The Breast Post NACT

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NACT

- Allows breast conservation in patients who otherwise would require mastectomy

- Improved cosmesis in those having breast conserving surgery

- Allows oncologist to evaluate tumour response and change treatment

- Prognostic information obtained on imaging which can complement conventional prognostic data such as initial staging, tumour grade and receptor status

- Allows time for genetic testing and subsequent surgical management

Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) CTNeoBC*

- 12 NACT randomised trials identified (n=13,125)
- Key objectives
  - Relationship of pCR to EFS and OS
  - Definition of pCR that correlates best with long term outcomes
  - Breast cancer subtypes in which pCR is best correlated with long term outcome

- pCR defined as
  - ypT0ypN0, absence of invasive or insitu cancer in the breast and axillary nodes
  - ypT0/isypN0, absence of invasive cancer in the breast and axillary nodes with DCIS allowed
  - ypT0/is, absence of invasive cancer in the breast with DCIS allowed irrespective of nodal involvement

*Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, Bonnefoi H, Cameron D, Gianni L, Valagussa P, Swain SM. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. The Lancet. 2014 Jul 12;384(9938):164-72.

CTNeoBC

- Results
  - 13%, 18% and 22% achieved pCR defined as ypT0ypN0, ypT0/isypN0, and ypT0/is
  - Absence of tumour from both breast and lymph nodes was better associated with improved EFS and OS
  - Patients who achieved pCR had an improved EFS (HR=0.48) and OS (HR=0.36) compared to those who did not
  - pCR was uncommon in patients with low grade hormone receptor +ve (7%)
  - pCR more common in High Grade hormone receptor +ve(16%), triple negative (34%), HR+ve/HER2+ve (30%) and hormone receptor -ve/HER 2+ve (50%)
- Individuals who attain pCR have a more favourable long term outcome
- Data shows comparable EFS or OS regardless of the presence or absence of DCIS

EBCTG

- The Early Breast Cancer Trialists' Collaborative Group[*] have gathered individual patient data for 4756 women randomly allocated in ten trials to either neoadjuvant chemotherapy (NACT) or adjuvant chemotherapy, with a median follow-up of 9 years (IQR 5–14).

- The results of this meta-analysis substantiate that NACT results in higher rates of breast-conserving therapy than does adjuvant chemotherapy (rate ratio 1·28 [95% CI 1·22–1·34]), without compromising on distant recurrence, breast cancer survival, or overall survival.

[*]

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from randomised trials. Lancet Oncol 2017; published online Dec 11. http://dx.doi.org/10.1016/ S1470-2045(17)30777-5

Role of Imaging

- Determine disease extent and monitor response to treatment
- MRI Gold standard compared to mammography/US
  - Sizing of tumour
  - Determining disease extent
  - Monitoring response to chemotherapy

- No national guidance on appropriate protocols

- Has been widely introduced into routine clinical practice despite a relative lack of prospective studies

Role of imaging in detecting imaging CR

- MRI Gold standard compared to mammography/US
- Accuracy for determining pathological complete response[1] is
  - 57% clinical examination
  - 74% mammography
  - 79% ultrasound
  - 80% mammography+US
  - 84% MRI

[1]Croshaw R, Shapiro-Wright H, Svensson E, Erb K, Julian T. Accuracy of clinical examination, digital mammogram, ultra-sound, and MRI in determining postneoad- juvant pathologic tumor response in opera- ble breast cancer patients. Ann Surg Oncol 2011;18(11):3160–3163.

INTENS Trial*

- Methods: Patients with invasive breast cancer were enrolled in the INTENS study between 2006 and 2009. 182 patients includes in whom data was available for post-NAC MRI (n155), US (n123), and histopathological tumour size.

- Results: MRI estimated residual tumour size with <10-mm discordance in 54% of patients, overestimated size in 28% and underestimated size in 18% of patients. With US, this was 63%, 20% and 17%, respectively. The negative predictive value in hormone receptor-positive tumours for both MRI and US was low, 26% and 33%, respectively.

- Conclusions: US was at least as good as breast MRI in providing information on residual tumour size post-neoadjuvant chemotherapy. However, both modalities suffered from a substantial percentage of over- and underestimation of tumour size and in addition both showed a low negative predictive value of pathologic complete remission

*Vriens BE, de Vries B, Lobbes MB, van Gastel SM, van den Berkmortel FW, Smilde TJ, van Warmerdam LJ, de Boer M, van Spronsen DJ, Smidt ML, Peer PG. Ultrasound is at least as good as magnetic resonance imaging in predicting tumour size post-neoadjuvant chemotherapy in breast cancer. European Journal of Cancer. 2016 Jan 1;52:67-76.

Assessing extent of residual disease

- MRI scan performed prior to surgery
  - Assess residual disease
  - Aid surgical planning
- MRI can cause overestimation
  - Due to sclerosis or necrosis
  - Multiple scattered lesions or foci
  - Reactive inflammation caused by tumour response and healing
  - DCIS
- MRI can cause underestimation
  - Lack of inflammatory response surrounding tumour (common in treatments using Docetaxol)
  - Antivascular effects of docetaxol
  - DCIS
  - Partial volume effects of small foci of residual disease

MRI post 2 cycles shows pCR
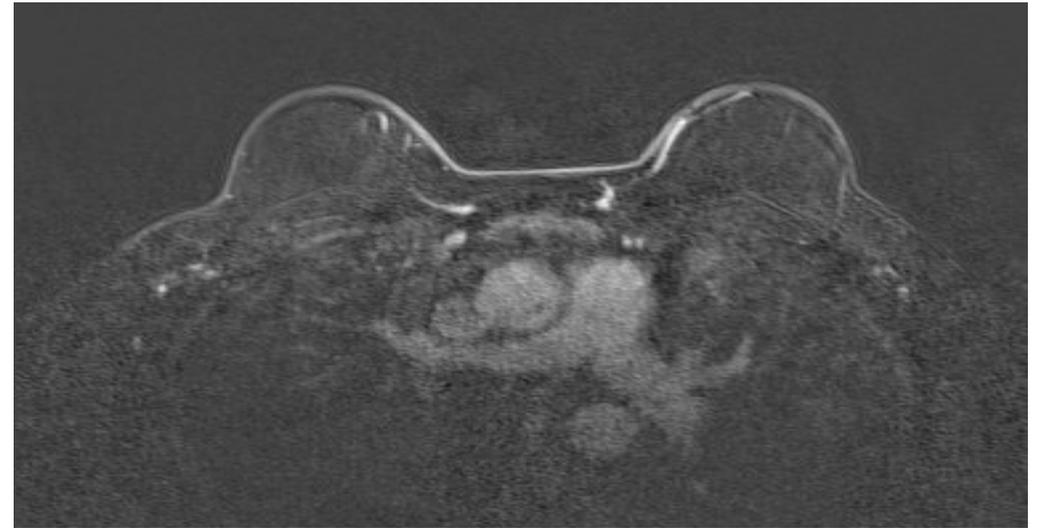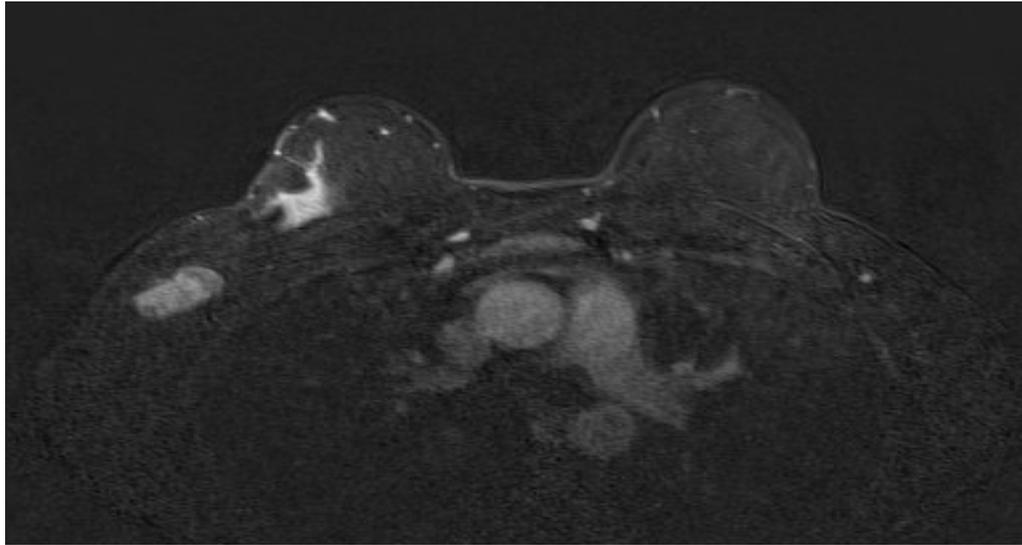
MRI scan shows progression
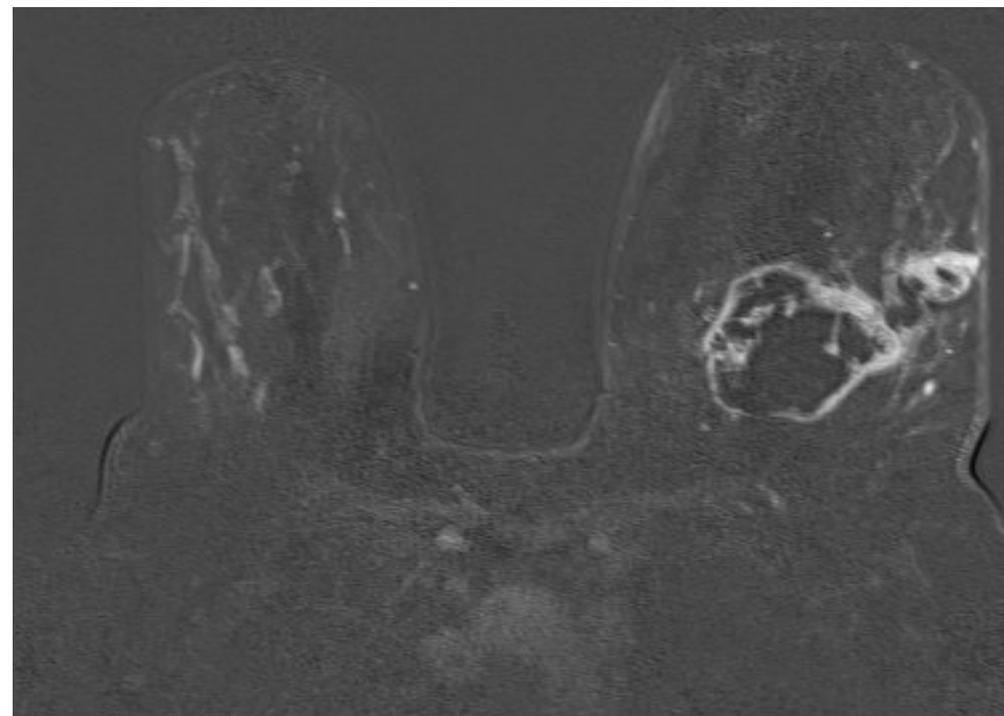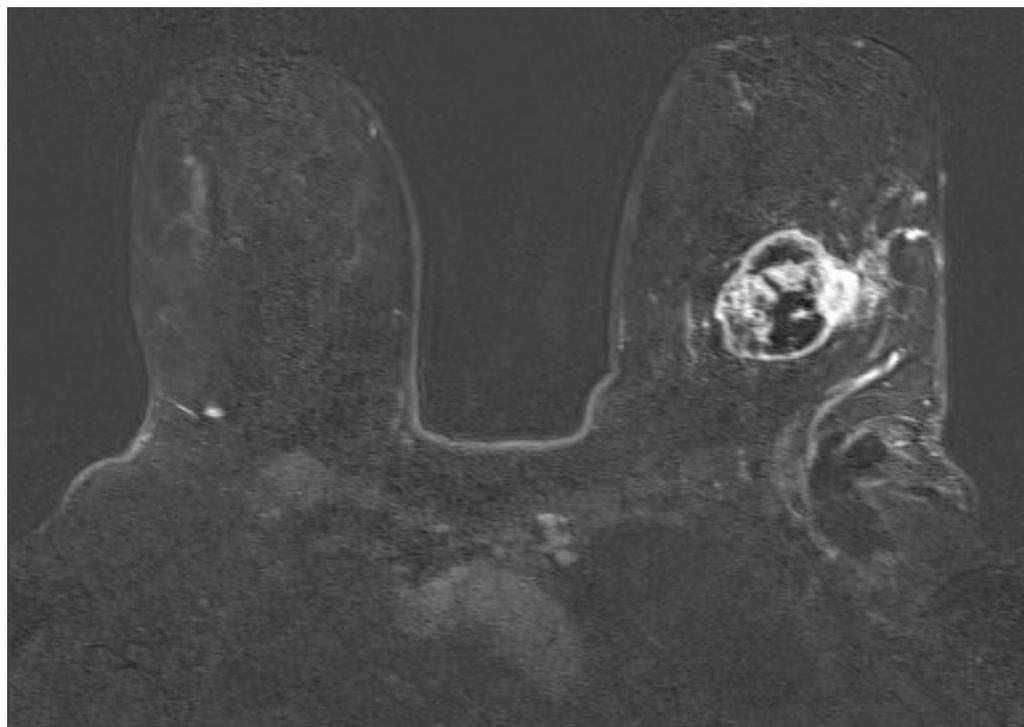
De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017[*]

- The Panel favoured several interventions that may reduce surgical morbidity, including acceptance of 2 mm margins for DCIS, **the resection of residual cancer (but not baseline extent of cancer) in women undergoing neoadjuvant therapy**, acceptance of sentinel node biopsy following neoadjuvant treatment of many patients, and the preference for neoadjuvant therapy in HER2 positive and triple-negative, stage II and III breast cancer

* Curigliano G, Burstein HJ, P Winer E, Gnant M, Dubsky P, Loibl S, Colleoni M, Regan MM, Piccart-Gebhart M, Senn HJ, Thürlimann B.. Annals of Oncology. 2017 Aug 1;28(8):1700-12.

NACT drives the changing role of surgery…..

Because it can facilitate <u>response adapted</u> surgery

| Chemotherapy Endocrine Rx | SURGERY | Radiotherapy | Endocrine |

Targeted therapies

Post NACT: surgery removes residual disease OR <u>confirms pCR</u>

Role of Imaging in detecting pCR

- We have established that imaging alone is inferior in determining imaging CR (iCR) post NACT

- Post NACT biopsy of the tumour bed is required to identify if there is any residual disease

Diagnosis of pathological complete response to neoadjuvant chemotherapy in breast cancer by minimal invasive biopsy techniques[*]

- Neoadjuvant chemotherapy (NACT) is widely used as an efficient breast cancer treatment. Ideally, a pathological complete response (pCR) can be achieved. Up to date, there is no reliable way of predicting a pCR. For the first time, we explore the ability of minimal invasive biopsy (MIB) techniques to diagnose pCR in patients with clinical complete response (cCR) to NACT in this study. This question is of high clinical relevance because a reliable pCR prediction could have direct implications for clinical practice.

- Methods: 164 patients were included. Core-cut (CC)-MIB or vacuum-assisted (VAB)-MIB were performed after NACT and before surgery. Negative predictive values (NPV) and false-negative rates (FNR) to predict a pCR in surgical specimen (diagnose pCR through MIB) were the main outcome measures.

[*] Heil J, Kümmel S, Schaefgen B, Paepke S, Thomssen C, Rauch G, Ataseven B, Große R, Dreesmann V, Kühn T, Loibl S. Diagnosis of pathological complete response to neoadjuvant chemotherapy in breast cancer by minimal invasive biopsy techniques. British journal of cancer. 2015 Dec;113(11):1565.

Diagnosis of pathological complete response to neoadjuvant chemotherapy in breast cancer by minimal invasive biopsy techniques[*]

- Results: Pathological complete response in surgical specimen was diagnosed in 93 (56.7%) cases of the whole cohort. The NPV of the MIB diagnosis of pCR was 71.3% (95% CI: (63.3%; 79.3%)). The FNR was 49.3% (95% CI: (40.4%; 58.2%)). Existence of a clip marker tended to improve the NPV. None of the mammographically guided VABs (n ¼ 16) was false-negative (FNR 0%, NPV 100%).

- Conclusions: Overall accuracy of MIB diagnosis of pCR was insufficient to suggest changing clinical practice. However, subgroup analyses (mammographically guided VABs) suggest a potential capacity of MIB techniques to precisely diagnose pCR after NACT. Representativity of MIB could be a crucial factor to be focused on in further analyses

[*]Heil J, Kümmel S, Schaefgen B, Paepke S, Thomssen C, Rauch G, Ataseven B, Große R, Dreesmann V, Kühn T, Loibl S. Diagnosis of pathological complete response to neoadjuvant chemotherapy in breast cancer by minimal invasive biopsy techniques. British journal of cancer. 2015 Dec;113(11):1565.

Diagnosis of pathological complete response to neoadjuvant chemotherapy in breast cancer by minimal invasive biopsy techniques

- pCR was absence of invasive and non-invasive cancer
  - Did not state if microcalcifications were evident on the mammogram
- Core biopsy – 116
  - US 112
  - Stereo 4
- VAB – 46
  - US 30
  - Stereo 16

Diagnosis of pathological complete response to neoadjuvant chemotherapy in breast cancer by minimal invasive biopsy techniques

- The MIB procedures guided by a clip marker tended to achieve a higher rate of true-negative results (OR 1.98; 95% CI: (0.81; 4.85), P-0.137) than without the use of a clip marker.

- The use of a clip marker also improved the NPV (74.2% (95% CI: 65.3%; 83.1%) with clip marker vs 62.1% (95% CI: 44.4%; 79:7%) without clip marker).

- More than three biopsies taken by MIB did not lead to a higher accuracy compared with patients with less than three biopsies taken (OR 0.67; 95% CI: (0.20; 2.26), P-0.516).

- **Confident that you were sampling the tumour bed as this seem to pose the biggest challenge and hence the results obtained.**

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Life demands excellence

Post neoadjuvant chemotherapy vacuum assisted biopsy in breast cancer: Can it determine pathologic complete response before surgery?

Marios-Konstantinos Tasoulis[1], Nicola Roche[1], Jennifer E Rusby[1], Romney Pope[2], Steve Allen[2], Kate Downey[2], Ashutosh Nerurkar[3], Peter Osin[3], Robin Wilson[2], Fiona MacNeill[1]

[1]Department of Breast Surgery, [2]Radiology and [3]Pathology, The Royal Marsden NHS Foundation Trust, London, UK

Abstract #567

BACKGROUND

- Neoadjuvant chemotherapy (NAC) is increasingly used in phenotype appropriate early operable breast cancer

- Pathologic complete response (pCR) rates up to 60% in certain phenotypes suggest a proportion of patients may require less or no surgery

- Image-guided vacuum assisted biopsy (VAB) has been used in our practice after completion of NAC, in patients with good imaging response, to assess residual disease and facilitate risk-adaptive surgery

AIM

To investigate if post-NAC VAB can reliably predict pCR and identify exceptional responders who may not require surgical intervention

METHODS

- Retrospective, single – institution, cohort study

- Breast cancer patients treated with NAC, who had partial/complete imaging response and underwent post-NAC VAB to aid surgical planning between 01/2013-01/2018

- pCR defined as ypT0

- Diagnostic accuracy of VAB calculated using final surgical pathology as reference standard

- Simple descriptive statistics and non-parametric statistical analyses were performed

RESULTS

- 53 patients underwent post-NAC VAB followed by surgery (45 breast conserving surgery – 8 mastectomy)

- The overall pCR rate was 41.5% (0% for HR positive / HER2 negative, 53.8% for HER2 positive, 72.8% for Triple Negative phenotypes)

- No significant associations were identified between tumour (histopathology, grade, size, phenotype) and VAB technique characteristics (biopsy needle size – number of samples obtained) and diagnostic performance of VAB

VAB diagnostic accuracy	Value% (95% Confidence Intervals)		
	Total cohort (N=53)	HER2 positive (N=26)	Triple Negative (N=11)
Overall Accuracy	84.9 (75.3 – 94.5)	84.6 (70.8 – 98.5)	90.9 (73.9 – 100)
Sensitivity	80.6 (64.7 – 94.6)	75 (50.5 – 99.5)	100 (100 – 100)
Specificity	90.9 (78.9 – 100)	92.9 (79.4 – 100)	87.5 (64.6 – 100)
False Negative Rate	19.3 (5.4 – 34.5)	25 (5 – 46.2)	0 (0 – 0)
Negative Predictive Value	76.9 (60.7 – 93.1)	81.3 (62.1 – 100)	100 (100 – 100)

Cohort clinical characteristics (N=53)

Age in years, median (range)	49 (28 – 70)
Histology, No (%)	
Invasive Ductal Carcinoma	51 (96.2)
Invasive Lobular Carcinoma	2 (3.8)
Nuclear Grade, No (%)	
Grade 2	21 (39.6)
Grade 3	32 (60.4)
Tumour Receptors Subtype, No (%)	
HR+/HER2+	19 (35.8)
HR+ / HER2-	16 (30.2)
HR-/HER2+	7 (13.2)
HR-/HER2-	11 (20.8)
Tumour size in mm, median (range)	38 (13 – 100)
VAB needle size in gauge, median (range)	10 (9 – 14)
No of VAB samples, median (range)	6.5 (4 – 18)

CONCLUSION

Post-NAC VAB may reliably predict pCR in patients with Triple Negative breast cancer. Diagnostic accuracy was not maintained across all phenotypes. Refinements and standardization in patient selection and VAB technique and more prospective trials are warranted to further explore the role of post-NAC VAB in supporting minimal or no surgery trials

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Nostra Trial

- Primary outcome: To determine whether patients with residual cancer can be identified by histological examination of multiple ultrasound-guided tumour bed core biopsy following dual-targeted neoadjuvant treatment HER2-positive, ER-negative early primary breast cancer

The Radiological Aim

- Is to widely sample the tumour bed, in a systematic and reproducible way.

Abstract P5-16-14: NOSTRA PRELIM: A non randomised pilot study designed to assess the ability of image guided core biopsies to detect residual disease in patients with early breast cancer who have received neoadjuvant chemotherapy to inform the design of a planned trial

- **METHODS**
- 23 consecutive patients with operable primary breast cancer scheduled for neoadjuvant chemotherapy were approached to take part in the study and 20 gave consent.
- All 20 patients had a clip inserted into the tumour bed under ultrasound(USS) guidance at diagnosis as is standard procedure.
- The number of cores taken ranged from 2-6. The median number of biopsies was 4
- Tumour size range at diagnosis was 15-61mm with USS. All received neo-adjuvant chemotherapy and those who were Her2 positive received neoadjuvant trastusumab. At completion all patients had USS guided tumour bed biopsy. They then went on to have surgery, after which pathology was assessed and an RCB score calculated for each patient.
- For this study patients all tumour types were included as non pCR outcomes were required to determine accuracy and inform changes to the biopsy protocol for future use.

Abstract P5-16-14: NOSTRA PRELIM: A non randomised pilot study designed to assess the ability of image guided core biopsies to detect residual disease in patients with early breast cancer who have received neoadjuvant chemotherapy to inform the design of a planned trial*

- **RESULTS**

- Only 2 patients in this study achieved a pCR

- Residual disease was correctly identified in 16/20 patients.

- Four patients had no tumour in their post treatment biopsies but had small residual invasive tumour at surgery. The size of residual disease in these patients ranged from 0.5 -9mm and all these patients had 3 core biopsies.

- One patient had negative post treatment biopsies and a PCR of their invasive tumour. This patient had a diagnostic biopsy that confirmed separate area of DCIS several centimetres from the invasive component. This area did not undergo post treatment tumour bed biopsies (although both areas were clipped at diagnosis).

- **CONCLUSION**

- A protocol for biopsy in the upcoming NOSTRA feasibility study has been designed to both take more biopsies and sample a larger area of the tumour bed in order minimise the false negative rate.

* Francis A, Herring K, Molyneux R, Jafri M, Trivedi S, Shaaban A, Rea DW. Abstract P5-16-14: NOSTRA PRELIM: A non randomised pilot study designed to assess the ability of image guided core biopsies to detect residual disease in patients with early breast cancer who have received neoadjuvant chemotherapy to inform the design of a planned trial.

Predict pCR with needle biopsy: the lessons

- KEY is obtaining 'representative' sample

- Radiology: being sure biopsied the tumour bed

- Pathology: evidence of post treatment fibrosis/reaction

Method

- Image-guided tumour marking with clips,
- Receive an approved chemotherapy, trastuzumab and pertuzumab schedule.
- Clinical and Radiological assessment of response
- After completion of neo-adjuvant chemotherapy but prior to surgical resection, multiple image-guided biopsies will be performed to sample across the tumour bed.
- After surgery, the amount of residual disease (if not pCR) using Residual Cancer Burden scoring will be correlated with the detection of tumour in the pre-surgical biopsies.
- Blood and tissue samples will be collected for central review and translational research.

NOSTRA-Feasibility Study

Obtain Informed Consent

Register Patient
☎ 0121 414 3604 or 0121 414 3797 (9.00 am till 5.00 pm Monday to Friday)

Mark and document tumour

Neoadjuvant chemotherapy plus dual anti-HER2 therapy. Treating clinician to use one of the 3 approved combination regimens:

Regimen 1	Regimen 2	Regimen 3
FEC* with Trastuzumab and Pertuzumab followed by Trastuzumab & Pertuzumab with Docetaxel	FEC* followed by Trastuzumab & Pertuzumab with Docetaxel	Docetaxel and Carboplatin with Trastuzumab & Pertuzumab

*Omission of 5-Fluorouracil at the discretion of the treating Investigator

Clinical and radiological assessment of response

**Clinical Response**   **No Clinical Response**

Multiple image-guided tumour bed core biopsies

Standard surgical treatment

Marking the tumour

In order to identify the site of the original tumour bed after completion of NAC it is important to:

1. Place an ultrasound visible clip as close to the centre of the cancer as possible unless local practice dictates clips at margins of the tumour in order to facilitate subsequent bracketing localisation.

2. Document position of the tumour and clip(s) prior to cycle 1 diagrammatically on the tumour bed core biopsy form

3. Document the maximum size of the long axis of the tumour and the distance of the clip from each of the long axis margins
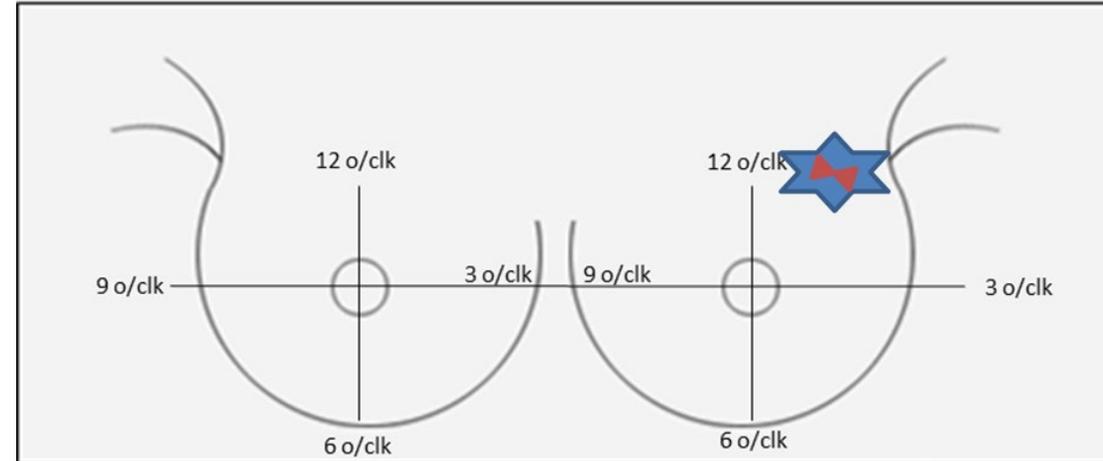

Size (mm)	Long axis: 75	Short axis (at 90°): 25
	Position in breast (clock face)	**(mm)**
Margin closest to nipple	1	15 mm from clip
Marker clip	2	24 mm from nipple
Margin furthest from nipple	2	60 mm from clip

The needle biopsy

- The aim is to widely sample the tumour bed, in a systematic and reproducible way.
- This is why we are taking a 'fan of 14G cores' rather than attempting to remove the 'centre of the tumour' using vacuum needle.

Performing the biopsy

Zone 1   2   3   4

- Using ultrasound and the pre-treatment diagram from the tumour bed core biopsy form. Identify the long axis of the original tumour bed, mentally divide this in to quarters and then take a fan of 14g needle core biopsies across the original tumour bed aiming for 2 biopsies from each quadrant.

- The cores obtained from each zone should be placed in separate histology pots
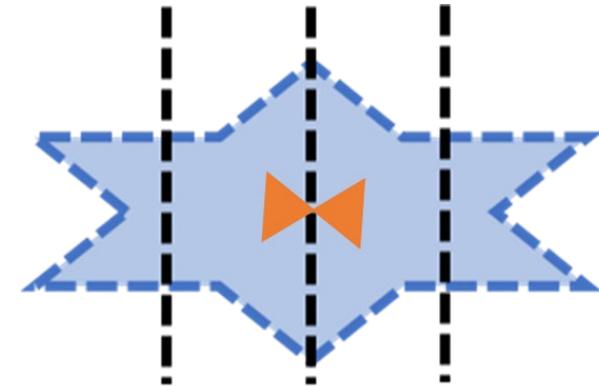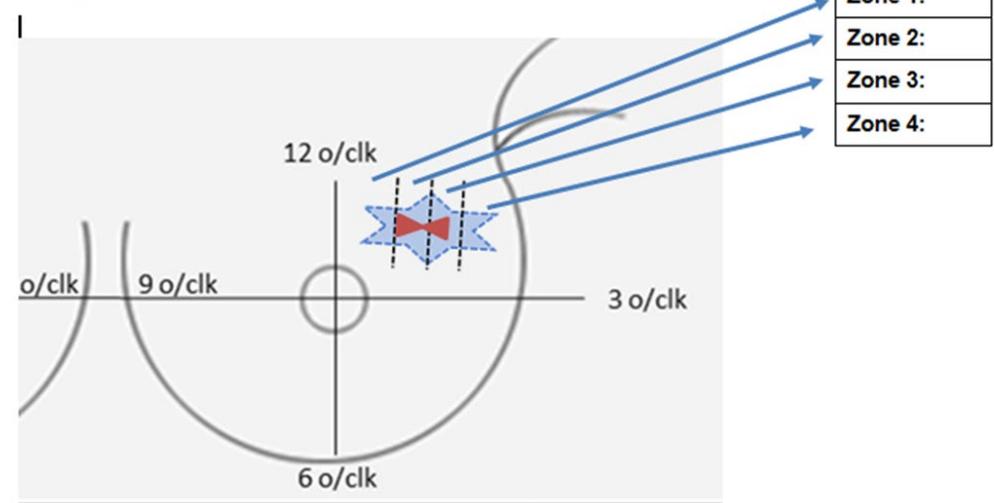
MDT Dilemma: what if we 'get it wrong'?

Post NACT under-staging (false negative clinical CR) may lead to inadequate surgery which risks......

- Leaving drug resistant clinically occult disease in the breast/axilla
- The patient pays a high price...?

  - ?More local recurrence ?Reduction in survival

  - BUT women with a poor response to neoadjuvant drug therapy are at highest risk for metastatic recurrence and death from their occult systemic disease, not local disease

- Any Questions