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Original Article

Pathological Complete Response Patients after Neoadjuvant Chemotherapy in Breast Cancer

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Cases of breast cancer metastasis after achieving a pathological complete response (pCR) with neoadjuvant chemotherapy (NAC) are sometimes encountered in clinical practice. We investigated the prognostic factors for pCR in patients with breast cancer after NAC. This retrospective cohort study included patients with localized breast cancer who underwent NAC followed by surgery between 2004 and 2020 and achieved a pCR. The associations between clinical factors and distant metastasis-free survival rate were statistically analyzed. We analyzed data for 127 patients. Twelve patients (9.4%) had distant metastases, and seven (5.5%) died. For estrogen receptor (ER)-positive patients, the distant metastasis-free survival rate was 94.6% for both 5 and 8 years. In contrast, ER-negative patients had a distant metastasis-free survival rate of 87.6% and 85.4% for 5 and 8 years ($p=0.094$), respectively. In cT0-2 patients, the distant metastasis-free survival rate was 92.4% for 5 years and 90.5% for 8 years, whereas in cT3-4 patients, the distant metastasis-free survival rate was 83.5% for 5 years and 83.5% for 8 years ($p=0.301$). This study suggested that patients with ER-negative, pre-NAC cT3 or T4 breast cancer who had achieved a pCR after NAC tended to have a worse prognosis.

Key words: breast, carcinoma, neoadjuvant therapy, prognosis

Neoadjuvant chemotherapy (NAC) was initially introduced to downstage locally advanced or inflammatory breast cancer and make it operable. However, NAC is currently being extended to operable breast cancer to allow breast-conserving surgery and serve as an option for human epidermal receptor 2 (HER2)-positive or triple-negative breast cancer. Patients with a pathological complete response (pCR) have better disease-free and overall survival than those with residual disease. However, cases of breast cancer metastases after achieving a pCR with NAC are sometimes encountered in clinical practice. Prognostic factors in patients with pCR after NAC are not well known. Therefore, we investigated the prognostic factors for pCR in patients with breast cancer after NAC.

Materials and Methods

This retrospective cohort study included 127 patients with localized breast cancer who underwent NAC followed by surgery and achieved a pCR at the National Hospital Organization Shikoku Cancer Center between June 2004 and September 2020. A pCR was defined as no residual invasive breast cancer in the histopathological specimens of the breast and axillary lymph nodes (ypT0/ypTisypN0). The analyzed clinical and biological factors were age, pre-NAC clinical T factor, pre-

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NAC clinical N factor, pre-NAC clinical stage, estrogen receptor (ER) status, HER2 status, subtype, and use of molecular targeted drugs. We analyzed the association between these factors and the distant metastasis-free survival rate. Since the survival rate of metastatic breast cancer is relatively good, we used the distant metastasis-free survival rate instead of survival-related indicators such as overall survival. At our hospital, metastasis before NAC is evaluated by Positron Emission Tomography - Computed Tomography (PET-CT) in accordance with published guidelines [http://www.nccn.org/professionals/physician_gls/. Accessed 2 September, 2021]. If brain metastasis is suspected due to neurological symptoms, contrast-enhanced head magnetic resonance imaging (MRI) is performed. Distant metastasis-free survival was defined as the time from operation to metastasis, death, or the last follow-up without metastasis before these end points. Patient death without metastasis or recurrence was censored at the time of death. One patient had a resected local recurrence and was alive without metastasis or recurrence at the time of writing. We did not regard her as a case of distant metastasis. We excluded patients who were diagnosed with stage IV breast cancer before NAC. The median follow-up time was 79 months (range, 1-184 months).

ER and HER2 statuses were evaluated using immunohistochemical (IHC) analysis. For ER status, positivity was defined as expression in >1% of the tumor cells. For HER2 status, IHC staining with a score of 3+(moderate to intense complete membrane staining observed in 10% of the tumor cells) or a positive *in situ* hybridization test result for IHC staining with a score of 2+(weak to moderate complete membrane staining in 10% of the tumor cells) was defined as positive.

Time-to-event endpoints were tested using log-rank tests (two-sided *p*-values). We used the Kaplan–Meier method to estimate the annual event-free survival. Statistical significance (p) was set at <0.05. All statistical analyses were performed using JMP®16 (SAS Institute Inc., Cary, NC, USA).

This study was approved by the Institutional Review Board of the National Hospital Organization Shikoku Cancer Center (approval number: 2021-15). We obtained informed consent for participation and data publication.

Results

We analyzed 127 patients with localized breast cancer who underwent NAC followed by surgery and achieved a pCR. Table 1 shows the patient and tumor characteristics. The median patient age was 52 years (range, 28-75 years), and there were 95 (74.8%) primary tumors measuring ≤50 mm. Further, only 19 (15.0%) patients did not have clinically involved adenopathy, 45 (35.4%) had ER-positive tumors, and 72

Table 1 Patient and tumor characteristics

Female sex—no.(%)	127 (100)
Median age—year. (range)	52 (28–75)
Clinical T factor—no. (%)	
≦T2	95 (74.8)
≧T3	32 (25.2)
Clinical N factor—no. (%)	
N0	19 (15.0)
≧N1	108 (85.0)
Clinical Stage—no. (%)	
≦Stage Ⅱ	65 (51.2)
Stage Ⅲ	62 (48.8)
ER status—no. (%)	
Positive	45 (35.4)
Negative	81 (63.8)
Unknown	1 (0.8)
HER2 status—no. (%)	
Positive	72 (56.7)
Negative	54 (42.5)
Unknown	1 (0.8)
NAC regimen—no. (%)	
Anthracycline plus taxane	104 (81.9)
Anthracycline only	3 (2.4)
Taxane only	19 (15.0)
Non-anthracycline or taxane	1 (0.8)
Surgery—no. (%)	
Bt+Ax or Bt+SN	47 (37.0)
Bp+Ax or Bp+SN or Bp only	80 (63.0)
Postoperative whole breast irradiation—no. (%)	
Yes	76 (95.0)
No	4 (5.0)
Metastasis or local recurrence—no. (%)	
Yes	17 (13.4)
No	110 (86.6)
Metastatic organ—no.	
Brain	7
Bone	5
Liver	3
Lung	2
Breast cancer death—no.	7

Bt, breast total mastectomy; Ax, axillary dissection; SN, sentinel lymph node biopsy; Bp, breast partial mastectomy.

(56.7%) had HER2-positive tumors. Most of them used anthracycline and taxane-based regimens, and HER2-positive patients used trastuzumab and pertuzumab accordingly. Eighty (63.0%) patients underwent breast-conserving surgery, and 76 of them (95.0%) underwent radiotherapy.

Twelve (9.4%) patients had distant metastases and seven (5.5%) died. The site of distant metastases was the brain in seven patients, bone in five, liver in three, and lungs in two. All seven patients with brain metastases were ER-negative, and four of these were HER2-positive. In addition, only brain metastases were found in four patients, of whom three were HER2-positive. Further, five (3.9%) patients had local recurrences, including three chest walls and two ipsilateral intramammary recurrences (Table 2).

In total, the distant metastasis-free survival rate was 90.1% for 5 years and 88.8% for 8 years. Regarding ER-positive patients, the distant metastasis-free survival rate was 94.6% for both 5 and 8 years. In contrast, ER-negative patients had a distant metastasis-free survival rate of 87.6% for 5 years and 85.4% for 8 years ($p = 0.094$). Patients with luminal tumors might have a tendency for a better prognosis. In cT0-2 patients, the distant metastasis-free survival rate was 92.4% for 5 years and 90.5% for 8 years, whereas in cT3-4 patients, the distant metastasis-free survival rate was 83.5% for 5 years and 83.5% for 8 years ($p = 0.301$). Hence, this study suggests that patients with larger tumors have a worse prognosis. There were no significant differences observed in age (< 52 years vs ≥ 52 years), clinical T factor (≤ T2 vs > T2), clinical N factor (N0 vs ≥ N1), clinical stage (≤ Stage II vs Stage III), ER status (positive vs negative), HER2 status (positive vs negative), subtype (luminal-non HER2 vs HER2 vs triple negative, pure HER2 vs non-pure HER2), and use of neoadjuvant molecular targeted drugs (use vs non-use) (Table 3, Figure 1).

Discussion

NAC is recommended for locally advanced breast cancer. Recently, NAC has also found a role in treating operable breast cancers. The National Surgical Adjuvant Breast and Bowel Project Protocol B-18, a clinical trial comparing preoperative and postoperative chemotherapy results, showed no statistically significant between-group differences in disease-free survival (DFS) or overall survival (OS) over a long-term follow-up [1]. Currently, NAC is an option for patients with early breast cancer when adjuvant chemotherapy is expected to be needed for the evaluation of tumor sensitivity to chemotherapy. Advances in chemotherapy due to the availability of taxanes, in addition to anthracyclines, have also promoted preoperative treatment.

pCR is generally considered a predictor of DFS and OS. Previously, pCR was defined in relation to the breast tumor only. However, several studies have shown that patients treated with NAC who achieve a pCR in both the breast and axilla have superior long-term outcomes [2-4]. Therefore, pCR was defined as the state of no residual invasive breast cancer in the breast or axillary lymph nodes. This definition was adopted for the analysis in our study.

In the Capecitabine for Residual cancer as Adjuvant Therapy trial, after standard NAC involving anthracycline, taxane, or both, the addition of adjuvant capecitabine therapy was effective in prolonging DFS and OS among patients with HER2-negative breast cancer who had residual invasive disease [5]. In the KATHERINE trial, among patients with HER2-positive early breast cancer who had residual invasive disease after NAC, the risk of recurrence of invasive breast cancer or death was 50% lower with adjuvant T-DM1 than with trastuzumab alone [6]. Thus, the purpose of NAC is to increase the breast-conserving surgery rate and the precision of prognosis according to the efficacy of NAC. These developments make NAC more important than ever before. With the progress of NAC, the pCR rate has reached approximately 20% [7].

In the I-SPY2 trial, patients who achieved a pCR showed a 3-year event-free survival (EFS) of 93-97%, with EFS being slightly higher in ER-positive patients [8]. In addition, there has been a study on prognosis in non-pCR patients [9], and another study has suggested that younger age (< 50 years) is a prognostic factor for locoregional recurrence-free survival [10]. However, the prognostic factors for death, metastasis, and local recurrence are not certain. In our study, ER negativity, cT3, and T4 were probable factors associated with a poor prognosis. However, this result may apply not only to pCR patients but to breast cancer patients as a whole, and no significant difference was found statistically. Our sample size was prohibitively small. Therefore, further studies such as comparisons with non-pCR patients would be useful.

Table 2 Patients of breast cancer metastases or recurrences after achieving a pCR with NAC

Age-year.	Clinical T factor	Clinical N factor	Clinical Stage	ER status	HER2 status	NAC regimen	Srurgery	RT
68	T2	N3c	IIIC	−	+	EC→DTX + Trastuzumab	Bt + Ax	−
70	T4b	N2a	IIIB	−	+	EC→DTX + Trastuzumab	Bp + Ax	+
58	T2	N1	IIB	−	+	EC→DTX + Trastuzumab	Bp + Ax	+
48	T3	N3b	IIIC	−	−	ddAC→ddPTX	Bt + Ax	−
47	T4d	N3a	IIIC	−	+	FEC→DTX + Trastuzumab	Bt + Ax	−
46	T2	N0	IIA	−	−	EC→DTX	Bp + SN	+
54	T2	N1	IIB	−	−	ddAC→ddPTX	Bt + Ax	−
47	T4b	N2a	IIIB	−	+	EC→DTX + Trastuzumab	Bt + Ax	+
48	T2	N1	IIB	−	−	FEC→DTX	Bt + Ax	+
36	T2	N1	IIB	−	+	FEC→DTX + Trastuzumab	Bp + Ax	+
46	T2	N1	IIB	+	−	EC→DTX	Bp + Ax	+
29	T2	N3a	IIIC	+	+	FEC→DTX + Trastuzumab	Bp + Ax	+
60	T4d	N3b	IIIC	−	−	AC→wPTX	Bt + Ax	+
38	T2	N2a	IIIA	+	−	FEC→DTX	Bt + Ax	−
58	T2	N0	IIA	−	−	FEC→wPTX	Bp + SN	+
30	T2	N1	IIB	+	−	DTX→FEC	Bp + Ax	+
75	T1c	N1	IIA	+	+	EC→wPTX	Bt + Ax	+

Age-year.	Metastatic organ or recurrence	Distant metastasis-free or recurrence-free survival-month	Outcome
68	brain	29	death
70	brain	10	death
58	brain	8	survival
48	brain	8	death
47	brain, bone, chest wall	2	death
46	brain, bone, liver, lung, distant lymph nodes	14	death
54	brain, bone, liver	8	survival
47	bone, mediastinal lymph nodes	20	survival
48	bone, axilla/parasternal/mediastinal/abdominal lymph nodes, peritoneal/meningeal dissemination	61	death
36	liver	105	survival
46	lung, axilla lymph nodes	22	survival
29	mediastinal lymph nodes, lymphangiosis carcinomatosa	24	survival
60	chest wall	3	death
38	chest wall	101	survival
58	ipsilateral breast	13	survival
30	ipsilateral breast	77	survival
75	contralateral breast	14	survival

EC, Epirubicin + Cyclophosphamide; DTX, Docetaxel; ddAC, dose-dense Adriamycin + Cyclophosphamide; ddPTX, dose-dense Paclitaxel; FEC, Fluorouracil + Epirubicin + Cyclophosphamide; wPTX, weekly Paclitaxel; Bt, breast total mastectomy; Ax, axillary dissection; Bp, breast partial mastectomy; SN, sentinel lymph node biopsy; RT, radiotherapy.

Previous studies have shown that bone is the most common distant metastatic organ in patients with breast cancer, with the liver, lung, and brain also being common sites of distant metastasis [11, 12]. In this study, the brain was the most common metastatic organ, and most of these metastases were ER-negative and HER2-positive. In Japan, molecular targeted drugs such as trastuzumab and pertuzumab are used as HER2-positive neoadjuvant and adjuvant therapies. These are large-molecule HER2 kinase inhibitors, which may have a low inhibitory effect on brain metastasis. Although not approved in Japan, small-molecule HER2

Table 3 Distant metastasis-free survival rate in all patients

	Number	5 year distant metastasis-free survival rate	8 year distant metastasis-free survival rate	*P* value
Total	127	90.1%	88.8%	–
Age				
≦51	63	89.2%	86.6%	0.445
≧52	64	91.0%	91.0%	
Clinical T factor				
≦T2	95	92.4%	90.5%	0.301
≧T3	32	83.5%	83.5%	
Clinical N factor				
N0	19	93.8%	93.8%	0.470
≧N1	108	89.5%	88.0%	
Clinical Stage				
≦Stage II	65	93.1%	90.1%	0.751
Stage III	62	87.1%	87.1%	
ER status				
Positive	45	94.6%	94.6%	0.094
Negative	81	87.6%	85.4%	
HER2 status				
Positive	72	90.1%	90.9%	0.578
Negative	54	88.9%	85.0%	
Luminal-non HER2 or HER2 or TN				
Luminal-non HER2	15	91.7%	91.7%	
HER2	72	90.9%	90.9%	0.524
TN	39	87.9%	81.1%	
pure HER2 or non pure HER2				
pure HER2	42	87.6%	87.6%	0.476
non pure HER2	84	91.5%	89.2%	
Use of neoadjuvant molecular targeted drugs				
Yes	74	90.7%	90.7%	0.65
No	53	89.2%	85.6%	

TN, triple negative.

kinase inhibitors such as neratinib and tucatinib potentially prevent brain metastases. In ExteNET, which compared the effects of 1-year administration of neratinib with placebo in patients who had completed trastuzumab-based adjuvant therapy in women with HER2-positive breast cancer, the 5-year cumulative incidence of central nervous system events was 1.3% in the neratinib group and 1.8% in the placebo group respectively ($p = 0.333$) [13]. In HER2CLIMB (which compared tucatinib with placebo, in combination with trastuzumab and capecitabine, in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine), among patients with brain metastases involving untreated brain metastases of 2 cm in diameter, progression-free survival (PFS) at 1 year was 24.9% in the tucatinib-combination group and 0% in the placebo-combination group ($p < 0.001$), with median PFS values of 7.6 (95% CI, 6.2 to 9.5) and 5.4 months (95% CI, 4.1 to 5.7), respectively [14].

In this study, of the 80 patients who underwent breast-conserving surgery, 2 had ipsilateral breast tumor recurrence and both received postoperative radiotherapy. In postoperative radiotherapy, the 10-year locoregional recurrence rate of patients with clinical stage III who achieved a pCR significantly improved with radiotherapy (7.3% vs. 33.3%; $p = 0.040$) [15]. This study suggests that pretreatment conditions contribute to local and regional lymph node recurrence, regardless of the effect of NAC. In this study, the intramammary recurrence rate was not low; therefore, postoperative whole-breast irradiation is essential.

There were some limitations to our study. First, the sample size was relatively small. Second, this study

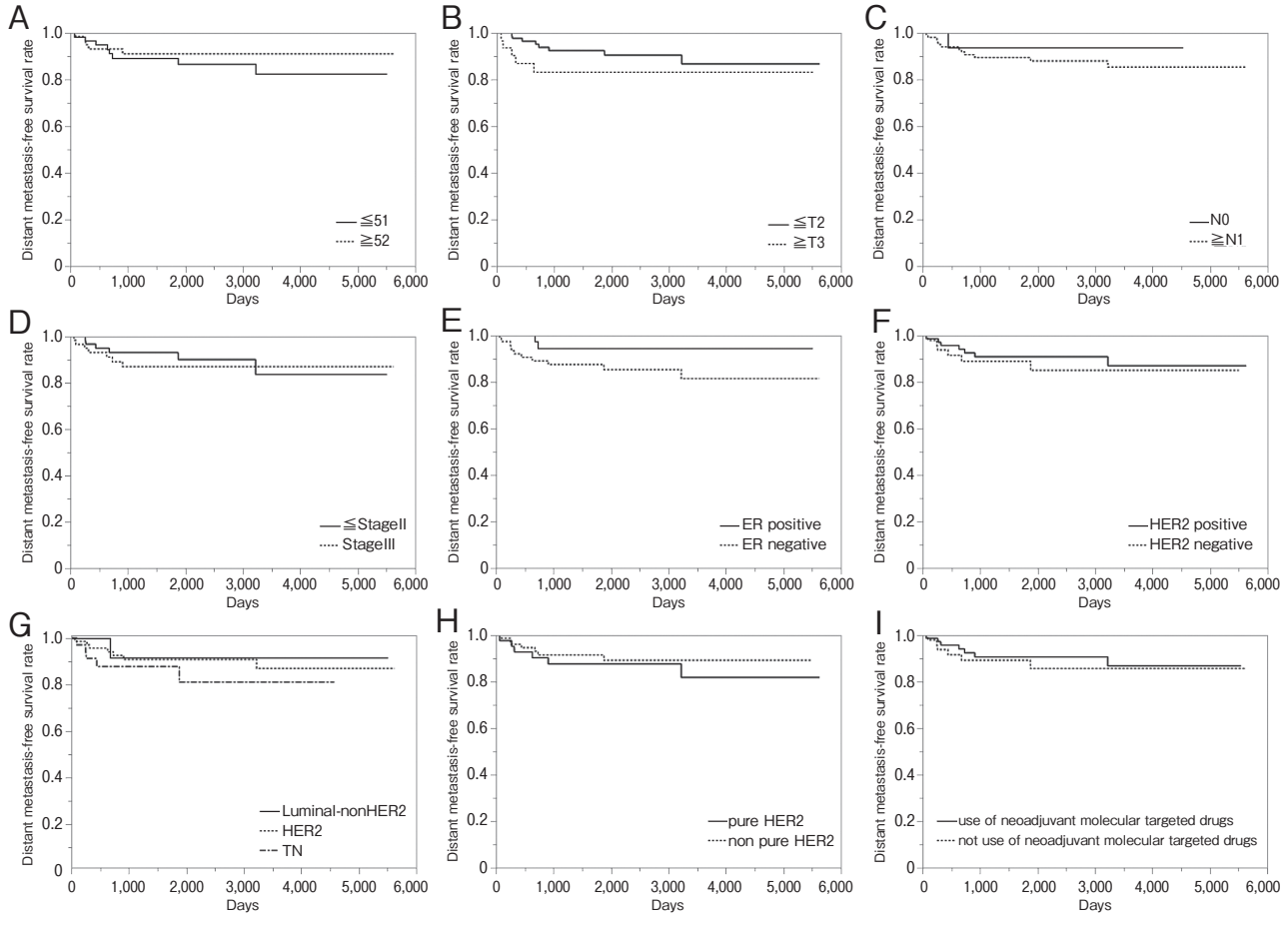

Fig. 1 Kaplan-Meier Estimates of Distant Metastasis-Free Survival. Distant metastasis-free survival according to **A**) age, **B**) clinical T factor, **C**) clinical N factor, **D**) clinical Stage, **E**) ER status, **F**) HER2 status, **G**) luminal-non HER2 or HER2 or TN, **H**) pure HER2 or non-pure HER2, and **I**) use of neoadjuvant molecular targeted drugs.

involved retrospective analysis at a single institution, which might result in selection bias. Third, the follow-up time for data collection was short.

In conclusion, patients with ER-negative, pre-NAC cT3, or T4 breast cancer who had achieved a pCR after NAC tended to have a worse prognosis. The brain was the most common metastatic organ in patients with pCR after NAC, and most of the metastases observed were ER-negative and HER2-positive. Therefore, small-molecule HER2 kinase inhibitors such as neratinib and tucatinib may have the potential to prevent brain metastases. Larger prospective studies should be conducted in the future to draw more definitive conclusions in this regard.

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