Evaluation of Breast Specimens after Neoadjuvant Chemotherapy

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Indications of Neoadjuvant Chemotherapy

• Management of locally advanced invasive breast cancer including inflammatory breast cancer
• ‘Down-staging’ of large inoperable cancers to permit surgical resection
• Routine management of women with high risk disease who would require adjuvant chemotherapy based on biological tumor characteristics and clinical-radiological findings
Advantages of Neoadjuvant Therapy

• Potential for tumor down sizing with an increase in the rate of breast conserving surgery

• Ability to monitor treatment response and tailor subsequent locoregional and systemic therapy - more individualized patient care
  • Patients with pCR may not benefit from further regional therapy such as adjuvant radiotherapy
  • Patients with poor response can be identified and entered into trials of novel targeted agents
Advantages of Neoadjuvant Therapy

• Evaluation of treatment response to new agents using pathological complete response (pCR) as a surrogate marker of outcome

• Neoadjuvant studies smaller, cheaper, faster results
Guidance for Industry
Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2014
Clinical/Medical

E. Recommendations for Pathology Standard Operating Procedures

Pre Treatment Evaluation - Breast

- Pre treatment breast CNB must be adequate for unequivocal diagnosis of invasive carcinoma and assessment of key prognostic/predictive factors
  - Histological type and grade
  - ER/ PR /HER2 status
  - Other biomarkers- Ki67, multigene assays
- If multiple lesions biopsy of at least 2 foci is advised to confirm multifocality and look for heterogeneity
- Additional biopsies for translational research studies
Pre Treatment Evaluation - Axilla

- Routine axillary U/S with histological assessment of abnormal nodes by CNB or FNA
- Pre-treatment SLNB not advised unless positive result will influence decision to give chemotherapy
- Nodal response is an important prognostic factor independent of response in the breast
Specimen Handling

• One of the most critical steps in accurately evaluate response to NAC is the macroscopic (gross) assessment of the specimen

• A multidisciplinary approach with close clinical/radiological correlation to map the precise location of the tumor bed is preferable to exhaustive blind sampling
Specimen Handling

• To achieve this it is essential that the surgical request form contains adequately detailed clinical information

• Access to radiological images, particularly MRI scans, at the time of specimen dissection is also useful
• 38 yrs female presented with a 2.5 cm palpable breast mass. Physical exam revealed prominent ALN

• She had a core bx of her breast mass and FNA of ALN

• Her breast bx showed a high-grade IDC and ALN FNA was positive for metastatic carcinoma
AJCC Clinical Stage: T2N2M0
Classification: Stage III

Her expected survival is 40%
• The patient was treated with neoadjuvant chemotherapy including four cycles of cytoxan adriamycin and taxol
• Clinically the mass became softer and smaller
• Lymph nodes were no longer palpable
• MRI showed complete resolution of the mass
• Patient underwent an excision of the mass and complete axillary node dissection
Neoadjuvant Chemotherapy

• The tumor bed consisted of an area of histiocytes and lymphocytes. No residual carcinoma was identified
• Sixteen lymph nodes were excised
• All were negative for metastatic carcinoma
Neoadjuvant Chemotherapy

Her expected survival is over 90%
Neoadjuvant Chemotherapy

- Standard therapy for locally advanced breast carcinoma
- Increasingly used for early stage operable disease
- A wide range of pathologic changes can occur after neoadjuvant chemotherapy
Methods to Determine Response to NAC

- Clinical examination
- Imaging methods (mammographs, US, MRI)
- Histopathologic evaluation
Neoadjuvant Chemotherapy

Clinical Response

• 60-80% patients with locally advanced breast carcinoma show measurable clinical response

• Imprecise
• Clinical/imaging methods
  – False negative 40-60%
  – False positive 20-30%

Histopathologic evaluation is gold standard
Neoadjuvant Chemotherapy

Pathological Response

• PCR is defined as complete absence of invasive carcinoma in the breast and no residual metastatic carcinoma in lymph nodes
• PCR occurs 5-30% of patients with locally advanced breast carcinoma after NAC
Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group

Proenzano E et al. Mod Pathol 2015;1185-201
pCR = no invasive cancer in breast or lymph nodes

What do we look at in the pathologic examination after NAC?

All prognostic factors important before treatment are also important after treatment

- Residual Tumor pattern
- Tumor size
- LVI
- Lymph node status
- Histologic type and grade
- Tumor biomarkers
Pathological Response

- Less than complete response (partial response) is difficult to classify
- There are different classification systems
Patterns of Tumor Response

Concentric shrinking
• Tumor size more difficult to assess after NAC
• If there is a single lesion present on pre-treatment imaging, then treat residual disease as a single tumor, especially if tumor cells are present within a reactive stromal background consistent with a solitary tumor bed
Patterns of Tumor Response

Scatter pattern
7th edition AJCC – largest contiguous area of tumour cells (B)

The combination of size and residual tumor cellularity is the best indicator of response
Measuring Tumor Size post NAC

(A) 2 dimensions of largest cross-section of entire area involved by scattered residual tumor foci

(B) Extent of largest contiguous focus
Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group

Provenzano E et al. Mod Pathol 2015;1185-201
Placement of clip prior to treatment is very helpful
Neoadjuvant Chemotherapy

- Identification of “Tumor Bed” essential
- Can be very difficult if there is a marked clinical/imaging response
- Requires thorough evaluation
How extensively these specimens need to be sampled?

- If gross tumor is present limited sampling is adequate to establish the presence, size and cellularity of residual tumor
- 1-2 sections/cm of tumor is reasonable
- If tumor bed is ill defined more extensive sampling is necessary
Neoadjuvant Chemotherapy

Responses Are Not Uniform

Complete Response
- No Residual Disease

Partial Response
- Residual Nidus over small area
- Residual Scatter Cells Over Original Volume
NSABP B-18

pCR: No recognizable invasive tumor cells present

pPR: The presence of scattered individual or small clusters of tumor cells in a demosplastic or hyaline stroma

pNR: Tumors not exhibiting therapy related changes
• Grade 1: no reduction in overall cellularity
• Grade 2: a minor loss in overall cellularity (up to 30% loss)
• Grade 3: 30-90% reduction in cellularity
• Grade 4: >90% reduction in cellularity
• Grade 5: no residual invasive carcinoma
Classification of Breast Ca After NAC

Miller-Payne Grading System

Overall survival compared with histological response to chemotherapy

Disease free survival compared with histological response to chemotherapy

• Pts with grade 4 response have a significantly worse prognosis
• Identification of small foci of residual invasive carcinoma is important
• Main limitation is that it does not include response in lymph nodes
Residual Cancer Burden System MDACC

- Cellularity of residual carcinoma over the tumor bed
- Presence of lymph node metastasis
- Size of the largest lymph node metastasis

<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>
Pathologic Assessment of Tumor Bed

- **tumor bed**
- **section code**
  - A1
  - A2
  - A3
  - A4
  - A5
- **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 %CIS**
- 30%

See downloadable protocol and illustrations at www.mdanderson.org/breastcancer_RCB
Pathologic Assessment of Tumor Bed
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: [ ] (mm) X [ ] (mm)
- Overall Cancer Cellularity (as percentage of area): [ ] (%)
- Percentage of Cancer That Is In-situ Disease: [ ] (%)

(2) Lymph Nodes
- Number of Positive Lymph Nodes: [ ]
- Diameter of Largest Metastasis: [ ] (mm)
- Residual Cancer Burden: [ ]
- Residual Cancer Burden Class: [ ]

The following parameters are required from pathologic examination in order to calculate Residual Cancer Burden (RCB) after...
Residual Cancer Burden System (MDACC)

RCB-0  No carcinoma in breast or lymph nodes (pCR)
RCB-1  Minimal residual disease (marked response)
RCB-2  Moderate response
RCB-3  Minimal or no response (chemoresistant)
Residual Cancer Burden

Likelihood of distant relapse in patients with residual cancer burden
A: entire paclitaxel plus fluorouracil, doxorubicin, and cyclophosphamide cohort
B: subset without adjuvant hormone treatment
C: subset who received adjuvant hormone treatment

TNBC

Class | N  | %
--- | --- | ---
pCR  | 43  | 34
RCB-I | 18  | 14
RCB-II | 42  | 34
RCB-III | 22  | 18

HR+/HER2-

Class | N  | %
pCR  | 26  | 10
RCB-I | 34  | 13
RCB-II | 156 | 60
RCB-III | 45  | 17

HER2+

Class | N  | %
pCR  | 38  | 37
RCB-I | 17  | 17
RCB-II | 30  | 29
RCB-III | 17  | 17
Residual Disease in Breast and Nodes (RDBN)

• Modification of the Nottingham Prognostic Index (NPI)

RDBN = 0.2 x Tumor size (cm) + LN stage (0-3) + Histologic grade (1-3)

Residual Disease in Breast and Nodes (RDBN)

• Lymph node stage:
  – 0 = neg
  – 1 = 1-4 LNs
  – 2 = 5-7 LNs
  – 3 = ≥ 8 LNs

• Grade is determined after therapy

Residual Disease in Breast and Nodes (RDBN)

4 groups are identified with significant prognostic differences

Provide the following information:

1. pCR (ypT0 ypN0 and ypT0/is ypN0) versus residual disease

2. ypT and ypN Stage using the current AJCC/UICC staging system

A single standardized approach to macroscopic and microscopic pathologic examination makes it easy to reliably provide information for clinical practice.
Neoadjuvant Chemotherapy

Histopathological Changes

- Lobular atrophy and calcification
- Epithelial atypia
- Stromal fibrosis
- Inflammation
- Cytoplasmic vacuolization
- Pigmented and foamy macrophages
- Interlobular fibrosis
- Fat necrosis
- Duct ectasia
Neoadjuvant Chemotherapy

Cytomorphologic Changes

- Biologic and clinical significance poorly understood
- 50% of cases nuclear grade changes after NAC
- ? malignant potential to grow and metastasize
Neoadjuvant Chemotherapy

Cytomorphologic Changes

Similar changes can occur in lymph node metastases
Lymph node changes

Partial response LN

pCR breast
Significance of nodal response

Nodal status post NAC a strong predictor of outcome

von Minckwitz G et al. JCO 2012;30:1796-1804
Neoadjuvant Chemotherapy

Lymph Node Metastases

- Number of positive nodes
- Even small clusters are significant
- Evaluation of ENE can be difficult
• Limited data about correlation of hormone receptor and HER2 status pre and post treatment

• ER - 2-30% change in status

• Similar outcome in patients who converted from ER+ vs to ER-ve after treatment

• PR - 5-50% change in status
Receptor Testing post NAC

- HER2 - results vary depending upon whether IHC or ISH is used
- 0-21% conversion on HER2 IHC
- 0-43% loss of HER2 gene amplification
- Association between loss of HER2 positivity and worse outcome – resistance vs negative subclone

Mittendorf et al, Clin Cancer Res 2009
Receptor Testing post NAC

Consider retesting if:

- Identification of morphologically distinct areas on final excision
- Inadequate tumor on CNB
- If there is a change in status which is predictive of response to therapy?

Treat positive result
Neoadjuvant Chemotherapy

Take Home Messages

• NAC is being used more frequently
• Pathologic response is an important predictor of survival
• pCR provides the best prognosis
• Better classification of pPR category is needed
Neoadjuvant Chemotherapy

Take Home Messages

• Pathologists should be familiar to ensure that chemotherapy induced changes in non-neoplastic tissue is not mistaken for residual tumor or that residual tumor is not confused with non-neoplastic cells.
• Record pretreatment phenotype and grade
• Accurate assessment of residual tumor requires multidisciplinary teamwork
• Require standardized procedures to evaluate the gross specimen, record a map of the tissue sections related to the gross & imaging findings, and relate the histopathologic findings to that map
Summary

• Uniform terminology is helpful
  - pCR in breast and nodes
  - Report presence and extent of in situ residual disease
Summary

• Pathology reports should include:
  ▪ Histologic type
  ▪ Size (as a single focus or tumor bed)
  ▪ Cellularity
  ▪ Margins
  ▪ LVI
  ▪ Lymph nodes
Thank You!

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