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Biologically Informed Decision-Making for PMRT in pT3N0M0 Luminal Breast Cancers (Protocol MF22-02): International Multicenter Real-World Data

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Abstract

Two hundred and 2 women from 16 centers with pT3N0M0 hormone receptor (HR) positive, HER2 negative BC who underwent mastectomy were retrospectively analyzed. Patients were divided into 2 groups: PMRT ($n = 130$) and no PMRT ($n = 69$). Groups were compared in terms of overall survival (OS), loco-regional recurrence (LRR) rate, and distant metastases (DM) in light of Magee Equations Score (MS). At a median follow-up of 51.3 months for the no PMRT group and 65.9 months for the PMRT group ($P = .041$), 9% ($n = 6$) of patients from the no PMRT group and 2% ($n = 3$) from the PMRT group developed LRR ($P = 0.047$). There was no difference in local recurrence (1% in no PMRT group vs. 2% in PMRT group; $P = .7$) and distant recurrence (7% in no PMRT group vs. 3% in PMRT group; $P = .16$) in patients who received PMRT and no PMRT. Further comparison of the LRR in the no PMRT and PMRT groups in patients with an MS < 18 did not show a significant difference (3% vs. 4%; $P = .64$). However, among patients with an MS ≥ 18, no PMRT group had a higher LRR rate compared to the PMRT group (11% vs. 2%; $P = .01$). In patients with an MS ≥ 18, the administration of PMRT correlates with statistically significantly better LRR-free survival (HR 0.19; 95% CI 0.05-0.79; $P = .02$). Patients with MS<18 experience a comparable rate of recurrence irrespective of PMRT, while those with MS≥ 18 have higher rates of LRR and thus should not omit PMRT.

Background: Current guidelines do not list definitive recommendations for postmastectomy radiation therapy (PMRT) in patients with luminal pT3N0M0 breast cancer (BC). Increased data suggests de-escalation of radiation therapy (RT) in genomically defined biologically favorable luminal BCs. The goal of this study is to determine whether PMRT can be safely omitted for this specific subgroup of patients. **Methods and materials:** Two hundred and 2 women from 16 centers with pT3N0M0 hormone receptor (HR) positive, HER2 negative BC who underwent mastectomy were retrospectively

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analyzed. No patients received neoadjuvant chemotherapy. Three patients were excluded because of positive surgical margins. Patients were divided into 2 groups: PMRT ($n = 130$) and no PMRT ($n = 69$). Groups were compared in terms of overall survival (OS), loco-regional recurrence (LRR) rate, and distant metastases (DM) in light of the Magee Equations Score (MS), menopausal status/age, axillary surgery, pathology, lymphovascular invasion (LVI), adjuvant chemotherapy, and adjuvant endocrine therapy. **Results:** The majority of the patients had invasive ductal carcinoma (49%, $n = 98$). There was no significant difference regarding tumor size, axillary surgery, and adjuvant endocrine therapy between the 2 groups ($P = .82$, $P = .28$, $P = .12$, respectively). LVI was 19% ($n = 39$), and it was greater in the PMRT group (25% vs. 10%; $P = .01$). Patients in the PMRT group received more chemotherapy (66% vs. 30%; $P < .001$), had more grade 3 tumors (28% vs. 9%, $P = .005$), and were more premenopausal (49% vs. 22%; $P = .0001$). At a median follow-up of 51.3 months for the no PMRT group and 65.9 months for the PMRT group ($P = .041$), 9% ($n = 6$) of patients from the no PMRT group and 2% ($n = 3$) from the PMRT group developed LRR ($P = .047$). There was no difference in local recurrence (1% in no PMRT group vs. 2% in PMRT group; $P = .7$) and distant recurrence (7% in no PMRT group vs. 3% in PMRT group; $P = .16$) in patients who received PMRT and no PMRT. Further comparison of the LRR in the no PMRT and PMRT groups in patients with an MS < 18 did not show a significant difference (3% vs. 4%; $P = .64$). However, among patients with an MS ≥ 18, no PMRT group had a higher LRR rate compared to the PMRT group (11% vs. 2%; $P = .01$). In patients with an MS ≥ 18, the administration of PMRT correlates with statistically significantly better LRR-free survival (HR 0.19; 95% CI 0.05-0.79; $P = .02$). **Conclusions:** Our findings imply that when considering PMRT for patients with pT3N0M0, HR-positive, and HER2-negative BC, clinicians can benefit from a combination of pathological risk factors and recurrence prediction models. Patients with MS < 18 experience a comparable rate of recurrence irrespective of PMRT, while those with MS ≥ 18 have higher rates of LRR and thus should not omit PMRT.

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Keywords: Luminal type, Magee score, Postmastectomy radiotherapy, pT3N0M0 breast cancer, Risk-adapted radiotherapy

Introduction

In the modern era, risk-adapted radiotherapy (RT) in breast cancer (BC) has become increasingly important, with de-escalated approaches favored for those at low risk of locoregional recurrence (LRR). This strategy aims to reduce treatment-related morbidity and increase the quality of life of patients without compromising oncological outcomes. In the presence of T3-T4 BC, positive surgical margins, and axillary lymph node metastasis after mastectomy, adjuvant postmastectomy radiotherapy (PMRT) is recommended as standard of care. In high-risk cases, adjuvant PMRT reduces LRR and improves survival.[1-4] However, the risk of LRR is generally low in lymph node-negative cases.[5]

According to the recently published updated clinical practice guideline of the American Radium Society, high-risk lymph node-negative cases (large tumor, triple-negative, or surgical margin positive) benefit from PMRT.[6] Within this group, pT3N0 cases are uncommon and heterogeneous.[7,8] The role of PMRT is controversial due to the lack of randomized controlled trials specific to these cases.[7-16] Studies showing survival benefits often use outdated RT techniques and suboptimal systemic treatment. Today, with modern RT techniques and effective systemic treatment, the role of PMRT may be limited in select patients with low LRR rates.[17] Therefore, the American College of Radiology recommends that treatment decisions should be individualized in these cases.[18]

Today, when deciding on PMRT, the risk of LRR is tried to be determined by considering classical clinicopathological risk factors such as patient age, histological grade, presence of lymphovascular invasion (LVI) and surgical margin status, as well as tumoral biomarkers such as estrogen receptor (ER)/ progesterone receptor (PR) or human epidermal growth factor receptor 2 (HER2) status and molecular features. Thus, PMRT especially in low risk pT3N0 cases where the role of PMRT controversial.[19] Although various nomograms have been tried to developed for this purpose, there is currently no clear method of distinguishing low-risk from high-risk cases.[15,20]

Multigene assays play an important role in determining the prognosis and adjuvant systemic treatment decision in BC cases. With these methods, patients with lymph node-negative, hormone receptor (HR) positive, and HER2-negative tumors are tried to be identified who have a high risk of distant recurrence and, therefore, may benefit from chemotherapy. In the recently published prospective TAILORx (Trial Assigning IndividuaLized Options for Treatment) study, the benefit of chemotherapy could not be demonstrated in cases with a 21-gene expression assay (Oncotype DX, Genomic Health, Redwood City, California) recurrence score (RS) of 25 or less. Therefore, the harmful effects of chemotherapy can be avoided in cases with low RS. However, there is no standard recommendation yet regarding its use in adjuvant RT decisions. In NSABP B14, B20 and B28 studies, the RS was shown to be associated with the risk of LRR in both lymph node-negative and positive patients.[21,22] In the ongoing prospective randomized MA.39 TAILOR RT study (NCTNCT00005957), the role of regional RT in those with non–high-risk Oncotype DX RS is being assessed.

However, genomic assays have some drawbacks, such as a high cost and a long turnaround time to get results. For this reason, alter-

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native methods have been investigated, and the Magee equations score (MS) has been developed using classical clinicopathological factors (tumor size, grade, ER, PR, HER2, and Ki67)[23-27] It is shown to be an affordable and reliable method for predicting the Oncotype DX RS. Studies have shown that MS can be used to predict pathologic complete response (pCR) and clinical outcomes in HR) positive, HER2 negative BC.[28-31]

To date, no study has used this method to predict the PMRT benefit in patients with pT3N0M0 BC. The goal of this study is to determine whether PMRT could be safely omitted in cases with low risk for MS for the luminal subgroup of BC patients.

Materials and Methods

Patients

We conducted a retrospective analysis of women > 18 years old with pT3N0M0 luminal BC (Luminal A or B: ER / PR + Her 2 neu (−) and all Ki67 and grades were included) who underwent a mastectomy. The Protocol MF22-02 is a Breast Health Working Group International multicenter study that included 202 female patients treated in 16 centers across the US and Türkiye. Eligibility criteria included patients with ER/PR positive and HER2-negative BC ≥ 5 cm with no history of NACT. Exclusion criteria included the presence of lymph node metastasis, both micro and macro metastasis, positive surgical margins, metastatic disease, in situ cancer alone, recurrent BC, and prior history of any cancer. Patients were categorized into 2 groups: those undergoing PMRT and those not undergoing PMRT. Details of patient, tumor and treatment characteristics were recorded from each hospital's records. This study was approved by the local Institutional Review Board and conducted in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Radiation fields (treatment to the chest wall alone or treatment to the chest wall and regional lymphatics) were not assessed in this study.

Magee Equations

Data required for MS calculation, such as H-scores for ER and PR, HER2, Ki67, tumor grade, and tumor size, were obtained from pathology reports. The H-score used in the MS multiplied the percentage (0–100) of positive cells for each particular intensity (0 = no staining, 1 = weak, 2 = moderate and 3 = strong), then added all the percentages to produce a score (eg, [20 × 3] + [40 × 2] + [10 × 1] = 150). The MS was calculated for all cases and divided into 2 categories: low (< 18) and intermediate/high (≥ 18) risk (http://path.upmc.edu/onlineTools/mageeequations.html).

Follow-Up

Patients were followed every 3 months for the first 2 years, every 6 months for the next 3 years, and annually after that. During follow-up visits, routine follow-up assessments, including medical history, physical examination, and laboratory tests, were performed. If intact, the contralateral breast was monitored with annual mammography. In case of suspicion of recurrence, appropriate imaging studies, including computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET)/CT, were performed as indicated per the standard of care.

Statistical Analysis

Groups were compared in terms of overall survival (OS) and locoregional recurrence-free survival (LRRFS). OS was defined as the time from pathological diagnosis to death due to any cause or the last follow-up. Locoregional recurrence (LRR) was defined as cancer reappearance or progression in the chest wall (local recurrence-LR), as well as regional lymph nodes (regional recurrence-RR). Recurrences at any other sites were categorized as distant metastases (DM). LRRFS was calculated from the date of diagnosis to the occurrence of LRR or the last follow-up, respectively. Patients who were alive or who did not recur were censored at the date of the last follow-up.

Kaplan–Meier survival curves for OS and LRRFS were generated. The impact of patient, tumor, and treatment-related variables, including age at diagnosis, menopausal status, histopathologic subtype, tumor size, tumor grade, LVI, axillary surgery, receipt of adjuvant chemotherapy, and receipt of adjuvant endocrine therapy and MS on OS and LRRFS were compared using the log-rank test. The univariate analysis (UVA) of each covariate with the use of PMRT was assessed using the chi-squared or Fisher's test for categorical covariates and analysis of variance for numerical covariates. A multivariable Cox proportional hazards model (MVA) considered variables with univariate P-values < .2, along with variables that were significant on UVA. Statistical analyses were conducted with R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria, https://www.r-project.org) software, and a 2-tailed P-value of < .05 was considered statistically significant.

Results

The study included 202 patients, but 3 were excluded because of positive surgical margins. One hundred and thirty (65%) patients received PMRT of the 199 patients, while 69 (35%) did not receive PMRT. The median age in the entire group was 54 years (range 44-69 years). The majority of the patients had invasive ductal carcinoma (49%, $n = 98$). Patient, tumor and treatment characteristics are summarized in Table 1.

Considering the patient characteristics, the cases who received PMRT were younger (median age 49.5 vs. 59, $P = .005$) and premenopausal (49% vs. 22%, $P = .0001$) compared to the cases who did not receive PMRT. In terms of tumor characteristics, grade 3 tumors (28% vs. 9%, $P = .005$) and LVI (25% vs. 10%, $P = .01$) were observed more frequently in cases treated with PMRT than in cases without PMRT. Finally, regarding treatment characteristics, patients treated with PMRT were more likely to undergo axillary lymph node dissection (ALND) (35% vs. 17%, $P = .007$) and receive chemotherapy (66% vs. 30%, $P < .001$). There was no significant difference regarding histopathology, tumor size, axillary surgery, and adjuvant endocrine therapy between the 2 groups ($P = .67$, $P = .82$, $P = .28$, $P = .12$, respectively) (Table 1).

At a median follow-up of 51.3 (range, 33-94) months for the no PMRT group and 65.9 (range, 39-111) months for the PMRT group ($P = .041$), 9% ($n = 6$) of patients from the no PMRT group and 2% ($n = 3$) from the PMRT group developed locoregional recurrence (LRR) ($P = .047$). Although LR rates were similar

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Table 1 Comparison of Patient, Tumor and Treatment Characteristics in no PMRT versus PMRT Groups

Characteristic	PMRT (-) *n* = 69 (%)	PMRT (+) *n* = 130 (%)	*P*-Value[a]
Median age (years)	59	49.5	**.005**
Menopausal status			**.0001**
Pre-	15 (22)	64 (49)	
Post-	54 (78)	66 (51)	
Axillary surgery			.28
No	2 (3)	1 (1)	
Yes	67 (97)	128 (99)	
ALND			**.007**
No	57 (83)	85 (65)	
Yes	12 (17)	45 (35)	
Histopathology			.67
Invasive ductal carcinoma	35 (51)	63 (48)	
Invasive lobular carcinoma	20 (29)	40 (31)	
Mix carcinoma (IDC+ILC)	9 (13)	22 (17)	
Others	5 (7)	5 (4)	
Median tumor size (cm)	6	6	.82
Grade			**.005**
1	13 (19)	23 (18)	
2	50 (72)	70 (54)	
3	6 (9)	37 (28)	
LVI			**.01**
Negative	62 (90)	98 (75)	
Positive	7 (10)	32 (25)	
Adjuvant chemotherapy			**< .001**
No	47 (70)	44 (34)	
Yes	20 (30)	86 (66)	
Adjuvant endocrine therapy			.121
No	3 (4)	1 (1)	
Yes	66 (96)	129 (99)	
Median Magee score	20.2	20.5	.27
Magee score <18			.13
No	45 (65)	96 (74)	
Yes	24 (36)	34 (26)	
Ki-67 level			.18
<15	38 (55)	58 (45)	
≥15	31 (45)	72 (55)	

Boldface indicates Statistically significant.
Abbreviations: ALND = axillary lymph node dissection; LVI = Lymphovascular invasion; *n* = number; PMRT = postmastectomy radiotherapy.
[a] Nonparametric Mann-Whitney U test result.

between the groups (1% vs. 2%, $P = .7$), the difference in LRR was due to the fact that RRs were observed at a higher rate in patients who were not treated with PMRT (4% vs. 0%, $P = .04$). However, there was no significant difference in DM rates (7% in the no PMRT group vs. 3% in the PMRT group; $P = .16$) in patients who received PMRT and did not have PMRT.

There was no significant difference in OS (HR 0.64, 95% CI 0.24-1.65, $P = .35$), and the 5-year OS remained comparable in patients treated with (89%, 95% CI: 79,100) and without PMRT (88%, 95% CI: 80, 96). LRRFS was statistically significantly higher

Table 2 Comparison of Locoregional Recurrence Between no PMRT and PMRT Groups According to Magee Scores 18 and 25, and ALND

	LRR (-) n (%)	LRR (+) n (%)	*P*-Value
Magee score < 18			
PMRT			.63
No	23 (96)	1 (4)	
Yes	33 (97)	1 (3)	
Magee score ≥ 18	45 (65)	96 (74)	
PMRT			**.01**
No	40 (89)	5 (11)	
Yes	94 (98)	2 (2)	
Magee score ≤ 25			
PMRT			.141
No	51 (93)	4 (7)	
Yes	90 (97)	3 (3)	
ALND			.451
No	134 (71)	8 (89)	
Yes	56 (29)	1 (11)	

Boldface indicates Statistically significant.
Abbreviations: ALND = axillary lymph node dissection; LRR = loco-regional recurrence; n = number; PMRT = postmastectomy radiotherapy.

in patients treated with PMRT (HR 0.196, 95% CI 0.05-0.79, $P = .02$) (Figures 1 and 2). When comparing patients with or without ALND, no significant difference was observed in terms of LRRFS (HR 0.17, 95% CI 0.02-1.42, $P = .1$) and LRR (Table 2).

Further comparison of the LRR in the no PMRT and PMRT groups in patients with an MS <18 did not show a significant difference (3% vs. 4%, $P = .63$). However, among patients with an MS ≥18, the no PMRT group had a significantly higher LRR rate compared to the PMRT group (11% vs. 2%; $P = .01$) (Table 2). Although no significant difference was observed between the PMRT and no PMRT groups in terms of LRRFS rates in patients with MS < 18 (HR 0.52, 95% CI 0.03-8.29, $P = .64$), the administration of PMRT was found to be correlated with statistically significantly better LRRFS rates in patients with MS ≥18 (HR 0.15, 95% CI 0.03-0.79, $P = .025$) (Figure 3).

PMRT is the sole significant factor in the entire study group when Magee Score is not taken into account. Other factors, including axillary dissection, menopause, lymph vascular invasion, adjuvant systemic therapy and tumor grad do not appear to have an effect (Table 3). However, analyses indicated that PMRT has no effect on LRR in patients with a Magee score < 18. Since there is no variable significantly associated with LRR in patients with a Magee score < 18, multivariable analysis could not be performed. In patients with a Magee score ≥ 18, PMRT shows a trend towards significance with a *P*-value of .052, HR 0.167, and 95% CI 0.028 to 1.012 (Table 4).

Discussion

Our results showed improved locoregional control and LRRFS with PMRT in patients with pT3N0 BC. This benefit was independent of patient, tumor, or treatment-related factors. However, there was no improvement in OS with PMRT. Exploratory subgroup

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Figure 1 Overall Survival according to PMRT. There was no significant difference in OS (HR 0.64, 95% CI 0.24-1.65, $P = .35$), and the 5- year OS remained comparable in patients treated with (89%, 95% CI: 79, 100) and without PMRT (88%, 95% CI: 80, 96). CI = confidence interval; HR = hazard ratio; OS = overall survival; PMRT = postmastectomy radiation therapy.

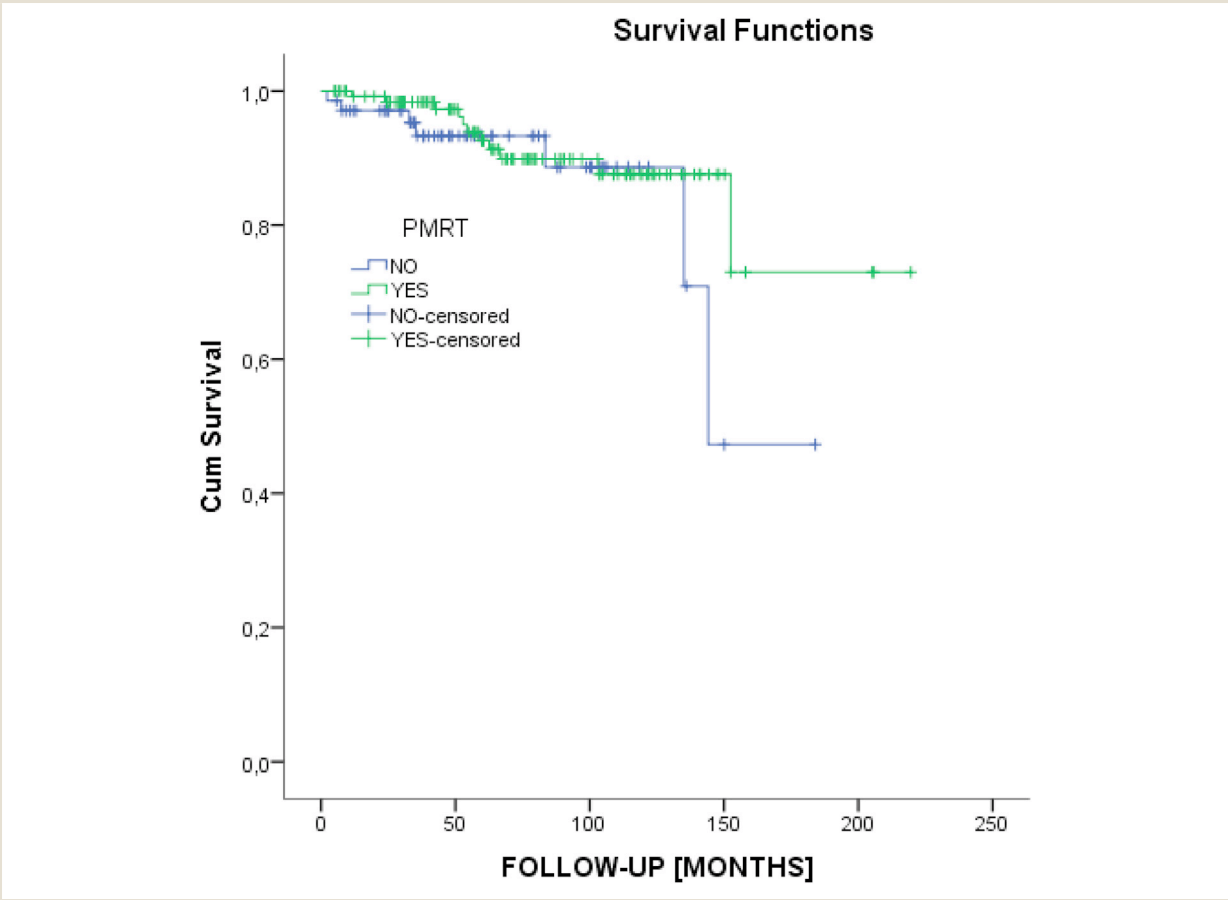


Table 3 Cox Multivariable Analysis for Locoregional Recurrence

	P	Exp(B)	95.0% CI for Exp(B)	
			Lower	Upper
Menopause	.345	0.454	0.088	2.335
Lymphovascular invasion	.546	1.678	0.313	8.994
PMRT	**.035**	**0.177**	0.035	0.888
Adjuvant systemic therapy	.883	0.877	0.154	4.998
Grade	.597	0.638	0.121	3.377
ALND	.260	0.283	0.031	2.547

Boldface indicates Statistically significant.
ALND = axillary lymph node dissection; PMRT = postmastectomy radiation therapy.
PMRT is the sole significant factor in the entire study group when Magee Score is not taken into account.

analysis showed a significant LRRFS advantage for PMRT in patients with MS ≥ 18. To the best of our knowledge, this is the first study to examine the role of PMRT in patients with pT3N0 BC, according to the MS.

Due to the rarity of pT3N0 presentation, no randomized data compares PMRT with no PMRT, and the optimal treatment paradigm remains controversial. However, many retrospective and population-based studies have shown a survival benefit with PMRT in pT3N0M0 BC.[6,9,10,12,20,31] In most of these studies, PMRT benefit was independent of age, tumor size, grade, and systemic therapy.[7,9,31] Alternatively, there are several retrospective studies in which no improvement in OS with the addition of PMRT

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Figure 2 Locoregional recurrence-free survival according to PMRT. LRRFS was statistically significantly higher in patients treated with PMRT (HR 0.196, 95% CI 0.05-0.79, $P = .02$). CI = confidence interval; HR = hazard ratio; LRRFS = locoregional recurrence-free survival; OS = overall survival; PMRT = postmastectomy radiation therapy.

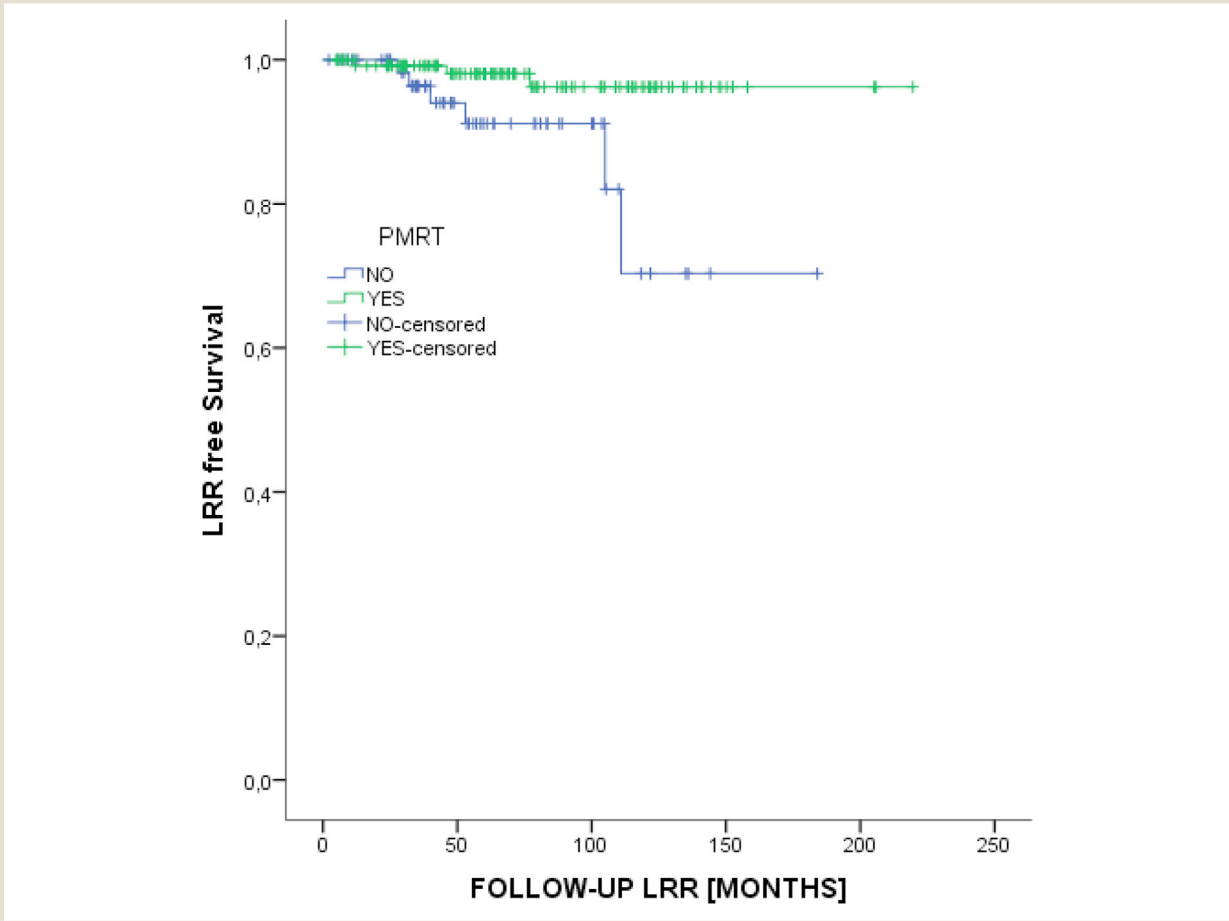


Table 4 Cox Multivariable Analysis for locoregional Recurrence for Patients With Magee Score ≥ 18

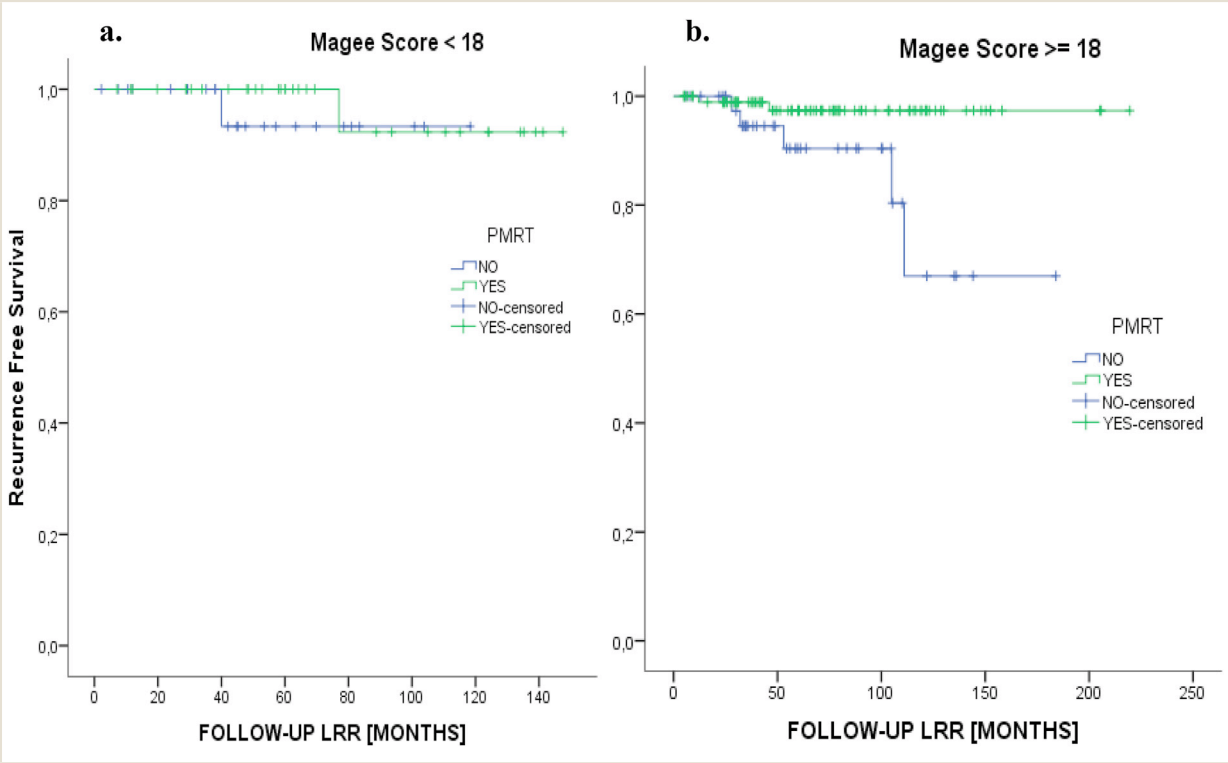
	P	Exp(B)	95.0% CI for Exp(B)	
			Lower	Upper
Menopause	.947	1.077	0.123	9.391
Lymphovascular invasion	.757	0.706	0.078	6.413
PMRT	**.052**	0.167	0.028	1,012
Adjuvant chemotherapy	.794	1.315	0.168	10.277
Grade	.971	0.960	0.110	8.386
ALND	.278	0.291	0.031	2.706

Boldface indicates Statistically significant.
ALND = axillary lymph node dissection; PMRT = postmastectomy radiation therapy.
PMRT has no effect on LRR in patients with a Magee Score <18. Since there is no variable significantly associated with locoregional recurrence in patients with a Magee score <18, multivariable analysis could not be performed. In patients with a Magee Score ≥18, PMRT shows a trend towards significance with a *P*-value of .052, HR 0.167, and 95% CI 0.028-1.012.

in patients with pT3N0 BC.[11,16,17] According to the Surveillance, Epidemiology, and End Results (SEER) database analysis, no survival benefit was shown with the addition of PMRT in pT3N0 BC.[11] Pooled analysis of NSABP B-13, B-14, B-19, B-20, and B-23 trials had 313 patients with 5 cm or larger node-negative tumors and treated with mastectomy. The 10-year locoregional failure rate was 7%. There was no difference in locoregional recurrence rates based on receipt of adjuvant systemic therapy.[32] However, it has been shown that PMRT may be beneficial in select cases, such as those < 40 years of age and ER/PR negative tumors.

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Figure 3 Locoregional recurrence-free survival for patients with MS < 18 and MS ≥ 18 according to PMRT. (A) No significant difference was observed between the PMRT and no PMRT groups in terms of LRRFS rates in patients with MS <18 (HR 0.52, 95% CI 0.03-8.29, $P = .64$). (B) The administration of PMRT was found to be correlated with statistically significantly better LRRFS rates in patients with MS ≥ 18 (HR 0.15, 95% CI 0.03-0.79, $P = .025$). CI = confidence interval; HR = hazard ratio; LRRFS = locoregional recurrence-free survival; MS = Magee score; OS = overall survival; PMRT = postmastectomy radiation therapy.



These studies are often criticized for their outdated diagnostic methods, surgical procedures and systemic treatment regimens. It is thought that the role of PMRT may be limited in the modern era with advancements in oncologic therapy. In some patients with pT3N0 BC, the risk of LRR is low, and PMRT can be omitted in these cases. Studies are ongoing to identify patients who will benefit most from PMRT in pT3N0 cases. In 2024, Meng et al.[15] developed a novel risk stratification model to identify high-risk patients with pT3N0M0 BC. This study included 2,062 patients with pT3N0M0 BC from the SEER database. OS benefit was shown with PMRT in the overall cohort. The 5-year OS was 84.2% for those who had received PMRT and 76.6% for those who had not ($P < .001$). Nomogram-based risk stratification included age (≥ 18-65 years vs. > 65 years), race, marital status, tumor size, histological grade, ER status, PR status, HER2 status, molecular subtype, chemotherapy and RT as variables and classified patients into low- and high-risk groups. However, OS benefit was not demonstrated with PMRT in the low-risk group, with an OS improvement in young and elderly patients by 10.1% and 12.4%, respectively, in the high-risk group ($P < .05$).

Today, both predictive and prognostic multigene assays are widely used to inform systemic therapy decisions in the adjuvant setting for ER-positive/HER2-negative early-stage BC. One of the most widely used commercial assays for this purpose is the Oncotype DX.[21] It is a 21-gene assay based on the expression of cancer-related genes. According to this assay, cases are classified as low (scores 0-≤ 18), intermediate (scores > 18-31), and high (scores > 31) risk groups (17). In parallel with the systemic therapy studies, studies are ongoing to identify BC patients who will benefit most from adjuvant RT in order to reduce unnecessary exposure to RT and its possible side effects. The clear benefit of these assays in identifying high-risk patients who will benefit most from RT has not yet been demonstrated. In a retrospective study published by Mamounas et al.,[22] the Oncotype DX RS was shown to be associated with the risk of LRR in ER/PR positive patients with lymph node metastasis who underwent adjuvant chemotherapy and endocrine therapy (NSABP B28). During a median follow-up of 11.2 years, 10-year LRR rates were 3.3% in cases with low RS (< 18), 7.2% in cases with intermediate RS (18-30), and 12.2% in cases with high RS (≥ 31) ($P < .001$). According to this study, RS was found to be an independent predictor of LRR.

Biomarker low-risk, ER-positive, HER2-negative BC is associated with good outcomes, and PMRT may be omitted in these cases. However, PMRT may be particularly useful in cases with a

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low risk of DM where the primary recurrence pattern is LRR. A study published by Goodman et al.[33] showed that PMRT in patients with pT1-2N1 ER-positive BC was associated with longer OS in patients with low RS but not in patients with an intermediate or a high RS. In the retrospective analysis of the Phase 3 randomized Southwest Oncology Group S8814 study, it was shown that RS was an independent prognostic factor for LRR in ER/PR-positive and lymph node-positive postmenopausal patients.[34] Among patients who did not receive PMRT, the 10-year LRR rate was higher in those with RS ≥18 compared to those with RS 0-17 (16.8% vs. 7.7%, $P = .03$). In a secondary analysis of the SWOG S1007 trial, in patients with HR-positive, HER2-negative BC with an Oncotype DX RS of 25 or less with 1-3 lymph nodes, the cumulative LRR was 0.11% after mastectomy with PMRT and 1.7% after mastectomy without RT. These low recurrence rates were maintained in patients irrespective of receipt of chemotherapy or hormonal therapy. In the ongoing biomarker-directed randomized phase III MA.39/TAILOR RT trial comparing BC recurrence-free interval in patients with ER-positive/HER2-negative BC that is low risk as defined by Oncotype DX RS. This study includes patients with ER ≥ 1%, HER2- negative, pT1-2N1 or pT3N0, and Oncotype DX RS ≤25. All patients will receive endocrine therapy. The patients were stratified as breast-conserving surgery vs. mastectomy, ALND vs. SLNB, whether they received adjuvant chemotherapy or not, and RS 0-10 vs. 10-25. The patients were randomized to receive regional nodal irradiation postlumpectomy and locoregional RT to the chest wall and regional nodes following mastectomy[35] Soft tissue deposits in the axilla have been correlated with increased risk of local recurrence and distant metastasis. It is imperative to routinely report axillary soft tissue involvement, beyond lymph nodes and extra capsular extension, especially when considering de-escalation of therapy. The extent of lympho-vascular invasion has not been well validated in the absence of nodal involvement in defining the risk of subsequent recurrence patterns. It needs to be assessed while considering the de-escalation of PMRT.[36]

The financial toxicity of multigene assays, especially for those in low- and middle-income countries (LMIC), has led to the development of different multivariable models that are clinically useful and cost-effective. For this purpose, MS, which was found to be highly correlated with Oncotype-DX® RS, was developed and validated.[23,24,34] It is easily accessed and available online for free for anyone to use. MS is a multivariable model that uses histopathologic and immunohistochemical data to predict Oncotype-DX® RS. Although studies in the literature have shown that it plays a role in predicting pCR after NACT in ER-positive and HER2-negative cases, there are no studies to predict patients who will most benefit from RT.[28–30] In our study, we tried to determine the cases that would benefit the most from PMRT, and we found a significant LRRFS advantage for PMRT in patients with MS ≥18.

Our study has several limitations, including the low number of patients and the short follow-up period. In BC, a much longer follow-up period is required for the locoregional control benefit for PMRT to be translated into a survival benefit. Although multi-institutional, another limitation is the study's retrospective design and the imbalances between the treatment groups. Patients who underwent PMRT were younger, premenopausal, and had more grade 3 and LVI-positive tumors. ALND and chemotherapy were also performed more frequently in cases that underwent PMRT. Therefore, there was an inherent potential selection bias and heterogeneity associated with our study. We were also not able to collate information on the radiation fields, such as the treatment of supraclavicular and internal mammary lymph node irradiation, which may impact the locoregional outcomes.

In conclusion, PMRT is recommended for pT3N0 BC patients in the presence of predictive factors for high risk of LRR. Such factors may include young age, LVI, high tumor grade, "triple-negative" subtype, and MS ≥ 18, as demonstrated for the first time in our study. Although PMRT could be safely omitted in patients with MS < 18, for patients with pT3N0 BC, it was associated with improvement in LRRFS in patients with MS ≥18. A large prospective multi-institutional study with a large cohort size and more homogeneity is required to validate the use of MS in PMRT decisions in daily practice.

Clinical Practice Points

- Pooled analysis of NSABP B-13, B-14, B-19, B-20, and B-23 trials had 313 patients with 5 cm or larger node-negative and treated with mastectomy. The 10-year locoregional failure rate was 7%. However, it has been shown that PMRT may be beneficial in select cases, such as those <40 years of age and ER/PR negative tumors.
- Oncotype DX RS was shown to be associated with the risk of LRR in ER/PR positive patients with lymph node metastasis who underwent adjuvant chemotherapy and endocrine therapy (NSABP B28). During a median follow-up of 11.2 years, 10-year LRR rates were 3.3% in cases with low RS (< 18), 7.2% in cases with intermediate RS (18-30), and 12.2% in cases with high RS (≥ 31) ($P < .001$). According to this study, RS was found to be an independent predictor of LRR.
- The financial toxicity of multigene assays, especially for those in low- and middle-income countries (LMIC), has led to the development of different multivariable models that are clinically useful and cost-effective such as the Magee score.
- PMRT is recommended for pT3N0 BC patients in the presence of predictive factors for high risk of LRR. Such factors may include young age, LVI, high tumor grade, "triple-negative" subtype, and MS ≥18, as demonstrated for the first time in our study.
- Although PMRT could be safely omitted in patients with MS <18 for the patients with pT3N0 BC, it was associated with improvement in LRRFS in patients with MS ≥18.

CRediT authorship contribution statement

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tualization. **Parul Nafees Barry:** Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis, Data curation, Conceptualization. **Caleb King:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Rohit Bhargava:** Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis, Data curation, Conceptualization. **Hasan Karanlik:** Writing – review & editing, Writing – original draft, Visualization, Data curation, Conceptualization. **Ferah Yildiz:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Formal analysis, Data curation, Conceptualization. **Aykut Soyder:** Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis, Data curation, Conceptualization. **Berk Goktepe:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Kazim Senol:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Caglar Guzel:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Ebru Sen:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Levent Yeniay:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Ahmet Dag:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Didem Can Trabulus:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Alper Coskun:** Writing – review & editing, Writing – original draft. **Hagigat Veliyeva:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Zafer Utkan:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Berkay Demirors:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Efe Sezgin:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **John Austin Vargo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Data curation, Conceptualization.

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