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ORIGINAL RESEARCH

Therapeutic value of postmastectomy radiation therapy for T1–2 breast cancer with 1–3 positive lymph nodes

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Abstract

Purpose Postmastectomy radiation therapy (PMRT) reduces locoregional recurrence (LRR) and breast cancer mortality for node-positive breast cancer, but its indication remains controversial in patients with 1–3 positive lymph nodes.

Methods We retrospectively analyzed LRR and survival rates in T1–2 breast cancer with 1–3 positive lymph nodes according to PMRT. The prognostic factors and the impact of the current standard systemic therapy (early period: 2000–2007 and late period: 2008–2015) were assessed because adjuvant trastuzumab has only been approved in 2008 in Japan.

Results Between 2000 and 2015, 162 patients with T1–2N1 breast cancer underwent mastectomy, and 32 (19.8%) underwent PMRT. The 5-year LRR rates were 5.3% in the no PMRT group and 0% in the PMRT group ($P = 0.272$). Meanwhile, the disease-free survival rates were 80.6% in the no PMRT group and 96.6% in the PMRT group ($P = 0.095$), and the benefit of PMRT was low in the late period. The significant prognostic factors were larger tumor size (T2) and estrogen receptor negativity.

Conclusions PMRT tended to improve LRR and disease-free survival. The omission of PMRT is carefully determined.

Keywords Breast cancer · Lymph node metastasis · Postmastectomy radiation therapy

Introduction

Postmastectomy radiation therapy (PMRT) provides significant clinical advantages for the patients with node-positive breast cancers who received mastectomy and systemic therapy and is recommended in many treatment guidelines [1–4]. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis has shown that PMRT reduced not only locoregional recurrence (LRR), but also breast cancer mortality [5]. However, their meta-analysis has certain shortcomings, including a high 5-year LRR rate of 16.5%, inadequate axillary and systemic managements, and stage migration via sentinel node biopsy [6]. The indication of PMRT remains controversial in T1–2 breast cancers with 1–3 positive lymph nodes. In the United States, only 30–40% of patients with 1–3 positive lymph nodes received PMRT, while over 60% of patients with 4 and more positive lymph nodes received the treatment [7, 8]. In a Japanese survey, PMRT was performed to only 20% of T1–2 breast cancers with limited positive lymph nodes in 2016 [9].

Recent studies reported low LRR rates of only up to 5% with and without PMRT in breast cancers with 1–3 positive lymph nodes [10–12]. The Japanese Breast Cancer Society reported in 2006 a 5-year relapse-free survival rate of 93.7% and overall survival (OS) of 93.3% [13]. A retrospective cohort study showed that PMRT no longer reduced LRR from 2000 to 2007 owing to advancements in systemic therapy, such that the 5-year LRR rates were 2.8% without PMRT and 4.2% with PMRT [11].

This study aimed to investigate the impact of PMRT for breast cancers with 1–3 positive lymph nodes. We hypothesized that PMRT did not improve the survival of the patients with T1–2 breast cancer with 1–3 positive lymph nodes who received systemic therapy.

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Materials and methods

Patients

Among breast cancer patients who underwent mastectomy between 2000 and 2015 at Hiroshima University Hospital, those with T1–2 breast cancers that involved 1–3 lymph nodes were eligible. The patients who received neoadjuvant chemotherapy were excluded. The medical records were retrospectively reviewed, and the clinicopathological characteristics, LRR rate, and survival rate were assessed. We divided the study period into the early (2000–2007) and the late periods (2008–2015) because adjuvant trastuzumab has only been approved in 2008 in Japan.

The Institutional Review Board approved this study. All procedures performed involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Radiation therapy

During the study period, we have not routinely performed PMRT for T1–2 breast cancers with 1–3 positive lymph nodes, and the performance of PMRT for high-risk cases decided by the cancer board composed of breast surgeons, radiation oncologists, and pathologists. The radiation fields were the chest wall and supraclavicular fossa, and the internal mammary field was included if metastasis was suspected or confirmed. The total radiation dose was 50 Gy in 25 fractions, and the discretionary electron beam boost of 10 Gy was performed when the deep margin was positive.

Statistics

Summarized data are presented as numbers and percentages unless otherwise stated. Frequencies were compared using Fisher's exact test for categorical variables and unpaired *t* test for continuous variables. The survival rates were analyzed via the Kaplan-Meier method using the log-rank test. LRR was defined as breast cancer recurrence in the ipsilateral chest wall, skin, axilla, infraclavicular, supraclavicular, or internal mammary lymph nodes. Distant recurrence was defined as recurrence outside the regions identified as LRR. Disease-free survival (DFS) was defined as the interval from the surgery to the first event (breast cancer recurrence or death from any cause). If no events occurred, the last observation was censored. Predictive factors for DFS and OS were assessed via univariate and multivariate analyses using the Cox proportional hazards model. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [14].

Results

A total of 162 patients were assessed in this study, and 32 (19.8%) received PMRT. Omission of axillary dissection was due to micrometastasis (22 patients) and only intramammary lymph node metastasis (one patient). The median follow-up period was 6.2 years. The patients' characteristics and the treatment are shown in Table 1. Although the patients with human epidermal growth factor receptor 2 (HER2)-positive disease did not receive PMRT, many of HER2-positive breast cancer patients were excluded because of neoadjuvant chemotherapy. The frequency of PMRT did not differ by tumor size, number of positive node, estrogen receptor (ER) status, and Ki-67 labeling index.

Local, regional, and distant recurrences occurred in 4, 2, and 17 patients, respectively. The 5-year LRR rates were 5.3% in the no PMRT group and 0% in the PMRT group ($P = 0.272$) (Fig. 1). DFS and OS were not significantly different between the two groups (5-year DFS: 80.6% vs 96.6%, $P = 0.095$; 5-year OS: 91.6% vs 93.3%, $P = 0.540$) (Fig. 2).

In the univariate analysis, larger tumor size (T2), ER negativity, and HER2 positivity were significantly related to worse DFS. Meanwhile, the negative prognostic factors on multivariate analysis were T2 and ER negativity (Table 2). The number of positive nodes, axillary dissection, and PMRT had no significant impact on DFS. No factors were not significantly related with OS in multivariate analysis.

The DFS curves according to the study period are shown in Fig. 3. The 5-year DFS in the early period was 77.2% and 100% ($P = 0.293$) and that in the late period was 85.7% and 96.0% ($P = 0.488$) in the no PMRT and PMRT groups, respectively. Although PMRT did not significantly improve DFS in both groups, the difference in the late period was smaller than that in the early period.

Discussion

This study demonstrated that the LRR rate was low regardless of PMRT implementation and PMRT tended to improve LRR and DFS in T1–2 breast cancers with 1–3 positive lymph nodes.

Many breast cancer guidelines recommend to strongly consider PMRT for breast cancers with 1–3 positive lymph nodes [1–4]. The sub-analysis of the Danish Breast Cancer Cooperative Group 82b/c trials reported that PMRT reduced LRR and improved OS for patients with node-positive breast cancer, and the survival benefit was similar in patients with 1–3 and ≥ 4 positive lymph nodes [15]. A meta-analysis from EBCTCG demonstrated the benefits of PMRT for LRR and

Table 1 Patient characteristics

	No PMRT ($n = 130$)	PMRT ($n = 32$)	P
Age (year), median (range)	60 (29–88)	59 (33–81)	0.529
T status			0.695
1	59 (78.7)	19 (21.3)	
2	71 (81.6)	16 (18.4)	
Number of positive node			0.558
1	74 (83.1)	15 (16.9)	
2	38 (77.6)	11 (22.4)	
3	18 (75.0)	6 (25.0)	
Nuclear grade			0.275
1	16 (80.0)	4 (20.0)	
2	66 (84.6)	12 (15.4)	
3	44 (73.3)	16 (26.7)	
Ly positive	93 (80.2)	23 (19.8)	1
ER positive	95 (77.2)	28 (22.8)	0.159
HER2 positive	25 (96.2)	1 (3.8)	0.017
Ki-67 labeling index	38.7 ± 25.6	32.2 ± 18.3	0.394
<Treatment>			
Axillary procedure			0.150
Sentinel node biopsy only	15 (68.2)	7 (31.8)	
Axillary dissection	115 (82.1)	25 (17.9)	
Chemotherapy			0.390
No	37 (75.5)	12 (24.5)	
Yes	93 (82.3)	20 (17.7)	
Hormonal therapy			0.327
No	29 (87.9)	4 (12.1)	
Yes	101 (78.3)	28 (21.7)	
Anti-HER2 therapy			0.694
No	120 (79.5)	31 (20.5)	
Yes	10 (90.9)	1 (9.1)	

ER estrogen receptor, *HER2* human epidermal growth factor receptor 2, *Ly* lymphatic invasion, *PMRT* postmastectomy radiation therapy

mortality in patients with breast cancer with 1–3 positive lymph nodes (5-year LRR: 16.5% to 2.8%, $P < 0.00001$; 5-year breast cancer mortality: 22.0% to 18.1%, $P = 0.01$) [5]. However, in the present study, the 5-year LRR, DFS, and OS were 5.3%, 83.0%, and 91.9%, respectively. These differences of outcomes may be based on improvement of radiological diagnosis, surgical management, and systemic therapy. Low LRR can lead to reduce the impact of PMRT for DFS and OS. In addition, the majority of recurrence patterns was distant metastasis. According to NSABP B-04 trial, recurrence of patients with clinically positive nodes who underwent axillary dissection or regional irradiation after mastectomy was more frequent in distant metastasis (74%) than in local (9%) and regional (17%) recurrence, and more than 80% of relapses occurred within 5 years of follow-up [16]. These findings suggest the importance of systemic treatment in the modern times.

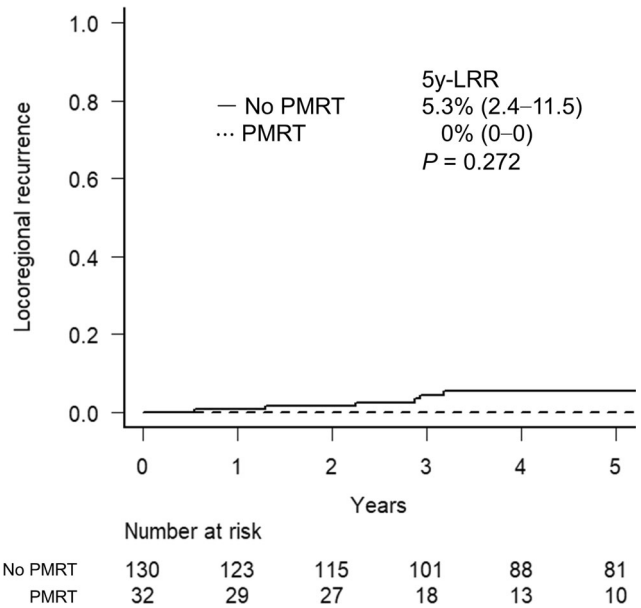

Fig. 1 Incidence of cumulative locoregional recurrence according to postmastectomy radiation therapy

Recent studies reported the low therapeutic impact of PMRT for breast cancers with 1–3 positive lymph nodes since 2000 [10, 11]. In Japan, anastrozole, an aromatase inhibitor, has been approved in 2000, and trastuzumab, an anti-HER2 monoclonal antibody, has been approved for metastatic breast cancer in 2001 and for adjuvant treatment in 2008. Therefore, we divided the study period into the early (2000–2007) and the late periods (2008–2015). Only eight patients underwent PMRT in the early period, and no recurrence occurred. The DFS of patients who did not undergo PMRT in the late period tended to be better than that in the early period (5-year DFS: 85.7% vs 77.2%, $P = 0.242$). Our data indicate that PMRT has a small impact for reducing recurrence. This study also

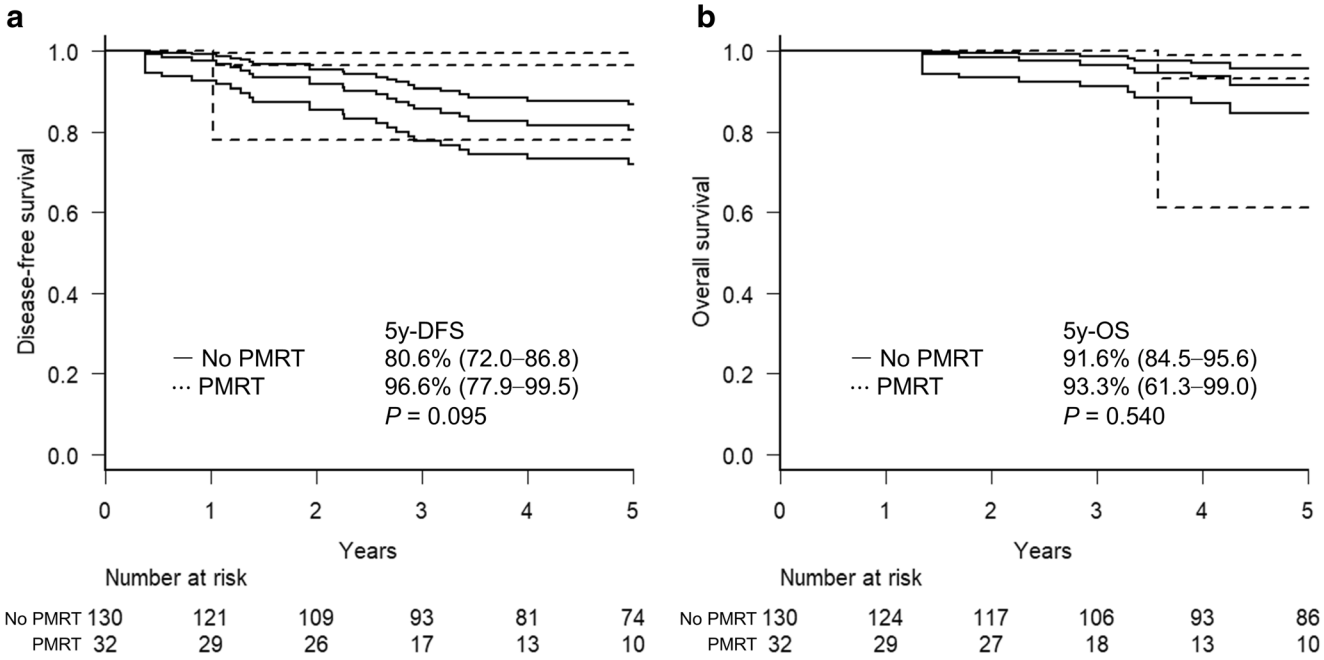

Fig. 2 Disease-free survival (**a**) and overall survival (**b**) curves according to postmastectomy radiation therapy

showed that the independent risk factors of DFS events were larger size (T2) and ER negativity. Other studies reported that the risk factors of LRR were younger age, lymphatic invasion, tumor grade, progesterone receptor negativity, number of

Table 2 Cox proportional hazards regression analysis for disease-free and overall survivals

Factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
<Disease-free survival>				
Age ≥ 65 years	0.89 (0.38–2.06)	0.781	0.92 (0.29–2.96)	0.894
T2	8.33 (2.49–27.9)	< 0.001	4.72 (1.35–16.5)	0.015
Number of positive node ≥ 2	0.84 (0.38–1.86)	0.66	1.02 (0.40–2.61)	0.962
Nuclear grade 3	0.43 (0.16–1.13)	0.087	0.45 (0.16–1.25)	0.125
Ly positive	2.07 (0.71–6.02)	0.184	2.05 (0.62–6.82)	0.241
ER positive	0.25 (0.11–0.55)	< 0.001	0.31 (0.11–0.87)	0.026
HER2 positive	2.98 (1.32–6.75)	0.009	1.58 (0.60–4.16)	0.359
Axillary dissection	0.95 (0.28–3.19)	0.935	0.51 (0.13–2.02)	0.340
Adjuvant chemotherapy	1.14 (0.46–2.86)	0.777	0.52 (0.13–2.05)	0.349
PMRT	0.21 (0.03–1.58)	0.13	0.32 (0.04–2.62)	0.288
<Overall survival>				
Age ≥ 65 years	2.00 (0.74–5.44)	0.173	2.68 (0.65–11.0)	0.172
T2	7.68 (1.74–33.8)	0.007	4.54 (0.96–21.5)	0.056
Number of positive node ≥ 2	0.94 (0.35–2.52)	0.901	1.04 (0.29–3.79)	0.953
Nuclear grade 3	0.66 (0.21–2.04)	0.467	0.67 (0.20–2.31)	0.530
Ly positive	4.24 (0.56–32.3)	0.164	3.54 (0.43–29.2)	0.241
ER positive	0.28 (0.10–0.75)	0.011	0.27 (0.07–1.07)	0.062
HER2 positive	1.78 (0.61–5.18)	0.293	0.69 (0.17–2.81)	0.602
Axillary dissection	0.70 (0.16–3.11)	0.639	0.77 (0.14–4.11)	0.762
Adjuvant chemotherapy	0.83 (0.27–2.61)	0.754	0.66 (0.12–3.58)	0.628
PMRT	0.53 (0.07–4.10)	0.547	0.70 (0.08–6.28)	0.752

CI confidence interval, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *HR* hazard ratio, *Ly* lymphatic invasion, *PMRT* postmastectomy radiation therapy

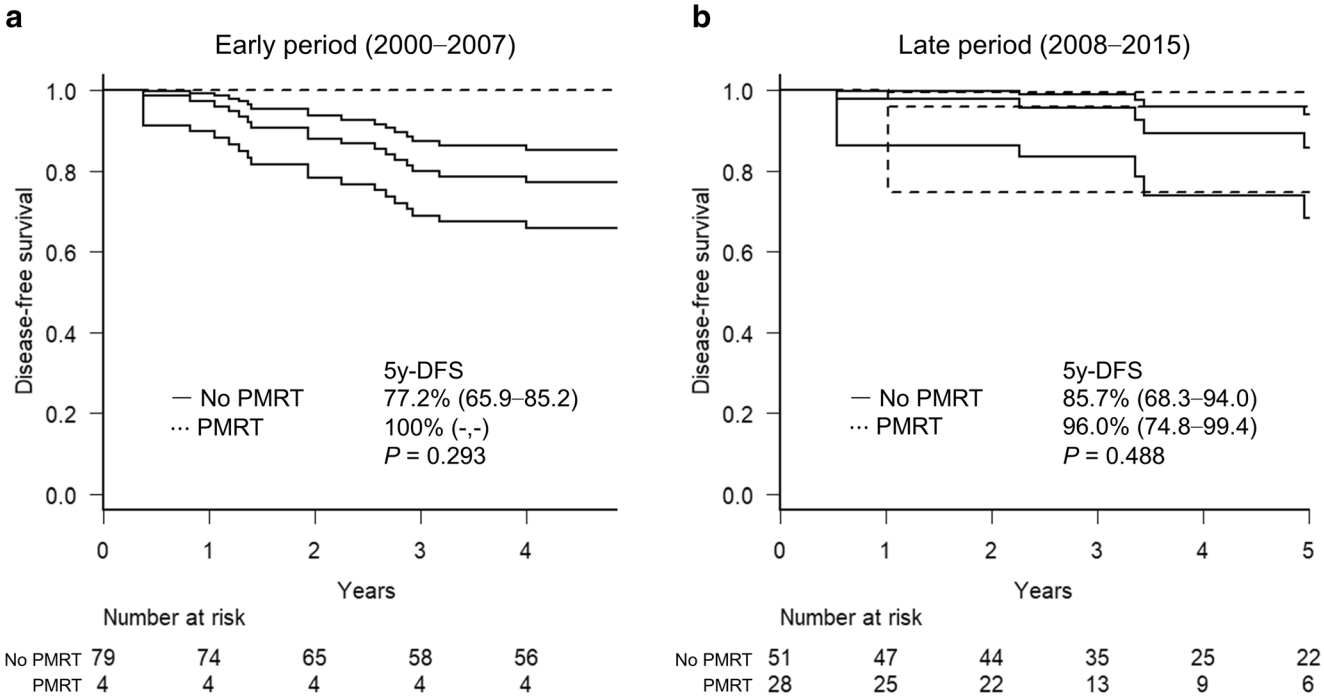

Fig. 3 Comparison of disease-free survival in the postmastectomy radiation therapy group and no postmastectomy radiation therapy group between the early (**a**) and late (**b**) study periods

positive lymph nodes, and extracapsular extension [10, 12, 17, 18]. However, the most adequate indication for performing PMRT has not been established [2]. Because strategies for systemic therapy have been rapidly progressing, large cohort studies are required for determining the indication for PMRT. We excluded the patients who received neoadjuvant chemotherapy in this study because it is impossible to pathologically assess the exact number of lymph node metastases. The therapeutic value of PMRT after neoadjuvant chemotherapy should also be evaluated in another cohort. Currently, tumor shrinkage is obtained via preoperative chemotherapy in many patients with HER2-positive and triple-negative breast cancers. The effect of PMRT on LRR might be small in triple-negative and HER2-positive breast cancers [19]. The ongoing phase III clinical trial (NSABP B51/RTOG 1304) will provide important information on the benefit of PMRT in patients who received preoperative chemotherapy.

Recently, the number of patients undergoing breast reconstruction surgery are increasing, and approximately 30% of patients with 1–3 positive lymph nodes have received in 2011 [7]. PMRT is associated with an increased number of complications after breast reconstruction, such as wound infection, skin flap necrosis, capsular contracture, revisional surgery, and removal or replacement of the implant [20, 21]. Therefore, the administration of PMRT must be adequately justified.

The present study has some limitations, such as its retrospective design, a relatively small patient cohort, and short follow-up period particularly in the late period cohort. Although the treatment strategy for breast cancer has changed with time, the standard treatment during the study period selected based on the decision of the cancer board.

In conclusion, the LRR rate was low and PMRT tended to improve LRR and DFS in T1–2 breast cancers with 1–3 positive lymph nodes. The omission of PMRT is carefully determined.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of ethical approval All human and animal studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the study. This article does not contain any studies with animals performed by any of the authors.

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