

Omission of Surgical Staging of the Axilla in Breast Cancer: When and Why

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85 yo woman with a 1.5 cm, ER/PR(+)HER2(-) breast cancer with a clinically negative axilla (US and PE)

75 yo woman with a 1.5 cm, ER/PR(+)HER2(-) breast cancer with a clinically negative axilla (US and PE)

65 yo woman with a 1.5 cm, ER/PR(+)HER2(-) breast cancer with a clinically negative axilla (US and PE)

55 yo woman with a 1.5 cm, ER/PR(+)HER2(-) breast cancer with a clinically negative axilla (US and PE)

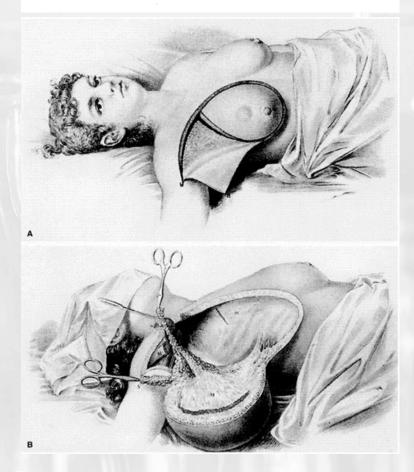
75 yo woman with a 1.5 cm, ER/PR(-)HER2(+) breast cancer with a clinically negative axilla (US and PE)

THE VIRCHOW-HALSTED THEORY

- Henri Francois Le Dran (1757)
 - One of the first surgeons to describe axillary nodal dissection for breast cancer
- Rudolph Virchow
 - Hypothesized that axillary nodes are the point of spread for distant disease
- William Halstead (Johns Hopkins Hospital)(1907)
 - Radical mastectomy to remove all disease (5-year survival with radical mastectomy 40% (6% LRR))
- Led to the utilization of axillary dissections for all breast cancer patient regardless of stage for the next 50 years

THE RESULTS OF OPERATIONS FOR THE CURE OF CANCER OF THE BREAST PERFORMED AT THE JOHNS HOPKINS HOSPITAL FROM JUNE, 1889, TO JANU-ARY, 1894.

By WILLIAM'S. HALSTED, M.D.,

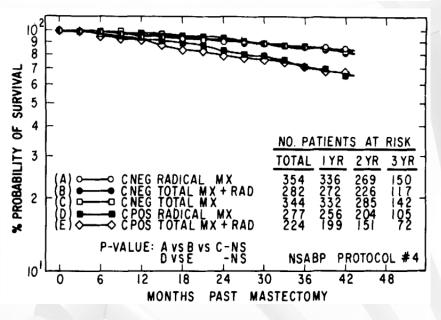


A CHANGE IN THEORY

COMPARISON OF RADICAL MASTECTOMY WITH ALTERNATIVE TREATMENTS FOR PRIMARY BREAST CANCER

A First Report of Results from a Prospective Randomized Clinical Trial

Bernard Fisher, MD, Eleanor Montague, MD, Carol Redmond, ScD,
Bruce Barton, MS, Donna Borland, RN, Edwin R. Fisher, MD,
Melvin Deutsch, MD, George Schwarz, MD, Richard Margolese, MD.,
William Donegan, MD, Herbert Volk, MD, Carl Konvolinka, MD,
Bernard Gardner, MD, Isidore Cohn, Jr, MD, Gerson Lesnick, MD,
Anatolio B. Cruz, MD, Walter Lawrence, MD, Thomas Nealon, MD,
Harvey Butcher, MD, Richard Lawton, MD, (and other NSABP investigators)*

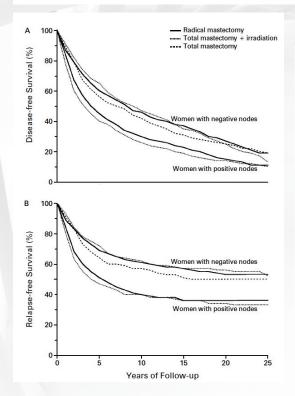


"positive axillary lymph nodes are not the predecessor of distant tumor spread but represent one manifestation of disseminated disease"

RADICAL VERSUS TOTAL MASTECTOMY

TWENTY-FIVE-YEAR FOLLOW-UP OF A RANDOMIZED TRIAL COMPARING RADICAL MASTECTOMY, TOTAL MASTECTOMY, AND TOTAL MASTECTOMY FOLLOWED BY IRRADIATION

BERNARD FISHER, M.D., JONG-HYEON JEONG, Ph.D., STEWART ANDERSON, Ph.D., JOHN BRYANT, Ph.D., EDWIN R. FISHER, M.D., AND NORMAN WOLMARK, M.D.



(Regional Recurrences @ 25 Years)	Radical Mastectomy	Mastectomy	Mastectomy plus Radiation
Negative Nodes	4%	6%	4%
Positive Nodes	8%	n/a	11%

(Overall Survival @ 25 Years)	Radical Mastectomy	Mastectomy	Mastectomy plus Radiation
Negative Nodes	25%	26%	19%
Positive Nodes	14%	n/a	14%

Fisher, et al., Cancer 1977; 39:2827-2839; Fisher, et al., N Engl J Med 2002;347:567-75

CHANGES IN AXILLARY SURGERY

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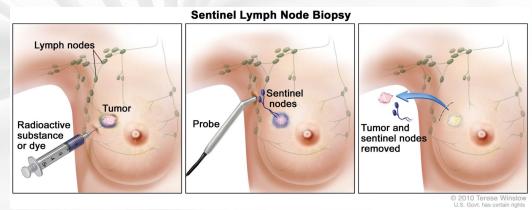
COMBINATION CHEMOTHERAPY AS AN ADJUVANT TREATMENT IN OPERABLE BREAST CANCER

GIANNI BONADONNA, M.D., ERCOLE BRUSAMOLINO, M.D., PINUCCIA VALAGUSSA, B.S., ANNA ROSSI, M.D., LUISA BRUGNATELLI, M.D., CRISTINA BRAMBILLA, M.D., MARIO DE LENA, M.D., GABRIELE TANCINI, M.D., EMILIO BAJETTA, M.D., RENATO MUSUMECI, M.D., AND UMBERTO VERONESI, M.D.

 Randomized control trial stratified by age, number of positive lymph nodes (1-3 versus 4+), and extent of surgery (radical mastectomy versus extended radical mastectomy)

(Failures)	Control	CMF	p-value
Total	24%	5.3%	<10 ⁻⁶
1-3 nodes	16.8%	3.6%	<10-3
4(+) nodes	40.7%	8.8%	<10-4

"Our data indicate that patients with potentially curable breast cancer and with positive axillary lymph nodes at the time of mastectomy show a statistically significant reduction in recurrence rate....." Sentinel lymph node resection compared with conventional axillary lymph node dissection in clinically node negative patients with breast cancer: overall findings from the NSABP B-32 randomised phase 3 trial

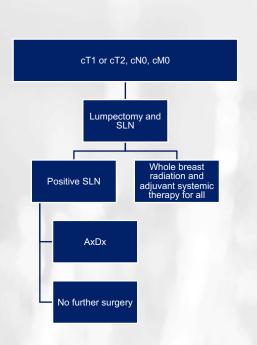


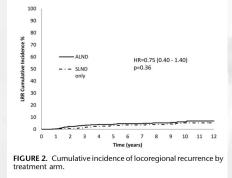
SLN SLN + AxDx (n=1975)alone (n=2011) 2.4% 2.7% Recurrences Local 0.4% 0.7% Regional Nodal 3.2% Distant 2.8% **Overall Survival** 91.8% 90.3 (95 CI; 90.4-93.3) (95 CI; 88.8-91.8)

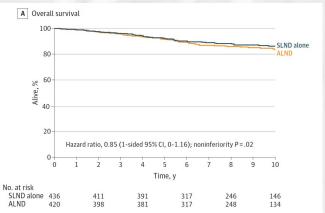
Bonadonna, et al., N Engl J Med 1976; 294: 405-410; https://nci-media.cancer.gov/pdg/media/images/661757.jpg; Krag et al., Lancet Oncol, 2010; 11: 927-933

CHANGES IN AXILLARY SURGERY

Locoregional Recurrence After Sentinel
Lymph Node Dissection With or
Without Axillary Lymph Node Dissection in
Patients with SLN Metastasis: ACOSOG Z0011







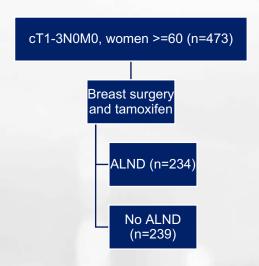
- Despite this de-escalation of axillary intervention, problems persist.
 - Surgical complications that can persist 2 years after surgery

Lymphedema (<6%)
Numbness and tingling 2X
Shoulder abduction issues 2X

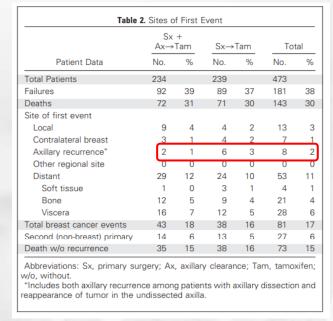
- What are we gaining?
- o Can we de-escalate further?

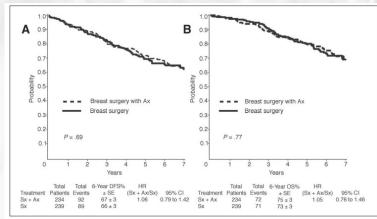
Giuliano et al, JAMA. 2017 Sep 12;318(10):918-926; Lucci et al., J Clin Oncol 2007; 25(24):3657-3663; Krag et al., Lancet Oncol, 2010; 11: 927-933; de Boniface, et al., N Engl J Med 2024;390:1163-1175; Verbelen, et al., Breast Cancer Res Treat 2014;144:21-3:

RANDOMIZED TRIAL COMPARING AXILLARY CLEARANCE WITH NO AXILLARY CLEARANCE IN OLDER PATIENTS WITH BREAST CANCER (IBCSG TRIAL 10-93)



- Randomized
- Tamoxifen (20 mg) for 5 years
- Radiation recommended for breast conserving surgery
- o 80% HR(+)
- o 98% T1/2
- 28% of ALND group had positive nodes (29% with >3 nodes positive)





- Quality of life metrics
- Lymphedema and shoulder/arm issues
- Short term improvements that resolve over time
- DFS and OS
 - 6-year DFS 67% vs 66%, ALND vs
 no (HR 1.06, 95% CI, 0.79-1.42, p=0.69)
 - 6-year OS 75% vs 73%, ALND vs no (HR 1.05, 95% CI, 0.76-1.46, p=0.77)
- Avoidance of ALND in clinically node negative women who receive adjuvant tamoxifen improves short term quality of life and provides equivalent outcomes

Rudenstam, et al., J Clin Oncol 2006;24(3):337-344

AXILLARY DISSECTION VERSUS NO AXILLARY DISSECTION IN ELDERLY PATIENTS WITH BREAST CANCER AND NO PALPABLE NODES

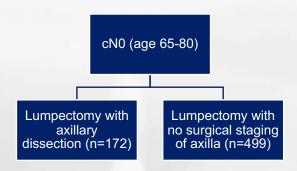


TABLE 2 Unfavorable events in 671 elderly patients with operable breast cancer, by axillary treatment group

The figures in each cell are: number of patients and 15-year

crude cumulative incidence

Events	No axillary dissection $(N = 499)$	Axillary dissection $(N = 172)$	Overall group $(N = 671)$
First event			
Ipsilateral axillary disease	30, 5.8%	0, 0%	30, 4.3%
Distant metastasis	49, 9.9%	20, 11.6%	69, 10.3%
Ipsilateral breast tumor recurrence	33, 6.3%	13, 7.7%	46, 6.7%
Contralateral breast cancer	9, 1.8%	4, 2.3%	13, 1.9%
Second primary malignancy	27, 5.6%	5, 2.9%	32, 4.9%
Death for unrelated condition	251, 49.6%	82, 41.9%	333, 47.6%
Mortality			
Breast cancer	71, 14.0%	23, 13.6%	94, 13.9%
Other malignancy	22, 4.3%	3, 1.8%	25, 3.6%
Unrelated condition	284, 56.4%	92, 47.8%	376, 54.2%

- 33.7% undergoing axillary dissection had occult axillary disease (72% one node)
- Yet only 5.8% of the no axillary surgery group had an axillary failure in 15 years (only 3.7% in T1 tumors)
- Multivariable analysis
- Receptor status, radiation, and axillary dissection were not significant in terms of distant metastasis or breast cancer death
- But lobular histology and larger tumor size was related to both
- Conclusion: Limit axillary dissection to those with clinically positive disease

- Non-randomized
- All prescribed tamoxifen (20 mg/day) for at least 2 years
- Median age 70
- ~93% of tumors T1-2
- ~92% HR(+)
- Median follow-up 180 months

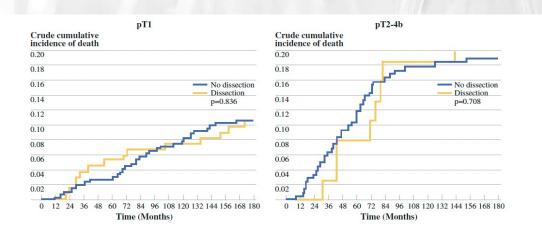
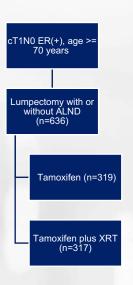


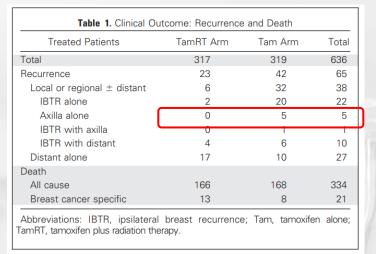
FIG. 1 Crude cumulative incidence curves of breast cancer death for patients given and not given axillary dissection. pT1 (left); pT2-4b (right)

Martelli, et al., Ann Surg Oncol. 2011;18(1):125-33

LUMPECTOMY PLUS TAMOXIFEN WITH OR WITHOUT IRRADIATION IN WOMAN AGE 70 YEARS OR OLDER WITH EARLY BREAST CANCER (CALGB 9343)



- Median follow-up 12.6 years
- 98% ER(+)
- 98% T1
- Median age ~75
- 90% white
- 38% ALND (n=244) (left to discretion of surgeon)



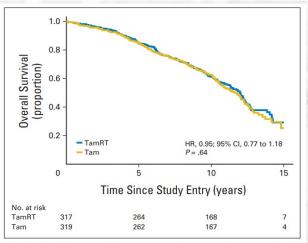


Fig 5. Overall survival. HR, hazard ratio; Tam, tamoxifen alone; TamRT tamoxifen plus radiation therapy

- No axillary recurrences in the ALND group (0/244)
- No axillary recurrences in the no axillary group who received tamoxifen and radiation (0/192)
- **Axillary failure rate in those** with no radiation and no ALND was 3% (6/200)

"If the results of a sentinel lymph node biopsy are not likely to change the choice of systemic therapy, it is questionable whether this 3% decrement warrants the use of sentinel node biopsy in this population."

Hughes, et al., J Clin Oncol 2013;31(19):2382-7

Choosing Wisely (ABIM/SSO/ASCO):

Don't routinely use sentinel node biopsy in clinically node negative women ≥70 years of age with early-stage hormone receptor positive, HER2 negative invasive breast cancer.

EMBRACING THE OMISSION OF SLN OVER 70 HR(+)

Survey of surgeons

- A lack of familiarity or skepticism toward the recommendation to avoid sentinel-node biopsy in women ≥ 70 years of age
- The influence of other collaborating oncology providers as justification for continued use

Survey of ASBS members (mostly community surgeons)

- In a healthy female with clinical T1N0 hormone receptorpositive (HR+) IBC, 83% favored SLNB if the patient was 75 years of age, versus 35% if the patient was 85 years of age.
- For DCIS, 32% endorsed SLNB in women undergoing lumpectomy, with breast surgical oncologists and academic surgeons being less likely to endorse this procedure (OR 0.54 [0.36-0.82], p = 0.028; and OR 0.53 [0.34-0.83], p = 0.005, respectively).

Retrospective chart review of ~1000 patients

- SLN surgery rate significantly decreased from 90.6% (2010-2016) to 62.8% in 2020 (p < 0.001) driven by breastconserving surgery
- During 2017-2020, SLN use varied by risk within BCS patients: 52.2% low-risk, 81.9% higher-risk, p < 0.001. In contrast, in mastectomy patients SLN was performed in ≥ 98% regardless of risk level.
- After adjusting for age and clinical risk, SLN use was not associated with adjuvant radiation [odds ratio (OR) 1.61, p = 0.11] or endocrine therapy (OR 1.12, p = 0.71).

Survey of oncology specialists

- 1. Shared decision making a major factor in older patients
- 2. Difficulties in navigating multidisciplinary care, "Will omission of SLN make adjuvant therapy more challenging?"
- 3. One theme was "supporting data are perceived as being weak"

Smith et al., Ann Surg Oncol, 2020; 27:2653-2663; Armani at al., Ann Surg Oncol 2021; 28(10):5580-5587; Tonneson et al., Ann Surg Oncol 2021;28(13):8766-8774; Minami et al., JAMA Network Open, 2022; 5(8):e2228524

A PROSPECTIVE STUDY OF SENTINEL NODE BIOPSY OMISSION IN WOMEN AGE ≥ 65 YEARS WITH ER+ BREAST CANCER

- Prospective, observational study with 125 patients
 - >= 65 years of age
 - cT1-2N0 ER(+) invasive breast cancer
 - Underwent breast conserving therapy
 - Radiation in only 29.6% (37/125)
 - Omission of SLN
- Median age 77; median follow-up 36.7 months; median tumor size 1 cm
- Endocrine therapy compliance only 48% at 2 years
- Chemotherapy in 4.8% (6/125)
- Axillary recurrences in 2/125 (1.6%) (both associated with distant recurrence in patients over 80)
- 3-year survivals

o RFS: 98.2%

BCSS: 99.2%

OS: 94.8%

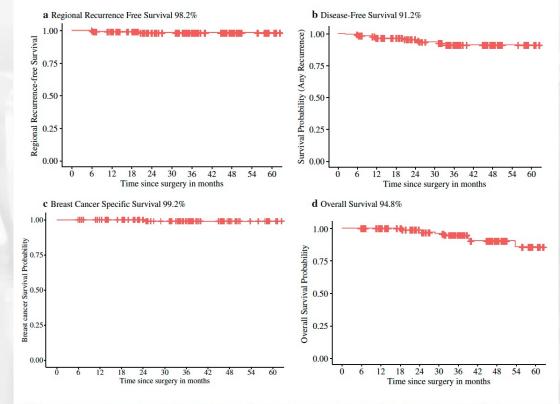
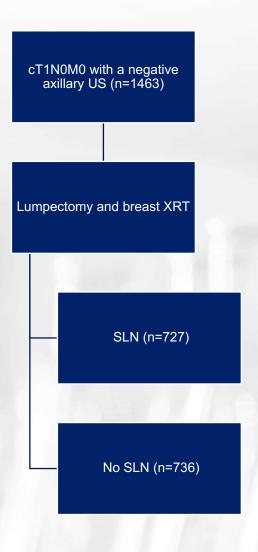


FIG. 2 Kaplan—Meier curves of estimated 3-year outcomes for regional recurrence-free survival (a), disease-free survival (b), breast cancer-specific survival (c), and overall survival (d)

Women older than aged 65 years with clinically staged T1-2N0 ER(+) breast cancer undergoing breast conservation surgery are unlikely to gain benefit from SLN.

SLN VERSUS NO AXILLARY SURGERY IN PATIENTS WITH SMALL BREAST CANCERS AND NEGATIVE RESULTS ON AXILLARY ULTRASOUND: THE SOUND RANDOMIZED CLINICAL TRIAL



- 18 centers, 2012 2017
- Exclusion criteria
 - Preoperative presence of multiple doubtful or suspicious lymph nodes
 - Extensive multifocality or multicentricity
 - Bilateral BC
 - Diagnosis of synchronous distant metastases
 - Previous cancer
 - Ongoing pregnancy or lactation
- Accrued 94% of targeted population
 - Intention to treat analysis
 - SLN group: 708 patients
 - Observation group: 697 patients

THE SOUND RANDOMIZED CLINICAL TRIAL

Patients, No. (%)		
Characteristic	SLNB (n = 708)	No axillary surgery (n = 697)
Age at surgery, y		
<40	10 (1.4)	10 (1.4)
40-49	114 (16.1)	128 (18.4)
50-64	324 (45.8)	298 (42.8)
≥65	260 (36.7)	261 (37.4)
Median (IQR)	60 (52-68)	60 (51-68)
Menopausal status ^a		==
Premenopausal	145 (20.6)	154 (22.3)
Perimenopausal or postmenopausal	558 (79.4)	538 (77.7)
Histotype		
Ductal	551 (77.8)	543 (77.9)
Lobular	61 (8.6)	59 (8.5)
Tubular	27 (3.8)	33 (4.7)
Other	69 (9.7)	62 (8.9)
Pathological tumor size		
pT1mic or pT1a	71 (10.0)	61 (8.8)
pT1b	251 (35.5)	240 (34.4)
pT1c	355 (50.1)	361 (51.8)
pT2	31 (4.4)	35 (5.0)
Median (IQR), cm	1.1 (0.8-1.5)	1.1 (0.8-1.5)
No. of positive SLNs		
0	599 (84.6)	12 (1.7)
1	83 (11.7)	10 (1.4)
≥2	14 (2.0)	0

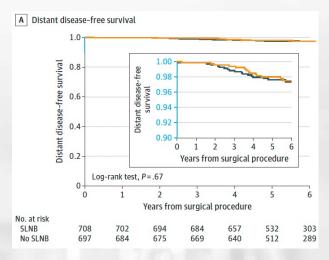
	Patients, No. (%)		
Characteristic	SLNB (n = 708)	No axillary surgery (n = 697)	
Ki-67 index ^c			
<20	455 (64.4)	439 (63.2)	
≥20	252 (35.6)	256 (36.8)	
Median (IQR)	15 (10-23)	15 (10-24)	
ERBB2 overexpression			
Not overexpressed	660 (93.2)	650 (93.3)	
Overexpressed	48 (6.8)	47 (6.7)	
Surrogate subtype			
Luminal ERBB2-negative	617 (87.1)	617 (88.5)	
ERBB2-enriched	48 (6.8)	47 (6.7)	
Triple-negative	43 (6.1)	33 (4.7)	
Grade ^b			
1	194 (27.7)	204 (29.9)	
2	377 (53.8)	356 (52.2)	
3	130 (18.5)	122 (17.9)	
ER status			
0	56 (7.9)	44 (6.3)	
>0	652 (92.1)	653 (93.7)	
PgR status			
0	108 (15.3)	95 (13.6)	
>0	600 (84.7)	602 (86.4)	

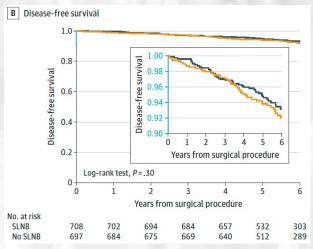
- For the SLN group
 - 82.5% were node negative
 - 2.1% pNi+, 5.1% pN1, 8.1% pN1
 - Only 0.6% were pN2
- Adjuvant treatments
 - Majority received endocrine therapy (98% for HR(+))
- Chemotherapy for ~19% of patients (~96% of HER2(+) received trastuzumab)
- Radiation therapy for 98%
 - 10.8% received partial breast (IORT) and ~4% IORT plus hypo-fractionated whole breast
 - 81.1% (SLN) 83.8% (No SLN) with conventional fractionation whole breast

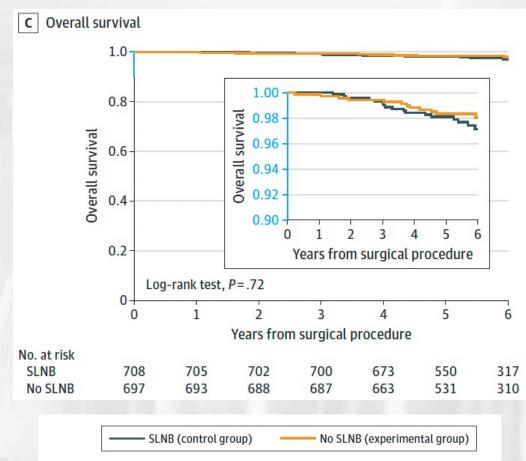
Gentilini et al., JAMA Oncol 2023;9(11):1557-1564

THE SOUND RANDOMIZED CLINICAL TRIAL

Table 3. Summary of First Events, Deaths, and Follow-Up Time Events, No. (%) SLNB No axillary surgery (n = 708)(n = 697)Outcome First events 7 (1 0) Ipsilateral breast recurrence 6 (0 9) Axillary recurrence 3 (0.4) 5 (0.7) Ipsilateral breast and axillary 2 (0.3) 0 recurrence 13 (1.8) Distant metastasis 14 (2.0) 5 (0.7) 7 (1.0) Contralateral breast cancer 22 (3.2) 17 (2.4) Nonbreast primary tumors 0 Death from breast cancer Death from cause other than 5 (0.7) 6(0.9)breast cancer Death from unknown cause 1 (0.1) 1 (0.1) Follow-up, median (IQR), y 5.7 (5.0-6.8) 5.7 (5.0-6.6) All deaths, cause 7 (1.0) 4 (0.6) Breast cancer Cause other than breast cancer 10 (1.4) 12 (1.7) 2 (0.3) Unknown cause 4 (0.6) Follow-up, median (IQR), y 5.8 (5.0-6.9) 5.8 (5.0-6.8) Abbreviation: SLNB, sentinel lymph node biopsy.







THE SOUND RANDOMIZED CLINICAL TRIAL

- Omission of axillary surgery was not inferior in DDFS for patients with <2 cm, hormone positive tumors and a negative axillary US
 - Axillary failure rate only 0.4% @ 5 years
 - Matches with Choosing Wisely guidance
 - Points to the importance of multi-disciplinary approaches to breast cancer patients
- Caution that this data may not apply to premenopausal women
 - In this patient population SLN data may alter treatment
 - RxPonder points to the benefit of chemotherapy for node positive premenopausal patients regardless of Oncotype
 - May also guide length of endocrine therapy
- Questions arise regarding adjuvant radiation fields
 - Overall risk of >3 nodes is very low (only 0.6% in the SLN group)
 - May not be a significant concern in older patients
- Await 10-year data to confirm results

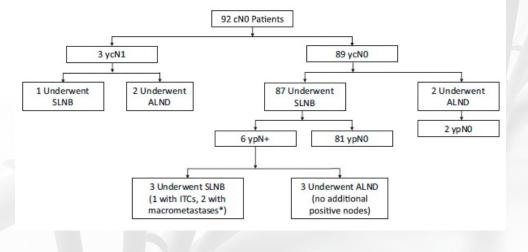
Gentilini et al., JAMA Oncol 2023;9(11):1557-1564; Kalinsky, et al., N Engl J Med 2021;385(25):2336-2347; Gnant, et al., N Engl J Med 2021; 385(5):395-405; Davies, et al., Lancet. 2013;381(9869):805-816

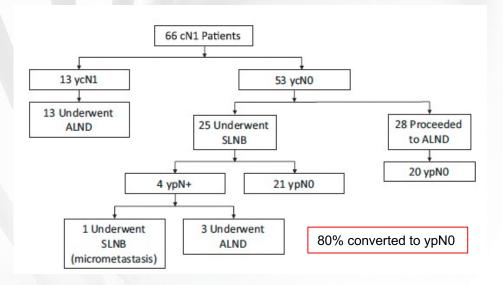
WHAT ABOUT OTHER BREAST CANCERS?

- Larger hormone positive, clinically node negative tumors
 - Data from the previously presented trials included T1 T3 tumors with similar results
 - Although not many larger tumors accrued to any of the trials
 - The risk of occult nodal disease rises with T stage although this may not alter treatment.....
- cN0 triple negative and HER2(+) breast cancers
 - Most of these patients will receive systemic therapy so maybe a SLN is not that important
 - But systemic therapy can be markedly altered based on the nodal status of a tumor
 - Additional / changes in chemotherapeutic agents
 - Addition of immunotherapy
 - Addition / changes in anti-HER2 therapy
 - On the other hand, the overall response rates for these tumor can be high
 - If therapy won't be affected......

AXILLARY NODAL RESPONSE TO NEOADJUVANT T-DM1 COMBINED WITH PERTUZUMAB IN A PROSPECTIVE PHASE II MULTI-INSTITUTION CLINICAL TRIAL

- Single-arm phase II prospective trial examining HE R2 heterogeneity
- 158 patients examined
 - Nodal status via physical exam and US
 - 92 cN0
 - 66 cN1





- Overall pCR rate 49.4%
- 100% of those with breast pCR had nodal pCR
- ypN0 rates overall:
 - 91.3% for cN0
 - 66.7% for cN1
- Allows for a discussion of selective omission of surgical staging of the axilla
 - With caveats for cN1
 - cN0 though with very low rates of disease, especially with a breast pCR

Weiss, et al., J Am Coll Surg 2024; 238:303-311

THE FUTURE.....

- Machine learning/Al
 - Prediction of SLN positivity
 - Applications for breast imaging and pathology
- Broadening of clinical trials to include other receptor subtypes
- Improvement in genomic testing

INSEMA Trial

Comparison of Axillary Sentinel Lymph Node Biopsy Versus no Axillary Surgery in Patients With Early-stage Invasive Breast Cancer and Breast-conserving Surgery: a Randomized Prospective Surgical Trial

NAUTILUS Trial

No axillary surgical treatment for lymph node negative patients after ultrasonography [NAULITUS]: protocol for a prospective randomized clinical trial

ASLAN Trial

Selective avoidance of sentinel lymph node biopsy after neoadjuvant chemotherapy in human epidermal growth factor 2 positive / triple negative breast cancer patients with excellent response

EURBREAST-01 Trial

Omission of SLNB in triple negative and HER2-positive breast cancer patients with radiologic and pathologic complete response in the breast after NAST: a singlearm, prospective surgical trial

SOAPET

Prospective study designed to evaluate the negative predictive value of LymphPET and to verify whether sentinel lymph node biopsy can be spared in patients with negative preoperative axillary assessment

Avoiding Sentinel Lymph Node Biopsy in Breast Cancer Patients After Neoadjuvant Chemotherapy (ASICS)

This study evaluates whether SLNB can safely be omitted in breast cancer patients with HER2+ or TN tumors who achieve a radiological complete response on MRI after neoadjuvant systemic therapy

BOOG 2013-08 Trial

Omittting Sentinel Node Procedure in Breast Cancer Patients Undergoing Breast Conserving Therapy

- Remember: Nodal disease is prognostic for certain patients
 - But the knowledge of nodal status may be enough
- For cT1-2N0, HR(+)HER2(-) breast cancers in patients 70 and over, SLN should not be routinely performed
- For cT1N0, HR(+)HER2(-) breast cancers in younger, post-menopausal women, SLN may not add to adjuvant therapy decision making and could be omitted
- All decisions regarding the possible omission of SLN should be via a multidisciplinary approach
- The challenge of modern surgical oncology is to develop the de-escalation of old surgical procedures while at least maintaining, if not improving, outcomes

Just because you CAN do something doesn't mean you should.



Omission of Surgical Staging of the Axilla in Breast Cancer: When and Why

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Department of Surgery

EMORY
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