

Panel Discussion:

Early Breast Cancer EBC- St Gallen's

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14th St.Gallen International Breast
Cancer Conference 2015

Primary Therapy of Early Breast Cancer
Evidence, Controversies, Consensus

18-21 March 2015, Vienna/Austria





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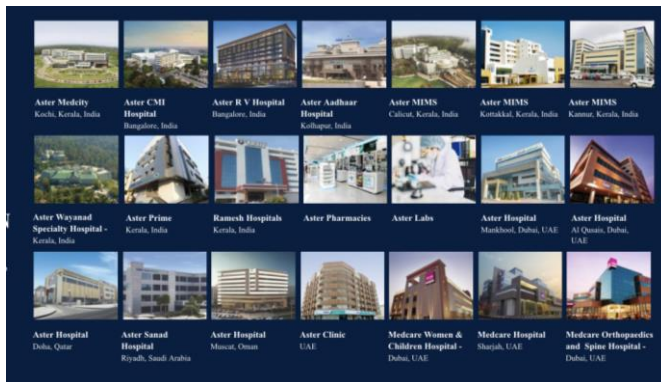
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Tailoring Therapy: Towards Precision Treatment of Patients with Early Breast Cancer



BCC 2015

14th St.Gallen International Breast Cancer Conference 2015

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Q .What is the definition of early Breast Cancer: EBC ?

1. Definition

- What is Early Breast Cancer ?

10^5 cells or < 10 mm Invasive cancer, N0, M0

- AJCC/UICC 9TH edition: Stage I and II
 - T1N0
 - T1N1
 - T2N0
 - T2N1
 - Early breast cancer is defined as tumours of not more than 5 cm diameter, with either impalpable or palpable but not fixed lymph nodes and no evidence of distant metastases.

TNM Stage and Operability at diagnosis

Overall Stage	Common Name	T	N	M	Operable at diagnosis
Stage 0	eBC	Tis	N0	M0	Yes
Stage I		T1	N0	M0	
Stage IIA		T0	N1	M0	
		T1	N1	M0	
		T2	N0	M0	
Stage IIB	T2	N1	M0		
	T3	N0	M0		
Stage IIIA	LABC	T0	N2	M0	No
		T1	N2	M0	
		T2	N2	M0	
	eBC	T3	N1	M0	Yes
	LABC	T3	N2	M0	No
Stage IIIB		T4	Any N	M0	No
Stage IIIC		Any T	N3	M0	
Stage IV	Metastatic	Any T	Any N	M1	

Approach to lump in breast



Premenopausal Lady 40 years , Lump right breast 2x2.5 cms

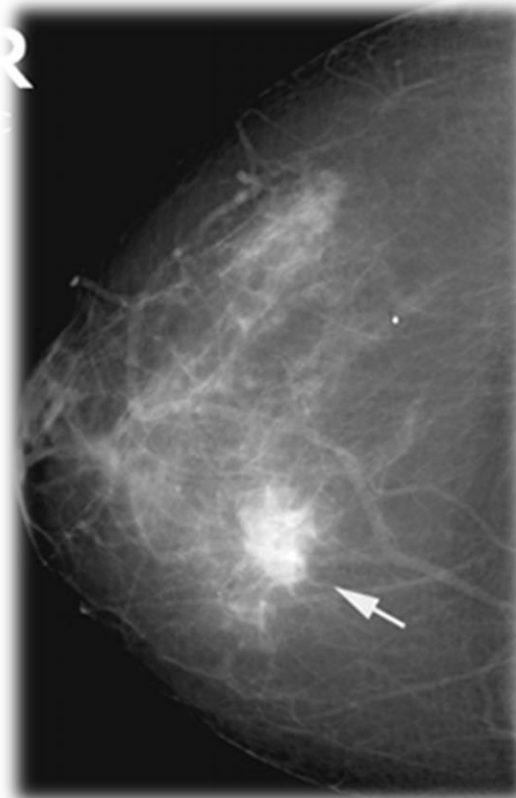
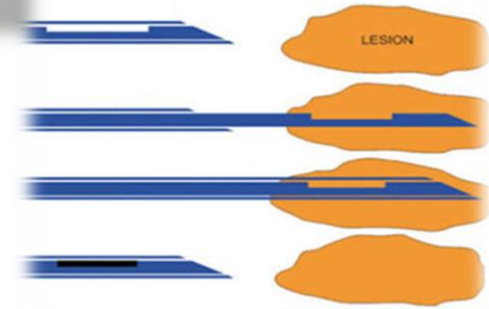
Q. How will you diagnose?

Triple assessment

Clinical examination

Radiological examination

Pathological examination

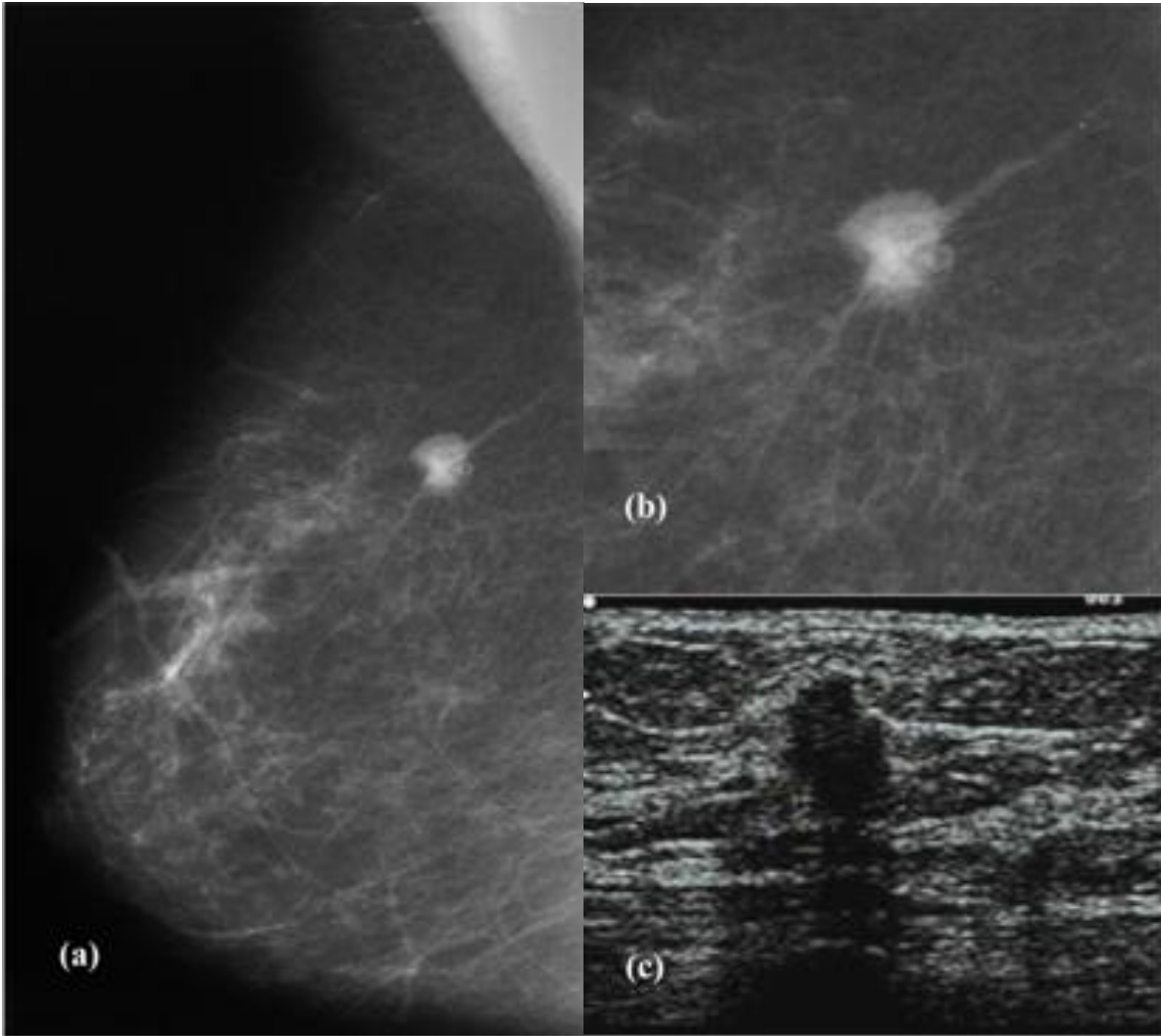


Diagnosis

- Clinical examination - most important

- Simple Triple Test:

Clinical + Mammography + Core Biopsy



For younger women with dense breasts

Use additional ultrasound (and rarely MRI) of breast

Triple Assessment of Breast

- Gold standard of breast cancer diagnosis
- > 95% of symptomatic breast cancers diagnosed using TABC^{1,2,3}

1) Merion Thomas J et al. *Br Med J* 1978; ii:1139 – 1141

2) Dixon JM et al. *Br J Surg* 1984; 71:593 – 596

3) Hermansen C et al. *Cancer* 1987; 60:1866 – 1871

TRIPLE ASSESSMENT

CLINICAL EXAMINATION

Sensitivity = 68-80%



RADIOLOGICAL EXAMINATION

PATHOLOGICAL EXAMINATION

FNAC

CORE BIOPSY (CNB)

SONOMAMMOGRAM

MAMMOGRAM

MRI

Sensitivity 75%, but 54-58% < 40years, and 81-94% > 65 yrs

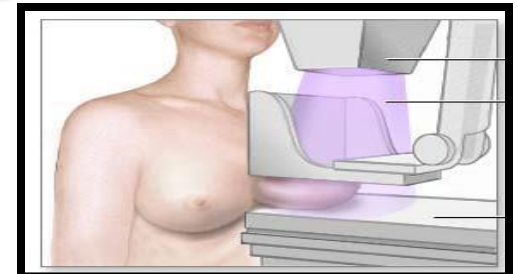
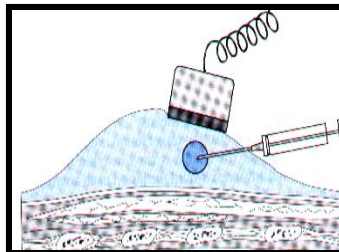
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IMAGE GUIDED

VACUUM ASSISTED CORE BIOPSY

ULTRASOUND / MRI GUIDED BIOPSY

STEREOTACTIC BIOPSY



6. Metastatic Survey

- Bone scan: yes or no
- CT Scan: Yes or no
- PET- CT Scan: yes or no

Q. Work Up???

Additional Work up

- Bone Scan → Localised bone pain / Elevated ALP
 - Metastasis identified by bone scan Stage I- 5.1%, Stage II- 5.6% and Stage III- 14%

[Puglisi F¹](#), [Follador A](#), [Minisini AM](#), [Cardellino GG](#), [Russo S](#), [Andreetta C](#), [Di Terlizzi S](#), [Piga A](#).
Baseline staging tests after a new diagnosis of breast cancer: further evidence of their limited indications. [Ann Oncol](#). 2005 Feb;16(2):263-6.

- PET/ PET-CT → Not recommended due to High false positive results

C. E. Carr, E. F. Conant, M. A. Rosen, M. D. Schnall and R. Davidson The impact of FDG PET in the staging of breast cancer, *Journal of Clinical Oncology*, 2006 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 24, No 18S (June 20 Supplement), 2006: 530

Metastatic Survey

- Performance of Breast MRI, bone scan (category 2B), and abdominal imaging with diagnostic CT (with or without pelvic CT) or MRI (all category 2A) are optional unless directed by symptoms or other abnormal study results.
- PET/CT scan is optional (category 2B);
 - useful when standard imaging are equivocal/suspicious
 - Bone scan may be omitted if PET CT shows osseous metastases

Bone scan vs PET scan

- Bone scan may be omitted if FDG PET/CT results are positive for bone metastasis.

7

- Role of MRI breast based response evaluation

Q. Is breast MRI necessary before BCS?

MRI not necessary Before BCS

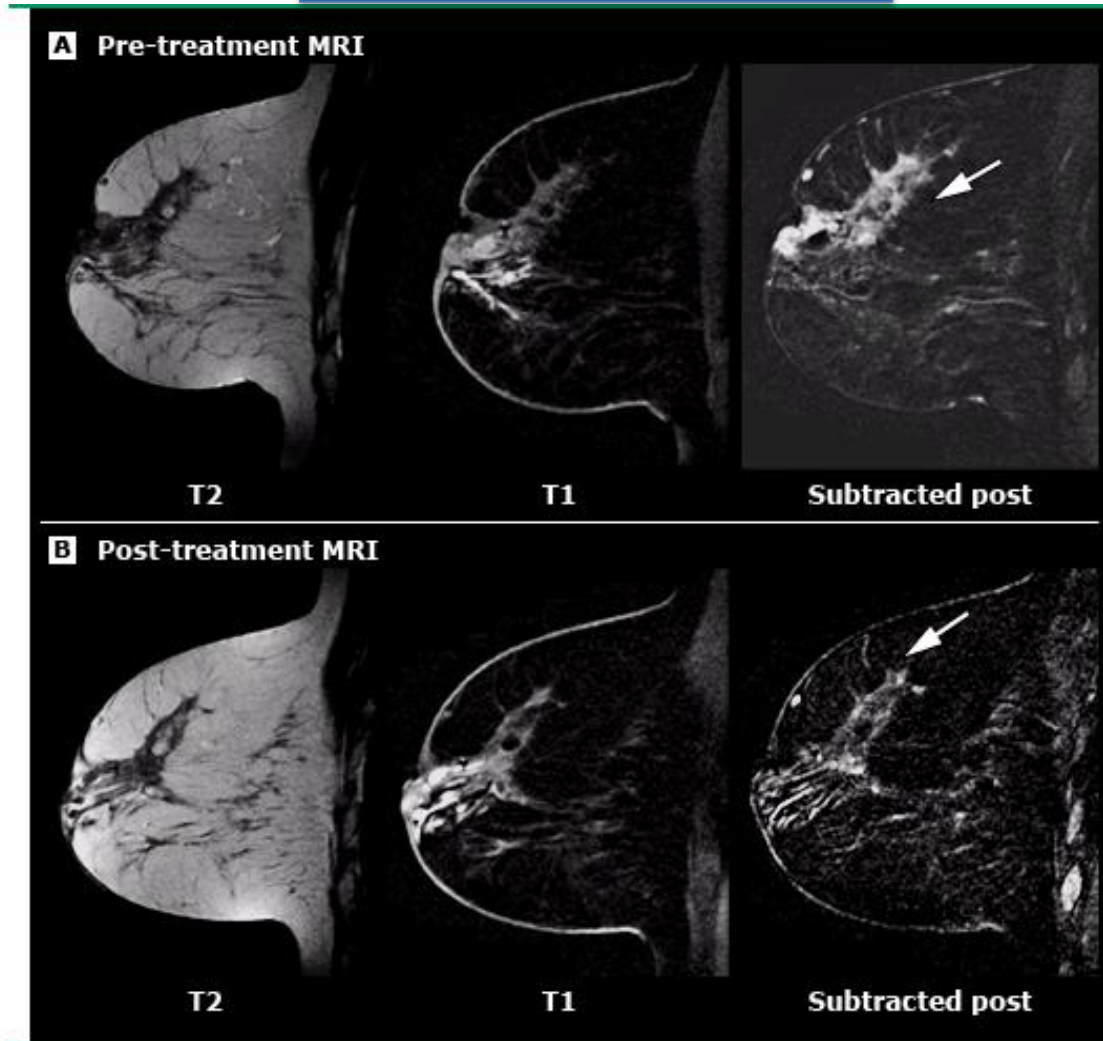
- Breast MRI staging alter surgical treatment in 7.8% to 33.3% of women
- PPV was 66% (95% CI, 52% to 77%)
- True Positive :False Positive ratio was 1.91 (95% CI, 1.09 to 3.34)

All Abnormal sites should be biopsied before surgical decision

[Houssami N](#), [Ciatto S](#), [Macaskill P](#), [Lord SJ](#), [Warren RM](#), [Dixon JM](#), [Irwig L](#). Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. [J Clin Oncol](#). 2008 Jul 1;26(19):3248-58. doi: 10.1200/JCO.2007.15.2108. Epub 2008 May 12.

MRI response assessment

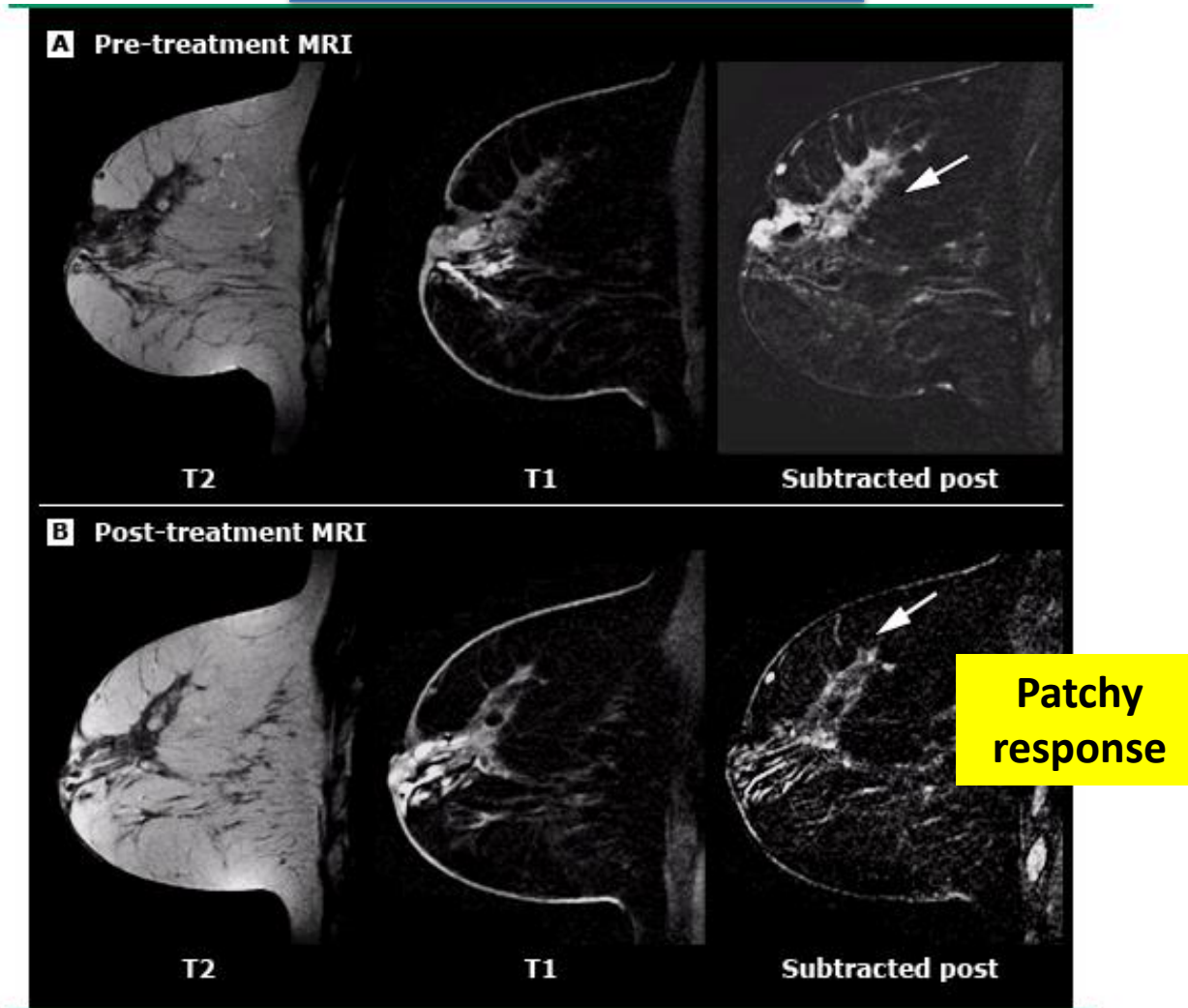
Invasive Lobular carcinoma



Patchy
response

MRI response assessment

Invasive Lobular carcinoma



MRI

Type of response

- Patchy response
- Concentric response

Better for Lobular carcinoma-LABC

- Predicting pCR
 - Sensitivity : 25-100%
 - Specificity : 50-97%
 - PPV : 47-73%
 - NPV : 71-100%

Conclusion: accuracy better than others. But both over estimation and underestimation occur.

It has not altered local recurrence rate

Accuracy of MR imaging for revealing residual breast cancer in patients who have undergone neoadjuvant chemotherapy.

*Partridge SC, Gibbs JE, Lu Y, Esserman LJ, Sudilovsky D, Hylton NM
AJR Am J Roentgenol. 2002 Nov; 179(5):1193-9.*

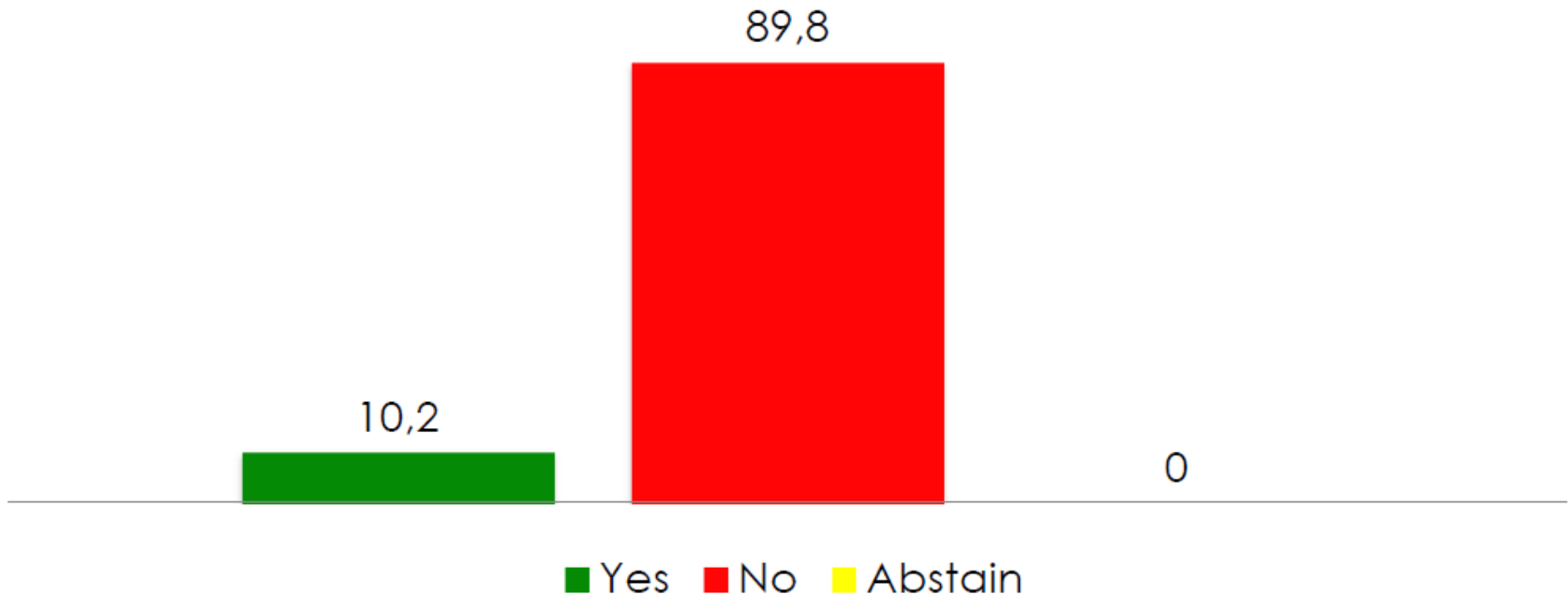
MRI tends to overestimate the size of residual disease

and, because of the antiangiogenic effects of certain chemotherapeutic agents on tumor, the ability of MRI to evaluate lesion enhancement can be significantly decreased

- *Accuracy of MRI in the detection of residual breast cancer after neoadjuvant chemotherapy.*
- *Rosen EL, Blackwell KL, Baker JA, Soo MS, Bentley RC, Yu D, Samulski TV, Dewhirst MW*
- *AJR Am J Roentgenol. 2003 Nov; 181(5):1275-82.*

Surgery of the primary breast cancer

Should MRI be routine for patients with newly diagnosed disease (to assess decision on BCS)?



Q. Whom you will send for genetic counseling and BRCA testing?

Guideline for BRCA testing

- Non Ashkenazic Jewish women
 - Two first degree relatives with breast cancer, one < 50 yrs
 - Three or more first / second degree relatives with breast cancer, any age
 - Breast / ovarian cancer in 1st or 2nd degree relatives
 - 1st degree relative with B/L breast cancer
 - Breast cancer in male relative
 - Two /More 1st or 2nd degree relatives with ovarian cancer
- Ashkenazic Jewish women
 - 1st degree relative with Breast / ovarian cancer
 - Two 2nd degree relatives with Breast / ovarian cancer

Q. Is BRCA positivity contraindication for breast conservation?

NO, BCS is possible

- Overall median F/U 161 months
- **After 13.4 years of F/U No significant difference in ITBR between mutation carriers, non-carriers and controls (P = 0.13)**
- On multivariate analysis, age was the most significant predictor for ipsilateral recurrence (P < 10⁽⁻³⁾)
- **The rate of CBC is higher in familial cases: 40.7% (mutation carriers), 20% (non-carriers), and 11% (controls) (P < 10⁽⁻⁴⁾) regardless of hormonal intervention.**
- As tumours in BRCA1/2 mutation carriers might be more sensitive to radiation

[Kirova YM¹](#), [Savignoni A](#), [Sigal-Zafrani B](#), [de La Rochefordiere A](#), [Salmon RJ](#), [This P](#), [Asselain B](#), [Stoppa-Lyonnet D](#), [Fourquet A](#). Is the breast-conserving treatment with radiotherapy appropriate in BRCA1/2 mutation carriers? Long-term results and review of the literature. [Breast Cancer Res Treat.](#) 2010 Feb;120(1):119-26. doi: 10.1007/s10549-009-0685-6. Epub 2009 Dec 24.

Not Contraindications for Breast Irradiation

- Young age
- Non-biopsied MRI findings
- Systemic lupus
- BrCa1 or 2 mutation carrier
- Contralateral breast or chest irradiation
- Node positive disease
- High grade histology
- Triple negative subtype
- T3 disease
- Retroareolar location

Q. Multifocal and multicentric (unilateral) tumors are contraindicated for breast conservation surgery?

- NO → Multifocal and multicentric (unilateral) tumors can be treated with breast conservation provided margins are clear and whole breast RT is planned.

St.Gallen Consensus 2015

When considering breast conserving surgery the following basic factors ARE NOT ABSOLUTE contraindications

- ❖ Young Age <35; <40
- ❖ Extensive or diffuse microcalcifications
- ❖ Multifocal disease
- ❖ Multicentric disease
- ❖ Tumor close to nipple
- ❖ Extensive vascularization
- ❖ Extensive intraductal component
- ❖ Lobular histology



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Is breast conservation therapy contraindicated in *BRCA1/BRCA2* mutation carriers?

- No
- Treatment of primary tumor should not be confused with prophylactic surgery to reduce the risk of a second primary tumor
- Issue to consider:
 - Risk of systemic disease and death from primary tumor
 - Risk of second primary breast cancer
 - Need for therapeutic mastectomy and decisions related to the type of reconstruction that will be used
 - Patient preference

Less Than 1% Absolute Survival Benefit at 20 Years Found for Contralateral Prophylactic Mastectomy

By Charlotte Bath

<http://www.ascopost.com/>

Is prophylactic mastectomy mandatory for *BRCA1* and *BRCA2* mutation carriers?

- No
- Risk reducing mastectomy (RRM) substantially reduces the risk of developing breast cancer by >90%
- Survival analysis by Kurian et al *JCO 2010*
 - Best survival with RRM at age 25 and RRSO at age 40
 - *BRCA1* mutation carriers
 - RRSO at 40 plus screening compared to RRSO and RRM at age 40: survival difference of 3% by age 70
 - *BRCA2* mutation carriers
 - Difference is 2%

Kurian et al JCO 2010

Q.

1. When you advice Pre operative

chemo to downstage the tumor???

2. In this setting Sentinel node biopsy

indicated???

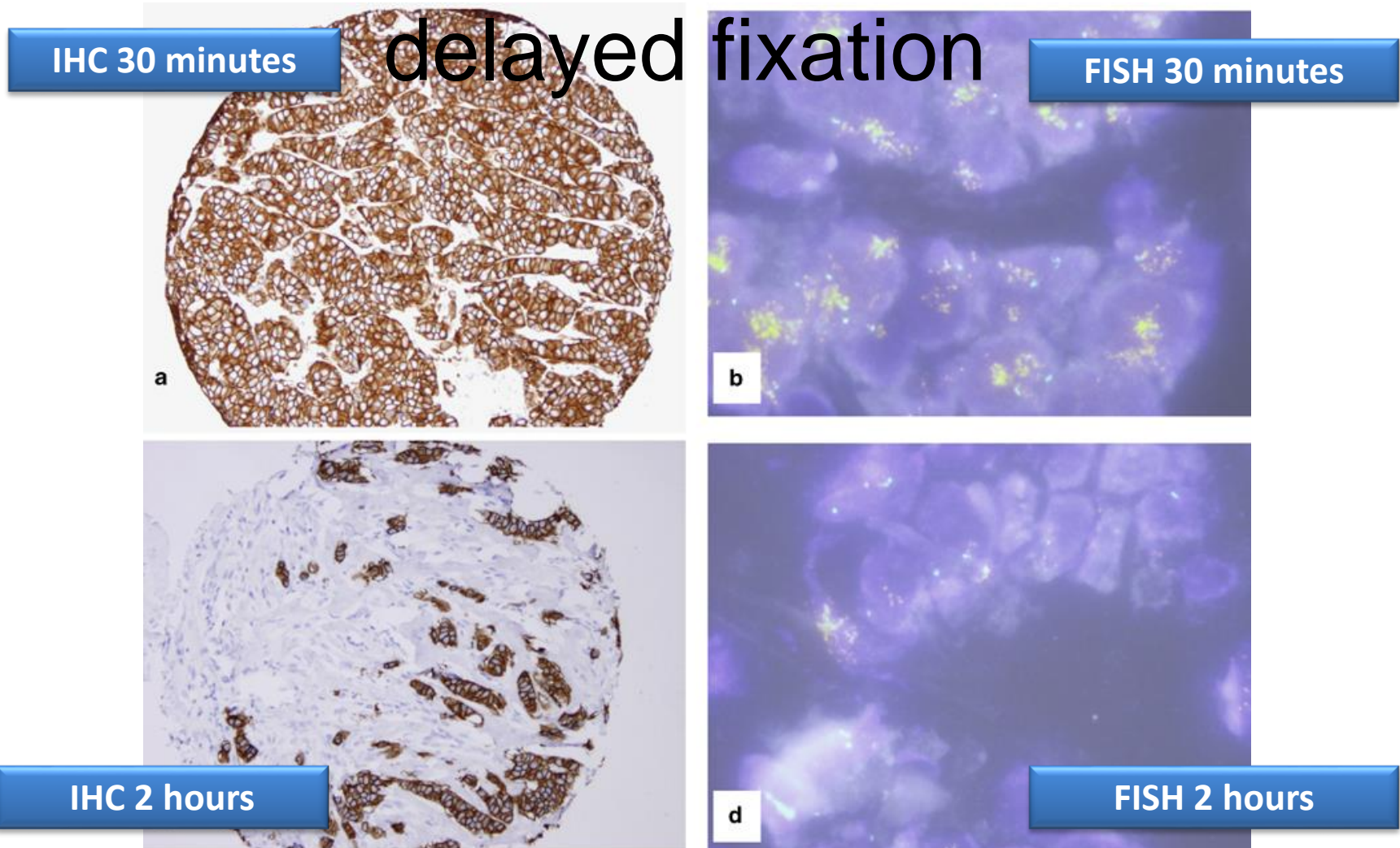
3. Timing Of SLNB???



EBC Planned for NACT for BCT

- Is core biopsy and IHC-4 mandatory: If NACT planned
- If upfront surgery is planned without neoadjuvant chemotherapy: Is still Core biopsy mandatory

HER2 IHC and FISH results in breast cancer specimens of delayed fixation



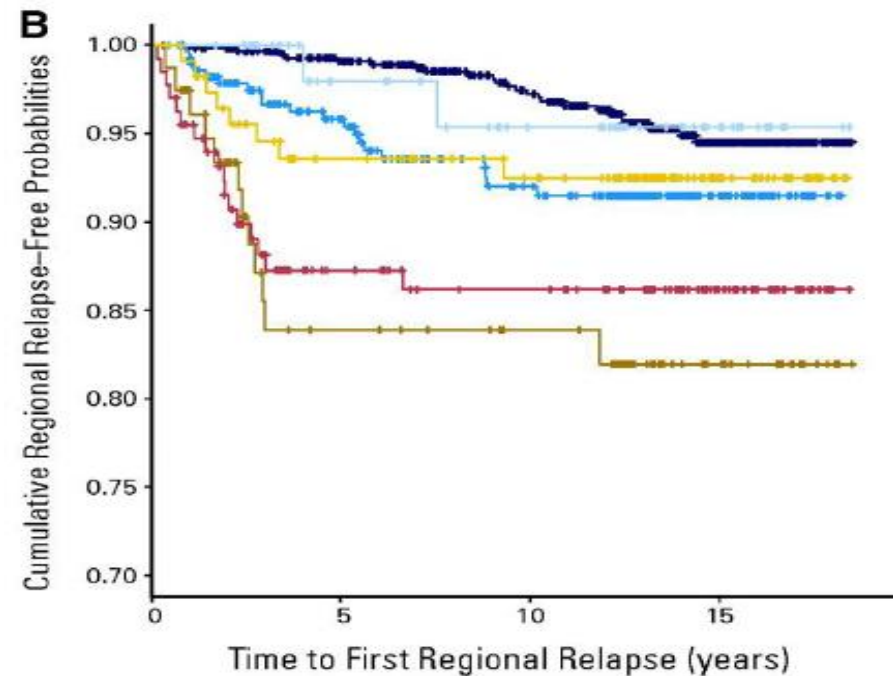
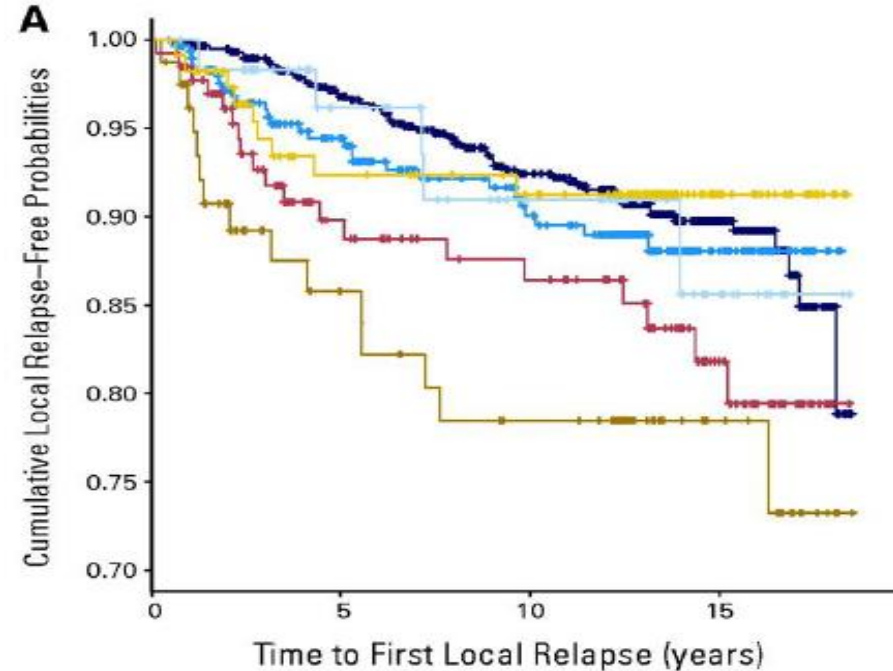
For Prognostication- it helps

- Meta analysis of 15 outcomes studies recording molecular subtypes
 - BCS n= 7174
 - Mastectomy n=5418
- Relative risk of LRR for Luminal A/B cancers was less after both BCS & MRM than TNBC and Her 2 Neu positive cancers
- Her 2 Neu positive cancers had higher LRR than TNBC after BCS but not MRM

**Univariate analysis of LRR
free survival after **BCS** with
breast cancer subtypes
shows statistically
significant difference Log
rank test $p=0.00515$**

Violet- Luminal A
Light Blue- Luminla Her2
Dark Blue-Luminal B
Gold- Five Marker Neagtive
Red- Basal
Biege- Her2 Enriched

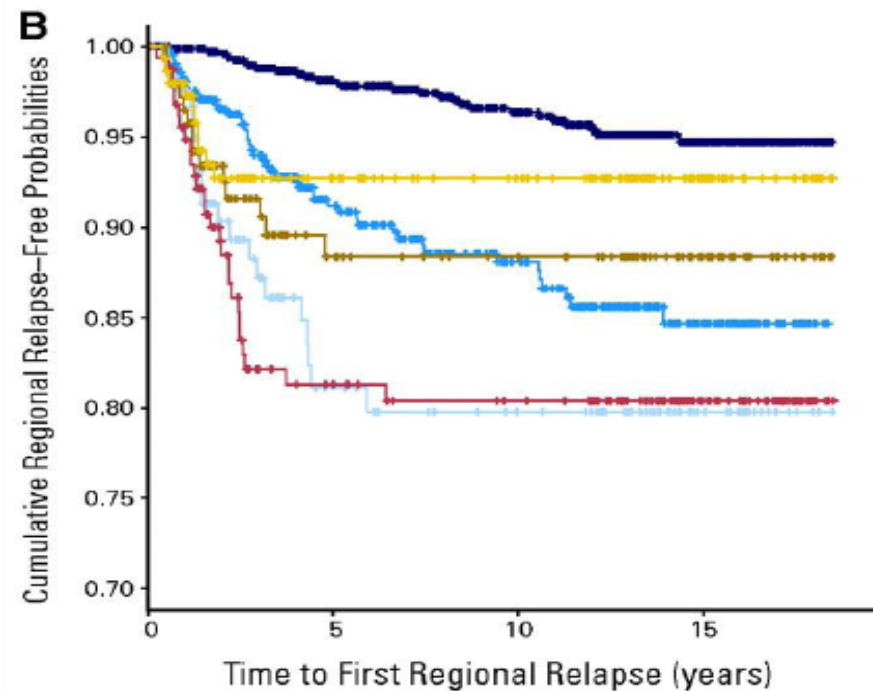
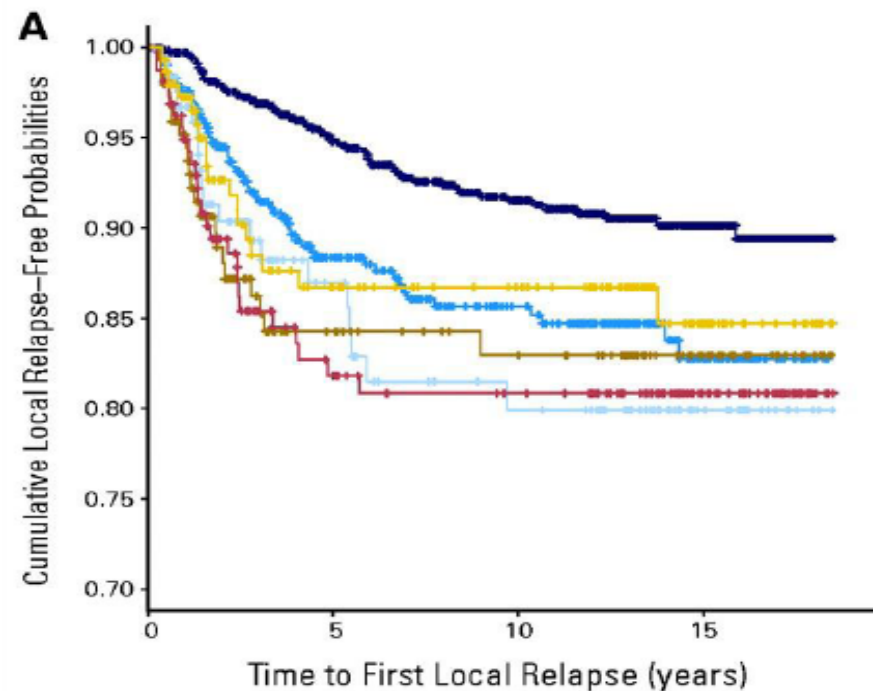
Voduc K D et al. JCO 2010; 28:1684-91



Univariate analysis of LRR free survival after **MASTECTOMY** with breast cancer subtypes shows statistically significant difference Log rank test $p < 0.001$

Violet- Luminal A
Light Blue- Luminla Her2
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Gold- Five Marker Neagtive
Red- Basal
Biege- Her2 Enriched

Voduc K D et al. JCO 2010; 28:1684-91



LRR & Molecular subtype

- British Columbia Cancer Agency cohort
n= 2985 with early breast cancer treated with BCS or MRM
underwent tissue microarray; Median F/U 12 years; chemo
underused; No Herceptin

Subtype	# Patients	# Events	10 Y LRFS (%)
Luminal A	587	55	92
Luminal B	295	27	90
Luminal-Her2	61	5	91
Her2+	80	15	79
Basal-like	134	19	86
TN-nonbasal	114	9	92

Voduc K D et al. JCO 2010;28:1684-1691

Luminal Subtyping useful in the setting of Pre
operative treatment plan

Luminal type does not Influence type of surgery
or margin status

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What is RCB Index?

RCB quantifies residual disease(RD) following Neoadjuvant
Chemotherapy in Breast Cancer.

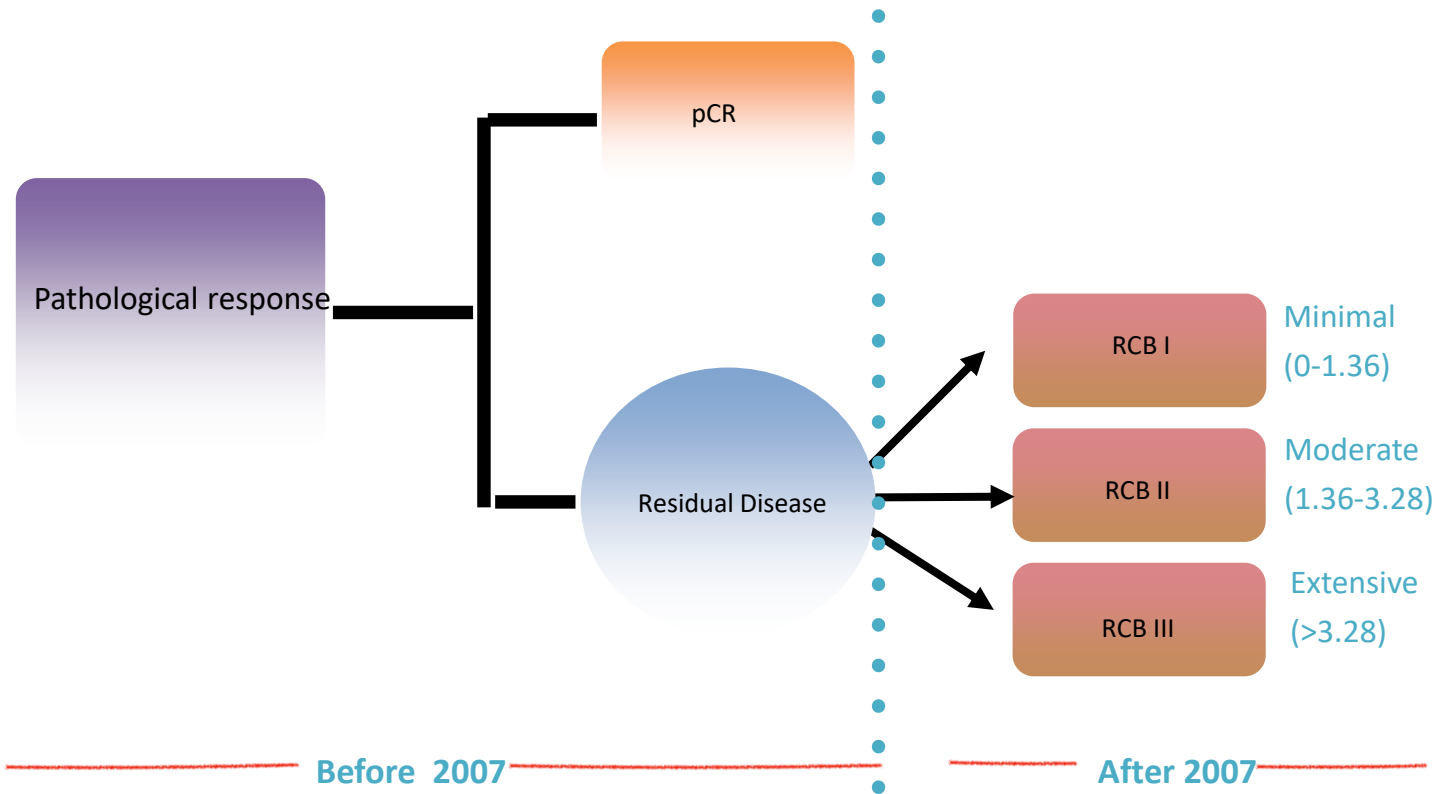
Assessed by

Primary Tumor size

% of Tumor invasive
V/s in situ.

Lymph Node Metastasis

RCB -Predictive model



Residual Cancer Burden Calculator

*Values must be entered into all fields for the calculation results to be accurate.	
(1) Primary Tumor Bed	
Primary Tumor Bed Area:	<input type="text" value="40"/> (mm) X <input type="text" value="20"/> (mm)
Overall Cancer Cellularity (as percentage of area):	<input type="text" value="2"/> (%)
Percentage of Cancer That Is <i>in situ</i> Disease:	<input type="text" value="0"/> (%)
(2) Lymph Nodes	
Number of Positive Lymph Nodes:	<input type="text" value="0"/>
Diameter of Largest Metastasis:	<input type="text" value="0"/> (mm)
<input type="button" value="Reset"/> <input type="button" value="Calculate"/>	
Residual Cancer Burden:	<input type="text" value="1.271"/>
Residual Cancer Burden Class:	<input type="text" value="RCB-I"/>

TNBC and Her-2-neu adjuvant modification based on RCB index

Q. Will you discuss Fertility preservation options in premenopausal women?

And

What Options you will give?

No Definitive evidence

- POEMS trial confirming the protective value of an LHRH agonist for ovarian function

LHRH analogue during chemotherapy for patients with receptor-negative breast cancer reduced the incidence of premature ovarian failure, confirming the report of Del Mastro et al., but contrary to the findings of the ZORO study of the German Breast Group.

Moore HCF, Unger JM, Phillips KA et al. Goserelin for Ovarian Protection during Breast-Cancer Adjuvant Chemotherapy. N Engl J Med 2015; 372: 923-32.

- Pre Chemo ovum retrieval and preservation

Q. Is Pre Operative Luminal typing
Necessary???

Does it impact Surgery???

Q.

How many cycles of
neoadjuvant chemotherapy???

- Complete tumor may disappear
- TNBC – To complete all cycles before surgery
- Her2 +ve : To complete all cycles before surgery with trastuzumab and postop only trastuzumab
- ER –ve: To complete all the cycles before surgery
- ER +ve: To give chemo until it becomes operable and do surgery. Remaining cycles after surgery

EBC with NACT for BCT

- If NACT – how many cycles to be given?
 - Sandwich therapy or Complete all
- NSABP B-27**
- In TNBC – NACT- CR – surgery
Any OS benefit?

GEPARDUO Trial

- In TNBC -pCR after NACT has survival advantage
- Completing all cycles (planned before local treatment (i.e. Surgery))

!) pCR rate in the 23% of patients with TNBC was double that of the non-TNBC subset (22% versus 11%)

2) However, patients with TNBC who achieved a pCR had similar 3 year overall survival as the non-TNBC (94% and 98%, $p=0.24$), whereas patients with TNBC who had residual disease after neoadjuvant therapy had a significantly worse 3 year OS (68% vs. 88%, $p=.0001$).

Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. Liedtke C, Mazouni C, Hess KR, André F, Tordai A, Mejia JA, Symmans WF, L J Clin Oncol. 2008 Mar 10; 26(8):1275-81.

NACT

- Neo-adjuvant: Platinum: Carboplatin
TNBC
BRCA +ve
pCR: 70-80% **CALGB40603: Ongoing**

German GeparSixto trial,
Vinorelbine + Capecetabine

- Recommended is 3-4 cycles for response assessment → before lumpectomy
- For TNBC → complete all cycles of chemotherapy before surgery → pCR will improve DFS and OS

Liedtke C et al, Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. [J Clin Oncol](#). 2008 Mar 10;26(8):1275-81. doi: 10.1200/JCO.2007.14.4147. Epub 2008 Feb 4.

Neoadjuvant Studies Summary

- No improvement in overall survival
 - Pts with pCR have improved survival
- Triple negative disease has highest pCR with chemotherapy
 - Carboplatin increases pCR in TNBC with BRCA+
- Luminal A disease outcome not related to pCR

- Role of trastuzumab in NACT
- How many cycles to be given?

All before surgery or sandwich

- Response assessment: pCR rate and ORR
- pCR in Her2neu positive patients

11. Neoadjuvant hormonal therapy

- Indications
- Trials
- Response rates
- Duration
- Role in lobular carcinoma

Neoadjuvant hormone therapy

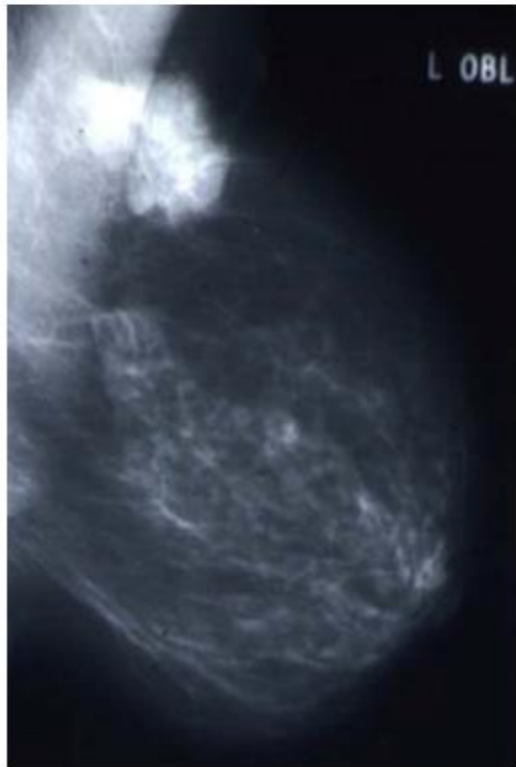
- Endocrine therapy is only effective for ER-positive disease
 - may be most effective in the **luminal A** molecular subtype and **lobular breast cancer**.

Seo JH, Kim YH, Kim JS. Meta analysis of pre-operative aromatase inhibitor versus tamoxifen in postmenopausal women with hormone receptor positive breast cancer. Cancer Chemother Pharmacol 2009; 63: 261–266.

- Optimal duration of Neoadjuvant AIs in postmenopausal women = **4–6 months for most women**
 - although 37% of patients achieve maximal response after 6–12 months letrozole

Llonbart-Cussac A, Guerrero A, Galan A et al. Phase II trial with letrozole to maximum response as primary systemic therapy in postmenopausal patients with ER/PgR[+] operable breast cancer. Clin Transl Oncol 2012; 14:125–131.

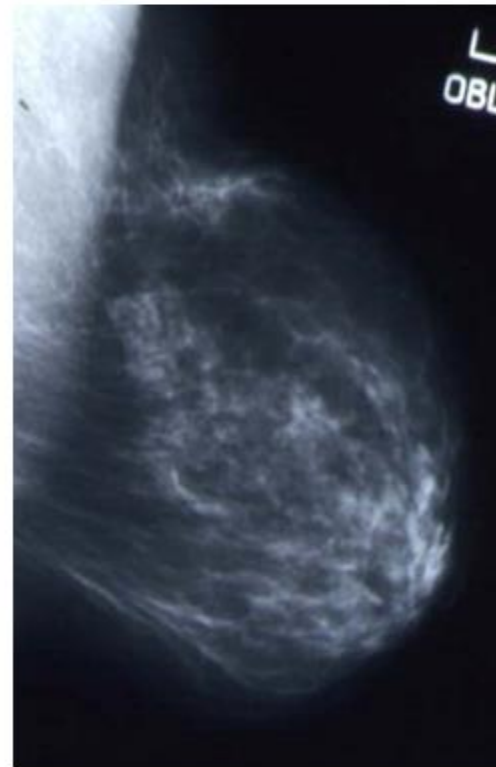
Efficacy of Neoadjuvant Endocrine Therapy



Before treatment



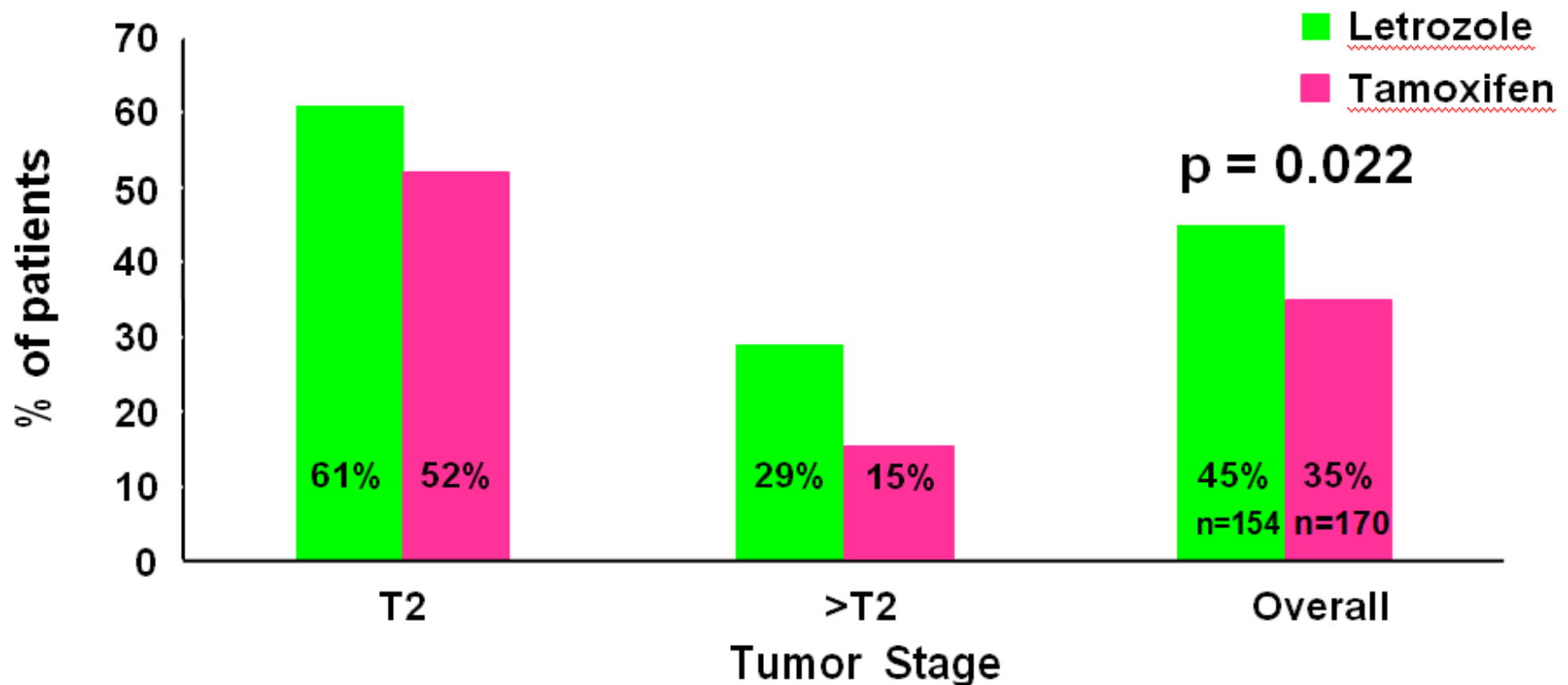
PROACT trial



After treatment with letrozole
for three months

Multidisciplinary Cancer Breast Management

Neoadjuvant Tamoxifen Compared with Letrozole: Breast-Conserving Surgery



Eiermann W, et al. *Ann Oncol*. 2001;12:1527-1532; Newman LA, et al. *Ann Surg Oncol*. 2002;9:228-234.

Neoadjuvant hormone therapy

A pCR to chemotherapy may be achieved in only 8% of ER +positive cancers compared with 24% in ER-negative tumors

Trial	N patients	Regimen	BCT rate (%)
Eiermann	337	Letrozole / Tamoxifen	45 / 35
Smith (IMPACT)	330	Anastrozole / Tamoxifen / Anastrozole + Tamoxifen	46 / 22 / 26
Gil	55	Exemestane	42
Paepke	33	Letrozole 4 months/ letrozole 8 months	67
Semiglazov	121	Chemotherapy/Anastrozole/Exemestane	24 / 32 / 34
PROACT trial	451	Anastrozole / tamoxifen	39.5% / 35.4%

Neoadjuvant Chemotherapy Vs Hormonal therapy

Overall Objective Response in Patients With High Levels of Estrogen Receptor Expression*

Response	Endocrine therapy, n=70	Chemotherapy, n=63	<i>P</i>
	No. (%)	No. (%)	
Clinical objective response	49 (70)	38 (60)	.068
Mammography	46 (66)	38 (60)	.088
Breast-conserving surgery	30 (43)	15 (24)	.054

*High levels of estrogen receptor expression are defined as ≥ 6 Allred score or ≥ 120 fmol/g.

NeoCENT trial results awaited! Neoadjuvant Chemotherapy versus Endocrine Therapy (NeoCENT) trial comparing letrozole to FEC100 for the treatment of postmenopausal women with ER-positive breast cancers.

- What if inspite of Taxol + Anthracycline Based NACT: No response ?

Preoperative paclitaxel and radiotherapy for LABC

- Well tolerated
- Provides significant pathological response, in up to 33% of patients with locally advanced breast cancer
- Significant postoperative morbidity rate

[Ann Surg Oncol.](#) 2000 Mar;7(2):145-9.

Preoperative paclitaxel and radiotherapy for locally advanced breast cancer: surgical aspects.

[Skinner KA](#)¹, [Silberman H](#), [Florentine B](#), [Lomis TJ](#), [Corso F](#), [Spicer D](#), [Formenti SC](#).

- If CCR after NACT

What next

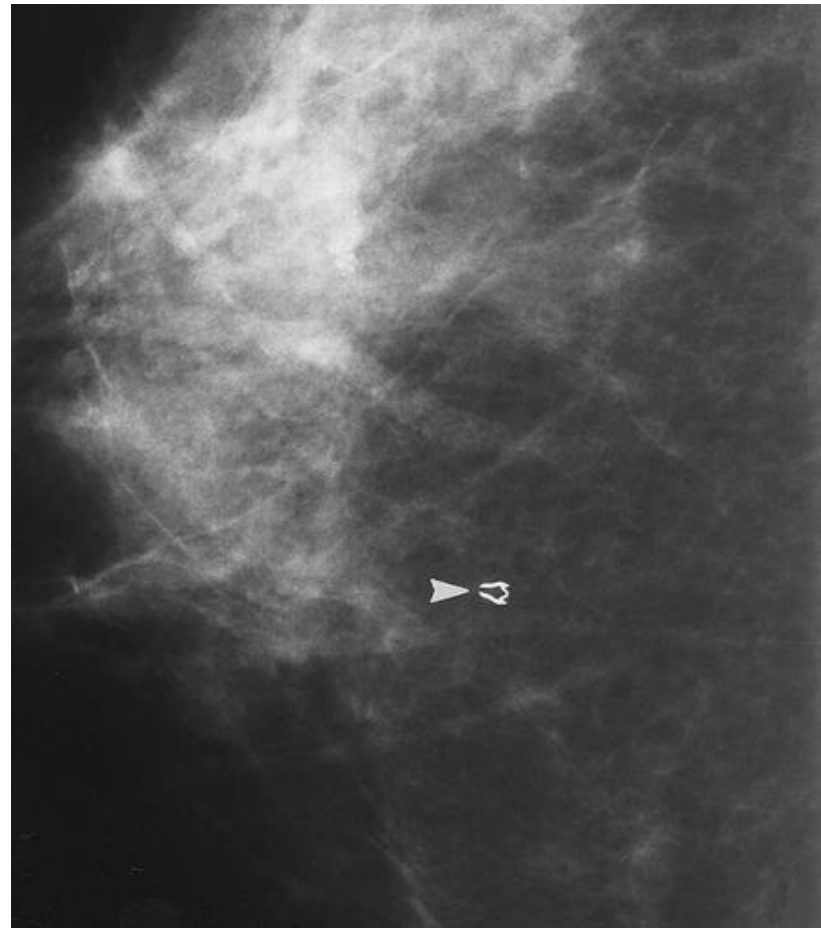
pCR is not more than 30%

Gohstectomy – So importance of Pre-chemo Clip marker

Q. Is Radio opaque marker localization of tumor is necessary ???

8.Role of stereotactic clip placement ?

- Clip placement prior to administration of NACT - to localize the site of the original tumor bed, in case the patient has a clinical & radiographic complete response.



- What is the importance of getting ER/PR/Her 2 neu before starting NACT ?

Has Gene Expression based Classification:

Luninal A

Luninal B

Her-2-neu +ve

Basal type

TNBC

Has impact on Surgery ?

Has impact on Neoadjuvant / Adjuvant

Role of Ki-67

- patients with estrogen receptor (ER)-positive, HER2-negative breast cancers are less likely to have a clinical or pathologic complete response to neoadjuvant chemotherapy (NACT)

Q. BCS and proceeding to standard radiation and adjuvant systemic therapy the *minimum acceptable surgical margin is:*

- No ink on invasive tumor?
- 1 – 2 mm clearance?
- > 2 – 5 mm clearance?
- > 5 mm clearance?

No ink on invasive tumor

91% Accepted → inked margin should be free of tumour

1. **St.Gallen Consensus 2015**
2. **Moran MS, Schnitt SJ, Giuliano AE et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol 2014; 32: 1507-15**



Should the margin required be

- dependent on tumor biology?
- dependent on neoadjuvant chemotherapy
- greater if age < 40?
- greater if lobular?
- greater after neoadjuvant therapy?
- greater in presence of extensive intraductal component?
- greater for pure DCIS than for invasive disease?

No

This conclusion applies regardless of tumour characteristics such as lobular histology, extensive intraductal component, young age, multifocality or multicentricity and unfavourable biological subtype

1. St.Gallen Consensus 2015

2. Moran MS, Schnitt SJ, Giuliano AE et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol 2014; 32: 1507-15.

Following neoadjuvant chemotherapy, not necessary to resect the entire area of the original primary if down-staging had occurred.

St.Gallen Consensus 2015

Q. How will you assess margin status???

Frozen section analysis (FSA)

Advantages

- Most widely used method for margin status
- Sensitivity 75-85%
- Specificity 90-100%

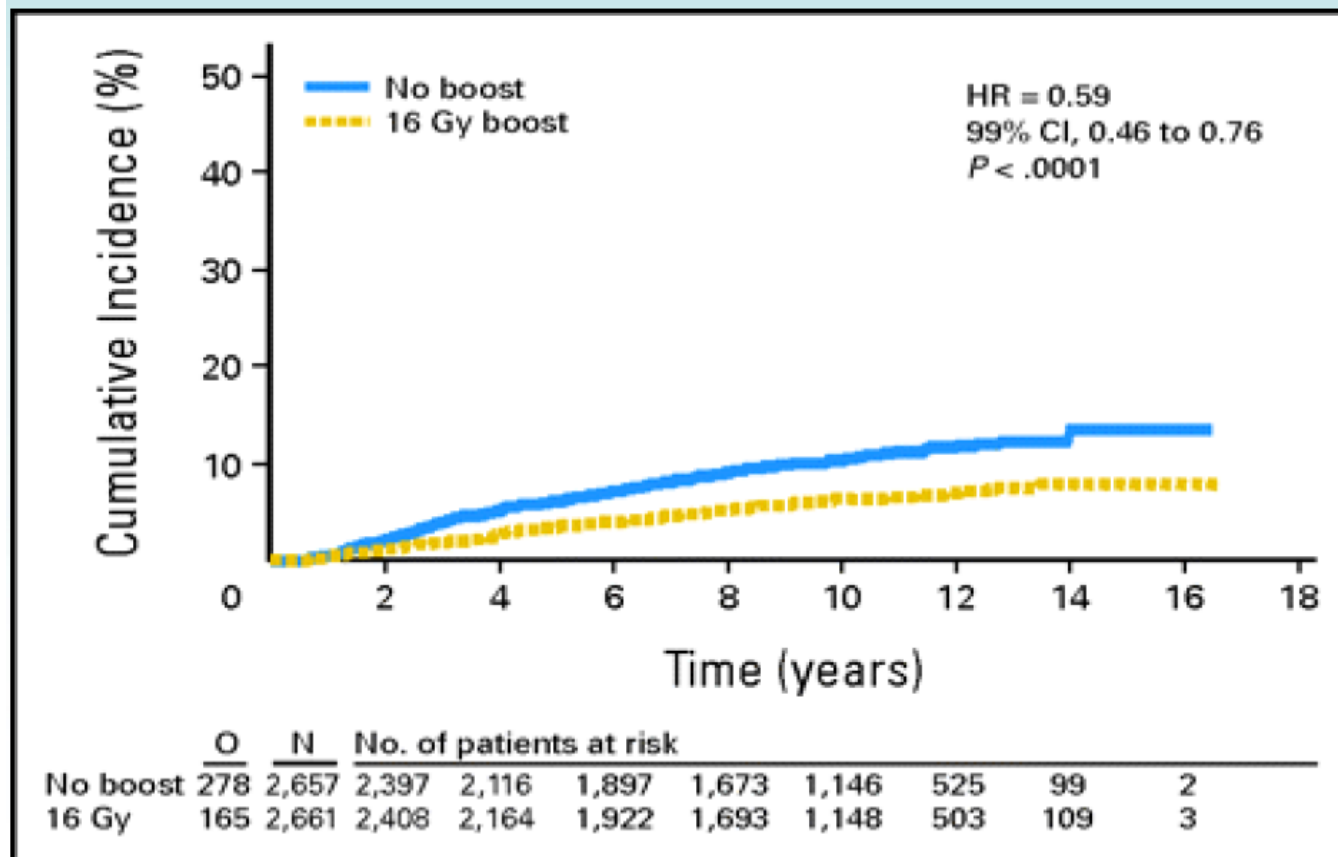
Disadvantages

- Not widely available
- Loss of specimen in small tumors
- Frozen artifacts
- 10% may still require resurgery after FSA

Q. If Margin positive on Frozen what next???

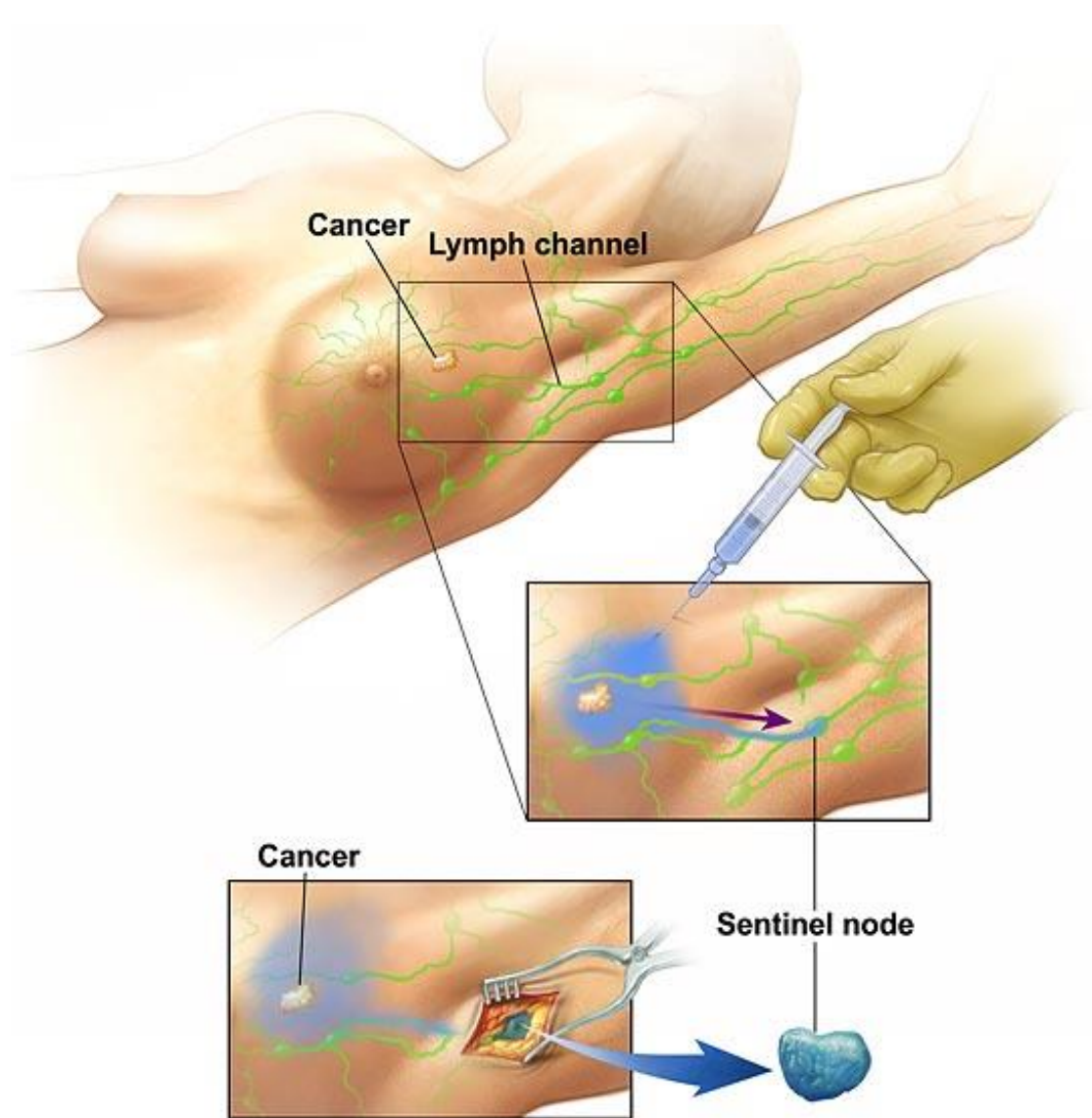
- Re-excision??
- Cavity Shave??
- Focal positivity??
- Multiple margins positive??
- Roll of RT boost???

Roll of Boost to the lumpectomy cavity



Bartelink, JCO, 2007

Procedure



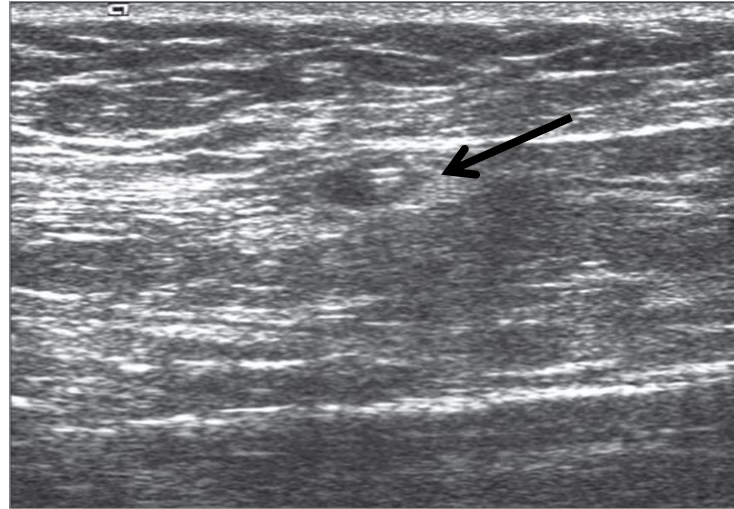
Q. Indications & contraindications
for SLNB???

SLNB

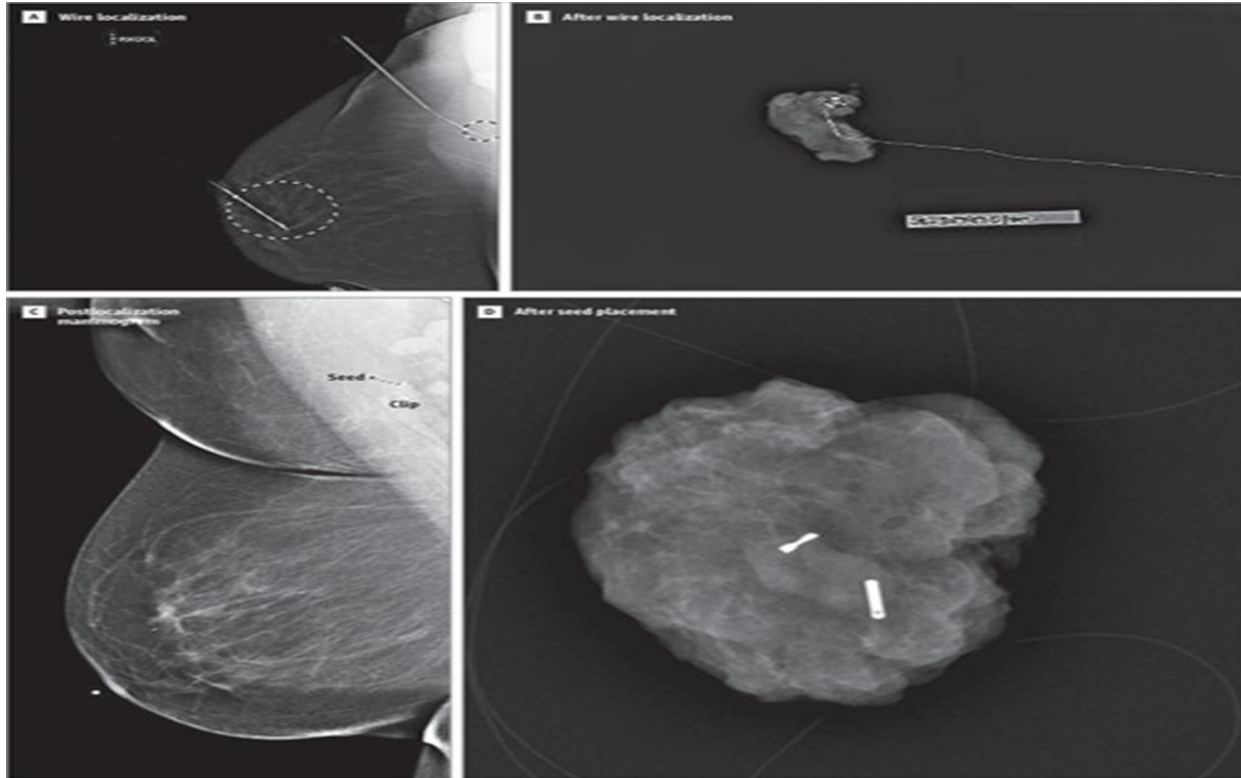
- Indications
 - Node Negative axilla
- Contraindications
 - Pregnancy
 - Lactation
 - LABC
 - Allergy to Lymphazurin / Blue dye

Multicentric cancers and T3 Primary tumors initially thought to be contraindications to Lymphatic mapping → Now studies have proven its accuracy in these settings

Targeted Axillary Dissection



Ultrasonographic Image of the Clip in a Lymph Node After Neoadjuvant Chemotherapy The clip marker was placed within the sampled lymph node under ultrasonographic guidance.



Images of Lymph Node Localization A, Wire localization (circles) of the lymph node. B, Intraoperative radiograph confirming removal of the clip-containing lymph node. C, Postlocalization mammogram of the iodine I 125–labeled seed placement. D, Intraoperative radiograph confirming removal of the clip-containing lymph node and seed

Axillary Recurrence After Negative SLN Biopsy and No ALND

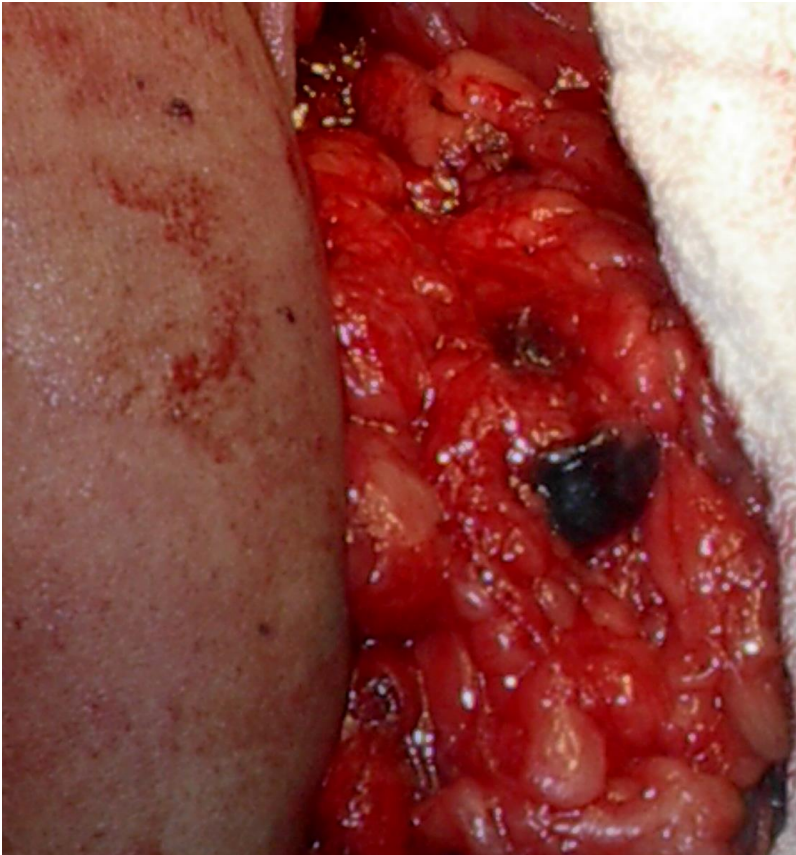
Author	No.	Median Follow-Up (Months)	Axillary Recurrence, No. (%)
Giuliano 2000	67	39	0
Veronesi 2001	285	14	0
Roumen 2001	100	24	1 (1)
Reitsamer 2002	116	22	0
Chung 2002	206	26	3 (1.4)
Veronesi 2003	167	46	0
Blanchard 2003	685	29	1 (0.1)
Winchester 2004	614	28	1 (0.16)
Janssen 2004	401	26	2 (0.5)

SLN, sentinel lymph node; ALND, axillary lymph node dissection.

Naik AM, Fey J, Gemignani M, et al. The risk of axillary relapse after sentinel lymph node biopsy for breast cancer is comparable with that of axillary lymph node dissection: a follow-up study of 4008 procedures. *Ann Surg.* 2004;240:462–468.

Q. Is ALND necessary for all patients with metastatic findings on SNB?

How do you address Axilla in LABC N0



Role of SLNB ?

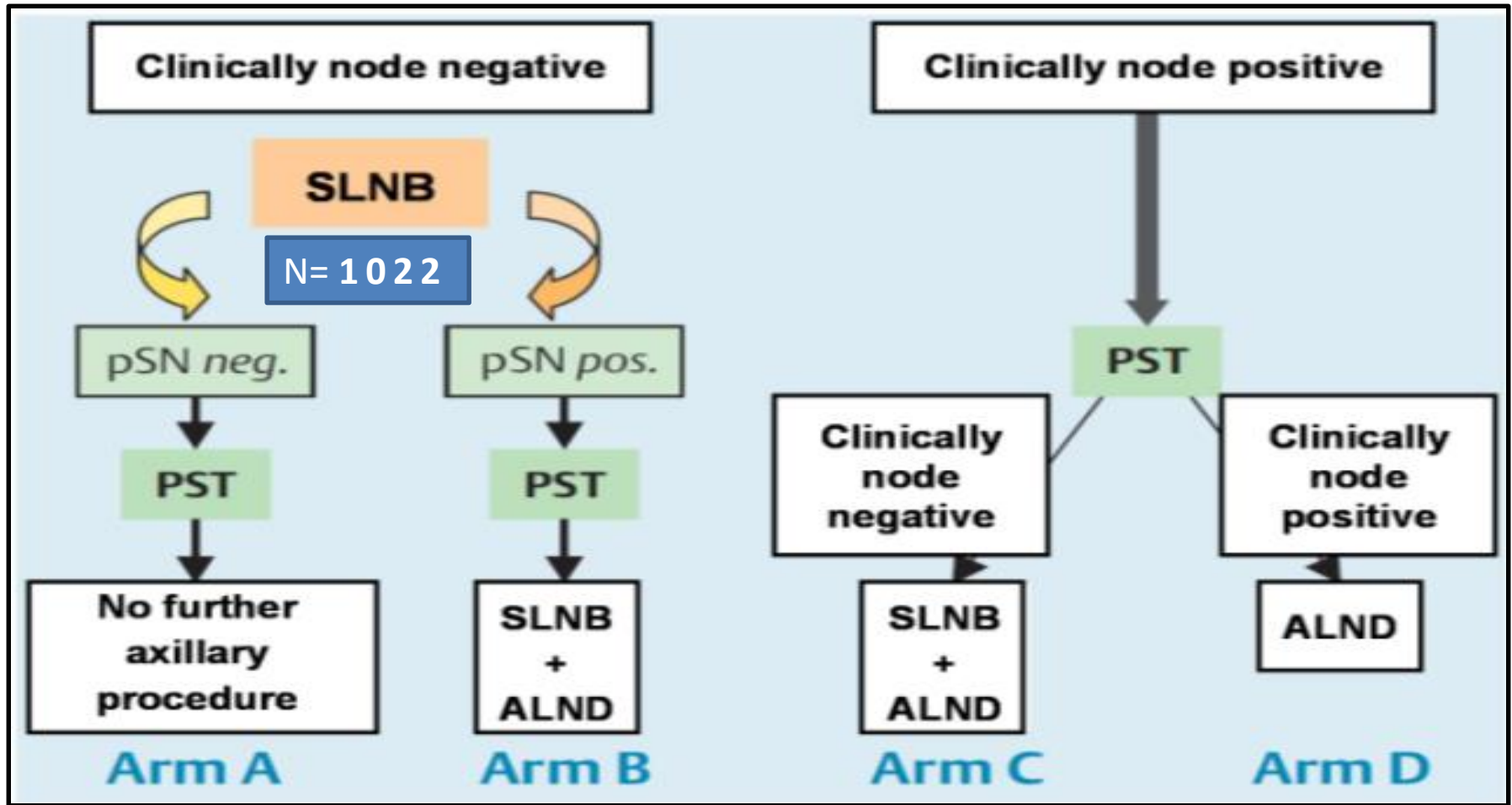
Pre-Chemo v/s Post Chemo ?

Pros and Cons of each

For SLNB after NACT

- NSABP B-27 trial supports SLNB after neoadjuvant chemotherapy
 - N=428
 - Lymph node identification rate 85%
 - False Negative Rate 11%

SENTINA- Supports SLNB before NACT



Detection rate 99.1% (95% CI 98.3-99.6; 1013 of 1022)

Detection rate = 80.1% (95% CI 76.6—83.2; 474 of 592)
FNR= 14.2% (95% CI 9.9—19.4; 32 of 226)

Against SLNB after NACT

- In 2006, a meta-analysis (n=1300)- SLNB after NACT reported a **false-negative rate of 12%**,
- **ACOSOG Z1071 trial** (2012), which also examined the procedure after NACT, reported a **false-negative rate of 12.6%**.

This is in contrast to the 5% to 9.5% false-negative rate reported when the sentinel node procedure is performed prior to any therapy

- **High FNR D/t uneven sterilization of the lymph nodes by the chemotherapy**

Against SLNB after NACT

- **Poorer identification rate** - prior to chemotherapy (87% vs 97%-100%)-
postulated to be caused by structural changes in lymphatic drainage, such as fibrosis within the axilla
- pretreatment determination of the pathological status of the lymph nodes can impact decisions

Recent trials of Axillary management

	ACOSOG Z0011	AMAROS	MA.20
No. Of patients	891	1425	1832
Surgery	BCS	BCS, Mastectomy	BCS
Control arm	ALND	ALND	ALND
Experimental arm	SN only	SN, RT Axilla and SC nodes	ALND, RT SC, IM nodes Axillary apex
DFS	No	No	Yes
OS	No	No	No

Axillary Recurrence After Positive SLN Biopsy With No ALND

Author	No.	Median Follow-Up (Months)	Axillary Recurrence, No. (%)
Guenther 2003	46	32	0
Fant 2003	31	30	0
Winchester 2004	73	28	0

SLN, sentinel lymph node; ALND, axillary lymph node dissection.

Naik AM, Fey J, Gemignani M, et al. The risk of axillary relapse after sentinel lymph node biopsy for breast cancer is comparable with that of axillary lymph node dissection: a follow-up study of 4008 procedures. *Ann Surg.* 2004;240:462–468.

ALND can be avoided in positive Sentinel node if BCS and ADJUVANT RADIATION planned

1. ACOSOG (American College of Surgeons Oncology Group) Z0011
2. IBCSG 23-01
3. Whelan T, Olivetto I, Ackerman I. NCIC-CTG MA.20: An Intergroup Trial of Regional Nodal Irradiation in Early Breast Cancer. 29, 779s. 011. Proceedings of the American Society of Clinical Oncology. 2011.
4. Poortmans P, Struikmans S, Collette S. Lymph node radiotherapy improves survival in breast cancer: 10 year results of the EORTC Radiation Oncology and Breast Cancer Groups phase III trial 2922/10925.6. 2013. ESTRO Congress Report.

Q. In patients with macro-metastases in 1-2 sentinel nodes, completion axillary dissection can be *omitted* ???

- Mastectomy (no radiotherapy planned) → NO
- Mastectomy (radiotherapy planned) → YES
- Conservative resection with radiotherapy using standard tangents → YES
- Conservative resection with radiotherapy using high tangents to include the lower axilla → YES

Controversy still exists concerning post mastectomy radiotherapy for pN1 (intermediate-risk) patients³

1. St.Gallen Consensus 2015

2. Nordenskjold AE, Fohlin HI, Albertsson P et al. No clear effect of postoperative radiotherapy on survival of breast cancer patients with 1-3 positive nodes: A population-based study. Ann Oncol 2015; mdv159.

3. Kunkler IH, Canney P, van Tienhoven G, et al: Elucidating the role of chest wall irradiation in 'intermediate-risk' breast cancer: The MRC/EORTC SUPREMO trial. Clin Oncol (R Coll Radiol) 20:31-34, 2008

Q. Can ALND be avoided if SLNB positive??

ALND Can be avoided

- Multivariate analysis shows that the administration of chemotherapy is mainly based on age, tumor grade, multifocality, and the size of sentinel node metastasis and not by the nodal extent
- The Danish and Canadian studies showed that patients with one to three positive nodes and patients with more than four positive nodes have a similar absolute survival benefit of 9% after 15 years.

FNR of SLNB 4.6% to 16.7%

- **NSABP B32**
- **ALMANAC** (Axillary Lymphatic Mapping Against Nodal Axillary Clearance)
- **Sentinella/GIVOM** (Gruppo Interdisciplinare Veneto di Oncologia Mammaria)
- **Canavese et al**
- **RACS** (Royal Australasian College of Surgeons)/SNAC (Sentinel Node Versus Axillary Clearance)
- **NCT00970983**
- **Cambridge/East Anglia Study Group**

Q.

1. When you advice Pre operative

chemo to downstage the tumor???

2. In this setting Sentinel node biopsy

indicated???

3. Timing Of SLNB???

St.Gallen Consensus

- Sentinel node biopsy was **appropriate**, but that in this situation **ALND** → **if even one sentinel node were positive**
- **False negative rates** however remain high unless 3 or more sentinel nodes are examined.

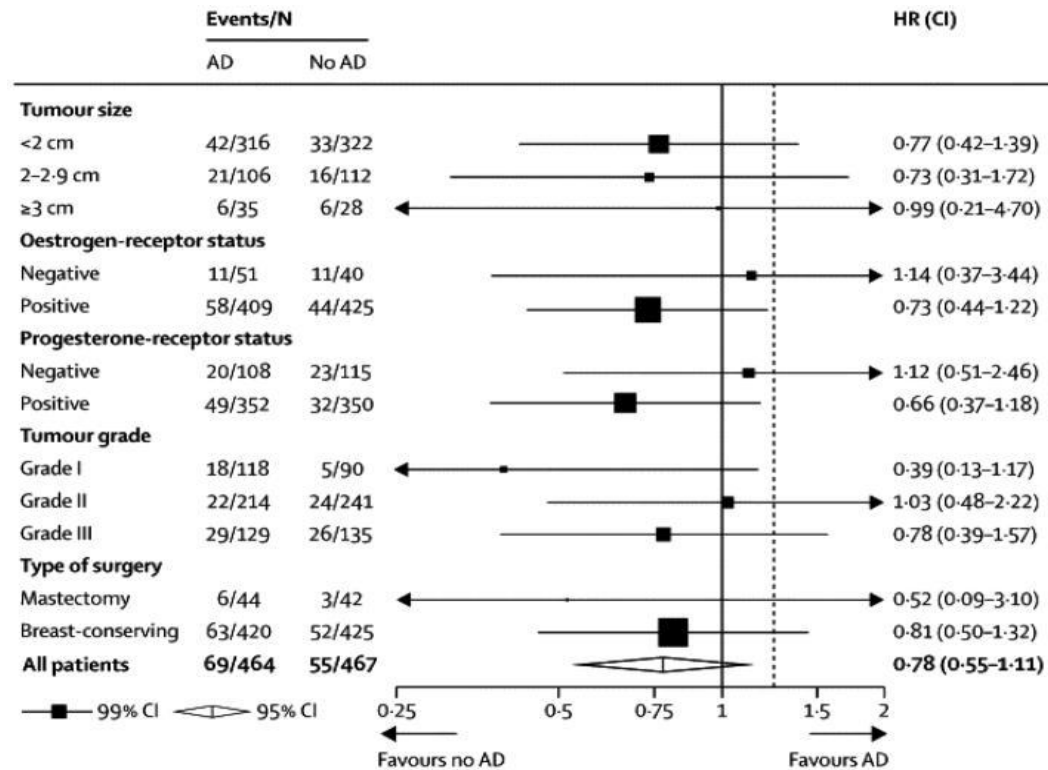
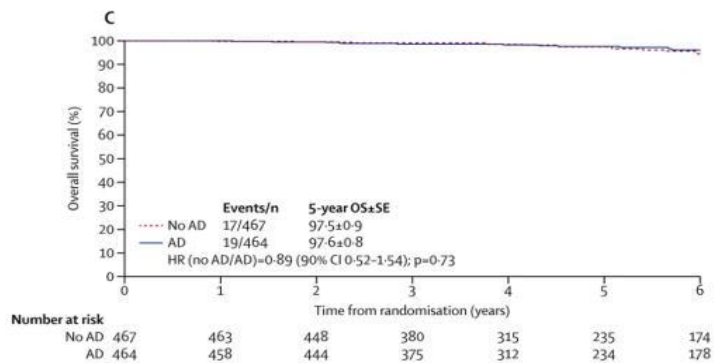
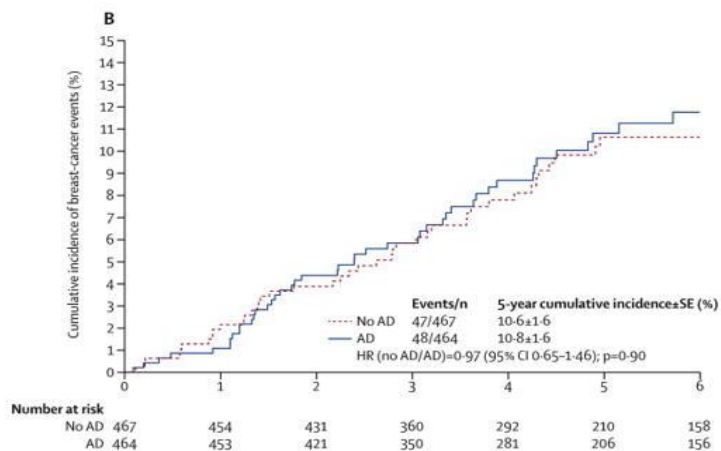
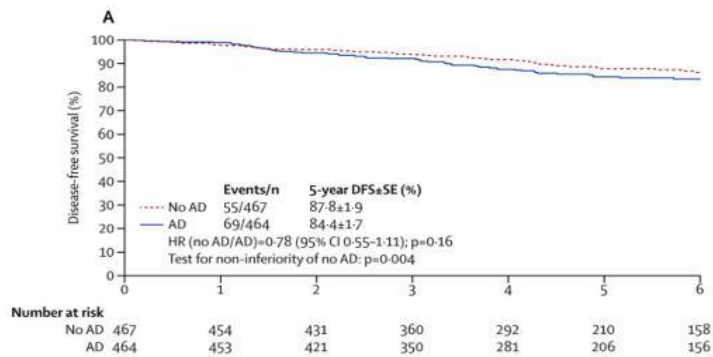
Accuracy of SLNB after NACT in patients with lymph nodes involvement at presentation

# of sentinel nodes removed	% False negative Rate ACOSOG Z1071	% False negative Rate SENTINA
1	32	24
2	21	19
≥3	9	7

Q. If Micrometastasis found in SLNB –
What Next???

ALND can safely avoided if adjuvant WBI planned

Galimberti V et al, Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. [Lancet Oncol.](#) 2013 Apr;14(4):297-305. doi: 10.1016/S1470-2045(13)70035-4. Epub 2013 Mar 11.



Galimberti V et al, Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. [Lancet Oncol.](https://doi.org/10.1016/S1470-2045(13)70035-4) 2013 Apr;14(4):297-305. doi: 10.1016/S1470-2045(13)70035-4. Epub 2013 Mar 11.

Skin Sparing Mastectomy (SSM)

PRE- OP



INTRA-OP

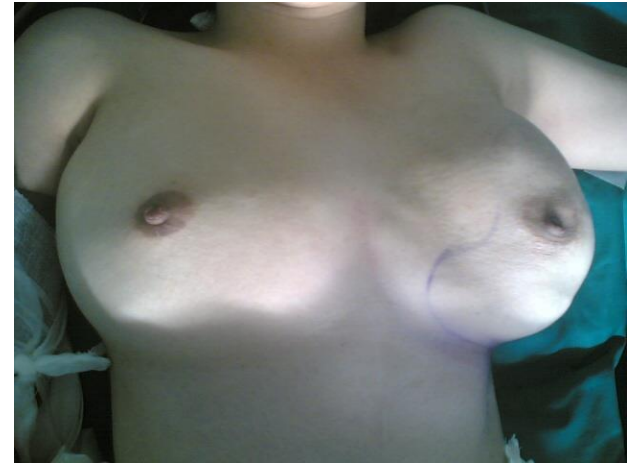


EARLY POST OP



LATE POST OP

Nipple Sparing (NSM) Mastectomy

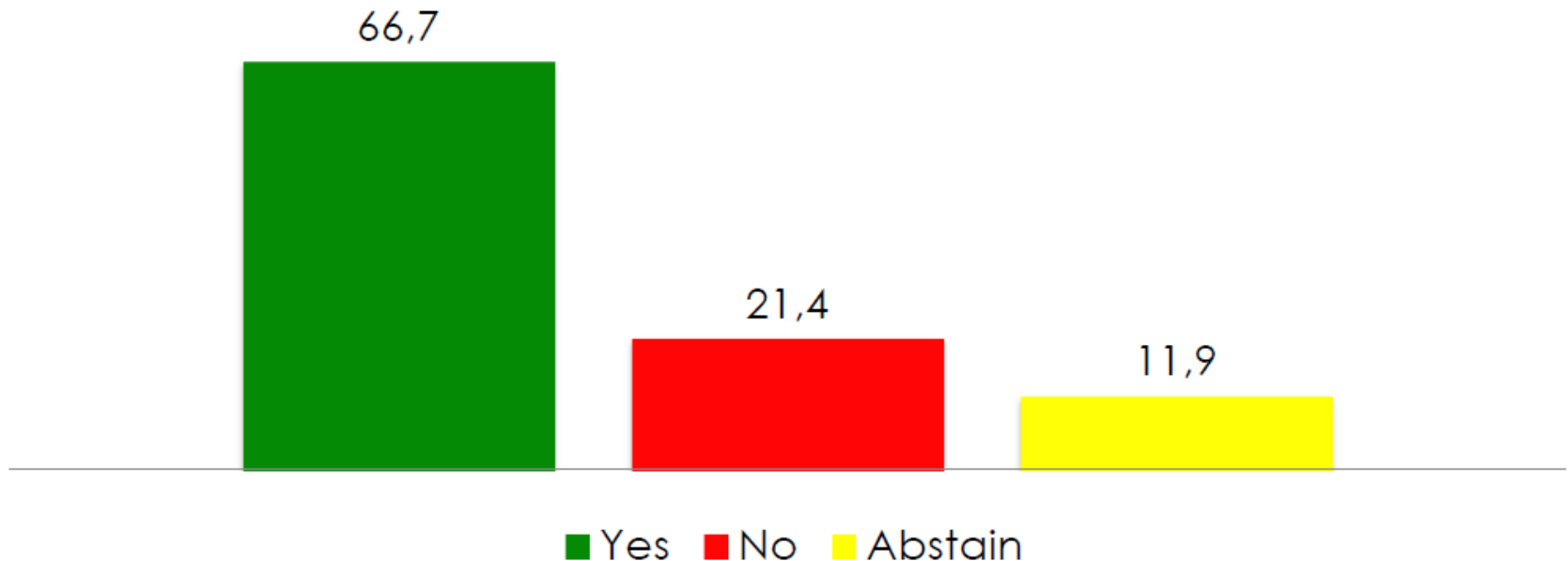


Q. What are the factors you will consider for Nipple sparing mastectomy???

- Peripherally located IDC/DCIS > 2cm from nipple
- With Favorable prognosis (Nottingham grade 1 or 2, node negative, Her2neu negative, no LVSI)
- Nipple margin assessment is mandatory

Surgery of the primary breast cancer

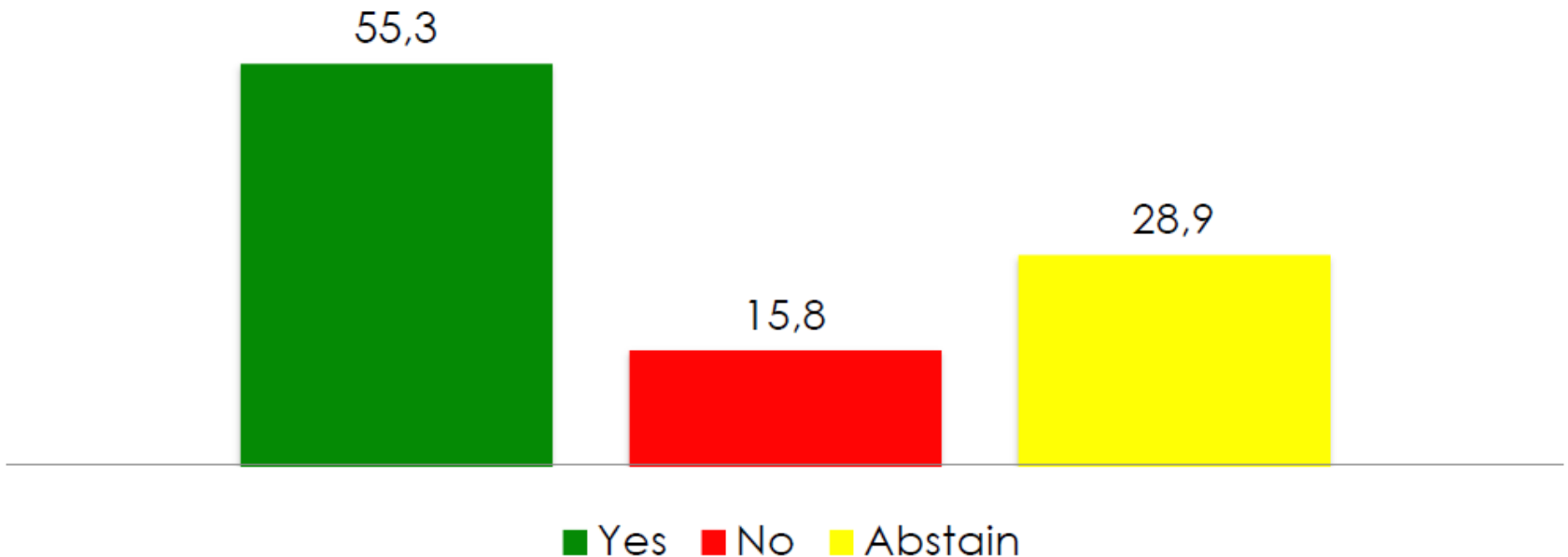
Is skin nipple sparing mastectomy an acceptable treatment without RT?



St Gallens

Surgery of the primary breast cancer

Is skin nipple sparing mastectomy an acceptable treatment if only margin toward nipple is tumor free and immediate reconstruction planned?



14. Reconstruction

- Prosthesis
- TRAM
- **Immediate vs. delayed**
- If adjuvant EBRT required ?
 - Atrophy of breast tissue
 - Long term asymmetry
 - Poor quality of skin envelop

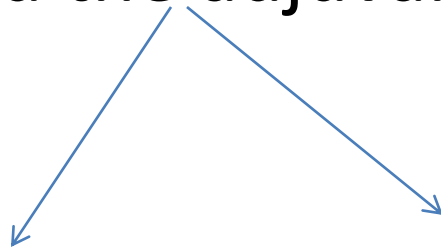
- Immediate prosthesis reconstruction associated with contracture and recurrent infection
- Radiated TRAM flaps shows late onset fibrosis & contracture
 - Styblo TM et al, Immediate breast reconstruction for stage III breast cancer using transverse rectus abdominis musculocutaneous (TRAM) flap, *Ann Surg Oncol*. 1996 Jul;3(4):375-80.
- Delayed reconstruction is preferred in the view of cosmesis

TRAM-Flap



15. Adjuvant chemotherapy

- If pCR: Should the adjuvant chemo be given



If 2-3 cycles given
before surgery

If all cycles finished
before surgery

And Sequencing of Chemo and Radiation and Hormonal therapy ?

Adjuvant Hormonal therapy

TAM v/s AI

Duration: 5 years v/s 10 years

Sequencing

ATLAS / aTOM

Conclusion and Take Home Message

- Core Biopsy mandatory in LABC: IHC: ER, PR, Her-2-neu
- MRI is not Mandatory or High level evidence
- PET CT scan metastatic survey still investigational
- Role of Neoadjuvant Hormonal therapy in : Lumina A, Postmenopausal ER +ve
- Role of Gene profile based management
- TNBC: preferable to complete all Neoadjuvant chemo:
- Transtuzumab in Her-2-neu +ve NACT pCR high
- SLNB in LABC is not level I evidence: But Pre chemo is better than post chemo
- Reconstuction is not contraindicated: Immediate v/s Delayed
- Sequencing: Chemo NACT : ER +ve v/s TNBC
- BCT is not standard of care in LABC still

Conclusion and Take Home Message

- Sequencing of Chemo and RT and Harmonal therapy
- Adjuvant External Beam RT mandatoy:
Chest wall and Supraclavicular : Int. Mammary: Not level I evidence
- Adjuvant Harmonal therapy: extended for 10 years

Important point: In Stage IIIB LABC:

if pCR:

75%-80% 5 year survival and 50% 10 year Survival:

So no Pessimisim:

,

Surgical benefits of NACT

Neoadjuvant chemotherapy (NACT) results in

- 40% increase of breast conserving therapy¹
- (40% reduction of axillary dissection²)
- 60% reduction in reoperation rate³



Thus, we reduce the extent of surgery after NACT



When dark clouds loom overhead, just remember.....

Every cloud has a silver lining

THANKS