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Scientific Article

Clinical outcomes and prognostic factors in patients with stage II-III breast cancer treated with neoadjuvant chemotherapy followed by surgery and postmastectomy radiation therapy in the modern treatment era

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Abstract

Purpose: There are no randomized studies on the indication for postmastectomy radiation therapy (PMRT) in patients who receive neoadjuvant chemotherapy (NAC) followed by a mastectomy. The aim of this study was to determine clinical outcomes and identify reliable prognostic factors in patients with locally advanced breast cancer treated with NAC followed by a mastectomy and PMRT.

Methods and materials: We retrospectively evaluated the relationship between clinicopathological factors and outcomes in 351 patients with stage II or III breast cancer who underwent NAC followed by radical mastectomy and PMRT between March 2005 and December 2013.

Results: The median follow-up duration was 81 months (Range, 12-156 months). For all patients, the 5-year locoregional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and overall survival (OS) rates were 91.3 %, 69.8 %, and 83.4 %, respectively. On multivariate analysis, estrogen-receptor positivity, and complete response of cancer in axillary nodes (ypN0) were significant prognostic factors for better LRFS, while lympho-vascular invasion and clinical stage IIIC were independent prognostic factors for worse LRFS. The number of axillary node

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metastasesafter surgery was an independent prognostic factor of DMFS and OS. Patients with hormone receptor- and human epidermal growth factor receptor 2 positivity had significantly better 5-year LRFS rates.

Conclusions: We identified several prognostic factors in our study. In particular, the number of axillary node metastases is significantly related to OS.

Introduction

Neoadjuvant chemotherapy (NAC) is widely used for patients with locally advanced, operable breast cancer to eradicate micrometastases before surgery. NAC also has the advantage of increasing breast conservation rates with acceptable local control and allows oncologists to evaluate tumor response to chemotherapy.[1-5] Several randomized trials have demonstrated that postmastectomy radiation therapy (PMRT) significantly reduces both recurrence and mortality in patients with positive lymph nodes even when systemic therapy was administered.[6-10]

There are no published randomized trials to guide the indication of PMRT in the NAC setting. The National Comprehensive Cancer Network indications for radiation therapy and fields of treatment are based on the worst stage pre- or posttreatment tumor characteristics in patients with NAC and the Japanese Breast Cancer Society Clinical Practice Guideline recommends PMRT for patients who show a response after NAC on the basis of the pretreatment stage. Despite the lack of reliable evidence, PMRT is recommended on the basis of pretreatment tumor characteristics for patients with advanced breast cancer even if a favorable response is achieved with chemotherapy.[11]

Although a few retrospective studies have suggested that an initial clinical stage or treatment response (ie, pathological complete response [pCR] of the primary tumor and lymph node metastasis or no evidence of residual pathologic nodal disease [ypN0])) is associated with good locoregional control, whether patients could omit PMRT remains controversial.[12-16] Many studies were conducted on patients before the standard use of aromatase inhibitors, trastuzumab, and anthracycline/taxane-based chemotherapy, which have improved clinical outcomes in adjuvant settings.[17-20]

The impact of PMRT on patients treated with modern NAC and systemic therapy is not known. Therefore, we investigated clinical outcomes and prognostic predictors that would help identify higher- or lower-risk subpopulations among patients with breast cancer who were treated with NAC followed by mastectomy and PMRT.

Methods and materials

We retrospectively analyzed 351 consecutive patients with clinical stage II-III breast cancer treated with NAC followed by mastectomy and PMRT between March 2005 and December 2013 at our institution. Eleven patients with bilateral invasive ductal breast cancer and 4 patients with another malignancy were excluded. Twenty-two patients with >365 days between NAC initiation and PMRT were also excluded. The American Joint Commission of Cancer 7th Edition staging system was used to classify patients into each breast cancer stage.

All patients received a radical modified mastectomy. Patients were typically treated with anthracycline and taxane-based chemotherapy (cyclophosphamide 500 mg/m^2, epirubicin 100 mg/m^2, and fluorouracil 500 mg/m^2 [4 courses] followed by weekly paclitaxel 80 mg/m^2 [12 courses] or cyclophosphamide 500 mg/m^2, epirubicin 100 mg/m^2, and fluorouracil 500 mg/m^2 [4 courses] followed by 3 weeks of docetaxel 75 mg/m^2 [4 courses]) before surgery. The indications for PMRT were a diagnosis of ≥4 positive axillary (Ax) lymph nodes by clinical evaluation including ultrasonography before treatment, diagnosis of a positive ipsilateral supraclavicular (SC) lymph node, or internal mammary region (IMN) and a T4 or positive surgical margin of the chest wall (CW).

All radiation planning was performed with 3-dimensional conformal radiation therapy techniques. PMRT was performed with up to 50 Gy with photon beams using the partially wide tangential technique to the CW and anterior supraclavicular region. If the surgical margin was positive, an electron boost of 10 Gy to16 Gy was added for the involved area of the CW. Between 2005 and 2007, the IMN (intercostal space 1-3) was prophylactically irradiated if a patient had ≥10 positive lymph nodes or if ≥4 positive lymph nodes and the tumor were located on the inner part of the breast. Between 2007 and 2013, we included the IMNs in the clinical target volumes for all patients.

Our institutional review board approved this study and waived the requirement for informed consent on the basis of the study's retrospective design.

Pathological assessment

Pathological assessment after NAC was performed by 2 expert breast cancer pathologists. At our hospital, lymphovascular invasion (LVI) is diagnosed initially by an expert pathologist and subsequently reviewed by 2 pathologists. In the present study, LVI status was classified as LVI-0 (ie, no LVI) where no evidence of LVI was found on any slides,

LVI-1 (ie, low LVI) where 1 to 9 LVI areas were detected, and LVI-2 (ie, high LVI) where ≥10 areas were detected.[21] Estrogen receptor (ER) and progesterone receptor (PgR) were assessed by immunohistochemistry and reported as positive or negative (cutoff: 10%). Human epidermal growth factor receptor 2 (HER2) positivity was defined as an immunohistochemical score of 3 + or 2 + with positive results on fluorescence in situ hybridization. Triple negative (TN) status was defined as negative for ER, PgR, and HER2 overexpression. pCR was defined as no evidence of residual invasive cancer in the primary tumor or axillary nodes with or without residual ductal carcinoma in situ.

Statistical analysis

We evaluated the relationship between the clinicopathological factors and clinical outcomes. Locoregional recurrence-free survival (LRFS) includes ipsilateral invasive or noninvasive chest wall tumor recurrence (ie, breast cancer that involves the same parenchyma as the original primary) and regional breast cancer recurrence (ie, invasive or noninvasive breast cancer in regional lymph nodes including the ipsilateral axilla, supra- or infra-clavicular, or internal mammary lymph nodes). Distant metastasis-free survival (DMFS) includes the events of metastatic disease-breast cancer that has either been biopsy-confirmed or clinically diagnosed as recurrent breast cancer. Overall survival (OS) includes death that is attributable to any cause including breast cancer, nonbreast cancer, or unknown cause. LRFS and DMFS were calculated from the date of chemotherapy initiation to the date of the documented initial recurrence. Observations were censored on the date that the patient was last known to be alive and LRFS, DMFS, and OS were estimated with the Kaplan-Meier method. Differences were compared using the log-rank test. Univariate and multivariate Cox regression analyses were used to determine the prognostic factors.

JMP software version 11 for Windows (SAS Institute, Cary, NC) was used for statistical analyses. Two-sided *P*-values of < .05 were considered statistically significant.

Results

Patients and treatments

The baseline characteristics of patients are listed in Table 1. The median follow-up duration was 81 months (Range, 12-156 months). All 249 patients who were hormone receptor (HR)-positive received hormonal therapy and 79 of 81 HER2-positive patients (97.5%) received trastuzumab. The median duration between the initiation of NAC and PMRT was 275 days (Range, 155-365 days). The median nodal ratio (positive divided by removed nodes, multiplied by 100) was 23%.

Table 1 Patient and treatment characteristics

Characteristic	Patients (n = 351)	%
Age (year)		
Range	25-80	
Median	49	
Tumour size		
Range	11-125 mm	
Median	47 mm	
NG		
1	123	35.0
2	100	28.5
3	74	21.1
unknown	54	15.4
LVI		
0	180	51.3
1	90	25.6
2	81	23.1
Clinical T stage		
T1	22	6.3
T2	158	45.0
T3	88	25.1
T4	83	23.6
Clinical N stage		
N0	16	4.6
N1	198	56.4
N2	29	8.3
N3	108	30.8
N3a	20	18.5
N3b	28	25.9
N3c	60	55.6
Clinical Stage		
IIA	22	6.3
IIB	81	23.1
IIIA	83	23.6
IIIB	57	16.2
IIIC	108	30.8
Hormone receptor status		
ER-positive	251	71.5
PgR-positive	135	38.5
HER2 overexpression	81	23.1
Subtype		
HR+, HER2+	33	9.4
HR+, HER2−	216	61.5
HR−, HER2+	44	12.5
HR−, HER2−	51	14.5
Unknown	7	2.0
Histology		
Invasive ductal carcinoma	328	93.4
Mucinous carcinoma	7	2.0
Lobular carcinoma	7	2.0
Others	9	2.6
Number of removed nodes		
Range	7-45	
Median	18	

(*continued on next page*)

Table 1 (*continued*)

Characteristic	Patients (n = 351)	%
Number of pathological positive nodes		
0	80	22.8
1-3	83	23.6
4-9	123	35.0
10 or more	65	18.5
Nodal ratio (%)		
(positive nodes/ removed nodes)x 100		
Range	0 - 100	
Median	23	
Response to NAC		
RECIST evaluation:		
CR	28	8.0
PR	222	63.2
SD	83	23.6
PD	18	5.1
ypT0	38	10.8
ypN0	79	22.5
pCR	18	5.1

Abbreviations: NG = nuclear grade, LVI = lymphovascular invasion, ER = estrogen receptor, PgR = progesterone receptor, HER2 = human epidermal growth factor receptor type 2, HR = hormone receptor, NAC = neoadjuvant chemotherapy, RECIST = Response Evaluation Criteria in Solid Tumours, CR = complete remission, PR = partial response, SD = stable disease, PD = progressive disease, pCR = pathological complete remission.

A total of 127 patients experienced recurrence as follows: locoregional recurrence (LRR) in 2 patients, locoregional and distant recurrence in 29 patients, and isolated distant failure in 96 patients. A total of 93 patients died of breast cancer.

Locoregional recurrence

Local failure occurred in 1 patient and local and regional failure occurred in 9 patients (CW + Ax: 4 patients, CW + Sc: 3 patients, and CW + IMN: 2 patients). Regional failure occurred in 22 patients (Sc + Ax: 8 patients; Ax: 8 patients; IMN: 4 patients; and Sc + IMN: 2 patients). The median time to LRR was 22 months and the 5-year LRFS rate was 91.3% for the entire group. On univariate analyses (Table 2), internal mammary chain irradiation, ER positivity, PgR positivity, early clinical N stage, and complete response of metastatic axillary nodes ypN0 were significantly associated with a higher LRFS rate. Large tumor, TN status, high LVI, advanced clinical N stage, number of axillary nodes metastases (AxLN mets), and clinical stage IIIC disease were significantly related to a lower LRFS rate (all $P < .05$). On multivariate analysis (Table 2), ER positivity, ypN0, high LVI, and clinical stage IIIC disease were independent predictors of LRFS.

The 5-year LRFS rate was 94.9% for ER positive patients (n = 251) and 81.9 % for ER negative patients (n = 100; $P = .0004$). The 5-year LRFS rate was 97.2 % for yp N0 (n = 79) and 89.5 % for ypN + (n = 272; $P = .03$). The 5-year LRFS rate was 92.9 % for the fewer lympho-vascular invasion group (n = 267) and 85.4 % for the higher lympho-vascular invasion group (n = 82; $P = .03$). Patients with clinical Stage IIIC disease had worse LRFS rates than those with another clinical stage disease. The 5-year LRFS rate was 79.8% for patients with clinical Stage IIIC disease (n = 108) and 96.2 % for patients with another stage disease (n = 243; $P < .0001$).

The 5-year LRFS rate for patients with pathologically proven no positive axillary node (ypN0; n = 79) was 97.2 %, with 1-3 positive axillary nodes (n = 83) 92.0 %, with 4 to 9 positive nodes (n = 123) 92.3 %, and with ≥10 positive nodes (n = 65) 81.0 %, respectively (number of positive axillary nodes: 0 vs ≥10 [$P = .0005$]; 1-3 vs ≥10 [$P = .03$]; 4-9 vs ≥10 [$P = .03$], 0 vs 1-3 [$P = .15$]; 0 vs 4-9 [$P = .06$], and 1-3 vs 4-9 [$P = .72$], respectively; Fig 1).

Survival

The 5-year DMFS and OS rates for the entire group were 69.8 % and 83.4 %, respectively. On multivariate analyses (Table 3), ypN0 and the number of AxLN mets. were independent predictors of DMFS. For OS, the number of AxLN mets. was the only significant predictor. The 5-year DMFS and OS rates for patients with ≥10 AxLN mets. were significantly inferior to patients with <9 AxLN mets. ($P < .0001$). The 5-year DMFS and OS rates for patients with pathologically proven negative axillary nodes were 87.3% and 91.2%, respectively; for 1 to 3 positive nodes 76.0 % and 91.2 %, respectively, for 4 to 9 positive nodes 70.3 % and 87.6 %, respectively, and for ≥10 positive nodes 39.8 % and 56.8%, respectively.

The 5-year DMFS, and OS rates were statistically compared with the number of axillary positive nodes with the following results: DMFS and OS of 0 versus 1 to 3 ($P = .11$ and $P = .61$, respectively); 0 versus 4 to 9 ($P = .006$ and $P = .38$, respectively); 0 versus ≥10 ($P < .0001$ and $P < .0001$, respectively), 1 to 3 versus 4 to 9 ($P = .32$ and $P = .75$, respectively), 1 to 3 vs. ≥10 ($P < .0001$ and $P < .0001$, respectively) 4 to 9 versus ≥10 ($P < .0001$ and $P < .0001$, respectively; (Fig 1).

Clinical outcomes by subtype

In our analyses of LRFS by subtypes, patients with HR and HER2 positivity (n = 33) had significantly better 5-year LRFS rates (100.0 %) than patients with another subtype, patients with HR positivity and HER2 negativity (n = 216; 94.1 %; $P = .04$), patients with HR negativity and HER2 positivity (n = 44; 85.7 %; $P = .007$), and patients with triple negativity (n = 51; 77.4 %; $P = .0004$), respectively.

Patients with triple negativity had a significantly worse 5-year OS rate (66.4 %) than patients with another

Table 2 Univariate and multivariate Cox regression analysis of locoregional recurrence-free survival in post-mastectomy breast cancer patients treated with neoadjuvant chemotherapy

Variables	Categories	HR	LRFS 95% CI	p-value
Univariate analysis				
Age (years)	continuous	0.25	0.037-1.599	0.15
IMN irradiation	yes vs. no	0.35	0.084-0.999	0.05
ER	(+) vs. (−)	0.30	0.146-0.611	0.001
PgR	(+) vs. (−)	0.37	0.136-0.837	0.02
HER2 overexpression	(+) vs. (−)	0.89	0.353-1.957	0.78
clinical N stage	N0 vs. N1 vs. N2 vs. N3	12.19	3.773-45.017	<0.0001
ypT0	yes vs. no	0.26	0.014-1.203	0.09
ypN0	yes vs. no	0.23	0.037-0.755	0.01
pCR	yes vs. no	0.58	0.033-2.709	0.56
RECIST CR	yes vs. no	0.82	0.133-2.730	0.78
Tumour size	continuous	1.01	1.019-26.15	0.05
Triple negativity	(+) vs. (−)	3.62	1.623-7.571	0.003
LVI	2 vs. 0-1	2.23	1.052-4.538	0.04
No. of Ax nodes mets.	continuous	28.8	5.505-120.63	0.0002
Clinical Stage IIIC	yes vs. no	4.60	2.241-9.946	<0.0001
Time to PMRT (days)	continuous	0.28	0.052-1.587	0.15
Multivariate analysis				
ER	(+) vs. (−)	0.18	0.063-0.556	0.004
PgR	(+) vs. (−)	0.83	0.245-2.460	0.75
ypN0	yes vs. no	0.02	0.001-0.396	0.003
pCR	yes vs. no	0.08	0.004-3.719	0.19
Triple negativity	(+) vs. (−)	0.95	0.353-2.718	0.93
LVI	2 vs. 0-1	2.59	1.104-5.983	0.03
clinical N stage	N0 vs. N1 vs. N2 vs. N3	0.53	0.188-1.844	0.30
No. of Ax node mets	continuous	1.05	0.998-1.096	0.06
Clinical Stage IIIC	yes vs. no	15.33	1.435-134.87	0.02

Abbreviations: LRFS = locoregional recurrence-free survival, HR = hazard ratio, CI = confidence interval, IMN = internal mammary node, RECIST = Response Evaluation Criteria in Solid Tumours, ER = estrogen receptor, PgR = progesterone receptor, HER2 = human epidermal growth factor receptor type 2, LVI = lymphovascular invasion, No. = number, Ax = axilla, mets. = metastases, PMRT = post mastectomy radiation therapy.

subtypes. The 5-year OS rate for TN patients and pathologically proven negative axillary nodes (n = 16) was 87.1 %. The OS for TN patients with 1 to 3 positive nodes (n = 10), TN and 4 to 9 positive nodes (n = 9), and TN and ≥10 positive nodes (n = 13) were 90.0 %, 77.8 %, and 15.4 %, respectively ($P = .0002$). The responses to treatment by subtype are shown in Table 4.

Discussion

There are no published randomized trials to guide the indication of PMRT in the NAC setting and the impact of PMRT on patients treated with modern NAC and systemic therapy is not known. In our study, all patients were typically treated with anthracycline and taxane-based chemotherapy before surgery followed by PMRT with a median follow-up duration of 81 months. The unique points of our study are the high consistency among treatments and more advanced stage patients compared with other studies.[14,16,22,23]

In one of the earliest and largest retrospective studies, Huang et al reported the outcomes of 542 patients treated with NAC followed by mastectomy and PMRT with a median follow-up duration of 69 months.[14] In their study, the pCR rate after NAC was 14 % in patients who received PMRT versus 6 % in those who did not receive PMRT. The 10-year LRR rate was 11 % in patients who received PMRT compared with 22 % in those who did not ($P = .0001$) and OS was also improved with PMRT. For the 46 patients who achieved pCR, the 10-year LRR rate was 3% with PMRT compared with 33% without PMRT ($P = .006$), which indicates that the most significant predictive factor for LRR was the omission of PMRT.

In another study, McGuire et al reported the clinical outcomes of 106 patients with clinical stage II–III breast cancer treated with NAC followed by mastectomy and achieved pCR at the time of surgery.[16] With a median follow-up duration of 62 months, the 10-year LRR rate did not statistically differ between the PMRT and non-PMRT groups. However, PMRT significantly reduced the 10-year LRR rate in patients with clinical stage III disease

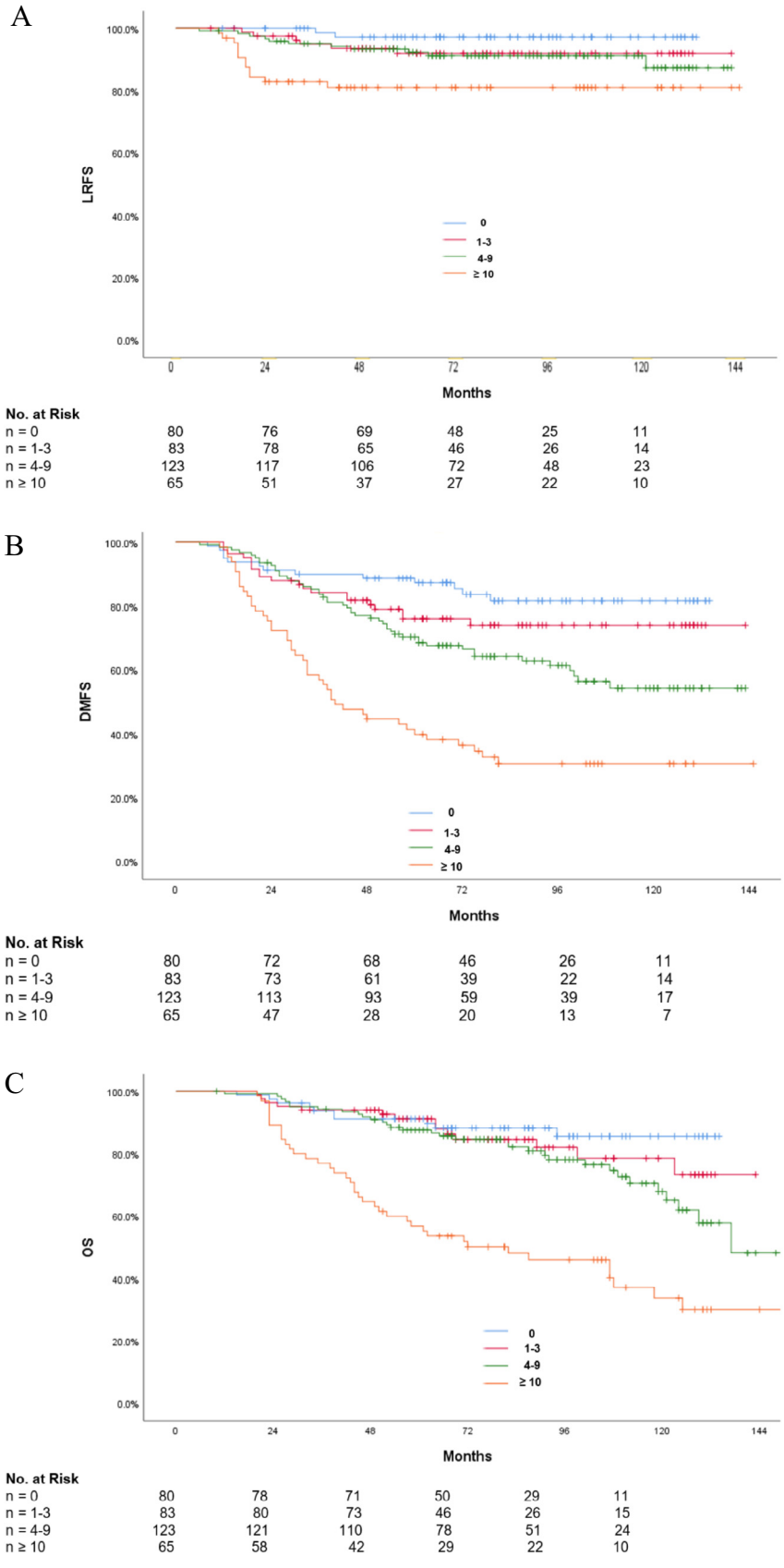

Figure 1 Kaplan-Meier analysis of locoregional recurrence-free survival. (A) Distant metastasis-free survival. (B) Overall survival. (C) By number of axillary node metastasis.

Table 3 Univariate and multivariate Cox regression analysis of distant metastasis-free survival and overall survival in postmastectomy breast cancer patients treated with neoadjuvant chemotherapy

Variables	Categories	DMFS	OS
		HR, 95%CI, p-value	HR 95%CI p-value
Univariate analysis			
Age (year)	continuous	0.76, 0.304-1.891, 0.56	1.44, 0.506-4.066, 0.49
IMN irradiation	yes vs. no	1.44, 0.934-2.327, 0.10	1.56, 0.954-2.702, 0.08
ER	(+) vs. (–)	0.85, 0.587-1.269, 0.43	0.65, 0.432-1.003, 0.05
PgR	(+) vs. (–)	0.96, 0.668-1.378, 0.84	0.86, 0.560-1.291, 0.46
HER2 overexpression	(+) vs. (–)	0.57, 0.344-0.899, 0.01	0.59, 0.333-0.983, 0.04
clinical N stage	N0 vs. N1 vs. N2 vs. N3	1.89 1.092-3.253 0.02	1.26 1.018-1.546 0.03
ypT0	yes vs. no	0.38, 0.150-0.794, 0.008	0.27, 0.065-0.706, 0.005
ypN0	yes vs. no	0.36, 0.190-0.607, < .0001	0.40, 0.195-0.736, 0.002
pCR	yes vs. no	0.43, 0.106-1.133, 0.09	0.42, 0.068-1.314, 0.15
RECIST CR	yes vs. no	1.12, 0.548-2.025, 0.74	0.75, 0.291-1.598, 0.49
Tumour size	continuous	2.00, 0.852-4.572, 0.11	2.36, 0.895-6.033, 0.08
Triple negativity	(+) vs. (–)	1.47, 0.882-2.314, 0.13	1.99, 1.170-3.229, 0.01
LVI	2 vs. 0 - 1	1.44, 0.967-2.103, 0.07	1.49, 0.950-2.289, 0.08
No. of Ax nodes mets	continuous	29.62, 12.15-68.30, < .0001	37.79, 13.66-98.461, <.0001
clinical Stage IIIC	yes vs. no	1.56, 1.072-2.237, 0.02	1.54, 1.001-2.331, 0.05
Time to PMRT (days)	continuous	0.85, 0.361-2.053, 0.72	0.99, 0.378-2.684, 0.99
Multivariate analysis			
ER	(+) vs. (–)	0.69, 0.391-1.279, 0.23	0.62, 0.326-1.249, 0.18
PgR	(+) vs. (–)	1.16, 0.760-1.786, 0.48	1.26, 0.756-2.124, 0.37
ypN0	yes vs. no	0.48, 0.221-0.965, 0.04	0.69, 0.292-1.482, 0.36
pCR	yes vs. no	0.88 0.199-2.806 0.85	0.71 0.108-2.750 0.65
Triple negativity	(+) vs. (–)	1.04, 0.531-2.059, 0.91	1.35, 0.670-2.750, 0.65
LVI	2 vs. 0 - 1	1.11, 0.724-1.663, 0.63	0.86, 0.175-4.284, 0.86
clinical N stage	N0 vs. N1 vs. N2 vs. N3	0.70 0.175-2.905 0.63	0.86 0.175-4.284 0.86
No. of Ax node mets	continuous	14.8, 5.13-40.02, <.0001	18.2, 5.506-57.17, <.0001
clinical Stage IIIC	yes vs. no	2.42, 0.938-6.229, 0.07	1.78, 0.625-5.182, 0.29

Abbreviations: DMFS = distant metastasis-free survival, OS = overall survival, HR = hazard ratio, CI = confidence interval, ER = estrogen receptor, PgR = progesterone receptor, HER2 = human epidermal growth factor receptor type 2, IMN = internal mammary node, LVI = lymphovascular invasion, RECIST = Response Evaluation Criteria in Solid Tumours, CR = complete response, Ax = axilla, mets = metastases.

(7% vs 33%; $P = .04$). The OS rate was also improved for patients with clinical stage III disease who received PMRT (77.3% vs 33.3%; $P = .002$). The authors concluded that PMRT is warranted in patients with clinical stage III disease who achieve pCR after NAC. In our study, patients with clinical Stage IIIC disease had significantly worse 5-year LRFS rates than those with other clinical stage diseases, even when treated with PMRT. Therefore, clinical stage III disease should be treated intensively including with PMRT.

Notably, the use of NAC modifies the pathologic extent of disease at the time of surgery. Given that NAC achieves a treatment response of up to 80%,[24] other studies showed that 20% to 40% of patients with lymph node-positive disease converted to lymph node-negative disease after NAC.[19,25] One argument to indicate PMRT for patients with clinically lymph node-positive disease before NAC regardless of the pathologic lymph node status at the time of surgery is evidence that PMRT reduces breast cancer mortality in patients with clinically lymph node-positive

Table 4 Treatment response and 5-year survival rates according to subtypes

Subtypes	n	ypT0/Tis	ypN0	pCR	LRFS	DMFS	OS
HR + HER2+	33	8 (24.0 %)	15 (45.5%)	3 (9.1%)	100.0%	81.8%	93.8%
HR+HER2–	216	5 (2.3%)	22 (10.2%)	3 (1.4%)	94.1%	69.4%	85.1%
HR–HER2+	44	20 (46.5 %)	22 (51.2%)	8 (18.6%)	85.7%	72.0%	83.7%
HR–HER2–	51	5 (10.4 %)	16 (33.3%)	4 (8.3%)	77.4%	57.8%	66.4%

Abbreviations: HR = hormone receptor, pCR = pathological complete response, LRFS = locoregional recurrence-free survival, DMFS = distant metastasis-free survival, OS = overall survival.

disease. Therefore, omission of radiation therapy in these patients potentially places them at an increased risk of mortality.

Le Scodan et al analyzed the outcomes of 134 patients with clinical stage II-III disease who achieved ypN0 disease after NAC.[22] A total of 78 of these patients received PMRT and the 5- and 10- year LRFS rates were high with or without PMRT. Additionally, the 10-year OS rate did not statistically differ between the 2 groups. The authors concluded that the omission of PMRT in women who achieve ypN0 status does not increase the risk of LRR or death.

Similarly, Shim et al analyzed the clinical outcomes and risk factors for LRR and DFS in 151 patients with clinical stage II and III breast cancer who achieved ypN0 after NAC,[23] and found PMRT not to be a significant prognostic factor. In our study, the 5-year LRFS rate for patients with ypN0 disease was significantly better than those with ypN + disease (97.2% vs 89.5 %, respectively; $P = .03$). Nevertheless, whether PMRT for patients with ypN0 disease can be omitted after NAC is unclear. The results of prospective, randomized studies such as the NSABP B 51/ Radiation Therapy Oncology Group (RTOG) 1304 phase 3 clinical trial and the Alliance A011202 trial will help address this issue.

The Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) pooled analysis enrolled approximately 12,000 patients and aimed to establish the association between pCR and event-free survival (EFS) and OS to determine the definition of pCR that best correlates with EFS or OS.[26] The analysis found that the best definition of pCR is the absence of invasive disease in the breast and lymph nodes (ypT0/ypTis ypN0). Using this definition, achieving a pCR resulted in a 64% reduction in the risk of death and a 52% reduction in relapse or death. In the trial-level analysis, the authors recorded little association between increases in the frequencies of pCR and EFS and OS. This pooled analysis did not validate pCR as a surrogate endpoint for improved EFS and OS.

In our study, we defined pCR as the absence of invasive disease in the breast and lymph nodes (ypT0/ypTis ypN0) and found that the predictive value of pCR was not statistically significant. Although the rate of achieving pCR was the greatest in HR-negative/HER2-positive patients, the clinical outcomes of these group were worse than those of the HR-positive/HER2-positive or HR-positive/HER2-negative groups. Therefore, we could not designate pCR as a surrogate marker for survival in concordant with the results of these studies. In our analysis, the clinical outcomes of patients with HR-positive/HER2-positive subtypes were the best among the 4 subtypes; therefore, PMRT could potentially be omitted for these patients even though their pCR rates were not high.

In accordance with our results, a recent meta-analysis of clinical outcomes for neoadjuvant chemotherapy by the Early Breast Cancer Trialists' Collaborative Group compared adjuvant chemotherapy in patients with early breast cancer[27] and suggested that pCR was higher with ER-negative biopsies than with ER-positive biopsies ($P < .0001$). Of the 4756 women included in the analysis, 3838 patients (81%) were in trials of regimens that included an anthracycline, one of which (902 women) also gave a taxane with similar regimens to our study. A noteworthy result of the study was that the incidence of local recurrence was significantly higher with NAC than with adjuvant chemotherapy in years 0 to 4 (risk ratio: 1.35; 95% confidence interval [CI], 1.11-1.64; $P = .003$) and 5 to 9 (risk ratio: 1.53; 95% CI, 1.08-2.17; $P = .02$) with few local recurrences after year 10. In the study, the details of radiation therapy were not available but the effect of radiation therapy on local recurrence could be important.

Recently, 2 randomized trials that were conducted by the Canadian Cancer Trials Group and the European Organisation for Research and Treatment of Cancer (EORTC) evaluated the addition of irradiation of the supraclavicular nodes, axillary apical nodes, and IMNs to whole-breast irradiation after breast-conserving surgery (both trials) or CW or no-CW irradiation after mastectomy (EORTC trial) in patients with early-stage breast cancer.[28,29] The crude rates of any breast cancer event were reduced from 20% to 16% at 10 years in the Canadian trial[20] and from 33% to 30% at 10 years in the EORTC trial with the addition of regional nodal irradiation with reductions in overall death rate of 1% and 2%, respectively. However, the addition of reginal nodal irradiation did not significantly improve OS. For delayed adverse events, no increases in rates of cardiac disease were observed.

Since 2007, we have included the IMNs in the clinical target volumes for all patients. On univariate analysis, IMN irradiation was significantly related to LRFS. On multivariate analysis, IMN irradiation was not a significant predictor of LRFS, which may be due to the inhomogeneous retrospective nature of the study. Most of our patients had more advanced stages of cancer compared with the patients in these trials; therefore, regional nodal irradiation would have contributed to improve breast cancer events. In the current study, there were no cardiac late adverse events. Nevertheless, the period of follow-up was not sufficiently long and further follow-up would be needed.

The PMRT guideline that was updated by the American Society of Clinical Oncology recommends that patients with axillary nodal involvement after neoadjuvant systemic therapy receive PMRT. The panel also recommends that treatment generally is administered to both the IMN and supraclavicular axillary apical nodes in addition to the CW or reconstructed breast.[30] In our study, almost all patients were treated in accordance with this PMRT guideline.

Our study has several limitations including a short follow-up period, limited sample size, and its retrospective nature. Therefore, our findings should be validated in larger, prospective trials. Nevertheless, our results show an important correlation between clinicopathological factors and the

clinical outcomes of patients with locally advanced breast cancer who were treated with NAC followed by mastectomy and PMRT.

Conclusions

We identified several predictive factors in patients with locally advanced breast cancer who were treated with NAC followed by surgery and PMRT in the modern treatment era. The number of axillary node metastases was significantly related to DMFS and OS and especially triple-negative patients with ≥10 positive nodes should receive more intensive treatments including PMRT or systemic therapy as well as more careful follow-up.

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