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Breast Cancer: Management of the Axilla in 2016

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SON Vancouver
Oct 2016

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- No Disclosures

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Principle #1

- There is no point talking about surgical therapy in isolation. From a patient point of view, successful treatment must be a team effort.

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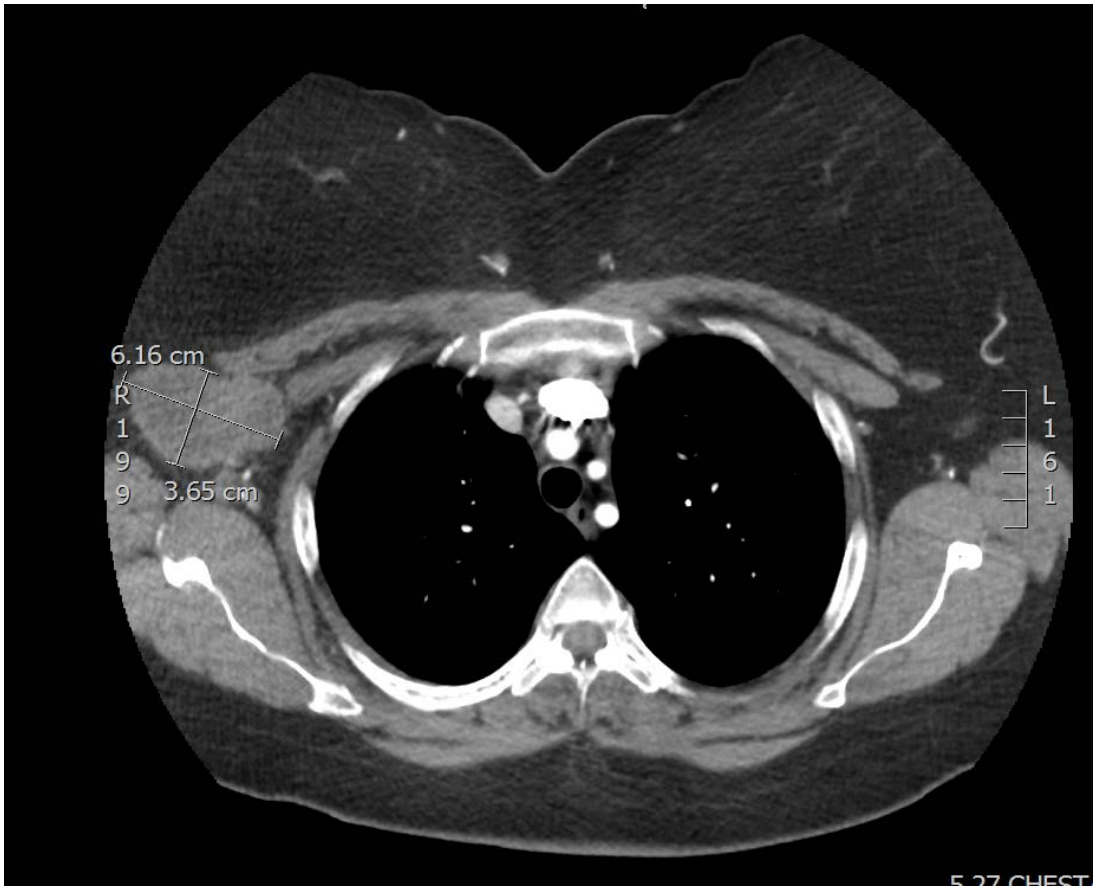
Questions

- Who needs an axillary node dissection?

Uncontrolled axillary disease



37 yo after negative SNB, regional RT and chemotherapy

Scenario #1

- 50 yo. with T1, ER/PR + Her-2 –
- clinically negative axilla
- Lumpectomy
- Negative SNB

NSABP B 32

- 694 (+) SLN patients went on to ALND
  - 39% had at least 1 further LN (+) in ALND
  - SLN was the ONLY positive node in 61%

False Neg Rate 9.8%
Accuracy Rate of SLNBx 97.2%

NSABP B-32: SLNB vs ALND

- With SLNB:
  - Improved neuropathy/paresthesia (11 vs 31%)
  - Improved lymphedema (8 vs 13%)
  - No difference DFS, OS, LR

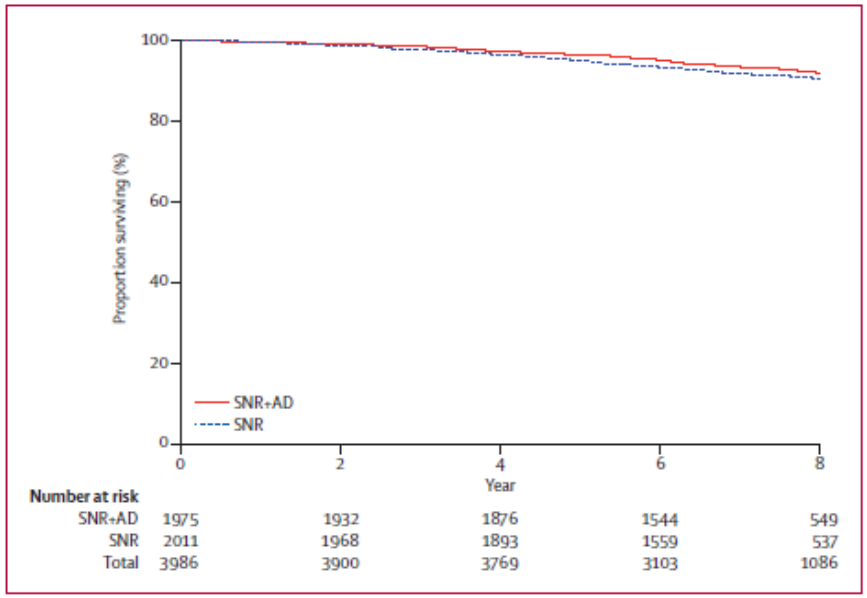


Figure 2: **Overall survival for sentinel-node (SLN)-negative patients**
Data as of Dec 31, 2009. For sentinal node resection (SNR) plus axillary dissection (AD), N=1975, 140 deaths. For SNR, N=2011, 169 deaths. Hazard ratio 1·20, 95% CI 0·96–1·50; p=0·12.

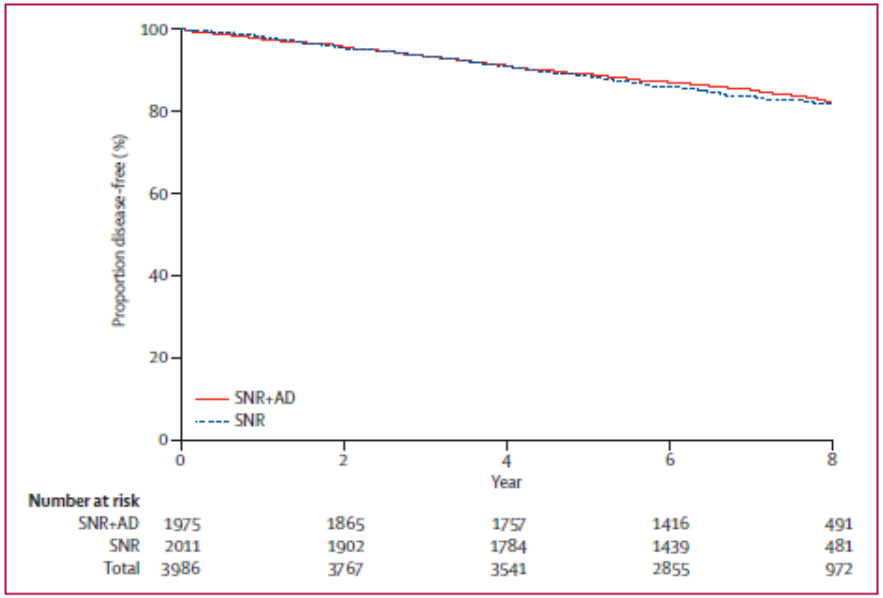


Figure 3: **Disease-free survival for sentinel-node (SLN)-negative patients**
Data as of Dec 31, 2009. For sentinal node resection (SNR) plus axillary dissection (AD), N=1975, 315 events. For SNR, N=2011, 336 events. Hazard ratio 1·05, 95% CI 0·90–1·22; p=0·54.

Scenario #2

- 50 yo. with T1, ER/PR + Her-2 –
- clinically negative axilla
- Lumpectomy
- Positive SNB (1/3)

ACOSOG Z0011

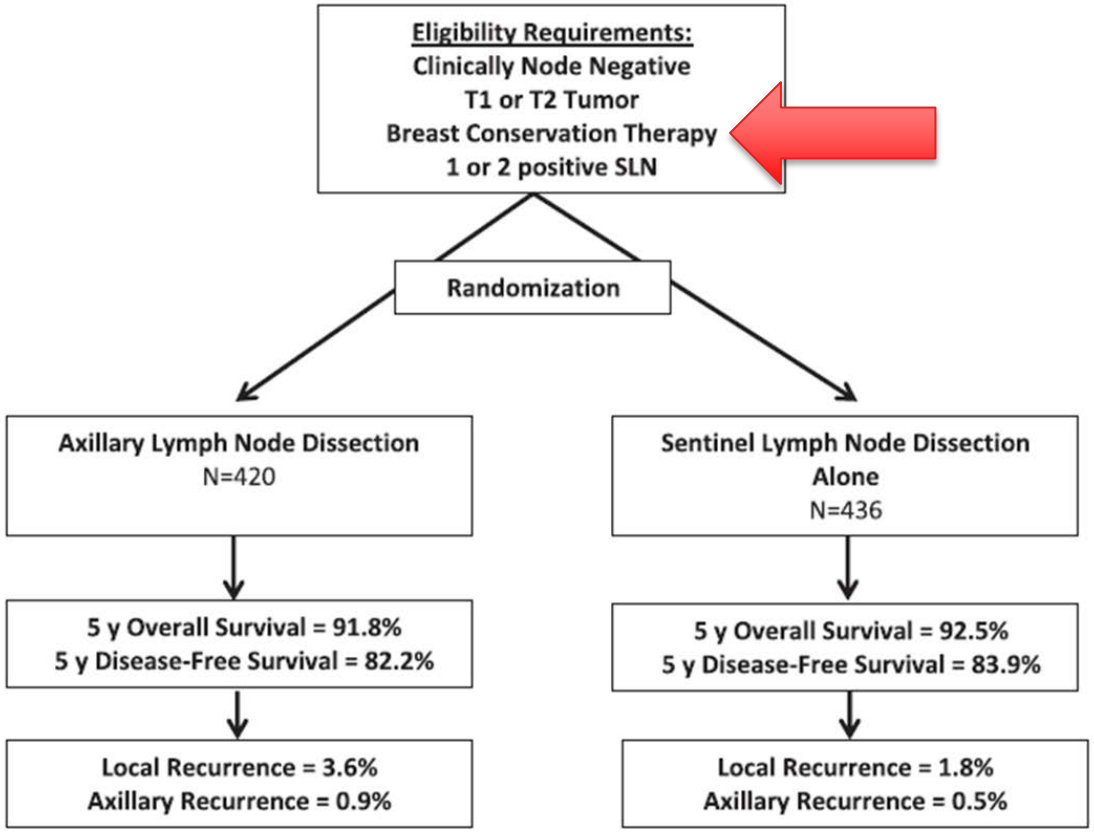


Fig. 1. Schema for the ACOSOG Z0011 Trial. The ACOSOG Z0011 trial was designed to determine whether there was a difference in overall survival or locoregional recurrence in patients with early breast cancer and 1 or 2 positive SLN who underwent axillary lymph node dissection versus those that had no further axillary therapy. (*Data from* Giuliano A,

ACOSOG Z0011

- Multicenter RCT (856 patients)

Inclusion Criteria:
- T1/T2 IBC with clinically neg axilla
- Tx BCS + SLNB and adjuvant RTx

Exclusion Criteria:
- ≥3 (+) SLN
- Matted/bulky nodes
- Neoadjuvant Tx

ACOSOG Z0011 2016 update

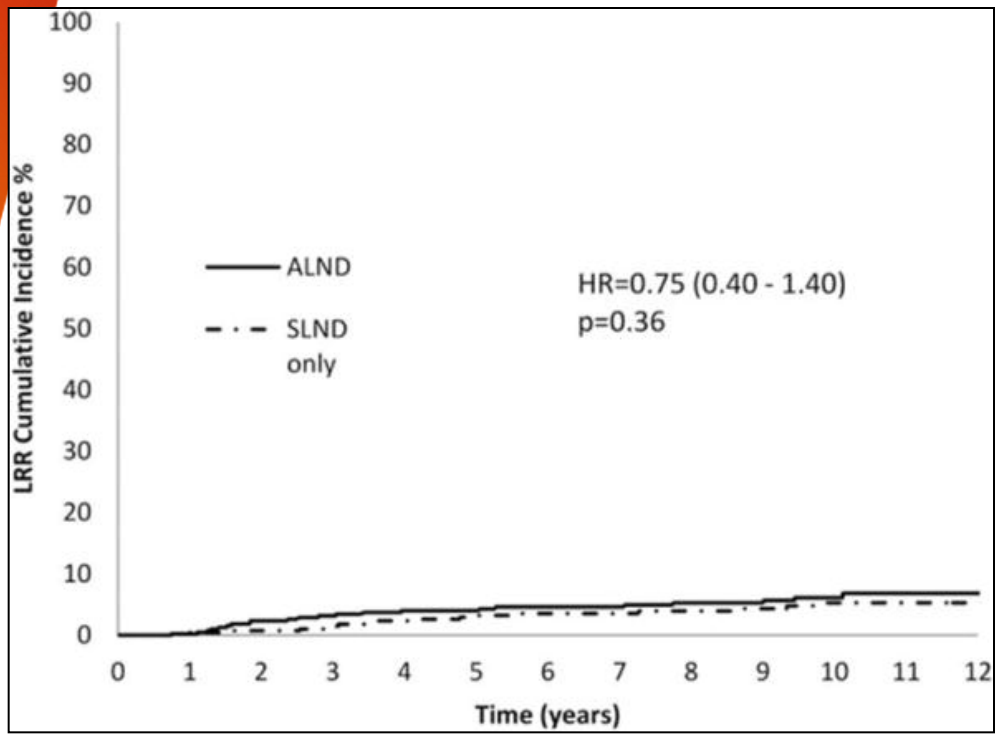


FIGURE 2 . Cumulative incidence of locoregional recurrence by treatment arm.

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.

Giuliano, Armando; Ballman, Karla; McCall, Linda; Beitsch, Peter; Whitworth, Pat; Blumencranz, Peter; Leitch, A; Saha, Sukamal; Morrow, Monica; Hunt, Kelly

Annals of Surgery. 264(3):413-420, September 2016.
DOI: 10.1097/SLA.0000000000001863

IBCSG 23-01

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, Camelia Chifu, Manuela Sargenti, Mattia Intra, Oreste Gentilini, Mauro G Mastropasqua, Giovanni Mazzarol, Samuele Massarut, Jean-Rémi Garbay, Janez Zgajnar, Hanne Galatius, Angelo Recalcati, David Littlejohn, Monika Bamert, 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

Lancet Oncol 2013; 14: 297–305

- SLNBx alone vs SLNBx followed by ALND
- 934 pts T1-2, $pN1_{mic}$
  - 91% BCS with 98% receiving RT
  - 13% of patients had further disease on ALND

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IBCSG 23-01

- No Difference OS / DFS
- No Difference LR recurrence

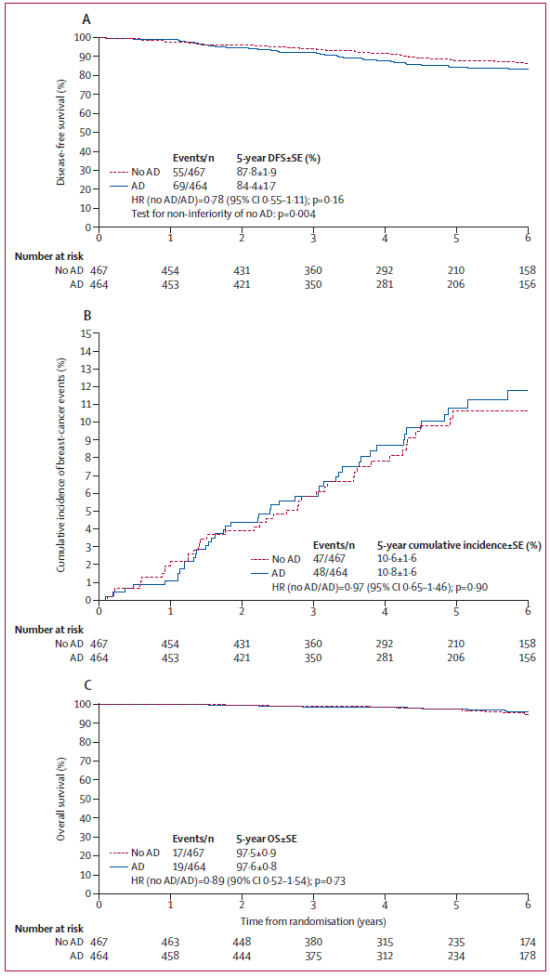


Figure 2: **Analysis of disease-free survival, cumulative incidence, and overall survival by intention to treat (n=931 patients)**
AD=axillary dissection. DFS=disease-free survival. OS=overall survival. (A) Disease-free survival. (B) Cumulative incidence of breast-cancer events. (C) Overall survival in the intention-to-treat population of 931 patients.

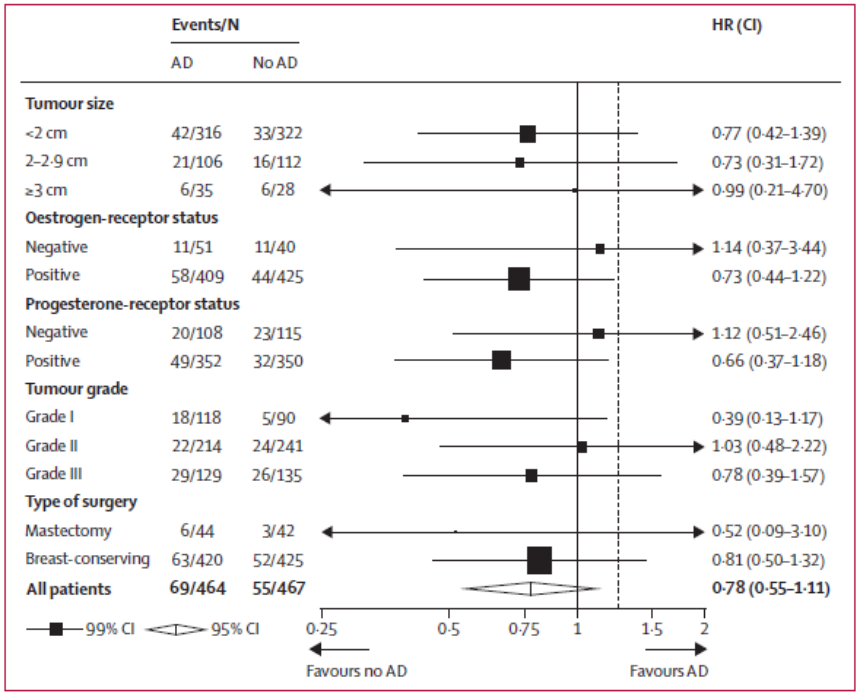


Figure 3: **Analysis of subgroups defined by tumour size, oestrogen-receptor status, progesterone-receptor status, tumour grade, and type of surgery, by intention to treat (n=931)**
HRs compare no axillary dissection versus axillary dissection among subgroups of the intention-to-treat population. Each subgroup HR is shown as a black square with the size of the square being inversely proportional to the variance of the corresponding log-HR estimate (ie, larger squares indicate lower variability in the estimate). The HR for all patients is shown as a diamond. The horizontal axis is displayed on a logarithmic scale.

Scenario #3

- 50 yo. with T1, ER/PR + Her-2 –
- clinically negative axilla
- Mastectomy
- Positive SNB (1/3)

EORTC - AMAROS

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

Mila Donker, Geertjan van Tienhoven, Marieke E Straver, Philip Meijnen, Cornelis J H van de Velde, Robert E Mansel, Luigi Cataliotti, A Helen Westenberg, Jean H G Klinkenbijl, Lorenzo Orzalesi, Willem H Bouma, Huub C J van der Mijle, Grard A P Nieuwenhuijzen, Sanne C Veltkamp, Leen Slaets, Nicole J Duez, Peter W de Graaf, Thijs van Dalen, Andreas Marinelli, Herman Rijna, Marko Snoj, Nigel J Bundred, Jos W S Merkus, Yazid Belkacemi, Patrick Petignat, Dominic A X Schinagl, Corneel Coens, Carlo G M Messina, Jan Bogaerts, Emiel J T Rutgers

***Lancet Oncol* 2014**

- RCT between ALND vs RNI after positive SLNB
- 4823 participants
  - T1-2, cN0
  - 18% mastectomy / 82% BCS combined with SLNB

EORTC - AMAROS

- Higher rates of lymphedema in the ALND group (23 vs 13%)
- No diff ROM, QOL (pain, body image etc)

	Axillary lymph node dissection	Axillary radiotherapy	p value
Clinical sign of lymphoedema in the ipsilateral arm			
Baseline	3/655 (<1%)	0/586 (0%)	0·25
1 year	114/410 (28%)	62/410 (15%)	<0·0001
3 years	84/373 (23%)	47/341 (14%)	0·003
5 years	76/328 (23%)	31/286 (11%)	<0·0001
Arm circumference increase ≥10% of the ipsilateral upper or lower arm, or both			
Baseline	33/655 (5%)	24/586 (4%)	0·497
1 year	32/410 (8%)	24/410 (6%)	0·332
3 years	38/373 (10%)	22/341 (6%)	0·080
5 years	43/328 (13%)	16/286 (6%)	0·0009

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

Table 2: Lymphoedema

EORTC - AMAROS

After median F/U of 6.1 years:

- No diff in OS/DFS

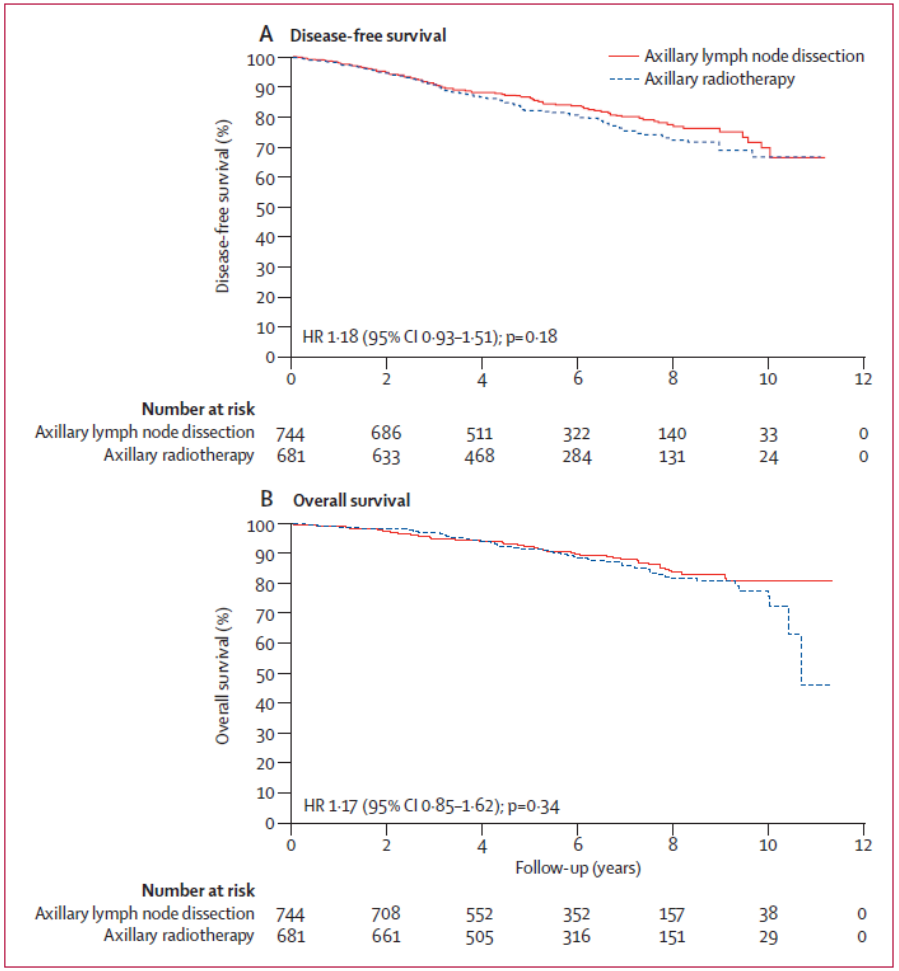


Figure 2: Disease-free survival and overall survival
HR=hazard ratio.

Axillary RT for 1-3 positive nodes: Meta-analysis

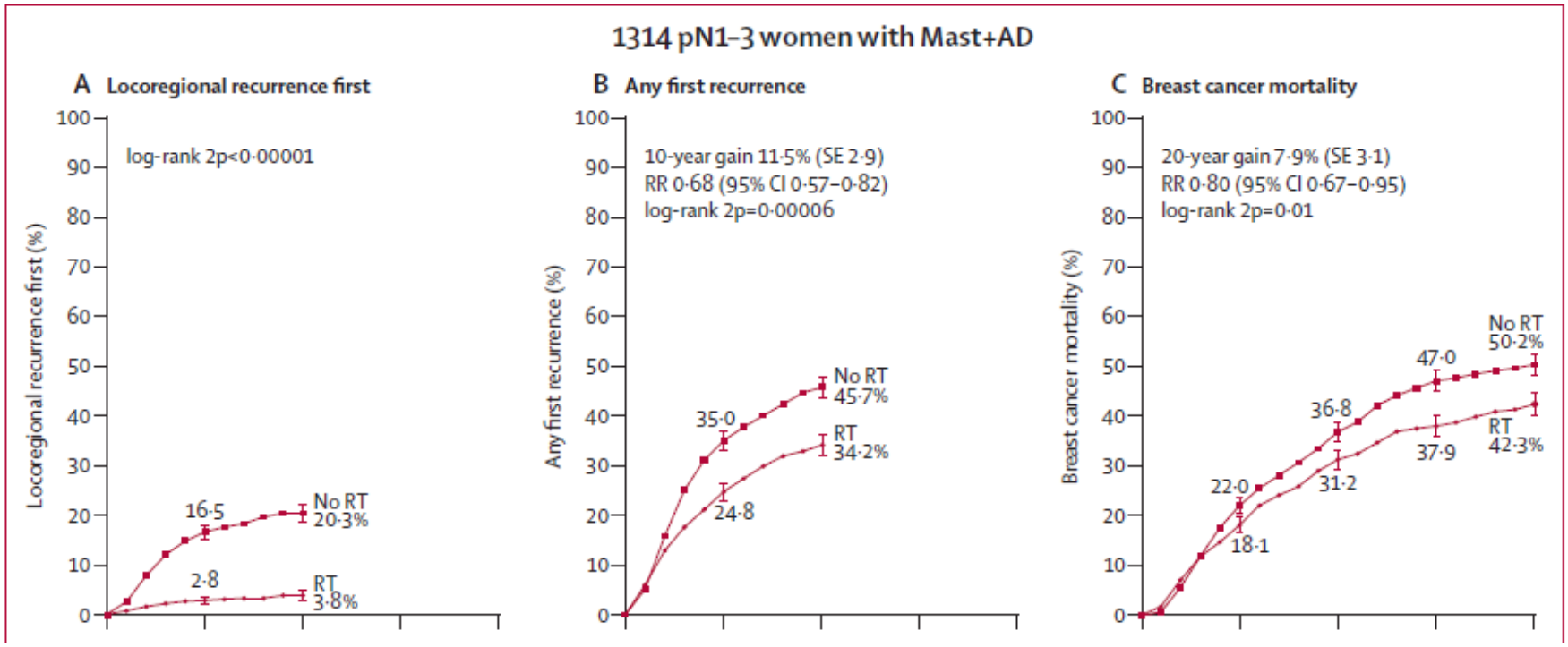
Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials

*EBCTCG (Early Breast Cancer Trialists' Collaborative Group)**

Summary

Background Postmastectomy radiotherapy was shown in previous meta-analyses to reduce the risks of both recurrence

Lancet 2014; 383: 2127–35



Nodal RT after dissection 1-3 positive nodes

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 23, 2015 VOL. 373 NO. 4

Regional Nodal Irradiation in Early-Stage Breast Cancer

Timothy J. Whelan, B.M., B.Ch., Ivo A. Olivotto, M.D., Wendy R. Parulekar, M.D., Ida Ackerman, M.D.,

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MA-20 Trial

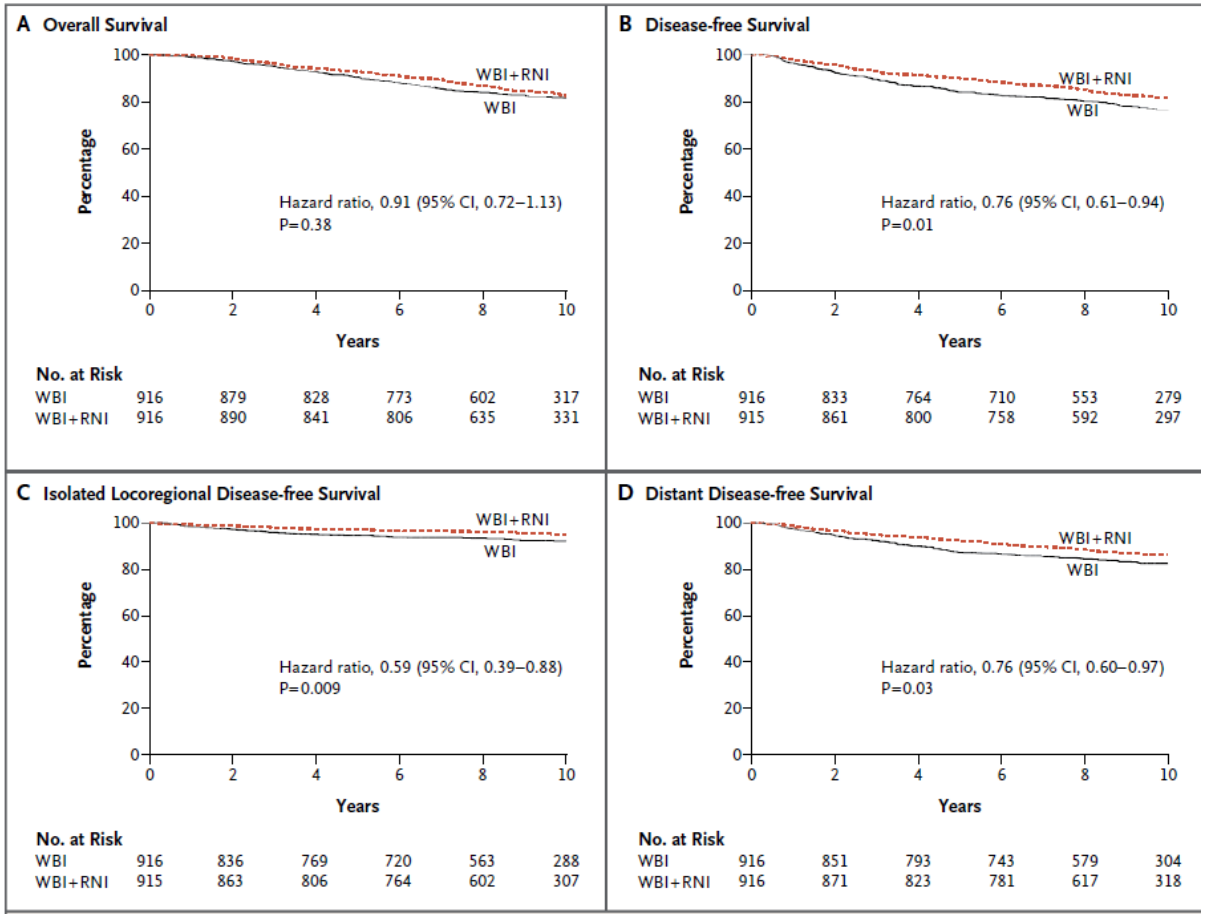

Figure 1. 10-Year Kaplan–Meier Estimates of Survival.

Shown are rates of overall survival (Panel A), disease-free survival (Panel B), isolated locoregional disease-free survival (Panel C), and distant disease-free survival (Panel D) among patients who underwent whole-breast irradiation plus regional nodal irradiation (WBI+RNI) and those who underwent whole-breast irradiation alone (WBI, control group).

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- In some centers, all node positive patients will receive regional nodal RT regardless of dissection.
- This must be taken into account when deciding on AND or not

New RCTs: “Z-11 including mastectomies”

- POSNOC (POsitive Sentinel NOde: adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy) trial
- Holland (BOOG 2013-07) for patients with 1 to 3 positive SLN
- Both trials will randomize 1-3 positive node patients to RT/ALND versus none

New Guidelines

Published Ahead of Print on September 19, 2016 as 10.1200/JCO.2016.69.1188
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2016.69.1188

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update

Abram Recht, Elizabeth A. Comen, Richard E. Fine, Gini F. Fleming, Patricia H. Hardenbergh, Alice Y. Ho, Clifford A. Hudis, E. Shelley Hwang, Jeffrey J. Kirshner, Monica Morrow, Kilian E. Salerno, George W. Sledge Jr, Lawrence J. Solin, Patricia A. Spears, Timothy J. Whelan, Mark R. Somerfield, and Stephen B. Edge

Abram Recht, Beth Israel Deaconess Medical Center, Boston, MA; Elizabeth A. Comen, Alice Y. Ho, Clifford A. Hudis, Monica Morrow, Memorial Sloan Kettering Cancer Center; New York; Jeffrey J. Kirshner, Hematology Oncology Associates of Central New York, East

New Guidelines

Clinical Question 1

Is PMRT indicated in patients with T1-2 tumors with one to three positive axillary lymph nodes who undergo ALND?

Recommendations

Recommendation 1a. The panel unanimously agreed that the available evidence shows that PMRT reduces the risks of locoregional failure (LRF), any recurrence, and breast cancer mortality for patients with T1-2 breast cancer and one to three positive lymph nodes. However, some subsets of these patients are likely to have such a low risk of LRF that the absolute benefit of PMRT is outweighed by its potential toxicities. In addition, the acceptable ratio of benefit to toxicity varies among patients and physicians. Thus, the decision to recommend PMRT or not requires a great deal of clinical judgment. The panel agreed clinicians making such recommendations for individual patients should consider factors that may decrease the risk of LRF, attenuate the benefit of reduced breast cancer–specific mortality, and/or increase the risk of complications resulting from PMRT. These factors include: patient characteristics (age > 40 to 45 years, limited life

New Guidelines

Clinical Question 2

Is PMRT indicated in patients with T1-2 tumors and a positive SNB who do not undergo completion ALND?

Recommendation

For patients with clinical T1-2 tumors with clinically negative nodes, SNB is now generally performed at the time of mastectomy, with omission of ALND if the nodes are negative. ALND has generally been performed if the nodes are positive, but there is increasing controversy about whether this is always necessary, especially if there is limited disease in the affected nodes. The panel recognizes that some clinicians omit axillary dissection with one or two positive sentinel nodes in patients treated with mastectomy. This practice is primarily based on extrapolation of data from randomized trials of patients treated exclusively or predominantly with breast-conserving surgery and whole-breast irradiation or breast plus axillary irradiation. In such cases where clinicians and patients elect to omit axillary dissection, the panel recommends that these patients receive PMRT only if there is already sufficient information to justify its use without needing to know that additional axillary nodes are involved (type: informal consensus; evidence quality: weak; strength of recommendation: moderate).

Scenario #3

- 50 yo. with T1, ER/PR + Her-2 –
- clinically negative axilla
- Mastectomy
- Positive SNB (1/3)

- So..
- In this patient not perform AND but instead refer to RT

Scenario #4

- *40 yo. with T2, ER/PR - Her-2 –*
- clinically negative axilla
- Lumpectomy
- Positive SNB (1/3)

What about high risk patients?

- "Z=11 eligible" patients undergoing BCT
- 5 year prospective cohort of node positive patients
- 31 month median follow up
- High risk (<50 , Her2+ or TN) v.s. average risk
- > 2 positive node or ECE triggered ALND

Ann Surg Oncol (2016) 23:3481–3486
DOI 10.1245/s10434-016-5259-3

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Age and Receptor Status Do Not Indicate the Need for Axillary Dissection in Patients with Sentinel Lymph Node Metastases

Anita Mamtani, MD[1], Sujata Patil, PhD[2], Kimberly J. Van Zee, MS, MD[1], Hiram S. Cody III, MD[1], Melissa Pilewskie, MD[1], Andrea V. Barrio, MD[1], Alexandra S. Heerdt, MD[1], and Monica Morrow, MD[1]

[1]Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

MSK series

- 242 high risk
- 459 average
- 15% of high risk patients underwent ALND
- 18% of average risk had ALND
- At ALND additional positive nodes found in 62% of high risk patients and 65% average risk
- At 31 months no axillary recurrence in either group

- Conclusion: ALND is not indicated based on age or subtype

Scenario #4

- *40 yo. with T2, ER/PR - Her-2 –*
- clinically negative axilla
- Lumpectomy
- Positive SNB (1/3)

- Plan: treat as Z0011 patient with Breast RT -/+ Axillary RT

Scenario #5

- 50 yo. with T1, ER/PR + Her-2 –
- clinically positive axilla
- Lumpectomy

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ACOSOG Z1071 ALLIANCE

Original Investigation

Sentinel Lymph Node Surgery After Neoadjuvant Chemotherapy in Patients With Node-Positive Breast Cancer

The ACOSOG Z1071 (Alliance) Clinical Trial

Judy C. Boughey, MD; Vera J. Suman, PhD; Elizabeth A. Mittendorf, MD, PhD; Gretchen M. Ahrendt, MD; Lee G. Wilke, MD; Bret Taback, MD; A. Marilyn Leitch, MD; Henry M. Kuerer, MD, PhD; Monet Bowling, MD; Teresa S. Flippo-Morton, MD; David R. Byrd, MD; David W. Ollila, MD; Thomas B. Julian, MD; Sarah A. McLaughlin, MD; Linda McCall, MS; W. Fraser Symmans, MD; Huong T. Le-Petross, MD; Bruce G. Haffty, MD; Thomas A. Buchholz, MD; Heidi Nelson, MD; Kelly K. Hunt, MD; for the Alliance for Clinical Trials in Oncology

JAMA October 9, 2013 Volume 310, Number 14

Sentina Trial

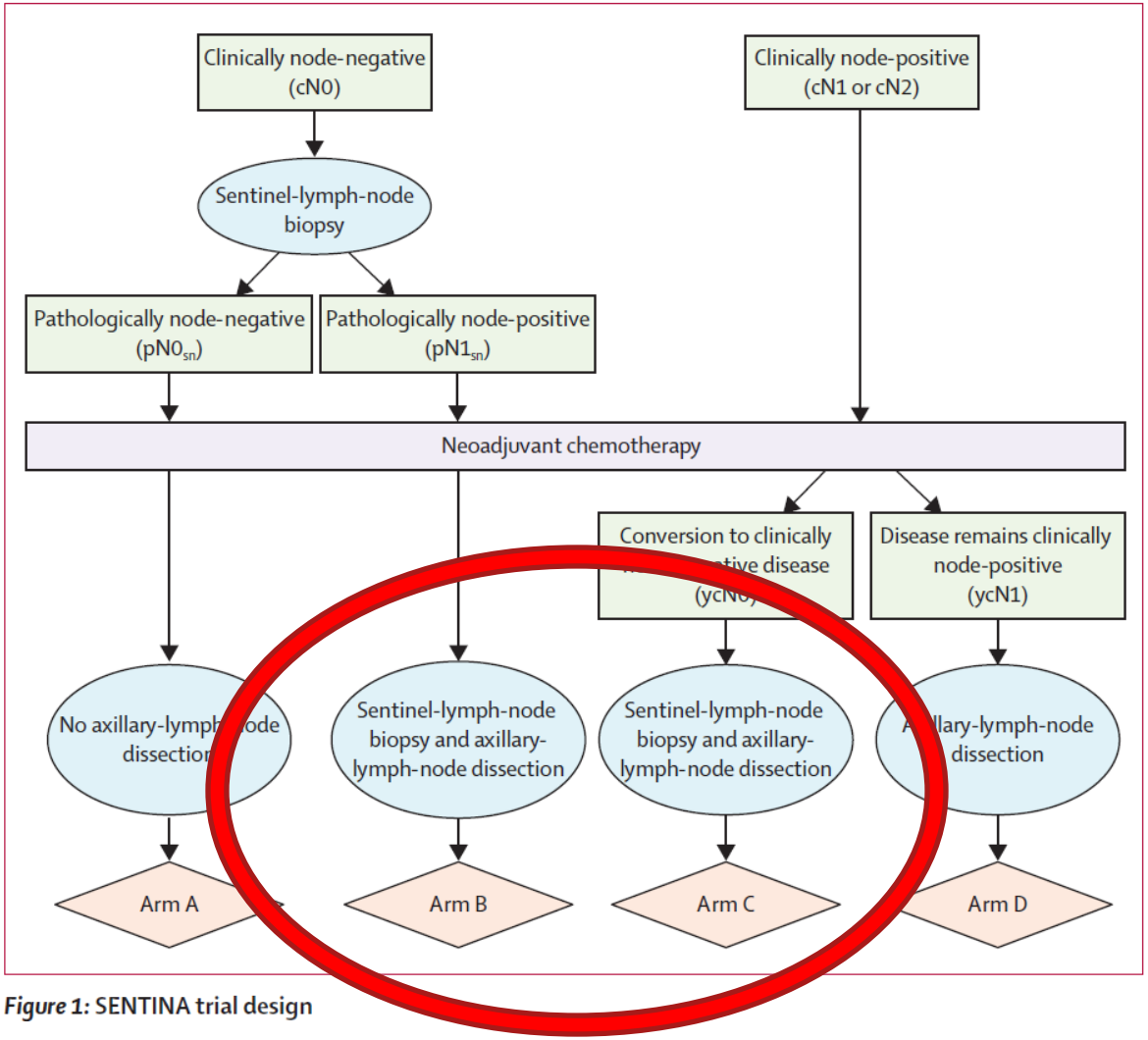

Figure 1: SENTINA trial design

SENTINA Trial

- Arm B (Pre and Post CTx SLNBx - ALND)
  - 35% of patients cN0 were pN1
  - 51% false neg rate for 2nd SLNBx
  - 60% detection rate

- Arm C (SLNBx-ALND post cN1-2 converted to ycN0)
  - 83% clinical conversion rate with Neoadj CTx
    - 36% pCNR

- SLNBx – If dual technique used (Tc99 & blue dye)
    - 88% detection rate

False neg rate :

if 1 SLN ⇒ 24.3%

If 2 SLN ⇒ 18.5%

If 3 SLN ⇒ 7.3%

MSK series : ALND after Neoadjuvant therapy

Ann Surg Oncol (2016) 23:3467–3474
DOI 10.1245/s10434-016-5246-8

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

How Often Does Neoadjuvant Chemotherapy Avoid Axillary Dissection in Patients With Histologically Confirmed Nodal Metastases? Results of a Prospective Study

Anita Mamtani, MD[1], Andrea V. Barrio, MD[1], Tari A. King, MD[2], Kimberly J. Van Zee, MD[1], George Plitas, MD[1], Melissa Pilewskie, MD[1], Mahmoud El-Tamer, MD[1], Mary L. Gemignani, MD[1], Alexandra S. Heerdt, MD[1], Lisa M. Sclafani, MD[1], Virgilio Sacchini, MD[1], Hiram S. Cody III, MD[1], Sujata Patil, PhD[3], and Monica Morrow, MD[1]

[1]Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY ; [2]Department of Breast Surgery, Dana Farber/Brigham and Women's Cancer Center, Boston, MA; [3]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

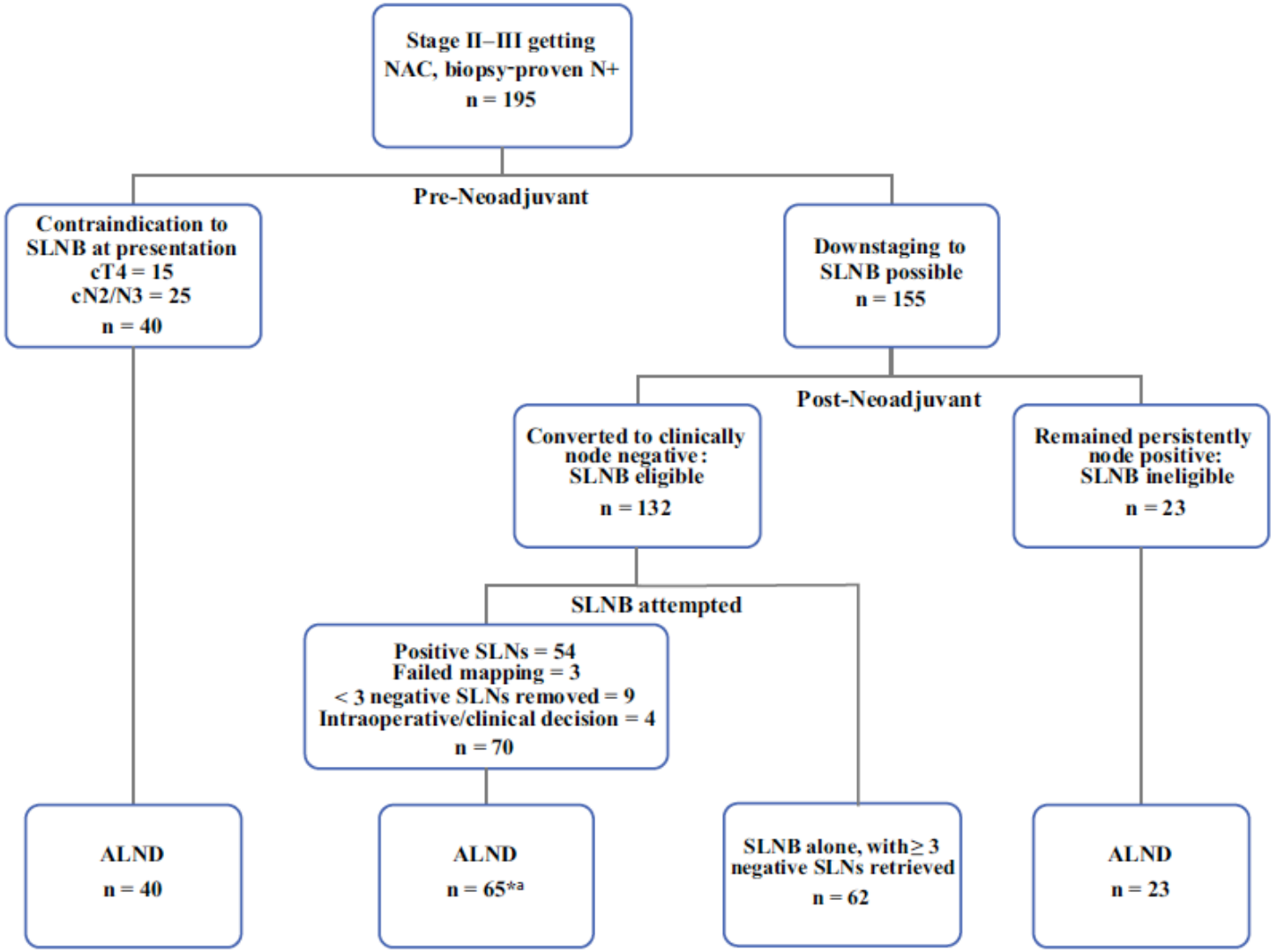

FIG. 1 Flow diagram. *NAC* neoadjuvant chemotherapy, *N+* confirmed nodal metastases at presentation, *SLNB* sentinel lymph node biopsy, *SLNs* sentinel lymph nodes, *ALND* axillary lymph node dissection. *Two patients were randomized to radiation therapy in the Alliance A011202 trial. [a]ALND was deferred for three patients with fewer than three negative SLNs, two by clinical judgment and one by patient preference

Scenario #5

- 50 yo. with T1, ER/PR + Her-2 –
- clinically positive axilla
- Lumpectomy

- Proceed to NAC
- If no response ALND
- If clinical response (or obese) U/S to assess nodes
- If nodes OK proceed to SNB
- Aim for 3 SNs with dye, probe and palpation
- If SNB negative or minimal disease RT to regional nodes (or clinical trial)
- If disease is bulky ALND

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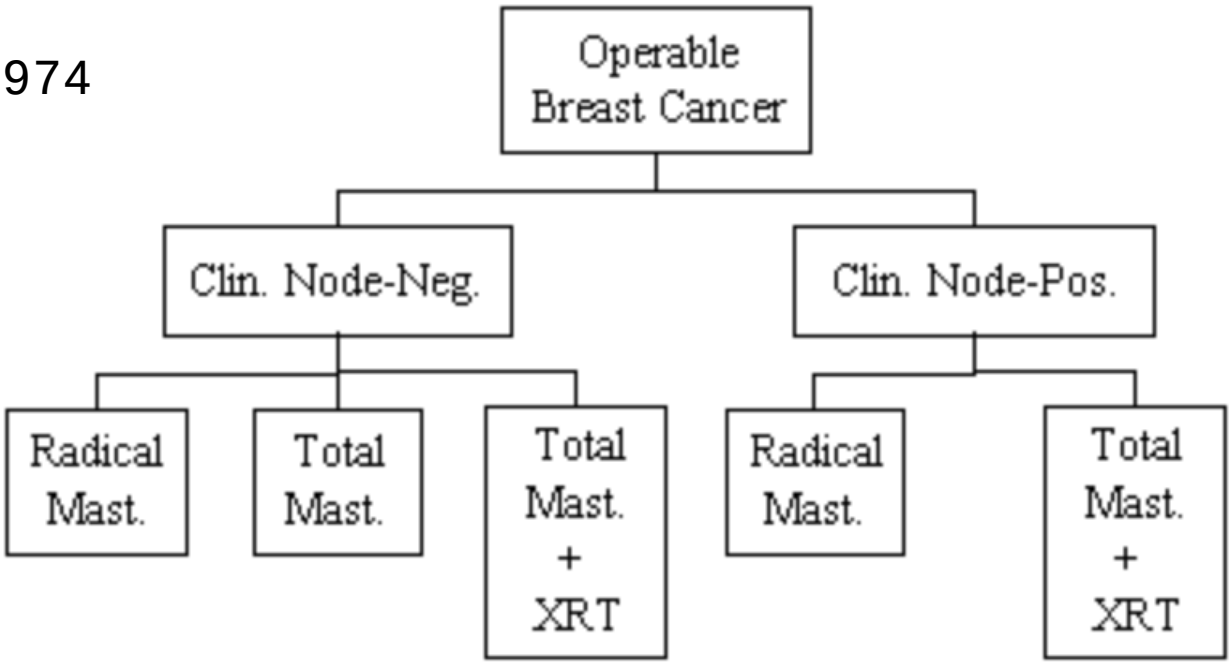
TWENTY-FIVE-YEAR FOLLOW-UP OF A RANDOMIZED TRIAL COMPARING RADICAL MASTECTOMY, TOTAL MASTECTOMY, AND TOTAL MASTECTOMY FOLLOWED BY IRRADIATION

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 · www.nejm.org

NSABP B-04 Trial

1971-1974



1159 cN0 patients

606 cN+ patients

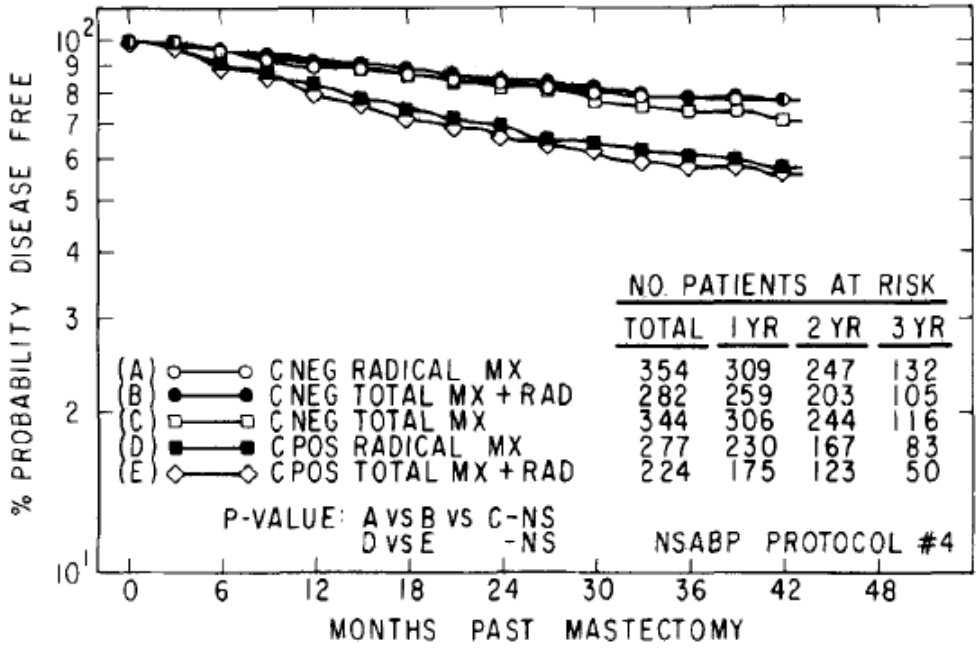


FIG. 3. Probability (%) of survival without disease.

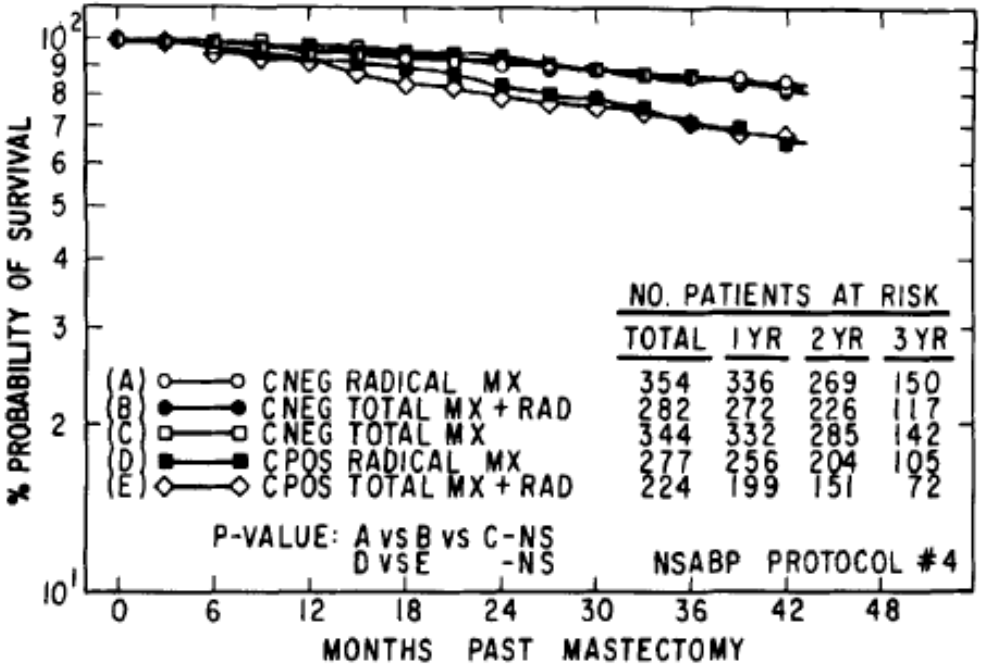


FIG. 4. Probability (%) of survival.

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Conclusion 1:Non-controversial Scenarios

- Clinical negative axilla, T1 or T2 tumor, lumpectomy and - SNB. (NSABP B-32)
- Clinical negative axilla, T1 or T2 tumor, lumpectomy and + SNB. (ACOSOG Z-0011)
- Bulky nodal disease after neoadjuvant chemotherapy - ALND
- Recurrent nodal disease after RT Chemo - ALND

Conclusions 2:Controversial Scenarios

- Total mastectomy with positive SNB: ALND or RT (AMAROS)
- U/S+ and FNA+ or clinically node positive: Neoadjuvant therapy followed by SNB(triple technique)
- If still positive ALND(?)

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Questions?

- Thank you!

NSABP B-04

- cN0 Group
  - 40% Radical Mastectomy Group were LN +
  - Only 18% of the TM group had LN recurrence at 25yrs
    - All salvaged by ALND with **NO DIFFERENCE IN SURVIVAL**

Clinical LN status is a strong predictor of DFS and OS

Not all regional disease is clinically relevant

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer

P.M. Poortmans, S. Collette, C. Kirkove, E. Van Limbergen, V. Budach, H. Struikmans, L. Collette, A. Fourquet, P. Maingon, M. Valli, K. De Winter, S. Marnitz, I. Barillot, L. Scandolaro, E. Vonk, C. Rodenhuis, H. Marsiglia, N. Weidner, G. van Tienhoven, C. Glanzmann, A. Kuten, R. Arriagada, H. Bartelink, and W. Van den Bogaert, for the EORTC Radiation Oncology and Breast Cancer Groups*

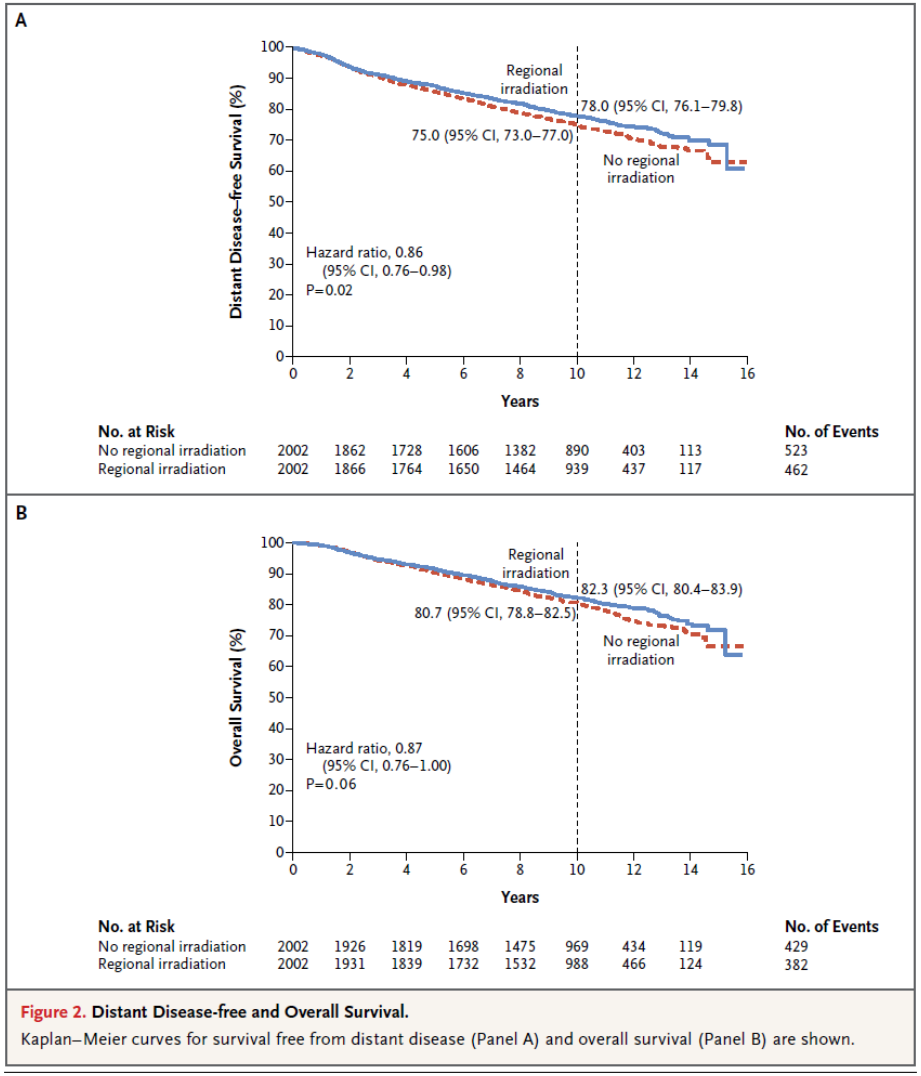

Figure 2. Distant Disease-free and Overall Survival.
Kaplan–Meier curves for survival free from distant disease (Panel A) and overall survival (Panel B) are shown.

EORTC 22922 Trial
2015
DFS and OS with and without Regional nodal irradiation

OS at 10 years 82.3% v.s. 80.7%
p = .06

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Principles

- Regional control by surgery is important
- Nodal surgery for non-clinically evident disease probably does not affect survival
- RT to regional node has a small effect on survival
- Chemotherapy and herceptin have a significant effect or regional control
- Axillary nodal dissection is more morbid than regional radiation at least in the short term
- AND + RT are much more likely to produce significant morbidity

Other scenarios

- Mastectomy with immediate reconstruction positive SN

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- Scenarios:
- 50 yo. with T1, ER/PR + Her-2 –
- 1. clinically negative axilla
- 2. U/S positive axillary node
- 3. palpable node
- What are the local RT guidelines
- What if the patient wants or needs a mastectomy

ACOSOG Z1071 ALLIANCE

- Is SNB accurate after Neoadjuvant?
- 649 pts T0-T4, cN1-2
- NeoAdj CTx followed by SLNBx and ALND
  - Had to have at least 2 SLN removed
  - Encouraged the use double technique