SINGAPORE 2018 ESMO ASIA

PRINCIPLES OF BREAST SURGERY / ONCOPLASTIC SURGERY

ESMO Preceptorship on Breast Cancer

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DISCLOSURE INFORMATION

No disclosures to declare

PRINCIPLES OF BREAST SURGERY

Therapeutic intent

Excise primary (local-regional cancer)

Clear margins

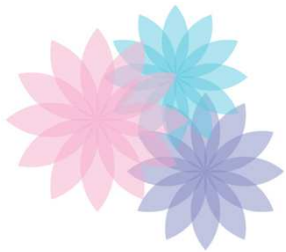
Maintain form / aesthetics

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

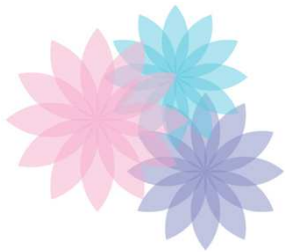
- Impt prognostic factors
  - Lymph node status
  - Tumour size
  - Tumour grade
  - Age
  - Lymphovascular invasion

  - 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

≤2.4	Excellant	93% 5YSR
≤3.4	Good	84%
≤4.4	Moderate I	70%
≤5.4	Moderate II	50%
>5.4	Poor	19%

INOPERABLE CANCER



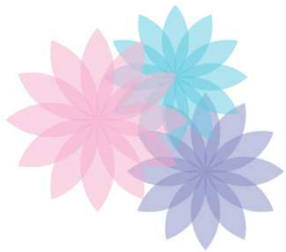
Metastatic

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

SINGAPORE 2018 ESMO ASIA

BREAST SURGERY

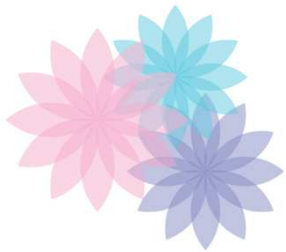
Choice of surgery depends entirely on extent of disease

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

Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, et al. Society of Surgical OncologyeAmerican Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irra- diation in stages I and II invasive breast cancer. Int J Radiat Oncol Biol Phys 2014;88:553e64.

Kwaliteitsinstituut voor de gezondheidszorg CBO. Richtlijn mammacarci- noom. 2008. p. 76e113., http://www.oncoline.nl/uploaded/FILES/mammacarcinoom/Richtlijn Behandeling van het Mammacarcinoom oktober 2005.pdf.

Association of Breast Surgery at B. Surgical guidelines for the management of breast cancer. Eur J Surg Oncol 2009;35(Suppl. 1):1e22.

Interdisziplin€are S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. http://www.awmf.org/uploads/tx_szleitlinien/032045OL_k_S3__Brustkrebs_Mammakarzinom_Diagnostik_Therapie_ Nachsorge_2012-07.pdf; 2012

Reseau Espace Sante-Cancer Rh^one-Alpes. Les Referentiels Cancer du Sein [5- 12-2013], http://www.rrc-ra.fr/Ressources/referentiels/PRA-SEI-1312SEIN. pdf; 2013.

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

J Clin Oncol 2016;34(33):4040e6.

MARGINS

Factors associated positive margin rate

- Lobular histology
- Adjacent DCIS to IDC
- Tumour size > 2cm
- Young age
- LVI
- Multifocality

MARGINS

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

The Breast 24 (2015) 413–417

MARGINS

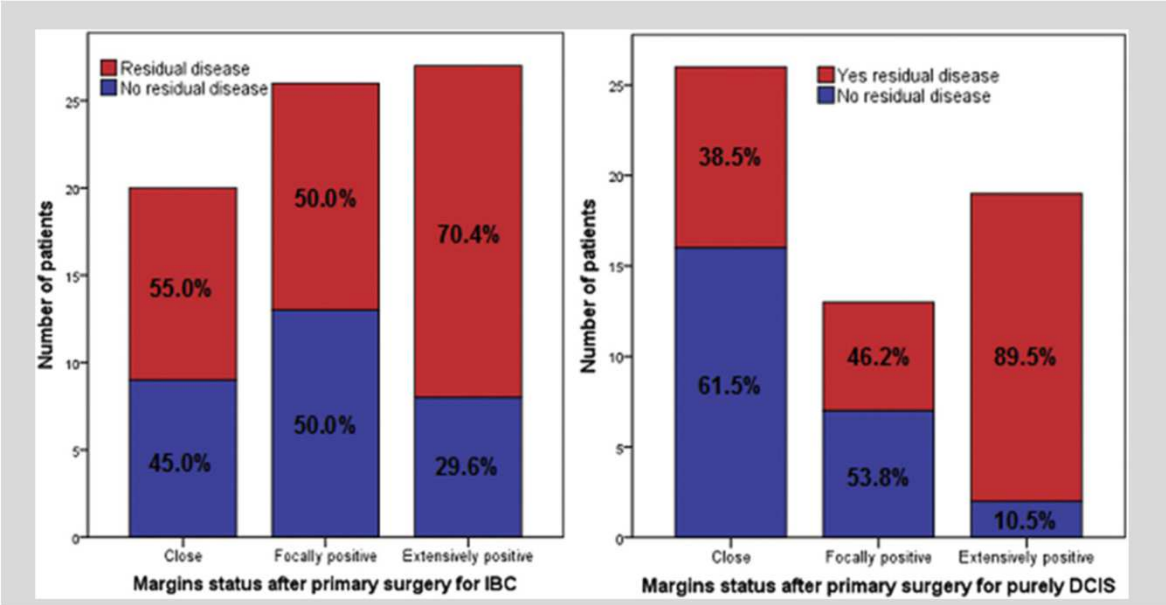
Impact of focally positive margins

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



EJSO 2017; 43: 1846-1854

Ann Surg Oncol (2014) 21:717–730
DOI 10.1245/s10434-014-3480-5

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GUIDELINE AND META-ANALYSIS

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, PhD[1], Petra Macaskill, PhD[1], M. Luke Marinovich, MPH[1], and Monica Morrow, MD[2]

[1]Screening and Test Evaluation Program (STEP), School of Public Health (A27), Sydney Medical School, University of Sydney, Sydney, Australia; [2]Breast 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

The Breast 25 (2016) 14-21

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

Localization technique	System components	Advantages	Disadvantages
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 (SAVI SCOUT)	• 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)

Br J Radiol 2018; 91: 20170740.

LESION LOCALIZATION

Other techniques

Intra-operative ultrasound

Annals of Surgical Oncology 2002; 9(10):994–8.

Modified ROLL – in combination with methylene blue dye

Annals of Surgical Oncology 2011;18(1):109–13

SAVI SCOUT® localization

Clin Imaging. 2018 Jul 24;52:280-286

Cryo-assisted localization

American Journal of Surgery 2006;192(4):462–70.

Haematoma associated localization (post VAB)

Ann Surg Oncol. 2010 Oct;17 Suppl 3:378-83.

LESION LOCALIZATION

Cochrane Database of Systematic Reviews 2015, Issue 12. Art. No.: CD009206.
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

European Journal of Surgical Oncology 1999; **25**: 464–469
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

Diagnostic Accuracy of Intraoperative Techniques for Margin Assessment in Breast Cancer Surgery: A Meta-Analysis – Annals of surgery Ann Surg. 2017 Feb;265(2):300-310

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 %

N Engl J Med. 2015 Aug 6;373(6):503-10.

MARGINS

Volume of Excision and Cosmesis with Routine Cavity Shave Margins Technique

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

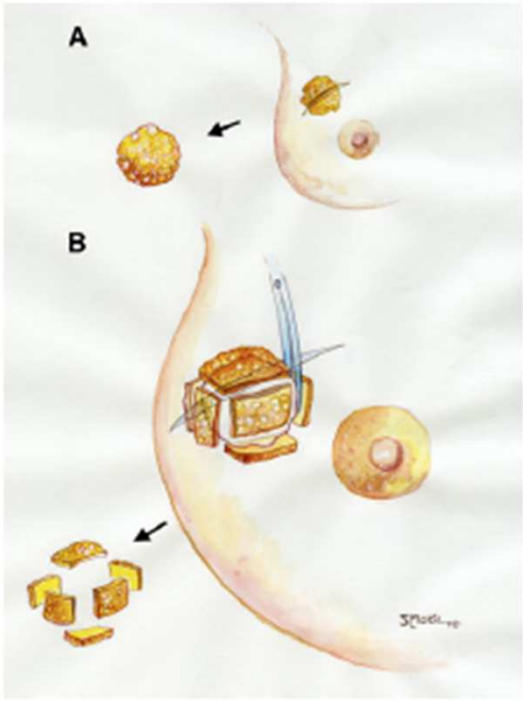
72 matched patients pairs-

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 165.1cm^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



Ann Surg Oncol (2012) 19:886–891

TARGET ACQUISITION

Intraoperative margin assessment

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

Ann Surg. 2017 Feb;265(2):300-310

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

Ann Surg Oncol (2016) 23:3290–3296

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)

Ann Surg. 2017 Feb;265(2):300-310

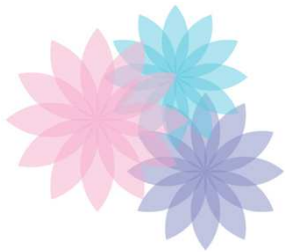
ONCOPLASTIC SURGERY

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

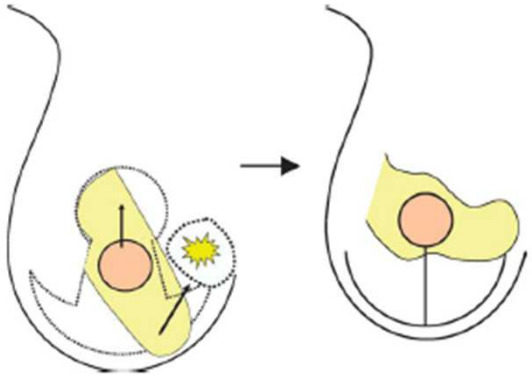


Figure 5 Scenario B. Filling the defect by extending the pedicle. The pedicle carries tissue normally excised into the defect.

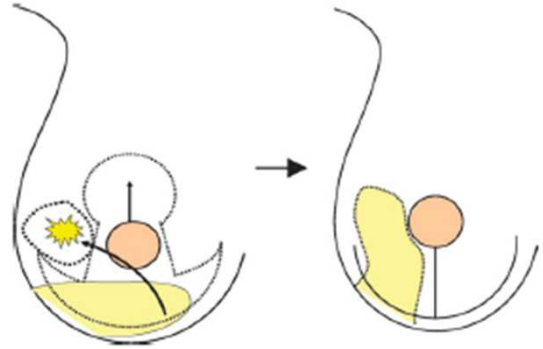


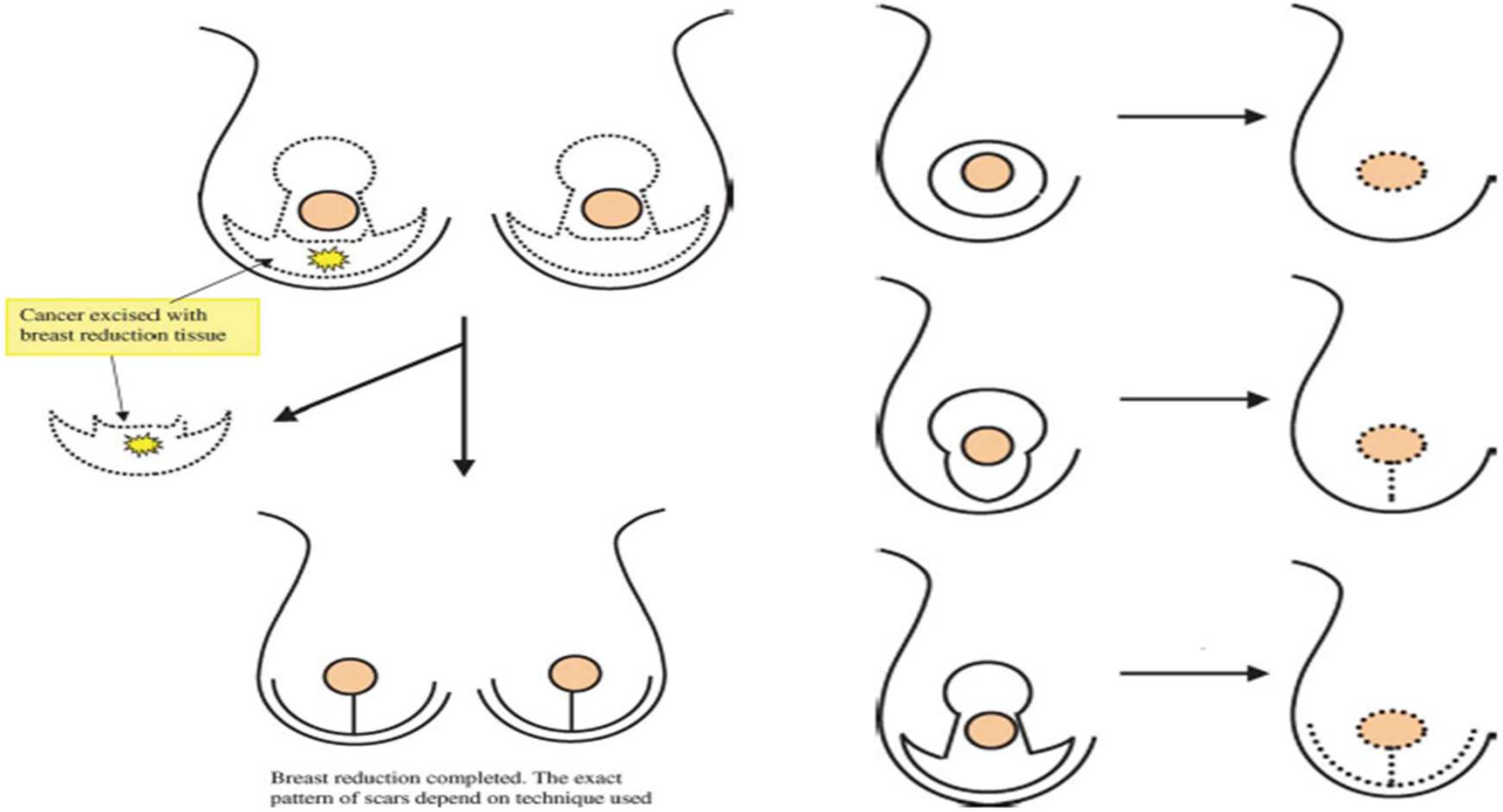
Figure 6 Scenario B. Filling defect by creating a secondary pedicle.

BJPS 58: 889-901, 2005

ONCOPLASTIC SURGERY

Level 2 techniques: Volume displacement

- Level II oncoplastic techniques



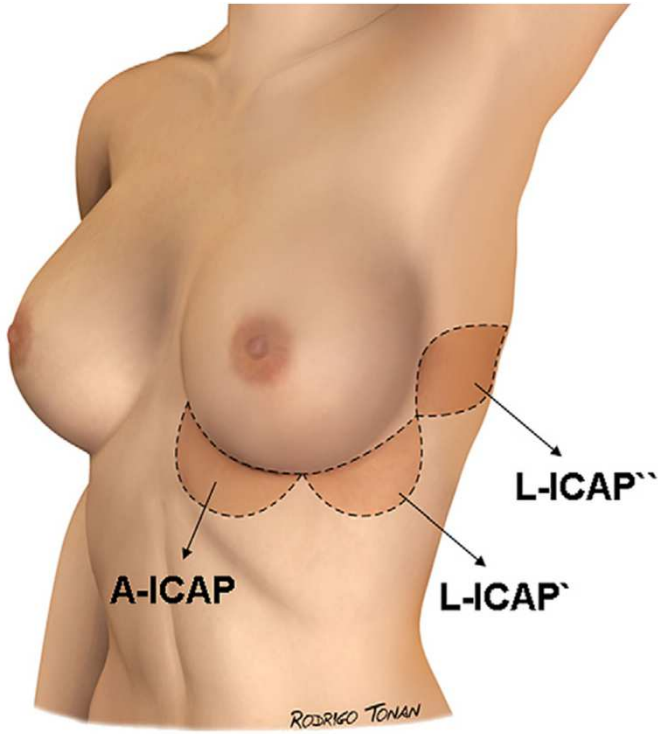
ONCOPLASTIC SURGERY

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



The Breast 20 (2011) 233–240

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 1
Recent data comparing BCS + RT to Mastectomy.

Author (ref number), year	Study Period	Data source	Inclusion criteria	N. of patients	Outcome Measure	Results		
						BCS+RT	M	M+RT
Agarwal [5], 2014	1998–2008	SEER database	T≤4cm N0-1	132.149	5y BCSS 10y BCSS	97 94	94 90	90% 83%
Hartman-Johnsen [5], 2015	1998–2008	Norway Cancer Registry	T1-2 N0-1	13.015	5yOS 10yOS 5y BCSS 10yBCSS	95 86 97 93	80 84 88 82	–
Chen [6], 2015	2004–2011	National Cancer Database	T1-2 N1-3	160.880	5y OS 8y OS	93.2 86.5	83.5 72.3	83 70.4
Lagendijk, Van Maaren [9,10], 2016, 2017	1999–2012	Netherlands Cancer Registry	T1-2 N0-2	129.692	11.7y OS and BCSS (1999-2005 cohort) 6y OS and BCSS (2006-2012 cohort)	OS:HR 0.74 BCSS: HR 0.72 OS: HR 0.67 BCSS: HR 0.75	HR 1 HR 1	–

BCSS=Breast Cancer-Specific Survival M = Mastectomy.

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[1]

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[2]
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

1. J Clin Oncol, 33 (2015), pp. 3938-3944
2. J Clin Oncol, 33 (2015), pp. 709-715

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

	LORD study (Europe)	COMET study (USA)	LORIS study (UK)
Age	>45 yrs of age	>40 yrs, non-pregnant	>46 yrs of age
DCIS grade	low grade DCIS	low / intermediate grade without comedo necrosis, ER/PR pos, HER2 neg	low grade DCIS / intermediate grade with low risk features
Pathology confirmation			Central pathology review
Diagnostic method	VAB biopsy	Core needle bx	diagnosed on VAB
Size of lesion			no size limit
Imaging criteria	asymptomatic, screen-detected DCIS		screen-detected or asymptomatic microcalcifications with no evidence of a mass
Monitoring criteria	Annual MMG, for 10 years		no endocrine tx, annual MMG, for 10 yrs
Recall criteria	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		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
Control arm	Standard treatment: Surgery / RT / endocrine tx		Standard Surgery and adj RT if indicated / endocrine tx permitted

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

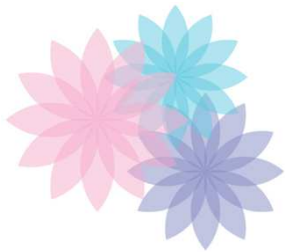
- Presence of multifocal patchy invasive foci – indicating patchy response
- Extensive DCIS

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
2. Lancet Oncol 2018; 19: 27-39

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. Cascinu [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

EJSO 2016

DE-ESCALATION OF SURGERY

Assessment of the axilla

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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

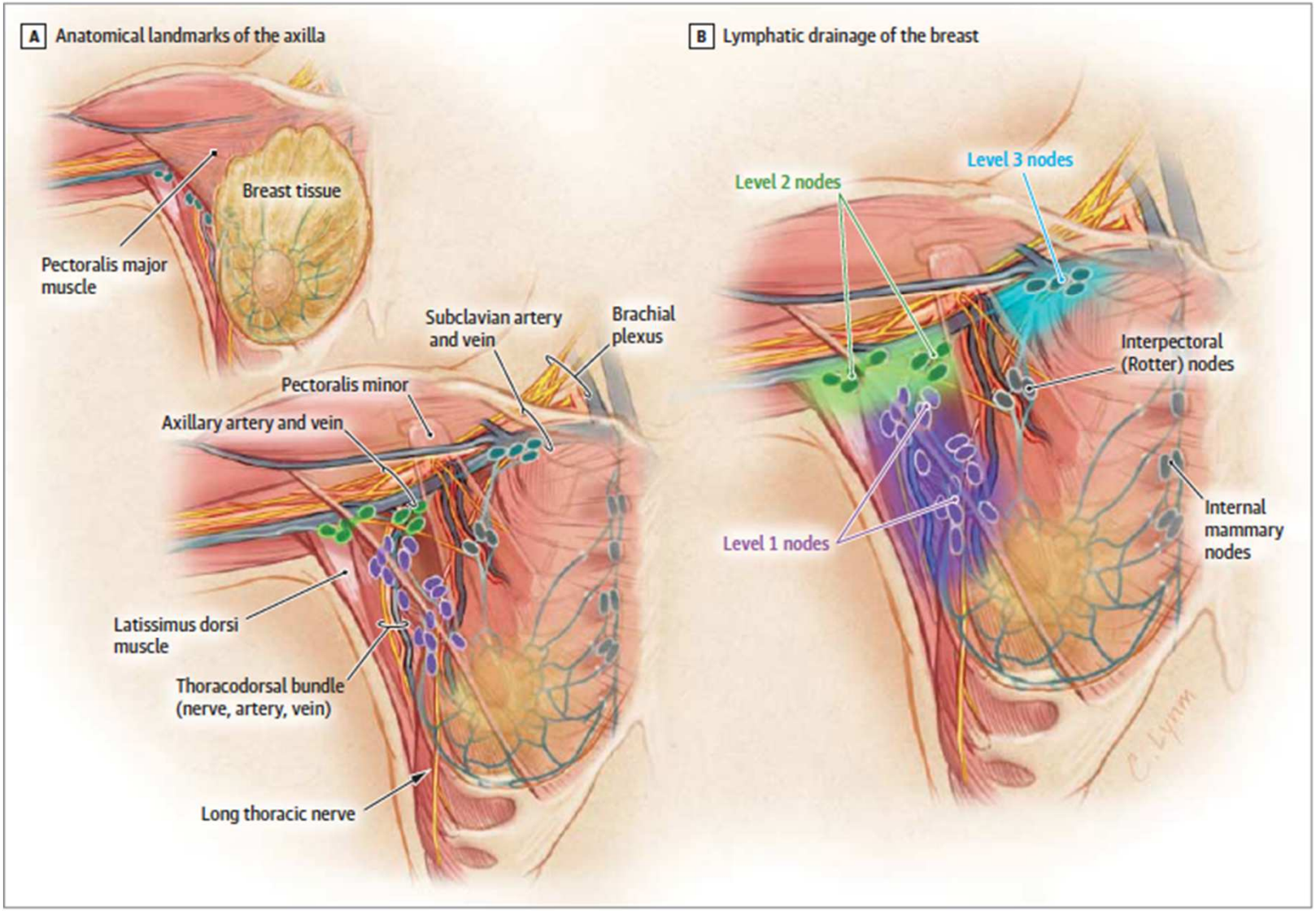
But - axillary dissection does not impact overall survival (NSABP- B04)

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

Figure 1. Anatomical Landmarks of the Axilla and Lymphatic Drainage of the Breast



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[1]

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.
Ann Surg 2016;264:413e20.

Z0011

Axillary dissection vs observation

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)

SLND	ALND
38% micromets	45% micromets
	27% had additional pos LN
LR 2%	LR 4%
Axillary recurrence 5 (0.9%)	Axillary recurrence 2 (0.5%)
10 yr OS 86.3%	10 yr OS 83.6%
10 yr DFS 80.2%	10 yr DFS 78.2%

IBCSG 23-01

Axilary 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 $\geq$ 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:

Tumour Size	Surgery First % BCS	Neoadjuvant Chemo % BCS
T1	79%	81%
T2	63%	71%
T3	8%	22%
All Patients	60%	67% P=0.002

Fisher B et al. JCO 1997; 15:2483-93

NSABP B-18

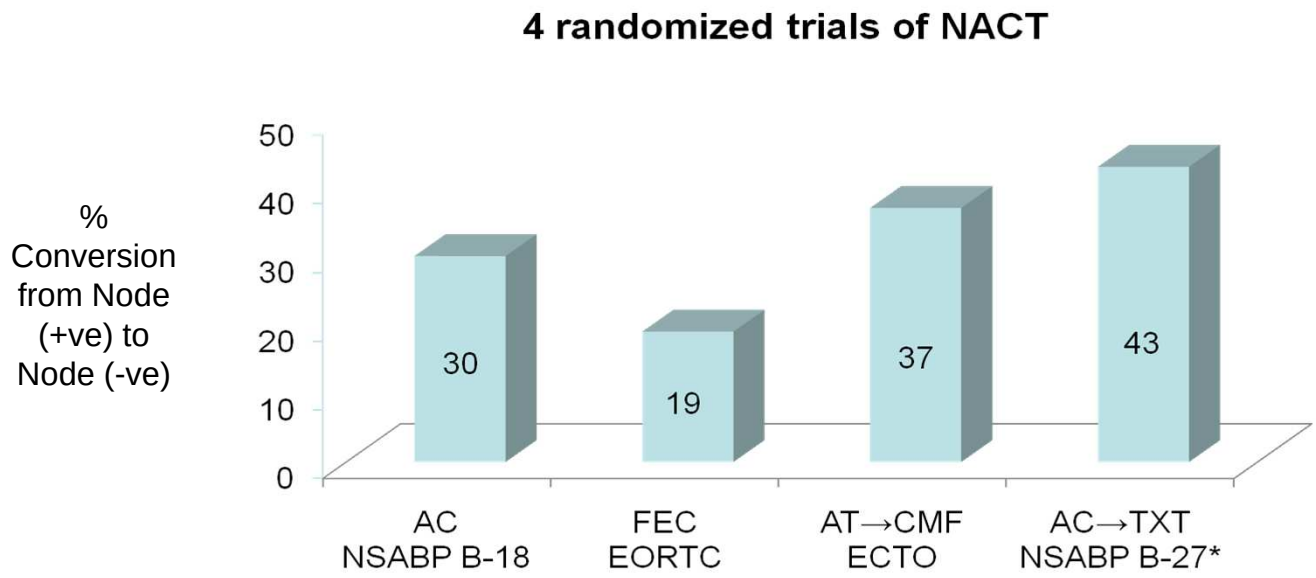
Axillary node downstaging

	Surgery First (n=743)	Neoadjuvant Chemo (n=743)
1-3 nodes +ve	30%	24%
4-9 nodes +ve	17%	12%
> 10 nodes +ve	10%	4%
Overall nodes +ve	57%	41% P<0.001

Fisher B et al. JCO 1997; 15:2483-93

AXILLARY NODE DOWNSTAGING

NSABP- B18



*Assuming 30% nodal down-staging with neoadjuvant AC

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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%[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

1. J Clin Oncol 2015;33: 258e63.
2. JAMA 2013;310:1455e61.
3. Ann Surg Oncol 2016;23:3467e74.

SLNB – Before or After NACT?

	PROs	CONs
SLN biopsy BEFORE NACT	-More accurate staging -Better patient selection for NACT	-2 operations -Unnecessary AC for 1/3 of node positive patients
SLN biopsy AFTER NACT	-1 operation -AC avoided for 1/3 of node positive patients	-less accurate staging -Dilemma for further adjuvant Tx : eg. RT

FEASIBILITY AND ACCURACY OF SLNB POST NACT

Various studies:

- Single institution trials
- Multicenter trials
- Meta-Analyses

SNB After NC: Single Institution Series

Author	# Pts (Node +)	Success Rate (%)	FN Rate (%)	Accurate	
Breslin, 2000	51 (25)	84	12	Yes	
Nason, 2000	15 (9)	87	33	No	
Stearns, 2002	34 (13)	85	14	Yes*	*Not in IBC
Fernandez, 2001	40 (16)	85	25	No	
Haid, 2001	33(18)	88	0	Yes	
Miller, 2002	35 (9)	86	0	Yes	
Reitsamer, 2003	30 (15)	87	7	Yes	
Brady, 2002	14 (11)	93	0	Yes	
Schwartz, 2003	21 (11)	100	9	Yes	
Balch, 2003	32 (19)	97	5	Yes	
Aihara, 2004	20 (12)	85	8	Yes	
Piato, 2003	42 (18)	98	17	Yes	
All	398 (182)	89.1	10.8		

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SNB After NC: Single Institution Series

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

- 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

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

Krag DN: Surg Oncol 1993
Mamounas EP: J Clin Oncol 2005
Veronesi U: N Engl J Med 2003
Tafra L: Am J Surg 2001
McMasters KM: J Clin Oncol 2000
Xing Y:Br J Surg 2005
Julian JB: SABCS 2004

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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, Tanja Fehm, Barbara Fleige, Maik Hausschild, Gisela Helms, Annette Lebeau, Cornelia Liedtke, Gunter von Minckwitz, Valentina Nekljudova, Sabine Schmatloch, Peter Schrenk, Annette Staebler, Michael Untch

Lancet Oncol 2013; 14: 609–18

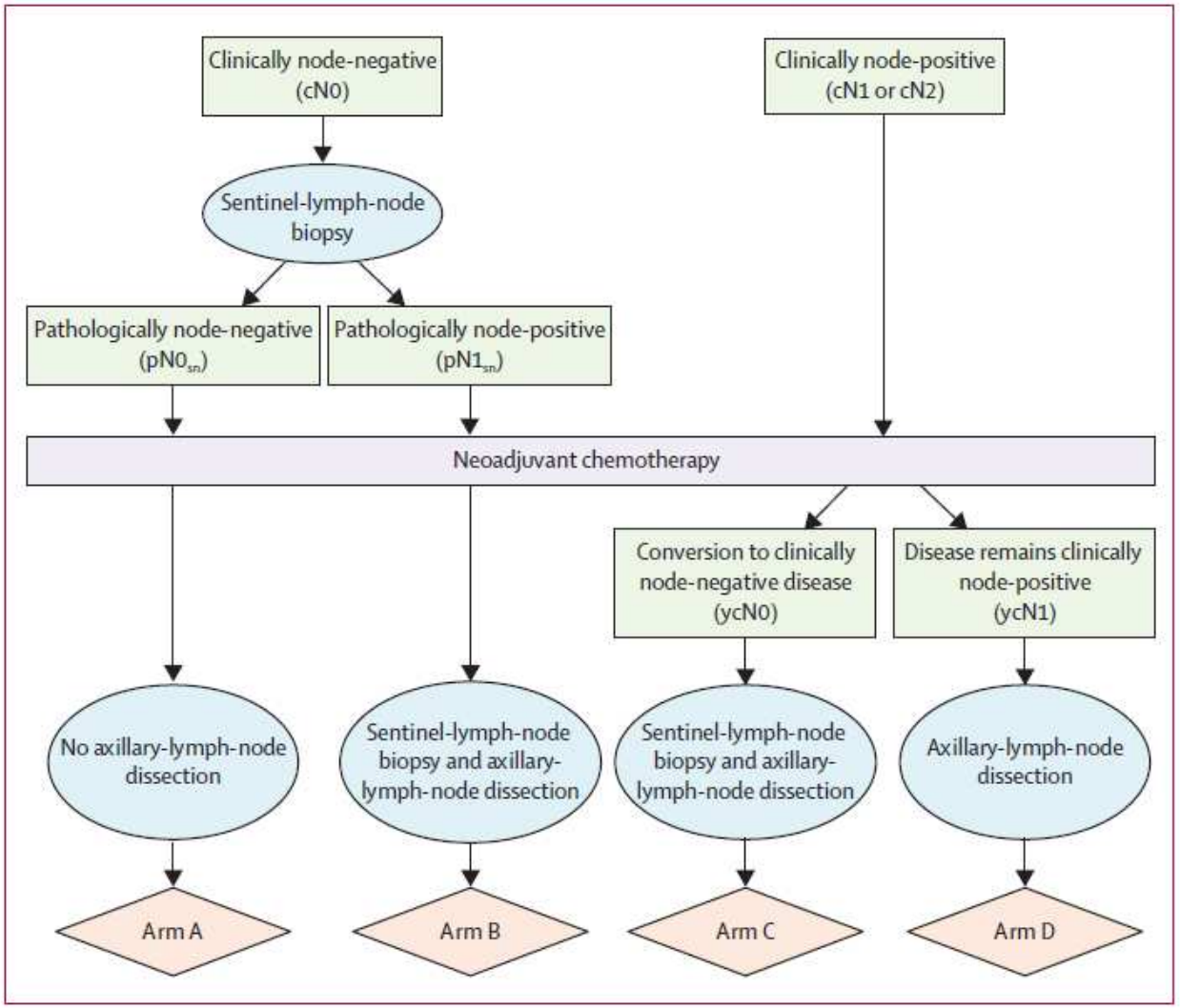
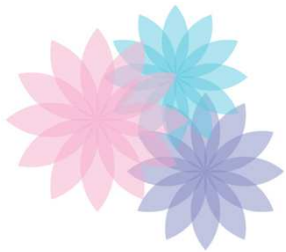


Figure 1: SENTINA trial design

SENTINA Trial

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

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. Haffty, MD; Thomas A. Buchholz, MD; Heidi Nelson, MD; Kelly K. Hunt, MD; for the Alliance for Clinical Trials in Oncology

JAMA. 2013;310(14):1455-1461. doi:10.1001/jama.2013.278932
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)

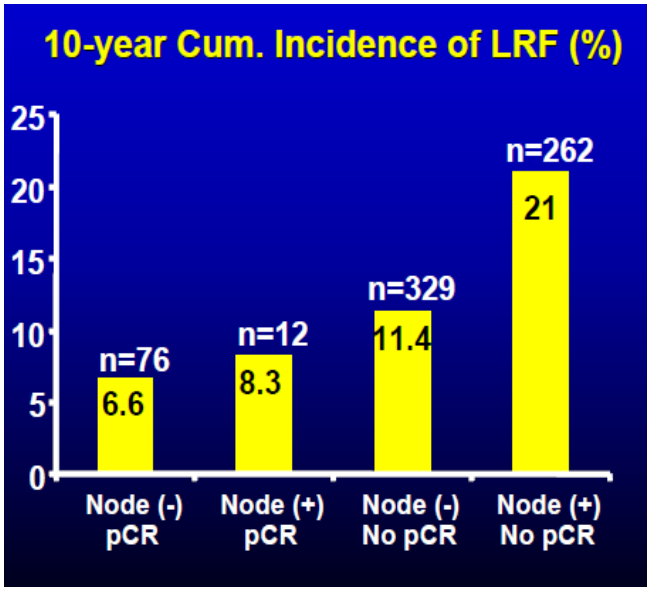
ACOSOG Z1071

- 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



Fisher B et al. JCO 1997; 15:2483-93

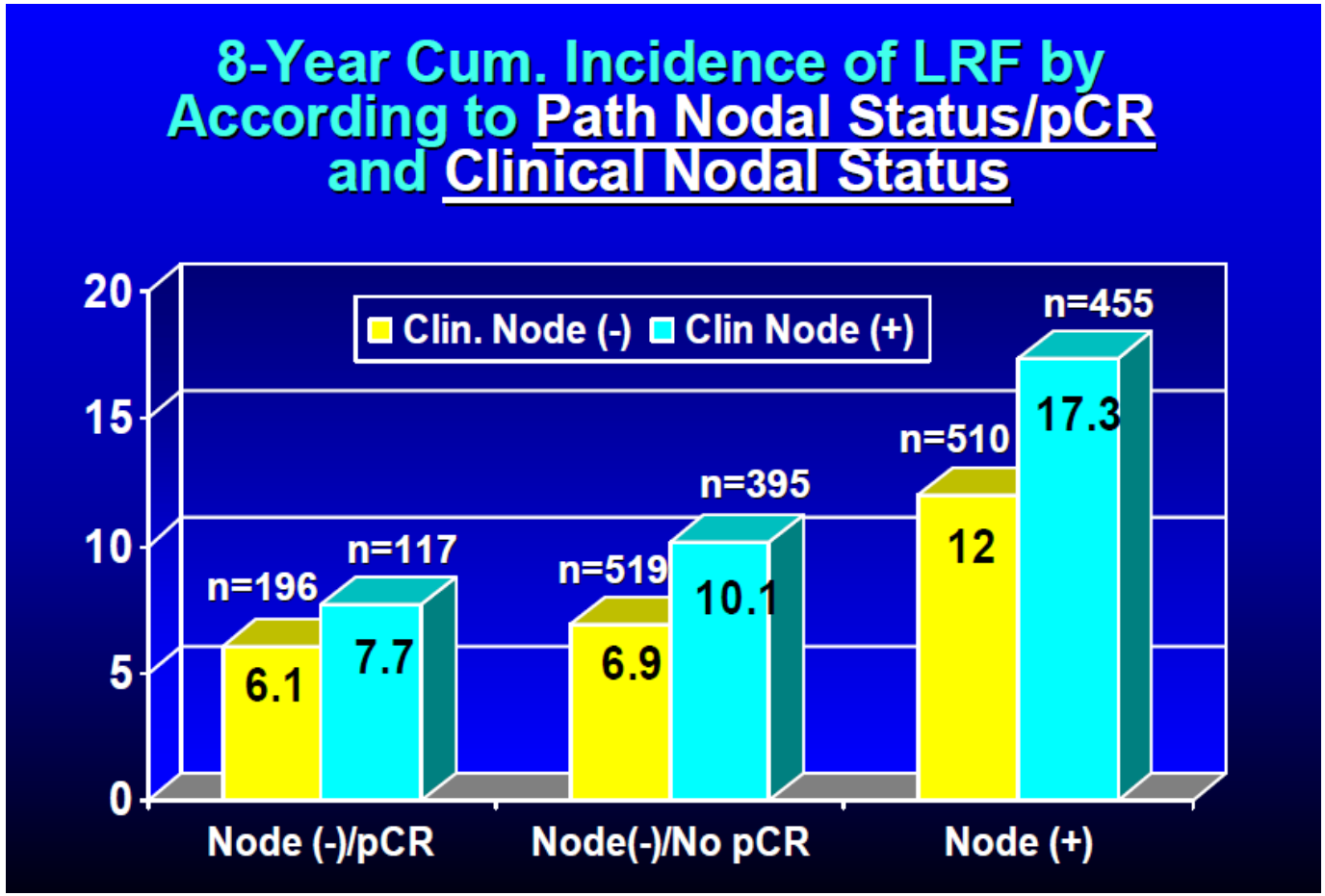
NSABP B-18 + B-27

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

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

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.

Mamounas EP; JCO 2012; 30(32): 3960-3966



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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)

Optimal Treatment Plan to Avoid Axillary Lymph Node Dissection in Early-Stage Breast Cancer Patients Differs by Tumor Subtype. In: Presented at the 2017 Society of Surgical Oncology Annual Cancer Symposium, March 15-18, 2017, Seattle, Washington.

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

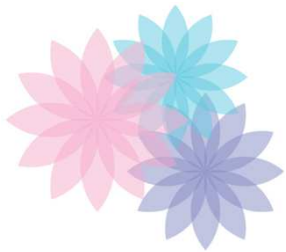
Definition of positive nodes: Atypia, ITC, micro- / macro-metastases

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



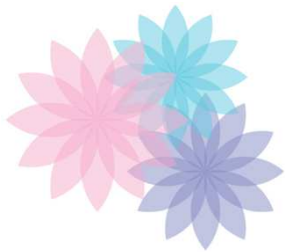
Skin sparing / Areolar sparing

- 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

Ann Surg 2010;251(4):632-9

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

Ann Surg Oncol 2015;22:3241-3249

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

Arch Plast Surg 2016;43(4):328-38

DE-ESCALATION OF THERAPY

De-escalation of surgery	De-escalation of radiotherapy	De-escalation of chemotherapy
Breast		
Improved cosmesis	Radiation related cancers	Neuropathy
Chronic pain	Telangiectasia	Cognitive decline
Sensory neuropathy	RT morphea	cardio-toxicity
body dysmorphea	Pigmentation	chronic fatigue
	Pneumonitis	
Axilla		
Less lymphedema		
No shoulder dysfunction		
local recurrence rates	local recurrence	distant relapse
nodal recurrence	distant relapse	local recurrence
survival impact		

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

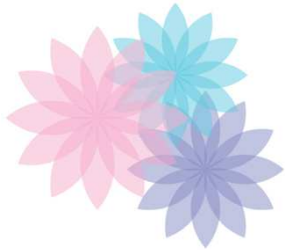
Balance gain with risk

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

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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

Literature reporting local recurrence rates following skin sparing mastectomy (chronological order of publication).

Authors et al.	SSM/vs. Mx (*n*); FU (follow-up) in months (m)	LR (%)
Newman et al., 1998[64]	372 SSM; median FU = 26 m	6.2%
Toth et al., 1999[3]	50 SSM; median FU = 51.5 m	0%
Medina-Franco et al., 2002[65]	173 SSM; median FU = 73 m	4.5%
Carlson et al., 2003[75]	539 SSM; median FU = 61.6 m	5.5% [0.6, 3.0, 10.4, 11.1, 0% in Stage 0, I, II, III, IV respectively]
Drucker-Zertuche et al., 2007[66]	105 SSM; mean FU = 51 m	1%
Vaughan et al., 2007[67]	210,206 SSM; median FU = 58.6 m	5.3% (9 of 11 in the index quadrant)
Lanitis et al., 2010[30] Meta-analysis of 7 studies[61,62,68–71,76]	825 SSM vs. 2518 Mx; median FU for studies = 37.5–101 m	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]
Kinoshita et al., 2011[72]	73 SSM vs.129 Mx; mean FU = 30 m	2.7% SSM vs. 3.9% Mx
Nava et al., 2011[13]	77 SSM; median FU = 36 m	0.5%/year
Sheikh et al., 2011[74]	177 SSM vs. 249 Mx; mean FU = 28 m	1.1% SSM vs. 0.8% Mx (non-significant); [positive or close margin, 29% SSM vs. 12% Mx; $p < 0.01$]
Peled et al., 2012[73]	126 SSM; median FU = 28 m	2.4%
Romics et al., 2012[24]	207 SSM; median FU = 119(14–163) m	2.9% (8.2% loco-regional, 10.6% systemic recurrence)

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, Rucha Kaushik, Vani Parmar, Shabina Siddique, Ashwini Budrukkar, Indraneel Mittra, Sudeep Gupta

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See Comment page 1284

See Online for podcast interview with Rajendra Badwe

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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

SINGAPORE 2018 ESMO ASIA

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

Pierce et al J Clin Oncol 2000;18:3360-3369

Is BCT possible?

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

Table 1: Risk for IBR in BRCA mutation carriers versus controls[5]

Cohort studies	**Risk Ratio (95% IC)**
Brekelmans 2007[6]	0.61 [0.33, 1.11]
Chappuis 2000[7]	0.97 [0.22, 4.15]
El-Tamer 2004[8]	3.22 [1.15, 9.01]
Haffty 2002[9]	2.15 [1.13, 4.07]
Robson 1998[10]	0.46 [0.06, 3.34]
Robson 2004[11]	1.57 [0.73, 6.36]
Subtotal (95% IC)	1.32 [0.70, 2.46]
Case-control studies	
Eccles 2001[12]	0.69 [0.30, 1.58]
Garcia-Etienne 2009[13]	4.50 [1.32, 15.35]
Kirova 2010[14]	1.90 [1.22, 2.97]
Pierce 2006[15]	1.51 [0.89, 2.56]
Subtotal (95% IC)	1.60 [0.94, 2.56]
Total (95% IC)	1.45 [0.98, 2.14]

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[1]

Cohort studies	**Risk Ratio (95% IC)**
Brekelmans 2007[6]	3.54 [2.28, 5.49]
Chappuis 2000[7]	7.97 [1.39, 45.81]
El-Tamer 2004[8]	1.74 [0.98, 3.11]
Haffty 2002[9]	4.77 [1.86, 12.24]
Robson 1998[10]	4.88 [1.89, 12.58]
Robson 2004[11]	3.51 [2.05, 6.01]
Stoppa-Lyonnet 2000[17]	0.89 [0.39, 2.04]
Subtotal (95% IC)	2.90 [1.85, 4.53]
Case-control studies	
Eccles 2001[12]	3.60 [2.15, 6.03]
Garcia-Etienne 2009[13]	15.0 [1.79, 125.57]
Kirova 2010[14]	3.67 [2.07, 6.48]
Pierce 2006[15]	8.34 [4.45, 15.63]
Subtotal (95% IC)	5.0 [2.97, 8.40]
Total (95% IC)	3.56 [2.50, 5.08]

Need for CPM in carriers?

- 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 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