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Original Article

Outcome of post-mastectomy radiotherapy after primary systemic treatment in patients with different clinical tumor and nodal stages of breast cancer: a cohort study

Jia-Qiang Zhang[1*], Chang-Yun Lu[2*], Lei Qin[3], Ho-Min Chen[4], Szu-Yuan Wu[4,5,6,7,8]

[1]Department of Anesthesiology and Perioperative Medicine, Henan Provincial People's Hospital, People's Hospital of Zhengzhou University, Zhengzhou, Henan, China; [2]Department of General Surgery, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, Yilan, Taiwan; [3]School of Statistics, University of International Business and Economics, Beijing, China; [4]Big Data Center, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, Yilan, Taiwan; Departments of [5]Food Nutrition and Health Biotechnology, [6]Healthcare Administration, College of Medical and Health Science, Asia University, Taichung, Taiwan; [7]Division of Radiation Oncology, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, Yilan, Taiwan; [8]School of Dentistry, College of Oral Medicine, Taipei Medical University, Taipei, Taiwan. [*]Equal contributors and co-first authors.

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Abstract: To evaluate the effect of post-mastectomy radiation therapy (PMRT) stratified by clinical tumor (T) or nodal (N) staging and determine predictors of overall survival (OS), locoregional recurrence (LRR), distant metastasis, and disease-free survival (DFS) in patients with breast cancer who received neoadjuvant chemotherapy (NACT) and total mastectomy (TM), we enrolled patients who received a diagnosis of breast invasive ductal carcinoma who received NACT followed by TM. Cox regression analysis was employed to calculate hazard ratios (HRs) and confidence intervals (CIs). Univariate and multivariate Cox regression analyses indicated that non-PMRT, Charlson comorbidity index ≥ 2, advanced clinical T or N stage, pathologic partial response, pathologic stationary disease, or pathologic progression disease were poor prognostic factors for OS. Well-differentiated tumor grade, pathologic complete response, and positive hormone receptors were better independent prognostic factors for OS. Adjusted HRs derived from PMRT for breast cancer after NACT and TM were 0.69 (0.53-0.89) and 0.74 (0.59-0.93) in clinical T3 and T4, respectively. aHRs derived from PMRT for breast cancer after NACT and TM were 0.67 (0.45-0.99), 0.75 (0.62-0.92), and 0.77 (0.60-0.98) in clinical N0, N1, N2-3, respectively. The aHRs (95% CI) of the PMRT group to the non-PMRT group for LRR-free survival and DFS were improved significantly. Our study indicated that PMRT significantly improved OS in clinical T3N0-T4N3 and for LRR-free survival and DFS in clinical T2N0-T4N3 from those of non-PMRT patients regardless of pathologic response and other predictors.

Keywords: Breast cancer, post-mastectomy radiation therapy, overall survival, locoregional recurrence, metastasis

Introduction

Neoadjuvant chemotherapy (NACT) is the systemic treatment of breast invasive intraductal carcinoma (IDC) before definitive surgical therapy [1]. Although all systemic therapy for nonmetastatic invasive breast cancer is intended to reduce the risk of distant recurrence, it is administered neoadjuvantly to assess the response to treatment, to downstage the cancer, and to reduce postoperative complications such as lymphedema [1-4]. For most patients who receive NACT, indications for post-mastectomy radiation therapy (PMRT) depend on various multifactors, such as the pretreatment stage and type of surgery (total mastectomy [TM] or breast conservative surgery), and consider pathologic responses to NACT [5-11]. In Taiwan, breast cancer is the most common cancer among women [12, 13]. Despite its increased incidence, its 5-year mortality rate has not significantly improved over the past decade (4.5% in 1997 and 4.4% in 2008) [13]. Over the last 10 years, NACT has become increas-

ingly popular in Taiwan and worldwide for patients with breast cancer [13, 14]. Therefore, an effective and optimal adjuvant therapy, including PMRT after NACT and TM, is crucial for such patients given the increasing incidence of breast cancer [5-11, 15] because no improvement in survival or local control has occurred over the past decade [13].

The incidence of breast cancer has decreased in North America but not in Asia, where it continues to increase [15]. A notable manifestation of the bimodal age distribution of breast cancer was observed in women [16]. The occurrence of early-onset breast cancer in the Asian or Taiwanese population is earlier than that in the Western population, which results in a higher incidence of breast cancer in young Taiwanese women [17-21]. Moreover, the late onset age distribution of patients with breast cancer in Asia or Taiwan (40-50 years) is earlier than that in Western countries (60-70 years) and peaks at an age of 45-50 years in most women [17-21]. The age-specific incidence rates of breast cancer increase sharply until the menopausal stage [22]. Younger patients with breast cancer typically have more aggressive tumors that are more likely to recur both locoregionally and distantly, and older patients with breast cancer tend to have less aggressive disease [23]. Determining suitable indications that PMRT improves survival in younger patients with breast cancer with aggressive tumors who receive aggressive treatments, such as NACT and TM, is crucial.

The benefits of PMRT remain unclear and controversial with variable indications including prechemotherapy staging, tumor size, nodal status, post-chemotherapy cancer staging, tumor size, nodal status, and pathologic response [5-11]. In addition, the benefits of PMRT are undetailed regarding outcomes of locoregional recurrence (LRR), overall survival (OS), distant metastasis (DM), and disease-free survival (DFS). Few studies have verified the effect of PMRT based on clinical tumor (T) or clinical nodal (N) staging, and we do not prefer to rely on pathologic staging or pathologic response because pathologic response depends on many complex factors [24-26]. In this study, we evaluated the effect of PMRT stratified by clinical T or N staging and discovered the predictors of OS, LRR, DM, and DFS in patients with breast cancer who received NACT and TM.

Patients and methods

In this study, we established a cohort by using data from the Taiwan Cancer Registry database (TCRD). We enrolled patients who received a diagnosis of breast IDC between January 1, 2007, and December 31, 2015. The follow-up duration was from the index date to December 31, 2016. The Cancer Registry database of the Collaboration Center of Health Information Application contains detailed cancer-related information of patients including clinical stage, treatment modalities, pathological data, radiation techniques, irradiation doses, and chemotherapy regimens used [27-35]. In the study, we included PMRT to both the chest wall and regional nodes with at least 50 Gy. Our protocols were reviewed and approved by the Institutional Review Board of Taipei Medical University. The diagnoses of enrolled patients were confirmed using their pathological data, and patients who received a new diagnosis of breast IDC were confirmed to have no other cancers. Patients diagnosed with breast IDC who received NACT followed by TM, were aged ≥ 20 years, and had American Joint Committee on Cancer (AJCC) clinical cancer stage I-IV were included. AJCC clinical tumor, node, and metastasis staging information was recorded in the TCRD. The breast cancer stages were all based on the seventh edition of the AJCC. Patients with metastasis, missing sex data, aged <20 years, undergoing nonstandard PMRT, with unclear differentiation of tumor grade, having unclear pathologic response, missing estrogen receptor (ER) or progesterone receptor (PR) status, missing human epidermal growth factor receptor 2 (HER2) status, and unclear staging were excluded. We also excluded patients with unclear regimens of NACT, who underwent fewer than four cycles of NACT, with ill-defined nodal surgery, and with nonrecorded hospital levels (medical center or nonmedical center hospitals) or hospital regions in our cohort. Being ER/PR-positive was defined as ≥ 1% of tumor cells exhibiting positive nuclear staining through immunohistochemistry [36], and being HER2 positive was defined as fluorescence in situ hybridization with a ≥ 2 ratio [37]. Finally, we enrolled patients with breast IDC who received NACT followed by TM and categorized them into the following groups according to their treatment modality to compare their outcomes: group 1 (control group), consisting of patients who did not receive

PMRT, and group 2 (case group), consisting of patients who received PMRT. The index date was the diagnosis date of breast cancer. The median total dose and fraction size of PMRT were 50 and 2 Gy per fraction in group 2. Comorbidities were scored using the Charlson Comorbidity Index (CCI) [38, 39]. Only comorbidities observed 6 months before the index date were included. Comorbidities were identified and included according to the main International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes for the first admission or more than two repeated main diagnosis codes for visits to the outpatient department.

After adjustment for confounders, the time dependent Cox proportional method was used to model the time from the index date to all-cause death, LRR, DM, and DFS among patients who underwent PMRT or non-PMRT. Through multivariate analysis, hazard ratios (HRs) were adjusted for age, diagnosis year, CCI scores, tumor grade differentiation, clinical T stage, clinical N stage, pathologic response, NACT regimen, nodal surgery, ER or PR status, HER2 status, hospital level, and hospital region. The effect of PMRT on OS, LRR-free survival, DM-free survival, and DFS was determined through multivariable Cox regression analysis for patients who received NACT and TM with or without PMRT and stratified by clinical T or clinical N stage. Stratified analyses in different clinical T or N stages were performed to evaluate mortality, recurrence, metastatic risk associated with PMRT or non-PMRT, age, diagnosis year, CCI score, tumor grade differentiation, pathologic response, NACT regimen, nodal surgery, ER or PR status, HER2 status, hospital level, and hospital region used in the multivariate analysis. All analyses were performed using SAS (v9.3; SAS, Cary, NC, USA). A two-tailed value of $P<0.05$ was considered statistically significant.

Results

A final cohort of 4236 patients (2917 and 1319 patients in groups 1 and 2, respectively) were eligible for further analysis. Patient characteristics are summarized in **Table 1**. No statistical differences appeared in age, CCI score, tumor grade, and ER or PR status between PMRT and non-PMRT groups (**Table 1**). More patients had received PMRT in 2011-2015 than in 2007-2014. This indicated that more patients had received PMRT in recent years. The PMRT group had more patients with advanced breast cancer in clinical T or N stages. Fewer patients with pathological complete response (pCR) received PMRT. Moreover, more patients with pathological stationary disease (pSD) or pathological progression of disease (pPD) received PMRT. Fewer patients receiving NACT with anthracycline-based regimens received PMRT. More patients receiving NACT with taxane-based regimens received PMRT. More patients received axillary lymph node dissection as nodal surgery in the PMRT group. The PMRT group had more HER2-positive patients. More patients received PMRT in non-medical centers, and more patients were in the north of Taiwan (**Table 1**).

According to multivariate Cox regression analysis, PMRT was a significant independent predictor of OS, LRR, and DFS (**Table 2**) but was a nonsignificant predictor of DM. Both univariate and multivariate Cox regression analyses indicated that non-PMRT, CCI ≥ 2, advanced clinical T or N stages, pathologic partial response (pPR), pSD, and pPD were poor prognostic factors for OS. Well-differentiated tumor grade, pCR, and being ER/PR-positive were better independent prognostic factors for OS. Advanced clinical N stage, poorly differentiated tumor grade, pPR, pSD, and pPD were poor prognostic factors for DM. In addition, poor prognostic factors after multivariate analysis for LRR comprised non-PMRT, poorly differentiated tumor grade, advanced T stage, advanced N stage, pPR, pSD, pPD, and being HER2 positive. Poor prognostic factors for DFS in patients with breast IDC status post-NACT and TM were non-PMRT, poor differentiation, advanced clinical T or N stages, poor pathologic response (including pPR, pSD, and pPD compared to CR), being ER/PR negative, and being HER2 positive. According to both univariate and multivariate Cox regression analyses, the aHRs (95% confidence interval [CI]) of PMRT to non-PMRT were 0.75 (0.65-0.87), 0.86 (0.66-1.11), 0.42 (0.37-0.48), and 0.68 (0.58-0.80) in all-cause death, DM, LRR, and DFS, respectively.

For stratified different clinical T or N stages, multivariate Cox regression analyses revealed that PMRT in patients with breast cancer who received NACT and TM was a significant inde-

Table 1. Characteristics of breast invasive intraductal carcinoma after NACT and TM between patients who received PMRT and those who did not (non-PMRT)

Variable		*Total Mastectomy*		
		PMRT (N = 2917)	*Non-PMRT (N = 1319)*	*P*
Age	Mean (SD)	51.3 (10.3)	52.0 (10.9)	0.1108
	Median (IQR; Q1, Q3)	51 (44.58)	51 (44.59)	
	20-49 years	1301 (44.6%)	562 (42.6%)	0.2263
	50+ years	1616 (55.4%)	757 (57.4%)	
Diagnosis year	2007-2010	956 (32.8%)	556 (42.2%)	<0.0001
	2011-2015	1961 (67.2%)	763 (57.8%)	
CCI score	0	2423 (83.1%)	1042 (79.0%)	0.0065
	1	350 (12.0%)	196 (14.9%)	
	2+	144 (4.9%)	81 (6.1%)	
Differentiation	Well	185 (6.3%)	86 (6.5%)	0.9504
	Moderate	1505 (51.6%)	690 (52.3%)	
	Poor	1227 (42.1%)	543 (41.2%)	
Clinical T stage	0-1	66 (2.3%)	48 (3.6%)	<0.0001
	2	956 (32.8%)	688 (52.2%)	
	3	998 (34.2%)	287 (21.8%)	
	4	897 (30.8%)	296 (22.4%)	
Clinical N stage	0	391 (13.4%)	436 (33.1%)	<0.0001
	1	1515 (51.9%)	636 (48.2%)	
	2	647 (22.2%)	186 (14.1%)	
	3	364 (12.5%)	61 (4.6%)	
Pathologic response	pCR	804 (27.6%)	758 (57.5%)	<0.0001
	pPR	822 (28.2%)	326 (24.7%)	
	pSD	738 (25.3%)	128 (9.7%)	
	pPD	553 (19.0%)	107 (8.1%)	
NACT regimen	Taxane-based	1176 (40.3%)	331 (25.1%)	<0.0001
	Anthracycline-based	772 (26.5%)	533 (40.4%)	
	Both	833 (28.6%)	306 (23.2%)	
	Neither	136 (4.7%)	149 (11.3%)	
Nodal surgery	ALND	2104 (72.1%)	890 (67.5%)	<0.0001
	SLND	813 (27.9%)	429 (32.5%)	
ER/PR status	Negative	1401 (48.0%)	653 (49.5%)	0.3726
	Positive	1516 (52.0%)	666 (50.5%)	
HER2 status	Negative	1876 (64.3%)	915 (69.4%)	0.0013
	Positive	1041 (35.7%)	404 (30.6%)	
Hospital level	Medical center	1595 (54.7%)	946 (71.7%)	<0.0001
	Nonmedical Center	1322 (45.3%)	373 (28.3%)	
Hospital area	North	1633 (56.0%)	644 (48.8%)	<0.0001
	Middle	477 (16.4%)	250 (19.0%)	
	South/East	807 (27.7%)	425 (32.2%)	
Mean follow-up time, months (SD)		59.6 (30.1)	65.5 (32.8)	
Death		754 (25.8%)	318 (24.1%)	0.2279
Distant metastasis		224 (7.7%)	106 (8.0%)	0.6879
Locoregional recurrence		706 (24.2%)	417 (31.6%)	<0.0001
DFS		578 (19.8%)	268 (20.3%)	0.7042

PMRT, post-mastectomy radiation therapy; T, tumor; N, nodal; DFS, disease-free survival; NACT, neoadjuvant chemotherapy; TM, total mastectomy; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; pCR, pathological complete response; pPR, pathologic partial response; pSD, pathological stationary disease; pPD, pathological progression of disease; ALND, axillary lymph node dissection; SNLD, Sentinel Lymph Node Dissection; IQR, interquartile range; SD, Standard Deviation.

Table 2. Multivariate Cox proportional hazards mode analysis of breast invasive intraductal carcinoma after NACT and TM

		OS		DM		LRR		DFS	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
PMRT	No	ref	0.0001	ref	0.24	ref	<0.0001	ref	<0.0001
	Yes	0.75 (0.65-0.87)		0.86 (0.66-1.11)		0.42 (0.37-0.48)		0.68 (0.58-0.80)	
Age	20-49 years	ref	0.61	ref	0.34	ref	0.18	ref	0.43
	50+ years	1.04 (0.91-1.18)		0.79(0.56-1.89)		0.92 (0.81-1.04)		0.94 (0.81-1.09)	
Diagnosis year	2007-2010	ref	0.90	ref	0.38	ref	0.40	ref	0.41
	2011-2015	0.99 (0.87-1.13)		0.90 (0.71-1.14)		1.06 (0.93-1.20)		1.06 (0.92-1.24)	
CCI score	0	ref	0.0008	ref	0.1393	ref	0.47	ref	0.66
	1	0.94 (0.77-1.14)		1.23 (0.88-1.71)		1.06 (0.88-1.27)		0.98 (0.79-1.22)	
	2+	1.53(1.21-1.93)		1.44 (0.21-1.93)		1.16 (0.90-1.50)		1.15 (0.84-1.55)	
Differentiation	Poor	ref	<0.0001	ref	0.0059	ref	0.0106	ref	0.0162
	Moderate	0.74 (0.64-0.85)		0.90 (0.98-1.72)		0.90 (0.78-1.03)		0.98 (0.83-1.15)	
	Well	0.44 (0.30-0.63)		0.83 (0.81-0.91)		0.65 (0.47-0.89)		0.62 (0.43-0.89)	
Clinical T stage	0-1	ref	<0.0001	ref	0.43	ref	<0.0001	ref	0.0334
	2	1.88 (1.03-3.45)		0.77 (0.38-1.54)		1.26 (0.79-1.98)		1.56 (0.89-2.73)	
	3	2.42 (1.32-4.45)		0.67 (0.33-1.35)		1.58 (1.00-2.51)		1.77 (1.00-3.12)	
	4	2.80 (1.52-5.15)		0.82 (0.41-1.67)		1.87 (1.18-2.98)		1.93 (1.09-3.41)	
Clinical N stage	0	ref	0.0001	ref	0.0001	ref	<0.0001	ref	<0.0001
	1	1.36 (1.11-1.66)		1.08 (1.01-1.35)		1.51 (1.24-1.83)		1.44 (1.16-1.80)	
	2	1.45 (1.15-1.82)		1.17 (1.03-1.57)		1.43 (1.14-1.79)		1.36 (1.05-1.77)	
	3	1.82 (1.40-2.35)		1.45 (1.09-2.26)		1.75 (1.35-2.26)		1.95 (1.46-2.60)	
Pathologic response	pCR	ref	<0.0001	ref	0.26	ref	<0.0001	ref	<0.0001
	pPR	1.52 (1.26-1.84)		1.29 (0.95-1.74)		1.41 (1.18-1.68)		1.32 (1.08-1.62)	
	pSD-pPD	2.42 (2.02-2.90)		1.16 (0.85-1.59)		2.34 (1.97-2.79)		1.90 (1.56-2.32)	
NACT regimen	Anthracycline-based	ref	0.47	ref	0.16	ref	0.99	ref	0.24
	Taxane-based	1.12 (0.95-1.31)		1.34 (0.85-1.56)		1.07 (0.73-1.30)		1.28 (0.87-1.53)	
	Both	1.03 (0.88-1.21)		1.14 (0.98-1.34)		1.03 (0.77-1.36)		1.09 (0.91-1.30)	
	Neither	1.14 (0.88-1.47)		1.32 (0.83-1.70)		1.08 (0.62-1.56)		1.19 (0.66-1.25)	
Nodal surgery	SLND	ref	0.70	ref	0.1109	ref	0.37	ref	0.44
	ALND	1.17 (0.79-1.73)		1.10 (0.92-1.55)		1.28 (0.91-1.82)		1.31 (0.86-1.98)	
ER/PR positive		0.67 (0.59-0.76)	<0.0001	0.94 (0.89-1.15)	0.30	0.82 (0.69-1.01)	0.08	0.44 (0.24-1.38)	<0.0001
HER-2 positive		1.07 (1.03-1.15)	0.0087	1.79 (1.42-2.26)	<0.0001	1.54 (1.36-1.75)	<0.0001	1.72 (1.49-1.99)	<0.0001
Hospital level	Medical center	ref	0.21	ref	0.20	ref	0.61	ref	0.0385
	Nonmedical Center	0.92 (0.81-1.05)		0.86 (0.67-1.09)		1.03 (0.91-1.17)		0.86 (0.74-0.99)	

HRs, hazard ratios; CI, confidence interval; PMRT, post-mastectomy radiation therapy; T, tumor; N, nodal; NACT, neoadjuvant chemotherapy; TM, total mastectomy; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; pCR, pathological complete response; pPR, pathologic partial response; pSD, pathological stationary disease; pPD, pathological progression of disease; ALND, axillary lymph node dissection; SNLD, sentinel lymph node dissection; OS, overall survival; LRR, locoregional recurrence; DM, distant metastasis; DFS, disease-free survival.

pendent predictor of better OS, except for clinical T1 and T2 (**Figure 1A**). Regardless of the pathologic response and other predictors adjusted in the model, PMRT resulted in better OS in clinical T3, T4, N0, N1, N2, and N3. aHRs derived for PMRT for breast cancer after NACT and TM were 0.69 (0.53-0.89) and 0.74 (0.59-0.93) in clinical T3 and T4, respectively (**Figure 1A**). Moreover, aHRs derived for PMRT for breast cancer after NACT and TM were 0.67 (0.45-0.99), 0.75 (0.62-0.92), and 0.77 (0.60-0.98) in clinical N0, N1, N2, and N3, respectively (**Figure 1A**). The aHRs (95% CI) of the PMRT group to the non-PMRT group for LRR-free survival were 0.48 (0.37-0.61), 0.37 (0.29-0.48), 0.40 (0.32-0.50), 0.41 (0.27-0.61), 0.41 (0.34-0.49), and 0.44 (0.35-0.56) in clinical T2, T3, T4, N0, N1, N2, and N3, respectively (**Figure 1C**). The aHRs of DFS derived for PMRT for breast cancer after NACT and TM were 0.67 (0.50-0.88), 0.71 (0.52-0.97), and 0.68 (0.52-0.89) in clinical T2, T3, and T4, respectively (**Figure 1D**). Moreover, the aHRs of DFS derived for PMRT for breast cancer after NACT and TM were 0.58 (0.36-0.92), 0.72 (0.58-0.89), and 0.70 (0.52-0.93) in clinical N0, N1, N2, and N3, respectively (**Figure 1D**). The aHRs of DM-free survival derived for PMRT for breast cancer after NACT and TM were 0.55 (0.34-0.89) and 0.51 (0.28-0.95) in patients with clinical T3 and N0, respectively (**Figure 1B**). There were no statistical differences between the PMRT and non-PMRT groups for DM-free survival after multivariate analysis of clinical T0, T1, T2, T4, N1, N2, and N3 (**Figure 1B**).

Discussion

Indications of PMRT in patients with breast IDC who received NACT followed by TM remain controversial [5, 6, 8-10, 40-43]. Indications of PMRT after NACT and TM in patients with breast cancer have deepened by clinical tumor size, lymph node status, and pathologic response in tumor or lymph nodes in previous studies but no solid conclusions on indications of PMRT have produced clear outcome benefits regarding PMRT on OS, DFS, LRR, or DM [5, 6, 8-10, 40-43]. In some studies, PMRT has been considered for patients with any residual pathologic N stages after NACT, based on retrospective evidence that suggests a higher rate of recurrence in such patients [40]. PMRT has also been considered in patients with residual pathologic breast T stages, although the threshold to omit PMRT in such patients is lower than that for patients with residual pathologic N stages [6, 8, 10, 40-43]. Without prospective data to guide the approach for patients with a pCR to NACT, some retrospective studies have suggested that patients who presented with clinical stage III disease based on AJCC stages be treated with PMRT, regardless of pathologic response [6, 8, 10, 40-43]. The clinical AJCC stages appear to be valuable markers for indications of adjuvant PMRT in patients with breast cancer who receive NACT and TM [6, 8, 10, 40-43]. Thus, most retrospective data in women with clinical stage III disease suggest that PMRT improves LRR, even in patients who have a pCR to NACT; however, the endpoints of previous studies have rarely been OS or DM [6, 8, 10, 40-43]. For example, in one retrospective study that included over 670 women treated with NACT followed by TM, PMRT was associated with a significantly lower rate of LRR over 10 years (22% vs 11%) [6]. Among 46 patients who presented with stage III or IV disease and achieved a pCR with NACT, PMRT was associated with a decreased 10-year rate of LRR (3% vs 33% among patients not receiving PMRT) [6]. By contrast, other retrospective data suggested that certain patients who achieve a pCR with NACT have low rates of LRR following TM without using PMRT [5, 9]. A large retrospective study of 3000 women treated with TM with or without PMRT discovered that PMRT was associated with only a modest reduction in 10-year LRR (10.3% vs 12.6% among patients who did not receive PMRT) [5]. Thus, PMRT may not be considered for such patients [5]. Therefore, pretreatment factors and patients' pathologic response to NACT were evaluated, with a lower threshold of omission from PMRT [5, 9]. In addition, another study reported that post-chemotherapy pathologic nodal status was not predictive of relative survival benefits obtained from PMRT [7]. Therefore, clear evidence and outcome benefits of PMRT with pretreatment factors is needed to better inform recommendations for PMRT after NACT and TM. Until now, the effects of PMRT on patients after NACT and TM in pretreatment clinical T and N stages after pathologic response is adjusted have been controversial. In this study, we estimated the effects of PMRT

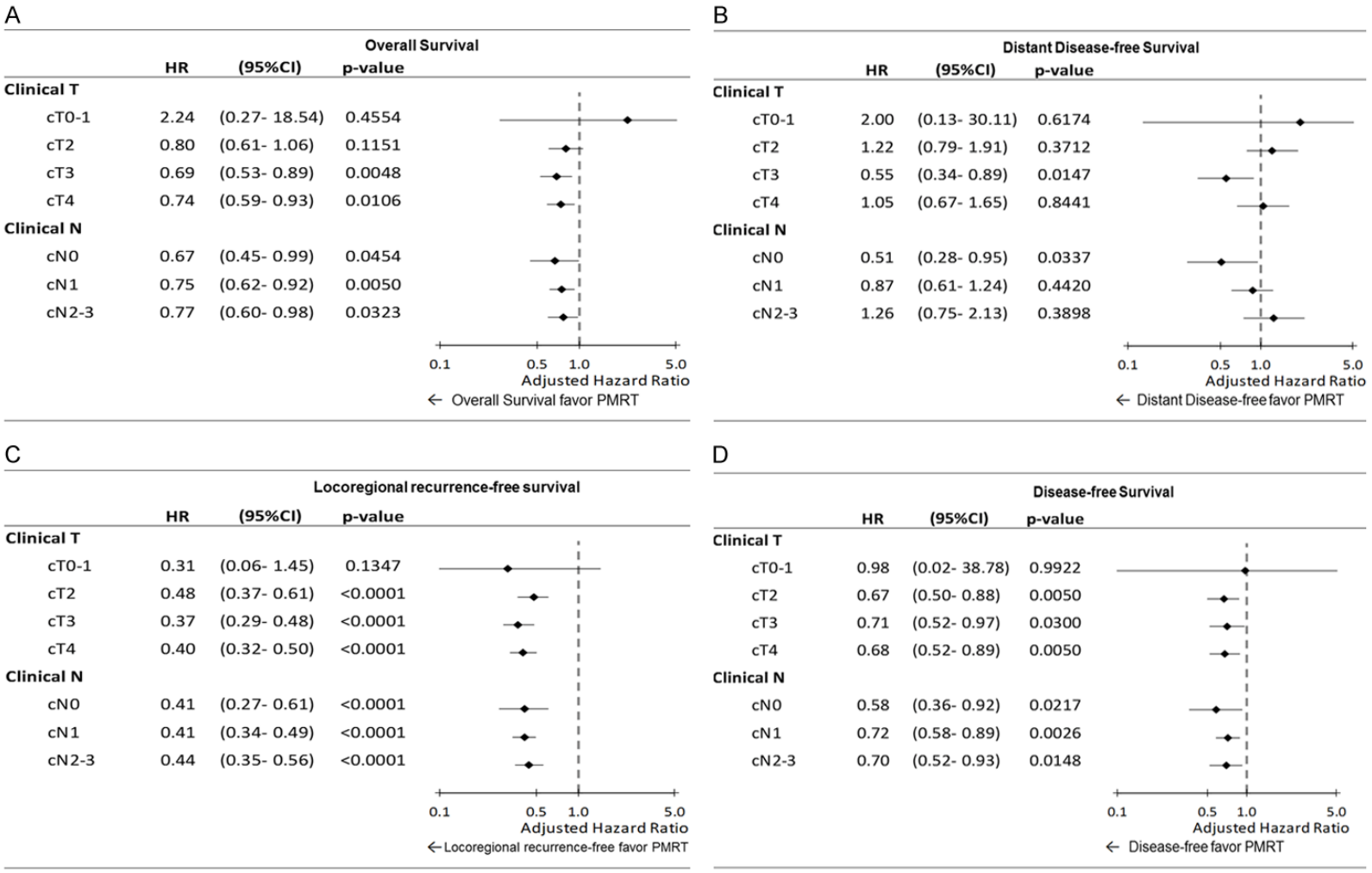

Figure 1. Effect of post-mastectomy radiation therapy (PMRT) on overall survival, locoregional recurrence-free survival, distant disease-free survival, and disease-free survival from multivariable Cox regression analysis in patients who received neoadjuvant chemotherapy and total mastectomy with or without PMRT stratified by clinical tumor and nodal stage. A. Effect of post-mastectomy radiation therapy on overall survival. HR Ratio: All variables presented in **Table 2** were used in the multivariate analysis. HRs, hazard ratios; CI, confidence interval; PMRT, post-mastectomy radiation therapy; T, tumor; N, nodal; OS, overall survival; LRR, locoregional recurrence; DM, distant metastasis; DFS, disease-free survival. B. Effect of post-mastectomy radiation therapy on distant metastasis-free survival. Adjusted HR: All variables presented in **Table 2** were used in the multivariate analysis. HRs, hazard ratios; CI, confidence interval; PMRT, post-mastectomy radiation therapy; T, tumor; N, nodal; OS, overall survival; LRR, locoregional recurrence; DM, distant metastasis; DFS, disease-free survival. C. Effect of post-mastectomy radiation therapy on

locoregional recurrence-free survival. Adjusted HR: All variables presented in **Table 2** were used in the multivariate analysis. HRs, hazard ratios; CI, confidence interval; PMRT, post-mastectomy radiation therapy; T, tumor; N, nodal; OS, overall survival; LRR, locoregional recurrence; DM, distant metastasis; DFS, disease-free survival. D. Effect of post-mastectomy radiation therapy on disease-free survival. Adjusted HR: All variables presented in **Table 2** were used in the multivariate analysis. HRs, hazard ratios; CI, confidence interval; PMRT, post-mastectomy radiation therapy; T, tumor; N, nodal; OS, overall survival; LRR, locoregional recurrence; DM, distant metastasis; DFS, disease-free survival.

by determining the effects of pretreatment clinical T and N stages on patients receiving NACT and TM regardless of pathologic response because complex pathologic responses after NACT depend on various physiologic or molecular factors [44-47].

The is the first study to estimate clinical T or N stages and the effect of PMRT on OS, DM, LRR, and DFS in patients with breast cancer who received NACT and TM. The multivariate Cox proportional hazards model analysis of breast IDC after NACT and TM revealed some significant predictors of OS, DFS, DM, and LRR (**Table 2**). PMRT, pathologic response, tumor grade, CCI score, clinical T or clinical N stage, and being ER/PR-positive were independent predictors of OS. PMRT resulted in better OS, LRR, and DFS after multivariate analysis in patients with breast cancer who received NACT and TM (**Table 2**). No significant benefits appeared from applying PMRT on DM in patients with breast cancer who received NACT and TM. According to our literature review, no sufficient data support the advantages of PMRT in OS, LRR, DM, or DFS for patients with breast cancer who received NACT and TM. This is the first data to show the benefits of PMRT on OS, DFS, and LRR in patients with breast cancer who received NACT and TM, but no association appeared between PMRT and the risk of DM in these patients.

Our findings are compatible with those of previous studies in which PMRT, pathologic response, and clinical T or N stage were independent predictors of OS in patients with breast cancer who received NACT and TM [7, 10]. Moreover, tumor grade, CCI ≥ 2, and being ER/PR negative were the first reported independent poor prognostic factors of OS for patients with breast cancer who received NACT and TM (**Table 2**). In our study, the predictors of OS in such patients were PMRT, tumor grade, being ER/PR negative, and clinical T or N stage before chemotherapy. In the past, whether these predictors of OS were attributed to distant or locoregional failure was unclear. In the current study, we clarified the effects of these predictors on distant and locoregional failure in patients with breast cancer who received NACT and TM. Poorly differentiated appearance resulted in poor OS because of a higher risk of DM and LRR. These findings are compatible with those of previous studies that have shown poorly differentiated breast cancer to result in a high risk of DM and a high LRR rate [48-50]. CCI ≥ 2 was an independent poor prognostic factor for OS but not a significant predictor of DM and LRR (**Table 2**). Higher CCI scores were associated with poor OS, which is compatible with the findings of previous studies that present comorbidity at breast cancer diagnosis as an independent adverse prognostic factor for death [51]. Our finding was reasonable regarding poor OS in patients with breast cancer with multicomorbidities who received NACT and TM compared with relatively healthy patients with CCI = 0. No association appeared between the risk of DM and LRR in patients with CCI ≥ 2. Clinical T stage before NACT was a predictor of OS, LRR, and DFS but not a significant predictor of DM (**Table 2**). Clinical T stage was a predictor of OS, LRR, and DFS for patients with breast cancer who received NACT and TM. The outcomes are similar to those of previous studies [5, 6, 8, 52]. Moreover, a higher advanced clinical T stage was associated with a higher risk of LRR in breast cancer, rather than the risk of DM (**Table 2**). Clinical N stage was an independent predictor of OS, DM, LRR, and DFS in patients with breast cancer who received NACT and TM, which is compatible with similar outcomes from previous studies [5, 6, 8, 52]. The difference between clinical T and N stage was in the effect of DM on patients who received NACT and TM. Higher advanced clinical N stage was proportional to a higher risk of DM; however, higher advanced T stage was not associated with a higher risk of DM. Pathologic response after NACT was a key predictor of OS, DM, LRR, and DFS in patients who receiv-

ed NACT and TM. This is the first study to discover that pCR and pPR were predictors of OS, DM, LRR, and DFS in patients with breast cancer who received NACT and TM. In addition, being ER/PR positive was a good predictor of OS and DFS in such patients, and this result is similar to that of a study by Buchholz et al., who reported a lower LRR risk in ER/PR-positive patients with hormone therapy [6]. Our study is the first to indicate that being HER2 positive was a poor prognostic factor of OS, DM, DFS, and LRR in patients with breast cancer who received NACT and TM. This finding may have resulted because having a HER2-positive disease (along with a negative disease) is associated with a lower pathologic response rate after NACT [44, 53, 54].

In summary, this is the first study to show significant predictors of OS, LRR, DM, and DFS in patients with breast cancer who received NACT and TM. Moreover, PMRT is a crucial adjuvant treatment and improved OS, LRR, and DFS in such patients regardless of their pathologic response after multivariate analysis. We clarified the benefits of PMRT by using clinical stage instead of pathologic response (**Figure 1**) because different chemotherapy regimens, tumor differentiation, molecular appearance (HER2 and ER/PR-positivity), and body index mass are associated with different pathologic responses [24-26, 45, 55, 56]. Indications of PMRT in patients can undergo interference from complicated factors in pathologic response [6, 8, 10, 40-43]. Thus, simplifying indications of PMRT by using clinical T or N stages can be valuable and help make further decisions regarding PMRT. The clear benefits of PMRT in OS, DM, LRR, and DFS are clarified in **Figure 1**.

Our study is the first to estimate the effect of PMRT on OS, LRR, DM, and DFS in patients with breast cancer who received NACT and TM who were stratified by clinical T and N stage after multivariable Cox regression analysis. Our study is a good reference for using clinical T or N stages for adjuvant PMRT in patients with breast cancer after receiving NACT and TM. Our study showed that PMRT for clinical T3N0 improved OS regardless of pathologic response (**Figure 1A**). The findings are compatible with those of previous studies [10, 57]. However, previous studies have not focused on detailed outcomes of OS, LRR, DM, or DFS [10, 57], and our study presented the clear benefits of PMRT in patients with breast IDC who received NACT and TM. In our study, PMRT was beneficial for OS for clinical T3N0 (**Figure 1A**), for LRR for clinical T2N0 (**Figure 1C**), and for DFS for clinical T2N0 (**Figure 1D**). No clear benefits appeared from PMRT for DM in patients with breast cancer who received NACT and TM (**Figure 1B**). Differences in PMRT in DM for patients with breast cancer who received NACT and TM may have been attributed to complex reactions between NACT and pathologic responses associated with various risks from DM.

Our study is the largest cohort study in Taiwan to estimate outcomes of PMRT for patients with breast cancer regarding OS, LRR, DM, and DFS depending on clinical T or N stages. The treatment of PMRT and regimens of NACT were homogenous in our study. Few studies have estimated the effects of PMRT for detailed outcomes of OS, LRR, DFS, and DM in patients with breast cancer who received NACT and TM, and all covariates including pathologic response were adjusted. In our study, poor prognostic factors for OS in such patients were non-PMRT, higher clinical T or N stage before NACT, poorly differentiated tumor grade, pPR, pSD, pPD, CCI $\geq$ 2, being ER/PR negative, and being HER2 positive (**Table 2**). Clinical T stage and CCI were not associated with DM, but clinical T stage was associated with LRR and DFS. From the multivariable Cox regression analysis for patients who received NACT and TM with or without PMRT, PMRT resulted in superior OS in clinical T3, T4, and N0-3 regardless of pathologic response and other predictors (**Figure 1A**). In our study, the effect of PMRT was significantly superior for OS in clinical T3N0-T4N3, for LRR-free survival in clinical T2N0-T4N3, and for DFS in clinical T2N0-T4N3 to non-PMRT patients regardless of pathologic response and other predictors (**Figure 1A-D**).

This study has some limitations. First, because all patients with breast IDC were enrolled from an Asian population, the corresponding ethnic susceptibility compared with the non-Asian population remains unclear; hence, our results should be cautiously extrapolated to non-Asian populations. However, no evidence indicates any differences in outcomes from

PMRT among patients with breast cancer who received NACT and TM between Asian and non-Asian populations. Second, the diagnoses of all comorbid conditions were based on ICD-9-CM codes. Nevertheless, the Taiwan Cancer Registry Administration randomly reviews charts and interviews patients to verify the accuracy of these diagnoses, and hospitals with outlier chargers or practices may be audited and subsequently be heavily penalized if malpractice or discrepancies are identified. Third, to prevent the creation of several subgroups, various neoadjuvant treatments were not categorized separately during analysis. Thus, the effects of different neoadjuvant treatments remain unclear. Accordingly, to obtain crucial information on population specificity and disease occurrence, a large-scale randomized trial comparing carefully selected patients undergoing suitable treatments is essential. Finally, the TCRD does not contain information regarding dietary habits, socioeconomic status, or body mass index, all of which may be risk factors for mortality. However, given the magnitude and statistical significance of observed effects in this study, these limitations are unlikely to affect conclusions.

Conclusions

PMRT significantly improved OS in clinical T3N0-T4N3 and LRR-free survival and DFS in clinical T2N0-T4N3 from those of non-PMRT patients regardless of pathologic response and other predictors.

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Disclosure of conflict of interest

None.

Abbreviations

PMRT, post-mastectomy radiation therapy; T, tumor; N, nodal; OS, overall survival; LRR, locoregional recurrence; DM, distant metastasis; DFS, disease-free survival; NACT, neoadjuvant chemotherapy; TM, total mastectomy; HRs, hazard ratios; CI, confidence intervals; IDC, invasive intraductal carcinoma; TCRD, Taiwan Cancer Registry database; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; pCR, pathological complete response; pPR, pathologic partial response; pSD, pathological stationary disease; pPD, pathological progression of disease; ALND, axillary lymph node dissection; SNLB, sentinel lymph node biopsy.

Address correspondence to: Dr. Szu-Yuan Wu, Division of Radiation Oncology, Department of Medicine, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, No. 83, Nanchang St., Luodong Township, Yilan County 265, Taiwan. E-mail: szuyuanwu5399@gmail.com

References

[1] Gralow JR, Burstein HJ, Wood W, Hortobagyi GN, Gianni L, von Minckwitz G, Buzdar AU, Smith IE, Symmans WF, Singh B and Winer EP. Preoperative therapy in invasive breast cancer: pathologic assessment and systemic therapy issues in operable disease. J Clin Oncol 2008; 26: 814-819.

[2] Kaufmann M, Hortobagyi GN, Goldhirsch A, Scholl S, Makris A, Valagussa P, Blohmer JU, Eiermann W, Jackesz R, Jonat W, Lebeau A, Loibl S, Miller W, Seeber S, Semiglazov V, Smith R, Souchon R, Stearns V, Untch M and von Minckwitz G. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. J Clin Oncol 2006; 24: 1940-1949.

[3] Schwartz GF and Hortobagyi GN. Proceedings of the consensus conference on neoadjuvant chemotherapy in carcinoma of the breast, April 26-28, 2003, Philadelphia, Pennsylvania. Cancer 2004; 100: 2512-2532.

[4] Mamtani A, Barrio AV, King TA, Van Zee KJ, Plitas G, Pilewskie M, El-Tamer M, Gemignani ML, Heerdt AS, Sclafani LM, Sacchini V, Cody HS 3rd, Patil S and Morrow M. How often does neoadjuvant chemotherapy avoid axillary dis-

section in patients with histologically confirmed nodal metastases? results of a prospective study. Ann Surg Oncol 2016; 23: 3467-3474.
[5] Mamounas EP, Anderson SJ, Dignam JJ, Bear HD, Julian TB, Geyer CE Jr, Taghian A, Wickerham DL and Wolmark N. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of national surgical adjuvant breast and bowel project B-18 and B-27. J Clin Oncol 2012; 30: 3960-3966.
[6] Buchholz TA, Tucker SL, Masullo L, Kuerer HM, Erwin J, Salas J, Frye D, Strom EA, McNeese MD, Perkins G, Katz A, Singletary SE, Hunt KK, Buzdar AU and Hortobagyi GN. Predictors of local-regional recurrence after neoadjuvant chemotherapy and mastectomy without radiation. J Clin Oncol 2002; 20: 17-23.
[7] Rusthoven CG, Rabinovitch RA, Jones BL, Koshy M, Amini A, Yeh N, Jackson MW and Fisher CM. The impact of postmastectomy and regional nodal radiation after neoadjuvant chemotherapy for clinically lymph node-positive breast cancer: a national cancer database (NCDB) analysis. Ann Oncol 2016; 27: 818-827.
[8] Huang EH, Tucker SL, Strom EA, McNeese MD, Kuerer HM, Buzdar AU, Valero V, Perkins GH, Schechter NR, Hunt KK, Sahin AA, Hortobagyi GN and Buchholz TA. Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. J Clin Oncol 2004; 22: 4691-4699.
[9] Huang EH, Tucker SL, Strom EA, McNeese MD, Kuerer HM, Hortobagyi GN, Buzdar AU, Valero V, Perkins GH, Schechter NR, Hunt KK, Sahin AA and Buchholz TA. Predictors of locoregional recurrence in patients with locally advanced breast cancer treated with neoadjuvant chemotherapy, mastectomy, and radiotherapy. Int J Radiat Oncol Biol Phys 2005; 62: 351-357.
[10] McGuire SE, Gonzalez-Angulo AM, Huang EH, Tucker SL, Kau SW, Yu TK, Strom EA, Oh JL, Woodward WA, Tereffe W, Hunt KK, Kuerer HM, Sahin AA, Hortobagyi GN and Buchholz TA. Postmastectomy radiation improves the outcome of patients with locally advanced breast cancer who achieve a pathologic complete response to neoadjuvant chemotherapy. Int J Radiat Oncol Biol Phys 2007; 68: 1004-1009.
[11] EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y, Wang Z and Darby S. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 2014; 383: 2127-2135.
[12] Health Promotion Administration MoHaW. Taiwan Cancer Registry Annual Report. 2017.
[13] Kuo CN, Liao YM, Kuo LN, Tsai HJ, Chang WC and Yen Y. Cancers in Taiwan: Practical insight from epidemiology, treatments, biomarkers, and cost. J Formos Med Assoc 2019; 12: S0929-6646.
[14] Ikeda T, Jinno H, Matsu A, Masamura S and Kitajima M. The role of neoadjuvant chemotherapy for breast cancer treatment. Breast Cancer 2002; 9: 8-14.
[15] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017; 67: 7-30.
[16] Korde LA, Zujewski JA, Kamin L, Giordano S, Domchek S, Anderson WF, Bartlett JM, Gelmon K, Nahleh Z, Bergh J, Cutuli B, Pruneri G, McCaskill-Stevens W, Gralow J, Hortobagyi G and Cardoso F. Multidisciplinary meeting on male breast cancer: summary and research recommendations. J Clin Oncol 2010; 28: 2114-2122.
[17] Parkin DM, Bray F, Ferlay J and Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74-108.
[18] Leong SP, Shen ZZ, Liu TJ, Agarwal G, Tajima T, Paik NS, Sandelin K, Derossis A, Cody H and Foulkes WD. Is breast cancer the same disease in Asian and Western countries? World J Surg 2010; 34: 2308-2324.
[19] Youlden DR, Cramb SM, Yip CH and Baade PD. Incidence and mortality of female breast cancer in the Asia-Pacific region. Cancer Biol Med 2014; 11: 101-115.
[20] Yu JM, Hsieh MC, Qin L, Zhang J and Wu SY. Metformin reduces radiation-induced cardiac toxicity risk in patients having breast cancer. Am J Cancer Res 2019; 9: 1017-1026.
[21] Lee CH, Zhang JF, Yuan KS, Wu ATH and Wu SY. Risk of cardiotoxicity induced by adjuvant anthracycline-based chemotherapy and radiotherapy in young and old Asian women with breast cancer. Strahlenther Onkol 2019; 195: 629-639.
[22] Matsuno RK, Anderson WF, Yamamoto S, Tsukuma H, Pfeiffer RM, Kobayashi K, Devesa SS and Levine PH. Early- and late-onset breast cancer types among women in the United States and Japan. Cancer Epidemiol Biomarkers Prev 2007; 16: 1437-1442.
[23] Beadle BM, Woodward WA and Buchholz TA. The impact of age on outcome in early-stage breast cancer. Semin Radiat Oncol 2011; 21: 26-34.
[24] Liedtke C, Mazouni C, Hess KR, Andre F, Tordai A, Mejia JA, Symmans WF, Gonzalez-Angulo

AM, Hennessy B, Green M, Cristofanilli M, Hortobagyi GN and Pusztai L. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 2008; 26: 1275-1281.

[25] Uematsu T, Kasami M, Watanabe J, Takahashi K, Yamasaki S, Tanaka K, Tadokoro Y and Ogiya A. Is lymphovascular invasion degree one of the important factors to predict neoadjuvant chemotherapy efficacy in breast cancer? Breast Cancer 2011; 18: 309-313.

[26] Keskin S, Muslumanoglu M, Saip P, Karanlik H, Guveli M, Pehlivan E, Aydogan F, Eralp Y, Aydiner A, Yavuz E, Ozmen V, Igci A and Topuz E. Clinical and pathological features of breast cancer associated with the pathological complete response to anthracycline-based neoadjuvant chemotherapy. Oncology 2011; 81: 30-38.

[27] Chang CL, Tsai HC, Lin WC, Chang JH, Hsu HL, Chow JM, Yuan KS, Wu ATH and Wu SY. Dose escalation intensity-modulated radiotherapy-based concurrent chemoradiotherapy is effective for advanced-stage thoracic esophageal squamous cell carcinoma. Radiother Oncol 2017; 125: 73-79.

[28] Chang WW, Hsiao PK, Qin L, Chang CL, Chow JM and Wu SY. Treatment outcomes for unresectable intrahepatic cholangiocarcinoma: nationwide, population-based, cohort study based on propensity score matching with the Mahalanobis metric. Radiother Oncol 2018; 129: 284-292.

[29] Chen TM, Lin KC, Yuan KS, Chang CL, Chow JM and Wu SY. Treatment of advanced nasopharyngeal cancer using low- or high-dose concurrent chemoradiotherapy with intensity-modulated radiotherapy: a propensity score-matched, nationwide, population-based cohort study. Radiother Oncol 2018; 129: 23-29.

[30] Lin YK, Hsieh MC, Chang CL, Chow JM, Yuan KS, Wu ATH and Wu SY. Intensity-modulated radiotherapy with systemic chemotherapy improves survival in patients with nonmetastatic unresectable pancreatic adenocarcinoma: a propensity score-matched, nationwide, population-based cohort study. Radiother Oncol 2018; 129: 326-332.

[31] Lin YK, Hsieh MC, Wang WW, Lin YC, Chang WW, Chang CL, Cheng YF and Wu SY. Outcomes of adjuvant treatments for resectable intrahepatic cholangiocarcinoma: chemotherapy alone, sequential chemoradiotherapy, or concurrent chemoradiotherapy. Radiother Oncol 2018; 128: 575-583.

[32] Yen YC, Hsu HL, Chang JH, Lin WC, Chang YC, Chang CL, Chow JM, Yuan KS, Wu ATH and Wu SY. Efficacy of thoracic radiotherapy in patients with stage IIIB-IV epidermal growth factor receptor-mutant lung adenocarcinomas who received and responded to tyrosine kinase inhibitor treatment. Radiother Oncol 2018; 129: 52-60.

[33] Lin WC, Ding YF, Hsu HL, Chang JH, Yuan KS, Wu ATH, Chow JM, Chang CL, Chen SU and Wu SY. Value and application of trimodality therapy or definitive concurrent chemoradiotherapy in thoracic esophageal squamous cell carcinoma. Cancer 2017; 123: 3904-3915.

[34] Yen YC, Chang JH, Lin WC, Chiou JF, Chang YC, Chang CL, Hsu HL, Chow JM, Yuan KS, Wu ATH and Wu SY. Effectiveness of esophagectomy in patients with thoracic esophageal squamous cell carcinoma receiving definitive radiotherapy or concurrent chemoradiotherapy through intensity-modulated radiation therapy techniques. Cancer 2017; 123: 2043-2053.

[35] Wu SY, Fang SC, Shih HJ, Wen YC and Shao YJ. Mortality associated with statins in men with advanced prostate cancer treated with androgen deprivation therapy. Eur J Cancer 2019; 112: 109-117.

[36] Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, Fitzgibbons PL, Francis G, Goldstein NS, Hayes M, Hicks DG, Lester S, Love R, Mangu PB, McShane L, Miller K, Osborne CK, Paik S, Perlmutter J, Rhodes A, Sasano H, Schwartz JN, Sweep FC, Taube S, Torlakovic EE, Valenstein P, Viale G, Visscher D, Wheeler T, Williams RB, Wittliff JL and Wolff AC. American society of clinical oncology/college of American pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 2010; 28: 2784-2795.

[37] Fehrenbacher L, Cecchini RS, Geyer CE Jr, Rastogi P, Costantino JP, Atkins JN, Crown JP, Polikoff J, Boileau JF, Provencher L, Stokoe C, Moore TD, Robidoux A, Flynn PJ, Borges VF, Albain KS, Swain SM, Paik S, Mamounas EP and Wolmark N. NSABP B-47/NRG oncology phase III randomized trial comparing adjuvant chemotherapy with or without trastuzumab in high-risk invasive breast cancer negative for HER2 by FISH and with IHC 1+ or 2. J Clin Oncol 2020; 38: 444-453.

[38] Charlson M, Szatrowski TP, Peterson J and Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994; 47: 1245-1251.

[39] Chen JH, Yen YC, Yang HC, Liu SH, Yuan SP, Wu LL, Lee FP, Lin KC, Lai MT, Wu CC, Chen TM, Chang CL, Chow JM, Ding YF and Wu SY. Curative-intent aggressive treatment improves survival in elderly patients with locally advanced head and neck squamous cell carcinoma and high comorbidity index. Medicine (Baltimore) 2016; 95: e3268.

[40] Liu J, Mao K, Jiang S, Jiang W, Chen K, Kim BY, Liu Q and Jacobs LK. The role of postmastectomy radiotherapy in clinically node-positive, stage II-III breast cancer patients with pathological negative nodes after neoadjuvant chemotherapy: an analysis from the NCDB. Oncotarget 2016; 7: 24848-24859.

[41] Abdel-Wahab M, Wolfson A, Raub W, Mies C, Brandon A, Morrell L, Lee Y, Ling S and Markoe A. The importance of postoperative radiation therapy in multimodality management of locally advanced breast cancer: a phase II trial of neoadjuvant MVAC, surgery, and radiation. Int J Radiat Oncol Biol Phys 1998; 40: 875-880.

[42] Ring A, Webb A, Ashley S, Allum WH, Ebbs S, Gui G, Sacks NP, Walsh G and Smith IE. Is surgery necessary after complete clinical remission following neoadjuvant chemotherapy for early breast cancer? J Clin Oncol 2003; 21: 4540-4545.

[43] Panades M, Olivotto IA, Speers CH, Shenkier T, Olivotto TA, Weir L, Allan SJ and Truong PT. Evolving treatment strategies for inflammatory breast cancer: a population-based survival analysis. J Clin Oncol 2005; 23: 1941-1950.

[44] Untch M, Fasching PA, Konecny GE, Hasmuller S, Lebeau A, Kreienberg R, Camara O, Muller V, du Bois A, Kuhn T, Stickeler E, Harbeck N, Hoss C, Kahlert S, Beck T, Fett W, Mehta KM, von Minckwitz G and Loibl S. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. J Clin Oncol 2011; 29: 3351-3357.

[45] Litton JK, Gonzalez-Angulo AM, Warneke CL, Buzdar AU, Kau SW, Bondy M, Mahabir S, Hortobagyi GN and Brewster AM. Relationship between obesity and pathologic response to neoadjuvant chemotherapy among women with operable breast cancer. J Clin Oncol 2008; 26: 4072-4077.

[46] Sanchez-Munoz A, Plata-Fernandez YM, Fernandez M, Jaen-Morago A, Fernandez-Navarro M, de la Torre-Cabrera C, Ramirez-Tortosa C, Lomas-Garrido M, Llacer C, Navarro-Perez V, Alba-Conejo E and Sanchez-Rovira P. The role of immunohistochemistry in breast cancer patients treated with neoadjuvant chemotherapy: an old tool with an enduring prognostic value. Clin Breast Cancer 2013; 13: 146-152.

[47] Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, Pusztai L, Green MC, Arun BK, Giordano SH, Cristofanilli M, Frye DK, Smith TL, Hunt KK, Singletary SE, Sahin AA, Ewer MS, Buchholz TA, Berry D and Hortobagyi GN. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 2005; 23: 3676-3685.

[48] Diel IJ, Kaufmann M, Goerner R, Costa SD, Kaul S and Bastert G. Detection of tumor cells in bone marrow of patients with primary breast cancer: a prognostic factor for distant metastasis. J Clin Oncol 1992; 10: 1534-1539.

[49] Harahap WA and Nindrea RD. Prognostic factors of local-regional recurrence in patients with operable breast cancer in Asia: a meta-analysis. Open Access Maced J Med Sci 2019; 7: 690-695.

[50] Cserni G. Tumour histological grade may progress between primary and recurrent invasive mammary carcinoma. J Clin Pathol 2002; 55: 293-297.

[51] Land LH, Dalton SO, Jensen MB and Ewertz M. Influence of comorbidity on the effect of adjuvant treatment and age in patients with early-stage breast cancer. Br J Cancer 2012; 107: 1901-1907.

[52] Buchholz TA, Katz A, Strom EA, McNeese MD, Perkins GH, Hortobagyi GN, Thames HD, Kuerer HM, Singletary SE, Sahin AA, Hunt KK, Buzdar AU, Valero V, Sneige N and Tucker SL. Pathologic tumor size and lymph node status predict for different rates of locoregional recurrence after mastectomy for breast cancer patients treated with neoadjuvant versus adjuvant chemotherapy. Int J Radiat Oncol Biol Phys 2002; 53: 880-888.

[53] von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, Fasching PA, Gerber B, Eiermann W, Hilfrich J, Huober J, Jackisch C, Kaufmann M, Konecny GE, Denkert C, Nekljudova V, Mehta K and Loibl S. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012; 30: 1796-1804.

[54] Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, Bonnefoi H, Cameron D, Gianni L, Valagussa P, Swain SM, Prowell T, Loibl S, Wickerham DL, Bogaerts J, Baselga J, Perou C, Blumenthal G, Blohmer J, Mamounas EP, Bergh J, Semiglazov V, Justice R, Eidtmann H, Paik S, Piccart M, Sridhara R, Fasching PA, Slaets L, Tang S, Gerber B, Geyer CE Jr, Pazdur R, Ditsch N, Rastogi P, Eiermann W and von Minckwitz G. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014; 384: 164-172.

[55] Bertucci F, Finetti P and Birnbaum D. Basal breast cancer: a complex and deadly molecular subtype. Curr Mol Med 2012; 12: 96-110.

[56] Onitilo AA, Engel JM, Greenlee RT and Mukesh BN. Breast cancer subtypes based on ER/PR and Her2 expression: comparison of clinicopathologic features and survival. Clin Med Res 2009; 7: 4-13.

[57] Nagar H, Mittendorf EA, Strom EA, Perkins GH, Oh JL, Tereffe W, Woodward WA, Gonzalez-Angulo AM, Hunt KK, Buchholz TA and Yu TK. Local-regional recurrence with and without radiation therapy after neoadjuvant chemotherapy and mastectomy for clinically staged T3N0 breast cancer. Int J Radiat Oncol Biol Phys 2011; 81: 782-787.