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Clinical and pathological predictors of recurrence in breast cancer patients achieving pathological complete response to neoadjuvant chemotherapy

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ABSTRACT

Introduction: Despite the excellent prognosis associated with pathological complete response (pCR) to neoadjuvant chemotherapy (NAC), some patients still develop recurrence. Here, we investigated the outcomes of breast cancer patients with pCR, as well as the clinical and pathological predictors of cancer recurrence in these patients.

Materials and methods: Of the 1599 breast cancer patients treated with NAC, we evaluated 394 patients who achieved pCR between January 2007 and December 2016. pCR was defined as no evidence of invasive cancer in breast. Residual *in situ* ductal and axillary lymph node diseases were not considered. We analyzed the outcomes using the Kaplan–Meier method. We assessed the association of clinical and pathological predictors with cancer recurrence using the cox proportional hazards regression model.

Results: The median follow-up time was 63 months. The 5-year disease-free survival rate was 92.3%. Cancer recurrence was observed in 28 patients (7.1%): local recurrence 8 patients (2.0%), visceral metastasis 10 patients (2.5%), and brain metastasis 10 patients (2.5%). Brain metastases were found in patients with HER2 type breast cancer. The significant predictors of cancer recurrence were HER2 positivity ($p = 0.04$), clinical tumor size ($p < 0.01$), and lymph node metastasis ($p < 0.01$) before NAC on univariate analysis and only lymph node metastasis on multivariate analysis.

Conclusion: Patients achieving pCR to NAC showed excellent outcomes. Advanced clinical stage, large tumor size, presence of lymph node metastasis, and HER2 positivity before NAC were identified as significant predictors of cancer recurrence. Residual *in situ* ductal and lymph node diseases after NAC were not significant predictors.

Introduction

Neoadjuvant chemotherapy (NAC) refers to systemic chemotherapy administered as an initial treatment before surgery. With recent advances in drug development and systemic therapies, the

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rate of patients achieving pathological complete response (pCR) after NAC for breast cancer has significantly improved. This has been particularly evident in hormone-receptor (HR)-negative or human epidermal growth factor receptor 2 (HER2)-positive breast cancer. The *Collaborative Trials in Neoadjuvant Breast Cancer*, which is the first large pooled analysis of NAC, demonstrated that patients who achieved pCR have improved event-free survival and overall survival (OS), with the prognostic value being the highest for aggressive cancer subtypes [1].

Despite the excellent prognosis of patients with pCR, breast cancer may still recur locally or as distant metastases. At present, the frequency and predictors of breast cancer recurrence after achieving pCR remain unclear. Moreover, the primary objective of surgery for patients who have potentially achieved pCR as evaluated by imaging is still concentrated on obtaining samples for pathological examination to assess whether local cancer control has been achieved. Importantly, there is an interesting argument in the field of breast cancer that surgery can be omitted in these patients if the achievement of pCR can be accurately diagnosed by imaging [2,3] and if the rate of local recurrence is low. However, if the frequency of local recurrence is high, the omission of surgical control should never be considered even if pCR could be accurately confirmed.

We hypothesize that the primary cancer has clinical features that are associated with recurrence after achieving pCR. If cancer recurrence were reasonably rare after achieving pCR, then the omission of surgical control following NAC would be justifiable.

In this study, we performed a retrospective analysis of one of the largest cohorts of patients in Japan who have achieved pCR after NAC to investigate their outcomes and identify the clinical and pathological predictors of cancer recurrence.

Materials and Methods

Study cohort

The medical information of all the patients was collected from Yokohama City University Medical Center, Yokohama Rosai Hospital, Kanagawa Cancer Center, and Tokyo Medical University Hospital, Japan. The study protocol was approved by the institutional review board of each institution. The clinical and pathological staging of breast cancer was based on the Cancer Staging Manual (7th ed.) of the American Joint Commission on Cancer.

A total of 1599 patients diagnosed as having operable breast cancer were treated with NAC at the 4 institutions mentioned above between January 2007 and December 2016. Patients with a second primary breast cancer, a medical history of other cancers, and suspected distant metastases during NAC were excluded. Clinical data regarding tumor characteristics and patients' demographics were obtained from the medical charts and analyzed. A final cohort of 394 patients who achieved pCR was analyzed in this study. Being a retrospective study, informed consent was not required.

Pathological assessments

All biopsies and surgical specimens of the patients were prepared by 5-mm step serial sectioning and then examined. HR status was assessed by immunohistochemistry (IHC) and categorized as positive when more than 1.0% of cancer cells were stained. HER2 positivity was defined according to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) [4] guidelines. This was indicated as a 3 + score on immunohistochemistry by HercepTest™ immunohistochemical assay (Dako Italia, Milan, Italy) or a positive result on HER2 gene amplification by fluorescence *in situ* hybridization or silver-enhanced *in situ* hybridization assay [4].

Breast cancers were classified into 4 subtypes based on the HR and HER2 statuses as follows: luminal subtype (HR-positive and HER2-negative), luminal-HER2 subtype (HR-positive and HER2-positive), HER2 subtype (HR-negative and HER2-positive), and triple negative subtype (both HR-negative and HER2-negative) [5]. pCR was defined as no residual invasive carcinoma in the breast even if there is residual ductal carcinoma *in situ* (DCIS: ypTis) or there is residual metastatic cancer in the axillary lymph nodes (ypN1) upon surgical resection.

Treatment and disease assessments

Patients received a standard anthracycline- and taxane-based chemotherapy regimen for NAC − 4 cycles of a combination of epirubicin and cyclophosphamide with or without 5-fluorouracil every 3 weeks, combined with either 4 cycles of docetaxel every 3 weeks or 12 cycles of paclitaxel every week. Trastuzumab was added to the taxane cycles at the NAC setting and continued for a total of 1 year in most of the HER2 cases. HR-positive cases received adjuvant endocrine therapy for ≥5 years. The surgical procedure consisted of mastectomy or breast-conserving surgery. Axillary lymph node dissection was performed for most of the cases with clinically positive nodes before NAC. Sentinel lymph node biopsy was conducted in all cases with clinically negative nodes using combined methods of blue dye and radioisotope. Axillary dissection was added when nodes were pathologically positive. Radiation therapy was administered to the ipsilateral remaining breast or tumor bed of patients who underwent partial mastectomy and to the axilla of patients with ≥4 axillary lymph node metastases. Cancer recurrence and distant metastasis were assessed regularly by history taking, physical test, and imaging. Disease-free survival (DFS) was defined as the time interval from surgery to the first documented cancer recurrence.

Statistical analysis

All statistical analyses were conducted using R (version 3.5.1). The Kaplan-Meier method with the logrank test was used for survival analyses. Group comparisons for categorical variables were carried out using Fisher's exact test. The Cox proportional hazards regression model was used to assess the association of clinical and pathological predictors with cancer recurrence. All tests were two-tailed and a p-value of ≤0.05 was considered to indicate a statistically significant difference.

Results

Patient and cancer characteristics

Of the 1599 patients diagnosed with clinical stage I–III breast cancer and treated with NAC, 394 (24.6%) achieved pCR. The median follow-up period for these 394 patients was 63 months (range = 16–161). The pCR rates for the various cancer subtypes were 52.9% (117/221) for HER2, 31.8% (97/305) for luminal HER2, 7.1% (49/690) for luminal, and 34.2% (131/383) for triple-negative.

The characteristics of the 394 patients are described in Table 1. The 5-year DFS and OS rates were 92.3% and 98.1%, respectively (Fig. 1A and B). Twenty-eight (7.1%) patients who achieved pCR eventually developed cancer recurrence, with 8 patients (28%) presenting with local recurrence in the breast and 10 patients (36%) each presenting with distant metastasis to brain or viscera (including the lungs, liver, and abdominal lymph nodes) as the first event (Fig. 1C). Bone or axillary lymph node metastasis was not observed as the first event.

Table 1
Demographics of patients who achieved pathological complete response.

Predictors		No. of patients		
		Total	Recurrence	
		(N)	(N)	(%)
Age at diagnosis (years)	≧ 50	260	15	5.8%
	<50	134	13	9.7%
Clinical stage	I/II	309	14	4.5%
	III	85	14	16.5%
Subtype	HER2	117	14	12.0%
	Luminal-HER	97	7	7.2%
	Luminal	49	1	2.0%
	TN	131	6	4.6%
HR status	Negative	248	20	8.1%
	Positive	146	8	5.5%
HER2 status	Negative	180	7	3.9%
	Positive	214	21	9.8%
Clinical T classification	cT1	77	7	9.1%
	cT2	259	24	9.3%
	cT3	40	5	12.5%
	cT4	18	4	22.2%
Clinical N classification	cN0	171	3	1.8%
	cN1-3	223	25	11.2%
Pathological T classification	ypT0	315	19	6.0%
	ypTis	79	9	11.4%
Pathological N classification	ypN0	350	24	6.9%
	ypN1	24	4	16.7%
	Unknown	20	0	
Type of mastectomy and Adjuvant RT	Partial/RT+	87	2	2.3%
	Total/RT+	140	14	10%
	Partial/RT-	110	9	8.2%
	Total/RT-	52	3	5.8%
	Unknown	5	0	

HR, hormone receptor; HER2, human epidermal growth factor type 2; RT, radiation therapy.

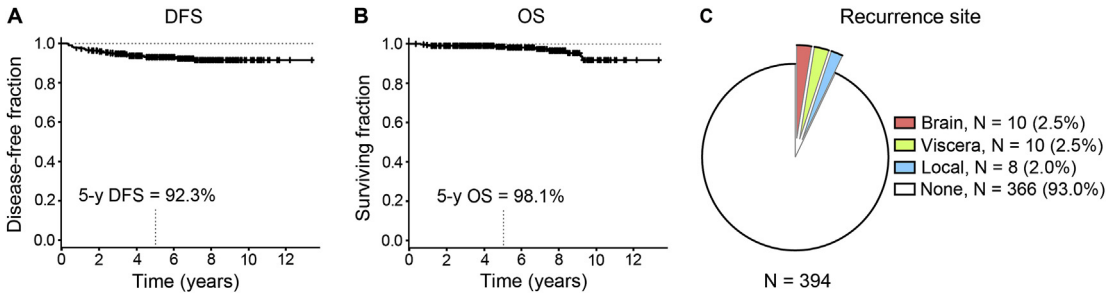

Fig. 1. Patients who achieved pathological complete response (pCR) to neoadjuvant chemotherapy had an excellent long-term outcome. The Kaplan-Meier plots and 5-year survival rates are shown for (**A**) disease-free survival (DFS) and (**B**) overall survival (OS) for the 394 patients who achieved pCR. (**C**) The pie chart indicates the incidence of recurrence after pCR has been achieved and the first recurrence site.

Univariate and multivariate analyses of predictors of cancer recurrence after achieving pCR

Advanced clinical stage (cStage), large tumor size (clinical T [cT] classification), and presence of lymph node metastasis (clinical N [cN] classification) before NAC were significantly associated with cancer recurrence. The hazard ratios for recurrence and their 95% confidence intervals (CIs) and associated *p*-values on univariate Cox regression analyses for cStage I-II vs. cStage III, cT1-2 vs. cT3-4, and cN0 vs. cN1-3 comparisons were 4.0 (1.9–8.4, $p < 0.01$), 2.9 (1.3–6.1, $p < 0.01$), and 9.4 (2.2–39.0, $p < 0.01$), respectively.

The presence of residual breast DCIS (pathological ypT) or residual lymph node metastasis (ypN) after NAC showed no significant association with recurrence – ypT0 vs. ypTis: hazard ratio = 1.7; 95% CI = 0.8–3.9, $p = 0.15$; ypN0 vs. ypN1: hazard ratio = 1.8, 95% CI = 0.5–6.0, $p = 0.33$.

Furthermore, the incidence of cancer recurrence was significantly higher in the HER2 breast cancer subtype than in the other 3 subtypes (hazard ratio = 2.6, 95% CI = 1.1–6.0, $p = 0.02$). Subsequently, HER2 positivity was also significantly associated with cancer recurrence (HER2+ vs. HER2-: hazard ratio = 2.5, 95% CI = 1.4 1–8.9; $p = 0.04$), whereas the HR status was not significantly associated with cancer recurrence (positive vs. negative-: hazard ratio = 0.5, 95% CI = 0.2–1.1, $p = 0.09$).

Age at diagnosis (≥50 vs. < 50 years), type of mastectomy (partial vs. total), and adjuvant radiation therapy showed no significant association with cancer recurrence. On the multivariate Cox analysis including only the significant predictors, clinical N classification was found to be the most significant predictor (cN0 vs. cN1-3: hazard ratio = 9.3, 95% CI = 2.0–43, $p < 0.01$). The complete results of the analyses are shown in Table 2.

HER2 positivity is associated with a higher risk of brain metastasis and a worse DFS.

Among the 4 subtypes of breast cancer, the HER2 subtype was

Table 2
Cox proportional hazard model of predictors of cancer recurrence in patients who achieved pCR.

Predictors		Univariate analysis			Multivariate analysis		
		Hazard ratio	95%CI	*p*-value	Hazard ratio	95%CI	*p*-value
Age at diagnosis (years)	≧ 50	Ref.					
	<50	1.7	0.8–3.7	0.16			
Clinical Stage	I/II	Ref.					
	III	4.0	1.9–8.4	**< 0.01**	1.2	0.2–2.4	0.73
Subtype	HER2	Ref.					
	Luminal-HER	0.5	0.2–1.3	0.15			
	Luminal	0.2	0.02–1.2	0.07			
	TN	0.4	0.1–0.9	**0.03**			
Subtype	HER2 type	2.6	1.1–6.0	**0.02**	2.1	0.1–1.2	0.12
	Other 3 types	Ref.			Ref.		
HR status	Negative	Ref.					
	Positive	0.5	0.2–1.1	0.09			
HER2 status	Negative	Ref.			Ref.		
	Positive	2.5	1.1–5.9	**0.04**	1.6	0.5–4.8	0.39
Clinical T classification	cT1/2	Ref.			Ref.		
	cT3/4	2.9	1.3–6.1	**< 0.01**	2.2	0.6–7.3	0.48
Clinical N classification	cN0	Ref.			Ref.		
	cN1-3	9.4	2.2–39	**< 0.01**	9.3	2.0–43	**< 0.01**
Pathologic T classification	ypT0	Ref.					
	ypTis	1.7	0.8–3.9	0.2			
Pathologic N classification	ypN0	Ref.					
	ypN1	1.8	0.5–6.0	0.33			
Type of mastectomy	Partial	Ref.					
	Total	1.8	0.8–3.9	0.15			
Adjuvant RT	No	Ref.					
	Yes	1.0	0.48–2.2	0.95			

CI, confidence interval; HR, hormone receptor; HER2, human epidermal growth factor type 2; RT, radiation therapy.

significantly associated with worse DFS as indicated by the Kaplan-Meier analysis (logrank $p = 0.048$; Fig. 2A). Furthermore, patients with HER2-positive breast cancer were significantly associated with a worse DFS compared with patients with HER2-negative breast cancer ($p = 0.03$; Fig. 2A and B). Cancer recurrence after achieving pCR was observed in 14 patients (12%) for the HER2, 1 (2%) for the luminal, 7 (7.2%) for the luminal-HER2, and 6 (4.6%) for the triple-negative subtypes. Details of the first site of cancer recurrence for the 4 cancer subtypes are shown in Fig. 2C.

Advanced clinical stage before NAC worsens DFS and OS

Advanced clinical stage as determined by the tumor size (cT) and lymph node metastasis (cN) was significantly associated with a less favorable outcome in terms of DFS and OS (Fig. 3A–F). The logrank test *p*-values in the Kaplan-Meier analyses were all <0.01 for DFS for cStage I-II vs. cStage III, cT1-2 vs. cT3-4, and cN0 vs. cN1–3 comparisons. For OS, the *p*-values were 0.03 for the cStage I-II vs. cStage III comparison, and ≤0.01 for the cT1-2 vs. cT3-4 and cN0 vs. cN1-3 comparisons. Surprisingly, the presence of residual

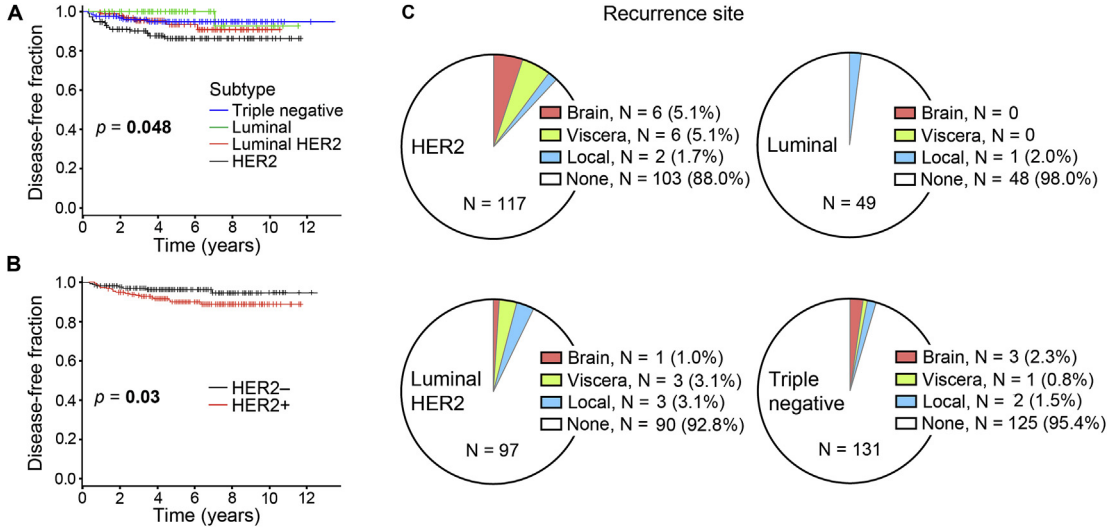

Fig. 2. After pathological complete response (pCR) was achieved, recurrence was most frequent for the HER2 subtype of cancer. The Kaplan-Meier plots and logrank test *p*-values are shown for the comparison of disease-free survival (DFS) by (**A**) cancer subtype and (**B**) HER2 positivity. (**C**) The pie charts indicate the incidence of recurrence after pCR has been achieved and its first recurrence site among patients with different cancer subtypes.

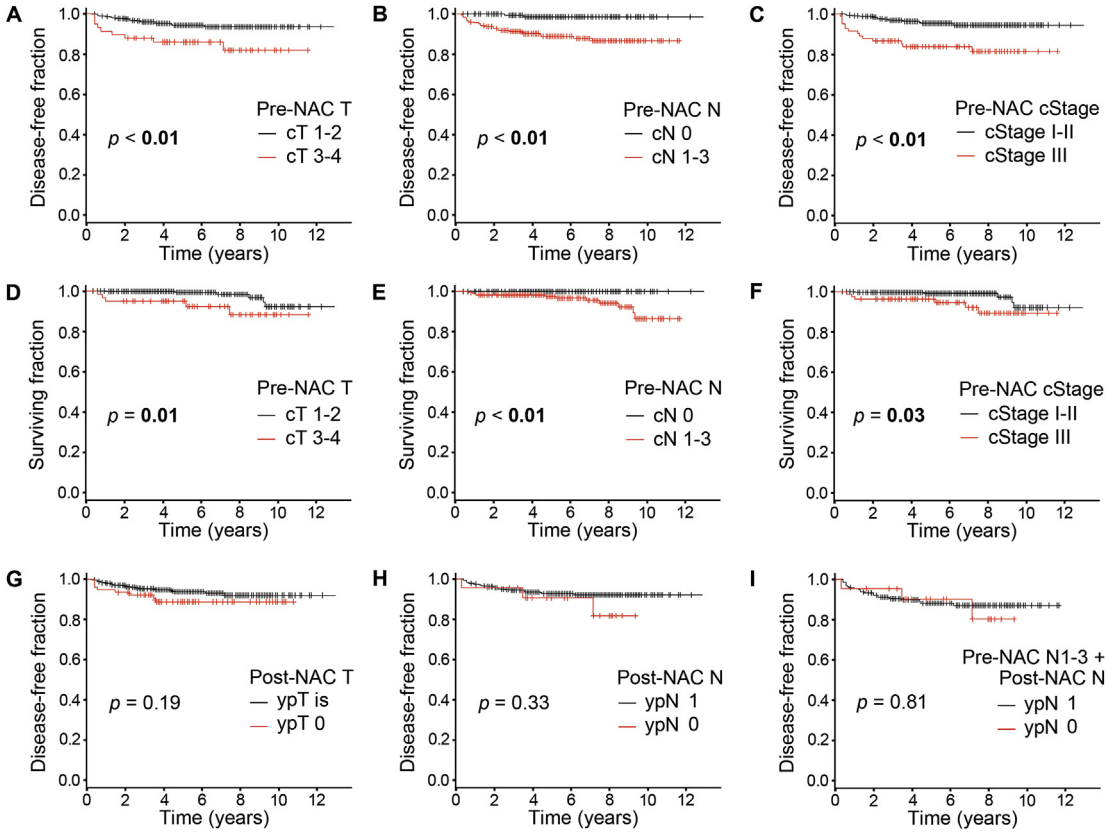

Fig. 3. The results showed that residual ductal carcinoma *in situ* (DCIS) and lymph node metastasis after neoadjuvant chemotherapy (NAC) are not significant predictors of cancer recurrence in patients who achieved pathological complete response (pCR). The Kaplan-Meier plots and logrank test *p*-values are shown for the comparison of disease-free survival (DFS) or overall survival (OS) among patients stratified by pre-NAC (**A, D**) clinical tumor size (cT 1–2 vs. 3–4), (**B, E**) clinical node metastasis status (cN 0 vs. 1–3), and (**C, F**) clinical stage (cStage I-II vs. III). DFS comparisons by post-NAC are shown in (**G**) for patients without and with residual DCIS in the breast (ypT0 vs. ypTis), and (**H**–**I**) for patients without and with residual lymph node metastasis (ypN0 vs. ypN1) in (**H**) the entire cohort or (**I**) among only those with pre-NAC lymph node metastasis.

breast DCIS or residual lymph node metastasis after NAC showed no significant effect on DFS (ypT0 vs. ypTis: $p = 0.19$; ypN0 vs. ypN1, $p = 0.33$; Fig. 3G and H). Even among only those who had lymph node metastasis before NAC, residual lymph node metastasis after NAC showed no significant effect on DFS (ypN0 vs. ypN1: $p = 0.81$; Fig. 3I).

Discussion

Cancer recurrence was rare after achieving pCR (7.1%). Both the 5-year DFS (92.3%) and OS (98.1%) rates of the patients were excellent, which are in agreement with previous reports [6–10], despite the definition of pCR as having no invasive disease in the breast regardless of lymph node metastasis. We found that advanced clinical stage before NAC, as determined by tumor size and axillary lymph node metastasis, and HER2 positivity are significant predictors of cancer recurrence after achieving pCR (Table 2).

The largest study that investigated the risk factors of cancer recurrence after achieving pCR was performed in MD Anderson Cancer Center at the University of Texas. The study analyzed 749 patients and showed the 5-year DFS and OS rates of 93% and 96%, respectively. The findings showed that younger patients and those with clinical stage IIIB and IIIC cancers at the time of diagnosis were at increased risk of developing distant metastasis, although no significant difference was found based on the HR or HER2 status [11]. In another study of 226 patients who achieved pCR after NAC, clinical stage IIIB and IIIC cancers, inflammatory breast cancer, premenopausal status, and axillary lymph node dissection (<10 lymph nodes) were found to be associated with an increased risk of developing distant metastasis [9]. Our present results are consistent with the results of these 2 previous studies, showing that breast cancer occasionally recurred in clinically advanced diseases even after achieving pCR.

Nevertheless, our present study has some inconsistencies with these 2 previous reports, these inconsistencies may be partly explained by the different pCR definition and the absence of invasive cancer in the breast and lymph nodes (ypT0/is ypN0) in the 2 previous studies. It is possible that patients with no invasive cancer in the breast and lymph nodes have an excellent prognosis regardless of the cancer subtype [11]. However, the advantages of our present study over these previous studies were the longer follow-up time and the contemporary and uniform use of chemotherapy regimens with the addition of trastuzumab to all HER2-positive cases.

It has been reported that patients with ypT0/is ypN0 had significantly better clinical outcome than patients with ypT0/is ypN1 [8]. We found that the recurrence rate of patients who had remnant lymph node metastasis after NAC (ypT0/is ypN1) were twice higher compared to those who achieved pCR in both breast and lymph nodes (ypT0/is, ypN0) (16.7 vs 6.9%). This is in agreement with previously published data [8,12], however, our data did not reach statistical significance. This is probably due to the small population size of our study. Nevertheless, clinical lymph node

metastasis prior to NAC was significantly associated with cancer recurrence in our study.

Taking together the results of the present and previous studies, the clinical stage before NAC is more important than the definition of pCR. Trastuzumab was given to all HER2-positive patients at the neoadjuvant setting. Therefore, we observed a pCR with the highest percentage of 54.3% in the HER2-positive patients. Although trastuzumab was given for a total of 1 year, post-pCR cancer recurrence was observed more frequently and the prognosis was worse in the HER2-positive patients than in the HER2-negative patients (Fig. 2B). Notably, HER2 diseases most frequently metastasized to the brain as the first site. This may be due to the affinity between HER2-positive breast cancer and brain metastasis [13,14]. This supports the suggestion of previous reports [15–17] that trastuzumab does not pass through the blood-brain barrier, at least until the barrier is disrupted by brain metastases or whole-brain radiation.

An important observation of our present study is that local recurrence was rare among the patients with pCR (2%). If local recurrence occurs frequently after achieving pCR, more substantial local control would be necessary. However, if local recurrence occurs rarely, we can assume that local control does not significantly affect the development of cancer recurrence after achieving pCR. Recently, it has been reported that image-guided fine-needle aspiration biopsy and vacuum-assisted core biopsy can identify a breast pCR with an accuracy of 98% (95% CI, 87%–100%) [2]. Furthermore, pCR following NAC can be identified with highly accuracy by developed multi-parametric MR imaging, regardless of the definition of pCR as ypT0 or ypT0/is [3,18]. Thus, our observations highlight the importance of conducting a future observational study to determine whether surgery can be omitted if pCR could be diagnosed accurately by image-guided percutaneous biopsies. We included residual lymph node metastasis in the assessment of pCR because it is possible to assess residual cancer in the breast without surgery using current technologies. However, the detection of residual cancer in lymph nodes is difficult without performing axillary dissection. We believe that our outcome assessment approach is practically useful when considering future observational studies regarding the possibility of omitting surgery in patients of whom pCR is highly expected.

This study also provided important materials for further understanding of the molecular and genetic changes of paired tumor samples from the primary lesion before NAC and from the recurrent lesion. These materials will provide important information and insights regarding the characteristics associated with a drug response or tumor recurrence.

In conclusion, in this study, breast cancer patients achieving pCR after NAC showed excellent long-term outcomes. The clinical stage, particularly the lymph node status before NAC, and HER2 positivity were more important predictors of cancer recurrence in patients with pCR than residual ductal lesion in the breast and lymph node metastasis after NAC.

Declarations of interest

None.

Disclosure

There are no financial or other interests with regard to the submitted manuscript that might be construed as a conflict of interest.

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