

### Management of the Axilla in 2023

From ALND to SLNBx to None?

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# Disclosures: Endomag



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Local-regional Treatment of Breast Cancer Has Become Progressively

> Less drastic More focused More conservative More precise Less morbid



# William Halsted: The Radical Mastectomy: 1890s







**Compared to breast amputation** 

Halsted performed a meticulous, almost bloodless operation; and reduced the operative mortality from 18% to 2%.

He improved 3-year disease free survival from 4.7% to 42.4%.

The results of operations for the cure of cancer of the breast performed at the Johns Hopkins Hospital from June, 1889 to January, 1894. Johns Hopkins Hospital Bulletin, 4:297, 1894-95

By William S. Halsted, M.D.

## Jerome Urban: The Extended Radical Mastectomy



### Is an even bigger operation better?



Urban JA. Cancer 1951;5:992-1008

## Internal Mammary Node Resection: The Milan Trial

737 patients 1964-68 Randomized to RM vs ERM No systemic rx 30 yr f/u No survival difference





Veronesi et.al. Eur J Cancer 1999;35:1320-1325

# Bernard Fisher: The NASBP and the Alternative Hypotheses

#### "Halstedian"

Tumor spread is orderly

Nodes are barriers

Breast cancer is a loco-regional disease

Extent/nuances of surgery dominate outcome

#### "Alternative" (Fisher)

Tumor spread is disorderly Nodes are not barriers



Breast cancer is a systemic disease "Variations in locoregional therapy are unlikely to substantially affect survival"



### **NSABP B-04**





## NSABP B-04 Influence of Nodal Treatment on Survival



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Fisher B, NEJM 2002;347:567

### **NSABP B-04 Results**

Variations in extent of surgery did not affect survival; No survival advantage for immediate ALND

Less than 50% of patients with positive nodes left behind at the initial surgery developed a nodal recurrence

40% in radical mastectomy group 18.5% in total mastectomy group

#### **Axillary recurrence**

75% within 2 years 67/68 underwent successful delayed ALND

#### **Paradigm shift:**

Not all residual/unresected disease becomes clinically significant Metastatic progression not dependent on regional spread Radical surgery may not be better

#### Axillary node status was the single most important prognosticator

Axillary surgery was mainly for staging, perhaps for local control, and probably not for survival

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# A New Operation: Sentinel Lymph Node Biopsy



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# **Sentinel Lymph Node Biopsy Origins**





Morton DL et.al. Arch Surg 1992;392-99 SLNB for

melanoma, blue dye

Krag DN et.al. Surg Oncol 1993;2:335-40 SLNB for breast, isotope Giuliano AE et.al. Ann Surg 1994;220:391-401 SLNB for breast, blue dye

Albertini JJ et.al. JAMA 1996;276:1818-22 SLNB for breast, blue dye + isotope



## Sentinel Node Biopsy Early Concerns

Can we do it? For whom? How? Is it accurate? Is the morbidity less? Is it safe? short term? long term?





## SLNBx is Feasible 69 observational studies in 8059 patients

# pts	SLN found	SLN false-neg (SLN-/AX+)	Accuracy (SLN correct/total)
8059	96%	7%	97%



Kim T et.al. Cancer 2006;106:4-16

### **NSABP B-32**





# NASBP B-32 DFS: SLN Negative (8 yr Results)



Krag, DN et.al. Lancet Oncology 2010;11:927-33z

# NSABP B-32 OS: SLN Negative (8 yr Results)



Krag, DN et.al. Lancet Oncology 2010;11:927-33z

# There was NO survival benefit to complete ALND in women with negative SLNs

# There was no benefit from the identification of occult tumor cells in H&E negative SLNs



### Sentinel Node: Spectrum of Micrometastases





"Classic" 2 mm micromet (pN1mi) 4,000,000 cells? IHC-positive micromet (pN0i+) 1 cell?



## Z0010: Survival by IHC

Method	H&E negative	H&E positive	IHC negative	IHC positive
	(3945/5184)	(1239/5184)	(3595)	(350)
5 year survival (95% CI)	95.6% (95.0-96.3)	92.8% (91.3-94.3) p=0.0002	95.8% (95.0-96.5)	95.1% (92.7-97.5) p=0.53

### **5 Randomized Trials of SLN Biopsy**

Trial	# pts	SLN found	SLN false- negative	Accuracy
EIO	532	99%	9%	97%
B-32	5611	97%	10%	97%
ALMANAC	836	96%	7%	98%
GIVOM	749	95%	17%	95%
SNAC	1088	94%	5%	98%

61-73% had SLN-only disease







# Sentinel Node Biopsy Sensory Morbidity (18 sensations)





Temple LK, Ann Surg Oncol 2002;9:654-62

# Sentinel Node Biopsy Morbidity/lymphedema

Outcome 5 yr median f/u	SLNB n=600	SLNB/ALND n=336
Lymphedema measured	5%	16%
Lymphedema reported	3%	27%

Lymphedema was related to

- a) Weight
- b) BMI
- c) H/o trauma
- d) H/o infection

NYU Grossman Long Island School of Medicine Lymphedema present in

- a) 41% of pts who reported arm swelling
- b) 5% of patients reporting no arm swelling

# De-escalation No ALND for SLN+ Patients



# Sentinel Node Biopsy False-negative > Axillary LR

	# pts	# axillary LR (%)	median f/u
SLN-/no ALND 48 series*	14,959	0.3%	3 yr
SLN-/no ALND IEO (RCT)	167	1.2%	8 yr
SLN-/no ALND B-32 (RCT)	2011	0.7%	8 yr

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\*all with >3 yrs follow up

### **Time Course of Axillary LR**



Meta-analysis of 48 studies

14,959 SLN-negative pts

Axillary LR in 67 (0.3%)

34 mo median f/u

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van der Ploeg IMC, et.al. EJSO 2008;34:1277-84



# Do patients undergoing breast conserving therapy who have 1 or 2 positive SLNs require ALND?

## **Does omitting ALND after a positive sentinel node biopsy decrease patient survival?**



### Z0010-Z0011 Trials (ACOSOG)



suspended 12/04 at n=889 due to slow accrual and too few events



www.acosog.org



### **Eligible**

Clinical T1-2N0 breast cancer

H&E-detected SLN metastases

Lumpectomy + whole breast RT

Adjuvant systemic therapy by choice

### **Ineligible**

Nodal RT

IHC-detected SLN metastases

Matted nodes

3 or more involved SN



Giuliano AE et.al. Ann Surg 2010;252:439

### **Z0011 Patient and Tumor Characteristics**

	SLN+/ALND (n=420)	SLN+/no ALND (n=436)
Median age	56 (24-92)	54 (25-90)
cT1	68%	71%
ER+/PR+	83% / 68%	83% / 70%
LVI+	41%	36%



### **Z0011 Patient and Tumor Characteristics**

	SLN+/ALND	SLN+/no ALND
Grade 1	22%	26%
Grade 2	49%	47%
Grade 3	29%	28%
IDC	83%	84%
ILC	7%	9%
Other Histology	11%	8%



### **Z0011 Systemic Therapy**

Systemic Therapy	SLN+/ALND	SLN+/no ALND
Chemotherapy	58%	58%
Hormonal	46%	47%
Chemo and/or Hormonal	96%	97%



### **Z0011 Locoregional Recurrence**

Recurrence @ 6.3 yrs median follow- up	SLN+ ALND (n=388)	SLN+ no ALND (n=425)
Local	3.6%	1.9%
<b>Regional</b> (Ax, Supraclav, IM)	0.5%	0.9%
Local+Regional	4.1%	<b>2.8%</b> p=0.47

Additional positive nodes in 27% of ALND's



### Z0011 and RT

Radiation field design	SLNB arm n=124	SLNB+ALND arm n=104
Tangents only	83%	79%
Proportion high tangents*	53%	50%
Supraclavicular field	17%	21%
Posterior axillary boost	10%	6%

\*sufficient records to determine field height



Jagsi R et.al. JCO 2014;32:385-93

### **Z0011 Overall Survival**





Giuliano AE et.al. JAMA 2011;305:569-75
Median f/u 6.3 yrs		<u>Median f/u</u>	<u>Median f/u 9.25 yrs</u>		
<u>ALND</u>	<u>SN</u>	ALND	<u>SN</u>		
0.5%	0.9%	0.5%	1.1%		
p =	0.45	p = 0	.45		

#### **10 yr Cumulative Nodal Recurrence**

0.5% ALND	1.5% SN	p = 0.28
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#### One axillary recurrence after initial 6 yrs



Giuliano A, Ann Surg 2016;264:413-20

#### **Z0011 Surgical Morbidity:** Why Not Do an Axillary Dissection?

	SLNBx%	ALND%	p-value
Wound Infection	3	8	0.0016
Axillary Paresthesia	9	39	<0.0001
Lymphedema: Patient Perceived	6	19	<0.0001
Lymphedema: Measured	6	11	0.0786





#### **ACOSOG Z0011 Conclusions**

#### For women with cT1-2N0:

### ALND was unnecessary (not inferior) in women with 1 or 2 positive sentinel lymph nodes

As long as the lymph nodes were not:

- grossly positive
- matted
- with extra-capsular extension

### If they planned to be treated with lumpectomy and whole breast radiotherapy



### So, Can ALND Be Safely Omitted In SLN+ Patients?

Should we change our treatment on the basis of one study? Well ...



#### Use of ALND - NCDB 1998-2005 (Note: Z-11 Results Reported in 2011)



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Bilimoria KY et.al. JCO 2009;27:2946-53

#### Outcome +/- ALND (NCDB)

	Axillary local recurrence	5 yr relative survival
SLN n	n <mark>icrometastases (</mark> <	2 mm)
SLN only (n=802)	0.4%	99%
SLN+ALND (n=2357)	0.2%	98%
SLN m	nacrometastases (>	2 mm)
SLN only (n=5596)	1.0%	90%
SLN+ALND (n=22591)	1.1%	89%



### **IBCSG 23-01**



#### IBCSG trial 23-01 SLN *micromet*/no ALND

cN0, T1-2, SLN micromets (<2 mm)

#### Randomize to ALND (n=464) vs no ALND (n=467)

95% had 1 SLN+ 91% had BCT (98% with RT)

#### Additional positive nodes in 13% of ALND



Galimberti V et.al. Lancet Oncol 2013;14:297-305

#### IBCSG trial 23-01 SLN *micromet*/no ALND

Event at 10 years	ALND n=464	No ALND n=467
Local	3%	3%
Regional	1%	2%
Distant	10%	9%
Death	13%	10%



Galimberti V et.al. Lancet Oncol 2018; 19: 1385-93



### IBCSG trial 23-01 SLN *micromet*/no ALND

#### Axillary LR at 10 yrs

2% for mastectomy (2/86)

<1% for BCT (7/845)

5/7 axillary LR had partial breast RT

Galimberti V et.al. Lancet Oncol 2018; 19: 1385-93

## Numerous Other Studies Have Also Replicated These Findings



#### SLN micromet/no ALND

2001-2010	# pts	BCT (%)	follow-up (mo)	axillary LR
SEER	1767	79%	50	0.1% (2)
NCDB	530	81%	64	0.6% (3)
Z0011	160	100%	76	0.9% (1)
6 series	526 (63-157)	60-84%	30-76	0.4% (2)
17 series	412 (4-50)	49-100%	14-79	0.5% (2)
TOTAL	3395	44-100%	42	0.3% (10)



Francissen CMTP et.al. Ann Surg Oncol 2012;19:4140-49

#### SLN macromet/no ALND

2003-2010	# pts	BCT (%)	follow-up (mo)	axillary LR
SEER	1473	79%	50	0.2% (3)
NCDB	1458	81%	79	1.2% (18)
Z0011	199	100%	76	0.9% (2)
5 series	113 (11-39)	60-100%	30-58	1% (1)
8 series	25 (1-7)	29-92%	30-47	0
TOTAL	3268	29-100%	43	0.7% (24)



Francissen CMTP et.al. Ann Surg Oncol 2012;19:4140-49

#### Axillary Management in cT1-2N0 Patients Undergoing BCT

Patients with 1-2 (?3) + SLNs (without gross extracapsular extension) should NOT undergo cALND

Role of axillary US + FNA/core which identifies a solitary +LN needs to be evaluated in the context of the use of neoadjuvant chemotherapy

Role of frozen section evolving but confirmation of multiple + LNs useful



Z0011 for non-Z0011 Patients?

# Can the policy of "SLN+/no ALND" be extended to patients outside the Z0011 criteria?

Mastectomy without RT?

Partial breast RT?

Neoadjuvant chemotherapy?



### **Z0011 for Mastectomy?**



#### SLNB "Z0011 for mastectomy" trials

Trial	Mastectomy %	Status	ALND+	Axillary LR 10 yr
Z0011	0	complete	27%	1.5%
IBCSG	9%	complete	13%	2%
AMAROS	15%	complete	33%	1.8%*
SENOMAC	ns	accruing	35%	-
POSNOC	ns	accruing	-	-
BOOG 2013- 07	100%	closed (slow accrual)	-	-



\*results for BCT+mastectomy+nodal RT

## Axillary Management in Patients Undergoing a Mastectomy

- For patients with the delayed recognition of SLN metastasis decision to perform ALND influenced by
- Burden of disease
- Likelihood of additional involved nodes by nomogram
- Plan for post-mastectomy XRT

#### **Consensus acceptance will be unlikely**

RCTs of "Z0011 for mastectomy" will be difficult Prospective well-characterized cohort studies may be informative



#### Sloan-Kettering - Breast Nomogram - Microsoft Internet Explorer



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Memorial Sloan-Kettering Cancer Center

#### Breast Cancer Prediction Tool



# Can Radiation Replace Surgery?



## AMAROS Trial After Mapping of the Axilla: Radiotherapy Or Surgery?





#### Stratification: institution Adjuvant systemic therapy by choice



#### AMAROS: Axillary Recurrence



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Donker M et.al. Lancet Oncol 2014;15:1303-10

#### AMAROS: DFS and OS





Donker M et.al. Lancet Oncol 2014;15:1303-10

#### AMAROS: Lymphedema (clinical observation)



Years after randomization



Donker M et.al. Lancet Oncol 2014;15:1303-10

#### Z0011 and AMAROS: Conclusions

#### if SLN negative, SLNBx is sufficient

for almost all cT1-3N0 patients

#### if SLN positive, SLNBx is sufficient

if Z0011 eligible: cN0 and 1-2 SLN+ and BCT/WBRT if AMAROS eligible: cN0 and 1-3 SLN+ and BCT or mastectomy

cN0 = normal to palpation!





#### **1-3 SLN+ (pN1) were eligible BUT** 95% had 1-2 SLN+

#### **BCT or mastectomy were eligible BUT** 85% had BCT



#### SLNB+ 4 trials of ALND vs none

	IBCSG 23-01	ACOSOG Z0011	AMAROS	OTOASOR
experimental arm	SN only	SN only	SN + RT	SN + RT
additional N+	13%	27%	33%	39%
axillary recurrence at 10 yrs	2%	1.4%	1.8%	1.7%
riangle DFS, OS	No	No	No	No
			Galimbe	erti V, Lancet Oncol 2



Galimberti V, Lancet Oncol 2018;19:1385 Giuliano A, JAMA 2017;318:918 Rutgers E, SABCS 2018 Savolt A, Eur J Surg Oncol 2017;43:672

#### **Z0011 for non-Z0011?**

# Can the policy of "SLN+/no ALND" be extended to patients outside the Z0011 criteria?

Abnormal axillary imaging?

Mastectomy (without RT)?

cN+ axilla?

Neoadjuvant chemotherapy?



### **Z0011 for Partial Breast Irradiation?**



#### **PBI: Some Caveats**

#### **PBI** is usually limited to node-negative cancers

Axillae staged by SLNB and/or ALND

#### "First event" reporting underestimates event rates But, event rates to date are very low

SLN negative/no ALND: axillary LR <<1% SLN positive/no ALND: axillary LR <1%



#### **PBI Trials**

	Follow Up	Node Neg.	Ax LR #	Ax LR %
Mammosite Registry n=1449	59 mo	97%	10	0.79%
TARGIT RCT n=1113	60 mo	83%	4	0.35%



Ann Surg Oncol 2011; 18: 3415 Lancet 2013; 383: 603-613

#### **PBI: The Issues**

#### Were the good results in Z0011 due to WBRT?

89% received WBRT (11% no RT)
18.9% received RT using ≥ 3 fields
15% received supraclavicular RT
50% had high tangents used
Distribution for all techniques equivalent in both arms

#### If so, is PBI really safe?

Unlikely to be evaluated in RCTs Prospective well-characterized cohort studies may be informative



**Z0011 for Patients Receiving Neoadjuvant Chemotherapy?** 

### no ALND for N+ pN0 post neo?



#### B-18 and B-27 Update: Survival, DFS, RFS



### No difference between pre- and post-op chemo

Rastogi P et.al. JCO 2008;26:778-85

#### Neoadjuvant Meta-analysis Survival +/- pCR



12 trials, 11955 patients

#### Cortazar P et.al. Lancet 2014;384:164-172
#### NSABP B-18 Rate of Breast Conservation

Tumor Size	Surgery First	Chemo First
	% BCT	% BCT
T1	79%	81%
( <b>≤2.0 cm</b> )		
T2	63%	71%
(2.1-5.0 cm)		
Т3	8%	22%
(>5 cm)		
All patients	60%	67%
		p=0.002



#### NSABP B-18 Axillary Node Downstaging

	Surgery First	Chemo First
	(n=743)	(n=735)
1-3 Nodes+	30%	24%
4-9 Nodes+	17%	12%
>10 Nodes+	10%	4%
<b>Overall Node+</b>	57%	41%
		p<0.001



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

### Axillary Downstaging: Results of 4 Trials



\*Assuming 30% nodal down-staging with neoadjuvant AC

Mamounas EP, NCI State of the Science

#### SLN Biopsy After Neoadjuvant Chemotherapy

Review of 27 studies	SLN Found	SLN False Negative (SLN-/axilla+)
2148 patients*	90.5%	10.5%
2000-2009	(88-92)	(8-14)

Review of	SLN	SLN	Pathologic
8 studies	found	false-neg	CR (axilla)
2007-2015	92%	15%	37%
	(91-94)	(13-18)	(34-40)



van Deurzen CHN et.al. Eur J Cancer 2009;45:3124-30 van Nijnatten TJA et.al. Eur J Surg Oncol 2015;41:1278-87

#### SLN Biopsy NSABP B-27 vs B-32

	# pts	SLN Found	SLN False-Neg
B-27* SLN biopsy <i>after</i> chemo	428	89%	10.7%
B-32** SLN biopsy upfront	720	97%	9.7%

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\*JCO 2005;23:2694-2702 \*\* Lancet Oncol 2007;8:881-8



#### **SENTINA**

#### **SN FNAC**

#### **GANEA 2**



## Neo trials N+ upfront, SLNBx/ALND post-NAC

	ACOSOG 1071 n=663	SENTINA n=360	SN FNAC n=153	GANEA 2 n=307
# SLN examined	Fals	se negative ra	ate (SLN-/Axil	la+)
1	31%	24%	18%	19%
2	21%	19%		
<u>&gt;</u> 3	9%	5%	5%	8%
Mapping				
Single agent	20%	16%	16%	ns
Dual agent	11%	9%	5%	ns



Kuehn T et.al. Lancet Oncol 2013;14:609-618 Boileau J-F et.al. JCO 2014;33:258-64 Classe J-M et.al. BCResTreat 2019;173:243-52

## Neo trials Axillary US post-NAC Instead of SLNBx? No!

post neoadjuvant axillary US vs path	ACOSOG 1071 (pN+ on entry)	SENTINA (cN+ on entry)	SN FNAC (pN+ on entry)
US false negative	<b>56%</b>	50%	47%
(US-/axilla+)	(243/430)	(296/595)	(39/83)
US false positive	28%	23%	19%
(US+/axilla-)	(57/181)	(27/120)	(10/54)

"the diagnostic accuracy of US... following neoaduvant systemic therapy is unacceptably low"\*



Boughey J. JCO 2015;33:3386-93 Schwentner L. The Breast 2017;31:202-7\* Boileau J-F et.al. JCO 2014;33:258-64

## SLN biopsy *alone* N+ upfront, neo, SLN-/no ALND

Center	SLN neg/no ALND #	median follow up months	axillary local recurrence
Мауо	139	34	0.7% (1/139)
IEO/Milan	123	110	1.6% (2/123)
MSKCC	234	40	0.4% (1/234)*
NCI/Milan	81	87	0% (0/81)

Piltin MA et.al. ASO 2020; 27: 4795-4801 Ribeiro-Fontana SK et.al. EJSO 2021; 47: 804-12 Barrio AV et.al. JAMA Oncol 2021; 7: 1851-55 Martelli G et.al. Ann Surg 2022; 276: 554-552



#### **Two Neoadjuvant RCTs: Results Still Unavailable**



cN+ axilla: a Prospective Study at MSKCC

> Z0011 extended to cN+ cT1-2N1, upfront BCT ER+/her2-≤ 2 susp nodes on US ALND only for >2 SLN+

## Primary: what proportion avoided ALND? Secondary: LRR, DFS



## Sequencing of Treatment - BCT Upfront Surgery vs Neoadjuvant? Rate of cALND

subtype	upfront BCT MSKCC 2010-2015 n=669	neoadjuvant MSKCC 2009-2016 n=271
ER/PR+/her2-	15%	34% (p<0.001)
her2+	13%	8%
triple negative	14%	7%

for patients who can have BCT and are ER/PR+/her2-, a Z0011 strategy of upfront surgery minimizes the rate of ALND



Pilewskie, M et.al. Ann Surg Oncol 2017 epub July 31

## **Z0011 for Patients Receiving Neoadjuvant Chemotherapy?**

#### **Present evidence for SLNBx post-NAC is sufficient**

Success rate *somewhat lower* than SLNB in general False negative rate *comparable* to SLNB in general

- Technique matters!
  - Remove >1 SLN
  - Map with dye + isotope
  - TAD

- But +SLN after NAC should proceed to cALND



# SLNBx should NOT be used in Inflammatory Breast Cancer

Limited data bec not expected to work base on disease

#### Small MDACC trial, SLNBx only successful in 25% of pts dual tracer used preop imaging could not predict success



DeSnyder S Clin Breast Ca 2018; Feb 18(1): e73

# Moving on Can We Omit SLNBx Entirely?



## Sentinel Node Bx Is FNR (SLN-/axilla+) meaningful?

#### positive nodes left behind

if	FNR 5%	FNR 10%
N+ = 10%	0.5% (5% of 10%)	1%
N+ = 20%	1%	2%
N+ = 40%	2%	4%
N+ = 80%	4%	8%

#### B-04 trial (1980's)

N+ left behind in 40% axillary LR in 20% 25 yr survival unaffected

#### Z0011 trial (2000's)

N+ left behind in 27% axillary LR in 1% 10 yr survival unaffected

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## SOUND Trial (2102-2017) No Therapeutic Benefit to SLNBx



Gentilini O, JAMA Oncol 2023, 3759

#### Role of Genomics Based on the results of the RxPONDER Trial

For postmenopausal women with ER+/Her2 – breast cancer RS is the primary determinant in the recommendation for chemotherapy Since cN0 women have a low incidence of LN+, maybe slnbx can be omitted



#### Delayed SLNBx: Magtrace The SentiNot Study

Intraoperative injection of SPIO during breast surgery In women with DCIS: undergoing a mastectomy or G2 and > 2 cm or G3 any size or associated with a mass If invasion was identified delayed SLNBx was performed (9-46 days) 78.7% avoided SLNBx SPIO had a higher SLN detection rate vs Tc<sup>99</sup> (with BD 93.9% vs 41.4%, p<0.001) Only 27.9% of SPIO detected and Tc<sup>99</sup> detected LNs were the same



#### We Can't De-escalate Everything Who Still Needs ALND?

failed SLNB (and node status necessary) Z0011 and AMAROS ineligible node + and ineligible for neoadjuvant node + after neoadjuvant regional node recurrence Inflammatory breast cancer









