Int. J. Radiation Oncology Biol. Phys., Vol. 62, No. 4, pp. 1035–1039, 2005
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0360-3016/05/$–see front matter

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.

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