How does neoadjuvant therapy change the management of the axilla?
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Disclosures
• Nil
Does neoadjuvant therapy change the management of the axilla?

What to expect:
- Background (historical) review
- Evidence from the SENTINA and Z1071 trials
- Missing data for the post neoadjuvant chemotherapy setting
- Where to next?

Pretreatment assessment of the axilla
- Originally SLNBx was for T0-2 clinical N0, level I nodes, not medial cancers
- Superiority of dual technique*

- USS FNA/Core biopsy (+clip)
- MRI; CT; PET
- Mammogram; tomosynthesis
- Beware other causes of axillary lymphadenopathy - silicone, sarcoid, lymphoma………

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Historical evidence

- Conversion of N+ to N- in ~40% after neoadjuvant chemotherapy (NAC)
- SLN identification in 90%, false negative in 8-10% in 3 meta analyses*
- Changes in node on USS (MRI)(clinically)
- N0 or N1 to N0
- SNBx (+/- frozen section) ?OSNA
- ALND level I and level II (& III)

*King Y et al Br J Surg 2006; 93: 539-546
*Kelly AM et al Acad Radiol 2009; 16: 551-563
*van Duerzen DH et al Eur J Cancer 2009; 45; 31124-30

Historical evidence

- SLN identification improved from 56% to 94% 1994-1999 in 51 patients post NAC *
- 42% pCR correlates with normalised axillary node US post NAC; removing <2 SLNs has higher false negative rate** (n=150)
- FNR 9.8% with axillary US and SLNB***

*Breslin et al J Clin Oncol 2000 18:3480-6
***Boughey JC et al J Clin Oncol 2015; JCO.2014.57.8401

SENTINA trial*:

- 1737 pts, 103 hospitals, 6+ Anthracyclin NAC
- cN0, before NAC SNBx detection (dual) 99.1%
- SNB-, n=662
- SNB+, n=360

*Kuehn T et al Lancet Oncol 2013; 14: 609-618
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- cN0, before NAC SNBx detection (dual) 99.1%
- SNB-, n=662
- SNB+, n=360
- SNB2/ALND later ~ 70.8% became negative;

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Z1071 trial*:
- 649 (756) pts, 136 hospitals; T0-4, N1-2 clinically N1
- NAC then US axilla then SLB (dual technique in 79%) + ALND in all
- SLN not identified in 7.1%; Only 1 node excised in 12%
- Where 2+ nodes identified, pCR (nodes) of 41% (CI 37-45%)
- False negative rate of 12.6% (9.9-16%) (0 in cN2, 2SNs)

*Boughey JC et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: The American College of Surgeons Oncology Group (ACOSOG) Z1071 Clinical Trial JAMA 2013; 310: 1455-1461

**Cody HS Lancet Oncol 2013; 14: 567-8
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- “Given the FNR, changes in approach and patient selection are required for SLNB to replace ALND”

* Boughey JC et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: The American College of Surgeons Oncology Group (ACOSOG) Z1071 Clinical Trial. JAMA 2013; 310: 1455-1461

Imaging response:
In 272 patients post NAC *, detection of persistent LN metastases (47%) for cN1 axillary US/FNA+ patients:
- Axillary US: 69.8% sensitivity (n=146); MRI: 61.0% (n=139); PET/CT: 63.2% (n=38)

“Only patients with normal AUS undergo SLN surgery would potentially reduce the FNR in Z1071 patients with ≥ two SLNs removed from 12.6% to 9.8% when preoperative AUS results are considered as part of SLN surgery”**

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Hieken TJ et al Ann Surg Oncol 2013 20: 3199-204
Boughey JC et al J Clin Oncol 2015; JCO.2014.57.8401

**no substitute yet for surgical assessment of sentinel nodes 😊**
Where to next?

• Biological subtype matters: in Z1071, (n=694)
  – pCR 38.2% in TNBC,
  – 45.4% in HER2+,
  – 11.4 in HR+/HER2- (p<0.0001)*


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• Targeted axillary dissection: clip placed in positive axillary node(s) pre NAC; clipped node localised (wire, I^{131} seed) and during the SLNB SLNs and these (if not the SLN) removed**

**Mittendorf EA et al Ann Surg Oncol 2014; 21: 2468-2473

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• Successful in 12/12***........SSO, 8:10 Friday March 27th
Caudle et al

*Gooch Ann Surg Oncol 2014; 21:2897-2903
**Mittendorf EA et al Ann Surg Oncol 2014; 21: 2468-2473
***Caudle et al JAMA Surg 2015; 150: 137-43

Other (missing) evidence:

• Extracapsular extension*
• 2006-2013 pT1-2, cN0, <3 +SLN excluding NAC
• 7,865 women: 778 1-2 N+, no ECE; 2.8% extracapsular extension, 180<2mm 151>2mm
• Older, larger, ER+, lymphovascular invasion
• ECE associated with greater axillary burden: 33% with >2mmEC had ≥4 additional +nodes 9% with <2mm EC had ≥4 additional +nodes
• OR 14.2...............what about after NAC?

*Gooch Ann Surg Oncol 2014; 21:2897-2903
Where to next?

- NSABP/RTOG trial: conversion to clinically N0 post NAC on SLNB or ALND: RTx v no RTx
  Q: does the addition of RTx significantly reduce invasive breast cancer recurrence free interval*

- Alliance trial: positive SLNB: ALND v axillary irradiation (+SCF +internal mammary radiation)
  Q: is axillary radiation alone non-inferior to RTx + ALND for invasive breast cancer recurrence free interval*


Summary

- Post NAC ~40% conversion from N+ to N-
- Biological subtype matters (TNBC, HER2+)
- SLNB should be done after NAC (not before)
- Need to use dual technique and retrieve 3+ nodes (FNR 9.8%)
- Future: targeted axillary axillary dissection (clipped node localized + dual technique)?
- Ongoing trials of the role(s) of radiotherapy underway
Conclusions

• All axillary options can be performed after NAC*
• Clear evidence for SLNBx post NAC**
• Best where NAC likely to change the node status: TNBC, HER2+ (rarely in ER+, N2 or N3)
• There remains a need to optimise locoregional management

*Fontein et al EJSO 2013; 39: 417-424
**Cody HS Lancet Oncol 2013; 14: 567-8