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CLINICAL INVESTIGATION **Breast**

PREDICTORS OF LOCOREGIONAL RECURRENCE IN PATIENTS WITH LOCALLY ADVANCED BREAST CANCER TREATED WITH NEOADJUVANT CHEMOTHERAPY, MASTECTOMY, AND RADIOTHERAPY

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Purpose: To identify the clinical and pathologic factors predictive of locoregional recurrence (LRR) after neoadjuvant chemotherapy, mastectomy, and radiotherapy.

Methods and Materials: We retrospectively reviewed the hospital records of 542 patients treated on six consecutive institutional prospective trials using neoadjuvant chemotherapy and postmastectomy radiotherapy. The clinical stage (American Joint Committee on Cancer, 1988) was Stage II in 17%, Stage IIIA in 30%, Stage IIIB in 43%, and Stage IV (ipsilateral supraclavicular disease) in 10%. All LRRs were considered events, irrespective of the timing to distant metastases.

Results: The median follow-up was 70 months. The 5-year and 10-year actuarial LRR rate was 9% and 11%, respectively. The clinical factors associated with LRR included combined clinical stage, clinical T stage, ipsilateral supraclavicular nodal disease, chemotherapy response, physical examination size after chemotherapy, and no tamoxifen use ($p \leq 0.04$ for all factors). The pathologic predictors of LRR included the number of positive nodes, dissection of <10 nodes, multifocal/multicentric disease, lymphovascular space invasion, extracapsular extension, skin/nipple involvement, and estrogen receptor-negative disease ($p \leq 0.05$ for all factors). Multivariate Cox regression analysis revealed that five factors independently predicted for LRR: skin/nipple involvement, supraclavicular nodal disease, no tamoxifen use, extracapsular extension, and estrogen receptor-negative disease (hazard ratio, 2.1–2.8; $p \leq 0.02$ for all factors). The 10-year LRR rate was only 4% for patients with one or none of these five independent factors, 8% for those with two factors, and 28% for those with three or more factors ($p < 0.0001$).

Conclusion: Although the long-term rate of LRR after neoadjuvant chemotherapy, mastectomy, and radiotherapy is low, we identified a number of factors that correlated independently with greater rates of LRR. Patients with three or more of these factors may benefit from research protocols investigating alternative treatment strategies.

Neoadjuvant chemotherapy, Locoregional recurrence, Breast cancer.

INTRODUCTION

We recently presented the first large series of data regarding the efficacy of postmastectomy radiotherapy (RT) in the setting of neoadjuvant chemotherapy (1). In a retrospective analysis of 713 patients treated on six consecutive institutional trials using doxorubicin-based neoadjuvant chemotherapy and mastectomy, the addition of RT reduced the 10-year rate of locoregional recurrence (LRR) from 22% to 12% ($p < 0.0001$). Although the rate of LRR after RT was low in the entire population, some subgroups of patients with specific risk factors may be at greater risk of developing LRR. The identification of such subgroups would be of clinical benefit in that alternative locoregional treatment strategies could be investigated.

The clinical and pathologic predictors of LRR have al-

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Table 1. Neoadjuvant chemotherapy regimens

Protocol	Study years	Neoadjuvant chemotherapy regimen	Cycles (*n*)	Patients (*n*) CHT + M + RT	Patients (*n*) Total study population*
Advanced primary	1974–1985	FAC	3	91	191
85-01	1985–1989	VACP	3	141	200
89-007	1989–1991	FAC	4	104	203
91-015	1991–1994	FAC or dose-escalated FAC	4	101	202
94-002	1994–1998	FAC or paclitaxel	4	41	174
97-099	1998–2000	AT	6	64	88
Total	1974–2000			542	1058

Abbreviations: CHT + M + RT = neoadjuvant chemotherapy, mastectomy, and radiotherapy (population analyzed in current study); FAC = 5-fluorouracil, doxorubicin, cyclophosphamide; VACP = vincristine, doxorubicin, cyclophosphamide, and prednisone; AT = doxorubicin, docetaxel.

* Total study population included other patients not analyzed in this paper, such as those receiving breast-conserving surgery with or without RT.

ready been identified in patients treated with initial surgery followed by adjuvant chemotherapy (2–6). However, for patients treated with neoadjuvant chemotherapy and postmastectomy RT, no data have been published identifying the risk factors for LRR. As neoadjuvant chemotherapy has become a common treatment approach, particularly for patients with intermediate or advanced locoregional disease, data regarding the risk factors for LRR are urgently needed. It is likely that these risk factors will be different from those determined from patients treated with adjuvant chemotherapy. Specifically, for patients treated with surgery first, the extent of disease is assessed pathologically. In contrast, for patients treated with chemotherapy first, the disease extent is assessed both clinically (before treatment) and pathologically (after chemotherapy). In this study, we analyzed a series of 542 women treated with neoadjuvant chemotherapy, mastectomy, and RT to identify the clinical and pathological factors predictive of LRR.

METHODS AND MATERIALS

Patient population

We retrospectively analyzed the data of patients treated on six consecutive institutional prospective trials conducted at the University of Texas M. D. Anderson Cancer Center (Houston, TX) between 1974 and 2000. These trials investigated the role of neoadjuvant chemotherapy for patients with nonmetastatic, noninflammatory breast cancer (Table 1). The institutional review board approved each protocol, and participating patients gave written informed consent. The review board also approved this analysis.

Of the patients enrolled into these prospective trials, 713 underwent mastectomy with (n = 579) or without (n = 134) RT; a comparison of their outcomes has been previously reported (1). For this analysis, we studied only the 542 patients who underwent postmastectomy RT (Table 2), excluding the 37 patients who required preoperative RT for extensive residual disease after chemotherapy.

All patients underwent clinical staging according to the TMN classification and the staging system set by the American Joint Committee on Cancer in 1988. The clinical stage at diagnosis was Stage II in 17%, Stage IIIA in 30%, Stage IIIB in 43%, and Stage IV (ipsilateral supraclavicular [SCV] lymph node disease) in 10%. Only patients without systemic metastases were eligible for these trials.

Treatment details

Table 1 shows the neoadjuvant chemotherapy regimens that the patients received. All patients received doxorubicin as part of a combination chemotherapy regimen, with 15% also receiving a taxane. The details regarding these regimens have been published in earlier reports (7–9). In brief, 5-fluorouracil, Adriamycin (doxorubicin), and cyclophosphamide (FAC) chemotherapy was given, consisting of 500 mg/m^2 5-fluorouracil given on Days 1 and 4 or Days 1 and 8, 50 mg/m^2 doxorubicin given as a Day 1 bolus or as a 48–72-h continuous infusion, and 500 mg/m^2 cyclophosphamide given on day 1. For those who received dose-escalated FAC, the corresponding doses of these drugs were increased to 600, 60, and 1000 mg/m^2. The VACP regimen consisted of 1.5 mg/m^2 of vincristine, 60–75 mg/m^2 of doxorubicin, 600–750 mg/m^2 of cyclophosphamide, and 40 mg of prednisone. Finally, the doxorubicin and docetaxel regimen consisted of 60 mg/m^2 of doxorubicin and 60 mg/m^2 of docetaxel given as intravenous boluses. The chemotherapy regimens were administered every 3 weeks.

For this article, we limited our study to the patients in these trials who were treated with both mastectomy and RT. These treatment modalities were not randomized variables in the prospective trials. The decision to undergo RT and mastectomy (rather than breast-conserving surgery) were determined by the patient and her physicians, and thus were subject to selection biases.

In our study population, the median number of recovered axillary lymph nodes after mastectomy was 15. With respect to RT, the treatment volumes included the chest wall and draining lymphatics (median dose, 50 Gy), followed by a chest wall boost (median dose, 10 Gy). Typically, the draining lymphatics were treated using two separate appositional fields, one targeting the supraclavicular fossa/axillary apex and the second targeting the internal mammary chain. A posterior boost supplementing the high axilla was used only in selected patients, such as those who had undergone inadequate axillary dissection. The volume of the chest wall boost typically treated the mastectomy scar with a margin around the scar of at least 5 cm. RT was delivered at an outside institution for 94 patients.

Table 2. Patient, tumor, and treatment characteristics (n = 542)

Characteristic	Value
Age (y)	
Median	50
Interquartile range	41–57
≤40	131 (24)
41–50	150 (28)
51–60	178 (33)
>60	83 (15)
Clinical T stage*	
T1	13 (2)
T2	73 (14)
T3	195 (36)
T4	261 (48)
Clinical N stage*	
N0	97 (18)
N1	213 (39)
N2	217 (40)
N3	15 (3)
Clinical stage*	
IIA	8 (2)
IIB	83 (15)
IIIA	164 (30)
IIIB	233 (43)
IV	54 (10)
Neoadjuvant chemotherapy regimen	
FAC (3 cycles)	91 (17)
VACP (3 cycles)	141 (26)
FAC (4 cycles)	104 (19)
FAC or dose-escalated FAC (4 cycles)	101 (19)
FAC or paclitaxel (4 cycles)	41 (8)
AT (6 cycles)	64 (12)
Response to neoadjuvant chemotherapy	
CR	78 (14)
PR	354 (65)
MR	88 (16)
NC	16 (3)
PD	6 (1)
Pathologic size (cm)	
Median	2.4
Interquartile range	0.5–4
≤1	176 (32)
1.1–2	79 (15)
2.1–3	95 (18)
3.1–4	70 (13)
4.1–5	44 (8)
>5	75 (14)
Unknown	3 (1)
Positive lymph nodes (n)	
Median	2
Interquartile range	0–6
0	141 (26)
1–3	185 (35)
4–9	138 (25)
≥10	73 (13)
Unknown	5 (1)
Lymph nodes sampled (n)	
Median	15
Interquartile range	10–19
<10	99 (18)
≥10	443 (82)
Positive lymph nodes	
<20%	281 (52)
≥20%	255 (47)
Unknown	6 (1)
Margin status	
Free/negative	477 (88)
Involved/positive	19 (4)
Close	41 (8)
Unknown	5 (1)
Estrogen receptor status	
Positive	240 (44)
Negative	213 (40)
Unknown	89 (16)
Hormonal treatment	
Yes	172 (32)
No	356 (66)
Unknown	14 (3)

Abbreviations: FAC = 5-fluorouracil, doxorubicin; cyclophosphamide; VACP = vincristine, doxorubicin, cyclophosphamide, prednisone; AT = doxorubicin, docetaxel; CR = complete response; PR = partial response; MR = minimal response; NC = no change; PD = progressive disease.

Data presented as number of patients, with percentages in parentheses, unless otherwise noted; because of small differences in rounding numbers, percentages do not always equal 100%.

* 1988 American Joint Committee on Cancer TNM classification and staging system.

In addition to neoadjuvant chemotherapy, mastectomy, and RT, 516 patients (95%) received adjuvant chemotherapy. These chemotherapy regimens changed during the period of the clinical trials and initially began with FAC (similar to the preoperative regimen). Subsequently, adjuvant cyclophosphamide, methotrexate, and 5-fluorouracil was investigated. Thereafter, either vinblastine and methotrexate or vinblastine, methotrexate, and 5-fluorouracil was used. Finally, the most recent approach adopted for this cohort investigated the use of taxanes. Additionally, 172 patients (32%) were also treated with adjuvant tamoxifen. During the period of these trials, tamoxifen use was limited to postmenopausal women with estrogen receptor (ER)-positive disease.

Statistical analysis

Locoregional recurrence was defined as disease recurrence on the ipsilateral chest wall or in the ipsilateral axillary, supraclavicular, infraclavicular, or internal mammary lymph nodes. Any other site of recurrence was considered distant metastasis. For this analysis, all LRRs were considered as events, irrespective of their timing relative to the development of distant metastases. All survival statistics were measured from the date of diagnosis. The actuarial rates of LRR were calculated according to the Kaplan-Meier method, and comparisons were made using the log–rank test (10). The clinical and pathologic factors that were statistically significant (two-tailed $p \leq 0.05$) on univariate analysis of LRR were included in a multivariate analysis using the Cox proportional hazards regression model (10).

RESULTS

The median follow-up period was 70 months. The 5-year and 10-year actuarial LRR rate was 9% and 11%, respectively. Table 3 summarizes the patterns of LRR and shows that most failures occurred on the chest wall or in the SCV

Table 3. Sites of locoregional recurrence

Site	Isolated first recurrences* (*n*)	Total recurrences†‡	
		n	%
Chest wall	16	34	68
Supraclavicular	6	16	32
Axilla	1	3	6
Infraclavicular	0	4	8
Internal mammary	0	1	2
Any site	22	50	100

* Those who presented as first site of failure without any evidence of distant metastases.

† Included both isolated first recurrences and locoregional recurrences discovered after, or simultaneously with, distant metastases.

‡ Percentages represent fraction of total locoregional recurrences that included specific site as a component of recurrence; because some patients experienced more than one site of recurrence, percentages do not total 100%.

lymph nodes (68% and 32%, respectively). Axillary, infraclavicular, and internal mammary lymph node failures as a component of LRR were relatively rare (≤8%).

Table 4 shows the LRR rates according to various clinical factors. The factors that significantly correlated with greater rates of LRR were as follows: combined clinical stage, clinical T stage, SCV nodal involvement, physical examination size after chemotherapy, clinical response to neoadjuvant chemotherapy, and no tamoxifen use.

Table 5 shows the rates of LRR according to the pathologic factors. The factors that were significantly associated with LRR were multifocal/multicentric disease, number of positive axillary nodes, axillary dissection of <10 nodes, lymphovascular space invasion, extracapsular extension, skin or nipple involvement, and ER-negative disease. Patients who achieved a pathologic complete response had a lower rate of LRR (2% vs. 12%), but this factor was not statistically significant ($p = 0.08$).

In a multivariate Cox regression analysis of LRR (Table 6), five factors were independently associated with developing LRR: skin/nipple involvement, SCV nodal involvement, no tamoxifen use, extracapsular extension, and ER-negative disease (hazard ratio, 2.1–2.8; $p = 0.001$–0.020). The 10-year rate of LRR for the 200 patients (37% of the population) with one or none of these five independent factors was only 4%, but the 202 patients (37% of the population) with two factors had a rate of 8%, and the 140 patients (26% of the population) with three or more factors had a rate of 28% ($p = 0.13$ for 0–1 factor vs. 2 factors; $p < 0.0001$ for 0–1 factor vs. 3–5 factors; and $p < 0.0001$ for 2 factors vs. 3–5 factors; Fig. 1).

DISCUSSION

This series identified the clinical and pathologic predictors of LRR after neoadjuvant chemotherapy, mastectomy, and RT. Although the overall rate of LRR was low (11% at 10 years), we were able to identify several factors that predicted for LRR: skin/nipple involvement, SCV nodal involvement, no tamoxifen use, extracapsular extension, and ER-negative disease.

Recent data have indicated that achievement of locoregional control is an important determinant of survival (11–15). Most data suggesting that locoregional treatment can improve survival have been obtained from patients treated with mastectomy with or without RT and adjuvant chemotherapy. However, we recently reported that the use of RT after mastectomy might achieve a similar survival benefit for selected subgroups of patients treated with neoadjuvant chemotherapy (1).

In this study, we demonstrated that multimodality therapy can achieve long-term locoregional control for most patients with locally advanced breast cancer. Specifically, 74% of our population had two or fewer LRR risk factors and the 10-year LRR in this subgroup was <8%. However, we were able to identify certain patients who remain at especially

Table 4. Locoregional recurrence rates according to clinical factors

Factor	10-y Rate	*p*
Neoadjuvant chemotherapy protocol	—	NS
Race	—	NS
Contralateral breast cancer before diagnosis	—	NS
Bilateral cancers at diagnosis	—	NS
Combined stage (1988 AJCC)		0.003
II	6	
IIIA	9	
IIIB	12	
IV	21	
T stage		0.04
T1–T2	7	
T3	8	
T4	14	
N stage	—	NS
Supraclavicular nodal involvement		0.001
No	10	
Yes	21	
Physical examination size at diagnosis (cm)	—	NS
Physical examination size after chemotherapy (cm)		<0.0001
0–2.0	9	
2.1–5.0	7	
5.1–9.9	23	
≥10.0	47	
Clinical response to neoadjuvant chemotherapy		0.008
CR	6	
PR	10	
MR	17	
NC	17	
PD	58	
Hormonal therapy		0.008
Yes	5	
No	13	

Abbreviations: NS = not significant; AJCC = American Joint Committee on Cancer; other abbreviations as in Table 2.

Table 5. Locoregional recurrence rates according to pathologic factors

Factor	10-y Rate	*p*
Histologic type	—	NS
Nuclear grade	—	NS
Multifocal/multicentric		0.05
No tumor	3	
Single tumor	9	
Multicentric-microscopic only	13	
Multifocal-gross	16	
Multifocal-microscopic only	25	
Multicentric-gross	30	
Pathologic CR		NS (0.08)
Yes	2	
No	12	
Pathologic size	—	NS
Positive lymph nodes		0.006
0	4	
1–3	11	
≥4	16	
Axillary lymph nodes sampled (*n*)		0.004
0–9	19	
≥10	9	
Margin status	—	NS
Lymphovascular space invasion		0.02
Absent	5	
Present	15	
Unknown	13	
Extracapsular extension		0.0002
Absent	6	
Present (any extent)	15	
Unknown	22	
Perineural invasion	—	NS
Chest wall or pectoral fascia invasion	—	NS
Skin or nipple involvement		0.0002
Absent	7	
Present	19	
Unknown	11	
Estrogen receptor status		0.04
Negative	15	
Positive	10	
Unknown	5	
Progesterone receptor status	—	NS
Her-2 neu status	—	NS

Abbreviations: NS = not significant; CR = complete response.

high risk of recurrence. Our data showed that patients with three or more risk factors (26% of our study population) had a LRR rate of 28%, despite receiving comprehensive standards of conventional chemotherapy, surgery, and RT.

The need for data such as those reported in this study has become increasingly important. Neoadjuvant chemotherapy is becoming an increasingly popular treatment strategy for patients with Stage II or III breast cancer. Although other studies have investigated predictors of LRR after postmastectomy RT, this is the first study to evaluate this question in patients treated with neoadjuvant chemotherapy. Investigating predictors of outcome in the setting of neoadjuvant chemotherapy is inherently more complex than similar studies investigating patients treated with adjuvant chemotherapy. This is because for patients treated with chemotherapy first, it is important to consider the disease extent both at

Table 6. Multivariate analysis of locoregional recurrence

Factor	Hazard ratio	95% Confidence interval	*p*
Skin or nipple involvement	2.8	1.5–5.2	0.001
Supraclavicular nodal involvement	2.7	1.3–5.6	0.009
No tamoxifen use	2.7	1.2–6.0	0.019
Extracapsular extension	2.1	1.1–4.0	0.020
Estrogen receptor negative disease	2.1	1.2–3.7	0.013

diagnosis and again after neoadjuvant treatment. Previously, we had found this to be true for patients treated with neoadjuvant chemotherapy and mastectomy without RT (16). In this study, for patients treated with RT, we also found that both pretreatment and postchemotherapy variables were associated with LRR. For example, the clinical identification of SCV nodal involvement at the initial diagnosis had a high association with developing LRR (hazard ratio of 2.7). In addition, ER-negative disease assessed at diagnosis independently correlated with LRR. With respect to the pathologic variables assessed after neoadjuvant chemotherapy, skin/nipple involvement and extracapsular extension independently predicted for LRR. Finally, we found an association between a lack of tamoxifen use and a greater risk of LRR. However, we do not believe this association has clinical implications. Tamoxifen, or an alternative hormonal treatment, would currently be indicated for all patients with ER-positive disease who require postmastectomy RT, and the data from numerous previous studies have consistently failed to show a clinical benefit of tamoxifen for patients with ER-negative disease (17).

Some of the same factors we identified as significantly correlating with LRR have also been correlated with LRR for patients treated with postmastectomy RT and adjuvant chemotherapy. One such observation concerns ER-negative disease. In a study analyzing the outcome of 470 women

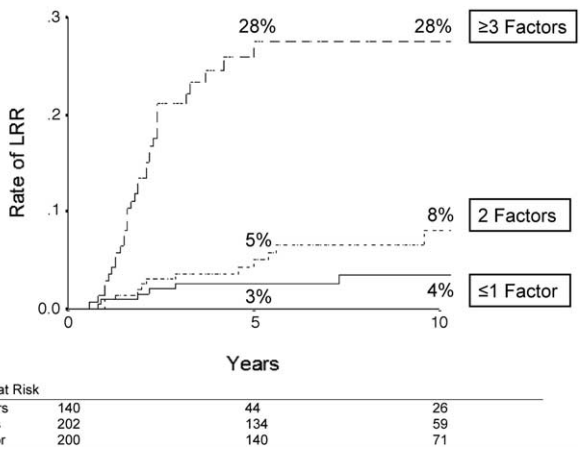

Fig. 1. Locoregional recurrence (LRR) rates according to number of independent risk factors.

treated with postmastectomy RT and adjuvant chemotherapy, we previously found that the presence of ER-negative disease was the strongest predictor for LRR (4). A number of groups have recently demonstrated that ER-negative breast cancer is genetically quite distinct from ER-positive breast cancer (18, 19).

Other factors that have previously been associated with LRR after postmastectomy RT (for patients treated with surgery first) include the presence of $\geq$10 positive axillary nodes (4), young age, increased tumor size, axillary nodal involvement, high nuclear grade, and lymphovascular space invasion (2, 3, 20). Given that most patients have a significant change in their disease extent with neoadjuvant chemotherapy, correlations between the pathologic disease extent and LRR are likely to be significantly different for patients treated with neoadjuvant chemotherapy than for those treated with surgery first. We previously demonstrated this for patients treated with mastectomy without RT (21), and it is very likely that this distinction is also true when assessing LRR after postmastectomy RT.

Our findings are clinically relevant because we identified a relatively small subgroup of patients for whom conventional treatments fail to achieve optimal locoregional disease control. In these patients, investigations should be pursued that explore alternative treatment strategies such as radiation dose escalation or treatment with concurrent radiosensitizing agents. These findings can serve as a tool for selecting which patients may benefit from research protocols investigating such alternative strategies.

CONCLUSION

The long-term rate of LRR is low for most patients with locally advanced breast cancer after multimodality treatment incorporating neoadjuvant chemotherapy, mastectomy, and RT. Despite this low rate, we were able to identify five factors that independently correlated with significantly greater rates of LRR. Patients with three or more of these factors may benefit from research protocols investigating alternative strategies such as radiation dose escalation or treatment with concurrent radiosensitizing agents.

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