Prognostic Significance of Modified Residual Disease in Breast and Nodes (mRDBN) Algorithm After Neoadjuvant Chemotherapy for Breast Cancer

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Key Words: Breast carcinoma; Neoadjuvant chemotherapy; Residual disease

ABSTRACT

Objectives: We hypothesized that prognostic accuracy of the residual disease in breast and lymph nodes (RDBN) method, which is calculated using residual tumor size, nodal involvement, and tumor grade, may be improved by incorporating residual tumor cellularity.

Methods: Cases included 614 patients who underwent neoadjuvant therapy for breast cancer. Tumor size was adjusted for residual cellularity of invasive carcinoma and used to calculate modified RDBN (mRDBN) and compared with unmodified gross tumor size (gRDBN).

Results: RDBN could be calculated in 428 cases. Relative risks of recurrence and death were significantly higher for RDBN-3 and RDBN-4 compared with RDBN-1. Kaplan-Meier analysis showed significant differences in disease-free survival and overall survival for estrogen receptor (ER)-negative/human epidermal growth factor receptor 2 (HER2)-negative and ER-positive/HER2-negative subgroups (P < .0001).

Conclusions: Both mRDBN and gRDBN provide prognostic information, particularly in HER2-negative carcinoma; however, mRDBN showed better stratification of RDBN-3 and RDBN-4 patients.

Following neoadjuvant systemic therapy for primary breast carcinoma, the pathologist must approach breast resection specimens differently from specimens in which no preoperative treatment is given. Location and evaluation of prior biopsy site(s)/tumor bed is essential, particularly in cases of complete or near-complete response, and some measure of tumor response to therapy should be given. Confirmation that previously involved lymph nodes have been removed and evaluated is also crucial to posttherapy staging. Evaluation of tumor response to systemic therapy is important to define prognosis, and many methods have been described in an attempt to maximize the prognostic information that can be obtained from these specimens. While the presence of residual ductal carcinoma in situ (DCIS) remains somewhat controversial, a pathologic complete response (pCR) is most commonly defined as absence of invasive tumor cells and lymphovascular space invasion in both the breast and sampled lymph nodes.1-3 pCR is associated with better event-free survival and overall survival compared with patients with residual disease.3-8 The presence and extent of residual disease in lymph nodes also have been shown to have prognostic significance, and methods of evaluation that incorporate lymph node status may therefore be preferable in clinical practice to those that do not.7-9,12
One published method to pathologically evaluate residual disease in surgical resection specimens is residual disease in breast and nodes (RDBN).\(^\text{13}\) First described by Chollet et al\(^\text{13}\) in 2008, the RDBN method classifies tumors into four risk levels and uses pathologic factors that retain prognostic value when assessed after neoadjuvant chemotherapy. These factors include number of involved lymph nodes, residual size of tumor in breast, and tumor grade. As originally published, and in contrast to the commonly used residual cancer burden method, RDBN does not attempt to quantify tumor cellularity as a part of its stratification into response classifications.\(^\text{14,15}\)

At Magee-Womens Hospital of University of Pittsburgh Medical Center, the degree of response to neoadjuvant systemic therapy is reported as percent tumor size/volume reduction to account for reduction in cellularity as well as tumor size. Using this method, a revised tumor size is calculated by multiplying the largest dimension in centimeters of the gross tumor bed by the cellularity of the tumor bed compared with the tumor cellularity in the pretherapy core biopsy specimen.\(^\text{16}\) In this study, we hypothesized that incorporating change in tumor cellularity by using the “revised tumor size” may further improve the prognostic accuracy of RDBN.

**Materials and Methods**

The institutional review board at the University of Pittsburgh approved this study. A retrospective review of a prospectively maintained database identified 614 consecutive female patients who received neoadjuvant systemic therapy from 2010 to 2014. Patients with incomplete surgical pathology information such that RDBN could not be calculated were excluded. The RDBN defines four prognostic levels using the following equation: RDBN = 0.2 (residual breast tumor size in centimeters) + index of involved nodes + tumor grade.\(^\text{13}\) Residual tumor size was recorded as the largest dimension of grossly identified lesion (gross tumor size). At our institution, reduction in tumor size/volume in the breast is determined using the following equation: estimated % tumor size/volume reduction = [(pretherapy clinical size – “revised” pathology tumor size) / pretherapy clinical size] * 100. A “revised” pathologic tumor size is calculated by multiplying the largest dimension of the gross tumor bed by the cellularity of the tumor bed compared with the cellularity observed in the pretherapy core biopsy sample. For example, if a 3-cm tumor bed has only 50% cellularity for invasive cancer (in comparison to the pretherapy core biopsy specimen), the revised tumor size is 1.5 cm. From pathology reports, both the gross tumor size and the “revised tumor size” were available. To evaluate the prognostic value of adjusting the RDBN for change in tumor cellularity, we calculated the modified RDBN index (mRDBN) by using the “revised” tumor size rather than the largest dimension of residual tumor. Gross and microscopic assessment of residual tumor size involves sampling of gross residual tumor and adjacent grossly uninvolved tissue. In cases with no residual tumor, the grossly identifiable tumor bed is typically entirely submitted for histologic examination. For RDBN, index of involved lymph nodes is scored as 0 for no positive nodes, 1 for one to four positive lymph nodes, 2 for five to seven positive lymph nodes, and 3 for eight or more positive lymph nodes. Methods of regional lymph node sampling, with either sentinel lymph node biopsy or axillary lymph node dissection, were performed at the surgeon’s discretion based on the burden of disease. Tumor grading was performed using the Nottingham grade that classifies the tumor into three grades (1-3).\(^\text{17}\) When RDBN was calculated using the gross tumor size (ie, not taking tumor cellularity into account), it was termed gRDBN. RDBN levels were defined as follows: RDBN-1 (equivalent to pCR) = index of 0, while RDBN-2 is an index between 0.1 and 2.9, RDBN-3 is an index between 3.0 and 4.3, and RDBN-4 is an index 4.4 or more.\(^\text{13}\)

Relative risk of recurrence (locoregional or distant) and death were calculated for RDBN 2 to 4 compared with RDBN-1 (pCR) using \(\chi^2\) statistical analysis. Analysis of cases recategorized to a different RDBN level using the revised tumor size was performed. Kaplan-Meier survival analysis with log-rank test for trend analysis was also performed on all cases and on cases divided by tumor phenotype (estrogen receptor [ER] positive/human epidermal growth factor receptor 2 [HER2] positive, ER-/HER2-, ER+/HER2-, and ER-/HER2+) using GraphPad Prism 7 software (GraphPad Software, La Jolla, CA). \(P \leq .05\) was considered statistically significant.

**Results**

Both mRDBN and gRDBN could be calculated on 459 cases. Twenty-nine cases were excluded because the patients had received neoadjuvant hormonal therapy rather than chemotherapy, and two cases were excluded because the patients were clinically staged as M1 at
presentation. This resulted in a total of 428 cases available for analysis. Characteristics of the studied patients, their management, and tumor characteristics are shown in Table 1 and Table 2. Median age of the patients was 54 years (range, 24-88 years), with approximately equal proportions of premenopausal and postmenopausal women. Mean follow-up was 33 months (median, 31 months; range, 4-70 months). For patients receiving neoadjuvant chemotherapy, the patients were treated at the discretion of treating oncologists. Of the patients for whom exact chemotherapy was known, 55% of patients received doxorubicin and cyclophosphamide-based chemotherapy, with most (90%) of those patients also receiving a taxane and 39% of patients receiving combination chemotherapy with at least one targeted anti-HER2 agent. Exact chemotherapy regimen is unknown in 13.7% of patients. Over the study period, in the entire cohort, 68 (16%) recurrences were observed, and 40 (9%) patients died.

Relative risks of recurrence and death using the gRDBN and mRDBN calculations are reported in Table 3. Using the gRDBN calculation, 156 (36%), 55 (13%), 139 (32%), and 78 (18%) of the 428 patients were grouped into gRDBN-1 (pCR), gRDBN-2, gRDBN-3, and gRDBN-4, respectively. Compared with patients with tumor response classified as gRDBN-1 (pCR), relative risk of recurrence for patients with tumor response classified as gRDBN-2 was 1.4 (95% confidence interval [CI], 0.3-7.5, \( P = .68 \)), 8.7 for gRDBN-3 (95% CI, 3.2-24.0, \( P < .0001 \)), and 15.5 for gRDBN-4 (95% CI, 5.7-42.4, \( P < .0001 \)). Relative risk of death

<table>
<thead>
<tr>
<th>Table 1: Clinical Characteristics</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>52</td>
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<tr>
<td>Median</td>
<td>53.5</td>
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<tr>
<td>Range</td>
<td>24-88</td>
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<tr>
<td><strong>Menopausal status, No. (%)</strong></td>
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</tr>
<tr>
<td>Premenopausal</td>
<td>215 (50)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>207 (48)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (1)</td>
</tr>
<tr>
<td><strong>Genetic testing (available for 64 patients), No. (%)</strong></td>
<td></td>
</tr>
<tr>
<td>BRCA negative</td>
<td>35 (8)</td>
</tr>
<tr>
<td>BRCA1 mutation</td>
<td>18 (4)</td>
</tr>
<tr>
<td>BRCA2 mutation</td>
<td>8 (2)</td>
</tr>
<tr>
<td>BRCA VUS</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>TP53 mutation</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td><strong>Breast laterality, No. (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>232 (54)</td>
</tr>
<tr>
<td>Right</td>
<td>185 (43)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7 (2)</td>
</tr>
<tr>
<td><strong>Surgical management of the breast, No. (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Breast-conserving surgery</td>
<td>190 (44)</td>
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<tr>
<td>Total or skin-sparing mastectomy</td>
<td>162 (38)</td>
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<tr>
<td>Nipple-sparing mastectomy</td>
<td>13 (3)</td>
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<tr>
<td>Modified radical mastectomy</td>
<td>55 (13)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (2)</td>
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<tr>
<td><strong>Axillary dissection, No. (%)</strong></td>
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<tr>
<td>No</td>
<td>248 (58)</td>
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<tr>
<td>Yes</td>
<td>178 (42)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (0.4)</td>
</tr>
</tbody>
</table>
compared with gRDBN-1 was 1.9 for gRDBN-2 (95% CI, 0.3-11.0, \( P = .5 \)), 6.0 for gRDBN-3 (95% CI, 1.7-20.1, \( P = .004 \)), and 12.0 for gRDBN-4 (95% CI, 3.6-39.5, \( P < .0001 \)).

Using the mRDBN calculation, 156 (36%), 63 (14%), 153 (35%), and 56 (13%) of the 428 patients were grouped into mRDBN-1 (pCR), mRDBN-2, mRDBN-3, and mRDBN-4, respectively. Using mRDBN-1 as the reference value, the relative risk of recurrence was 1.9 (95% CI, 0.4-8.1, \( P = .41 \)) for mRDBN-2, 8.2 (95% CI, 3.0-22.5, \( P = .0001 \)) for mRDBN-3, and 20.2 (95% CI, 7.4-54.9, \( P < .0001 \)) for mRDBN-4, while relative risk of death was 3.3 (95% CI, 0.8-14.3, \( P = .11 \)) for mRDBN-2, 5.1 (95% CI, 1.5-17.3, \( P = .0088 \)) for mRDBN-3, and 15.8 (95% CI, 4.8-51.8, \( P < .0001 \)) for mRDBN-4.

The results of reclassification of RDBN categories using mRDBN compared with gRDBN are shown in Table 4. Patients with pCR (RDBN-1) were classified as such using both gRDBN and mRDBN calculations. No RDBN-2 cases were reclassified using mRDBN compared with gRDBN. In the gRDBN-3 cases, nine (6.0%) of 139 cases were reclassified: one case reclassified to RDBN-4 and eight cases reclassified to RDBN-2. Of the 78 cases in the RDBN-4 category using the gRDBN calculation, 24 (31%) were reclassified to the RDBN-3 category using the mRDBN calculation. In the gRDBN-4 category, 39.7% of patients experienced a recurrence compared with 51.7% of patients in the mRDBN-4 category. Over the follow-up period, 23.1% of patients in the gRDBN-4 category died, while 30.4% of patients in the mRDBN-4 category died.

Results of Kaplan-Meier analysis for disease-free survival (DFS) and overall survival (OS) for all cases studied are depicted in Figure 2. DFS and OS curves were significantly different using both gRDBN and mRDBN calculations (\( P < .0001 \)). DFS was similar for patients with RDBN-1 and RDBN-2. While the curves for DFS were somewhat similar, mRDBN calculation shows a greater difference in OS between mRDBN-3 and mRDBN-4 than the gRDBN calculation. Similar results for DFS and OS were obtained for both mRDBN and gRDBN calculations in patients with ER+/HER2– breast carcinomas in phenotype-specific analysis (\( P < .0001 \)). Figure 3, while in ER+/HER2– tumors Figure 4, a significant difference in OS curve was noted with the mRDBN calculation (\( P = .0193 \)) but not with the gRDBN calculation (\( P = .0511 \)). In patients with ER+/HER2+ breast carcinomas, RDBN categories predicted DFS but not OS Figure 5. With somewhat better separation of the RDBN-4 category with mRDBN, while in ER+/HER2+ breast carcinomas, both RDBN-1 and RDBN-2 category patients had excellent DFS and OS, but analysis of RDBN-2 and RDBN-4 was limited due to very few cases in these categories Figure 6.
**Discussion**

Systemic therapies (chemotherapy and hormonal therapy) are given in breast cancer to decrease the risk of distant relapse and improve overall survival. When given in the neoadjuvant setting, chemotherapy can be used to facilitate primary surgery, enable breast-conserving surgery and better cosmetic outcome, downstage axillary nodal disease, and also permit assessment of sensitivity of the tumor to various treatments. Published methods for assessment of residual disease following systemic therapy use variable histopathologic characteristics. The prognostic value of pathologic complete response has been well established; however, the value of quantifying lesser degrees of response remains less clear, and tumor phenotype based on hormone receptor and HER2 status plays a role. $^{7,16,18-23}$ Few comparisons of the described methods have been performed. Corben et al $^{24}$ reported that methods incorporating posttherapy lymph node status provided the most prognostic information and that age-unadjusted RDBN predicted both distant DFS and OS.

Residual cancer burden (RCB) has been recommended as the preferred method for use in clinical trials. $^{1}$ This method, first described by Symmans et al $^{14}$ in 2007, uses primary tumor dimension, cellularity of the tumor bed corrected for proportion of DCIS, and axillary nodal burden to calculate an RCB index, which is then divided into four risk groups. This method has been found to identify prognostic subgroups independently of and within the American Joint Committee on Cancer (AJCC) staging system. Reproducibility of this method has been studied, and among five pathologists using 100 cases, good agreement was demonstrated. $^{25}$ The classification system of response after neoadjuvant therapy used in the current study, the RDBN method, first published in 2008, also uses factors that have been individually shown to retain prognostic value following neoadjuvant systemic therapy: number of involved lymph nodes, residual tumor in the breast, and tumor grade. $^{10,13,26}$ A major difference between the RCB and RDBN methods is the incorporation of posttherapy tumor grade into the calculation. Mitotic activity is one
of three components of histologic grade in breast carcinoma. High posttherapy mitotic counts (>13 mitotic figures per 10 high-power fields) have been associated with a significantly higher risk of development of distant metastasis. In a more recent study by Choi et al., posttherapy histologic grade was associated with worse OS, suggesting that the addition of posttherapy tumor grade could provide important prognostic information in patients with residual disease after neoadjuvant systemic therapy. Therefore, the RDBN method may also contribute important information in this setting. Direct comparison of RCB and RDBN methods with a focus on tumor grade may represent an important next step in understanding the most important prognostic factors; however, this comparison could not be performed in the current cases due to the absence of information in pathology reports required to calculate RCB.

In this study, we calculated RDBN level using both the maximum gross tumor size and a modified tumor size based on change in cellularity with systemic therapy to ascertain the added value of including this parameter, as reduction in cellularity can be dramatic in post-neoadjuvant resection specimens, without appreciable change in maximum gross tumor size. Overall, both gRDBN and mRDBN calculations provided prognostic information for DFS and OS in 428 cases of invasive breast carcinoma treated with neoadjuvant chemotherapy. Relative risk of recurrence and mortality increased with increasing burden of residual carcinoma in the breast and lymph nodes. Using the modified tumor size resulted in 31% of RDBN-4 cases being reclassified to RDBN-3. Both gRDBN-3 and mRDBN-3 patients had similar recurrence and mortality rates, while responses classified as mRDBN-4 had higher recurrence.
and mortality rates, suggesting that the prognostic significance of level 4 classification using the mRDBN calculation may be more meaningful in predicting the patient’s prognosis. Similarly, Peintinger et al caution against overestimation of cellularity and/or tumor bed size when using the RCB method to preserve the prognostic value of the RCB-III category.

In subgroup analysis based on tumor phenotype using hormone receptor and HER2 status, both gRDBN and mRDBN provided prognostic information in both ER-/HER2- (triple-negative) and ER+/HER2- breast carcinomas. In patients with ER-/HER2+ tumors, the RDBN method showed significant differences in OS among RDBN levels, although analysis was limited by small numbers of patients in RDBN-2 and RDBN-4. DFS was not significantly different among RDBN categories using either calculation. Similarly, among patients with ER+/HER2+ tumors, significant overlap of survival curves using both calculations was observed for patients with residual disease. These findings are similar to those recently reported in a comparison of methods for assessment of response by tumor phenotype, including RDBN, in which response categories were most prognostically meaningful in ER-/HER2- tumors and least meaningful in HER2+ breast carcinomas. Anti-HER2 therapy was not a component of the treatment regimens in that study, but most patients with HER2+ tumors in the current study received treatment containing targeted anti-HER2 therapy. It is conceivable that the availability of adjuvant-targeted therapy options in ER+/HER2+ breast carcinomas may diminish the prognostic significance of residual disease burden. Similar results were also seen in a comparison study of Chevallier’s method and RDBN...
in 318 patients with tumor phenotype subgroups, in which RDBN groups were prognostically significant for triple-negative but not HER2+-like breast carcinomas. Correction for tumor size and quantification of residual tumor in general may not give as much prognostic information in patients with HER2+ tumors. We have hypothesized that mRDBN would significantly improve prognosis estimates compared with gRDBN. Our findings validate the prognostic value of the RDBN method; however, our results show only marginal improvement with mRDBN and appears to offer the greatest advantage over gRDBN in ER+/HER2– tumors. This is likely because of the weightage given to residual breast tumor size in calculating the RDBN index. The residual tumor size in centimeters is multiplied by a factor of 0.2, resulting in a difference of only 0.8 units for a 5-cm residual tumor size vs a 1-cm residual tumor size. Significantly more weight is given to posttherapy tumor grade and residual tumor in the axillary lymph nodes. Change in tumor grade after chemotherapy is a less well-defined phenomenon. Much is known about nuclear enlargement after chemotherapy, resulting in a higher overall tumor grade, but little is known or published about lower tumor grade after chemotherapy, a phenomenon we label as “tumor differentiation.” In small proportion of cases, a poorly differentiated and highly proliferative tumor can “differentiate” to form tubules, lined by lower grade and mitotically inactive nuclei in response to chemotherapy. This obviously results in a lower RDBN index and improved DFS.
and OS, although it is unclear whether in some cases, this finding is the result of preferential targeting of higher grade tumor cells by chemotherapy agents. One of the most significant components of RDBN is the presence and amount of residual tumor in axillary lymph nodes. It is critical for the surgeon to obtain the pretherapy positive lymph node at the time of resection and for the pathologist to document the presence of biopsy clip and/or biopsy site to ensure the lymph node removed is in fact the previously positive node.

Strengths of the current study include the large sample size, standardized grossing procedure for neoadjuvant breast specimens, and detailed clinicopathologic data available. This study was limited by heterogeneity of tumor phenotype and, therefore, the treatment regimens used in these patients. This may be particularly important in patients with HER2+ tumors, as treatment regimens advanced to include dual HER2 blockade with trastuzumab and pertuzumab during the time that the study database was collected. This heterogeneity is somewhat addressed by phenotype-specific analysis and exclusion of patients receiving neoadjuvant hormonal treatment. Longer length of follow-up may also be helpful in further elucidating the effects of residual tumor on prognosis. Assessment of interobserver variability in assessing cellularity may also be important in further refinement of the method used at our institution. Assessment of posttherapy cellularity in resection specimens with heterogeneous residual cellularity may be particularly challenging. Likewise, specimens with minimal residual

Figure 5A Disease-free survival (DFS) (A, B) and overall survival (OS) (C, D) for estrogen receptor–positive/human epidermal growth factor receptor 2–positive cases using unmodified gross tumor size residual disease in breast and lymph nodes (gRDBN) (A, C) and modified residual disease in breast and lymph nodes (mRDBN) (B, D) calculations. A, P = .0123. B, P = .0152. C, P = .3413. D, P = .8271.
disease showed the least concordance among pathologists in a study of interobserver variability of the RCB method.²⁵

The results reported here and previously reported for RCB and posttherapy AJCC staging establish that reporting of pCR vs residual disease alone is insufficient for quantification of risk in patients who have received systemic therapy, as varying degrees of response have prognostic significance.¹⁴,³²,³³ In particular, patients with a near-complete response (equivalent to RDBN-2) have a much better prognosis compared with patients with a high burden of residual disease.¹⁴ These findings also suggest that, similar to the RCB method, some indicator of residual cellularity, either in absolute terms or by comparing with the pretherapy core biopsy specimen, adds additional prognostic information and may help to maintain the prognostic significance of RDBN-4. Future directions may include comparison of the RDBN method with the RCB method and further studies to understand the significance of the decrease in tumor grade following neoadjuvant systemic therapy. Our study supports reporting of traditional pathologic parameters such as tumor size, tumor grade, lymph node status, and number of positive lymph nodes in the posttherapy resection specimen for prognostic purposes and suggests that residual tumor cellularity should also be included in the pathology report after neoadjuvant systemic therapy of primary breast cancer.
Case 151 illustrates a dramatic decrease in cellularity between the pretherapy core biopsy specimen (A) and the posttherapy resection specimen (B).


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References


