

Clinical Investigation: Breast Cancers

# Locoregional Recurrence Risk for Patients With T1,2 Breast Cancer With 1-3 Positive Lymph Nodes Treated With Mastectomy and Systemic Treatment

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## Summary

Randomized trials have indicated that post-mastectomy radiation therapy (PMRT) improves the outcome for patients with T1,2 breast cancer with 1 to 3 positive lymph nodes. However, since the completion of these trials, overall event rates have decreased. In this study, we demonstrated that PMRT reduced locoregional recurrence in patients treated from 1978-1997 but not in patients treated from 2000-2007. In this later era, the 5-year rate of locoregional recurrence in

**Purpose:** Postmastectomy radiation therapy (PMRT) has been shown to benefit breast cancer patients with 1 to 3 positive lymph nodes, but it is unclear how modern changes in management have affected the benefits of PMRT.

**Methods and Materials:** We retrospectively analyzed the locoregional recurrence (LRR) rates in 1027 patients with T1,2 breast cancer with 1 to 3 positive lymph nodes treated with mastectomy and adjuvant chemotherapy with or without PMRT during an early era (1978-1997) and a later era (2000-2007). These eras were selected because they represented periods before and after the routine use of sentinel lymph node surgery, taxane chemotherapy, and aromatase inhibitors.

**Results:** 19% of 505 patients treated in the early era and 25% of the 522 patients in the later era received PMRT. Patients who received PMRT had significantly higher-risk disease features. PMRT reduced the rate of LRR in the early era cohort, with 5-year rates of 9.5% without PMRT and 3.4% with PMRT (log-rank  $P = .028$ ) and 15-year rates 14.5% versus 6.1%, respectively; (Cox regression analysis: adjusted hazard ratio [AHR] 0.37,  $P = .035$ ). However, PMRT did not appear to benefit patients treated in the later cohort, with 5-year LRR rates of 2.8% without PMRT and 4.2% with PMRT ( $P = .48$ ; Cox analysis: AHR 1.41,  $P = .48$ ). The most significant factor predictive of LRR for the patients who did not receive PMRT was the era in which the patient was treated (AHR 0.35 for later era,  $P < .001$ ).

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the patients who did not receive PMRT was only 2.8%.

**Conclusion:** The risk of LRR for patients with T1,2 breast cancer with 1 to 3 positive lymph nodes treated with mastectomy and systemic treatment is highly dependent on the era of treatment. Modern treatment advances and the selected use of PMRT for those with high-risk features have allowed for identification of a cohort at very low risk for LRR without PMRT. © 2014 Elsevier Inc.

## Introduction

Postmastectomy radiation therapy (PMRT) has been demonstrated to offer clinically significant benefits for selected patients treated with mastectomy and systemic treatments. For patient cohorts with a clinically relevant locoregional recurrence (LRR) risk after mastectomy and systemic treatments, randomized clinical trials have shown that PMRT can significantly reduce LRR, decrease the subsequent risk of distant metastases, and improve overall survival (1-6). However, other patient cohorts, such as those with early-stage lymph node–negative disease, have a much lower risk of LRR after mastectomy. For such patients, data from clinical trials suggest that the potential toxicities of PMRT outweigh any potential benefit (7).

Consensus statements by the American Society for Radiation Oncology and the American Society of Clinical Oncology recommend PMRT for patients with 4 or more positive lymph nodes and recommend against PMRT for patients with early-stage lymph node–negative disease (8, 9). However, there continues to be significant controversy over whether patients with T1,2 tumors with 1 to 3 positive lymph nodes should be recommended to receive PMRT.

The data from the Danish 82B/C trials and the Vancouver British Columbia trial suggest that patients with 1 to 3 positive lymph nodes achieve significant LRR and overall survival benefits from adjuvant PMRT (1-7, 10). Moreover, these data contributed to an update of the Early Breast Cancer Trialists' Collaborative Group meta-analyses of PMRT randomized trials. These investigators have presented data showing that PMRT led to improvements in the 10-year rates of LRR and overall survival in patients with 1 to 3 positive lymph nodes (11). Accordingly, when these data are published they are likely to lead to a greater use of PMRT for all patients with 1 to 3 positive lymph nodes.

Several groups have previously reported a lower risk of LRR for patients with 1 to 3 positive lymph nodes who were treated in the United States with a standard modified radical mastectomy and adjuvant chemotherapy. Specifically, data from MD Anderson, the Eastern Cooperative Oncology Group, and the National Surgical Adjuvant Breast and Bowel Project reported 10-year LRR rates without PMRT to range from 10% to 13% (12-14). Although this risk is significantly lower than that reported by the Danish trials, the British Columbia trial, and the Early Breast Cancer Trialists' Collaborative Group meta-analysis, it is still possible that PMRT may be of some

benefit for patients with this degree of LRR risk. For example, in a previous analysis of MD Anderson patients with T1,2 disease with 1 to 3 positive lymph nodes, we demonstrated that PMRT reduced the 10-year LRR risk from 13% to 3% ( $P = .003$ ) (15).

Rather than adopting a universal recommendation for PMRT for patients with positive lymph nodes, our institutional philosophy over the past decade has been to selectively recommend PMRT for subcategories of patients with 1 to 3 positive lymph nodes who have higher-risk features. For example, we found the following cofactors to increase the risk of LRR for patients with 1 to 3 positive lymph nodes who did not receive PMRT: tumor size 4 cm, lymphovascular space invasion, 3 positive lymph nodes, close (<2 mm)/positive margins, patient age under 40, gross extracapsular extension of disease, and skin or nipple invasion (16). One purpose of this study was to assess whether by using these criteria to help select patients for PMRT, we have been effective in identifying a large percentage of patients with 1 to 3 positive lymph nodes who can be safely spared the potential toxicity, costs, and inconveniences of PMRT. A second focus of this study was to investigate whether patients treated in a more modern era who did not receive PMRT have a lower risk of LRR.

Our hypothesis was that modern treatment approaches, such as the use of sentinel lymph node surgery and improvements in systemic treatments, have also contributed to a lower risk of LRR and have provided further evidence that not all patients with 1 to 3 positive lymph nodes require PMRT.

## Methods and Materials

We retrospectively reviewed the records of breast cancer patients treated with mastectomy followed by adjuvant systemic therapy for patients with T1,2 disease with 1 to 3 positive lymph nodes. We evaluated the LRR outcome for patients treated in 2 eras: 1978-1998 (early era) and 2000-2007 (later or modern era). We selected these eras to pick periods of time before and after selective modern-day treatment advances, including the routine use of sentinel lymph node surgery and improvements in systemic treatment such as taxanes and aromatase inhibitors.

We included only patients who came to our institution at the time of their primary presentation. We excluded the 51 patients who were treated at an outside facility with mastectomy for a T1,2 breast cancer with 1 to 3 positive lymph nodes and who subsequently presented for a second opinion after experiencing a recurrence. Patients who were given

neoadjuvant systemic treatment before mastectomy were likewise excluded. The patients treated in the early era were identified through a multidisciplinary clinical trials database. Therefore, all these patients were treated on a phase 2 or 3 clinical trials investigating adjuvant systemic treatment questions. We previously reported the LRR outcome in these patients (15, 16), but for this study we updated the results to permit 15-year outcome data. The patients included in the later era were identified in a multidisciplinary database that enrolled all consecutively treated patients. The LRR outcome in some of the patients who did not receive PMRT in the later era were previously reported (17), but again, these data were updated and new patients were added.

We divided the patients into 4 populations based on the time of diagnosis and the use of adjuvant PMRT: (1) early cohort (1978-1997) without PMRT; (2) early cohort with PMRT; (3) later cohort (2000-2007) without PMRT; and (4) later cohort with PMRT. The differences between these populations were studied with a  $\chi^2$  test. The primary outcome analyzed was LRR, which was defined in this study as evidence of disease in the ipsilateral chest wall/skin/axilla, disease in the ipsilateral internal mammary/axillary/supraclavicular/infraclavicular nodes, and disease in the sternum that showed evidence of local tissue involvement on radiographic imaging. LRR rates were calculated by Kaplan-Meier analysis and compared by use of a 2-sided log-rank test. We used a Kaplan-Meier method over a competing risk method because we were interested in estimating the total risk of LRR, inasmuch as this has relevance in radiation decision making (18). One variable we were not able to adequately assess was the size of disease within the lymph node because it was not consistently reported in the same fashion over time. In addition, this precluded us from designating patients into the subcategories of the N1 staging system. We performed a Cox logistic regression analysis on the patients divided according to treatment eras. We also repeated a Cox analysis on all patients from both eras who did not receive PMRT, and then again only those without PMRT who were treated in the later era.

## Results

The study population consisted of 1027 patients with T1,2 breast cancer with 1 to 3 positive lymph nodes treated with mastectomy and adjuvant chemotherapy with or without PMRT. Five hundred five patients were treated in the early era, 98 (19%) of whom received PMRT, and 522 patients were treated in the later era, 137 (26%) of whom received PMRT ( $\chi^2$  for this difference,  $P = .009$ ). Full details concerning the patients' clinical, pathologic, and treatment characteristics for each of the 4 groups are given in Table E1 (available online at [www.redjournal.org](http://www.redjournal.org)), and the differences between radiation use patterns in the early and later eras are highlighted in Table 1. Patients in the early era

**Table 1** Use of radiation in adverse features during later era versus earlier era

Factor	Percentage who received postmastectomy radiation	
	Early era	Later era
Age $\leq 40$	22%	36%
T2 disease	22%	44%
3 positive lymph nodes	23%	50%
ER-negative disease	16%	30%
ECE $> 2$ mm	18%	67%
+LVSI	16%	32%
Overall rate of use	19%	26%

Abbreviations: ECE = extracapsular extension; ER = estrogen receptor; LVSI = lymphovascular space invasion.

were treated before the routine use of taxanes, sentinel lymph node surgery, and aromatase inhibitors; therefore, no patient in the early era received any of these treatments. By contrast, 65% of the patients in the later era underwent sentinel lymph node surgery, 85% were treated with taxanes, and 50% were treated with aromatase inhibitors (Table E1, available online at [www.redjournal.org](http://www.redjournal.org)). None of the patients in either era were treated with dose-dense therapy, although taxanes were frequently given on a weekly schedule. The radiation treatment fields and radiation dose for the patients who received PMRT was relatively consistent during both eras. PMRT gave 50 Gy in 2-Gy fractions to the chest wall, level III and supraclavicular fossa, and internal mammary lymph nodes, followed by a 10-Gy chest wall boost dose. One difference between the eras was that in the early era, fluoroscopic simulation was performed. In the later era, patients receiving PMRT had computed tomography simulation and 3-dimensional dose calculation algorithms.

The median follow-up times for the early era group and the later era group were 205 months and 84 months, respectively.

The use of PMRT during both eras was determined by the treating physicians. Accordingly, there are significant differences between the PMRT and no-PMRT subgroups in both eras. Namely, patients who were treated with radiation more commonly were younger, more commonly had T2 disease, and more commonly had a higher number of involved lymph nodes. How factors influenced PMRT treatment decisions also varied by era. For example, in the early era, only 22.5% of patients with T2 tumors received PMRT, whereas in the later era 44.1% of patients with T2 tumors received PMRT. In addition, in the early era, only 23.7% of patients with 3 positive lymph nodes received PMRT, whereas in the later era, 50.0% of patients with 3 positive lymph nodes received PMRT. Other groups who more commonly received PMRT in the later era included younger patients, patients with gross extracapsular extension of disease, and patients with estrogen receptor-negative disease.

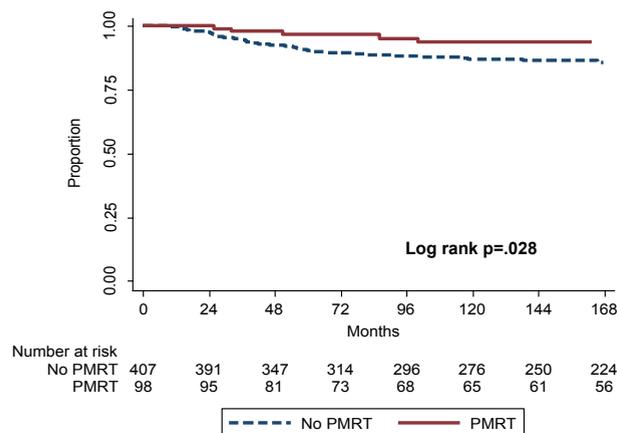
### Locoregional recurrence according to PMRT

Table E2 (available online at [www.redjournal.org](http://www.redjournal.org)) shows the LRR rates for the various patient, pathologic, and treatment groups. Crude numbers showed that within the population of 1027 patients there were 82 (8%) LRR events. The early cohort that did not receive PMRT had 56 events (13.8%); the early cohort PMRT treatment group had 5 events (5.1%); the later cohort no-PMRT group had 15 events (3.9%), and the later cohort that received PMRT had 6 events (4.4%). In the patients who had the site of LRR clearly documented, the chest wall was the most common site of LRR, followed by the infraclavicular/supraclavicular fossa, internal mammary region, and finally the level I/II axilla. Figure 1 shows the Kaplan Meier local-control curve for the patients treated in the early cohort. The 5-year LRR rate for the patients in the early cohort was 9.5% without PMRT and 3.3% with PMRT, and the respective 15-year rates were 14.5% versus 6.1% (log-rank  $P=.028$ ). A Cox regression analysis of the early cohort revealed PMRT use to be a significant factor predictive of LRR (adjusted hazard ratio [AHR] 0.37,  $P=.035$ ). Figure 2 shows the local control curves for the later cohort of patients. In contrast to the early cohort, in the later cohort there was not a statistical difference in the LRR according to use of PMRT. In addition, in the later cohort, PMRT use was not significant in a Cox analysis (AHR 1.41,  $P=.48$ ).

### Locoregional recurrence in patients who did not receive PMRT

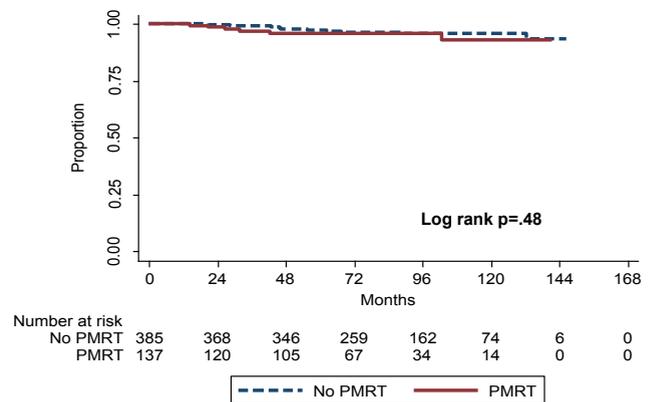
Figure 3 shows the local control curves for the patients who did not receive PMRT divided according to era of

#### Locoregional control in the early cohort patients according to use of PMRT



**Fig. 1.** Local control curves for patients treated in the early era with mastectomy and adjuvant systemic treatment with or without postmastectomy radiation therapy (PMRT). As shown, PMRT led to a statistically improved local control rate.

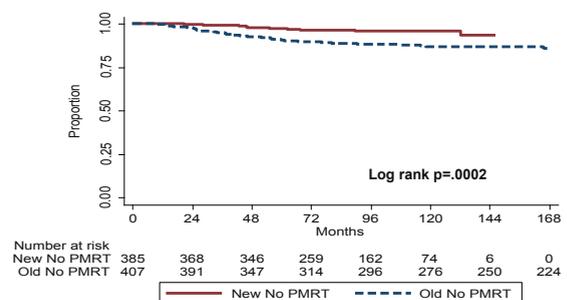
#### Locoregional control in the later cohort patients according to use of PMRT



**Fig. 2.** Local control curves for patients treated in the later era with mastectomy and adjuvant systemic treatment with or without postmastectomy radiation therapy (PMRT). As shown, there were no statistical differences in local control according to PMRT use.

treatment. As shown in the figure, patients treated in the later cohort had a statistically significant lower rate of LRR than did those treated in the early cohort. This in part reflects selection biases in the populations because in the later era more patients with adverse features were treated with PMRT (Table 1). We next conducted multivariable Cox analyses to gain insights into cofactors that predict for LRR specifically in the patients who were not treated with PMRT. In an analyses that included no PMRT from both eras, the most significant factor predictive of LRR for the patients who did not receive PMRT was the era in which the patient was treated (AHR 0.35 for later era,  $P<.001$ ).

#### Locoregional control in patients who were not treated with PMRT according to treatment era



**Fig. 3.** Local control curves for patients treated with mastectomy and adjuvant systemic treatment without postmastectomy radiation therapy (PMRT) divided according to era of treatment. As shown, there was a much higher local control rate in the patients treated in the more modern era.

To help refine the selection criteria for radiation use in modern patients, we then conducted a Cox analysis limited to the data from the later era no-PMRT cohort. The following 2 factors were independently associated with higher rates of LRR in this cohort: pathologic tumor size >3 cm (AHR 4.56,  $P=.019$ ) and no sentinel lymph node dissection performed (AHR 4.74,  $P=.005$ ). For patients with both of these factors, the 5-year LRR without PMRT ( $n=14$ ) was 9.9%.

### Total breast cancer event rates

The 5-year and 10-year breast cancer event rates (determined as development of any breast cancer recurrence or a breast cancer death) for the 4 groups were as follows: early era no-PMRT 22% and 31%; early era with PMRT 27% and 34%; later era no-PMRT 8% and 13%; later era with PMRT 14% and 27%.

### Discussion

There remains a significant controversy as to whether all patients treated with mastectomy and adjuvant systemic therapy for T1,2 disease with 1 to 3 positive lymph nodes should be recommended to receive PMRT. In this article, we report an outstanding local control rate in a group of patients with this stage of disease treated in the modern era who did not receive PMRT. Specifically, the respective 5-year and 10-year LRR rates for patients who did not receive PMRT and were treated in the modern era were only 2.8% and 4.3%. Moreover, only 26% of patients with this stage of disease received PMRT, indicating that with careful selection criteria, nearly three quarters of patients with T1,2 breast cancer with 1 to 3 positive lymph nodes avoided the toxicities, costs, and inconveniences of PMRT without having an unacceptable LRR rate.

There are many potential reasons why the rate of LRR in patients in our report who did not receive PMRT was much lower than historically reported rates. First, many patients with grossly evident lymph node–positive disease are currently treated with neoadjuvant chemotherapy. This has the potential of causing patients treated with an initial mastectomy to have a smaller volume of disease compared with those treated before the use of neoadjuvant chemotherapy. For example, we found that 65% of the patients treated in the more modern era were candidates for sentinel lymph node surgery. In addition, the pathologic processing and serial sectioning of sentinel lymph nodes has led to the detection of very small metastatic disease foci, which often may have not been detected with standard pathologic processing of dissected axillary lymph nodes. Therefore, it is possible that some patients with 1 to 3 positive lymph nodes in the later era may have been considered to be lymph node–negative if their lymph nodes had undergone the same pathologic examination techniques used in the early era. This results in a form of stage migration, which

can lower risk the risk of LRR in the later era cohort. Another clear contributor to the low LRR risk in the later cohort was the increased use of PMRT in the patients with higher-risk features. This of course selects for a more favorable group in the later cohort of patients who did not receive PMRT. Finally, it is likely that the numerous advances in systemic treatments, such as the incorporation of taxanes and aromatase inhibitors, likely also have had locoregional benefits. When we conducted a Cox regression analysis of LRR for the entire group of patients who did not receive radiation, treatment era was the most significant independent factor. Specifically, the no-PMRT patients treated in the more modern era had a 63% proportionally lower risk of LRR than did the no-PMRT patients in the earlier era. It is important to recognize that the randomized trials suggesting a benefit from PMRT for patients with 1 to 3 positive lymph nodes were conducted before to these treatment advances and changes in treatment strategies occurred.

In our previous studies of LRR in patients treated with mastectomy and radiation, we reported a 13% rate for patients with T1,2 with 1 to 3 positive lymph nodes (15, 16). These rates were lower than those reported in the Danish and British Columbia trials but were consistent with similar rates reported by investigators from the Eastern Cooperative Oncology Group and the National Surgical Adjuvant Breast and Bowel Project (1-6, 10, 12-14). We also found that larger T2 tumors, lymphovascular space invasion, 3 positive lymph nodes, close/positive margins, patient age under 40, gross extracapsular extension of disease, and skin or nipple invasion all were important cofactors that increased the LRR to clinically relevant rates (12). Accordingly, these factors influenced decisions concerning PMRT in our more modern era of patients. For example, in our earlier era cohort, PMRT was used in 19% of patients, whereas in the more recent years, the use increased to 26% of patients. In addition, the majority of patients with T2 disease received PMRT in the later cohort but not in the earlier cohort. When we analyzed the cofactors predictive of LRR only in the later cohort who did not receive radiation, we again demonstrated the importance of tumor size and also highlighted the importance of sentinel lymph node surgery. Specifically, the only higher-risk cohort we were able to find were those with T2 disease who were not candidates for sentinel lymph node surgery.

The degree to which adequate risk stratification versus modern treatment played a role in reducing the LRR rate without PMRT is uncertain. However, both clearly seem to be contributing to the improved outcomes of patients in the modern treatment era. A recent article from the Cleveland Clinic also reported a 5-year LRR rate of only 8.9% in 271 modern-day patients with 1 to 3 positive lymph nodes treated without PMRT (19). They identified 2 factors that further increased the risk: Bloom-Richardson grade 3 and extracapsular extension. For the patients who had neither of these factors, the 5-year LRR risk was only 4.1%. Another recent report from Memorial

Sloan-Kettering also examined the LRR recurrence rate in 1331 patients with T1,2 disease with 1 to 3 positive lymph nodes (20). They also reported a 5-year LRR recurrence rate of less than 5% in the patients who were not treated with PMRT. The risk, however, was higher in the younger patients ( $\leq 50$  years) and those with lymphovascular space invasion. Other authors have reported that tumor size over 4 cm, 3 positive lymph nodes, inadequate lymph node dissection, lymphovascular space invasion, young patient age, triple negative disease, and size of lymph node metastasis also increase the LRR risk without PMRT (12-24). Together, these studies suggest that patients with 1 to 3 positive lymph nodes are a heterogeneous group, and recommendations concerning PMRT should consider cofactors such as those just stated. On the basis of these data, our institutional policy is to be selective in the use of PMRT for patients with T1,2 disease with 1 to 3 positive lymph nodes. We consider treatment for younger patients and those with lymphovascular space invasion (except those specified as having it in only 1 focal area), 3 positive lymph nodes (determined by any pathologic method), triple negative disease, tumor size of 4 cm, skin or nipple invasion, or a combination of these factors.

There are limitations that should be considered when the results of this study are interpreted. Because of its retrospective nature, we could not directly test the benefits of PMRT in specific subgroups of patients with T1,2 with 1 to 3 positive lymph nodes. Indeed, in the later era, important cofactors helped determine why 26% of the patients received PMRT, and our study could not test whether radiation clearly benefited these patients. The use of these cofactors to select treatment also led to selection bias of the patients who did not receive PMRT. Therefore, these results should not be generalized to all patients with 1 to 3 positive lymph nodes. Although we offer hypotheses that improved systemic agents, and the use of sentinel lymph node surgery contributed to these low rates, we were not equipped to specially test these hypotheses. Our retrospective study was also unable to examine a potential for improved systemic outcomes that are independent from an LRR benefit.

In conclusion, breast cancer patients with T1,2 disease with 1 to 3 positive lymph nodes who received modern treatments had a lower risk for LRR than is suggested by the historical data.

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