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ORIGINAL REPORT

Low Locoregional Recurrence Rate Among Node-Negative Breast Cancer Patients With Tumors 5 cm or Larger Treated by Mastectomy, With or Without Adjuvant Systemic Therapy and Without Radiotherapy: Results From Five National Surgical Adjuvant Breast and Bowel Project Randomized Clinical Trials

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ABSTRACT

Purpose

Lymph node (LN) –negative breast cancer tumors ≥ 5 cm occur infrequently, and their optimal management is not well defined. In this study, we assess patterns of locoregional failure (LRF) in LN-negative patients who underwent mastectomy, either with or without adjuvant chemotherapy or hormonal therapy and without postmastectomy radiation therapy (PMRT).

Patients and Methods

Of 8,878 breast cancer patients enrolled onto National Surgical Adjuvant Breast and Bowel Project B-13, B-14, B-19, B-20, and B-23 node-negative trials, 313 had tumors that were 5 cm or larger (median, 5.5 cm; range, 5.0 to 15.5 cm) at pathology and were treated by mastectomy. Median follow-up time was 15.1 years. Therapy included adjuvant chemotherapy in 34.2% of patients; tamoxifen in 21.1%; chemotherapy plus tamoxifen in 19.2%; and no systemic therapy in 25.5%.

Results

Twenty-eight patients experienced LRF. The overall 10-year cumulative incidences of isolated LRF, LRF with and without distant failure (DF), and DF alone as first event were 7.1%, 10.0%, and 23.6%, respectively. Cumulative incidences for isolated LRF as first event for patients with tumors of 5 cm or more than 5 cm were 7.0% and 7.2%, respectively ($P = .9$). For patients who underwent no systemic treatment, chemotherapy alone, tamoxifen alone, or chemotherapy plus tamoxifen, the incidences were 12.6%, 5.6%, 4.6%, and 5.3%, respectively ($P = .2$). The majority of failures occurred on the chest wall (24 of 28 patients). Multivariate analysis did not identify significant prognostic factors for LRF.

Conclusion

In patients with LN-negative tumors ≥ 5 cm who are treated by mastectomy with or without adjuvant systemic therapy and no PMRT, LRF as first event remains low. PMRT should not be routinely used for these patients.

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INTRODUCTION

Patients with node-negative breast cancer and primary tumors 5 cm or larger represent less than 1% of new breast cancer patients,[1] and optimal management for these patients is not well defined. Although standard recommendations for these patients include systemic treatment in addition to surgery, the addition of radiation therapy for improved local control or survival is debatable. The postmastectomy radiation therapy (PMRT) guidelines of the American Society of Clinical Oncology[2] provide no recommendations for T3N0 tumors because of a lack of information and conflicting data. Yet, the majority of practicing radiation oncologists recommend PMRT for these tumors.[3]

In this study, we examine the rates and patterns of locoregional failure (LRF) in 313 breast cancer patients whose tumors were ≥ 5 cm at pathology and who, per protocol, did not receive PMRT as part of five randomized clinical trials conducted by the National Surgical Adjuvant Breast and

Bowel Project (NSABP). These patients underwent axillary lymph node (LN) dissection and were treated with modified radical mastectomy (MRM), with or without adjuvant chemotherapy or adjuvant hormonal therapy.

PATIENTS AND METHODS

Study Population

Patients included in this report were treated in five NSABP node-negative trials (B-13, B-14, B-19, B-20, and B-23) evaluating adjuvant chemotherapy and/or hormonal therapy but not allowing for adjuvant PMRT. To be included in this analysis, a patient had to be eligible with follow-up, had to have undergone MRM, and had to have had a pathologic tumor ≥ 5 cm in diameter. A brief summary of each of the five trials is provided in Table 1. Treatment details, outcome, and other aspects of each trial have been reported in previous publications (B-13,[4] B-14,[5,6] B-19,[7] B-20,[8] and B-23[9]). All trials were approved by local human investigations committees or institutional review boards in accordance with assurances filed with and approved by the Department of Health and Human Services, when appropriate. Written informed consent was required for participation in the trials.

Statistical Methods

In NSABP studies, local failure after mastectomy is defined as any recurrence of tumor in the ipsilateral chest wall or in the mastectomy scar. Regional failure is defined as any recurrence of tumor in the ipsilateral supraclavicular, infraclavicular, axillary, or internal mammary nodes. Recurrence in any other site is considered distant failure (DF). For our study, isolated LRF was defined as any first local or regional failure without evidence of simultaneous DF. Simultaneous DF is defined as any subsequent DF that occurred within 4 months after the diagnosis of the isolated LRF. The occurrence of contralateral events and other second primary cancers was ignored in the determination of (isolated) locoregional recurrences. LRF with or without DF (LRF ± DF) was defined as any first LRF with or without any subsequent DF.

Time to isolated LRF was defined as time from definitive surgery to the first diagnosis of an isolated LRF. Time to DF was defined as time from surgery to the first DF. Local or regional failures occurring without a subsequent DF but with additional follow-up of less than 4 months were counted as isolated events.

The nonparametric method[10] was used to estimate 10-year cumulative incidence for isolated LRF, LRF ± DF, and DF alone. For the analysis of cumulative incidence for each end point, competing events were defined as (1) any first isolated recurrence, (2) any first other recurrence followed by a DF within 4 months, (3) any first DF, and (4) any death without evidence of previous recurrence. Gray's K-sample statistic was used to test whether any statistical significance of differences existed in cumulative incidence among groups stratified by protocols (univariate analysis).[11] The Cox proportional hazards model[12] was used to test the association between cause-specific hazard functions and selected patient and tumor characteristics and to estimate the magnitude of such association, stratified by protocols. All P values were two tailed, and $P \leq .05$ was considered to be significant. Analyses were based on all follow-up information received at the NSABP Biostatistical Center as of June 30, 2005.

RESULTS

A total of 8,878 node-negative patients enrolled onto these five NSABP trials were eligible with follow-up. Of these, 313 patients met our predetermined criteria and are included in this analysis (Table 1). Patients in this study were treated between 1981 and 1998. Table 2 lists patient and tumor characteristics. Two hundred sixteen and 169 patients were at risk for any first recurrence at 5 and 10 years, respectively. Of the 313 patients considered for this analysis, 28 (8.9%) presented with isolated LRF as the first event. The overall 10-year cumulative incidences of isolated LRF, LRF ± DF, and DF alone as first event were 7.1%, 10.0%, and 23.6%, respectively. The median times to develop isolated LRF and DF were 2.3 and 1.8 years, respectively. The majority of LRFs (62.2%) occurred within the first 4 years, and 18.9%, 10.8%, and 8.1% of LRFs occurred at 4 to 8, 8 to 12, and more than 12 years of follow-up, respectively.

The rates of isolated LRF, LRF ± DF, and DF according to different patient and tumor characteristics are listed in Table 3. Results from univariate analyses indicated that age, menopausal status, estrogen receptor status, pathologic tumor size, number of LNs removed, and the type of treatment were not significant predictors for either LRF or DF. Patients who had one to five LNs removed had a 10-year isolated LRF cumulative incidence estimate of 16.7% compared with 7.3% for patients who had ≥ 10 LNs removed. However, this difference was not significant ($P = .21$). Also, patients who were randomly assigned to no adjuvant systemic treatment arms had a 12.6% isolated LRF rate compared with a 5.3% rate in patients who received systemic treatment with chemotherapy, tamoxifen, or both ($P = .2$). Using multivariate analysis, we were unable to identify any independent prognostic factors for LRF ± DF. The majority of recurrences (24 of 28 patients) occurred in the chest wall and around the mastectomy scar (85.7%); two patients experienced recurrences in the supraclavicular fossa, one patient experienced a recurrence in the axilla, and one patient experienced a recurrence in the parasternal area.

Table 1. Summary of NSABP Treatment Protocols and No. of Patients Included in This Report

Trial	No. of Patients With Tumors ≥ 5 cm	Total No. of Patients	Period of Accrual	Patient ER Status (fmol/mg)	Trial Treatment Groups
B-13	51	731	1981-1988	< 10	No further therapy *v* M → F + LV
B-14	103	2,817	1982-1994	> 10	Placebo *v* Tam (5 or 10 years)
B-19	54	1,074	1988-1990	< 10	M → F + LV *v* CMF
B-20	45	2,301	1988-1993	> 10	M → F + Tam *v* CMF + Tam *v* Tam
B-23	60	1,955	1991-1998	< 10	Six CMF ± Tam *v* 4 AC ± Tam
Total	313	8,878*	1981-1998	—	—

Abbreviations: NSABP, National Surgical Adjuvant Breast and Bowel Project; ER, estrogen receptor; M, methotrexate; F, fluorouracil; LV, leucovorin; AC, doxorubicin 60 mg/m^2 intravenously and cyclophosphamide 600 mg/m^2 intravenously; CMF, cyclophosphamide 100 mg/m^2 orally, methotrexate 40 mg/m^2 intravenously, and fluorouracil 600 mg/m^2 intravenously; Tam, tamoxifen.
*No. of patients eligible with follow-up and analyzed.

Table 2. Patient, Tumor, and Treatment Characteristics of the Study Population

Characteristics	No. of Patients	%
Age, years		
< 50	162	51.8
50-59	89	28.4
≥ 60	62	19.8
Median	49	
Range	29-74	
Menopausal status		
Premenopausal	164	52.4
Postmenopausal	145	46.3
Unknown	4	1.3
Tumor ER status		
Positive	147	47.0
Negative	166	53.0
Pathologic tumor size, cm		
5	144	46.0
5.1-7.0	130	41.5
7.1-10.0	34	10.9
> 10.0	5	1.6
Median	5.5	
Range	5.0-15.5	
No. of LN removed		
1-5	12	3.8
6-9	39	12.5
≥ 10	262	83.7
Median	16	
Range	1.0-39.0	
Treatment regimen		
No systemic treatment	80	25.5
Chemotherapy only	107	34.2
Tam only	66	21.1
Chemotherapy + Tam	60	19.2

Abbreviations: ER, estrogen receptor; LN, lymph nodes; Tam, tamoxifen.

DISCUSSION

Because of the rarity of reports and information about the efficacy of radiotherapy for the treatment of patients with T3N0 breast cancer, Recht et al[2] avoided giving recommendations for this group of patients in the American Society of Clinical Oncology guidelines for PMRT. Nevertheless, many clinicians choose to treat T3N0 patients with radiotherapy. In a recent survey[3] of radiation oncologists, 1,137 respondents from North America and Europe (88.3% and 84.8%, respectively) would recommend PMRT for patients with T3N0 breast cancer despite the lack of clinical evidence regarding its benefit; furthermore, of these oncologists, 47.7% and 20.2%, respectively, would recommend supraclavicular radiation.

The study we carried out was designed to contribute to the base of clinical decision-making knowledge about the use of radiation therapy in node-negative patients with large tumors. We found 169 patients with tumors (T3N0) larger than 5 cm among 8,878 patients enrolled onto five node-negative trials (Table 1), representing less than 2% of node-negative patients. We decided to include patients with 5-cm tumors (large T2N0) to increase the number of patients to 313, which represented 3.5% of LN-negative patients enrolled onto these trials (Table 1). The isolated LRF and LRF ± DF rates were similar whether the tumor was 5 cm or larger than 5 cm (Table 3). Although the total number of patients in this series is relatively small, to our knowledge, because of the infrequency of this clinical scenario, this is the largest series to date on patients with tumors of 5 cm or larger with negative LNs treated by mastectomy without PMRT.

In Finland, Helinto et al[1] identified 38 patients with T3N0 tumors treated by MRM from among 4,190 new breast cancer patients (representing < 1% of the patients). Mignano et al[13] reported the LRF rate in his series of 101 patients with T3N0 breast cancer treated from 1974 to 1994 with MRM who received no radiation and of whom, only 9% received adjuvant systemic therapy. Isolated LRF as first event was reported in 12 patients (12%); six of these patients experienced chest wall recurrence, and six experienced regional LN failure. The authors concluded that the risk of LRF in T3N0 is low and does not warrant the routine use of PMRT. In a combined analysis from the Massachusetts General Hospital, M.D. Anderson Cancer Center, and Yale University, Floyd et al,[14] with a median follow-up time of 85 months, found that the 5-year actuarial cumulative rates of LRF in 70 node-negative patients with tumors ≥ 5 cm was 7.6%; four of the five failures occurred in the chest wall, and one occurred in the axilla. Tumor size and menopausal status were not found to be significant prognostic factors of LRF, but in a multivariate analysis, lymphatic vessel invasion (LVI) was found to be an independent prognostic factor for LRF, disease-free survival, and overall survival (OS). Although the low LRF rate in that series is in agreement with what we found, the study by Floyd et al[14] was a retrospective study, and the omission of PMRT for the patients in their series was determined by patient and physician biases that may have affected the selection of the cohort analyzed.

All the patients in our series received no PMRT, as required by the different protocols. One might argue that, between 1981 and 1998, physicians who had patients at particularly high risk for LRF when PMRT was not an option might have been disinclined to enroll them in these NSABP studies. This is an unlikely scenario because in the same period (1984 to 1994) 5,758 patients with MRM and positive LNs (ie, considered higher risk patients) were accrued to node-positive NSABP trials that also did not allow PMRT.[15] Almost 50% of the latter group had ≥ four positive LNs, and 11% had larger than 5 cm tumors with positive LNs. Therefore, it is unlikely that only node-negative, low-risk patients for LRF were selected to enroll onto the node-negative NSABP trials included in this analysis.

Several randomized studies have suggested that PMRT reduces the risk of LRF by two thirds and potentially increases OS.[16-18] These trials have targeted mainly patients with positive LNs. However, the randomized clinical trial reported by Overgaard et al,[16,17] in which patients were randomly assigned to cyclophosphamide, methotrexate, and fluorouracil chemotherapy versus cyclophosphamide, methotrexate, and fluorouracil plus PMRT, included 135 premenopausal[16] and 132 postmenopausal[17] patients with T3N0 tumors. The results in that group showed that PMRT decreased the LRF rate from 17% to 3% in premenopausal patients and from 23% to 6% in postmenopausal patients.[16,17] In addition, PMRT significantly increased the OS rate from 70% to 82% in premenopausal patients[16] but did not significant increase OS in postmenopausal patients. However, in those studies, axillary LN dissection was considered suboptimal because an average of only seven LNs were removed[16,17] compared with 15 to 17 LNs removed in other studies.[15,19-21] Thus, it is possible that some of the T3N0 patients in the Overgaard et al[16,17] series may have been found to be node positive if additional axillary LNs had been removed

Table 3. Ten-Year Cumulative Incidence Rates and Raw Estimates at Year 10 of ILRF, LRF ± DF, and DF

Factor	No. of Patients	ILRF Incidence %	ILRF Incidence SE	ILRF No. of Events	LRF ± DF Incidence %	LRF ± DF Incidence SE	LRF ± DF No. of Events	DF Incidence %	DF Incidence SE	DF No. of Events
Age, years*										
< 49	162	8.1	2.2	13	10.0	2.4	16	25.5	3.5	41
50-59	89	5.7	2.5	5	11.4	3.4	10	22.8	4.5	20
≥ 60	62	6.5	3.2	4	8.1	3.5	5	19.5	5.1	12
P		.71			.28			.98		
Menopausal status*										
Pre-/perimenopausal	164	7.4	2.1	12	9.3	2.3	15	22.8	3.3	37
Postmenopausal	145	6.2	2.0	9	10.4	2.6	15	23.7	3.6	34
P		.29			.58			.82		
ER status*										
Positive	147	7.7	2.2	11	9.7	2.5	14	23.2	3.5	34
Negative	166	6.6	1.9	11	10.3	2.4	17	23.7	3.3	39
P		.57			.60			.26		
Pathologic tumor size, cm*										
5.0	144	7.0	2.1	10	9.8	2.5	14	26.7	3.7	38
5.1-7.0	130	8.6	2.5	11	10.1	2.7	13	20.2	3.6	26
> 7.0	39	2.6	2.6	1	10.3	4.9	4	23.1	6.9	9
P		.34			.90			.42		
No. of axillary LN dissected*										
1-5	12	16.7	11.4	2	16.7	11.4	2	41.7	15.1	5
6-9	39	2.6	2.6	1	5.1	3.6	2	18.3	6.4	7
≥ 10	262	7.3	1.6	19	10.4	1.9	27	23.5	2.6	61
P		.21			.28			.28		
Treatment regimen										
No systemic treatment	80	12.6	3.7	10	16.3	4.2	13	27.7	5.1	22
Chemotherapy only	107	5.6	2.3	6	7.5	2.6	8	21.5	4.0	23
Tam only	66	4.6	2.6	3	7.7	3.3	5	25.9	5.5	17
Chemotherapy + Tam	60	5.3	3.0	3	8.6	3.8	5	18.6	5.1	11
P		.21			.32			.60		

NOTE. *P* values compare overall cumulative incidence during the entire follow-up period. The events were counted only up to year 10 for a fair comparison with the corresponding 10-year cumulative incidence estimates.

Abbreviations: ILRF, isolated local and/or regional failure as first events with no distant failure within the first 4 months of diagnosis; LRF ± DF, local and/or regional failure with or without distant failure; DF, distant failure; ER, estrogen receptor; LN, lymph nodes; Tam, tamoxifen.

*Unknowns, if any, were omitted from each analysis.

at surgery. In our series, patients who had had one to five axillary LNs removed had a 16.7% isolated LRF rate, in contrast to 7.3% in patients who had had 10 or more LNs removed. Although the difference was not statistically significant because of the small number of patients who had one to five LNs removed (12 patients), the trend suggests that adequate LN dissection may be able to identify T3N0 patients with a lower risk for LRF.

As discussed earlier, the rate of LRF in T3N0 patients randomly assigned to the nonradiation arm in the Overgaard et al[16,17] trials was higher (17% to 23%) than the rate observed in our series (7.1%) or in other similar series (Floyd et al,[14] 7.6%; and Mignano et al,[13] 12%). This discrepancy between the randomized trials[16,17,22] and other series[15,19-21] in the LRF rate in patients who did not receive PMRT was also found in patients with one to three and ≥ four positive axillary LNs.[15] Thus, the applicability of the findings from the randomized trials to current practice about the routine use of PMRT in patients with tumors larger than 5 cm and negative axillary nodes (by an adequate axillary dissection) who are treated with systemic therapy has been questioned.

As mentioned earlier, the univariate and multivariate analyses in our study did not show any significant prognostic factors for LRF or LRF ± DF. Although an adequate number of removed axillary LNs and the use of systemic treatment were found to be associated with better locoregional control, these associations were not statistically significant. This could be because the number of patients and, more importantly, the number of events were relatively small in our study. It is also possible that some potentially prognostic factors were not studied because of the lack of information in our database. These factors include LVI,[14,21,23,24] tumor grade,[21,23] human epidermal growth factor receptor 2 expression,[25,26] close margins,[24] *p53* expression,[27] and presence of extensive intraductal component.[28] Floyd et al[14] found that LVI was an independent prognostic factor for LRF. Nevertheless, tumor size, as long as the LNs were negative, was not found to be an independent prognostic factor for LRF in either of our series or the study by Floyd et al.[14] In a recent retrospective analysis of 877 patients with T1-3 node-negative tumors treated at Massachusetts General Hospital with mastectomy without adjuvant PMRT, Jagsi et al[29] suggested that patients with multiple risk factors, including close margins, T2 or larger tumors, premenopausal status, and LVI, are at higher risk for LRF. However, only 25 patients (0.55%) had tumors larger than 5 cm.

Large breast tumors that present without the involvement of regional LNs may be a distinct clinical and biologic entity. It is possible that the inability of these tumors to spread to regional nodes despite their ability to grow to large size may indicate a more indolent biologic nature. This clinical presentation is clearly in contrast to the one in which small tumors have already spread to regional LNs and/or distant sites at the time of clinical presentation. The study of biologic differences and gene fingerprinting[30] between these extremes of tumor presentation may help in the understanding of the nature of the invasive and metastatic potential of breast tumors and in the identification of patients who would benefit from PMRT.

The most common PMRT approach used by radiation oncologists and in the cooperative group studies includes the area of the chest wall and regional LNs.[16,17,22] The risk of radiation pneumonitis increases with the number of radiation fields used as well as with the use of chemotherapy.[31,32] Furthermore, the risk for arm lymphedema increases when radiotherapy includes the regional lymph node.[33,34] All these facts raise the question of the need for regional radiation should radiation be used in this group of patients. Because the chest wall was by far the most common site of failure in this study (86%) as well as in the study by Floyd et al,[14] it may be reasonable to consider treating the chest wall only, without radiating the regional LNs, in subsets of patients thought to be at higher risk, thereby minimizing the adverse effects of PMRT.

In our series, the 10-year cumulative incidence for LRF ± DF in patients who did not receive systemic treatment was 16.3% (13 of 80 patients) compared with 7.5% (eight of 107 patients), 7.7% (five of 66 patients), and 8.6% (five of 60 patients) in patients who received systemic adjuvant chemotherapy, adjuvant tamoxifen, or both, respectively (Table 3). However, the number of events was small, and these differences were not statistically significant. Most patients with ≥ 5-cm N0 tumors would now receive systemic treatment.[8] Therefore, with systemic therapy, the overall LRF ± DF rate without PMRT in our study would be in the range of 6% to 7.7%, and the isolated LRF as first event rate would be in the range of 4.6% to 5.6% (Table 3). This rate is low enough that the benefit from routine PMRT might not outweigh its potential adverse effects. Furthermore, it is possible that a majority of this population might be treated with neoadjuvant chemotherapy because there would be a better chance for them under that circumstance to undergo conservative surgery.[35] To identify these low-risk patients, it might be reasonable for them to undergo up-front sentinel-node surgery; if the node is negative, the patient might not require PMRT or regional radiation if conservative approaches are used. A recent meta-analysis[36] suggested that an absolute reduction in LRF rate of approximately 20% is needed to improve survival by approximately 5%. Thus, it is unlikely that PMRT in this population will yield a significant improvement in survival.

In conclusion, the locoregional recurrence rate in this small population of node-negative patients with large tumors is lower than what radiation oncologists have perceived.[3] We found no statistically significant risk factors for locoregional recurrence in this study. These data should be interpreted with caution because of the small number of patients and events and because LVI, grade, and margins were not among the factors that were included in our database, but the data suggest that pathologic tumor size alone, in the absence of positive LNs, should not be a basis for PMRT.

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