Evaluación de la respuesta patológica completa tras tratamiento neoadyuvante en cáncer de mama

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**Pathological Response**

- Pathological response is measured by the amount of tumor cells persisting in the surgical specimen after treatment (breast and lymph node).

- Different classification systems to assess pathological response are used.

- Non standardized gross sampling protocols.

- Non standardized Pathology report.
# Assessment of Pathological Response

<table>
<thead>
<tr>
<th>Classification system</th>
<th>Primary tumor</th>
<th>pCR in the breast</th>
<th>Lymph nodes</th>
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</table>
| **NSABP B-18**        | pCR: no invasive tumor cells  
                        | pPR: scattered/small clusters of tumor cells in a desmoplastic or hyaline stroma | No invasive carcinoma | Yes, number, size of metastasis |
| **Chevallier**        | Ch(1). no tumor either in the macroscopic or microscopic evaluation  
                        | Ch(2). in situ carcinoma but no invasive tumor or metastatic lymph nodes  
                        | Ch(3). Invasive carcinoma with  
                        | Ch(4). few modifications | No invasive or in situ carcinoma | Yes |
| **Sataloff**          | T-A. minimal residual tumor, scattered cells <5% either focal or widespread (sampling!)  
                        | T-B. >50%  
                        | T-C. <50% but  
                        | T-D. no therapeutic effect | Total or near total therapeutic effect | Yes |
| **Penault-Llorca**    | Class 1. Ch(1+2)+TA-NA-NB. almost/complete response, no node involvement  
                        | Class 2. Ch(3)+TA-NC-ND, TB or TC any N. partial response, no class 1 or 2  
                        | Class 3. Ch(4)+T-D any N. no therapeutic effect | Total or near total therapeutic effect, absence node involvement | Yes |
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<td><strong>AJCC/pTNM (y)</strong></td>
<td>ypT</td>
<td>No invasive carcinoma</td>
<td>ypN</td>
</tr>
<tr>
<td><strong>MNPI (modified Nottingham prognostic index)</strong></td>
<td>0.2 x tumor size (cm) + lymph node status (1. node negative, 2. 1-3 positive lymph nodes, 3. ≥4 positive lymph nodes) + grade</td>
<td>No invasive carcinoma</td>
<td>Yes</td>
</tr>
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</table>
| **Pinder et al.**     | 1. cPR. no residual carcinoma, DCIS allowed  
2. pPR. i. minimal residual disease (<10%), ii. response to therapy 10-50%, iii. >50% tumor cellularity remains with features of response  
3. no evidence of response | No invasive carcinoma | Yes |
| **Miller y Payne system** | Grade 1. no change or some alteration to individual cells but no reduction  
Grade 2. minor loss of tumor cells but still high, up to 30% of loss  
Grade 3. 30-90% reduction  
Grade 4. marked disappearance, small clusters or scattered cells, >90% loss  
Grade 5. no malignant cells in the site of the tumor, fibroelastosis, macrophages, DCIS allowed | No invasive carcinoma, may be present DCIS | No |
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<td><strong>RCB (residual cancer burden)</strong></td>
<td>RCB index (a continuous index combining pathological measurements of primary tumor -size, cellularity- and nodal metastasis -number and size- for prediction of distant relapse free survival (DRFS) in multivariate Cox regression analyses. in breast or lymph node RCB-I. partial response RCB-II. partial response RCB-III. chemoresistant</td>
<td>No invasive carcinoma</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Rouzier et al.</strong></td>
<td>Nomogram developed to predict residual tumor size and eligibility for breast conservation surgery calculated in a multivariate model initial tumor size, grade, histologic type were associated with a residual tumor &lt;3cm. initial tumor diameter, histologic type, multicentricity and ER status were independently associated with breast conservation</td>
<td>No invasive carcinoma</td>
<td>No</td>
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<td><strong>Jeruss et al.</strong></td>
<td>Cox proportional hazards models were used to create the clinical pathological scoring system (CPS) clinical stages ≥IIB or IIIB and pathological stages ≥ypIIA or ypIIIC were independently associated with a decreased DSS</td>
<td>No invasive carcinoma</td>
<td>Yes</td>
</tr>
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</table>
Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group


Recommendations for standardized pathological characterization of residual disease for neoadjuvant clinical trials of breast cancer by the BIG-NABCG collaboration

**pCR Definition**
* (FDA, 2013 y BIG-NABCG, 2015)

- Pathological complete response (pCR) is defined as no residual invasive breast cancer in the breast (DCIS can be present), and no evidence of lymph node metastasis.

- ypT0/ypTis ypN0 (AJCC staging).


Proenzano E, et al. Mod Pathol 2015; 28: 1185-201
Measurement of Residual Breast Cancer Burden to Predict Survival After Neoadjuvant Chemotherapy

W. Fraser Symmans, Florentia Peintinger, Christos Hatzis, Radhika Rajan, Henry Kuerer, Vicente Valero, Lina Assad, Anna Poniecka, Bryan Hennessy, Marjorie Green, Aman U. Buzdar, S. Eva Singletary, Gabriel N. Hortobagyi, and Lajos Pusztai

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<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
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<td>Primary tumor bed dimensions ($\sqrt{d_1d_2}$)</td>
<td>1.24 (1.04 to 1.48)</td>
<td>.02</td>
</tr>
<tr>
<td>Cellularity fraction of invasive cancer ($f_{inv}$)</td>
<td>7.37 (2.16 to 25.1)</td>
<td>.001</td>
</tr>
<tr>
<td>Size of largest metastasis ($d_{met}$)</td>
<td>1.17 (0.99 to 1.38)</td>
<td>.06</td>
</tr>
<tr>
<td>No. of positive lymph nodes</td>
<td>1.11 (1.04 to 1.19)</td>
<td>.002</td>
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Handling of macroscopic samples

- Orientation (according to a pre-defined surgical protocol)
- Good fixation (mastectomy)
- Detailed clinical information is essential
  i. site of tumor /tumors may be especially difficult to determine in the macroscopic specimen when good responses
  ii. marker such a wire coil or seed.
Summary of Key Points for Pathologic Assessment of the Primary Tumor Bed

Define the dimensions of residual tumor bed and estimate the percent of that area that is cancer.

1. **GROSS**: Identify the probable tumor bed and describe this macroscopic finding:
   a. Report the measurements of the largest gross dimensions (prefer three dimensions, but minimum is two dimensions).
b. Submit the largest cross-sectional area for histology and specifically describe those blocks in the Section Code:
   i. Try to indicate how they are oriented by photography, radiography, photocopy, or intelligent description (e.g., “sections B1 – B7 cross section of tumor bed in rows from antero-superior to postero-inferior”).
   ii. If additional sections are from surrounding tissues, then describe those as well.
   iii. Five representative sections from a big, obvious tumor bed should be sufficient.
2. **MICROSCOPY.** Review the slides that correspond to the tumor bed (± surrounding tissues):
   a. Estimate the extent of spread of residual cancer relative to the gross tumor bed:
      i. If similar to the gross description, then keep the original measurements.
      ii. If obviously different, then revise the dimensions of the tumor bed based on
          the microscopic review of the tumor bed.
iii. Suggestion: Dotting the perimeter of cancer in each slide can be helpful to reconstruct the tumor extent across multiple slides (see point 1-b-i).
b. Using the microscope, make visual snapshots of cancer cellularity as you go from field to field across the defined tumor bed from one end to the opposite (e.g., left to right, then top to bottom) to estimate the:

i. Average cancer cellularity (%) across the entire tumor bed. This is all cancer, whether invasive or in situ.

ii. Average percent of the cancer within the tumor bed that is in situ.

```
tumor bed section code slides
A1 A2 A3 A4 A5
Average %CA per Slide
Slide A1 20%
Slide A2 30%
Slide A3 40%
Slide A4 20%
Slide A5 30%
OVERALL 30%
%CIS 1%
```
Residual Cancer Burden Calculator

*Values must be entered into all fields for the calculation results to be accurate.

(1) Primary Tumor Bed
- Primary Tumor Bed Area: 2.5 (mm) X 2 (mm)
- Overall Cancer Cellularity (as percentage of area): 30 (%)
- Percentage of Cancer That Is in situ Disease: 5 (%)

(2) Lymph Nodes
- Number of Positive Lymph Nodes: 3
- Diameter of Largest Metastasis: 3 (mm)

Residual Cancer Burden: 2.687
Residual Cancer Burden Class: RCB-II
pCR predictive factors

• Histological type.
• Histological grade.
• TILs.
• RE/PR.
• HER2.
• Ki67.
• Subrogate IHC molecular subtype.
• Molecular subtype.
Should we analyze predictive markers after treatment?

- RE change (13-18%)
- RP change (26-32%)
- Her-2 change (6-9%)
  - Her-2 lost associates to poor prognosis
- High Ki67 associates to poor prognosis.
- Change to TNBC associates to poor prognosis.
- TILs.
- There is not a formal recommendation to analyse predictive markers after neoadyuvan therapy.

Provenzano E, et al, 2015