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Original article

Breast-conserving surgery with or without irradiation in women with invasive ductal carcinoma of the breast receiving preoperative systemic therapy: A cohort study

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ABSTRACT

Purpose: To investigate the outcomes of adjuvant whole breast radiation therapy (WBRT) in patients with invasive ductal carcinoma of the breast (breast IDC) receiving preoperative systemic therapy (PST) and breast-conserving surgery (BCS), and their prognostic factors, considering overall survival (OS), locoregional recurrence (LRR), distant metastasis (DM), and disease-free survival.

Patients and methods: Patients diagnosed as having breast IDC and receiving PST followed by BCS were recruited and categorized by treatment into non-breast radiation therapy [BRT] (control) and WBRT (case) groups, respectively. Cox regression analysis was used to calculate hazard ratios (HRs) and confidence intervals (CIs).

Results: Multivariate Cox regression analyses indicated that non-BRT, cN3, and pathologic residual tumor (ypT2–4) or nodal (ypN2–3) stages were poor prognostic factors for OS. The adjusted HRs (aHRs; 95% CIs) of the WBRT group to non-BRT group for all-cause mortality were 0.14 (0.03–0.81), 0.32 (0.16–0.64), 0.43 (0.23–0.79), 0.23 (0.13–0.42), 0.52 (0.20–1.33), and 0.34 (0.13–0.87) in the ypT0, ypT1, ypT2–4, ypN0, ypN1, and ypN2–3 stages, respectively. The aHRs (95% CIs) of the WBRT group to non-BRT group for all-cause mortality were 0.09 (0.00–4.07), 0.46 (0.26–0.83), 0.18 (0.06–0.51), 0.28 (0.06–1.34), 0.25 (0.10–0.63), 0.47 (0.23–0.88), and 0.32 in the cT0–1, cT2, cT3, cT4, cN0, cN1, and cN2–3 stages, respectively. The WBRT group exhibited significantly better LRR-free and DM-free survival than the non-BRT group, regardless of the clinical T or N stage or pathologic response after PST.

Conclusion: WBRT might lead to superior OS and LRR-free and DM-free survival compared with the non-BRT group, regardless of the initial clinical TN stage or pathologic response.

Abbreviations: WBRT, whole breast radiation therapy; BRT, breast radiation therapy; BCS, breast-conserving surgery; RT, radiation therapy; T, tumor; N, nodal; cT, clinical tumor stages; cN, clinical nodal stages; ypT, pathological tumor stages after preoperative systemic therapy; ypN, pathological nodal stages after preoperative systemic therapy; OS, overall survival; LRR, locoregional recurrence; DM, distant metastasis; PST, preoperative systemic therapy; TM, total mastectomy; HRs, hazard ratios; CIs, 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; ALND, axillary lymph node dissection; SNLB, sentinel lymph node biopsy; CCI, Charlson comorbidity index; IIT, intention-to-treat.

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1. Introduction

Breast-conserving surgery (BCS) allows women with early invasive breast cancer to preserve their breasts without sacrificing the oncologic outcome [1–3]. Successful BCS requires complete surgical removal of the tumor with negative surgical margins followed by adjuvant whole breast radiation therapy (WBRT) to eradicate any residual disease [4]. Patient selection is crucial for the success of BCS [5–7]. Cosmetic concerns do not dictate but can influence the choice of procedure, such as a large tumor in a small breast, breast asymmetry, or postradiation fibrosis [8].

Preoperative systemic therapy (PST) increases the eligibility for BCS [9]. Before initiation of PST, a clip is placed in the tumor bed to guide BCS [10]. After completion of PST, breast imaging should be repeated to determine a patient's candidacy for BCS [11]. All patients should undergo definitive breast surgery, either BCS or total mastectomy (TM), including those who can achieve a pathologic complete response (pCR) [12]. Postmastectomy radiation therapy (PMRT) has two potential benefits, namely a decrease in the rate of locoregional recurrence (LRR) and increase in long-term breast cancer-specific survival and overall survival (OS) among certain patient populations [1,13,14]. These benefits have been consistently reported previously [1,13,14]. 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 [1,13,14].

No study, however, has estimated the requirement of WBRT for patients with invasive ductal carcinoma of the breast (breast IDC) receiving PST and BCS. All evidence of BCS followed by WBRT is based on observations in patients with breast cancer not receiving PST [1–3,15–18]. The detailed outcomes of OS, LRR, or distant metastasis (DM) are still unclear in patients with breast cancer receiving PST and BCS with or without WBRT. Thus far, observations in patients with breast cancer receiving PST and BCS followed by WBRT are consistent with those of earlier studies that included patients who did not receive PST but received BCS followed by WBRT [1–3,15–18]. The necessity of WBRT in patients with breast cancer receiving PST and BCS has never been investigated. Therefore, in this study, we aimed to estimate the effects of WBRT in these patients and clarify the benefits of WBRT in terms of OS, LRR, or DM in such patients receiving PST and BCS.

2. Patients and methods

In this study, we identified a cohort of patients with breast cancer from the Taiwan Cancer Registry database (TCRD). Patients diagnosed as having breast IDC between January 1, 2007, and December 31, 2015 were enrolled in the study. They were followed up 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 the clinical stage, treatment modalities, pathological data, radiation techniques, irradiation doses, hormone receptor status, human epidermal growth factor receptor 2 (HER2) status, and chemotherapy regimens used [19–27]. In this study, we included WBRT to the whole breast in patients with pathologic N0 after PST (ypN0) and to the whole breast and regional nodes with 50 Gy at least in patients positive for pathologic lymph nodes after PST (ypN1–3). Our protocols were reviewed and approved by the Institutional Review Board of Taipei Medical University. The diagnoses of the enrolled patients were confirmed using their pathological data, and patients newly diagnosed as having breast IDC were confirmed to have no other cancer. Patients with a diagnosis of breast IDC receiving PST followed by BCS, those aged ≥20 years, and those with clinical cancer stage I–IV as per the American Joint Committee on Cancer (AJCC) were included. BCS involves the excision of the primary tumor (i.e., lumpectomy) and evaluation of the axillary lymph nodes (most commonly with sentinel lymph node biopsy) for invasive tumors. The AJCC clinical and pathological staging is also recorded in the TCRD. The breast cancer stages were all based on the seventh edition of the AJCC. We excluded patients if they had metastasis; were missing sex data; were aged <20 years; received nonstandard WBRT, partial breast radiation therapy (BRT), or total mastectomy; had unclear tumor grade differentiation or pathologic response; had missing estrogen receptor (ER)/progesterone receptor (PR) or HER2 status data; and had unclear tumor staging data. Those with unclear regimens of PST, fewer than four cycles of PST, ill-defined nodal surgery, and nonrecorded hospital levels (academic center or community hospitals) [28] were also excluded. ER or PR positivity was defined when ≥1% of tumor cells demonstrated positive nuclear staining according to immunohistochemistry [29], and HER2 positivity was defined as an immunohistochemistry score 3+ or a fluorescence in situ hybridization ratio of ≥2 [28,30]. Finally, patients with breast IDC receiving PST followed by BCS were enrolled and categorized into the following groups according to the treatment modality to compare their outcomes: group 1 (control group, non-breast radiation therapy [non-BRT]), consisting of patients who did not receive adjuvant WBRT, and group 2 (case group, WBRT), consisting of patients who received adjuvant WBRT. The index date was the date of diagnosis of breast cancer. Comorbidities were scored using the Charlson comorbidity index (CCI) [31,32]. 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 WBRT or non-BRT. In the multivariate analysis, hazard ratios (HRs) were adjusted for adjuvant WBRT, age, diagnosis year, CCI scores, tumor differentiation, cT, cN, ypT, ypN, PST regimens, nodal surgery, ER/PR status, HER2 status, and hospital levels. The impact of WBRT on OS and LRR-free and DM-free survival for patients who received PST and BCS with or without WBRT, stratified by cT, cN, ypT, or ypN, was evaluated using a multivariable Cox regression analysis. Stratified analyses in cT, cN, ypT, and ypN stages were performed to evaluate the OS, LRR, and DM risk associated with WBRT or non-BRT. Age, diagnosis year, CCI scores, tumor differentiation, cT, cN, ypT, ypN, PST regimens, nodal surgery, ER/PR status, HER2 status, and hospital levels were used in the multivariate analysis. All analyses were performed using SAS (version 9.3; SAS, Cary, NC, USA). A two-tailed $p < 0.05$ was considered statistically significant.

3. Results

The final cohort comprised 1544 patients (108 and 1436 in groups 1 and 2, respectively), who were eligible for further analysis. Patient characteristics are summarized in Table 1. No statistical differences were observed in age, CCI scores, tumor differentiation, cT, cN, ypT, ypN, nodal surgery, ER/PR status, and HER2 status between the WBRT and non-BRT groups (Table 1). More patients received WBRT from 2011 to 2015 compared with those from 2007 to 2010. In the WBRT group, more patients with breast cancer received the anthracycline-based PST regimen, whereas fewer patients received adjuvant WBRT in academic hospitals compared with the non-BRT group (Table 1). More deaths, LRR, and DM were

observed in the non-BRT group than in the WBRT group.

According to the multivariate Cox regression analysis, adjuvant WBRT was a significant independent predictor of OS, LRR, and DM (Tables 2–4). Both univariate and multivariate Cox regression analyses indicated that non-BRT, cN3, and pathologic residual tumor (ypT2–4) or nodal (ypN2–3) stage were poor prognostic factors (Table 2), whereas ER/PR positivity was an independent better prognostic factor for OS. In addition, poor prognostic factors for LRR after multivariate analysis were non-BRT, residual pathologic tumor (ypT1–4), and HER2 positivity (Table 3). As presented in Table 4, non-BRT, poorly differentiated tumors, cN2–3, ypT1–4, ypN1–3, and HER2 positivity were poor prognostic factors for DM. Old age was an independent better prognostic factor for DM (Table 4). According to both univariate and multivariate Cox regression analyses, the adjusted hazard ratios (aHRs; 95% confidence intervals [CIs]) of WBRT to non-BRT were 0.39 (0.26–0.60), 0.39 (0.24–0.63), and 0.11 (0.08–0.15) for all-cause mortality, LRR, and DM, respectively (Tables 2–4).

Table 1
Characteristics of Patients With Breast Cancer Who Received Preoperative systemic therapy and Underwent Breast-Conserving Surgery With or Without Adjuvant Whole Breast Radiation therapy.

Variable		BCS		
		WBRT (n = 1436)	Non-BRT (n = 108)	*p* value
Age (y)	Mean (SD)	46.7 (10.2)	47.2 (9.1)	0.6025
	Median (Q1,Q3)	46 (39,54)	47 (41, 54)	
	20–49	875 (60.9%)	66 (61.1%)	0.9708
	50+	561 (39.1%)	42 (38.9%)	
Diagnosis year	2007–2010	271 (18.9%)	30 (27.8%)	0.0243
	2011–2015	1165 (81.1%)	78 (72.2%)	
CCI score	0	1229 (85.6%)	87 (80.6%)	0.3473
	1	152 (10.6%)	16 (14.8%)	
	2+	55 (3.8%)	5 (4.6%)	
Differentiation	Well	76 (5.3%)	8 (7.4%)	0.5092
	Moderate	608 (42.3%)	42 (38.9%)	
	Poor	452 (31.5%)	39 (36.1%)	
	Missing	300 (20.9%)	19 (17.6%)	
cT	cT0-1	78 (5.4%)	3 (2.8%)	0.4347
	cT2	1030 (71.7%)	76 (70.4%)	
	cT3	226 (15.7%)	18 (16.7%)	
	cT4	102 (7.1%)	11 (10.2%)	
cN	cN0	460 (32.0%)	31 (28.7%)	0.4828
	cN1	763 (53.1%)	57 (52.8%)	
	cN2	136 (9.5%)	15 (13.9%)	
	cN3	77 (5.4%)	5 (4.6%)	
ypT	ypT0	285 (19.8%)	18 (16.7%)	0.2654
	ypT1	705 (49.1%)	45 (41.7%)	
	ypT2	398 (27.7%)	40 (37.0%)	
	ypT3	29 (2.0%)	5 (4.7%)	
	ypT4	19 (1.3%)		
ypN	ypN0	889 (61.9%)	63 (58.3%)	0.6322
	ypN1	374 (26.0%)	28 (25.9%)	
	ypN2	132 (9.2%)	14 (13.0%)	
	ypN3	41 (2.9%)	3 (2.8%)	
Pathologic AJCC stages	pCR	260 (18.1%)	17 (15.7%)	0.5399
	IA	438 (30.5%)	30 (27.8%)	
	IB	29 (2.0%)	0	
	IIA	351 (24.4%)	25 (23.1%)	
	IIB	164 (11.4%)	17 (15.7%)	
	IIIA	134 (9.3%)	14 (13.0%)	
	IIIB	19 (1.3%)	5 (4.7%)	
	IIIC	41 (2.9%)		
PST regimen	Taxane based	563 (39.2%)	48 (44.4%)	0.0033
		496 (34.5%)	24 (22.2%)	
	Both	251 (17.5%)	17 (15.7%)	
	Neither	126 (8.8%)	19 (17.6%)	
Nodal surgery	ALND	1113 (77.5%)	78 (72.2%)	0.4379
	SLNB	275 (19.2%)	26 (24.1%)	
	None	48 (3.3%)	4 (3.7%)	
ER/PR	Negative	662 (46.1%)	54 (50.0%)	0.4332
	Positive	774 (53.9%)	54 (50.0%)	
HER2	Negative	1030 (71.7%)	73 (67.6%)	0.3590
	Positive	406 (28.3%)	35 (32.4%)	
Hospital level	Academic center	910 (63.4%)	79 (73.1%)	0.0411
	Others	526 (36.6%)	29 (26.9%)	
Mean follow-up time, months (SD)		56.7 (26.8)	54.1 (29.1)	
Death		144 (10.0%)	29 (26.9%)	<0.0001
local recurrence		124 (8.6%)	21 (19.4%)	0.0002
distant metastasis		215 (15.0%)	61 (56.5%)	<0.0001

WBRT, whole breast radiation therapy; BRT, breast radiation therapy; BCS, breast-conserving surgery; T, tumor; N, nodal; PST, preoperative systemic therapy; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; pCR, pathological complete response; ALND, axillary lymph node dissection; SNLB, sentinel lymph node biopsy; IQR, interquartile range; SD, standard deviation; CCI, Charlson comorbidity index.

Fig. 1A–C presents Kaplan–Meier survival curves of all-cause mortality and LRR-free and DM-free survival for patients with breast IDC who received PST and BCS with or without adjuvant WBRT. Compared with patients who did not receive WBRT, patients who received WBRT had superior OS and LRR-free and DM-free survival. The 5-year OS in patients who received WBRT and those who did not receive WBRT was 92.47% and 69.33%, respectively (Fig. 1A). The 5-year LRR-free survival of the WBRT and non-BRT groups was 94.01% and 76.41%, respectively (Fig. 1B), whereas the 5-year DM-free survival of the WBRT and non-BRT groups was 86.89% and 39.48%, respectively (Fig. 1C).

After stratification of patients according to different clinical T (cT0–4), clinical N (cN0–3), pathologic T (ypT0–4), and pathologic N (ypN0–3) stages, multivariate Cox regression analyses also revealed that adjuvant WBRT was a significant independent predictor of better OS in patients with breast cancer who received PST and BCS, irrespective of their clinical T or N stage or pathologic T or N stage, even in patients who achieved pCR (Fig. 2). The aHRs (95% CIs) of the WBRT group to non-BRT group for all-cause mortality were 0.14 (0.03–0.81), 0.32 (0.16–0.64), 0.43 (0.23–0.79), 0.23 (0.13–0.42), 0.52 (0.20–1.33), and 0.34 (0.13–0.87) in the ypT0, ypT1, ypT2–4, ypN0, ypN1, and ypN2–3 stages, respectively (Fig. 2). The aHRs (95% CIs) of the WBRT group to the non-BRT group for all-cause mortality were 0.09 (0.00–4.07), 0.46 (0.26–0.83), 0.18 (0.06–0.51), 0.28 (0.06–1.34), 0.25 (0.10–0.63), 0.47 (0.23–0.88), and 0.32 in the cT0–1, cT2, cT3, cT4, cN0, cN1, and cN2–3 stages, respectively (Fig. 2). In addition, compared with the non-PMRT group, the WBRT group showed significant locoregional control and DM-free survival, regardless of the TN stage or pathologic response (even ypT0, ypN0, or pCR; Supplemental Figs 1 and 2). The aHRs (95% CIs) of the WBRT group to the non-BRT group for LRR-free survival were 1.26 (0.21–7.73), 0.42 (0.19–0.93), 0.33 (0.16–0.66), 0.34 (0.18–0.63), 0.31 (0.12–0.77), 0.68 (0.07–6.28), 0.26 (0.01–4.96), 0.41 (0.23–0.73), 0.30 (0.09–1.02), 0.31 (0.12–0.85), 0.29 (0.16–0.55), and 0.98 (0.24–3.96) in the ypT0, ypT1, ypT2–4, ypN0, ypN1, ypN2–3, cT0–1, cT2, cT3, cN0, cN1, and cN2–3 stages, respectively (Supplemental Fig 1). The aHRs (95% CIs) of the WBRT group to the non-BRT group for DM-free survival were 0.07 (0.02–0.24), 0.09 (0.06–0.15), 0.09 (0.06–0.15), 0.08 (0.06–0.13), 0.11 (0.06–0.21), and 0.13 (0.05–0.31) in the ypT0,

Table 2
Multivariate Analysis of All-Cause Mortality in Patients Who Received Preoperative systemic therapy and Underwent Breast-Conserving Surgery.

		All-cause mortality		
		HR	(95%CI)	*p* value
Adjuvant WBRT	No	Ref		<0.0001
	Yes	0.39	(0.26–0.60)	
Age (y)	20–49	Ref		0.32
	50+	0.84	(0.60–1.18)	
Diagnosis year	2007–2010	Ref		0.13
	2011–2015	0.75	(0.52–1.08)	
CCI score	0	Ref		0.28
	1	1.09	(0.96–1.93)	
	2+	1.14	(0.42–1.99)	
Differentiation	Poor	Ref		0.30
	Moderate	0.90	(0.62–1.31)	
	Well	0.47	(0.20–1.13)	
cT	cT0–1	Ref		0.07
	cT2	0.60	(0.30–1.19)	
	cT3	0.89	(0.42–1.89)	
	cT4	1.03	(0.46–2.34)	
cN	cN0	Ref		0.09
	cN1	1.03	(0.68–1.55)	
	cN2	1.48	(0.86–2.55)	
	cN3	1.91	(1.01–3.63)	
ypT	ypT0	Ref		0.0012
	ypT1	1.61	(0.91–2.86)	
	ypT2	1.51	(1.36–2.63)	
	ypT3–4	1.75	(1.37–3.41)	
ypN	ypN0	Ref		<0.0001
	ypN1	1.47	(0.99–2.19)	
	ypN2–3	3.06	(1.93–4.83)	
PST regimen	Anthracycline	Ref		0.40
	Taxanes	0.73	(0.50–1.08)	
	Both	0.77	(0.49–1.19)	
	Neither	1.07	(0.44–1.35)	
Nodal surgery	SLNB	Ref		0.99
	ALND	0.99	(0.59–1.63)	
	None	1.05	(0.41–2.70)	
ER/PR positive		0.47	(0.34–0.66)	<0.0001
HER2 positive		0.83	(0.58–1.21)	0.34
Hospital level	Academic center	Ref		0.93
	Others	0.98	(0.70–1.38)	

WBRT, whole breast radiation therapy; BCS, breast-conserving surgery; T, tumor; N, nodal; HRs, hazard ratios; CI, confidence interval; PST, preoperative systemic therapy; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; pCR, pathological complete response; ALND, axillary lymph node dissection; SNLD, sentinel lymph node dissection; OS, overall survival; LRR, locoregional recurrence; DM, distant metastasis; CCI, Charlson comorbidity index.

Table 3
Multivariate Analysis of Locoregional Recurrence in Patients Who Received Preoperative systemic therapy and Underwent Breast-Conserving Surgery.

		Locoregional recurrence		
		HR	(95%CI)	*p* value
Adjuvant WBRT	No	ref		0.0001
	Yes	0.39	(0.24–0.63)	
Age (y)	20–49	ref		0.99
	50+	1.00	(0.69–1.44)	
diagnosis year	2007–2010	ref		0.88
	2011–2015	0.97	(0.63–1.49)	
CCI score	0	ref		0.50
	1	0.99	(0.59–1.68)	
	2+	1.56	(0.74–3.30)	
Differentiation	Poor	ref		0.25
	Moderate	1.03	(0.70–1.52)	
	Well	0.24	(0.06–1.01)	
cT	cT0–1	ref		0.25
	cT2	0.68	(0.33–1.39)	
	cT3	0.70	(0.32–1.57)	
	cT4	0.32	(0.10–0.98)	
cN	cN0	ref		0.42
	cN1	1.08	(0.71–1.65)	
	cN2	1.06	(0.55–2.03)	
	cN3	1.81	(0.88–3.72)	
ypT	ypT0	ref		0.0019
	ypT1	1.79	(1.02–3.12)	
	ypT2	1.97	(1.62–3.45)	
	ypT3–4	2.13	(1.25–4.22)	
ypN	ypN0	ref		0.54
	ypN1	1.01	(0.63–1.42)	
	ypN2–3	1.02	(0.41–1.28)	
PST regimen	Anthracycline	ref		0.91
	Taxanes	0.89	(0.59–1.33)	
	Both	0.92	(0.56–1.51)	
	Neither	0.93	(0.44–1.55)	
Nodal surgery	SLNB	Ref		0.54
	ALND	1.10	(0.68–1.78)	
	None	1.68	(0.67–4.23)	
ER/PR positive		0.72	(0.51–1.04)	0.08
HER2 positive		1.95	(1.35–2.80)	0.0003
Hospital level	Academic center	ref		0.71
	Others	0.93	(0.65–1.34)	

WBRT, whole breast radiation therapy; BCS, breast-conserving surgery; T, tumor; N, nodal; HRs, hazard ratios; CI, confidence interval; PST, preoperative systemic therapy; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; pCR, pathological complete response; ALND, axillary lymph node dissection; SNLD, sentinel lymph node dissection; OS, overall survival; LRR, locoregional recurrence; DM, distant metastasis; CCI, Charlson comorbidity index.

Table 4
Multivariate Analysis of Distant Metastasis in Patients Who Received Preoperative systemic therapy and Underwent Breast-Conserving Surgery.

		Distant metastasis		
		HR	(95%CI)	*p* value
Adjuvant WBRT	No	ref		<0.0001
	Yes	0.11	(0.08–0.15)	
Age	20–49	ref		0.0276
	50+	0.73	(0.56–0.97)	
Diagnosis year	2007–2010	ref		0.22
	2011–2015	0.83	(0.62–1.12)	
CCI Scores	0	ref		0.18
	1	1.37	(0.96–1.97)	
	2+	1.31	(0.71–2.40)	
Differentiation	Poor	ref		0.0050
	Moderate	0.78	(0.58–1.04)	
	Well	0.28	(0.13–0.59)	
cT	cT0–1	ref		0.93
	cT2	0.85	(0.47–1.52)	
	cT3	0.85	(0.44–1.64)	
	cT4	0.93	(0.46–1.88)	
cN	cN0	ref		0.0020
	cN1	1.00	(0.73–1.36)	
	cN2	1.88	(1.21–2.90)	
	cN3	1.98	(1.02–3.11)	
ypT	ypT0	ref		<0.0001
	ypT1	2.89	(1.75–4.79)	
	ypT2	4.40	(2.59–7.50)	
	ypT3–4	5.70	(2.75–11.82)	
ypN	ypN0	ref		0.0221
	ypN1	1.33	(1.08–1.80)	
	ypN2–3	1.66	(1.15–2.41)	
PST regimen	Anthracycline	ref		0.88
	Taxanes	0.79	(0.52–1.23)	
	Both	0.86	(0.38–1.38)	
	Neither	1.12	(0.84–1.72)	
Nodal surgery	SLNB	ref		0.98
	ALND	1.04	(0.72–1.50)	
	None	1.04	(0.51–2.11)	
ER/PR positive		0.80	(0.61–1.04)	0.10
HER2 positive		1.84	(1.41–2.40)	<0.0001
Hospital level	Academic center	ref		0.99
	Others	1.00	(0.77–1.30)	

WBRT, whole breast radiation therapy; BCS, breast-conserving surgery; T, tumor; N, nodal; HRs, hazard ratios; CI, confidence interval; PST, preoperative systemic therapy; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; pCR, pathological complete response; ALND, axillary lymph node dissection; SNLD, sentinel lymph node dissection; OS, overall survival; LRR, locoregional recurrence; DM, distant metastasis; CCI, Charlson comorbidity index.

ypT1, ypT2–4, ypN0, ypN1, and ypN2–3 stages, respectively (Supplemental Fig 2), and they were 0.07 (0.00–1.99), 0.09 (0.06–0.13), 0.03 (0.01–0.09), 0.15 (0.04–0.56), 0.09 (0.05–0.17), 0.12 (0.08–0.19), and 0.04 (0.02–0.09) in the cT0–1, cT2, cT3, cT4, cN0, cN1, and cN2–3 stages, respectively (Supplemental Fig 2).

4. Discussion

No study thus far has reported the necessity and benefits of adjuvant WBRT for patients with breast cancer receiving PST and BCS. All evidence of adjuvant WBRT is dependent on the findings of earlier studies enrolling patients who did not receive PST [1–3,15–18]. To the best of our knowledge, this study is the first to show the effects of adjuvant WBRT in these patients. The current study provided a therapeutic reference for further adjuvant WBRT in patients receiving PST and BCS. Moreover, physicians and patients with breast cancer receiving BCS with or without PST should understand the importance of adjuvant WBRT (Fig. 2, Supplemental Figs 1 and 2).

As shown in Table 1, compared with those in the non-BRT group, more patients were receiving the anthracycline-based PST regimen, were in nonacademic hospitals, and were diagnosed in 2011–2015 in the WBRT group. This could be attributed to more experiences with PST and increased observations regarding the safety and benefits of WBRT in recent years. In addition, the anthracycline-based PST regimen is the standard regimen [33,34], and the use of standard PST regimens might be proportional to the use of adjuvant WBRT. In academic hospitals, fewer patients with breast cancer received PST and BCS in the WBRT group than those in the non-BRT group, which may explain the insufficient evidence for these patients. Thus, physicians had no consensus on further decisions regarding adjuvant WBRT for these patients in academic hospitals. Our study findings resolved the problem of insufficient evidence regarding WBRT in patients with breast cancer receiving PST and BCS (Fig. 2, Supplemental Figs 1 and 2). Physicians in nonacademic hospitals always followed therapeutic guidelines reported in earlier studies [1–3,15–18]; however, the patients without PST included in those studies were different from our population of patients who were receiving PST and BCS. However, no significant differences were observed in PST regimens, academic hospitals, or years since diagnosis in OS, LRR, and DM (Tables 2–4). These factors are not confounding factors for our outcomes and do not bias the conclusions of the study.

Adjuvant WBRT is highly effective for reducing all-cause mortality in patients with breast cancer status after PST and BCS, regardless of their clinical stage or pathologic response after PST (Figs. 1A and 2). In our study, other predictors were significantly poor prognostic factors for OS (Table 2) such as non-BRT, cN3, ypT2–4, ypN2–3, and ER/PR negativity. A systemic review of literature revealed that no study has demonstrated cN3, ypT2–4, ypN2–3, and ER/PR negativity as poor prognostic factors for OS in patients with breast cancer receiving PST and BCS. Our results demonstrated that cN3, residual tumor stages (ypT2–4), and residual nodal stages (ypN2–3) were poor predictors of OS in patients with breast cancer receiving PST and BCS. These findings might reflect that clinical advanced nodal stages (cN3) were a more significant valuable predictor than clinical tumor stages (cT1–4) in these patients. The ypN stage was a superior predictor than ypT stage, corroborating the previous results [35,36]. A poor pathologic response (ypT2–4 and ypN2–3) also reflected the poor survival of patients receiving PST and BCS, and these outcomes are compatible with those of earlier studies, in which most of the patients with breast cancer received PST and TM, and the patient populations in these studies differed from those in the current study [37,38]. The present study demonstrated that a poor pathologic response was associated with poor OS in patients with breast cancer receiving PST and BCS (Table 2, Figs. 1 and 2). In Table 2, ER/PR positivity was a better predictor of OS, consistent with the findings of an earlier study [39], which demonstrated that ER/PR positivity results in better OS in patients who did not receive PST. Taken together, we strongly recommend adjuvant WBRT for patients with breast cancer receiving PST and BCS because it would reduce all-cause mortality, irrespective of the clinical or pathologic stage.

Adjuvant WBRT also reduced LRR risk in multivariate analysis (Table 3). The LRR-free survival curve showed significant differences between WBRT and non-BRT (Fig. 1B). In the multivariable Cox regression analysis, adjuvant WBRT reduced LRR risk (Supplemental Fig 1). Compared with the non-BRT group, the WBRT group did not reach statistical significance at stages ypN1, cT0–1, and cT4 owing to the small sample size in the subgroups of the non-BRT group (Table 1 and Supplemental Fig 1). The ypT1–4 stage and HER2 positivity were also poor prognostic factors of LRR (Table 3). Notably, rather than the ypN stages, the ypT1–4 stages were proportional to LRR risk. Our findings indicated that the ypT stages, but not the ypN stages, were important predictors of LRR;

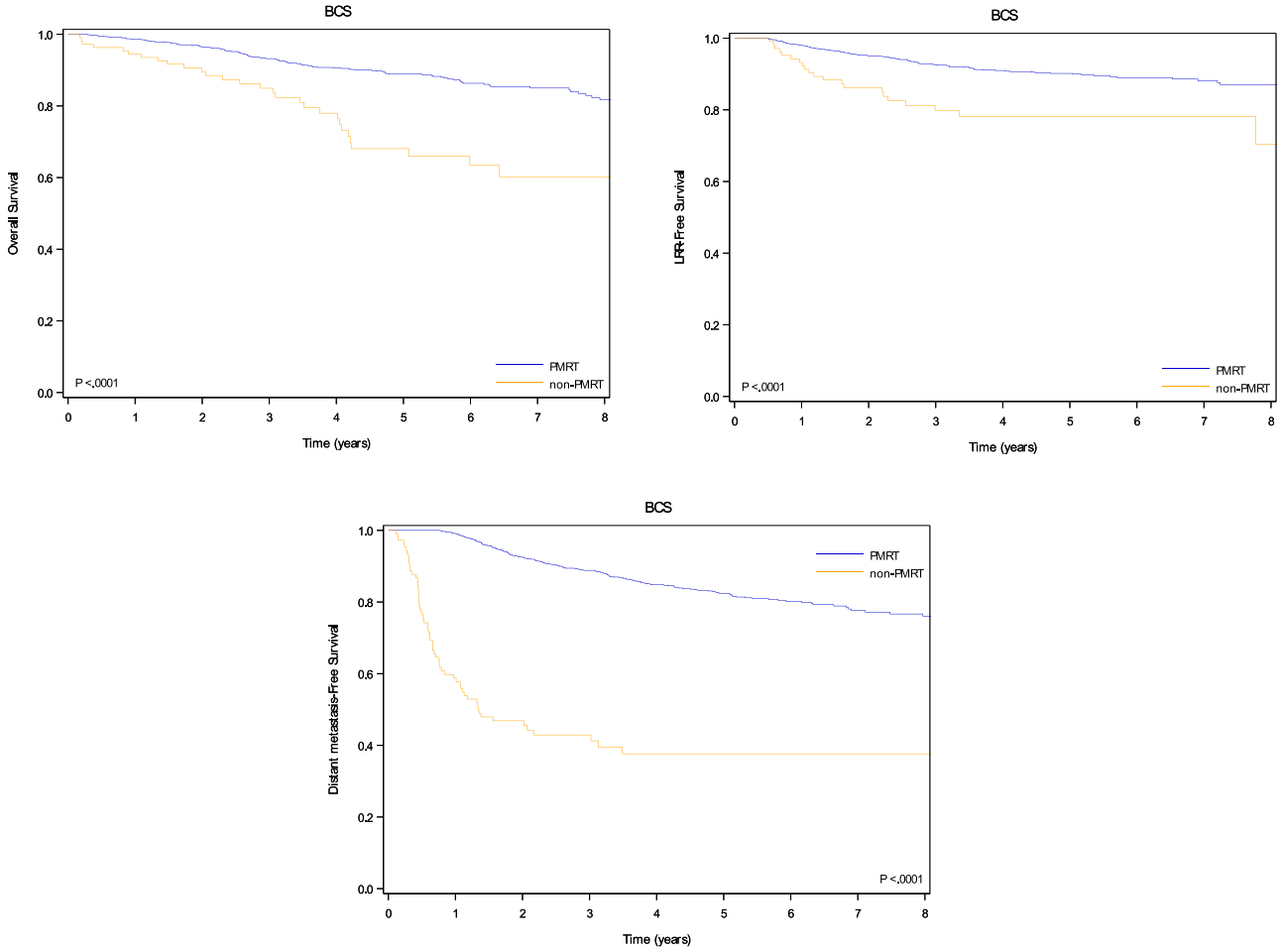

Fig. 1. Kaplan–Meier survival curves of patients who underwent breast-conserving surgery.

these findings can provide physicians with references that can be used to closely monitor local recurrence in patients with residual pathologic tumor stages (ypT1–4) in the future. HER2 positivity was a predictor of LRR, and it might be associated with high LRR risk, as observed previously [40]. This is the first study to demonstrate that HER2 positivity is a risk factor for LRR in patients with breast cancer receiving PST and BCS.

Few studies have shown that adjuvant RT might be associated with the reduction of DM in breast cancer [41–43]. The advantage in OS appeared to be a consequence of the decreased DM rate, rather than the decreased LRR rate, as indicated by the almost identical effects of WBRT on LRR-free and DM-free survival in our study (Supplemental Figs 1 and 2). A meta-analysis demonstrated that RT reduced the LRR and DM rates at 5 years by 2.3% and 5.4%, respectively [43]. Whether this effect is real or an artifact remains unclear. The meta-analysis proposed two hypotheses to explain this finding. The first one indicated the possibility of considerable underestimation of the recurrence rate in the internal mammary lymph nodes. The other hypothesis is that micrometastasis in the internal mammary lymph nodes and medial supraclavicular lymph nodes represented a source for metastatic spread without growing to a clinically detectable size before DM diagnosis [43]. Recurrences in these nodal regions are not detected by routine follow-up programs [43]. The clinical appearance of DM using positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography demonstrated high rates of unsuspected mediastinal lymph node involvement [44], which may have originated in the internal mammary lymph nodes as a source of further dissemination. Another possibility is the so-called abscopal effect of WBRT, which is due to an immune reaction against the tumor induced by tumor cell necrosis or necroptosis after exposure to ionizing irradiation [45,46] (Supplemental Figs 1 and 2). This would, however, implicate that relatively few tumor cells in clinically negative lymph nodes can initiate a substantial immune response, which appears to be unlikely considering the lack of clinical evidence for such a reaction after RT for macroscopic disease in breast cancer. Determining the accurate hypothesis or understanding whether the combined effects of all these hypotheses exist or a completely different mechanism prevails will be the subject of further research. Our study demonstrated significant reduction of DM in patients with breast cancer receiving PST and BCS followed by WBRT in the multivariate analysis (Table 4) and in the analysis stratified according to clinical or pathological tumor and nodal stages (Supplemental Fig 2). Other studies have also demonstrated that local RT could reduce DM risk in patients with breast cancer [41–43]. Adjuvant WBRT could be recommended for reduction in LRR and DM risk (Tables 3 and 4). Young age, poor tumor differentiation, clinically advanced nodal stage (cN2–3), poor pathologic response of the tumor (ypT1–4) and nodal (ypN1–3) stages, and HER2 positivity were poor prognostic factors for DM (Table 4). Adjuvant WBRT could be recommended for improving DM-free survival (Fig. 1C). The fact that old age is a better prognostic factor for DM might be associated with the competing risk of death in older patients [47]. Moreover, breast cancer biology

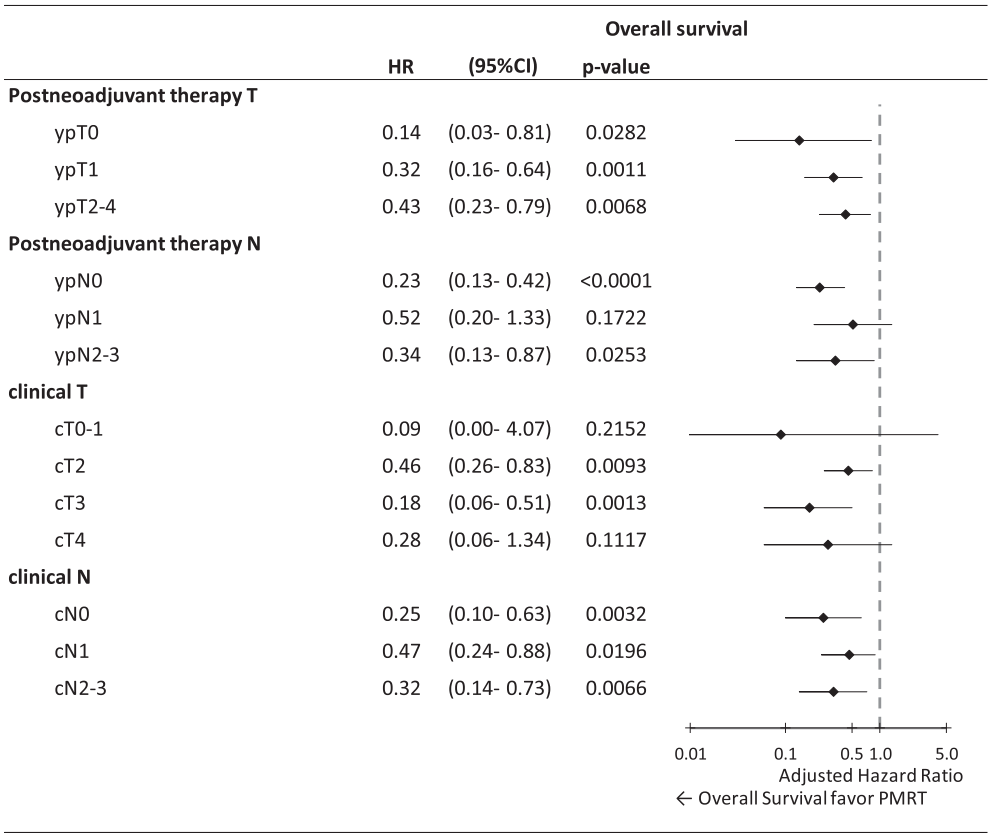

Fig. 2. Impact of adjuvant whole breast radiation therapy on overall survival of patients who underwent breast-conserving surgery with or without adjuvant whole breast radiation therapy, in multivariable Cox regression analysis.Adjusted hazard ratio: All variables presented in Table 2 were used in the multivariate analysis.
HRs, hazard ratios; CI, confidence interval; WBRT, whole breast radiation therapy; BCS, breast-conserving surgery; T, tumor; N, nodal; OS, overall survival; LRR, locoregional recurrence; DM, distant metastasis.

might be different, with less aggressive behavior, in older patients [48]. Notably, clinical tumor stages (cT0–4) were not associated with DM risk, whereas clinical nodal stages (cN2–3) were associated with DM risk; these outcomes might echo earlier theories stating that lymph node status is a more important predictor of DM than tumor stage [36]. However, the pathologic response of tumor (ypT1–4) as well as nodal (ypN1–3) stage was DM risk predictor (Table 4). To the best of our knowledge, this study was the first to demonstrate that cN2–3, ypT1–4, and ypN1–3 stages and HER2 positivity were poor prognostic factors for DM. Patients with HER2 positivity also showed high DM risk in an earlier study [49].

This study has some limitations. First, because all patients with breast IDC were enrolled from an Asian population, the corresponding ethnic susceptibility compared with a non-Asian population remains unclear; hence, our results should be cautiously extrapolated to non-Asian populations. However, no evidence exists to demonstrate the differences in outcomes of WBRT between Asian and non-Asian patients with breast cancer receiving PST and BCS. 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 be heavily penalized if malpractices or discrepancies are identified. Third, to prevent the creation of several subgroups, various neoadjuvant treatments were not categorized separately during the analyses. Some patients with breast IDC were receiving cisplatin-based regimens or endocrine therapy, such as hormone therapy, as PST regimens instead of anthracycline- or taxane-based regimens because of underlying heart disease or other comorbidities in our study. Thus, the effects of different neoadjuvant treatments remain unclear. However, CCI scores, including underlying heart disease, were adjusted in our study. Fourth, our study enrolled patients receiving breast IDC treatments in academic hospitals (63.4% in WBRT group and 73.1% in non-BRT group); therefore, their corresponding susceptibility compared with a population in nonacademic hospitals remains unclear; hence, our results should be cautiously extrapolated to patients in nonacademic hospitals. Nevertheless, more patients were receiving non-BRT in academic hospitals; therefore, the risks of all-cause mortality, LRR, and DM might be high in nonacademic hospitals [50,51]. Moreover, cancer care might be better in academic hospitals [50,51]; this analysis is likely to underestimate the beneficial effects of WBRT on survival because more patients in the non-BRT group received treatments in academic hospitals. Hence, our conclusions cannot be overturned. In addition, hospital levels were adjusted in the multivariate analysis for all-cause mortality, LRR, and DM. No statistical significance was observed in the multivariate analysis. Fifth, some patients in Taiwan refused further adjuvant RT after PST because of excellent pathologic response after PST; severe side effects from previous treatments, such as chemotherapy and surgery; or fear of further adjuvant RT because of poor health education. Thus, such patients might not receive adjuvant RT. Patients receiving non-BRT may have had a bias against completion of all treatment protocols because of poor self-confidence, unknown physical susceptibility to PST or BCS, or poor health education and thus believed that if PST and BCS demonstrate excellent response, then adjuvant breast RT is not necessary. This bias might be associated with patient education,

personal mental health, or family support. However, our analysis is identical to an intention-to-treat (ITT) analysis. In an ITT analysis, data from all participants initially enrolled in a clinical trial are used for analyzing efficacy and safety. Therefore, with the bias in the non-BRT group not measured as is observed in the real world, we estimated the true treatment effectiveness of adjuvant WBRT in the current study for patients with breast IDC receiving PST and BCS. Moreover, no evidence indicates the association of poor health education or poor mental support with survival outcomes in patients with breast cancer receiving PST followed by BCS. All potential confounding factors for survival outcomes in patients with breast cancer receiving PST were adjusted for in the multivariate analysis. Accordingly, to obtain crucial information on population specificity and disease occurrence, a large-scale randomized trial comparing carefully selected patients undergoing suitable treatments is required. Finally, the TCRD does not contain information on dietary habits, socioeconomic status, or body mass index of patients, 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

The effects of WBRT might be associated with superior OS and LRR-free and DM-free survival compared with the non-BRT group, regardless of the initial clinical TN stage or pathologic response, even in patients who achieved pCR of tumor or nodal stages.

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.

For Software

Project name: Not applicable.
Project homepage: Not applicable.
Archived version: Not applicable.
Operating system(s): Not applicable.
Programming language: Not applicable.
Other requirements: Not applicable.
License: Not applicable.
Any restrictions to use by nonacademicians: Not applicable.

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Condensed abstract

We investigated the detailed outcome patterns of adjuvant whole breast radiation therapy (WBRT) for patients with breast cancer receiving preoperative systemic therapy (PST) and breast-conserving surgery (BCS), as well as their prognostic factors, stratified by clinical tumor (T), nodal (N), and pathological response of ypT or ypN staging. The endpoints were overall survival (OS), locoregional recurrence (LRR), distant metastasis (DM), and disease-free survival. Non-breast radiation therapy (BRT), cN3, pathologic residual tumor (ypT2–4), or nodal (ypN2–3) stages are poor prognostic factors for OS. The beneficial effects of WBRT are superior OS and LRR-free and DM-free survival compared with the non-BRT group, regardless of the initial clinical T or N stage or pathologic response.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2020.09.010.

References

[1] 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.
[2] Early Breast Cancer Trialists' Collaborative G. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. N Engl J Med 1995;333:1444–55.
[3] Morris AD, Morris RD, Wilson JF, White J, Steinberg S, Okunieff P, et al. Breast-conserving therapy vs mastectomy in early-stage breast cancer: a meta-analysis of 10-year survival. Canc J Sci Am 1997;3:6–12.
[4] Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol : Off J Am Soc Clin Oncol 2014;32:1507–15.
[5] Waljee JF, Rogers MA, Alderman AK. Decision aids and breast cancer: do they influence choice for surgery and knowledge of treatment options? J Clin Oncol : Off J Am Soc Clin Oncol 2007;25:1067–73.
[6] Morrow M, Strom EA, Bassett LW, Dershaw DD, Fowble B, Giuliano A, et al. Standard for breast conservation therapy in the management of invasive breast carcinoma. Ca - Cancer J Clin 2002;52:277–300.
[7] McLaughlin SA. Surgical management of the breast: breast conservation therapy and mastectomy. Surg Clin 2013;93:411–28.
[8] Fitzal F, Mittlboeck M, Trischler H, Krois W, Nehrer G, Deutinger M, et al. Breast-conserving therapy for centrally located breast cancer. Ann Surg 2008;247:470–6.
[9] Newman LA. Decision making in the surgical management of invasive breast cancer-Part 2: expanded applications for breast-conserving surgery. Oncology (Williston Park) 2017;31:415–20.
[10] Aebi S, Davidson T, Gruber G, Cardoso F, Group EGW. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2011;22(Suppl 6):12–24.
[11] 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.
[12] Thompson AM, Moulder-Thompson SL. Neoadjuvant treatment of breast cancer. Ann Oncol 2012;23(Suppl 10):x231–6.
[13] 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.
[14] 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.
[15] Agarwal S, Pappas L, Neumayer L, Kokeny K, Agarwal J. Effect of breast conservation therapy vs mastectomy on disease-specific survival for early-stage breast cancer. JAMA Surg 2014;149:267–74.
[16] Hartmann-Johnsen OJ, Karesen R, Schlichting E, Nygard JF. Better survival after breast-conserving therapy compared to mastectomy when axillary node status is positive in early-stage breast cancer: a registry-based follow-up study of 6387 Norwegian women participating in screening, primarily operated between 1998 and 2009. World J Surg Oncol 2017;15:118.
[17] Vila J, Gandini S, Gentilini O. Overall survival according to type of surgery in young (</=40 years) early breast cancer patients: a systematic meta-analysis comparing breast-conserving surgery versus mastectomy. Breast 2015;24:175–81.
[18] Hofvind S, Holen A, Aas T, Roman M, Sebuodegard S, Akslen LA. Women treated with breast conserving surgery do better than those with mastectomy independent of detection mode, prognostic and predictive tumor characteristics. Eur J Surg Oncol 2015;41:1417–22.
[19] 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.
[20] 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.
[21] 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.
[22] 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.
[23] 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.
[24] 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.
[25] 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.
[26] 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.
[27] 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.
[28] 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.
[29] 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.
[30] 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.
[31] Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47:1245–51.
[32] 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.
[33] Untch M, Loibl S, Bischoff J, Eidtmann H, Kaufmann M, Ju Blohmer, et al. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): a randomised phase 3 trial. Lancet Oncol 2012;13:135–44.
[34] Romond EH, Perez EA, Bryant J, Suman VJ, Geyer Jr CE, Davidson NE, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673–84.
[35] Ellis MJ, Tao Y, Luo J, A'Hern R, Evans DB, Bhatnagar AS, et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. J Natl Cancer Inst 2008;100:1380–8.
[36] 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.
[37] Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384:164–72.
[38] Cortazar P, Geyer Jr CE. Pathological complete response in neoadjuvant treatment of breast cancer. Ann Surg Oncol 2015;22:1441–6.
[39] 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.
[40] 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.
[41] Cao L, Ou D, Shen KW, Cai G, Cai R, Xu F, et al. Outcome of postmastectomy radiotherapy after primary systemic treatment in patients with clinical T1-2N1 breast cancer. Canc Radiother 2018;22:38–44.
[42] 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.
[43] Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials. Radiat Oncol 2013;8:267.
[44] Eubank WB, Mankoff DA, Takasugi J, Vesselle H, Eary JF, Shanley TJ, et al. 18fluorodeoxyglucose positron emission tomography to detect mediastinal or internal mammary metastases in breast cancer. J Clin Oncol : Off J Am Soc Clin Oncol 2001;19:3516–23.
[45] Lauber K, Ernst A, Orth M, Herrmann M, Belka C. Dying cell clearance and its impact on the outcome of tumor radiotherapy. Front Oncol 2012;2:116.
[46] Frey B, Rubner Y, Kulzer L, Werthmoller N, Weiss EM, Fietkau R, et al. Antitumor immune responses induced by ionizing irradiation and further immune stimulation. Cancer Immunol Immunother 2014;63:29–36.
[47] Hoag JR, Hegde U, Zweifler R, Berwick M, Swede H. Competing risks survival of older patients with metastatic cutaneous melanoma: a SEER population-based study. Melanoma Res 2016;26:505–12.
[48] Azim Jr HA, Partridge AH. Biology of breast cancer in young women. Breast Cancer Res 2014;16:427.
[49] 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.
[50] van der Linden N, Bongers ML, Coupe VMH, Smit EF, Groen HJM, Welling A, et al. Treatment patterns and differences in survival of non-small cell lung cancer patients between academic and non-academic hospitals in The Netherlands. Clin Lung Canc 2017;18:e341–7.
[51] Chaudhry R, Goel V, Sawka C. Breast cancer survival by teaching status of the initial treating hospital. CMAJ (Can Med Assoc J) 2001;164:183–8.