# **Residual cancer burden (RCB)** (Core)

Multivariable response predictors combine individual prognostic elements. The residual cancer burden (RCB) index combines residual carcinoma in the breast (tumour size and cellularity) and in the lymph nodes (number of lymph nodes with carcinoma and extent of largest lymph node metastasis) into a single continuous RCB score that can be divided into RCB class 0 corresponding to pCR, RCB I minimal residual disease, RCB II moderate residual disease, and RCB III extensive residual disease. After neoadjuvant chemotherapy (with anti-HER2 therapy when applicable) the RCB score and classes are prognostic overall, within American Joint Committee on Cancer (AJCC) anatomic stage groups[1] and within breast cancer subtypes (triple negative, HR+ HER2-, HR+ HER2+, and HR- HER2+). RCB was originally described in 2007.[2] A standard operating procedure (SOP), teaching materials and a calculator are freely available at: http://www.mdanderson.org/breastcancer_RCB.[3] RCB is widely used in a variety of settings and is reproducible.[2,4,5] A recent pooled meta-analysis including over 5,000 patients confirmed that RCB score and classes were independently and strongly prognostic in all breast cancer subtypes.[6] The AJCC 8$^{th}$ edition Staging System[1] recommends adding additional descriptions to staging, such as the number of foci, total area of involvement, RCB, etc. AJCC stage and RCB provide complementary information.

Residual cancer burden (RCB) score and class can be included in the pathology report. For best results it is important to follow the SOP including appropriate sampling of the tumour bed and to use uniform definitions for the elements as explained in the SOP and this dataset. It is preferable if the pathologist interpreting the RCB can also report the calculated result. It is also helpful to provide the core elements used to calculate RCB when RCB class and score are reported. If the RCB score is not calculated, then the required information should be provided and formatted in the report such that any member of the clinical team reading the report would exactly enter the correct information and obtain the correct result from the calculator, as this facilitates calculation of RCB at a later date by the clinical team or when access to the online calculator is not available at the site of reporting.

Combining the core prognostic elements from the surgical specimen into a single score with corresponding prognosis improves reproducibility by dampening the effects of variable results of individual elements due to differences in interpretation or sampling (for example, if there are multiple foci of invasive carcinoma in an area of fibrosis this would give a large tumour with low cellularity if they are interpreted as a single tumour or a small tumour with high cellularity if only the largest individual focus is assessed (see Figure 1, **TUMOUR DIMENSIONS**), and facilitates interpretation, comparisons, and clinical decisions. Other factors such as pre-treatment burden of disease and tumour biology may also be important predictors of prognosis in a given situation.

When multiple separate lesions are present the one with the greatest burden of residual disease determines RCB. This is often the largest lesion. It is useful to also calculate the RCB score for the smaller lesions if they are more cellular and may yield a higher RCB score. If the separate invasive carcinomas are distinct by tumour type, grade and/or receptor status then RCB should be reported for each. For example, after neoadjuvant therapy with chemotherapy and anti-HER2 therapy in a patient with a synchronous HER2 positive tumour and HR positive HER2 negative tumour response in both tumours is expected to be different. RCB is expected to be prognostic in both tumours. In particular, the response in the HER2 positive tumour will determine the need to escalate subsequent therapy.

Residual cancer burden (RCB) cannot be reliably calculated if the positive lymph nodes were removed prior to neoadjuvant therapy as the number of lymph nodes with carcinoma and the extent of the largest lymph node metastasis are needed. Areas of fibrosis and extracapsular extension are included in the measurement. The 'RCB size of the largest lymph node metastasis' may be different from the size used to determine AJCC[1] N categories. For ITCs, a number <1 can be entered for the extent of the largest lymph node metastasis. The number of involved nodes used to calculate RCB includes the number of lymph nodes with macrometastases, micrometastases and ITCs. Involved internal mammary lymph nodes are included in the lymph node count to calculate RCB.

At this time, pathology response endpoints following neoadjuvant endocrine therapy are insufficiently validated to be considered as core elements. The PEPI is recommended as a non-core element when reporting response from neoadjuvant endocrine therapy. PEPI has not been extensively validated for prognosis, but the results to date with PEPI are promising and it combines parameters that have known prognostic information: tumour size, involved nodes, proliferative suppression, and persistence of estrogen receptor (ER) positive status of the residual invasive cancer.

Residual cancer burden (RCB) and yp stage (Union for International Cancer Control (UICC)[7]/AJCC[1] TNM) were not designed for prognosis after neoadjuvant endocrine therapy, and their prognostic value has not been demonstrated in this setting. It is already clear that patients with ER positive disease who achieve a low RCB or ypStage from chemotherapy-based treatment will have an excellent prognosis with adjuvant endocrine therapy. However it remains unproven whether achieving that same response with neoadjuvant endocrine therapy would impart the same excellent prognosis with continued adjuvant endocrine therapy as there are currently no data. The elements to determine RCB and the RCB score can still be used to describe the findings in the surgical specimen post neoadjuvant endocrine therapy but it would be prudent to add a note to the report that the prognostic value of RCB score and class has not been demonstrated in the setting of neoadjuvant endocrine therapy.

There are insufficient data to support specific prognostic tools as core elements for other types of neoadjuvant therapy. However, the elements in this dataset are reasonable to describe the pathological findings in these more unusual or investigational treatment settings.

**References**


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