PRINCIPLES OF BREAST SURGERY / ONCOPLASTIC SURGERY

ESMO Preceptorship on Breast Cancer

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DISCLOSURE INFORMATION

No disclosures to declare
THERAPEUTIC INTENT
- Excise primary (local-regional cancer)
- Clear margins
- Maintain form / aesthetics

PALLIATIVE INTENT / SYMPTOM CONTROL
- Toilet – convert an open infected wound into a clean wound
- Symptom palliation
ROLE OF SURGERY

Disease control
- Removal of the cancer
- Decrease tumour burden
- Symptom control

Preservation of form / function
- Choice of surgery
  - Conservation
  - Reconstruction

Side effects of surgery
- Physical
- Mental

Prophylactic surgery
SURGICAL ALGORITHM

1. Is it operable?
2. Is it conservable?
3. Does she want recon?
4. Advanced / stage IV
5. Are symptoms palliatable?
STAGING

Manchester Staging

- Stage 1
  - Tumour confined to breast
- Stage 2
  - Tumour confined to breast with mobile LN axilla
- Stage 3
  - Tumour in the breast with fixed axillary nodes
- Stage 4
  - Metastatic disease
Staging

• Impt prognostic factors
  • Lymph node status
  • Tumour size
  • Tumour grade
  • Age
  • Lymphovascular invasion

• NPI LN status
  • No nodes = 1pt
  • 1-3 nodes = 2 pts
  • 4 or more nodes = 3pts

• Nottingham Prognostic Index
  (Sum of the following)
  • Tumour grade (1-3)
  • LN status (1-3)
  • Tumour size x0.2

<table>
<thead>
<tr>
<th></th>
<th>Excellant</th>
<th>93% 5YSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2.4</td>
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<tr>
<td>≤3.4</td>
<td>Good</td>
<td>84%</td>
</tr>
<tr>
<td>≤4.4</td>
<td>Moderate I</td>
<td>70%</td>
</tr>
<tr>
<td>≤5.4</td>
<td>Moderate II</td>
<td>50%</td>
</tr>
<tr>
<td>&gt;5.4</td>
<td>Poor</td>
<td>19%</td>
</tr>
</tbody>
</table>
INOPERABLE CANCER

Metastatic
LABC

Neoadj chemo
- Margins
- Conservation
- Tumour biology
OPERABLE CANCER

Gradual progression towards less radical surgery
Halsted’s
Modified radical mastectomy
Breast conservation
Axillary clearance vs sentinel node biopsy
SURGERY FOR THE BREAST
BREAST SURGERY

Choice of surgery depends entirely on extent of disease

Volume of breast tissue needing resection (cancer with margins) relative to the volume of the breast

Conservation only if minimal / acceptable cosmetic impact on the operated breast achievable

- Not subject to molecular subtype, but concerns about adjacent DCIS are an important consideration
- Radiation is mandatory (although certain subgroups suitable for de-escalating therapy)
BREAST CONSERVATION SURGERY

- Aims:
  - Complete excision of malignant cells
  - Minimal excision of normal breast tissue
    - Only what is needed for clear margins
  - Minimal cosmetic impact of the affected breast
  - Clear margins are the issue
  - Re-operations have physical, psychological and economical repercussions
MARGINS

Invasive breast cancer

No international consensus internationally

ASTRO / ASCO / SSO guidelines – ‘no tumour on inked margin’

USA and Netherlands: No tumour on the inked margin

UK: >2mm

Germany / Scotland / France: > 1mm

1-2mm acceptable


MARGINS
DCIS

- Margins for DCIS: >2mm
- the extent of DCIS at the involved margin
- the margin which is involved
- presence of residual calcifications on mammogram
- impact of re-excision of the appearance of the breast
- life expectancy

MARGINS

Factors associated positive margin rate

- Lobular histology
- Adjacent DCIS to IDC
- Tumour size > 2cm
- Young age
- LVI
- Multifocality
Impact of close but negative margins in breast conserving surgery

- Review of patients from a prospective database, 2000-2012
- Re-excision at margins of < 2mm
- 2520 procedures, re-excision rate 12% for BCS, 2% for mastectomy
  - Residual disease found in 38% and 26% respectively

Residual disease rate in positive, 0.1-0.9mm, and 1.0-1.9mm margins were 40%, 38% and 33%

- Multiple margins <2mm trended towards significance for residual disease
- Age, race, menopausal status, tumour histology, HR status, triple negative disease, LVI were not associated with residual disease

5-year LR rates (median FU 43 mths) was 1.1% for TM, and 1.9% for BCS patients
MARGINS

Impact of focally positive margins

Margins classified as

- **Negative** >2mm, **close** <2mm, focally positive (<4mm length of tumour touching ink), **extensively positive** (>4mm length)

499 patients, Tis to T3, primary surgery (BCS)

- 43% (212) negative margins, 32% (161) close margins, 12% (59) focally positive, 13% (67) extensively positive margins
The Association of Surgical Margins and Local Recurrence in Women with Early-Stage Invasive Breast Cancer Treated with Breast-Conserving Therapy: A Meta-Analysis

Nehmat Houssami, MD, PhD¹, Petra Macaskill, PhD¹, M. Luke Marinovich, MPH¹, and Monica Morrow, MD²

¹Screening and Test Evaluation Program (STEP), School of Public Health (A27), Sydney Medical School, University of Sydney, Sydney, Australia; ²Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY
MARGINS

Cosmetic impact of clear margins

van den Tol et al analyzed surgical margins, and excision volumes of breast tissue following breast conservation surgery.

Central database data (PALGA – national registry in the Netherlands), 9274 reports:

- Involved margins: 5.4%
- Focal involvement 11% cases
- Unsatisfactory resections – 33.8% (<1mm)

Median excised volume 46cc, calculated resection ration was 2.3 => excision was 2.3 times the optimal resection volume.
MARGINS

Methods to decrease re-excision rates

- Better definition of the target
  - Determining the extent of disease
- Improve targeting of lesion
  - Localisation techniques
- Immediate assessment of margins
  - Cavity shave / Margin probe / Frozen section of margins
- Increase margin width *
  - Oncoplastic surgery
# LESION LOCALIZATION

<table>
<thead>
<tr>
<th>Localization technique</th>
<th>System components</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Wire-guided localization               | • Wire  
• Needle delivery system                          | • Safe  
• Effective  
• Well established  
• Inexpensive  
• Can be placed under mammogram, ultrasound or MRI guidance | • Depending on practice setting often same day procedure (limited scheduling)  
• Wire external to patient (wire may dislodge, migrate, kink, fracture, or become transected)  
• Patient discomfort  
• Potential worse cosmesis due to suboptimal incision placement depending on wire location |
| Radioactive seed localization          | • Iodine-125 labeled titanium seed implant  
• Needle delivery system  
• Detector: gamma probe/ion chamber | • Scheduling flexibility (half life I-125 = 59 days)  
• No external component limits the possibility of displacement or transection  
• No depth limitation  
• Compatible with sentinel lymph node mapping  
• Better cosmesis | • Radiation safety precautions  
• Radiation exposure to patient and staff  
• No repositioning once deployed  
• Cannot be placed under MRI guidance (gamma probe not MRI compatible) |
| Non-radioactive radar localization     | • Implantable non-radioactive reflector  
• Needle delivery system  
• Detector  
• Console | • Scheduling flexibility (FDA long-term implant clearance)  
• No external component limits the possibility of displacement or transection  
• No radiation exposure  
• No radiation safety precautions  
• Better cosmesis | • Cost  
• Depth limitation  
• No repositioning once deployed  
• No MRI compatible needle delivery system  
• Interference with older halogen lights in OR  
• Contain nickel (possible nickel allergy)  
• Limited published data |
| Magnetic seed (MagSeed)                | • Stainless steel seed implant  
• Needle delivery system  
• Detector probe magnetizes the seed and temporarily converts it to a magnet | • Scheduling flexibility (placed up to 30 days in advance)  
• No external component limits the possibility of displacement or transection  
• No radiation exposure  
• No radiation safety precautions  
• Stainless steel seed (no issue with nickel allergy)  
• Better cosmesis  
• Count indicates distance to the seed | • Cost  
• Depth limitation  
• No repositioning once deployed  
• No MRI compatible needle delivery system  
• No published data  
• Need for non-magnetizable surgical instruments  
• MRI bloom up to 4 cm (depending on sequence used) |
LESION LOCALIZATION

Other techniques

Intra-operative ultrasound

Modified ROLL – in combination with methylene blue dye

SAVI SCOUT® localization

Cryo-assisted localization

Haematoma associated localization (post VAB)
LESION LOCALIZATION

DOI: 10.1002/14651858.CD009206.pub2.

11 RCTs, assessed ROLL or RSL compared to WGL
Methods were comparable
No one better than the other, ROLL / RSL are reasonable alternatives, as reliable as WGL

ROLL vs WGL: differences were seen, in favour of ROLL, but not statistically significant
Successful localization: RR 0.66, CI 0.16-2.28; 869 patients; 6 trials
Positive excision margins: RR 0.74, CI 0.42 – 1.29; 517 patients; 5 trials
Re-operation rates: RR 0.51, CI 0.21-1.23; 583 patients; 4 trials
LESION LOCALIZATION
Cochrane review

WGL vs RSL:
Successful localization: RR 3.85, CI 1.21-12.19; 402 patients, 2 trials

RSL vs WGL:
Positive margins: RR 0.67, CI 0.43-1.06; 366 patients; 2 trials
Re-operation rates: RR 0.80, CI 0.48-1.32, 305 patients, 1 trial

However for successful excisions, all 3 methods were the same, RR 1.00

WGL – fewer postoperative complications compared to both ROLL / RSL, but not significant
BREAST CONSERVATION SURGERY

Better targeting

Non-palpable tumour
  - localization needed for excision
  - Issues for localization
    - 2D images for a 3D lesion
    - Accuracy of marker placement
    - Relation of the lesion to the marker
    - Marker migration
    - Marker transection
    - Needs to be placed as a separate procedure to surgery
    - Patient distress
  - Knowing where the lesion is, does not increase the chance of precise excision
MARGINS
Cavity shave trials / articles

Margin assessment by cavity shaving after breast-conserving surgery: analysis and follow-up of 543 patients
Do additional shaved margins at the time of lumpectomy eliminate the need for re-excision? *The American Journal of Surgery* (2008) 196, 556–558
MARGINS

Improving negative margin rates

RCT for margin shaves
- 1:1 comparison 235 patients, stage 0-stage 3 undergoing BCT
- Resection of routine cavity shaves vs no further resections
- Pos Margins = no ink on tumour for IDC, 1mm for DCIS

- Prior to randomization – both groups had similar positive margin rates – 36% and 34%
- After randomization for routine cavity shaves vs no further shaves, margin positive in the no shave group remained at 34%, however margin positive rates in the routine shave group were 19%

- Re-excision rates – no shave group 21%, shave group 10 %
**MARGINS**

Volume of Excision and Cosmeseis with Routine Cavity Shave Margins Technique

Analysed patients who had cavity shaving (CSM) vs patients treated with standard partial mastectomy (SPM)

72 matched patients pairs-

Mean tumour size for both groups were similar 1.52 cm$^3$ vs 1.51 cm$^3$

Volume excised in CSM was 80.66 cm$^3$, vs 165.1 cm$^3$ in SPM

Re-excision rates in CSM was 18.1% vs 34.6% in SPM

Cosmetic score in CSM was 2.3, vs 3.0 in SPM group

## TARGET ACQUISITION

Intraoperative margin assessment

<table>
<thead>
<tr>
<th>Technique</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUROC</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frozen section</td>
<td>86%</td>
<td>96%</td>
<td>0.96</td>
<td>Expensive, resource intensive, slow turnaround</td>
</tr>
<tr>
<td>Cytology</td>
<td>91%</td>
<td>95%</td>
<td>0.98</td>
<td>Unable to distinguish in-situ from invasive</td>
</tr>
<tr>
<td>Intraoperative US</td>
<td>59%</td>
<td>81%</td>
<td>0.78</td>
<td>Operator dependent, calcs not visible on US</td>
</tr>
<tr>
<td>Specimen radiography</td>
<td>53%</td>
<td>84%</td>
<td>0.73</td>
<td>Unable to define non-calcified cancer, benign calcs could be called malignant</td>
</tr>
<tr>
<td>Optical spectroscopy</td>
<td>85%</td>
<td>87%</td>
<td>0.88</td>
<td></td>
</tr>
</tbody>
</table>

TARGET ACQUISITION

Margin assessment

Frozen section:
- Time consuming
- Expensive
- Subject to sampling error – 4 margins minimum, maximum 12
- Snap freezing can also create compression, freezing and destructive artifacts

- However if possible, it is the most accurate way
TARGET ACQUISITION
Margin assessment techniques available

Imaging:
- high resolution scanners for specimen analysis
- microcomputed CT, high-frequency US, MRI

Optical:
- Light (of various frequencies ranging from visible to infra-red) directed on / into tissue produce spectra unique for each tissue type
- Raman spectroscopy, optical coherence tomography, confocal microscopy

Bioimpedancece / Radiofrequency:
- Tissue exposed to radiofrequency fields and generates an electromagnetic field which is recognized as a tissue spectral signature e.g. MarginProbe™ ClearEdge™

Mass Spectometry
- Measures tissue specific ionic content linked to cellular metabolism
- Rapid evaporative ionization mass spectrometry (REIMS) and Desorption electrospray Ionization (DESI)

ONCOPLASTIC SURGERY

Allows the excision of larger volumes of tissue, extends option of conservation to more patients

- Larger cancers
- Multifocal disease
- EIC

Patients who could potentially omit radiation
ONCOPLASTIC SURGERY

- Oncoplastic surgery techniques
  - If area that requires excision (inclusive of margins) is <20% of the breast volume
    - Level 1 oncoplastic technique

  - If volume excised is 20-50%, (50% if breast size is large) of total breast volume –
    - Level 2 oncoplastic technique
    - Usually entails excision of skin, and breast reduction surgery inclusive of the tumour
    - Partial reconstruction also possible with the use of local pedicled flaps (TDAP, LICAP)

  - If >50% of total breast volume will be removed, total mastectomy with or without reconstruction
ONCOPLASTIC SURGERY
Level 2 techniques: Volume displacement

Parenchymal mobilization to fill cavity
- Tissue flaps will be somewhat ischemic
- Prone to fat necrosis
- Increased likelihood scarring / fibrosis
- Cavity sides can be clipped
ONCOPLASTIC SURGERY
Level 2 techniques: Volume displacement

- Level II oncoplastic techniques
ONCOPLASTIC SURGERY
Level 2 techniques: Volume replacement

Breast conservation surgery and partial reconstruction
Using L-ICAP / A-ICAP flaps
- Cavity is not re-opposed but is filled with tissue instead
ONCOPLASTIC SURGERY
Surgical approach in early breast cancer

Issues
- Fat necrosis
- Tumour site
- Nipple necrosis – partial / complete
- Radiation – only to affected side
- Fibrosis
- Positive margins
- Asymmetry
- Residual volume
# BREAST CONSERVATION SURGERY

<table>
<thead>
<tr>
<th>Author (ref number), year</th>
<th>Study Period</th>
<th>Data source</th>
<th>Inclusion criteria</th>
<th>N. of patients</th>
<th>Outcome Measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal [5], 2014</td>
<td>1998–2008</td>
<td>SEER database</td>
<td>T≤4cm N0-1</td>
<td>132.149</td>
<td>5y BCSS</td>
<td>97</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>10y BCSS</td>
<td>94</td>
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<td>94</td>
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<td>10yOS</td>
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<td>5y BCSS</td>
<td>86</td>
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<td></td>
<td>8y OS</td>
<td>93.2</td>
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<td>11.7y OS and BCSS (1999–2005 cohort)</td>
<td>86.5</td>
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<td>BCSS: HR 0.74</td>
<td>72.3</td>
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<td>OS: HR 0.67</td>
<td>70.4</td>
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<td>BCSS: HR 0.75</td>
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<td>Chen [6], 2015</td>
<td>2004–2011</td>
<td>National Cancer Database</td>
<td>T1-2 N1-3</td>
<td>160.880</td>
<td>5y OS</td>
<td>93</td>
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<td></td>
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<td>72.3</td>
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<td>BCSS: HR 0.75</td>
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</tbody>
</table>

BCSS = Breast Cancer-Specific Survival M = Mastectomy.

The Breast 35 (2017) 32-33
BREAST CONSERVATION SURGERY

Personal reflections

1. Knowing where the target is and acquiring the target are 2 completely separate issues
2. Marker is seldom in the dead centre of the target, and where it is within or (if outside target) in relation to the target is difficult predict
3. Assessing distances on imaging and translating it to the patient on the table is not the same
4. Although I know ‘no ink on tumour’ is acceptable, 1cm gross margins are still the aim

5. Ideal localization marker:
   1. Mark the extent of disease in the patient – including DCIS
   2. Can be detected just outside the margins
   3. Can be visualized directly in the patient
DE-ESCALATION OF SURGERY

Early disease
EARLY STAGE BREAST CANCER
Recurrence risk for DCIS

ECOG E5194 – IBTR with omission of RT, margins >3mm

Low-intermediate grade DCIS, <25mm, recurrence at 12 years is 14.4%
High grade DICS, <10mm, recurrence rate at 12 years is 24.6%
(5.5% low grade, 6.7% intermediate grade, 11.7% high grade recurred with invasive disease)

RTOG 9804 IBTR with RT omission
In women aged >26 years, <25mm, >3mm margins, low-intermediate grade, not mammographically occult
7 years FU: IBTR with RT 0.9%, no RT -> 6.7%
However no impact on overall survival rates

EARLY STAGE BREAST CANCER

Active observation

Omission of surgery in low grade DCIS

- Screen detected low / intermediate grade DCIS (HR+/-, HER2 +/-)
- ≤10mm, aged 70yrs or older
  - Must be screen detected, diagnosed on VAB

- NOT for observation are
- Low grade DCIS in patients under 45 years of age, even with good molecular profile, <10mm in size
<table>
<thead>
<tr>
<th>Age</th>
<th>LORD study (Europe)</th>
<th>COMET study (USA)</th>
<th>LORIS study (UK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;45 yrs of age</td>
<td>&gt;40 yrs, non-pregnant</td>
<td>&gt;46 yrs of age</td>
<td>low grade DCIS / intermediate grade with low risk features</td>
</tr>
<tr>
<td>DCIS grade</td>
<td>low grade DCIS</td>
<td>low / intermediate grade without comedo necrosis, ER/PR pos, HER2 neg</td>
<td></td>
</tr>
<tr>
<td>Pathology confirmation</td>
<td>Central pathology review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic method</td>
<td>VAB biopsy</td>
<td>Core needle bx</td>
<td>diagnosed on VAB</td>
</tr>
<tr>
<td>Size of lesion</td>
<td>no size limit</td>
<td>no size limit</td>
<td></td>
</tr>
<tr>
<td>Imaging criteria</td>
<td>asymptomatic, screen-detected DCIS</td>
<td>screen-detected or asymptomatic microcalcifications with no evidence of a mass</td>
<td></td>
</tr>
<tr>
<td>Monitoring criteria</td>
<td>Annual MMG, for 10 years</td>
<td>no endocrine tx, annual MMG, for 10 yrs</td>
<td>New cluster of calcs, outside index lesion, new calcs in the contralateral breast, new non calcified lesion, development of a mass around the index calcifications. NOT progression of the index calcs</td>
</tr>
<tr>
<td>Recall criteria</td>
<td>Increase in size of largest index lesion by 30% on MMG, lesion must be at least 1cm in diameter, Bx if any suspicion of malignancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control arm</td>
<td>Standard treatment: Surgery / RT / endocrine tx</td>
<td>Standard Surgery and adj RT if indicated / endocrine tx permitted</td>
<td></td>
</tr>
</tbody>
</table>
DE-ESCALATION OF SURGERY

Advanced disease
ADVANCED BREAST CANCER
Role of neoadjuvant therapy

Effect of NACT: Meta-analysis of 10 NAC RCTs
Trials from 1983 – 2002
Median FU 9 yrs, last FU 2013
Most chemotherapy regimes were anthracycline based: 81%
69% had complete or partial clinical response
65% were able to have breast conserving surgery (vs 49% of those with adjuvant chemo)
LRR (15 yrs): 21.4% (NACT) vs 15.9% (adj chemo)
Distant recurrence (15 yrs): 38.2% (NACT) vs 38.0% (adj chemo)
Breast Ca mortality: 34.4% (NACT) vs 33.7% (adj chemo)
All cause mortality: 40.9% (NACT) vs 41.2% (adj chemo)
ROLE OF NEOADJUVANT THERAPY IN SURGERY

Who should receive neoadjuvant therapy?

Chemotherapy
Stage II / III HER2 positive or triple negative breast cancer

Endocrine therapy
CDK 4/6 inhibition with endocrine therapy?

Allows downsizing and downstaging of cancer
- Potential for breast conservation / makes it more feasible
- De-escalation of axillary surgery
- Elimination of micrometastatic disease
- Oligometastatic patients who are downstaged
ROLE OF NEOADJUVANT THERAPY IN SURGERY

Breast conservation after neoadjuvant therapy

Excision of residual tumour is sufficient, no need to excise the tumour footprint\(^1\)
Margins of ‘no tumour on ink’ largely acceptable however have to consider

- Presence of multifocal patchy invasive foci – indicating patchy response
- Extensive DCIS

However BCS post NACT associated with higher rates of local recurrence 21.4% vs 15.4% (patients who had BCS, followed by adjuvant chemotherapy), however there was no difference in distant recurrence rates or breast cancer mortality\(^2\)

Nipple-sparing mastectomy is safe – if there is adequate assessment of the retroareolar tissue to exclude disease

1. Annals Oncol 2017; 28: 1700-1712
SURGICAL CONSIDERATIONS

Disease factors
  - Optimal timing for surgery after chemo

Patient factors
  - Inherent Co-morbidities
  - Co-morbidities following chemotherapy
    - Altered immunity
    - Altered healing
    - Cardiotoxicity
Impact of time to surgery after neoadjuvant chemotherapy in operable breast cancer patients

C. Omarini a, G. Guaitoli a, S. Noventa a, A. Andreotti b, A. Gambini b, E. Palma b, S. Papi b, G. Tazzioli b, S. Balduzzi c, M. Dominici a, S. Cascini a, F. Piacentini a

- Retrospective study assessing time to surgery (TTS)
- 319 patients, Grp A TTS <21 days, Grp B >21 days
- Grp A: 61 patients, Grp B 258 patients
- Median TTS 34 days
- No association between clinical stage, nuclear grade, chemo regime, type or surgery with TTS was detected
- OS and RFS significantly worse for Grp B compared to Grp A, HR 3.1 (95% CI 1.1-8.6, p=0.03) and 3.1 (95% CI 1.3-7.1, p=0.008)
- Confirmed to be an independent variable on multivariate analysis
DE-ESCALATION OF SURGERY

Assessment of the axilla
EARLY BREAST CANCER

Assessment of lymph nodes

Assessing for nodal involvement allows staging of the patient
provides prognostic information
also has therapeutic implications

Need for chemo / RT

But - axillary dissection does not impact overall survival (NSABP- B04)
In this age of screening and detecting more early disease, negative AC are common
Removal of normal nodes come with significant physical morbidity, risk of lymphedema, with no benefit to the patient.
Hence SNB, omission of AC in the event of negative / low nodal burden, extending SNB to select patients post NACT
Sentinel nodes are identified within levels 1 and 2. Anatomical landmarks of the thoracodorsal bundle, long thoracic nerve, and axillary vein are used to delineate tissue removed during a level 1 and 2 complete axillary lymph node dissection.
SENTINEL NODE BIOPSY
ASCO guideline

7 RCTs
NSABP-B32, ALMANAC, Sentinella / GIVOM, RACS/ SNAC trial, NCT0097-983, Cambridge / East Anglia Study grp, Canavese et al

Survival / mortality
- No difference in OS
- B32: 8 YSR 90.3% (SNB) vs 91.8% (SNB+ALND), all cause mortality 4% in each arm

DFS / EFS
- No difference is DFS / EFS

Recurrence
- No difference in rates of IBTR / Ax recurrence or DM

J Clin Oncol 2014; 32:1365-1383
SENTINEL NODE BIOPSY

ASCO guideline

Adverse events
  - ALND associated with higher rates of AEs cf SNB
  - Lymphedema, seroma, neurologic and sensory deficits, shoulder pain, decreased ROM

Performance of SNB
  - FNR - 4.6% to 16.7%
  - NPV – 90.1%-96.1%

— Overall accuracy of SNB 93% - 97.6%

- Adverse events with SLN
  - Allergic reactions 1-2%,
  - 0.25% to 0.5% have anaphylaxis

Cording also occurs with SLN
SENTINEL NODE BIOPSY

SNB: in practice for many years
- Established to reflect the state of axillary nodal involvement
- Eligibility T1 / T2, cN0.
- Dual method: Radioactive colloid (usually $^{99}$TM), and Patent V blue dye
- Rate of sentinel node detection: at least 90%
- False negative rates should be <5%
POSITIVE SLNB

Full axilla dissection – up to level 3
- All positive – micromets and larger
- In the presence of a positive SLN – 48.3% had additional nodal disease
- 10% of patients with neg SLN upgraded to positive nodes when stained with IHC
  - ITC / micromets??
    - 10% of patients with ITC had additional metastatic nodes
    - Patients with micromets – 20-35% had additional metastatic nodes

Additional criteria for completion ALND
Failure to identify SLN
SENTINEL NODE BIOPSY
Primary surgery in early breast cancer

ASCOG Z011 trial
Omission of full axillary dissection in patients with <2 positive nodes, undergoing breast conserving surgery, radiation therapy and systemic therapy

AMAROS / EORTC trials
Post mastectomy patients, <2 positive nodes
Completion axillary dissection or axillary radiation offer equivalent control

JAMA 2011;305:569e75.
**Challenged need for ALND for positive SLN**

- Positive SLN is often the only positive node
- NSABP- B04: upfront ALND no benefit

**Criteria**

- T1, T2, N0, M0 (median size 17mm), undergoing BCS with 1-2 pos SLN (H&E)
- Randomized to ALND or no Sx
- All had WBI, and most (97%) had systemic tx
- 891 pat recruited (planned 1900)

<table>
<thead>
<tr>
<th>SLND</th>
<th>ALND</th>
</tr>
</thead>
<tbody>
<tr>
<td>38% micromets</td>
<td>45% micromets</td>
</tr>
<tr>
<td>27% had additional pos LN</td>
<td></td>
</tr>
<tr>
<td>LR 2%</td>
<td>LR 4%</td>
</tr>
<tr>
<td>Axillary recurrence 5 (0.9%)</td>
<td>Axillary recurrence 2 (0.5%)</td>
</tr>
<tr>
<td>10 yr OS 86.3%</td>
<td>10 yr OS 83.6%</td>
</tr>
<tr>
<td>10 yr DFS 80.2%</td>
<td>10 yr DFS 78.2%</td>
</tr>
</tbody>
</table>
IBCSG 23-01
Axillary dissection vs observation

- Need for ALND in patients w micromets (>0.2mm-<2mm)
- cALND vs observation
- Allowed patients with mastectomy (10%)
- 68% had T1 cancers, 90% ER+, 25% G3, 90% had RT (BCS).
- Patient who had cALND – 13% had more positive LN

- Median FU 5 yrs.
- OS: no ALND 97.5%, cALND 97.6%
- DFS: no ALND 87.8%, cALND 84.4%
- Axillary recurrence: no ALND 1.1%, cALND 0.2%
EORTC AMAROS
Axillary dissection vs RT

- T1b-T2, N0
- BCS & TM
- Completed accrual
  - 65% patients SNB neg, 29.7% patients SNB positive (1425)
  - 744 – ALND, 681 had AxRT
  - Median tumour size 17-18mm (13-23mm)
  - 80% BCS, 90% systemic tx, 85% RT
  - 1-3 LN removed in all cases, 60% macromet, 30% micromet, 10% ITC
  - cALND: 32% had additional positive LN, 7.8% had > 4.
- DFS / OS similar
  - 5-years axillary recurrence rate: ALND 0.43% (4 / 744 events (0.54%)) AxRT 1.19% (7 / 681 events (1.03%))
SNB AFTER NACT
## NSABP B-18

Breast Conservation rates:

<table>
<thead>
<tr>
<th>Tumour Size</th>
<th>Surgery First % BCS</th>
<th>Neoadjuvant Chemo % BCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>79%</td>
<td>81%</td>
</tr>
<tr>
<td>T2</td>
<td>63%</td>
<td>71%</td>
</tr>
<tr>
<td>T3</td>
<td>8%</td>
<td>22%</td>
</tr>
<tr>
<td>All Patients</td>
<td>60%</td>
<td>67%</td>
</tr>
</tbody>
</table>

Fisher B et al. JCO 1997; 15:2483-93
NSABP B-18
Axillary node downstaging

<table>
<thead>
<tr>
<th></th>
<th>Surgery First (n=743)</th>
<th>Neoadjuvant Chemo (n=743)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 nodes +ve</td>
<td>30%</td>
<td>24%</td>
</tr>
<tr>
<td>4-9 nodes +ve</td>
<td>17%</td>
<td>12%</td>
</tr>
<tr>
<td>&gt; 10 nodes +ve</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>Overall nodes +ve</td>
<td>57%</td>
<td>41%</td>
</tr>
</tbody>
</table>

Fisher B et al. JCO 1997; 15:2483-93
AXILLARY NODE DOWNSTAGING
NSABP- B18

% Conversion from Node (+ve) to Node (-ve)

4 randomized trials of NACT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC NSABP B-18</td>
<td>30</td>
</tr>
<tr>
<td>FEC EORTC</td>
<td>19</td>
</tr>
<tr>
<td>AT→CMF ECTO</td>
<td>37</td>
</tr>
<tr>
<td>AC→TXT NSABP B-27*</td>
<td>43</td>
</tr>
</tbody>
</table>

*Assuming 30% nodal down-staging with neoadjuvant AC

Mamounas EP, NCI State of the Science
SENTINEL NODE BIOPSY – POST NACT

After neoadjuvant therapy

cN0 at presentation, SNB recommended post NACT
cN1 at presentation, downstaged to cN0 after NACT, SNB is feasible
Nodal pCR rates are between 35-49%\textsuperscript{1,2,3}
  - Sentina trial
  - TAD: targeted axillary dissection
Axillary dissection can be spared if 3 lymph nodes negative at the time of SNB
Fewer than 3 nodes results in unacceptably high false negative rates

\textsuperscript{1} J Clin Oncol 2015;33: 258e63.
\textsuperscript{2} JAMA 2013;310:1455e61.
\textsuperscript{3} Ann Surg Oncol 2016;23:3467e74.
### SLNB – Before or After NACT?

<table>
<thead>
<tr>
<th></th>
<th><strong>PROs</strong></th>
<th><strong>CONs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SLN biopsy BEFORE</strong></td>
<td>- More accurate staging</td>
<td>- 2 operations</td>
</tr>
<tr>
<td></td>
<td>- Better patient selection for NACT</td>
<td>- Unnecessary AC for 1/3 of node positive patients</td>
</tr>
<tr>
<td></td>
<td><strong>SLN biopsy AFTER NACT</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 1 operation</td>
<td>- less accurate staging</td>
</tr>
<tr>
<td></td>
<td>- AC avoided for 1/3 of node positive patients</td>
<td>- Dilemma for further adjuvant Tx : eg. RT</td>
</tr>
</tbody>
</table>
FEASIBILITY AND ACCURACY OF SLNB POST NACT

Various studies:

- Single institution trials
- Multicenter trials
- Meta-Analyses
<table>
<thead>
<tr>
<th>Author</th>
<th># Pts (Node +)</th>
<th>Success Rate (%)</th>
<th>FN Rate (%)</th>
<th>Accurate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breslin, 2000</td>
<td>51 (25)</td>
<td>84</td>
<td>12</td>
<td>Yes</td>
</tr>
<tr>
<td>Nason, 2000</td>
<td>15 (9)</td>
<td>87</td>
<td>33</td>
<td>No</td>
</tr>
<tr>
<td>Stearns, 2002</td>
<td>34 (13)</td>
<td>85</td>
<td>14</td>
<td>Yes*</td>
</tr>
<tr>
<td>Fernandez, 2001</td>
<td>40 (16)</td>
<td>85</td>
<td>25</td>
<td>No</td>
</tr>
<tr>
<td>Haid, 2001</td>
<td>33 (18)</td>
<td>88</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>Miller, 2002</td>
<td>35 (9)</td>
<td>86</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>Reitsamer, 2003</td>
<td>30 (15)</td>
<td>87</td>
<td>7</td>
<td>Yes</td>
</tr>
<tr>
<td>Brady, 2002</td>
<td>14 (11)</td>
<td>93</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>Schwartz, 2003</td>
<td>21 (11)</td>
<td>100</td>
<td>9</td>
<td>Yes</td>
</tr>
<tr>
<td>Balch, 2003</td>
<td>32 (19)</td>
<td>97</td>
<td>5</td>
<td>Yes</td>
</tr>
<tr>
<td>Aihara, 2004</td>
<td>20 (12)</td>
<td>85</td>
<td>8</td>
<td>Yes</td>
</tr>
<tr>
<td>Piao, 2003</td>
<td>42 (18)</td>
<td>98</td>
<td>17</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>All</strong></td>
<td><strong>398 (182)</strong></td>
<td><strong>89.1</strong></td>
<td><strong>10.8</strong></td>
<td></td>
</tr>
</tbody>
</table>
**SNB After NC: Single Institution Series**

<table>
<thead>
<tr>
<th>Author</th>
<th># Pts (Node +)</th>
<th>Success Rate (%)</th>
<th>FN Rate (%)</th>
<th>Accurate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kang, 2004</td>
<td>54 (27)</td>
<td>72</td>
<td>11</td>
<td>Yes</td>
</tr>
<tr>
<td>Jones, 2005</td>
<td>36 (18)</td>
<td>81</td>
<td>11</td>
<td>No</td>
</tr>
<tr>
<td>Kinoshita, 2006</td>
<td>77 (27)</td>
<td>94</td>
<td>11</td>
<td>Yes</td>
</tr>
<tr>
<td>Shimazu, 2004</td>
<td>47 (33)</td>
<td>94</td>
<td>12</td>
<td>Yes</td>
</tr>
<tr>
<td>Julian, 2004</td>
<td>42 (19)</td>
<td>95</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>Lang, 2004</td>
<td>53 (24)</td>
<td>94</td>
<td>4</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>All</strong></td>
<td><strong>309 (160)</strong></td>
<td><strong>88.7</strong></td>
<td><strong>8.1</strong></td>
<td></td>
</tr>
</tbody>
</table>

- Rates of SLN identification: 72 – 100%
- Rates of False negative SLN: 0 – 33%
MULTICENTER TRIAL: NSABP B-27

Identification Rate: 85%
- With blue dye only: 78%
- With radioisotope +/- blue dye: 88-89%

False Negative Rate: 11%
- With blue dye only: 14%
- With radioisotope +/- blue dye: 5 – 9.3%

Mamounas EP; JCO 2005; 23(12): 2694-2702
## Comparison of False Negative Rates Between SN Multicenter Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>FNR</th>
<th>(SN-/N+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter SB-2 Trial</td>
<td>11%</td>
<td>(13/114)</td>
</tr>
<tr>
<td>Italian Randomized Trial</td>
<td>9%</td>
<td>(8/91)</td>
</tr>
<tr>
<td>Ann Arundel</td>
<td>13%</td>
<td>(25/193)</td>
</tr>
<tr>
<td>University of Louisville</td>
<td>7%</td>
<td>(24/333)</td>
</tr>
<tr>
<td>NSABP B-32 Randomized Trial</td>
<td>10%</td>
<td>(75/766)</td>
</tr>
<tr>
<td>NSABP B-27 (After NC)</td>
<td>11%</td>
<td>(15/140)</td>
</tr>
<tr>
<td>Meta-Analysis (After NC)</td>
<td>12%</td>
<td>(65/540)</td>
</tr>
</tbody>
</table>

Krag DN: Surg Oncol 1993
Mamounas EP: J Clin Oncol 2005
McMasters KM: J Clin Oncol 2000
Xing Y: Br J Surg 2005
Julian JB: SABCS 2004

Mamounas EP, NCI State of the Science
SLN: BEFORE OR AFTER NACT
Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study

Thorsten Kuehn, Ingo Bauerfeind, Tarja Fehm, Barbara Fleige, Maija Hauschild, Gisela Helms, Annette Lieben, Cornelia Liedtke, Guntav von Minckwitz, Valentina Neklyudova, Sabine Schmalbach, Peter Schrenk, Annette Steebner, Michael Unich

Lancet Oncol 2013; 14: 609-18
Figure 1: SENTINA trial design
## SENTINA Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Arm A</th>
<th>Arm B</th>
<th>Arm C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1737 pts 103 institutions</td>
<td>cN0/pN0 SLNB upfront N=1022</td>
<td>cN0/SLN+ve NACT Re-SLNB + AC n=360</td>
<td>cN1-2 NACT SLNB + AC N=592</td>
</tr>
<tr>
<td>SLN Identification rate</td>
<td>99%</td>
<td>61%</td>
<td>80%</td>
</tr>
<tr>
<td>False negative rate (SLN –ve / AC +ve)</td>
<td>52%</td>
<td></td>
<td>14%</td>
</tr>
</tbody>
</table>
SENTINA TRIAL

- False negative rate:
  - By mapping technique:
    - Single method (radioisotope) – 16%
    - Dual method – 8.6%
  - By no. of SLN removed:
    - 1 SLN 24%
    - 2 SLN 18%
    - 3 SLN 7%
LYMPH NODE POSITIVE DISEASE BEFORE NACT
Original Investigation

Sentinel Lymph Node Surgery After Neoadjuvant Chemotherapy in Patients With Node-Positive Breast Cancer
The ACOSOG Z1071 (Alliance) Clinical Trial

Judy C. Boughey, MD; Vera J. Suman, PhD; Elizabeth A. Mittendorf, MD, PhD; Gretchen M. Ahrendt, MD; Lee G. Wilke, MD; Bret Taback, MD; A. Marilyn Leitch, MD; Henry M. Kuerer, MD, PhD; Monet Bowling, MD; Teresa S. Flippo-Morton, MD; David R. Byrd, MD; David W. Ollila, MD; Thomas B. Julian, MD; Sarah A. McLaughlin, MD; Linda McCall, MS; W. Fraser Symmans, MD; Huong T. Le-Petross, MD; Bruce G. Hauffty, MD; Thomas A. Buchholz, MD; Heidi Nelson, MD; Kelly K. Hunt, MD; for the Alliance for Clinical Trials in Oncology

Published online October 7, 2013.
ACOSOG Z1071

- Phase 2 trial
- 701 patients (2009 – 2011)
- cT0-4, N1-2, M0 disease
- All had neoadjuvant chemotherapy (commonly AC + taxane) followed by SLNB + AC

- Clinical CR – 83%
- Pathologic CR – 41%

- SLN identification rate – 92.5%
  - 79% of patients had dual method (radiocolloid + blue dye)
False negative rate:

By mapping technique
- Single method – 20.3%
- Dual method – 10.8%

By no. of SLN removed:
- 1 SLN 31.5%
- 2 SLN 21%
- ≥2 SLN 12.6%
- ≥3 SLN 9.1%
Prognosis post NACT

NSABP B-18

NSABP B-18 + B-27

Table 2. Multivariate Analysis of Independent Predictors of 10-Year LRR in the Combined Data Set

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 50 v &lt; 50 years†</td>
<td>0.78</td>
<td>0.63 to 0.98</td>
<td>.03</td>
</tr>
<tr>
<td>Clinical tumor size &gt; 5 v ≤ 5 cm†</td>
<td>1.51</td>
<td>1.19 to 1.91</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Clinical nodal status cN(+) v cN(−)†</td>
<td>1.61</td>
<td>1.28 to 2.02</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Nodal/breast pathologic status</td>
<td></td>
<td>&lt; .001</td>
<td></td>
</tr>
<tr>
<td>ypN(−)/no breast pCR v ypN(−)/breast pCR†</td>
<td>1.55</td>
<td>1.01 to 2.39</td>
<td></td>
</tr>
<tr>
<td>ypN(+) v ypN(−)/breast pCR†</td>
<td>2.71</td>
<td>1.79 to 4.09</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. The total No. of patients was 2,961, with 320 locoregional recurrence (LRR) events.
Abbreviations: HR, hazard ratio; pCR, pathologic complete response.
*Includes only patients for whom surgery type and all covariates are known.
†Category used as baseline for comparison of risk.

Fisher B et al. JCO 1997; 15:2483-93
Mamounas EP; JCO 2012; 30(32): 3960-3966
8-Year Cum. Incidence of LRF by According to Path Nodal Status/pCR and Clinical Nodal Status

Mamounas EP, NCI State of the Science
NACT TO AVOID AXILLARY DISSECTION

Use of NAC allows avoidance of ALND in some patients

669 cN0 patients, initial BCS vs 271 patients who received NACT

- In ER+, HER2 neg patients, need for ALND reduced from 34% (initial Sx/BCS by Z011 criteria) to 15% (NACT) p <0.0001
- In TNBC, ALND rate was 14% for initial BCS vs 7% post NACT p=0.26
- In HER2+ disease, rate was 13% for initial BCS, 8% post NACT p=0.26
- In patients undergoing mastectomy, NACT reduced need for ALND from 36% to 8%, p<0.001 in HER2 pos, and from 25% to 7% in TNBC patients p=0.001, BUT not in ER+ cancers (37% vs 34%, p=0.62)

PREDICTORS OF RESPONSE TO NACT

- Her 2 +ve / triple negative disease is responsive
  - 68 - 74% axillary pCR in Her 2 +ve disease
  - 57% axillary pCR in triple negative disease
- ER +ve disease is poorly responsive
  - <10% axillary pCR
- Invasive Lobular Carcinoma is poorly responsive
  - <5% breast / axillary pCR
- Oncotype Dx may be able to predict response to chemotherapy

Straver ME, EJC 2009; 45(13):2284-2292
Chehade HEH, Anticancer Research 2016; 36:1461-1472
J Clin Oncol 2005;23:7265e77.
Breast Cancer Res Treat 2015;154:299e308
AXILLARY CLEARANCE POST NACT

When it should be done

1. Clinically positive nodes after chemotherapy
2. Failure to detect lymph nodes at SLNB
3. Failure to find 3 lymph nodes
4. Lymph node positive at SLNB

Definition of positive nodes: Atypia, ITC, micro- / macro-metastases

Future: possible to avoid ALND in patients with indolent disease and low nodal burden post NACT?
Total Mastectomy

- Surgical considerations
- Clear margins
  - Skin involvement
    - Dermal infiltration
  - Pectoralis muscle
- Closure of wound
  - Reconstruction
CONSERVATIVE MASTECTOMY

Skin sparing / Areolar sparing
- Maximal excision of breast tissue
- Aesthetically not so normal

Nipple sparing
- Best results for aesthetic satisfaction
- There will be some breast tissue left in the nipple mound
- Nipple will be numb
CONSERVATIVE MASTECTOMY

Conditions for nipple sparing mastectomy:
- Early stage / Prophylactic for BRCA carriers
- Favourable biology
- IDC or DCIS at least 2 cm away from nipple
- Imaging negative for nipple involvement
- No nipple discharge
- No Paget's disease
- Nipple base assessed and not involved with malignancy
ONCOLOGICAL SAFETY
Nipple sparing mastectomy

Lanitis et al 2010:

- Meta-analysis of 9 studies, 3739 patients
- LRR similar between SSM and NSM
- But SSM groups had lower proportion of distant relapse
ONCOLOGICAL SAFETY
Nipple sparing mastectomy

De La Cruz et al 2015:
Meta-analysis of 20 studies, 5594 patients

- 7 studies comparing OS
  - 3.4% risk difference between NSM and SSM/MRM
- 5 Studies comparing DFS
  - 9.6% risk difference between NSM and SSM/MRM
- 8 studies comparing LR
  - 0.4% risk difference between the groups

Risk differences for all outcomes not statistically significant
ONCOLOGICAL SAFETY

Nipple sparing mastectomy

De La Cruz et al 2015

- At <3 yrs, 3-5 yrs, and > 5yrs
- For NSM, MRM, SSM
  - OS 97.2, 97.9, 86.8%
  - DFS 93.1, 92.3, 76.1%
  - LR 5.4, 1.4, 11.4%
  - NAR 2.1, 1.0, 3.4%

Good biological profile – safe to undergo NSM

Age 35.6 to 61yrs, with DCIS or stage I/II IDC and TND > 2cm

Can be considered in BRCA mutation carriers however no long term FU available – so far < 5years.
COMPLICATIONS SPECIFIC TO NSM

Nipple necrosis
Flap necrosis
Headon et al: 12,358 patients pooled analysis
Overall complication rate 22.3%
Nipple necrosis rate 5.9%
However appeared to decrease over time suggesting that surgeon expertise is a factor
## DE-ESCALATION OF THERAPY

<table>
<thead>
<tr>
<th>De-escalation of surgery</th>
<th>De-escalation of radiotherapy</th>
<th>De-escalation of chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved cosmesis</td>
<td>Radiation related cancers</td>
<td>Neuropathy</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>Telangiectasia</td>
<td>Cognitive decline</td>
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<tr>
<td>Sensory neuropathy</td>
<td>RT morphea</td>
<td>cardio-toxicity</td>
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<tr>
<td>body dysmorphea</td>
<td>Pigmentation</td>
<td>chronic fatigue</td>
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<td></td>
<td>Pneumonitis</td>
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<td>Axilla</td>
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<tr>
<td>Less lymphedema</td>
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<tr>
<td>No shoulder dysfunction</td>
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<tr>
<td>local recurrence rates</td>
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<td>distant relapse</td>
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<tr>
<td>survival impact</td>
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</table>
EARLY BREAST CANCER
De-escalation of treatment

With the observation of increased survival benefit and decreased local recurrence rates from long term adjuvant radiation trials, time to question if gold standard should now be breast conservation and radiation, over mastectomy

Patient choice?

Trade of side effects / morbidity:
Less surgery, usually means addition of RT / systemic therapy or both
DE-ESCALATION OF THERAPY

Patient discussion

Balance gain with risk
Decreased side effects vs increased recurrence risk
Need to identify patient goals
Acceptable morbidity vs relapse rates
Take into account tumour biology, anticipated lifespan, current co-morbidity
THANK YOU
Reconstruction

- Autologous vs Non-autologous
Reconstruction

- Autologous
- Free
  - require microvascular anastomosis
  - Increased operating time
  - Flap failure rates 1.9%
  - TRAM or DIEP
- Pedicled
  - Failure rates 0.2%
  - LD / TRAM
Reconstruction

- Autologous
- Complication rates (15-18%)
  - Wound infection
  - Seroma
  - Wound dehiscence
  - Chronic pain
Non-autologous

- Implants
- Expanders
  - silicon shell with saline core that can be expanded
- Mostly silicon
- Newer ones textured
  - Risk of anaplastic large cell lymphoma
  - 1/1000 to 1/10,000 patients
  - Presents as late, persistent seroma
  - No need for prophylactic removal at present
Non-autologous

- Consequences
  - Early
    - Seroma
    - Infection
  - Late
    - Tissue is stiffer – will not droop naturally
    - Capsular contracture
    - Implant pocket is too big
    - Granuloma
    - Distortion with RT
    - 49% will require revision surgery
Safety of IBR

- Most guidelines recommend that IBR should be offered to all patients contemplating a mastectomy
<table>
<thead>
<tr>
<th>Authors et al.</th>
<th>SSM vs. Mx (n); FU (follow-up) in months (m)</th>
<th>LR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newman et al., 1998</td>
<td>372 SSM; median FU = 26 m</td>
<td>6.2%</td>
</tr>
<tr>
<td>Toth et al., 1999</td>
<td>50 SSM; median FU = 51.5 m</td>
<td>0%</td>
</tr>
<tr>
<td>Medina-Franco et al., 2002</td>
<td>173 SSM; median FU = 73 m</td>
<td>4.5%</td>
</tr>
<tr>
<td>Carlson et al., 200375</td>
<td>539 SSM; median FU = 61.6 m</td>
<td>5.5% [0.6, 3.0, 10.4, 11.1, 0% in Stage 0, I, II, III, IV respectively]</td>
</tr>
<tr>
<td>Drucker-Zeruche et al., 200766</td>
<td>105 SSM; mean FU = 51 m</td>
<td>1%</td>
</tr>
<tr>
<td>Vaughan et al., 200757</td>
<td>210,206 SSM; median FU = 58.6 m</td>
<td>5.3% (9 of 11 in the index quadrant)</td>
</tr>
<tr>
<td>Lanitis et al., 201010</td>
<td>825 SSM vs. 2518 Mx; median FU for studies = 37.5−101 m</td>
<td>5.7% SSM (3.8−10.4) vs. 4.0% Mx (1.7−11.5) OR = 1.14 (95% CI 0.78−1.68) [Systemic recurrence = 8.3% SSM vs. 12.1% Mx; OR = 0.63, 95% CI 0.43−0.92]</td>
</tr>
<tr>
<td>Meta-analysis of 7 studies61,62,68−71.76</td>
<td></td>
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</tr>
<tr>
<td>Kinoshita et al., 201172</td>
<td>73 SSM vs. 129 Mx; mean FU = 30 m</td>
<td>2.7% SSM vs. 3.9% Mx</td>
</tr>
<tr>
<td>Nava et al., 201113</td>
<td>77 SSM; median FU = 36 m</td>
<td>0.5%/year</td>
</tr>
<tr>
<td>Sheikh et al., 201174</td>
<td>177 SSM vs. 249 Mx; mean FU = 28 m</td>
<td>1.1% SSM vs. 0.8% Mx (non-significant), [positive or close margin, 29% SSM vs. 12% Mx; p &lt; 0.01]</td>
</tr>
<tr>
<td>Peled et al., 201273</td>
<td>126 SSM; median FU = 28 m</td>
<td>2.4%</td>
</tr>
<tr>
<td>Rometes et al., 201224</td>
<td>207 SSM; median FU = 119(14−163) m</td>
<td>2.9% (8.2% loco-regional, 10.6% systemic recurrence)</td>
</tr>
</tbody>
</table>
Local Recurrence following IBR

- Rate varies from institution to institution
- Risk factors:
  - Young age
  - Multiple tumours
  - Larger tumours
  - High grade DCIS, however most recurrences a/w invasive disease
  - Higher stage disease
- Close or positive margins (<2mm)
- Median time to recurrence about 36 (7-128) months

Agrawal et al EJSO 2013;39;320-328
Prophylactic surgery
Prophylactic Surgery

- Increasing trends in the past decade
- Not just in high risk groups
- Perceived benefit
  - Reduction of contralateral breast cancer risk
  - ? Potential survival benefit
  - Improved personal effect
  - Presumed health care costs savings
- NICE guidelines
  - proven genetic mutation, or
  - high risk family history without a proven genetic mutation
Prophylactic Surgery

- Risks factors a/w increased risks of CBC
  - BRCA mutation
    - (15 year actuarial risk of CBC in BRCA 1 is 36.5%, BRCA 2 28.5%)
  - High risk FHx without mutation
  - Young age at first cancer
  - Previous radiation

- Patients with sporadic EBC
  - Lifetime risk of CBC is 13% in those under 50
  - 3.5% for those over 50 yrs
Prophylactic Surgery

- CBC
  - Increased surveillance
  - Increased awareness
  - Tend to present earlier – no survival impact
  - Risk of death is greater from ipsilateral metastatic disease rather than from new primary
- Even with patients with BRCA mutations, no OS benefit in patients older than 50 years
- In BRCA mutation patients > 35 years with co-morbidities, no OS benefit as well
Prophylactic Surgery

- Alternatives:
  - Surveillance
    - Regular CBE, MMG and MRI
    - HR of death from screen detected cancers is half that of symptomatic detection
    - MRI – more sensitive but lower specificity compared to MMG
      - Increase risk of false positives
      - Increased anxiety
Prophylactic Surgery

- Alternative:
  - Chemoprevention
  - STAR trial – comparing Tamoxifen vs Raloxifene in 19747 women
    - 50% reduction of CBC as long as age >35 yrs, postmenopausal, or both.
    - Tamoxifen slightly more effective, but higher risk of endometrial cancer and thromboembolic events
    - Similar effects noted with AIs
    - ATAC trial, 2.5% CBC rates in patients on anastrozole vs 4.2% in patients on Tam at 9 years
Prophylactic Surgery

- Morbidity incurred
  - Longer surgery time (can be shortened)
  - Increased hospital stay
  - Double the surgical risk for wound infection, dehiscence, flap necrosis
  - Chronic pain
  - Persistent seroma
Prophylactic Surgery

- Potential drivers of prophylactic surgery
  - Psychological factors
  - Perception of outcome
    - Balance of risk of future cancer and effect on mortality
    - vs incurred morbidity from additional surgery, psychological effect of loss of breast
    - vs surveillance anxiety – biopsies etc
Palliative surgery
Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial

Rajendra Badwe, Rohini Hawaldar, Nita Nair, Ruchika Kaushik, Voni Parmar, Shabina Siddique, Ashwini Budnikar, Indranil Mittra, Sudesh Gupta

Summary

Background: The role of locoregional treatment in women with metastatic breast cancer at first presentation is unclear. Preclinical evidence suggests that such treatment might help the growth of metastatic disease, whereas many retrospective analyses in clinical cohorts have suggested a favourable effect of locoregional treatment in these patients. We aimed to compare the effect of locoregional treatment with no treatment on outcome in women with metastatic breast cancer at initial presentation.

Methods: In this open-label, randomised controlled trial, we recruited previously untreated patients (≥65 years of age with an estimated remaining life expectancy of at least 1 year) presenting with de-novo metastatic breast cancer from Tata Memorial Centre, Mumbai, India. Patients were randomly assigned (1:1) to receive locoregional treatment directed at their primary breast tumour and axillary lymph nodes, or no locoregional treatment, by a computer-generated block randomisation sequence (block size of four). Randomisation was stratified by site of distant metastases, number of metastatic lesions, and hormone receptor status. Patients with resectable primary tumour in the breast that could be treated with endocrine therapy were randomly assigned upfront, whereas those with an unresectable primary tumour were planned for chemotherapy before randomisation. Of the patients who had chemotherapy before randomisation, we randomly assigned patients who had an objective tumour response after six to eight cycles of chemotherapy. The primary endpoint was overall survival analysed by intention to treat. This study is registered with ClinicalTrials.gov, NCT00193778.

No survival benefit found with removal of primary cancer in Stage IV breast cancer
Breast cancer treatment in mutation carriers
In BCT possible?

- Conflicting results from studies
  - Recent meta-analysis of 5326 carriers, 2320 controls
    - no difference in IBR rates (17.3% in carriers, 11% in controls, RR 1.45)
  - However if stratify by length of FU –
    - similar rates if < 7yrs,
    - but IBR increases markedly after this
    - Carriers – 23.9% vs 15.9% in controls
Is BCT possible?

- Comparing IBR in carriers after BCT vs mastectomy
  - Cumulative risk IBR in patients with BCT is 23.5% vs 5.5% in patients who had TM at 15 years
  - But BCSS with BCT was 93.5% vs 92.8%
  - And OS with BCT was 91.8% vs 89.8%
    - indicative of increased new primaries in patients who had BCT, unlike patients with TM who would have had true recurrence
Is BCT possible?

- Factors associated with reduced risk of IBR after BCT in BRCA carriers
  - Adj chemo
  - Oophorectomy

<table>
<thead>
<tr>
<th>Cohort studies</th>
<th>Risk Ratio (95% IC)</th>
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<tbody>
<tr>
<td>Brekelmans 2007</td>
<td>0.61 [0.33, 1.11]</td>
</tr>
<tr>
<td>Chappuis 2000</td>
<td>0.97 [0.22, 4.15]</td>
</tr>
<tr>
<td>El-Tamer 2004</td>
<td>3.22 [1.15, 9.01]</td>
</tr>
<tr>
<td>Haffty 2002</td>
<td>2.15 [1.13, 4.07]</td>
</tr>
<tr>
<td>Robson 1998</td>
<td>0.46 [0.06, 3.34]</td>
</tr>
<tr>
<td>Robson 2004</td>
<td>1.57 [0.73, 6.36]</td>
</tr>
<tr>
<td><strong>Subtotal (95% IC)</strong></td>
<td>1.32 [0.70, 2.46]</td>
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<tr>
<th>Case-control studies</th>
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<tr>
<td>Eccles 2001</td>
<td>0.69 [0.30, 1.58]</td>
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<tr>
<td>Garcia-Etienne 2009</td>
<td>4.50 [1.32, 15.35]</td>
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<tr>
<td>Kirova 2010</td>
<td>1.90 [1.22, 2.97]</td>
</tr>
<tr>
<td>Pierce 2006</td>
<td>1.51 [0.89, 2.56]</td>
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<tr>
<td><strong>Subtotal (95% IC)</strong></td>
<td>1.60 [0.94, 2.56]</td>
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<tr>
<td><strong>Total (95% IC)</strong></td>
<td>1.45 [0.98, 2.14]</td>
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Need for CPM in carriers?

- Carriers have a higher risk of CBC compared to non-carriers

Table 3: risk for CBC: BRCA-mutation carriers versus non-carriers

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<td>Chappuis 2000</td>
<td>7.97 [1.39, 45.81]</td>
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<td>El-Tamer 2004</td>
<td>1.74 [0.98, 3.11]</td>
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<td>Haffty 2002</td>
<td>4.77 [1.86, 12.24]</td>
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<td>Robson 2004</td>
<td>3.51 [2.05, 6.01]</td>
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<td>Stoppa-Lyonnet 2000</td>
<td>0.89 [0.39, 2.04]</td>
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<td>Kirova 2010</td>
<td>3.67 [2.07, 6.48]</td>
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<tr>
<td>Pierce 2006</td>
<td>8.34 [4.45, 15.63]</td>
</tr>
<tr>
<td>Subtotal (95% IC)</td>
<td>5.0 [2.97, 8.40]</td>
</tr>
<tr>
<td>Total (95% IC)</td>
<td>3.56 [2.50, 5.08]</td>
</tr>
</tbody>
</table>
BRCA 1 carriers higher risk than BRCA 2

Comparing BRCA 1 vs BRCA 2
  - 1532 BRCA 1 vs 950 BRCA 2 carriers
  - CBC rates were 21.1% and 15.1% respectively at 5 years
  - Risk increases with time from diagnosis

CPM did not affect OS
  - but small studies, short FU

Valachis et al Breast Cancer Res Treat 2014;144:443-455
Need for CPM in carriers?

- Protective factors against CBC in carriers
  - Use of adj Tamoxifen
  - Oophorectomy
  - Older age at first diagnosis