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CLINICAL INVESTIGATION

POSTMASTECTOMY RADIATION IMPROVES THE OUTCOME OF PATIENTS WITH LOCALLY ADVANCED BREAST CANCER WHO ACHIEVE A PATHOLOGIC COMPLETE RESPONSE TO NEOADJUVANT CHEMOTHERAPY

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Purpose: **The aim of this study was to investigate the role of postmastectomy radiation therapy in women with breast cancer who achieved a pathologic complete response (pCR) to neoadjuvant chemotherapy.**
Methods and Materials: **We retrospectively identified 226 patients treated at our institution who achieved a pCR at surgery after receiving neoadjuvant chemotherapy. Of these, the 106 patients without inflammatory breast cancer who were treated with mastectomy were analyzed. The patients' clinical stages at diagnosis were I in 2%, II in 31%, IIIA in 30%, IIIB in 25%, and IIIC in 11% (American Joint Committee on Cancer 2003 system). Of the patients, 92% received anthracycline-based chemotherapy, and 38% also received a taxane. A total of 72 patients received postmastectomy radiation therapy, and 34 did not. The actuarial rates of local-regional recurrence (LRR) and survival of the two groups were compared using the log-rank test.**
Results: **The median follow-up of surviving patients was 62 months. Use of radiation therapy did not affect the 10-year rates of LRR for patients with Stage I or II disease (the 10-year LRR rates were 0% for both groups). However, the 10-year LRR rate for patients with Stage III disease was significantly improved with radiation therapy (7.3% ± 3.5% with vs. 33.3% ± 15.7% without; $p = 0.040$). Within this cohort, use of radiation therapy was also associated with improved disease-specific and overall survival.**
Conclusion: **Postmastectomy radiation therapy provides a significant clinical benefit for breast cancer patients who present with clinical Stage III disease and achieve a pCR after neoadjuvant chemothearpy.** **© 2007 Elsevier Inc.**

Neoadjuvant chemotherapy, Pathologic complete response, pCR, Breast cancer, Postmastectomy radiation.

INTRODUCTION

Three randomized trials and three meta-analyses have established that adjuvant radiation therapy improves the outcome of patients with Stage II and III breast cancer treated with mastectomy and systemic therapies (1–6). For example, the Early Breast Cancer Trialists' Collaborative Group demonstrated that for patients with a risk of local-regional recurrence (LRR) after surgery in excess of 10%, the use of radiation therapy can reduce the relative risk of LRR by approximately two thirds and consequently improve overall survival (OS) (6). Historically, the determining factors used to select which patients have a clinically relevant LRR risk after mastectomy for patients treated with surgery first have been the pathologic extent of disease at the primary site and in the axillary lymph nodes at the time of initial surgery (7, 8).

The role of postmastectomy radiation therapy for patients treated with neoadjuvant chemotherapy remains less well studied, and the indications for using radiation after mastectomy are less clear. We previously reported our institutional experience with 150 patients treated with neoadjuvant

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chemotherapy and mastectomy without postmastectomy radiation therapy; we found that advanced clinical stage at presentation, pathologic involvement of four or more lymph nodes at surgery, and lack of tamoxifen use independently predicted for an increased risk of LRR (9). A subsequent comparison of this group of patients with a cohort of 542 patients treated with neoadjuvant chemotherapy, mastectomy, and postmastectomy radiation therapy demonstrated that adding postmastectomy radiation therapy reduced the absolute risk of LRR from 22% to 11%. Postmastectomy radiation therapy was found to enhance local-regional control in patients presenting with Stage IIB or greater disease (American Joint Committee on Cancer 1988 staging system), pathologic residual tumor size >2 cm, and four or more nodes positive at surgery (10).

An intriguing finding of both studies was that the small group of patients who presented with locally advanced disease and achieved a pCR after neoadjuvant chemotherapy, defined as no residual invasive disease in the breast or axilla, still experienced a significant LRR rate when radiation therapy was not used. However, the sample size of these initial analyses was limited. To improve our understanding of the role of postmastectomy radiation therapy for patients who achieve a pCR to neoadjuvant chemotherapy, we report here our updated institutional experience that includes additional patients and evaluates both LRR and survival outcomes. Patients with locally advanced disease are increasingly being treated with neoadjuvant chemotherapy, and newer chemotherapy regimens have increased the percentage of patients who achieve a pathologic complete response (pCR) (11, 12). Therefore, defining the role of postmastectomy radiation therapy in this subset of patients has become increasingly important to clinicians.

METHODS AND MATERIALS

Patients

We retrospectively reviewed the records of 226 patients with primary breast carcinoma who had a pCR after receiving neoadjuvant chemotherapy at The University of Texas M. D. Anderson Cancer Center between 1982 and 2002 identified from the institution's database. We focused this study on the 106 patients without inflammatory breast cancer who were treated with mastectomy after neoadjuvant chemotherapy to gain insights into the indications for the use of postmastectomy radiation therapy in such patients. Patients with inflammatory breast cancer were excluded because they all received postmastectomy radiation therapy. For the 106 patients, the clinical stage of the disease at the time of diagnosis, based on the 2003 American Joint Committee on Cancer criteria, was I, II, IIIA, IIIB, and IIIC in 2%, 31%, 30%, 25%, and 11% of the patients, respectively. Of the 74 patients with Stage III disease, 46 were included in a previous report (10). The data from these patients were updated for this analysis. The M. D. Anderson Cancer Center institutional review board approved our retrospective review of the patient's medical records for this study.

Histopathology

Pathologists at the M. D. Anderson center evaluated all diagnostic tissue specimens before therapy. The histologic type of the primary tumors was defined according to the World Health Organization system (13). Tumor grade was defined according to a modification of Black's nuclear grading system (14). Response to neoadjuvant chemotherapy was determined by pathologic assessment of the surgical specimen. A pCR was defined as a patient's having no evidence of invasive carcinoma in the breast or axillary lymph nodes (both negative).

Treatment

Details of the neoadjuvant chemotherapy regimens used in this study have been previously reported (15). Of the patients, 92% received an anthracycline as a component of the neoadjuvant chemotherapy, and 38% received a taxane either pre- or postoperatively. All patients underwent a modified radical mastectomy that included a level I or II axillary dissection. The patient and the physician determined whether postmastectomy radiation therapy would be used. For those receiving postmastectomy radiation therapy, the standard approach during this period was to treat the chest wall and draining lymphatics with 50 Gy in 25 fractions over 5 weeks, followed by a boost to the chest wall consisting of 10 Gy in five fractions over 1 week. The undissected draining lymphatics were typically treated with two separate fields, a photon field targeting the supraclavicular fossa/axillary apex, and an electron field targeting the internal mammary chain and medial chest wall.

Statistical analysis

Local-regional recurrence was defined as a recurrence of disease in the ipsilateral chest wall or the ipsilateral draining lymphatics. All LRRs were considered as events independent of the presence or absence of distant metastases (DM). There were no LRRs that developed subsequent to a DM. The Kaplan-Meier product-limit method was used to compute freedom from LRR, distant metastasis-free survival (DMFS), cause-specific survival (CSS), and OS curves. These endpoints were all calculated from the date of diagnosis. The log-rank test was used to compare Kaplan-Meier curves. Values of $p \leq 0.05$ were considered statistically significant. Statistical analyses were carried out using the SPSS 12.0 software program, version 12.0 (SPSS Inc, Chicago, IL). Because of the relatively small sample sizes and low total number of events, a multivariate analysis was not performed.

RESULTS

Patient and primary tumor data

The median age of the patients was 46 years (range, 23–74 years), and the median follow-up time for surviving patients was 62 months. Characteristics of the study population are summarized in Table 1. There were no significant differences between the patients in the irradiated and nonirradiated groups with respect to age, menopausal status, histologic subtype, estrogen receptor (ER) status, progesterone receptor (PR) status, HER-2/neu receptor status, presence of lymphovascular space invasion (LVI), tumor grade, or use of hormone therapy. A greater percentage of patients in the irradiated than the nonirradiated group had more advanced clinical disease stages at presentation ($p < 0.001$).

Correlation between clinical variables and LRR

Despite the greater percentage of patients with advanced disease in the irradiated group, the 10-year actuarial rates of

Table 1. Patient and tumor characteristics

Characteristic	Nonirradiated (n = 34) No. of patients	%	Irradiated (n = 72) No. of patients	%	*p* Value
Age					
≤50 years	21	(62)	44	(61)	0.949
>50 years	13	(38)	28	(39)	
Menopause					
Pre	22	(65)	39	(54)	0.155
Post	12	(35)	32	(45)	
Male sex	0	(0)	1	(1)	
Clinical T stage					
T1	5	(15)	3	(4)	<0.001
T2	18	(53)	9	(13)	
T3	4	(12)	36	(50)	
T4	7	(20)	24	(33)	
Clinical N stage					
N0	15	(44)	14	(19)	0.057
N1	12	(35)	30	(42)	
N2	6	(18)	16	(22)	
N3	1	(3)	11	(15)	
NX	0	(0)	1	(2)	
Clinical stage					
IB	2	(6)	0	(0)	<0.001
IIA	13	(38)	1	(1)	
IIB	7	(21)	9	(17)	
IIIA	5	(15)	29	(37)	
IIIB	6	(17)	21	(29)	
IIIC	1	(3)	12	(15)	
Histology					
Ductal	29	(85)	63	(87)	0.687
Lobular	1	(3)	2	(3)	
Other	0	(0)	4	(6)	
Unknown	4	(12)	3	(4)	
ER status					
Positive	8	(23)	14	(19)	0.828
Negative	19	(56)	40	(56)	
Unknown	7	(21)	18	(25)	
PR status					
Positive	12	(35)	11	(15)	0.055
Negative	12	(35)	38	(53)	
Unknown	10	(30)	23	(32)	
HER-2/neu					
Positive	6	(18)	12	(17)	0.210
Negative	9	(26)	14	(22)	
Equivocal	0	(0)	1	(1)	
Unknown	19	(50)	45	(60)	
LVI					
Positive	5	(15)	4	(6)	0.115
Negative	29	(85)	68	(94)	
Grade					
1	1	(3)	0	(0)	0.399
2	5	(15)	15	(20)	
3	25	(73)	53	(74)	
Unknown	3	(9)	4	(6)	
Hormone therapy					
Yes	13	(38)	20	(29)	0.310
No	21	(62)	52	(71)	

Abbreviations: ER = estrogen receptor; LVI = lymphovascular space invasion; PR = progesterone receptor.

LRR did not differ significantly between the irradiated (5%) and nonirradiated (10%) patients ($p = 0.40$). None of 32 patients who had clinical Stage I or II disease at presentation and who achieved a pCR had a LRR (10-year LRR rates were 0% for both the patients treated with radiation therapy and those not receiving radiation). However, for those who initially presented with Stage III disease ($n = 74$), the use of radiation therapy was associated with a significantly lower 10-year rate of LRR (7.3% ± 3.5% in the irradiated patients vs. 33.3% ± 15.7% in those who did not receive radiation therapy, $p = 0.040$, Fig. 1).

Table 2 shows the rates of LRR according to clinical and pathologic factors among the 74 patients with clinical Stage III disease. Age, menopausal status, histology, ER status, PR status, nuclear grade, and number of lymph nodes did not predict for differences in the rate of LRR. The presence or absence of LVI at the time of initial biopsy showed a trend toward association with LRR, although this did not reach statistical significance (45% ± 24.8% with and 8.6% ± 3.6% without, $p = 0.063$).

The DMFS, CSS, and OS rates differed significantly between irradiated and nonirradiated patients who presented with Stage III disease. In this cohort, the 10-year DMFS rate was 87.9% ± 4.6% for the irradiated patients and 40.7% ± 15.5% for the nonirradiated patients ($p = 0.0006$, Fig. 2). The 10-year CSS rate was 87% ± 5% for the irradiated patients and 40% ± 16% for the nonirradiated patients ($p = 0.0014$). Finally, the 10-year OS rate was 77.3% ± 6% for the irradiated patients and 33.3% ± 14% for the nonirradiated patients ($p = 0.0016$, Fig. 3).

One patient in the nonirradiated group with a clinical T4N1 breast cancer developed DM 6 months after diagnosis (see first event in Fig. 2). A metastatic workup including bone scan, chest x-ray, and computed tomography of the

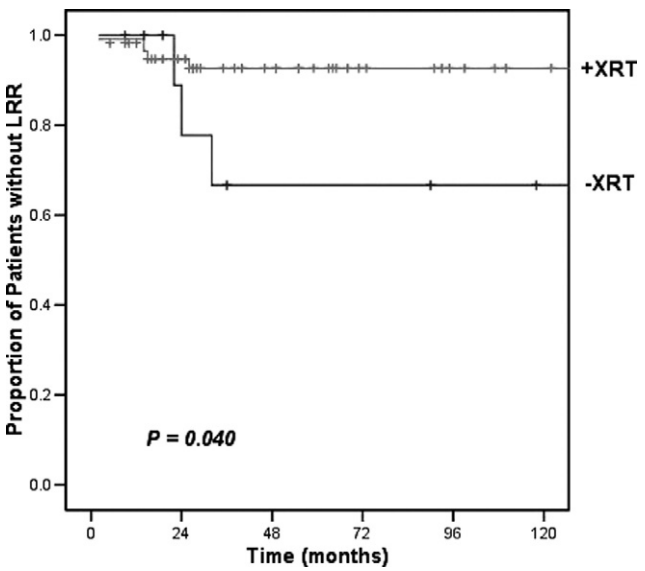

Fig. 1. Freedom from local-regional recurrence (LRR) in patients presenting with clinical Stage III breast cancer treated with neoadjuvant chemotherapy and mastectomy with or without radiation therapy (+XRT, $n = 62$ and −XRT, $n = 12$ respectively).

abdomen and pelvis had been negative for DM at the time of diagnosis. After three cycles of neoadjuvant chemotherapy, the patient underwent a mastectomy and was found to have a pCR. The patient then received adjuvant chemotherapy as planned but developed leptomeningeal metastatic disease 3 months after surgery. It could not be retrospectively determined whether the development of DM discouraged the use of postmastectomy radiation therapy. To account for this potential source of bias, we recalculated the outcome statistics excluding the data on this patient. For patients with clinical Stage III disease, the LRR rates did not change, and the differences in DMFS, CSS, and OS remained significantly different.

Table 2. Univariate analysis of factors associated with local-regional recurrence (LRR) after a pathologic complete response (pCR) in patients with Stage III disease treated with mastectomy

Characteristic	No. of patients	10-Year actuarial LRR rate	p Value
Age			0.27
≤50 years	50	14.3	
>50 years	24	5.3	
Clinical T stage			0.43
T1	3	0	
T2	8	27	
T3	30	7	
T4	31	12	
Clinical N stage			0.46
N0	5	20	
N1	31	4.2	
N2	22	11.5	
N3	13	15.4	
Menopausal status			0.55
Premenopausal	44	13.9	
Postmenopausal	28	8.0	
Histology			0.67
Ductal	61	11.5	
Lobular	2	0	
Estrogen receptor status			0.24
Positive	12	0	
Negative	42	14.3	
Progesterone receptor status			0.36
Positive	9	0	
Negative	37	12.5	
Lymphovascular invasion status			0.063
Yes	6	45	
No	68	8.5	
Nuclear grade			0.23
2	13	0	
3	54	13.0	
No. of lymph nodes examined			0.68
≤10	18	6	
>10	55	11.1	
Radiation therapy given			0.04
Yes	62	7.2	
No	12	33.4	

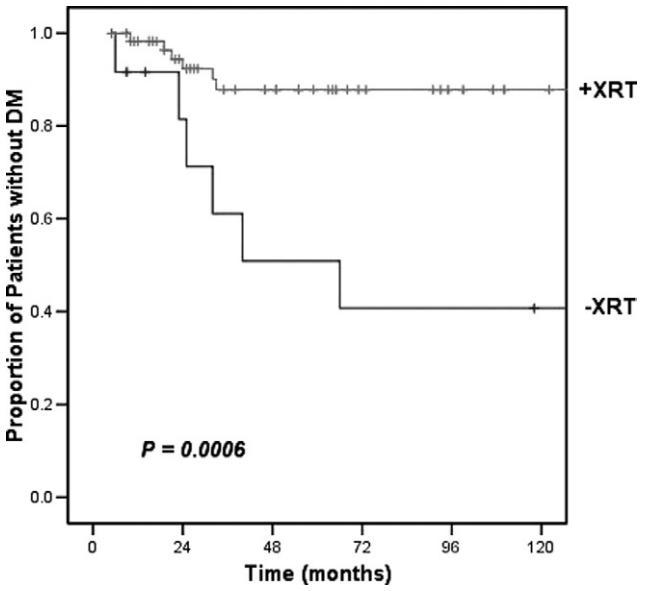

Fig. 2. Freedom from distant metastases (DM) in patients with clinical Stage III breast cancer treated with neoadjuvant chemotherapy and mastectomy with or without radiation therapy (+XRT and −XRT, respectively).

DISCUSSION

A number of studies have indicated that patients who achieve a pCR after neoadjuvant chemotherapy have an excellent prognosis, with a significantly lower risk of developing a distant metastases and a lower risk of dying compared with patients who have residual disease after neoadjuvant chemotherapy. However, few published studies have addressed how an achievement of pCR should affect local-regional treatment decisions. In this study, we showed

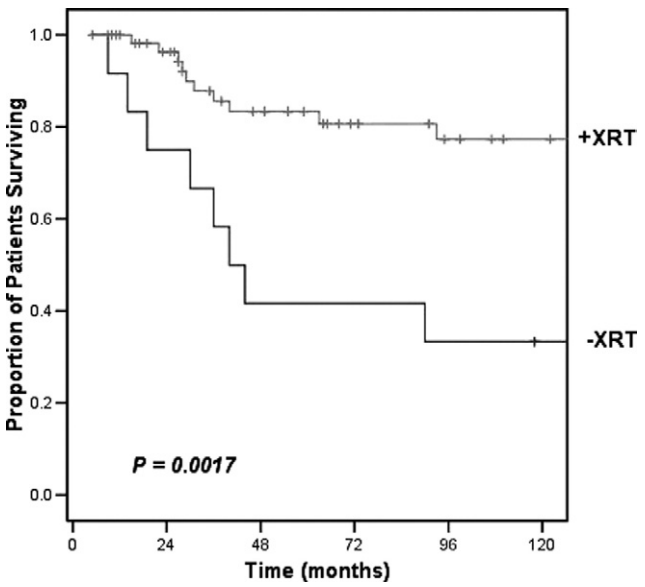

Fig. 3. Overall survival in patients with Stage III breast cancer treated with neoadjuvant chemotherapy and mastectomy with or without radiation therapy (+XRT and −XRT, respectively).

that patients with clinical Stage III breast cancer who experience a pCR maintain a clinically relevant risk of LRR after mastectomy, and that radiation therapy provides a significant clinical benefit. The 10-year LRR rate for patients who initially presented with Stage III disease was greater than 30% without postmastectomy radiation therapy vs. a risk of 7% when radiation therapy was used. These data reinforce earlier findings from our group that suggest that the LRR risk after neoadjuvant chemotherapy and mastectomy is determined not just by the extent of residual disease after treatment but also by the extent of disease before treatment (9, 10). These findings are also consistent with numerous studies that have demonstrated postmastectomy radiation therapy can significantly improve local-regional control for patients at elevated risk for LRR.

In this study, radiation use was also associated with a statistically significant reduction in the rate of DM and an improved CSS and OS in the patients with Stage III disease. The significant survival advantage associated with the use of radiation therapy in the cohort of patients with Stage III disease was somewhat surprising, given the relative modest sample size of this population. The recent meta-analysis results of the Early Breast Cancer Trialists' Collaborative Group indicated that radiation therapy can improve DMFS and OS in patients with an elevated risk of LRR. However in that study, an absolute reduction of 4% in the LRR rate corresponded to a reduction in breast cancer mortality of 1% (6). It is possible that this ratio may be different in patients who have a pCR to neoadjuvant chemotherapy. The ability of radiation therapy to favorably affect survival is dependent on three factors. First, it must be given to patients with a high risk of persistent local-regional disease after neoadjuvant chemotherapy and mastectomy. In our study cohort, the risk of LRR without radiation therapy for patients with Stage III disease exceeded 30%. Second, the radiation therapy must eradicate the residual local-regional disease. In our study, the absolute reduction in LRR for patients with Stage III disease was 26% at 10 years. Finally, patients must have a low competing risk of incurable persistent disease at distant sites. Patients who achieve a pCR are known to have a markedly lower risk of DM compared with patients with similar stages of disease who do not achieve a pCR, and the lower competing risk of DM may allow for improvements in LRR to have a greater impact on survival.

Our study also found that none of the 20 patients with Stage I or II breast cancer who achieved a pCR and did not receive postmastectomy radiation therapy developed an LRR. Although the sample size of this subgroup was limited and did not provide sufficient statistical power to establish equivalence between the irradiated and nonirradiated groups, it represents the largest such patient cohort in the literature. The preliminary insights from this analysis suggest that postmastectomy radiation therapy may not be required in patients like those in our Stage II cohort, although additional data are needed to confirm these findings. One source of such data will be an analysis of the LRR outcome of patients treated with mastectomy in National Surgical Adjuvant Breast and Bowel Project (NSABP) studies. The majority of patients enrolled in the NSABP B-18 trial and the subsequent NSABP B-27 trial had Stage II disease, and postmastectomy radiation therapy was not used in these trials. Therefore, a report on the long-term local-regional outcomes of patients who had a pCR to neoadjuvant chemotherapy in those trials will be a valuable addition to the existing literature.

It is important to note that this study has several limitations. The use of radiation therapy was not a randomized variable; therefore the differences in outcomes between the irradiated and nonirradiated stage III patients may have been affected by the selection biases that are inherent in retrospective research. However, as indicated by the imbalances with respect to stage of disease between the two groups, radiation therapy was used preferentially for patients with worse disease characteristics. Also, the follow-up of the patients in this study was relatively modest. In addition, HER-2/neu amplification was not routinely assayed in these patients, and trastuzumab was not used in the primary treatment of the patients. Recent evidence has demonstrated that the addition of trastuzumab to neoadjuvant chemotherapy regimens produces high rates of pathologic complete response, and might have further reduced rates of local recurrence by eliminating residual microscopic disease in patients whose tumors demonstrated HER-2/neu amplification (16).

CONCLUSION

In conclusion, although the overall rate of LRR after mastectomy is low for patients with breast cancer who achieve a pCR to neoadjuvant chemotherapy, the risk of LRR after mastectomy for patients with clinical Stage III disease appears to be high in this updated analysis. In our institution, our current practice is to offer comprehensive postmastectomy radiation treating the chest wall and undissected draining nodal basins to patients who present with clinical Stage III breast cancer and are found to have obtained a pCR at the time of mastectomy. In the future, a prospective Phase III trial is warranted to clarify the role of postmastectomy radiation after neoadjuvant chemotherapy, particularly for those with Stage II disease.

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