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Original article

Effect of pathologic stages on postmastectomy radiation therapy in breast cancer receiving neoadjuvant chemotherapy and total mastectomy: A Cancer Database Analysis

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ABSTRACT

Purpose: To use pathologic indicators to determine which patients benefit from postmastectomy radiation therapy (PMRT) for breast cancer after neoadjuvant chemotherapy (NACT) and total mastectomy (TM).

Patients and methods: We enrolled 4236 patients with breast invasive ductal carcinoma who received NACT followed by TM. Cox regression analysis was used to calculate hazard ratios (HRs) and confidence intervals; independent predictors were controlled for or stratified in the analysis.

Results: After multivariate Cox regression analyses, the adjusted HRs derived for PMRT for all-cause mortality were 0.65 (0.52–0.81, $P < 0.0001$) and 0.58 (0.47–0.71, $P < 0.0001$) in postchemotherapy pathologic tumor stages T2–4 (ypT3–4) and postchemotherapy pathologic nodal stages N2–3 (ypN2–3), respectively. Moreover, adjusted HRs derived for PMRT with all-cause mortality were 0.51 (0.38–0.69, $P < 0.0001$), 0.60 (0.40–0.88, $P = 0.0096$), and 0.64 (0.48–0.86, $P = 0.0024$) in pathological stages IIIA, IIIB, and IIIC, respectively. Additionally, the PMRT group showed significant locoregional control irrespective of the pathologic response, even ypT0, ypN0, or pathological complete response (pCR), compared with the No-PMRT group. The multivariate analysis showed no statistical differences between the PMRT and No-PMRT groups for distant metastasis-free survival in any pathologic response of ypT0–4, ypN0–3, and pathologic American Joint Committee on Cancer stages pCR to IIIC.

Conclusion: For patients with breast cancer ypT3–4, ypN2–3, or pathologic stages IIIA–IIIC receiving NACT and TM, benefit from PMRT if it is associated with OS benefits, regardless of the clinical stage of the disease. Compared with No-PMRT, PMRT improved locoregional recurrence-free survival, even pCR, in patients with breast cancer receiving NACT and TM.

Abbreviations: PMRT, postmastectomy radiation therapy; T, tumor; N, nodal; ypT, postchemotherapy pathologic tumor stages; ypN, postchemotherapy pathologic nodal stages; OS, overall survival; LRR, locoregional recurrence; DM, distant metastasis; NACT, neoadjuvant chemotherapy; TM, total mastectomy; HRs, hazard ratios; CI, confidence interval; IDC, invasive ductal 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; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; CCI, Charlson comorbidity index; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; pCR, pathological complete response.

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1. Introduction

Most patients with locally advanced breast cancer, and some with early-stage disease, particularly with triple negative or human epidermal growth factor receptor 2 (HER2) positive status, are treated with neoadjuvant chemotherapy (NACT) [1,2]. The goal of the treatment is to induce a tumor response before surgery and enable breast conservation [1,2]. Moreover, NACT provides information regarding response to therapy that may be useful in the future if the disease recurs. NACT results in long-term distant disease-free survival and overall survival (OS) comparable with those achieved with primary surgery followed by adjuvant systemic therapy [3,4]. However, the choice between breast conservation and total mastectomy (TM) after NACT is dependent on the pathologic response and patients' breast size in relation to residual tumor size [5,6]. Therefore, the surgical approach to the primary tumor depends on the size of the tumor and breast [5,6]. Asian women have relatively smaller breasts compared with women in Western countries [7]. Thus, TM rates among women receiving NACT in Asia have been high [8]. Therefore, the number of Taiwanese patients with breast cancer receiving NACT followed by TM is high [9]. The effect of postchemotherapy pathologic tumor stages (ypT), postchemotherapy pathologic nodal stages (ypN), or overall pathologic American Joint Committee on Cancer (AJCC) stages would be valuable for further adjuvant treatment in Taiwan or Asia because most patients in Taiwan still receive TM after NACT [8,9].

Postmastectomy radiation therapy (PMRT) has two potential benefits, namely a decrease in the rate of locoregional recurrence (LRR) and increases in long-term breast cancer-specific survival and OS for certain patient populations (one or more of the following: involvement of axillary lymph nodes, a tumor size of more than 5 cm, and invasion of the cancer to skin or pectoral fascia) [10–13]. These benefits have been consistently reported in multiple studies [10–13]. Decisions on who should receive PMRT depend on the baseline risk for recurrence, such as women who have >3 involved lymph nodes, 1–3 involved lymph nodes, or high-risk primary tumors [10–13]. However, the indications of PMRT for patients who received neoadjuvant therapy have been controversial, especially in patients receiving TM [14,15]. LRR benefits have been presented in patients with any degree of residual macroscopic nodal disease after NACT with PMRT because retrospective evidence suggests that recurrence is high in such patients [16]. PMRT has been offered to patients with residual breast disease (ypT1–4), although the threshold to omit PMRT in such patients is lower than that for patients with residual nodal (ypN1–3) disease [16,17]. Evidence with ypT or ypN as indicators is insufficient for determining further PMRT, and a combination of ypT and ypN as indicators has not been considered for determining further PMRT.

Until now, no detailed outcome analysis is available regarding PMRT for breast cancer after NACT and TM depending on different pathologic responses and stratification based on ypT, ypN, and overall pathologic AJCC stages. In our study, we estimated the detailed outcomes of OS, LRR, and distant metastasis (DM) in PMRT for breast cancer status after NACT and TM with various pathologic responses of ypT, ypN, or overall pathologic AJCC stages. Moreover, we prefer using pathologic indicators to determine conditions for PMRT for breast cancer after NACT and TM.

2. Patients and methods

In this study, we established a cohort of breast cancer using data from the Taiwan Cancer Registry database (TCRD). The final cohort eligible for further analysis consisted of 4236 patients (2917 and 1319 patients in PMRT and No-PMRT, respectively). We enrolled patients with breast invasive ductal carcinoma (IDC) diagnosis between January 1, 2007 and December 31, 2015. The follow-up duration was from the index date (the date of breast cancer diagnosis) to December 31, 2016. The Cancer Registry database of the Collaboration Center of Health Information Application contains detailed cancer-related information of patients, including the clinical stage, treatment modalities, pathological data, radiation techniques, irradiation doses, hormone receptor status, HER2 status, and chemotherapy regimens used [18–26]. In the study, we included PMRT of both the chest wall and regional nodes with a minimum of 50 Gy. Patients with no evidence of lymph node involvement prior to or during NACT, or those who had negative needle biopsies of any suspicious nodes at diagnosis, should undergo post-NACT sentinel lymph node biopsy (SLNB). If the SLNB post-treatment is positive, surgeons in Taiwan suggest proceeding with axillary lymph node dissection (ALND). Our protocols were reviewed and approved by the Institutional Review Board of Taipei Medical University. The diagnoses of the enrolled patients were confirmed through their pathological data, and patients who received a new diagnosis of breast IDC were confirmed to have no other cancer. Patients with a diagnosis of breast IDC receiving NACT followed by TM, age $\geq$20 years, and AJCC clinical cancer stage I–IV were included. Moreover, the AJCC clinical staging was recorded in the TCRD. The breast cancer stages were based on AJCC, seventh edition. Patients with metastasis, missing sex data, age <20 years, nonstandard PMRT, unclear differentiation of tumor grade, unclear pathologic response, missing estrogen receptor (ER), progesterone receptor (PR) status, missing HER2 status, and unclear staging were excluded. Furthermore, we excluded patients with unclear NACT regimen, fewer than four cycles of NACT, ill-defined nodal surgery (neither SLNB nor ALND), and nonrecorded hospital type [27] (academic center or community hospitals) in our cohort. ER or PR positive was defined as $\geq$ 1% of tumor cells demonstrating positive nuclear staining through immunohistochemistry [28], and HER2 positive was defined as immunohistochemistry score 3+ or fluorescence in situ hybridization ratio $\geq$ 2 [27,29]. Finally, we enrolled patients with breast IDC receiving NACT followed by TM and categorized them into the following groups according to the 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. Index date means the date met inclusion criteria and also the start of follow-up. The index date was the date of breast cancer diagnosis. Comorbidities were scored using the Charlson comorbidity index (CCI) [30,31]. 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 mortality, LRR, and DM among patients who underwent PMRT or No-PMRT. In the multivariate analysis, hazard ratios (HRs) were adjusted for PMRT, age, diagnosis year, CCI scores, tumor differentiation, AJCC clinical stages, ypT, ypN, NACT regimen, nodal surgery, ER/PR, HER2 status, and hospital type. The effects of PMRT on OS, LRR-free survival, and DM-free survival in multivariable Cox regression analysis, in patients who received NACT and TM with or without PMRT, were stratified according to ypT, ypN, or pathologic AJCC stages. Stratified analyses in different pathologic T or N stages were performed to evaluate the OS, LRR, and DM risk associated with PMRT or No-PMRT; furthermore, in the multivariate analysis, we used age, diagnosis year, CCI scores, tumor differentiation, AJCC clinical stages, ypT, ypN, NACT regimen, nodal surgery, ER/PR, HER2 positive, and hospital type. All analyses were

performed using SAS (version 9.3; SAS, Cary, NC, USA). A two-tailed value of $p < 0.05$ was considered statistically significant.

3. Results

The final cohort eligible for further analysis consisted of 4236 patients (2917 and 1319 patients in groups 1 and 2, respectively). The patient characteristics are summarized in Table 1. No statistical differences were noted between the PMRT and No-PMRT groups in terms of age, tumor grade, and ER/PR status (Table 1). The number of patients receiving PMRT in 2011–2015 was higher than that in 2007–2010. In the PMRT group, the number of patients with breast cancer with AJCC clinical stages III–IV was high. Few patients with pathological complete response (pCR) received PMRT. Moreover, most patients with breast cancer receiving PMRT received NACT and TM irrespective of the pathologic response. Patients receiving PMRT included those with advanced residual T or N stages. Most patients in the PMRT group received ALND as nodal surgery. Most patients receiving NACT with a taxane-based regimen received PMRT. The PMRT group mostly consisted of HER2-positive patients. Most patients receiving PMRT were treated in nonacademic hospitals (Table 1).

According to the multivariate Cox regression analysis, PMRT was a significantly independent predictor of OS and LRR but a nonsignificant predictor of DM (Tables 2–4). Both univariate and multivariate Cox regression analyses indicated that No-PMRT, CCI ≥2, poor differentiation, AJCC clinical stages III–IV, and pathologic residual tumor (ypT1–4) or nodal (ypN1–3) stages are poor prognostic factors for OS (Table 2). Well-differentiated tumor grade, namely ypT0, ypN0, or ER/PR positive, was an independent good prognostic factor for OS. In addition, according to a multivariate analysis, poor prognostic factors for LRR were No-PMRT, poor differentiation of tumor grade, AJCC clinical stages III–IV, residual ypT1–4 or ypN1–3, and ER/PR positive status (Table 3). Table 4 shows that AJCC clinical stage IV, poor differentiation of tumor grade, ypT2–4, ypN1–3, and HER2 positive status were poor

Table 1
Characteristics of patients with breast cancer who received neoadjuvant chemotherapy followed by total mastectomy stratified into PMRT and No-PMRT groups.

Variable		TM		
		PMRT ($N = 2917$)	No-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	1301 (69.8%)	562 (30.2%)	0.2263
	50+	1616 (68.1%)	757 (31.9%)	
Diagnosis year	2007–2010	956 (63.2%)	556 (36.8%)	<0.0001
	2011–2015	1961 (72.0%)	763 (28.0%)	
CCI scores	0	2423 (69.9%)	1042 (30.1%)	0.0065
	1	350 (64.1%)	196 (35.9%)	
	2+	144 (64.0%)	81 (36.0%)	
Differentiation	Well	185 (6.3%)	86 (6.5%)	0.9504
	Moderate	1505 (51.6%)	690 (52.3%)	
	Poor	1227 (42.1%)	543 (41.2%)	
AJCC clinical stages	I	66 (57.9%)	48 (42.1%)	<0.0001
	II	995 (77.7%)	285 (22.3%)	
	III	959 (58.2%)	690 (41.8%)	
	IV	897 (75.2%)	296 (24.8%)	
ypT	ypT0	197 (60.2%)	130 (39.8%)	<0.0001
	ypT1	749 (64.1%)	419 (35.9%)	
	ypT2	1163 (68.6%)	532 (31.4%)	
	ypT3–4	808 (77.2%)	238 (22.8%)	
ypN	ypN0	822 (71.6%)	326 (28.4%)	<0.0001
	ypN1	1291 (84.6%)	235 (15.4%)	
	ypN2–3	66 (57.9%)	48 (42.1%)	<0.0001
yp pathologic AJCC stage	pCR	154 (56.0%)	121 (44.0%)	<0.0001
	IA	277 (50.5%)	272 (49.5%)	
	IB	36 (65.5%)	19 (34.5%)	
	IIA	448 (53.6%)	388 (46.4%)	
	IIB	456 (71.3%)	184 (28.8%)	
	IIIA–IIIC	1546 (82.2%)	335 (17.8%)	
NACT regimen	Taxanes	1176 (78.0%)	331 (22.0%)	<0.0001
	Anthracycline	772 (59.2%)	533 (40.8%)	
	Both	833 (73.1%)	306 (26.9%)	
	Neither	136 (47.7%)	149 (52.3%)	
Nodal surgery	ALND	2104 (70.3%)	890 (29.7%)	<0.0001
	SLNB	813 (65.5%)	429 (34.5%)	
ER/PR	Negative	1401 (68.2%)	653 (31.8%)	0.3726
	Positive	1516 (69.5%)	666 (30.5%)	
HER2	Negative	1876 (67.2%)	915 (32.8%)	0.0013
	Positive	1041 (72.0%)	404 (28.0%)	
Hospital level	Academic/research facility	1595 (62.8%)	946 (37.2%)	<0.0001
	Others	1322 (78.0%)	373 (22.0%)	

PMRT, postmastectomy 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; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; SD, standard deviation; CCI, Charlson comorbidity index; AJCC, American Joint Committee on Cancer; ypT, postchemotherapy pathologic tumor stages; ypN, postchemotherapy pathologic nodal stages; IQR, interquartile range.

Table 2
Multivariate analysis of all-cause mortality in patients with breast cancer who received neoadjuvant chemotherapy followed by total mastectomy.

		All-cause mortality		
		HR	(95% CI)	p value
PMRT	No	Ref		0.0001
	Yes	0.71	(0.56–0.77)	
Age	20–49	Ref		0.59
	50+	1.02	(0.89–1.16)	
Diagnosis year	2007–2010	Ref		0.88
	2011–2015	0.97	(0.89–1.11)	
CCI scores	0	Ref		0.0004
	1	0.91	(0.73–1.11)	
	2+	1.54	(1.24–1.90)	
Differentiation	Poor	Ref		<0.0001
	Moderate	0.73	(0.66–0.86)	
	Well	0.43	(0.32–0.61)	
AJCC clinical stages	I	Ref		<0.0001
	II	1.86	(0.92–2.88)	
	III	2.08	(1.29–3.77)	
	IV	2.80	(1.44–3.75)	
ypT	ypT0	Ref		<0.0001
	ypT1	1.59	(1.11–2.32)	
	ypT2	1.79	(1.22–1.98)	
	ypT3–4	2.59	(2.01–3.70)	
ypN	ypN0	Ref		<0.0001
	ypN1	1.44	(1.16–1.84)	
	ypN2–3	2.33	(2.01–2.77)	
NACT regimen	Anthracycline	Ref		0.39
	Taxanes	1.10	(0.93–1.29)	
	Both	1.04	(0.87–1.20)	
	Neither	1.13	(0.89–1.37)	
Nodal surgery	SLNB	Ref		0.88
	ALND	1.07	(0.89–1.33)	
ER/PR	Negative	Ref		<0.0001
	Positive	0.65	(0.55–0.74)	
HER2 positive	Negative	Ref		0.88
	Positive	1.02	(0.88–1.14)	
Hospital level	Academic	Ref		0.29
	Others	0.91	(0.82–1.07)	

HR, hazard ratio; CI, confidence interval; PMRT, postmastectomy radiation therapy; T, tumor; N, nodal; NACT, neoadjuvant chemotherapy; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; CCI, Charlson comorbidity index; AJCC, American Joint Committee on Cancer; ypT, postchemotherapy pathologic tumor stages; ypN, postchemotherapy pathologic nodal stages.

prognostic factors for DM. According to both univariate and multivariate Cox regression analyses, the adjusted HRs (95% confidence interval [CI]) of PMRT and No-PMRT were 0.71 (0.56–0.77), 0.51 (0.41–0.58), and 0.91 (0.77–1.21) for all-cause mortality, LRR, and DM, respectively.

For stratified pathologic T (ypT0–4), pathologic N (ypN0–3), or pathologic AJCC stages, multivariate Cox regression analyses revealed that PMRT was a significant independent predictor of improved OS in patients with breast cancer who received NACT and TM with pathologic ypT3–4, ypN2–3, or pathologic AJCC stage IIIA–IIIC (Fig. 1). Adjusted HRs for PMRT for all-cause mortality were 0.65 (0.52–0.81) and 0.58 (0.47–0.71) in ypT3–4 and ypN2–3, respectively (Fig. 1). Moreover, adjusted HRs for PMRT for all-cause mortality were 0.51 (0.38–0.69), 0.60 (0.40–0.88), and 0.64 (0.48–0.86) in pathological AJCC stages IIIA, IIIB, and IIIC, respectively (Fig. 1). Additionally, PMRT showed significant locoregional control irrespective of the pathologic response, even ypT0, ypN0, or pCR, compared with the No-PMRT group (Fig. 2). The adjusted HRs (95% CI) of the PMRT group to No-PMRT group for LRR-free survival were 0.36 (0.18–0.74), 0.39 (0.30–0.52), 0.64 (0.52–0.80), 0.42 (0.33–0.53), 0.60 (0.46–0.80), 0.46 (0.36–0.60), and 0.28 (0.23–0.34) in ypT0, ypT1, ypT2, yoT3–4, ypN0, ypN1, and ypN2–3, respectively (Fig. 2). The adjusted HRs of LRR-free survival derived for PMRT for breast cancer after NACT and TM were 0.28 (0.12–0.64), 0.36 (0.21–0.60), 0.690(0.43–0.84), 0.61 (0.44–0.85), 0.24 (0.18–0.31), 0.40 (0.26–0.62), and 0.34 (0.25–0.46) in patients with pathologic AJCC stage pCR, stage IA, IB–IIA, IIB, IIIA, IIIB, and IIIC, respectively (Fig. 2). A multivariate analysis revealed no statistical differences between PMRT and No-PMRT groups for DM-free survival in any pathologic response of ypT0–4, ypN0–3, and pathologic AJCC stages pCR to IIIC (Supplemental Figure 1).

4. Discussion

PMRT has been prevalent in patients with breast cancer receiving NACT and TM in recent years (Table 1). However, the definitive indications of adjuvant PMRT are controversial in these patients [14,15]; clinical stages did not provide convincing evidence for performing PMRT in patients with breast cancer who have received NACT and TM [32–38]. Because controversy exists regarding clinical stages for indicating PMRT [14,15,32–38], pathologic tumor or nodal stages might be important basic references for further PMRT in patients with breast cancer receiving NACT and TM. Therefore, we focused on the pathologic stages after NACT as indicators for performing further PMRT in these patients.

According to Table 1, the clinical stage or pathologic stages were more advanced in the PMRT group than those in the No-PMRT group. Patients in the PMRT group had higher CCI scores than did those in the No-PMRT group (Table 1). Advanced clinical stages, pathologic stages, and higher CCI scores were poor prognostic factors for OS or LRR in patients with breast cancer after NACT and TM (Tables 2 and 3). Although there were more patients with

Table 3
Multivariate analysis of locoregional recurrence in patients with breast cancer who received neoadjuvant chemotherapy followed by total mastectomy.

		Locoregional recurrence		
		HR	(95% CI)	p value
PMRT	No	Ref		<0.0001
	Yes	0.51	(0.41–0.58)	
Age	20–49	Ref		0.28
	50+	0.93	(0.84–1.06)	
Diagnosis year	2007–2010	Ref		0.43
	2011–2015	1.05	(0.92–1.18)	
CCI scores	0	Ref		0.54
	1	1.03	(0.91–1.26)	
	2+	1.16	(0.90–1.50)	
Differentiation	Poor	Ref		0.0081
	Moderate	0.88	(0.75–0.94)	
	Well	0.64	(0.46–0.88)	
AJCC clinical stages	I	Ref		<0.0001
	II	1.25	(0.76–1.97)	
	III	1.52	(1.01–2.34)	
	IV	1.85	(1.17–2.89)	
ypT	ypT0	Ref		<0.0001
	ypT1	1.61	(1.15–2.29)	
	ypT2	1.81	(1.29–2.51)	
	ypT3–4	2.48	(1.70–3.24)	
ypN	ypN0	Ref		0.0013
	ypN1	1.40	(1.16–1.72)	
	ypN2–3	2.22	(1.84–1.93)	
NACT regimen	Anthracycline	Ref		0.19
	Taxanes	1.03	(0.96–1.09)	
	Both	1.10	(0.94–1.30)	
	Neither	1.12	(0.98–1.65)	
Nodal surgery	SLNB	Ref		0.44
	ALND	1.29	(0.93–1.80)	
ER/PR positive	Negative	Ref		0.22
	Positive	1.03	(0.93–1.27)	
HER2 positive	Negative	Ref		<0.0001
	Positive	1.56	(1.34–1.70)	
Hospital level	Academic	Ref		0.59
	Others	1.02	(0.90–1.16)	

HR, hazard ratio; CI, confidence interval; PMRT, postmastectomy radiation therapy; T, tumor; N, nodal; NACT, neoadjuvant chemotherapy; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; CCI, Charlson comorbidity index; AJCC, American Joint Committee on Cancer; ypT, postchemotherapy pathologic tumor stages; ypN, postchemotherapy pathologic nodal stages.

advanced stages or high CCI scores in the PMRT group compared with in the No-PMRT group, OS was superior in the PMRT group compared with the No-PMRT group. The survival benefits of OS in the PMRT group were only underestimated and null to the hypothesis. PMRT leads to improved OS and LRR, and the conclusions could not be overturned.

According to Table 2, the AJCC clinical stage was an independent poor prognostic factor of OS, especially in stages III–IV. In addition, clinical stage III–IV was a poor prognostic factor for LRR (Table 3), and clinical stage IV was a poor prognostic factor for DM (Table 4). The clinical stage is an important factor indicating the risk of OS, LRR, and DM (Tables 2–4). Our findings were compatible with previous studies [32–38]. Retrospective data of women with clinical stage III receiving PMRT have indicated improved local control even for patients who had a pCR to NACT [32,34,37,38]. In one retrospective study consisting of >670 women treated with NACT followed by TM, PMRT was associated with a significantly low rate of LRR at 10 years (22% versus 11%) and a low risk of death from breast cancer (HR 0.5, 95% CI 0.34–0.71) [34]. Among the 46 patients who presented with clinical stage III or IV and achieved a pCR with NACT, PMRT was associated with a reduced 10-year rate of LRR (3% versus 33% among patients not receiving PMRT). By contrast, other retrospective data have suggested that certain patients who achieve a pCR with NACT have low rates of LRR following TM without PMRT [14,15]. The conclusions are conflicting regarding the need for PMRT in patients with breast cancer who received NACT and TM, especially pCR [14,15]. For example, a large retrospective study of 3000 women treated with mastectomy with or without PMRT revealed that PMRT was associated with a modest reduction in 10-year LRR (10.3% versus 12.6% among patients who did not receive PMRT), with predictors of recurrence being clinical node involvement prior to NACT and tumor size > 5 cm [15]. Patients lacking these features were at low risk of LRR [15]. Taken together, whether PMRT is advantageous for patients with breast cancer after NACT and TM based on clinical stages is still debatable. Thus, pathologic findings might be crucial indicators of PMRT. Our study showed that PMRT improves OS in patients with ypT3–4, ypN2–3, or pathologic stage IIIA–IIIC compared with the No-PMRT group, and clinical stages were adjusted (Fig. 1). Regardless of clinical stages, we recommend that PMRT is necessary for patients with breast cancer who received NACT and TM with ypT3–4, ypTN1–3, or pathologic stages IIIA–IIIC, and PMRT could result in greater OS than could No-PMRT.

Other predictors of OS in these patients with breast cancer who received NACT and TM are also presented in Table 2, with poor differentiation, CCI ≥2, and ER/PR negative being poor prognostic factors for OS. No study has shown that poor differentiation, CCI ≥2, and ER/PR negative are poor prognostic factors in breast cancer after NACT and TM, but previous studies have considered high CCI scores [39], ER/PR negative [40], and poor tumor differentiation [41–43] as poor prognostic factors for OS, DM, or LRR in patients with breast cancer who received various treatments. Our study

Table 4
Multivariate analysis of distant metastasis in patients with breast cancer who received neoadjuvant chemotherapy followed by total mastectomy.

		Distant metastasis		
		HR	(95% CI)	p value
PMRT	No	Ref		0.33
	Yes	0.91	(0.77–1.21)	
Age	20–49	Ref		0.37
	50+	0.89	(0.88–1.21)	
Diagnosis year	2007–2010	Ref		0.45
	2011–2015	0.93	(0.73–1.16)	
CCI scores	0	Ref		0.1386
	1	1.22	(0.87–1.69)	
	2+	1.43	(0.23–1.89)	
Differentiation	Poor	Ref		0.0039
	Moderate	0.78	(0.39–0.85)	
	Well	0.69	(0.35–0.79)	
AJCC clinical stages	I	Ref		0.0048
	II	1.29	(0.97–1.69)	
	III	1.34	(0.82–2.20)	
	IV	1.77	(1.19–2.39)	
ypT	ypT0	Ref		<0.0001
	ypT1	1.90	(0.94–3.66)	
	ypT2	2.73	(1.45–5.51)	
	ypT3–4	4.41	(2.21–7.87)	
ypN	ypN0	Ref		<0.0001
	ypN1	1.19	(1.11–1.59)	
	ypN2–3	1.28	(1.07–2.90)	
NACT regimen	Anthracycline	Ref		0.89
	Taxanes	0.98	(0.74–1.39)	
	Both	1.04	(0.78–1.30)	
	Neither	1.01	(0.72–1.46)	
Nodal surgery	SLNB	Ref		0.1098
	ALND	1.08	(0.91–1.43)	
ER/PR positive	Negative	Ref		0.35
	Positive	1.13	(0.90–1.44)	
HER2 positive	Negative	Ref		<0.0001
	Positive	1.80	(1.39–2.21)	
Hospital level	Academic	Ref		0.26
	Others	0.87	(0.69–1.12)	

HR, hazard ratio; CI, confidence interval; PMRT, postmastectomy radiation therapy; T, tumor; N, nodal; NACT, neoadjuvant chemotherapy; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; CCI, Charlson comorbidity index; AJCC, American Joint Committee on Cancer; ypT, postchemotherapy pathologic tumor stages; ypN, postchemotherapy pathologic nodal stages.

showed that ER/PR negative, CCI ≥2, or poor tumor differentiation are poor prognostic factors for OS in patients with breast cancer receiving NACT and TM (Table 2). In addition, poor differentiation and HER2 positive status are poor prognostic factors for LRR (Table 3), and our outcomes were similar to those of previous studies in different treatments for breast cancer [41,44]. Moreover, poor differentiation and HER2 positive status were high risk factors for DM (Table 4), and our findings were compatible with those of other studies in different treatments for breast cancer [42,45]. Thus, poor differentiation was a poor prognostic factor for OS, LRR, and DM; HER2 positive was a poor prognostic factor for LRR and DM; and CCI ≥2 and ER/PR positive were poor prognostic factors for OS. Furthermore, our study showed that not only were clinical stages, pathologic stages, ypT, and ypN significant factors for survival but also poor differentiation, CCI ≥2, and HER2 positive status were poor prognostic factors for survival (Tables 2–4).

According to Tables 2–4, pathologic stages are significant factors for PMRT in patients with breast cancer receiving NACT and TM. The effects of PMRT on OS, LRR-free survival, and distant metastasis-free survival in multivariable Cox regression analysis for patients who received NACT and TM with or without PMRT were analyzed (Figs. 1 and 2 and Supplemental Figure 1). After the adjustment of all predictors mentioned in Table 2, PMRT was found to be superior for OS in patients with breast cancer receiving NACT and TM with ypT3–4, ypN1–3, and pathologic AJCC stages IIIA–IIIC compared with the No-PMRT group. Our findings suggest that PMRT might be necessary for patients with breast cancer receiving NACT and TM with ypT3–4, ypN2–3, or pathologic stages IIIA–IIIIC. Thus, PMRT is not required for patients with breast cancer receiving NACT and TM with pCR, early pathologic stages IA–IIB, ypT0–2, or ypN0–1 regardless of clinical stages or other predictors (Fig. 1). Moreover, PMRT is significantly superior for LRR-free survival in patients with breast cancer receiving NACT and TM with pCR, ypT0–4, or ypN0–3 (Fig. 2). Our findings were compatible with some retrospective studies, indicating that PMRT is beneficial for lowering LRR irrespective of the pathologic response [32–38]. In addition, PMRT is not significant for the reduction of DM risk in patients with breast cancer receiving NACT and TM (Supplemental Figure 1). Our findings suggest that PMRT associated with improved OS should be a necessary factor for ypT3–4, ypN2–3, or pathologic stage IIIA–IIIC patients with breast cancer receiving NACT and TM regardless of clinical stages. PMRT could improve LRR-free survival, even pCR, in patients with breast cancer receiving NACT and TM compared with No-PMRT (Fig. 2).

The strength of our study is that it is the largest cohort study in Taiwan to estimate the detailed outcomes of PMRT for patients with breast cancer, including OS, LRR, and DM, depending on the pathologic response of ypT, ypN, or pathologic stages. The PMRT treatment and NACT regimens were relatively homogenous in our study. Scarce studies have estimated the effects of PMRT for detailed outcomes of OS, LRR, and DM in patients with breast cancer receiving NACT and TM and adjustment of all predictors including clinical stages. In our study, poor prognostic factors for OS in these patients were no PMRT, advanced clinical stages III–IV before NACT,

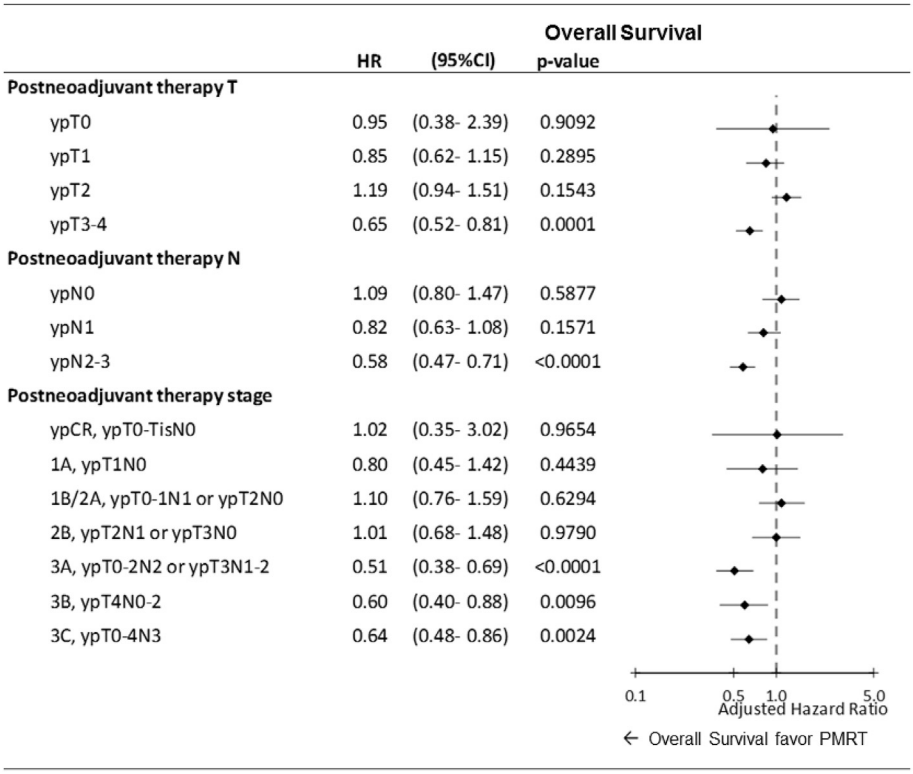

Fig. 1. Impact of PMRT on overall survival in multivariate Cox regression analysis for patients who received total mastectomy with or without PMRT. Adjusted hazard ratio: All variables presented in Table 2 were used in the multivariate analysis. HR, hazard ratio; CI, confidence interval; PMRT, postmastectomy radiation therapy; T, tumor; N, nodal.

poor differentiation, ypT1–4, ypN1–3, CCI ≥2, ER/PR negative, and HER2 positive status (Table 2). Multivariate Cox regression analysis for patients who received NACT and TM with or without PMRT revealed that PMRT led to superior OS in ypT3–4, yN1–3, or stage IIIA–IIIC irrespective of clinical stages and other predictors (Fig. 1). Our study is the first to estimate the OS, LRR, and DM of PMRT for patients with breast cancer receiving NACT and TM with different ypT, ypN, and overall AJCC pathological stages. The beneficial effects of PMRT were improved OS and LRR-free survival compared with the No-PMRT group based on the multivariate analysis.

This study has some limitations. First, because all patients with breast IDC were Asian, the corresponding ethnic susceptibility compared with non-Asian populations remains unclear; hence, our results should be cautiously extrapolated to non-Asian populations. However, no evidence demonstrates the differences in outcomes of PMRT for patients with breast cancer receiving 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 the diagnoses, and hospitals with outlier chargers or practices may be audited and subsequently heavily penalized if malpractice or discrepancies are identified. Third, to prevent the creation of several subgroups, various neoadjuvant treatments were not categorized separately during the analyses. Thus, the effects of different neoadjuvant treatments remain unclear. Fourth, the selection bias in the study were patients in the PMRT group had higher CCI scores than did those in the No-PMRT group. However, there were more patients with advanced stages or high CCI scores in the PMRT group compared with in the No-PMRT group, OS was superior in the PMRT group compared with the No-PMRT group. The survival benefits of OS in the PMRT group were only underestimated and null to the hypothesis. PMRT leads to improved OS and LRR, and the conclusions could not be overturned. 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, considering the magnitude and statistical significance of the observed effects in this study, these limitations are unlikely to affect the conclusions.

5. Conclusions

In patients with breast cancer type ypT3–4, ypN2–3, or pathologic stage IIIA–IIIC receiving NACT and TM, benefit from PMRT if it is associated with improved OS. Compared with No-PMRT, PMRT improved LRR-free survival, even pCR, in patients with breast cancer receiving NACT and TM.

Ethics approval and consent

Our protocols were reviewed and approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB No. 201712019).

Consent for publication

Not applicable.

Availability of data and material

The datasets supporting the study conclusions are included within this manuscript and its additional files.

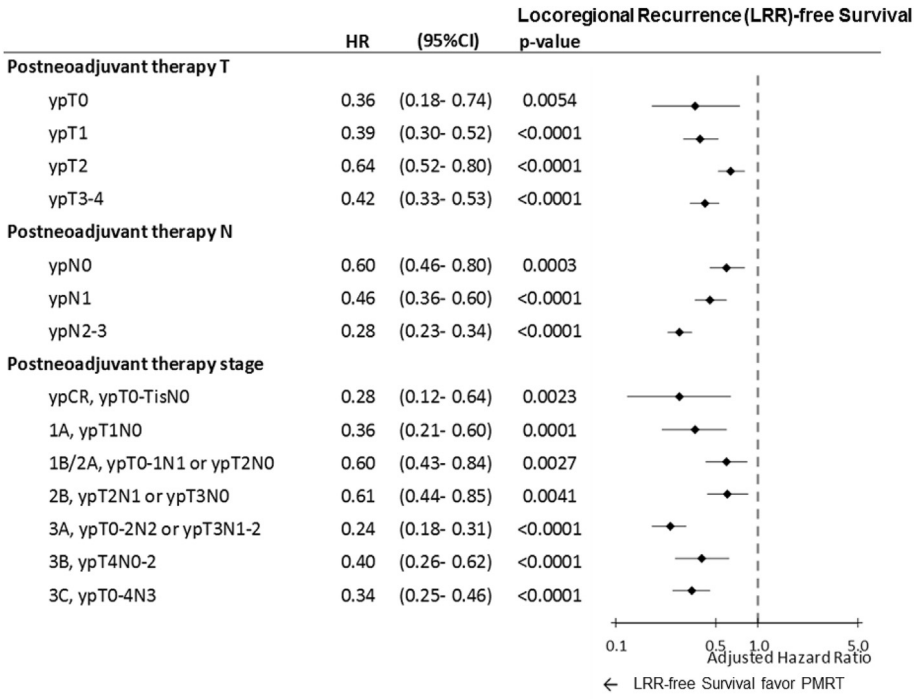

Fig. 2. Impact of PMRT on locoregional recurrence-free survival in multivariate Cox regression analysis for patients who received total mastectomy with or without PMRT. Adjusted hazard ratio: All variables presented in Table 2 were used in the multivariate analysis. HR, hazard ratio; CI, confidence interval; PMRT, postmastectomy radiation therapy; T, tumor; N, nodal.

Author contributions

Conception and Design: Jiaqiang Zhang, MD, PhD; Chang-Yun Lu, MD; Chien-Hsin Chen, MD; Szu-Yuan Wu, MD, MPH, PhD, Financial Support: Lo-Hsu Medical Foundation, LotungPoh-Ai Hospital, supports Szu-Yuan Wu's work (Funding Number: 10908 and 10909). Collection and Assembly of Data: Chang-Yun Lu, MD; Ho-Min Chen, MS; Szu-Yuan Wu, MD, MPH, PhD*, Data Analysis and Interpretation: Ho-Min Chen, MS; Szu-Yuan Wu, MD, MPH, PhD*, Administrative Support: Szu-Yuan Wu*, Manuscript Writing: Jiaqiang Zhang, MD, PhD; Chien-Hsin Chen, MD; Szu-Yuan Wu, MD, MPH, PhD, Final Approval of Manuscript: All authors.

Condensed abstract

No large-scale study has estimated detailed outcome patterns of postmastectomy radiation therapy (PMRT) stratified based on postchemotherapy pathologic tumor or nodal stages (ypT and ypN, respectively) for overall survival (OS), locoregional recurrence, or distant metastasis in patients with breast cancer receiving neoadjuvant chemotherapy (NACT) and total mastectomy (TM). We used pathologic indicators to determine which patients benefit from PMRT for breast cancer after NACT and TM. For patients with breast cancer ypT3–4, ypN2–3, or pathologic stages IIIA–IIIC receiving NACT and TM, PMRT should be performed if it is associated with OS benefits, regardless of their clinical stages. Compared with No-PMRT, PMRT improved locoregional recurrence-free survival and even pathological complete response in patients with breast cancer receiving NACT and TM.

Declaration of competing interest

The authors have no potential conflicts of interest to declare. The datasets supporting the study conclusions are included within the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2020.08.017.

References

[1] Teshome M, Hunt KK. Neoadjuvant therapy in the treatment of breast cancer. Surg Oncol Clin 2014;23:505–23.
[2] Guarneri V, Dieci MV, Barbieri E, Piacentini F, Omarini C, Ficarra G, et al. Loss of HER2 positivity and prognosis after neoadjuvant therapy in HER2-positive breast cancer patients. Ann Oncol 2013;24:2990–4.
[3] Thompson AM, Moulder-Thompson SL. Neoadjuvant treatment of breast cancer. Ann Oncol 2012;23(Suppl 10):x231–6.
[4] Cance WG, Carey LA, Calvo BF, Sartor C, Sawyer L, Moore DT, et al. Long-term outcome of neoadjuvant therapy for locally advanced breast carcinoma: effective clinical downstaging allows breast preservation and predicts outstanding local control and survival. Ann Surg 2002;236:295–302. discussion -3.
[5] Chen JH, Feig BA, Hsiang DJ, Butler JA, Mehta RS, Bahri S, et al. Impact of MRI-evaluated neoadjuvant chemotherapy response on change of surgical recommendation in breast cancer. Ann Surg 2009;249:448–54.
[6] Murugappan K, Saboo A, Kuo L, Ung O. Paradigm shift in the local treatment of breast cancer: mastectomy to breast conservation surgery. Gland Surg 2018;7:

506–19.
[7] Maskarinec G, Meng L, Ursin G. Ethnic differences in mammographic densities. Int J Epidemiol 2001;30:959–65.
[8] Sun Y, Liao M, He L, Zhu C. Comparison of breast-conserving surgery with mastectomy in locally advanced breast cancer after good response to neoadjuvant chemotherapy: a PRISMA-compliant systematic review and meta-analysis. Medicine (Baltim) 2017;96:e8367.
[9] National Health Insurance Administration. Ministry of Health and welfare, Taiwan, R.O.C. 2015. 2017.
[10] Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;366:2087–106.
[11] Danish Breast Cancer Cooperative G, Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. J Clin Oncol : Off J Am Soc Clin Oncol 2006;24:2268–75.
[12] Ragaz J, Olivotto IA, Spinelli JJ, Phillips N, Jackson SM, Wilson KS, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst 2005;97:116–26.
[13] Ebctcg, McGale P, Taylor C, Correa C, Cutter D, Duane F, et al. 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;383:2127–35.
[14] Huang EH, Tucker SL, Strom EA, McNeese MD, Kuerer HM, Hortobagyi GN, et al. 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;62:351–7.
[15] Mamounas EP, Anderson SJ, Dignam JJ, Bear HD, Julian TB, Geyer Jr CE, et al. 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 : Off J Am Soc Clin Oncol 2012;30:3960–6.
[16] Liu J, Mao K, Jiang S, Jiang W, Chen K, Kim BY, et al. 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;7:24848–59.
[17] Rusthoven CG, Rabinovitch RA, Jones BL, Koshy M, Amini A, Yeh N, et al. 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;27:818–27.
[18] Chang CL, Tsai HC, Lin WC, Chang JH, Hsu HL, Chow JM, et al. Dose escalation intensity-modulated radiotherapy-based concurrent chemoradiotherapy is effective for advanced-stage thoracic esophageal squamous cell carcinoma. Radiother Oncol 2017.
[19] Chang WW, Hsiao PK, Qin L, Chang CL, Chow JM, 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.
[20] Chen TM, Lin KC, Yuan KS, Chang CL, Chow JM, 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 2017.
[21] Lin YK, Hsieh MC, Chang CL, Chow JM, Yuan KS, Wu ATH, et al. 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.
[22] Lin YK, Hsieh MC, Wang WW, Lin YC, Chang WW, Chang CL, et al. Outcomes of adjuvant treatments for resectable intrahepatic cholangiocarcinoma: chemotherapy alone, sequential chemoradiotherapy, or concurrent chemoradiotherapy. Radiother Oncol 2018.
[23] Yen YC, Hsu HL, Chang JH, Lin WC, Chang YC, Chang CL, et al. 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.
[24] Lin WC, Ding YF, Hsu HL, Chang JH, Yuan KS, Wu ATH, et al. Value and application of trimodality therapy or definitive concurrent chemoradiotherapy in thoracic esophageal squamous cell carcinoma. Cancer; 2017.
[25] Yen YC, Chang JH, Lin WC, Chiou JF, Chang YC, Chang CL, et al. 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;123:2043–53.
[26] Wu SY, Fang SC, Shih HJ, Wen YC, Shao YJ. Mortality associated with statins in men with advanced prostate cancer treated with androgen deprivation therapy. Eur J Canc 2019;112:109–17.
[27] Bahreini F, Soltanian AR, Mehdipour P. A meta-analysis on concordance between immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) to detect HER2 gene overexpression in breast cancer. Breast Cancer 2015;22:615–25.
[28] Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. 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 : Off J Am Soc Clin Oncol 2010;28:2784–95.
[29] Fehrenbacher L, Cecchini RS, Geyer Jr CE, Rastogi P, Costantino JP, Atkins JN, et al. 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 : Off J Am Soc Clin Oncol 2020;38:444–53.
[30] Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47:1245–51.
[31] Chen JH, Yen YC, Yang HC, Liu SH, Yuan SP, Wu LL, et al. Curative-intent aggressive treatment improves survival in elderly patients with locally advanced head and neck squamous cell carcinoma and high comorbidity index. Medicine (Baltim) 2016;95:e3268.
[32] Huang EH, Tucker SL, Strom EA, McNeese MD, Kuerer HM, Buzdar AU, et al. 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 : Off J Am Soc Clin Oncol 2004;22:4691–9.
[33] Abdel-Wahab M, Wolfson A, Raub W, Mies C, Brandon A, Morrell L, et al. 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;40:875–80.
[34] Buchholz TA, Tucker SL, Masullo L, Kuerer HM, Erwin J, Salas J, et al. Predictors of local-regional recurrence after neoadjuvant chemotherapy and mastectomy without radiation. J Clin Oncol : Off J Am Soc Clin Oncol 2002;20:17–23.
[35] Ring A, Webb A, Ashley S, Allum WH, Ebbs S, Gui G, et al. Is surgery necessary after complete clinical remission following neoadjuvant chemotherapy for early breast cancer? J Clin Oncol : Off J Am Soc Clin Oncol 2003;21:4540–5.
[36] Panades M, Olivotto IA, Speers CH, Shenkier T, Olivotto TA, Weir L, et al. Evolving treatment strategies for inflammatory breast cancer: a population-based survival analysis. J Clin Oncol : Off J Am Soc Clin Oncol 2005;23:1941–50.
[37] McGuire SE, Gonzalez-Angulo AM, Huang EH, Tucker SL, Kau SW, Yu TK, et al. 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;68:1004–9.
[38] Pierce LJ, Lippman M, Ben-Baruch N, Swain S, O'Shaughnessy J, Bader JL, et al. The effect of systemic therapy on local-regional control in locally advanced breast cancer. Int J Radiat Oncol Biol Phys 1992;23:949–60.
[39] Land LH, Dalton SO, Jensen MB, Ewertz M. Impact of comorbidity on mortality: a cohort study of 62,591 Danish women diagnosed with early breast cancer, 1990-2008. Breast Canc Res Treat 2012;131:1013–20.
[40] Onitilo AA, Engel JM, Greenlee RT, 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.
[41] Medina-Franco H, Vasconez LO, Fix RJ, Heslin MJ, Beenken SW, Bland KI, et al. Factors associated with local recurrence after skin-sparing mastectomy and immediate breast reconstruction for invasive breast cancer. Ann Surg 2002;235:814–9.
[42] Schoppmann SF, Bayer G, Aumayr K, Taucher S, Geleff S, Rudas M, et al. Prognostic value of lymphangiogenesis and lymphovascular invasion in invasive breast cancer. Ann Surg 2004;240:306–12.
[43] Elston CW. The assessment of histological differentiation in breast cancer. Aust N Z J Surg 1984;54:11–5.
[44] Gonzalez-Angulo AM, Litton JK, Broglio KR, Meric-Bernstam F, Rakkhit R, Cardoso F, et al. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. J Clin Oncol : Off J Am Soc Clin Oncol 2009;27:5700–6.
[45] Duchnowska R, Dziadziuszko R, Czartoryska-Arlukowicz B, Radecka B, Szostakiewicz B, Sosinska-Mielcarek K, et al. Risk factors for brain relapse in HER2-positive metastatic breast cancer patients. Breast Canc Res Treat 2009;117:297–303.