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Original contribution

# Modulatory effect of neoadjuvant chemotherapy on biomarkers expression; assessment by digital image analysis and relationship to residual cancer burden in patients with invasive breast cancer☆

**Amber Cockburn MD[a], Jingsheng Yan PhD[b], Dewi Rahardja PhD[b], David Euhus MD[c], Yan Peng MD, PhD[a], Yisheng Fang MD, PhD[a], Venetia Rumnong Sarode MD[a,*]**

[a]*Department of Pathology, UT Southwestern Medical Center, Dallas, TX 77843, USA*
[b]*Department of Clinical Science, UT Southwestern Medical Center, Dallas, TX 77843, USA*
[c]*Department of Surgery, UT Southwestern Medical Center, Dallas, TX 77843, USA*

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**Summary** The use of digital imaging techniques for biomarker assessment has gained recognition as a valid tool for clinical use. In this study, we used image analysis for evaluation of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor (HER2), Ki-67 index, and p53 in 172 patients with invasive breast cancer treated with neoadjuvant chemotherapy and compared it with an untreated group (100 cases). We also examined the relationship between biomarker expression and the extent of residual disease using the Web-based MD Anderson residual cancer burden (RCB) calculator. Residual disease was classified as RCB 0/I, II, and III corresponding to complete/near-complete response, moderate, and extensive residual disease, respectively. Overall change in ER, PR, and HER2 status in the treated group was seen in 9.02% ($P$ = .0148), 18.4% ($P$ = .011), and 12.0% ($P$ = .0042), respectively. Change in HER2 status, positive to negative and negative to positive, occurred in 27.2% and 7.0%, respectively. The group with RCB 0/I was frequently younger ($P$ = .0057) and showed higher ER(−) status ($P$ = .0316), lower ER scores ($P$ = .0103), higher Ki-67 index ($P$ = .0008), and p53 ($P$ = .0055) compared with those with RCB II and III. Pathologic tumor stage ($P$ = .0072), lumpectomy versus mastectomy ($P$ = .0048), and p53 expression ($P$ = .0190) were independent predictors of recurrence-free survival. The RCB categories ($P$ = .0003) and tumor grade ($P$ = .0049) were independent predictors of overall survival. This is the first study to conduct a comprehensive analysis of biomarkers in neoadjuvant chemotherapy–treated patients versus an untreated group using the digital image analysis method. We have demonstrated for the first time the relationship between RCB, tumor biomarkers expression, and clinical outcome.
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## 1. Introduction

The primary objective of neoadjuvant chemotherapy (NAC) is to reduce tumor size, improve operability, and

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* Corresponding author. Department of Pathology, UT Southwestern Medical Center at Dallas, Dallas, TX 75235, USA.
*E-mail address:* venetia.sarode@utsouthwestern.edu (V. Rumnong Sarode).

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assess tumor response. Evaluation of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER2) by immunohistochemistry (IHC) is routinely performed before NAC for therapy planning. Knowledge of biomarker status after NAC is important because this may influence adjuvant systemic therapy. There are conflicting reports on the effect of NAC on biomarker expression. Some studies have shown that NAC can alter biomarker expression, whereas others reported no significant change [1-3]. However, the major limitations of the previous studies were the small number of cases. Also, biomarker assessment was performed by manual methods, which is subjective and lacked reproducibility. Digital image analysis (IA) provides objective, reproducible, and quantitative measurement of biomarker expression with less interobserver and intraobserver variability than manual methods [4-6]. In addition, preanalytic variables such as tissue processing, tumor heterogeneity, and sampling error can lead to inconsistencies in biomarker results [7-9]. The lack of a control group in many of these studies makes it difficult to conclude if change in expression was caused by the effect of NAC or preanalytic variables.

The pathologic measurement of residual disease after NAC is an important prognostic parameter that can influence the outcome of these patients. In several studies, pathologic complete response (pCR) was a predictor of long-term survival [10-13]. However, in patients with incomplete response, residual disease can range from minimal to extensive. Recently, Symmans et al [14] described a method for estimating residual tumor in post-NAC surgical specimens using routine pathologic parameters such as tumor size and cellularity, extent of nodal involvement, and size of metastasis. The residual cancer burden (RCB) classification stratified residual disease into 4 groups, from 0 (pCR) to III (extensive residual disease). The RCB was shown to be a prognostic indicator of distant relapse–free survival and also provided prognostic value for patients with stage II and stage III disease [14].

The main objectives of this study were to investigate the effect of NAC on the expression of ER, PR, HER2, Ki-67, and p53 evaluated by IA in patients with stage 2 to 4 invasive breast cancer analysis (IBCA). We explored the relationship between baseline biomarker expression and extent of residual disease using the RCB classification and also determined if change in expression was associated with tumor response. Relationship between biomarkers and RCB with recurrence-free survival (RFS) and overall survival (OS) was also analyzed.

## 2. Materials and methods

We retrospectively identified 203 patients with clinical stage 2 to 4 IBCA treated with NAC at our institution between the years 2000 and 2010. Pathology information including tumor size, nodal status, histologic subtypes (World Health Organization classification), and Nottingham tumor grade were obtained from the surgical pathology files. Results of ER, PR, HER2, Ki-67, and p53 were obtained from the IA laboratory database. Clinical information including race/ethnicity, age at diagnosis, clinical tumor size and stage, presurgical chemotherapy, surgery, and follow-up was obtained from the electronic medical records. The institutional review board of UT Southwestern Medical Center approved this study.

### 2.1. Measurement of RCB

Two pathologists performed a retrospective review of archived histology slides and pathology reports. For estimation of RCB, the largest 2 dimensions (in millimeters) of tumor/tumor bed, overall percentage of tumor cellularity and in situ component, number of positive lymph nodes, and size of the largest metastasis were assessed for each case. The Web-based MD Anderson RCB calculator was used for estimation of RCB (http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3).

The RCB class was assigned using the RCB index and RCB 0, RCB I, RCB II, and RCB III corresponding to pCR, near-complete response, moderate, and extensive residual disease, respectively.

We also analyzed 100 consecutive cases of IBCAs without NAC (control group) diagnosed during the same period with biomarker results on core biopsies and subsequent excisions to minimize the effect of tissue fixation, tumor heterogeneity, and sampling error. A comparison of biomarkers on the paired specimens was performed in the treated versus control groups.

### 2.2. Chemotherapy regimens

Patients received standard anthracycline/taxane-based therapy in 125 (72.6%) of 172. Also, 28 (16.2%) of 172 HER2-positive patients received trastuzumab-based treatment. Fourteen patients received other combinations of chemotherapy.

### 2.3. IHC and quantification of biomarkers

All biomarker analyses were performed in the Clinical Laboratory Improvement Act–certified laboratory. Immunohistochemical staining was performed using standardized automated techniques on 4-$\mu$m paraffin-embedded sections. The scoring and quantification of biomarkers was performed by IA according to the manufacturer's guidelines. The Automated Cellular Imaging System (ACIS; Clarient, Inc, San Juan Capistrano, CA) was used from 2000 to November 2009, and the Ventana Imaging System (VIAS; Ventana, Medical Systems, Tuscon, AZ) from December 2009 onward. Both systems were validated before clinical use.

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