THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Surgical Approach to the Axilla in 2018

Cancer De Mama
Sao Paulo, Brazil 2018

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Objectives

- Discuss changes in staging of breast cancer.
- Discuss management of the axilla in patients undergoing surgery first.
- Discuss the role of nodal staging after chemotherapy.

Timeline for Breast Cancer Treatment

1890

Radical mastectomy

1960

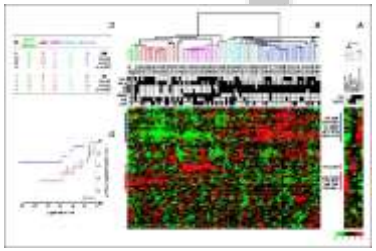
Trials in Breast Conserving Therapy

Introduction of adjuvant therapy

1980 - Tamoxifen

1990-2000

Trials in Sentinel Node Surgery



2000

Description of breast cancer subtypes

1990 -Trastuzumab

Prognostic Factors

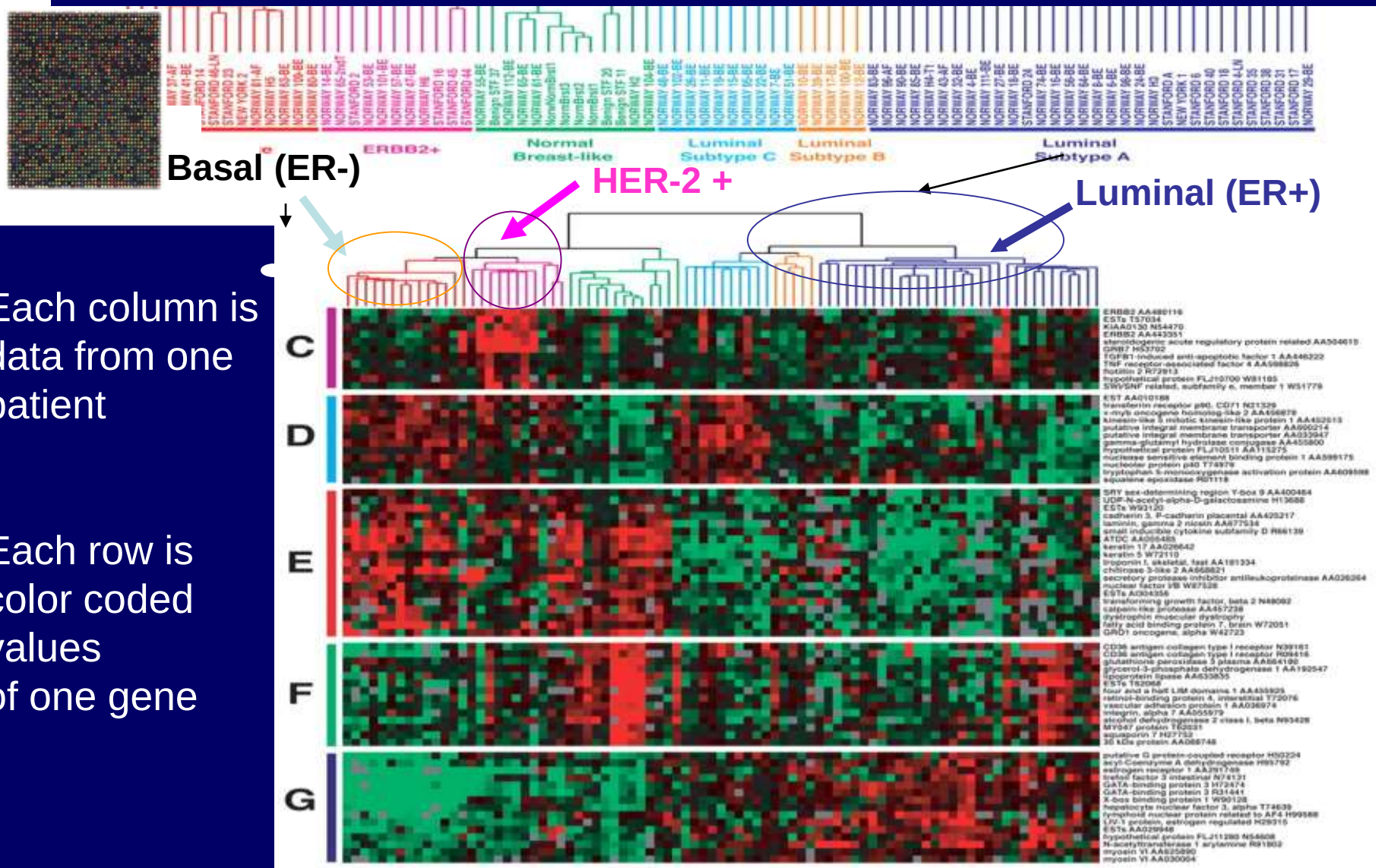
- Tumor size
- Lymph node status
- Histologic type
- Angiolymphatic invasion
- Age and comorbidities
- Race
- Grade
- Estrogen receptor
- Progesterone receptor
- HER2 status
- 21 gene recurrence score
- Mammaprint

Prognosis and Staging

- AJCC TNM stage:
  - T: primary tumor
  - N: regional (ipsilateral) lymph nodes
  - M: distant Metastasis

- Pathologic stage (PS): Definitive stage is determined after surgery by pathologic evaluation of the primary tumor and regional lymph nodes.

Hierarchical Clustering Reveals Clinically Relevant Gene Expression Profiles in Breast Cancer



Each column is data from one patient

Each row is color coded values of one gene

Sorlie et al., PNAS, 2001

Case Considerations

- 49 yo female undergoes BCT and SLN disssection, pT1cN0M0 invasive ductal carcinoma, intermediate grade, ER 90%, PR 30%, HER-2/neu negative

- 54 yo female undergoes BCT and SLN dissection, pT1cN0M0 invasive ductal carcinoma, high grade, ER negative, PR negative and HER-2/ neu negative

- Same TNM, anatomic stage
- Different prognosis

Novel Staging Systems

- Six different staging systems were assessed: (1) PS; (2) PS and grade; (3) PS, grade, and LVI; (4) PS, grade, and ER; (5) PS, grade, and combination of ER and PR; and (6) PS, grade, and combination of ER, PR, and HER2.
- Model performance was quantified using Harrell's concordance index (C-index).
- Similar to area under the receiver operating characteristic (ROC) curve, C-index can range from perfect concordance (1.0) to random predictions (0.5).

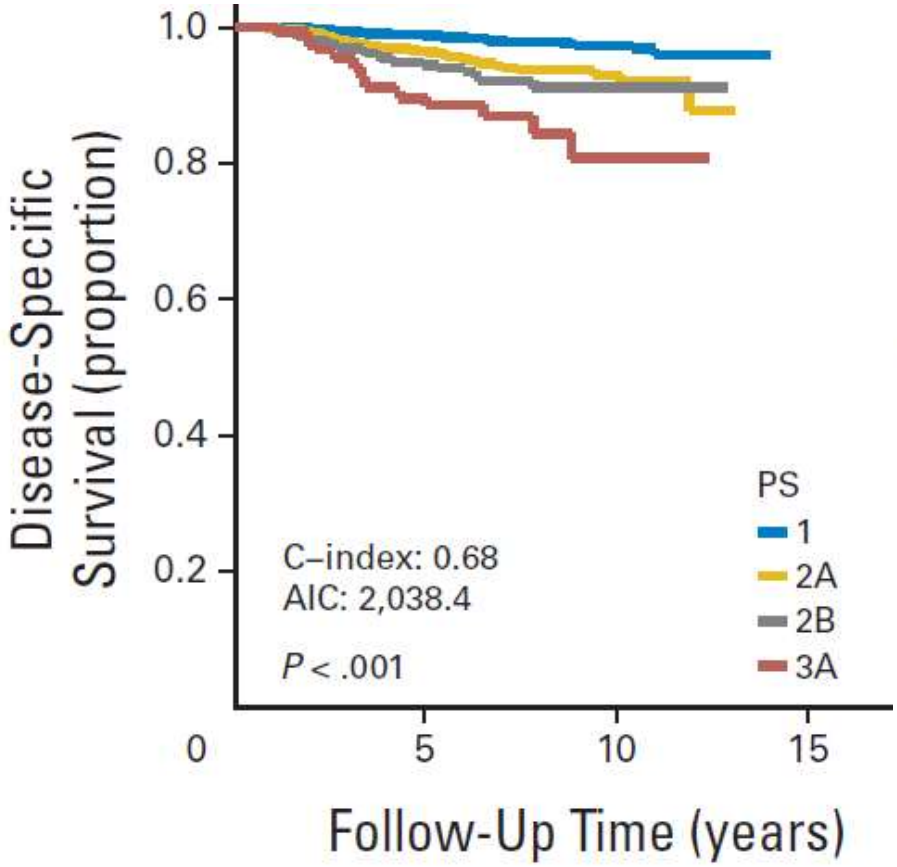
External Validation

- SEER database - Patients were included if they had stage I–IIIA breast cancer.
- Patients with unknown stage, grade, ER status, or PR status and those lost to follow-up within 2 years were excluded.
- There were 26,711 in the external validation cohort.

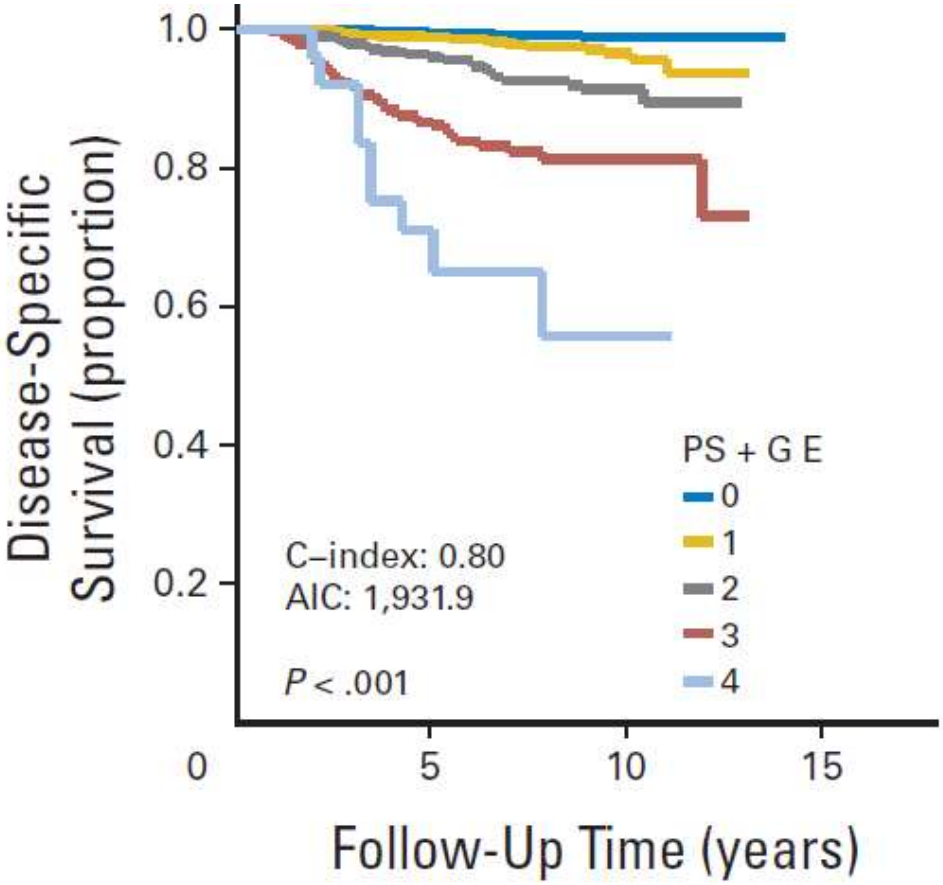
Yi M, et al. *J Clin Oncol* 2011

Incorporation of Biologic Factors into Novel Staging System

Pathologic Stage



PS + GE



Yi M, et al. J Clin Oncol 2011

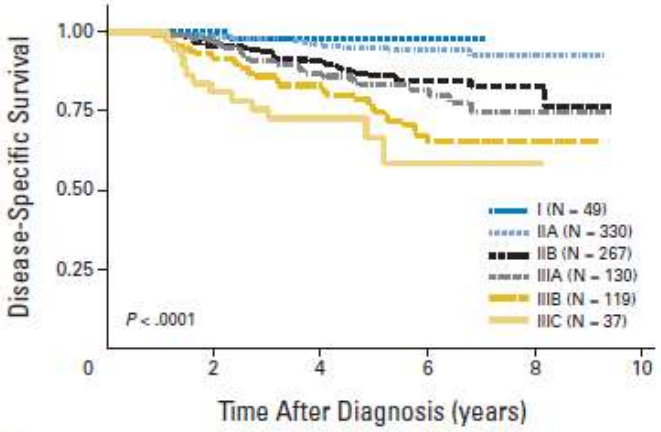
Staging Following Neoadjuvant Chemotherapy

- Hypothesis: Patients treated with neoadjuvant therapy could be better stratified incorporating the following:
  - Clinical stage
  - Pathologic stage
  - Biologic factors

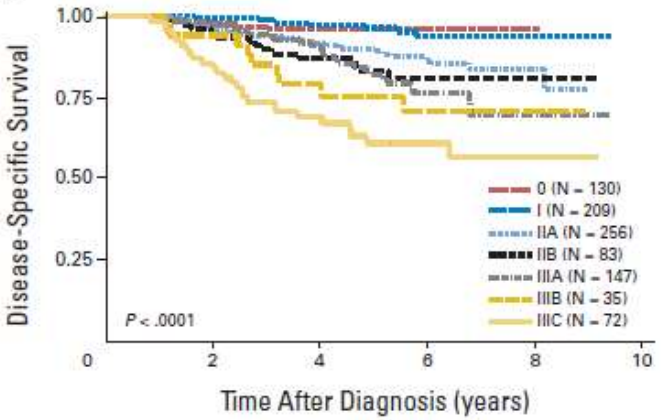
Jeruss J, et al. *J Clin Oncol* 2008

Staging Following Neoadjuvant Chemotherapy

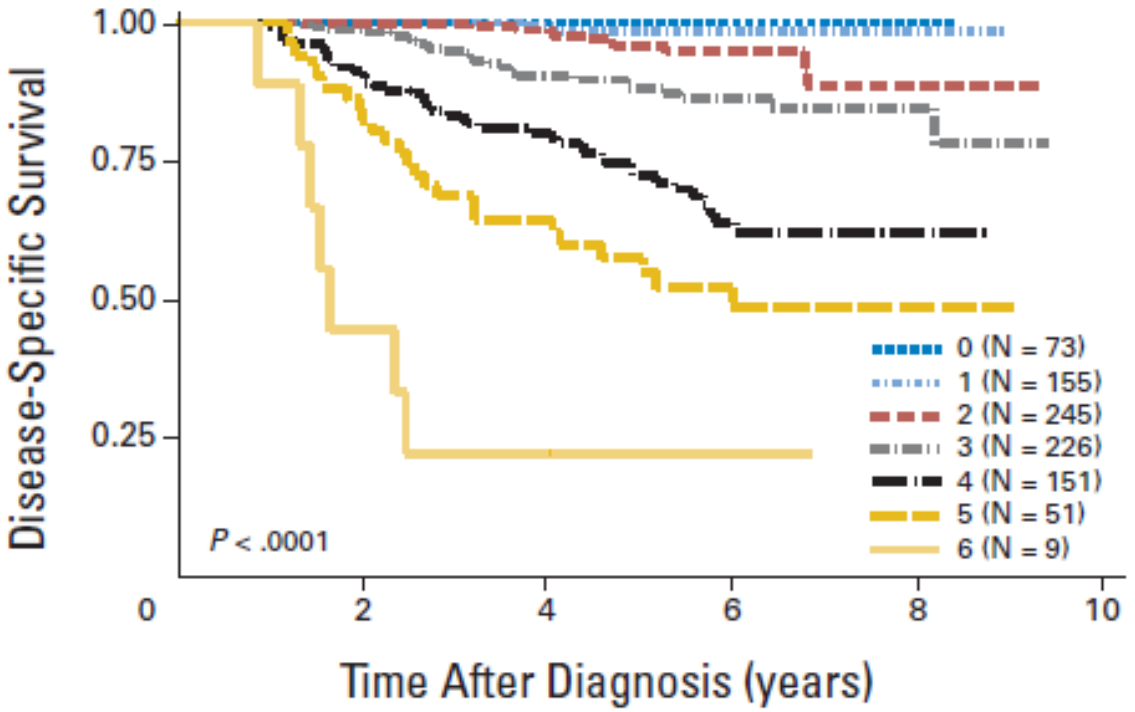
Clinical Stage



Pathologic Stage



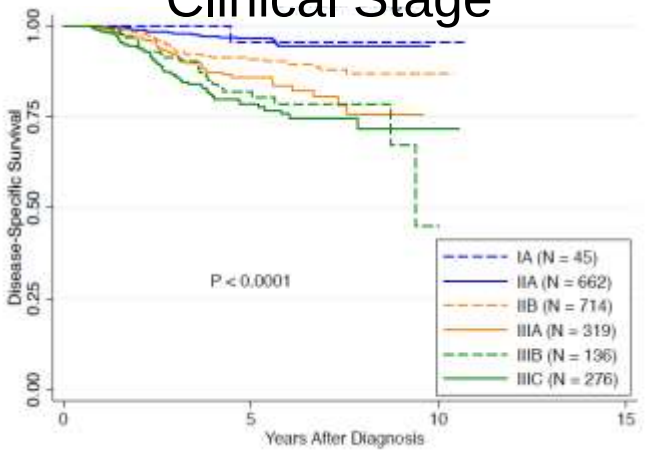
CPS+EG



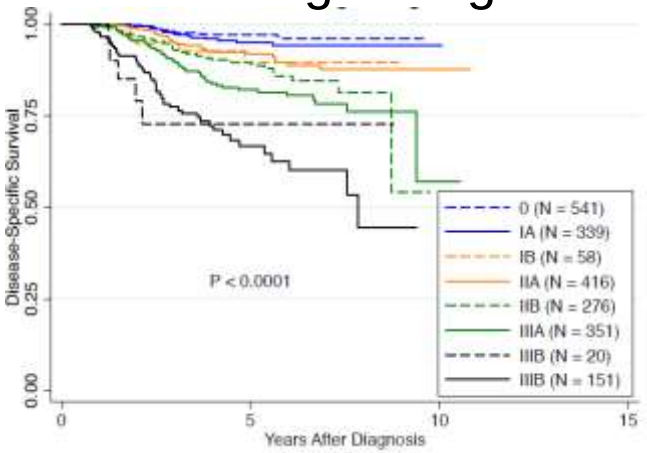
Neo-Bioscore

Stage	Score
Clinical Stage	
I	0
IIA	0
IIB	1
IIIA	1
IIIB	2
IIIC	2
Pathologic Stage	
0	0
I	0
IIA	1
IIB	1
IIIA	1
IIIB	1
IIIC	2
Tumor marker	
ER neg	1
Grade 3	1
HER2 neg	1

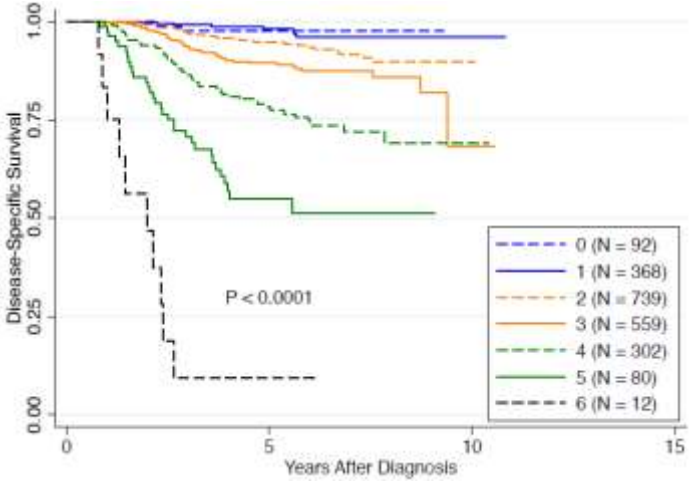
Clinical Stage



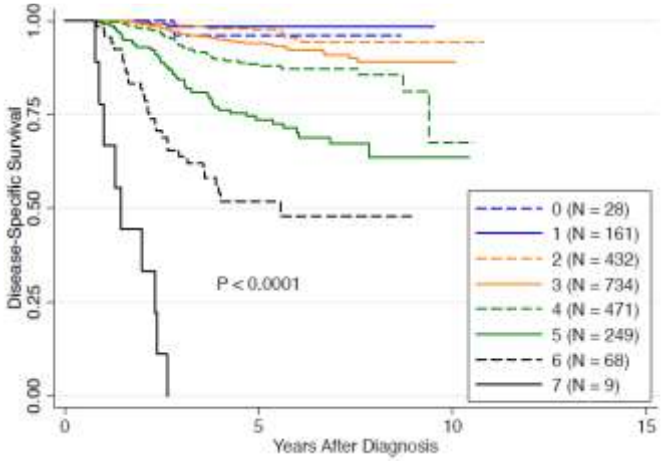
Pathologic Stage



CPS+EG Stage



Neo-Bioscore



Mittendorf EA, et al. *JAMA Oncol*, 2016

Management of the Regional Nodes

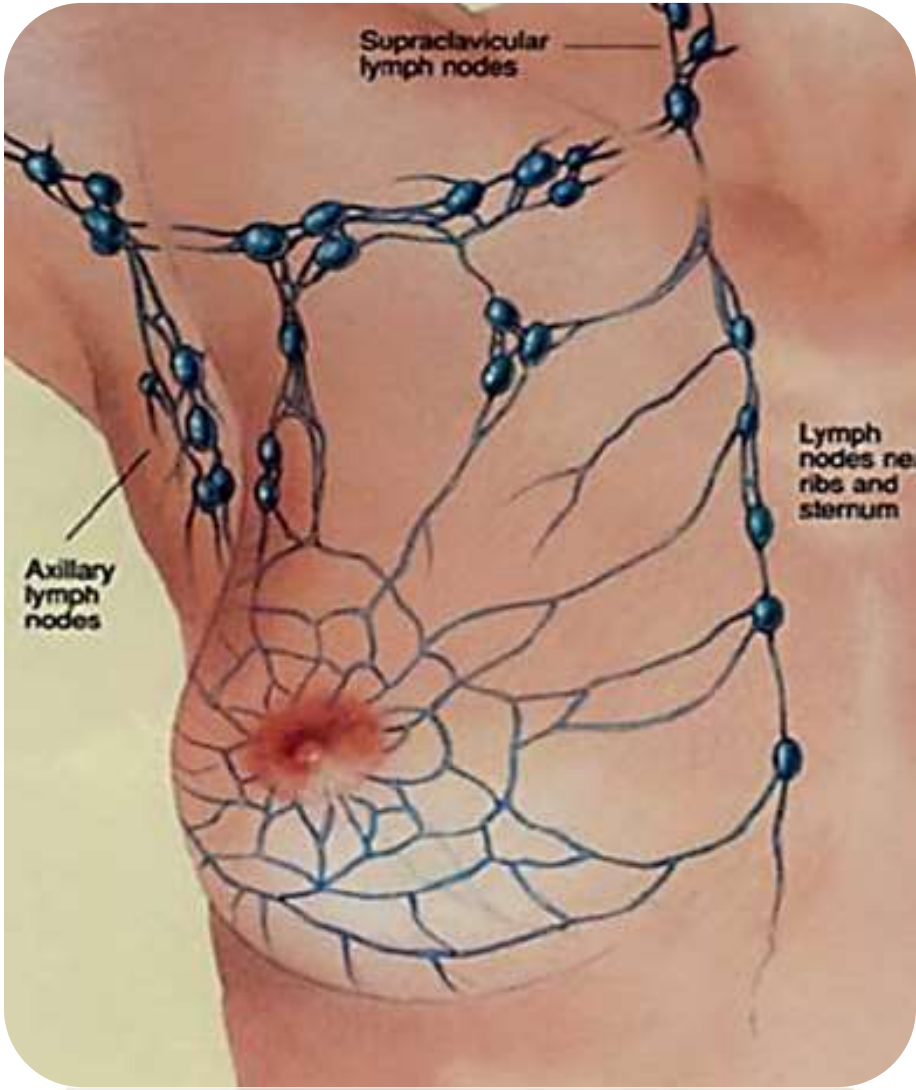
Assessment of Nodal Basins

- False negative rate of physical exam: 45%
- Ultrasound with FNA of abnormal nodes[1]:
  - Sensitivity: 86.4%
  - Specificity: 100%
  - Diagnostic Accuracy: 79%
  - False Negative Rate: 11.6%
- Ultrasound identified metastases in:
  - 93% nodes if metastases >0.5 cm
  - 44% nodes if metastases <0.5 cm

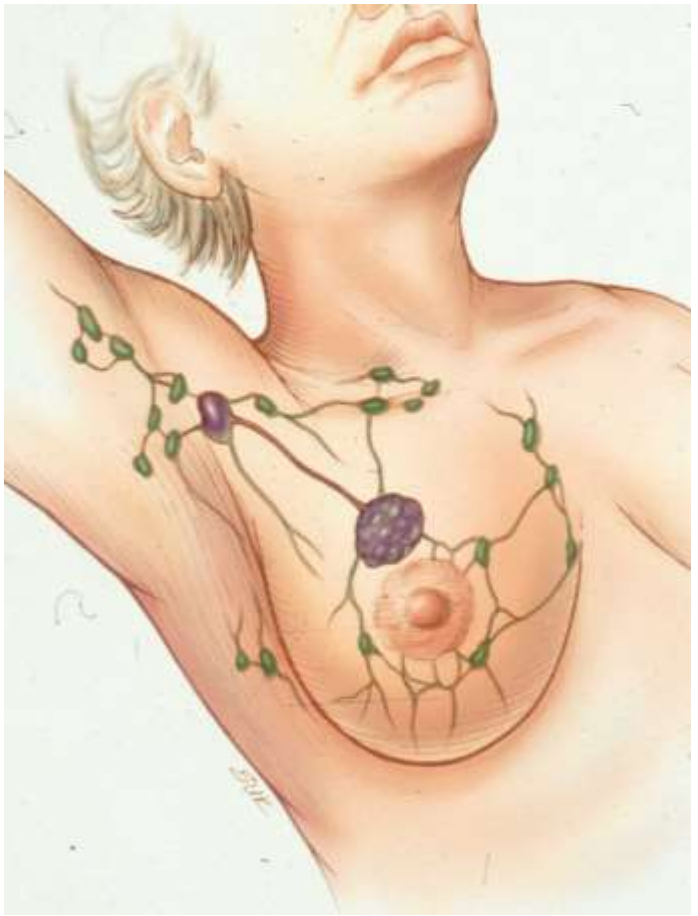
[1]Krishnamurthy S, et al. *Cancer 2002*

MD Anderson Approach

- All patients with invasive breast cancer undergo US evaluation of regional nodal basins:
  - Axilla
  - Infraclavicular
  - Internal mammary chain
- If abnormal axillary nodes seen, supraclavicular is added

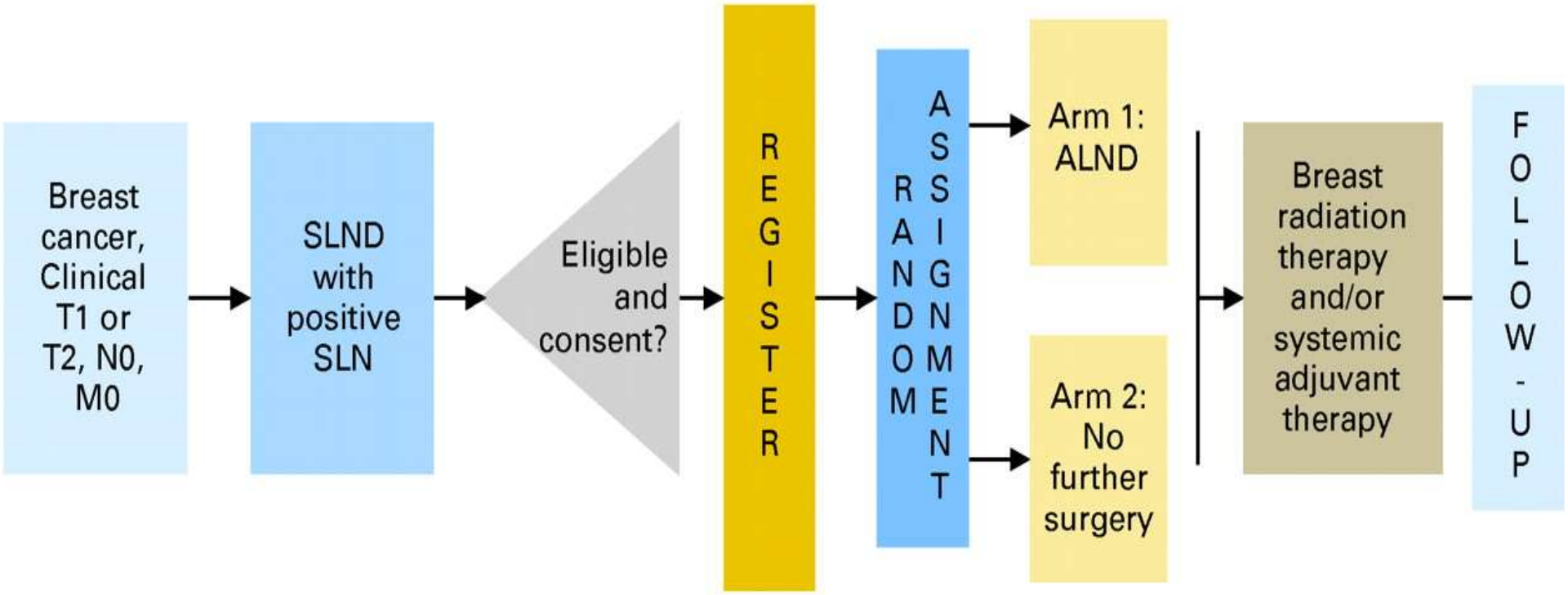


Sentinel Lymph Node Dissection



Meric and Hunt, Breast Cancer, 2007

ACOSOG Z0011



Primary Objective: To assess whether OS after SLND alone was not inferior to that for patients who underwent completion ALND for a positive SLN

Z0011 Results – 10 Year Follow-up

- 27% of SLND+ALND had additional +nodes
- 14% had 4 or more positive nodes

Cumulative Locoregional recurrence at 10 years		
	Local Recurrence	**Regional Recurrence**
SLNB only	**12 (3.8%)**	**5 (1.5%)**
ALND	**19 (5.6%)**	**2 (0.5%)**
	P = 0.13	**P = 0.36**

Giuliano A, et al. *Ann Surg* 2016

Radiation to Regional Nodes?

TABLE 5. Recurrence Rates for Patients With Known Radiation Protocol Deviations

	Total Patients	Local		Regional		Total LRR	
		No. of Events (10-y CI)	*P*	No. of Events (10-y CI)	*P*	No. of Events (10-y CI)	*P*
WBI done (from CRF)							
Yes	540	16 (3.3%)	0.002	5 (1.0%)	—	21 (4.3%)	0.002
No	65	6 (12.2%)		0 (0.0%)		6 (12.2%)	
RT done (355 pts with extra info)							
Yes	228	4 (1.9%)	0.004	4 (1.9%)	0.80	8 (3.8%)	0.015
No	107	8 (9.1%)		1 (1.1%)		9 (10.2%)	
High Tangents (228 pts with extra info)							
Yes	73	3 (4.3%)	0.64	1 (1.4%)	0.82	4 (5.8%)	0.59
No	69	1 (1.5%)		1 (1.6%)		2 (3.0%)	
N/A or Unknown	86	0 (0.0%)		2 (2.8%)		2 (2.8%)	
Supraclavicular (228 pts with extra info)							
Yes	43	0 (0.0%)	—	0 (0.0%)	—	0 (0.0%)	—
No	185	4 (2.3%)		4 (2.3%)		8 (4.6%)	

Giuliano A, et al. *Ann Surg* 2016

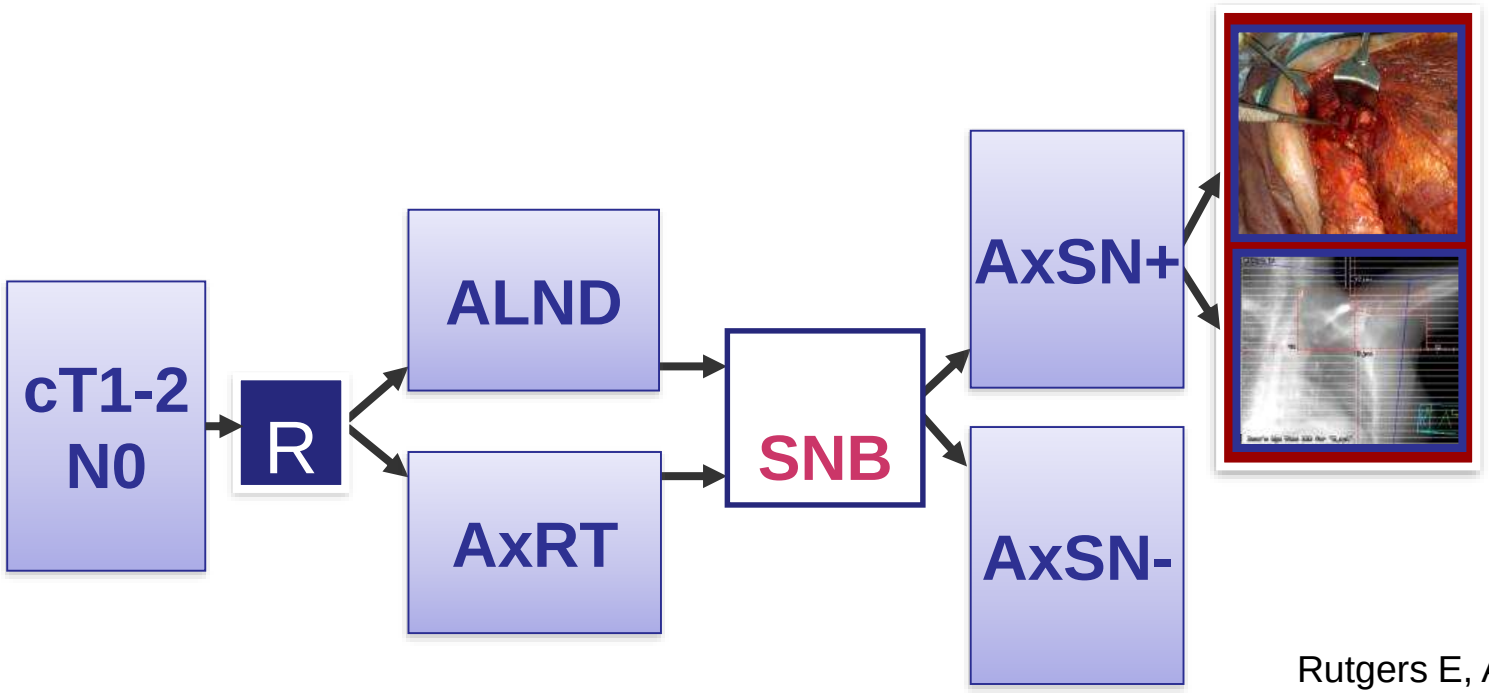
Radiation to Axilla/Regional Nodes?

As previously reported by Jagsi et al,[6] there were radiation protocol deviations among 335 patients in both treatment arms. Of the 335 patients, 228 had port films available for review and 107 had no radiation treatment. There were no significant differences between treatment arms in the use of protocol-prohibited nodal fields. High tangents were used in 51% of patients. Fifteen percent of patients received third-field treating supraclavicular nodes. There were no differences between the 2 treatment arms related to patient or tumor characteristics and prevalence of supraclavicular irradiation. Further analysis of the recurrence data from these 335 patients revealed that only "no radiation" was associated with an increased risk of local recurrence ($P = 0.004$) but not regional recurrence ($P = 0.80$) (Table 5).

Giuliano A, et al. *Ann Surg* 2016

AMAROS

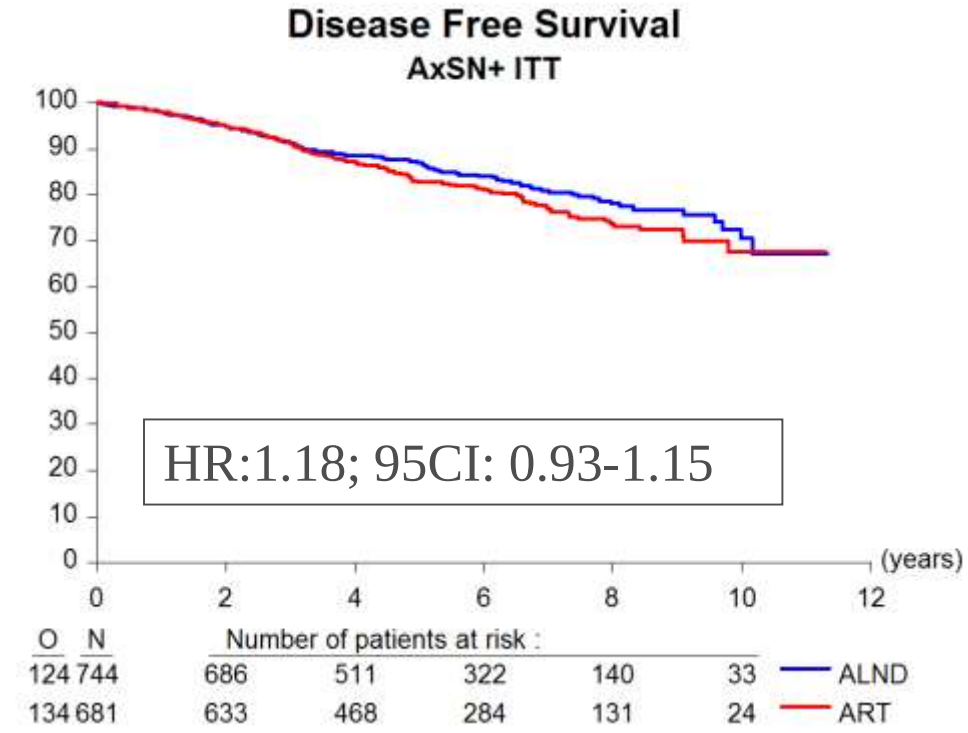
- Hypothesis: AxRT provides comparable local control and survival as ALND with fewer side effects
- cT1b-2 N0
- BCT or mastectomy
- Pts with ≥ 1+ SLN randomized to ALND or AxRT

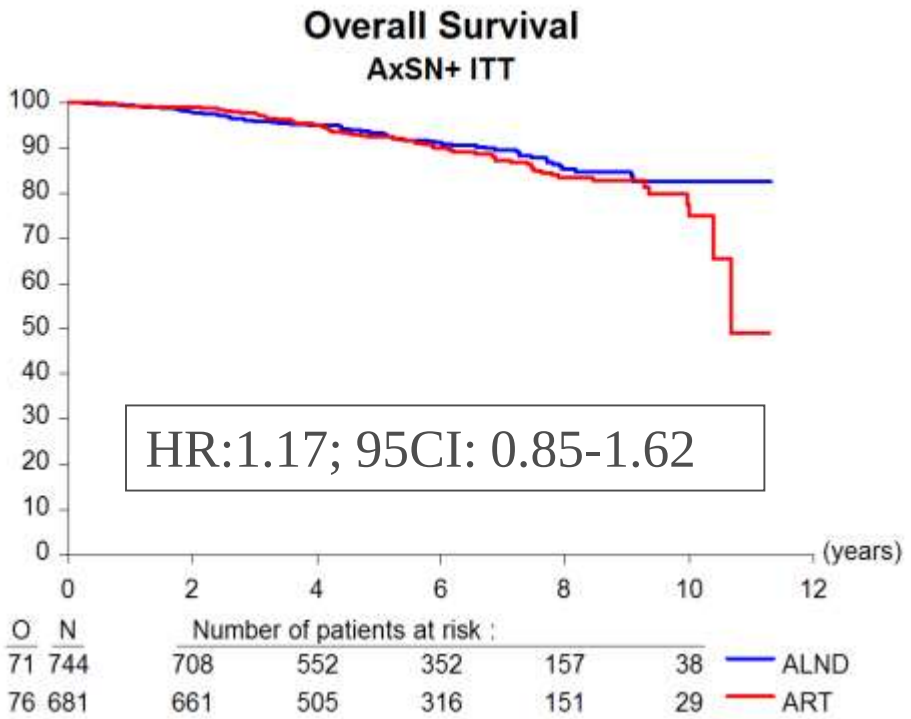


Rutgers E, ASCO 2013

AMAROS

- No difference in DFS or OS

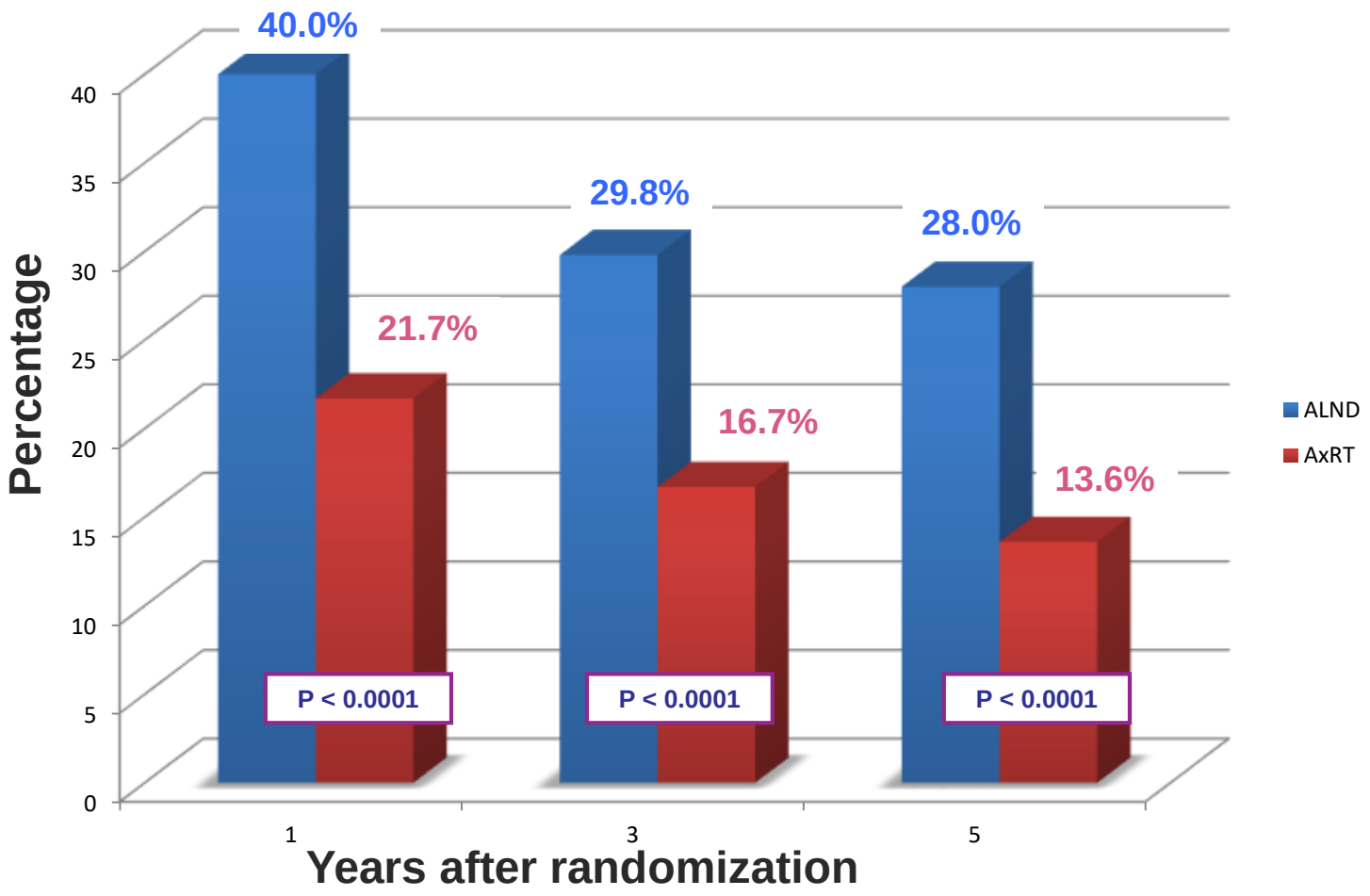




Rutgers E, ASCO 2013

AMAROS

- Decreased lymphedema with AxRT



***lymphedema observed or treated**

Rutgers E, ASCO 2013

Indications for Axillary Node Dissection?

- Clinically node negative axilla with positive SLN
  - Some patients undergoing mastectomy (AMAROS and IBCSG 23-01)
  - BCT patients not meeting Z0011 criteria
- Axillary recurrence
- Inflammatory breast cancer
- Locally advanced breast cancer

➢ PRACTICE EVOLVING *Paradigm Shifting*

  - Targeted axillary surgery
  - Node positive before/after preoperative systemic therapy

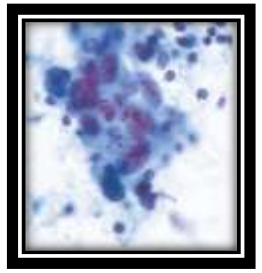
Axillary Management after Chemotherapy

Nodal Ultrasound

Negative

Positive

FNA



Neoadjuvant Chemotherapy

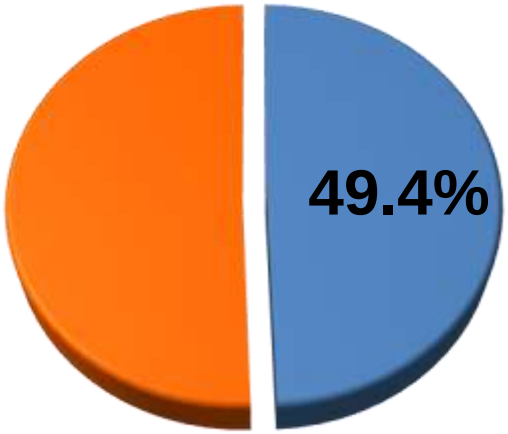
Sentinel Node Dissection

Axillary Node Dissection??

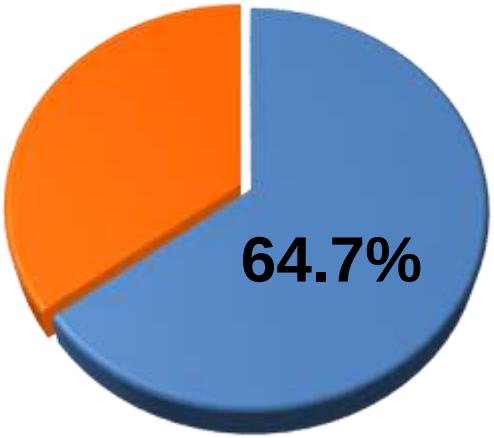
Alternatives to ALND…

Pathologic Complete Response Rates in the Axilla

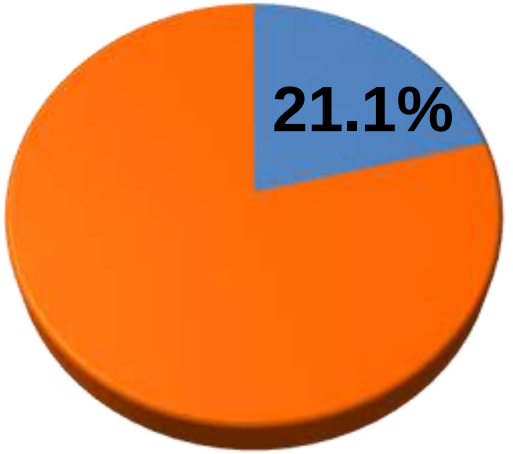
Triple Negative



HER2 Positive



HR Positive, HER2 Negative



p<0.0001

Boughey J, et al. *Ann Surg* 2015

SLND After Chemotherapy in Clinically Node Positive Patients

- 3 recently published trials:
  - ACOSOG Z1071[1] – USA
  - SENTINA[2] - Europe
  - SN FNAC[3] - Canada

[1]Boughey et al. *JAMA*, 2013
[2]Kuehn et al. *Lancet Oncology*, 2013
[3]Boileau et al. JCO, 2015

Trial Design

cT1-4 N1-2 invasive breast cancer

↓

Neoadjuvant Chemotherapy

↓

SLN and ALND

Endpoint: Compare SLN pathology to the remaining axillary nodes (FNR)

Clinically Node Positive Patients

- Neoadjuvant chemotherapy (NAC) is often used
- 40-70% of clinically node-positive patients convert to node-negative with NAC[1-3]
- Use of SLND in patients who convert to node-negative is limited by high false negative rate (FNR)

$$\text{FNR} = \frac{\text{SLN-negative but lymph node+}}{\text{Total lymph node+}}$$

[1]Kuerer et al. *Ann Surg*, 1999
[2]Hennessy et al. *J Clin Oncol*, 2005
[3]Dominici et al. Cancer, 2010

SLND for Clinically Node Positive Patients

	ACOSOG Z1071[1]	SENTINA (Arm C)[2]	SN FNAC[3]
Nodal Eligibility Criteria	cN1-2 *Endpoints reported for cN1	cN1-2	cN1-2
Biopsy required to confirm metastases?	Yes	No	Yes
Number of Patients	cN1=603 cN2=34	592	153
SN Identification Rate	92.7%	87.8%	87.6%
Overall FNR (No IHC)	12.6%	14.2%	13.4%

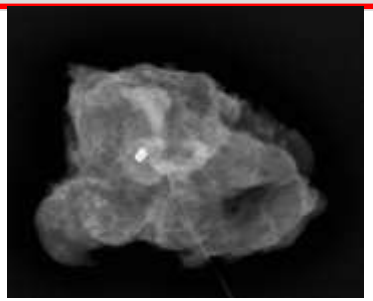
[1]Boughey et al. *JAMA*, 2013

[2]Kuehn et al. *Lancet Oncology*, 2013

[3]Boileau et al. JCO, 2015

ACOSOG Z1071
Clip placement in cN1 patients and 2+ SLNs examined

170 patients had clip placed in the node at the time of biopsy

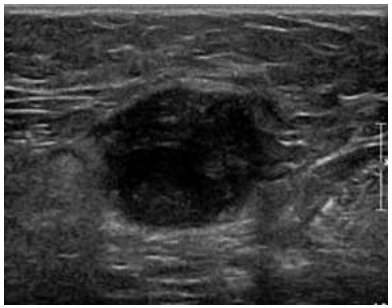


	N	Residual Nodal Disease	FNR	95% CI
Clip found in SLN	107	59	6.8%	1.9-16.5
Clip in ALND specimen	34	21	19%	5.4-41.9
Clip location unknown	29	21	14.3%	3-36.3

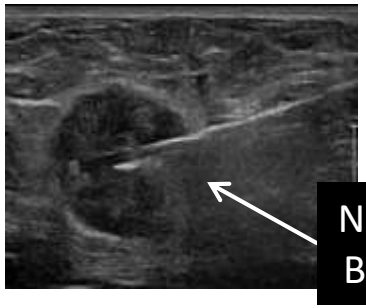
Boughey J, et al. *Ann Surg*, 2015

Prospective Registry of Breast Cancer Patients with Axillary Nodal Metastases Identified at Ultrasound

Staging US shows abnormal lymph nodes



Needle Biopsy confirms metastases



Clip placed in sampled node[1]

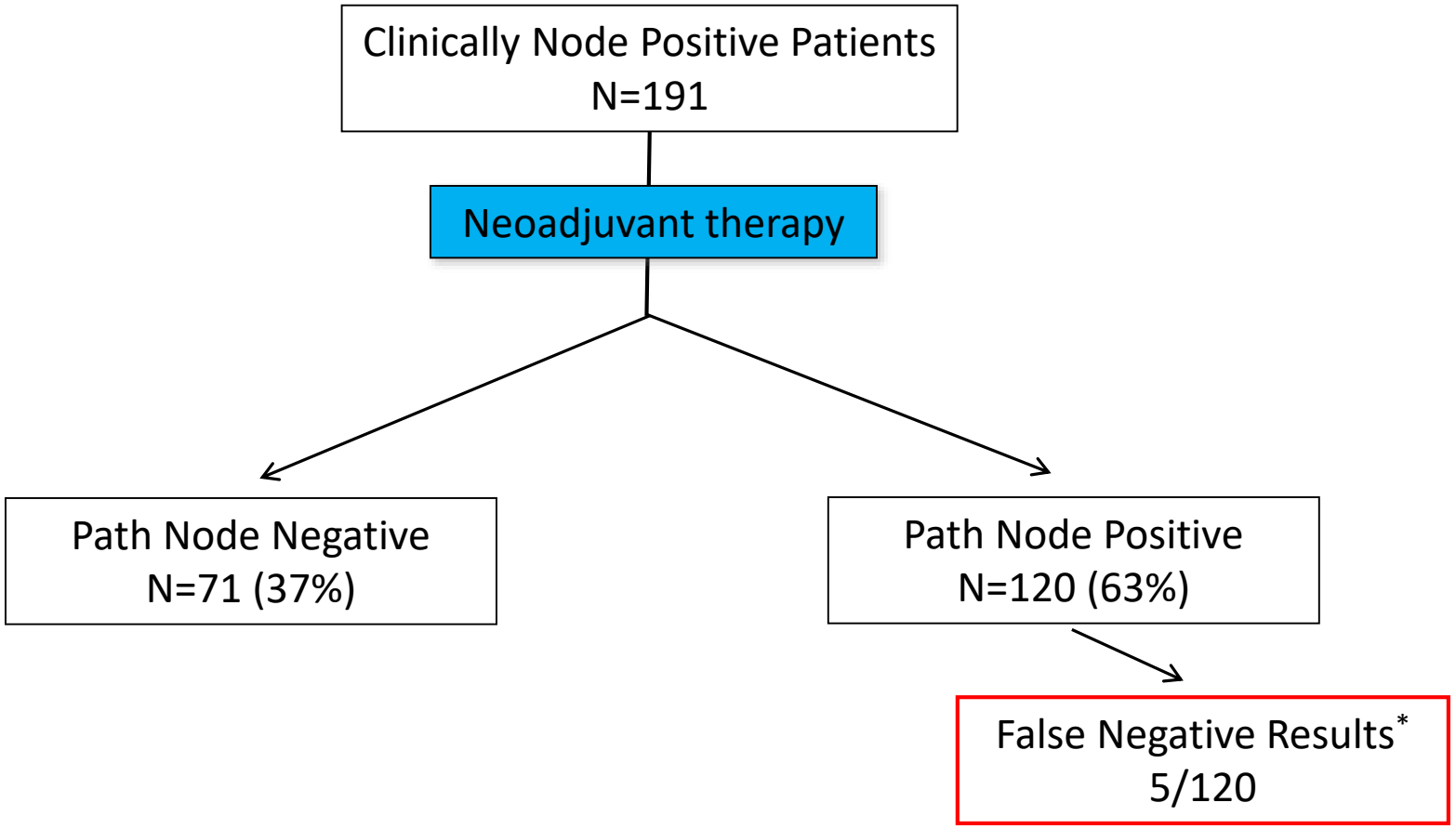
Patient receives neoadjuvant chemotherapy

Surgery
Axillary LNs removed

Xray to identify the clipped node
Clipped node pathology reported separately

[1]NCCN Guidelines, Version 2.2014

Pathologic Evaluation of Clipped Node



False Negative Rate

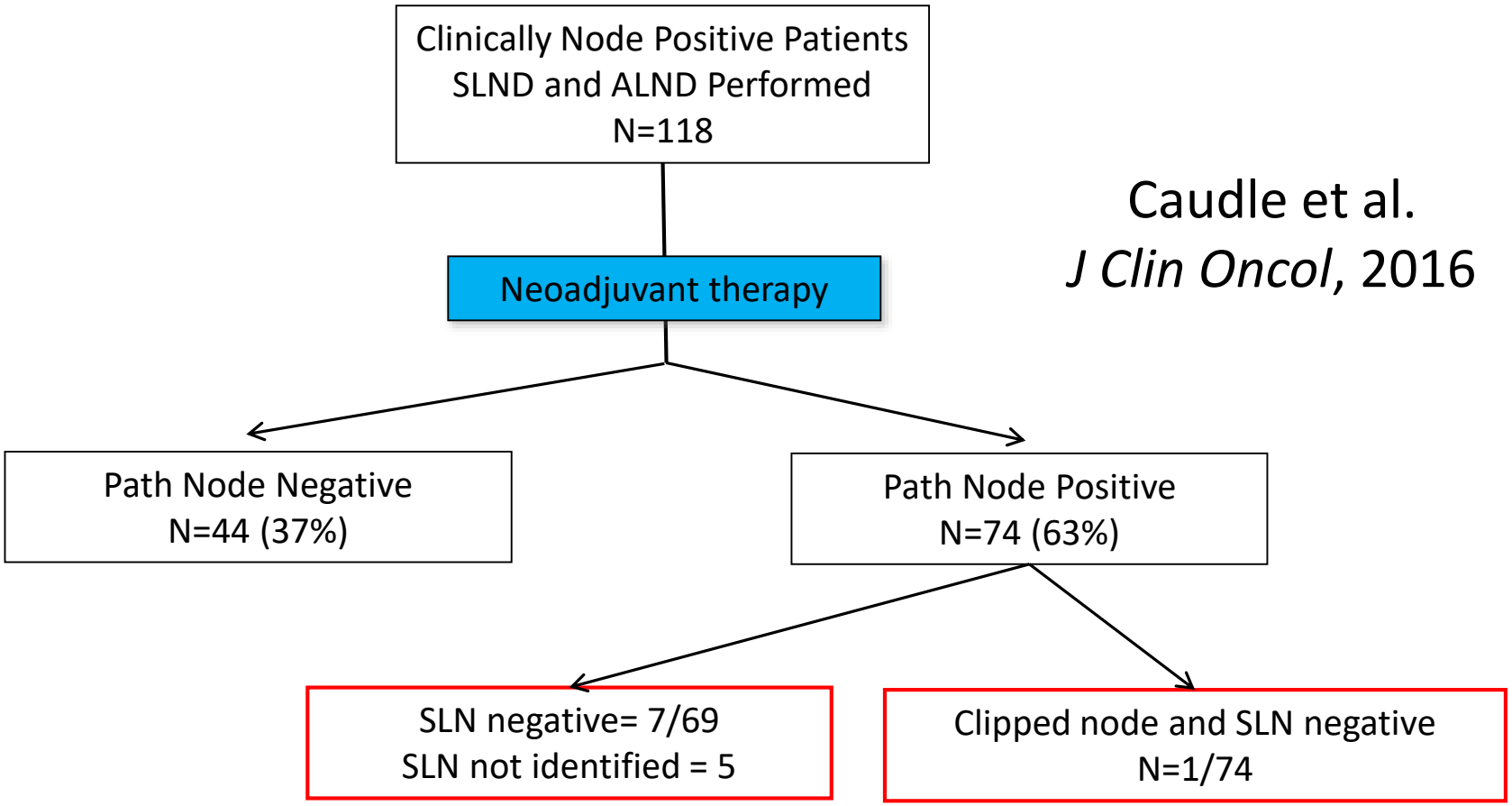
4.2% (95% CI 1.4 – 9.5)

*Clipped node showed no disease but other nodes in axillary specimen contained metastases

Caudle A, et al. *J Clin Oncol*, 2016

Does evaluation of the clipped node improve axillary staging over SLND?

Patients Undergoing SLND



Caudle et al.
J Clin Oncol, 2016

False Negative Rate

SLND Alone = 10.1% (95% CI 4.2 – 19.8)

SLND + Evaluation of Clipped Node = 1.4% (95% CI 0.03-7.3)

P=0.03

Why Localize the Clipped Node?

Clipped node not retrieved as a SLN:

- MDACC[1]: 23% (31/134)
- Pittsburgh[2]: 27% (8/30)
- ACOSOG Z1071[3]:
  - Clipped node was a SLN: 63% (107/170)
  - Clipped node in ALND: 20% (34/170)
  - Unknown: 17% (29/170)

[1]Caudle et al. *J Clin Oncol*, 2016
[2]Diego et al. *Ann Surg Oncol*, 2016
[3]Boughey et al. *Ann Surg*, 2015

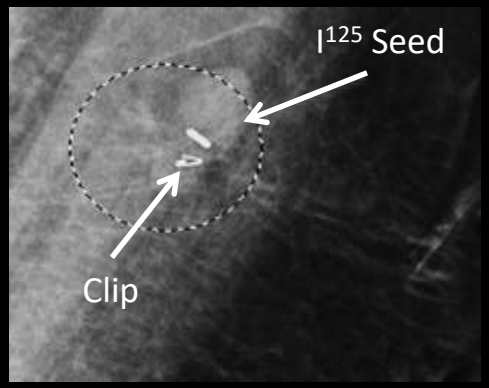
Can we selectively remove clipped nodes at surgery?

Targeted Axillary Dissection

1-5 Days Before Surgery

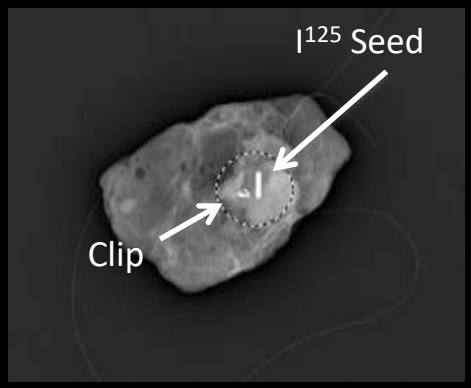
Day of Surgery

Breast Imaging
I^{125} seed placed in marked node



Nuclear Medicine
Radioisotope injection for SLND

Node containing I^{125} seed selectively removed

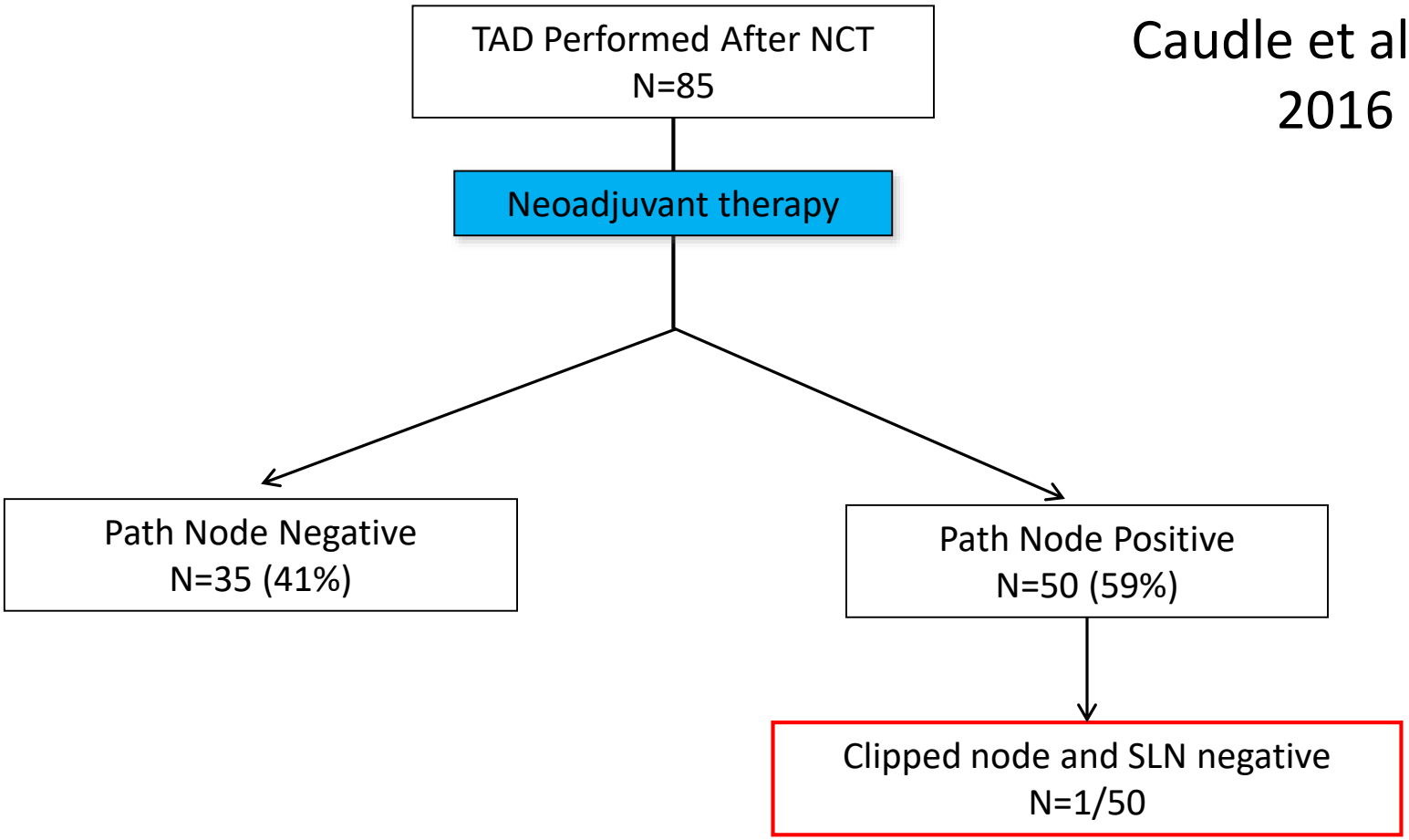


SLNs removed

Remaining axillary nodes removed

Caudle A, et al. *JAMA-Surg.* 2015. 150(2): 137-43

Patients Undergoing TAD



Caudle et al. *JCO*, 2016

False Negative Rate

TAD (SLNs + Clipped Node) = 2.0% (95% CI 0.05-10.7)

Conclusions

- False Negative Rates:
  - SLND Alone = **10.1%**
  - Evaluation of clipped node alone = **4.2%**
  - Targeted Axillary Dissection = **2.0%**
- Evaluation of the clipped node is valuable in nodal staging after neoadjuvant chemotherapy
- Targeted axillary dissection (TAD) improves axillary staging over SLND alone

Is TAD better in some patients than others?

Accuracy of TAD
Burden of Nodal Disease at Diagnosis

	< 4 Abnormal Nodes on US	≥4 Abnormal Nodes on US
Number	227	86
Nodal pCR	33.5%	31.4%
FNR of clipped node	**2.0%** 3/151 (95% CI 0.4-5.7)	**11.9%** 7/59 (95% CI 4.9-22.9)
FNR of TAD	**1.1%** 1/92 (95% CI 0.03 – 5.9)	**5.7%** 2/35 (95% CI 0.7-19.2)

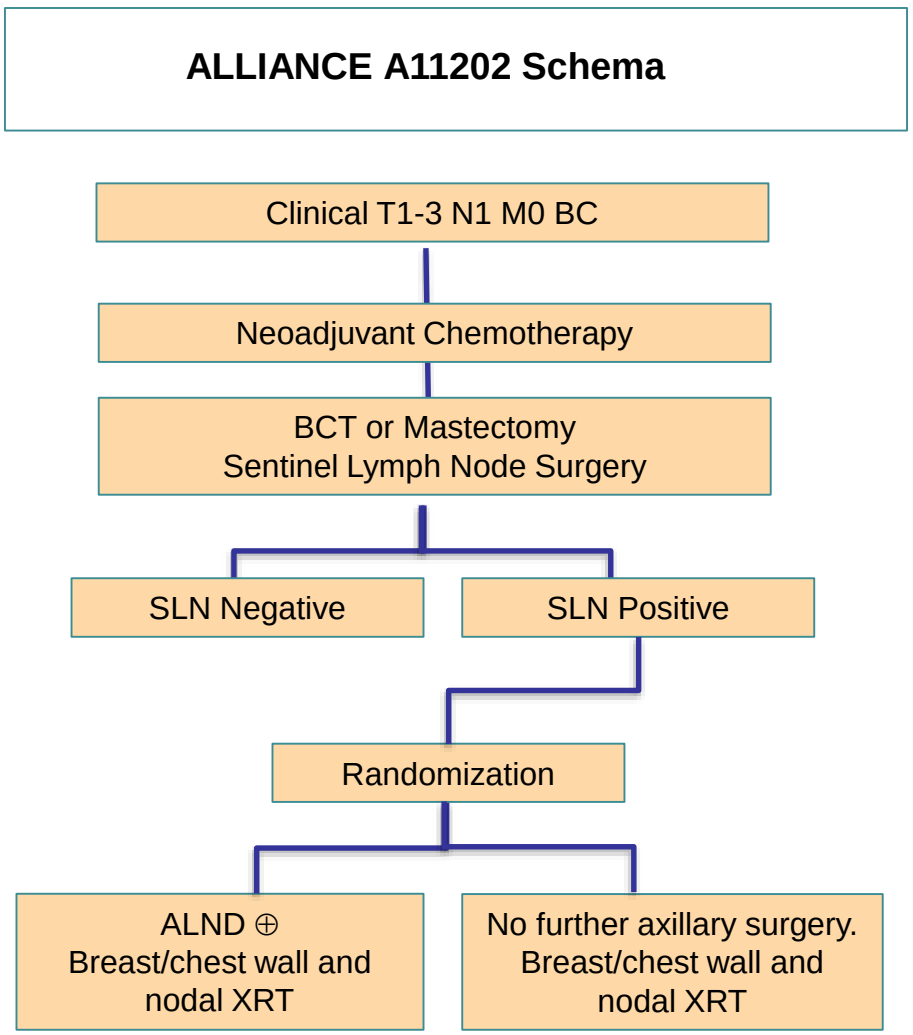
Accuracy of TAD

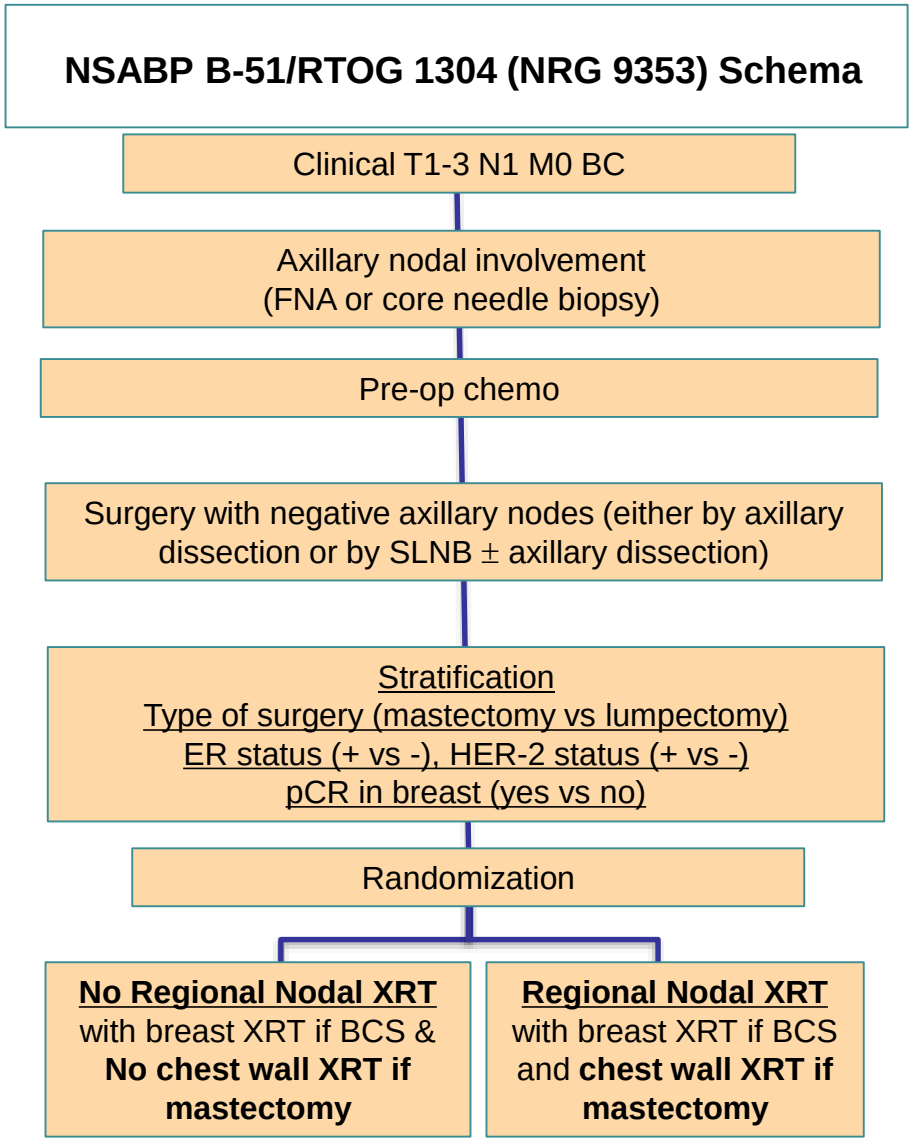
	T1-2 with < 4 nodes
Number	167
Nodal pCR	24.1%
FNR of clipped node	**1.8%** 2/112 (95% CI 0.2-6.3)
FNR of TAD	**0%** 0/69 (95% CI 0 – 5.2)

TAD in Clinical Practice

- Offer TAD with possible omission of ALND if < 4 abnormal nodes on initial US
- Recommend ALND for those with ≥4 nodes
- Multidisciplinary discussion is important
  - Radiation Oncology
  - Plastic Surgery
- **No outcome data available**

Important Ongoing Cooperative Group Trials





Surgery followed by adjuvant therapy

surgery

Adjuvant therapy

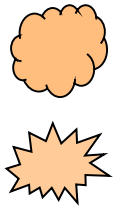
Follow-up

*

Outcome assessed as events occur over time

Neoadjuvant approach

Systemic therapy



surgery

Follow-up

*

Pathologic assessment of response

Thank you!

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