Int. J. Radiation Oncology Biol. Phys., Vol. 62, No. 4, pp. 1035–1039, 2005

0360-3016/05/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2004.12.014

CLINICAL INVESTIGATION **Breast**

LOCOREGIONAL RECURRENCE RATES AND PROGNOSTIC FACTORS FOR FAILURE IN NODE-NEGATIVE PATIENTS TREATED WITH MASTECTOMY: IMPLICATIONS FOR POSTMASTECTOMY RADIATION

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Purpose: Postmastectomy radiation therapy (PMRT) reduces locoregional recurrence (LRR) of breast cancer. Survival appears improved in patients at higher risk for LRR. This study addresses whether subsets of node-negative patients with sufficiently high risk of LRR might benefit from PMRT.

Methods: Retrospective analysis of a cohort of 877 cases of node-negative breast cancer treated with mastectomy, without adjuvant radiation, from 1980 to 2000.

Results: Median follow-up was 100 months. Ten-year cumulative incidence of LRR as first event was 6.0%. Size greater than 2 cm, margin less than 2 mm, premenopausal status, and lymphovascular invasion (LVI) were independently significant prognostic factors. Ten-year LRR was 1.2% for those with 0 risk factors, 10.0% for those with 1 risk factor, 17.9% for those with 2 risk factors, and 40.6% for those with 3 risk factors. The chest wall was the site of failure in 80% of patients.

Conclusion: Postmastectomy radiation therapy has not been recommended for node-negative patients because the LRR rate is low in that population overall. This study suggests, however, that node-negative patients with multiple risk factors, including close margins, T2 or larger tumors, premenopausal status, and LVI, are at higher risk for LRR and might benefit from PMRT. Because the chest wall is the most common site of failure, treating the chest wall alone in these patients to minimize toxicity is reasonable. © 2005 Elsevier Inc.

Breast cancer, Radiation therapy, Node negative, Local failure, Mastectomy.

INTRODUCTION

Multiple retrospective and prospective studies have shown that postmastectomy radiation therapy (PMRT) leads to a statistically significant reduction in locoregional recurrence (LRR) of breast cancer by approximately two thirds (1). Recent randomized trials as well as a large meta-analysis have indicated that survival is also improved in patients who are at higher risk for LRR (2–5).

Postmastectomy radiation therapy has generally not been recommended in node-negative patients who have undergone mastectomy, in light of the low LRR rates in that group as a whole (6). Yet, axillary nodal involvement, although clearly an important prognostic factor, is not the sole predictor of LRR in breast cancer patients. Indeed, the American Society of Clinical Oncology's PMRT guidelines consider size as another potential risk factor, insofar as they recommend PMRT in all node-positive women with T3 tumors, including the controversial group of patients with only 1 to 3 positive lymph nodes. Still, little support currently exists for the role of PMRT in node-negative women, regardless of tumor size or other prognostic factors. Previous studies have failed to show benefit from PMRT in node-negative women (7), but these studies failed to select for the subgroups of node-negative women at highest risk for LRR.

Retrospective studies have identified a number of potential prognostic factors for LRR after mastectomy other than nodal status. Such prognostic factors include not only tumor size but also vessel invasion and margin status (8–12). Unfortunately, the absolute rates of LRR in node-negative women with these adverse prognostic factors have not been as well documented. Recent data suggests that even node-negative women with certain other adverse prognostic factors may have LRR risks in excess of 20% (10).

This study seeks to document the prognostic factors for LRR in node-negative patients after mastectomy, as well as

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These results were presented in preliminary form as an oral presentation at the 2003 annual ASTRO meeting in Salt Lake City, UT.

Received Nov 10, 2004, and in revised form Dec 14, 2004. Accepted for publication Dec 14, 2004.

the absolute risks of LRR in patients identified to be at higher risk, to identify whether a subset of node-negative patients might be at sufficiently high risk of LRR that PMRT might be of benefit.

METHODS AND MATERIALS

This article presents the retrospective analysis of a cohort of 877 cases of node-negative invasive breast carcinoma in 870 patients treated at Massachusetts General Hospital between 1980 and 2000. Treatment consisted of mastectomy and axillary nodal dissection. No patients received PMRT. Patients with T4 tumors were excluded from this series.

Patients who met these criteria were identified through the hospital tumor registry and breast center databases, in an attempt to include all possible cases that were treated at the institution during the study period. Hospital and clinic charts were then reviewed to obtain information regarding a number of potential clinical and pathologic prognostic factors, as listed in Table 1, as well as clinical outcomes in follow-up. This study was approved by the appropriate institutional review board.

Cases in which information regarding a particular prognostic feature was not available were excluded from analyses that included that feature as an independent variable. The exception was analysis based on lymphovascular invasion (LVI). After discussion with the senior pathologist who personally examined the majority of the breast cancer slides in this series, we decided that pathologists routinely examined the slides to determine whether LVI was present throughout the time period of this study. In the earlier years of the study, the tendency was only to record LVI when present and not document its absence. Because LVI was routinely sought and recorded when present, we analyzed the cases in which LVI was not recorded as part of the same group as those in whom it was recorded as absent.

The rates of "isolated" LRR (LRR as the first event, without evidence of distant metastases for at least 4 months after the date of LRR) and "total" LRR (LRR as first event, with or without simultaneous distant metastases) were calculated by both Kaplan-Meier and cumulative incidence frequency (CIF) analysis, and a number of characteristics were examined as potential prognostic factors. Multivariate analysis was performed by application of a Cox proportional-hazards model. All factors that were statistically significant on univariate analysis were included in the initial model, and then those that did not achieve a significance of $p < 0.05$ were removed stepwise until the remaining factors were all found to be statistically significant at the 0.05 level. R version 1.9.1 (The R Project for Statisitcal Computing, Vienna, Austria) was utilized for the cumulative incidence frequency analyses, and SAS version 8.2 (SAS, Cary, NC) was utilized for the remainder of the analyses.

RESULTS

The median follow-up was 100 months, with a median patient age of 64. The median number of lymph nodes examined was 15. Adjuvant systemic treatment was utilized in a subset of 276 cases, whereas no form of systemic treatment was administered in the other 601 cases. Of the 276 cases that received systemic therapy, 148 received hormonal therapy alone, 74 received chemotherapy alone, and 54 received both chemotherapy and hormonal therapy. Table 1 summarizes the characteristics of the case population.

Table 1. Patient characteristics

	Number
Menopausal status	
Premenopausal	165
Postmenopausal	584
Unknown	128
Margin status	
Positive	19
Close (≤2 mm)	45
Negative (>2 mm)	662
Unknown	151
Tumor stage	
T1	461
T2	296
T3	25
Unknown	95
Lymphovascular invasion	
Present	59
Absent	215
Not described	603
Systemic treatment	
Hormonal therapy alone	148
Chemotherapy alone	74
Both chemo and hormones	54
Neither chemo nor hormones	601

The proportion of isolated LRR in the entire cohort was 32 of 877, and the proportion of total LRR was 46 of 877. The cumulative incidence of "isolated" LRR at 10 years was 4.3% and the cumulative incidence of "total" LRR was 6.0% in the entire node-negative cohort. The chest wall was the site of failure in the vast majority of these cases: 87.5% of the "isolated" failures and 80.4% of the "total" failures. Site of failure is documented in Table 2.

A number of potential prognostic factors were then examined. Because the differences between "isolated" and "total" LRR rates were minimal, only "total" LRR rates are presented here. As shown in Fig. 1, menopausal status was significantly correlated to LRR rates, with 10-year cumulative incidence rates of 11.1% in premenopausal patients compared with 5.1% in postmenopausal patients ($p = 0.01$).

Table 2. Sites of failure

	Number of isolated locoregional recurrences (%)	Number of total locoregional recurrences (%)
Chest wall	28 (87.5%)	37 (80%)
Axilla	2 (6%)	3 (7%)
Supraclavicular region	1 (3%)	5 (11%)
IMC	1 (3%)	1 (2%)
Total	32 (100%)	46 (100%)

Abbreviation: IMC = internal mammary chain.

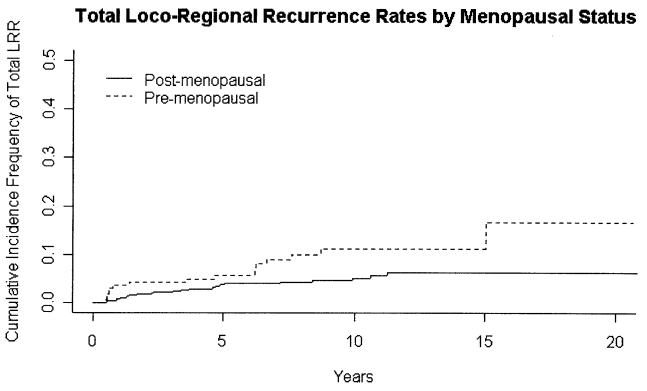

Fig. 1. Premenopausal patients had a higher rate of locoregional recurrence ($p = 0.01$, log-rank).

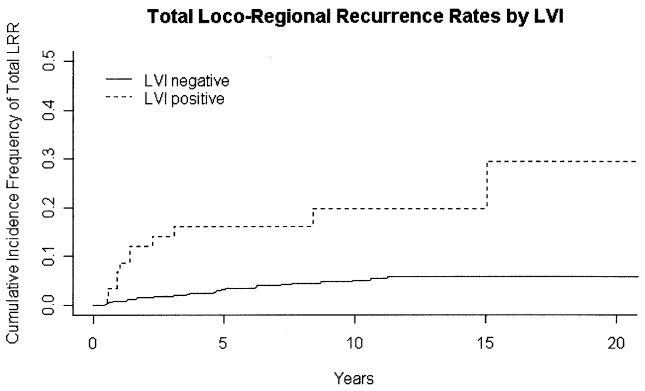

Fig. 3. Patients in whom lymphovascular invasion was identified had a higher rate of locoregional recurrence ($p = 0.0001$, log-rank).

Figure 2 shows that pathologic deep-margin status was strongly correlated with LRR. Patients with negative margins had a 10-year LRR of 5.1%, as compared with 22% in patients with close margins and 21% in patients with positive margins ($p < 0.001$). Lymphovascular invasion (LVI) was also significantly correlated with LRR, with 10-year LRR of 19.8% in patients documented to have LVI compared with 5.0% in the other patients ($p = 0.0001$), as shown in Fig. 3.

Tumor size was correlated to LRR, with 10-year LRR rates of 11% in patients with tumors greater than 2 cm vs. 3.1% in patients with tumors up to 2 cm in size ($p = 0.001$), as shown in Fig. 4. Pathologic grade was also correlated to LRR, with 10-year LRR of 0% in patients with Grade 1 tumors, 5.3% in patients with Grade 2 tumors, and 10% in patients with Grade 3 tumors ($p = 0.03$).

When cases treated with systemic therapy were compared as a group against those that were not treated with systemic therapy, no statistically significant difference was seen ($p = 0.37$). When the systemic therapy cases were broken down into subgroups based on type of systemic therapy, a statistically significant difference was seen, with 10-year actuarial rates of failure of 6.5% in the group that received no systemic therapy, 4% in the group that received chemotherapy alone, 2.4% in the group that received hormonal therapy alone, and 12.6% in the group that received both treatments ($p = 0.04$).

Multivariate analysis by a Cox proportional-hazards model revealed that only size, margin, LVI, and menopausal status were independently significant predictors of LRR. The hazard ratios for the 4 risk factors identified were similar, as shown in Table 3.

The rates of LRR with 0, 1, 2, or 3 risk factors are shown in Fig. 5. The 10-year LRR rate was 1.2% ± 0.9% for those with 0 risk factors, 10.0% ± 2.9% for those with 1 risk factor, 17.9% ± 7.5% for those with 2 risk factors, and 40.6% ± 13.8% for those with 3 risk factors. Only 1 patient had all 4 risk factors, and this patient experienced an isolated LRR.

DISCUSSION

Adjuvant radiation therapy has not been routinely recommended for node-negative patients after mastectomy because the rate of LRR has been low in that population as a

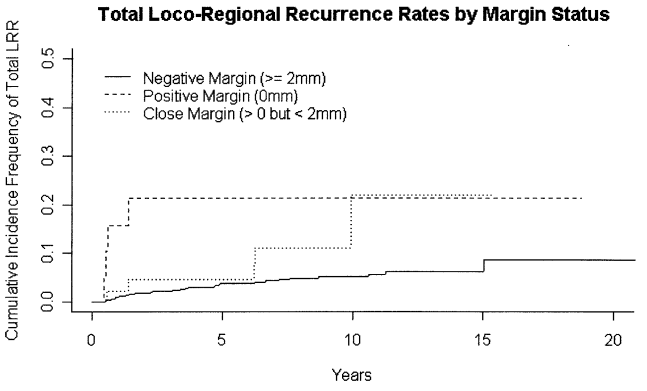

Fig. 2. Patients with close or positive deep margins of resection (<2 mm) had a higher rate of locoregional recurrence ($p < 0.001$, log-rank).

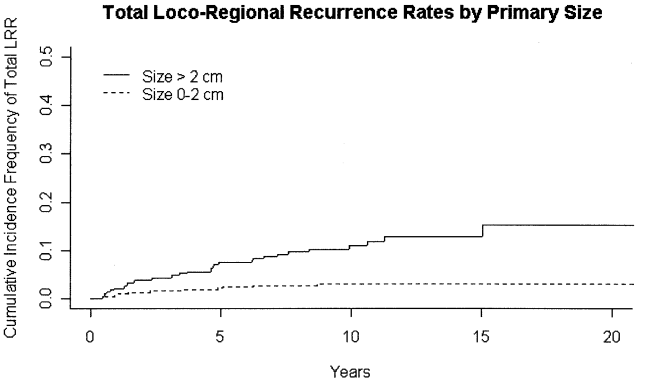

Fig. 4. Patients with larger tumors had a higher rate of locoregional recurrence ($p = 0.001$, log-rank).

Table 3. Multivariate analysis

	Hazard ratio	*p* Value
Margin (≥2 mm vs. <2 mm)	2.6	0.0210
Menopausal status (pre vs post)	2.8	0.0051
Size (>2 cm vs. ≤2 cm)	3.8	0.0024
Lymphovascular invasion (positive vs. negative)	3.2	0.0088

whole. This study confirms the low overall rates of LRR in node-negative patients treated with mastectomy.

This study also suggests, however, that a subset of even node-negative patients exist who are at higher risk for LRR, for whom further treatment such as PMRT might be considered. Strikingly, this study found LRR rates well in excess of 30% when node-negative patients had 3 or more of the identified risk factors for recurrence. Thus, to only consider nodal involvement when determining whether to proceed with measures to reduce LRR seems overly simplistic.

The recent analysis of 1,275 node-negative women treated on the International Breast Cancer Study Group (IBSCG) protocols found size, LVI, and menopausal status to be predictive of failure (10). The influence of margin status could not be assessed by the IBSCG investigators because of the exclusion of patients with positive margins from their trials. Other investigators, however, including those in 2 other single institutional studies that worked with smaller numbers of node-negative patients, (9, 11) have identified the importance of margin status as a predictor of LRR. This study emphasizes the quantification of risk of recurrence by using multiple factors.

Absolute quantification of LRR rates is important because different clinicians have different thresholds for recommending PMRT, and patients should be given as much information as possible to allow them to balance the risks and benefits of treatment in their own cases. In light of the randomized studies (2–4) that showed a 9% absolute increase in survival from PMRT in patients with positive nodes and T3 tumors whose LRR rates approached 30%, a consideration of PMRT in node-negative patients with a similar risk of LRR seems reasonable. Our study shows that node-negative patients with 3 or more risk factors appear to have similar risk of LRR as the node-positive patients included in the randomized trials that showed a survival advantage with PMRT.

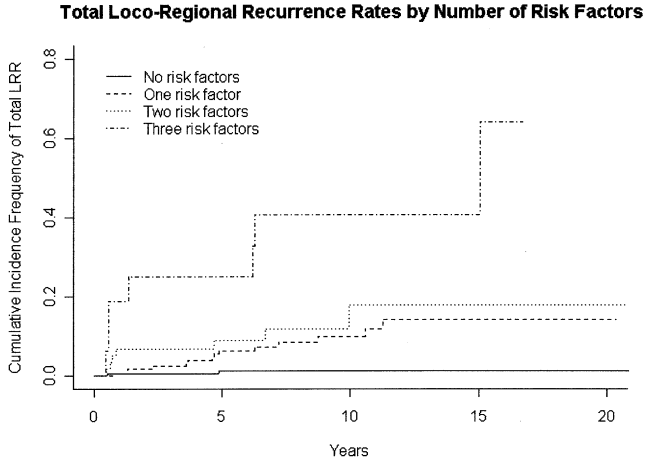

Fig. 5. Risk of locoregional recurrence increased with increasing number of risk factors ($p < 0.0001$, log-rank).

This study has certain limitations, however. Many patients in this study were treated before the era in which chemotherapy and hormonal therapy were routinely employed. To the extent that the systemic therapy now commonly employed may reduce LRR rates, the risks faced by the patients in this study may be higher than the risks faced by patients who uniformly receive systemic therapy.

Published findings regarding the effect, if any, of systemic therapy upon LRR after mastectomy are mixed. Of the 2 other large studies of LRR in node-negative patients treated with mastectomy, the M. D. Anderson study, which included 141 node-negative patients, included adjuvant chemotherapy (9). In the IBSCG study, patients received either no chemotherapy or only 1 cycle of perioperative chemotherapy on trial (10). Unfortunately, the M. D. Anderson study, which also included a large number of node-positive patients, did not report individual absolute LRR rates for their node-negative subset. Furthermore, the patients who received chemotherapy in that era for node-negative disease may have had more aggressive disease than those who would receive chemotherapy today. Therefore, data regarding the absolute risks of LRR in node-negative patients treated with mastectomy and systemic therapy are not available. Systemic therapy was utilized in only a minority of patients in this study, and selection bias almost certainly plays a role in explaining the higher rate of LRR in the group that received both chemotherapy and hormonal therapy in our series. Thus, definitive conclusions regarding the impact of systemic therapy based upon these results are not possible. Because systemic therapy has become more widespread in recent years, future studies will be better able to address this question, as more recent cohorts of patients mature.

The statistical analysis in this study was performed by application of both Kaplan-Meier and cumulative incidence frequency estimates. The 2 methods differ in the way in which competing events are treated. Because competing events such as distant failure are censored in Kaplan-Meier analyses, thereby reducing the denominator from which the LRR rates are calculated, the concern has been raised that Kaplan-Meier analysis may overestimate the risk of LRR. Because of the considerable debate on this point (13), and because the other 2 large studies of LRR in node-negative patients after mastectomy have differed in the statistical methods used, we initially analyzed the data by both methods. In cases such as that of node-negative patients who have undergone mastectomy, the risks of competing events is low, so that the difference between the 2 methods was expected to be relatively insignificant. This expectation was

ultimately the case, with the Kaplan-Meier results generally slightly higher but not substantially different from the CIF estimates. Therefore, only the CIF results are actually presented in this manuscript.

In summary, this study suggests that although LRR is uncommon in node-negative patients as a whole, a subset of node-negative patients appears to be at sufficiently high risk of LRR that PMRT might be beneficial. Relevant factors that should be considered in addition to axillary involvement include tumor size, vessel invasion, margin status, and menopausal status. Specifically, physicians should consider PMRT for postmenopausal patients with all 3 of the other risk factors: T2 or larger tumors, close or positive margins, and LVI. For premenopausal patients with any 2 of the other 3 risk factors, PMRT should be considered. Because the chest wall was by far the most common site of failure in this study, treatment of the chest wall, without regional lymph nodes, in the subsets of patients identified as higher risk, may be reasonable. The side effects of PMRT might thus be minimized.

While research is ongoing to identify biomarkers that will one day allow us to tailor our therapies in response to highly accurate predictions of risk for failure (14–16), we must muddle through for the time being with the best estimates that can be devised from the clinical and pathologic factors currently discernible. By including a larger number of factors in our assessments, we may improve the accuracy of our risk estimates and, thereby, formulate more appropriate treatment recommendations. Studies such as this one are useful in refining models for risk estimation.

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