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Original

Histological Evaluation of Therapeutic Effect and RCB (Residual Cancer Burden) Index in Primary Breast Cancer Operated after Neoadjuvant Chemotherapy : Retrospective Study of the Clinicopathological Findings and Prognosis

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Abstract : The therapeutic effect found histologically after surgery following neoadjuvant chemotherapy (NAC) correlates with patient prognosis. Such correlations must consider the remaining invasive lesions as well as intra-ductal components and lymph node metastasis. To this end, we compared the residual cancer burden (RCB) index with the conventional method of judging the histopathological therapeutic effect. We also took into account the clinicopathological features of patients related to recurrence and prognosis by the RCB index. We studied 244 cases of primary breast cancer in 238 patients who had undergone surgery after NAC in Showa University Hospital from 2005 to 2014. We classified the cases into groups based on the Japanese Breast Cancer Society's criteria for evaluating the histological therapeutic effect and the RCB index. The cases were also analyzed in regard to various clinicopathological factors. The prognosis was evaluated by drawing recurrence-free survival curves using the Kaplan-Meier method, and the log rank test was used to test statistical significance. The RCB index was evaluated for cases of Grade 0–1b that had a certain degree of residual tumor tissue. Comparison of the recurrence-free survival rates in each of the RCB index groups indicated a significant correlation, although only for patients with some degree of residual malignancy even after chemotherapy. We conclude that the RCB index can be used for providing a more precise prediction of recurrence.

Key words : breast cancer, neoadjuvant chemotherapy (NAC), RCB (residual cancer burden) index, pathology, surgery

Introduction

Patients with invasive breast cancer that is operable show similar survival whether they

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undergo surgery following neoadjuvant chemotherapy (NAC) or have surgery first and then receive chemotherapy[1–3]. Also, the histological therapeutic effect seen in surgical specimens following NAC correlates with patient prognosis, with long-term survival achieved particularly in patients diagnosed as having achieved a pathological complete response (pCR)[2,4]. A meta-analysis of 12 recent clinical studies of NAC for breast cancer reported that pCR can serve as a surrogate endpoint for event-free survival (EFS) and / or overall survival (OS)[5]. In general, the most commonly used criteria for histological evaluation are the diagnostic criteria of Fisher *et al*[4] used in the NSABP B-18 study ; however, that study assumed that no invasive lesions remained, and intra-ductal components and lymph node metastasis were not taken into account. The later NSABP B-27 study evaluated intraductal components in addition to the diagnostic criteria of Fisher *et al*[6]. In addition, a recent report recommended that the residual presence of lymph node metastases should also be evaluated[5]. We therefore consider that the histological evaluation criteria used in such cases need to be clarified, of course taking into account the objectivity and reproducibility of histological evaluations.

The residual cancer burden (RCB) index proposed by Symmans *et al*[7] has been used in numerous large-scale clinical studies, including I-SPY (1, 2), GEICAM, ACOSOG (Z11103), CALGB (40601, 40603), NSABP (B-40, B-41), and ABCSG (3, 4), and its reproducibility has been evaluated[8]. Based on this background, we compared the RCB index with the conventional method of judging the histopathological therapeutic effect, that is, by evaluating the status of residual invasive lesions. We also investigated the significance of clinicopathological features and recurrence for prognosis by the RCB index.

Materials and methods

Methods

The subjects of this study were 244 cases of primary breast cancer in 238 patients who had undergone surgery after NAC in Showa University Hospital from 2005 to 2014. All the subjects were women, and 6 patients had bilateral synchronous breast cancer.

We collected the clinical and pathological information about the study subjects into a database, and then performed a retrospective survey of the medical records regarding postoperative recurrence and death. We classified the cases into two groups (Grade 0, 1a, 1b, 2a and Grade 2b, 3) based on the Japanese Breast Cancer Society's criteria for evaluating the histological therapeutic effect. We also classified them into two groups (RCB-0, 1 and RCB-2, 3) after calculating the RCB index for each case. The cases were analyzed in regard to various clinicopathological factors including age, clinical stage, histological type, vascular invasion, lymph node metastasis, biomarkers, chemotherapy regimen, surgical procedure, recurrence, and death, and analyzed using the t-test and chi-square test. Prognosis was evaluated by drawing recurrence-free survival curves using the Kaplan-Meier method, and the log rank test was used to test for statistical significance.

The biomarker findings were classified as follows : ≥ 10% ER•PgR was defined as positive, for HER2 only score 3 was considered positive, and ≥ 30% Ki67 was defined as positive.

Japanese Breast Cancer Society's criteria

These criteria classify cases into Grade 0 to Grade 3 based on the histological therapeutic effect. Details are described in Table 6[9].

RCB index

The extent of residual disease (RD) in the post-treatment surgical resection specimen could be determined from the bi-dimensional diameters of the primary tumor bed in the resection specimen (d_1 and d_2), the proportion of the primary tumor bed that contains invasive carcinoma (f_{inv}), the number of axillary lymph nodes containing metastatic carcinoma (LN), and the diameter of the largest metastasis in an axillary lymph node (d_{met}). If multiple tumors were present, the dimensions of the largest tumor were recorded. Bi-dimensional measurements of the primary tumor bed (millimeters) were combined as follows:

$$d_{prim} = \sqrt{d_1 d_2}$$

The proportion of invasive carcinoma (f_{inv}) within the cross sectional area of the primary tumor bed was estimated from the overall percent area of carcinoma ($\%CA$), and then corrected for the component of *in situ* carcinoma ($\%CIS$):

$$f_{inv} = (1-(\%CIS / 100)) \times (\%CA/100)$$

From the above, we defined the RCB index as follows:

$$\text{RCB} = 1.4\ (f_{inv}\, d_{prim})^{0.17} + [4(1-0.75^{LN})\ d_{met}]^{0.17}\ \text{(Fig. 1, 2)}$$

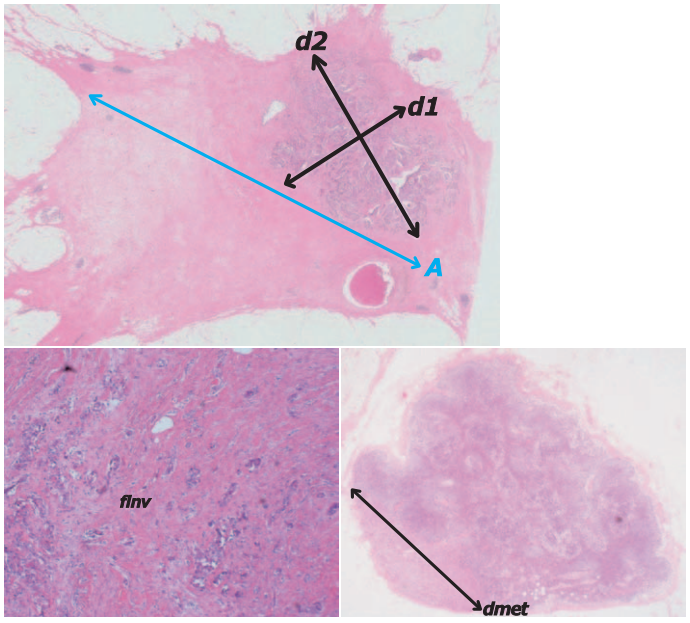
They identified two cutoff points to assign patients with RD (not RCB-0) after NAC into one of three classes: RCB-1 (minimal RD), RCB-2 (moderate RD), and RCB-3 (extensive RD). Two cutoff points were determined sequentially by maximizing the profile log-likelihood of a multivariate Cox model that included the clinical covariates and the dichotomized RCB index. The first cutoff point (RCB-3 and RCB-1/2) was selected as the 87th percentile (RCB, 3.28), and the second (RCB-1 and RCB-2) corresponds to the 40th percentile (RCB, 1.36)[7].

Results

Data on patient background characteristics for the 244 cases are compiled in Table 1. The mean patient age was 51.6 years, and the mean duration of follow-up was 30.5 (6–120) months. Recurrence was seen in 38 cases, and 11 cases died. The mean time from surgery until recurrence was 28.2 months, and the mean time until death was 46.1 months.

No striking differences were found in the distributions of the disease stage in each group based on the pretreatment stage, using the defined criteria for evaluating the histological therapeutic effect according to the General Rules for Clinical and Pathological Recording of Breast Cancer or when using the RCB index (Table 2).

Table 3 details the clinicopathological factors for each of the histological therapeutic effect evaluation criteria of the General Rules for Clinical and Pathological Recording of Breast Cancer.



$$\mathrm{RCB} = 1.4\ (f_{inv} d_{prim})^{0.17} + [4(1-0.75^{LN})\ d_{met}]^{0.17}$$

$$d_{prim} = \sqrt{d_1 d_2}$$

$$f_{inv} = (1-(\%\ CIS\ /\ 100)) \times (\%\ CA\ /\ 100)$$

Fig. 1. RCB index

The pathological variables included bi-dimensional diameters of the primary tumor bed (d_1, d_2), the proportion of primary tumor area containing invasive carcinoma (f_{inv}), the number of positive lymph nodes (LN), and the diameter of the largest nodal metastasis (d_{met}). The diameter indicated the tumor that existed before NAC (A). The proportion of invasive carcinoma (f_{inv}) within the cross-sectional area of the primary tumor bed was estimated from the overall percent area of carcinoma (% CA), and then corrected for the component of in situ carcinoma (% CIS).

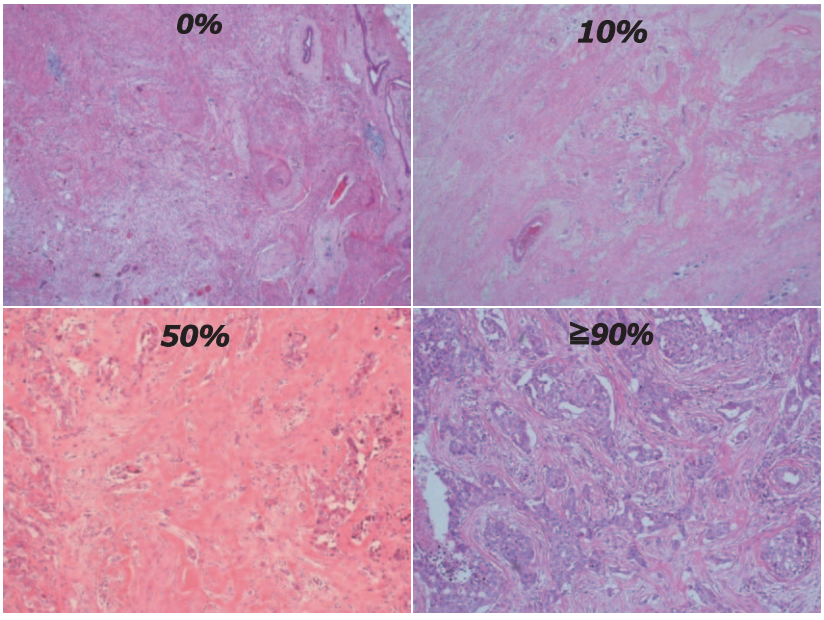


Fig. 2. The overall percent area of carcinoma (% CA)

We evaluated the overall percent area of carcinoma (% CA) like these figures to calculate RCB index.

Table 1. Patient background characteristics

		n = 244	
Age	Mean (Range)	51.6 (26–74)	
T stage	T1	60	24.6%
	T2	124	50.8%
	T3	22	9.0%
	T4	36	14.8%
	Uncertain	2	0.8%
N stage	N0	137	56.1%
	N1	97	39.8%
	N2	3	1.2%
	N3	5	2.0%
	Uncertain	2	0.8%
M stage	M (+)	3	1.2%
	M (−)	239	98.0%
	Uncertain	2	0.8%
Histlogic type	IDC	227	93.0%
	Special type	17	7.0%
Biomarker	ER (+)	138	56.6%
	ER (−)	97	39.8%
	Uncertain	9	3.6%
	PgR (+)	106	43.4%
	PgR (−)	127	52.0%
	Uncertain	11	4.6%
	HER2 (+)	58	23.8%
	HER2 (−)	177	72.5%
	Uncertain	9	3.7%
	Ki67 (+)	106	43.4%
	Ki67 (−)	93	38.1%
	Uncertain	45	18.5%
Chemotherapy	FEC	9	
	FEC→PTX (+Her)	67(+9)	
	FEC→DTX (+Her)	88(+31)	
	FEC→TC+Her	1	
	FEC→GEM+Carboplatin	4	
	Bev+PTX	3	
	Pertuzumab+DTX+Her	2	
	Bev+PTX+Eribulin	1	
	DTX+CPA+HER	1	
	TC (+Her)	12(+5)	
	PTX (+Her)	5(+1)	
	DTX	3	
	Uncertain	2	
Operation	Partial resection	111	45.5%
	Total resection	133	54.5%
Recurrence	None	206	84.2%
	Local recurrence	2	1.0%
	Distant recurrence	36	14.8%
Death	None	233	95.3%
	Death with recurrence	10	4.3%
	Death of other disease	1	0.4%

(Lung metastasis of ovarian cancer)

There was a tendency for the diameter of invasive tumor and the degree of vascular invasion and lymph node metastasis to increase as the percentage of residual invasive lesions increased. Stratification of the biomarker findings indicated that, compared with the overall distributions, the group diagnosed with Grade 0, 1a, 1b, 2a showed a tendency for more ER (+), HER2 (−), ki67 $<$ 30% cases, while the Grade 2a, 3 group showed a tendency for more ER (−), HER2 (+) and ER (−), HER2 (−), ki67 $\geq$ 30% cases. In addition, the rates of recurrence and death were low for the Grade 2b, 3 cases, at 7.7% and 0.0%, whereas the rates were 17.7% and 5.8%, respectively, in the Grade 0, 1a, 1b, 2a group of patients; however, these differences were not significant.

Table 4 represents the stratification of clinicopathological factors for each RCB index group. Stratification of the biomarker findings indicated that, compared with the overall distributions, RCB-0, 1 showed a tendency for more cases of ER (−), HER2 (+), while RCB-2, 3 showed a tendency for more cases of ER (+), HER2 (−), ki67 $<$ 30%. In addition, there were no significant differences between the groups for rates of recurrence and death.

Table 2. The pretreatment stages

	T					N					M		
	T 1	T 2	T 3	T 4	Uncertain	N 0	N 1	N 2	N 3	Uncertain	M(+)	M(−)	Uncertain
Grade 0, 1	38	76	13	25	1	83	65	2	2	1	2	150	1
153	24.8%	49.7%	8.5%	16.3%	0.7%	54.2%	42.5%	1.3%	1.3%	0.7%	1.3%	98.0%	0.7%
Grade 2	11	25	5	6	0	31	16	0	0	0	0	47	0
47	23.4%	53.1%	10.6%	12.8%	0.0%	66.0%	34.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%
Grade 3	11	23	4	5	1	23	16	1	3	1	1	42	1
44	25.0%	52.3%	9.1%	11.4%	2.3%	52.3%	36.4%	2.3%	6.8%	2.3%	2.3%	95.4%	2.3%
RCB-0	9	20	4	4	1	22	13	1	1	1	0	37	1
38	23.7%	52.6%	10.5%	10.5%	2.6%	57.9%	34.2%	2.6%	2.6%	2.6%	0.0%	97.4%	2.6%
RCB-1	14	25	6	5	1	36	13	0	1	1	1	49	1
51	27.5%	49.0%	11.8%	9.8%	2.0%	70.6%	25.5%	0.0%	2.0%	2.0%	2.0%	96.0%	2.0%
RCB-2	29	60	9	17	0	69	44	1	1	0	1	114	0
115	25.2%	52.2%	7.8%	14.8%	0.0%	60.0%	38.3%	0.9%	0.9%	0.0%	0.9%	99.1%	0.0%
RCB-3	8	19	3	10	0	10	27	1	2	0	1	39	0
40	20.0%	47.5%	8.7%	25.0%	0.0%	25.0%	67.5%	2.5%	5.0%	0.0%	2.5%	97.5%	0.0%
All cases	60	124	22	36	2	137	97	3	5	2	3	239	2
244	24.6%	50.8%	9.0%	14.8%	0.8%	56.1%	39.8%	1.2%	2.0%	0.8%	1.2%	98.0%	0.8%

Table 3. Clinicopathological data for the Grade 0, 1a, 1b, 2a and Grade 2b, 3 groups

			All cases 244		Grade 0, 1, 2a 192 (78.7%)		Grade 2b, 3 52 (21.3%)		*p value* < 0.05
Age	Mean (Range)		51.6 (26-74)		52.1 (26-74)		51 (34-71)		0.2176
Tumor diameter (mm)	Mean (Range) (mm)		17.9 (0-105)		22.1 (0-105)		0.09 (0-3)		< 0.0001*
Vessel invasion	ly (+)		29	11.9%	29	15.1%	0	0.0%	0.0023*
	v (+)		3	1.2%	3	1.6%	0	0.0%	0.3644
Lymph node metastasis	N (+)		82	33.6%	78	40.6%	0	0.0%	< 0.0001*
Biomarker	ER+, HER2−	ki67 ≧ 30%	31	12.7%	26	13.5%	5	9.6%	0.4508
		ki67 < 30%	68	27.9%	66	34.4%	2	3.8%	< 0.0001*
		Uncertain	16	6.6%	16	8.3%	0	0.0%	
	ER+, HER2+	ki67 ≧ 30%	11	4.5%	8	4.2%	3	5.8%	0.6213
		ki67 < 30%	9	3.7%	6	3.1%	3	5.8%	0.3695
		Uncertain	3	1.2%	3	1.6%	0	0.0%	
	ER−, HER2+	ki67 ≧ 30%	21	8.6%	10	5.2%	11	21.2%	0.0003*
		ki67 < 30%	6	2.5%	2	1.0%	4	7.7%	0.0060*
		Uncertain	8	3.3%	6	3.1%	2	3.8%	
	ER−, HER2−	ki67 ≧ 30%	43	17.6%	28	14.6%	15	28.8%	0.0166*
		ki67 < 30%	10	4.1%	10	5.2%	0	0.0%	0.0929
		Uncertain	9	3.7%	5	2.6%	4	7.7%	
	Uncertain		9	3.7%	6	3.1%	3	5.8%	
Recurrence	−		206	84.4%	158	82.3%	48	92.3%	
	+		38	15.6%	34	17.7%	4	7.7%	0.0772
Death	−		233	95.5%	181	94.2%	52	100.0%	
	+		11	4.5%	11	5.8%	0	0.0%	0.0773
Observation period	Mean (Range) (Months)		30.5 (6-120)		31.6 (6-120)		28.1 (6-93)		0.4842

Table 4. Clinicopathological data for the RCB-0, 1 and RCB-2, 3 groups

			All cases 244		RCB-0, 1 89, 36.5%		RCB-2, 3 155, 63.5%		*p value* < 0.05
Age	Mean (Range)		51.6 (26–74)		51.8 (31–74)		51.5 (26–74)		0.9809
Tumor diameter (mm)	Mean (Range) (mm)		17.9 (0–105)		4.47 (0–35)		27.1 (0–105)		< 0.0001*
Vessel invasion	ly (+)		29	11.9%	2	2.2%	27	17.4%	0.0013*
	v (+)		3	1.2%	0	0.0%	3	1.9%	0.1866
Lymph node metastasis	N (+)		82	33.6%	2	2.2%	80	51.6%	< 0.0001*
Biomarker	ER+, HER2−	ki67 ≧ 30%	31	12.7%	11	12.4%	20	12.9%	0.6016
		ki67 < 30%	68	27.9%	7	7.9%	61	39.4%	< 0.0001*
		Uncertain	16	6.6%	3	3.4%	13	8.4%	
	ER+, HER2+	ki67 ≧ 30%	11	4.5%	4	4.5%	7	4.5%	0.9937
		ki67 < 30%	9	3.7%	6	6.7%	3	1.9%	0.0552
		Uncertain	3	1.2%	0	0.0%	3	1.9%	
	ER−, HER2+	ki67 ≧ 30%	21	8.6%	14	15.7%	7	4.5%	0.0026*
		ki67 < 30%	6	2.5%	5	5.6%	1	0.6%	0.0158*
		Uncertain	8	3.3%	7	7.9%	1	0.6%	
	ER−, HER2−	ki67 ≧ 30%	43	17.6%	20	22.5%	23	14.8%	0.132
		ki67 < 30%	10	4.1%	2	2.2%	8	5.2%	0.2691
		Uncertain	9	3.7%	5	5.6%	4	2.6%	
	Uncertain		9	3.7%	5	5.6%	4	2.6%	
Recurrence	−		206	84.4%	78	87.6%	128	82.6%	
	+		38	15.6%	11	12.4%	27	17.4%	0.2941
Death	−		233	95.5%	86	93.3%	147	94.2%	
	+		11	4.5%	3	6.7%	8	5.8%	0.5164
Observation period	Mean (Range) (Months)		30.5 (6–120)		31.3 (6–120)		29.9 (8–110)		0.3378

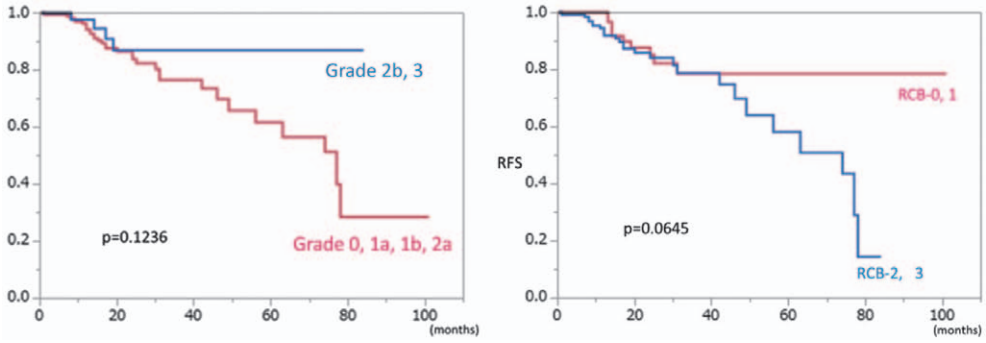


Fig. 3. Recurrence-free survival (RFS) analysis
The left graph represents the analysis for the Grade 0, 1a, 1b, 2a and Grade 2b, 3 groups based on the histological therapeutic effect evaluation criteria of the Japanese Breast Cancer Society. The right graph represents the analysis for the RCB-0, 1 and RCB-2, 3 groups based on the RCB index. The recurrence-free survival plots were compared, but the analyses revealed no statistically significant differences ($P = 0.1236$ and $P = 0.0645$).

Analysis of the recurrence-free survival plots is represented in Fig. 3, with the graph on the left showing the Grade 0, 1a, 1b, 2a and Grade 2a, 3 groups based on the histological therapeutic effect evaluation criteria of the Japanese Breast Cancer Society. The right plot shows the curves

Table 5. Clinicopathological data of the RCB-0, 1 and RCB-2, 3 group for cases of Grade 0-1b

			Grade 0-1b 153		RCB-1 17, 11.1%		RCB-2, 3 136, 88.9%		*p value* < 0.05
Age	Mean (Range)		52.3 (31-74)		57.2 (38-74)		51.7 (31-74)		0.1037
Tumor diameter (mm)	Mean (Range) (mm)		27.2 (1-105)		11.8 (1-35)		29.2 (4-105)		< 0.0001*
Vessel invasion	ly (+)		24	15.7%	2	11.8%	22	16.2%	0.6928
	v (+)		3	2.0%	0	0.0%	3	2.2%	0.5641
Lymph node metastasis	N (+)		69	45.1%	0	0.0%	69	50.7%	0.0002*
Biomarker	ER+, HER2-	ki67 ≧ 30%	19	12.4%	3	17.6%	16	11.8%	0.9099
		ki67 < 30%	59	36.8%	2	11.8%	57	41.9%	0.0075*
		Uncertain	14	5.7%	2	11.8%	12	8.8%	
	ER+, HER2+	ki67 ≧ 30%	5	3.3%	0	0.0%	5	3.7%	0.4535
		ki67 < 30%	5	3.3%	2	11.8%	3	2.2%	0.021*
		Uncertain	1	0.7%	0	0.0%	1	0.7%	
	ER-, HER2+	ki67 ≧ 30%	6	3.9%	0	0.0%	6	4.4%	0.41
		ki67 < 30%	1	0.7%	0	0.0%	1	0.7%	0.7408
		Uncertain	2	1.3%	1	5.9%	1	0.7%	
	ER-, HER2-	ki67 ≧ 30%	22	14.4%	1	5.9%	21	15.4%	0.3701
		ki67 < 30%	8	5.2%	1	5.9%	7	5.1%	0.7922
		Uncertain	5	3.3%	3	17.6%	2	1.5%	
	Uncertain		6	3.9%	2	11.8%	4	2.9%	
Recurrence	-		129	84.3%	16	94.1%	113	83.1%	
	+		24	15.7%	1	5.9%	23	16.9%	0.3118
Death	-		147	96.1%	17	100.0%	130	95.6%	
	+		6	3.9%	0	0.0%	6	4.4%	0.41
Observation period	Mean (Range) (Months)		30.4 (6-120)		37.2 (9-120)		30 (6-110)		0.0755

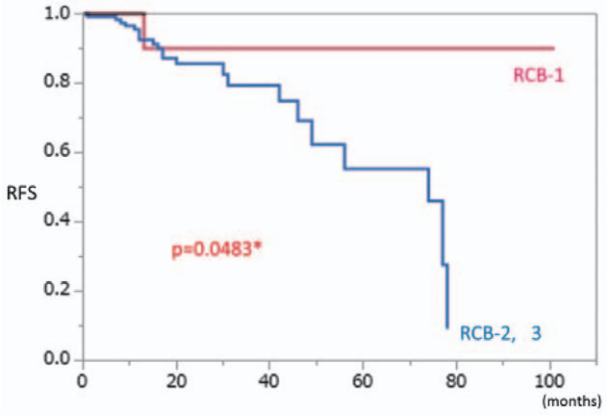


Fig. 4. Recurrence-free survival (RFS) analysis for cases of Grade 0-1b
This graph represents the analysis of the RCB-1 and RCB-2, 3 groups based on the RCB index for cases of Grade 0-1b. Comparison of recurrence-free survival rates between the RCB index groups indicated a significant correlation ($P = 0.0483^*$).

for the RCB-0, 1 and RCB-2, 3 groups based on the RCB index. Analyses of these recurrence-free survival plots revealed no statistically significant differences ($P = 0.1236$ and $P = 0.0645$).

Table 5 presents the stratification of clinicopathological factors for each RCB index group

for cases of Grade 0–1b that had a certain degree of residual tumor tissue, after excluding the cases of pCR and near pCR, which are considered to have a good prognosis. Stratification of the biomarker findings indicated that the percentage of ER (+), HER2 (−), ki67 < 30% cases tended to increase as the RCB index increased, whereas, conversely, the percentage of ER (+), HER2 (+), ki67 < 30% cases tended to decrease. There were no significant differences between the groups for rates of recurrence and death.

Analysis of the recurrence-free survival plots for cases of Grade 0–1b that had a certain degree of residual tumor tissue (Fig. 4) was performed for the RCB-1 and RCB-2, 3 groups based on the RCB index for cases of Grade 0–1b. Comparison of the recurrence-free survival rates in each of the RCB index groups indicated a significant correlation ($P = 0.0483$). These results indicate that RCB index can be used to predict outcomes. In addition, it seems that we can treat the cases of RCB-1 group almost equally to RCB-0 (pCR) cases.

Discussion

In this study, we used the RCB index as a means for evaluating the status of residual tumors and investigated the histological therapeutic effect based on criteria of the General Rules for Clinical and Pathological Recording of Breast Cancer, the clinical histopathological data, recurrence, and prognosis.

Reports to date have identified various prognostic factors in patients undergoing surgery following NAC. Those factors include the clinical stage, histological type, tumor diameter, axillary lymph node metastasis, vascular invasion, multifocal pattern of residual tumor, tumor necrosis, hormone receptors, positive rate of HER2, ki67 cells, menopausal status, and race (African-American)[10–15]. With respect to hormone receptors and positive rate of HER2, ki67 cells, our study supported these past reports. Concretely, the cases that had better effects of NAC showed a tendency for more cases in which estrogen receptor was negative, HER2 was positive, and ki-67 was high. In addition, most of these previous reports rated the tumor diameter and axillary lymph node metastasis as the most important prognostic factors[10–13], while a more recent study stated that it is better to use T0 N0 or T0/is N0 as the definition of pCR[5]. In our present paper, we used the RCB index, which not only considers the primary lesion and axillary lymph node metastasis, but also might represent a more accurate prognostic index since it is a numerical rating. Table 6 shows the other criteria used for evaluating the histological therapeutic effect[16].

The RCB index that we used herein has been employed in numerous clinical studies[8]. In addition, the reproducibility of the RCB index has been evaluated as high, with an RCB category concordance rate of 0.989[8]. One report stated that the following are important items that should be included in pathology reports: pCR/non-pCR, the T stage, N stage, and RCB index if not available, 2 perpendicular diameters of the tumor[17].

Our present results found a significant correlation between the RCB index and the recurrence-free survival period, although only for patients with some degree of residual malignancy even after chemotherapy. We therefore conclude that the RCB index can be used to elicit a more precise prediction of recurrence. However, the RCB index did not show a significant correlation with

Table 6. Other criteria used for evaluating the histological therapeutic effect

	Year	Criteria for evaluating the histological therapeutic effect		
The Japanese Breast Cancer Society's criteria	2012	Grade 0 (No Response)		Presence of little change in cancer cells
		Grade 1 (Partially Effective)	1a (Mild Effect)	Pleasence of changes in cancer cells inspite of the area, or severe changes in less than 1/3 cancer cells
			1b (Moderate Effect)	Presence of severe changes in more than 1/3 and less than 2/3 cancer cells
		Grade 2 (Quite Effective)	2a (High Effect)	Presence of severe changes in more than 2/3 cancer cells, but presence of cancer nest clearly
			2b (Extremely High Effect)	Presence of effect nearly Complete Response (Grade 3), but presence of extremely a little cancer cells
		Grade 3 (Complete Response)		Presence of necrosis, disappearance or replacement of glomerous or fibrous tissue in all cancer cells
NSABP B-18 criteria	1997	pCR		No recognizable invasive tumor cells present
		pPR		The presence of scattered individual or small clusters of tumor in a desmoplastic or hyaline stroma
		pNR		Tumors not exhibiting the changes listed above
Chevallier's grading system	1993	Class 1 (pCR)		Disappearance of all tumor
		Class 2 (pCR)		Presence of DCIS in the breast, no invasive carcinoma and negative lymph node
		Class 3 (pPR)		Presence of invasive carcinoma with stromal alteration
		Class 4 (pNR)		Few modifications of the tumoral appearance
Miller-Payne's grading system	2003	Grade 1 (pNR)		No change or some alteration to individual malignant cells, but no reduction in overall cellularity
		Grade 2 (pPR)		A minor loss of tumor cells, but overall cellularity still high ; up to 30% loss
		Grade 3 (pPR)		Between an estimated 30% and 90% reduction in tumor cells
		Grade 4 (almost pCR)		A marked disappearance of tumor cells such that only small clusters or widely dispersed indivisual cell remains ; >90% loss of tumor cells
		Grade 5 (pCR)		No malignant cells identifiable in sections from the site of the tumor ; only vascular fibroelastotic dstroma remains, often containing macrophages; however, ductal carcinoma in situ may be present
Sataloff's grading system	1995	Tumor	T-A	Total or near total therapeutic effect (pCR)
			T-B	>50% therapeutic effect, but less than total or near total (pPR)
			T-C	<50% therapeutic effect, but effect evident (pPR)
			T-D	No therapeutic effect (pNR)
		Node	N-A	Evidence of therapeutic effect, no metastatic disease
			N-B	No nodal metastasis or therapeutic effect
			N-C	Evidence of therapeutic effect, but nodal metastatasis present
			N-D	Viable metastatic disease, no therapeutic effect

survival. Noting that the mean 5-year survival was in excess of 90% for stage II breast cancer[18], for which chemotherapy is indicated, it is difficult to claim that a mean follow-up period of 30.5 months is even close to being sufficient. Thus, the issue of the duration of follow-up warrants further investigation.

Conflict of interest disclosure

The authors have declared no conflict of interest.

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