# De-escalation of Axillary Therapy for Breast Cancer

1894 – 2022 and Beyond

***No financial disclosures***

1

## Guidelines for Axillary Management in Breast Cancer

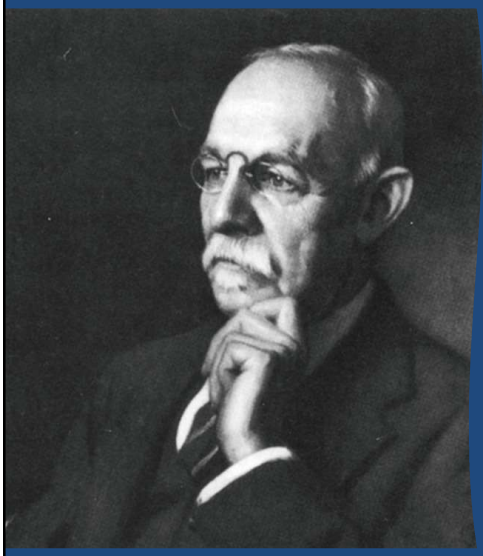
- **https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf**
- **Brackstone M, Baldassarre FG, Perera FE et.al. Management of the Axilla in Early-Stage Breast Cancer: Ontario Health (Cancer Care Ontario) and ASCO Guideline. J Clin Oncol 2021; 39: 3056-82.**
- **https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-the-Management-of-the-Axilla-Concise-Overview.pdf**

2

# Informed Consent

The surgeon's role is to give the patient the information she needs in order to know whether she wants to strictly follow guidelines or to choose a reasonable alternative.

3



**William Stewart Halsted, MD**
**1852 - 1922**

First Professor of Surgery
Johns Hopkins Hospital

Developed Surgical
Residency Training

Halsted WS. The Results of Operations for the Cure of Cancer of the Breast Performed at the Johns Hopkins Hospital from June, 1889, to January, 1894. *Ann Surg* 1894;20:497-555.

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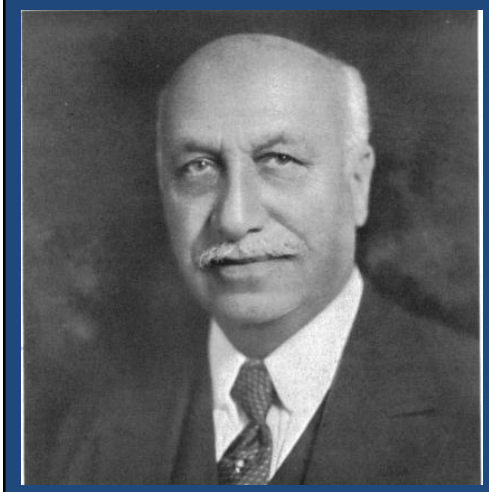

**Willy Meyer, MD**
**1858 - 1932**

Attending Surgeon
New York Skin and Cancer Hospital

Professor of Surgery
Woman's Medical College
New York

Meyer W. An improved method of the radical operation for carcinoma of the breast. *Med Rec* 1894;46:746.

5

# Halsted/Meyer Radical Mastectomy

Level I through III axillary dissection

"The axillary vein should be stripped absolutely clean."

"Furthermore, these patients are old. Their average age is nearly fifty-five years. They are no longer very active members of society."

Halsted WS. The Results of Operations for the Cure of Cancer of the Breast Performed at the Johns Hopkins Hospital from June, 1889, to January, 1894. *Ann Surg* 1894;20:497-555.

6

Radical mastectomy, including axillary dissection of Levels I, II, and III became a standard operation in many institutions over the next 75 years.

Some institutions used radiation to control local and regional disease.

7

# Axillary Radiation Without ALND (cN0)

| Institute | Follow-up (yrs) | Patients | Recurrence (%) |
|---|---|---|---|
| Royal Marsden | 10 | 211 | 3 (1) |
| Institute Curie | 4.5 | 332 | 7 (2) |
| Santiago | 5.2 | 171 | 4 (2) |
| Charlebourg | 5 | 281 | 4 (1) |
| Henri Mondor | 10 | 446 | 0 (0) |
| Groupe Europeen | 5 | 1,040 | 19 (2) |
| Tufts | 4.5 | 73 | 1 (1) |
| JCRT | 6 | 335 | 3 (1) |

Adapted from

Recht A, Houlihan MJ. Axillary lymph nodes and breast cancer. Cancer 1995; 76(9):1491-1511.

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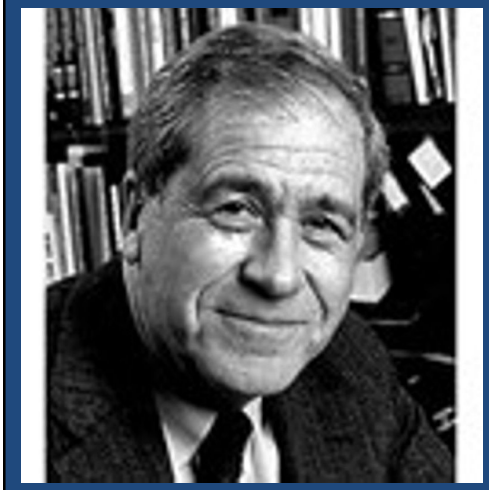

**Bernard Fisher, MD**
**1918 - 2019**

Chairman

National Surgical Adjuvant Breast Project (NSABP)

"I discovered how little information there was related to the biology of breast cancer and what a lack of interest there was in understanding the disease."

9

# NSABP B-04

**Clinically node negative**

- Radical mastectomy
- Total mastectomy + radiation
- Total mastectomy alone

**Clinically node positive**

- Radical mastectomy
- Total mastectomy + radiation

**No systemic treatment for any patient**

Fisher B, Montague E, Redmon C, et.al. Comparison of radical mastectomy with alternative treatments for primary breast cancer: a first report of results from a prospective randomized clinical trial. Cancer 1977; 39:2827–39.

10

# NSABP B-04

**"No significant differences were observed among the three groups of women with negative nodes or between the two groups of women with positive nodes with respect to disease-free survival, distant disease-free survival, or overall survival."**

Fisher B, Montague E, Redmon C, et.al. Comparison of radical mastectomy with alternative treatments for primary breast cancer: a first report of results from a prospective randomized clinical trial. Cancer 1977; 39:2827–39.

11

# NSABP B-04

## Delayed ALND Arm

- **There was *no survival detriment* compared to patients who had immediate ALND.**
- **Only half of the patients with positive nodes left behind developed palpable nodes in the axilla.**

Fisher B, Montague E, Redmon C, et.al. Comparison of radical mastectomy with alternative treatments for primary breast cancer: a first report of results from a prospective randomized clinical trial. Cancer 1977; 39:2827–39.

12

# Lymphedema

**Prospective, randomized (Edinburgh)**

**395 patients**

| | |
|---|---|
| **Radical mastectomy** | **10 %** |
| **Mastectomy and radiation** | **5 %** |

**Bruce J. Operable cancer of the breast. Cancer 1971; 28:1443-51**

13

# Neoadjuvant chemotherapy with CMF for node positive breast cancer

| | Treatment failure (at 27 months) |
|---|---|
| Control group | 24% |
| CMF | 5.3% (p = 0.000001) |

Bonadonna G, Brusamolino E, Valagussa P. Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 1976;294:405-10.

14

Despite the findings of NSABP B-04 in 1977, axillary dissection remained necessary for *staging*, not therapeutic, purposes.

15

## De-escalation of Standard Level III Dissection Randomized Trials

| | # Pts | Follow-up years | Overall Survival | Disease-free Survival |
|---|---|---|---|---|
| **Tominaga (Level III vs Level II)** | **1209** | **10** | **Level III 85.7%<br>Level II 86.6% (p = 0.93)** | **III 77.8%<br>II 73.3 % (p = 0.67)** |
| **Kodoma (Level III vs Level I)** | **514** | **10** | **Level III 89.6%<br>Level I 87.8% (p = NS)** | **III 76.6%<br>I 74.1% (p = NS)** |

Tominaga T, Takashima S, Danno M. Randomized clinical trial comparing level II and level III axillary node dissection in addition to mastectomy for breast cancer. Br J Surg 2004;91(1):38-43.

Kodoma H, Nio Y, Iguchi C, Kan N. Ten-year follow-up results of a randomised controlled study comparing level-I vs level-III axillary lymph node dissection for primary breast cancer. British Journal of Cancer 2006;(95):811–816.

16

## No Axillary Dissection (IBCSG 10-93) cN0; 60 years and older

| | # Pts | Follow-up years | Overall Survival | Disease-free Survival |
|---|---|---|---|---|
| No ALND | 239 | 6.6 | 73 % | 66 % |
| ALND | 234 | 6.6 | 75 % (p = 0.77) | 67 % (p = 0.69) |

Rudenstam C, Zahrieh D, Forbes J, et al. Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10-93. J Clin Oncol 2006;24(3):337-44.

17

## Sentinel Node Biopsy

| | False Negative Rate |
|---|---|
| Blue dye only | 8.6 % |
| Radioactive tracer only | 7.4 % |
| Combination dye and tracer | 5.9 % |

Pesek S, Ashikaga T, Krag L, Krag D. The false-negative rate of sentinel node biopsy in patients with breast cancer: a meta-analysis. World J Surg 2012;36(9):1385-93.

Petrelli F, Lonati V, Barni S. Axillary dissection compared to sentinel node biopsy for the treatment of pathologically node-negative breast cancer: a meta-analysis of four randomized trials with long-term follow up. Oncol Rev 2012;6(2):e20 Published online 2012 Oct 8. doi: 10.4081/oncol.2012.e20

18

# Sentinel Node Biopsy

Axillary recurrence after 10 years

1.6%

Boniface J, Frisell J, Bergvist L, Andersson Y. Ten-year report on axillary recurrence after negative sentinel node biopsy for breast cancer from the Swedish Multicentre Cohort Study. Brit J Surg 2017;104(3):238-47.

19

# Sentinel Node Biopsy

SNB substantially decreased morbidity compared to ALND and became standard for axillary staging.

Burak WE, Hollenbeck ST, Zervos EE, et al: Sentinel lymph node biopsy results in less postoperative morbidity compared with axillary lymph node dissection for breast cancer. Am J Surg 2002;183::23,2002-27, Crossref, Medline.

Peintinger F, Reitsamer R, Stranzl H, et al: Comparison of quality of life and arm complaints after axillary lymph node dissection vs sentinel lymph node biopsy in breast cancer patients. Br J Cancer 2003;89::648,2003-652, Crossref, Medline.

Schijven MP, Vingerhoets AJ, Rutten HJ, et al: Comparison of morbidity between axillary lymph node dissection and sentinel node biopsy. Eur J Surg Oncol 2003; 29::341,2003-350, Crossref, Medline.

Ashikaga T, Krag D, Land S, et al. Morbidity results from the NSABP B-32 trial comparing sentinel lymph node dissection versus axillary dissection. J Surg Oncol 2010;102:111-8. doi: 10.1002/jso.21535.

20

# IBCSG 23-01 Trial

## 10-year follow-up

cT1-2 cN0 patients; TM or PM plus SNB

Micrometastases only (≤ 2 mm) with no ECE

| | DFS | AX Recurrence | Lymphedema |
|---|---|---|---|
| ALND (464 pts) | 74.9 % | 1 (0.2%) | 13 % |
| SNB only (467 pts) | 76.8 %(NS) | 4 (0.8%)NS | 4% |

Galimberti V, Cole B, Viale G, et al. Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 trial. Lancet Oncol 2018;19(10):1385-1393.

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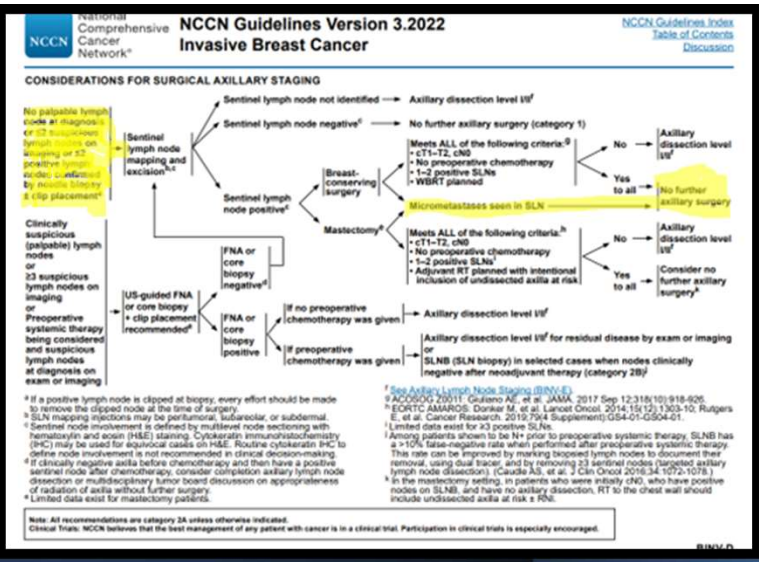
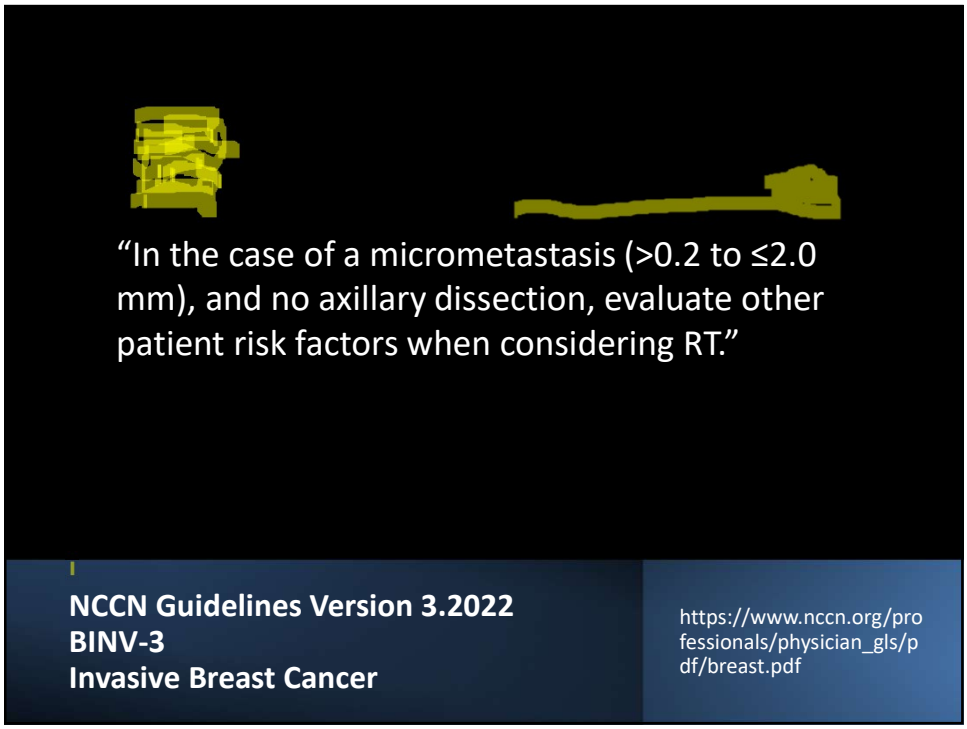



**NCCN Guidelines Version 3.2022**
**BINV-D**
**Invasive Breast Cancer**

https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

22




23

## ACOSOG Z-0011 (Alliance)
### 10-year follow-up

cT1-2 patients; cN0

PM plus breast radiation; systemic therapy planned

No more than 2 positive sentinel nodes; No gross ECE

| | OS | DFS | Regional Recurrence |
|---|---|---|---|
| SNB alone | 86.3% | 80.2% | 1.2% |
| ALND | 83.6% (NS) | 78.2% (NS) | 0.5% (NS) |

Guiliano A, Ballman K, McCall L, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis; The ACOSOG Z0011 (Alliance) randomized clinical trial. JAMA 2017;318(10):918-926. doi:10.1001/jama.2017.11470

24

# AMAROS Trial

## After Mapping of the Axilla: Radiotherapy Or Surgery?

### 10-year follow-up

cN0, cT1-2, SN+; TM or PM

| | Axillary Recurrence | Lymphedema |
|---|---|---|
| AR (681 pts) | 1.82 % | 11 % |
| ALND (744 pts) | 0.93 % (NS) | 23 % |

Donker M, van Tienhoven G, Straver M., et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS):a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014;15(12):1303-10.

Rutgers E, et al. 2018 San Antonio Breast Cancer Symposium (Abstract GS4-01)

25

# OTOASOR Trial

## Optimum Treatment Of Axilla: Surgery Or Radiotherapy?

### 8-year follow up

cT $\leq$ 3 cm, cN0; Partial or Total Mastectomy, SNB

| | Ax Recurrence | OS | DFS | Morbidity |
|---|---|---|---|---|
| AR (230 pts) | 1.7 % | 84.8 % | 77.4 % | 4.7% |
| ALND (244 pts) | 2.0 % (NS) | 77.9 % (NS) | 72.1 % (NS) | 15.3% |

Savolt A, Peley G, Polgar C. Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla - Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III, non-inferiority trial. Eur J Surg Oncol 2017;43(4):672-9.

26

# Lymphedema in NSABP B-04

| | |
|---|---|
| Radical mastectomy | 30.7% |
| Mastectomy and radiation | 14.8% |
| Mastectomy alone | 15.5% |

(p = 0.001)

Deutsch M, Land S, Begovic M, et al. The incidence of arm edema in women randomized on the National Surgical Adjuvant Breast and Bowel project study B-04 to radical mastectomy versus total mastectomy and radiotherapy versus total mastectomy alone. Int J Radiat Oncol Biol Phys 2008;70(4):1020-4.

27

# Criticism of NSABP B-04

1. Underpowered to detect small differences.
   Z-0011, AMAROS, OTOASOR underpowered

2. Axillary recurrence was first event only.

3. One third of patients had nodes removed.
   – 2/3 of patients had no nodes removed

Fisher B, Jeong J, Anderson S, et al. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. N Engl J Med 2002; 347:567-575 DOI: 10.1056/NEJMoa020128

28

## Criticism of NSABP B-04

### Mastectomy Only Group

| | Delayed palpable nodes |
|---|---|
| No axillary treatment (overall) | 19% |
| No axillary treatment (Zero nodes removed) | 21% |

Fisher B, Wolmark N, Bauer M, Redmond C, Gebhardt M. The accuracy of clinical nodal staging and of limited axillary dissection as a determinant of histologic nodal status in carcinoma of the breast. Surg Gynecol Obstet 1981;152:765-72.

29

## Furthermore…

SNB removes the nodes most likely to contain tumor including all intraoperatively palpated nodes.

Only 27% of patients are node positive now.*

Residual tumor burden after SNB now is almost surely lower than it was in NSABP B-04.

*DeSantis C, Gaudet M, Newman L, et al. Breast cancer statistics, 2019. **https://doi.org/10.3322/caac.21583**

30

**Consensus guideline on axillary management for patients with in situ and invasive breast cancer: a concise overview. American Society of Breast Surgeons 2022.**

**https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-the-Management-of-the-Axilla-Concise-Overview.pdf**

31

## 2022 ASBrS Axillary Guideline

**Omit Sentinel Node Biopsy:**

- ER positive patients 70 years or older with clinically negative axilla and tumors up to 5 cm in size

Hughes KS, Schnaper LA, Bellon JR, et.al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol 2013;31(19):2382-7.

32

# CALGB 9343

## 10 year follow-up

- Patients 70 years and older
- All were to take tamoxifen
- Randomized to breast radiation or not after PM
- LRR 10% without radiation; 2% with radiation
- No difference in survival

Axillary dissection allowed but discouraged.

62% did not have ALND.

No difference in survival; 3% axillary recurrence

Hughes K, Schnaper L, Bellon J, et al. Lumpectomy Plus Tamoxifen With or Without Irradiation in Women Age 70 Years or Older With Early Breast Cancer: Long-Term Follow-Up of CALGB 9343. J Clin Oncol 2013;31(19):2382-7.

33

# CALGB 9343

## 10 year follow-up

- ER+ patients 70 years and older
- All were to take tamoxifen
- Randomized to breast radiation or not after PM
- LRR 10% without radiation; 2% with radiation
- No difference in survival

Axillary dissection allowed but discouraged.

62% did not have ALND.

No difference in survival; 3% axillary recurrence

Hughes K, Schnaper L, Bellon J, et al. Lumpectomy Plus Tamoxifen With or Without Irradiation in Women Age 70 Years or Older With Early Breast Cancer: Long-Term Follow-Up of CALGB 9343. J Clin Oncol 2013;31(19):2382-7.

34

# 2022 ASBrS Axillary Guideline

**Omit Sentinel Node Biopsy:**

- Patients 70 years or older with clinically negative axilla and hormone receptor positive tumor 5 cm or smaller in size
- Patients with DCIS undergoing partial mastectomy unless suspicion of invasion is present

Hughes KS, Schnaper LA, Bellon JR, et.al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol 2013;31(19):2382-7.

van Roozendaal LM, Goorts B, Klinkert M et.al. Sentinel lymph node biopsy can be omitted in DCIS patients treated with breast conserving therapy. Breast Cancer Res Treat 2016;156:517-25.

35

# 2022 ASBrS Axillary Guideline

**Omit Sentinel Node Biopsy:**

- Patients 70 years or older with clinically negative axilla and hormone receptor positive tumor 5 cm or smaller in size
- Patients with DCIS undergoing partial mastectomy unless suspicion of invasion is present
- Patients undergoing prophylactic mastectomy (1.2% node +)

Hughes KS, Schnaper LA, Bellon JR, et.al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol 2013;31(19):2382-7.

van Roozendaal LM, Goorts B, Klinkert M et.al. Sentinel lymph node biopsy can be omitted in DCIS patients treated with breast conserving therapy. Breast Cancer Res Treat 2016;156:517-25.

Nagaraja N, Edirimanne S, Eslick GD. Is Sentinel Lymph Node Biopsy Necessary in Patients Undergoing Prophylactic Mastectomy? A Systematic Review and Meta-Analysis. Breast J 2016; 156: 517-25.

36

## 2022 ASBrS Axillary Guideline

**Perform Sentinel Node Biopsy:**

- Clinically node negative patients who meet ACOSOG Z-0011 criteria, even if image detected nodes positive on FNA or core biopsy.

*Patients in ACOSOG Z-0011 did not have axillary ultrasound.

*At MSKCC 47% of patients who met Z-0011 criteria, but had image guided positive node biopsy, had only 1 or 2 positive nodes.

Pilewskie M, Mautner S, Stemple M, Eaton A, Morrow M. Does a Positive Axillary Lymph Node Needle Biopsy Result Predict the Need for an Axillary Lymph Node Dissection in Clinically Node-Negative Breast Cancer Patients in the ACOSOG Z0011 Era? Ann Surg Oncol 2016;23(4):1123–8

37

## 2022 ASBrS Axillary Guideline
## No Neoadjuvant Chemotherapy
## 3 or more positive nodes

Majority opinion:

ALND only recommended option

38

## Judicial System

Criminal

Evidence beyond a reasonable doubt

Civil

Preponderance of evidence

39

## Standard Treatment

Tort law does not compel us to follow guidelines.

Standard care is what a *reasonable* person would do under the same or similar circumstances.

40

## Ontario Health/ASCO Guidelines
## 3 or more positive nodes (No NAC)

"The management of the axilla for patients with four or more positive lymph nodes (N2 and N3 disease) falls outside the scope of this guideline….***For exactly three positive lymph nodes, there is not enough evidence to make a recommendation, and therefore, we recommend proceeding with ALND*** *and considering* LRNI."

**Brackstone M, Baldassarre FG, Perera FE et.al. Management of the Axilla in Early-Stage Breast Cancer: Ontario Health (Cancer Care Ontario) and ASCO Guideline. J Clin Oncol 2021; 39: 3056-82.**

41

## Ontario Health/ASCO Guidelines
## 3 or more positive nodes (No NAC)

***"Even in patients with three <u>or more</u> positive sentinel lymph nodes*** (25% of patients in the AMAROS trial), ***LRNI was equivalent to ALND; thus, either treatment strategy is an option. However, radiotherapy has lower lymphedema risk, and therefore, we recommended it."***

**Brackstone M, Baldassarre FG, Perera FE et.al. Management of the Axilla in Early-Stage Breast Cancer: Ontario Health (Cancer Care Ontario) and ASCO Guideline. J Clin Oncol 2021; 39: 3056-82.**

42

# Multiple nodes in AMAROS

- 25% of patients had 4 or more ***additional*** positive nodes in group randomized to AR who crossed over to ALND arm.
  Not representative of entire AR group.
- 8% of patients in ALND arm (and therefore the AR arm as well) had 4 or more ***additional*** positive nodes (total of at least 5 positive nodes).
- AMAROS was not a trial that contained only small volume disease.

Donker M, van Tienhoven G, Straver M., et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS):a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014;15(12):1303-10.

43

# 2022 ASBrS Axillary Guideline
## Management of node positive axilla after NAC

Majority opinion:

Only ALND until publication of Alliance 11202.

44

# Alliance 11202

Axillary node positive by core or FNA

All received NAC

No palpable axillary nodes after NAC

SNB positive

Randomized to: ALND vs Axillary Radiation

Boughey J, Haffty B, Buchholz T, et al. Alliance A011202: A Randomized Phase III Trial Comparing Axillary Lymph Node Dissection to Axillary Radiation in Breast Cancer Patients (cT1-3 N1) Who Have Positive Sentinel Lymph Node Disease After Receiving Neoadjuvant Chemotherapy

https://www.allianceforclinicaltrialsinoncology.org/main/cmsfile?cmsPath=/Public/Annual%20Meeting/files/A011202-Boughey-May2019.pdf

45

# Alliance 11202

- After new guidelines posted in March, 2022, Alliance 11202 re-opened for accrual because of low event rate then closed again 7/1/22.
- Publication likely to be in 2030 at the earliest.

46

# 10-year Regional Recurrence after NAC
## (Analysis of NSABP B-18 and B-27 neoadjuvant trials)

All patients had
- TM or PM/breast only radiation
- No nodal radiation
- ALND

Nodal recurrence (includes AX, SC, IM)
- cN0; ypN0 0.9 – 3.0%
- cN0; ypN+ 0.5 – 3.4%
- cN1; ypN0 1.3 – 2.0%
- cN1; ypN+ 4.8 – 8.7 %

Mamounas EP, Anderson SJ, Dignam JJ, et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. J Clin Oncol 2012;30(32):3960-6.

47

## cN0; ypN+

[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.

**NCCN Guidelines Version 3.2022**
**BINV-D**
**Invasive Breast Cancer**

https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

48

## 10-year Regional Recurrence after NAC
### (Analysis of NSABP B-18 and B-27 neoadjuvant trials)

All patients had
- TM or PM/breast radiation
- ALND with no nodal radiation

Nodal recurrence (includes AX, SC, IM)
- cN0; ypN0 0.9 – 3.0%
- cN0; ypN+ 0.5 – 3.4%
- cN1; ypN0 1.3 – 2.0%
- cN1; ypN+ 4.8 – 8.7 %

Mamounas EP, Anderson SJ, Dignam JJ, et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. J Clin Oncol 2012;30(32):3960-6.

49

## 10-year Regional Recurrence after NAC
### (Analysis of NSABP B-18 and B-27 neoadjuvant trials)

- Pre-menopausal patients in B-18 did not receive tamoxifen.
- Patients in B-27 received concurrent tamoxifen.
- No patients received:
  - aromatase inhibitors
  - trastuzumab
  - pertuzumab
  - pembrolizumab
  - trastuzumab emtansine (T-DM1)
  - CDK 4/6 inhibitors (abemaciclib, etc.)
  - capecitabine

50

# Sentinel Lymph Node Dissection following Neo-adjuvant Chemotherapy

False Negative Rate

| | |
|---|---|
| Single tracer, removing 1 or 2 nodes | 12 – 14 % |
| Dual tracer, removing at least 3 nodes | 9.1 % |
| SNB plus targeted removal of clipped node | 2 % |

Boughey J, Suman V, Mittendorf A. Sentinel Lymph Node Surgery after Neoadjuvant Chemotherapy in Patients With Node-Positive Breast Cancer: The American College of Surgeons Oncology Group (ACOSOG) Z1071 Clinical Trial. JAMA 2013;310(14):1455-61.

Caudle A, Yang W, Krishnamurthy S, et al. Improved Axillary Evaluation Following Neoadjuvant Therapy for Patients With Node-Positive Breast Cancer Using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection. J Clin Oncol. 2016;34(10):1072-8.

51

# Patients SNB Negative after NAC Follow-up without ALND

Barrio AV, Montagna G, Mamtani A, et al. Nodal recurrence in patients with node-positive breast cancer treated with sentinel node biopsy alone after neoadjuvant chemotherapy-a rare event. JAMA Oncol 2021;7(12):1851-1855. Doi.10.1001/jamaoncol.2021.4394

Fontana S, Pagan E, Magnoni F. Long-term standard sentinel node biopsy after neoadjuvant treatment in breast cancer: a single institution ten-year follow-up. Euro J Surg Oncol 2021;47(4):804-12. doi:https://doi.org/10.1016/j.ejso.2020.10.014

Martelli G, Barretta F, Miceli R. Sentinel node biopsy alone or with axillary dissection in breast cancer patients after primary chemotherapy; Long-term results of a prospective interventional study. Ann Surg 2020. doi:10.1097/SLA.0000000000004562

52

# Sentinel Lymph Node Dissection

Axillary recurrence after 10 years

1.6%

Boniface J, Frisell J, Bergvist L, Andersson Y. Ten-year report on axillary recurrence after negative sentinel node biopsy for breast cancer from the Swedish Multicentre Cohort Study. Brit J Surg 2017;104(3):238-47.

53

# Patients with Negative SNB after NAC Follow-up without ALND

| Institute | # Pts | # Sentinel Nodes | Predicted False Negative rate | Follow up years | | | Initially cN0 | Initially cN1-2 |
|---|---|---|---|---|---|---|---|---|
| MSKCC, Barrio | 234 | Dual Tracer Minimum 3 nodes | 9% | 3.3 | | | NA | 0.4% |
| European Institute Oncology, Milan, Fontana | 439 | Radiocolloid Only Minimum 1 node | 12-14% | 9.2 | | | 1.5% | 1.8% |
| National Tumor Institute, Milan Martelli | 176 | Radiocolloid Only Minimum 1 node | 12-14% | 7.25 | | | 0% | 0% |

54

# National Cancer Database

## Retrospective Review 2012-2015

cT1-3N1M0 and ypT0-3N1M0

All Received RNI

| | 5-year OS | Propensity matched 5-year OS |
|---|---|---|
| ALND | 73% | 69% |
| SNB | 76% (p=0.39) | 79% (p=0.33) |

Kharouta MZ, Damico N, Miller M, Harris EE, Lyons J. Impact of Axillary Lymph Node Dissection (ALND) on survival in patients with ypN1 breast cancer that receive regional nodal irradiation (RNI): A national cancer database (NCDB)analysis. Int J Radiation Oncol Biol Phys 2020;108. DOI: https://doi.org/10.1016/j.ijrobp.2020.07.1140

55

# ALND or AR after NAC?

## What patients need to know.

- If cN0 before NAC, no increase in LRR. NCCN guidelines allow radiation which will cut her risk of lymphedema in half.
- If cN+ before NAC and ypN+ after NAC, increased LRR 25 years ago but nothing suggested ALND better than AR for control.
- No published trials comparing ALND vs AR after NAC.
- Alliance 11202 publication delayed due to low recurrence rate.
- Other than lymphedema, if trial shows difference in the two arms, likely to be small and perhaps clinically insignificant.

56

# ALND or AR after NAC?

What patients need to know

- Axillary recurrence with modern systemic therapy is low.
- AR excellent for microscopic disease in all other scenarios, and no reason to believe it would be different in her.
- Neoadjuvant chemotherapy plus ALND leads to very high lymphedema rates.

57

## Lymphedema in ACOSOG (Alliance) Z1071

- All patients had neoadjuvant chemotherapy and SNB followed by ALND.
- Radiation at discretion of local physicians, and omission of axilla recommended.

Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer The ACOSOG Z1071 (Alliance) clinical trial. JAMA. 2013;310(14):1455-1461.

Haffty BG, McCall LM, Ballman KV, et al. Impact of Radiation on Locoregional Control in Women with Node-Positive Breast Cancer Treated with Neoadjuvant Chemotherapy and Axillary Lymph Node Dissection: Results from ACOSOG Z1071 Clinical Trial. Int J Radiation Oncol Biol Phys 2019;105(1):174-182.

58

## Lymphedema in ACOSOG (Alliance) Z1071
### (at 3 years)

| | |
|---|---|
| Arm heaviness | 31% |
| Volume increase ≥ 10% | 60% |
| Increase in circumference ≥ 2 cm | 75% |

Armer JM, Ballman KV, McCall L, et al. Lymphedema symptoms and limb measurement changes in breast cancer survivors treated with neoadjuvant chemotherapy and axillary dissection: results of ACOSOG (American College of Surgeons Oncology Group) Z1071(Alliance) substudy. Support Care Cancer 2019;27(2) 495-503.

59

## Decrease Risk of Lymphedema

Axillary Reverse Mapping

LYMPHA Procedure

60

# ALND to determine if N2?

RxPONDER Trial

MonarchE Trial

Kalinsky K, Barlow WE, Gralow JR, et al: 21-Gene assay to inform chemotherapy benefit in node-positive breast cancer. N Engl J Med 385:2336-2347, 2021 Crossref, Medline

Harbeck N, Rastogi P, Martin M, et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol 2021;32(12):1571-1581. doi: 10.1016/j.annonc.2021.09.015. Epub 2021 Oct 14.

61

# MonarchE

Randomized to +/- **abemaciclib (CDK 4/6 inhibitor**)

High risk if N2

High risk if N1 and

- T ≥ 5cm
- Grade III
- Ki 67 ≥ 20 %

Absolute Benefit for abemaciclib at 3 years

| | |
|---|---|
| Invasive disease-free survival | 5.4% (p = 0.0009) |
| Distant relapse-free survival | 4.2 % (p = 0.0001) |

Harbeck N, Rastogi P, Martin M, et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol 2021;32(12):1571-1581. doi: 10.1016/j.annonc.2021.09.015. Epub 2021 Oct 14.

62

# RxPONDER and MonarchE

"…routine ALND is not indicated to safely apply the results of RxPONDER or monarchE to determine systemic therapy recommendations for patients with HR+/HER2– breast cancer."

Mittendorf E, King T, Tolaney S. Impact of RxPONDER and monarchE on the Surgical Management of the Axilla in Patients With Breast Cancer. J Clin Oncol 2022;JCO2200173. doi: 10.1200/JCO.22.00173. Online ahead of print.

63

# PlanB and SUCCESS C Analysis

Her2 negative; High risk patients

N2 patients benefited from **anthracyclines** only if they had lobular histology.

de Gregorio A, Janni W, Friedl T, et al. The impact of anthracyclines in intermediate and high-risk HER2-negative early breast cancer-a pooled analysis of the randomised clinical trials PlanB and SUCCESS C. Br J Cancer 2022;126(12):1715-1724. https://doi.org/10.1038/s41416-021-01690-6

64

## ~~ALND?~~

- SNB is now the accepted standard for axillary staging established by multiple prospective, randomized trials.
- We accept the fact that a small number of patients will be under-staged and perhaps under-treated due to a false negative rate of approximately 6%.
- ALND triples the morbidity compared to SNB, so we accept under-staging and potential under-treatment to avoid morbidity.
- Goal should be to get risk of undetected N2 disease under 6%.

65

## MSKCC Database
## 11,596 tumors

## ≥ 4 positive nodes

| | |
|---|---|
| HR+/HER2− | 9% |
| HR−/HER2− | 13% |

Ugras S, Stempel M, Patil S, et al. Estrogen receptor, progesterone receptor, and HER2 status predict lymphovascular invasion and lymph node involvement. Ann Surg Oncol 2014;21:3780-3786. Crossref, Medline

66

# Targeted Axillary Dissection

If important to determine N2 disease

Obtain axillary ultrasound; biopsy and clip any suspicious nodes.

Perform TAD to remove clipped nodes.*

Use dual tracers and carefully search for sentinel and palpable nodes.

Assure the patient and the medical oncologist that the chance of undetected N2 disease is low.

*Caudle A, Yang W, Krishnamurthy S, et al. Improved Axillary Evaluation Following Neoadjuvant Therapy for Patients With Node-Positive Breast Cancer Using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection. J Clin Oncol 2016;34(10):1072-1078. doi: 10.1200/JCO.2015.64.0094

67

# Personal Experience

- When SNB replaced ALND in late 1990s, ALND no longer needed for staging and systemic therapy decisions.
- If patients were getting radiation anyway, axillary control could be obtained without morbidity of ALND.
- Discussed guidelines and offered AR in lieu of ALND.
- Included PM or TM patients; NAC; multiple positive nodes.
- Goal was to render axilla free of palpable disease.

68

## Personal Series
## 1998 - 2011

| | Patients | Axillary Recurrence | Lymphedema |
|---|---|---|---|
| SNB Only | 630 | 4 (0.6%) | 1.9% |
| ALND | 180 | 1 (0.6%) | 30.4% |
| Axillary radiation | 70 | 0 (0%) | 6.9% |

Snider H. American Society of Breast Surgeons Presidential Address: could quality measures impede quality care? Ann Surg Oncol 2012;19(10):3125-30.

69

## 1894 – 2022
### De-escalation (guideline supported)

1894:

Level I-III ALND, stripping vein absolutely clean

2022:

**SNB** --- Most patients under 70 years with invasive disease; image-detected, non-palpable positive node (Z-11)

**SNB without ALND**--- micrometastases; low volume macrometastases (Z-11, AMAROS, OTOASOR)

**No axillary operation** --- 70 years and over; PM for DCIS without suspicion of invasion; prophylactic mastectomy

70

# 1894 – 2022

## De-escalation (supported by preponderance of evidence)

2022:

**Axillary radiation**

No NAC: 3 or more positive sentinel nodes (ASCO equivocal)

NAC: Any positive nodes

Cuts risk of lymphedema in half with no data suggesting any harm.

71

# and Beyond….

TAXIS Trial

34 sites; 4 countries

Clinically node positive patients at presentation or after NAC undergo Tailored Axillary Surgery (TAS) to decrease volume of disease.

Randomized to ALND plus RNI (excluding axilla) or No ALND with RNI (including axilla)

Henke G, Knauer M, Ribi K, et al. Tailored axillary surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-positive breast cancer (TAXIS): study protocol for a multicenter, randomized phase-III trial. Trials 2018;19. 667

72

## The Bottom Line….

Axillary dissection is becoming an operation of historical interest only.

73

# Primum Non Nocere

74