Stratification of Prognosis by Biological Features Following Neoadjuvant Chemotherapy in Luminal Breast Cancer

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Abstract. *Background/Aim:* There are few models predicting breast cancer prognosis among patients receiving neoadjuvant chemotherapy (NAC) for estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative (luminal) breast cancer. We examined whether biological features (BFs) of residual tumors are prognostic factors following NAC. *Patients and Methods:* We enrolled patients with remnant tumors following NAC for luminal breast cancer and evaluated clinical stage, pathological stage, BFs prior to NAC, and BFs following NAC as prognostic factors. BFs were divided into high and low risk using the previously reported YR-IHC4 model calculated according to ER, progesterone receptor (PgR), HER2, and the proliferation marker Ki-67. *Results:* A total of 57 patients were enrolled in the current study. We observed a statistically significant difference in relapse-free survival (RFS) between the BF risk categories via YR-IHC4 predictions following NAC ($p=0.044$). The 5-year RFS rates of the BF low- and high-risk groups following NAC were 84.2% and 52.5%, respectively. *Conclusion:* BFs of residual tumors following NAC may be important prognostic factors in luminal breast cancer.

Patients with breast cancer who achieve pathological complete response (pCR) following neoadjuvant chemotherapy (NAC) are reported to have improved event-free survival and overall survival (OS) (1). However, response-guided treatment

following NAC has recently been administered to patients without pCR. For example, in patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer who present with residual invasive disease following NAC, prognoses were improved by changing the postoperative treatment to trastuzumab emtansine (from trastuzumab) (2).

Estrogen receptor (ER)-positive/HER2-negative (luminal) breast cancer, which accounts for 60-70% of all breast cancers (3, 4), has a low pCR rate (5) and lacks management evidence with respect to non-pCR cases. Thus, there is a need to identify non-pCR luminal breast cancer cases with high risk of recurrence.

Biological features (BFs) and conventional anatomical factors are important prognostic factors (6). Oncotype DX recurrence scores (RS) are available as a means of expressing the BFs as predictive factors with respect to chemotherapy and overall prognostic factors (7). There are some reports that RS can be predicted using four immunostaining markers [ER, progesterone receptor (PgR), HER2, and Ki-67] that are measured in daily clinical practice (8, 9). We also previously reported a model based on these four factors to predict RS ≥ 26 (10). The cutoff value of 26 points is a guide in the TAILORx (11) and RxPONDER (12) trials.

Ueno *et al.* (13) reported that, in neoadjuvant endocrine therapy (NET), the combination of pre- and post-treatment RS provides pivotal information for predicting prognosis. However, to our knowledge, no study has examined the prediction of prognosis based only on the BFs of the residual tumors following NAC, in which physiology changes more dramatically than that following NET. In cases where NAC is performed, the BFs of remnant tumors following chemotherapy, compared to the initial BFs, may correlate with prognosis more strongly.

Herein, we examined whether the BFs of residual tumors following NAC could be a prognostic factor in luminal breast cancer. Our previously reported model was used to represent these BFs.

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Key Words: Breast cancer, biological features, neoadjuvant chemotherapy, prognostic factors.

Patients and Methods

Patients. Of 1,874 consecutively presenting patients who underwent surgery for primary breast cancer at Yokohama Rosai Hospital between June 2012 and August 2020, 63 had luminal breast cancer and underwent NAC. Six patients achieved pCR, and the remaining 57 patients had remnant tumors; these 57 patients were enrolled in this study. The study was approved by the Yokohama Rosai Hospital Ethics Committee (no. 2021-25) and was conducted in accordance with the principles of the Declaration of Helsinki and its later amendments. Consent was obtained using an opt-out system.

Immunohistochemical staining. Immunohistochemical (IHC) staining for ER, PgR, and Ki-67 was conducted using a Benchmark Ultra automated stainer and an Aperio ScanScope AT Turbo within the I-VIEW DAB Universal Kit (Roche Diagnostics KK, Tokyo, Japan). Quantitative scores, which were expressed as the proportion of positively stained cells for each marker, were calculated. Five areas were randomly selected, and approximately 1,000 cells were counted in each area to obtain the average scores for each marker. According to previous research, ER positivity is defined as an ER-positive cell rate of >10% (14). IHC staining for HER2 was performed using a DAKO Autostainer Link 48 (Agilent Technologies, Ltd., Tokyo, Japan) and the DAKO HercepTest II Kit (DAKO, Glostrup, Denmark). IHC staining for HER2 was evaluated based on the following scoring system: 0+, 1+, 2+, and 3+. The criterion for HER2 negativity was a score of 0+, 1+, or 2+, with a fluorescence *in situ* hybridization score of <2.0 (15).

Risk categories of BF_s via the discriminant function. We previously demonstrated that a model based on four markers (ER, PgR, HER2, Ki-67) could predict RS ≥ 26 (10). The discriminant function was as follows: $YR-IHC4 = 1 / \{1 + \exp[-(4.611 + 1.2342 \times HER2 - 0.0813 \times ER - 0.0489 \times PgR + 0.0857 \times Ki-67)]\}$. Quantitative values (*i.e.*, the proportion of positively stained cells for each marker) were used for the above modes for ER, PgR, and Ki-67, whereas scores of 0, 1, and 2 were used for HER2. The cut-off point for YR-IHC4 was 0.5. If YR-IHC4 was ≥ 0.5 , the case was defined as high risk; and if YR-IHC4 was <0.5, the case was defined as low risk.

TNM classification. Anatomical staging was assessed using the Union for International Cancer Control (UICC) tumor node metastasis (TNM) classification, 8th edition (16).

Neoadjuvant chemotherapy indication and regimens. NAC was performed according to BF_s and anatomical staging, based on the physician's discretion. NAC includes both anthracycline-based and taxane-based regimens. Dose modification was performed because of adverse events according to patient or physician request.

One of the following regimens was implemented as an anthracycline-based regimen: four cycles of FEC (cyclophosphamide 500 mg/m², epirubicin 100 mg/m², fluorouracil 500 mg/m²) every 3 weeks, four cycles of EC (cyclophosphamide 600 mg/m², epirubicin 90 mg/m²) every 3 weeks, or four cycles of dose-dense EC (cyclophosphamide 600 mg/m², epirubicin 90 mg/m²) every 2 weeks.

One of the following regimens was used as a taxane-based regimen: four cycles of docetaxel (75 mg/m²) every 3 weeks, 12 cycles of

paclitaxel (80 mg/m²) on a weekly basis, or 4 cycles of dose-dense paclitaxel (175 mg/m²) every 2 weeks.

Adjuvant therapy following surgery. Endocrine therapy was performed postoperatively. Tamoxifen was used for premenopausal patients, and aromatase inhibitors were used for postmenopausal patients. However, this regimen was changed as appropriate based on occurrence of adverse events. Irradiation was performed for cases requiring breast-conserving surgery and in those with axillary lymph node metastasis prior to NAC. In cases that had undergone total mastectomy with three or fewer lymph node metastases following NAC, radiation therapy was not administered following a discussion between the patient and the physician. Capecitabine was likewise administered following discussions between the physician and the patient.

Prognostic factors. We evaluated the following prognostic factors in the present study: clinical stage prior to NAC, pathological stage following NAC, risk category of BF *via* YR-IHC4 predictions prior to NAC, and risk category of BF *via* YR-IHC4 predictions following NAC.

Statistical analysis. Cox proportional hazard models were used to examine prognostic factors with respect to relapse-free survival (RFS) and OS *via* hazard ratios (HR) and 95% confidence intervals (CIs). RFS and OS were estimated using the Kaplan-Meier method. Statistical significance was defined based on a two-sided *p*-value <0.05. All statistical analyses were performed using Bell Curve software (version 3.20) for Excel (Social Survey Research Information, Tokyo, Japan).

Results

Patient characteristics. The medical and demographic characteristics of the patients included in the present study are shown in Table I. We enrolled 24 (42.1%) and 33 (57.9%) patients with cStage II and cStage III, respectively, as well as 16 (28.1%), 25 (43.8%), and 16 (28.1%) patients with pStage I, pStage II, and pStage III, respectively. Prior to NAC, there were 34 (59.6%) and 22 (38.5%) patients at low risk and high risk, respectively, according to the YR-IHC4 model. There was insufficient data to calculate YR-IHC4 predictions for one case. Following NAC, there were 43 (75.4%) and 14 (24.5%) patients at low risk and high risk, respectively.

Information regarding therapy after surgery is shown in Table II. Endocrine therapy after surgery was performed in 56 patients (98.3%). Radiation therapy was administered to 50 patients (87.7%). Capecitabine was administered to 23 patients (40.3%).

Relapse-free and overall survival. The median follow-up time in the current study was 46 months (range=8-110 months). The results of Cox proportional hazard analysis are shown in Table III. We observed a statistically significant difference in RFS between risk categories of BF *via* YR-

Table I. Patient medical and demographic characteristics.

Variable	Number of patients (%)
Age (year; median)	51 (29-71)
Menopausal status	
Premenopausal	31 (54.4)
Postmenopausal	26 (45.6)
Histological type	
Invasive ductal carcinoma	51 (89.4)
Other	3 (5.3)
Unknown	3 (5.3)
Nuclear grade before NAC	
1	7 (12.3)
2	26 (45.6)
3	23 (40.3)
Unknown	1 (1.7)
LVI before NAC	
Present	23 (40.3)
Absent	29 (50.9)
Unknown	5 (8.8)
cStage before NAC	
II	24 (42.1)
III	33 (57.9)
pStage after NAC	
I	16 (28.1)
II	25 (43.8)
III	16 (28.1)
BF prior to NAC	
Low-risk	34 (59.6)
High-risk	22 (38.5)
Unknown	1 (1.7)
BF following NAC	
Low risk	43 (75.4)
High risk	14 (24.5)

NAC: Neoadjuvant chemotherapy; LVI: lymphovascular invasion; BF: biological feature.

IHC4 predictions following NAC, with an HR of 3.578 (1.033-12.388; $p=0.044$). No statistically significant differences in OS were observed for any of the prognostic factors. Kaplan-Meier curves for RFS are shown in Figure 1. The 5-year RFS rates were 84.2% and 52.5% in the low-risk and high-risk groups of BFs *via* YR-IHC4 predictions following NAC, respectively.

Discussion

To the best of our knowledge, this is the first report to show that prognosis is stratified only by BFs of residual tumors following NAC.

Several previous studies have examined prognosis prediction following NAC. Colleoni *et al.* (17) reported a nomogram predicting disease-free survival (DFS) in patients without pCR following NAC. In their study, five-year DFS was predicted based on factors including pathological tumor size, the number of positive lymph nodes, ER expression, HER2 status, Ki-67,

Table II. Descriptive statistics for adjuvant therapy performed following surgery.

Therapy	Number of patients (%)
Endocrine therapy	
Performed	56 (98.3)
Not performed	1 (1.7)
Radiation therapy	
Performed	50 (87.7)
Not performed	7 (12.3)
Chemotherapy (Capecitabine)	
Performed	23 (40.3)
Not performed	34 (59.6)

Table III. Associations observed within Cox proportional hazard models.

Variable	RFS		OS	
	HR (95%CI)	p -Value	HR (95%CI)	p -Value
cStage		0.240		0.613
Stage II	Referent		Referent	
Stage III	2.259 (0.579-8.819)		2.048 (0.126-33.075)	
pStage		0.068		0.255
Stage I/II	Referent		Referent	
Stage III	3.189 (0.916-11.096)		5.000 (0.312-79.937)	
BF prior to NAC		0.898		-
Low-risk	Referent		-	
High-risk	0.920 (0.259-3.265)		-	
BF following NAC		0.044		0.325
Low-risk	Referent		Referent	
High-risk	3.578 (1.033-12.388)		4.053 (0.249-65.798)	

HR: Hazard ratio; NAC: neoadjuvant chemotherapy; OS: overall survival; RFS: relapse-free survival; BF: biological feature.

and vascular invasion. Another evaluation method, the CPS+EG staging system incorporating ER status, tumor grade with pretreatment clinical stage (CS), and post-treatment pathologic stage (PS), has likewise been reported and is well discussed (18-21). These studies differ from the present study in that they addressed anatomical factors and included HER2-positive cases and did not evaluate PgR, which is a strong prognostic factor for luminal breast cancer (22). In addition, ER status prior to NAC was evaluated using the CPS+EG Staging System. In contrast, our research focuses on luminal breast cancer and only on the BFs of residual tumors.

We observed that clinical stage and BFs prior to NAC did not stratify prognoses. There may be bias underlying these

Figure 1. Kaplan-Meier curves for relapse-free survival (RFS). The 5-year RFS rates were 84.2% and 52.5% in the low-risk and high-risk groups of biological features via YR-IHC4 predictions following neoadjuvant chemotherapy, respectively.

findings in that patients with a good prognosis who do not require chemotherapy or pCR following NAC were not enrolled in the current investigation. On the contrary, although a statistically significant difference was not observed, we found that RFS was stratified based on pathological stage. Thus, if the number of cases is large, pathological stage may also be an important factor. With respect to OS, no statistically significant differences were observed for any of the prognostic factors in the current investigation. This could be because the sample size was small, and the prognosis for luminal breast cancer is relatively long, therefore, it is hard to make a significant difference.

Recently, response-guided treatment following NAC has been performed for non-pCR cases as an escalation therapy. Masuda *et al.* (23) reported that the addition of capecitabine, an oral fluoropyrimidine, prolongs DFS and OS among patients with HER2-negative breast cancer who present with residual tumors following NAC. In our study, capecitabine was administered to 23 of the 57 enrolled patients (40.3%). We note that the present study includes cases enrolled prior to the initiation of the above trial. Rather than administering capecitabine to all non-pCR cases, the strategy of

administering capecitabine only to high-risk cases among non-pCR cases may be beneficial to patients as well as in consideration of medical costs. In the present study, as the number of enrolled cases was small, it was not possible to examine the additional benefit of capecitabine. The results of the Monarch E trial were announced in 2020 (24); the results demonstrated that in patients with luminal high-risk breast cancer, the CDK4/6 inhibitor abemaciclib in addition to endocrine therapy demonstrated superior DFS compared to endocrine therapy alone. For high-risk cases following NAC, CDK4/6 inhibitors have shown promise. Conversely, low-risk cases may not require escalation therapy even in non-pCR cases. The present study results provide important insights for identifying cases requiring additional treatment among non-pCR cases following NAC for luminal breast cancer. This is important as a de-escalation within escalation therapy. Evaluating the kind of additional treatment that should be administered to various non-pCR cases is an urgent issue that should be addressed comprehensively in future investigations.

The present study has several limitations. First, the YR-IHC4 model used in the present study has not been proven or validated in a large-scale clinical trial. Originally, RS have been shown to predict prognosis based on specimens obtained prior to chemotherapy; therefore, it is unclear whether these predictions are applicable to specimens obtained following NAC. In addition, the current study was conducted at a single institution with a small patient population; furthermore, the study design was retrospective. Future prospective multi-center studies with larger cohorts are necessary in order to validate our findings.

Conclusion

In the current study, we demonstrated that the biological features of residual tumors evaluated following NAC may be important prognostic factors in luminal breast cancer. In the future, we aim to create a model identifying vulnerable sub-populations with poor prognoses following NAC for luminal breast cancer in a high-powered multi-center investigation with a larger number of enrolled patients and to conduct prospective randomized trials regarding additional treatment modalities for this population with a poor prognosis.

Conflicts of Interest

The Authors have no conflicts of interest to disclose in relation to this study.

Authors' Contributions

SY designed the study, collected the samples and clinical data, performed statistical analyses, and wrote the article. TC collected the samples and clinical data, designed the study, and revised the

article. YS, SI, FH, and HT collected samples and clinical data. AY, KN, and IE have revised the manuscript. All Authors have read and approved the final version of the manuscript.

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