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CLINICAL INVESTIGATION **Breast**

SELECTING BREAST CANCER PATIENTS WITH T1-T2 TUMORS AND ONE TO THREE POSITIVE AXILLARY NODES AT HIGH POSTMASTECTOMY LOCOREGIONAL RECURRENCE RISK FOR ADJUVANT RADIOTHERAPY

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Purpose: To define the individual factors and combinations of factors associated with increased risk of locoregional recurrence (LRR) that may justify postmastectomy radiotherapy (PMRT) in patients with T1–T2 breast cancer and one to three positive nodes.

Methods and Materials: The study cohort comprised 821 women referred to the British Columbia Cancer Agency between 1989 and 1997 with pathologic T1-T2 breast cancer and one to three positive nodes treated with mastectomy without adjuvant RT. The 10-year Kaplan-Meier estimates of isolated LRR and LRR with or without simultaneous distant recurrence (LRR ± SDR) were analyzed according to age, histologic findings, tumor location, size, and grade, lymphovascular invasion status, estrogen receptor (ER) status, margin status, number of positive nodes, number of nodes removed, percentage of positive nodes, and systemic therapy use. Multivariate analyses were performed using Cox proportional hazards modeling. A risk classification model was developed using combinations of the statistically significant factors identified on multivariate analysis.

Results: The median follow-up was 7.7 years. Systemic therapy was used in 94% of patients. Overall, the 10-year Kaplan-Meier isolated LRR and LRR ± SDR rate was 12.7% and 15.9%, respectively. Without PMRT, a 10-year LRR risk of >20% was identified in women with one to three positive nodes plus at least one of the following factors: age <45 years, Stage T2, histologic Grade 3, ER-negative disease, medial location, more than one positive node, or >25% of nodes positive (all $p < 0.05$ on univariate analysis). On multivariate analysis, age <45 years, >25% of nodes positive, medial tumor location, and ER-negative status were statistically significant predictors of isolated LRR and LRR ± SDR. In the classification model, the first split was according to age (<45 years vs. ≥45 years), with 29.3% vs. 13.7% developing LRR ± SDR ($p < 0.0001$). Of 123 women <45 years, the presence of >25% of nodes positive was associated with a risk of LRR ± SDR of 58.0% compared with 23.8% for those with ≤25% of nodes positive ($p = 0.01$). Of 698 women >45 years, the presence of >25% of nodes positive also conferred a greater LRR ± SDR risk (26.7%) compared with women with ≤25% of nodes positive (10.8%; $p < 0.0001$). In women >45 years with ≤25% of nodes positive, tumor location and ER status were factors that could be used to further distinguish low-risk from higher risk subsets.

Conclusion: Clinical and pathologic factors can identify women with T1-T2 breast cancer and one to three positive nodes at high LRR risk after mastectomy. Age <45 years, >25% of nodes positive, a medial tumor location, and ER-negative status were statistically significant independent factors associated with greater LRR, meriting consideration and discussion of PMRT. Combinations of these factors further augmented the LRR risk, warranting recommendation of PMRT to optimize locoregional control and potentially improve survival. The absence of high-risk factors identifies women who may reasonably be spared the morbidity of PMRT. © 2005 Elsevier Inc.

Breast cancer, Radiotherapy, Mastectomy, Locoregional recurrence.

INTRODUCTION

The role of postmastectomy radiotherapy (PMRT) in breast cancer patients with T1-T2 tumors and one to three positive axillary nodes is among the most controversial issues in adjuvant breast cancer management facing radiation oncologists today. PMRT, which generally encompasses the chest wall and regional lymph nodes, has been demonstrated to improve locoregional control in patients with high-risk breast cancer (1–3). In the absence of adjuvant systemic therapy, trials have not demonstrated improved survival with PMRT compared with surgery alone (1, 2). In the past two decades, systemic therapy for breast cancer has evolved, with broader indications for adjuvant chemotherapy and hormonal therapy (4, 5). Re-

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cently, three randomized trials (6–8) and a meta-analysis (3) demonstrated that PMRT improved not only locoregional control, but also survival, among patients with high-risk disease treated with systemic therapy. The results of these trials have prompted reevaluation of prior policies and launched a number of position statements and treatment guidelines addressing the role of PMRT in modern practice (9–14).

Although consensus has been reached that PMRT is indicated for patients with advanced primary tumors >5 cm or four or more positive axillary nodes, the role of PMRT in patients with tumors ≤5 cm and one to three positive axillary nodes is controversial (9–14). In the Danish Breast Cancer Cooperative Group 82b and 82c trials, the locoregional recurrence (LRR) rate without PMRT of approximately 30% at 10 years (7, 8) was considerably greater than rates observed in the British Columbia Cancer Agency (BCCA) trial (16% at 10 years and 33% at 15 years) (6) and in cohort studies of patients enrolled in systemic therapy trials (12–20% at 10 years) (15–20). This discrepancy has been attributed to heterogeneous practices in axillary staging, systemic therapy, and patient selection (6–8, 9–14). The relative reduction in LRR of approximately two-thirds associated with PMRT is of a similar magnitude in women with one to three positive nodes compared with women with four or more positive (1–3, 6–8). However, the absolute reduction in LRR with PMRT would be smaller if the baseline risk of LRR were lower in this subgroup, and the associated survival implication is unclear.

Owing to the inconsistencies in the available evidence, the role of PMRT in women with one to three positive nodes is currently undefined. It is, thus, disappointing that an Intergroup trial designed to address this question directly by randomizing patients with one to three positive nodes to locoregional PMRT or observation was prematurely closed because of a lack of accrual (21). The reasons for the trial's poor accrual were likely multifactorial, but may have included patient refusal, physician biases, and divergent opinions and practice patterns. In a Canadian study comparing regional RT use before and after the publication of the Danish Breast Cancer Cooperative Group and BCCA trials in 1997, Chua *et al.* (22) reported that among women with one to three positive nodes, regional PMRT use increased from 32% to 54%. Similar findings were apparent in a survey of radiation oncologists in the United States and Europe that reported that 50% of European responders and 55% of American responders indicated they would use PMRT in patients with one to three positive nodes (23). The selection criteria in using or withholding PMRT among these clinicians were not specified.

Because PMRT optimizes locoregional control and may affect survival (3, 6–8), strategies that use patient and pathologic characteristics, other than tumor and nodal stage, to distinguish subsets at high risk of LRR (justifying use of PMRT) from those at sufficiently low risk of LRR (who may be spared PMRT) warrant investigation. This study reports an analysis of the individual prognostic factors and combinations associated with a high risk of LRR in patients with T1-T2 breast cancer and one to three positive nodes that may be used to select patients for adjuvant RT.

METHODS AND MATERIALS

The Breast Cancer Outcomes Unit database of the BCCA identified 1117 women diagnosed between January 1, 1989 and December 31, 1997 and referred with pT1-T2 breast cancer and one to three positive axillary nodes who were treated with mastectomy. The analysis excluded patients with established indications for PMRT, including pT3-T4 tumors and/or four or more positive nodes, patients presenting with distant metastasis, and patients with unknown pTN stage. Because our objective was to evaluate the prognostic factors for increased LRR in the absence of PMRT, patients who received RT (n = 296) were also excluded. The remaining 821 women with Stage T1-T2 breast cancer and one to three positive nodes formed the cohort for this analysis.

The primary outcomes examined were isolated LRR (ILRR), defined as the first site of tumor recurrence involving the ipsilateral chest wall (local) and/or axillary, superior infraclavicular, and internal mammary nodes (regional); and LRR with or without simultaneous distant recurrence (LRR ± SDR). LRR events that occurred >1 month after distant recurrence were not recorded. The secondary outcomes were breast cancer–specific survival and overall survival.

Patient age at diagnosis was initially examined by 5-year intervals and subsequently dichotomized at <45 vs. ≥45 years, the cutoff at which the most statistically significant difference in LRR was observed on univariate analysis. The tumor factors analyzed were histologic features (ductal, lobular, other); T stage (T1, T2); tumor location (medial, central, lateral, unknown); histologic grade (1, 2, 3, unknown); lymphovascular invasion status (present, absent, unknown); and estrogen receptor (ER) status (positive, negative, unknown). The nodal factors analyzed included the number of positive axillary nodes (one to three), number of axillary nodes removed (≤5, 6–10, 11–15, ≥16, unknown), and percentage of positive nodes (≤25%, >25%). Adjuvant systemic therapy was analyzed as tamoxifen alone, chemotherapy alone, both, or none.

Statistical analysis

The patient characteristics of those who did and did not experience LRR were compared using chi-square tests. To examine the effect of possible predictors of recurrence, 10-year Kaplan Meier risk of ILRR and LRR ± SDR and the associated standard errors (SEs) were computed for each patient and tumor characteristic. Statistical significance of survival differences was determined using the log–rank test. Multivariate analyses of the prognostic variables for ILRR and LRR ± SDR were performed using the Cox proportional hazards model. The proportional hazards assumptions were checked using *cox.zph* in S-PLUS, version 6.1. Using the statistically significant factors identified on multivariate analysis, a classification model of combinations of patient, tumor, and nodal factors associated with statistically significant different risks was constructed. At each level of the classification model, the 10-year Kaplan-Meier LRR-free survival curves were generated for different combinations of risk factors and compared using log–rank statistics. Each breakpoint was chosen by examining the degree of statistical significance of differences and sample sizes within the subgroups being compared. All analyses were conducted using Statistical Package for Social Sciences, version 11.0.1 (SPSS, Chicago, IL).

RESULTS

The median follow-up time was 7.7 years. The median patient age at diagnosis was 62 years (range, 26–94 years).

Tumor and treatment characteristics

Table 1 summarizes the data on the tumor and treatment characteristics of the study cohort. All patients underwent modified radical mastectomy with axillary dissection. The median number of nodes removed was 10 (range, 1–39). None of the study subjects received adjuvant locoregional RT.

Adjuvant systemic therapy, delivered according to the BCCA guidelines (24), was used in 94% of patients (21.7% chemotherapy alone, 57.1% hormonal therapy alone, and 15.1% both chemotherapy and hormonal therapy). Of 302 patients treated with chemotherapy, 202 received adriamycin and cyclophosphamide; 91 received cyclophosphamide, methotrexate, and fluorouracil; and 4 received fluorouracil, adriamycin, and cyclophosphamide. Hormonal therapy consisted of tamoxifen in 581 patients, ovarian ablation in 9 patients, and both ovarian ablation and tamoxifen in 2 patients.

Comparisons of cohorts with and without LRR

Table 1 also presents comparisons of the clinical characteristics of patients with and without ILRR and LRR ± SDR. For both LRR endpoints, women who experienced relapse were significantly younger with a greater proportion of medial tumors, Stage T2, histologic Grade 3, and ER-negative disease (all $p < 0.05$). The nodal characteristics more frequently associated with LRR were more than one positive node and >25% positive nodes ($p < 0.05$). The distributions of histologic type, surgical margin status, number of nodes removed, and systemic therapy use were comparable between cohorts with and without LRR.

Crude and Kaplan-Meier recurrence and survival outcomes

Overall, 8.2% ($n = 67$) and 6.9% ($n = 57$) of patients experienced local recurrence and regional recurrence, respectively. LRR ± SDR occurred in 113 patients (crude rate, 13.8%). Of these, 90 had ILRR (crude rate, 11.0%). The median time to relapse was 1.78 years (range, 0.19–12.11 years) for ILRR and 1.98 years (range, 0.19–12.11 years) for LRR ± SDR. Of 57 regional recurrences, 36 (63%) involved the axillary nodes, 19 (33%) the clavicular nodes, and 2 (3%) the internal mammary nodes. Distant recurrence occurred in 31.2% ($n = 256$) of subjects.

The 10-year Kaplan-Meier estimate of ILRR and LRR ± SDR was 12.7% (SE, 1.3) and 15.9% (SE, 1.5), respectively. The 10-year Kaplan-Meier breast cancer-specific survival and overall survival rate was 71.3% (SE, 1.8) and 58.2% (SE, 1.9), respectively.

Table 2 presents comparisons of the 10-year Kaplan-Meier ILRR and LRR ± SDR rate stratified by age, pathologic characteristics, and systemic therapy type. Age <45 years, >25% positive nodes, medial tumor location, and ER-negative disease were factors statistically significantly associated with both ILRR and LRR ± SDR. In the univariate analysis, the 10-year Kaplan-Meier LRR ± SDR risk was approximately ≥30% in the presence of age <45 years, >25% positive nodes, and medial tumor location; a risk of approximately 20–25% was observed for patients with Stage T2, histologic Grade 3, ER-negative disease, and more than one positive node.

Multivariate analysis

Table 3 presents the multivariate analyses of patient, tumor, and treatment variables on postmastectomy LRR using Cox proportional hazards modeling. Statistically significant independent predictors of ILRR and LRR ± SDR were age <45 years, >25% positive nodes, medial tumor location, and ER-negative disease (all $p < 0.05$).

Classification of risk groups using combinations of prognostic factors

Figure 1 depicts the classification schema separating patients at varying LRR risk using combinations of the statistically significant prognostic variables. The first split stratified subjects by age; women <45 years had statistically significant greater 10-year Kaplan-Meier risk of LRR compared with women ≥45 years (ILRR, 22.8% vs. 10.8%, $p = 0.0004$; and LRR ± SDR 29.3% vs. 13.7%, $p < 0.0001$; Fig. 2).

Of 123 women <45 years, the presence of >25% of nodes positive was associated with increased LRR compared with ≤25% positive nodes (ILRR, 47.6% vs. 18.5%, $p = 0.04$; LRR ± SDR 58.0% vs. 23.8%, $p = 0.01$; Fig. 3a). Of 698 women ≥45 years, the presence of >25% of nodes positive also conferred a greater risk of recurrence (ILRR, 20.6% vs. 8.7%, $p = 0.0003$; and LRR ± SDR 26.7% vs.10.8%, $p < 0.0001$; Fig. 3b). In women ≥45 years with ≤25% nodes positive, tumor location (medial vs. all others) and ER status (negative vs. positive) may also be used to distinguish further those at moderate risk (approximately 20%) from those at low risk (LRR <10%).

DISCUSSION

Advances in locoregional and systemic therapies in the past two decades have revolutionized breast cancer management. Recent trials have demonstrated that, in women receiving systemic therapy, PMRT improves not only locoregional control, but also disease-free and overall survival (3, 6–8). This survival benefit supports the hypothesis that when distant micrometastasis is controlled by systemic therapy and the locoregional tumor burden is reduced by RT, the effects combine to enhance disease control and survival (9). The key association between locoregional control and improved survival warrants investigation of strategies to define the selection criteria of high-risk disease to justify the use of PMRT. The current study has identified that, in the absence of adjuvant RT, age <45 years, >25% of nodes positive, a medial tumor location, and ER-negative disease

Table 1. Patient, tumor, and treatment characteristics of entire cohort and comparisons of patients with and without locoregional recurrence

Characteristic	Entire cohort (n = 821)	ILRR Absent (n = 731)	ILRR Present (n = 90)	p	LRR ± SDR Absent (n = 708)	LRR ± SDR Present (n = 113)	p
Age (y)							
Median	62	63	59	0.004	63	58	0.001
Range	27–94	27–94	26–88		27–94	25–85	
Histologic type							
Ductal	762 (92.8)	679 (92.9)	83 (92.2)	0.75	657 (92.8)	105 (92.9)	0.96
Lobular	57 (6.9)	50 (6.8)	7 (7.8)		49 (6.9)	8 (7.1)	
Other	2 (0.2)	2 (0.3)			2 (0.3)	0 (0)	
Tumor location				0.001*			0.001*
Medial	115 (14.0)	93 (12.7)	22 (24.4)		86 (12.1)	29 (25.7)	
Central	119 (14.5)	105 (14.4)	14 (15.6)		102 (14.4)	17 (15.0)	
Lateral	424 (51.6)	386 (52.8)	38 (42.2)		378 (53.4)	46 (40.7)	
Unknown	163 (19.9)	147 (20.1)	16 (17.8)		142 (20.1)	21 (18.6)	
Tumor stage							
T1	376 (45.8)	344 (47.1)	32 (35.6)	0.04	335 (47.3)	41 (36.3)	0.03
T2	445 (54.2)	387 (52.9)	58 (64.4)		373 (52.7)	72 (63.7)	
Grade				0.01*			<0.0001*
1	61 (7.4)	58 (7.9)	3 (3.3)		57 (8.1)	4 (3.5)	
2	373 (45.4)	343 (46.9)	30 (33.3)		337 (47.6)	36 (31.9)	
3	322 (39.2)	274 (37.5)	48 (53.3)		259 (36.6)	63 (55.8)	
Unknown	65 (7.9)	56 (7.7)	9 (10.0)		55 (7.8)	10 (8.8)	
LVI				0.18*			0.04*
Absent	370 (45.1)	337 (46.1)	33 (36.7)		330 (46.6)	40 (35.4)	
Present	386 (47.0)	340 (46.5)	46 (51.1)		325 (45.9)	61 (54.0)	
Unknown	65 (7.9)	54 (7.5)	11 (12.2)		53 (7.5)	12 (10.6)	
ER status				0.02*			0.002*
Positive	568 (69.2)	147 (20.1)	28 (31.1)		500 (70.6)	68 (60.2)	
Negative	175 (21.3)	514 (70.3)	54 (60.0)		138 (19.5)	37 (32.7)	
Unknown	78 (9.5)	70 (9.6)	8 (8.9)		70 (9.9)	8 (7.1)	
Surgical margins				0.51*			0.60*
Positive	26 (3.2)	22 (3.0)	4 (4.4)		21 (3.0)	5 (4.4)	
Negative	724 (88.2)	643 (88.0)	81 (90.0)		624 (88.1)	100 (88.5)	
Unknown	71 (8.7)	66 (9.0)	5 (5.6)		63 (8.9)	8 (7.1)	
Positive nodes (n)							
1	483 (58.8)	447 (61.1)	36 (40.0)	0.001	439 (62)	44 (38.9)	0.001
2	229 (27.9)	193 (26.4)	36 (40.0)		181 (25.6)	48 (42.5)	
3	109 (13.3)	91 (12.4)	18 (20.0)		88 (12.4)	21 (18.6)	
Nodes removed (n)				0.12*			0.14*
≤5	104 (12.7)	92 (12.6)	12 (13.3)		88 (12.5)	16 (14.5)	
6–10	312 (38.0)	271 (371)	41 (45.6)		264 (37.4)	48 (43.6)	
11–15	256 (31.2)	228 (31.2)	28 (31.1)		221 (31.3)	35 (31.8)	
≥16	143 (17.4)	135 (18.5)	8 (8.9)		132 (18.7)	11 (10.0)	
Unknown	6 (0.7)	5 (0.7)	1 (1.1)		3 (0.4)	3 (2.7)	
Positive nodes (%)				<0.0001*			<0.0001*
≤25%	674 (82.1)	613 (83.9)	61 (67.8)		598 (84.5)	76 (67.3)	
>25%	141(17.2)	113 (15.5)	28 (31.1)		107 (15.2)	34 (30.1)	
Unknown	6 (0.7)	5 (0.7)	1 (1.1)		3 (0.4)	3 (2.7)	
Systemic therapy				0.44			0.06
CHT alone	178 (21.7)	153 (20.9)	25 (27.8)		143 (20.2)	35 (31.0)	
HT alone	469 (57.1)	424 (58.0)	45 (50.0)		414 (58.5)	55 (48.7)	
Both	124 (15.1)	110 (15.0)	14 (15.6)		109 (15.4)	15 (13.3)	
None	50 (6.1)	44 (6.0)	6 (6.7)		42 (5.9)	8 (7.0)	

Abbreviations: ILRR = isolated locoregional recurrence; LRR = locoregional recurrence; SDR = simultaneous distant recurrence; LVI = lymphovascular invasion; ER = estrogen receptors; CHT = chemotherapy; HT = hormonal therapy.

Data presented as number of patients, with percentage in parentheses.

* Test statistics applied to patients with known values only.

are statistically significant prognostic factors of postmastectomy LRR in women with T1-T2 tumors and one to three positive nodes. When each of these factors was examined individually, the associated Kaplan-Meier 10-year LRR risk was ≥20%.

Acknowledging that a universally accepted definition of low

Table 2. Subgroup analyses of 10-year Kaplan-Meier locoregional recurrence outcomes

Variable	*n*	10-year Kaplan-Meier Isolated LRR rate (%)	10-year Kaplan-Meier LRR ± SDR (%)
All patients	821	12.7 (1.3)	15.9 (1.5)
Age (y)			
<40	52	24.4 (6.2)	27.4 (6.7)
≥40	769	11.9 (1.4)	15.1 (1.5)
p		0.001	0.006
<45	123	22.8 (4.2)	29.3 (4.7)
≥45	698	10.8 (1.3)	13.7 (1.5)
p		0.0004	<0.0001
<50	215	17.7 (29)	21.2 (3.1)
≥50	606	10.8 (1.4)	13.8 (1.6)
p		0.02	0.007
Histologic type			
Ductal	762	12.4 (1.4)	15.8 (1.5)
Lobular	57	15.9 (5.5)	21.9 (5.5)
p		0.89	0.90
Tumor location			
Medial	115	23.7 (4.9)	31.5 (5.2)
Central	119	11.6 (3.0)	15.1 (3.6)
Lateral	424	10.5 (1.7)	13.5 (1.9)
p		0.004	0.0001
Tumor stage			
T1	376	9.2 (1.7)	11.6 (1.8)
T2	445	15.9 (2.0)	20.6 (2.4)
p		0.01	0.005
Grade			
1–2	434	8.7 (1.5)	10.9 (1.7)
3	322	17.7 (2.5)	23.5 (2.8)
p		0.0004	<0.0001
LVI			
Absent	370	10.4 (1.8)	13.1 (2.2)
Present	386	13.4 (1.9)	18.4 (2.1)
p		0.11	0.02
ER status			
Positive	568	10.0 (1.5)	14.5 (1.8)
Negative	175	19.0 (3.3)	24.5 (3.6)
p		0.004	0.004
Surgical margin status			
Positive	26	16.8 (7.7)	16.8 (7.7)
Negative	724	12.9 (1.4)	16.5 (1.6)
p		0.52	0.64
Positive nodes (*n*)			
1	483	8.6 (1.4)	10.2 (1.5)
2	229	18.7 (3.1)	25.8 (3.5)
3	109	18.9 (4.2)	23.7 (4.9)
p		0.0002	<0.0001
Nodes removed (*n*)			
≤5	104	15.2 (4.4)	18.4 (4.6)
6–10	312	15.3 (2.3)	18.8 (2.6)
11–15	256	12.6 (2.3)	15.8 (2.6)
≥16	143	5.4 (2.0)	8.9 (3.0)
p		0.08	0.09
Positive nodes (%)			
≤25%	674	10.2 (1.3)	12.9 (1.5)
>25%	141	25.1 (4.6)	32.0 (5.1)
p		<0.0001	<0.0001
Systemic therapy			
CHT alone	178	16.7 (3.2)	22.7 (3.7)
HT alone	469	11.3 (1.7)	14.3 (1.9)
Both	124	12.2 (3.1)	13.0 (3.2)
None	50	13.8 (5.2)	18.2 (3.7)
p		0.47	0.08

Abbreviations as in Table 1.
Data in parentheses are standard errors.

Table 3. Multivariate analysis of locoregional recurrence

	ILRR		LRR ± SDR	
Variable	*p*	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)
Age (<45 vs. ≥45 y)	0.001	3.44 (1.68–7.07)	0.002	3.22 (1.54–6.75)
Positive nodes (>25% vs. ≤25%)	0.05	2.00 (0.99–4.05)	0.006	2.61 (1.31–5.22)
Tumor location (medial vs. lateral)	0.002	2.46 (1.15–5.26)	0.0001	3.69 (2.17–6.29)
ER status (negative vs. positive)	0.01	2.02 (1.16–3.54)	0.03	1.82 (1.05–3.17)
Grade (3 vs. 1–2)	0.11		0.08	
Tumor stage	0.15		0.26	
Histologic type	0.69		0.47	
LVI	0.31		0.15	
Surgical margin status	0.16		0.47	
Positive nodes	0.74		0.75	
Dissected nodes	0.24		0.63	
Systemic therapy	0.92		0.93	

Abbreviations: CI = confidence interval; other abbreviations as in Table 1.

and high LRR risk status is lacking and that the thresholds of absolute and relative risk reductions at which clinicians should recommend adjuvant locoregional therapy are also undefined, we suggest that LRR risk appraisals be guided by both the established knowledge that RT reduces LRR by approximately two-thirds and the relationship between locoregional control and survival demonstrated in the available meta-analyses of local therapies (1–3). In the Early Breast Cancer Trialists' Collaborative Group Overview, absolute improvements in locoregional control of 20% corresponded to absolute improvements of 5% in breast cancer-specific survival, suggesting a 1 to 4 relationship between survival and locoregional control improvement (2). In addition, if vascular mortality hazards related primarily to outdated techniques are avoided, the expected absolute increase in 20-year survival has been estimated at 2–4% (2). In another meta-analysis restricted to patients receiving systemic therapy, locoregional RT reduced the risk of LRR (odds ratio 0.25) and mortality (odds ratio 0.83) (3).

We thus venture to propose that patients with a 10-year LRR estimate of <10% constitute a low-risk subgroup that may be spared PMRT and that patients with a LRR risk of >30% constitutes a high-risk subgroup, justifying PMRT

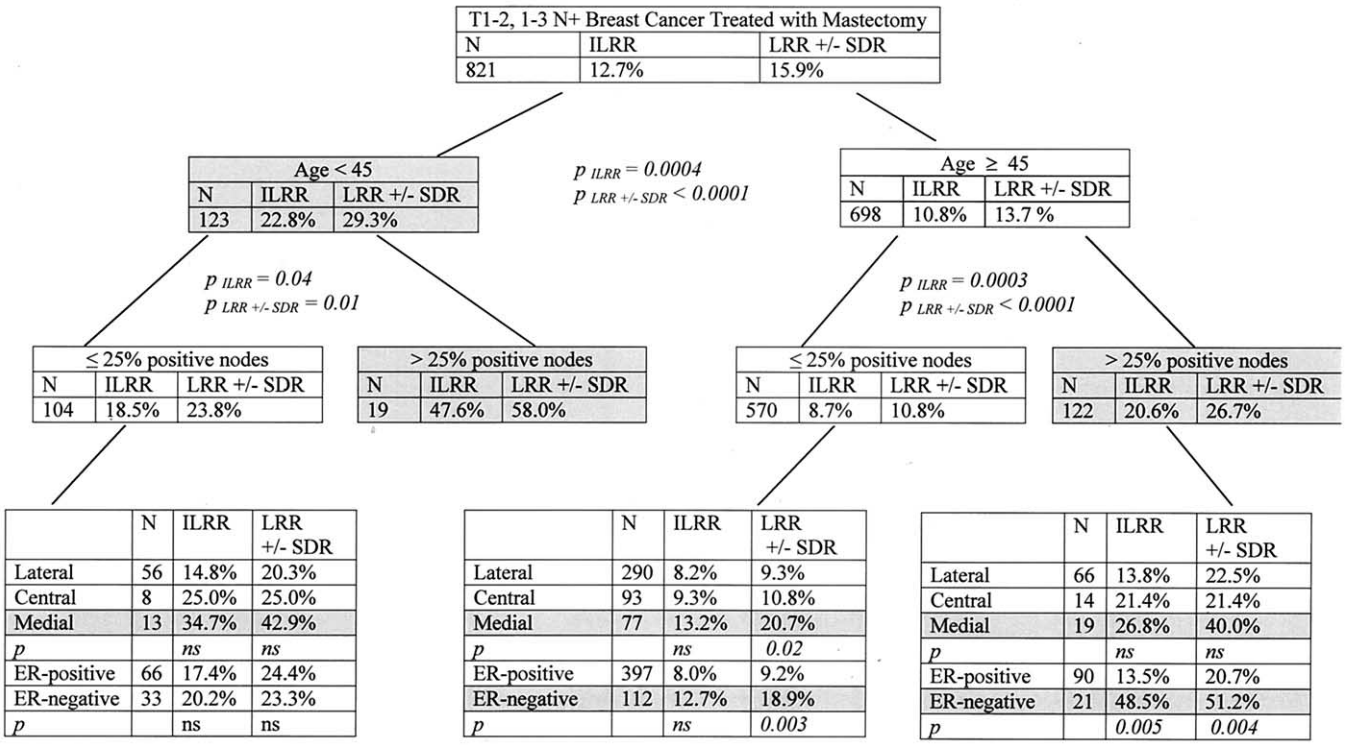

Fig. 1. Risk classification model of ILRR and LRR ± SDR using combinations of the significant patient, tumor, and nodal factors identified on multivariate analysis.

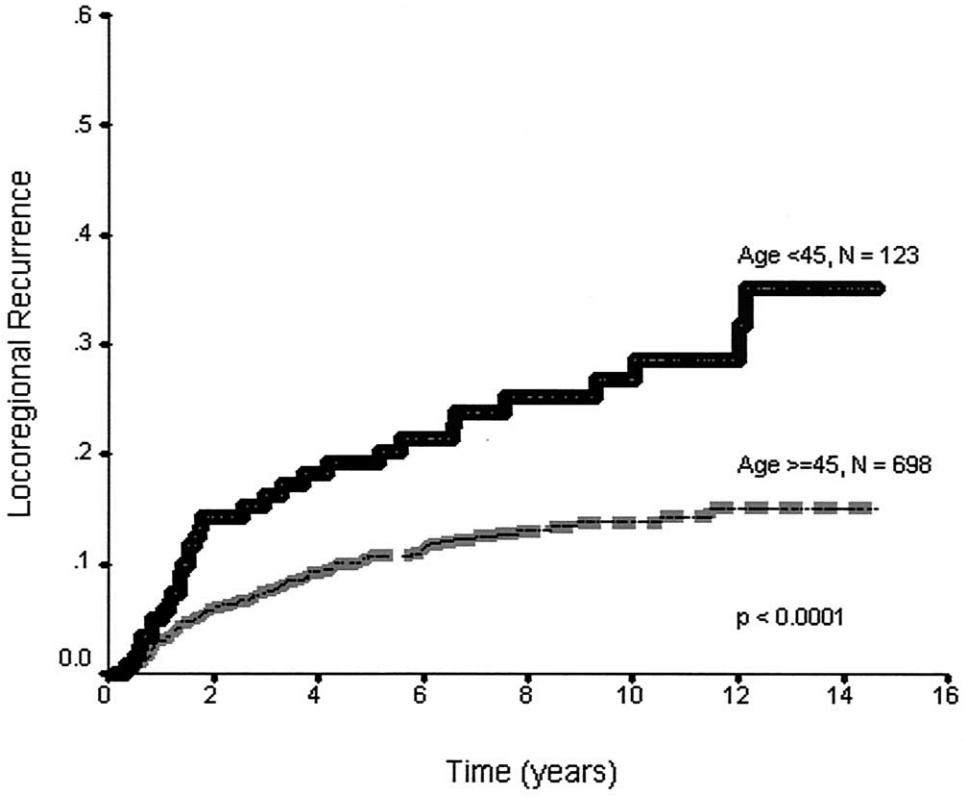

Fig. 2. Kaplan-Meier locoregional recurrence ± simultaneous distant recurrence in women aged <45 and ≥45 years.

recommendations since a two-thirds relative reduction (absolute 20%) may translate to 10-year absolute survival improvements of 4–5%. A 15–20% LRR risk may arguably be a reasonable threshold at which PMRT should be considered and discussed, with careful balancing of the benefits and risks and attention to the patient's goals and preferences.

Using this framework, our risk classification model supports consideration of PMRT in all patients <45 years (LRR >20%) and the recommendation of PMRT for women in this age group with >25% positive nodes (LRR >50%).

For women ≥45 years (LRR 14%), the presence of >25% of nodes positive conferred a greater risk of LRR of 27%, meriting PMRT consideration. Within this subgroup,

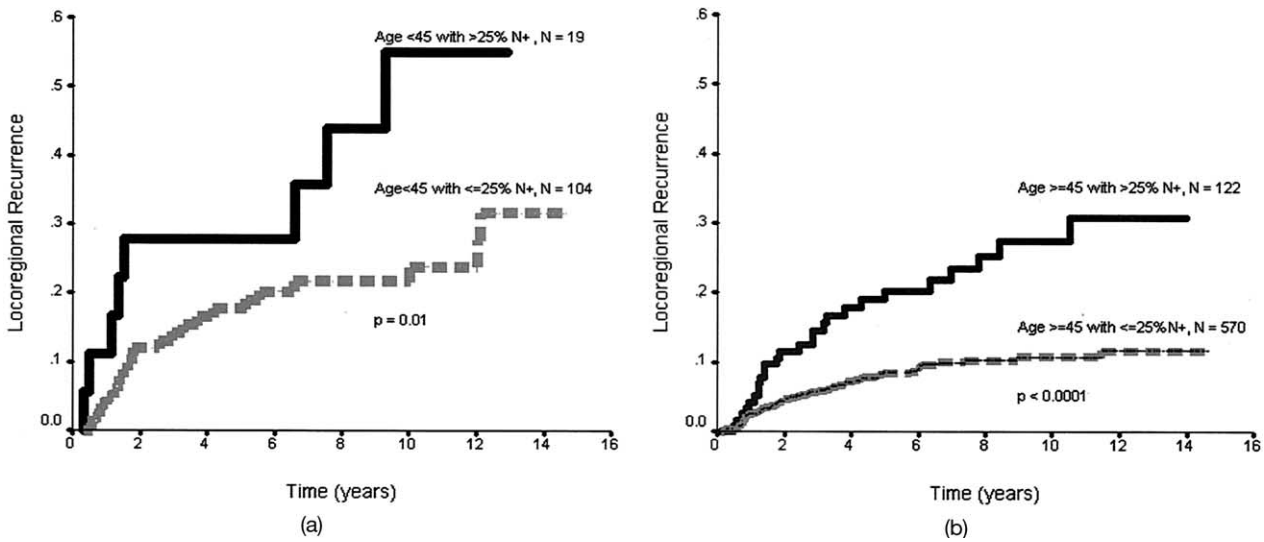

Fig. 3. Kaplan-Meier locoregional recurrence and simultaneous distance recurrence (LRR ± SDR) stratified by percentage positive nodes in (a) women aged <45 years and (b) women aged ≥45 years.

a medial tumor location and ER-negative disease were also associated with a LRR risk of 40–50%, warranting recommendation of PMRT.

In women ≥45 years with ≤25% of nodes positive, tumor location and ER status may also be used to distinguish moderate-risk (LRR ~20%) from low-risk (LRR <10%) cohorts.

Table 4 summarizes the data of contemporary studies of postmastectomy LRR in patients with one to three positive nodes treated without PMRT, most of whom received systemic therapy (6–8, 15–20, 25, 26). A direct comparison with the current study was difficult, because these analyses varied in sample size, follow-up time, and type of surgical and systemic therapies. The definitions and calculation methods for LRR also varied, but the 10-year risk of approximately 15% was strikingly consistent across the studies, including the present series. However, few studies performed multivariate analyses restricted specifically to patient cohorts with T1-T2 tumors and one to three positive nodes.

Pisansky *et al.* reported on 342 women with T1-T2 tumors and one to three positive nodes treated with nonanthracycline-based chemotherapy with or without tamoxifen. With a median follow-up of 9.3 years, the risk of ILRR was 17% (15).

Recht *et al.* (16) reported on the outcomes of 2016 patients, including 983 subjects with T1-T2 tumors and one to three positive nodes, who were enrolled in four randomized systemic therapy trials conducted by the Eastern Cooperative Oncology Group. The median follow-up time was 12.1 years. The 10-year risk of LRR with or without simultaneous distant recurrence was 12% in patients with T1-T2 breast cancer and one to three positive nodes. Multivariate analysis was performed of the entire sample, including patients with T3 disease and four or more positive nodes. Increasing tumor size, increasing numbers of positive nodes, ER-negative status, and decreasing numbers of nodes examined were independent predictors of LRR (16).

Katz *et al.* (17) analyzed 1031 patients in five trials of doxorubicin-based chemotherapy at the M. D. Anderson Cancer Center, 404 of whom had T1-T2 tumors with one to three positive nodes. On multivariate analysis restricted to these patients, extranodal extension ≥2 mm, <10 nodes removed, and tumor size >4 cm were independent predictors of LRR. In another analysis of the same patient cohort, but including 466 patients with T1-T3 tumors and one to three positive nodes, the primary tumor factors that were statistically significant adverse prognostic factors for greater LRR were skin or nipple invasion, pectoral fascia invasion, and close or positive surgical margins (18). In a third report using recursive partitioning analysis of the entire sample of 1031 patients, including those with T3 tumors and four or more positive nodes, patients with ≥20% of nodes positive and patients with <20% of nodes positive and tumors ≥5 cm were identified as high-risk subsets with 40% LRR at 8 years (19).

Wallgren *et al.* (20) reported on 2250 women with one to three positive nodes enrolled in seven International Breast Cancer Study Group trials of systemic therapy. Factors associated with increased LRR risk were high histologic grade and vascular invasion among premenopausal patients and high histologic grade and tumor size >2 cm among postmenopausal patients (20).

In addition to these large series of patients enrolled in prospective systemic therapy trials, two small community-based studies have focused on patients with T1-T2 tumors and one to three positive nodes. Both reported a 16% rate of LRR, but at 4 years and 15 years, respectively (25, 26). In the multivariate analyses conducted in these studies, one series of 110 patients with a short median follow-up of 4.5 years found tumor size to be associated with LRR risk (25), but the other series, with only 74 patients, identified tumor size and age ≤45 years to be prognostic for LRR (26).

Similar to other retrospective analyses, our study was subject to biases in patient and treatment selection. However, because the current knowledge has largely been gleaned from subjects enrolled in prospective trials of systemic therapy who may have inherently different characteristics compared with patients in the community, our population-based approach offers a distinct set of information on risk estimates and outcomes in a large, potentially more representative, sample of patients encountered in community practice. Although the vast majority of patients with one to three positive nodes received some form of systemic therapy, our study identified a small minority (6%) who did not. We chose to include these patients in the analysis to provide comprehensive information regarding patients with this disease stage who were treated in the community. This approach also served to highlight differences in patient and treatment characteristics in population-based studies compared with studies in which patients were treated using systemic therapy protocols.

Variations in surgical techniques have the potential to affect LRR risk. Although consensus has been reached that Level I and II nodes (located lateral to and deep to the pectoralis minor muscle) should be removed for accurate staging and to reduce axillary recurrence, less agreement has been reached on the number of nodes that must be removed (27). In the National Surgical Adjuvant Breast Project B-04 study, the qualitative nodal status (negative vs. positive) could be estimated accurately with removal of 3–5 nodes, but the estimate of quantitative nodal status (1–3 vs. ≥4) was more reliable when at least 10 nodes were removed (28). Accordingly, the disproportionately greater incidence of LRR in the Danish randomized clinical trials compared with other series has been attributed to limited axillary surgery that removed a median of seven nodes (7, 8), potentially resulting in disease understaging. Although the median number of nodes removed in the BCCA randomized clinical trial (6) and the current population-based study from the same institution was 11 and 10, respectively, the 10-year ILRR rate of 13% and LRR ± SDR rate of 16% in the absence of PMRT were comparable to that of other series in which >15 nodes were removed (16–20). In the current study's multivariate analysis, the number of nodes removed did not emerge as a statistically significant LRR predictor, but the percentage of positive nodes correlated highly with LRR

Table 4. Summary of contemporary data published from 1990 to present of postmastectomy locoregional recurrence in patients with 1–3 positive nodes treated without radiotherapy

Study	Subjects with 1–3N+ treated with no PMRT (*n*)	Median nodes removed (*n*)	Systemic therapy	Median follow-up (y)	LRR definition and calculation methods	LRR without radiotherapy (%)	Multivariate analysis of LRR
Randomized trials of PMRT vs no PMRT							
Ragaz *et al.*, BCCA, 1997 (6)	92 T1–T3	11	CMF	12.5	LRR without prior or DR or SDR (Kaplan-Meier)	16% at 10 y 33% at 15 y	Not performed
Overgaard *et al.*, DBCG 82b, 1997 (7)	516 T1–T3	7	CMF	9.5	LRR ± SDR (crude rates)	30% at 10 y	NA*
Overgaard *et al.*, DBCG 82c, 1998 (8)	403 T1–T3	7	Tamoxifen	9.9	LRR ± SDR (crude rates)	31% at 10 y	NA*
Retrospective analyses of randomized trials of systemic therapy							
Pisansky *et al.*, NCCTG and Mayo Clinic, 1993 (15)	342 T1–T2	Not reported	Premenopausal: CFP ± Tam Postmenopausal: observation vs. P vs. P + Tam	9.3	ILRR without SDR (cumulative incidence)	17% at 8 y	NA†
Recht *et al.*, ECOG, 1999 (16)	983 T1–T2	15	CMF-based CHT and/or HT	12.1	ILRR without SDR	7–9% at 10 y	NA†
					LRR ± SDR (cumulative incidence)	12% at 10 y	
Katz *et al.*, MDACC, 2000 and 2001 (17)	404 T1–T2	17	Doxorubicin-based CHT	9.7	ILRR = LRR without prior DR or SDR	10% at 10 y	Extranodal extension ≥ 2 mm (17)
					Total LRR = all LRR with or without prior DR or SDR (Kaplan-Meier)	14% at 10 y	<10 nodes removed (17)
							T > 4cm (17)
Wallgren *et al.*, IBCSG, 2003 (20)	2250 T1–T2	15	CMF or Tam	12–15.5	LRR ± SDR (cumulative incidence)	16–20% at 10 y premenopause 13–19% at 10 y postmenopause	NA†
Retrospective population-based analyses							
Cheng *et al.*, Taipei, 2002 (25)	110 T1–T2	17	CHT and/or HT in all subjects	4.5	LRR ± SDR (Kaplan-Meier)	16% at 4 y	Tumor size
Fodor *et al.*, Budapest, 2003 (26)	74 T1–T2	11	CHT and/or HT in 82% (*n* = 61) subjects	15.7	ILRR (crude rates)	16% at 15 y	Age ≤ 45 y
							Tumor size
Present series, BCCA, 2004	821 T1–T2	10	CHT and/or HT in 94% (*n* = 771) subjects	7.7	ILRR	16% at 10 y	Age < 45 y
					LRR ± SDR (Kaplan-Meier)		>25% N+ Medial location ER-negative

Abbreviations: BCCA = British Columbia Cancer Agency; DBCG = Danish Breast Cancer Cooperative Group; NCCTG = North Central Cancer Treatment Group; ECOG = Eastern Cooperative Oncology Group; MDACC = M. D. Anderson Cancer Center; IBCSG = International Breast Cancer Study Group; ILRR = isolated locoregional recurrence; LRR = locoregional recurrence; DR = distant recurrence; PMRT = postmastectomy radiotherapy; C = cyclophosphamide, M = methotrexate; F = fluorouracil; P = prednisone; CHT = chemotherapy; HT = hormone therapy; Tam = tamoxifen; N+ = positive nodes; premen = premenopausal; postmen = postmenopausal; other abbreviations as in Table 1.

* Not applicable because endpoint used was any recurrence and multivariate analysis performed on overall sample, including patients with T3 tumor, ≥4 positive nodes, and those treated with radiotherapy.

† Not applicable because multivariate analysis performed on overall sample, including patients with T3 tumors and ≥4 positive nodes.

and was useful in classifying patients in different risk groups. This finding was corroborated by the M. D. Anderson Cancer Center's recursive partitioning analysis of node-positive patients with T1-T3 disease (19).

Other clinical factors identified in the current multivariate analysis (young age, ER-negative status, and, to a lesser extent, high histologic grade) have been demonstrated in some studies, but not in others, to be associated with greater LRR in patients with node-positive disease (Table 4). Unlike most studies, the present series and the smaller series from Fodor *et al.* were the only studies that identified young age (<45 years) to be a statistically significant prognostic factor of postmastectomy LRR in women with one to three positive nodes. This disparity may have been related to patient selection, particularly in the age differences between patients enrolled in prospective trials compared with patients in population-based series. For example, in the Eastern Cooperative Oncology Group and M. D. Anderson Cancer Center systemic therapy trials, the median age of patients enrolled was 50 years and 48 years, respectively (16–19). In contrast, in the present series, the median age was 62 years. Because the current study included patients with a wider age range, it may have had greater potential to detect age-related variations in outcomes compared with prospective trials in which patients were generally younger and older populations were underrepresented.

Compared with other contemporary series, the present analysis is the sole study to demonstrate that a medial tumor location is a predictor of postmastectomy LRR in patients with one to three positive nodes. A medial tumor location has been reported in other studies to be associated with inferior distant disease control (29), breast cancer–specific survival (30, 31), and overall survival (31). These hazards have been attributed to untreated occult metastasis of the internal mammary nodes (29–31) and emphasize the importance of ongoing clinical trials, conducted by the European Organization for Research and Treatment of Cancer (EORTC 22922) and the National Cancer Institute of Canada (NCIC MA20), evaluating the effects of internal mammary nodal RT on locoregional control and survival after mastectomy or breast-conserving surgery. The NCIC MA20 study randomized patients after breast-conserving surgery to RT to the breast or breast plus regional nodes and stratified patients according to the number of positive nodes and systemic therapy use (32). The nodal treatment volume varied according to the number of positive nodes and number of nodes removed. Although not directly applicable to the postmastectomy setting, this study has the potential to provide valuable insight into nodal recurrence patterns according to regional RT use and volume in women with one to three positive nodes.

As surgical techniques evolve toward more limited nodal staging procedures, including sentinel node biopsy with or without axillary sampling (33–35), and the systemic therapy armamentarium expands to include newer agents with varying schedules and dose intensities, the role of PMRT and its integration with these other modalities will undoubtedly also evolve. Advances in conformal techniques that limit normal tissue exposure (36–38) have created the potential for RT to exert an even greater impact on survival by optimizing locoregional control while minimizing toxicity. Ultimately, however, adjuvant therapy decisions require the complex balancing of benefits and risks from the perspectives of the patient and her oncologist. These decision-making processes require not only clinical judgment and skills in estimating risks (39), but also effective communication and careful consideration of the patient's values and preferences (40). Computer-based tools using patient's prognostic characteristics to provide estimates of efficacy of adjuvant systemic therapy have been developed to assist clinicians and patients with individualized decision-making (41–43). Analogous decision aids applicable to adjuvant locoregional therapy may also be of substantial clinical and educational value and should be explored.

CONCLUSION

Patients with T1-T2 tumors and one to three positive nodes in this population-based analysis experienced overall LRR risk of 13–16% at 10 years. Although the magnitude of this risk may not be sufficiently great to justify routine PMRT in all patients, subgroups with age <45 years, >25% positive nodes, medial tumor location, and ER-negative disease experienced LRR of >20%. Women with these individual characteristics should be considered for PMRT. Combinations of these prognostic factors conferred even greater LRR risks, justifying recommendation of PMRT to optimize locoregional control and potentially improve survival.

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