VOLUME 25 · NUMBER 28 · OCTOBER 1 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Measurement of Residual Breast Cancer Burden to Predict Survival After Neoadjuvant Chemotherapy

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Submitted January 5, 2007; accepted June 29, 2007; published online ahead of print at www.jco.org on September 4, 2007.

Supported by a research Grant No. DAMD17-02-1-0458 01 from Department of Defense Breast Cancer Research Program (W.F.S.) and the Nellie B. Connally Breast Cancer Research Fund.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/07/2528-4414/$20.00

DOI: 10.1200/JCO.2007.10.6823

ABSTRACT

Purpose
To measure residual disease after neoadjuvant chemotherapy in order to improve the prognostic information that can be obtained from evaluating pathologic response.

Patients and Methods
Pathologic slides and reports were reviewed from 382 patients in two different treatment cohorts: sequential paclitaxel (T) then fluorouracil, doxorubicin, and cyclophosphamide (FAC) in 241 patients; and a single regimen of FAC in 141 patients. Residual cancer burden (RCB) was calculated as a continuous index combining pathologic measurements of primary tumor (size and cellularity) and nodal metastases (number and size) for prediction of distant relapse-free survival (DRFS) in multivariate Cox regression analyses.

Results
RCB was independently prognostic in a multivariate model that included age, pretreatment clinical stage, hormone receptor status, hormone therapy, and pathologic response (pathologic complete response [pCR] *v* residual disease [RD]; hazard ratio = 2.50; 95% CI 1.70 to 3.69; $P < .001$). Minimal RD (RCB-I) in 17% of patients carried the same prognosis as pCR (RCB-0). Extensive RD (RCB-III) in 13% of patients was associated with poor prognosis, regardless of hormone receptor status, adjuvant hormone therapy, or pathologic American Joint Committee on Cancer stage of residual disease. The generalizability of RCB for prognosis of distant relapse was confirmed in the FAC-treated validation cohort.

Conclusion
RCB determined from routine pathologic materials represented the distribution of RD, was a significant predictor of DRFS, and can be used to define categories of near-complete response and chemotherapy resistance.

J Clin Oncol 25:4414-4422. © 2007 by American Society of Clinical Oncology

INTRODUCTION

A central tenet of neoadjuvant clinical trials is that tumor response, as a surrogate end point, should be strongly correlated with long-term patient survival.[1,2] Pathologic complete response (pCR) is associated with long-term survival, and has been adopted as the primary end point for neoadjuvant trials.[3-12] While it is generally held that a definition of pCR should include patients without residual invasive carcinoma in the breast (pT0), the presence of nodal metastasis, minimal residual cellularity, and residual in situ carcinoma are not consistently defined as pCR or residual disease (RD).[11-15] When there is no residual invasive cancer in the breast, the number of involved axillary lymph nodes is inversely related to survival.[11] Conversely, patients who convert to node-negative status after treatment have excellent survival, even if there is RD in the breast.[17] Consequently, the combination of tumor size and nodal status after neoadjuvant treatment is prognostic.[18]

Alternatively, the Miller and Payne classification ignores tumor size and nodal status altogether, and estimates only the decrease in cancer cellularity after treatment.[10] However, the reduction in cellularity is often greatest when the residual tumor is small, suggesting a relationship between residual size and cellularity.[19] While microscopic RD, altered cytologic appearance, and estimated tumor volume less than 1 cm^3 also indicate good response, these tend to be descriptive parameters and are also difficult to apply to tumor beds with dispersed microscopic foci of carcinoma.[3-6,9,20] Finally, there is no evidence that residual in situ carcinoma alone increases risk of future distant relapse.[12,21,22]

Table 1. Population Characteristics of the Cohorts Used for Development and Validation of the Residual Cancer Burden Index

Characteristic	Cohort			
	Development (n = 241)		Validation (n = 141)	
	No.	%	No.	%
Treatment				
Neoadjuvant				
T/FAC*	241	100	0	0
FAC†	0	0	141	100
Adjuvant hormone‡				
Yes	160	66	57	40
No	81	34	80	57
Unknown	0	0	4	3
Demographic and clinical				
Age, years				
Mean		50.8		48.8
SD		10.6		10.4
≤ 50	119	49	79	56
> 50	122	51	62	44
ER status				
Positive	151	63	79	56
Negative	90	37	55	39
Unknown	0	0	7	5
PR status				
Positive	112	47	57	40
Negative	126	52	51	36
Unknown	3	1	33	23
HER-2 status				
Positive	49	20	0	0
Negative	181	75	3	2
Unknown	11	5	138	98
Tumor characteristics before treatment				
Lymph node status				
Positive	114	47	89	63
Negative	127	53	52	37
Clinical tumor size§, mm				
Mean		24.9		39.2
SD		13.5		17.1
Unknown	39	16	12	5
Clinical AJCC stage				
0	0	0	0	0
I	23	10	0	0
II	196	81	76	54
III	22	9	65	46
Tumor pathology after neoadjuvant treatment				
T stage				
yT0	67	28	26	18
yT1	117	49	54	38
yT2	46	19	52	37
yT3	11	5	9	6
Lymph node status				
Positive	100	41	75	53
Negative	141	59	66	47
Pathologic yAJCC stage				
0	55	23	23	16
I	70	29	28	20
II	78	32	48	34
III	38	16	42	30
f_{inv}				
Mean		0.16		0.27
SD		0.21		0.27
Unknown	0	0	0	0
Primary tumor bed size§, mm				
Mean		12.8		19.6
SD		14.7		19.5
Unknown	0	0	0	0

(continued on following page)

Table 1. Population Characteristics of the Cohorts Used for Development and Validation of the Residual Cancer Burden Index (continued)

Characteristic	Cohort			
	Development (n = 241)		Validation (n = 141)	
	No.	%	No.	%
Treatment outcomes				
Response to neoadjuvant treatment				
Complete response	55	23	23	16
Residual disease	186	77	118	84
Events within 5 years				
Distant relapse	38	16	28	20
Local recurrence	1	0	0	0
Death	1	0	5	4
Censored	201	84	108	76
Events within 10 years				
Distant relapse	43	18	44	31
Local recurrence	1	0	1	0
Death	2	1	8	6
Censored	195	81	88	63
Median follow-up, months	67.3		104.7	

Abbreviations: T/FAC, paclitaxel plus fluorouracil, doxorubicin, and cyclophosphamide; SD, standard deviation; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2; AJCC, American Joint Committee on Cancer; yAJCC, revised American Joint Committee on Cancer; f_{inv}, fraction invasive cancer.

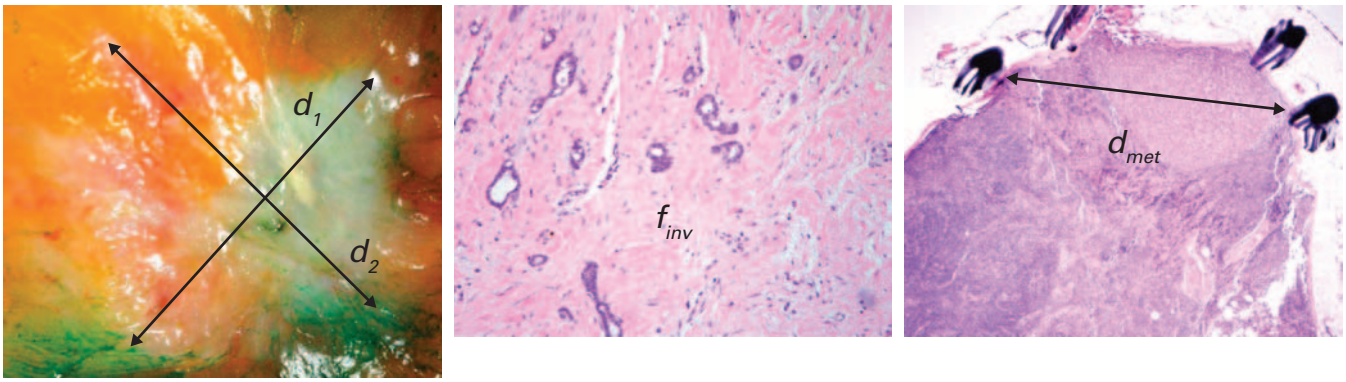
*T given in four cycles of 3-weekly intervals or in 12 cycles of weekly intervals followed by four cycles of FAC given at 3-weekly intervals.

†Four cycles of FAC given at 3-weekly intervals followed by surgery and then by four more cycles of adjuvant FAC (for 111 women) or other chemotherapy given at 3-weekly intervals.

‡Ninety-one percent of patients with hormone receptor–positive cancer (ER positive or PR positive) received 5 years of adjuvant tamoxifen after the completion of all chemotherapy.

§Calculated as the geometric mean of the largest two pathologic diameters of the primary tumor bed.

Stronger prognostic information from pathologic response can increase the clinical and scientific information learned from neoadjuvant clinical trials. Dichotomization of response as pCR or RD is overly simplistic for these objectives because RD after neoadjuvant treatment includes a broad range of actual responses from near pCR to frank resistance. More effective or prolonged neoadjuvant treatments should reduce the extent of RD in many patients, possibly blurring the prognostic distinction between pCR and RD. In contrast, it should be possible to identify patients with resistant disease in order to develop predictive tests for this adverse outcome. Therefore, we proposed to measure residual cancer burden (RCB) as a continuous variable derived from the primary tumor dimensions, cellularity of the tumor bed, and axillary nodal burden.



Variable	Hazard Ratio (95% CI)	*P*
Primary tumor bed dimensions ($\sqrt{d_1 d_2}$)	1.24 (1.04 to 1.48)	.02
Cellularity fraction of invasive cancer (f_{inv})	7.37 (2.16 to 25.1)	.001
Size of largest metastasis (d_{met})	1.17 (0.99 to 1.38)	.06
No. of positive lymph nodes	1.11 (1.04 to 1.19)	.002

Fig 1. The pathological variables included bidimensional 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}). These covariates were included in a multivariate analysis of distant relapse-free survival in the paclitaxel plus fluorouracil, doxorubicin, and cyclophosphamide (T/FAC) cohort.

Table 2. Multivariate Cox Proportional Hazards Analyses of Prognostic Factors of Distant Relapse-Free Survival in T/FAC Treated Cohort

Variable	Analysis Without RCB Index			Analysis With RCB Index*		
	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
Age (> 50 *v* ≤ 50)	0.32	0.16 to 0.64	.001	0.41	0.20 to 0.83	.01
Stage pre (III *v* I or II)	3.01	1.33 to 6.84	.008	2.27	0.96 to 5.35	.06
Hormone receptor status† (positive *v* negative)	0.48	0.14 to 1.67	.25	0.54	0.16 to 1.85	.33
Hormone treatment (yes *v* no)	0.54	0.16 to 1.85	.33	0.33	0.09 to 1.16	.08
Paclitaxel schedule (3-weekly *v* weekly)	1.50	1.08 to 2.08	.02	1.48	1.04 to 2.04	.03
Response (RD *v* pCR)	4.82	1.77 to 13.1	.002	0.54	0.12 to 2.32	.41
RCB index	—		—	2.50	1.70 to 3.69	< .001

Abbreviations: T/FAC, paclitaxel plus fluorouracil, doxorubicin, and cyclophosphamide; RCB, residual cancer burden; RD, residual disease; pCR, pathologic complete response; ER, estrogen receptor; PR, progesterone receptor.
*$P < .001$ and $\chi^2 = 24.8$ (by the likelihood ratio test) for the comparison with the analysis without the RCB index.
†Defined as positive if ER positive or PR positive.

PATIENTS AND METHODS

Pathologic Review

The authors proposed that the extent of RD in the post-treatment surgical resection specimen could be determined from bidimensional 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}; Appendix 1, online only). Largest bidimensional measurements of the residual primary tumor bed were recorded from the macroscopic description in the pathology report and confirmed after review of corresponding slides. If multiple tumors were present, the dimensions of the largest were recorded. Bidimensional 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*): $f_{inv} = (1 - (\%CIS/100)) \times (\%CA/100)$. Pathologic stage after treatment was determined using the revised American Joint Committee on Cancer (yAJCC) staging system for breast cancer.[23]

Patients and Materials

Four authors (W.F.S., R.R., L.A., A.P.) contributed to a review of the pathology reports and hematoxylin and eosin (H&E) stained slides from the surgical resection specimens of 382 patients who completed neoadjuvant chemotherapy for invasive breast carcinoma (T1-3, N0-1, M0). One cohort included 241 patients treated for 6 months with a regimen including paclitaxel (T) followed by fluorouracil, doxorubicin, and cyclophosphamide (FAC), then surgical resection of the residual tumor and either sentinel lymph node biopsy procedure or axillary dissection (protocol MDACC DM 98-240).[24] Data from this developmental cohort were used to develop the formula for RCB index and to identify thresholds of RCB that identify corresponding risk groups (Table 1).

An independent validation cohort (Table 1) included 141 patients treated for 3 months with FAC alone, followed by surgical resection of the residual tumor and axillary dissection, and then 3 additional months of adjuvant chemotherapy (FAC for 129 patients and other noncrossresistant chemotherapy for 12 patients who had clinically stable or progressive disease; protocols MDACC DM 91-015, DM 94-002.[25,26] This cohort included patients with more advanced disease (63% node positive *v* 47%; 100% stage II/III *v* 90%) and larger size tumors (mean diameter, 3.9 *v* 2.5 cm). The pCR rate was lower in the validation cohort (16%), consistent with the shorter duration of preoperative chemotherapy and the absence of a taxane.

Patients with hormone receptor–positive breast cancer were offered 5 years of adjuvant tamoxifen according to treatment guidelines at the time. The institutional review board of MDACC approved these protocols and all patients signed an informed consent form before initiation of therapy. Pathologic review and data analyses were conducted in accordance with a separately approved institutional review board protocol (MDACC LAB02-010).

Statistical Analysis

Distant relapse-free survival (DRFS) was recorded as the interval from initial diagnostic biopsy until distant metastasis. Patients who did not relapse were censored at the time of last follow-up or death. The significance of the RCB index as a predictor of DRFS was evaluated by comparing full multivariate Cox models with and without the RCB term based on the likelihood ratio test. Details of the statistical methods used are provided in Appendix 2, online only.

RESULTS

Development of RCB Index

The four parameters of residual tumor (d_{prim}, f_{inv}, *LN*, and d_{met}) were individually associated with significantly higher risk of distant relapse ($P < .001$) after T/FAC chemotherapy in univariate Cox regression analyses and maintained significance as independent predictors in the main effects multivariate Cox regression model (Fig 1 and Appendix 3, online only). To calculate a single index of RCB, we first combined the covariates to terms that measure RCB in the primary tumor bed ($RCB_{prim} = f_{inv}\, d_{prim}$) and in regional metastases ($RCB_{met} = 4\,(1 - 0.75^{LN})\, d_{met}$). The metastatic term is intended to be proportional to the sum of diameters of the affected lymph nodes, but since only the size of the largest metastasis is routinely measured we assumed that additional nodal metastases each have 75% of the diameter of the next-largest metastasis (Appendix 3, online only).

The distributions of the primary and metastatic RCB components were highly right skewed (Appendix 3, online only) and so an unconditional power transformation on the two components was applied.[27] The transformed terms were then scaled to match the 95th percentiles of their respective distributions, and added to define the RCB index:

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

Residual Cancer Burden Index As a Predictor of Distant Relapse

Patients had almost a two-fold increase in relapse risk for each unit of increase in the RCB index (hazard ratio [HR], 1.94; 95% CI,

1.47 to 2.55; $P < .001$). When the RCB index was included in a multivariate Cox regression model that included clinical and treatment covariates (Table 2), the overall predictive power of the model was significantly improved ($P < .001$), and the RCB index was significantly associated with the risk of disease recurrence (HR, 2.50; 95% CI, 1.70 to 3.69; $P < .001$). Both the primary and metastatic contributions to the RCB index were independently prognostic after adjusting for other risk factors in multivariate Cox regression analysis (primary term HR, 2.84; 95% CI, 1.47 to 5.48; $P = .002$; metastatic term HR, 2.57; 95% CI, 1.58 to 4.17; $P < .001$).

There appeared to be a disproportionate increase in the risk of 5-year distant relapse with increasing RCB values after T/FAC chemotherapy (Fig 2A). A similar analysis stratified by hormone treatment status demonstrated an overall increased risk of relapse with increasing RCB levels for patients who did not receive adjuvant hormone therapy (Fig 2B). The likelihood of 5-year relapse in patients who received hormone treatment was lower for the entire range of RCB values, and it increased more gradually through the lower spectrum of RCB values (Figs 2A and 2B). However, both groups had similar gradients of increasing risk through the higher spectrum of RCB values, indicating comparatively greater risk of relapse with more extensive RD.

RCB Index Identifies Near pCR and Resistant Groups

We identified two cutoff points to assign patients with RD (RCB > 0) after T/FAC treatment into one of three classes: RCB-I (minimal RD), RCB-II (moderate RD), and RCB-III (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 (Appendix 2, online only). The first cutoff point (RCB-III *v* RCB-I/II) was selected as the 87th percentile (RCB, 3.28), and the second (RCB-I *v* RCB-II) corresponds to the 40th percentile (RCB, 1.36). The cutoff points defined subgroups of RCB-0 to RCB-III with increasingly poor prognosis (Appendix Table A1, online only, and Fig 3A). The cumulative incidence estimate of the overall probability of relapse within 5 years adjusted for the competing risk of death events was 5.4% for the pCR group and 2.4% for the group with minimal RD (RCB-I), whereas it was 53.6% for the group with extensive RD (RCB-III). The difference in the rates of distant relapse at 5 years between the groups with the worst (RCB-III) and best (RCB-0) prognoses was 48.2% (95% CI, 28.1 to 65.6), providing sufficient separation to reliably classify patients into groups with different prognosis.[28]

Because adjuvant hormone therapy likely affects relapse-free survival, we evaluated the risk of relapse within groups who did or did not receive adjuvant hormone treatment. All hormone receptor–positive patients were eligible for treatment and 91% of them underwent adjuvant hormone therapy. Women with RCB-0 or RCB-I after neoadjuvant T/FAC had excellent 5-year relapse-free prognosis irrespective of whether or not they received adjuvant hormone treatment (Figs 3B and 3C). It is noteworthy that nine patients with hormone receptor–negative breast cancer and RCB-III after neoadjuvant T/FAC chemotherapy all relapsed within 27 months (Fig 3B). The prognosis of those with RCB-II was improved in the group treated with adjuvant hormone therapy (Fig 3C).

RCB Groups Stratify Prognosis of Revised yAJCC Stage After Chemotherapy

We evaluated the contribution of the RCB group to the prognostic power of each post-therapy yAJCC stage group (Fig 4).[29] Of course, RCB-0 and stage 0 both identify those patients with pCR. RCB did not add significant prognostic information for stage I patients ($P = .38$; Fig 4A), but RCB classified stage II patients in three subgroups ($P = .005$; Fig 4B) and stage III patients in two subgroups ($P = .025$; Fig 4C) with significantly different prognoses. Similarly, RCB stratified the prognosis within yAJCC stage groups in the validation FAC-treated cohort (Figs 4D to 4F). Furthermore, the RCB provided a more refined prognosis within subcategories of yAJCC stage for both cohorts (Appendix 4, online only). Therefore, RCB classification appears to add significant prognostic power compared with post-treatment

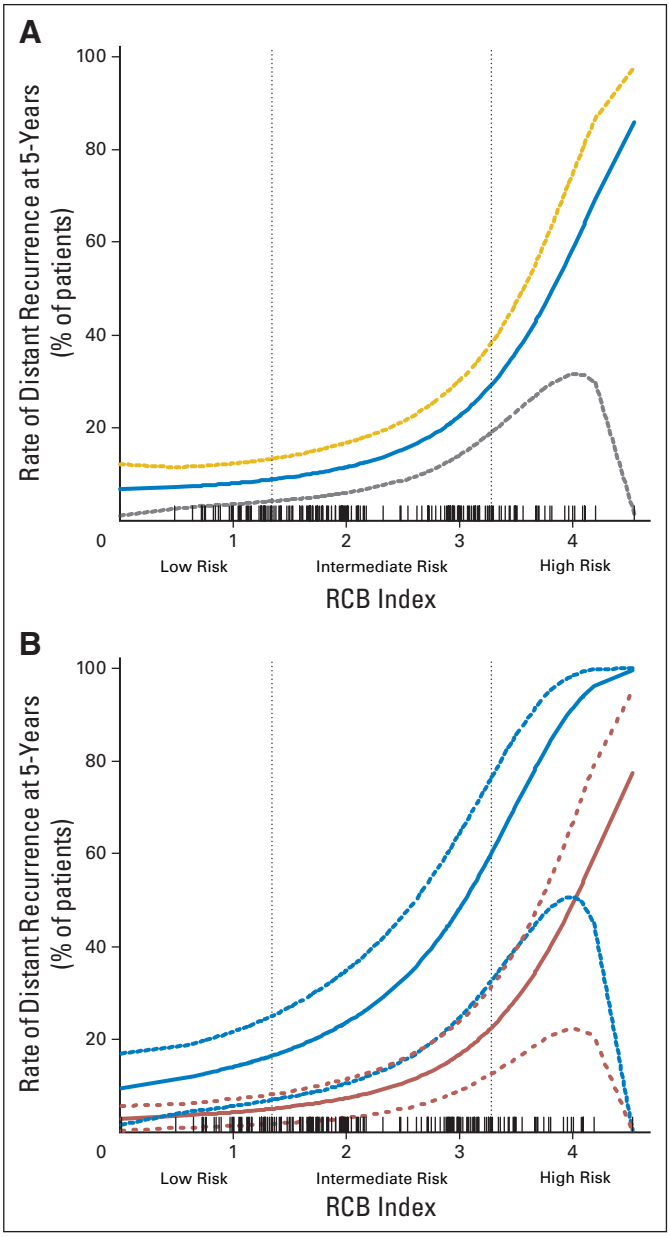


Fig 2. Likelihood of 5-year distant recurrence as a continuous function of residual cancer burden (RCB; solid curves) and the corresponding point-wise 95% CI (dashed lines) were estimated using a smoothing spline approximation: (A) entire paclitaxel plus fluorouracil, doxorubicin, and cyclophosphamide (T/FAC) cohort; (B) subsets who either received adjuvant hormone treatment (91% of receptor-positive patients; red lines) or did not (blue lines).

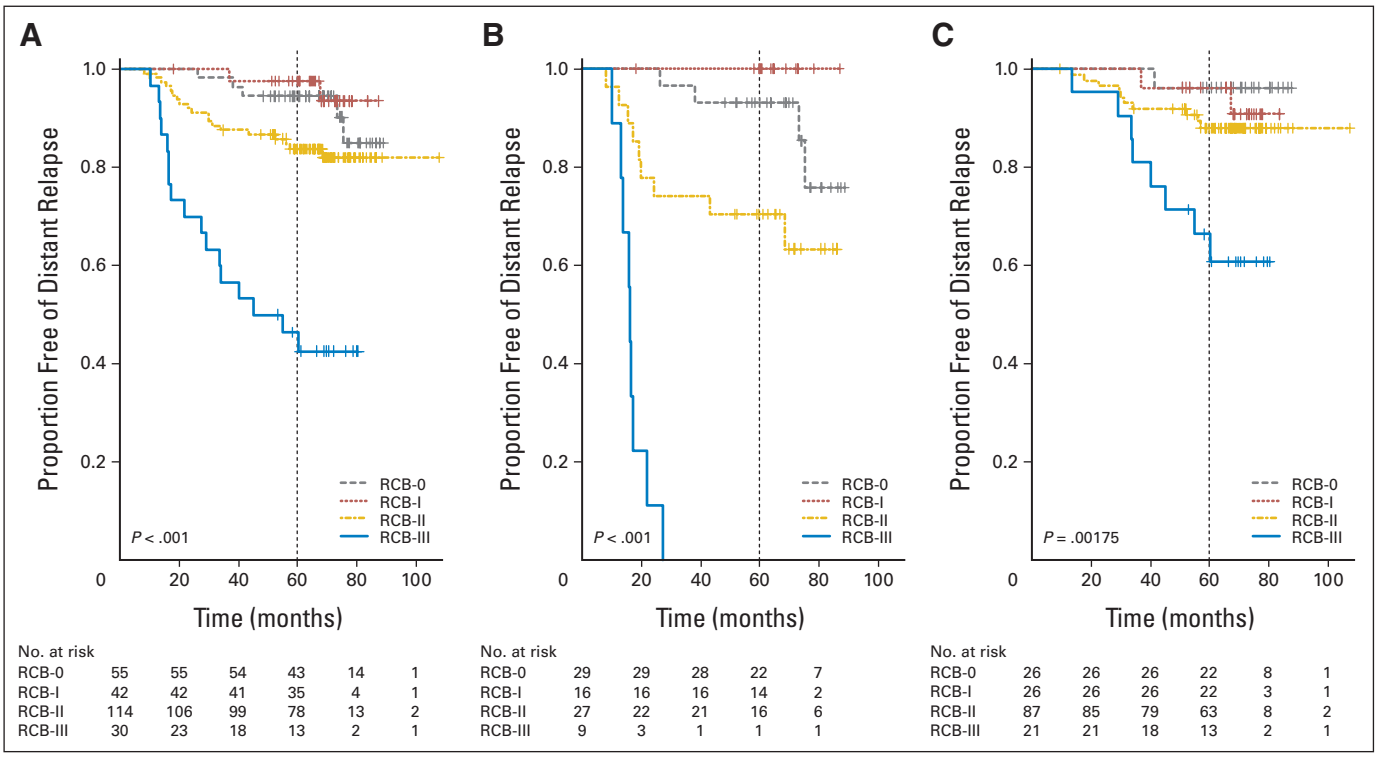


Fig 3. Likelihood of distant relapse in patients with residual cancer burden (RCB) -0 (pathologic complete response), RCB-I, RCB-II, or RCB-III in: (A) entire paclitaxel plus fluorouracil, doxorubicin, and cyclophosphamide (T/FAC) cohort; (B) subset without adjuvant hormone treatment; (C) subset who received adjuvant hormone treatment (91% of hormone receptor–positive and no hormone receptor–negative patients). *P* values are from a log-rank test for difference between all survival curves.

pathologic yAJCC stage, at least for stage II/III tumors that represent 48% of the T/FAC-treated cohort.

Validation of RCB As Predictor of Distant Relapse

We evaluated the intrinsic prognostic accuracy of the RCB-based survival model by calibrating the predicted probabilities of distant relapse at 5 years produced by the full multivariate Cox regression model (including RCB group) to the observed probabilities of relapse (Appendix 2, online only).[30] The calibration plot suggested that the predicted probabilities of distant relapse by the RCB survival model were similar to the empirical Kaplan-Meier estimates (Fig A1, online only; cross symbols). Next, we adjusted for potential overoptimism in the predictions from bias introduced by "using the data twice" first, for selecting cutoff points and subsequently for evaluating the model's predictive accuracy.[31,32] The estimated global shrinkage factor of 0.871 indicated only moderate overfitting. The adjusted prognostic model and its calibration is shown in Figure A1, online only (filled symbols), and appears to predict accurately the relapse-free rates at 5 years in the T/FAC cohort.

Discrimination of this prognostic model between relapsed and nonrelapsed patients was measured using Harrell's *c* index (Appendix 2, online only).[30] The bias-adjusted *c*-index in the development cohort was estimated to be 0.77 (95% CI, 0.69 to 0.84), indicating statistically significant discrimination ($c = 0.5$ for random predictions, $c = 1$ for perfectly discriminating model).[32]

Generalizability of the RCB system was evaluated in the independent validation cohort of patients treated with neoadjuvant FAC chemotherapy. RCB defined groups with increasingly poor 5-year and 10-year prognoses (Appendix Table A1 and Appendix 5, online only). The difference in the rates of distant relapse between the worst (RCB-III) and best (RCB-0) prognosis groups was 36.3% (95% CI, 21.4 to 51.4) at 5 years and 52.2% (95% CI, 35.1 to 66.9) at 10 years. The separation of the 5-year relapse rates is somewhat smaller in the FAC cohort than for the T/FAC cohort (48.2%), indicating some optimism in those predictions and possibly benefit from additional postoperative chemotherapy. No systematic bias was apparent in the calibration plot (Fig A1B, online only), especially for the optimism-adjusted model. The *c*-index of the prognostic model on the validation cohort was 0.70 (95% CI, 0.61 to 0.79) suggesting similar discriminatory ability. Taken together, these results validate the prognostic ability of the RCB system for predicting distant relapse in breast cancer patients treated with neoadjuvant T/FAC or FAC chemotherapy.

DISCUSSION

The lack of uniform methods to report pathologic response is a contributing factor in the recent erosion of confidence in the value of neoadjuvant trials to anticipate the results of larger adjuvant trials.[11] Although pCR (including node-negative status) has consistently imparted an excellent prognosis in published studies, meaningful reporting of RD has been an elusive goal. This problem is accentuated when evaluation of pathologic response is limited to the review of archival pathology reports. This is because asymmetry of RD and variable

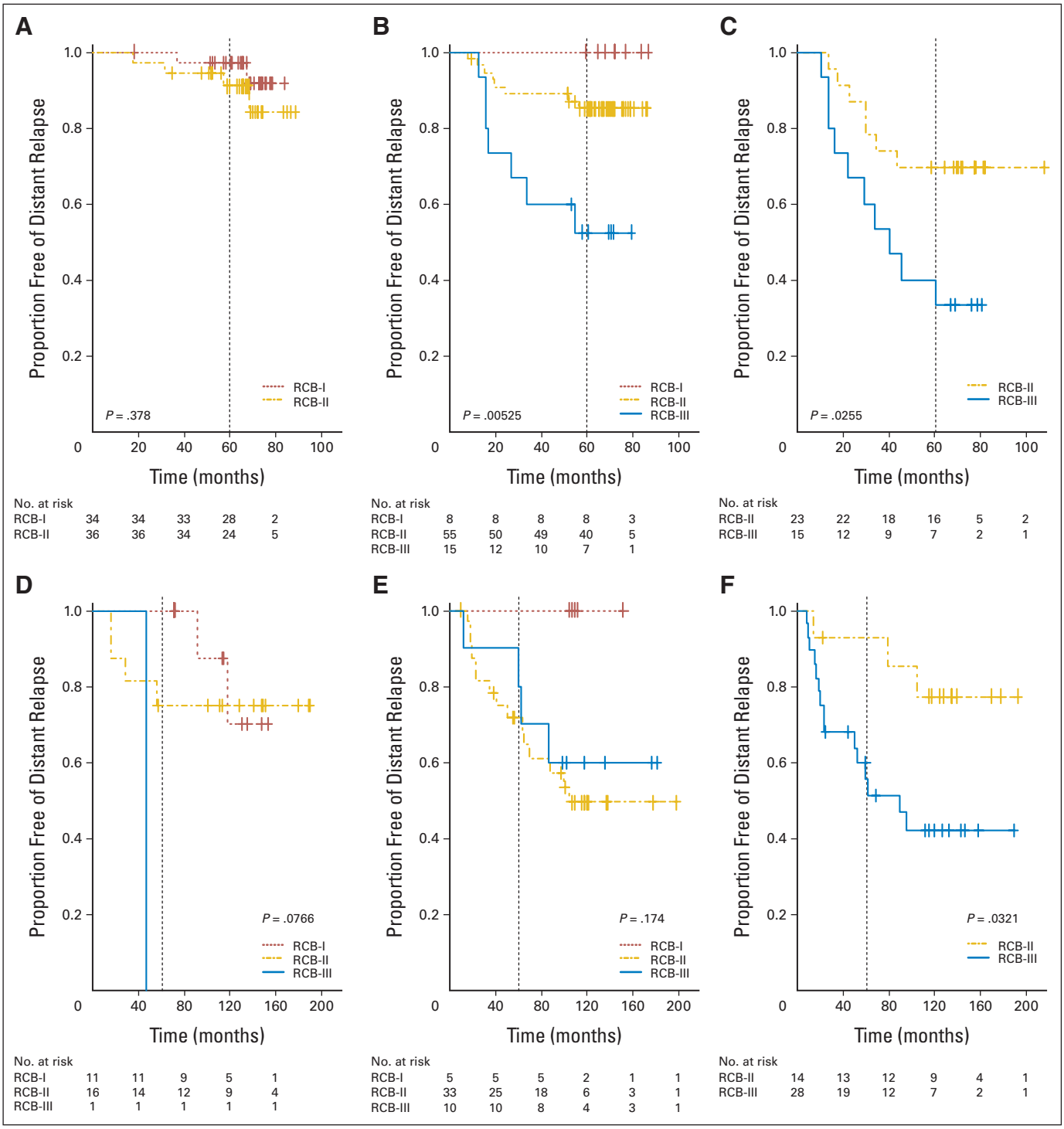


Fig 4. Kaplan-Meier distant relapse curves for each American Joint Committee on Cancer (yAJCC) stage group after chemotherapy as a function of residual cancer burden (RCB) class. yAJCC stage 0, residual cancer burden (RCB) -0, and pathologic complete response (pCR) all define the same outcome. The *P* values are from a log-rank test for difference between survival curves. (A, B, C) Paclitaxel plus fluorouracil, doxorubicin, and cyclophosphamide (T/FAC)-treated patients; (D, E, F) independent cohort of FAC-treated patients. (A, D) Stage I, (B, E) stage II, and (C, F) stage III residual disease.

hypocellularity after treatment are not usually quantified in the report, and are not captured by tumor diameter and nodal status alone.

We have attempted to combine relevant pathological characteristics of RD into a composite index of RCB. Each variable in the equation for RCB has prognostic significance, and the calculated primary and metastatic terms in the equation are equivalently and independently prognostic. As a result, RCB is strongly prognostic, and represents the continuum of RD in a treated population. Our analyses of intrinsic prognostic accuracy (Fig A1, online only), discrimination, and generalizability (Tables 2 and A1 [online only], Fig A1 [online

only]) did not demonstrate any major bias in our model of RCB to predict distant relapse, even though the FAC-treated patients received additional postoperative chemotherapy. Furthermore, RCB extends the prognostic value of our current dichotomous assessment of response as pCR or RD (Table 1), and the revised yAJCC stage classifications of RD (Fig 4).

We have also been careful to employ methods of pathologic assessment that could feasibly be incorporated in routine diagnostic practice without adding to the cost of patient care. The variables used to calculate RCB can be simply obtained from pathologic review and entered into a calculation script that is freely available on the internet (www.mdanderson.org/breastcancer_RCB). A stepwise guide for the pathologic evaluation of post-treatment breast specimens is provided, along with links to illustrative examples. This Web site could be a useful tool for pathologists, and could also be employed in multicenter trials of neoadjuvant treatment to standardize sampling and reporting of pathologic findings from post-treatment specimens.

Further studies should address interobserver variability of RCB measurements (and prognostic power), and evaluate RCB when used by other groups in other study populations. One must also consider whether incomplete pathologic data might invalidate the utility of RCB. For example, assessment of the residual primary tumor bed in patients who had pretreatment surgical biopsy might overestimate the response in the breast. Alternatively, assessment of the residual nodal cancer burden in patients who had a positive lymph node excised before neoadjuvant treatment might overestimate the nodal response.

RCB measurements provide a continuous parameter of response, so that all subject responses contribute to the analysis. Therefore, small, phase II studies, treatment regimens with low pCR rates (such as hormone therapy), or with similar pCR rates, can be compared to identify differences in the extent of RD. RCB can also be divided into four classes (RCB-0 to RCB-III). We note that patients with minimal RD (RCB-I) had the same 5-year prognosis as those with pCR (RCB-0), irrespective of the type of neoadjuvant chemotherapy administered, adjuvant hormone therapy (Fig 3), or the pathologic stage of RD (Fig 4). Therefore, the combination of RCB-0 (pCR) and RCB-I expands the subset of patients who can be identified as having benefited from neoadjuvant chemotherapy.

Extensive RD (RCB-III) was associated with poor prognosis, irrespective of the type of neoadjuvant chemotherapy administered, adjuvant hormone therapy (Fig 3), or the pathologic stage of RD (Fig 4). In particular, all patients with RCB-III after T/FAC chemotherapy, who did not receive adjuvant hormone therapy, suffered distant relapse within 3 years (Fig 3B). However, it should also be noted that 13% of patients with receptor-positive disease had RCB-III after T/FAC chemotherapy (21 of 160), with a 5-year distant relapse rate of 40% despite receiving adjuvant hormone treatment (Fig 3C). This identifies an important subset of patients with combined insensitivity to chemotherapy and hormone therapy, or with RD (after surgery) that is too extensive to be controlled by hormone therapy alone. Conversely, even a moderate response from chemotherapy (RCB-II) appears to improve the survival benefit from subsequent hormone therapy (Figs 2B, 3C). This illustrates how identification of the subset of receptor-positive patients who might correctly be spared (denied) adjuvant chemotherapy despite consensus treatment recommendations will require very careful selection based on the tumor's predicted chemosensitivity and the predicted endocrine sensitivity.[33,34]

It has been recommended that the predictive ability of a new marker should be evaluated based on whether the marker improves an already optimized multivariate model of available risk factors.[35] On this basis, the RCB index is an independent new risk factor that improves the prediction of distant relapse after neoadjuvant chemotherapy compared with currently used risk factors. Although RCB could supplement existing methods to define pathologic response, independent validation of RCB is needed before it can be broadly used as a surrogate end point for patient survival.[36]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).