# Axillary Nodal Evaluation Following Neoadjuvant Chemotherapy

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**Amy Rivere, MD FACS**
**October 29, 2022**

# What is the History?

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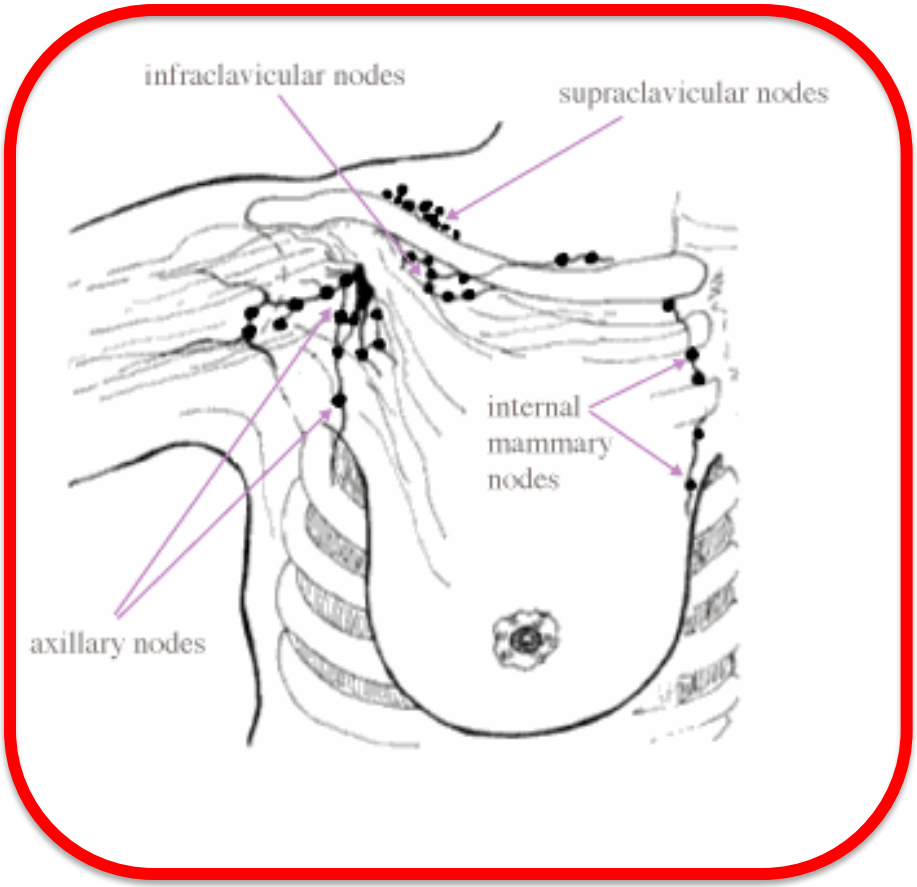
# Purpose of Axillary Evaluation

- To guide adjuvant therapy- both systemic and radiation treatments
- Remove the disease to provide regional control
- Provide prognostic information

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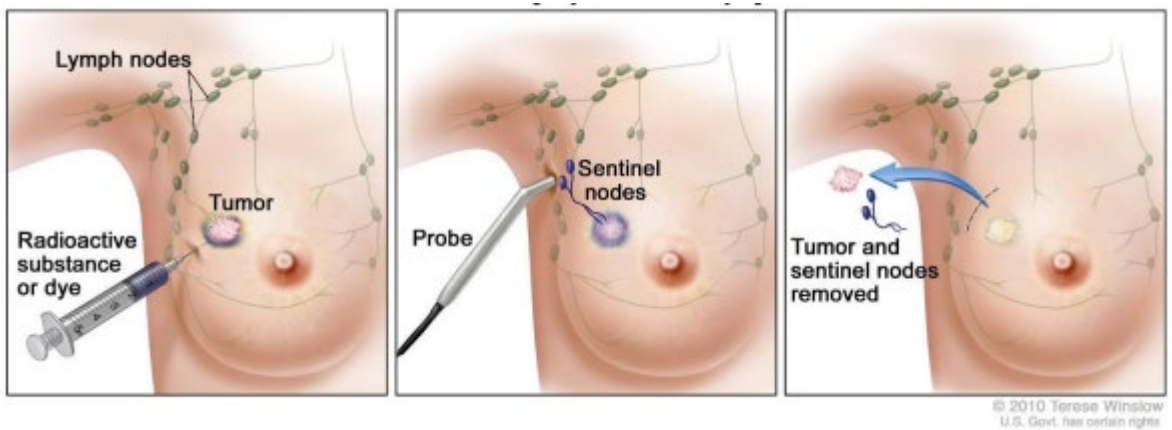
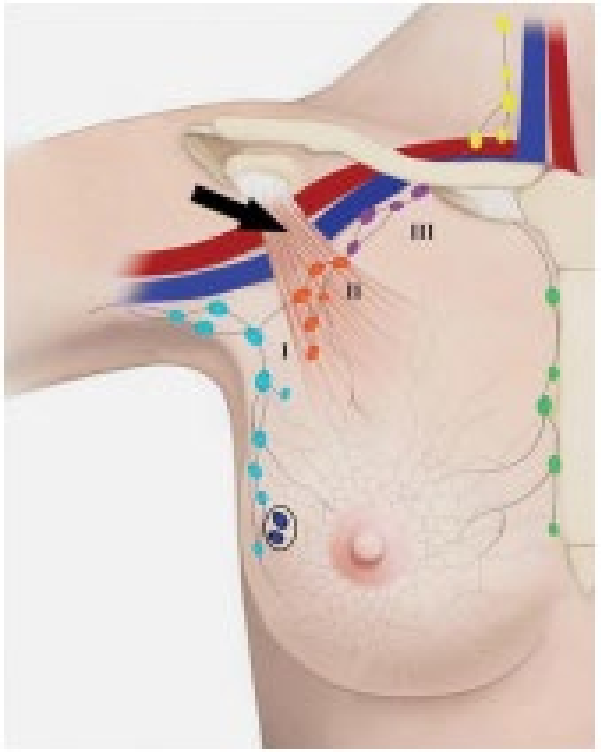
# Two Traditional Axillary Surgical Options:

- 1) Sentinel Lymph Node Biopsy (SLNB)




- 2) Axillary Node Dissection

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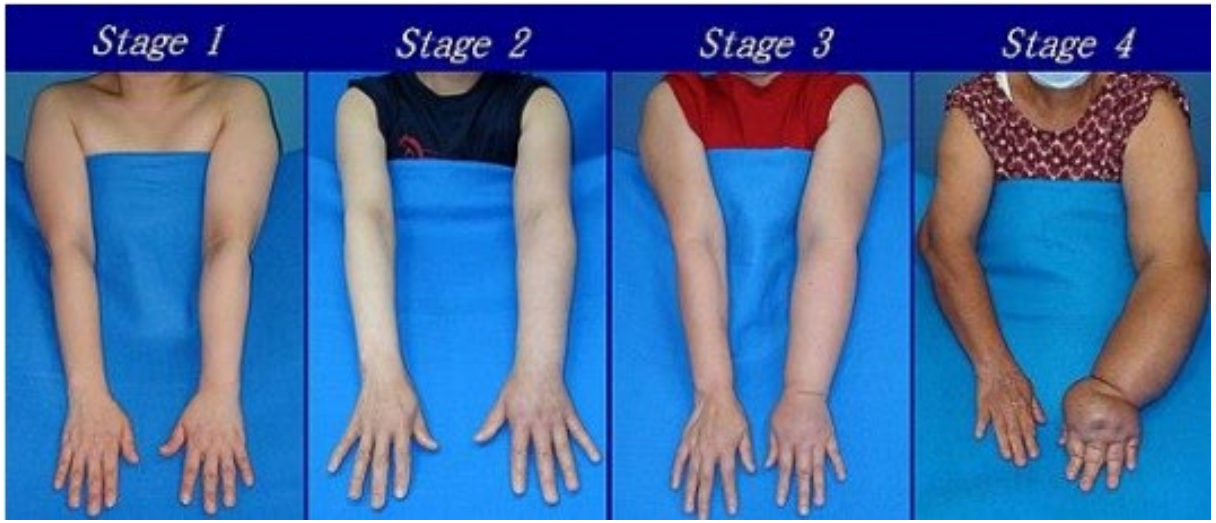
# Challenges of Axillary Dissection

- 1) Eventual development of arm lymphedema (up to 25%)




- 2) **Impact:** limited arm mobility, pain, sensation of heaviness, numbness, negative self-perception of body image, emotional distress, impact on employment, increased health care costs, etc.

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# Non-Operative Detection of Axillary Metastasis

| Modality | Sensitivity |
| --- | --- |
| PE + Mammo | 21-40% |
| MRI | 36-78% |
| PET | 50-70% |
| Axillary U/S | 40-85% |
| U/S + needle biopsy | 42-68% |

***There are No Biologic Predictors of Nodal Metastasis***

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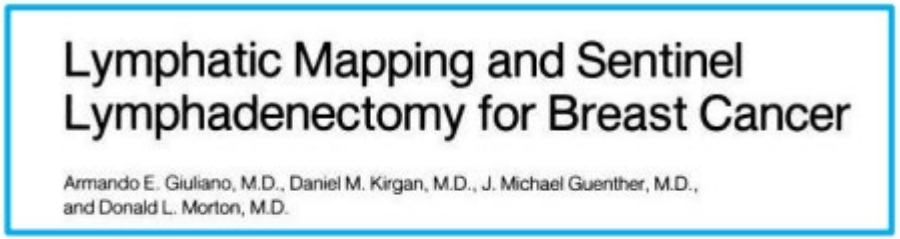
# Sentinel Node Biopsy (SNB):
# No Axillary Dissection for pN0

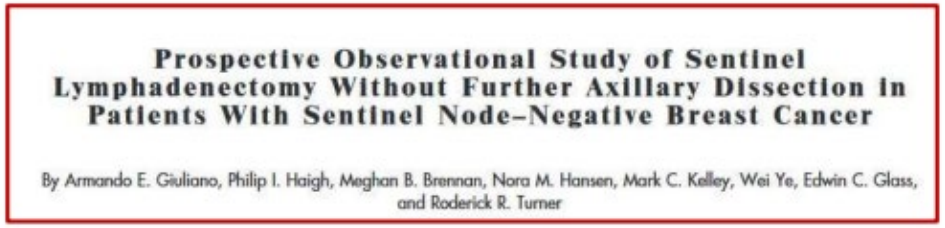
**Axillary dissection had been used for over a century to stage and treat patients with breast cancer. SNB (1991) was the first major innovation. Adequate treatment for pN0.**

## Evidence based!


Lymphatic Mapping and Sentinel Lymphadenectomy for Breast Cancer

Armando E. Giuliano, M.D., Daniel M. Kirgan, M.D., J. Michael Guenther, M.D., and Donald L. Morton, M.D.

ANNALS OF SURGERY
Vol. 220, No. 3, 391–401
© 1994 J. B. Lippincott Company


Prospective Observational Study of Sentinel Lymphadenectomy Without Further Axillary Dissection in Patients With Sentinel Node–Negative Breast Cancer

By Armando E. Giuliano, Philip I. Haigh, Meghan B. Brennan, Nora M. Hansen, Mark C. Kelley, Wei Ye, Edwin C. Glass, and Roderick R. Turner

J Clin Oncol 18:2553-2559. © 2000 by American Society of Clinical Oncology.

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**Sentinel Node Biopsy is the Foundation of Axillary Surgery!**

# Randomized Multicenter Trial of Sentinel Node Biopsy Versus Standard Axillary Treatment in Operable Breast Cancer: **The ALMANAC Trial**

**3.1** ALMANAC Trial Comparing Sentinel Node Biopsy to Conventional Axillary Treatment in Patients with Clinically Node-Negative Invasive Breast Cancer

| | Standard axillary procedure | Sentinel node biopsy | *p*-value |
|---|---|---|---|
| Nodal positivity[1] | 23% | 26% | — |
| Arm swelling (patient reported)[2]* | | | |
| 3 months — mild | 12% | 4% | <0.001† |
| 3 months — moderate or severe | 3% | 1% | |
| 6 months — mild | 14% | 4% | |
| 6 months — moderate or severe | 3% | 0.5% | |
| Sensory loss (patient reported)[1]* | | | |
| 1 month | 62% | 18% | <0.0001† |
| 3 months | 54% | 20% | |
| 6 months | 43% | 16% | |
| Sensory loss (physician assessed)[2]* | | | |
| 1 month | 42% | 14% | <0.0001† |
| 3 months | 38% | 14% | |
| 6 months | 37% | 14% | |
| Drain usage[2]* | 79% | 17% | <0.001† |
| Mean days of hospital stay[2]* | 5.4 days | 4.1 days | <0.001‡ |
| Return to normal activities in 6 months[2]* | 93% | 96% | <0.001‡ |

* Intention to treat; † Chi-square; ‡ Mann-Whitney test

SOURCES: [1] ALMANAC trialists'. Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 15.

[2] Mansel RE et al. Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 18.

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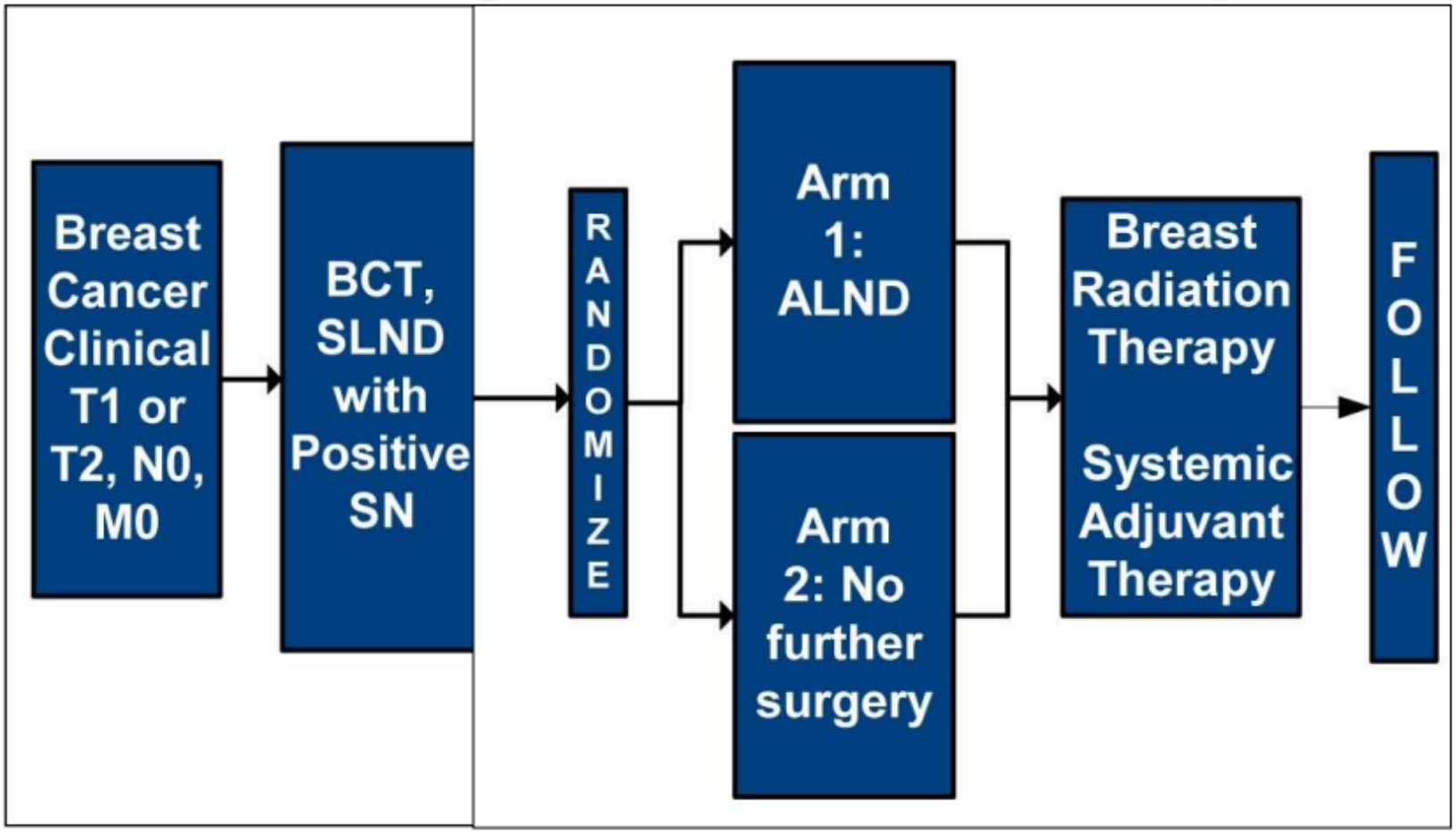
Journal of the National Cancer Institute, Vol. 98, No. 9, May 3, 2006

# Z0011: The Next Major Change
## No Axillary Dissection for pN+

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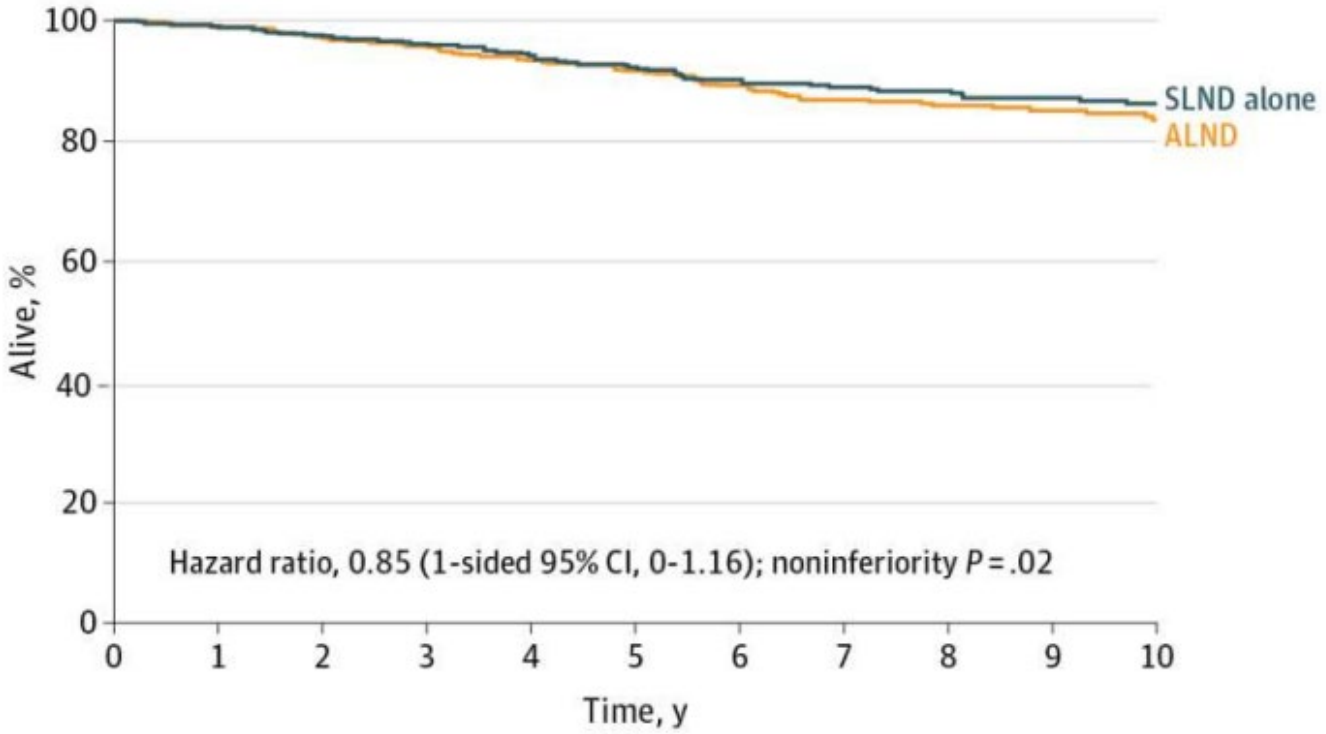
Giuliano AE, et al. JAMA 2011:569-75

# Z0011 10-Year Overall Survival




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| SLND alone | 436 | 411 | 391 | 317 | 246 | 146 |
| ALND | 420 | 398 | 381 | 317 | 248 | 134 |

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Giuliano AE. JAMA 318(10):918-926, 2017

# Z0011

- Z0011 showed that SNB is as effective as ALND for clinical T1T2N0 patients undergoing breast-conserving therapy and adjuvant systemic therapy.
- **Exclusions:**
  - Palpable nodes
  - Mastectomy
  - Gross extra-nodal extension
  - ≥ T3
  - Neoadjuvant therapy
  - 3 or more involved SN

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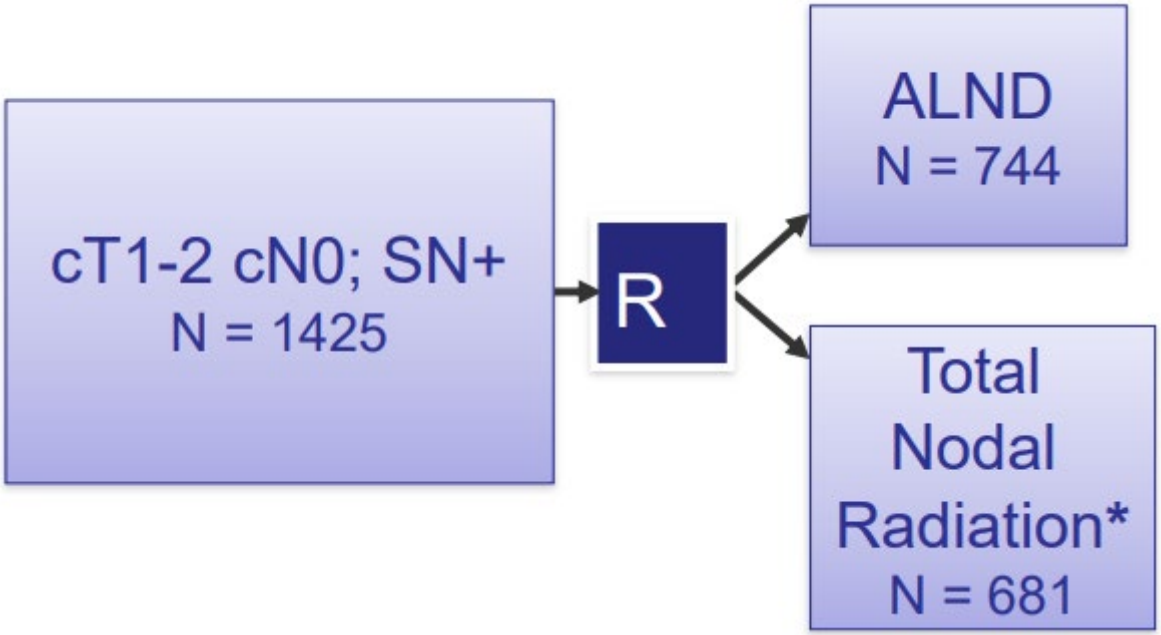
# AMAROS: Another Change




**Stratification: institution**
**Adjuvant systemic therapy by choice**
***axilla, supraclavicular, low neck**

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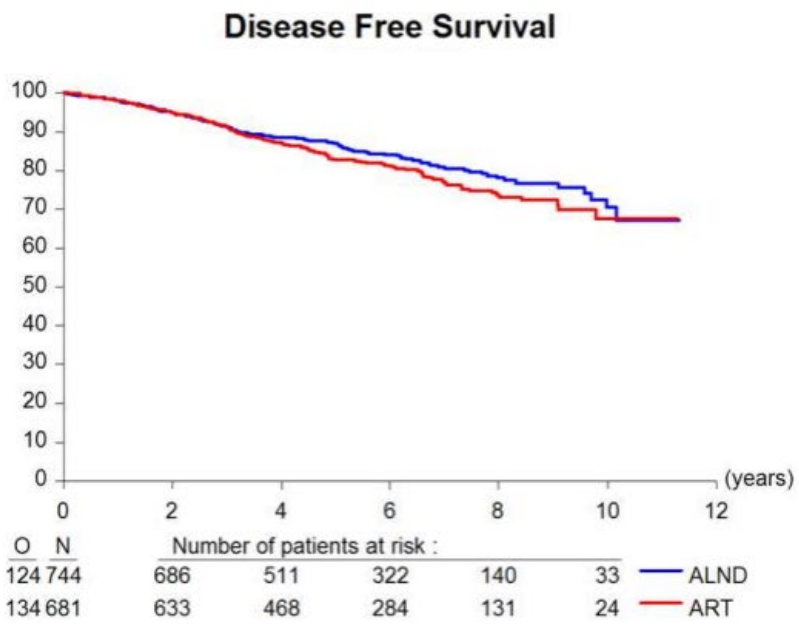
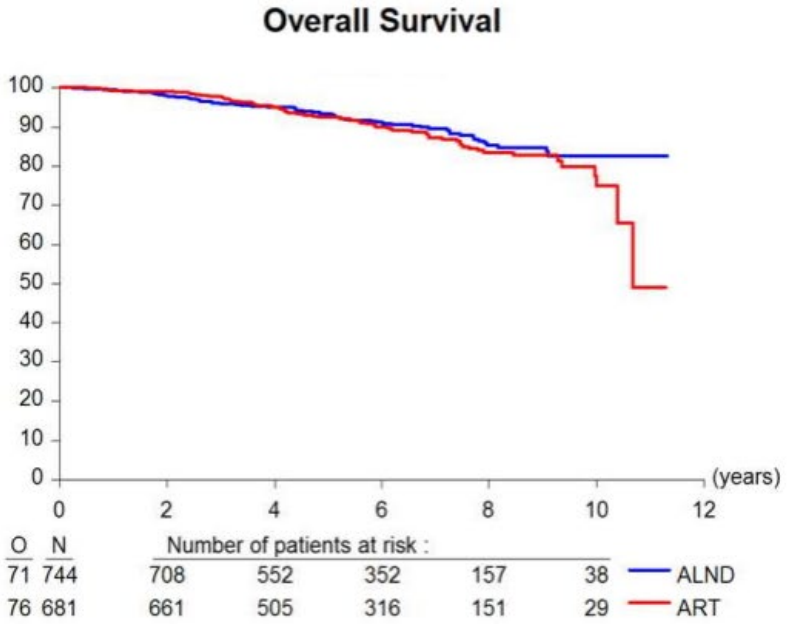
# AMAROS Survival Outcomes

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Donker et al. Lancet Oncol. 15(12): 1303-10, 2014.

# AMAROS

- Similar to Z0011
- AMAROS showed that SNB + irradiation is as effective as ALND
- **Mastectomy (17% of patients)**
- **Exclusions:**
  - Palpable nodes
  - T3
  - Neoadjuvant therapy

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# Z0011 and AMAROS

- These two prospective, randomized studies show that ALND is not necessary for some women with limited SN metastasis.

- All patients had an operation to determine axillary status.

- **These studies do not render axillary surgery obsolete.**

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# Omission of ALND is Yet Unproven

- ALL Clinically Node Positive
- Clinically Node Negative:
  - T3
  - 3 or more positive SN
  - Matted nodes
  - Contraindication for XRT

- **Positive node after NAC**

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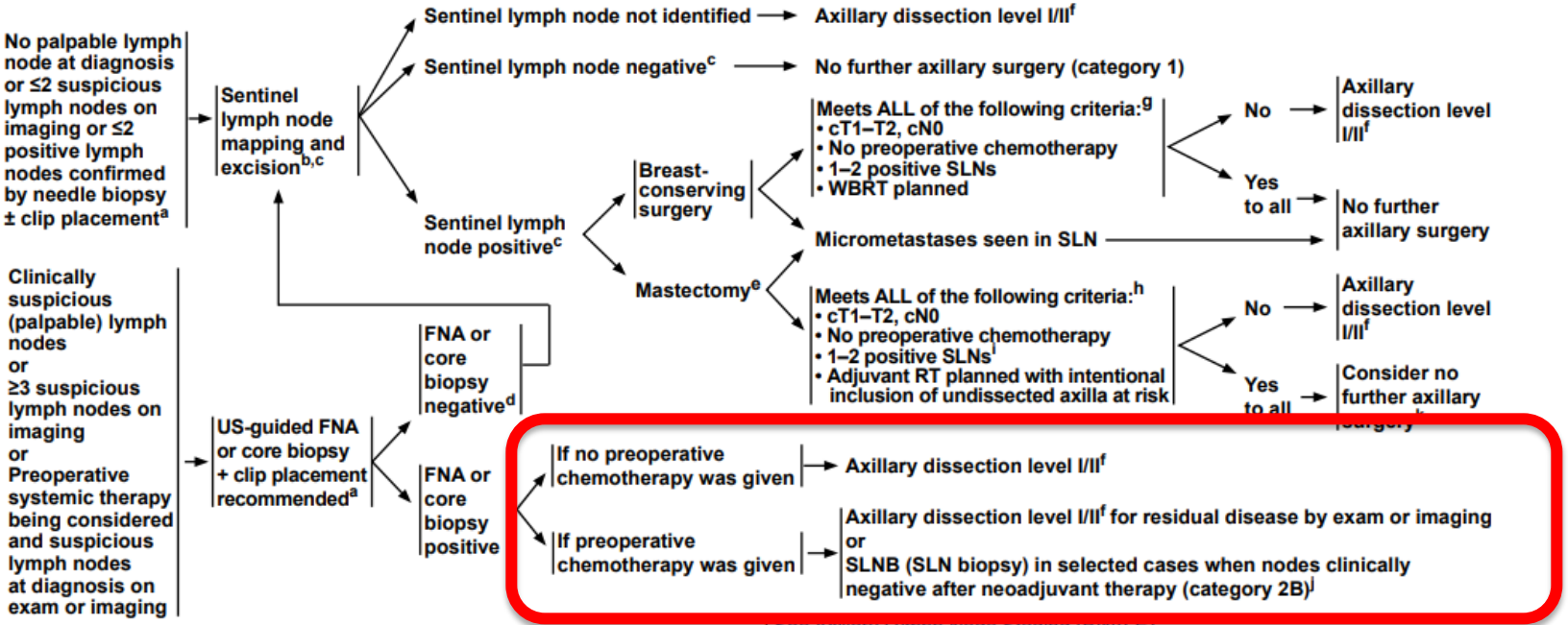
## CONSIDERATIONS FOR SURGICAL AXILLARY STAGING




[a] If a positive lymph node is clipped at biopsy, every effort should be made to remove the clipped node at the time of surgery.
[b] SLN mapping injections may be peritumoral, subareolar, or subdermal.
[c] Sentinel node involvement is defined by multilevel node sectioning with hematoxylin and eosin (H&E) staining. Cytokeratin immunohistochemistry (IHC) may be used for equivocal cases on H&E. Routine cytokeratin IHC to define node involvement is not recommended in clinical decision-making.
[d] If clinically negative axilla before chemotherapy and then have a positive sentinel node after chemotherapy, consider completion axillary lymph node dissection or multidisciplinary tumor board discussion on appropriateness of radiation of axilla without further surgery.
[e] Limited data exist for mastectomy patients.
[f] See Axillary Lymph Node Staging (BINV-E).
[g] ACOSOG Z0011: Giuliano AE, et al. JAMA. 2017 Sep 12;318(10):918-926.
[h] EORTC AMAROS: Donker M, et al. Lancet Oncol. 2014;15(12):1303-10; Rutgers E, et al. Cancer Research. 2019;79(4 Supplement):GS4-01-GS04-01.
[i] Limited data exist for ≥3 positive SLNs.
[j] Among patients shown to be N+ 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 ≥3 sentinel nodes (targeted axillary lymph node dissection). (Caudle AS, et al. J Clin Oncol 2016;34:1072-1078.)
[k] In the mastectomy setting, in patients who were initially cN0, who have positive nodes on SLNB, and have no axillary dissection, RT to the chest wall should include undissected axilla at risk ± RNI.

**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.**

# What About the False Negative Rate of SLNB after Neoadjuvant Chemotherapy?

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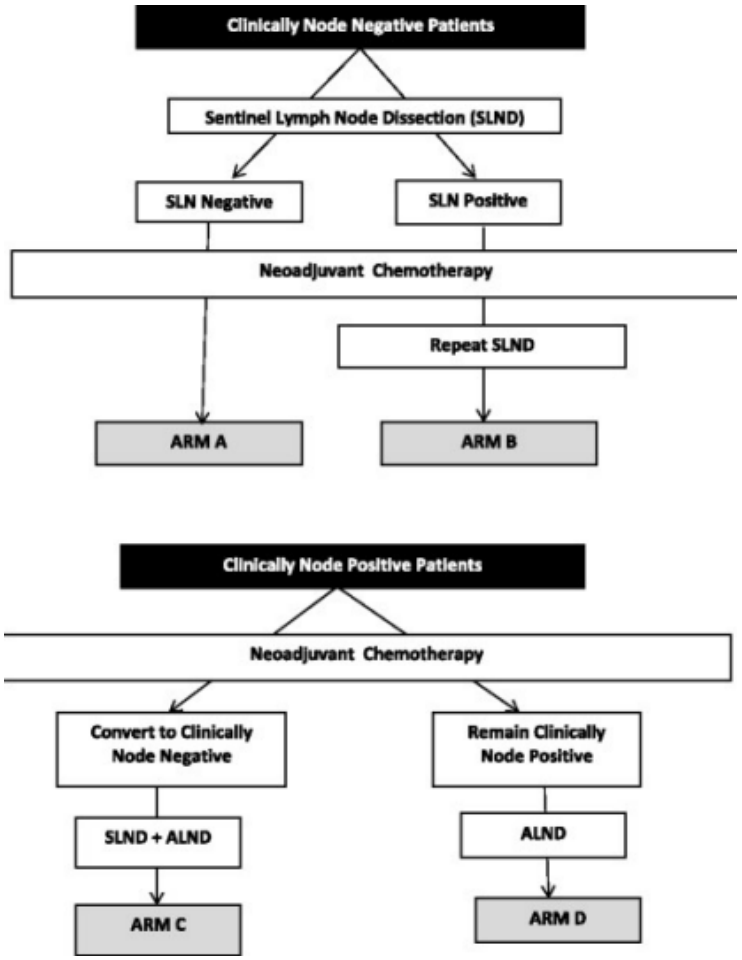
# SENTINA Trial

- Identification rate SLN was 81%
- False-negative rate was 14.2%
- The false-negative rate was 24.3% (17 of 70) for women who had one node removed and 18.5% (10 of 54) for those who had two sentinel nodes removed

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Kuehn et al Lancet Onc 2013

# SN FNAC

## (Sentinel Node Biopsy Following Neoadjuvant Chemotherapy)

- Canadian /US Study
- T0-T3 with N1-2 biopsy proven
- Neoadjuvant Chemotherapy
- SLNB + ALND
- The SNB IR was found in 87.6%
- The FNR was 8.4%
- If SN ypN0(i+)s had been considered negative, the FNR would have increased to 13%

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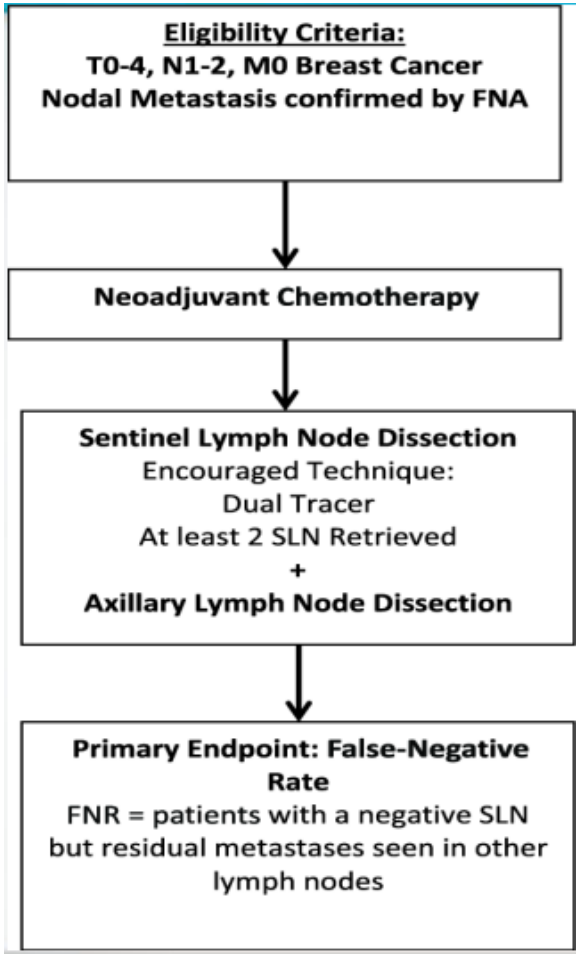
Boileau et al J Clin Onc 2015

# ACOSOG Z1071




- SLN detection rate was 93%
- 41% cN1 patients converted to N0 after NAC
- FN rate in cN1 with at least 2 SLN removed 12.6% dropped to 9.1% for 3 SLN removed
- FN rate lower with dual vs. single tracer ( 10.8 vs 20.3%)
- FN rate > or = 3 SLN removed was 9.1%

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Boughey, et al. JAMA 2013

# SLN trials in patients with clinically node positive breast cancer who underwent NAC

| | ACOSOG Z1071 | SN FNAC | SENTINA |
|---|---|---|---|
| N | 649 | 153 | 592 |
| ID | 92% | 87.6% | 81% |
| Nodal pCR | 41% | 25% | 52% |
| FNR% | 12.6 % | 8.4 % | 14.2 % |
| Single Tracer | 20.3% | 16 % | 27 % |
| Dual Tracer | 10.8 % | 5.2 % | 12 % |

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# What Can We Do to Minimize False Negative Rate?

1) Using dual-agent lymphatic mapping (radiotracer and blue dye)

2) Identifying three or more SLNs

3) Marking the metastatic lymph node with a clip before neoadjuvant therapy and then resecting it at the time of surgery reduces false-negative rates to less than 10%.

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

- Prospective study of patients with biopsy-confirmed nodal metastases with a clip placed in the sampled node
- Patients undergoing TAD had SLND and selective removal of the clipped node
- Of 208 patients enrolled in this study, 191 underwent ALND, with residual disease identified in 120 (63%)
- The clipped node revealed metastases in 115 patients, resulting in an FNR of 4.2% (95% CI, 1.4 to 9.5) for the clipped node
- In patients undergoing SLND and ALND (n = 118), the FNR was 10.1% (95% CI, 4.2 to 19.8), which included seven false-negative events in 69 patients with residual disease
- Adding evaluation of the clipped node reduced the FNR to 1.4%
- The clipped node was not retrieved as an SLN in 23% (31 of 134) of patients

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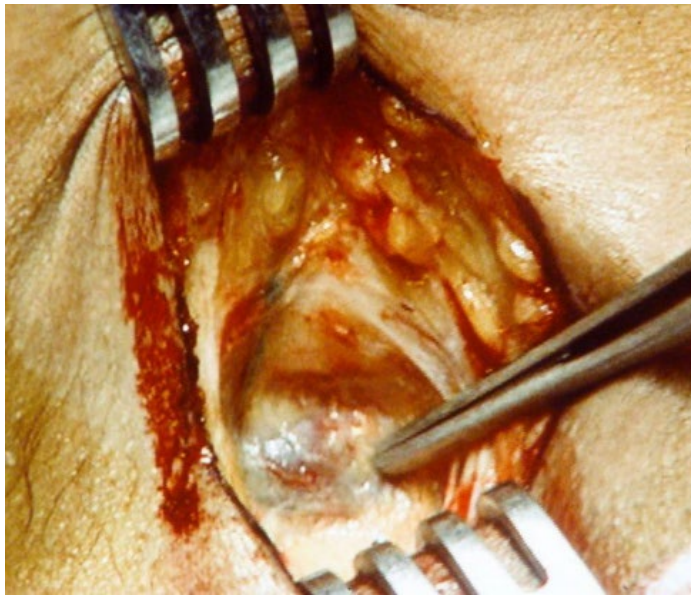
Caudle, A. J Clin Oncol. 2016 Apr 1;34(10):1072-8

# Targeted Axillary Dissection

- Targeted axillary dissection is a technique where the marked preNAC positive node is removed along with the sentinel nodes and its response to chemotherapy is evaluated
- Marking nodes with biopsy-confirmed metastatic disease allows for selective removal and improves pathologic evaluation for residual nodal disease after chemotherapy (FNR 2%)
- Increases accuracy since the marked lymph node appears not to be the SLN in 23-35% of cases



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Caudle A J Clin Oncol 2016

# Is Low-Volume Disease in the Sentinel Node After Neoadjuvant Chemotherapy an Indication for Axillary Dissection?

- From July 2008 to July 2017, 702 patients (711 cancers) had SLN biopsy after NAC.
- On FS, 181 had metastases, 530 were negative; 33 negative cases were positive on final pathology (false-negative rate 6.2%).
- Fifty-nine percent of patients with micrometastases and 63% with macrometastases had one or more additional positive nodes at ALND.
- Among those with a false-negative result, 10 (30%) had ITCs, 15 (46%) had micrometastases, and 8 (24%) had macrometastases

- **Overall, 1/6 (17%) patients with ITCs and 28/44 (64%) patients with micrometastases had additional nodal metastases at ALND.**
- **Low-volume SLN disease after NAC is not an indicator of a low risk of additional positive axillary nodes and remains an indication for ALND, even when not detected on intraoperative FS.**

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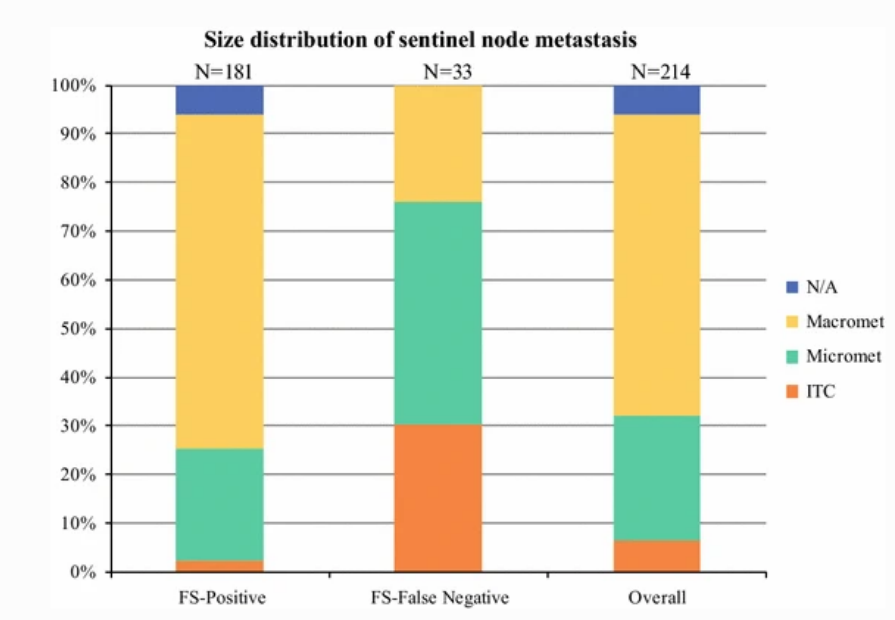
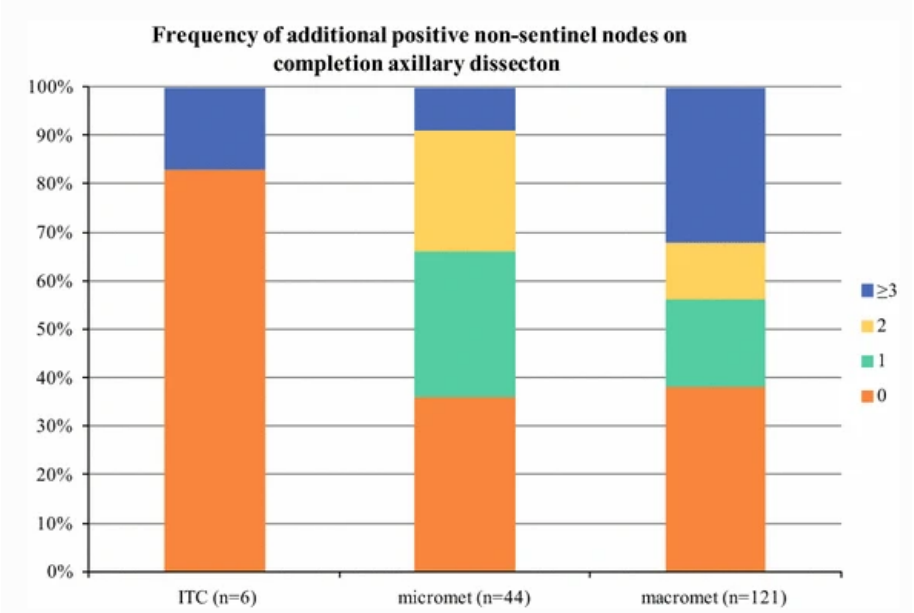
•Monica Morrow MD, *Annals of Surgical Oncology* **volume 25**, pages1488–1494 (2018)

## Comparison of sentinel lymph node metastases size based on detection by intraoperative frozen section.




## Overall frequency of additional positive non-sentinel nodes at completion axillary dissection based on sentinel lymph node metastasis size

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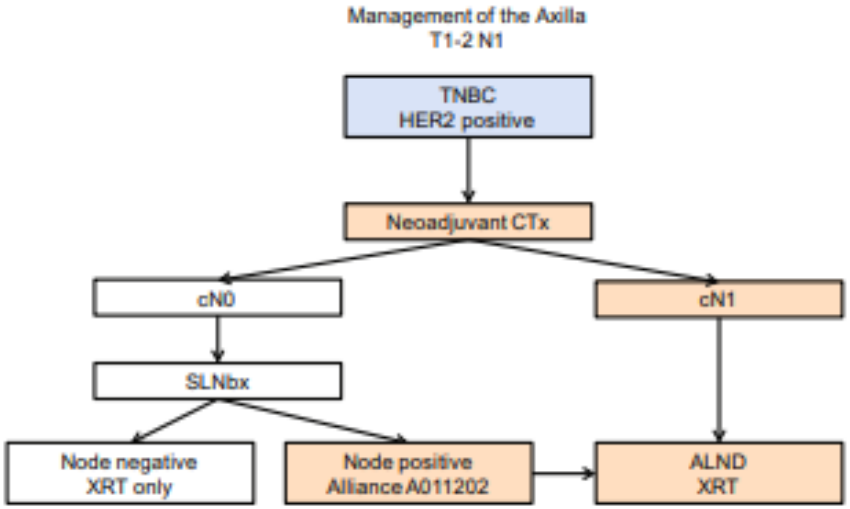
# Management of the axilla in T1-2N1 breast cancer

**Table 1.** Nodal pathologic complete response in triple-negative/HER2 positive breast cancers, and in hormone receptor-positive and HER2 negative breast cancers.

| Study | No. of patients (stage) | HR positive/ HER2 negative | TNBC | HER2 positive |
|---|---|---|---|---|
| Boughey 2013 | 756 (pN+) | 21% | 49% | 65% |
| Kim 2015 | 415 (pN+) | 29% | 54% | 49% |
| Montagna 2020 | 573 (pN+) | 20% | 44% | 63.3% |
| Simons 2019 | 139 (pN+) | 7.4% | 44% | 74% |

*HR* hormone receptor, *N* node, *TNBC* triple-negative phenotype, *HER2* human epidermal growth factor receptor 2.




The sensitivity of ultrasound, MRI, and PET/CT to identify residual lymph node disease has been reported to be 70%, 61%, and 63%, respectively

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El Tamer. npj Breast Cancer (2022) 8:69

# Residual Axillary Disease with Breast pCR

- NCDB
- 30,821 patients
- Axillary only disease after NAC
  - 12.4% Her2(+)
  - 14.1% TNBC

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Barron, A et al JAMA Surg.153:1120, 2018.

- No prospective randomized study has yet shown that axillary dissection can be eliminated after neoadjuvant therapy.

(B51 and Alliance)

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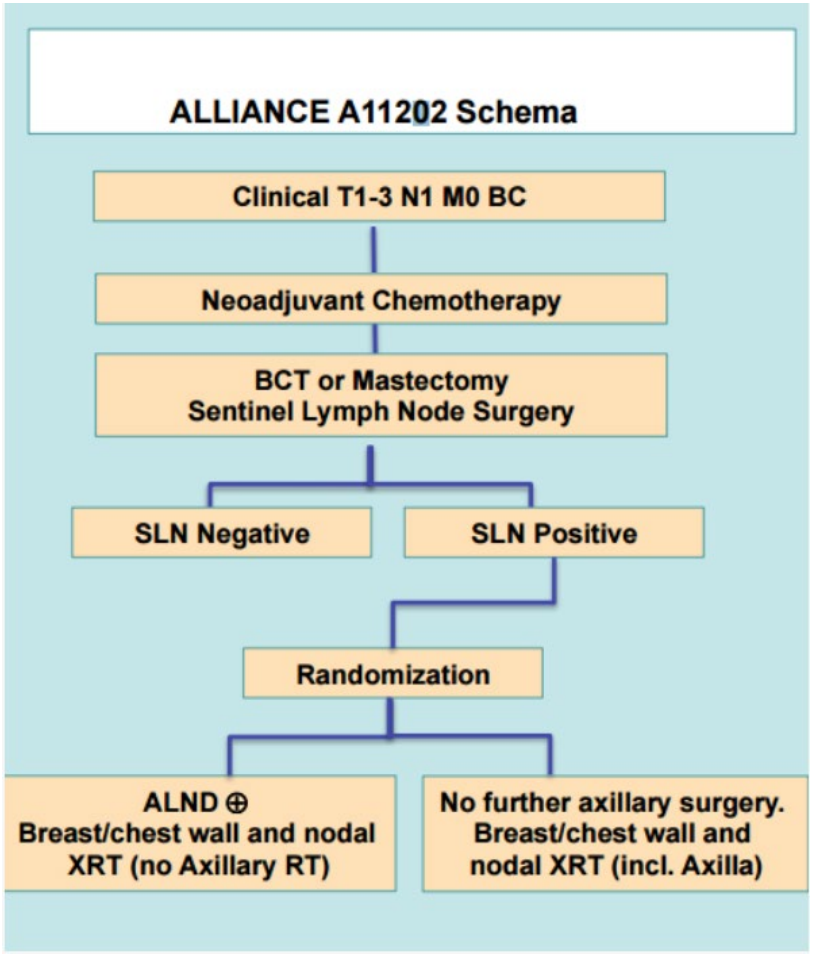
# Can We De-Escalate?

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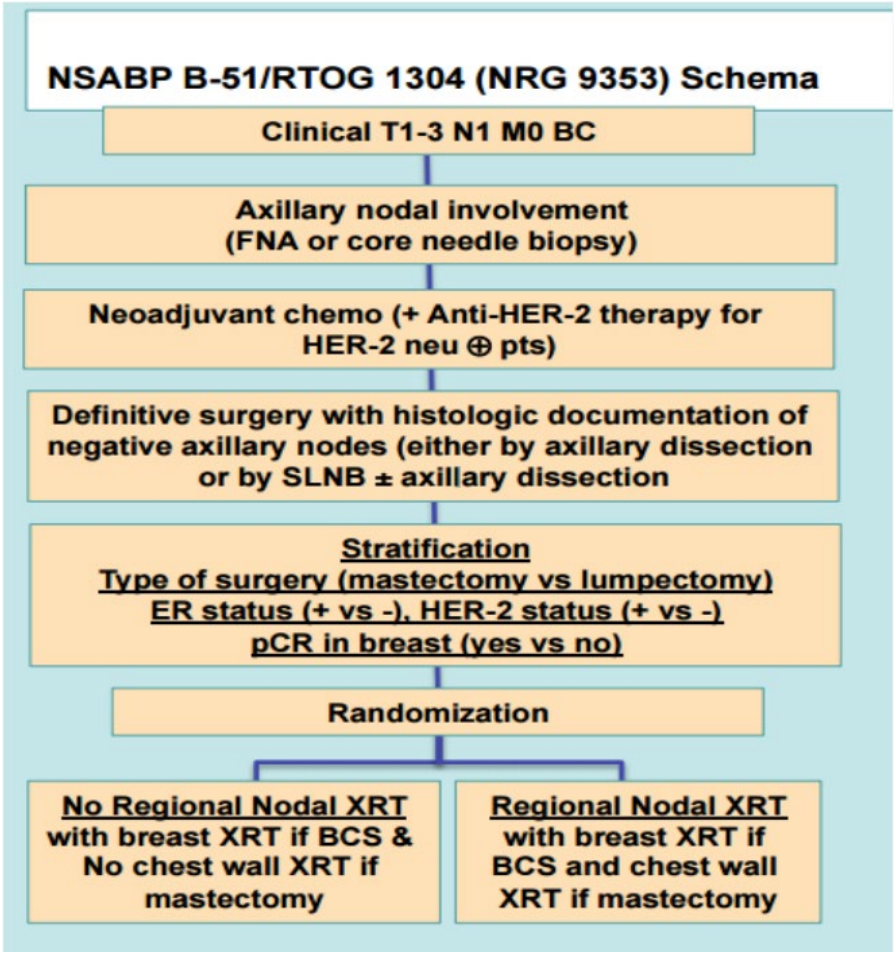
>2000 patients enrolled. Currently closed
Est Primary Completion Date is 1/1/24

# Can We De-Escalate?

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**Axillary recurrence is a rare event in node positive patients treated with sentinel node biopsy alone after neoadjuvant chemotherapy: results of a prospective study**

- MSKCC study reported on regional control of the axilla with dual-mapping following a negative sentinel lymph node biopsy after neoadjuvant chemotherapy.

- Among 234 patients with 3 or more negative sentinel nodes without an axillary dissection and a median follow-up of 40 months:
  - 13 patients developed distant metastasis
  - only 1 patient developed local recurrence (refused radiation)

- These data are supportive of the reliability of a sentinel node procedure after neoadjuvant chemotherapy in patients who became clinically node negative after neoadjuvant chemotherapy when proper techniques are used

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# Conclusion

- Targeted SLNbx after Neoadjuvant Chemotherapy is a Reasonable Approach with conversion to clinically negative disease
- De-escalation of surgery in the axilla prevents complications of ALND
- Completion axillary lymph node dissection is the **standard of care** for all patients in whom the sentinel node is positive or in whom there is a failure to identify 3 or more sentinel nodes

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# THANK YOU!!

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