

IMPORTANCE OF RADIATION THERAPY FOR BREAST CANCER PATIENTS TREATED WITH HIGH-DOSE CHEMOTHERAPY AND STEM CELL TRANSPLANT

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Purpose: To determine local-regional failure rates in breast cancer patients treated with surgery and high-dose chemotherapy with stem cell transplant and to relate local-regional failure to the use and timing of radiation treatment.

Methods and Materials: We retrospectively reviewed the records of 165 breast cancer patients treated on institutional protocols with surgery and high-dose chemotherapy with stem cell transplant. All patients had either Stage III disease, 10 or more positive axillary lymph nodes, or 4 or more positive axillary lymph nodes following neoadjuvant chemotherapy. Twelve patients had inflammatory breast cancer. Thirteen patients treated with breast preservation and 5 patients who died from toxicity within 30 days of transplant were excluded from the analyses of local-regional recurrences. In the remaining 147 patients, 108 were treated with adjuvant radiation and 39 were not. The disease stage distribution for these two groups was comparable. The median follow-up for surviving patients was 35 months.

Results: The 3- and 5-year actuarial disease-free survival (DFS) for the entire group was 60% and 51%, respectively. The 5-year rates of freedom from isolated local-regional recurrence were 95% in the patients treated with adjuvant radiation and 86% in the patients who did not receive radiation ($p = 0.014$, log rank comparison). The 5-year rates of any local-regional recurrence as a first event (isolated recurrences plus those with simultaneous local-regional and distant recurrences) were 92% versus 82%, respectively for patients whose treatment did and did not include radiation ($p = 0.038$). We could not demonstrate a correlation of the timing of radiation with the risk of local-regional recurrence.

Conclusions: These data indicate that high-dose chemotherapy does not negate the importance of radiation in optimizing local-regional control in patients with high-risk breast cancer. Given the results of recent randomized trials studying postmastectomy radiation, which show that improving local-regional control improves overall survival (OS), we believe that all breast cancer patients with high-risk primary breast cancer who are treated with high-dose chemotherapy with stem cell transplant should receive radiation as a component of their treatment. © 2000 Elsevier Science Inc.

Breast cancer, High-dose chemotherapy, Transplant, Radiation.

INTRODUCTION

Over the past decade, the use of high-dose chemotherapy with autologous stem cell transplant has increased dramatically in the United States. In 1989, the number of transplants registered with the Autologous Blood and Marrow Transplant Registry of North America for treatment of breast cancer was 272, and by 1994 the number had risen to 1513 (1). It is estimated that these figures represent only

about half of the transplants for breast cancer performed in the United States (1). Despite the widespread adoption of high-dose chemotherapy, its role in the treatment of high-risk breast cancer has not been established. There are now completed Phase III trials comparing standard adjuvant therapy with and without high-dose chemotherapy with transplant. The initial results from two large randomized trials suggest that high-dose chemotherapy should not be

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Presented at the 1999 ASTRO meeting, San Antonio, Texas, Oct. 1999.

This work was supported in part by Grants T32CA77050 and

P30CA16672 awarded by the National Cancer Institute, U.S. Department of Health and Human Services.

Acknowledgment—Richard Moore's contribution to this article was performed while he was working in the Department of Radiation Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX.

Accepted for publication 23 September 1999.

considered as a component of standard therapy (2, 3), but rather is more appropriate for protocol settings addressing specific scientific questions.

Most published data concerning high-dose chemotherapy with autologous stem cell transplant for breast cancer have focused on the endpoints of the development of distant metastatic disease and survival. Very little information is available concerning the impact of this treatment on local-regional control and on the need for adjuvant radiation. This retrospective study was undertaken to determine local-regional control rates in breast cancer patients treated with high-dose chemotherapy following mastectomy, and to relate local-regional control to the use of radiation. These data help address the question of whether the aggressive chemotherapy obviates the need for local-regional radiation. The second objective of this study was to determine how high-dose chemotherapy with transplant impacts the interval between diagnosis and the initiation of radiation, and whether radiation delay influences local-regional control. Recently, postmastectomy radiation has been shown in Phase III studies to improve survival for patients with high-risk breast cancer (4, 5). This second objective of our study, therefore, investigates whether treatment with high-dose chemotherapy plus transplant compromises the delivery and efficacy of a treatment now shown to improve survival rates.

METHODS AND MATERIALS

We performed a retrospective analysis of the outcome of breast cancer patients treated on institutional high-dose chemotherapy protocols. We included only patients without a history of local recurrence or distant metastases prior to transplant and only patients who had undergone surgical resection of all gross disease from the breast and level I–II axilla prior to transplant. All patients had Stage III disease, 10 or more positive axillary lymph nodes, or 4 or more positive axillary lymph nodes following neoadjuvant chemotherapy. From November 1989–October 1997, there were 165 patients who met these criteria. For some of these patients for whom clinic notes were not available from either 1998 or 1999, follow-up information concerning the disease status was obtained through a phone interview of the patient, family, or referring outside physician.

Only 13 of the 165 patients were treated with a breast-conserving surgery (the remaining patients had a modified radical mastectomy). This provided insufficient clinical data to assess local-regional control rates with this type of surgical therapy. An additional 5 patients died within 30 days of transplant from treatment toxicity. These patients did not have adequate follow-up to be at risk for local-regional recurrence. For these reasons, these 18 patients were not included in the analyses of local-regional control. None of these 18 patients developed a local-regional recurrence. Their data were included in the overall survival (OS) and disease-free survival (DFS) calculations.

The patients in this study represented a selected popula-

tion, in that eligibility for enrollment on our high-dose chemotherapy protocols was determined following completion of adjuvant chemotherapy treatment. We are aware of one patient who was not included in this report because she was found to have a local recurrence during pretreatment evaluation for high-dose chemotherapy. It was not possible to determine the total number of patients who were not offered high-dose chemotherapy because of development of recurrent disease or lack of response to neoadjuvant chemotherapy.

All patients in this study were treated with conventional chemotherapy and surgery prior to their high-dose chemotherapy. The treating physicians determined the sequencing of chemotherapy and surgery, as well as the chemotherapy agents used. Approximately half (49%) of the patients received neoadjuvant chemotherapy. A doxorubicin-based regimen was used in the conventional chemotherapy treatment in all but one case. Only 16% of the patients received both doxorubicin and a taxane.

High-dose chemotherapy with transplant was given according to institutional protocols. Patients underwent mobilization of peripheral blood stem cells for collection using either granulocyte colony-stimulating factor (G-CSF) alone (6 $\mu\text{g}/\text{kg}$ subcutaneously q12h) or after CVP chemotherapy (cyclophosphamide 1.5 $\text{gm}/\text{m}^2/\text{d}$ IV days 1–3, etoposide 250 $\text{mg}/\text{m}^2/\text{d}$ IV days 1–3, and cisplatin 40 mg/m^2 IV days 1–3, Mesna 1.5 $\text{g}/\text{m}^2/\text{d}$ by continuous IV infusion over 24 h for 3 days). Patients then received high-dose CBT chemotherapy (cyclophosphamide 2.0 gm/m^2 IV days –7, –6, –5; BCNU (carmustine) 150 mg/m^2 IV days –7, –6, –5; thiotepa 240 mg/m^2 IV days –7, –6, –5, with Mesna 2.0 $\text{mg}/\text{m}^2/\text{d}$ by continuous IV infusion for 3 days). The cryopreserved blood progenitor cells were then reinfused intravenously.

For the 43 patients treated with radiation in our institution, treatment was given in a standardized fashion. The chest wall was treated with opposed tangential photon fields or matched electron fields depending on the anatomy of the patient, with use of intermittent bolus to assure adequate skin dosage. A matched appositional electron field (energy determined using computer tomography planning) was used to treat the internal mammary lymph nodes and a matched photon field was used to treat the supraclavicular fossa and axillary apex. These fields received 50 Gy in 25 fractions over 5 weeks. For patients with extensive lymph node disease and extranodal extension, a posterior axillary boost was used to bring the midaxilla to 40–50 Gy. Subsequently, the chest wall was boosted with 1 or 2 electron fields to a 60 Gy total dose. These dosages and fields were modified for selected patients, such as those with inflammatory cancer. For the 65 patients treated outside of our institution, treatment field information was available in only 16. In these patients, 14 had the chest wall and supraclavicular regions treated to a minimal dose of 50 Gy, 1 had the chest wall only treated to 50 Gy, and 1 had the chest wall and supraclavicular region treated to 45 Gy. In the remaining 49 patients

Table 1. Patient characteristics

	RT Group	No RT Group
Number of patients	108	39
Stage II	35 (32%)	17 (44%)
Stage III	73 (68%)	22 (56%)
Inflammatory	8 (7%)	3 (8%)
≥10 lymph nodes	67 (62%)	28 (72%)
ER+, PR+*	32/89 (37%)	14/33 (42%)
ER+, PR−	12/89 (13%)	5/33 (12%)
ER−, PR+	9/89 (10%)	1/33 (3%)
ER−, PR−	36/89 (40%)	13/33 (39%)
Age <40 years	34 (32%)	11 (28%)

* ER, PR = estrogen and progesterone receptors; the fraction indicates the number of patients with the particular ER, PR status over the number of patients in whom ER, PR status was known.

treated with radiation, the only information concerning the radiation treatment were the dates of treatment.

To evaluate the efficacy of local-regional radiation in patients treated with high-dose chemotherapy, the 108 eligible patients treated with chemotherapy, mastectomy, high-dose chemotherapy, and radiation (RT group) were compared to the 39 patients treated with chemotherapy, mastectomy, and high-dose chemotherapy (no RT group). The majority of the patients in the no RT group did not receive radiation because this was the preference of their treating physician, although some did not receive radiation because of transplant toxicity. Only 9 of the 108 patients in the RT group received radiation prior to high-dose chemotherapy and transplant. For the 99 patients who received radiation after transplant, the median interval from diagnosis to radiation was 11 months with a range of 6–25 months, and the median interval from transplant to radiation was 2.2 months.

Table 1 displays patient and pathological characteristics of the RT and no RT groups. As can be seen, the disease extent and the percentage of patients with estrogen receptor (ER)- and progesterone receptor (PR)-negative tumors were comparable between the two groups. For the entire group, the median age at diagnosis was 45 with a range of 27–62. Median tumor size was 4.0 cm, with a range of 0–15 cm. The median number of positive lymph nodes was 11 with a range of 0–44. The median follow-up of surviving patients was 35 months with a range of 11–107 months.

Actuarial statistics using methods of Kaplan-Meier were used to estimate survival and local-regional control (6). For DFS, one patient was censored when she developed a second cancer. For the Kaplan-Meier local-regional analyses, patients were censored at the time of last follow-up or at the time of death. Isolated local-regional recurrences were defined as a chest wall or lymph node recurrence occurring as the first evidence of recurrent disease without simultaneous distant metastases. Overall local-regional recurrences were defined as a chest wall or lymph node recurrence occurring as a first event either as an isolated recurrence or with a simultaneous distant metastases. Local-regional recurrences

Overall and Disease-Free Survival

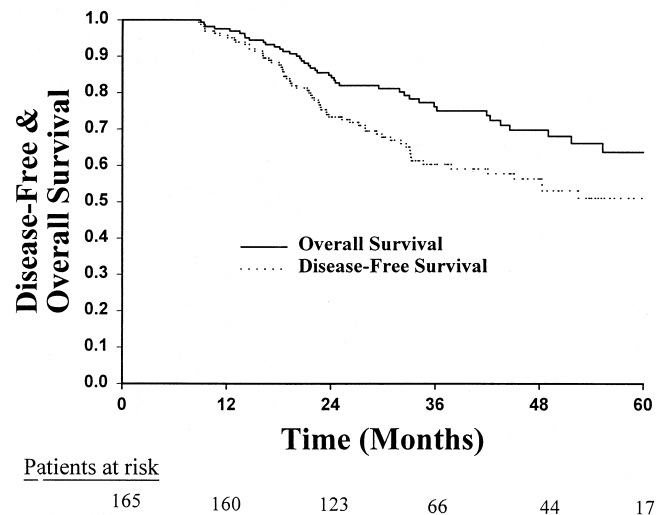


Fig. 1. Actuarial OS and DFS for the 165 patients in this series.

following the development of metastatic disease are not reliably recorded in medical records and therefore were not felt to be appropriate for this retrospective analysis. Actuarial data were compared with 2-sided log rank tests. Local-regional control rates using a cumulative incidence methodology that accounts for the competing risk of local-regional recurrence and distant metastases were also provided (7). Multivariate analysis was performed using a Cox regression analysis (8).

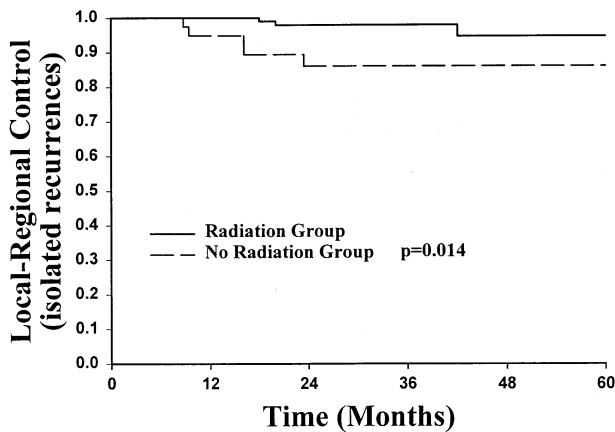
RESULTS

The OS and DFS for the 165 patients is shown in Fig. 1. At 3 years, the OS and DFS were 76% and 60%, respectively. At 5 years these figures were 64% and 51%, respectively. The actuarial overall local-regional control rates were 91% and 89%, respectively at 3 and 5 years. Using the cumulative incidence methodology, which accounts for the competing risk of death from metastatic disease, these rates of overall local-regional control were 92% and 91%, respectively at 3 and 5 years.

Figure 2 displays actuarial rates of freedom from isolated local-regional recurrence for the RT and no RT groups. The rates of freedom from isolated local-regional recurrences at 3 years were 98% (RT) and 86% (no RT), and at 5 years were 95% (RT) and 86% (no RT). These differences were statistically significant at a $p = 0.014$ level. The overall local-regional control rates at 5 years were 92% (RT) and 82% (no RT), $p = 0.038$. The 3- and 5-year OS for these two groups were 81% (RT) versus 71% (no RT), and 67% (RT) versus 59% (no RT), respectively ($p = 0.18$).

Table 2 shows how additional patient and pathological factors affected the incidence of isolated local-regional recurrences. The only other factors found to adversely impact local-regional control were inflammatory disease, ER-neg-

Freedom From Isolated Local-Regional Recurrence



Patients at risk						
Radiation	108	107	77	38	23	9
No Radiation	39	36	21	13	11	3

Fig. 2. Actuarial freedom from isolated local-regional recurrence curves for patients divided according to treatment with radiation. The solid curve represents the 108 patients who were treated with radiation. The dashed curve represents the 39 patients who did not receive radiation as a component of their initial treatment (no RT). The difference between these actuarial data was statistically significant at $p = 0.014$.

ative disease, and PR-negative disease. Since all of the local-regional recurrences occurred in patients with ER-negative and PR-negative disease, a multivariate analysis was performed on this subset of patients. The use of radiation continued to be significant with $p = 0.018$ for isolated local-regional recurrence and $p = 0.034$ for overall local-regional recurrence. Inflammatory disease was of marginal significance in the multivariate analysis ($p = 0.093$ for

Table 2. The relationship of patient and pathological characteristics and the incidence of local-regional recurrence

Characteristic	Isolated local-regional recurrence p Value*	Overall local-regional recurrence p Value*
Stage II vs. III	0.530	0.455
Tumor size ± 4.5 cm (median size)	0.513	0.538
Positive lymph nodes ± 11 (median number)	0.858	0.591
Inflammatory disease [†]	0.029	0.006
ER status [†]	0.013	0.002
PR status [†]	0.024	0.005
Age ± 44 (median age)	0.586	0.349

ER, PR = estrogen and progesterone receptors.
 * p values represent two-sided log rank tests.
[†] Patients with inflammatory disease, ER-negative disease, PR-negative disease did worse.

Table 3. Local-regional failure as a function of radiation delay

Radiation delay interval (months)	Diagnosis to radiation (recurrences/No. at risk)	Surgery to radiation (recurrences/No. at risk)
0-2	0/1	0/5
2-4	0/2	1/3
4-6	0/3	0/12
6-8	1/7	2/25
8-10	1/30	1/30
10-12	1/34	1/22
12-14	2/20	1/8
14-16	1/5	0/1
16-25	0/6	0/2

No. = number.

isolated local-regional recurrence and $p = 0.056$ for overall local-regional recurrence). These results indicate that the use of radiation is a prognostic factor independent of the ER and PR status and inflammatory disease.

Table 3 shows the crude incidences of overall local-regional recurrences as a function of radiation timing. Patients not treated with radiation were not included in this table. There was 1 local-regional recurrence in the 9 patients who received radiation prior to transplant compared to 5 events in the 99 patients who received radiation after transplant. The shortest diagnosis to radiation interval for which there was a local-regional recurrence was 7.4 months. A comparison of the local-regional control rates in the patients divided at any arbitrarily defined radiation delay interval did not show a statistically significant difference. However, the median diagnosis to radiation interval for all irradiated patients was 11 months, with only 8 patients having an interval shorter than 7 months.

DISCUSSION

From our cohort of 147 breast cancer patients treated with high-dose chemotherapy plus transplant, we demonstrated that radiation continues to play an important role in optimizing local-regional control. The patients in this report had pathological features that have been found to increase the risk both for local-regional recurrence following mastectomy and for the development of metastatic disease. Specifically, two of the most important prognostic features that simultaneously increase the distant and local recurrence risk are primary tumor stage and degree of involvement of axillary lymph nodes. Because conventional chemotherapy generally is able to achieve a one-third reduction in the risk of systemic treatment failure, the percentage of patients with advanced primary and/or nodal disease who develop metastatic disease following conventional chemotherapy remains high. Studies of high-dose chemotherapy with transplant have been specifically directed towards these patients in an effort to further reduce the risk of metastatic disease development. However, attainment of local-regional control for these patients is also of paramount importance. In a report of 2016 patients treated with mastectomy and adjuvant che-

motherapy, Recht *et al.* reported that patients with advanced primary and nodal disease may have greater than a 30% risk of local-regional recurrence following mastectomy and conventional chemotherapy without radiation (9). The median follow-up for the patients in this paper was 12.1 years. Furthermore, if high-dose chemotherapy with transplant were able to further reduce the competing risk of distant metastases, it is likely that the risk of local-regional recurrence would further increase.

The primary objective of high-dose chemotherapy trials has focused on increasing the rate of sterilizing preexisting distant micrometastases. Less attention has been directed at simultaneously optimizing local-regional control. In part, this reflects the fact that the role of radiation following mastectomy is still being defined. Initial trials comparing mastectomy to mastectomy and radiation were unable to demonstrate a survival advantage for the addition of radiation treatments (10–12). Meta-analyses of these early trials suggested that postmastectomy irradiation reduced local-regional recurrence and the risk of breast cancer deaths, but increased the risk of cardiovascular deaths (13, 14). However, radiation techniques have considerably evolved since these early trials, and the subset of patients predicted to benefit from radiation has become more clearly defined. In addition, adjuvant chemotherapy has decreased the competing risk of distant metastases, which increases the importance of attaining local-regional control.

The 1997 publication of the results from two randomized prospective trials provided data concerning the role of postmastectomy radiation using more modern radiotherapy techniques and proper patient selection. The largest of these trials, the Danish Cooperative Group 82b trial, randomized over 1700 premenopausal patients with high-risk breast cancer to mastectomy and chemotherapy versus mastectomy, chemotherapy, and chest wall and lymphatic irradiation (4). In this study, the addition of radiation improved 10-year local-regional control, DFS, and OS. The results of this trial were confirmed by a smaller similar study from Vancouver, British Columbia (5).

The results of the Danish trial have been criticized for the high local-regional failure rates seen in the patients treated with surgery and chemotherapy alone (15). In part this is explained by a less aggressive axillary surgery than that which is commonly used in the United States. However, one conclusion that can be drawn from these trials that is independent of this criticism, is that conventional chemotherapy is not an adequate substitute for local-regional radiation in postmastectomy patients who are at high risk for local-regional failure. This conclusion was further confirmed by Recht *et al.*, who reported local-regional recurrence rates in excess of 30% following mastectomy and conventional chemotherapy for patients with selected high-risk pathological features (such as involvement of 8 or more axillary lymph nodes) (9). Finally, in a retrospective analysis of 618 patients treated with mastectomy for breast cancer with 10 or more positive lymph nodes, Diab *et al.* reported local-regional failure rates of 41% following systemic therapy

alone compared to 17% following systemic therapy and radiation (16). Our data are consistent with these previous reports, and importantly demonstrate that radiation also reduces isolated local-regional recurrences for patients treated with both conventional chemotherapy and high-dose chemotherapy with autologous stem cell transplant.

A second important finding from the Danish and Vancouver trials was the demonstration that reducing isolated local-regional recurrences with postmastectomy radiation can lead to an improvement in OS. This makes our finding of a reduction in isolated local-regional recurrence in patients treated with high-dose chemotherapy of paramount importance. In our study, there was a higher 5-year survival rate for the RT group compared to the no RT group (67% versus 59%), but this difference was not statistically significant. The number of patients in this series did not provide sufficient statistical power to investigate whether radiation treatment impacted survival. In addition, potential biases inherent in retrospective analyses could possibly have an equal impact on survival data as any effect that resulted from radiation treatment.

While a number of studies have investigated the use of high-dose chemotherapy and breast cancer, few have analyzed local-regional recurrence patterns. Marks *et al.* have provided one of the only analyses investigating the use of radiation in the transplant setting (17). Initially their institutional adjuvant high-dose chemotherapy protocol omitted radiation treatment. Local-regional failure occurred in 3 of the first 9 patients treated. Radiation was then adopted for the remaining 40 patients of their study. Six patients required radiation doses under 44 Gy owing to treatment toxicity, with 1 experiencing a subsequent local-regional recurrence. Only 1 local-regional recurrence developed in the remaining 34 patients, who were treated to dosages over 44 Gy. Despite the small patient numbers of this series, the difference in local-regional control between the patients treated with radiation and those not receiving radiation was statistically significant. Our results, with a much larger number of patients, confirm the Marks *et al.* study.

Results of randomized trials thus far indicate that use of adjuvant high-dose chemotherapy with transplant must continue to be considered experimental. The second focus of our current study was to investigate whether this experimental modality compromised the efficacy of a treatment previously proven to benefit survival. We did not demonstrate that high-dose chemotherapy compromised radiation efficacy secondary to delaying the initiation of this treatment. We did not find a statistical relationship between the risk of local-regional recurrences and the timing of radiation. However, all patients in this series had a delay in the initiation of radiation (the median interval from diagnosis to radiation was 11 months). A more optimal way to address the question of whether transplants impair radiation efficacy due to delay in treatment, would be to compare a group of patients irradiated pretransplant to one irradiated after transplant. Unfortunately, we do not have sufficient data to make this comparison. However, the low rate of local-regional failure in our patients treated with radiation after transplant sug-

gests that if a difference existed favoring pretransplant radiation it would require a very large sample size to detect.

As highlighted in a recent review by Recht and Come, there are few published data on the timing of radiation in the postmastectomy setting (18). One study investigating this issue found that patients receiving postmastectomy radiation within 6 months from diagnosis had a local control rate of 96% at 8 years compared to a rate of 77% for those with a 6-month or greater delay (19). However, the patient numbers in this report were small and the difference was not statistically significantly different ($p = 0.19$). A second nonrandomized postmastectomy study (published only as an abstract) reported local recurrence rates of 10% for patients treated with radiation followed by chemotherapy, 18% for patients treated with chemotherapy followed by radiation, and 5% for those treated with 3 cycles of chemotherapy, radiation, then the final 3 cycles of chemotherapy (20).

An alternative method of judging whether radiation delay negatively impacted local-regional recurrences for our patients would be to compare our results with those obtained in the literature. The isolated and overall local-regional recurrence rates for patients treated with radiation in our series were respectively 5% and 8% at 5 years. The Kaplan-Meier statistical methodology we used may overestimate true rates of recurrences by assuming that patients who die from competing risks, such as distant metastatic disease, have an equivalent projected risk of local-regional recurrence as the remaining population in the study. This may not be true if additional systemic therapy is used to treat the metastatic recurrence. However, the Kaplan-Meier methodology does provide useful information for clinicians interested in estimations of total actuarial risk of an event independent from a competing risk.

Our local-regional control data, and the previously discussed data from Marks *et al.*, are the only available published data studying radiation efficacy in patients treated with high-dose chemotherapy and transplant. The results are similar to or better than the reported local-regional control rates for patients treated with mastectomy, chemotherapy and radiation for disease with similar high-risk features. In a retrospective study, Metz *et al.* reported an actuarial local-regional recurrence rate of 11% at 10 years in patients treated with postmastectomy radiation (21). However, in the Metz *et al.* study, only 68% of patients were treated with chemotherapy, and patients with N2 and N3 patients were excluded. Finally, Diab *et al.* reported an actuarial local-regional recurrence at 5 years of 17% in 214 patients with 10 or more positive lymph nodes treated with mastectomy, conventional systemic therapy, and radiation (16). Our more favorable local-regional control rate in a group of patients with similar adverse features may be indicative of a synergistic benefit of the high-dose chemotherapy systemic and radiation treatments in the local-regional area. However, given the limitations of comparing retrospective series, this hypothesis should be considered as speculative.

In conclusion, this study demonstrates that high-dose chemotherapy with transplant does not preclude the need for local-regional radiation for patients with high-risk breast cancer. All clinical trials investigating high-dose chemotherapy in patients with similar high-risk disease features should incorporate local-regional radiation into the treatment regimen. The sequencing of therapies remains uncertain, although we found no evidence that delaying the delivery of radiation diminished its efficacy in minimizing the development of isolated local-regional recurrences.

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