Locoregional Recurrence Patterns After Mastectomy and Doxorubicin-Based Chemotherapy: Implications for Postoperative Irradiation

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Purpose: **The objective of this study was to determine locoregional recurrence (LRR) patterns after mastectomy and doxorubicin-based chemotherapy to define subgroups of patients who might benefit from adjuvant irradiation.**

Patients and Methods: **A total of 1,031 patients were treated with mastectomy and doxorubicin-based chemotherapy without irradiation on five prospective trials. Median follow-up time was 116 months. Rates of isolated and total LRR (± distant metastasis) were calculated by Kaplan-Meier analysis.**

Results: **The 10-year actuarial rates of isolated LRR were 4%, 10%, 21%, and 22% for patients with zero, one to three, four to nine, or ≥ 10 involved nodes, respectively ($P < .0001$). Chest wall (68%) and supraclavicular nodes (41%) were the most common sites of LRR. T stage ($P < .001$), tumor size ($P < .001$), and ≥ 2-mm extranodal extension ($P < .001$) were also predictive of LRR. Separate analysis was performed for patients with T1 or T2 primary disease and one to three involved nodes (n = 404). Those with fewer than 10 nodes examined were at increased risk of LRR compared with those with ≥ 10 nodes examined (24% *v* 11%; $P = .02$). Patients with tumor size greater than 4.0 cm or extranodal extension ≥ 2 mm experienced rates of isolated LRR in excess of 20%. Each of these factors continued to significantly predict for LRR in multivariate analysis by Cox logistic regression.**

Conclusion: **Patients with tumors ≥ 4 cm or at least four involved nodes experience LRR rates in excess of 20% and should be offered adjuvant irradiation. Additionally, patients with one to three involved nodes and large tumors, extranodal extension ≥ 2 mm, or inadequate axillary dissections experience high rates of LRR and may benefit from postmastectomy irradiation.**

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RANDOMIZED TRIALS that date back to the early 1970s have established that adjuvant radiation therapy after mastectomy reduces the incidence of locoregional recurrence (LRR) of breast cancer by approximately two thirds.[1-11] Two more recent trials now suggest that the improved locoregional control achieved by using postmastectomy irradiation in appropriately selected patients improves survival rates.[10,11]

The patients most likely to benefit from adjuvant radiotherapy are presumed to be those with an increased risk of locoregional failure. Their identification requires analysis of the patterns of failure after standard modified radical mastectomy and adjuvant systemic therapy. In one such analysis, Fowble et al[12] reviewed the recurrence patterns of 627 patients treated with mastectomy and cyclophosphamide/methotrexate/fluorouracil (CMF) chemotherapy on Eastern Cooperative Oncology Group trials. Factors predictive of high rates of LRR were identified as four or more involved nodes, tumor size greater than 5 cm, the presence of tumor necrosis, negative estrogen receptor status, and involvement of the pectoral fascia. A recent update by Recht et al[13] that included over 2,000 patients treated with CMF on Eastern Cooperative Oncology Group trials suggested that the combination of prognostic factors, particularly tumor size and nodal involvement, was most predictive of the risk of LRR. These two reports of LRR patterns after mastectomy and CMF therapy remain the only large series in the literature. However, there is little information concerning recurrence patterns after other forms of systemic therapy, including anthracycline-based chemotherapy, which growing evidence suggests is superior to CMF for node-positive patients.[14]

In this report, we examine LRR patterns in 1,031 patients treated on prospective trials at the University of Texas M.D. Anderson Cancer Center with mastectomy and doxorubicin-based chemotherapy without irradiation. Our goal was to identify subgroups of patients at significant risk of LRR who might benefit from the addition of postmastectomy irradiation.

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PATIENTS AND METHODS

Patient, Tumor, and Treatment Characteristics

Between 1975 and 1994, 1,805 patients were treated with doxorubicin-based adjuvant systemic therapy with or without tamoxifen after mastectomy on prospective clinical trials at the University of Texas M.D. Anderson Cancer Center.[15-21] Each protocol was reviewed and approved by an institutional review board. Each participant gave written informed consent according to institutional guidelines. Referral for postoperative irradiation was at the discretion of the treating medical oncologists in most of these trials. A fraction of the patients on one protocol were randomized to receive postmastectomy irradiation. The results of this trial were previously published.[16] This report comprises the data from the records of the 1,031 patients who did not receive radiotherapy.

Eligibility criteria for these trials included resectable stages II and IIIA disease. Patients older than 75 years, those with evidence of distant dissemination at diagnosis, and those with a prior or concurrent malignancy were not eligible for inclusion in these trials. Informed consent was required before protocol entry. Patient, tumor, and treatment characteristics are listed in Table 1. The median age for all patients was 48 years (interquartile range, 42 to 56 years). Four hundred ninety-three (48%) of the patients were premenopausal, and 525 (51%) were postmenopausal; menopausal status was not recorded for 13 patients.

Pathology for each patient was reviewed at M.D. Anderson Cancer Center before treatment. Information concerning pathologic findings was obtained from the M.D. Anderson pathology reports; however, pathology materials were not re-examined for the purpose of this study. Pathologic tumor size was determined by postoperative gross and microscopic examination. The median tumor size was 2.5 cm, with an interquartile range of 1.9 to 3.9 cm. The median number of nodes examined was 17 (interquartile range, 13 to 22), and the median number of involved nodes was three (interquartile range, one to six). Nine hundred eighteen patients (89%) had 10 or more nodes examined. Nine patients (1%) had fewer than five nodes removed, and 91 (9%) had between five and nine nodes removed. The median pathologic size of the largest involved node was 1.6 cm (interquartile range, 1.0 to 2.5 cm). Extranodal extension was described as focal ($\leq$ 2 mm), gross ($>$ 2 mm), present, not otherwise specified, or absent.

Patients underwent radical mastectomy (n = 5) or modified radical mastectomy (n = 1,026) before adjuvant systemic therapy. They were then randomized to one of several treatment arms (Table 1), each of which consisted of combination chemotherapy that included doxorubicin. Each protocol stipulated a minimum of six cycles of fluorouracil/doxorubicin/cyclophosphamide and a minimum doxorubicin dose of 40 to 50 mg/m^2 per cycle. No patients received preoperative chemotherapy in these trials. The median number of chemotherapy cycles was seven (interquartile range, six to 10). In addition to chemotherapy, 318 patients (31%) who were estrogen receptor– and/or progesterone receptor–positive also received tamoxifen.

Follow-Up, End Points, and Statistical Analysis

Patient follow-up consisted of physical examination, routine laboratory studies, chest x-rays, and bone scans, according to protocol guidelines. Ultrasound and computerized tomography (CT) scans were not routinely ordered during the follow-up period but were performed when indicated. It should be noted that CT technology was not available for routine clinical use at M.D. Anderson Cancer Center before the early 1980s, and it was not used systematically for some time after this. Median follow-up time from the date of initial histologic diagnosis for all patients alive at the time of analysis was 116 months (range, 6 to 262 months). Seven hundred sixty-six patients were assessable at 5 years and 370 at 10 years. Thirteen patients were lost to follow-up within less than 3 years of treatment (range, 6 to 35 months). Of these, 11 were alive without evidence of disease and two were alive with disease as of the last date of contact.

All LRRs were recorded, as were the date and site of first distant metastasis. LRRs consisted of ipsilateral chest wall, axillary, supraclavicular, infraclavicular, or internal mammary node failures. Recurrence of any other site was considered distant metastasis.

Five- and 10-year actuarial rates of overall survival (OS), disease-free survival (DFS), distant metastasis, isolated LRR, and total LRR were calculated by the Kaplan-Meier method, with comparisons among groups performed using two-sided log-rank tests.[22] Total LRR consisted of all LRRs with or without prior or simultaneous distant metastasis. For the purpose of this study, an isolated LRR was defined as an LRR without prior or simultaneous distant metastasis. Multivariate analysis was performed using Cox logistic regression analysis.[22] All *P* values were two-tailed, with a value of $\leq$ .05 considered to be significant.

RESULTS

Overall Results

OS and DFS for all patients at 10 years were 65% and 55%, respectively. The actuarial rates of isolated and total LRR for the entire cohort were 14% and 19%, respectively, at 10 years (crude rates, 12% and 17%, respectively). Table 2 lists the sites of LRR. The chest wall and supraclavicular fossa were the most common sites of locoregional failure, which represents a component of failure in 68% and 40%, respectively, of those who experienced an LRR. Axillary, infraclavicular, and internal mammary node chain (IMC) recurrences were much less common, although the rates for these may be underreported because most patients were not routinely screened for regional recurrences with ultrasound or thoracic CT scans. Seventy-nine percent of recurrences were biopsy proven. Although the median interval to LRR was 29 months, 42% of failures occurred after 3 years and 21% after 5 years. The median interval to chest wall recurrence was 27 months, which was shorter than the interval to detection of regional nodal recurrence (median, 44 months). The 10-year actuarial rate of distant metastasis–free survival was 64%.

LRR With Regard to Prognostic and Treatment-Related Factors

The probability of isolated and total LRR was analyzed with regard to prognostic and treatment-related factors (Table 3). Increasing T stage, as well as 1-cm increments in tumor size, were predictive of both isolated and total LRR on univariate analysis ($P < .0001$). The number of involved nodes was also a significant predictor of the risk of LRR.

Table 1. Patient, Tumor, and Treatment Characteristics

Characteristic	No. of Patients	%
Age		
Median, years	48	
Interquartile range, years	42-56	
≤ 40 years	226	22
41-50 years	382	37
51-60 years	262	25
> 60 years	161	16
Menopausal status		
Premenopausal	493	48
Postmenopausal	525	51
Unknown	13	1
T stage		
T1	314	30
T2	509	50
T3	103	10
TX	105	10
Tumor size		
Median, cm	2.5	
Interquartile range, cm	1.9-3.9	
≤ 1.0 cm	44	6
1.1-2.0 cm	270	26
2.1-3.0 cm	280	27
3.1-4.0 cm	160	16
4.1-5.0 cm	69	7
> 5.0 cm	103	10
ER status		
Positive	466	45
Negative	391	38
Unknown	174	17
Location		
Central/inner	281	27
Outer	687	67
Entire breast	14	1
Unknown	49	5
Histology		
Ductal/mixed	932	91
Lobular	55	5
Other	22	2
Unknown	22	2
Grade		
Well differentiated	29	3
Moderately differentiated	401	39
Poorly differentiated	366	35
Unknown	235	23
No. of involved nodes		
Median	3	
Interquartile range	1-6	
0	141	14
1-3	466	45
4-9	263	26
≥ 10	156	15
Unknown	5	< 1
No. of nodes examined		
Median	17	
Interquartile range	13-22	
< 10	100	10
≥ 10	918	89
Unknown	13	1
Size of largest node*		
Median, cm	1.6	
Interquartile range, cm	1.0-2.5	
≤ 1 cm	159	18
1.1-2 cm	221	25
2.1-3 cm	126	14
> 3 cm	58	7
Unknown	326	32
Extranodal extension*		
None	573	64
< 2 mm	83	9
≥ 2 mm	141	16
Present, NOS	68	8
Unknown	25	3
Chemotherapy regimen		
FAC ± BCG	222	22
FAC + MV	262	25
FAC + CMF	75	7
FACVP	88	9
FACVP + MTX + VB	137	13
VACP	90	9
VACP + IFNα	112	11
Other	45	4
Hormonal treatment		
Yes	318	31
No	645	62
Unknown	68	7

Abbreviations: ER, estrogen receptor; NOS, not otherwise specified; FAC, fluorouracil/doxorubicin/cyclophosphamide; BCG, Bacillus-Calmette-Guerin vaccine; MV, methotrexate/vinblastine; FACVP, fluorouracil/doxorubicin/cyclophosphamide/vincristine/prednisone; MTX, methotrexate; VB, vinblastine; VACP, vincristine/doxorubicin/cyclophosphamide/prednisone; IFNα, interferon alfa.

*Excluding 141 node-negative patients.

The 10-year actuarial rate of isolated LRR was 4% for node-negative patients. Corresponding rates of isolated LRR for patients with one to three, four to nine, or ≥ 10 involved nodes were 10%, 21%, and 22%, respectively, at 10 years ($P < .0001$). The 10-year actuarial rate of total LRR was 7% for node-negative patients and 14%, 25%, and 33% for patients with one to three, four to nine, and ≥ 10 involved nodes, respectively ($P < .0001$). The probability of isolated and total LRR as a function of the number of axillary lymph nodes that contained tumor is displayed in Figs 1 and 2. Primary tumor size and number of nodes that contained tumor were interactive parameters predictive of LRR. Table 4 lists 10-year actuarial rates of isolated and total LRR with regard to traditional categories of tumor size and nodal status.

Pathologic size of the largest involved lymph node, of which 90% were less than 3 cm, was recorded in 564 patients. In these patients, the size of the largest involved

Table 2. Sites of LRR

Site	Median Interval (months)	Isolated LRR		Total LRR	
		No.	%	No.	%
Chest wall	27	122	98	122	68
Supraclavicular	35	41	33	71	40
Axilla	40	21	17	25	14
Infraclavicular	63	10	8	12	7
Internal mammary	39	—	—	15	8
Any site	29	124	100	179	100

NOTE. Percentages represent fraction of LRRs including the specific site as a component of failure. Individual patients may have experienced more than one site of failure, so percentages do not total 100%.

axillary lymph node did not predict the risk of LRR. The degree of extranodal extension was predictive of the risk of both isolated and total LRR. Focal extranodal extension was associated with a minimally increased risk of LRR. However, extranodal extension of $\geq$ 2 mm was associated with a significantly greater risk (27% risk of isolated LRR and 33% of total LRR). This increased rate of LRR was not entirely explained by an increased incidence of axillary failure. Axillary recurrences as a component of failure made up only 8% of all LRRs in the patients with extranodal extension $\geq$ 2 mm. This rate of axillary failure was not significantly different from that of the overall sample.

There was no association between age or menopausal status and the risk of isolated or total LRR. Neither histology nor estrogen receptor status, alone or when stratified by the addition of hormonal therapy to chemotherapy, was a significant prognostic factor for LRR. Central or inner quadrant tumors were marginally associated with increased risk of total LRR when compared with outer quadrant lesions (24% *v* 16%; $P = .04$). There were no significant differences in the rates of total or isolated LRR with regard to the specific regimen of combination chemotherapy, the number of cycles of chemotherapy, or the use of hormonal therapy.

On multivariate analysis by forward stepwise Cox logistic regression, significant predictors of isolated LRR included T stage ($P < .0001$), number of involved nodes ($P < .0001$), and extranodal extension $\geq$ 2 mm ($P = .007$). Tumor size, age, menopausal status, estrogen receptor status, tumor location, histology, grade, number of nodes examined, and hormonal use were not significant predictors of isolated LRR and were dropped from the model. Similar analysis was performed with total LRR as the end point. Significant predictors included T stage ($P < .0001$), number of involved nodes ($P < .0001$), and extranodal extension $\geq$ 2 mm ($P = .005$). All other variables failed to achieve significance.

LRR Patterns for Patients With One to Three Involved Nodes

LRR patterns were examined separately for the 404 patients with tumors $\leq$ 5 cm and one to three involved nodes (Table 5). The results were similar to those in the overall group, with several notable exceptions. Although the extent of axillary dissection was not prognostic for the overall group, patients with one to three involved nodes and fewer than 10 nodes examined were at significantly increased risk of total LRR when compared with those with 10 or more nodes examined (24% *v* 11%; $P = .02$). The sites of recurrence for patients with fewer than 10 nodes examined paralleled those of the overall group and of the patients with 10 or more nodes examined. Of the 47 patients with fewer than 10 nodes examined, 10 experienced LRR. The chest wall was the most common site of failure (a component of failure in 70% of those with LRR), followed by supraclavicular (10%), axillary (10%), and internal mammary nodal failures (10%). There were no differences in isolated or total LRR patterns among patients with one, two, or three involved nodes. In this subgroup, extranodal extension $\geq$ 2 mm was an important discriminant of the risk of LRR (33% for those with gross extracapsular extension *v* 0% for those without; $P = .01$). All of these cases were isolated LRRs, and the sites of recurrence were similar to those of the overall cohort of patients.

Patients with T2 tumors were significantly more likely to experience an isolated LRR or LRR with or without distant metastasis than were patients with T1 tumors ($P = .02$ and .01, respectively). The risk of isolated LRR increased with primary tumor size grouped in 1-cm increments. Patients with tumors $\leq$ 2 cm had the lowest rates of isolated LRR ($<$ 10%), those with tumors 2.1 to 4.0 cm had intermediate rates (10% to 13%), and those with tumors 4.1 to 5.0 cm had the highest rates (26%). These values reached marginal significance ($P = .05$), although there were few patients in the last group. There were no significant differences in LRR

Table 3. Ten-Year Actuarial and Crude Rates of Total and Isolated LRR With Regard to Prognostic and Treatment-Related Factors

Factor	Isolated LRR			Total LRR		
	10-Year Actuarial Rate (%)	Crude Rate	*P*	10-Year Actuarial Rate (%)	Crude Rate	*P*
Age						
≤ 40 years	12	23/226		15	31/226	
41-50 years	11	35/382	ns	17	57/382	ns
51-60 years	16	39/262		22	55/262	
> 60 years	16	23/161		24	36/161	
Menopausal status						
Premenopausal	13	50/493	ns	19	79/493	ns
Postmenopausal	14	68/525		18	97/525	
T stage						
T1	8	24/314		12	36/493	
T2	14	59/509	< .0001	20	89/509	< .0001
T3	27	23/103		34	34/103	
Tumor size						
≤ 1.0 cm	5	3/44		6	4/44	
1.1-2.0 cm	9	21/270		13	32/270	
2.1-3.0 cm	10	24/280	< .0001	16	42/280	< .0001
3.1-4.0 cm	18	24/160		23	32/160	
4.1-5.0 cm	19	11/69		26	15/69	
> 5.0 cm	27	23/103		34	34/103	
ER status						
Positive	15	55/466	ns	20	80/466	ns
Negative	12	43/391		18	66/391	
Location						
Central/inner	17	34/281		24	56/281	
Outer	11	70/687	< .0001*	16	104/687	< .0001†
Entire breast	37	6/14		45	7/14	
Histology						
Ductal/mixed	13	104/932		19	165/932	
Lobular	13	6/55	ns	19	11/55	ns
Other	5	1/22		5	1/22	
Grade						
Well differentiated	16	4/29		16	4/29	
Moderately differentiated	12	43/401	ns	16	63/401	ns
Poorly differentiated	11	37/366		16	57/366	
No. of positive nodes						
0	4	5/141		7	9/141	
1-3	10	38/466	< .0001	14	60/466	< .0001
4-9	21	49/253		25	63/263	
≥ 10	22	28/156		34	46/156	
No. of nodes examined						
< 10	14	11/100	ns	19	17/100	ns
≥ 10	13	105/918		18	157/918	
Size of largest node‡						
≤ 1 cm	9	11/159		15	21/159	
1.1-2 cm	13	27/221	ns	20	43/221	ns
2.1-3 cm	19	20/126		23	27/126	
> 3 cm	20	8/58		26	11/58	
Extranodal extension‡						
None	12	70/573		18	109/573	
< 2 mm	18	10/83	.007	22	15/83	.02
≥ 2 mm	27	29/141		33	38/141	
Present, NOS	14	8/68		22	14/68	
Hormonal treatment						
Yes, ER^+	13	33/248	ns	19	49/248	ns
No, ER^+	11	19/181		17	27/181	
Yes, ER^-	0	0/21	ns	0	0/21	ns
No, ER^-	16	42/346		21	63/346	

Abbreviation: ns, not significant.

*P = ns for univariate central/inner versus outer.

†P = .04 for univariate central/inner versus outer.

‡Excluding 141 node-negative patients.

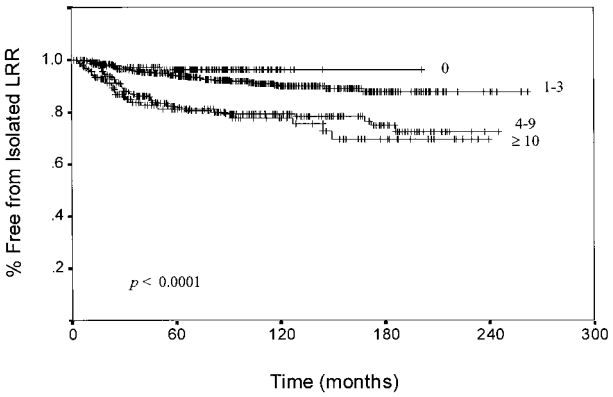

Fig 1. LRR with regard to number of involved nodes.

patterns with regard to other potential prognostic or treatment-related variables, including age, menopausal status, estrogen receptor status, tumor location, histology, grade, chemotherapy regimen, or the use of hormonal therapy.

On multivariate analysis by forward stepwise Cox logistic regression, significant predictors of isolated LRR for patients with one to three involved nodes included extranodal extension ≥ 2 mm ($P = .0001$), number of nodes removed ($P = .04$), and T stage ($P = .02$). Tumor size in 1-cm increments, age, menopausal status, estrogen receptor status, tumor location, histology, grade, and hormonal use were not significant predictors of isolated LRR and were dropped from the model. Similar analysis was performed with total LRR as the end point. Significant predictors included extranodal extension ≥ 2 mm ($P = .002$), number of nodes removed ($P = .02$), and T stage ($P = .01$). All other variables failed to achieve significance.

DISCUSSION

The history of postmastectomy radiation can be characterized as one of conflicting data and extensive debate.

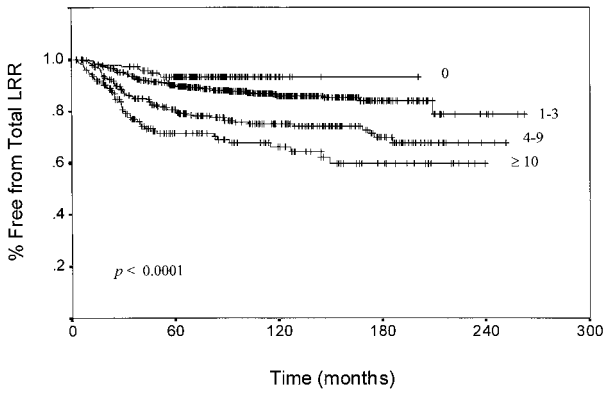

Fig 2. LRR with or without distant metastasis with regard to number of involved nodes.

Since the 1950s, a variety of prospective trials with conflicting results have been conducted.[1-11] After the publication in 1987 of a meta-analysis by Cuzick et al[23] that reported increased mortality in women who had received postmastectomy radiotherapy as a component of their treatment, its use was intensely challenged. An update published in 1994 reported no significant difference in overall mortality. A decrease in breast cancer–related deaths in those treated with radiation was offset by increased cardiac mortality.[24] A similar reduction in breast cancer mortality, as well as a two thirds reduction in LRR, was reported in a third meta-analysis, which was published by the Early Breast Cancer Trialists' Collaborative Group.[1] These authors also reported an increase in non–breast cancer deaths, which was most evident for women older than 60 years and which resulted in no difference in OS. These meta-analyses were strongly influenced by the results of several early trials, which were hampered by poor radiation technique, improper patient selection, and the infrequent use of adjuvant systemic therapy.[25]

More recently, two trials published in the *New England Journal of Medicine* have demonstrated superior locoregional control, DFS, and OS with the addition of postoperative radiotherapy to mastectomy and chemotherapy. The Danish 82b trial evaluated the use of postoperative radiotherapy in 1,708 high-risk premenopausal women treated with mastectomy and CMF.[8,9] At 10 years, there was a decrease in LRR from 32% to 9% in the patients who received radiation to the chest wall and regional lymphatics ($P < .001$). This translated into improvements in both DFS (48% *v* 34%; $P = .001$) and OS (54% *v* 45%; $P < .001$). Most surprising was the observation that these significant improvements in DFS and OS were evident for all subgroups of patients, including patients with one to three involved nodes. A second trial from British Columbia also reported improvements in locoregional control (87% *v* 67%; $P = .003$) and DFS (50% *v* 33%; $P = .007$) in node-positive premenopausal women treated with adjuvant radiation after mastectomy and CMF.[11] Similar benefits in postmenopausal women treated with mastectomy and tamoxifen were recently reported by the Danish Breast Cancer Cooperative Group.[10]

Together, these trials have demonstrated that the improvement in locoregional control observed with adjuvant irradiation translates into an improvement in OS. It is, therefore, imperative to identify those patients at significant risk of LRR who are most likely to realize the benefit of adjuvant irradiation. Unfortunately, few published data exist concerning LRR patterns in patients treated with modern chemotherapy. The only large series reported to date includes patients treated with various CMF-related regi-

Table 4. Ten-Year Actuarial Rates and Crude Rates of Isolated and Total LRR With Regard to Primary Tumor Size and Nodal Status

	No. of Involved Nodes							
	0		1-3		4-9		≥ 10	
T Stage	10-Year Actuarial Rate (%)	Crude Rate	10-Year Actuarial Rate (%)	Crude Rate	10-Year Actuarial Rate (%)	Crude Rate	10-Year Actuarial Rate (%)	Crude Rate
Isolated LRR								
T1	6	2/41	7	10/190	9	8/72	17	4/29
T2	11	1/81	12	23/214	23	24/132	17	11/79
T3	29	2/7	29	10/34	31	13/33	29	6/28
Total LRR								
T1	11	4/41	9	15/190	17	13/72	17	4/29
T2	14	3/81	16	33/214	27	31/132	34	22/79
T3	29	2/7	23	8/34	40	14/33	29	9/28

NOTE. Patients with unknown T stage and/or unknown number of involved nodes are excluded.

mens.[12,13] There is growing evidence that anthracycline-based chemotherapy is the treatment of choice for women with node-positive breast cancer.[14] Only a handful of small series have reported LRR rates after mastectomy and anthracycline-containing regimens.[14,16,21,26-38] Unlike these previous series, this report focuses specifically on prognostic factors predictive of LRR in patients treated with anthracycline-based chemotherapy after mastectomy and represents the largest data set currently available in this cohort of breast cancer patients.

Our analysis of recurrence patterns in 1,031 patients found that doxorubicin-based adjuvant systemic therapy does not obviate the need for postmastectomy irradiation for subsets of breast cancer patients at substantial risk of LRR. Patients with tumors larger than 4 cm or involvement of four or more axillary lymph nodes experienced rates of isolated LRR in excess of 20%. The results of the Danish trial demonstrated that the reduction in LRR observed with the addition of radiotherapy in patients with comparable LRR rates translated into an absolute benefit in DFS of 10% and an absolute benefit in OS of approximately 6%. This survival benefit is similar in magnitude to that achievable with adjuvant systemic therapy. Together, these data suggest that all patients with tumors larger than 4 cm or with four or more involved axillary lymph nodes should be offered postoperative radiotherapy.

The risk of LRR and, thus, the value of postmastectomy radiotherapy in patients with one to three involved nodes remain controversial. Although the Danish group observed an improvement in OS for this subset of patients, the reported LRR rate of 30%[8,9] was much greater than that reported in other studies, in which it ranged from 5% to 20%.[12,13,31,32,35,39-42] One possible explanation for the discrepancy in the LRR rates is the limited nature of axillary dissections performed in the Danish trial. The median number of nodes removed was seven, compared with the median of 17 in our series, which is more consistent with standard practice in the United States. Also, the proportion of LRRs that were axillary failures in the Danish trial (45% of LRRs) was also much greater than that observed in our report (14% of LRRs). Interestingly, patients with one to three involved nodes and fewer than 10 nodes examined in our cohort were at significantly increased risk of both isolated LRR and LRR with or without distant metastasis. One possible reason these patients are at increased LRR risk is that the axillary dissection is too limited and underestimates the actual disease extent.

As a group, patients with stage II breast cancer and one to three involved nodes experienced a low risk of LRR (10% isolated LRR and 14% total LRR). However, there were subsets of these patients who were observed to have a much higher risk of LRR. These include patients with tumors larger than 4.0 cm (26% isolated LRR risk) or with lymph node disease displaying extranodal extension ≥ 2 mm (33% isolated LRR risk). Because patients without these risk factors who have undergone an adequate axillary dissection have a low risk of LRR, any survival benefit from adjuvant radiotherapy is likely to be small. Although the proportional reduction in breast cancer deaths in these low-risk patients is likely to be similar to that of those at greater risk of LRR, the absolute benefit would be expected to be modest. Assuming the same proportional risk reductions observed in the British Columbia and Danish Cooperative Group trials, a reduction in LRR rates from 10% to 3% with comprehensive postmastectomy irradiation would be predicted to result in a 3% survival advantage for these low-risk patients. The specific threshold of LRR risk that warrants the addition of adjuvant irradiation is debatable and requires the clinical judgment of the physician in consultation with individual patients. In fact, the threshold for the recommendation of adjuvant systemic therapy has gradually been lowered over the years, and for many patients, absolute survival benefits

Table 5. Ten-Year Actuarial and Crude Rates of Total and Isolated LRR With Regard to Prognostic and Treatment-Related Factors for Patients With Tumors ≤ 5 cm and One to Three Involved Nodes (N = 404)

	Isolated LRR			Total LRR		
	10-Year Actuarial Rate (%)	Crude Rate	*P*	10-Year Actuarial Rate (%)	Crude Rate	*P*
Age						
≤ 40 years	7	5/82		8	6/82	
41-50 years	10	12/158	ns	14	19/158	ns
51-60 years	10	10/100		12	13/100	
> 60 years	11	6/64		17	10/64	
Menopausal status						
Premenopausal	11	15/188	ns	14	22/188	ns
Postmenopausal	9	17/208		12	25/208	
T stage						
T1	6	10/190		9	15/190	
T2	12	23/214	.02	26	33/214	.01
Tumor size						
≤ 1.0 cm	3	1/36		3	1/36	
1.1-2.0 cm	7	9/154		11	14/154	
2.1-3.0 cm	10	11/120	.05	15	18/120	ns
3.1-4.0 cm	13	8/69		15	11/69	
4.1-5.0 cm	26	4/25		26	4/25	
ER status						
Positive	9	17/214	ns	10	21/214	ns
Negative	11	11/130		16	18/130	
Location						
Central/inner	11	9/103		16	15/103	
Outer	11	20/281	.006*	18	28/281	.04*
Entire breast	50	1/2		50	1/2	
Histology						
Ductal/mixed	11	33/361		14	47/361	
Lobular	0	0/20	ns	5	1/20	ns
Other	0	0/9		0	0/9	
Grade						
Well differentiated	10	0/13		12	0/13	
Moderately differentiated	11	17/179	ns	14	23/179	ns
Poorly differentiated	7	9/136		13	17/136	
No. of nodes examined						
< 10	16	6/47	ns	24	10/47	.02
≥ 10	9	26/355		11	37/355	
Size of largest node						
≤ 1 cm	3	2/97		10	8/97	
1.1-2 cm	9	8/93	ns	10	10/93	ns
2.1-3 cm	16	5/35		18	6/35	
> 3 cm	20	3/23		29	5/23	
Extranodal extension						
None	7	19/301		11	31/301	
< 2 mm	6	1/31	.0002	9	2/31	.01
≥ 2 mm	33	10/36		33	10/36	
Present, NOS	4	2/23		13	4/23	
Hormonal use						
Yes, ER^+	9	11/107	ns	11	13/107	ns
No, ER^+	7	6/85		12	7/85	
Yes, ER^-	0	0/7	ns	0	0/7	ns
No, ER^-	12	10/113		18	17/113	

NOTE. Unknowns are excluded in each category.

*P = ns for univariate central/inner versus outer.

of less than 10% are considered acceptable indications for adjuvant therapy.

Consistent with most previous reports,[12,13] our study found that the chest wall and supraclavicular fossa are the most common sites of LRR. The low overall rates of axillary recurrence do not support the routine supplementation of axillary dose beyond that delivered by the supraclavicular/axillary apex field and the chest wall tangents. Although the rate of documented IMC failures in our cohort was quite low, CT scans and ultrasound were not routinely performed as screening procedures in these patients, many of whom were treated before the routine use of CT scans. It is, therefore, possible that many IMC recurrences went undetected. Indeed, despite the observation that these clinical recurrences are rare,[12,43-47] autopsy and surgical reports have documented microscopic involvement of the IMC nodes in up to 25% of node-positive patients with outer quadrant tumors and 50% of those with central/inner quadrant tumors.[48] Whether subclinical involvement of these nodes is a source of seeding for distant metastasis is also unknown. The indications for treatment to the regional lymphatics, particularly the use of a posterior axillary supplemental field and targeting of the IMC nodes, remain questions worthy of further study.

There has been considerable debate over the most appropriate method for reporting failure patterns such as LRR.[49-51] The Kaplan-Meier statistical methodology we used may overestimate true rates of recurrence by assuming that patients who die from a competing risk, such as distant metastatic disease, have a projected risk of LRR equivalent to that of the overall population in the study. This may not be the case, given that these patients may have more aggressive disease by nature and that additional systemic therapy delivered after the diagnosis of a distant metastasis potentially alters the subsequent risk of LRR. However, we have chosen to use the Kaplan-Meier methodology because it does provide useful information for clinicians interested in estimations of total actuarial risk of an event independent of a competing risk. Although there are limitations to any method of analysis of outcome other than survival, Kaplan-Meier analysis addresses most closely the clinical situation that physicians face in discussing the role of adjuvant therapy with their patients. Crude recurrence rates are also reported to allow readers to compare these results with other series in the literature. Given the long duration of follow-up in our study, the crude rates of LRR do not differ dramatically from the rates calculated by the Kaplan-Meier method, which indicates that this is a fair approximation of the true risk.

The results of this analysis demonstrate that doxorubicin-based chemotherapy does not obviate the need for postmastectomy irradiation. Patients with zero, one to three, four to nine, and 10 or more involved nodes experience isolated LRR rates of 4%, 10%, 21%, and 22%, respectively. The corresponding rates of total LRR are 7%, 14%, 25%, and 34%, respectively. Because of the longer duration of follow-up and precise definition of isolated and total LRR in the current series, these rates are consistent with previous reports from our institution. Our results also support the recently published recommendations of the American Society for Therapeutic Radiology and Oncology (ASTRO) consensus statement regarding the indications for postmastectomy irradiation.[52] We conclude that patients with stage II disease and four or more involved nodes or stage III disease are at the greatest risk of isolated LRR and are most likely to derive a benefit from the addition of postmastectomy irradiation. Taken as a whole, patients with stage II breast cancer and one to three involved lymph nodes are at low risk of LRR, and the corresponding absolute benefit in survival derived from postmastectomy irradiation is likely to be small. However, there may be a subset of these patients who are also at a significant risk of LRR and for whom adjuvant irradiation should be considered. These include patients with large tumors, those with extranodal extension $\geq$ 2 mm, and those who have not undergone an adequate axillary dissection.

The question of whether radiation benefits subgroups of stage II patients with one to three involved nodes takes on increased importance with the growing evidence that modern radiotherapy has the potential to improve survival in properly selected patients. Because our experience does not reproduce the findings of the recent prospective trials, it is difficult to justify the routine use of postmastectomy irradiation in patients with one to three involved nodes unless other risk factors are present. The results of this study support the need for a prospective, randomized trial to specifically assess the role of postmastectomy irradiation in this patient group.

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