

# Updates in Surgical Axillary Management

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Oncology Updates: CME Webinar Series

UC San Diego

# Disclosures

- **No disclosures**

## **Learning Objective(s):**

- **Describe current advances in surgical management of the axilla following neoadjuvant systemic therapy**
- **Describe the impact of clipping the positive lymph node in patients with clinically node positive breast cancer treated with neoadjuvant chemotherapy and impact on axillary surgery in the ISPY-2 clinical trial**
- **Describe the utility of sentinel lymph node frozen section diagnosis following neoadjuvant chemotherapy in patients with clinically node negative HER2-positive or triple negative breast cancer**
- **Describe when axillary staging may be omitted in primary breast cancer: Updates from the SOUND Trial and clinical impact**

# Role of Clipping the lymph node

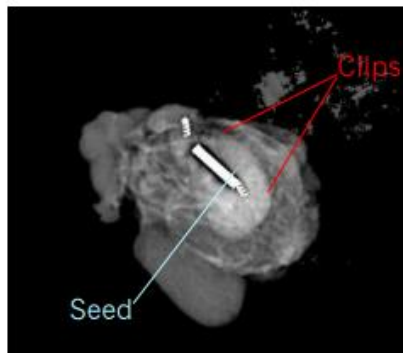
cN+ patients



SLN surgery can be used for reliable nodal staging after NAC



Targeted axillary dissection (TAD)



TAD can reduce false negative rates



Evaluate the **use of nodal clipping over time** and the relationship between **node clipping and surgical outcomes** in cN+ patient on the ISPY-2 neoadjuvant chemotherapy trial

# Surgical standards for management of the axilla in the ISPY-2 trials

## Management at diagnosis:

- Axillary ultrasound and needle biopsy of the most abnormal node is required
- Placement of a clip in the positive node is recommended

## Surgical management:

- Pre-operative localization of the clip is recommended
- ALND or SLN is permitted, but SLN requires use of dual tracer
- If clip was placed, resection of clipped node should be performed
- If no clip was placed, the resection of all SLNs and removal of at least 2 nodes is required
- Use of completion axillary dissection is at the discretion of the treating surgeon

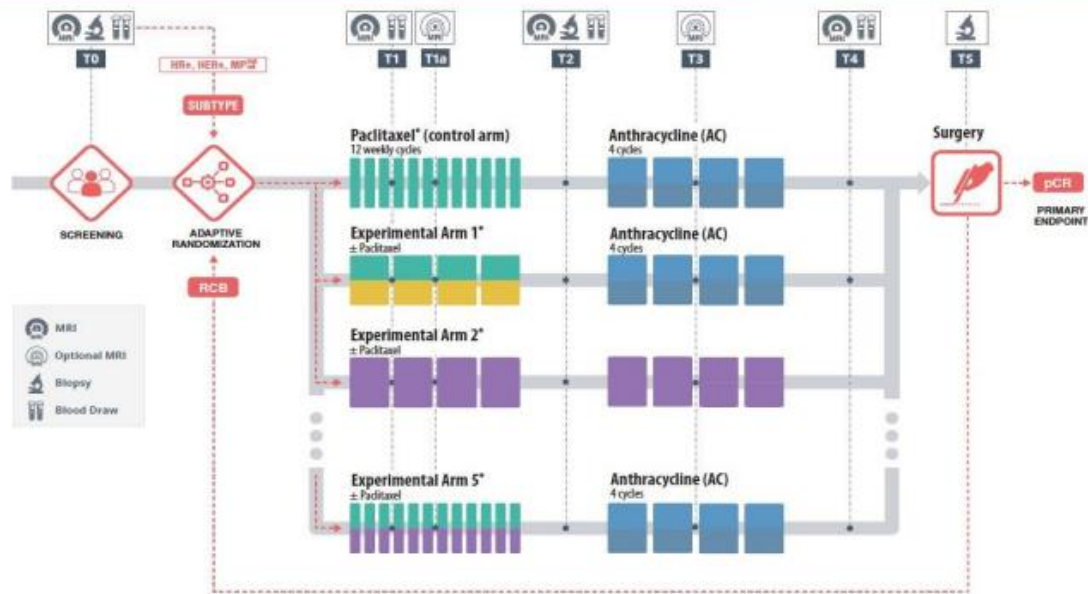
# ISPY-2 Trial Schema

Trial eligibility:

- Clinical stage II or III
- Molecularly high-risk

ISPY2 is an adaptively randomized trial of NAC followed by surgical resection

Primary endpoint = pCR rates



\* Patients who are HER2+ may also receive trastuzumab (Herceptin)

† An investigational combination of one or more agents may be used to replace all or some of the standard therapy

# Primary Study Questions



1

- Has the use of nodal clipping in patient on the ISPY-2 trial increased over the last 10 years?

2

- Is placement of a clip in the positive lymph node associated with a higher rate of SLN/TAD-only surgery?

3

- Does placement and/or retrieval of a clip in the positive lymph node (TAD) impact the FNR of the SLN procedure?

4

- Does placement and/or retrieval of a clip in the positive lymph node impact event-free survival(EFS?)



# Methods

## Inclusion criteria:

- Patients enrolled in ISPY-2 who were **cN+ in the axilla**
- Underwent NAC and surgery between 01/2011 and 12/2021



## Compared two groups:

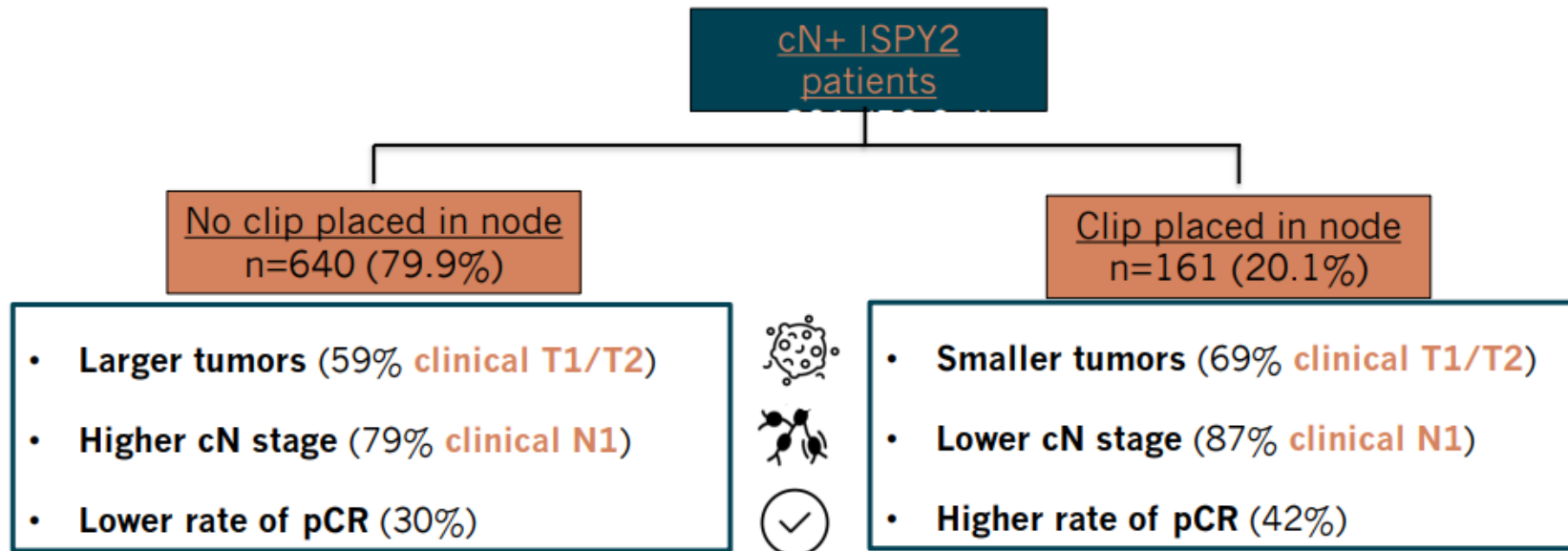
Patients with **clip** in lymph node  
versus  
Patients **without clip** in lymph node



## Statistical analyses:

- Clinicopathologic characteristics by group:
  - Pearson's chi-square test, fisher's exact test, Wilcoxon rank sum test, multivariable logistic regression
- Calculation of false-negative rate:
  - in those who underwent SLN and ALND
- Event free survival by group:
  - Log rank test, Kaplan Meier survival analysis, univariable and multivariable Cox proportional hazards models

# Patient population



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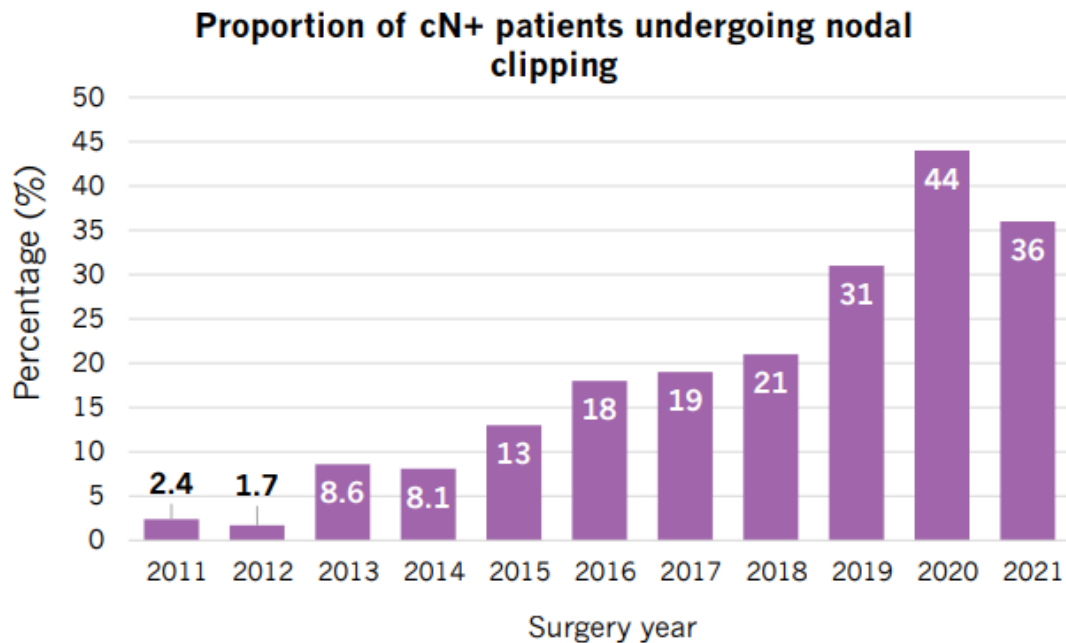
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# Results: Prevalence of Nodal Clipping by Year



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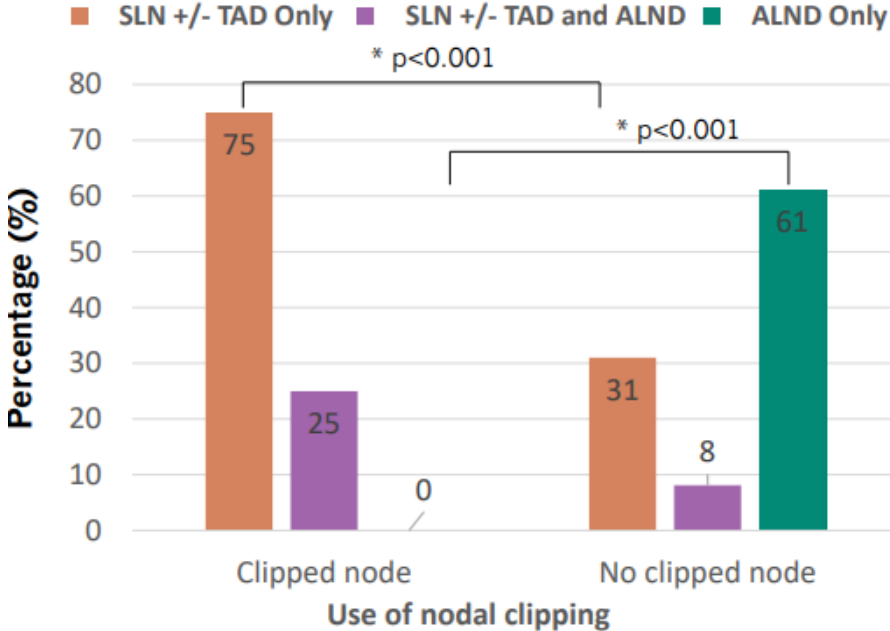
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# Results: Clip placement is independently associated with SLN-only surgery



Odds of SLN/TAD surgery

	OR (95% CI)	P value
<b>Nodal clip placement</b>		
No clipped node	—	
Clipped node	4.3 (2.8 - 6.8)	<0.001
<b>cN category at diagnosis</b>		
N1	—	
N2	0.48 (0.23 - 0.93)	
N3	0.56 (0.30 - 0.99)	
<b>Surgery Year</b>		
2011	—	
2012	1.59 (0.53 - 5.46)	
2013	1.54 (0.53 - 5.13)	
2014	1.70 (0.60 - 5.62)	
2015	2.70 (0.99 - 8.71)	
2016	2.69 (0.95 - 8.89)	
2017	4.14 (1.54 - 13.2)	
2018	4.06 (1.51 - 13.0)	
2019	6.94 (2.69 - 21.7)	
2020	6.27 (2.31 - 20.3)	
2021	4.48 (1.63 - 14.6)	

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# Results: FNR of SLN Procedure with and without clip placement

$$\text{False negative rate (FNR)} = \frac{\text{\# patients with pathologically negative SLNs but nodal disease in ALND}}{\text{Total \# patients with residual disease in SLN, ALND, or both}}$$

Note: The calculated FNRs were based only on patients who underwent **both SLN/TAD and ALND**

Use of nodal clipping	False-negative SLN events / Total # patients with residual disease	FNR (95% CI)	p-value versus without clip placement
cN+ without clip placement	5/39	12.8% (4 – 22%)	reference
cN+ with clip placement	3/32	9.4% (0.4 – 18%)	0.60
cN+ with clip placed and retrieved	1/26*	N/A	N/A
cN+ with clip placed but not retrieved	2/3*	N/A	N/A

\* 3 patients missing clip retrieval status



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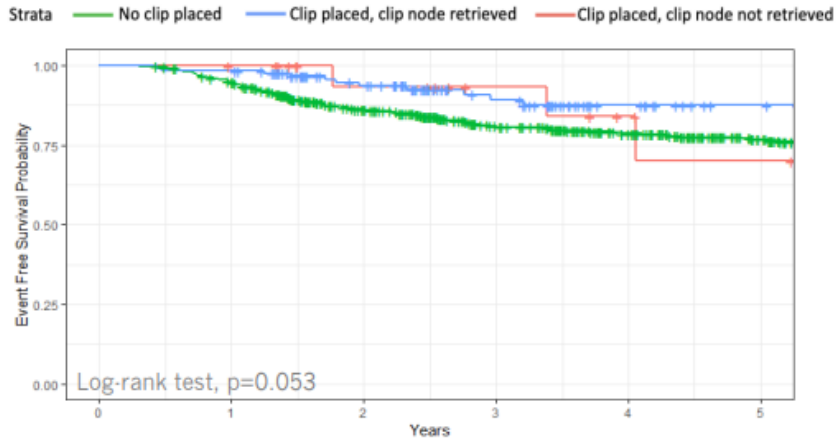
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- **Does placement and/or retrieval of a clip in the positive lymph node impact event-free survival(EFS?)**

### EFS in patients with and without nodal clipping by clip retrieval status



**EFS** = patient survival without local or distant breast cancer recurrence or death

### Multivariable Cox proportional Hazard model

**No significant difference in EFS** between patients with or without clip placement (HR 1.1, 95% CI 0.6 – 2.0,  $p=0.7$ )

## Clipped node cohort, compared to the no clipped node cohort, had...



Higher odds for **SLN**  
**+/- TAD only** surgery



Comparable **FNR**  
for SLN/TAD surgery




Comparable  
**EFS**

# Study Conclusions

- 
- Clip placement in the positive sentinel lymph node likely facilitates use of SLN/TAD and omission of ALND

- 
- Clip placement also confers a safe FNR and no negative impact on EFS

- 
- Clipping the + lymph node is associated with potential benefit without demonstrated harm and should be recommended

The utility of sentinel lymph node frozen section diagnosis following neoadjuvant chemotherapy in patients with clinically node negative HER2-positive or triple negative breast cancer

# SLN Frozen Section

## Pros

- **ALND is the current standard of care for any positive SLNs post neoadjuvant systemic therapy**
- **Frozen section diagnosis facilitates completion of all necessary axillary surgery during the index operation**

## Cons

- **Costly**
- **Time consuming**
- **Limited sampling, technically difficult**
- **Unavailable in some settings**

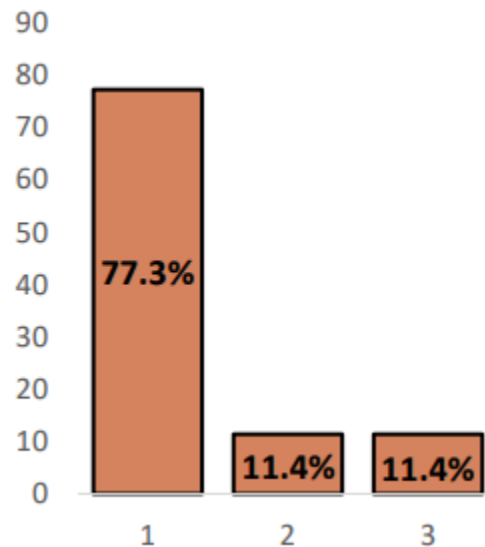
Evaluated the presence of SLN positivity and the test characteristics of frozen section diagnosis in patients with HER2+ and TNBC following neoadjuvant chemotherapy

# Results

## Final pathology results of sentinel lymph nodes

		Positive	Negative
Total No.		44 (6.6)	618 (93.4)
Approximated breast cancer subtype	Triple negative	27 (6.7)	376 (93.3)
	HR-, HER2+	5 (6.2)	76 (93.8)
	Triple positive	12 (6.7)	166 (93.3)

Numbers are No. (%)  
Fishers exact test p-value = >0.99





# From: The Prevalence of Sentinel Lymph Node Positivity and Implications for the Utility of Frozen Section Diagnosis Following Neoadjuvant Systemic Therapy in Patients with Clinically Node-Negative HER2-Positive or Triple-Negative Breast Cancer

	Final pathology SLN positive	Final pathology SLN negative	Total
<b>Receptor subtypes</b>			
Overall			
Frozen section SLN positive	19	0	19
Frozen section SLN negative	14	457	471
Total	33	457	490
	Sensitivity: 57.6%	Specificity: 100%	
<b>Triple-negative</b>			
Frozen section SLN positive	12	0	12
Frozen section SLN negative	8	272	280
Total	20	272	292
	Sensitivity: 60.0%	Specificity: 100%	
<b>Hormone receptor-negative, HER2-positive</b>			
Frozen section SLN positive	3	0	3
Frozen section SLN negative	1	58	59
Total	4	58	62
	Sensitivity: 75.0%	Specificity: 100%	
<b>Hormone receptor-positive, HER2-positive</b>			
Frozen section SLN positive	4	0	4
Frozen section SLN negative	5	127	132
Total	9	127	136
	Sensitivity: 44.4%	Specificity: 100%	

SLN sentinel lymph node, HER2 human epidermal growth factor receptor 2

## Test characteristics

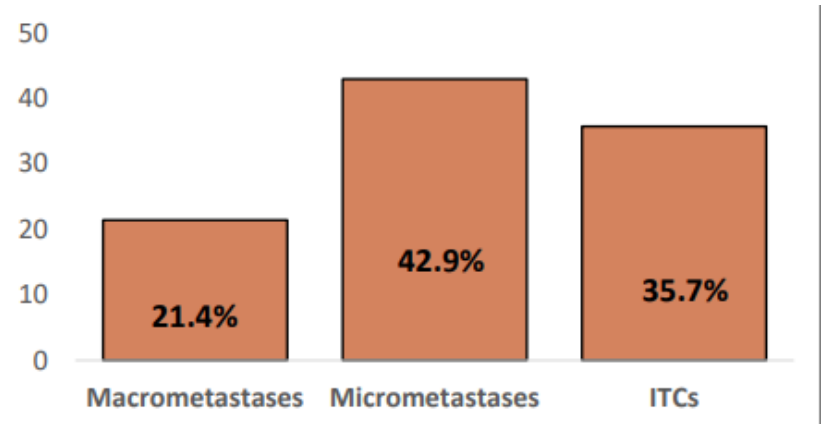
**Sensitivity: 57.6%**

**Specificity: 100%**

**PPV: 100%**


**NPV: 97%**


## False negatives




**1 in 26 patients undergoing frozen section are SLN+ and will test positive**

# Conclusions

- 
- The prevalence of SLN positivity is low in patients with clinically node negative HER2-positive or triple negative breast cancer who receive neoadjuvant systemic therapy
  - Sensitivity of frozen section Dx in this population is limited

- 
- Delaying ALND may allow for the review of new evidence, risks and benefits with patients
  - Lymphovenous bypass may be coordinated if staged approach taken

- 
- For this population, although intraoperative evaluation of SLNs may be worthwhile sometimes based on cost and patient preference, in general it may be **deferred to final pathology**

Sound Trial Overview: Is it safe to omit sentinel lymph node biopsy in patients with small breast cancer (BC) and a negative preoperative axillary ultrasonography result?

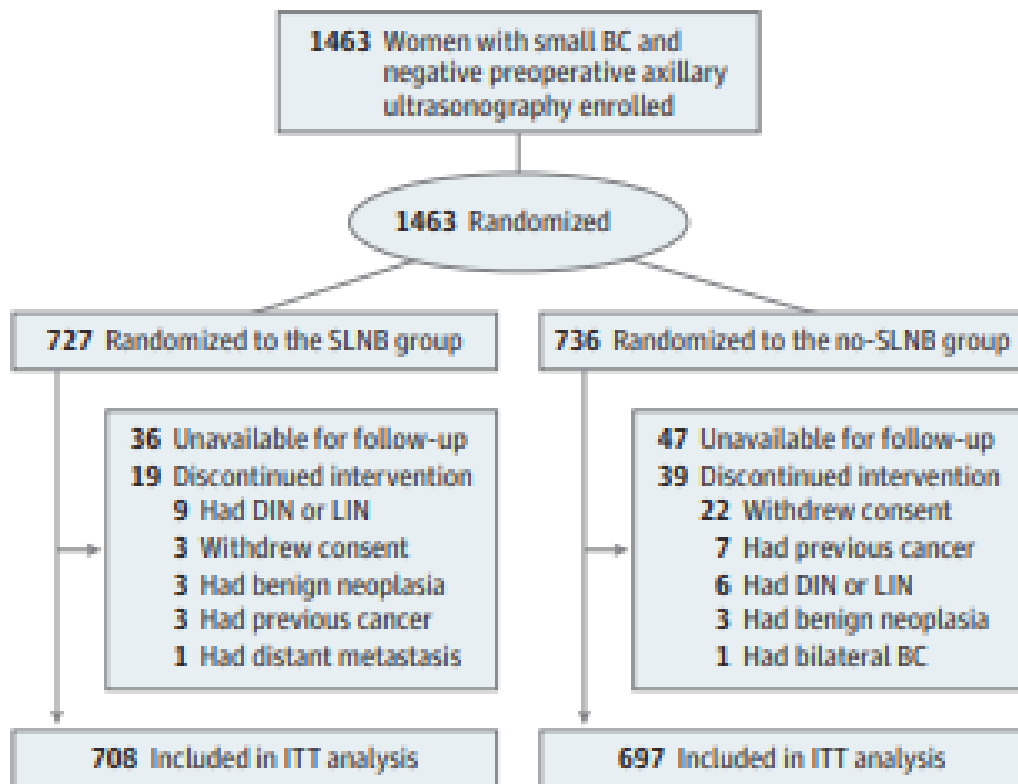
## Inclusion

Phase III Randomized Controlled Trial conducted at 18 European hospitals from 2012-2017

- Invasive breast cancer up to 2 cm
- cN0
- Planning for BCT and XRT and had axillary US showing no LN involvement(if doubtful, FNA performed and had to be negative)

## Randomization

- **SLN Surgery**
- **No axillary surgery**



BC indicates breast cancer; DIN, ductal intraepithelial neoplasia; ITT, intention to treat; LIN, lobular intraepithelial neoplasia; and SLNB, sentinel lymph node biopsy.

**Recommended adjuvant systemic therapy and radiotherapy were similar in the 2 groups**



**Table 2. Final Surgical Treatment and Recommended Adjuvant Therapy**

Treatment	Patients, No. (%)		P value
	SLNB (n = 708)	No axillary surgery (n = 697)	
<b>Surgery</b>			
Breast-conserving	12 (1.7)	675 (96.8)	
Breast-conserving and SLNB	646 (91.2)	13 (1.9)	NA
Breast-conserving, SLNB, and AD	45 (6.4)	5 (0.7)	
Mastectomy and SLNB	5 (0.7)	4 (0.6)	
<b>Hormone therapy</b>			
No	66 (9.3)	49 (7.0)	.12
Yes	642 (90.7)	648 (93.0)	
<b>Hormone therapy in ER-positive cases<sup>a</sup></b>			
No	14 (2.1)	7 (1.1)	.12
Yes	638 (97.9)	646 (98.9)	
<b>Chemotherapy</b>			
No	566 (79.9)	575 (82.5)	.22
Yes	142 (20.1)	122 (17.5)	
<b>Hormone therapy and chemotherapy</b>			
Neither hormone therapy nor chemotherapy	17 (2.4)	11 (1.6)	.35
Hormone therapy without chemotherapy	549 (77.5)	564 (80.9)	
Chemotherapy without hormone therapy	49 (6.9)	38 (5.5)	
Both hormone therapy and chemotherapy	93 (13.1)	84 (12.1)	
<b>Radiotherapy</b>			
No	14 (2.0)	17 (2.4)	.56
Yes	694 (98.0)	680 (97.6)	
<b>Trastuzumab</b>			
No	661 (93.4)	651 (93.4)	.98
Yes	47 (6.6)	46 (6.6)	
<b>Trastuzumab in overexpressed ERBB2-positive cases<sup>b</sup></b>			
No	3 (6.2)	1 (2.1)	.62
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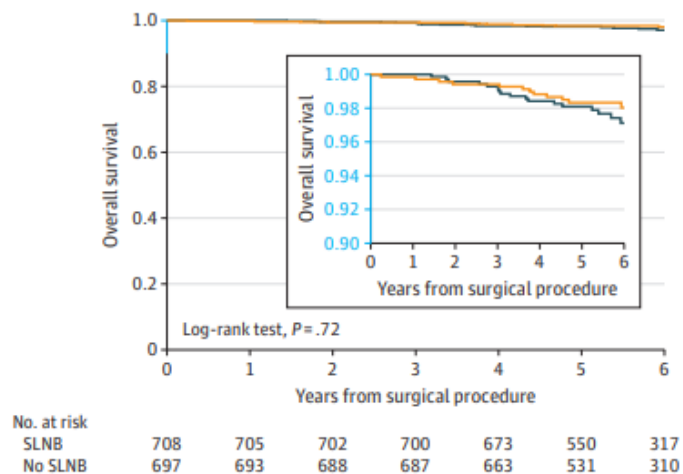
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	SLN surgery	No axillary surgery	
Locoregional relapse	12 (1.7%)	11 (1.6%)	
Distant metastases	13 (1.8%)	14 (2.0%)	
Deaths	21 (3.0%)	18 (2.6%)	
5-year DDFS	97.7%	98.0%	p=0.67
5-year DFS	94.7%	93.9%	p=0.30
5-year OR	98.2%	98.4%	p=0.72

**C** Overall survival



SLNB indicates sentinel lymph node biopsy.

— SLNB (control group) — No SLNB (experimental group)

## Conclusions

Patients with small breast cancer with sonographically normal appearing lymph nodes can be safely spared any axillary surgery whenever the lack of pathological information does not affect the postoperative treatment plan.

Study provides further data supporting that axillary sentinel lymph node surgery does not provide therapeutic benefit.

- In the no axillary surgery group, the cumulative incidence of lymph node recurrences in the axilla was very low (0.4% at 5 years), despite a 13.7% rate of nodal involvement in the SLNB group.

## Limitations/Considerations

LN surgery likely still has a role in certain patients for staging to guide adjuvant therapies:

- Young patients where chemotherapy is associated with survival benefit for node positive disease.

While adjuvant treatment recommendations in terms of rate of chemotherapy was similar between the two groups, identification of nodal positivity in ER+ breast cancer also influences treatment options in terms of CDK4/6 inhibitor eligibility as well as consideration of extended endocrine therapy (to 10 years).

Thank you

Questions?  
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