced the 10-year LRR rate from 19% to 10% ($P < .0001$).[14] In addition, three randomized trials investigating postmastectomy radiation in patients treated with systemic therapy demonstrated a reduction in LRR rates from approximately 30% to 10%.[3-5] It was not surprising that the benefits of postmastectomy radiation in the current study were similar to those reported after adjuvant chemotherapy. One would not anticipate that the sequencing of chemotherapy and surgery would necessarily affect the efficacy of radiation; however, until this report, there have been no published data to support this hypothesis.

Whether radiation therapy benefits patients with stage II breast cancer with one to three positive lymph nodes remains an area of controversy. In this study, we did not find that radiation provided any benefit to these patients; however, the sample size was limited. In our previous study

Table 6. Multivariate Analysis of CSS

Factor	Hazard Ratio	95% CI	*P*
Stage ≥ IIIB	2.35	1.77 to 3.11	< .0001
Pathological size > 0 cm	2.13	1.27 to 3.57	.004
No radiation	2.03	1.41 to 2.92	< .0001
No. of positive nodes ≥ 4	1.67	1.20 to 2.31	.002
Minimal or worse clinical response to neoadjuvant chemotherapy	1.62	1.21 to 2.17	.001
Nodes sampled < 10	1.53	1.15 to 2.06	.004
No tamoxifen	1.40	1.03 to 1.90	.030
Estrogen receptor–negative	1.39	1.06 to 1.82	.019

Abbreviation: CSS, cause-specific survival.

investigating radiation after mastectomy and adjuvant chemotherapy, radiation reduced the 10-year LRR rate for patients with stage II breast cancer and one to three positive lymph nodes from 13% to 3%, $P = .003$.[14] Clearly, more data from clinical trials are needed to guide treatment recommendations regarding this group of patients.

In addition to reducing LRR rates, we also found that radiation may improve survival from breast cancer death in certain subsets of patients. Lack of radiation treatment was independently associated with higher breast cancer mortality (hazard ratio 2.0). For patients with clinical stage IIIB to stage IV disease, clinical T4 tumors, or four or more pathologically positive nodes, the addition of radiation after neoadjuvant chemotherapy and mastectomy resulted in an absolute CSS advantage of approximately 20% (44% *v* 22%, 45% *v* 24%, and 44% *v* 18%, respectively).

The potential for LRR therapy, in conjunction with systemic therapy, to reduce metastases and deaths from breast cancer has long been recognized. The meta-analysis published by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that radiation treatment improved 20-year CSS rates by 13% ($P = .0001$), despite the fact that most of the trials included in the analysis used obsolete radiation techniques and did not include systemic treatment.[15,16] However, this CSS advantage of radiation therapy was historically counterbalanced by an increase in the number of deaths from other causes, particularly cardiovascular, which mitigated any OS benefit. Since the time of those early trials, modern radiation techniques have progressed significantly and overcome limitations associated with cardiovascular dose toxicity. Indeed, the two Danish trials have demonstrated that postmastectomy radiation, using more modern techniques, did not increase the risk of ischemic heart disease-related morbidity or mortality.[17] Correspondingly, the three most recent randomized trials investigating postmastectomy radiation have demonstrated an improvement in OS.[3-5] In general, the absolute survival benefit in these trials was about half as great as the absolute reduction in the rate of LRR. For the patients with four or more positive nodes, clinical T4 tumors, or stage IIIB to stage IV disease, our results showed a similar magnitude of benefit. The absolute reduction in LRR for these subsets of patients ranged from 30% to 40% (Table 3), and the absolute benefit in CSS was approximately 20% (Table 5). As previously stated, we chose to focus our analysis on CSS in this study rather than OS because patients who did not receive radiation more often died of nonbreast cancer-related causes.

It is important to recognize the limitations of this review. Foremost, this was a retrospective analysis where radiation was not a randomized variable. In an effort to reduce the potential for selection biases that may have affected whether patients were treated or not treated with radiation, we excluded any patients who had a recurrence within 2 months after mastectomy or completion of adjuvant chemotherapy. Because radiation was not a randomized variable, the two cohorts had significant differences in many factors that affected LRR and survival. The variables we identified that affected outcome biased the irradiated cohort to have a worse expected outcome; however, it is possible that there are other selection biases that we did not take into account. In addition, because of the limited number of patients in some subgroup analyses, we cannot conclude a lack of benefit from radiation, particularly for patients with earlier stage disease or lesser pathological extent of disease. Finally, our series had a median follow-up period of 69 months. Longer follow-up may help define other subsets of patients who can benefit from radiation therapy, particularly with respect to survival. An update of the Early Breast Cancer Trialists' Collaborative Group meta-analysis that extended follow-up from 10 to 20 years demonstrated an increasingly significant CSS benefit from radiation in the second decade after treatment ($P = .03$ *v* $P = .0001$).[15,16]

In conclusion, postmastectomy radiation plays an important role in the management of patients receiving neoadjuvant chemotherapy and mastectomy for locally advanced breast cancer. Radiation was found to benefit both local control and survival in patients presenting with clinical T3 tumors or stage III to stage IV disease, and in patients with four or more positive nodes after chemotherapy.

Radiation treatment should be considered for these patients regardless of their response to initial chemotherapy.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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