Criterios de respuesta patológica con los distintos subtipos de cáncer de mama. ¿Qué cambios se dan en el tejido postquimioterapia y qué dificultades se plantean para evaluar la respuesta?

José Palacios Calvo

Servicio de Anatomía Patológica
Pathological Response

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

• Non standardized gross sampling protocols.

• Non standardized Pathology report.

• Different classification systems to assess pathological response are used.
## 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>
</tr>
</thead>
<tbody>
<tr>
<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>
</tbody>
</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. up to 30% of loss  
Grade 3. 30-90% reduction  
Grade 4. >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 invasive carcinoma | Yes |
## Assessment of Pathological Response

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<tr>
<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. RCB-0. no carcinoma 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 No invasive carcinoma Yes 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>
</tr>
<tr>
<td><strong>Jeruss et al.</strong></td>
<td>Cox proportional hazards models were used to create the clinical pathological scoring system (CPS) clinical stages ≥IIIB 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>
</tbody>
</table>
## Assessment of Pathological Response

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</thead>
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<tr>
<td><strong>NSABP B-18</strong></td>
<td>pCR: no invasive tumor cells pPR: scattered/small clusters of tumor cells in a desmoplastic or hyaline stroma</td>
<td>No invasive carcinoma</td>
<td>Yes, number, size of metastasis</td>
</tr>
<tr>
<td><strong>Chevallier</strong></td>
<td>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</td>
<td>No invasive or in situ carcinoma</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Sataloff</strong></td>
<td>T-A. minimal residual tumor, scattered cells &lt;5% either focal or widespread (sampling!) T-B. &gt;50% T-C. &lt;50% but T-D. no therapeutic effect</td>
<td>Total or near total therapeutic effect</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Penault-Llorca</strong></td>
<td>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</td>
<td>Total or near total therapeutic effect, absence node involvement</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group

Elena Proenzano\textsuperscript{1}, Veerle Bossuyt\textsuperscript{2}, Giuseppe Viale\textsuperscript{3}, David Cameron\textsuperscript{4}, Sunil Badve\textsuperscript{5}, Carsten Denkert\textsuperscript{6}, Gaëtan MacGrogan\textsuperscript{7}, Frédérique Penault-Llorca\textsuperscript{8}, Judy Boughey\textsuperscript{9}, Giuseppe Curigliano\textsuperscript{10}, J Michael Dixon\textsuperscript{11}, Laura Esserman\textsuperscript{12}, Gerd Fastner\textsuperscript{13}, Thorsten Kuehn\textsuperscript{14}, Florentia Peintinger\textsuperscript{15,16}, Gunter von Minckwitz\textsuperscript{17}, Julia White\textsuperscript{18}, Wei Yang\textsuperscript{19} and W Fraser Symmans\textsuperscript{20} on behalf of the Residual Disease Characterization Working Group of the Breast International Group-North American Breast Cancer Group (BIG-NABC) collaboration

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

V. Bossuyt\textsuperscript{1*}, E. Proenzano\textsuperscript{2}, W. F. Symmans\textsuperscript{3}, J. C. Boughey\textsuperscript{4}, C. Coles\textsuperscript{5}, G. Curigliano\textsuperscript{6}, J. M. Dixon\textsuperscript{7}, L. J. Esserman\textsuperscript{8}, G. Fastner\textsuperscript{9}, T. Kuehn\textsuperscript{10}, F. Peintinger\textsuperscript{11,12}, G. von Minckwitz\textsuperscript{13}, J. White\textsuperscript{14}, W. Yang\textsuperscript{15}, S. Badve\textsuperscript{16}, C. Denkert\textsuperscript{17}, G. MacGrogan\textsuperscript{18}, F. Penault-Llorca\textsuperscript{19}, G. Viale\textsuperscript{20} & D. Cameron\textsuperscript{21} of the Breast International Group-North American Breast Cancer Group (BIG-NABC) 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).


Provenzano 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<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>
</tr>
</tbody>
</table>
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, Lisa Assad, Anna Poniecka, Bryan Hennessy, Marjorie Green, Aman U. Buzdar, S. Eva Singletary, Gabriel N. Hortobagyi, and Lajos Puzsztai
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 as a wire coil or seed.
Handling of macroscopic samples
clip de marcaje

lecho tumoral macroscópico (d1xd2)
Imágenes cedidas por Dr. Vicente Peg
Microscopic evaluation of tumor the tumor bed

(Supplemental Information)

(Supplemental Information)
Microscopic evaluation of tumor the tumor bed

Largest dimension of tumor bed

(A) Two dimensions of largest cross section of entire area involved by scattered residual tumor foci

(B) Extent of largest contiguous focus
## Microscopic evaluation of tumor cellularity

![Diagram showing the process of microscopic evaluation of tumor cellularity](image)

### Tumor Bed
- Section Code
- Slides

<table>
<thead>
<tr>
<th>Section Code</th>
<th>Slides</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>A1</td>
</tr>
<tr>
<td>A2</td>
<td>A2</td>
</tr>
<tr>
<td>A3</td>
<td>A3</td>
</tr>
<tr>
<td>A4</td>
<td>A4</td>
</tr>
<tr>
<td>A5</td>
<td>A5</td>
</tr>
</tbody>
</table>

### Cellularity and CIS

<table>
<thead>
<tr>
<th>Slide</th>
<th>%CA Per Slide</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>20%</td>
</tr>
<tr>
<td>A2</td>
<td>30%</td>
</tr>
<tr>
<td>A3</td>
<td>40%</td>
</tr>
<tr>
<td>A4</td>
<td>20%</td>
</tr>
<tr>
<td>A5</td>
<td>30%</td>
</tr>
</tbody>
</table>

**Overall %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
HER2

p63
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
Residual proliferative cancer burden to predict long-term outcome following neoadjuvant chemotherapy

A. Sheri¹,²,³*, I. E. Smith¹, S. R. Johnston¹, R. A’Hern⁴, A. Nerurkar⁵, R. L. Jones⁶, M. Hills², S. Detre², S. E. Pinder⁷, W. F. Symmans⁸ & M. Dowsett¹,²,³
Conclusions

- Pathological response should be evaluated in both breast and lymph node.
- Adequate clinical information and presurgical location of tumor is necessary.
- A standardized gross sampling protocol should be used.
- A standardized protocol for microscopic evaluation should be used.
- Residual Cancer Burden is the preferred method for quantification of residual disease.
- The final report should also include the ypT, ypN stages.