EVALUATION OF AXILLARY LYMPH NODES AFTER NEOADJUVANT SYSTEMIC THERAPY

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AXILLARY LYMPH NODE METASTASIS

- Axillary lymph node metastasis is one of the most important prognostic factors in breast cancer .

    - as an indicator of poor prognosis.

    - with the 5-year survival decreasing by approximately 28% to 40% in patients with such a condition

- Preoperative identification of LNM in the axilla

    - The surgical approach:

        - Axillary lymph node dissection

    - Neoadjuvant chemotherapy

NSABP B-04 TRIAL

- The aggressive axillary surgery for breast cancer patients with negative axillary lesions does not improve the overall survival of the patients

  - Routine ALND for patients with a clinically node-negative axilla is unnecessary

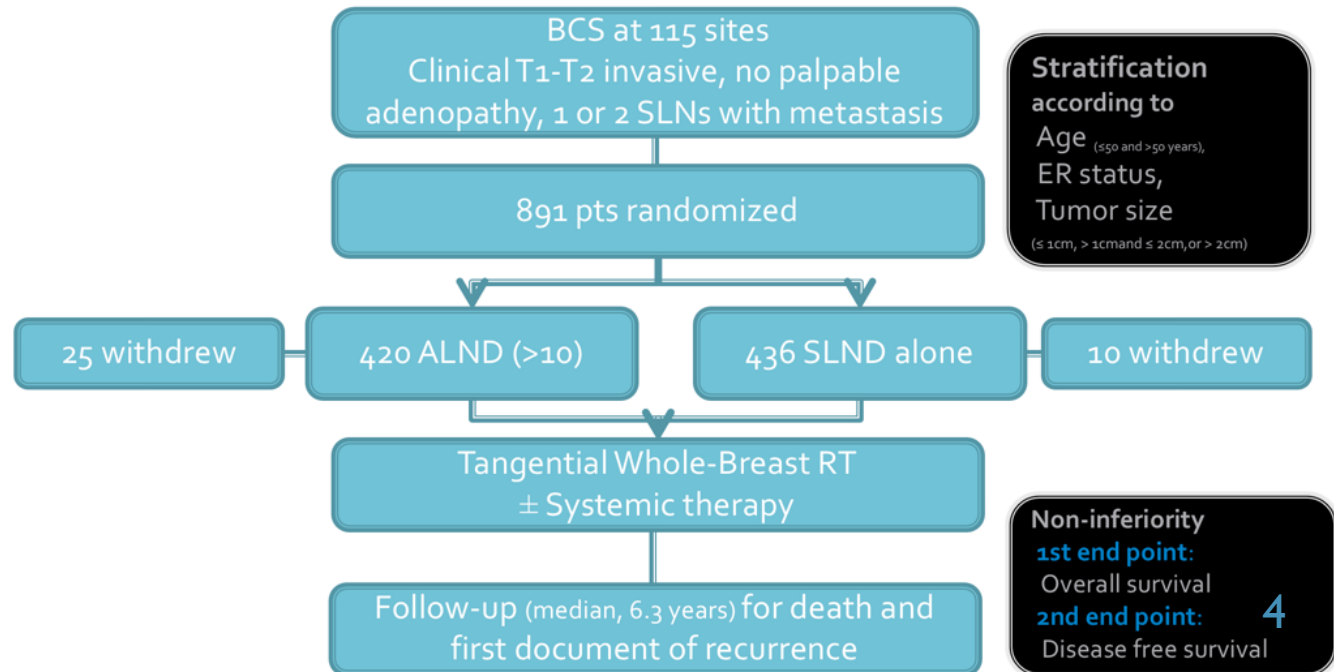 - Removing healthy lymph nodes renders no benefit on OS
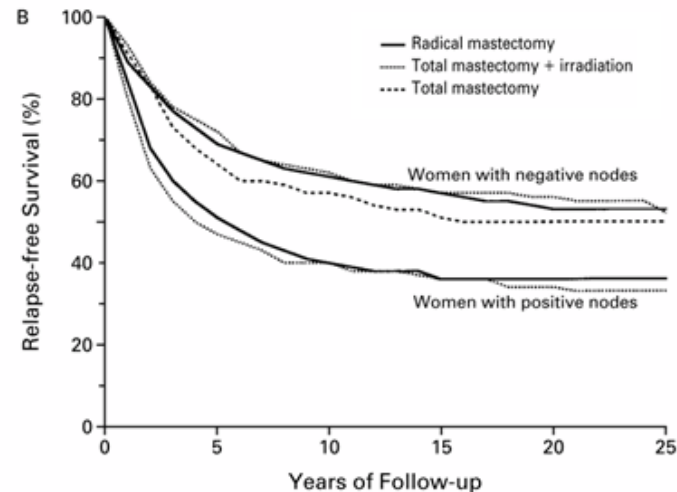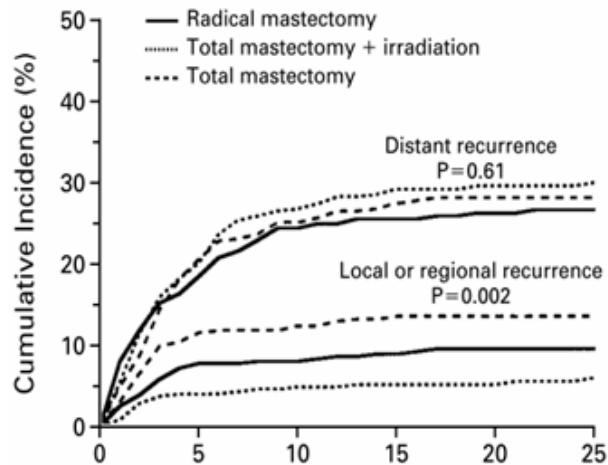
(P=0.46)

AMERICAN COLLEGE OF SURGEONS ONCOLOGY GROUP (ACOSOG) Z0011 TRIAL

- ALND provided no survival benefit over less invasive SLN dissection during a 6-year follow-up period in a selected cohort of patients with clinical T1–T2 invasive breast cancer, who had no palpable adenopathy and one or two biopsy-proven metastatic sentinel lymph nodes

BCS at 115 sites
Clinical T1-T2 invasive, no palpable adenopathy, 1 or 2 SLNs with metastasis

Stratification according to
Age (≤50 and >50 years),
ER status,
Tumor size
(≤ 1cm, > 1cm and ≤ 2cm, or > 2cm)

891 pts randomized

25 withdrew — 420 ALND (>10) — 436 SLND alone — 10 withdrew

Tangential Whole-Breast RT ± Systemic therapy

Non-inferiority
1st end point:
Overall survival
2nd end point:
Disease free survival

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Follow-up (median, 6.3 years) for death and first document of recurrence

SEVERANCE

Giuliano JAMA 2011, ACSOG Z0011

LYMPHATIC MAPPING AFTER NEOADJUVANT CHEMOTHERAPY

- Identification of an SLN (lymph node that initially harbored cancer) by lymphatic mapping after NAC can be difficult

- because obstructions occur from live or necrotic tumor emboli from the tumor itself and/or fibrosis of lymphatic channels from chemotherapy

SEVERANCE

NEOADJUVANT CHEMOTHERAPY (NAC)

- The increasing use of neoadjuvant chemotherapy (NAC) for operable breast cancer has raised questions about optimal local therapy for the axilla.

- **The poor identification rate of SLN** due to possible alteration of lymphatics as a result of NAC.

- **The high false negative rate** because upfront chemotherapy may show different effects on sentinel and non-sentinel nodes;

  - The malignancy may be eradicated in sentinel nodes, while residual disease may persist in non-sentinel nodes.

SEVERANCE

SLNB AFTER NAC IN CLINICALLY NEGATIVE AXILLA

- SLNB in patients with cN0 axilla before NAC (n=980) and post-NAC (n=203).

  - SLN identification rate : 98% before NAC and 95% after NAC (p = 0.032)

- Patients who underwent SLNB after NAC had a higher chance of having negative SLN than those who underwent SLNB before NAC (67% vs. 54%, *p*=0.001) and had lesser chance of undergoing ALND (33% vs. 45%, *p*=0.006).

- SLNB after NAC in patients with cN0 axilla is a feasible treatment option, and additional axillary treatment is not necessary in those with negative SLN.

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SEVERANCE

THE ACOSOG Z1071 TRIAL

- the utility of SLNB in the treatment of patients with bx-proven node(+) disease who underwent NAC(T0–T4,N1–N2,M0)

- phase 2 study of the clinical efficacy of substituting SLNB for ALND ; false-negative rate (FNR) of SLNB, 10% of goal

- Boughey SABCS 2012 : 31.5 % FNR with one SLN

- Boughey JAMA 2013: 21.1% FNR with 2 SLN and single agent

Studies evaluating the IDENTIFICATION RATE & FALSE-NEGATIVE RATE \ among patients with CLINICALLY NODE-POSITIVE DISEASE undergoing SLNB following NAC

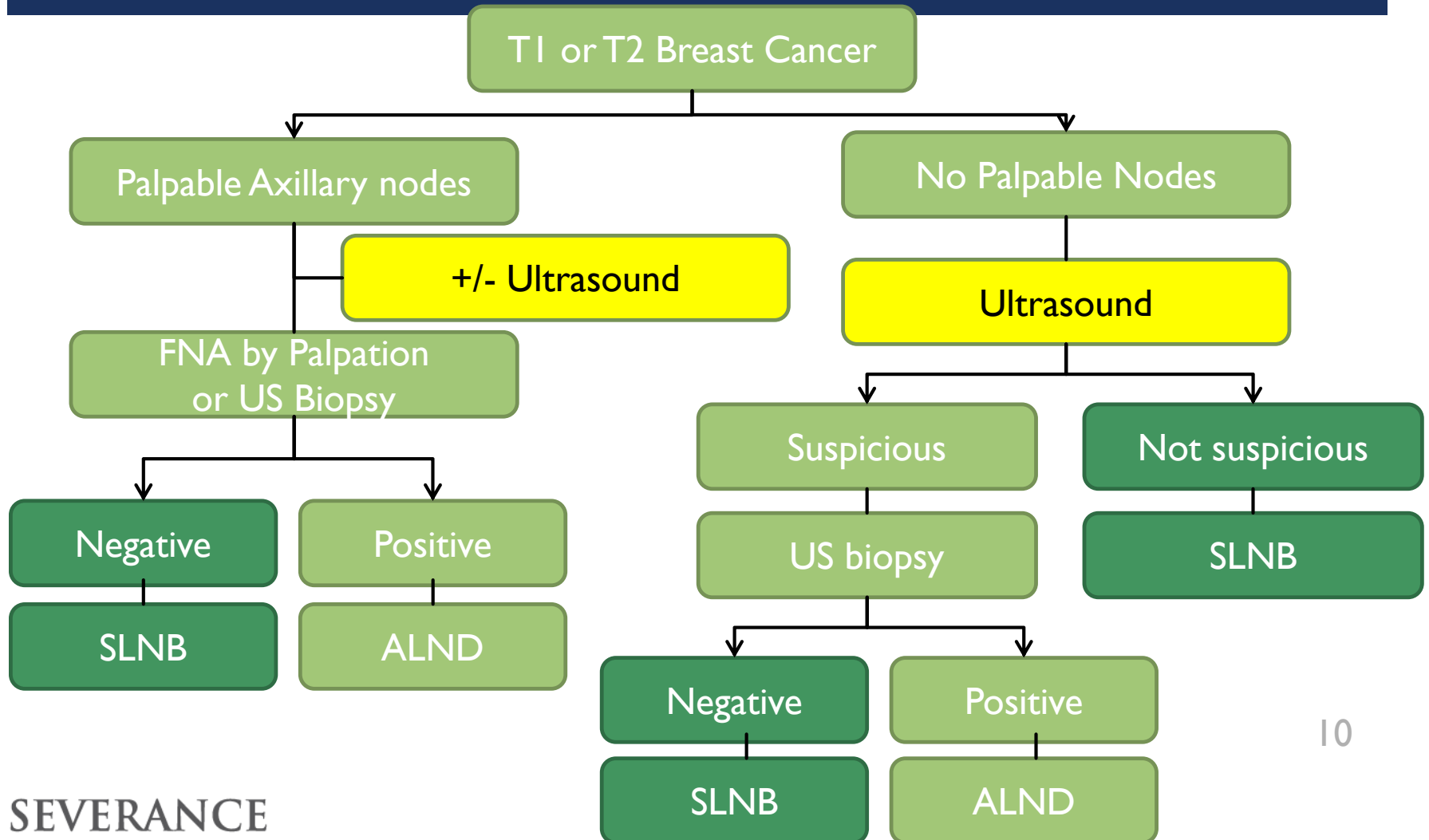| Study	ACOSOG Z1071	SENTINA	SN FNAC
Design	Single arm	4 Arms	Single arm
No. of patients	756	Arm C (592)	153
Patient population	T0-4, N1-2, M0	N1-2, M0	N1-2, M0
cN0 after NAC	100[a]	83	Unknown[a]
SLN identification rate (%)	92.9	80.1	87.6
False negative rate (%)	12.6	14.2	9.6
2 SLNs	21.1	18.5	4.9 (≥2 SLNs)
≥3 SLNs	9.1	7.3	-
Dual tracer technique	10.8	8.6	5.2
Inclusion of ypN0(i+)	8.7	-	8.4

[a] Ultrasound performed in all patients.

[b] False-negative rate excluding immunohistochemically detected isolated tumor cells.

SEVERANCE

IN CURRENT CLINICAL PRACTICE,
POSSIBLE ALGORITHM FOR AXILLARY STAGING IN PATIENTS WITH INVASIVE BREAST CANCER

T1 or T2 Breast Cancer

- **Palpable Axillary nodes**
  - +/- Ultrasound
  - **FNA by Palpation or US Biopsy**
    - Negative → SLNB
    - Positive → ALND

- **No Palpable Nodes**
  - Ultrasound
    - Suspicious → US biopsy
      - Negative → SLNB
      - Positive → ALND
    - Not suspicious → SLNB

SEVERANCE

US FINDINGS OF AXILLARY LN
- CORRELATED WITH FINAL SURGICAL RESULTS

	Surgical Results		
	Positive	Negative	PPV (%)
Cortical features			
Thin	6	16	27
Thick or lobular	16	6	73
Hypoechoic	33	1	97
Hilar features			
Central	9	22	29
Eccentric	15	1	94
Completely replaced	20	0	100

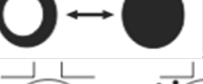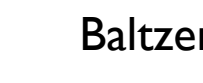**Maximal cortical thickness $\geq$ 2.3mm**

Deurloo 2003 EJC
Koelliker et al Radiology 2008

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SUSPICIOUS MR FINDINGS OF AXILLARY NODAL METASTASES

Descriptor	SN (%)	SP (%)	PPV (%)	
Irregular margin	41.2	95.2	77.8	
cortex				
Homogeneous	29.4	16.7	12.5	
Inhomogeneous	47.1	90.5	66.7	
Nodular thickening	23.5	92.9	57.1	
Hilus sign	52.9	4.3	20.0	
Perifocal edema	29.4	100.0	100.0	
Rim sign	23.5	100.0	100.0	
Asymmetry	76.7	85.7	68.4	

Meta-analysis

US criteria	Palpable	Non-palpable	Sensitivity	Specificity
size	+	+	69.2 (63.4–74.6)	75.2 (70.4–79.6)
morph	+	+	71.0 (65.2–76.3)	86.2 (82.6–89.3)

MRI			Prevalence	Sensitivity	Specificity
DCE	Kvistad et al. 2000	Hieken et al. 2013	12.0% - 61.4%	60.0 (33.3–97.0)	78.6 (14.0–98.5)
	Orguc et al. 2012	Abe et al. 2013			
	He et al. 2012	An et al. 2014			
	Hwang et al. 2013				

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IN CURRENT CLINICAL PRACTICE,
POSSIBLE ALGORITHM FOR AXILLARY STAGING IN PATIENTS WITH INVASIVE BREAST CANCER

No Palpable Nodes

Ultrasound/MR

Suspicious → US biopsy → Negative → SLNB → Negative / Positive → ALND

Not suspicious → SLNB

Positive → ALND

Chemotherapy → Ultrasound/MR → SLNB → ?

SLNB: sentinel lymph node biopsy
ALND: axillary lymph node dissection

SEVERANCE
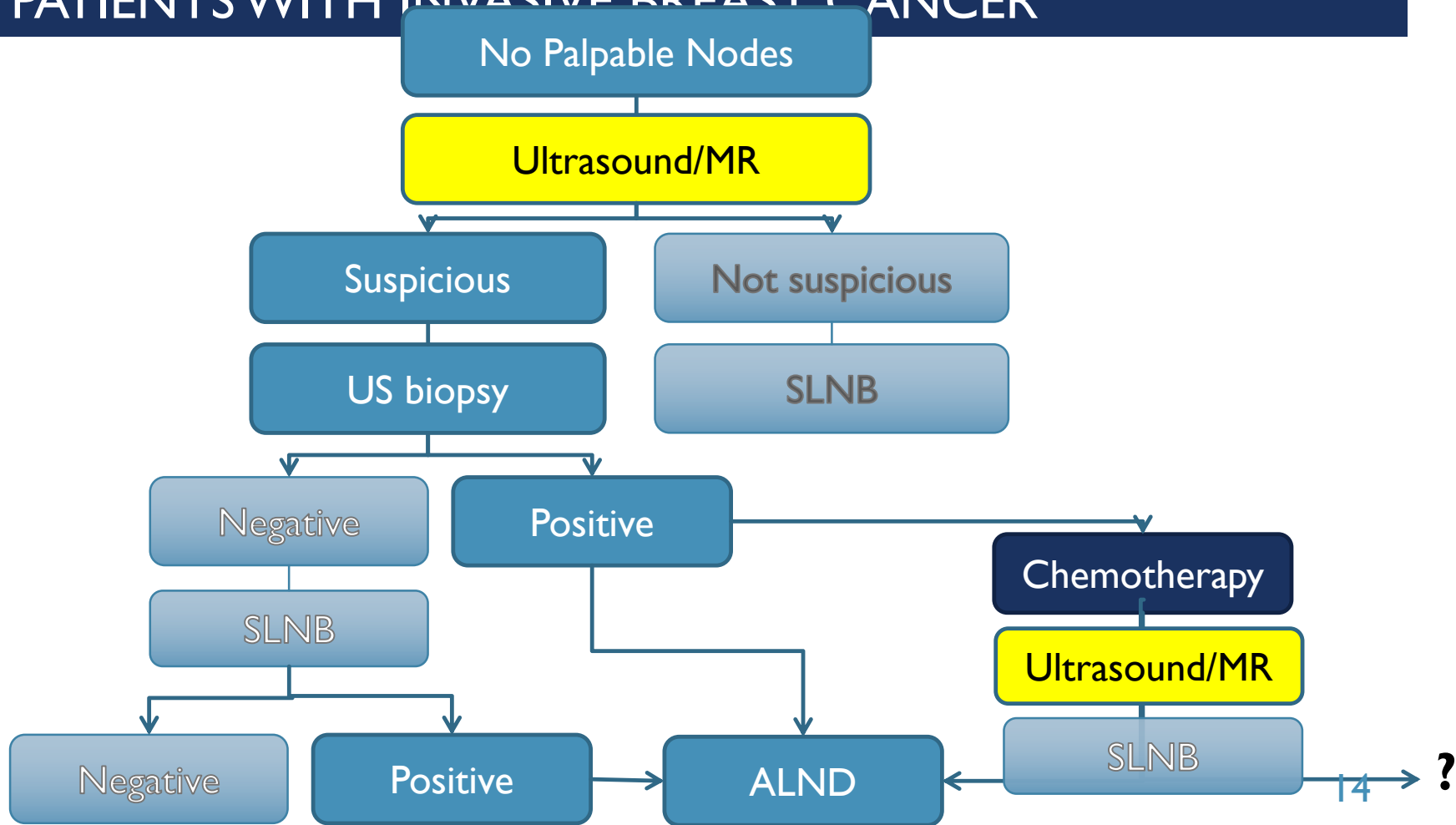
- Imaging Evaluation of Axillary Lymph Nodes after Neoadjuvant Systemic Therapy

- How to improve the performance of Sentinel Node Biopsy after Neoadjuvant
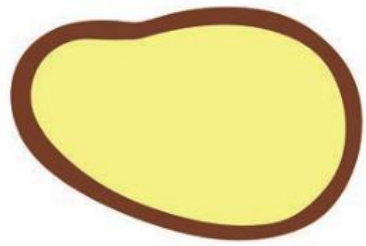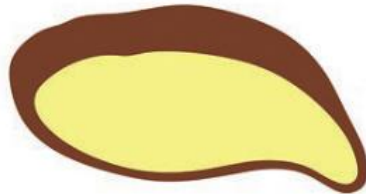
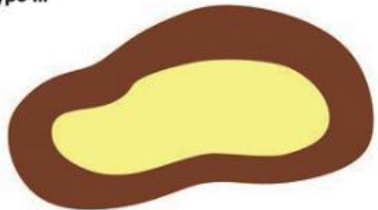 Chemotherapy: Targeted axillary dissection
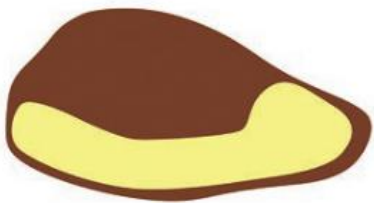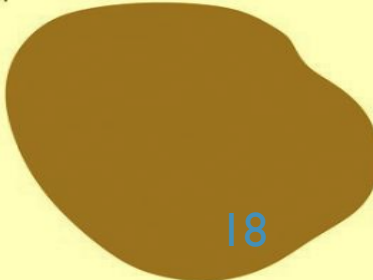
SEVERANCE

IMAGING EVALUATION OF AXILLARY LYMPH NODES AFTER NEOADJUVANT SYSTEMIC THERAPY

SEVERANCE

AXILLARY ULTRASOUND IDENTIFIES RESIDUAL NODAL DISEASE AFTER CHEMOTHERAPY: RESULTS FROM THE ACSOG Z1071 TRIAL (ALLIANCE)

- Lymph node features on axillary ultrasound (US) images obtained after neoadjuvant chemotherapy associated with residual nodal disease

  - Increased cortical thickness (mean, 3.5 mm for node-pos vs 2.5 mm for node-neg)

  - longer short-axis diameter, longer long-axis diameter, absence of fatty hilum

- Axillary US performed after neoadjuvant chemotherapy is useful for nodal response

  assessment, with longer short-axis diameter, longer long-axis diameter, increased cortical

  thickness, and absence of fatty hilum significantly associated with residual nodal disease after

  neoadjuvant chemotherapy.

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SEVERANCE

Le-Petross AJR 2018

AXILLARY ULTRASOUND IDENTIFIES RESIDUAL NODAL DISEASE AFTER CHEMOTHERAPY: RESULTS FROM THE ACSOG Z1071 TRIAL (ALLIANCE)

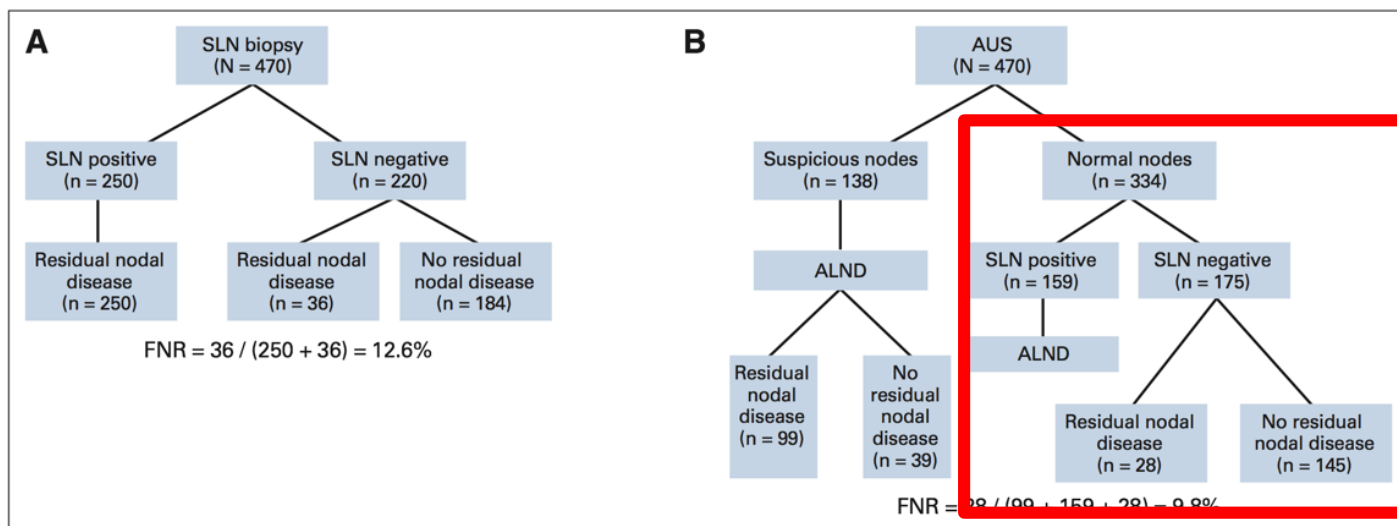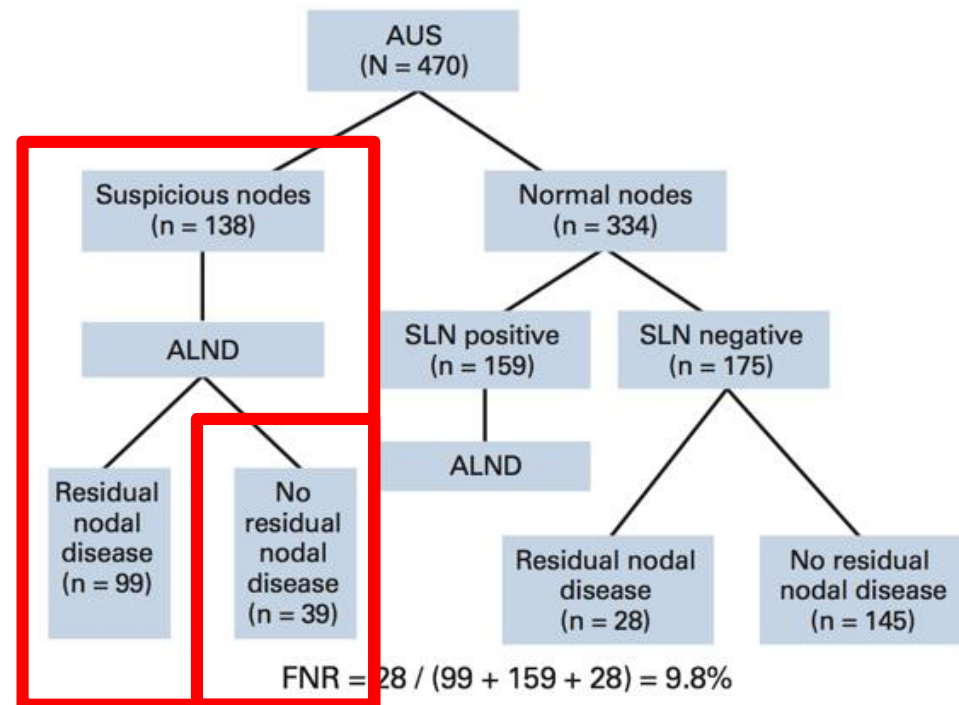|		PPV for residual	Odds Ratio for PCRn	
Node not seen		58%	Ref	
Type I	no visible cortex	56%	1.07	
Type II	a hypoechoic cortex </= 3 mm	56%	1.06	
Type III	a hypoechoic cortex > 3 mm	59%	0.94	
Type IV	a generalized lobulated hypoechoic cortex	80%	0.35	
Type V	focal hypoechoic cortical lobulation	68%	0.65	
Type VI	a totally hypoechoic node with no hilum	80%	0.34	

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Le-Petross AJR 2018

- Z1071 Pts with T0-4, N1-2, M0 BC underwent AUS after NAC

- The SLN FNR was not different based on AUS result

- The use of SLNB only when sonographic findings were negative, potentially reduce the FNR in Z1071 patients with 12.6% to 9.8%

- Preop/afterchemo AUS results are considered as part of SLN surgery.

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Boughey JCO 2015

- Question whether AUS has anything to do with it.

    - Among negative AUS, the FNR of SLN biopsy was 15% (28 of 187)

    - Among positive AUS, the false-positive rate of AUS was 29% (39 of 138 patients)

- *An abnormal AUS post-NAC is not sufficient for proceeding to ALND.*

AUS (N = 470)

Suspicious nodes (n = 138) → ALND → Residual nodal disease (n = 99) / No residual nodal disease (n = 39)

Normal nodes (n = 334) → SLN positive (n = 159) / SLN negative (n = 175)

SLN positive → ALND → Residual nodal disease (n = 28) / No residual nodal disease (n = 145)

FNR = 28 / (99 + 159 + 28) = 9.8%

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THE DIAGNOSTIC PERFORMANCE OF BREAST MRI FOR AXILLARY NODAL STAGING AFTER NAC

- A retrospective review using single institutional cancer registry.

- 135 Patients who started NAC from 2005 to 2010 with clinically node positive disease

Analysis	Total MRI, n = 135	Luminal, n = 73	HER2þ, n = 34	TN, n =28
True positive, n (%)	42 (31)	18 (25)	9 (27)	15 (54)
True negative, n (%)	23 (17)	8 (11)	11 (32)	4 (14)
False positive, n (%)	3(2)	0 (0)	1 (3)	2 (7)
False negative, n (%)	67 (50)	47 (64)	13 (38)	7 (25)
Sensitivity (%)	39	28	41	68
Specificity (%)	88	100	92	67
PPV (%)	93	100	90	88
NPV (%)	26	15	46	36
Accuracy (%)	48	36	59	68

SEVERANCE

PREOPERATIVE AXILLARY LYMPH NODE EVALUATION IN BREAST CANCER PATIENTS BY BREAST MAGNETIC RESONANCE IMAGING (MRI): *DIAGNOSTIC PERFORMANCE OF MRI ACCORDING TO NAC*

	Overall (%)	No-NAC (%)	NAC (%)	*p-value*
Sensitivity	51.3 (60/117)	51.7 (30/58)	50.8 (30/59)	0.911
Specificity	92.2 (284/308)	90.9 (229/252)	98.2 (55/56)	0.001
PPV	71.4 (60/84)	56.5 (30/53)	96.8 (30/31)	< 0.001
NPV	83.3 (284/341)	89.1 (229/257)	65.5 (55/84)	< 0.001
Advance (pN2/3)				
SN w/ cN1-3	80.0 (24/30)	91.7 (11/12)	83.3 (15/18)	
SN w/ cN2-3	36.7 (11/30)	33.3 (4/12)	38.9 (7/18)	
NPV w/cN0	98.2 (335/341)	99.6 (256/257)	94.0 (79/84)	0.039
NPV w/cN0/1	95.3 (388/407)	97.4 (294/302)	89.5 (94/105)	0.017

SEVERANCE

Hyun ER 2016

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PREDICTION OF ADVANCED AXILLARY LN METASTASES (ypN23) USING BREAST MR IMAGING AND PET/CT AFTER NEOADJUVANT CTX IN IDC PATIENTS

Characteristics	Univariate OR (95% CI)	Multivariate OR (95% CI)	P value
Number of positive ALNs on **initial staging** MR imaging*			
<4	1.00	1.00	
≥4	5.91	6.04	0.080
Number of positive ALNs on **restaging** MR imaging*			
<2	1.00	1.00	
≥2	12.04	8.06	0.015
Short diameter of the largest ALN on **restaging** MR imaging			
≤7.7mm	1.00	1.00	
>7.7mm	5.00	4.44	0.063

- A **higher number of positive ALNs on restaging MR imaging** was an independent **predictor for advanced ALN metastases** after NAC.

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SEVERANCE

PREDICTION OF ADVANCED AXILLARY LN METASTASES (ypN23) USING BREAST MR IMAGING AND PET/CT AFTER NEOADJUVANT CTx IN IDC PATIENTS

Imaging modalities	AUC	SN	SP	PPV	NPV
MR	0.792	83.3%	75.0%	29.4%	97.3%
PET/CT	0.729	58.3%	87.5%	36.8%	94.4%
MR+PET/CT	0.849	100.0%	69.8%	29.3%	100.0%

- The AUC and sensitivity of restaging MR imaging plus PET/CT was higher than that of each restaging MR imaging and PET/CT; however, the differences were not statistically significant (AUC, P = 0.318 and P = 0.119, respectively; sensitivity, P = 0.500 and 0.063, respectively).

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SEVERANCE

# HOW TO IMPROVE THE PERFORMANCE OF SENTINEL NODE BIOPSY AFTER NAC

SEVERANCE

- **Placing a clip in the positive lymph node could sole the high FNR?**

  - 31.5 % FNR with one SLN in Z1071 trial

- Data from Z1071: the FNR in cases with placing a clip in the positive lymph node was lower than that using dual tracer technique (7.4% vs 10.8%)

Targeted axillary dissection

- After completion of NAC, the clipped node is localized by using a wire or radioactive seed

- During the SLND procedure, taking both all SLNs and clipped node with localization

Mittendorf ASO 2014
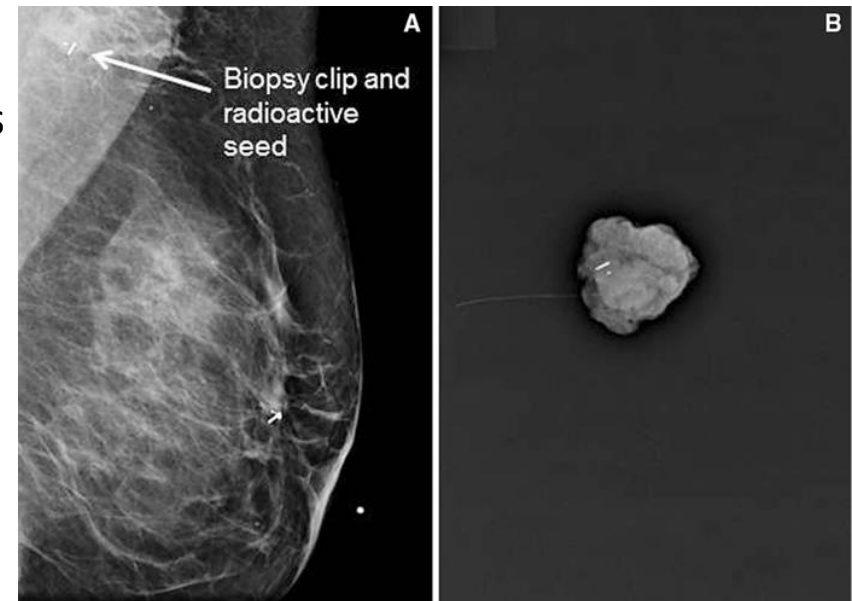
IDENTIFICATION AND RESECTION OF CLIPPED NODE DECREASES THE FNR OF SLNB IN NAC PTS PRESENTING WITH NODE (+) BC results from ACOSOG Z1071 (ALLIANCE)

False-negative Rate by Clip Location and Patient Group Analyzed

	N	Residual Disease identified in SLNs or ALND, n (%)	FNR (%)	95% CI
Patients with ≥ 2SLNs removed and cN1 disease				
Clip in SLN	107	59 (55.1)	6.8	1.9-16.5
Clip in ALND	34	21 (61.8)	19.0	5.4-41.9
Clip location unknown	29	21 (72.4)	14.3	3.0-36.3
Clip not placed	355	209 (59.0)	13.4	9.1-18.8

- 525 patients with cN1 disease and ≧2 SLNs confirmed

- 170 clip in LN vs 355 no clip in LN
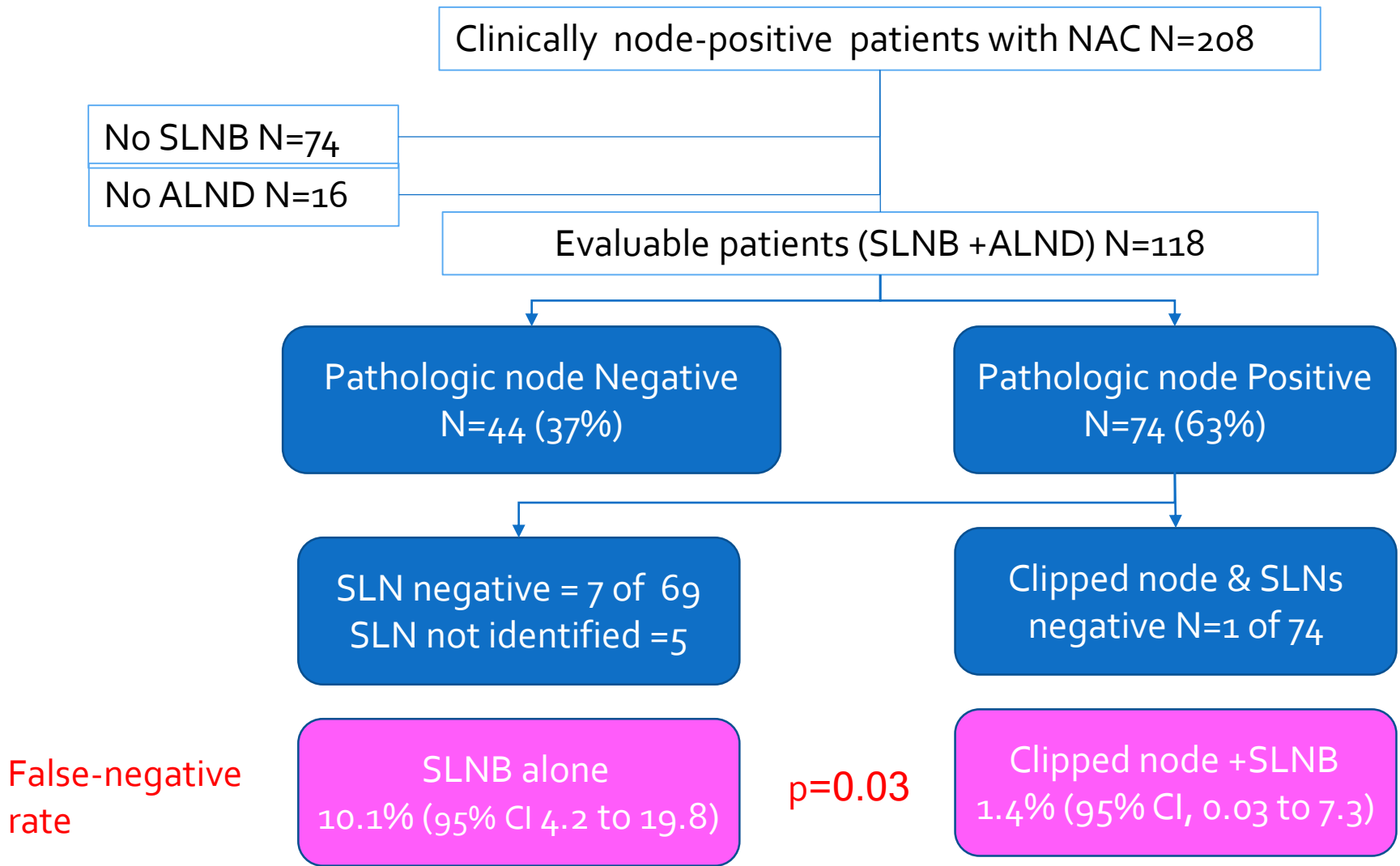
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Boughey AS 2016

SEVERANCE

Selective Surgical Localization of Axillary Lymph Nodes Containing Metastases in Patients With Breast Cancer

- the feasibility of image-guided localization and resection of lymph nodes containing known-metastases.

- 12 patients with ALN-meta confirmed by FNA, who had a clip placed in the lymph node targeted for biopsy.
  - US guided wire –needle localization (n=2) & radioactive iodine I $_{125}$ (n=10)

- Image-guided localization & selective removal were successful in all 12 patients.
  - 80% : the clipped node = one of the SLNs
  - 20% : the clipped node ≠ one of the SLNs

- Without clip-localization, the biopsy-proven metastatic axillary node with the clip would not have been included in surgery in these 20% of patients.
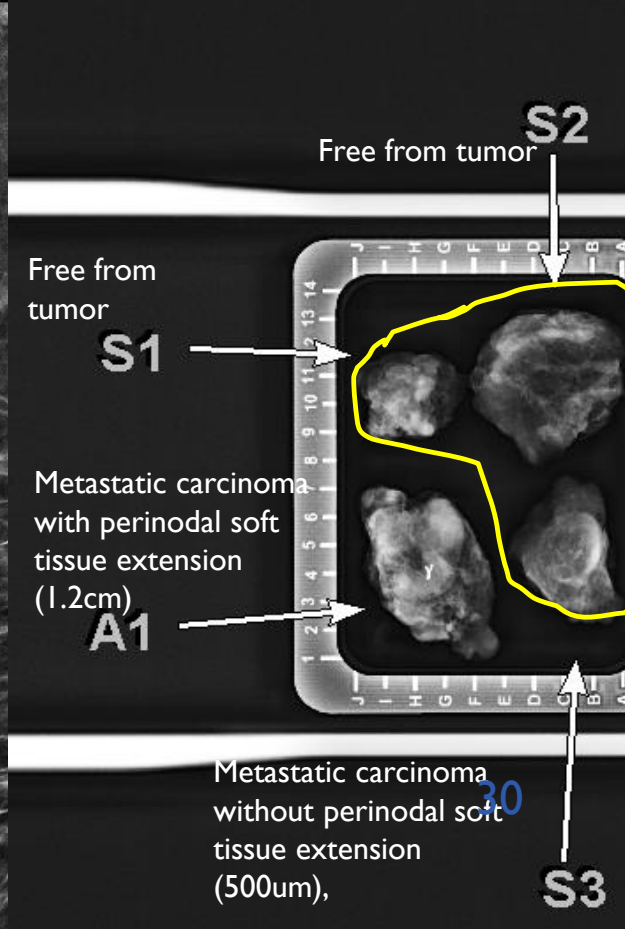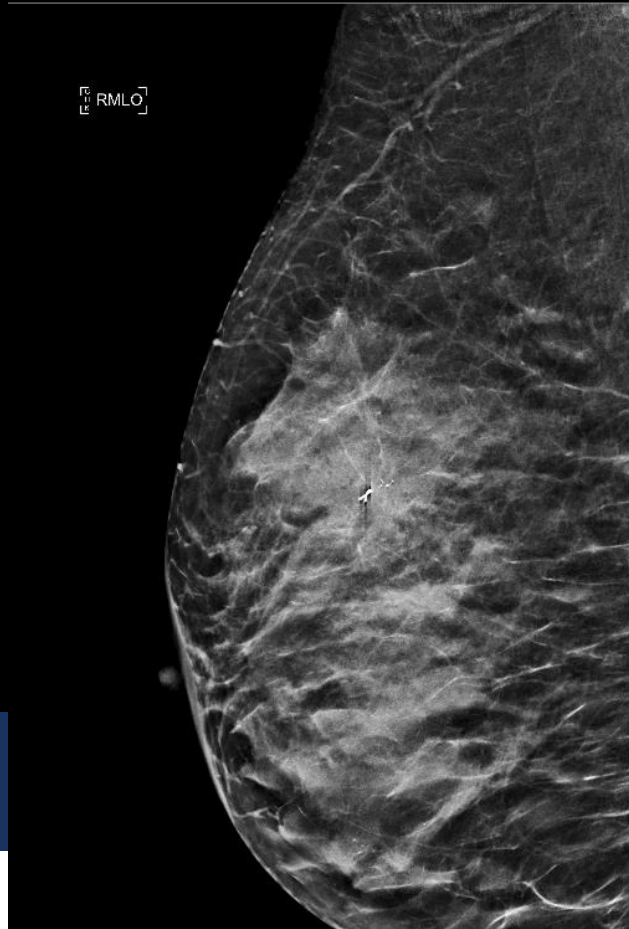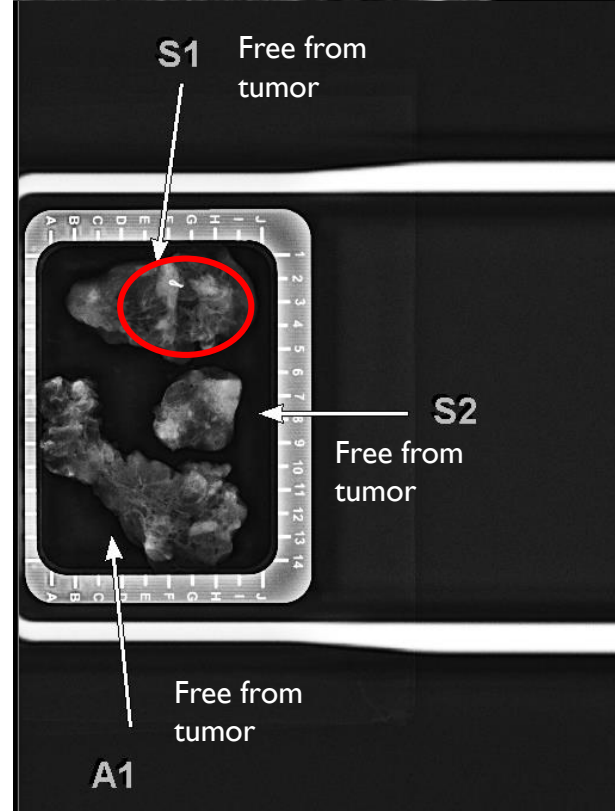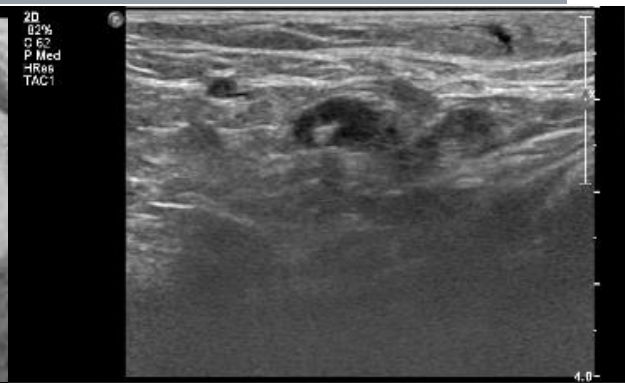
Caudle JAMA 2015

Targeted axillary dissection (TAD)

SLNB +/- Clip

Clinically node-positive patients with NAC N=208

No SLNB N=74

No ALND N=16

Evaluable patients (SLNB +ALND) N=118

Pathologic node Negative
N=44 (37%)

Pathologic node Positive
N=74 (63%)

SLN negative = 7 of 69
SLN not identified =5

Clipped node & SLNs
negative N=1 of 74

False-negative rate

SLNB alone
10.1% (95% CI 4.2 to 19.8)

p=0.03

Clipped node +SLNB
1.4% (95% CI, 0.03 to 7.3)

Caudle JCO 2016

47/f

59/f

S1 Free from tumor

S2 Free from tumor

A1 Free from tumor

S2

Free from tumor

Free from tumor S1

Metastatic carcinoma with perinodal soft tissue extension (1.2cm) A1

Metastatic carcinoma without perinodal soft tissue extension (500um), S3

30

C Postlocalization mammogram

Seed

Clip

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Park S & Kim MJ CRT epub
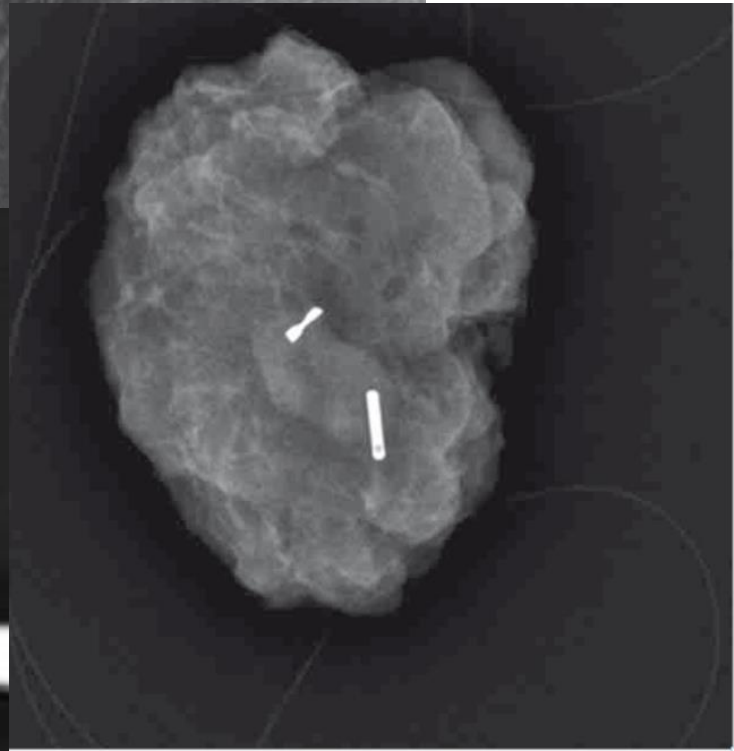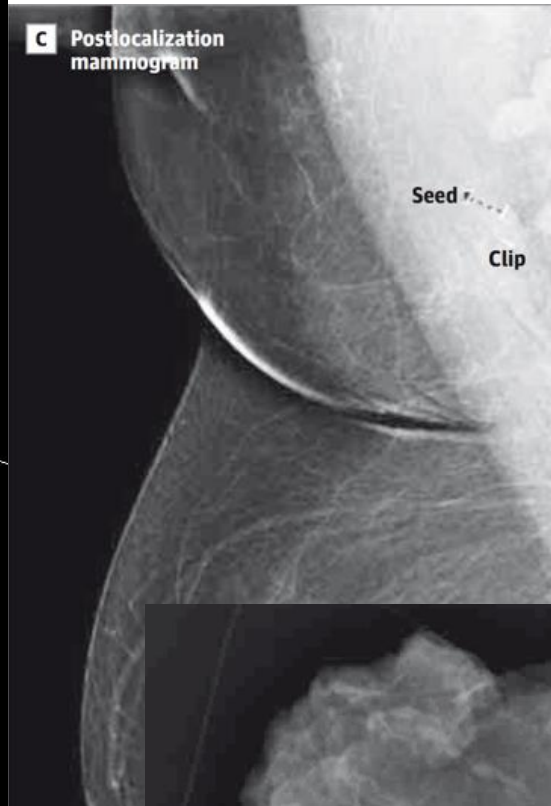
CHARCOAL TATTOOING OF METASTATIC ALN FOLLOWED BY SLNB AFTER NAC IN BREAST CANCERS IN YUHS

Tatoo node

Blue-dyed node

SEVERANCE

Park CRT epub
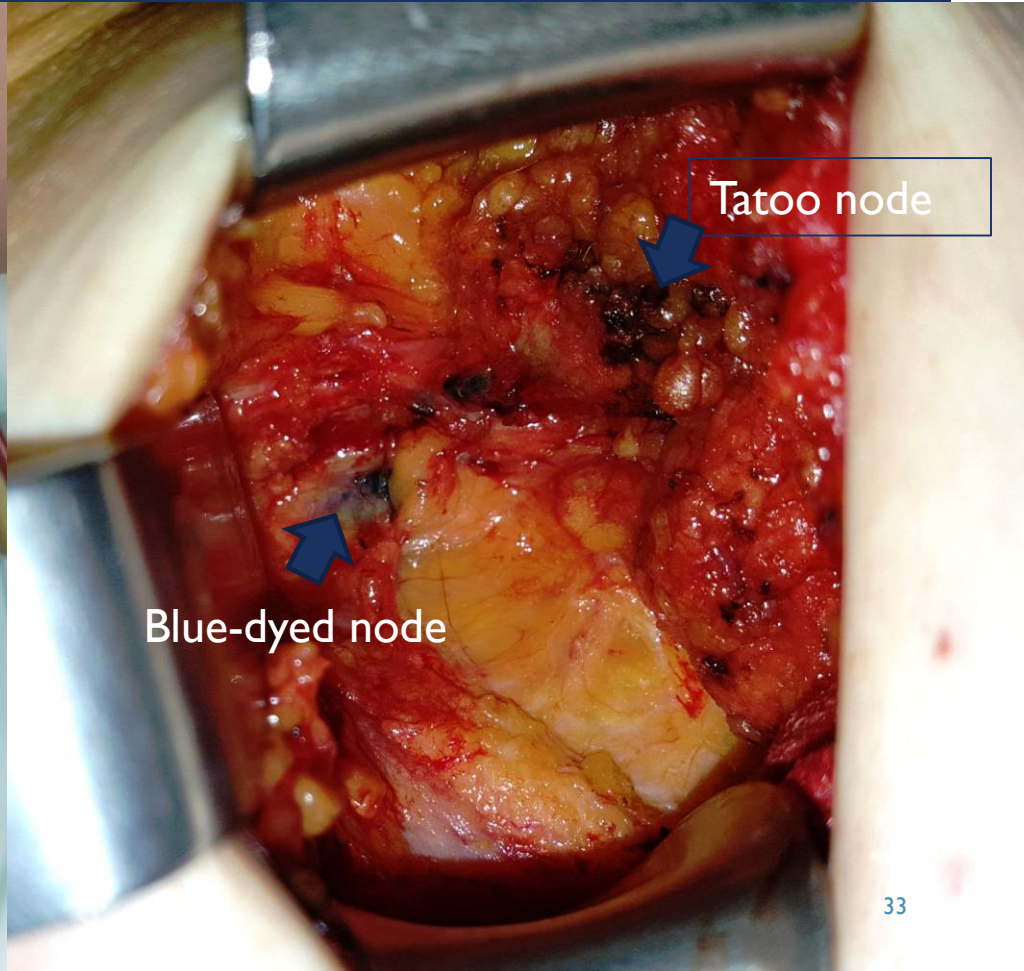
SLN 1
1st Hot LN ≠ Blue colored LN ≠ Tattoo LN

SLN 2
2nd Hot LN = Blue colored LN ≠ Tattoo LN

ALN 1
Cold LN = Tatto LN ≠ Blue LN

Blue-dyed node

Tatoo node

Metastasis , diameter 13mm

Parameter	Final ALN status after NCT			Total
	Positive (n=10)		Negative (n=10)	
	Non-sentinel ALN (+)	Non-sentinel ALN (-)		
SLNB				
Positive	3	5	-	8
Negative	2	-	10	12
Modified SLNB				
Positive	4	6	-	10
Negative	0	-	10	10

a)Modified SLNB is the final results of hot or blue-colored sentinel lymph nodes and initial cytology-proven, charcoal-tattooed lymph node excised during axillary sampling procedure.

Park CRT epub

TAKE HOME MASSAGE

- NAC is increasingly used for patients with operable breast cancer to allow more limited surgery in the breast and axilla.

- However, the diagnostic performance of imaging evaluation after NAC is limited. It could be helpful to exclude advanced nodal disease, but not sufficient to replace SLNB.

- A multidisciplinary approach is needed to evaluate re-staging of axillary lymph node after NAC, using imaging findings, tumor biology, and localization of proven metastatic lymph nodes.

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THANK YOU FOR YOUR ATTENTION!