Evaluation of Breast Specimens after Neoadjuvant Chemotherapy

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Indications of Neoadjuvant Chemotherapy

• Management of locally advanced invasive breast ca including inflammatory breast ca
• ‘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 tumour 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 individualised 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

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.

Neoadjuvant Chemotherapy

- 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.
Her expected survival is 40%

Neoadjuvant Chemotherapy

- 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

Neoadjuvant Chemotherapy

- 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
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

Methods to Determine Response to NAC

- 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 ca in lymph nodes
- PCR occurs 5-30% of patients with locally advanced breast carcinoma after NAC
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**Pathological Response**

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

**Patterns of Tumor Response**

**Concentric shrinking**

- [Images of concentric shrinking patterns]

**Scatter pattern**

- [Images of scatter pattern patterns]
Measuring Tumor Size post NAC

- 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.
Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group.

Measuring Tumor Size post NAC

- 7th edition AJCC – largest contiguous area of tumour cells (B)
- The combination of size and residual tumor cellularity is the best indicator of response

Significance of nodal response

Nodal status post NAC a strong predictor of outcome
Lymph node changes

Partial response LN  pCR breast

Systems of Categorizing Response to Neoadjuvant Treatment

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

Miller-Payne System

- 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

- 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
Residual Cancer Burden

Systems of Categorizing Response To Neoadjuvant Treatment

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)
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

Neoadjuvant Chemotherapy

- Identification of “Tumor Bed” essential
- Can be very difficult if there is a marked clinical/imaging response
- Requires thorough evaluation
Responses Are Not Uniform

Tumor Bed

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
Placement of clip prior to treatment is very helpful
Neoadjuvant Chemotherapy

Histopathological Changes

• Lobular atrophy and calcification
• Epithelial atypia
• Fibrous stromal involution
• Inflammation
• Cytoplasmic vacuolization
• Pigmented and foamy macrophages
• Interlobular fibrosis
• Fat necrosis
• Duct ectasia
Neoadjuvant Chemotherapy

Cytomorphologic Changes

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

Similar changes can occur in lymph node metastases
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Lymph Node Metastases

- Number of positive nodes
- Even small clusters are significant
- Evaluation of ENE can be difficult
Receptor Testing post NAC

- 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 – 2-59% 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)

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

Neoadjuvant Chemotherapy

Take Home Messages

- Pathology reports should include:
  - Histologic type
  - Size (as a single focus or tumor bed)
  - Cellularity
  - Margins
  - LVI
  - Lymph nodes
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