

Stadiazione dell'ascella in pazienti trattate con chemioterapia neoadiuvante

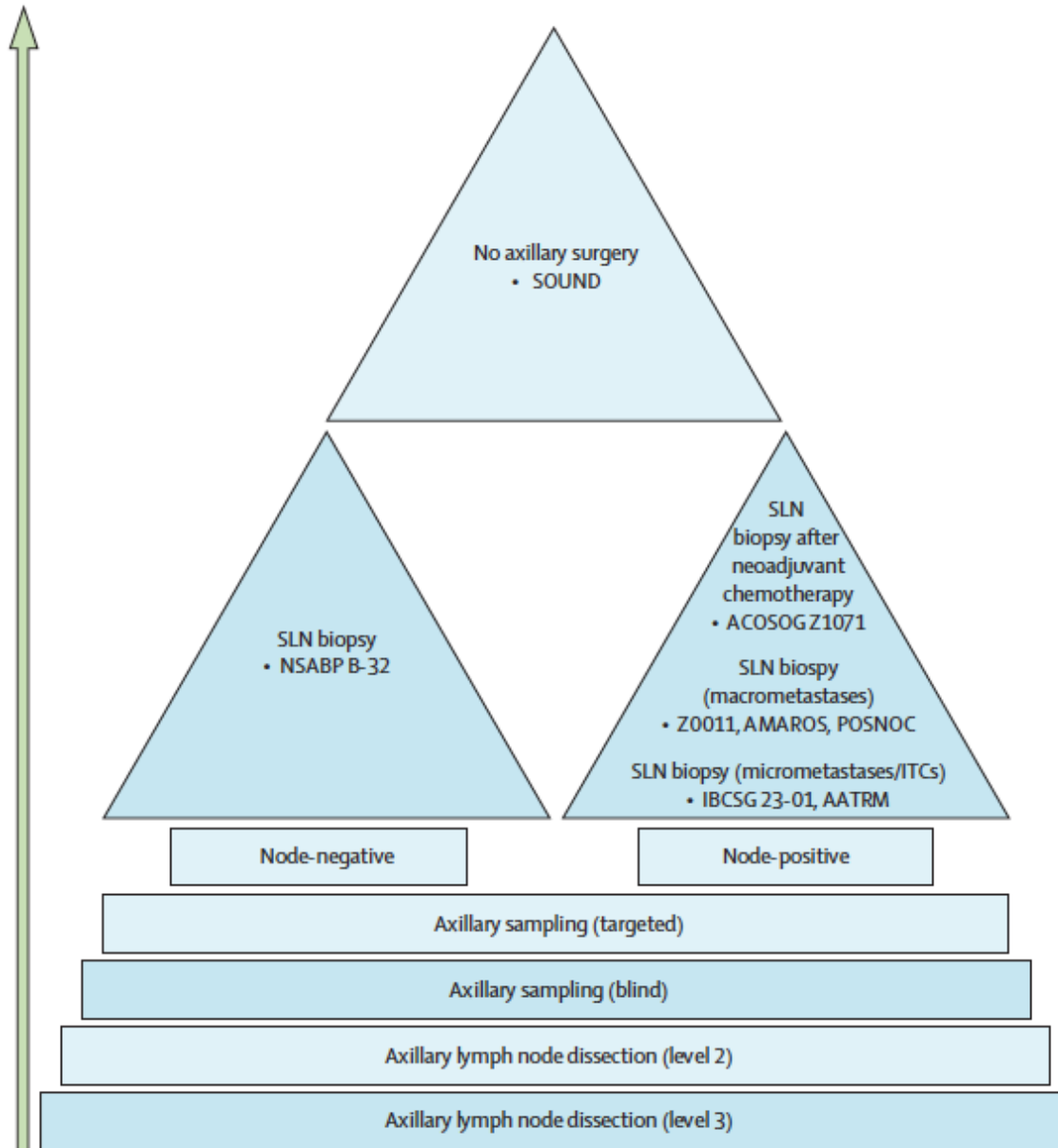
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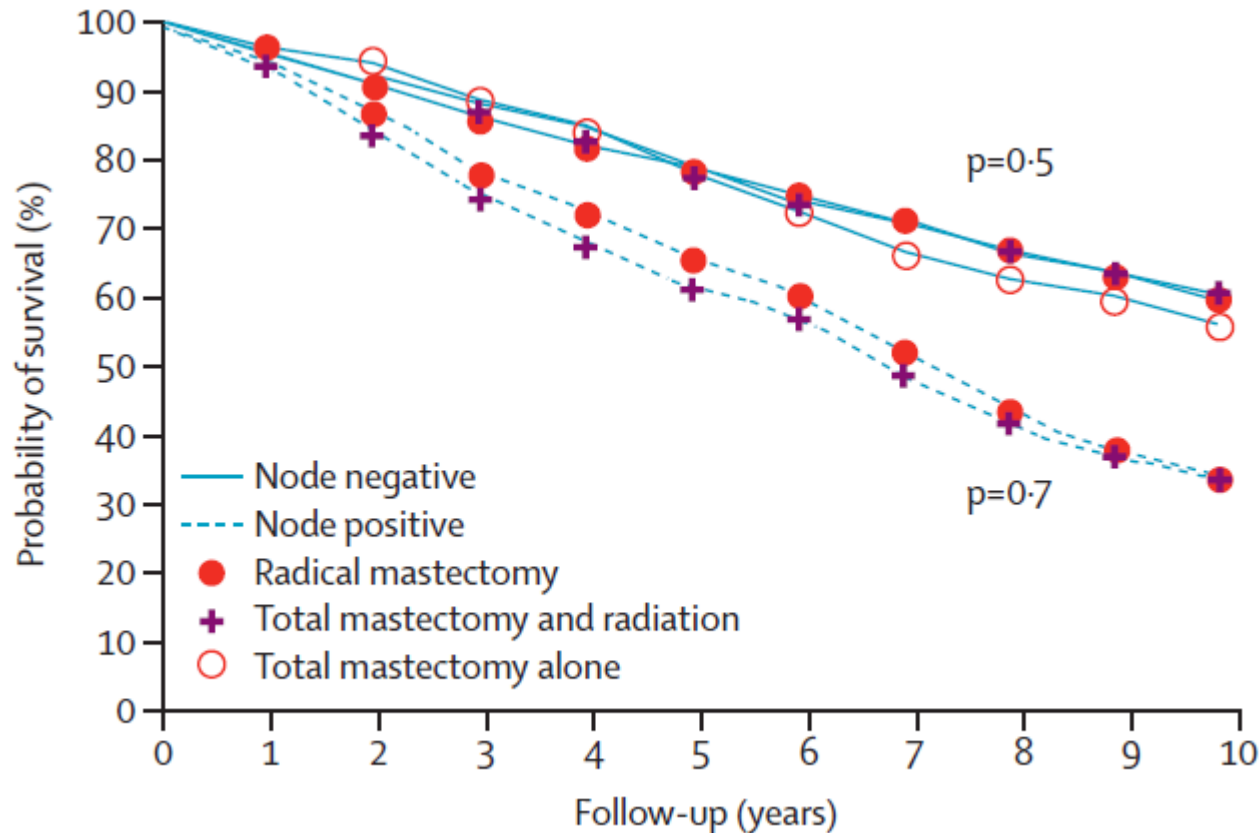
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Schematic of progressive de-escalation of axillary surgery



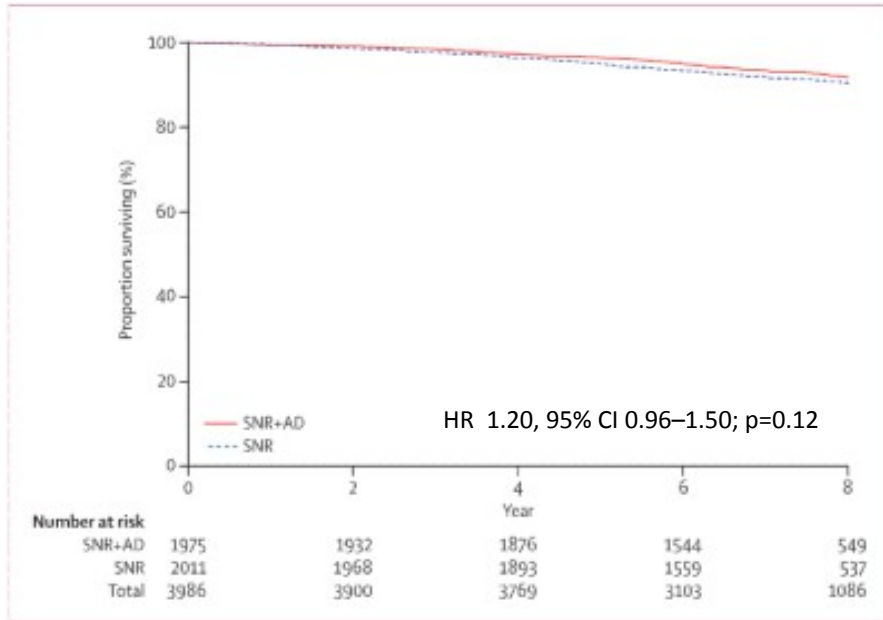
Overall survival for node-negative and node-positive patients in the NSABP B-04 study according to treatment



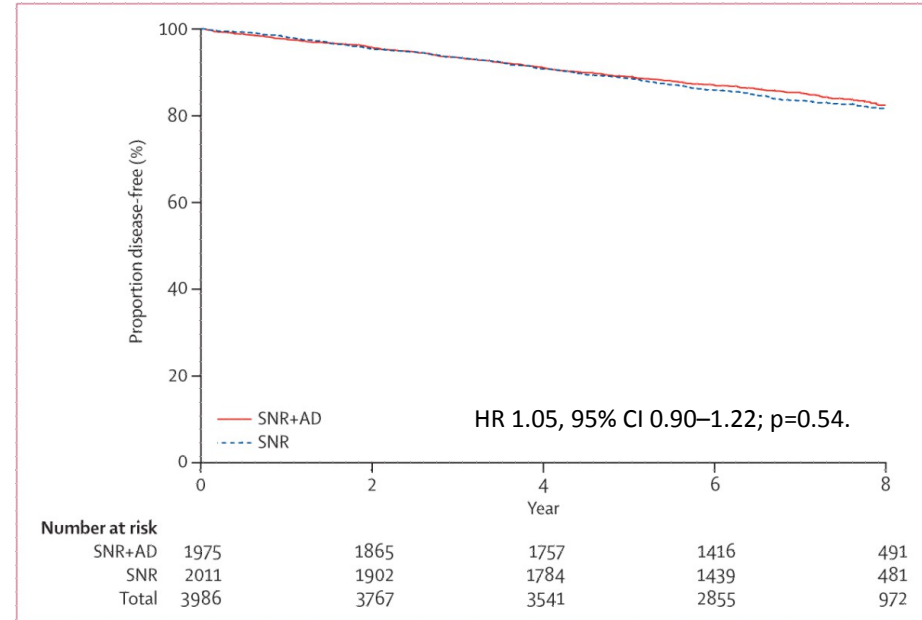
No significant differences were observed among **clinically node-negative patients** undergoing **radical mastectomy, total mastectomy and radiation or total mastectomy alone (around 40% pathologically node positive in each arm)**, nor between node-positive patients treated with either radical mastectomy or mastectomy and irradiation

Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial

Overall survival for sentinel-node (SLN)-negative patients



Disease-free survival for sentinel-node (SLN)-negative patients

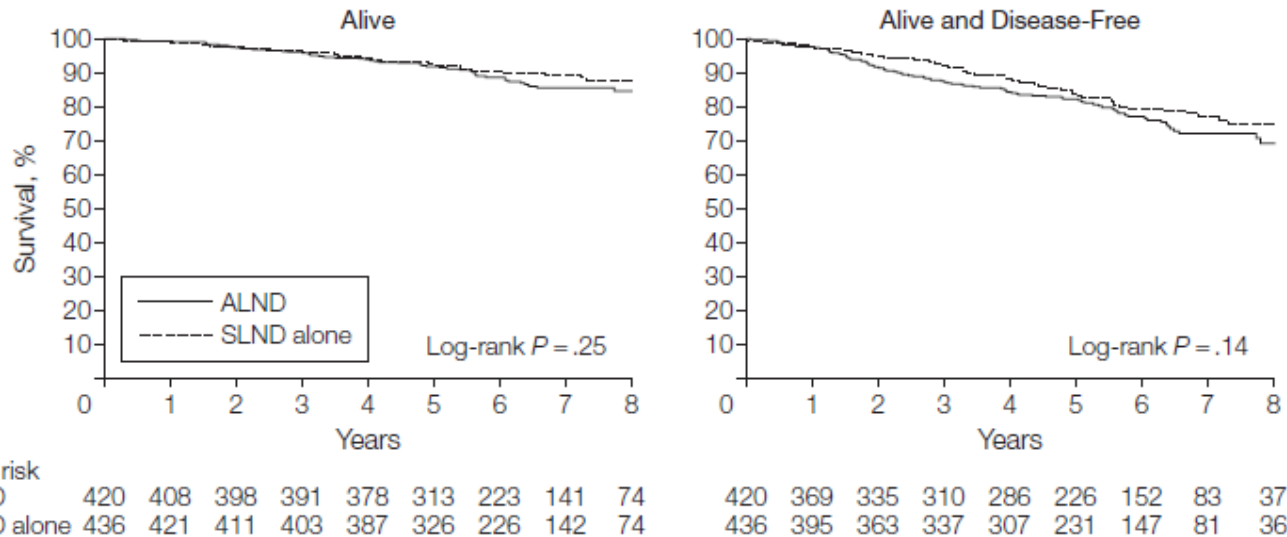


- SLNs were successfully removed in 97.2% with a **false-negative rate of 9.8%**
- **Overall survival, disease-free survival, and regional control** were statistically **equivalent** between groups.

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Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis

A Randomized Clinical Trial



- In the ALND group, **27.3% patients had additional metastasis in lymph nodes removed by ALND**
- In the, at a median follow-up of 6.3 years, **neither 5-year regional recurrence, nor 5-year overall survival differed significantly** between the two arms

Current approach of the axilla in patients with early-stage breast cancer

SLN biopsy BEFORE neoadjuvant chemotherapy

PROS

- provides pathological information about axillary nodal status without the confounding effects of NAC
- can help select pN0 patients *ab initio* for whom adjuvant locoregional radiotherapy may be spared

CONS

- Clinical utility limited, since it generally does not affect the decision regarding the choice of systemic therapy
- May preclude information that may help select locoregional radiotherapy Mohtai et al, Lancet 2017,
 - does not provide quantification of initial disease burden

Current approach of the axilla in patients with early-stage breast cancer

SLN biopsy AFTER neoadjuvant chemotherapy

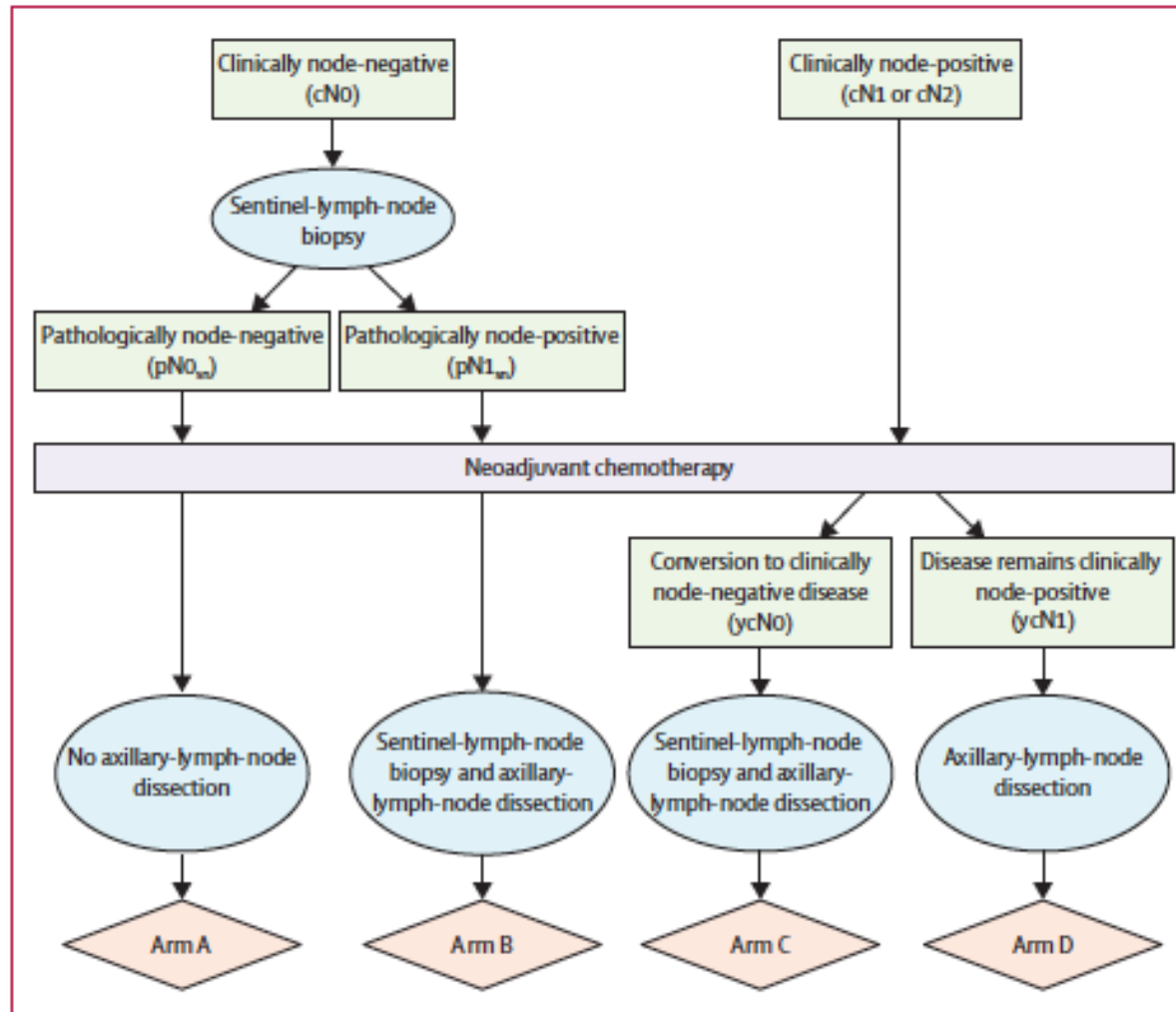
PROS

- Can potentially avoid the need for ALND in 30–40% of patients who experience cPR after NAC
- Can show pathological axillary downstaging by NAC, an important prognostic factor and surrogate marker for improved overall survival (particularly in patients with triple-negative or HER2- positive breast cancer)

CONS

- success rates in terms of identification rate and false negative rate slightly less favourable by comparison with upfront SLN biopsy

Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study



- SENTINA is a four-arm, prospective, multicentre cohort study undertaken at 103 institutions in Germany and Austria.
- 1737 women with breast cancer who were scheduled for neoadjuvant chemotherapy were enrolled into the study.

Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort

	Arms A and B	Arm B	Arm C	p
Hot spot on lymphoscintigraphy	1014/1022 (99%)	236/360 (66%)	476/592 (80%)	<0.0001
Overall surgical detection rate (n/N; 95% CI)	99.1% (1013/1022; 98.3–99.6)	60.8% (219/360; 55.6–65.9)	80.1% (474/592; 76.6–83.2)	<0.0001
Overall surgical detection rate with radiocolloid alone	98.8% (573/580; 97.5–99.5)	52.9% (126/238; 46.4–59.4)	77.4% (301/389; 72.9–81.4)	..
Overall surgical detection rate with radiocolloid and blue dye	99.5% (399/401; 98.2–99.9)	76.2% (80/105; 66.9–84.0)	87.8% (144/164; 81.8–92.4)	..
Sentinel lymph nodes removed				
0	9/1022 (1%)	141/360 (39%)	118/592 (20%)	..
1	284/1022 (28%)	96/360 (27%)	142/592 (24%)	..
2	294/1022 (29%)	56/360 (16%)	131/592 (22%)	..
3	186/1022 (18%)	22/360 (6%)	81/592 (14%)	..
4	114/1022 (11%)	20/360 (6%)	59/592 (10%)	..
>4	135/1022 (13%)	25/360 (7%)	61/592 (10%)	..
At least one sentinel node removed				
All patients	Mean 2.7, median 2.0	Mean 2.4, median 2.0	Mean 2.7, median 2.0	<0.0001
Radiocolloid alone	Mean 2.6, median 2.0	Mean 2.3, median 2.0	Mean 2.6, median 2.0	0.012
Radiocolloid and blue dye	Mean 2.8, median 2.0	Mean 2.6, median 2.0	Mean 2.9, median 3.0	0.059

Data are n/N (%), unless otherwise stated.

Table 3: Detection of sentinel lymph nodes, according to selected factors

- In women **SNLB before neoadjuvant chemotherapy (arm A + B) detection rate was 99.1%**
- In patients who had a **second SNLB after neoadjuvant chemotherapy (arm B), the detection rate was 60.8%**
- In patients who **converted after neoadjuvant CT from cN+ to ycN0 (arm C), the detection rate was 80.1%**

Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study

	Arm B (n=64)	Arm C (n=226)
Overall false-negative rate (n/N; 95% CI)	51.6% (33/64; 38.7–64.2)	14.2% (32/226; 9.9–19.4)
False-negative rate, according to number of sentinel nodes removed		
1	66.7% (16/24)	24.3% (17/70)
2	53.8% (7/13)	18.5% (10/54)
3	50.0% (5/10)	7.3% (3/41)
4	50.0% (3/6)	0.0% (0/28)
5	18.2% (2/11)	6.1% (2/33)
False-negative rate, according to detection technique		
Radiocolloid alone	46.2% (18/39)	16.0% (23/144)
Radiocolloid and blue dye	60.9% (14/25)	8.6% (6/70)

Data are rate (number of patients), unless otherwise stated.

Table 4: False-negative rate of sentinel-lymph-node resection in patients with positive nodes, according to selected factors

- In patients who **converted after neoadjuvant chemotherapy from cN+ to ycN0 (arm C), false-negative rate was 14.2%**
- In patients who had a **second sentinel-lymph-node biopsy** procedure after neoadjuvant chemotherapy (arm B), **false-negative rate was 51.6%**
- A **significant relation** was seen between the **number of resected sentinel lymph nodes and the false-negative rate**

- **Sentinel-lymph-node biopsy is a reliable diagnostic method before neoadjuvant chemotherapy.**
- **After systemic treatment or early sentinel-lymph-node biopsy, the procedure has a lower detection rate and a higher false negative rate**

Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer

Table 5 Within-study comparison of sentinel lymph node biopsy sensitivity for women with breast cancer treated with and without preoperative chemotherapy

Reference	Sensitivity after preoperative chemotherapy		Sensitivity without preoperative chemotherapy	
	No. of patients	%	No. of patients	%
11	6 of 9	67 (35, 88)	20 of 22	91 (72, 98)
12	16 of 20	80 (58, 92)	8 of 10	80 (48, 94)
13	15 of 15	100 (79, 100)	200 of 225	89 (84, 92)
25	19 of 19	100 (83, 100)	19 of 21	90 (71, 97)
26	24 of 27	89 (72, 96)	91 of 101	90 (83, 95)
Pooled	80 of 90	89 (81, 94)	338 of 379	89 (86, 92)

- Meta-analyses resulted in estimates for **identification rates of 91%** (95% IC 88 to 94) and **sensitivity of 88%** (95% IC 84 to 91) respectively.
- **SLNB is a reliable tool for planning treatment after preoperative chemotherapy.**

Is sentinel lymph node biopsy a viable alternative to complete axillary dissection following neoadjuvant chemotherapy in women with node-positive breast cancer at diagnosis? An updated meta-analysis involving 3,398 patients

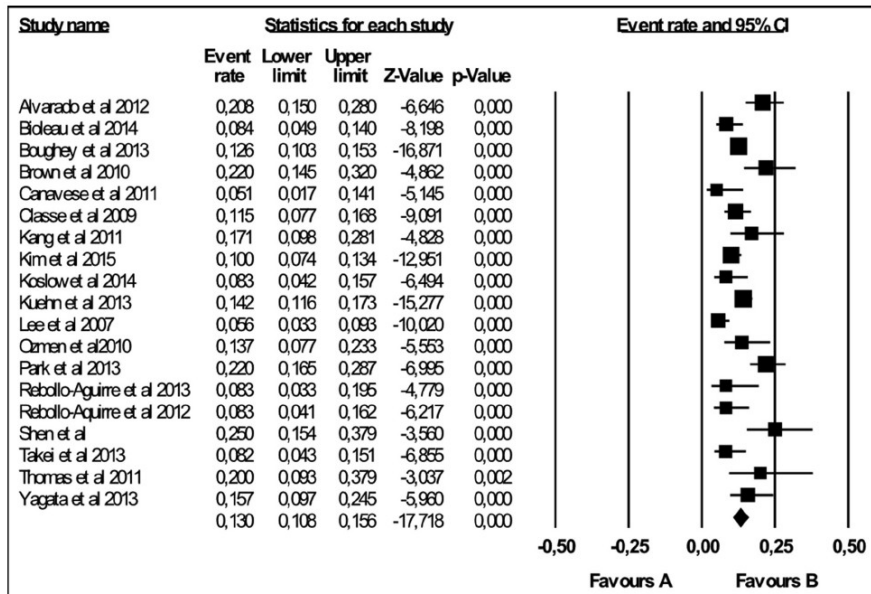


Figure 2 Forest plot showing event rate defined as FNR. Nineteen studies were included. The pooled estimate was found to be 13% (95 CI 10.8% to 15.6%).

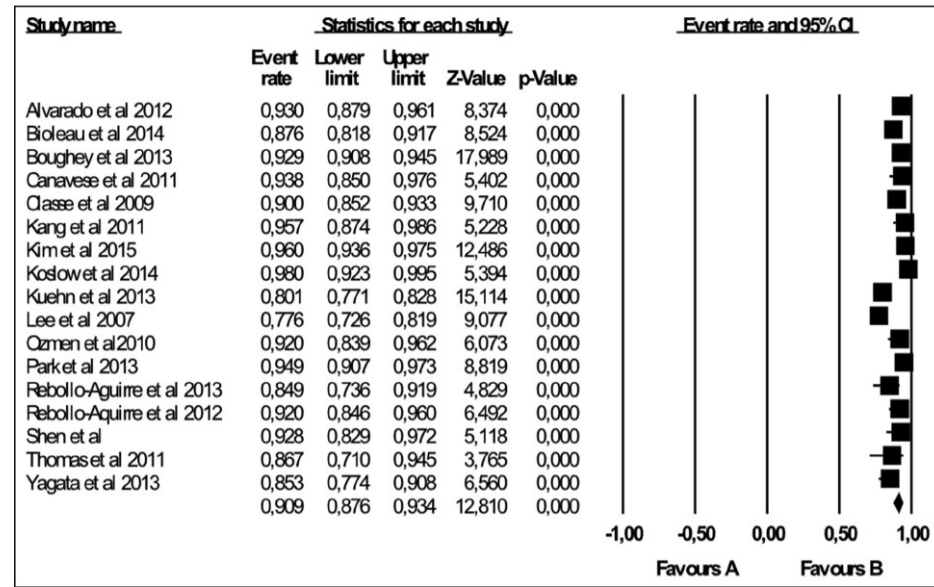


Figure 4 Forest plot showing event rate defined as IR. Seventeen studies were included. The pooled estimate was found to be 90.9% (95 CI 87.6% to 93.4%).

- The pooled estimate of the **IR** was **91%** and that of the **FNR** of **13%**
- **SLNB after NAC in biopsy-proven node-positive patients** results in reasonably acceptable FNR and IR, making it a **valid alternative management strategy to axillary dissection**

Sentinel Lymph Node Surgery After Neoadjuvant Chemotherapy in Patients With Node-Positive Breast Cancer The ACOSOG Z1071 (Alliance) Clinical Trial

Table 3. Factors Affecting the Likelihood of a False-Negative Sentinel Lymph Node Finding in the 310 Women With cN1 Disease at Presentation, 2 or More SLNs Examined, and Residual Nodal Disease After Neoadjuvant Chemotherapy

	False-Negative SLN Findings, No. (Total)	FNR (95% CI), %	Fisher Exact Test, P Value
Age, y			
18.0-49.9	20 (150)	13.3 (8.3-19.8)	.73
≥50.0	19 (160)	11.9 (7.3-17.9)	
BMI			
≥25.0	25 (227)	11.0 (7.3-15.8)	.18
<25.0	14 (83)	16.9 (9.5-26.7)	
Clinical T category prior to chemotherapy			
Tis, T0, T1, or T2	32 (225)	14.2 (9.9-19.5)	.18
T3 or T4	7 (85)	8.2 (3.4-16.2)	
Chemotherapy duration, mo			
≤4.0	20 (201)	10.0 (6.2-15.0)	.07
≥4.1	19 (109)	17.4 (10.8-25.9)	
Palpable, fixed, or matted nodes after chemotherapy ^a			
Yes	10 (52)	19.2 (9.6-32.5)	.17
No	28 (247)	11.3 (7.7-16.0)	
Mapping agents used			
Single	12 (59)	20.3 (11.0-32.8)	.05
Dual	27 (251)	10.8 (7.2-15.3)	
Multiple injection sites ^b			
Yes	5 (70)	7.1 (2.4-15.9)	.21
No	30 (225)	13.3 (9.2-18.5)	
No. of SLNs examined			
2	19 (90)	21.1 (13.2-31.0)	.007
≥3	20 (220)	9.1 (5.6-13.7)	

- 649 patients with cN1 disease, underwent chemotherapy followed by both SLN surgery and ALND.
- **Detection rate was 96.9% and FNR 12.6% (if ≥ 2 SNLNs were identified)**
- **Pathological complete nodal response was 41.0%**
- **both the use of dual-agent mapping and recovery of more than 2 SLNs were associated with a lower likelihood of false-negative SLN findings**
- **Until further data are available, we recommend that SLN surgery after chemotherapy not be performed in patients with clinically evident residual nodal disease or poor response to chemotherapy.**

Sentinel Node Biopsy After Neoadjuvant Chemotherapy in Biopsy-Proven Node-Positive Breast Cancer: The SN FNAC Study

Table 2. Impact of No. of SNs Removed, Method of SN Identification, Definition of Positive SN, and Clinical Stage at Presentation on FNR, NPV, and Accuracy of SNB After Neoadjuvant Chemotherapy

Factor	FNR		NPV		Accuracy		P
	No.	%	No.	%	No.	%	
No. of SNs removed							.076
1	4 of 22	18.2	11 of 15	73.3	29 of 33	87.9	
≥ 2	3 of 61	4.9	32 of 35	91.4	90 of 93	96.8	
Method of lymph node mapping							.190
Isotope only	4 of 25	16.0	10 of 14	71.4	31 of 35	88.6	
Dual tracers (isotope and blue dye)	3 of 58	5.2	34 of 37	91.9	89 of 92	96.7	
Definition of positive SN							
Any size (ypN0[i+] + ypN1mi + ypN1)	7 of 83	8.4	44 of 51	86.3	120 of 127	94.5	
> 0.2 mm (ypN1mi + ypN1)	11 of 83	13.3	44 of 55	80.0	116 of 127	91.3	
> 2 mm (ypN1)	14 of 83	16.9	44 of 58	75.9	113 of 127	89.0	
Clinical stage at presentation							
T stage							
T0	1 of 4	25.0	1 of 2	50.0	4 of 5	80.0	
T1	0 of 7	0.0	1 of 1	100.0	8 of 8	100.0	
T2	1 of 37	2.7	27 of 28	96.4	63 of 64	98.4	
T3	5 of 35	14.3	15 of 20	75.0	45 of 50	90.0	
N stage							
N0	0 of 11	0.0	3 of 3	100.0	14 of 14	100.0	
N1	7 of 67	10.4	38 of 45	84.4	98 of 105	93.3	
N2	0 of 4	0.0	3 of 3	100.0	7 of 7	100.0	

Abbreviations: FNR, false-negative rate; NPV, negative predictive value; SN, sentinel node; SNB, sentinel node biopsy.

- 153 patients with biopsy-proven node-positive breast cancer (T0-3, N1-2) underwent both SNB and CNB.
- **IHC use was mandatory, and SN metastases of any size, including isolated tumor cells (ypN0[i], 0.2 mm) were considered positive.**
- **The SNB IR was 87.6%, and the FNR was 8.4%.**
- **If SN ypN0(i)s had been considered negative, the FNR would have increased to 13.3%**
- **the FNR of SNB after NAC was decreased with the use of dual tracers and when ≥ 2 SLNs were removed**

Swedish prospective multicenter trial evaluating sentinel lymph node biopsy after neoadjuvant systemic therapy in clinically node-positive breast cancer

False negative SLN findings after NAC in different scenarios

Scenario	True pos (<i>n</i>)	False neg (<i>n</i>)	FNR ^a (%)
Overall	79	13	14.1
Dual mapping performed	71	11	13.4
IBC excluded (<i>n</i> = 15)	76	11	12.6
ITC considered ypN+	87	10	10.3
SLNB with 1 node retrieved	31	11	26.2
SLNB with ≥ 2 nodes	48	2	4.0
SLNB with ≥ 3 nodes	23	0	0.0

^a Calculated as the number of patients with a false negative SLN in each scenario divided by the number of false negative and true positive SLNs in the same scenario

NAST neoadjuvant systemic therapy, *FNR* false negative rate, *SLN* sentinel lymph node, *SLNB* sentinel lymph node biopsy, *IBC* inflammatory breast cancer, *ITC* isolated tumor cells, *FNR* false negative rate

- The **SLN identification rate was 77.9% but improved to 80.7% with dual mapping.**
- **A positive SLNB was found in 52%, almost 66% of whom had additional positive non-sentinel lymph nodes.**
- The **overall pathologic nodal response rate was 33.3% (66/195).**
- The **overall FNR was 14.1% but decreased to 4% when only patients with two or more sentinel nodes were analyzed.**
- **In biopsy-proven node-positive breast cancer, SLNB after NAC is feasible even though the identification rate is lower than in clinically node-negative patients**

Caveats of SLNB after NAC

- **For cN+ patients after NAC completion** the SLNB seems to be insufficient, with reported **FNRs ranging from 7% to 25%**.
- Because the SLNB aims to identify patients with an ax-pCR without missing residual disease, a **negative predictive value (NPV) of 95% would be desirable**.
- A high NPV is especially important because **residual tumor is considered resistant to administered chemotherapy and might require additional treatment**

How to decrease the FNR of SLNB after NAC in biopsy-proven node-positive breast cancer patients ?

- Selecting only patients with ≥ 2 **(3) SLNs identified**
- Broadening the definition of SLN metastasis after NAC to **include isolated tumor cells**
- Selecting only patients with **sonographically unsuspecting lymph nodes** for SLNB after NAC
- Use of **nomograms** for predicting nonsentinel lymph node metastasis after NAC
- **Pre-NAC marking** of the cytologically verified lymph node

Using ultrasound and palpation for predicting axillary lymph node status following neoadjuvant chemotherapy e Results from the multi-center SENTINA trial

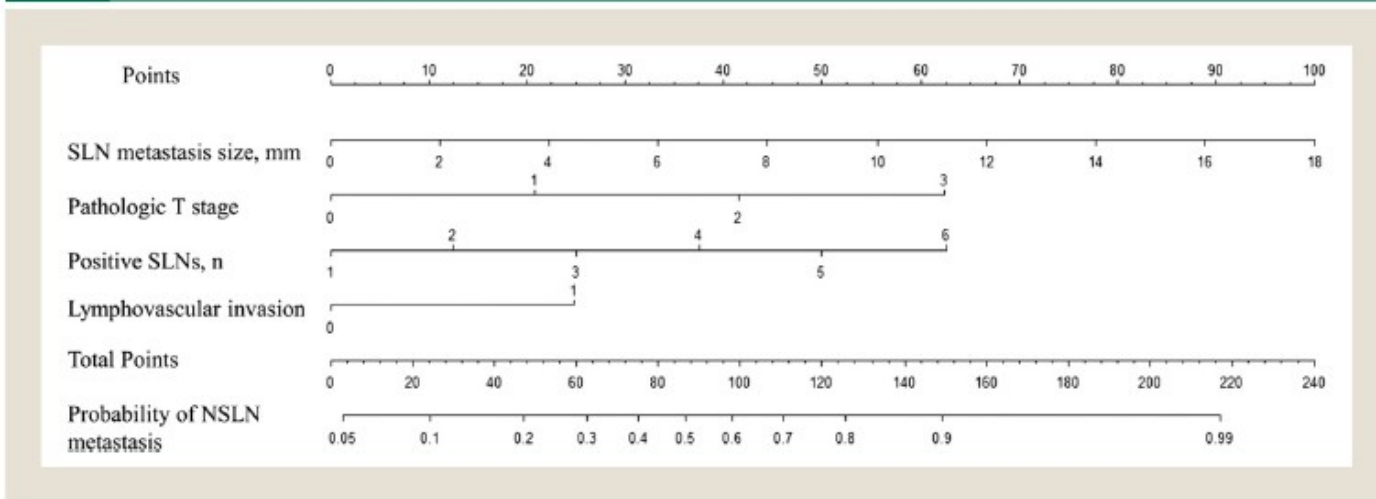
Arm C/D pathologic nodal status vs. investigator defined cN status.

	cN after NST overall evaluation											
	Negative					Positive						
	N					%	N					%
pN												
Negative	298					50.3	28					22.8
Positive	294					49.7	95					77.2
Predictive test	True negative	False negative	True positive	False positive	Sensitivity, %	False negative rate, %	Specificity, %	False positive rate, %	Positive predictive value, %	Negative predictive value, %		
cN after NACT overall evaluation	298	294	95	28	24.4	75.6	91.4	8.6	77.2	50.3		

- The investigators combined classification (palpation and ultrasound) resulted in a **sensitivity of 24.4%, specificity 91.4%, and a NPV of 50.3%.**
- Of 592 patients with **unsuspicious axillary nodes (cN0) following NST, 50.3% were pN0, 25.5%**

Predictive Factors for Nonsentinel Lymph Node Metastasis in Patients With Positive Sentinel Lymph Nodes After Neoadjuvant Chemotherapy: Nomogram for Predicting Nonsentinel Lymph Node Metastasis

Figure 2 Nomogram to Predict Nonsentinel Lymph Node (NSLN) Metastasis in Patients With Positive Sentinel Lymph Node (SLN) Metastasis After Neoadjuvant Chemotherapy (NAC)



- **Pathologic T stage, lymphovascular invasion, SLN metastasis size, and number of positive SLN metastases were independent predictors for NSLN metastases ($P < .05$)**
- **The NAC nomogram was based on these 4** myotep/pt/slno/medst Cancer 2017

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

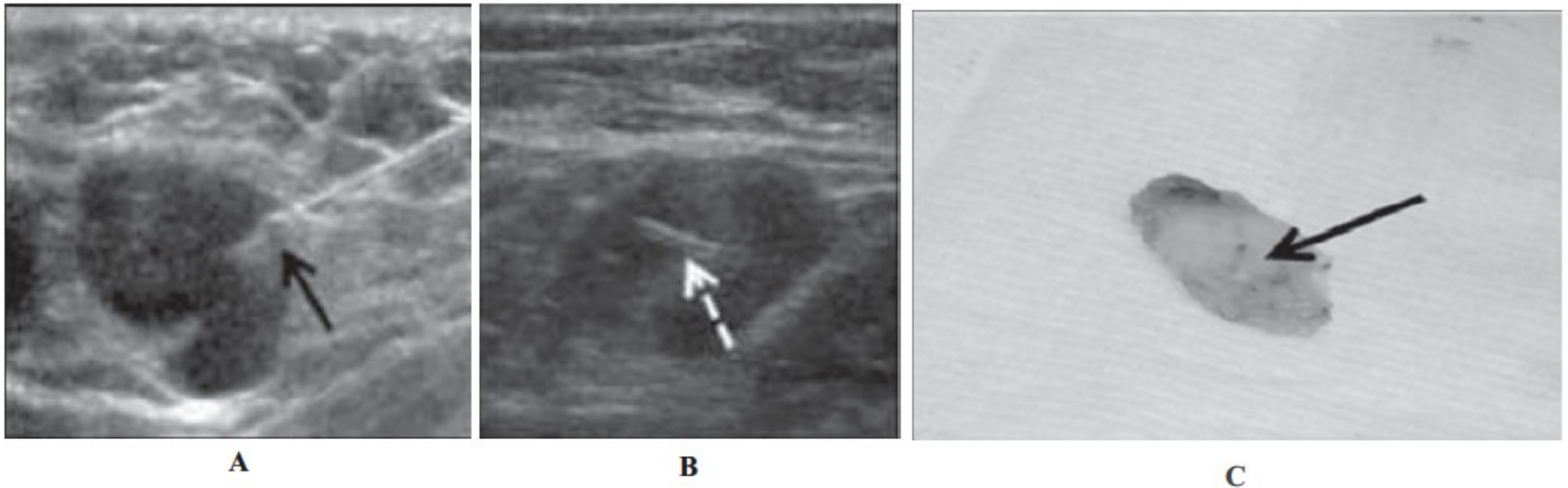
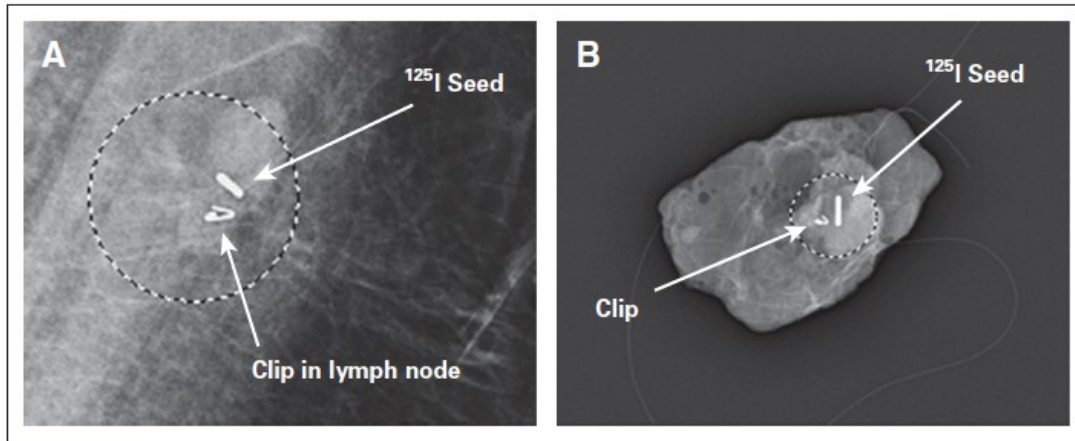


FIGURE 1. A, Insertion of a radioactive iodine seed in an axillary lymph node under ultrasound guidance. The black arrow indicates the tip of an 18-G needle through which the iodine seed is inserted in the lymph node. B, Position of the iodine seed in the lymph node. C, Excised lymph node with the iodine seed in situ.

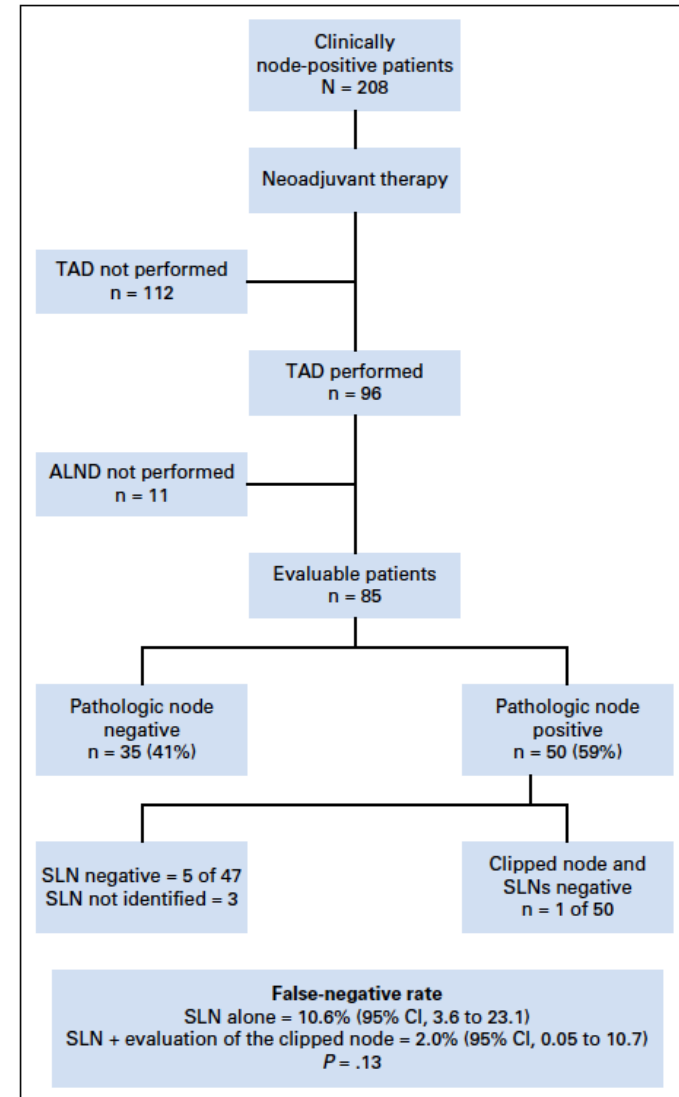
- **Prior to NST, proven tumor-positive axillary lymph nodes were marked with a 125I seed (MARI-node)**
- **After NST, the MARI node was selectively removed** using a γ -detection probe and a complementary axillary lymph node dissection was performed in all patients
- **Identification rate was 97% and false negative rate was 7%.**

Improved Axillary Evaluation Following Neoadjuvant Therapy for Patients With Node-Positive Breast Cancer Using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection (TAD)

Iodine-125 seed localized removal of clipped axillary lymph nodes

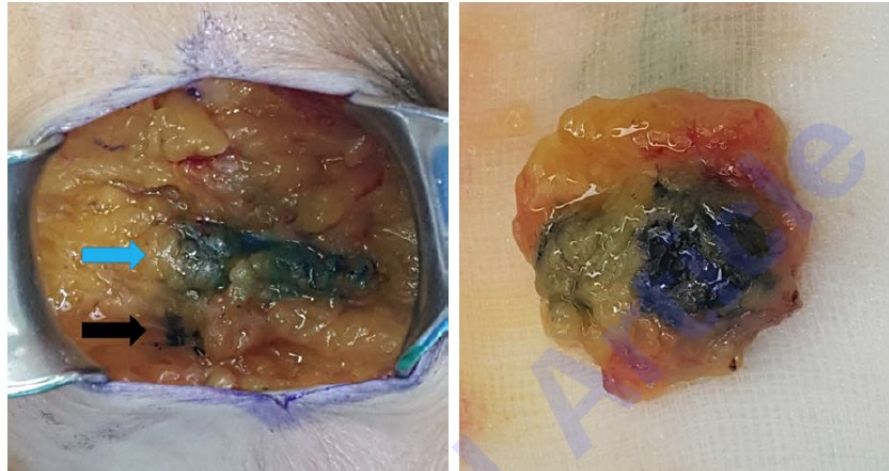


- Patients undergoing TAD had SLND and selective removal of the clipped node using iodine-125 seed localization placed in the clipped node under ultrasound guidance 1 to 5 days before surgery.
- FNR of the clipped node was 4.2% (95% CI, 1.4 to 9.5)
- FNR of SNLD was 10.1% (95% CI, 4.2 to 19.8)
- FNR of TAD was 2.0% (1 of 50; 95% CI, 0.05 to 10.7).
- Marking nodes with biopsy-confirmed metastatic disease allows for selective removal and improves pathologic evaluation for residual nodal disease after chemotherapy



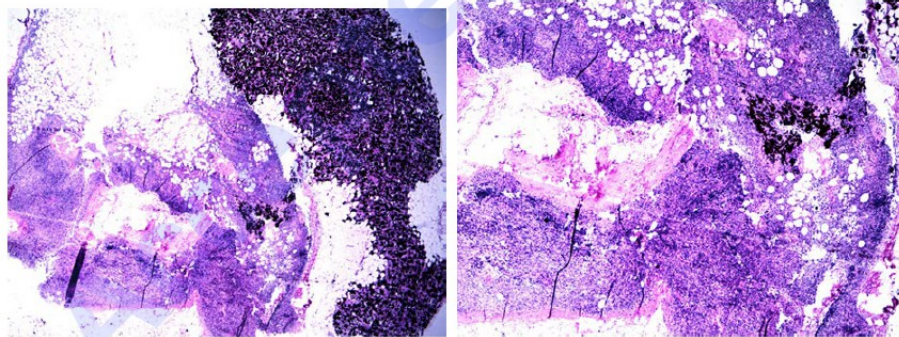
Feasibility of Charcoal Tattooing of Cytology-Proven Metastatic Axillary Lymph Node at Diagnosis and Sentinel Lymph Node Biopsy after Neoadjuvant Chemotherapy in Breast Cancer Patients

Fig. 2. Intraoperative photographs and pathologic slides of a sentinel lymph node. (A) Charcoal tattoo (black arrow) and blue dye (blue arrow) tracks during axillary surgery. (B) Excised sentinel node marked with the tattoo and blue dye. Low-power field (H&E staining, x20) (C) and high-power field (H&E staining, x100) (D) microscopic views show tattoo pigments with no residual metastatic carcinoma in the sentinel node.



(A)

(B)



(C)

(D)

- 20 patients with cytology-proven node metastases prospectively underwent **charcoal tattooing at diagnosis.**
- **SLNB using dual tracers and axillary surgery after NCT were then performed.**
- **False-negative rate (FNR), of hot/blue SLNB was 20.0%,**
- **When excised tattooed node and SNLB were calculated together FNR was 0.0%)**
- The tattooing procedure without additional preoperative localization is advantageous for improving the diagnostic performance of SLNB in this setting

Nodal axillary management N+ breast cancer patients undergoing NAC MARI vs TAD vs RISAS vs Charcoal tattooing

Kyoto Breast Cancer Consensus Conference 1

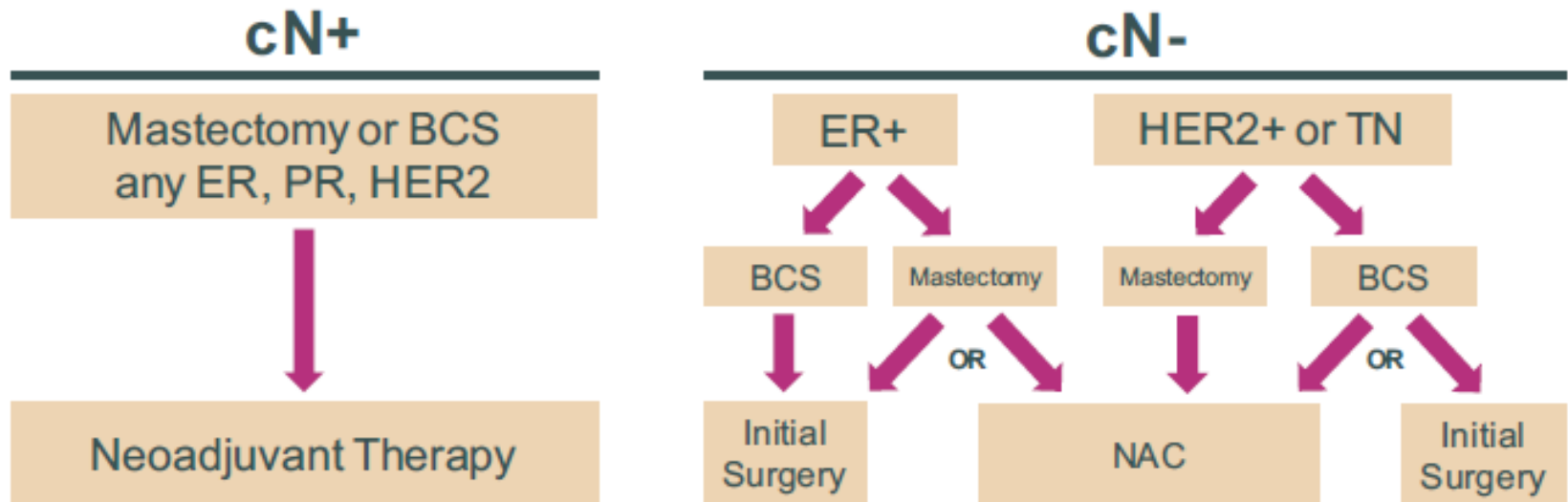
De-escalation of axillary surgery in early breast cancer

Ismail Jatoi, John R Benson, Masakazu Toi

“Downstaging of biopsy-proven node-positive patients with neoadjuvant chemotherapy could safely permit sentinel lymph node biopsy alone when the index node has been successfully retrieved at surgery, while nodal deposits of any size continue to mandate completion axillary lymph node dissection”

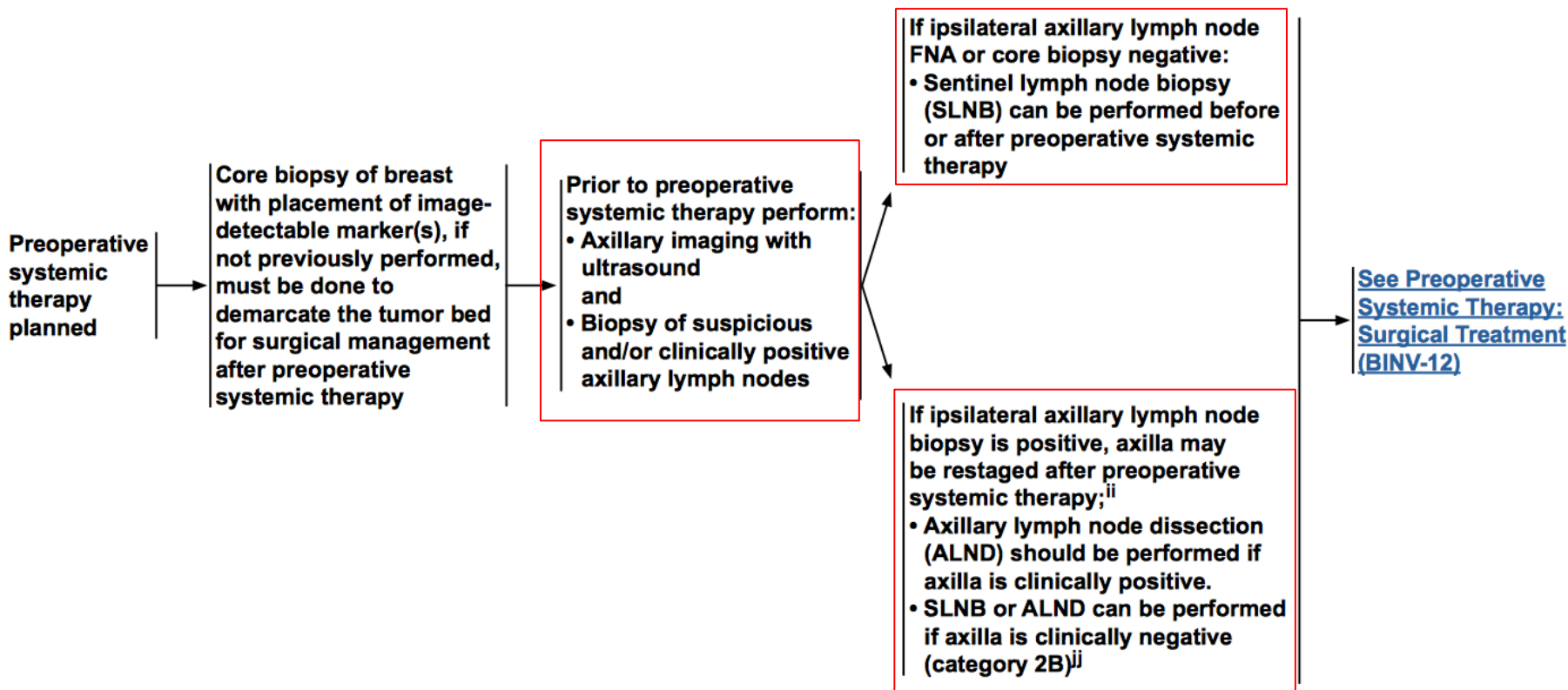
De-escalating and escalating surgery in the management of early breast cancer

Algorithm for Minimizing the Need for Axillary Node Dissection



- Patients presenting with **nodal disease (cN1)** have no option other than **neoadjuvant therapy to avoid axillary dissection**.
- Patients who are **cN0 and ER+ having BCS** should have **initial surgery**, while those who are **ER- or HER2+ having mastectomy** should receive **NAC**.
- For TN or HER2 + patients having breast conservation, the likelihood of ALND does not differ for initial surgery versus NAC and the same is true for ER + patients having mastectomy. *The Breast, in press 2017*

PREOPERATIVE SYSTEMIC THERAPY: BREAST AND AXILLARY EVALUATION



ⁱⁱMarking 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.

^{jj}Among patients shown to be node-positive prior to preoperative systemic therapy, SLNB has a >10% false-negative rate when performed after preoperative 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 patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SPECIAL ARTICLE

De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017

Axillary surgery following neoadjuvant therapy

- In a woman who presented with a **clinically negative axilla** and who received neoadjuvant treatment, the Panel **strongly believed sentinel node biopsy to be appropriate** and favored the biopsy be carried out **after neoadjuvant treatment**.
- **There was more controversy** regarding sentinel node surgery for women who presented with a **clinically positive axilla**, and had a clinical response **with down staging to a clinically negative axilla**. The Panel believed **sentinel node biopsy**, as opposed to axillary dissection, to be **adequate if at least three or more negative sentinel nodes were detected and examined**. Because of concerns for false-negative results with limited sampling, sentinel node surgery was generally considered **not adequate if only one or two negative sentinel nodes were identified**.
- The Panel recommended that **patients with a clinically positive axilla or with macrometastases identified in sentinel nodes after neoadjuvant therapy** undergo **completion axillary dissection**
- **The Panel was split on whether residual micro-metastatic lymph node involvement warranted completion dissection** after neoadjuvant therapy.

Work in progress

- The **NSABP B-51/RTOG1304** trial is currently evaluating the benefit of **locoregional radiotherapy** in patients who **initially** present with **axillary nodal involvement** and who have **histologically negative nodes after NAC**
- For patients who present with **documented axillary lymph node involvement** and have a **positive SLN biopsy after NAC**, The **ALLIANCE 11202 trial** (NCT01901094) randomly assigns to **completion ALND or to no further axillary surgery (assuming that regional nodal radiotherapy will be used)** to assess whether further decrease in the need for ALND can be achieved



Problemi aperti

- Utilizzo del doppio tracciante per la ricerca del LFNS
- Indicazione a DA in caso di micrometastasi/ITC del LFNS
- Numero di LFNS esaminati sufficiente ad evitare la DA di completamento
- Metodo di localizzazione del LFN MTS dopo CT neoadiuvante