Axillary lymph nodes, handling and reporting post-Z11 and TNM8: when is a micrometastasis not a micrometastasis?

Colin A Purdie

BDIAP Symposium on Breast Pathology

Friday 24th November 2017

Axillary lymph nodes, Z11 and TNM8

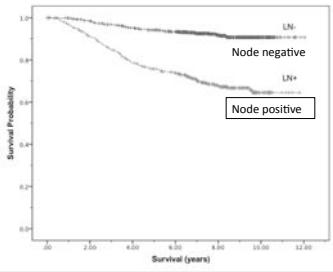
- Management of the axilla in early breast cancer
  - SNB negative
  - SNB positive
- Z11
  - What does it tell us about the management of a positive axilla?
- Pathological handling of the SNB
- TNM8 (AJCC 8th edition)

Management of the axilla in early breast cancer

- Nodal dissection
  - Radical (Halsted) mastectomy (1882-1970s)
- Purpose
  - Therapy
    - Removal of all breast tissue with overlying skin and underlying pectoral muscles
    - Removal of involved nodes

Lymph node status and survival

Tayside 2000-2004 operable breast cancer patients
n=1074



$p < 0.0001$

Lymph node status and survival

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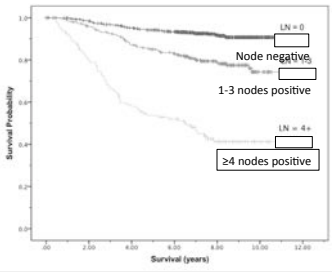
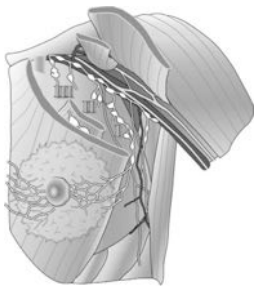


$p < 0.0001$

Axillary node clearance



- Definitive staging of the axilla
- Treatment of axillary disease
- Morbidity
  - Seroma
  - Lymphoedema (2-30%)
  - Numbness
  - Paraesthesia
  - ↓ROM at shoulder

NSABP B-04

RADICAL VERSUS TOTAL MASTECTOMY

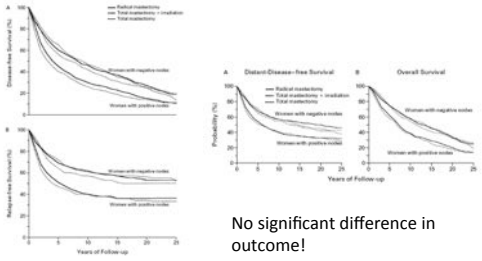
TWENTY-FIVE-YEAR FOLLOW-UP OF A RANDOMIZED TRIAL COMPARING RADICAL MASTECTOMY, TOTAL MASTECTOMY, AND TOTAL MASTECTOMY FOLLOWED BY IRRADIATION

BERNARD FISHER, M.D., JONG-HYEON JEONG, PH.D., STEWART ANDERSON, PH.D., JOHN BRYANT, PH.D., EDWIN R. FISHER, M.D., AND NORMAN WOLMARK, M.D.

N Engl J Med, Vol. 347, No. 8 · August 22, 2002

- Clinically node negative
  - Halsted Mx (incl ANC)
  - Simple Mx + XRT to axilla
  - Simple Mx only
- Clinically node positive
  - Halsted Mx (incl ANC)
  - Simple Mx + XRT to axilla
- 25 year follow-up
  - DFS
  - OS
- No adjuvant systemic therapy

NSABP B-04



No significant difference in outcome!

NSABP B-04

- Clinically node positive
  - Halsted Mx (incl ANC)
  - Simple Mx + XRT to axilla

No difference in outcome after 25 years

- Clinically node negative
  - Halsted Mx (incl ANC)
  - Simple Mx + XRT to axilla
  - Simple Mx only

No difference in outcome after 25 years

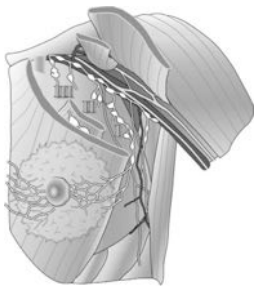
NSABP B-04

- Clinically node negative patients
  - Mx + ANC - 40% had positive nodes
  - Mx only - 18.6% presented with nodal metastasis during 25 years of follow-up!

NSABP B-04

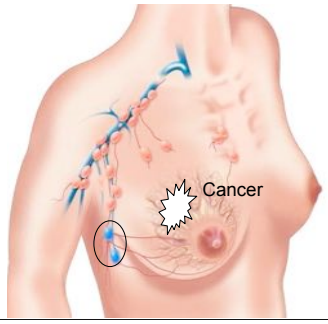
- Conclusions
  - Node positive disease
    - Radiotherapy is as good as surgery
    - Confirmed by AMOROS
  - Clinically node negative disease
    - No treatment to the axilla is necessary

Axillary node clearance



- Definitive staging of the axilla ✔
- Treatment of axillary disease **?**
- Morbidity ✔
  - Seroma
  - Lymphoedema (2-30%)
  - Numbness
  - Paraesthesia
  - ↓ROM at shoulder

Sentinel Node Biopsy



Sentinel Node Biopsy

- Things worth remembering about SNB
  - False negatives
    - 7% on meta-analysis of 9,220 patients (Pesek *et al* World J Surg 2012)
  - The positive SLN is frequently the only positive node (>50% in ALMANAC, 61% in NSABP B-32)
  - 10% of SLNs are internal mammary nodes (ALMANAC)
    - 6% had internal mammary node metastases with *negative* axillary nodes (ALMANAC)

Sentinel Node Biopsy

- Negative SNB
  - Does it matter that SNB has significant false negative rate?
- Positive SNB
  - Does the volume of metastatic disease matter?

Negative SNB

Outcome following negative SNB

TABLE 1. Incidence of Axillary Recurrence After Negative Sentinel Node Biopsy Without Completion Axillary Lymph Node Dissection in Patients With Primary Invasive Breast Cancer

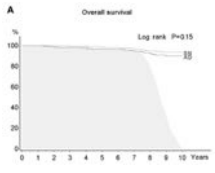
Publication (Author, Year)	Patients (N)	Median Follow-up (mo)	Design (No. Institutions)	Axillary Recurrences N (%)
Veronesi[34] (2001)	280	14	Single	0 (0)
Reunen[35] (2001)	100	24	Single	1 (1)
Chung[9] (2002)	208	26	Single	3 (1.4)
Reitsamer[17] (2003)	116	22	Single	0 (0)
Veronesi[18] (2003)	167	46	Single	0 (0)
Badgwell[7] (2003)	159	32	Single	0 (0)
Blanchard[8] (2003)	685	29	Single	1 (0.1)
Naik[19] (2004)	2340	31	Single	3 (0.12)
Reitsamer[36] (2004)	200	36	Single	0 (0)
Imoto[11] (2004)	112	52	Single	4 (3.6)
Torrenga[12] (2004)	104	57	Single	1 (0.96)
van der Vegt[23] (2004)	106	35	Single	1 (0.9)
Smidt[20] (2005)	439	26	Single	2 (0.46)
Jerusa[14] (2005)	592	27	Single	1 (0.17)
Zavagno[24] (2005)	479	36	Multicenter (5)	0 (0)
Langer[15] (2005)	122	42	Single	1 (0.8)
Veronesi[25] (2005)	953	38	Single	3 (0.3)
Kekke[16] (2005)	113	37	Single	1 (0.9)
Haid[26] (2006)	170	47	Single	1 (0.6)
Paleaty[39] (2006)	335	33	Single	2 (0.6)
Present study	*2246*	*37*	*Multicenter (25)*	*27 (1.2)*

Published trials including more than 100 patients.

Bergkvist *et al* , Ann Surg 2008; **247: 150-6**

SNB in node negative disease

- Similar survival to ANC
  - NSABP-B32 (Krag *et al*, Lancet Oncology 2010)
  - Milan (Veronesi *et al*, Ann Surg 2010)



SNB in node negative disease

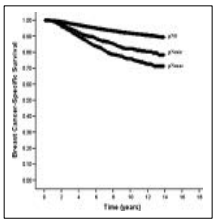
- Negative SNB requires no further local treatment
- What happens to the (~7%) false negatives?

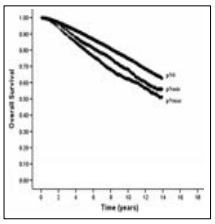
Positive SNB

Sentinel Node Biopsy

- Does the volume of metastatic disease matter?
  - Macrometastasis
  - Micrometastasis
  - Isolated tumour cells (ITCs)

Prognosis and volume of metastatic disease



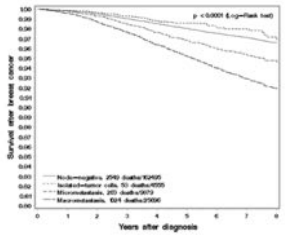


Truong PT, Vinh-Hung V, Cserni G, et al. The number of positive nodes and the ratio of positive to excised nodes are significant predictors of survival in women with micrometastatic node-positive breast cancer. *Eur J Cancer* 2006;**42**:1072–7

N = 62.500
SEER database

Prognosis and volume of metastatic disease

SEER database
N = 206,625



Iqbal J, *et al*. Breast Cancer Res Treat (2017) 161:103–115

Paradox

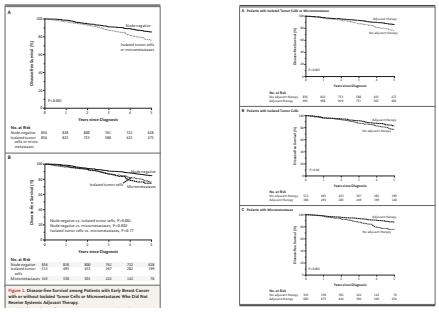
- Even low volume metastatic disease has a negative impact on prognosis
- SNB has a significant false negative rate but this does not influence prognosis

ITCs, micrometastases and prognosis

- De Boer *et al*. N Eng J Med 2009; 361: 653-663
  - MIRROR
    - (Micrometastases and Isolated Tumor Cells: Relevant and Robust or Rubbish)
  - 2707 patients with 5 year follow up
  - pN0, pN0(i+) and pN1mi
  - With and without adjuvant therapy

ITCs and micrometastases and prognosis

No adjuvant therapy **Adjuvant therapy**



De Boer *et al*. N Eng J Med 2009; 361: 653-663

ITCs and micrometastases and prognosis

	5 year DFS		
	No adjuvant therapy	Adjuvant therapy	
pN0	86%	N/A	
pN0(i+) and pN1mi	76%	86%	P<0.001

De Boer *et al*. N Eng J Med 2009; 361: 653-663

Paradox explained

Even low volume metastatic disease influences prognosis

SNB has a significant false negative rate

Adjuvant (systemic) therapy abrogates many of the prognostic implications of nodal metastatic disease

Trials of observation *Vs* ANC in positive SNB

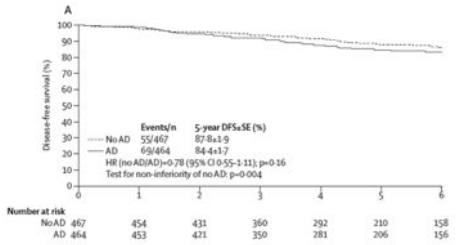
- IBCSG 23-01
  - ANC *Vs* observation
  - cN0 but micrometastasis on SNB
  - Opened 2001, closed 2010
- ACOSOG Z0011
  - ANC *Vs* observation
  - cN0 but 1 or 2 positive node(s) on SNB
  - Opened 1999, closed 2004

Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial

Viviana Galimberti, Bernard F Cole, Stefano Zurrida, Giuseppe Viale, Alberto Luini, Paolo Veronesi, Paola Baratella, Camillo Chifu, Manuela Sargenti, Mattia Intra, Orsola Gentilini, Mauro G Mastropasqua, Giovanni Mazzarol, Samuele Massarut, Jean-Rémi Garbay, Janet Zygmunt, Hanne Gelmbles, Angelo Bevilacqua, David L Wapnir, Monika Bonnet, Marco Colleoni, Karen N Price, Meredith M Regan, Aron Goldhirsch, Alan S Coates, Richard D Gelber, Umberto Veronesi, for the International Breast Cancer Study Group Trial 23-01 investigators

Target	Actual
• 1960 patients	• 934
• 558 events	• 124
• 70% DFS at 5 years	• 84%

IBCSG 23-01



Galimberti *et al.* Lancet Oncol 2013; 14:297-305

IBCSG 23-01

- Median follow-up 5 years
  - No difference in DFS, OS, LRR
  - 13 % of ANC group had non-SNB metastases
  - >99% of patients received adjuvant XRT and/or systemic therapy

Z11

- American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 Randomized Trial
- Alpha-numeric quality score
  - A – Z with A = best
  - 1 -10 with 1 = best
  - Hence quality score of Z11!

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

A Randomized Clinical Trial

Armando E. Giuliano, MD

JAMA. 2011;305(6):569-575

Locoregional Recurrence After Sentinel Lymph Node Dissection With or Without Axillary Dissection in Patients With Sentinel Lymph Node Metastases

The American College of Surgeons Oncology Group Z0011 Randomized Trial

Armando E. Giuliano, MD, Linda McCall, MS,† Peter Beitsch, MD,‡ Pat W. Whitworth, MD,§ Peter Blumencranz, MD,¶ A. Marilyn Leitch, MD,‖ Sukamal Saha, MD,** Kelly K. Hunt, MD,††*

Locoregional Recurrence After Sentinel Lymph Node Dissection With or Without Axillary Dissection in Patients With Sentinel Lymph Node Metastases

Long-term Follow-up From the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 Randomized Trial

Armando E. Giuliano, MD, Karla Ballman, PhD,† Linda McCall, MS,† Peter Beitsch, MD,‡ Pat W. Whitworth, MD,§ Peter Blumencranz, MD,‖ A. Marilyn Leitch, MD,** Sukamal Saha, MD,†† Monica Morrow, MD,‡‡ and Kelly K. Hunt, MD‡‡*

(*Ann Surg* 2016;264:413–420)

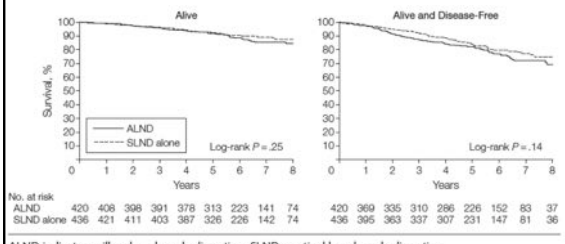
ACOSOG Z0011

- Study design
  - cT1/2, cN0
  - Breast conservation with breast XRT
  - 1 or 2 positive SNBs
  - ANC *Vs* observation
  - Overall survival as primary end-point
  - 500 deaths required to give 90% power to confirm non-inferiority

ACOSOG Z0011

Target	Actual
• 1900 patients	• 891
• 500 events	• 98
• 80% OS at 5 years	• 92%

ACOSOG Z0011



ALND indicates axillary lymph node dissection; SLND, sentinel lymph node dissection.

JAMA. 2011;305(6):569-575

ACOSOG Z0011

- Problems
  1. Overall survival not a good 1° endpoint
  2. Insufficient patients (813 *vs.* 1900) recruited to show a difference even if the event rate had been as high as predicted
  3. 146 (18%) ineligible patients retained in analysis (33 were pN0, 15 had ≥3 positive nodes and 98 were pNx)

Characteristic	No. (%) ALND (n = 420)	SLND Alone (n = 436)
Lymph node metastases		
0	4 (1.2)	29 (7.0)
1	199 (58.0)	295 (71.1)
2	68 (19.8)	76 (18.3)
3	25 (7.3)	11 (2.7)
≥4	47 (13.7)	4 (1.0)
Missing	77	21

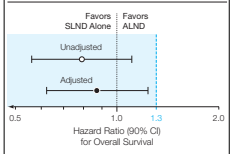
ACOSOG Z0011

- Problems (cont[d])
  4. 166 lost to follow-up.
  5. 25% had no tumour grade
  6. Tangential Field Irradiation treats the axilla and 51% received high tangents
     - This equates to full level I axillary radiotherapy
  7. 15% received SCF XRT
  8. 11% received no XRT at all!

ACOSOG Z0011 Conclusion

- SLNB was not inferior to ALND in patients with 1-2 positive nodes treated by BCS, breast XRT and systemic adjuvant therapy
  - LRR at 10 years
    - ANC – 6.2%
    - SNB – 5.3%
- Consistent with NSABP B-04

Figure 3. Hazard Ratios Comparing Overall Survival Between the ALND and SLND-Alone Groups



Blue dashed line at hazard ratio = 1.3 indicates non-inferiority margin; blue-tinted region to the left of hazard ratio = 1.3 indicates values for which SLND alone would be considered noninferior to SLND plus ALND. ALND indicates axillary lymph node dissection; CI, confidence interval; SLND, sentinel lymph node dissection.

CA CANCER J CLIN 2017;67:290–303

Breast Cancer—Major Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual

Armando E. Giuliano, MD[1]; James L. Connolly, MD[2]; Stephen B. Edge, MD[3]; Elizabeth A. Mittendorf, MD, PhD[4]; Hope S. Rugo, MD[5]; Lawrence J. Solin, MD[6]; Donald L. Weaver, MD[7]; David J. Winchester, MD[8]; Gabriel N. Hortobagyi, MD[9]

TNM 8

- ITCs
  - "Single tumour cells or small clusters of cells not more than 200µm in greatest extent that can be detected by routine H&E satins or IHC"
  - "Cluster fewer than 200 cells in a single histological cross section"
  - Nodes containing ITCs only are excluded from the positive node count but included in the total number evaluated
- pN0(i+)

TNM 8

- Micrometastases
  - Metastases larger than 200µm and/or more than 200 cells but none larger than 2.0mm
- pN1mi

TNM 8

- Macrometastases
  - Metastases larger than 2.0mm
- pN1-3

TNM 7 *Vs* 8

TNM 7	TNM 8
• pNX	• Unchanged
• pN0	• Unchanged
• pN0(i+)	• Unchanged
• pN1	• Unchanged
– pN1mi	– Unchanged
– pN1a	– Unchanged
– pN1b	– Changed
– pN1c	– Changed

TNM 7 *Vs* 8

TNM 7	TNM 8
• pN2	• Unchanged
– pN2a	– Unchanged
– pN2b	– Unchanged
• pN3	• Unchanged
– pN3a	– Unchanged
– pN3b	– Unchanged
– pN3c	– Unchanged

TNM 7 *Vs* 8

TNM 7	TNM 8
• pN1	• pN1
– Macro or micrometastases in 1-3 axillary nodes and/or internal mammary nodes	– Macro or micrometastases in 1-3 axillary nodes and/or internal mammary nodes
– pN1mi	– pN1mi
• Micrometastases	• Micrometastases
– pN1a	– pN1a
• Metastasis in 1-3 nodes; at least 1 larger than 2.0mm	• Metastasis in 1-3 nodes; at least 1 larger than 2.0mm
– pN1b	– pN1b
• Internal mammary nodes with micro- or macrometastases detected by SLNB	• Internal mammary nodes
– pN1c	– pN1c
• Metastasis in 1-3 axillary nodes and internal mammary nodes	• Metastasis in 1-3 axillary nodes and internal mammary nodes

Lymph Node Assessment

- All nodes treated in the same way
  - Grossly involved
    - 1 representative section
  - Not grossly involved
    - Process entire node
    - Cut at ≤ 2mm and embed non-opposing faces


The Royal College of Pathologists

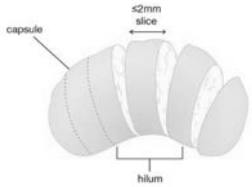
Pathology reporting of breast disease in surgical excision specimens incorporating the dataset for histological reporting of breast cancer

June 2016

The Royal College of Pathologists
Pathology: the science behind the cure

Pathology reporting of breast disease in surgical excision specimens incorporating the dataset for histological reporting of breast cancer

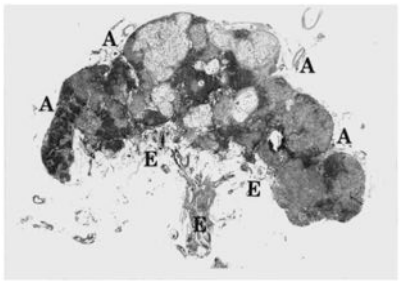
Sentinel Lymph Node: slicing perpendicular to the long axis



JOURNAL OF PATHOLOGY, VOL. 143: 187–191 (1984)

THE ROUTINE HISTOLOGICAL INVESTIGATION OF AXILLARY LYMPH NODES FOR METASTATIC BREAST CANCER

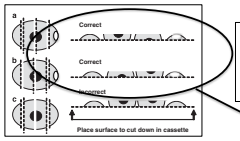
F. HARVEY



Modern Pathology (2000) 13, 516–522

Pathology evaluation of sentinel lymph nodes in breast cancer: protocol recommendations and rationale

Donald L Weaver[1,2,3]



Standard recommendation

in summary, only one standard protocol for evaluating SLNs can be supported and endorsed based on evidence, albeit old evidence, at this time. Thin sectioning of nodes at 2.0 mm intervals, embedding all sections, and examining one section from the surface of the block is a strategy designed to detect all metastases larger than 2.0 mm. The resulting

?

Postoperative Lymph Node Assessment

- All nodes treated in the same way
  - Grossly involved
    - 1 representative section
  - Not grossly involved
    - Process entire node
    - Cut at ≤ 2mm and embed non-opposing faces
    - H&E +/- deeper levels +/- IHC only to characterise suspicious cells and determine the maximum size of deposit(s)

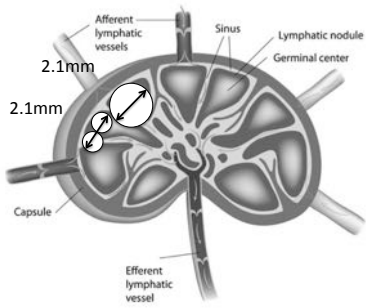

The Royal College of Pathologists
Pathology: the science behind the cure

Pathology reporting of breast disease in surgical excision specimens incorporating the dataset for histological reporting of breast cancer

June 2016

Lymph Node Assessment

- Measure maximum size of metastasis and categorize as *per* TNM
- Report each specimen separately
  - Number of positive nodes
  - Total number of nodes received



Metastatic Volume

- 1 metastasis 2.1mm diameter
  - 4.8mm^3 volume

- 2 metastases each 1.05mm diameter
  - 1.2mm^3 volume

TNM 8

- General rule 4
  - "If there is doubt concerning the correct T, N, or M category to which a particular case should be allotted, then the lower (i.e., less advanced) category should be chosen."

CA CANCER J CLIN 2017;67:290-303

Breast Cancer–Major Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual

Armando E. Giuliano, MD[1]; James L. Connolly, MD[2]; Stephen B. Edge, MD[3]; Elizabeth A. Mittendorf, MD, PhD[4]; Hope S. Rugo, MD[5]; Lawrence J. Solin, MD[6]; Donald L. Weaver, MD[7]; David J. Winchester, MD[8]; Gabriel N. Hortobagyi, MD[9]

Introduction

The TNM (primary tumor [T], regional lymph nodes [N], distant metastases [M]) staging system began in 1959 as a product of the American Joint Committee for Cancer (AJCC) staging end results reporting.[1]

References

1. Amin MB, Edge FL, Edge SB, et al. The eighth edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin.* 2017;67:93-99.

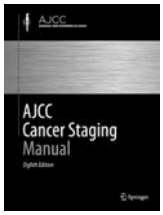
COMMENTARY

CA CANCER J CLIN 2017;67:93-99

The Eighth Edition AJCC Cancer Staging Manual: Continuing to Build a Bridge From a Population-Based to a More "Personalized" Approach to Cancer Staging

Mahul B. Amin, MD[1]; Frederick L. Greene, MD[2]; Stephen B. Edge, MD[3,4]; Carolyn C. Compton, MD, PhD[3,4]; Jeffrey E. Gershenwald, MD[5]; Robert K. Brookland, MD[6]; Laura Meyer, CAPM[6]; Donna M. Gress, RHIT, CTR[10]; David R. Byrd, MD[11]; David P. Winchester, MD[12]

the robust principles of cancer classification using the anatomic extent of disease tumor, lymph node, metastasis (TNM) concept first developed by Pierre Denoix in the 1940s and 1950s.[1] The First Edition of the *AJCC Cancer Staging Manual* was published in 1977



In this eighth edition, the term 'stage' is used when only descriptions of anatomic extent of disease are used and 'prognostic group' for when additional prognostic factors are incorporated.

The eighth edition of the staging system also uses genomic assays when available to downstage some estrogen receptor-positive, lymph node-negative tumors.

CA CANCER J CLIN 2017;67:290-303

Breast Cancer–Major Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual

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Changes for the eighth edition were based on evidence available from peer-reviewed literature and on findings from large, as yet unpublished databases

AJCC Cancer Staging Manual 8th Ed

- Classical LCIS

Lobular carcinoma in situ (LCIS) is removed as a pathologic tumor in situ (pTis) category for T categorization. LCIS is a benign entity and is removed from TNM staging.

- Pleomorphic LCIS

The expert panel debated whether to include this variant of LCIS in the pTis category; however, there are insufficient data in the literature regarding outcomes and reproducible diagnostic criteria for this LCIS variant.

Battle of the 8th editions' nomenclatures

UICC	AJCC
• Stage – Anatomical extent of disease	• Anatomic Stage Group – Anatomical extent of disease
• Prognostic Group – Classifications incorporating other prognostic factors	• Prognostic Stage Group – Anatomic + Grade + HER2, ER, PgR, multi-gene assays

Prognostic Tools

- Nottingham Prognostic Index (NPI)
  - T, N & grade
- Adjuvant! online
  - Currently offline!
  - T, N, grade, ER, age
- Predict
  - Age, method of detection, T, N, grade, ER, HER2, Ki67

Conclusions

1. Nodal staging in breast cancer is essential
2. Pathological assessment must identify all macrometastases and correctly classify smaller volume deposits
3. Do not add together the diameters of multiple deposits (if in doubt, err on the side of the lower stage)
4. Z11 does not constitute good evidence
5. Enter patients into POSNOC