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ORIGINAL ARTICLE – BREAST ONCOLOGY

Role of Postmastectomy Radiotherapy After Neoadjuvant Chemotherapy in Breast Cancer Patients: A Study from the Japanese Breast Cancer Registry

Minoru Miyashita, MD, PHD[1], Naoki Niikura, MD, PHD[2], Hiraku Kumamaru, MD, PHD[3], Hiroaki Miyata, MD, PHD[4], Takayuki Iwamoto, MD, PHD[5], Masaaki Kawai, MD, PHD[6], Keisei Anan, MD, PHD[7], Naoki Hayashi, MD, PHD[8], Kenjiro Aogi, MD, PHD[9], Takanori Ishida, MD, PHD[1], Hideji Masuoka, MD, PHD[10], Kotaro Iijima, MD, PHD[11], Shinobu Masuda, MD, PHD[12], Koichiro Tsugawa, MD, PHD[13], Takayuki Kinoshita, MD, PHD[14], Hitoshi Tsuda, MD, PHD[15], Seigo Nakamura, MD, PHD[16], and Yutaka Tokuda, MD, PHD[2]

[1]Department of Breast and Endocrine Surgical Oncology, Tohoku University School of Medicine, Sendai, Japan; [2]Department of Breast and Endocrine Surgery, Tokai University School of Medicine, Isehara, Japan; [3]Department of Healthcare Quality Assessment, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; [4]Department of Health Policy and Management School of Medicine, Keio University, Tokyo, Japan; [5]Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama, Japan; [6]Department of Breast Surgery, Miyagi Cancer Center, Natori, Japan; [7]Department of Surgery, Kitakyushu Municipal Medical Center, Kitakyushu, Japan; [8]Department of Breast Surgical Oncology, St. Luke's International Hospital, Tokyo, Japan; [9]Department of Breast Surgery, Shikoku Cancer Center, Matsuyama, Japan; [10]Sapporo-Kotoni Breast Clinic, Sapporo, Japan; [11]Department of Breast Surgery, Juntendo University School of Medicine, Tokyo, Japan; [12]Department of Pathology, Nihon University School of Medicine, Tokyo, Japan; [13]Division of Breast and Endocrine Surgery, Department of Surgery, St. Marianna University School of Medicine, Kawasaki, Japan; [14]Department of Breast Surgery, National Cancer Center Hospital, Tokyo, Japan; [15]Department of Basic Pathology, National Defense Medical College, Saitama, Japan; [16]Division of Breast Surgical Oncology, Department of Surgery, Showa University School of Medicine, Tokyo, Japan

ABSTRACT

Background. The role of postmastectomy radiotherapy (PMRT) in breast cancer patients receiving neoadjuvant chemotherapy (NAC) is controversial. We aimed to evaluate the effectiveness of radiotherapy in patients treated with NAC and mastectomy in the Japanese Breast Cancer Registry.

Methods. We enrolled patients who received NAC and mastectomy for cT1–4 cN0–2 M0 breast cancer. We evaluated the association between radiotherapy and outcomes, locoregional recurrence (LRR), distant disease-free survival (DDFS), and overall survival (OS) based on ypN status by multivariable analysis.

Results. Of the 145,530 patients, we identified 3226 who met the inclusion criteria. Among ypN1 patients, no differences were found in LRR, DDFS, or OS between groups with and without radiotherapy ($p = 0.72$, $p = 0.29$, and $p = 0.36$, respectively). Radiotherapy was associated with improved LRR-free survival ($p < 0.001$), DDFS ($p = 0.01$), and OS ($p < 0.001$) in patients with ypN2–3. Multivariable analysis demonstrated that use of radiotherapy was independently associated with improved LRR [hazard ratio (HR) 0.61, 95% confidence interval (CI) 0.45–0.82, $p = 0.001$] and OS [HR 0.69, 95% CI 0.53–0.89, $p = 0.004$) for ypN2–3 patients only. The association between radiotherapy and OS was not statistically significant among ypN0 ($p = 0.22$) and ypN1 patients ($p = 0.51$).

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M. Miyashita, MD, PHD
e-mail: atihsayim8m8@med.tohoku.ac.jp

Conclusions. The results from this nationwide database study did not show significant associations between PMRT and improved survival among ypN0 and ypN1 patients. Radiotherapy may be beneficial only for ypN2–3 breast cancer patients who receive NAC and mastectomy in the modern era.

The role of postmastectomy radiotherapy (PMRT) in the setting of adjuvant therapy has been studied in multiple randomized clinical trials, and it has been shown to provide survival benefits for breast cancer patients with positive lymph nodes.[1] In contrast, whether PMRT improves survival in patients treated with neoadjuvant chemotherapy (NAC) prior to mastectomy is unclear, because no data from randomized prospective trials are available. Some retrospective data for stage III breast cancer patients indicate that PMRT decreases locoregional recurrence (LRR) even for patients with pathologic complete response (pCR) to NAC.[2–4] However, other retrospective data suggest that patients who achieve pCR with NAC exhibit low rates of LRR without PMRT after surgery.[5,6] A recent analysis from the National Cancer Database (NCDB) of the American College of Surgeons and the American Cancer Society showed that PMRT was associated with improved overall survival (OS) for pathologic positive nodal subgroups, but no differences in OS were observed with addition of PMRT following NAC in patients with ypN0.[7,8] However, data for LRR, distant disease recurrence, and the association between these endpoints and OS are lacking in that report.

Multiple studies in adjuvant settings have reported that breast cancer patients with one to three positive lymph nodes who receive modern treatments exhibit a lower risk of LRR without PMRT.[9,10] The significance of PMRT may change in the modern treatment era as systemic therapy becomes more powerful and axillary staging becomes more accurate. The optimal indication for PMRT for management of patients treated with NAC remains controversial. The balance between benefit and harm, such as toxicity, cost, and geographic problems, may change depending on treatment advances.

The aim of this analysis using data from the Japanese Breast Cancer Registry (JBCR) is to evaluate the therapeutic effectiveness of PMRT for breast cancer patients treated with NAC based on the status of pathologically residual lymph nodes with survival information including LRR, distant disease-free survival (DDFS), and OS.

METHODS

Data Source

The present study was conducted using the JBCR database, which contains clinical records from more than 300,000 breast cancer patients from more than 800 institutions in Japan.[11,12] The Registration Committee of the Japanese Breast Cancer Society managed the registry with support from the Public Health Research Foundation (Tokyo, Japan) up to year 2011. The registry is currently maintained by the National Clinical Database, a registry platform for nationwide clinical registries with more than 15 specialty societies participating in its governance. Affiliated institutes provide data for newly diagnosed primary breast cancer patients through a web-based system covering patient demographics, clinicopathological characteristics, survival data, including OS, DDFS, and LRR-free survival (LRR-FS), and therapies, such as types of surgery, radiotherapy, chemotherapy, hormone therapy, and anti-human epidermal growth factor receptor (HER)2 therapy.

Study Patients

In the current study, we enrolled patients who received neoadjuvant chemotherapy (NAC) and mastectomy for cT1–4 cN0–2 M0 breast cancer between 2004 and 2009 from JBCR (Fig. 1). We excluded women < 18 years of age, male patients, and patients with bilateral breast cancer. We also excluded patients whose information for postoperative follow-up, radiotherapy, and lymph node resection was missing. The use of the data for retrospective observational studies was approved by the ethics committee of the Japan Surgical Society, and the Ethics Review Committee at the Japanese Breast Cancer Society approved the study.[13]

Study Outcomes

We assessed three survival endpoints: LRR, distant recurrence, and overall survival (OS). In this study, LRR was defined as disease in the ipsilateral chest wall, skin, or ipsilateral axillary/supraclavicular/infraclavicular/internal mammary lymph nodes identified on biopsy and/or imaging. We assessed patients' LRR-FS time as the time between NAC initiation and first local recurrence. DDFS time was defined as the time between NAC initiation and first distant metastasis. OS time was defined as the time from NAC initiation until date of death from any cause.

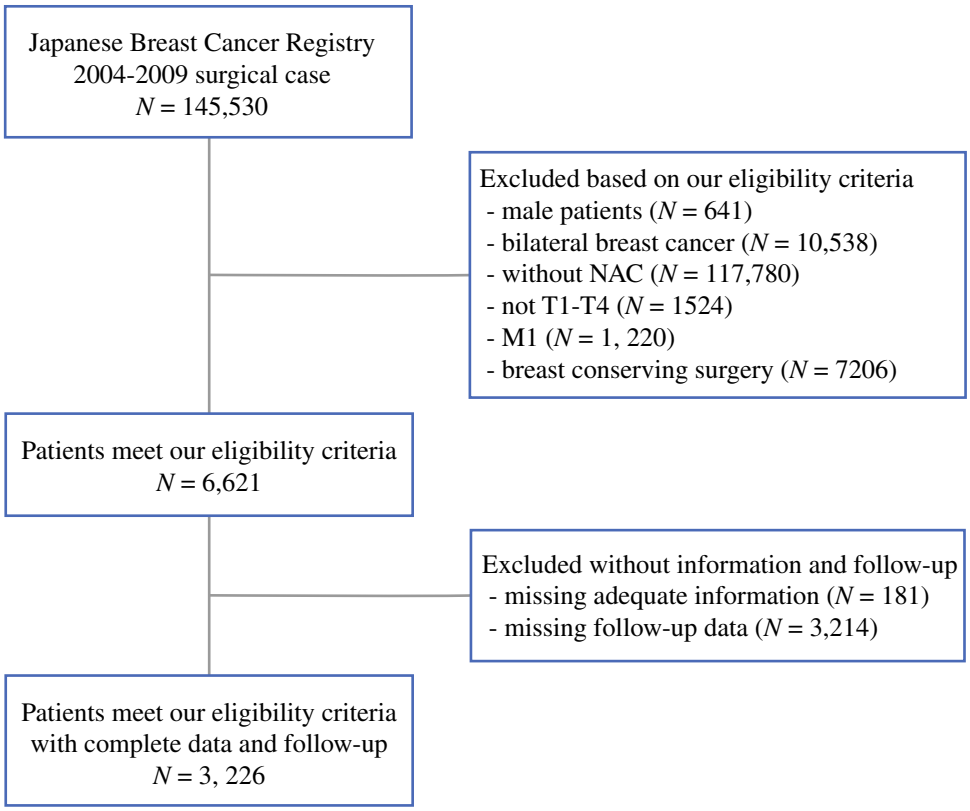

FIG. 1 CONSORT diagram. *NAC* neoadjuvant chemotherapy

Statistical Analysis

We first divided the patients into three groups based on their residual nodal status (ypN0, ypN1, and ypN2–3). We compared the differences in the clinicopathological features of patients with or without PMRT using Fisher's exact test or the Chi squared test for categorical variables and Wilcoxson rank-sum test, separately for each group. We compared crude survival between treatment groups using the Kaplan–Meier method and log-rank test. A small number of patients with erroneous date for recurrence before NAC initiation were excluded from the analysis. For each nodal group separately, we estimated the hazard ratio (HRs) and 95% confidence interval (CI) for those with and without PMRT using Cox proportional hazards regression, adjusting for the following potential confounding factors: age, clinical T stage, clinical N stage, and biological subtype. We assessed whether the association between PMRT and outcome was significantly different across nodal groups. We compared the likelihood ratio among all patients across the nodal groups with an interaction term between PMRT and nodal group. Finally, we conducted subgroup analyses comparing the crude survival of patients in the pN2–3 group with and without PMRT, using Kaplan–Meier curves and log-rank test, within three groups defined by estrogen receptor (ER), progesterone receptor (PgR), and HER2 status: HR+ (ER+, HER2−), HER2+ (ER±, HER2+), and triple-negative (TN) disease (ER−, PgR−, HER2−). All tests were two-sided, with p value < 0.05 considered significant. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient and Treatment Characteristics

Table 1 presents details of the patient and disease characteristics by pathological nodal status group. The median patient age was 53 years (range 23–92 years). A total of 1413 (43.8%) of the 3226 patients had cT2 tumors, and 1759 (54.5%) patients were diagnosed with cN1 prior to treatment. A total of 59.7% (N = 1925) of the tumors were ER positive, 41.8% (N = 1348) were PgR positive, and 24.4% (N = 787) were HER2 positive. A total of 2996 (92.9%) patients underwent axillary lymph node dissection (ALND), and 2307 (71.5%) patients were treated with NAC containing both anthracyclines and taxanes as current standard regimens (Supplementary Table 1). The radiation fields included the regional nodal fields, supra/infraclavicular fossa, and internal mammary lymph nodes for 593 (59.7%) of the 993 patients in the PMRT group.

TABLE 1 Patient characteristics categorized by pathological nodal status ($N = 3226$)

Factors	ypN0					ypN1					ypN2-3				
	PMRT		No PMRT		p value	PMRT		No PMRT		p value	PMRT		No PMRT		p value
	$N = 185$	%	$N = 1114$	%		$N = 265$	%	$N = 777$	%		$N = 543$	%	$N = 342$	%	
Age (years)					0.54					0.72					0.001*
Median	55		52			53		53			52		56		
Range	34–68		34–70			36–70		34–70			34–70		34–74		
Menopausal status					0.53					0.75					0.01*
Premenopausal	76	41.1	485	43.5		115	43.4	348	44.8		244	44.9	119	34.8	
Postmenopausal	105	56.8	592	53.1		141	53.2	409	52.6		283	52.1	214	62.6	
Unknown	4	2.2	37	3.3		9	3.4	20	2.6		16	2.9	9	2.6	
Clinical T stage at diagnosis					< 0.001*					< 0.001*					0.20
cT1	14	7.6	97	8.7		10	3.8	85	10.9		30	5.5	25	7.3	
cT2	49	26.5	565	50.7		94	35.5	377	48.5		214	39.4	114	33.3	
cT3	43	23.2	211	18.9		57	21.5	148	19		112	20.6	84	24.6	
cT4	79	42.7	241	21.6		104	39.2	167	21.5		187	34.4	119	34.8	
Clinical N stage at diagnosis					< 0.001*					< 0.001*					0.02*
cN0	47	25.4	495	44.4		30	11.3	165	21.2		59	10.9	32	9.4	
cN1	78	42.2	499	44.8		161	60.8	494	63.6		319	58.7	208	60.8	
cN2	23	12.4	61	5.5		39	14.7	78	10		96	17.7	73	21.3	
cN3	35	18.9	56	5		35	13.2	37	4.8		69	12.7	26	7.6	
Unknown	2	1.1	3	0.3		0	0	3	0.4		0	0	3	0.9	
Histologic type					0.06					0.32					0.44
Ductal	168	90.8	983	88.2		237	89.4	711	91.5		477	87.8	303	88.6	
Lobular	8	4.3	28	2.5		9	3.4	29	3.7		29	5.3	22	6.4	
Others	9	4.9	103	9.2		19	7.2	37	4.8		37	6.8	17	5	
ER status					0.07					0.01*					< 0.001*
Positive	107	57.8	543	48.7		199	75.1	491	63.2		401	73.8	184	53.8	
Negative	71	38.4	516	46.3		52	19.6	236	30.4		110	20.3	121	35.4	
Unknown	7	3.8	55	4.9		14	5.3	50	6.4		32	5.9	37	10.8	
PgR status					0.30					0.08					< 0.001*
Positive	72	38.9	379	34		138	52.1	343	44.1		284	52.3	132	38.6	
Negative	107	57.8	679	61		111	41.9	382	49.2		225	41.4	169	49.4	
Unknown	6	3.2	56	5		16	6	52	6.7		34	6.3	41	12	
HER2 status					0.02*					0.22					0.56
Positive	76	41.1	347	31.1		62	23.4	155	19.9		92	16.9	55	16.1	
Negative	100	54.1	684	61.4		186	70.2	550	70.8		401	73.8	248	72.5	

TABLE 1 continued

Factors	ypN0					ypN1					ypN2-3				
	PMRT		No PMRT		*p* value	PMRT		No PMRT		*p* value	PMRT		No PMRT		*p* value
	N = 185	%	*N* = 1114	%		*N* = 265	%	*N* = 777	%		*N* = 543	%	*N* = 342	%	
Unknown	9	4.9	83	7.5		17	6.4	72	9.3		50	9.2	39	11.4	
Pathological T stage after chemotherapy					0.004*					0.001*					0.86
pT0, pTis	24	13	138	12.4		1	0.4	25	3.2		10	1.8	4	1.2	
pT1	40	21.6	351	31.5		65	24.5	253	32.6		91	16.8	55	16.1	
pT2	51	27.6	326	29.3		101	38.1	272	35		197	36.3	132	38.6	
pT3	36	19.5	122	11		74	27.9	144	18.5		187	34.4	119	34.8	
Unknown	34	18.4	177	15.9		24	9.1	83	10.7		58	10.7	32	9.4	

ER estrogen receptor, *PgR* progesteron receptor, *HER2* human epidermal growth factor receptor 2, *PMRT* postmastectomy radiotherapy

*p value is significant

LRR-FS, DDFS, and OS

We included patients whose postoperative follow-up was more than 5 years. Locoregional events at the first recurrence site were identified in 412 (12.8%) patients at the cutoff date for the analysis (February 2017). The 5-year LRR-FS rates for the cohorts of patients with ypN0 and ypN1 were not significantly different between the PMRT group and the no PMRT group ($p = 0.81$ and $p = 0.72$, respectively). In contrast, the 5-year LRR-FS rates were significantly improved with PMRT for the ypN2–3 cohort ($p < 0.001$) (Fig. 2). A total of 679 (21.0%) of the patients in the entire cohort experienced distant recurrence first. The 5-year DDFS rates were not significantly different between the two groups in the ypN0 ($p = 0.15$) and ypN1 cohorts ($p = 0.29$). However, the 5-year DDFS rates significantly improved with PMRT in the ypN2–3 cohort ($p = 0.01$) (Fig. 2). A total of 561 (17.4%) patients died. No significant differences were found in the 5-year OS rates between the two groups in the ypN0 ($p = 0.05$) and ypN1 cohorts ($p = 0.36$). In contrast, the 5-year OS rates significantly improved with addition of PMRT in the ypN2–3 cohort ($p < 0.001$) (Fig. 2).

Multivariable Analysis of Survival

We performed multivariable analyses to assess the improvement in the outcome associated with PMRT by pathological nodal status; the results are shown in Table 2 and Fig. 3. PMRT independently remained associated with improved OS in the cohort of patients with ypN2–3 (HR 0.69, 95% CI 0.53–0.89, $p = 0.004$). The 5-year OS rate did not significantly differ between the PMRT and no PMRT groups in the ypN0 (HR 1.33, 95% CI 0.84–2.09, $p = 0.22$) and ypN1 cohorts (HR 0.88, 95% CI 0.60–1.29, $p = 0.51$) (Fig. 3). These results demonstrate a significant interaction between the association of PMRT with survival and the pathological nodal status ($p < 0.001$). Analysis of LRR-FS revealed a significant improvement in survival only in the ypN2–3 cohort (HR 0.61, 95% CI 0.45–0.82, $p = 0.001$), in agreement with the OS analysis. No LRR-FS differences were observed with addition of PMRT in the ypN0 (HR 0.86, 95% CI 0.46–1.50, $p = 0.623$) and ypN1 cohorts (HR 0.83, 95% CI 0.54–1.26, $p = 0.39$) (interaction $p < 0.001$) (Fig. 3). However, DDFS as the endpoint for distant recurrence first was not independently associated with presence or absence of PMRT in any subgroup, including the ypN0 (HR 1.10, 95% CI 0.72–1.67, $p = 0.67$), ypN1 (HR 1.03, 95% CI 0.75–1.41, $p = 0.86$), and ypN2–3 cohorts (HR 0.84, 95% CI 0.66–1.08, $p = 0.17$) (interaction $p = 0.04$) (Fig. 3).

Survival Based on Biological Subtype

A total of 487 of the 787 patients (61.9%) exhibited HR+ disease, 147 (18.7%) exhibited HER2+ disease, and 153 (19.4%) exhibited TN disease. Due to small numbers of patients, these analyses had insufficient power to validate the effect of radiotherapy in each subgroup. Among the HR+ subgroup, the 5-year LRR-FS, DDFS, and OS rates in the HR+ disease subgroup were not significantly different between the PMRT and no PMRT groups ($p = 0.14$, $p = 0.77$, and $p = 0.15$, respectively) (Supplementary Fig. 1). The same were true for TN disease (LRR-FS: $p = 0.32$, DDFS: $p = 0.14$, and OS: $p = 0.23$) (Supplementary Fig. 1). Among the HER2+ subgroup, LRR-FS was significantly better in the PMRT group compared with that in the no PMRT group ($p = 0.01$). However, no differences in DDFS and OS were observed between these two groups ($p = 0.89$ and $p = 0.73$, respectively) (Supplementary Fig. 1).

DISCUSSION

Currently, NAC is widely used in breast cancer patients with clinical stage II or III disease, but the role of PMRT in the survival of patients treated with NAC remains controversial. We have to decide the indication for radiotherapy depending on the clinical guidelines constructed based on retrospective data of patients treated from 1990 to the early 2000s.[14–16] Our results from this nationwide database study of breast cancer patients following modern NAC show that survival did not differ between the groups with and without PMRT among patients with ypN0 or ypN1 disease. Radiotherapy may be beneficial only for ypN2–3 breast cancer patients who receive NAC and mastectomy in the modern era.

We examined multiple survival endpoints, including LRR, DDFS, and OS. Previous nationwide database studies have assessed only the role of PMRT in OS but not LRR and DDFS due to data deficiencies.[7,8] Our study provides

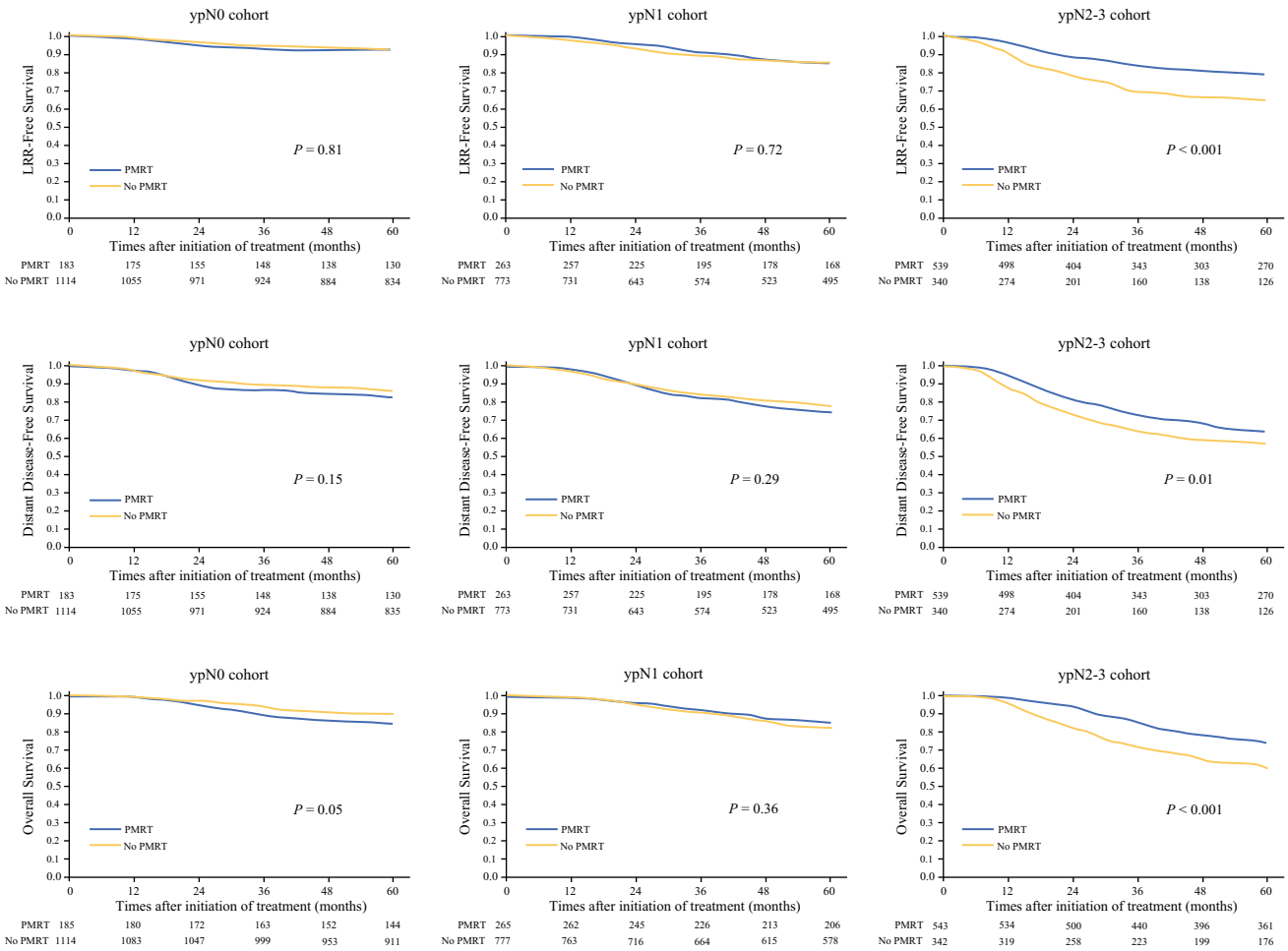

FIG. 2 Locoregional recurrence (LRR)-free survival, distant disease-free survival, and overall survival of breast cancer patients with or without PMRT in the ypN0, ypN1, and ypN2–3 cohort. *PMRT* postmastectomy radiotherapy, *ypN* pathologically lymph node status

TABLE 2 Multivariable analysis of survival (N = 3226)

Factors	ypN0				ypN1				ypN2-3			
	HR	95% Confidence interval		p value	HR	95% Confidence interval		p value	HR	95% Confidence interval		p value
		Low	High			Low	High			Low	High	
LRR-free survival												
Age (years)												
≥ 50	1				1				1			
< 50	0.67	0.44	1.04	0.07	0.73	0.51	1.03	0.07	1.20	0.87	1.65	0.27
Clinical T stage at diagnosis												
cT1	1				1				1			
cT2	2.17	1.03	4.55	0.04*	0.67	0.32	1.41	0.29	0.98	0.48	2.00	0.95
cT3	2.09	1.17	3.75	0.01*	0.96	0.60	1.55	0.88	1.55	1.02	2.36	0.04*
cT4	2.45	1.41	4.29	0.002*	1.47	0.97	2.23	0.07	2.16	1.51	3.09	< 0.001*
Clinical N stage at diagnosis												
cN0	1				1				1			
cN1	0.98	0.60	1.60	0.95	0.84	0.53	1.32	0.44	1.10	0.64	1.90	0.73
cN2	1.51	0.69	3.30	0.30	1.19	0.65	2.17	0.58	1.38	0.76	2.48	0.29
cN3	1.92	0.90	4.08	0.09	1.38	0.70	2.73	0.35	1.63	0.85	3.12	0.15
Unknown	5.48	0.72	41.73	0.10	N/A	N/A	N/A	0.98	1.70	0.22	13.07	0.61
Biological subtypes												
ER+, HER2−	1				1				1			
HER2+	0.93	0.53	1.64	0.81	2.42	1.61	3.64	< 0.001*	1.91	1.30	2.81	0.001*
ER−, HER2−	1.99	1.18	3.37	0.01*	2.29	1.43	3.68	0.001*	3.45	2.40	4.96	< 0.001*
Unknown	0.60	0.21	1.74	0.35	1.06	0.53	2.09	0.88	1.31	0.79	2.17	0.30
Radiation												
No PMRT	1				1				1			
PMRT	0.86	0.46	1.60	0.62	0.83	0.55	1.26	0.39	0.61	0.45	0.82	0.001*
Distant disease-free survival												
Age (years)												
≥ 50	1				1				1			
< 50	1.02	0.74	1.40	0.91	0.70	0.53	0.92	0.011*	0.90	0.70	1.14	0.37
Clinical T stage at diagnosis												
cT1	1				1				1			
cT2	0.84	0.40	1.77	0.64	0.86	0.49	1.52	0.60	0.90	0.53	1.52	0.68
cT3	1.80	1.20	2.72	0.005*	1.27	0.88	1.82	0.20	1.45	1.06	1.97	0.02*
cT4	2.04	1.39	3.00	< 0.001*	1.67	1.19	2.34	0.003*	1.40	1.06	1.86	0.02*

TABLE 2 continued

Factors	ypN0				ypN1				ypN2-3			
	HR	95% Confidence interval		*p* value	HR	95% Confidence interval		*p* value	HR	95% Confidence interval		*p* value
		Low	High			Low	High			Low	High	
Clinical N stage at diagnosis												
cN0	1				1				1			
cN1	1.16	0.81	1.65	0.42	1.08	0.73	1.60	0.71	1.44	0.90	2.29	0.13
cN2	1.54	0.88	2.71	0.13	1.47	0.89	2.43	0.13	1.57	0.94	2.63	0.09
cN3	1.79	1.03	3.11	0.04*	1.65	0.94	2.90	0.08	2.63	1.55	4.47	< 0.001*
Unknown	2.65	0.36	19.50	0.34	N/A	N/A	N/A	0.97	3.52	0.81	15.27	0.09
Biological subtypes												
ER+, HER2−	1				1				1			
HER2+	1.43	0.95	2.16	0.09	2.08	1.50	2.88	< 0.001*	1.43	1.04	1.97	0.028*
ER−, HER2−	2.30	1.52	3.47	< 0.001*	2.38	1.66	3.42	< 0.001*	3.05	2.27	4.09	< 0.001*
Unknown	1.13	0.57	2.21	0.73	0.59	0.30	1.17	0.13	1.36	0.92	2.03	0.13
Radiation												
No PMRT	1				1				1			
PMRT	1.10	0.72	1.67	0.67	1.03	0.75	1.41	0.86	0.84	0.66	1.08	0.17
Overall survival												
Age (years)												
≥ 50	1				1				1			
< 50	1.21	0.84	1.75	0.31	0.92	0.67	1.27	0.62	0.93	0.71	1.21	0.57
Clinical T stage at diagnosis												
cT1	1				1				1			
cT2	1.05	0.49	2.25	0.89	0.66	0.33	1.32	0.24	0.80	0.43	1.47	0.47
cT3	1.55	0.96	2.49	0.07	1.16	0.77	1.74	0.48	1.29	0.92	1.81	0.15
cT4	1.92	1.26	2.92	0.002*	1.24	0.85	1.82	0.27	1.47	1.09	1.98	0.01*
Clinical N stage at diagnosis												
cN0	1				1				1			
cN1	1.54	1.02	2.34	0.04*	1.38	0.85	2.22	0.19	0.91	0.59	1.39	0.66
cN2	1.40	0.69	2.84	0.35	1.86	1.04	3.32	0.04*	0.99	0.61	1.60	0.98
cN3	3.23	1.84	5.70	< 0.001*	2.27	1.21	4.25	0.01*	1.54	0.92	2.58	0.10
Unknown	3.27	0.44	24.24	0.25	N/A	N/A	N/A	0.97	2.01	0.46	8.67	0.35
Biological subtypes												
ER+, HER2−	1				1				1			
HER2+	1.28	0.76	2.15	0.36	2.26	1.50	3.39	< 0.001*	1.39	0.95	2.03	0.09
ER−, HER2−	3.97	2.47	6.37	< 0.001*	4.40	2.95	6.57	< 0.001*	4.93	3.64	6.67	< 0.001*

TABLE 2 continued

Factors	ypN0				ypN1				ypN2-3			
	HR	95% Confidence interval		*p* value	HR	95% Confidence interval		*p* value	HR	95% Confidence interval		*p* value
		Low	High			Low	High			Low	High	
Unknown	2.04	1.02	4.08	0.04*	1.28	0.66	2.47	0.46	2.17	1.48	3.18	< 0.001*
Radiation												
No PMRT	1				1				1			
PMRT	1.33	0.84	2.09	0.22	0.88	0.60	1.29	0.51	0.69	0.53	0.89	0.004*

ypN pathologically lymph node status, *HR* hazard ratio, *LRR* locoregional recurrence, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *PMRT* postmastectomy radiotherapy, *N/A* not available

*p value is significant

the first evidence of the impact of PMRT on LRR, DDFS, and OS and the association of these endpoints using the largest sample size. Multivariable analysis revealed that administration of PMRT to ypN2–3 women was associated with improved LRR-FS and OS. This result supports that locoregional control through radiotherapy produced an overall survival benefit for patients following NAC, which was previously demonstrated in adjuvant settings.[1] In contrast, PMRT did not reduce distant metastasis as the first disease recurrence in this patient subgroup. These findings support the survival benefit of PMRT as locoregional control in locally advanced breast cancer. One of the most significant findings of the present study is that PMRT did not improve survival in ypN0 and ypN1 patients, which contradicts the NCDB reports.[7,8] In our analysis, the rates of LRR for ypN0 with PMRT, ypN0 without PMRT, ypN1 with PMRT, and ypN1 without PMRT were 7.0%, 6.7%, 12.5%, and 13.1%, respectively. These results are very similar to those from the combined analysis of NSABP B-18 and B-27, which reported LRR rates for ypN0 and ypN1 of 7.8% (38 of 488 patients) and 15.6% (99 of 634 patients) without PMRT, respectively.[6,17] Another retrospective study of 676 breast cancer patients who received doxorubicin-based NAC and mastectomy at the MD Anderson Cancer Center indicated that PMRT was associated with improved LRR rates in select patients with clinical T3, T4, N2, or N3 disease at presentation and pathological T2, T3, or N2–3 disease at resection.[4] The lack of significant improvement in the outcomes for ypN0 and ypN1 in the present study confirms several previous reports, including the report from the MD Anderson Cancer Center.

We analyzed patient and disease characteristics and survival categorized by pathological nodal status but not clinical nodal status before chemotherapy, primarily due to the inaccuracy of the methods used to diagnose clinical nodal status as positive or negative. Indeed, 34.5% (N = 286) of the patients were diagnosed with pathological nodal involvement at resection in the cohort of patients considered clinical N0 at presentation (N = 828). Chemotherapy also modifies the disease extent of breast cancer in most patients. The NSABP B-18 and B-27 data suggest that the LRR rate is sufficiently low without PMRT in patients who exhibit a good response to NAC.[6] We propose that the indication for radiotherapy should be judged based on the pathological nodal status, which is the true status and reflects the response to chemotherapy.

The contribution of the biological subtype to the impact of radiotherapy on LRR, DDFS, and OS in the setting of NAC and mastectomy is not in clear agreement with the results obtained in adjuvant settings. A study from the Memorial Sloan Kettering Cancer Center suggested that TN breast cancer exhibited the highest LRR rate after

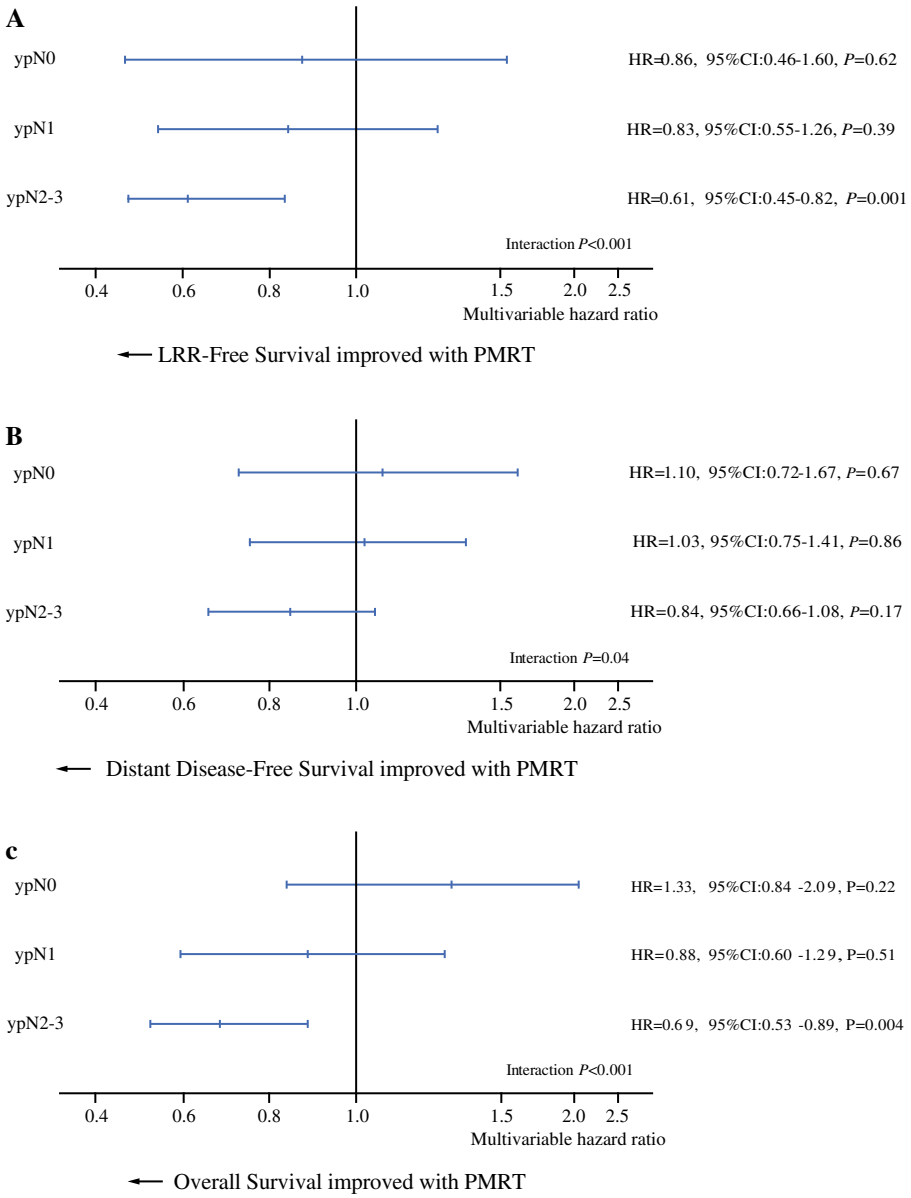

FIG. 3 Impact of PMRT on locoregional recurrence (LRR)-free survival (**a**), distant disease-free survival (**b**), and overall survival (**c**) by ypN status in multivariable Cox regression analysis. *PMRT* postmastectomy radiotherapy, *HR* hazard ratio, *CI* confidence interval

NAC, mastectomy, and PMRT, and that patients with HR+ and HER2+ breast cancer exhibited favorable LRR rates regardless of NAC response.[18] However, the effect of PMRT could not be evaluated, because patients without radiotherapy were excluded from this study. No previous study included a nationwide database in which the association between the survival effect of radiotherapy and the molecular subtype was evaluated. Radiotherapy significantly improved the LRR rate only for patients with HER2+ disease in our analysis ($p = 0.01$). Patients with TN disease exhibited a higher LRR rate after NAC and mastectomy regardless of the presence or absence of PMRT. Conversely, favorable LRR rates for HR+ patients were observed in both groups. High-risk subgroups for recurrence, such as those with TN disease and large tumor, are particularly recommended for radiotherapy. However, the sample size was relatively small to evaluate the effect of radiotherapy for each specific subgroup in the present registration study. The effect of the molecular subtype should be confirmed in a larger study.

The retrospective nature of the present study is an important limitation. The characteristics of the patients receiving and not receiving PMRT were different at baseline. While we adjusted for important risk factors such as patient age and clinical and biological subtypes, there may remain unmeasured confounders that may have biased our estimation. These results might be confirmed in an ongoing randomized trial (NSABP B-51/RTOG 1304) for women

with cN1 disease who converted to ypN0 10 years after NAC. The median follow-up time was also limited, and the results need to be confirmed with longer follow-up.

CONCLUSIONS

The results from this nationwide database study of breast cancer patients following modern NAC showed that PMRT was not associated with improved survival in patients with ypN0 or ypN1. Radiotherapy may be beneficial only for ypN2–3 breast cancer patients who receive NAC and mastectomy in the modern era. Randomized clinical trials are needed to optimize the use of PMRT for breast cancer patients treated with neoadjuvant chemotherapy.

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