NEXT GENERATION LEARNING

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USCAP
Creating a Better Pathologist
Assessment of the Axilla Post Neoadjuvant Chemotherapy

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Dr. Elena Provenzano declares she has no conflict(s) of interest to disclose.
Pre Treatment Evaluation - Axilla

- Routine axillary U/S with histological assessment of abnormal nodes by core biopsy 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
  - Invalidates post treatment grading of response using RCB
Assessment of axillary lymph nodes

• All nodes should be embedded in entirety
• Areas of myxoid change, fibrosis or collections of foamy macrophages suggestive of previous metastasis with response should be noted – intermediate prognosis compared with ‘true’ node negativity
• Low threshold for doing immunohistochemistry if suspicious of metastatic disease, especially if fibrosis
Lymph node changes
Lymph node changes
Lymph node changes – variable response

Complete response  Partial response  No response
Significance of nodal response

- Nodal status post chemotherapy is a strong predictor of outcome

von Minckwitz G et al. JCO 2012;30:1796-1804
Significance of nodal response

- Neo Tango – 44 patients (6%) residual disease in axilla despite pCR in the breast
- Residual nodal disease an independent predictor of poor prognosis, even in presence of pCR in the breast
Lymph node changes

Partial response LN

pCR breast
Significance of nodal response

- 403 pts proven node positive
- 22% axillary pCR (31% if ER neg) - 69% also pCR breast
- 4% of breast pCR had residual axillary disease
- Axillary node positive – 5 yr OS 72%, DFS 60%
- Axillary pCR – 5 yr OS 93%, DFS 87%

Hennessy et al., J Clin Oncol 2005;23:9304-11
Significance of nodal response

• Axillary conversion the MOST significant predictor of OS
• Size of residual breast tumour NOT predictive if residual nodal disease
• No influence of size of metastasis – prognosis still worse if < 0.1 mm
• Evidence of nodal response associated with improved DFS

Hennessy et al., J Clin Oncol 2005;23:9304-11
Significance of nodal response

- 277 pts, tumours > 3 cm
- 39% clinically node pos -> ypN0
- Number of positive nodes post chemo strongest predictor of survival
  Cure et al., Breast Ca Res Treatment 2002;76(1):37-45
- 122 pts, 52% node positive pre chemo
- Worse DFS/ OS with increased number of nodes and increasing size of metastasis
- Size of largest metastasis the strongest predictor of survival on multivariate analysis
- ITC’s regarded as node positive

ITC’s post chemotherapy

- Presence of isolated tumour cells in lymph nodes
- TNM – call ypN0(i+) BUT not pCR
- WHO – call node positive i.e. NOT pCR

- do NOT regard as pCR
- often background fibrosis indicating previous macrometastatic disease with regression – nodal equivalent of minimal residual disease
- measure size of entire deposit including intervening fibrosis
SLNB Timing: Pros and Cons

BEFORE Rx
Pros:
• Accurate staging before treatment – may guide decisions regarding need for chemo/ radio Rx
• More experience with SLN in this setting
• Low axillary recurrence rates
SLNB Timing: Pros and Cons

BEFORE Rx
Cons:

• Need for two operations
• May delay commencement of therapy
• Unnecessary ALND in patients who have axillary pCR (20-40%)
• Loss of information regarding chemotherapy response in axillary lymph nodes
• Can’t calculate RCB if SLN +ve
Pre Rx SLN

• Pre treatment SLN positive in 30-80% of patients
• Up to 80% of patients have negative clearance – disease removed by SLN versus response to therapy

SLNB Timing: Pros and Cons

AFTER Rx

Pros:

• Large series suggest comparable accuracy to SLN in adjuvant setting
• No delays to commencement of therapy
• Single procedure
• Information regarding nodal response – may be better predictor of survival
• Avoid unnecessary ALND in patients who have pCR in axilla
SLNB Timing: Pros and Cons

AFTER Rx

Cons:

• Limited data regarding axillary recurrence rates
• Variable false negative rate if node positive before Rx – up to 30% in some series
• Learning curve for procedure
Literature review

- Overview 27 studies including 4 large multicentre studies (2148 pts)
- IR 91% (71-100%)
- False negative 10.5% (0-39%)
- Accuracy 94% (77-100%)
- SLN involvement 49%, 40% only positive node (0-67%)
- Clinically N0 (266 pts) - IR 93%, accuracy 94.4%
- Clinically N1 (342 pts) – IR 88%, accuracy 94.5%

Van Deurzen et al. EJC 2009;45(18):3124-30
Node negative patients

- 3746 pts, 575 neoadjuvant chemoRx
- T1-3, clinically node negative (exam & U/S)
- NAC group younger, more T3 tumours
- IR – 99% adjuvant, 97% NAC
- False negative rate – 4% adjuvant, 6% NAC
- Fewer positive nodes in NAC group
  - T1 – 13% v 19%
  - T2 – 21% v 37%
  - T3 – 30% v 51%

- 55 months follow up – LRR 2.1% (1.2%), regional RR 1.2% (0.9%) and distant 7.5% (2.7%)

Literature review

• LN +ve patients
• Overview 19 studies including 793 pts
• IR 85% (68-100%)
• False negative 11% (0-33%)
• Axillary pCR rate 35%
• Authors own data - Axillary pCR rate 20%
  ER+/HER2-  4%
  triple –ve  33%
  ER-/HER2+  38%

NSABP-B27

- 2365 pts, 428 with SLN followed by ALND
- 76% clinically N0, smaller tumours = select group
- Identification rate 85% - improved to 90% in 2000 but trend N/S
- 67% 1-2 nodes sampled (1-12)
- 36% node positive; 56% SLN only positive node
- False negative rate 7% - N0 = 7%, N1-2 = 12% (N/S)
- pCR in breast, false negative 1.7%

Mamounas et al. JClin Onc 2005;23(12):2694-702
SENTINA study

cN0 → Pre NAC SLN (IR 99%)

- SLN -ve
  - No further axillary intervention

- SLN +ve
  - Repeat SLN post NAC
    - IR 61%
    - FNR 52%

cN+ → NAC

- Post NAC cN0
  - SLN
    - IR 80%
    - FNR 14.2%

- Post NAC cN+
  - ALND

Kuehn et al. Lancet Oncol 2013;14(7):609-18
• Eligibility – invasive breast cancer T0-4 N1-2 M0, proven axillary metastasis (Bx/FNA), no prior axillary surgery
• Axillary US pre and post Rx – *clip biopsied node*
• 701 women – 687 underwent SLNB post chemotherapy
• Detection rate 92.9% cN1 and 89.5% cN2
• Only significant factor in detection rate is use of dual agent mapping – blue dye only 77%, dye and radioisotope 94%

ACOSOG Z1071

- 585 women cN1 with at least 2 SLNs and completion axillary clearance
- Nodal pCR rate 41% - 21% ER+/ HER2-, 49% TN, 65% HER2+
- 20.6% residual nodal disease confined to SLN
- Overall FNR 12.6% (10.8% if dual mapping vs 20.8% single mapping only)
- FNR 9.1% if 3 or more SLNs examined compared with 21% if 2 nodes examined and 31% if only a single node examined

ACOSOG Z1071

• Conclusion – ‘changes in approach and patient selection that result in greater sensitivity would be necessary to support use of SLN as an alternative to ALND in this population’ -> avoid SLN if clinically evident residual nodal disease or poor response to therapy

Post treatment axillary US

- ACOSOG Z1071 - subsequent paper looking at results in relation to post treatment axillary US
- 30% of patients had an Abnormal AUS – 72% node positive, FNR 8.1%
- Abnormal AUS correlated with larger size of metastasis and more involved nodes
- 70% of patients had a Normal AUS – 56% node positive, FNR 15%
- If use AUS to triage patients for SLN, FNR = 9.8%

- Boughey J Clin Oncol 2015;33(30):3386-93
Post treatment axillary US

- 150 node positive patients
- 53% complete clinical response in the axilla
  88% palpation, 50% normalised U/S
- 26% pCR in the breast, 42% pCR in the axilla
- IR 93%, overall FNR 21%
- Normalised US – 50% pCR, FNR 16%
- Suspicious /indeterminate US – 33% pCR, FNR 28%

Targeted Axillary Dissection

• ACOSOG Z1071
• Follow up paper looking at patients with clip in biopsied node (n=170)
• 29 patients clip not located at time of axillary surgery
• 107 (76%) clip in SLN – FNR 6.8%
• 34 (24%) clip in non-SLN – FNR 19%
• 41% of cases clipped node was only positive node
• Correlation with overall LN status 93%

Targeted Axillary Dissection

• 12 patients with placement of clip in LN sampled by pre treatment FNA
• Removal of clipped node by wire localisation or placement of radioactive I\textsuperscript{125} labelled seeds
• All 12 nodes successfully removed
• 5 patients had concomitant SLN biopsy – in 4 clipped node was SLN
• 4/9 patients had residual nodal disease post NAC – clipped node positive in all

Caudle AS et al., JAMA Surg 2015;150(2):137-43
SN FNAC study

- 153 pts, T0-3, N1-2 with biopsy proven metastasis
- SLN cut at 2mm intervals, IHC on all negative nodes
- Axillary pCR rate 34.5%
- FNR 13.3%
- If ypN0(i+) included as node positive, FNR 8.4%
- ≥ 2 SLN FNR 4.9%
- Recommend ypN0(i+) be regarded as node positive
- Similar analysis on Z1071 – FNR becomes 8.7%

• Boileau et al., JClin Oncol 2015;33(3):258-64
SN FNAC

• HOWEVER no change in prognosis with occult metastasis identified by IHC alone
• 51 patients with axillary pCR
• Slide review with additional H&E level and cytokeratin immunohistochemistry
• Occult metastases identified by IHC in 8 patients
• 6 in 1 node only, 2 in 1 and 2 nodes respectively
• No difference in DFS or OS (100% DSS at 10 years)

Loya et al., Cancer, 2009;115:1605-12


