SAN ANTONIO BREAST CANCER SYMPOSIUM®

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AIOM Associazione Italiana di Oncologia Medica

What is the optimal current axillary management after NAC?

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Indications for NAC Are Changing

Absolute	Relative
• Inflammatory Cancer • Other T4 tumors • N2 or N3 disease	• Large tumor/breast ratio in patient desiring BCT • Reducing the need for ALND

King T, Morrow M, Nat Rev Clin Oncol 2015;12:335

SNB Feasibility In cN+ Patients After NAC

- 3 prospective single arm trials
- SNB ➔ back-up ALND
- No LRR data

	ACOSOG Z1071	SN FNAC	SENTINA
N	689	153	592 (cN+)*
cTN	cT0-4 N1/2	cT0-3 N1/2	cN0/N1/N2
FNR (Overall)	12.6%	13.4%	14.2%

Boughey J, Ann Surg 2014;260:608
Boileau J, J Clin Oncol 2015;33:258
Kuehn T, Lancet Oncol 2013;14:609

Methods to minimize the False Negative Rate (FNR) of sentinel lymph node dissection after neoadjuvant chemotherapy for node positive breast cancer

Practical approach to the axilla after neoadjuvant chemotherapy: What the clinical trials don't address

Axillary Surgery – Why?

- Staging of the axilla
  - Guide adjuvant systemic therapy
    - – pN0 vs pN+
    - – # of positive LNs
  - Guide adjuvant radiation (indication and fields)
- Resection of disease
  - To render patient NED – no evidence of disease
- Long-term regional control
- Survival?

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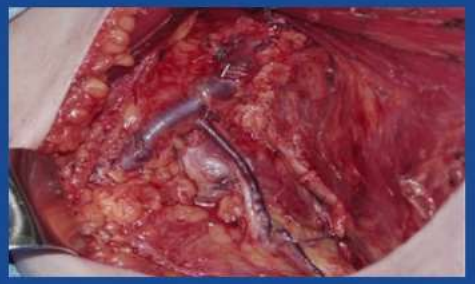
Evolution of Axillary Surgery

- Routine ALND
  - Removing all the LNs (10-25+)
  - Lymphedema risk 25%



- SLN surgery
  - 2-3 LNs
  - Lymphedema risk 6-8%

- No axillary surgery
  - Axillary Ultrasound
  - Patients at of low risk of +LNs
  - Patients where axillary status does not impact management

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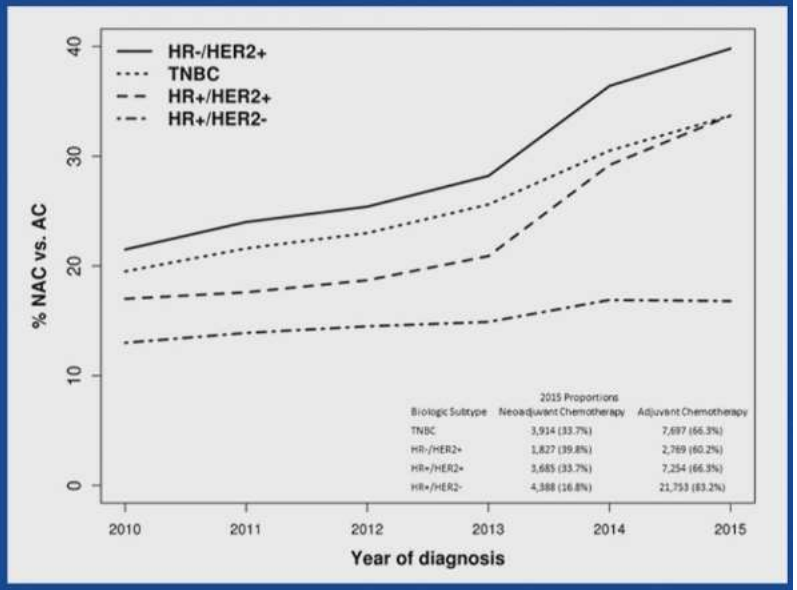
Neoadjuvant Chemotherapy

- Decrease extent of disease in the breast
  - Increase rate of breast conservation
- Decrease likelihood of nodal positivity
  - Increase use of sentinel node surgery
- Assess response of tumor to chemotherapy
  - Prognostic information
  - Adjust adjuvant therapies
- Drug development
  - Advance development of therapy to improve breast cancer survival



Murphy et al. ASO 2018 Aug;25(8):2241-2248

Neoadjuvant Chemotherapy

Clinical Stage → **Chemotherapy** → **Surgery** → **Pathologic Stage**

Physical examination
Axillary Ultrasound
MRI

Percutaneous biopsy – cN1(f)

AVOID axillary surgery

Repeat imaging to assess response

Axillary surgery to assess for residual nodal disease
SLN/TAD?
ALND?

AJCC –Definition of Regional Lymph Nodes

CLINICAL N CATEGORY

cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
cN2	Metastases in ipsilateral Level I, II axillary lymph nodes that are clinically fixed or matted; *or* in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN3	Infraclavicular (level III) or supraclavicular LN involvement *or* in ipsilateral internal mammary nodes with axillary lymph node metastases

PATHOLOGICAL N CATEGORY

pN0	No regional LN metastases identified or ITCs only
pN1	Micrometastases or metastases in 1-3 axillary LNs; and/or clinically negative internal mammary nodes with metastatic disease by SLN biopsy
pN2	Metastases in 4-9 axillary LNs; or positive internal mammary nodes by imaging in absence of axillary LN mets
pN3	Metastases in 10+ axillary LNs

SLN after NAC in cN0 patients

1,456 patients from 16 studies

- SLN identification rate 96% [95% CI: 95%-97%]
- **SLN FNR 6%** (95% CI: 3%-8%)
  - Sensitivity 94% (95% CI: 92%-97%)
  - NPV 98% (95% CI: 98%-99%)
  - Accuracy 99% (95% CI: 99%-100%)

- SLN after NAC compared to surgery first
  - Similar SLN identification rates
  - Similar FNR
  - Lower nodal positivity rates
    - Fewer axillary dissections in T2 and T3

    T2: 20.5% vs. 36.5%, p<0.0001
    T3: 30.4% vs. 51.4%, p=0.04
  - Does not lead to higher local-regional failure rates

SLN feasible and accurate in cN0 disease

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Geng et al PLoS One. 2016 Sep 8;11(9):e0162605
Hunt et al. Ann Surg 2009; 250 (4):558-66

Response to neoadjuvant chemotherapy

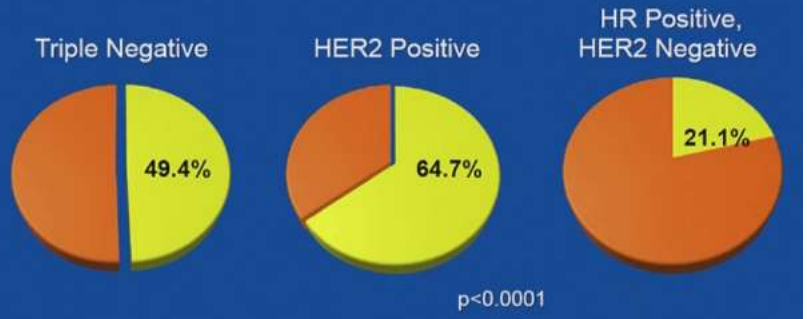
Increasing pCR rates:

- Anthracyclines 10-15%
- Anthracyclines + taxanes 25-30%
- Targeted anti-Her2 therapy:
  - Trastuzumab + chemo 40-50%
  - 2 anti-her2 agents + chemo 50-60%

Nodal response rates (cN1 to ypN0):

- Anthracyclines 30%
- Anthracyclines + taxanes 40%
- Anti-Her2 therapy up to 70-75%

Pathological Complete Response Rates in the Axilla



Boughey et al. Ann Surg. 2014 Oct;260(4):608-16

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Outline

- SLN after NAC in cN1 disease – the trials
- Optimizing identification of the SLNs
- Decreasing the FNR
  - Technique
    - Number of SLNs removed
    - Dual tracer
  - Pathology
    - Treatment effect
    - IHC of SLNs
  - Removal of the clipped node
    - Ensuring identification of the clipped node
- Incorporating into clinical practice

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SLN identification rate

Study	SLN identified	SLN ID rate
Z1071	639/689	92.7%
SENTINA	474/592	80.1%
SN FNAC	127/145	82.2%
Meta-analysis of these 3 trials	1240/1426	87.0%
Meta-analysis – pooled estimate across 17 studies		90.9%

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Boughey et al. JAMA 2013 Oct 9;310(14):1455-61; Kuehn et al. Lancet Oncol. 2013; 14 (7); 609-18; Boileau et al. JCO. 2015 Jan 20;33(3):258-64; El Hage et al. Am J Surg. 2016; 212(5):969-981

SLN identification rates after NAC in Z1071

- SLN identification rate in pts undergoing surgery after NAC is higher with use of dual tracers for mapping
  - SLN ID rate with single tracer = 88.9% (95%CI: 82.6-93.5%)
  - SLN ID rate with dual tracers = 93.8% (95%CI: 91.4-95.6%) p=0.048
- No other clinical or pathologic factors significantly impacted SLN identification

Use of dual tracer is recommended when performing SLN in patients who have received NAC

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Boughey et al. Ann Surg. 2015 Mar; 261(3); 547-52

FNR of SLN after NAC in cN1 patients

SENTINA	FNR overall	14.2%
SN FNAC	FNR overall including IHC	8.4%
Z1071	FNR with ≥ 2 SLNs removed	12.6%

Meta-analysis
3,398 patients

FNR 13%
-pooled estimate
across 19 studies

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Kuehn et al. Lancet Oncol. 2013; 14 (7); 609-18; Boileau et al. JCO. 2015 Jan 20;33(3):258-64;
Boughey et al. JAMA 2013 Oct 9;310(14):1455-61: El Hage et al. Am J Surg. 2016; 212(5):969-981

Number of SLNs removed

- Z1071

≥ 2 SLNs removed FNR = 12.6% (39/310)

- SENTINA

≥ 2 SLNs removed FNR = 9.6% (15/156)

- SN FNAC

≥ 2 SLNs removed FNR = 4.9% (3/61)

Meta-analysis of these 3 trials
≥ 2 SLNs removed FNR =
57/527 = 10.8%

How frequently were ≥ 2 SLNs identified

Z1071	310/388	79.9%
SENTINA	156/226	69.0%
SN FNAC	61/83	73.5%

Resect at least 2 SLNs

Boughey et al. JAMA 2013 Oct 9;310(14):1455-61; Kuehn et al. Lancet Oncol. 2013; 14 (7); 609-18;
Boileau et al. JCO. 2015 Jan 20;33(3):258-64; El Hage et al. Am J Surg. 2016; 212(5):969-981

Use of dual tracer on SLN FNR

Trial	Mapping agent	FN cases	FNR	P value
Z1071	Blue dye only	2/9	22.2%	0.046
	Radiolabeled colloid only	10/50	20.0%	
	Dual tracer	27/251	10.8%	
SENTINA	Radiocolloid only	23/144	16.0%	NR
	Dual tracer	6/70	8.6%	
SN FNAC	Isotope only	4/25	16.0%	0.19
	Dual tracer	3/58	5.2%	

Single tracer – 39/228 = 17.1%

Dual tracer – 36/379 = 9.5%

Use dual tracer

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Boughey et al. JAMA 2013 Oct 9;310(14):1455-61; Kuehn et al. Lancet Oncol. 2013; 14 (7); 609-18; Boileau et al. JCO. 2015 Jan 20;33(3):258-64; El Hage et al. Am J Surg. 2016; 212(5):969-981

WAYS TO ENSURE SLN IS A NODE THAT WAS POSITIVE PRIOR TO CHEMO AND NOT A BYSTANDER NODE

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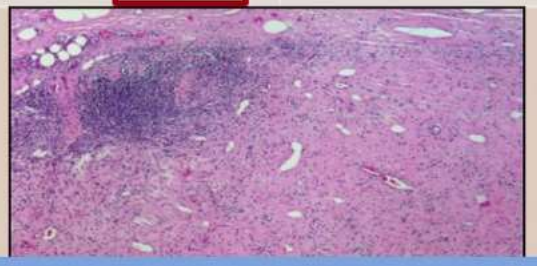
Treatment Effect / Histologic Changes

Histologic changes	N	FNR	95% CI
Not mentioned	339 (64.5%)	28/208 = 13.5%	9.1 – 18.9%
Present	186 (35.5%)	11/102 = **10.8%**	5.5 – 18.5%
Adipose tissue	33 (6.3%)		
Fat necrosis	15 (2.9%)		
Fibrosis	17 (3.2%)		
Histiocyte infiltrate	88 (16.8%)		
Treatment effect NOS	33 (6.3%)		



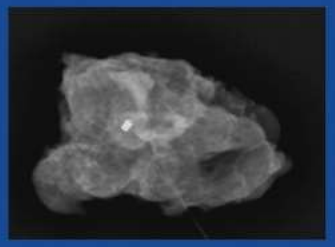
Consider pathologist to comment on presence of histologic changes in SLN

Bougney et al. SABCS 2012

Identification and Resection of Clipped Node Decreases the False-negative Rate of Sentinel Lymph Node Surgery in Patients Presenting With Node-positive Breast Cancer (T0–T4, N1–N2) Who Receive Neoadjuvant Chemotherapy

Results From ACOSOG Z1071 (Alliance)

Judy C. Boughey, MD, Karla V. Ballman, PhD,† Huong T. Le-Petross, MD,‡ Linda M. McCall,§ Elizabeth A. Mittendorf, MD, PhD,¶ Gretchen M. Ahrendt, MD,|| Lee G. Wilke, MD,** Bret Taback, MD,†† Eric C. Felíberti, MD,‡‡ and Kelly K. Hunt, MD¶*



170 of 525 (32.4%) patients with cN1 disease and 2+ SLNs removed had clip placed in LN at diagnosis

Clip	N	Nodal residual disease	FNR	95% CI
Clip placed and found in SLN	107	59	**6.8%**	1.9 – 16.5%
Clip placed and found in ALND	34	21	19.0%	5.4 – 41.9%

Resect the clipped node

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Boughey et al. Ann Surg. 2016 Apr;263(4):802-7

Clipped node not retrieved as a SLN

- ACOSOG Z1071: 24.1% (34/141)
- MDACC: 23.1% (31/134)
- UPMC: 26.7% (8/30)

OVERALL: 23.9% (73/305)

Boughey et al. Ann Surg, 2015
Caudle et al. JCO, 2016
Diego et al. ASO, 2016

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Clipped node not retrieved as a SLN

- ACOSOG Z1071: 24.1% (34/141)
- MDACC: 23.1% (31/134)
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Boughey et al. Ann Surg, 2015
Caudle et al. JCO, 2016
Diego et al. ASO, 2016

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Marking Axillary Lymph Nodes With Radioactive Iodine Seeds for Axillary Staging After Neoadjuvant Systemic Treatment in Breast Cancer Patients

The MARI Procedure

- 100 cN1+ patients after NAC
- I-125 seed placed at initial LN biopsy (before NAC)
- Half-life of seed is 59.6 days
- Seed in place: 17 weeks (9-31 weeks)
- No SLN surgery, removal of + LN only using seed localization
- Identification rate: 97% (97/100)
- ALND in 95 patients

- FNR of clipped node: **7%** (5/70)

Marking and removing the initial biopsy proven metastatic LN after NAC has a high identification rate and low FNR

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Donker et al. Ann Surg 2015 Feb;261(2):378-82

Resection of Clipped Node & SLN – Targeted Axillary Dissection

- Localize clipped node prior to surgery
- Remove SLNs and clipped node
- MDACC experience

  176 patients TAD and ALND

  - FNR SLN alone 7.9%
  - FNR clipped node alone 3.9%
  - FNR SLN + clipped node **2.4%**

Caudle et al. J Clin Oncol. 2016 Apr 1;34(10):1072-8
Caudle et al. SSO 2017

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Methods to identify biopsy proven node

Marking the positive node

- Clip
- Tattoo
  - India ink
  - Charcoal

Localizing the marked node

- Radioactive seed
- Other seeds
- Ultrasound
- Palpation

Impact of IHC in SN FNAC

- Primary endpoint included SLNs positive for ITCs – FNR 8.4%
- IF had limited to disease >0.2mm – then FNR would have been 13.3%

	FN cases	FNR
Definition of positive node		
Any size, including N0(i+)	7/83	8.4%
>0.2mm	11/83	**13.3%**
>2mm	14/83	16.9%

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Boileau et al. JCO 2015 Jan 20;33(3):258-64

Impact of IHC and ITCs on SLN FNR in Z1071

- SLNs from 17 patients revealed disease ≤0.2mm in size on H&E or IHC

Node positive definition	N	Residual disease identified in SLNs or ALND	FNR	95% CI	Pathologic nodal response
SLN metastasis >0.2mm by H&E	470	301 (64.0%)	11.3%	8.0-15.4	36.0% (169/470)
SLN metastasis any size (including ≤0.2mm)	470	311 (66.2%)	**8.7%**	5.6-11.8	33.8% (159/470)

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Boughey et al. SABCS 2014, updated data

Impact of IHC and ITCs on SLN FNR in Z1071

SLNs from 17 patients had disease ≤ 0.2mm identified on IHC or H&E

- 7 patients had positive nodes on ALND
  - changed from false negative to true positive
  - decreased the FNR of SLN surgery
  - did not impact the pathologic nodal response rate

In these 17 cases additional disease on ALND seen in 7 = 41%

- 10 patients were pN0 (negative SLNs and ALNs) pathologically
  - changed from pN0 to pN1
  - decreased the pathological nodal response rate
  - decreased the FNR of SLN surgery

Use IHC on SLNs

Axillary management

Without a clip in the LN at diagnosis

- If 0 or 1 SLN identified convert to ALND
- ≥2 SLNs – manage axilla based on pathology of SLNs

Clip in the LN at diagnosis

- If 0 SLNs or only 1 SLN without the clip convert to ALND
- If ≥2 SLNs or 1 SLN including the clip - manage axilla based on pathology of SLNs

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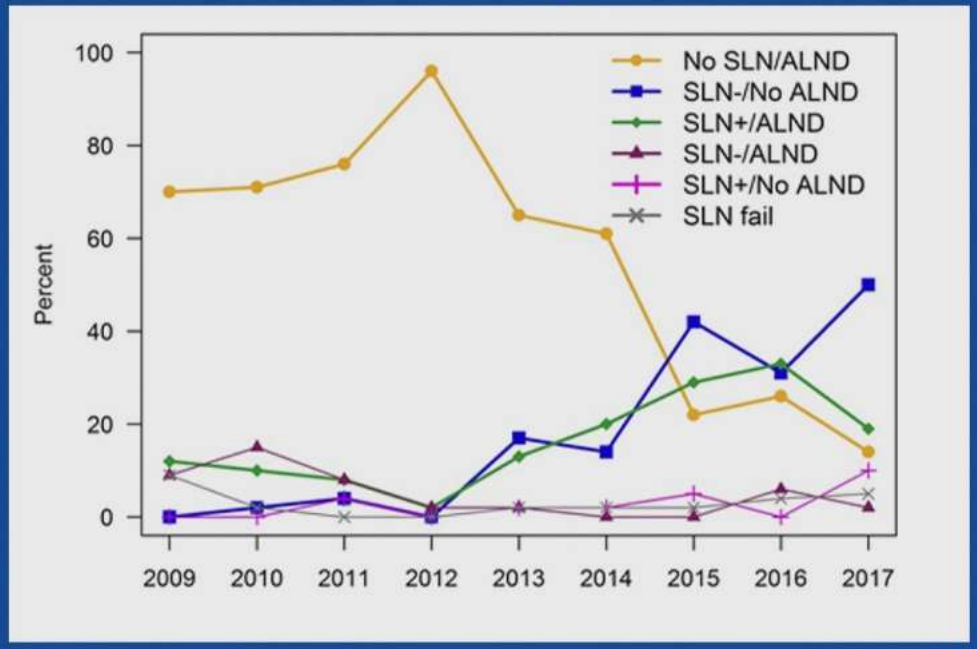
Evolution of axillary surgery for cN1 patients after NAC at Mayo Clinic Rochester



431 patients with biopsy-proven cN1 patients treated with NAC between 1/2009 to 12/2017

Use of SLN surgery (+/- ALND) increased from 30% in 2009 to 86% in 2017 ($p<0.001$)

Performance of ALND decreased from 97% in 2009 to 38% in 2017 ($p<0.001$)

With short-term follow up (median 9 months, range 0-8 years), no nodal recurrences have occurred in patients without ALND

Nyugen....Boughey ASO 2018 Sep;25(9):2596-2602

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Oncologic safety and locoregional recurrence

- 147 patients cN1/2 → cN0 after NAC at the European Institute of Oncology in Milan
- Median f/u 61 months
- Axillary recurrence (0.7%)
  - 1/77 SLN+ (ALND)
  - 0/70 SLN- (no ALND)
- Conclusion: SLN surgery is acceptable in cN1/2 patients who become cN0 after NAC

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Galimberti et al, EJSO 2015

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Invasive Breast Cancer

NCCN Guidelines Index
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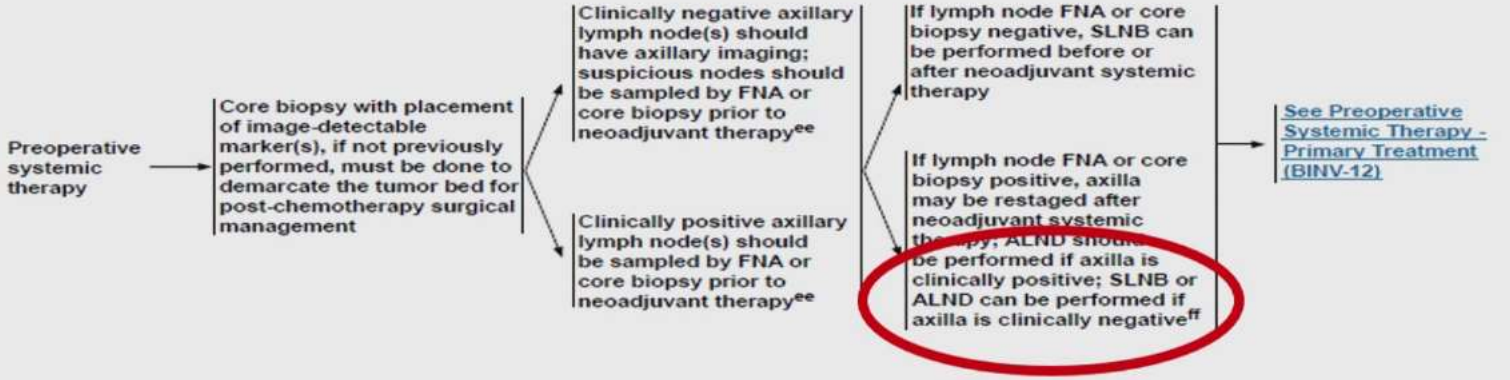
Discussion

Preoperative Systemic Therapy Breast and Axillary Evaluation



Surgical resection → See Locoregional Treatment of Clinical Stage I, IIA, or IIB Disease or T3, N1, M0 (BINV-3)

[ee] Marking of sampled axillary nodes with a tattoo or clip should be considered to permit verification that the biopsy-positive lymph node has been removed at the time of definitive surgery.

[ff] Among patients shown to be node-positive prior to neoadjuvant systemic therapy, SLNB has a >10% false-negative rate when performed after neoadjuvant systemic therapy. This rate can be improved by marking biopsied lymph nodes to document their removal, using dual tracer, and by removing more than 2 sentinel nodes.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

How to incorporate SLN after NAC in cN+ patients in your practice

- Radiology / Surgery: Consider placement of marker in LNs at time of percutaneous LN biopsy
  - Consider localization of biopsy positive node prior to surgery
- Surgery: Use dual tracer technique
  - Resect all SLNs (blue, radioactive, palpably abnormal)
- Pathology: Assessment of response to therapy effect in LNs
  - Incorporate IHC on the SLNs
- Which patients to consider:
  - Good clinical and radiological response in breast and LNs

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Surgical Standards for Management of the Axilla in Breast Cancer Clinical Trials with Pathological Complete Response Endpoint

BASELINE	Clinical Node Negative	Clinical Node Positive
PRE-CHEMO	Axillary ultrasound, if sonographic abnormal LNs FNA or CNB No axillary surgery prior to chemotherapy	Axillary ultrasound, if sonographic abnormal LNs FNA or CNB Strongly recommend placement of clip in positive LN No axillary surgery prior to chemotherapy
POST-CHEMO (PRE-SURGERY)		Strongly consider localization of clipped node

AXILLARY SURGERY	SLN surgery	SLN surgery or ALND
SLN SURGERY APPROACH	Recommended use of dual tracer Resection of all radioactive nodes >10% of hottest node Resection of all blue nodes Resection of all palpably abnormal nodes Resection of at least 2 SLNs recommended	Require use of dual tracer Resection of all radioactive nodes >10% of hottest node Resection of all blue nodes Resection of all palpably abnormal nodes If no clip placed, resection of at least 2 SLNs required If Bx proven positive node clipped, ensure resection of the clipped node

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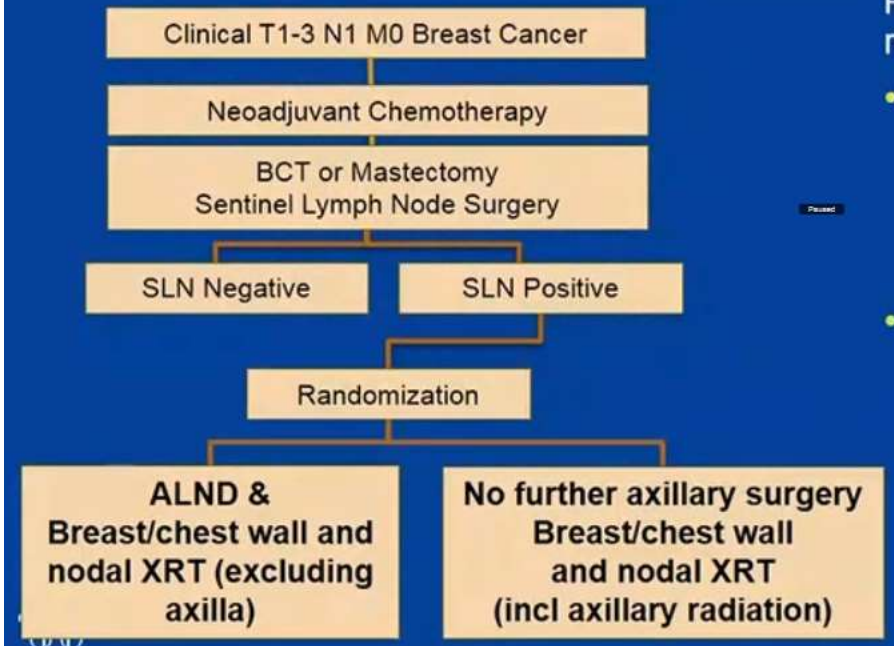
Slide 51

NPJ Breast Cancer. 2018 Aug 17;4:26. 2018

A011202 - A randomized phase III trial comparing axillary lymph node dissection to axillary radiation in breast cancer patients (cT1-3 N1) who have positive sentinel lymph node disease after receiving neoadjuvant chemotherapy



Primary endpoint: invasive breast cancer recurrence-free interval

- Arm 1
  - ALND – level I and II LNs
  - RT to the breast (BCS) or chest wall (mastectomy)
  - Regional nodal irradiation
    - level III LNs and supraclavicular fossa
- Arm 2
  - No ALND
  - RT to the breast (BCS) or chest wall (mastectomy)
  - Regional nodal irradiation
    - to level I, II, III LNs and supraclavicular fossa

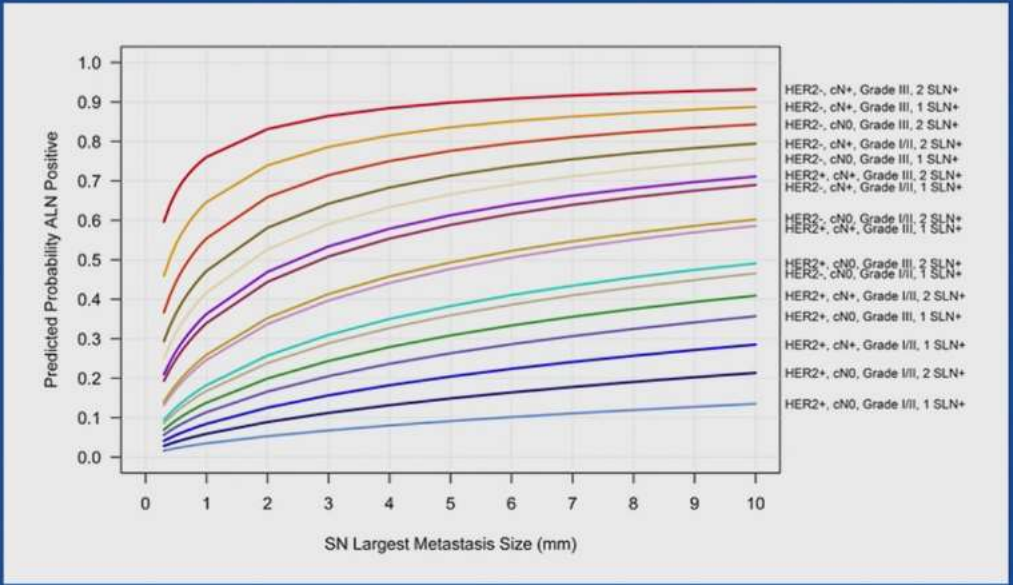
As of Dec 1 2018
Registered 1364/1576 (86.5%)

Positive SLN after NAC

- Additional nodal disease found in 50-63% with +SLN
- MDACC scoring system (n=104, 38 cN+)
  - LVI, method of detection of SLN metastasis, multicentricity, initial lymph node status, and pathologic tumor size
- S. Korea (n=140 cN+)
  - pathologic T stage, lymphovascular invasion, SLN metastasis size, and number of positive SLN metastases

Jeruss et al, Cancer 2008, 112(12): 2646-54
Ryu et al, Clin Breast Cancer 2017; 17(7): 550-8
Barron et al, ASO 2018 Oct;25(10):2867-2874

Risk of additional nodal disease in setting of positive SLN after NAC



120 patients, 58 cN+

- cN+ vs cN0
- Her2 – vs Her2+
- Tumor grade
- # +SLNs
- Size SLN metastasis

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Barron, Hoskin, Boughey. ASO 2018 Oct;25(10):2867-2874

Likelihood of additional positive nodes at ALND based on size of SLN metastasis

	ITCs	Micromets	Macromets
SN FNAC (all cN+)	4/7 (57%)	3/8 (37%)	34/61 (56%)
MSKCC (cN0 and cN+)	1/6 (17%)	28/44 (64%)	75/121 (62%)
Z1071	**4/11 (36.4%)**	**164/273 (60.1%)**	
OVERALL	**9/24 (37.5%)**	**31/52 (60%)**	**109/182 (60%)**

Boileau et al. JCO 2015 Jan 20;33(3):258-64
Moo et al. ASO 2018 Jun;25(6):1488-1494

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Role of IHC - Z1071 data

		SLN negative (n=186)	SLN positive ≤0.2mm (n=17)	SLN positive by H&E (>0.2mm) (n=267)	P value
Number of positive SLNs	Median (range)	0 (0-0)	1 (1-3)	2 (1 – 7)	<0.0001
Positive nodes on ALND		**27 (14.5%)**	**7 (41.2%)**	**161 (60.3%)**	<0.0001
Number of positive nodes on ALND	0	159 (85.5%)	10 (58.8%)	106 (39.8%)	<0.0001
	1	16 (8.6%)	3 (17.6%)	44 (16.5%)	
	2	11 (5.9%)	4 (23.5%)	116 (88.6%)	
Largest metastasis (SLN or ALN)	Median (range)	0.17 ± 0.49	0.41 ± 1.14	1.06 ± 0.88	<0.0001
LRR-free	HR (95% CI)	1.00 (ref)	1.89 (0.23-15.7)	2.86 (1.17-6.99)	0.070
	5 yr estimate (95% CI)	**96.0 (91.3 – 98.2)**	**91.7 (53.9-98.9)**	**91.0 (86.4-94.1)**	
BCSS	HR (95% CI)	1.00 (ref)	3.66 (1.30-10.33)	3.45 (1.90-3.28)	0.0002
	5 yr estimate	**94.1 (89.3–96.8)**	**88.2 (60.0 – 96.9)**	**81.6 (76.3-85.9)**	

Z1071 unpublished data

Positive SLN after NAC

- Risk of additional positive nodes is higher than in patients with upfront surgery
- Varies by:
  - cN stage, tumor biology (subtype & grade), # positive SLNs, LVI, breast response
- Consider A11202
- ALND standard of care outside of clinical trial

Overview

- Status of SLNB after NAC in cNo patients
- Management of cN+ axilla after NAC
  - How often is ALND avoided in cN+ patients after NAC?
  - Can we select ER+ subsets that have a better response to NAC?
  - Is axillary imaging a useful tool post-NAC to determine eligibility for SLNB?
  - Controversial indications for ALND after NAC
- What is the optimal strategy to avoid ALND in cNo patients?

Memorial Sloan Kettering Cancer Center.

SLNB Feasibility in cNo Patients after NAC

	Xing[1] 2006	Kelly[2] 2009	van Deurzen[3] 2009	Tan[4] 2011	Geng[5] 2016
No. of studies	21	24	27	10	16
No. of patients	1273	1799	2148	449	1456
IR (%)	**90**	**90**	**91**	**94**	**96**
FNR (%)	**12**	**8**	**10.5**	**7**	**6**

Identification rate similar with single-agent or dual-agent mapping

False-negative rate similar to upfront surgery setting

[1]Xing Y, Br J Surg, 2006;93:539
[2]Kelly A, Acad Radiol, 2009;16:551
[3]Van Deurzen C, Eur J Cancer, 2009;45:3124
[4]Tan V, J Surg Oncol 2011;104:97
[5]Geng C, PLoS One, 2016;11:e0162605

Decreased Nodal Positivity After NAC in cNo Patients

		n	Nodal positivity		P value
			Upfront surgery	NAC	
NSABP B-18		1097	48%	33%	<0.001
MDACC					
	T2	992	37%	21%	<0.0001
	T3	106	51%	30%	0.04

SLNB *after* NAC can decrease the likelihood of ALND

Fisher B, J Clin Oncol 1997;15:2483
Hunt K, Ann Surg 2009;250:558

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Outcomes of SLNB After NAC in cNo Patients

Although FNR similar to adjuvant setting, concerns for potential worse outcomes with SLNB alone after NAC due to possibility of leaving behind nodes with "chemo-resistant disease"

	n	Median F/U	Nodal recurrence
MD Anderson (2009)	575	47 months	1.2%
GANEA 2 (2018)	419	36 months	0.2%

Hunt K, Ann Surg 2009;250:558
Classe J, Breast Cancer Res Treat 2018 (Epub)

Management of the Clinically Node-Negative Axilla

- Sentinel lymph node biopsy should be performed *after* NAC
- Single agent or dual agent mapping
- High identification rate
- Acceptable false-negative rate

SLNB Feasibility in cN+ Patients after NAC

- 4 prospective, multi-institutional trials
- Primarily included cT1-3N1 patients
- SLNB ➔ back-up ALND

	ACOSOG Z1071	SN FNAC	SENTINA	GANEA 2
n	689	153	592 (cN+)	307
cTN	cT0-4 N1/N2	cT0-3 N1/N2	cN0/N1/N2	pN1*
IR	92.7%	87.6%	80.1%	79.5%
FNR (Overall)	**12.6%**	**13.3%**	**14.2%**	**11.9%**

The use of dual tracer and removal of ≥ 3 SLNs resulted in FNR < 10%

Boughey J, JAMA 2013;310:1455
Boileau J, J Clin Oncol 2015;33:258
Kuehn T, Lancet Oncol 2013;14:609
Classe J, Breast Cancer Res Treat 2018 (Epub)

How Often Are ≥ 3 SLNs Identified?

Use of SLNB in cN+ patients as a strategy to avoid ALND is appropriate if removal of ≥ 3 SLNs is feasible

Study	n	Removal of ≥ 3 SLNs
ACOSOG Z1071	651	57%
SENTINA	592	34%
Mamtani (2016)	**128**	**86%**

Boughey J, JAMA 2013;310:1455
Kuehn T, Lancet Oncol 2013;14:609
Mamtani A, Ann Surg Oncol 2016;23:3467

Optimizing the SLNB Procedure in cN+ Patients after NAC

Meta-analysis 13 studies

1921 cN+ patients (biopsy-proven)

SLNB/ALND after NAC

Pooled IR 90%

Pooled FNR 14%

FNR 11% (6%-15%) dual mapping

FNR 4% (0%-9%) (≥3 SLNs removed)

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Tee S, Br J Surg 2018;105:1541

Optimizing the SLNB Procedure in cN+ Patients after NAC

Meta-analysis 13 studies

1031 cN+ patients (biopsy proven)

None of the studies have reported benefit of nodal clipping with dual mapping and retrieval ≥ 3 SLNs

Pooled FNR 14%

FNR 11% (6%-15%) dual mapping

FNR 4% (0%-9%) (≥3 SLNs removed)

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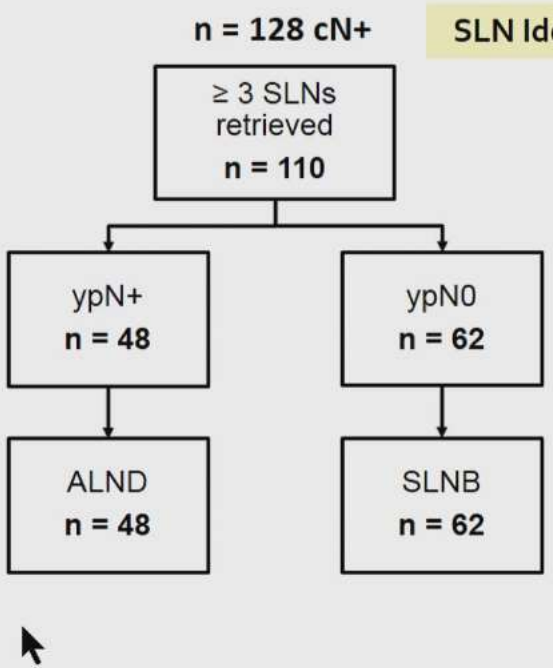
Tee S, Br J Surg 2018;105:1541

How Often Is ALND Avoided in cN+ Patients after NAC?



Mamtani A, Ann Surg Oncol 2016;23:3467 (Slide Courtesy of Mamtani A)

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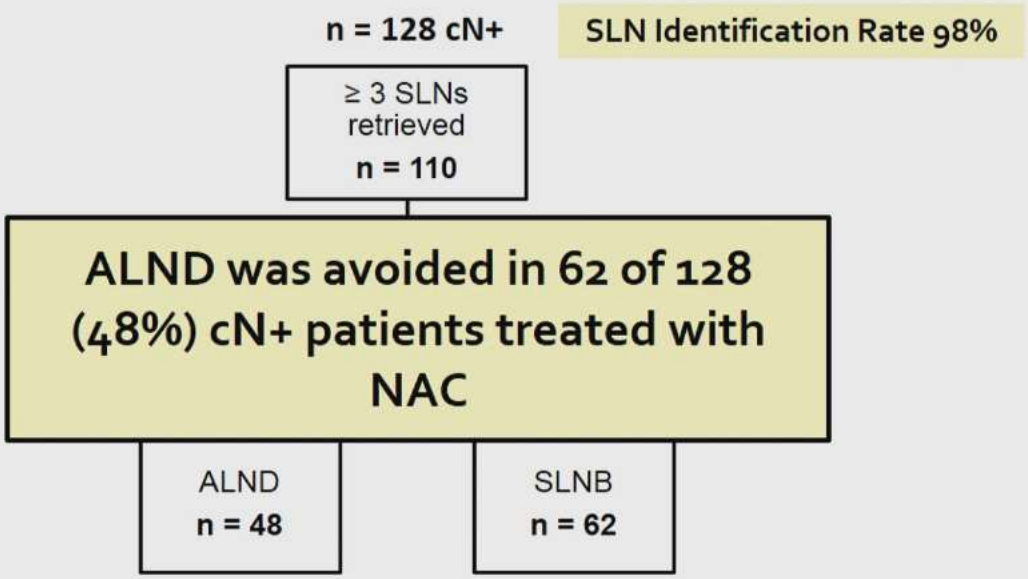
How Often Is ALND Avoided in cN+ Patients after NAC?



Mamtani A, Ann Surg Oncol 2016;23:3467 (Slide Courtesy of Mamtani A)

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Nodal pCR Varies by Receptor Subtype

Receptor Status	Nodal pCR (%)	
	ACOSOG Z1071 n = 694	MSKCC n = 195
All	41%	49%
HR+/HER2-	21%	21%
HER2+	65%	82%
Triple Negative	49%	47%

ACOSOG Z1071: 89% HER2+ patients received trastuzumab
MSKCC: 100% HER2+ received dual anti-HER2 therapy

Boughey J, Ann Surg 2014;260:608
Mamtani A, Ann Surg Oncol 2016;23:3467

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All	41%	49%
HR+/HER2-	**21%**	**21%**
HER2+	65%	82%
Triple Neg		%

Do all ER+ patients have similar response to NAC?

Boughey J, Ann Surg 2014;260:608
Mamtani A, Ann Surg Oncol 2016;23:3467

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Is There a Subset of ER+/HER2- Patients Likely to Benefit from NAC?

MSKCC
2007-2016
n = 402 ER+/HER2-
n = 301 (75%) cN+

Nodal pCR = 15%
16% (Ductal) vs 7% (Lobular), p = 0.09
Nodal pCR ↑ in PR-/high grade or poorly differentiated

Petruolo O, Ann Surg Oncol 2017;24:2446

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Is There a Subset of ER+/HER2- Patients Likely to Benefit from NAC?

Multivariable analysis of effect of pathologic characteristics on nodal pCR

Pathologic characteristics	Nodal pCR (OR)	P-value
Histology (lobular vs. ductal)	0.49	0.28
Differentiation (poor vs. well/moderate)	**2.67**	**0.014**
PR status (negative vs. positive)	1.89	0.08

Rates of nodal pCR by pathologic characteristics

Receptor/grade/differentiation	Nodal pCR	
	n	%
PR+/high or poor	16/117	14%
PR+/non-high or non-poor	8/98	8%
PR-/high or poor	**17/48**	**35%**
PR-/non-high or non-poor	0/29	0%

$P < 0.0001$

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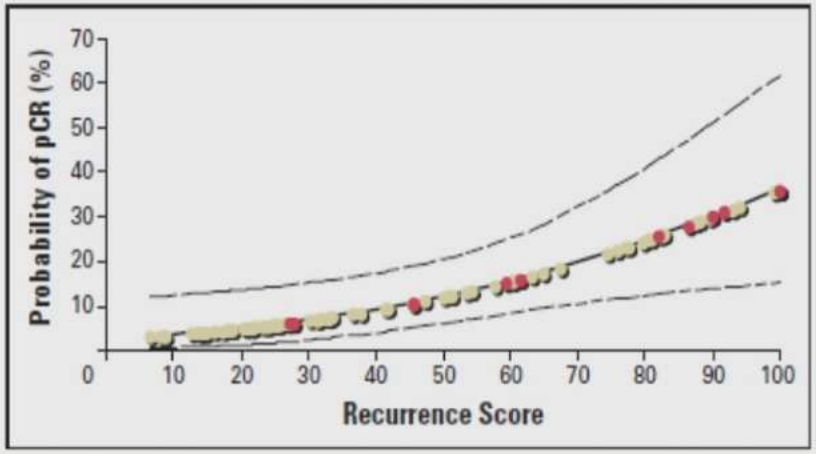
Petruolo O, Ann Surg Oncol 2017;24:2446

Can Oncotype be Used to Predict pCR in ER+ Patients Treated with NAC?

N = 89 patients with LABC
NAC = doxorubicin and paclitaxel
58% ER+



The probability of pCR increased with recurrence score (p = 0.005)

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Gianni L, J Clin Oncol 2005;23:7265

Is There a Subset of ER+/HER2- Patients Likely to Benefit from NAC?

PR- and/or poorly differentiated/high-grade features select patients with best response to NAC

pCR uncommon in node-positive lobular cancers or non-high-grade ductal cancers

What Are Nodal Recurrence Rates in cN+ Patients Treated with SLNB Alone after NAC?

Galimberti V et al
n = 147 cN1/N2
70 SLN negative after NAC, SLNB alone
Median f/u 61 months
No nodal failures

Nguyen TT et al
n = 430 cN1
n = 93 SLNB alone (88% SLN negative)
Median f/u 9 months
No nodal failures

Galimberti V, Eur J Surg Oncol 2016;41:361
Nguyen T, Ann Surg Oncol 2018;25:2596

MSK Approach to the Clinically Node-Positive Axilla after NAC

- cT1-3N1 breast cancer eligible for SLNB after NAC if convert to cNo
- SLNB performed with dual tracer mapping
- Do not require retrieval of clipped node
- Require retrieval of at least 3 SLNs to minimize false-negative rate

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Selecting cN+ Patients for SLNB after NAC

1. Physical exam

2. Imaging

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Is Palpable Adenopathy after NAC an Indication for ALND?

SN FNAC
n = 153 cN+
n = 19 palpable adenopathy after NAC
PPV 89% (17/19)

MSKCC cohort
n = 155 biopsy-proven cN1
n = 23 palpable adenopathy after NAC
PPV 78% (18/23)

Boileau J, J Clin Oncol 2015;33:258
Mamtani A, Ann Surg Oncol 2016;23:3467

Is Palpable Adenopathy after NAC an Indication for ALND?

Palpable nodes not all the same

If nodes clinically suspicious and poor response to NAC in breast → ALND

Doubt → needle biopsy post-NAC
→ SLNB

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Should Axillary Imaging Be Performed after NAC to Determine Eligibility for SLNB?

SN FNAC

n = 129 AUS + pathology

NPV = 48% (36/75)

PPV = 81% (44/54)

Accuracy = 62%

ACOSOG Z1071

n = 611 AUS + available pathology

n = 430 normal AUS, 57% pN+

n = 181 abnormal AUS, 72% pN+

If patients with abnormal AUS triaged to ALND, **28%** of patients would receive unnecessary ALND

Boileau J, J Clin Oncol 2015;33:258
Boughey J, J Clin Oncol 2015;33:3386

Should Axillary Imaging Be Performed after NAC to Determine Eligibility for SLNB?

MSKCC
n = 129 breast cancer patients
Pre- and post-NAC MRI

Axillary node status on MRI	pN- (n = 80)	pN+ (n = 49)
Normal pre- and post NAC (n = 32)	81%	19%
Abnormal pre-NAC, normal post-NAC (n = 50)	68%	32%
Abnormal pre- and post- NAC (n = 47)	43%	57%

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Weber J, J Am Coll Surg 2017;225:740

Should Axillary Imaging Be Performed after NAC to Determine Eligibility for SLNB?

Axillary imaging likely not a useful tool post-NAC as it can not reliably predict the status of the axilla

Abnormal axillary imaging post-NAC should not be used to triage patients directly to ALND

Controversial Indications for ALND

1. Locally advanced breast cancer
2. Low-volume disease in the SLN
3. Absence of treatment effect in the SLN

Can SLNB Be Performed in cT4 or cN2/N3 Disease after NAC?

Stearns V et al
n = 8 inflammatory breast cancer
IR = 75%
FNR = 25%

Hidar S
n = 20 inflammatory breast cancer
IR = 80%
FNR = 18%

DeSnyder SM
n = 16 inflammatory breast cancer
IR = 25% (limited FNR assessment)

Stearns V, Ann Surg Oncol 2002;9:235
Hidar S, Int J Surg 2009;7:272
DeSnyder S, Clin Breast Cancer 2018;18:e73

Can SLNB Be Performed in cT4 or cN2/N3 Disease after NAC?

ACOSOG Z1071

n = 33 cT4
FNR not specified for cT4

n = 38/701 cN2
n = 26 at least 2 SLNs removed
pCR = 46%
FNR: 0% (95% CI: 0%-23.2%)

SN FNAC

n = 10/153 cN2
FNR: 0% (0/4)

SENTINA

FNR not assessed for cN1 and cN2 separately

Boughey J, JAMA 2013;310:1455
Boileau J, J Clin Oncol 2015;33:258
Kuehn T, Lancet Oncol 2013;14:609

Nodal pCR Similar in LABC Compared to Non-LABC

MSKCC prospective neoadjuvant database
195 cN+(biopsy proven)
n = 40 cT4 or cN2/3
n = 155 cN1

	cT4 or cN2/N3 N= 40	cN1 N = 155
Nodal pCR	45%	50%

p = 0.5

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Mamtani A, Ann Surg Oncol 2016;23:3467

Tumor Biology Predicts Response to NAC in Locally Advanced Breast Cancer

n = 321 (2006-2016)
cT_4 and/or cN_2/N_3
All HER2+ patients received HER2 targeted therapy

	Nodal pCR	
Receptor Subtype	**n**	**%**
All	**310**	**38**

Nodal pCR: 43% (cN1) vs. 36% (cN2) vs. 32% (cN3) (p = 0.23)

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Gentile L, Ann Surg Oncol 2017;24:3896

Protocol 17-384: Sentinel Lymph Node Biopsy after Neoadjuvant Chemotherapy in Patients Presenting with Locally Advanced Breast Cancer: A Prospective Study

- Eligibility:
  - Female breast cancer patients
  - cT4 and/or cN2/N3 treated with NAC
  - Clinically node negative after NAC
- Design:
  - Single-arm prospective trial
  - Eligible patients undergo SLNB with dual tracer mapping, followed by completion axillary dissection
  - Attempt to retrieve ≥ 3 SLNs
- Primary Objective:
  - Prospectively determine false-negative rate of SLNB after NAC in locally advanced breast cancer patients

PI: Andrea V. Barrio; Co-PI: Monica Morrow

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Is ALND Needed for Low- Volume Disease in the SLN after NAC?

Patients having upfront surgery → volume of disease in SLN predictor of additional disease in non-SLN

Micrometastases or isolated tumor cells in SLN
10-20% risk of additional non-SLN metastases

MSKCC
pN1mic (n = 254): 20% non-SLN mets
pNoi+ (n = 250): 12% non-SLN mets

Cserni G, Br J Surg 2004;91:1245
van Deurzen C, J Natl Cancer Inst 2008;100:1574
Kumar S, Ann Surg Oncol 2010;17:2909

Is ALND Needed for Low- Volume Disease in the SLN after NAC?

July 2008-July 2017
n = 711 SLN procedures after NAC
Overall FNR of frozen section: 6.2%

76% of false negatives were micromets or ITCs

Moo T, Ann Surg Oncol 2018;25:1488

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Is ALND Needed for Low- Volume Disease in the SLN after NAC?

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pN1mic (n = 254): 20% non-SLN mets
pNoi+ (n = 250): 12% non-SLN mets

Cserni G, Br J Surg 2004;91:1245
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Moo T. Ann Surg Oncol 2018:25:1488

Is ALND Needed for Low- Volume Disease in the SLN after NAC?

July 2008-July 2017
n = 711 SLN procedures after NAC
Overall FNR of frozen section: 6.2%

Is return to OR for ALND necessary?

76% [illegible] Cs

Moo T, Ann Surg Oncol 2018;25:1488

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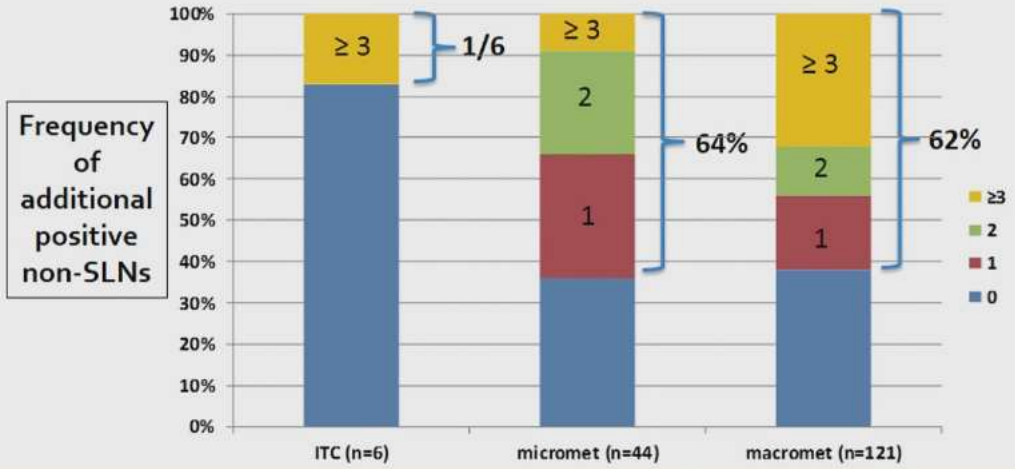
Is ALND Needed for Low- Volume Disease in the SLN after NAC?



Approximately 1/3 of NSLN metastases were macromets

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Moo T, Ann Surg Oncol 2018;25:1488 (Slide Courtesy of Moo T)

Is ALND Needed for Low- Volume Disease in the SLN after NAC?

ALND is indicated for low-volume disease in the SLN, even when not initially seen on FS, due to high likelihood of additional non-SLN disease

Is the Absence of Treatment Effect in the Nodes an Indication for ALND?

n = 528 biopsy-proven N+

n = 204 ypNo after NAC

Treatment effect in nodes identified in **192 (94%)** patients

	ALND (n = 135)		SLNB (n = 69)		P-value
	n	%	n	%	
Treatment effect	131	97	61	88	0.02

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Barrio A, Ann Surg Oncol 2016;23:3475

Is the Absence of Treatment Effect in the Nodes an Indication for ALND?

Characteristic		n	Treatment effect	No treatment effect	P-value
Tumor subtype	HR+/HER2-	30	**83%**	**17%**	0.05
	Triple neg	55	96%	4%	
	HER2+	119	96%	4%	
Breast pCR (pT0/is)	Yes	141	97%	3%	0.05
	No	63	**89%**	**11%**	

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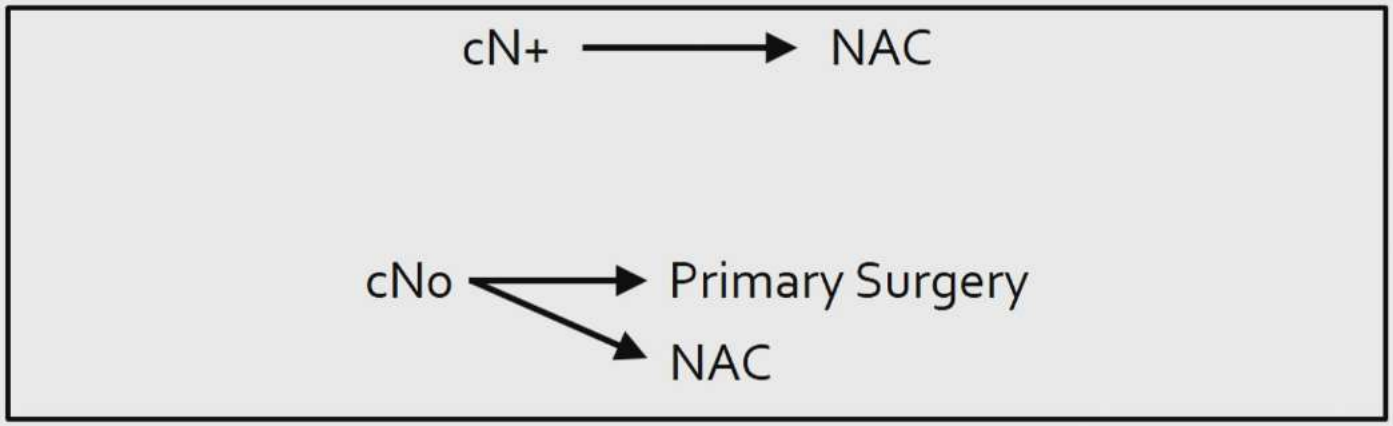
Barrio A, Ann Surg Oncol 2016;23:3475

Is the Absence of Treatment Effect in the Nodes an Indication for ALND?

The absence of treatment effect in the SLN is not an absolute indication for ALND, and may occur due to biologic differences in tumor response

What Is the Optimal Strategy to Avoid ALND in cNo Patients?



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Rates of ALND by Type of Surgery and Tumor Subtype

1944 cT1-2N0

Subtype	Upfront BCS n = 669	NAC n = 271	P value
HR+/HER2-	**15%**	**34%**	**<0.001**
HER2+	13%	8%	0.26
HR-/HER2-	14%	7%	0.26

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Pilewskie M, Ann Surg Oncol 2017;24:3527

Rates of ALND by Type of Surgery and Tumor Subtype

1944 cT1-2N0

Subtype	Upfront mastectomy n = 1004	NAC n = 271	P value
HR+/HER2-	37%	34%	0.62
HER2+	**36%**	**8%**	**<0.001**
HR-/HER2-	**25%**	**7%**	**0.001**

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Pilewskie M, Ann Surg Oncol 2017;24:3527

Rates of ALND by Type of Surgery and Tumor Subtype

1944 cT1-2N0

Multivariable analysis assessing likelihood of ALND

	Odds Ratio	P value
NAC vs. BCS (ER+/HER2-)	3.35	<0.001
NAC vs. mastectomy (HER2+)	0.19	<0.001
NAC vs. mastectomy (ER-/HER2-)	0.25	0.007

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Pilewskie M, Ann Surg Oncol 2017;24:3527

Summary

- SLNB is accurate in cNo patients and in cN+ patients if ≥3 SLNs retrieved, and reduces need for ALND
- Axillary imaging post-NAC unnecessary, as it cannot reliably predict status of the axilla
- Low-volume disease in the SLN *is* an indication for ALND
- The optimal strategy to avoid ALND in cNo patients is based largely on tumor subtype and type of breast surgery