Faculty Presenters

- **Seema A. Khan, MD**, is Professor of Surgery at Northwestern University Feinberg School of Medicine and the Bluhm Family Professor of Cancer Research. She also serves as the co-leader of the Women's Cancer Research Program at Robert H. Lurie Comprehensive Cancer Center. Dr. Khan is a member of the NCCN Breast Cancer Panel and the NCCN Ovarian Cancer Panel.
- **Kilian E. Salerno, MD**, is Assistant Professor of Radiation Oncology and Director of Breast Radiation and Soft Tissue/Melanoma Radiation at Roswell Park Cancer Institute in Buffalo, New York. Dr. Salerno is a member of the ASCO Postmastectomy Radiation Guidelines Panel and the NCCN Breast Cancer Panel.
- **Benjamin O. Anderson, MD**, is Professor of Surgery and Global Health Medicine at the University of Washington and Chair of the Breast Health Global Initiative in the Division of Public Health Sciences at Fred Hutchinson Cancer Research Center. He also serves as Director of the Breast Health Clinic at the Seattle Cancer Care Alliance. Dr. Anderson serves as Vice Chair on the NCCN Breast Cancer Panel and as Chair of the NCCN International Program Steering Committee. He also leads the NCCN Resource Stratification Working Group.

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National Comprehensive Cancer Network

SABCS Updates: Local Therapy

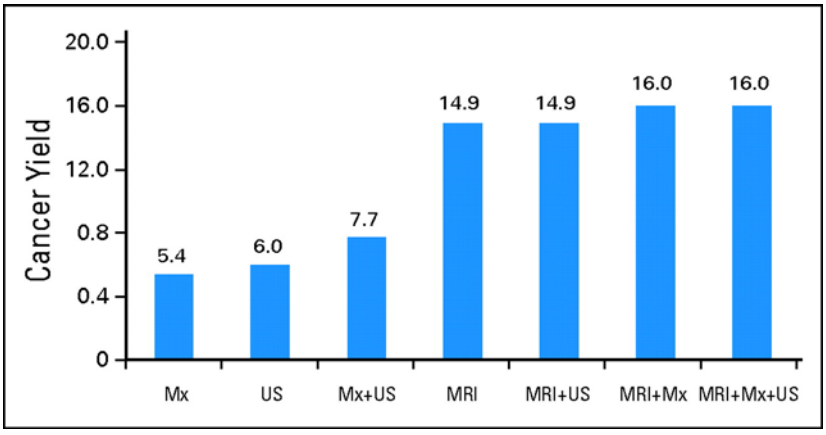
Surveillance, Prevention, & Local Therapy

Seema A. Khan, MD
Professor of Surgery
Bluhm Family Professor of Cancer Research
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Surveillance

Which surveillance modality?

- Cancer yield of the different imaging methods, alone or in combination
  - Women with a lifetime risk of >20%, based on the BRCAPro model.



Christiane Kuhl et al. JCO 2010;28:1450-1457

Surveillance of non-BRCA familial risk

Mark Robson, MD, *Memorial Sloan Kettering Cancer Center*

Actionability requires clinical validity

Summary: 2015

Gene	Breast	Ovary	Other
ATM	Y (OR 2.8)	N	?Pancreas
$CHEK_{2*}$	Y (OR 3.0)	N	?Colon
$PALB_2$	Y (OR 5.3)	N	?Pancreas
NBN*	Y (OR 2.7)	N	
BRIP1	N	Y (OR 3.4-11.2)	
RAD51C/D	N	Y (OR 5.2-12)	
RAD51B	N	N	
BARD1	N	N	
MRE11A/RAD50	N	N	

Robson M, et al. Symposium presentation at: San Antonio Breast Cancer Symposium; December 9-12, 2015; San Antonio, TX

Actionability is a matter of thresholds

Breast MRI guidelines for non-BRCA patients

Group	NCCN/ACS/ ACR	Ontario	NICE	GC-HBOC	Australia Medicare	IKNL 2012
Threshold	>20% LTR	>25% LTR	NR	>30% LTR	Strong FH (complex definition)	NR
Age Start	10 yrs prior (>30)	30	NA	25	Not specified	NA
Age Stop	--	69	NA	69 or ACR1	50	NA
Other					ATM 7271T>G PALB2 3113G>A	

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Estimated cumulative risks (%)
RR varying with age, no competing risk

Gene	30	40	50	60	70	80
No mutation	0.1%	0.5%	2.0%	4.4%	8.0%	12.0%
ATM (constant)	0.1%	1.4%	5.6%	11.8%	20.8%	30.0%
ATM (OR 5 to 50, then 2)	0.3%	2.4%	9.7%	14.0%	20.4%	27.1%
CHEK2 (constant)	0.2%	1.5%	5.9%	12.6%	22.1%	31.8%
CHEK2 (declining)	0.4%	1.6%	5.7%	10.5%	17.0%	23.4%

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Problems with "cumulative lifetime risk"

- No consensus on how to calculate
  - To what age?
  - Remaining risk falls as absolute risk rises
- Nearly impossible to do calibration studies
- Not helpful in deciding when to initiate

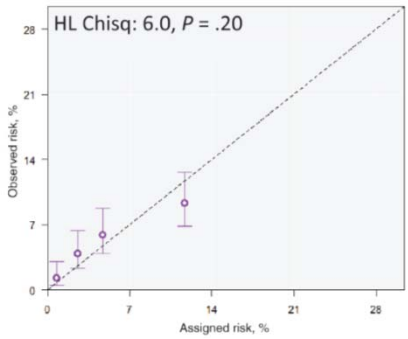
- Good for classification of risk from a gene
- Not so good for individual decision-making

Robson M, et al. Symposium presentation at: San Antonio Breast Cancer Symposium; December 9-12, 2015; San Antonio, TX

Advantages for shorter horizons

Less discordance
Calibrations studies are feasible
Guidance as to when to begin surveillance

A IBIS model

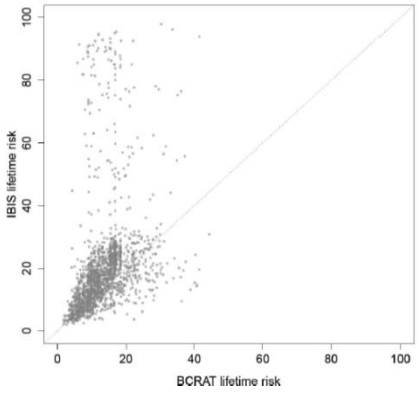


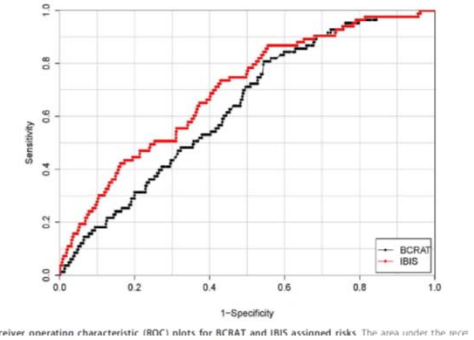
B BOADICEA model

- Observed BC risk (10 yr)
  - 4.8% (95% Cl 4.2-6.5%)
- Predicted Mean Risks
  - IBIS 3.9%
  - BOADICEA 3.0%

Robson M, et al. Symposium presentation at: San Antonio Breast Cancer Symposium; December 9-12, 2015; San Antonio, TX

Gail versus IBIS, lifetime estimates





Summary

- Proposed target 5-year risk of 2.5% for MRI
  - Likely to be relatively sensitive for detection
  - PPV will be low (<10%)(risk-benefit? Cost-effectiveness?)
  - Threshold met at age 45 by "average" mod pen carrier
  - "Average" PALB2 carriers meet at 35
  - Multiplicative effect of FH would move ~5 yrs younger

Robson M, et al. Symposium presentation at: San Antonio Breast Cancer Symposium; December 9-12, 2015; San Antonio, TX

Summary suggestions

Gene	Breast MRI*	RRSO*	Colonoscopy	Pancreas
ATM	45 years (40 w/ FH)	No	Population	No
CHEK2 truncating	45 years (40 w/ FH)	No	Consider at 40?	No
CHEK2 missense	No (FH model)	No	Population	No
PALB2	35 years (30 w/FH)	No	Population	No
NBN	45 years (40 w/ FH)	No	Population	No
BRIP1	No (FH model)	45-50	Population	No
RAD51C	No (FH model)	50-55	Population	No
RAD51D	No (FH model)	45-50	Population	No
APC I1307K	No (FH model)	No	Consider at 40?	No
MUTYH Mono	No (FH model)	No	Population	No

FH model: MRI if modeled 5 year risk >2.5%
Mutations in other genes should be managed according to FH

Robson M, et al. Symposium presentation at: San Antonio Breast Cancer Symposium; December 9-12, 2015; San Antonio, TX

Issues to resolve regarding thresholds for interventions

- Shorter thresholds make a lot of sense
- But they are very age dependent.
- Problem remains, which threshold?
- Which model?

Prevention

Anastrozole versus tamoxifen for the prevention of loco-regional and contralateral recurrence in postmenopausal women with Ductal Carcinoma In-Situ (IBIS-II DCIS)

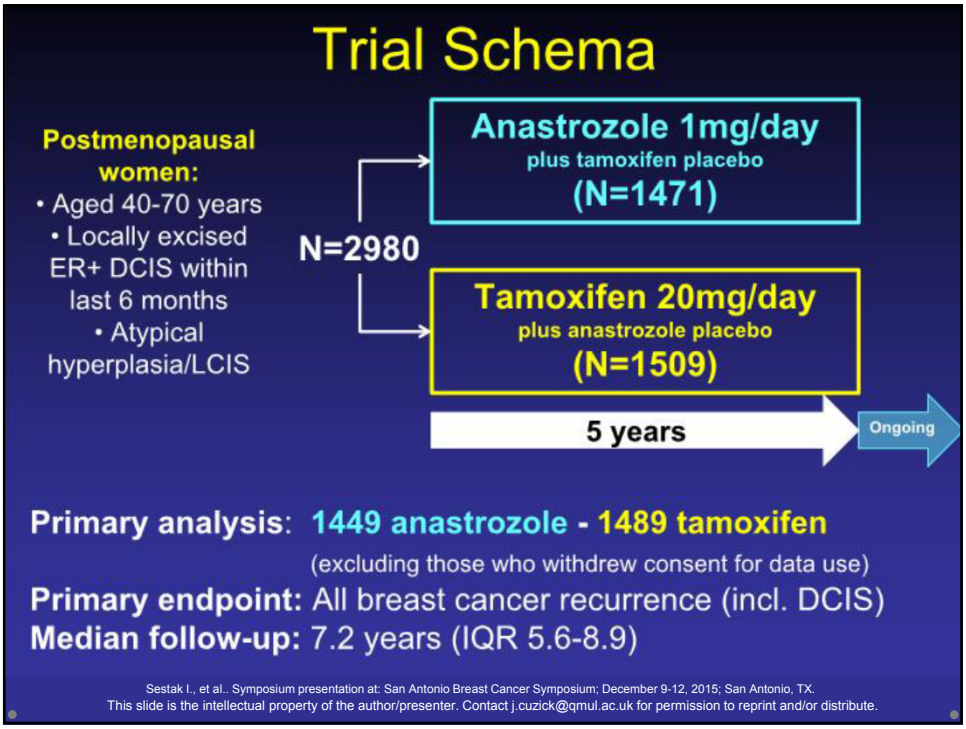
Jack Cuzick

Ivana Sestak, Anthony Howell, Bernardo Bonanni, Nigel Bundred, Christelle Levy, Gunter von Minckwitz, Wolfgang Eiermann, Patrick Neven, Michael Stierer, Chris Holcombe, Robert E. Coleman, Louise Jones, Ian Ellis, John F. Forbes on behalf of the IBIS-II investigators

Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University London, London, UK
Genesis Breast Cancer Prevention Centre, Manchester, UK
Division of Cancer Prevention and Genetics, European Institute of Oncology, Milan, Italy
South Manchester University Hospital, Manchester, UK
Centre François Baclesse, Caen, France
German Breast Group, Neu-Isenburg, Germany
Interdisciplinary Oncology Centre, Munich, Germany
University of Leuven, Leuven, Belgium
Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria
Royal Liverpool University Hospital, Liverpool, UK
Weston Park Hospital, Sheffield, UK
Barts Cancer Institute, John Vane Science Centre, London, UK
University of Nottingham, Molecular Medical Sciences, Nottingham, UK
University of Newcastle, Calvary Mater Hospital, Australia New Zealand Breast Cancer Trials Group Newcastle, Australia

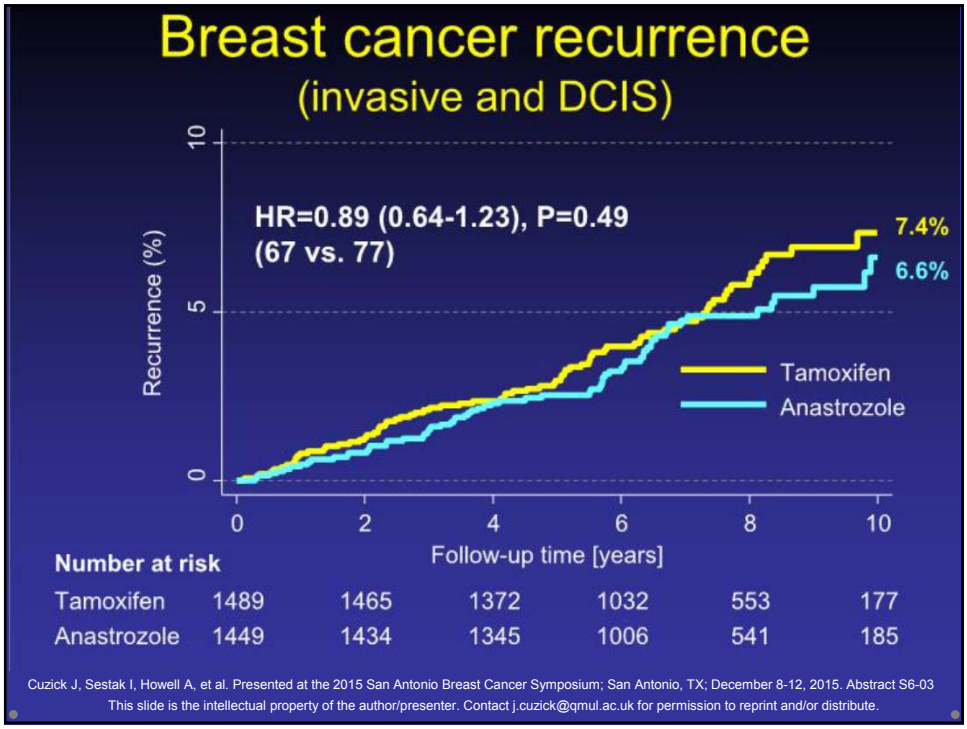
Cuzick J, Sestak I, Howell A, et al. Presented at the 2015 San Antonio Breast Cancer Symposium; San Antonio, TX; December 8-12, 2015. Abstract S6-03

Trial Schema

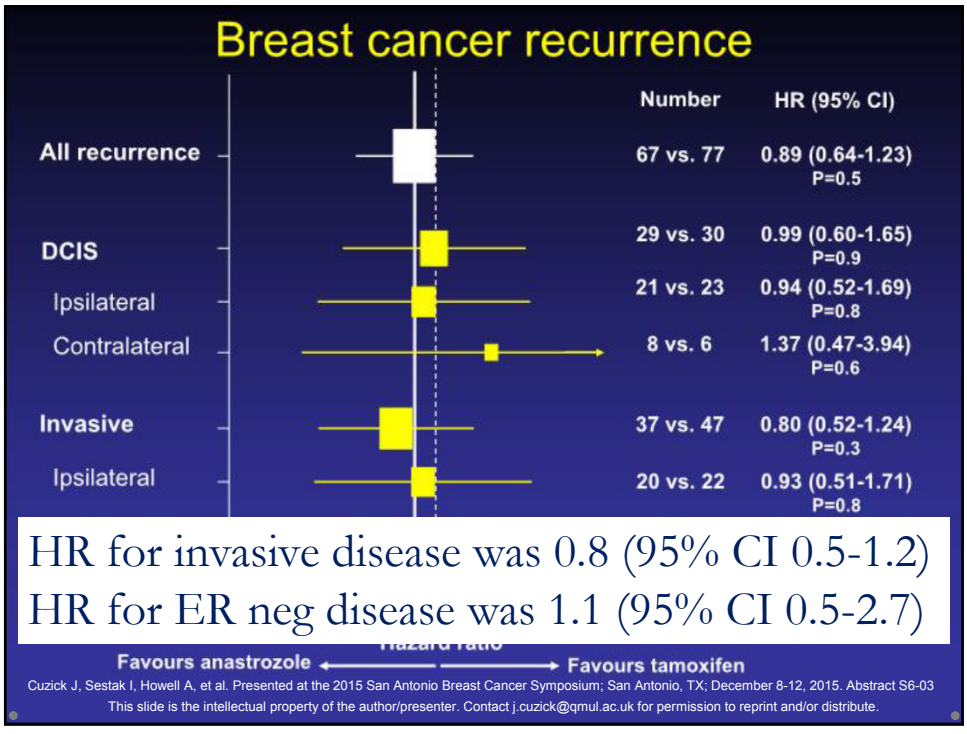


Primary analysis: 1449 anastrozole - 1489 tamoxifen
(excluding those who withdrew consent for data use)
Primary endpoint: All breast cancer recurrence (incl. DCIS)
Median follow-up: 7.2 years (IQR 5.6-8.9)

Sestak I., et al.. Symposium presentation at: San Antonio Breast Cancer Symposium; December 9-12, 2015; San Antonio, TX.

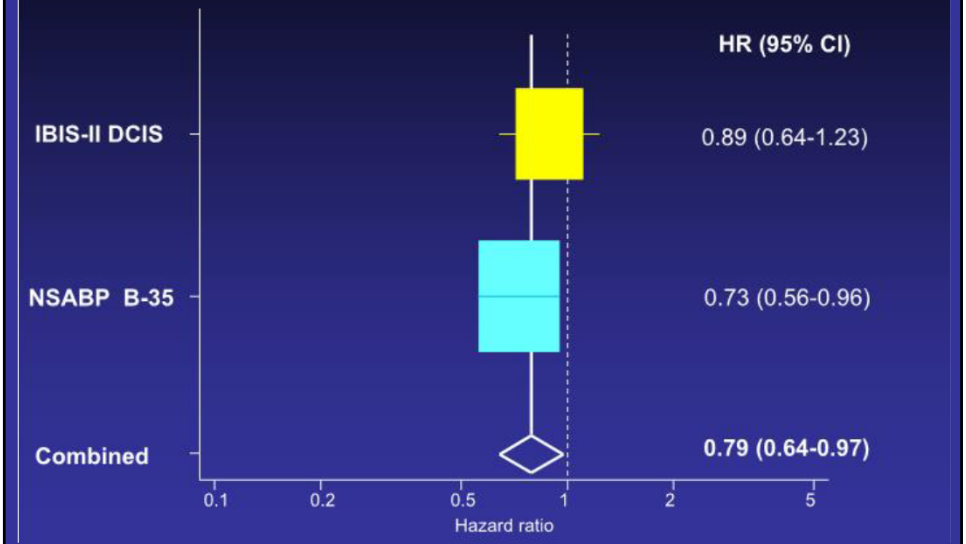


Cuzick J, Sestak I, Howell A, et al. Presented at the 2015 San Antonio Breast Cancer Symposium; San Antonio, TX; December 8-12, 2015. Abstract S6-03



Cuzick J, Sestak I, Howell A, et al. Presented at the 2015 San Antonio Breast Cancer Symposium; San Antonio, TX; December 8-12, 2015. Abstract S6-03

Meta-analysis



Cuzick J, Sestak I, Howell A, et al. Presented at the 2015 San Antonio Breast Cancer Symposium; San Antonio, TX; December 8-12, 2015. Abstract S6-03

IBIS-II adverse events

Other cancers

	Anastrozole (N=1449)	Tamoxifen (N=1489)	OR (95% CI)	P-value
Total	**61**	**71**	**0.88 (0.61-1.26)**	**0.5**
Gynaecological	1	17	0.06 (0.001-0.38)	0.0002
Endometrial	1	11	0.09 (0.002-0.64)	0.004
Ovarian	0	5	0.00 (0.00-0.79)	0.03

Fractures & clots

	Anastrozole (N=1449)	Tamoxifen (N=1489)	OR (95% CI)	P-value
Fractures	**129**	**100**	**1.36 (1.03-1.80)**	**0.03**
Pelvic, hip	11	4	2.84 (0.84-12.25)	0.06
Spine	6	6	1.03 (0.27-3.85)	0.9
Major thromboembolic	**7**	**24**	**0.30 (0.11-0.71)**	**0.003**
Cerebrovascular accident	13	4	3.36 (1.04-14.18)	0.025

Cuzick J, Sestak I, Howell A, et al. Presented at the 2015 San Antonio Breast Cancer Symposium; San Antonio, TX; December 8-12, 2015. Abstract S6-03

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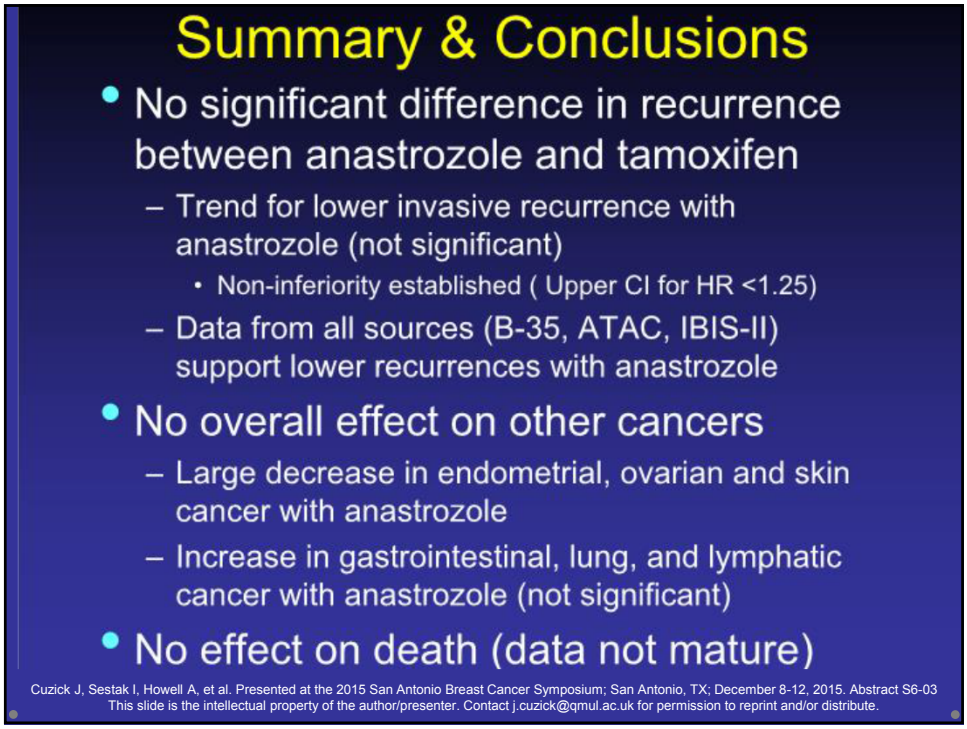

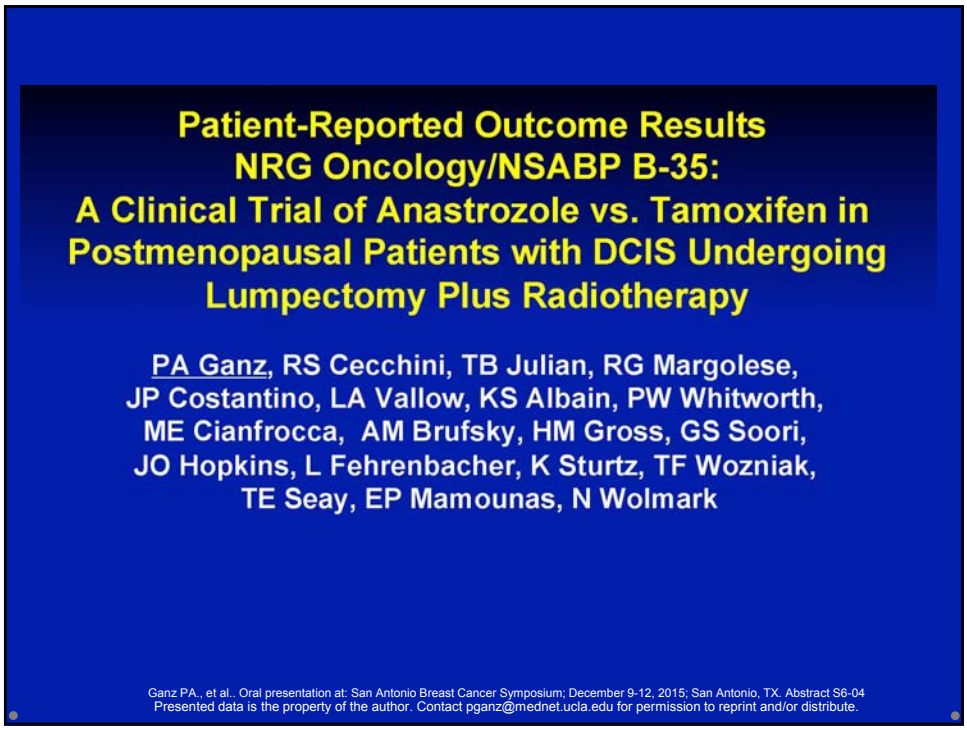

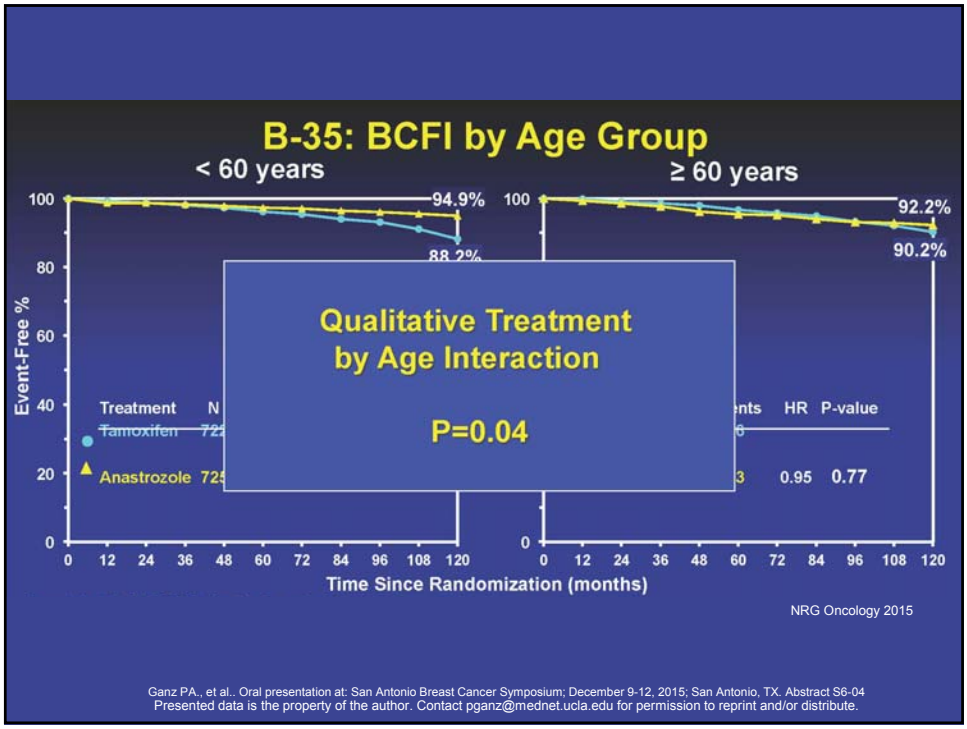

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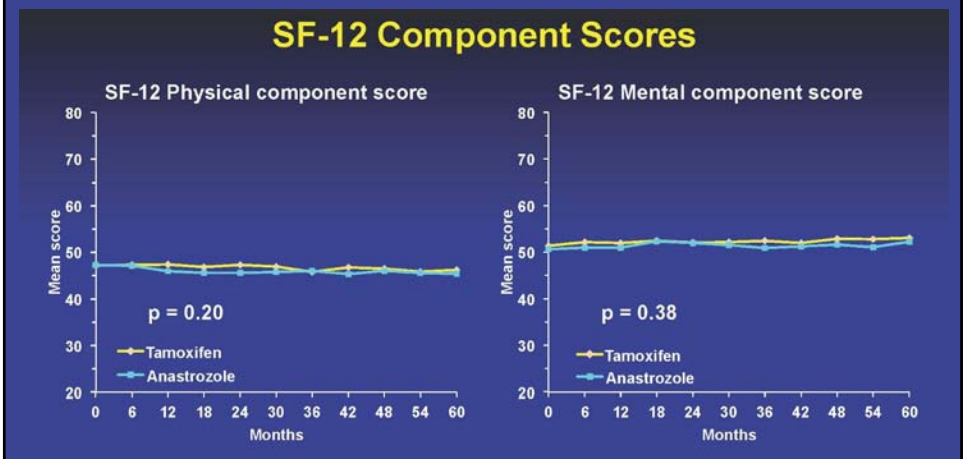
NSABP B-35 patient reported outcomes



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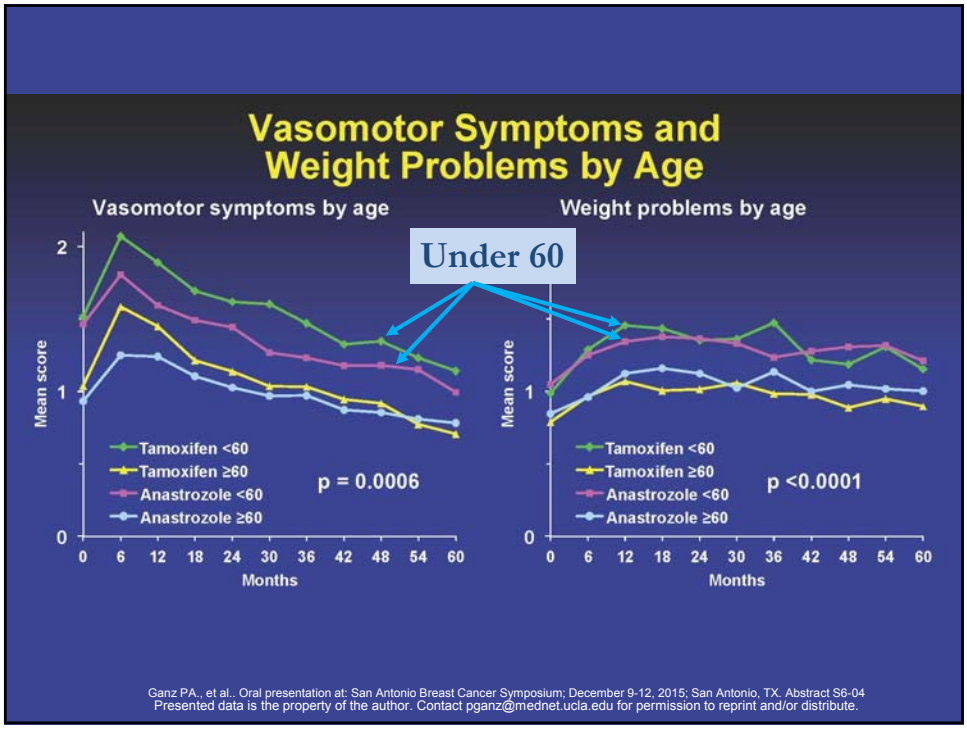
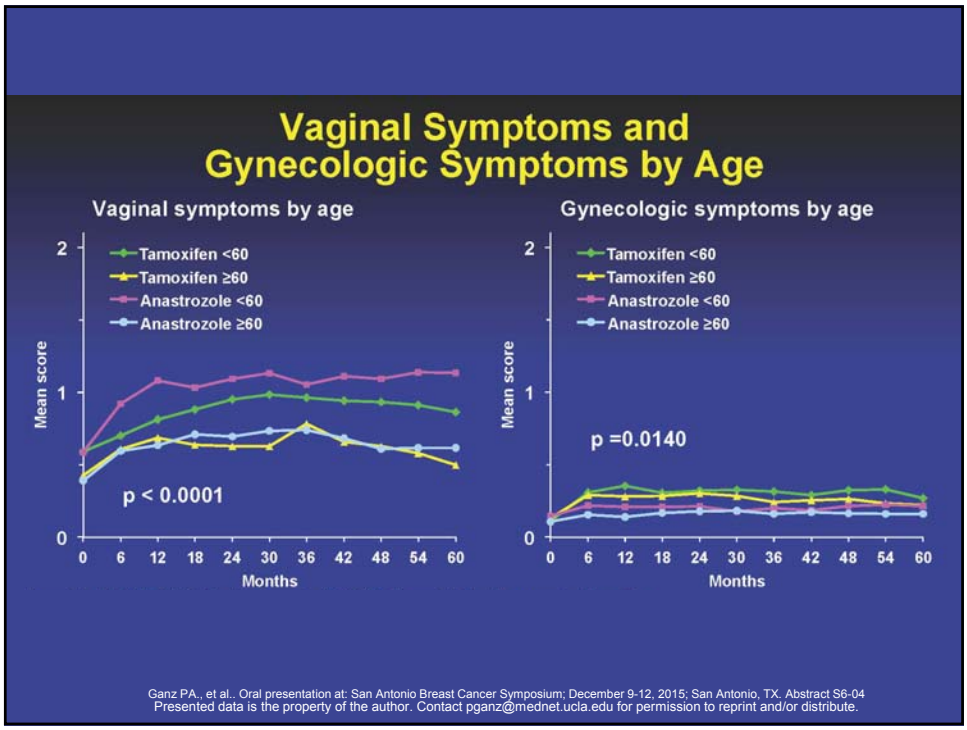




Conclusions from IBIS-II & B-35

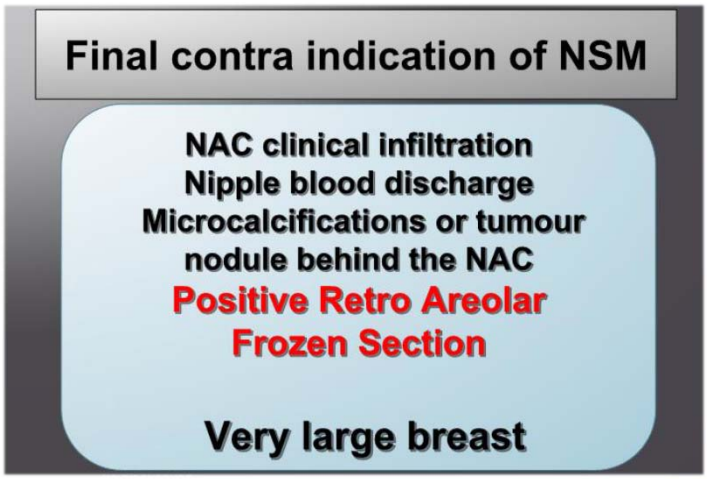
- Anastrozole may have an edge over tamoxifen in terms of efficacy, particularly for younger women.
- Adverse events as expected.
- Symptoms are worse with anastrozole for women under 60.
- These data are consistent regarding approximate equivalence of these agents
- Support personalized decisions based on age, patient preference, and co-morbidities.

Nipple-sparing mastectomy
reviewed by Petit, Milan.

- Complications
  - Nipple necrosis total 3%; partial 6%
  - Implant loss 5%
- Satisfaction
  - Better body image
  - Better sexual functioning
  - Less feeling of mutilation
- Recurrence
  - 772 invasive cancer patients, 5 year results
  - Non-nipple LR 3.6%
  - Nipple LR 0.8%

Petit J., et al. Symposium presentation at: San Antonio Breast Cancer Symposium; December 9-12, 2015; San Antonio, TX.

Nipple-sparing mastectomy
reviewed by Petit, Milan.



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Breast conservation & margins

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MARGIN WIDTH AND RE-EXCISION IN BREAST CONSERVING TREATMENT,
A DBCG BASED STUDY

A. Bodilsen, K. Bjerre, B.V. Offersen, P. Vahl, M. Mele, J.M. Dixon,
B. Ejlertsen, J. Overgaard, P. Christiansen

AARHUS UNIVERSITET

Bodilsen A., et al., Oral Presentation at: San Antonio Breast Cancer Symposium; December 9-12, 2015; San Antonio, TX. Abstract S2-01.

Margin width & breast conservation: a DBCG study

PURPOSE

- Investigate association between margin width and IBTR
- Identify factors associated with residual disease after re-excision
- Determine the effect of re-excision on IBTR in a population-based nationwide cohort

INCLUSION

- 2000-2009
- Age18-75
- Breast conserving surgery
- Invasive cancer
- Unilateral
- No prior cancer
- Treated according to DBCG guidelines
- **In total 11,900 patients**

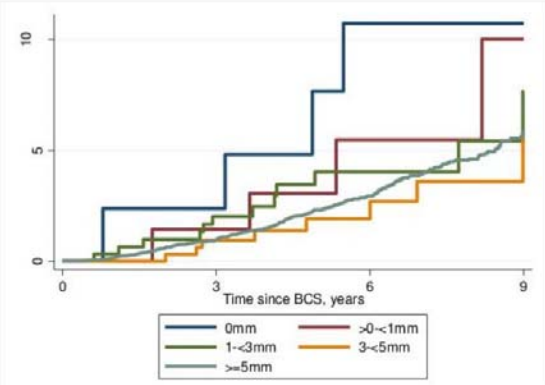
Bodilsen A., et al., Oral Presentation at: San Antonio Breast Cancer Symposium; December 9-12, 2015; San Antonio, TX. Abstract S2-01.

DBCSG results

- IBTR at 5 years 2.4% At 9 years 5.9%

MARGIN & IBTR

	HR	95% CI
0 mm	2.52	1.02-6.23
> 0-<1mm	1.40	0.62-3.79
1-<3 mm	1.40	0.79-2.47
3-<5mm	0.79	0.39-1.62
≥ 5 mm	1	



Cumulative incidence of IBTR by margin width in 11,900 women

Bodilsen A., et al., Oral Presentation at: San Antonio Breast Cancer Symposium; December 9-12, 2015; San Antonio, TX. Abstract S2-01.

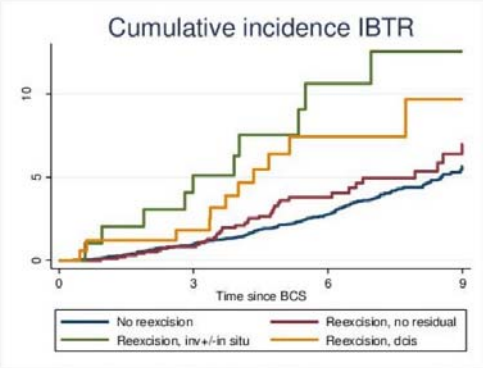
Additional significant co-variates

- Age
- Re-excision
- Nodal positivity
- ER status
- Use of chemotherapy
- Use of boost RT

Re-excision with residual disease indicates increased risk of IBTR

RE-EXCISION & IBTR

	HR	95% CI
No re-excision	1	
Re-ex, no res	1.21	0.86-1.70
Res – inv+/- DCIS	2.97	1.57-5.62
Res - DCIS	2.58	1.50-4.45



Cumulative incidence of IBTR after final BCS by surgery and residual finding

Bodilsen A., et al., Oral Presentation at: San Antonio Breast Cancer Symposium; December 9-12, 2015; San Antonio, TX. Abstract S2-01.

integraal kankercentrum Nederland

The effect of breast conserving surgery and mastectomy on 10-year survival

10-12-2015 | Marissa van Maaren

L. De Munck, G.H. de Bock, J.J. Jobsen, T. van Dalen, P. Poortmans, S.C. Linn, L.J.A Strobbe, S. Siesling

The effect of breast conservation & mastectomy on 10-year survival

- **Dutch guidelines:**

  T1-2N0-1 indication for BCT or MAST

-
  - Netherlands Cancer Registry
  - Women, 1st primary tumor, diagnosis 2000-2004
  - pT1-2N0-1 stage
  - Treated with BCT or MAST, all Dutch hospitals
  - No M. Paget
  - No macroscopic residual tumour
  - No neo-adjuvant systemic therapy

Van Maaren et al., Oral Presentation at: San Antonio Breast Cancer Symposium; December 9-12, 2015; San Antonio, TX. Abstract S3-05.

Characteristics of 37000+ patients

- 58.4% BCT
  - Younger
  - Smaller, well differentiated, unifocal, ductal tumors
  - Localised in inner or outer parts
  - Less hormonal therapy
  - Less axillary lymph node dissection

Median follow-up time 11.3 years

	n	HR [95% CI]	p-value
Overall cohort			
MAST	15,473	1	
BCT	21,734	0.81 [0.78-0.85]	**<0.001**

Corrected for confounding

- **Analyses stratified by T and N stage showed similar results**

Van Maaren et al., Oral Presentation at: San Antonio Breast Cancer Symposium; December 9-12, 2015; San Antonio, TX. Abstract S3-05.

Context and Discussion

- Radiotherapy was not used in this population.
- HER2 testing was not routine.
- Selection bias remains a viable explanation for the observed survival advantage with BCT use
- Nevertheless, this is reassuring information for women with early-stage breast cancer considering mastectomy

Van Maaren et al., Oral Presentation at: San Antonio Breast Cancer Symposium; December 9-12, 2015; San Antonio, TX. Abstract S3-05.

Conclusions

- Surveillance: lifetime estimates problematic; consider shorter timeframes for making recommendation for MRI.
- Prevention: anastrozole equivalent to tamoxifen for DCIS patients, adverse effects as expected, leaving room for personalized choices.
- Surgical treatment: no significant advantage of wide margins. Overall survival following BCT equivalent to mastectomy.
- Axillary management: the trend towards less surgery continues.

2016

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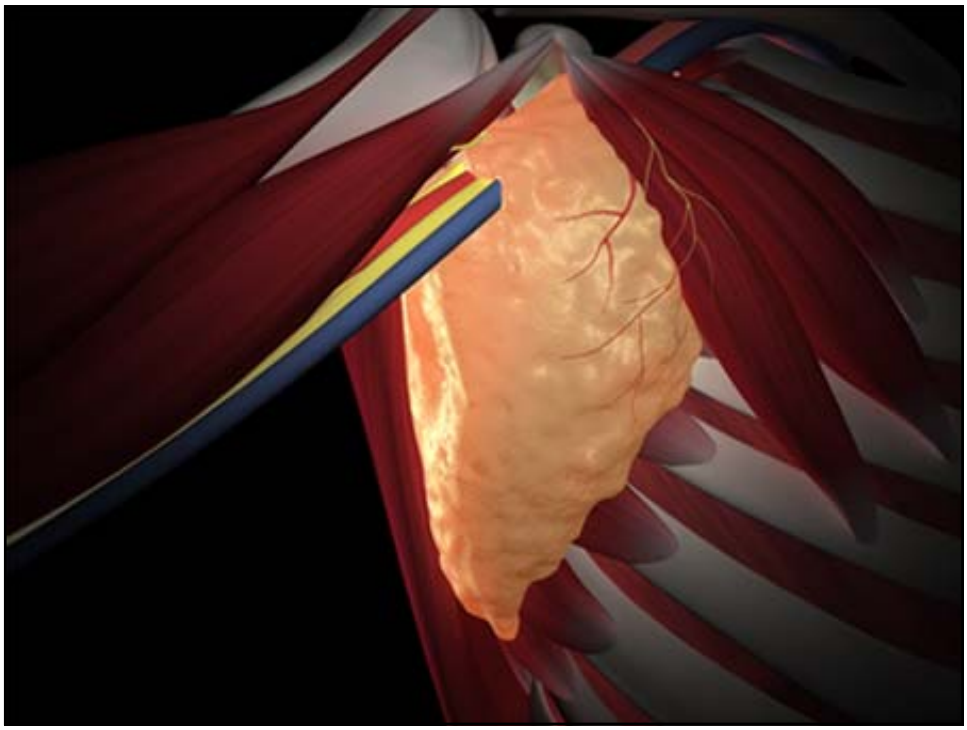
Surgical Management of the Axilla in Early Stage Breast Cancer

Benjamin O. Anderson, MD

Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance



BREAST CANCER 2016: Surgical Management of the Axilla

- Historical Perspective on the axilla
- Sentinel node excision for staging
- Sentinel node excision for treatment
- Sentinel node following neoadjuvant

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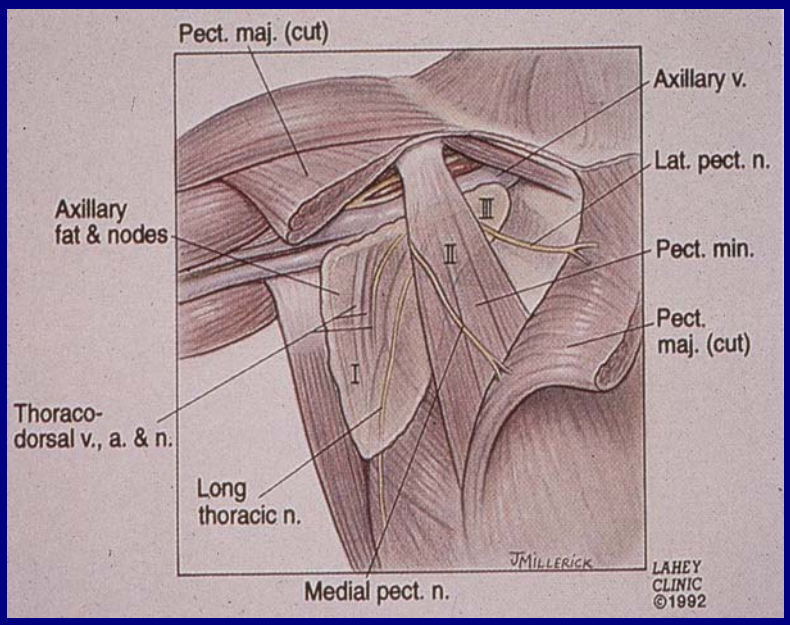


AXILLARY RECURRENCE:
NSABP B-04, 25 year follow-up

- 1,079 clinically node-negative patients
  1. Radical mastectomy
  2. Total mastectomy + axillary XRT
  3. Total mastectomy with salvage ALND (365 pts)
- 586 clinically node-positive patients
  1. Radical mastectomy
  2. Total mastectomy + axillary XRT
- No systemic therapy in either arm

Fisher, et al. NEJM 347:567, 2002

AXILLARY RECURRENCE:
NSABP B-04, 25 year follow-up

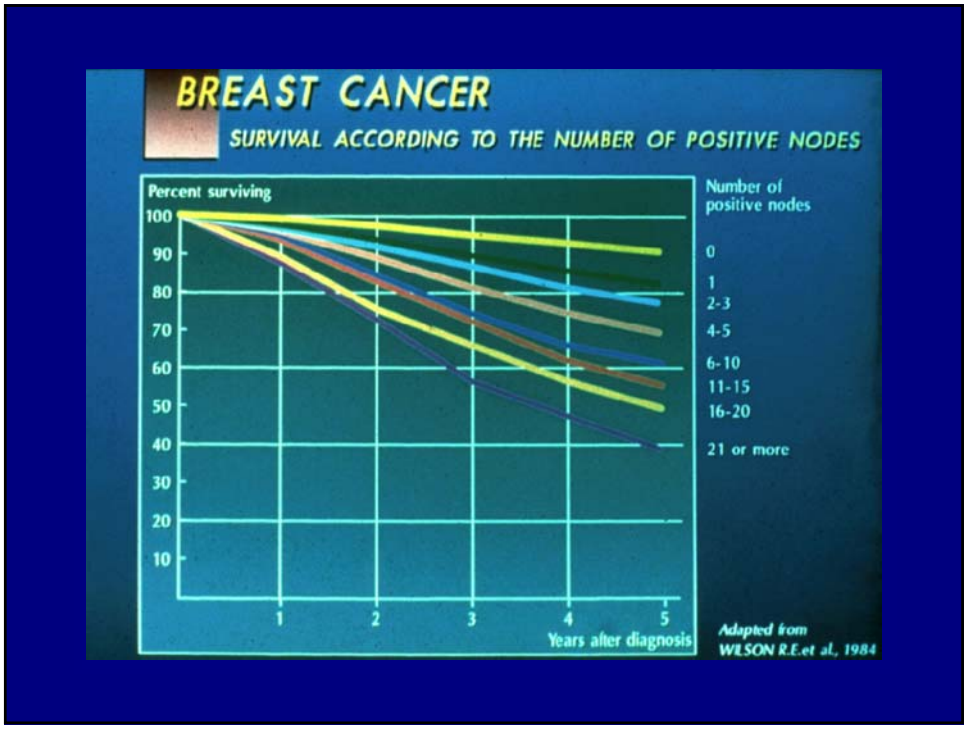
- Population
  - 70% over age 50
  - 3.3cm mean tumor size (T2)
  - 40% node positive in RM group
- Outcome comparing randomized groups
  - No difference in disease-free survival
  - No difference in overall survival

Fisher, et al. NEJM 347:567, 2002

AXILLARY RECURRENCE:
NSABP B-04, 25 year follow-up

- Axillary recurrence in 68 / 365 (18.6%)
  - Half of occult node positive cancers recurred
  - Median time to recurrence 14.8 months
  - One patient could not be resected
- TM specimens contained nodes in 35%
  - 23%: 1 - 5 lymph nodes
  - 12%: >5 lymph nodes

Fisher, et al. NEJM 347:567, 2002



AXILLARY NODE DISSECTION: Complication Rates

- Lymphedema
  - Acute: 40%
  - Chronic: 15-20%
- Paraesthesia: 40%
- Need for a drain: 100%
- Seroma formation: 10%

LYMPHEDEMA PRESENTATION

Mild - stage I (left)

Moderate – stage II (left)

Severe – stage III (right)

S. McLaughlin, "Lymphedema" in Diseases of the Breast 5th Ed, 2014

BREAST CANCER 2016: Surgical Management of the Axilla

- Historical Perspective on the axilla
- Sentinel node excision for staging
- Sentinel node excision for treatment
- Sentinel node following neoadjuvant

BREAST CANCER 2016: Surgical Management of the Axilla

- Historical Perspective on the axilla
- Sentinel node excision for staging
- Sentinel node excision for treatment
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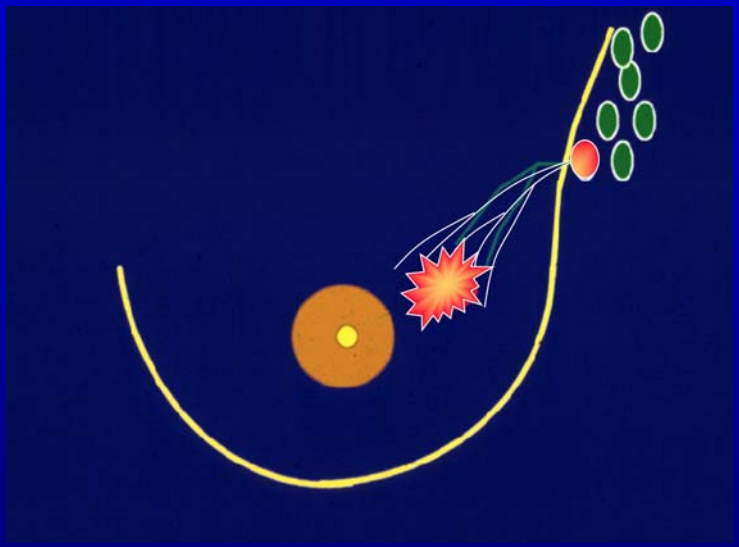
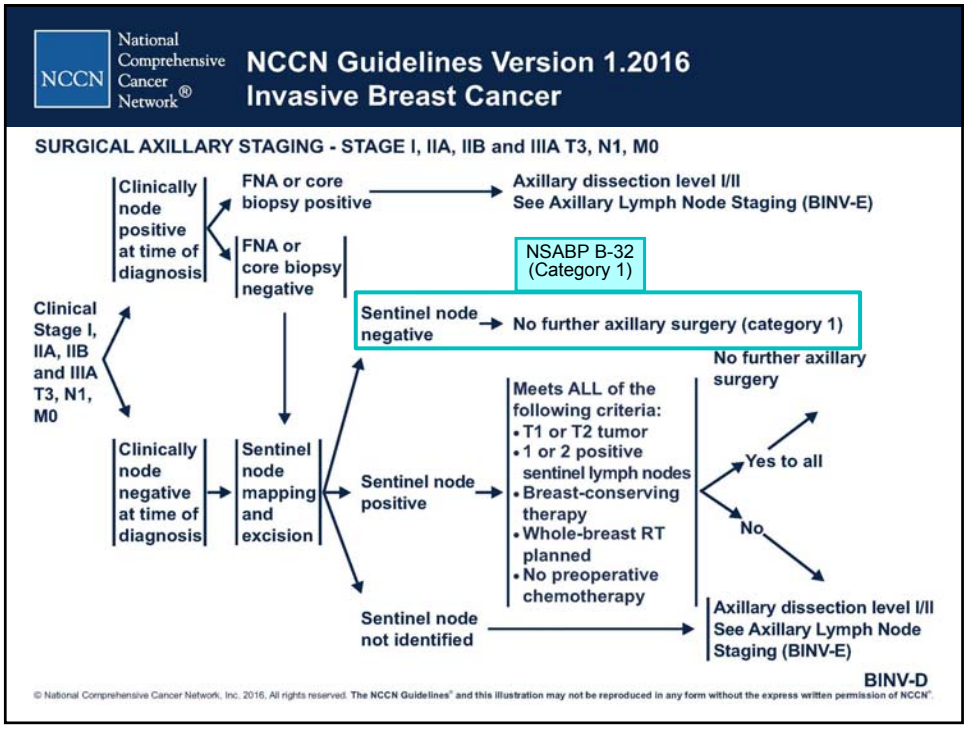
SENTINEL NODE CONCEPT

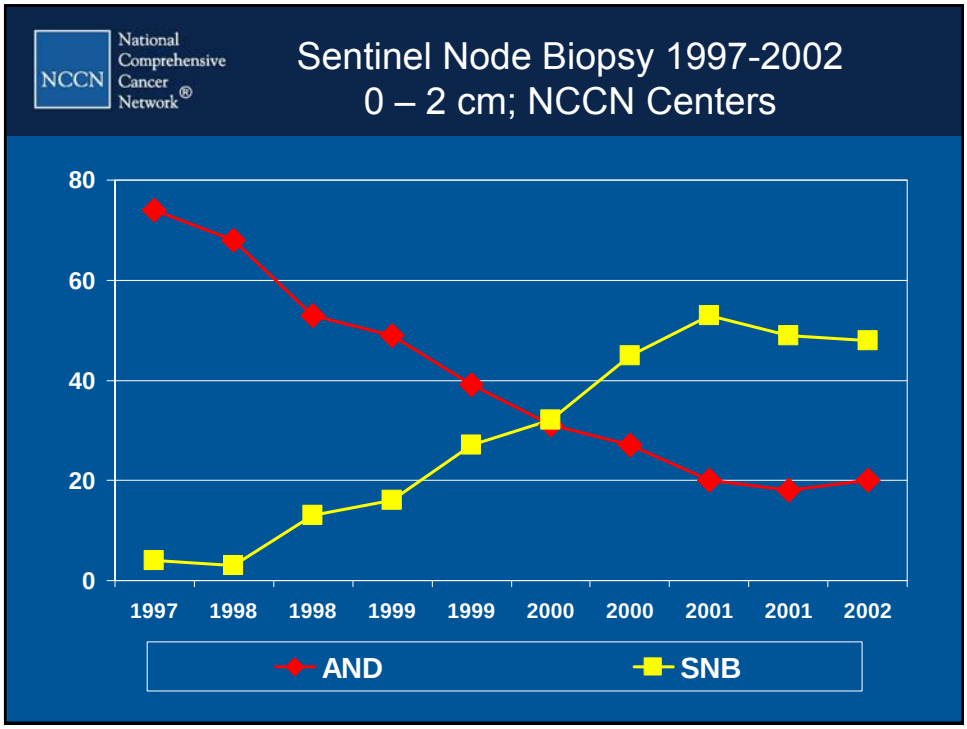




QUESTION

Was prospective randomized (category 1) evidence required before sentinel node biopsy was accepted as the standard of care in the U.S.?

1) Yes
2) No



NCCN Breast Guidelines

Sentinel node biopsy

- 1998: Incorporated as option in guideline footnote
  - Smaller tumor; negative node; trained team
- 2002: Included in primary guideline
  - Expanded indications
- 2007: Sentinel node biopsy preferred
  - Experienced team and appropriate candidate

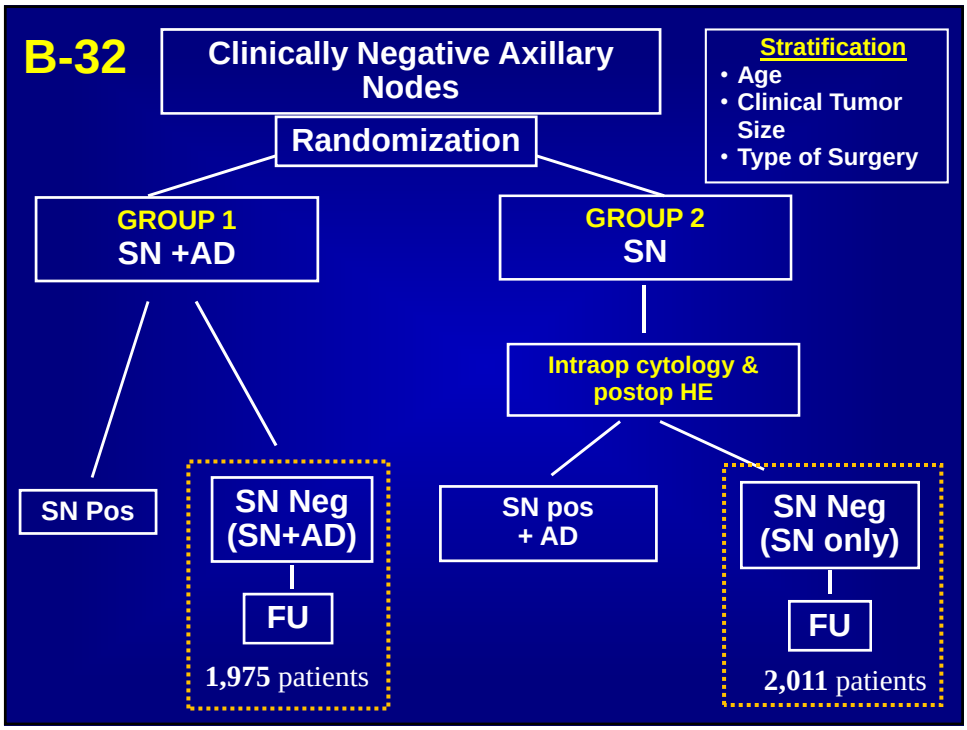
ASCO 2009 Abstract LBA505

NSABP PROTOCOL B-32

A Randomized, Phase III Clinical Trial to Compare Sentinel Node Resection to Axillary Dissection in Clinically Node-Negative Breast Cancer Patients

Definitive Analysis of the Primary Outcomes

DN Krag, SJ Anderson, TB Julian, A Brown, SP Harlow, JP Costantino, T Ashikaga, D Weaver, EP Mamounas, N Wolmark



NSABP Protocol B-32

Disease-Free Survival for Sentinel Node Negative Patients

Krag, et al., Lancet Oncol 11:927, 2010

Local and Regional Recurrences as First Events

	Group 1 SN + AD	Group 2 SN
Local	54 (2.7%)	49 (2.4%)
Axillary	2 (0.1%)	8 (0.3%)
Extra-axillary	5 (0.25%	6 (0.3%)

Krag, et al., Lancet Oncol 11:927, 2010

Residual Morbidity at End of Follow-up

- Lower in SN group
- Not nonexistent

	Group 1 SN + AD	Group 2 SN
Shoulder abduction deficit	19%	13%
Arm volume difference >5%	28%	17%
Arm numbness	31%	8%
Arm tingling	13%	7%

Ashikaga JSO 102:111, 2010

All differences p<0.001

Krag, et al., Lancet Oncol 11:927, 2010

NCCN Breast Guidelines

Sentinel node biopsy

- Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial *Lancet Oncol* 2007; 8: 881-88

  David N Krag, Stewart J Anderson, Thomas B Julian, Ann M Brown, Seth P Harlow, Takamaru Ashikaga, Donald L Weaver, Barbara J Miller, Lynne M Jalovec, Thomas G Frazier, R Dirk Noyes, André Robidoux, Hugh M C Scarth, Denise M Mammolito, David R McCready, Eleftherios P Mamounas, Joseph P Costantino, Norman Wolmark, for the National Surgical Adjuvant Breast and Bowel Project (NSABP)

- Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial *Lancet Oncol* 2010; 11: 927-33

  David N Krag, Stewart J Anderson, Thomas B Julian, Ann M Brown, Seth P Harlow, Joseph P Costantino, Takamaru Ashikaga, Donald L Weaver, Eleftherios P Mamounas, Lynne M Jalovec, Thomas G Frazier, R Dirk Noyes, André Robidoux, Hugh M C Scarth, Norman Wolmark

BREAST CANCER 2016: Surgical Management of the Axilla

- Historical Perspective on the axilla
- Sentinel node excision for staging
- Sentinel node excision for treatment
- Sentinel node following neoadjuvant

BREAST CANCER 2016: Surgical Management of the Axilla

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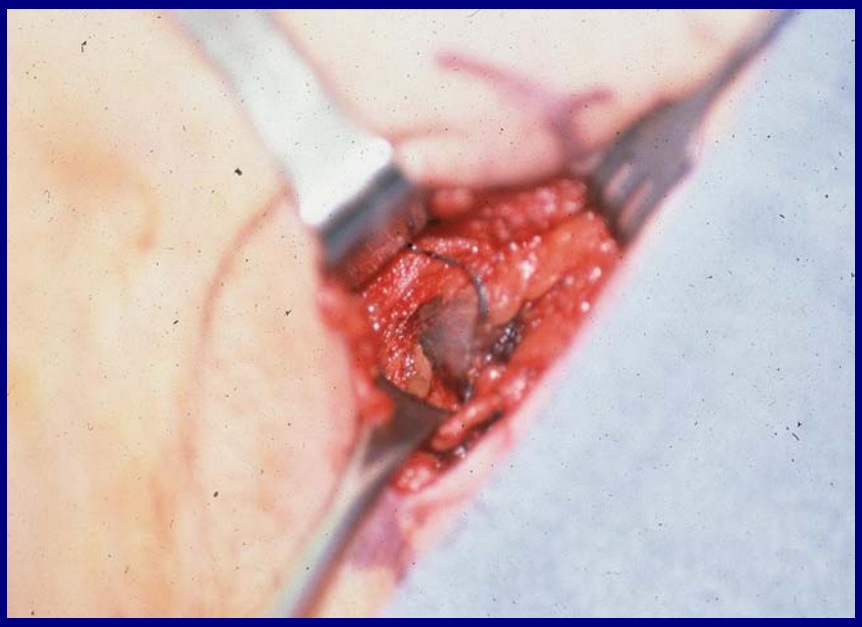
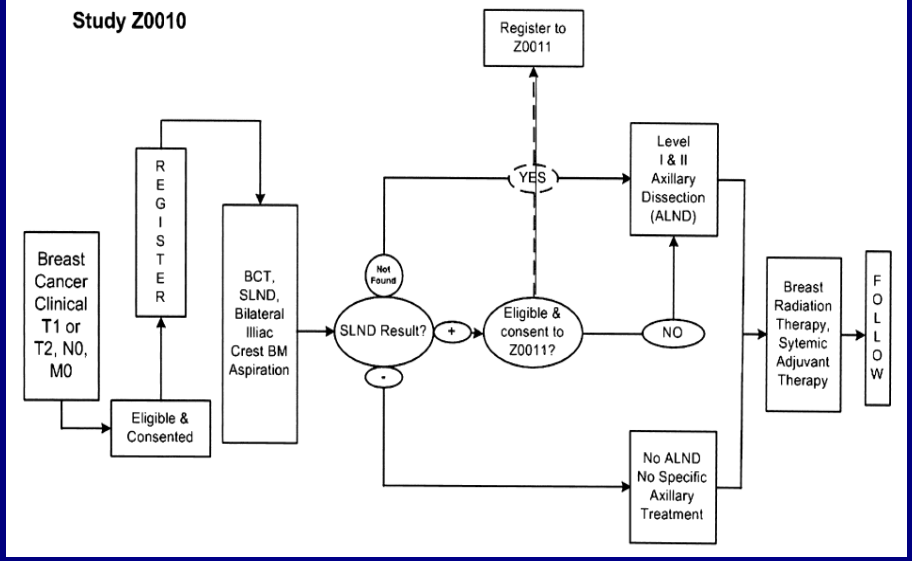


QUESTIONS

Does immunohistochemical staining of the sentinel lymph node improve therapeutic outcomes?

1) Yes
2) No

Peace and Love Hospital (Kumasi , Ghana) 2004
Recurrent breast cancer in axillary lymph node bed



Giuliano, et al. JAMA 306:385, 2011

ACOSOG Z0010
Methods

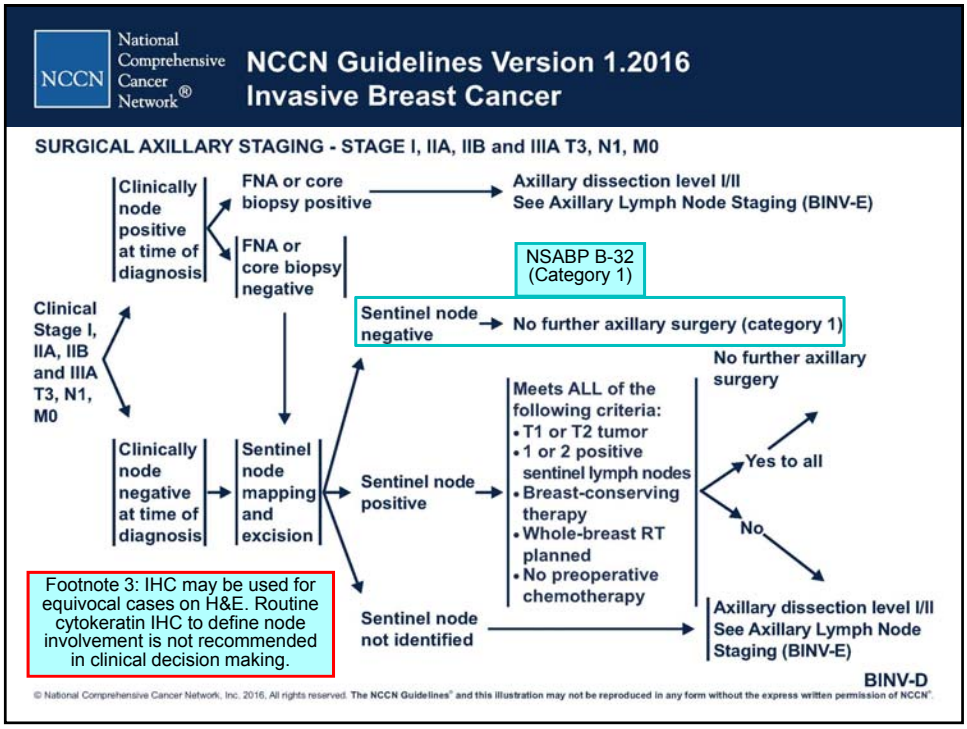
- Bone marrow aspiration prior to SLN bx
- Bone marrow specimens subjected to IHC (investigators blinded to results)
- SLN processed – standard pathology and H&E staining
- SLN neg by H&E subjected to IHC for cytokeratin (investigators blinded to results)

Giuliano, et al. JAMA 306:385, 2011

ACOSOG Z0010
Results

- Among SLN H&E negative patients, SLN IHC results (positive vs negative) was not significantly associated with differences in OS at 5 years.
- While bone marrow metastases were associated with worsened outcome, the results were not independent on multivariate analysis.
- Conclusion: Routine examination of SLNs by IHC is not supported by this study.

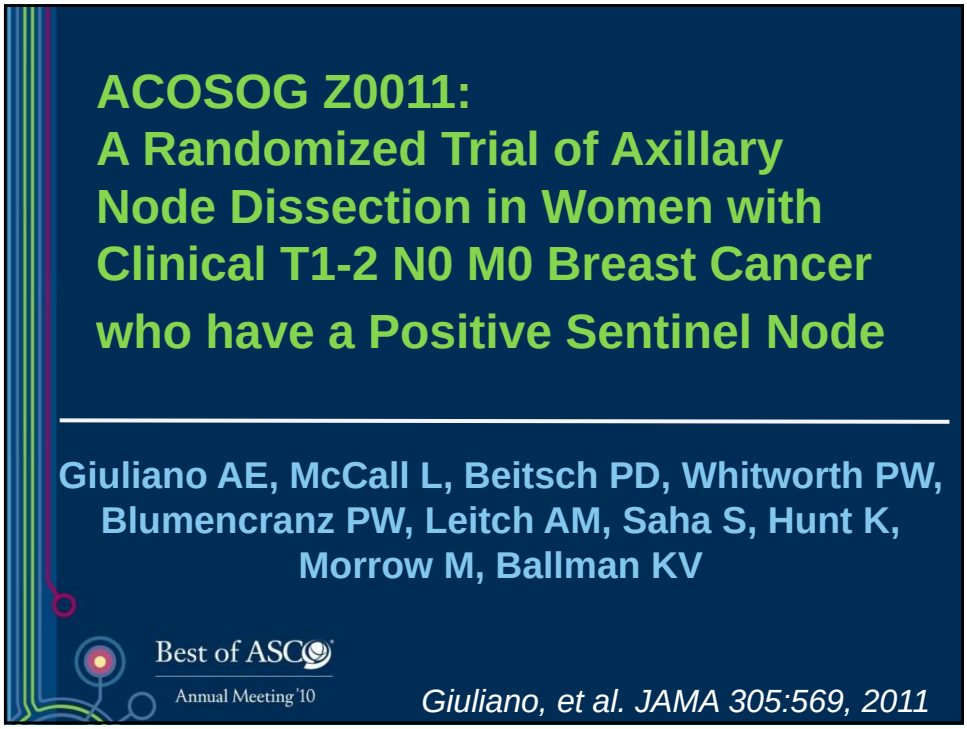
Giuliano, et al. JAMA 306:385, 2011

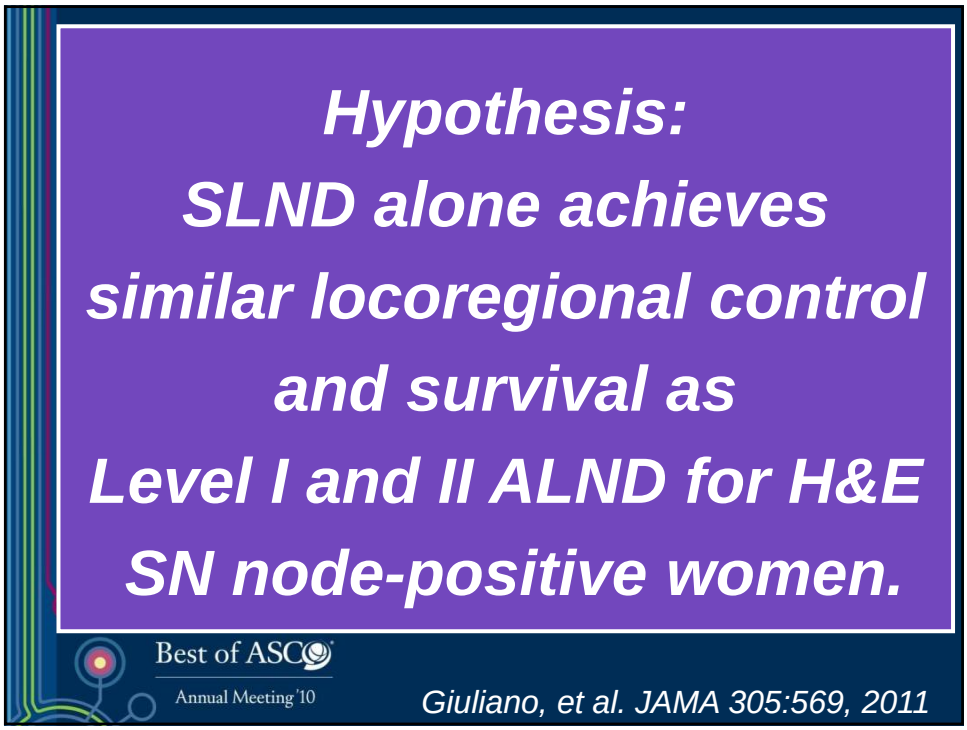


QUESTIONS

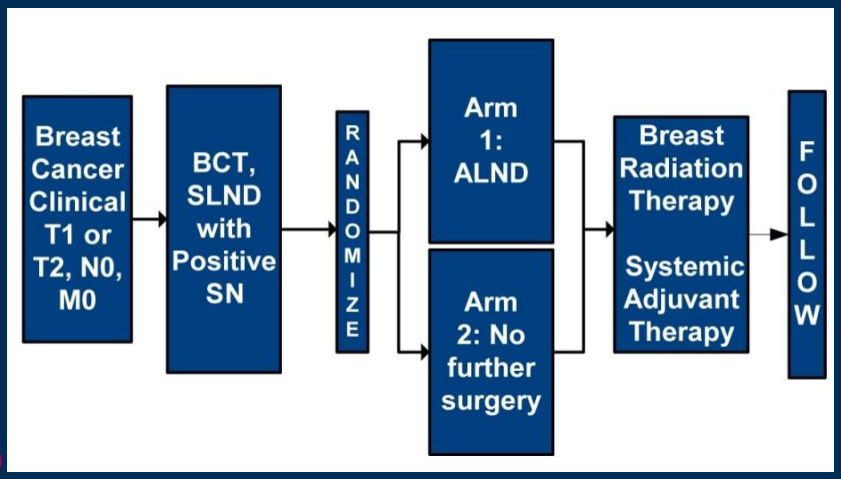
Is completion axillary node dissection necessary when positive axillary nodes remain after SLN biopsy?

1) Yes
2) No





Z0011 Study Design Schema



Best of ASCO Annual Meeting '10

Giuliano, et al. JAMA 305:569, 2011

Inclusion/Exclusion Criteria

Eligibility

- Clinical T1 T2 N0 breast cancer
- H&E-detected metastases in SN (AJCC 5th edition)
- Lumpectomy with whole breast irradiation
- Adjuvant systemic therapy by choice

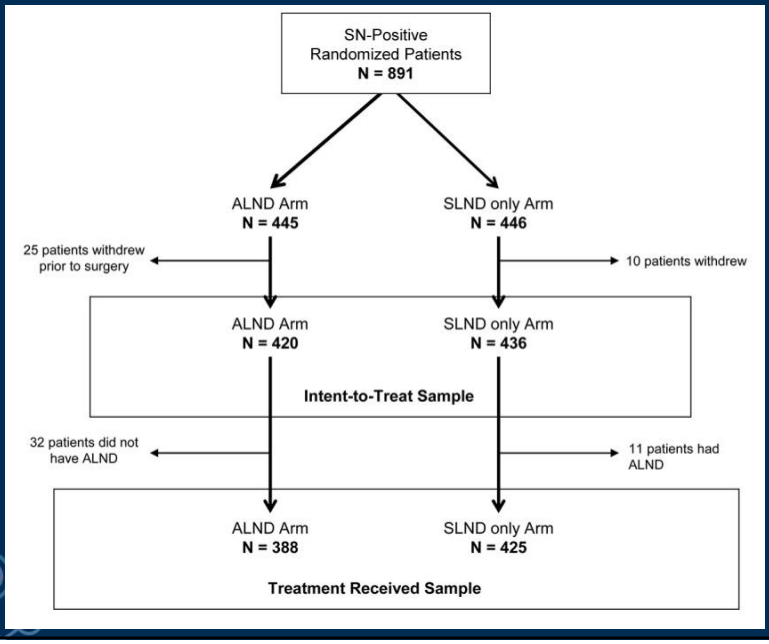
Ineligibility

- ***Third field (nodal irradiation) or APBI***
- ***Metastases in SN detected by IHC***
- ***Matted nodes***
- ***3 or more involved SN***

Best of ASCO Annual Meeting '10

Giuliano, et al. JAMA 305:569, 2011

Study Population Schema 5/99–12/04



Adjuvant Systemic Therapy

	ALND	SLND
Chemotherapy	57.9%	58.0%
Hormonal therapy	46.4%	46.6%
Either/Both	96.0%	97.0%

P = N.S.

Best of ASCO Annual Meeting '10

Giuliano, et al. JAMA 305:569, 2011

106 (27.4%) patients treated with ALND had additional positive nodes removed beyond SN.

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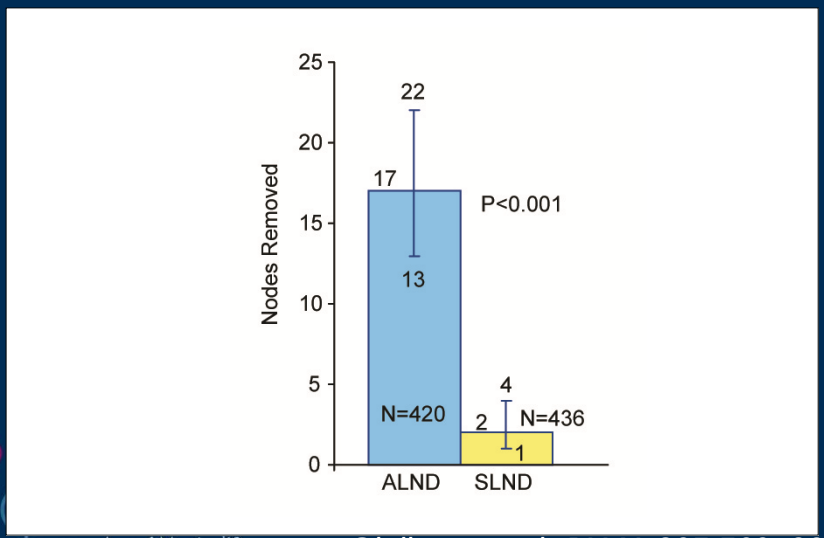
Giuliano, et al. JAMA 305:569, 2011

Median Number of Lymph Nodes Removed



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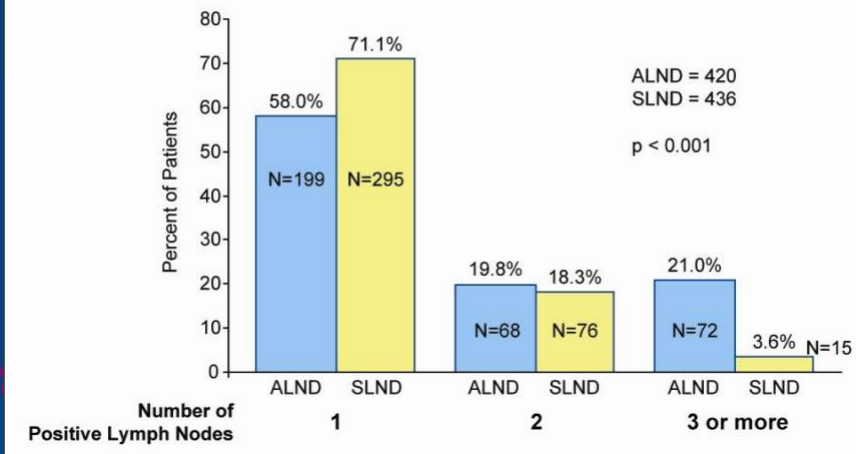
Giuliano, et al. JAMA 305:569, 2011

Number of Positive Lymph Nodes



Annual Meeting '10

Giuliano, et al. JAMA 305:569, 2011

Locoregional Recurrences

Recurrence	ALND (420 pts)	SLND (436 pts)
Local (Breast)	15 (3.6%)	8 (1.8%)
Regional (Axilla, Supraclavicular)	2 (0.5%)	4 (0.9%)
Total Locoregional	17 (4.1%)	12 (2.8%)
	P = 0.11	

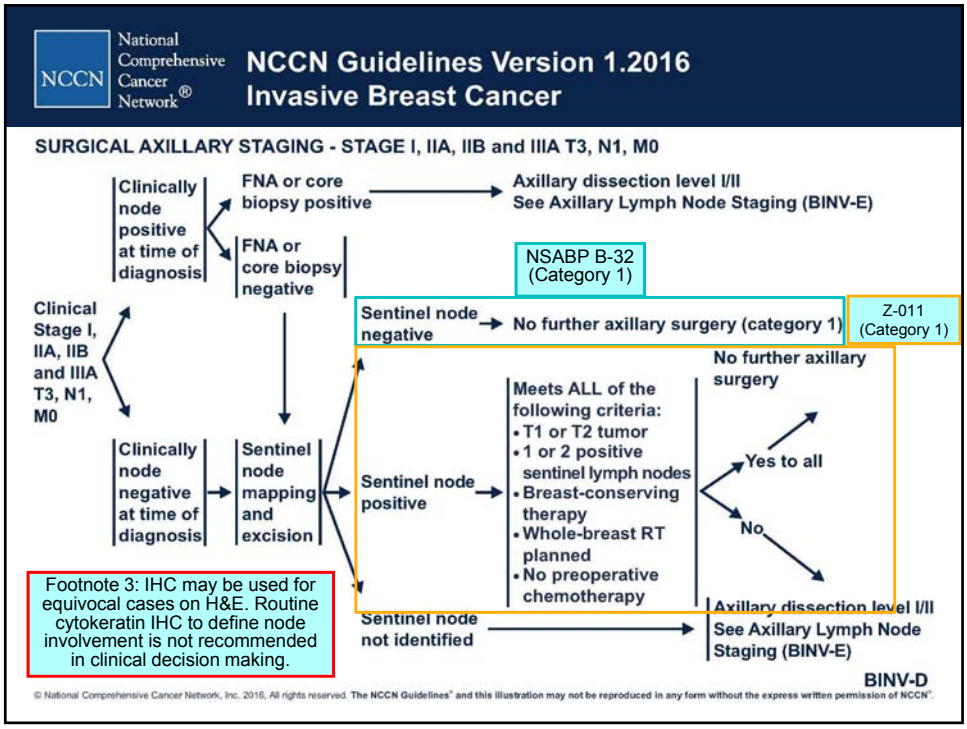
Median follow-up = 6.3 years

Regional recurrence seen in only 0.7% of the entire population

Best of ASCO

Annual Meeting '10

Giuliano, et al. JAMA 305:569, 2011

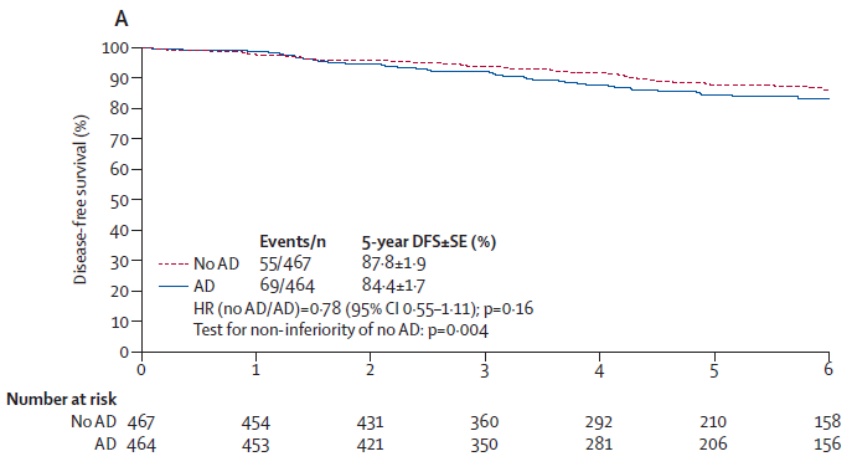


SLN / MICROMETS
IBCSG 23-01 TRIAL (2013)

- T1/T2, clinically node negative, > 1 micromet in SLN(s):
  - 934 patients randomized to ALND vs. no ALND
  - 9% had mastectomy; 13% had positive non-sentinel nodes
  - Median follow-up 57 months
- RESULTS:
  - No difference in disease-free survival or overall survival
  - Disease recurrence in the undissected axilla remained <1%

Galimberti, et al., Lancet Oncol 14:297,2013

SLN / MICROMETS
IBCSG 23-01 TRIAL (2013)



Galimberti, et al., Lancet Oncol 14:297,2013

DISSECTION vs. XRT
AMAROS TRIAL (2014)

- T1/T2, clinically node negative, positive SLN(s):
  - 4806 patients randomized to ALND vs. axillary radiotherapy
  - 1425 had positive SLN: 744 had ALND; 681 had axillary XRT
  - 33% had positive non-sentinel nodes; Median follow-up 6.1 years
- RESULTS
  - Low axillary recurrence rates (0.43% surgery vs 1.19% XRT)
  - Lymphedema more common in the axillary node dissection group

Donker, et al., Lancet Oncol 15:1303,2014

DISSECTION vs. XRT
AMAROS TRIAL (2014)

	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

Donker, et al., Lancet Oncol 15:1303,2014

BREAST CANCER 2016:
Surgical Management of the Axilla

- Historical Perspective on the axilla
- Sentinel node excision for staging
- Sentinel node excision for treatment
- Sentinel node following neoadjuvant

BREAST CANCER 2016: Surgical Management of the Axilla

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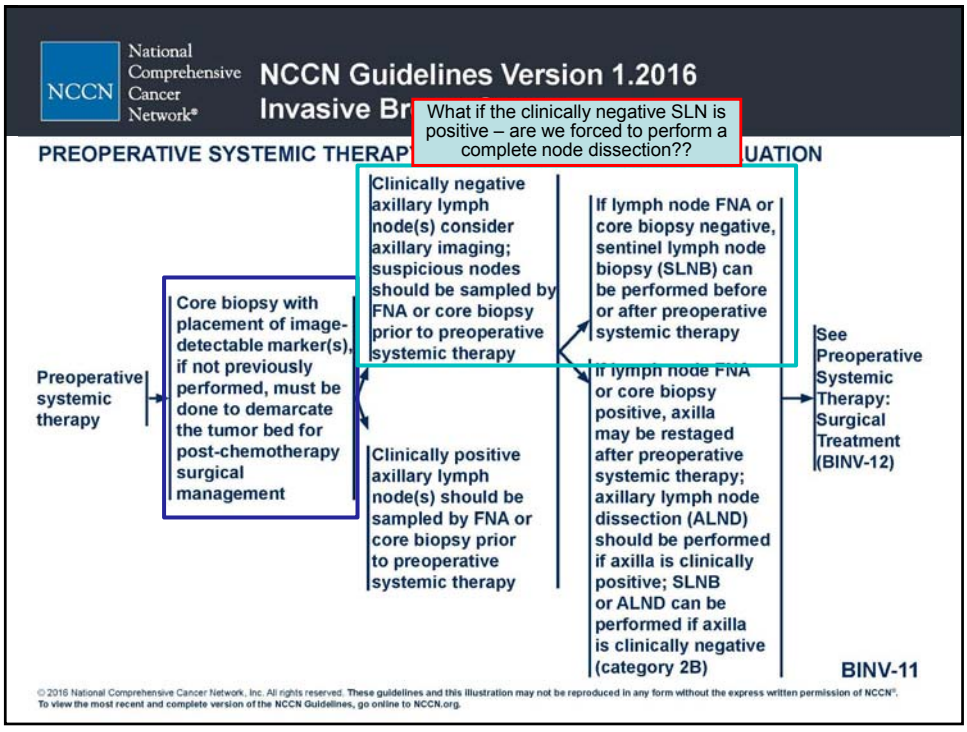
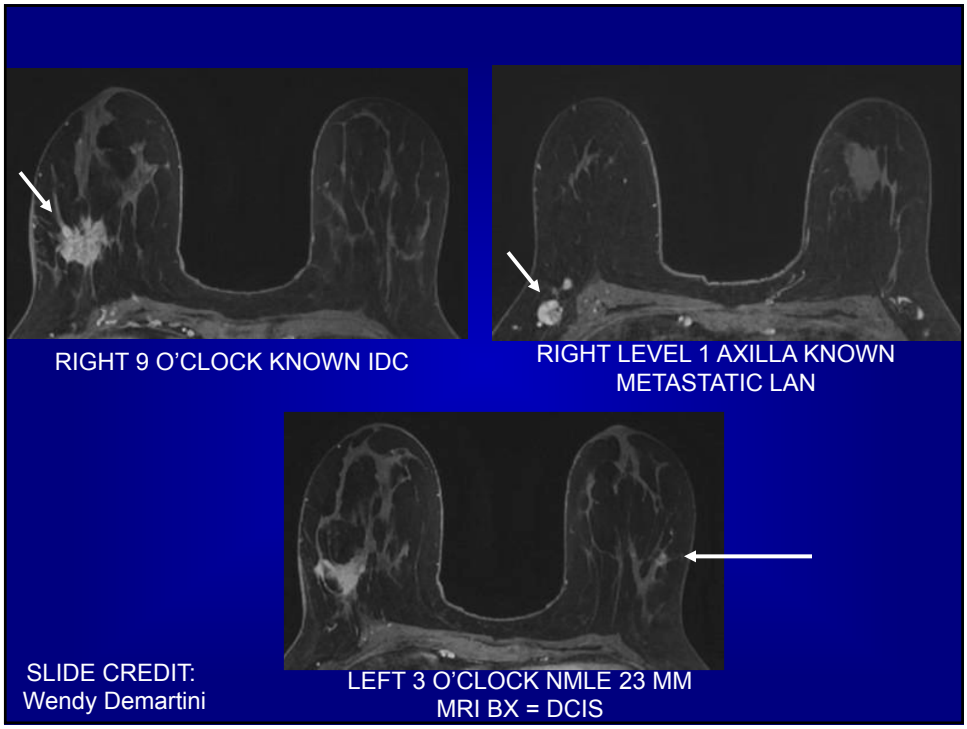
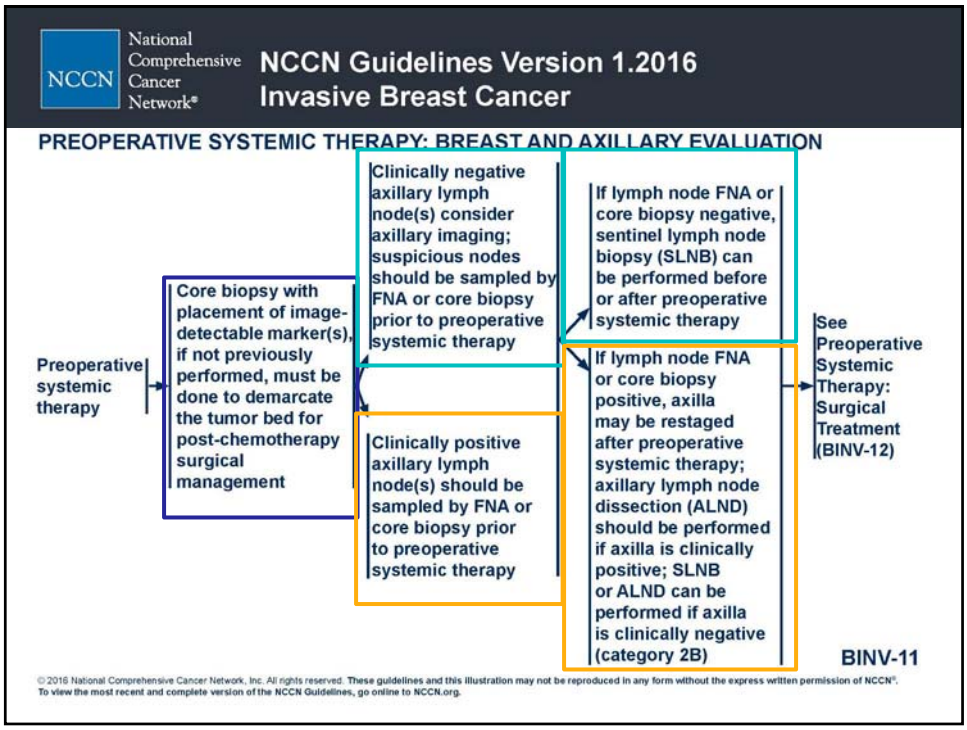






QUESTION

If a SLN biopsy or nodal sampling is positive *before* neoadjuvant therapy, is a complete axillary node dissection always required *after* neoadjuvant chemotherapy?

1) Yes
2) No

Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study

Thorsten Kuehn, Ingo Bauerfeind, Tanja Fehm, Barbara Fleige, Maik Hausschild, Gisela Helms, Annette Lebeau, Cornelia Liedtke, Gunter von Minckwitz, Valentina Nekljudova, Sabine Schmatloch, Peter Schrenk, Annette Staebler, Michael Untch

Summary

Background The optimum timing of sentinel-lymph-node biopsy for breast cancer patients treated with neoadjuvant chemotherapy is uncertain. The SENTINA (SENTinel NeoAdjuvant) study was designed to evaluate a specific algorithm for timing of a standardised sentinel-lymph-node biopsy procedure in patients who undergo neoadjuvant chemotherapy.

Kuehn, et al., Lancet Oncol 14:609,2013

SLN / NEOADJUVANT CHEMO SENTINA TRIAL (2013)

- Four-arm prospective trial at 103 institutions in Europe:
  - Arm A (cN0, pN0): Clinically node-negative disease (cN0) with negative SLN before neoadjuvant chemotherapy
  - Arm B (cN0, pN1): If the sentinel node was positive (pN1), a second SLN procedure done after neoadjuvant chemotherapy
  - Arm C (cN+, ycN0): Women with clinically node-positive disease (cN+) who converted to clinically node-negative disease after chemotherapy (ycN0) had SLN and axillary dissection
  - Arm D (cN+, ycN1): Clinical nodal status remained positive (ycN1) underwent complete axillary dissection without SLN

Kuehn, et al., Lancet Oncol 14:609,2013

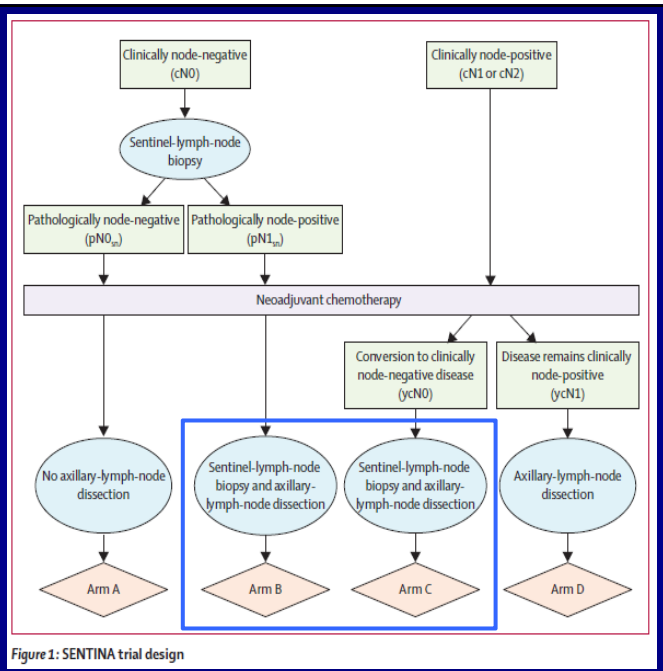


Figure 1: SENTINA trial design

Kuehn, et al., Lancet Oncol 14:609,2013

SLN / NEOADJUVANT CHEMO
SENTINA TRIAL (2013)

- Four-arm prospective trial at 103 institutions in Europe:
- 1737 patients received treatment, 1022 underwent SLN before chemo (arms A and B) - 99.1% detection rate
- 226 patients converted cN+ to ycN0 after chemo (Arm C):
  - 80.1% detection rate, 14.2% false-negative rate
  - 24·3% false-negative rate (17 of 70) for one node removed
  - 18·5% false-negative rate (10 of 54) for two nodes removed
- 64 patients who had a second SLN after chemo (arm B):
  - 60.8% detection rate, 51.6% false-negative rate

Kuehn, et al., Lancet Oncol 14:609,2013

	Arm B (n=64)	Arm C (n=226)
Overall false-negative rate (n/N; 95% CI)	51·6% (33/64; 38·7–64·2)	14·2% (32/226; 9·9–19·4)
False-negative rate, according to number of sentinel nodes removed		
1	66·7% (16/24)	24·3% (17/70)
2	53·8% (7/13)	18·5% (10/54)
3	50·0% (5/10)	7·3% (3/41)
4	50·0% (3/6)	0·0% (0/28)
5	18·2% (2/11)	6·1% (2/33)
False-negative rate, according to detection technique		
Radiocolloid alone	46·2% (18/39)	16·0% (23/144)
Radiocolloid and blue dye	60·9% (14/25)	8·6% (6/70)

Data are rate (number of patients), unless otherwise stated.

Table 4: **False-negative rate of sentinel-lymph-node resection in patients with positive nodes, according to selected factors**

Kuehn, et al., Lancet Oncol 14:609,2013

SLN / NEOADJUVANT CHEMO
SENTINA TRIAL (2013)

- Four-arm prospective trial at 103 institutions in Europe:
- Sentinel-lymph-node biopsy is a reliable diagnostic method before neoadjuvant chemotherapy
- After systemic treatment, SLN biopsy has a lower detection rate and higher false negative rate compared with SLN biopsy done before neoadjuvant chemotherapy
- The false negative rate of SLN biopsy decreased with number of SLNs found and was <10% when 3 or more SLNs were removed.

Kuehn, et al., Lancet Oncol 14:609,2013

SLN / NEOADJUVANT CHEMO
Z1071 TRIAL (2013)

- 136 institutions 2009-2011: T0-4, N1-2, neoadjuvant chemo:
  - 756 patients enrolled, 663 had cN1 disease, 649 had preop chemo
  - All patients underwent both SLN biopsy and completion ALND
- RESULTS:
  - SLN not identified in 46 pts (7.1%); 1 SLN excised in 78 pts(12.0%)
  - 525 had 2 or more SLNs: complete pathological response in 41%
  - 39 patients had a false-negative SLN biopsy (FNR 12.6%)
- CONCLUSION: Greater sensitivity necessary to avoid ALND

Boughey, et al., JAMA 310:1455,2013

SLN / NEOADJUVANT CHEMO Z1071 TRIAL (2015)

- 136 institutions 2009-2011: T0-4, N1-2, neoadjuvant chemo:
  - 756 patients enrolled, 663 had cN1 disease, 649 had preop chemo
  - All patients underwent both SLN biopsy and completion ALND
  - 203 patients had clip placed in node at initial biopsy
- RESULTS:
  - In 170 (83.7%) with cN1 disease and ≥2 SLN removed, FNR 6.8%
  - In 34 (24.1%) where clip was in ALND specimen, FNR 19%
  - No clip placed, FNR 13.4%; Clip placement not confirmed, FNR 14.3%

Boughey, et al., Ann Surg 261:547, 2015

BREAST CANCER 2016: Surgical Management of the Axilla

- Axillary recurrences seen in the 1970s have not continued in the era of modern adjuvant therapy.
- Sentinel node biopsy is now the standard of care for axillary staging with clinically node-negative cancers.
- Complete axillary node dissection has remained the standard of care with clinically node-positive cancers, even after a clinical response to neoadjuvant chemotherapy, but new approaches to avoiding complete node dissection are now emerging.

2016
NCCN CONGRESS SERIES™
National Comprehensive Cancer Network

Adjuvant Radiation Therapy in Early Stage Breast Cancer

Kilian E. Salerno, MD
Director of Breast, Soft Tissue/Melanoma Radiation Oncology
Roswell Park Cancer Institute

Adjuvant Radiation Therapy in Early Stage Breast Cancer

- Learning objectives:
  - To describe various adjuvant radiation treatment options in early stage breast cancer
  - To recognize patient and clinical factors that influence adjuvant radiation treatment selection

Adjuvant Radiation Therapy in Early Stage Breast Cancer

- Learning objectives:
  - To describe various adjuvant radiation treatment options in early stage breast cancer
  - Rationale
  - Targets, definitions, doses, modalities, techniques

Rationale

- Role of radiation in the setting of breast conservation and post mastectomy:
  - Improvement in local or locoregional control
  - Survival benefit for invasive carcinomas and in the post mastectomy setting
    - Disease free survival
    - Overall survival
    - Is this still true? For all patients?

EBCTCG Meta-Analysis 2005

- "Effects of RT and Extent of Surgery for Early Breast Cancer on LR and 15 yr Survival"
- 42,000 women, 78 randomized trials
- Can avoid 1 breast cancer death over next 15 yrs for every 4 local recurrences prevented

Clarke et al, Lancet 2005

EBCTCG Meta-Analysis 2011

- "Effects of RT after BCS on 10 yr Recurrence and 15 yr Breast Cancer Death"
- 10,801 women, 17 randomized trials
- RT reduces LR by 1/2 and breast cancer death rate by about 1/6
- Proportional reductions in risk with use of RT
- Actual absolute benefit differs among patients

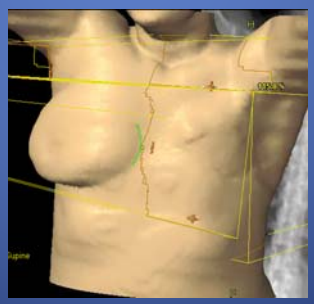
EBCTCG, Lancet 2011

Principles of Radiation Therapy

- Treatment options
  - Targets
  - Definitions
  - Techniques
- Optimizing treatment planning and delivery

Radiation Treatment Options

- TARGETS:
  - Whole breast
  - Partial breast
  - Chest wall
  - Regional nodes
    - SCV
    - ICV
    - Axilla at risk
    - IMNs
  - Boost



Radiation Treatment Options

- DOSE and FRACTIONATION
  - Conventional Fractionation
    - 1.8-2 Gy per fraction to total dose 45-50.4 Gy
  - Hypofractionation
    - Shorter course utilizing larger doses per fraction
    - >2 Gy per fraction to lower total dose
      - 40-42.5 Gy given in daily fxs for whole breast
      - 34-38.5 Gy given twice daily fxs for partial breast
  - Accelerated course
    - Treatment over shorter time course

Radiation Treatment Options

- MODALITIES:
  - External Beam
    - Photons
    - Electrons
    - Protons?
  - Brachytherapy
    - Radioactive source
    - Device
  - Intraoperative
    - Various means

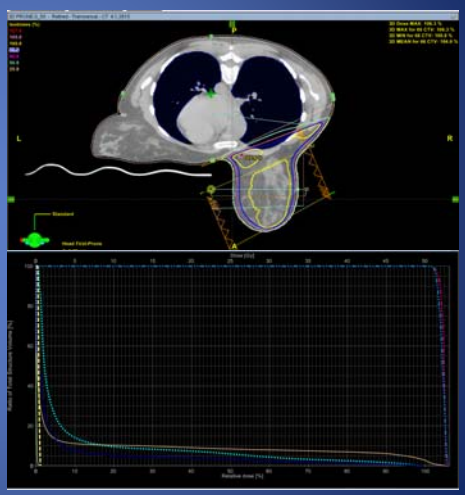
Radiation Treatment Options

- TECHNIQUES:
  - Positioning
    - Supine vs Prone
  - CT simulation and volume based planning
  - 3D conformal vs IMRT
  - Respiratory control with deep inspiration breath hold technique
    "respiratory gating"

Use of Prone Positioning

Use of prone positioning

- Use in select patients with early stage disease
- Breast is target
- Minimize normal tissue doses and treatment toxicity

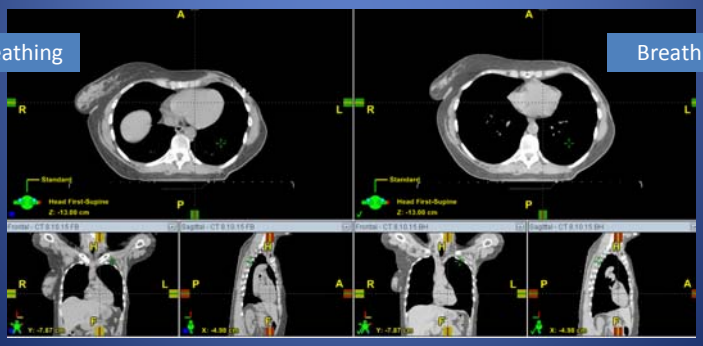


Use of “Respiratory Gating”

Breath hold technique

- Moderate deep inspiration
- Extra time, equipment, personnel, increased planning efforts and time for treatment

Free Breathing



Breath Hold

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Invasive Breast Cancer

PRINCIPLES OF RADIATION THERAPY

Optimizing Delivery of Individual Therapy:
It is important to individualize radiation therapy planning and delivery. CT-based treatment planning is encouraged to delineate target volumes and adjacent organs at risk. Greater target dose homogeneity and sparing of normal tissues can be accomplished using compensators such as wedges, forward planning using segments, and intensity-modulated radiation therapy (IMRT). Respiratory control techniques including deep inspiration breath-hold and prone positioning may be used to try to further reduce dose to adjacent normal tissues, in particular heart and lung. Boost treatment in the setting of breast conservation can be delivered using enface electrons, photons, or brachytherapy. Chest wall scar boost when indicated is typically treated with electrons or photons. Verification of daily setup consistency is done with weekly imaging. In certain circumstances, more frequent imaging may be appropriate. Routine use of daily imaging is not recommended.

BINV-I

Radiation Treatment Options

- In summary:
  - Many radiation treatment options
  - Consider what was involved and what is at risk for microscopic disease
  - Individual risk stratification and treatment selection

Adjuvant Radiation Therapy in Early Stage Breast Cancer

- Learning objectives:
  - To describe various adjuvant radiation treatment options in early stage breast cancer
  - To recognize patient and clinical factors that influence adjuvant radiation treatment selection

Radiation Treatment Options

- How is treatment tailored to the individual patient?
  - Patient factors
  - Treatment factors
  - Disease burden
  - Biology
  - Risks for disease morbidity vs treatment morbidity

Factors that Influence Radiation Treatment Selection

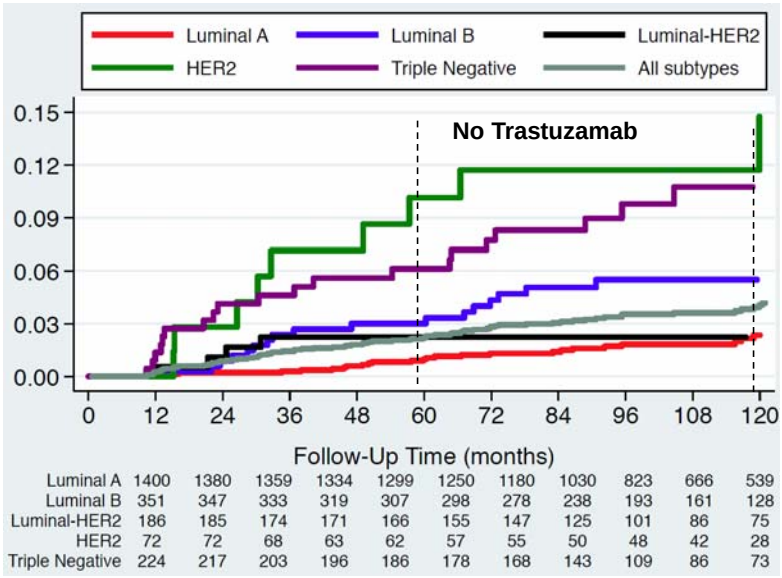
- Patient factors: age, comorbidities
- Treatment factors: type and extent of surgery, type of systemic therapy, response to neoadjuvant therapy
- Disease burden: T stage / size, N stage / # ratio / size, ECE, LVSI, EIC, margins
- Biology: grade, ER, PR, Her2, gene profile, recurrence score

Risk Factors for LR

- Effect of biologic subtype, age, nodal involvement on risk for local recurrence
- DFCI/MGH series of >2200 pts treated with BCT from 1996-2007
- Low LR of 2% at 5 yrs
- Following slides courtesy of Jay Harris

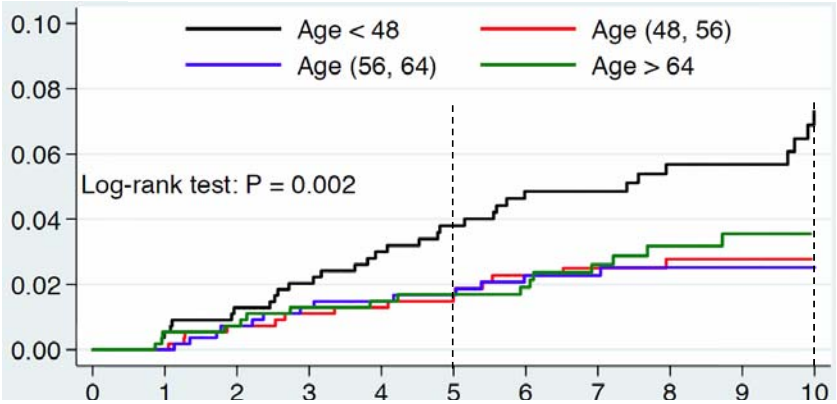
Nguyen et al, JCO 2008
Arvold et al, JCO 2011

K-M estimate of local recurrence by subtype



Slide courtesy of Jay Harris
SABCS 2015 Presentation

K-M estimate of local recurrence by age



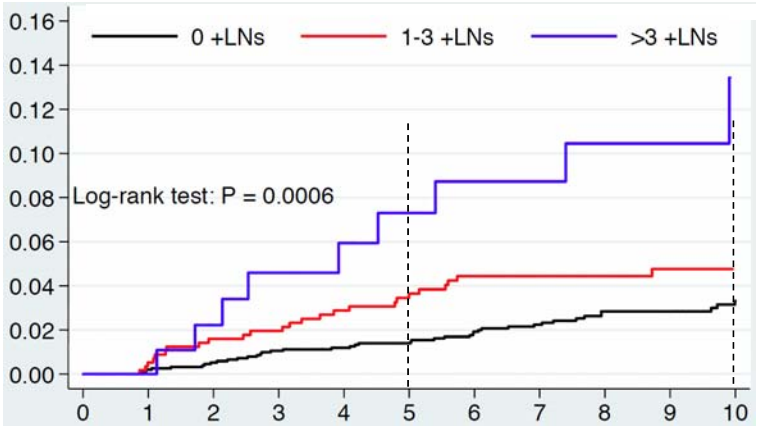
Time to local recurrence (years)

At risk

Age < 48	560	548	529	516	495	468	444	391	318	269	219
Age (48, 56)	557	550	541	528	513	500	472	413	342	274	225
Age (56, 64)	558	555	536	525	516	499	474	399	310	251	209
Age > 64	558	548	531	514	496	471	438	383	304	247	190

Slide courtesy of Jay Harris
SABCS 2015 Presentation

K-M estimate of local recurrence by nodal status



Time to local recurrence (years)

At risk

0 +LNs	1563	1545	1506	1469	1431	1374	1288	1106	883	720	585
1-3 +LNs	576	564	547	536	519	498	477	423	345	283	230
>3 +LNs	94	92	84	78	70	66	63	57	46	38	28

Slide courtesy of Jay Harris
SABCS 2015 Presentation

Multivariate Cox regression of Local Recurrence

Prognostic factor	HR	95% CI
Age: 23-46	1.00	
47-54 and 55-63	~0.50	NS
64-87	0.19	0.07 - 0.57
Subtype: Luminal A	1.00	
Luminal B and Luminal-HER2	~2	NS
HER2 (No trastuzumab)	4.27	1.04 – 17.48
TNBC	4.15	1.19 – 14.38
Node-positive vs N0 (p=0.008)	2.46	1.27 – 4.75
Tumor >2cm vs ≤2cm (p=0.03)	2.03	1.07 – 3.88
Adjuvant chemo (p=0.02)	0.44	0.22 – 0.89

Slide courtesy of Jay Harris
SABCS 2015 Presentation

Radiation Treatment Options

- How is treatment tailored to the individual patient?
  - Individual risk stratification and treatment selection

Clinical Case

71 yo lady with 1.8 cm right breast mass on screening mammogram. Bx proven invasive ca of NST, grade 2, ER/PR positive, Her2 negative.

cT1cN0M0. Opts for breast conservation.

pT1cN0 (0/2 slns), negative margins, no LVI, no EIC.

Low recurrence score. Plans for endocrine therapy.

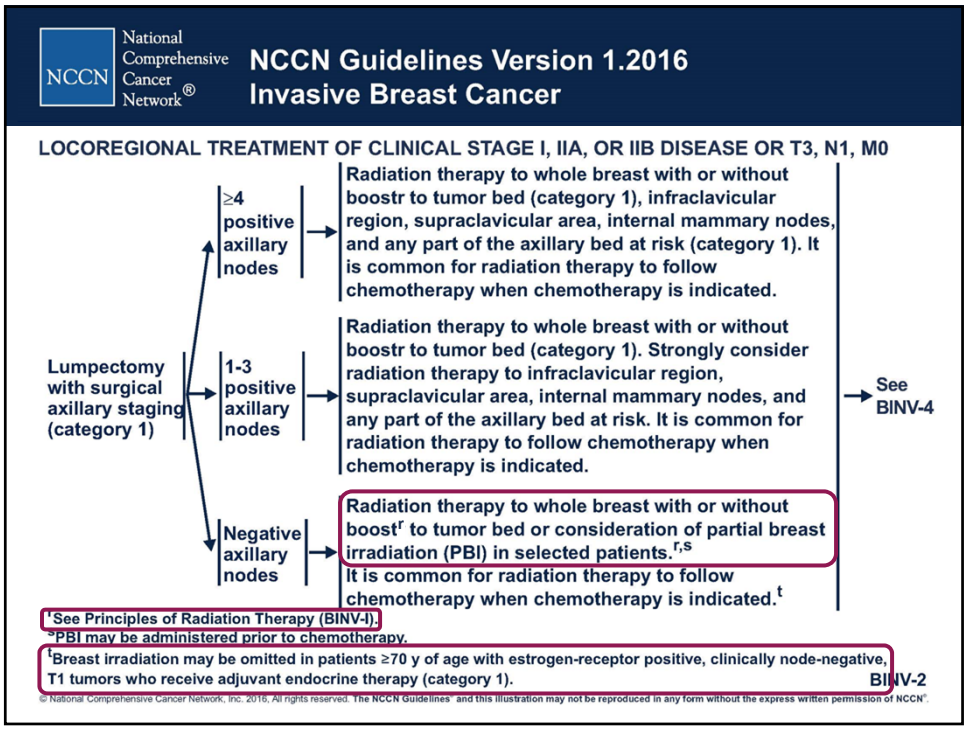
Sees you for breast RT recommendations…

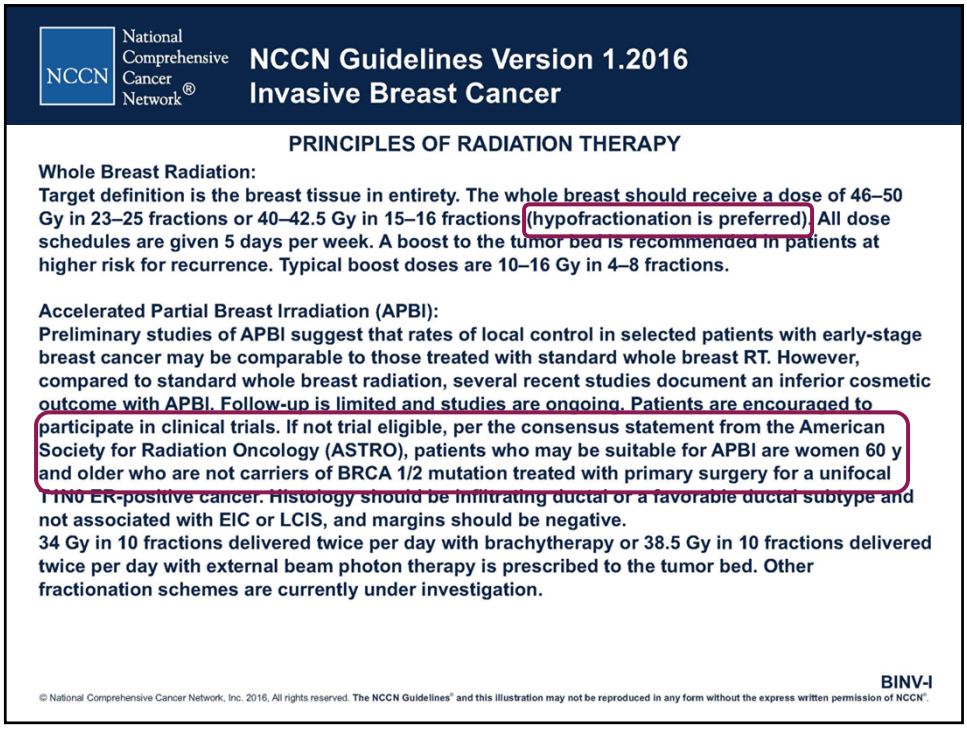
Clinical Case

1. Mastectomy
2. Conv fx whole breast radiation ± boost
3. Hypo fx whole breast radiation ± boost
4. Accelerated partial breast irradiation (APBI)
5. No radiation
6. Clinical trial

Treatment Options

- Mastectomy
  - Unlikely any indication for PMRT
  - If contraindication to RT
- Whole breast ± boost
  - Conv fx (5-6 wks)
  - Hypo fx (3-4 wks)
- APBI
  - Intraop, Brachy, EBRT (1-10 fxs)
- No radiation (omission of RT)





NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Invasive Breast Cancer

PRINCIPLES OF RADIATION THERAPY

Whole Breast Radiation:
Target definition is the breast tissue in entirety. The whole breast should receive a dose of 46–50 Gy in 23–25 fractions or 40–42.5 Gy in 15–16 fractions (hypofractionation is preferred). All dose schedules are given 5 days per week. A boost to the tumor bed is recommended in patients at higher risk for recurrence. Typical boost doses are 10–16 Gy in 4–8 fractions.

Accelerated Partial Breast Irradiation (APBI):
Preliminary studies of APBI suggest that rates of local control in selected patients with early-stage breast cancer may be comparable to those treated with standard whole breast RT. However, compared to standard whole breast radiation, several recent studies document an inferior cosmetic outcome with APBI. Follow-up is limited and studies are ongoing. Patients are encouraged to participate in clinical trials. If not trial eligible, per the consensus statement from the American Society for Radiation Oncology (ASTRO), patients who may be suitable for APBI are women 60 y and older who are not carriers of BRCA 1/2 mutation treated with primary surgery for a unifocal T1N0 ER-positive cancer. Histology should be infiltrating ductal or a favorable ductal subtype and not associated with EIC or LCIS, and margins should be negative.
34 Gy in 10 fractions delivered twice per day with brachytherapy or 38.5 Gy in 10 fractions delivered twice per day with external beam photon therapy is prescribed to the tumor bed. Other fractionation schemes are currently under investigation.

BINV-I

Hypofractionation

- *Whole breast radiation: why is hypofractionation now preferred in the guidelines?*
  - Long term results from Ontario and UK trials

    Canadian 42.5 Gy in 16 fractions, no boost
    START B 40 Gy in 15 fractions, ± boost

- At least equivalent or better disease outcomes
- At least equivalent or better cosmesis
- At least equivalent or better side effects

Whelan et al, NEJM 2010
Haviland et al, Lancet Oncol 2013

Hypofractionation

- Who can be treated with hypofractionated whole breast irradiation?
- ASTRO Guidelines 2011
  (following Ontario publication but prior to UK)

Table 1. Evidence supports the equivalence of hypofractionated whole breast irradiation with conventionally fractionated whole breast irradiation for patients who satisfy all of these criteria*

1. Patient is 50 years or older at diagnosis.
2. Pathologic stage is T1–2 N0 and patient has been treated with breast- conserving surgery.
3. Patient has not been treated with systemic chemotherapy.
4. Within the breast along the central axis, the minimum dose is no less than 93% and maximum dose is no greater than 107% of the prescription dose (±7%;) (as calculated with 2-dimensional treatment planning without heterogeneity corrections).

* For patients who do not satisfy all of these criteria, the task force could not reach consensus and therefore chose not to render a recommendation either for or against hypofractionated whole breast irradiation in this setting. Please see the text for a thorough discussion of tumor grade. Patients receiving any type of whole breast irradiation should generally be suitable for breast-conserving therapy with regards to standard selection rules (*e.g.*, not pregnant, no evidence of multicentric disease, no prior radiotherapy to the breast, no history of certain collagen-vascular diseases).

  - I treat more broadly than this since UK results
- ASTRO to update guidelines in 2017
- Not used routinely for nodal irradiation at this time

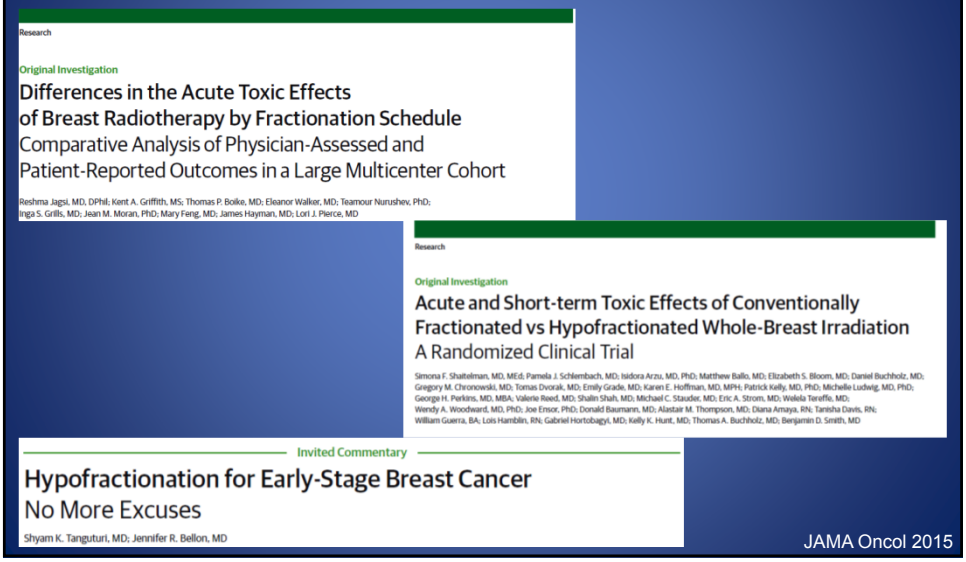
Smith et al, IJROBP 2011

ASTRO *Choosing Wisely*®

- One of the 2013 recommendations:
  - Don't initiate whole breast radiotherapy as a part of breast conservation therapy in women age >50 with early stage invasive breast cancer without considering shorter treatment schedules.

Choosing Wisely®
An initiative of the ABIM Foundation

Recent Publications: Hypofractionation



Research

Original Investigation

Differences in the Acute Toxic Effects of Breast Radiotherapy by Fractionation Schedule
Comparative Analysis of Physician-Assessed and Patient-Reported Outcomes in a Large Multicenter Cohort

Reshma Jagsi, MD, DPhil; Kent A. Griffith, MS; Thomas P. Boike, MD; Eleanor Walker, MD; Teamour Nurushev, PhD; Inga S. Grills, MD; Jean M. Moran, PhD; Mary Feng, MD; James Hayman, MD; Lori J. Pierce, MD

Research

Original Investigation

Acute and Short-term Toxic Effects of Conventionally Fractionated vs Hypofractionated Whole-Breast Irradiation
A Randomized Clinical Trial

Simona F. Shaitelman, MD, MEd; Pamela J. Schlembach, MD; Isidora Arzu, MD, PhD; Matthew Ballo, MD; Elizabeth S. Bloom, MD; Daniel Buchholz, MD; Gregory M. Chronowski, MD; Tomas Dvorak, MD; Emily Grade, MD; Karen E. Hoffman, MD, MPH; Patrick Kelly, MD, PhD; Michelle Ludwig, MD, PhD; George H. Perkins, MD, MBA; Valerie Reed, MD; Shalin Shah, MD; Michael C. Stauder, MD; Eric A. Strom, MD; Welela Tereffe, MD; Wendy A. Woodward, MD, PhD; Joe Ensor, PhD; Donald Baumann, MD; Alastair M. Thompson, MD; Diana Amaya, RN; Tanisha Davis, RN; William Guerra, BA; Lois Hamblin, RN; Gabriel Hortobagyi, MD; Kelly K. Hunt, MD; Thomas A. Buchholz, MD; Benjamin D. Smith, MD

Invited Commentary

Hypofractionation for Early-Stage Breast Cancer
No More Excuses

Shyam K. Tanguturi, MD; Jennifer R. Bellon, MD

JAMA Oncol 2015

Accelerated Partial Breast Irradiation (APBI)

- Different methods for delivery
  - IORT
  - Interstitial
  - Intracavitary
  - EBRT
- Different guidelines/consensus statements
  - ASTRO, ASBS, ABS, ESTRO
  - Inclusion/exclusion criteria for NSABP B39/ RTOG 0413
- ASTRO defines suitable, cautionary, unsuitable groups
- NCCN guidelines based on ASTRO suitable group

Smith et al, IJROBP 2009

ASTRO APBI Consensus Statement

Table 2. Patients "suitable" for APBI if all criteria are present

Factor	Criterion
Patient factors	
Age	≥60 y
BRCA1/2 mutation	Not present
Pathologic factors	
Tumor size	≤2 cm*
T stage	T1
Margins	Negative by at least 2 mm
Grade	Any
LVSI	No†
ER status	Positive
Multicentricity	Unicentric only
Multifocality	Clinically unifocal with total size ≤2.0 cm‡
Histology	Invasive ductal or other favorable subtypes§
Pure DCIS	Not allowed
EIC	Not allowed
Associated LCIS	Allowed
Nodal factors	
N stage	pN0 (i^-, i^+)
Nodal surgery	SN Bx or ALND‖
Treatment factors	
Neoadjuvant therapy	Not allowed

Currently being updated

New draft was open for public comment through March 2016

Smith et al, IJROBP 2009

Omission of Radiation

- In selected women with lower risk for recurrence
- No survival detriment
- CALGB 9343
  - 70 yrs or older, small cancers, negative nodes, negative margins, ER/PR positive
  - BCS → Tamoxifen ± RT
  - LRR 10% (no RT) vs 2 % (RT) at median 12.6 yrs
- PRIME II, Fyles et al, NSABP B-21

Hughes et al, JCO 2013; Kunkler et al, Lancet Oncol 2015; Fyles et al, NEJM 2004; Fisher et al JCO 2002

Omission of Radiation: Practice Patterns

- Among NCCN institutions
  - Wide variability by site (range <10% to 50%)
  - Increased adoption with change in guidelines
  - Multivariable analysis for RT omission
    - Dx after 2004, older age, comorbidities, smaller tumors, no axillary surgery, treating institution
    - 70-74 yrs of age
      - Receipt of RT in 2000 94% vs 88% in 2009
    - >80 yrs of age
      - Receipt of RT in 2000 80% vs 41% in 2009

McCormick et al, J Am Coll Surg 2014

Adjuvant Radiation Options Following BCS: Summary

- Hypofractionated Whole Breast Irradiation
  - ***PREFERRED***
- Accelerated Partial Breast Irradiation (APBI)
  - ***ASTRO suitable criteria***
- Omission of RT
  - ***YES in select patients***

Clinical Case redux

Now our patient has BCS with SLN Bx and 1/3 SLNs are positive.

Sees you for next treatment recommendations…

Clinical Case Redux

1. Axillary dissection
2. Whole breast radiation ± boost
3. High tangents radiation ± boost
4. Whole breast + regional nodal irradiation
5. Accelerated partial breast irradiation (APBI)
6. Clinical trial

Clinical Case Redux2

Or she opts for mastectomy with SLN Bx and 1/3 SLNs are positive…

Axillary dissection?

PMRT?

Systemic therapy options?

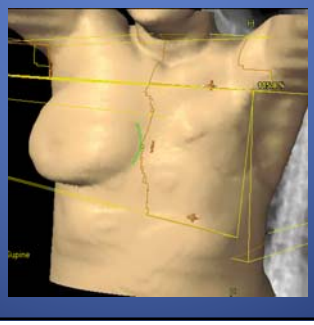
Which patients need regional nodal irradiation (or not)?

- What influence of surgical resection and axillary surgical staging?
- What about in setting of neoadjuvant chemotherapy?
- What extent of RNI?

Which patients need regional nodal irradiation (or not)?

TARGETS:

- Whole breast
  - Standard Tangents
  - High Tangents
- Chest wall
- ±
- Regional nodes
  - SCV
  - ICV
  - Axilla at risk
  - IMNs



Which patients need regional nodal irradiation (or not)?

- In setting of BCT?
  - ACOSOG Z11: cT1-2N0, 1-2 +SLNs, tangents
  - IBCSG 23-01: N1mic
  - MA 20: higher risk patients
  - EORTC 22922: higher risk patients

Giuliano et al, JAMA 2011; Galimberti et al, Lancet Oncol 2013; Whelan et al, NEJM 2015; Poortmans et al, NEJM 2015;

Which patients need regional nodal irradiation (or not)?

- In post mastectomy setting?
  - B-04, Danish 82b and 82c, British Columbia
  - ECOG and NSABP pooled analyses
  - Patients on more recent trials?
    - Few on IBCSG and some on EORTC
    - SUPREMO
  - EBCTCG: benefit to RT

Fisher et al, NEJM 2002; Overgaard et al, Radiother Oncol. 2007; Ragaz et al, JNCI 2005; Recht et al, JCO 1999; Taghian et al, JCO 2004; EBCTCG, Lancet, 2014

Which patients need regional nodal irradiation (or not)?

- AxLND vs Axillary RT?
  - AMAROS
- In setting of neoadjuvant chemo?
  - Currently based on maximal disease stage
  - SENTINA: axillary staging options
  - Current open trials
    - NSABP B51 / RTOG 1304
    - Alliance A011202

Donker et al, Lancet Oncol 2014

ACOSOG Z11

- RCT of AxLND vs observation for women with 1-2 positive SLNs
- 891 pts, cT1-2N0
- ~ 40% of +SLNs were micromets
- On AxLND, 27.4% of patients had additional +LNs
- Whole breast RT via tangents, no nodal
  - QARC analysis showed variation with 3rd field, high tangents use
- Median 6.3 yrs, no difference and low rates of LR / LRR (<5%), less lymphedema with SLN alone

Giuliano et al, JAMA 2011

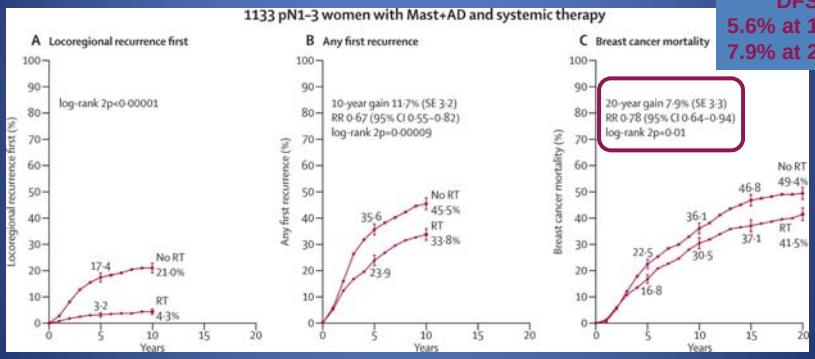
Jagsi et al, JCO 2014

EBCTCG Meta-Analysis 2014

- "Effects of RT after Mastectomy and Axillary Surgery on 10 yr Recurrence and 20 yr Breast Cancer Mortality"
- 8,135 women, 22 randomized trials
- In women with 1-3 N+ and ≥4 N+
  - RT reduced LRR, OR, and breast cancer mortality
- Are the risks for recurrence the same now?
- Does this mean everyone should be treated?

EBCTCG, Lancet 2014

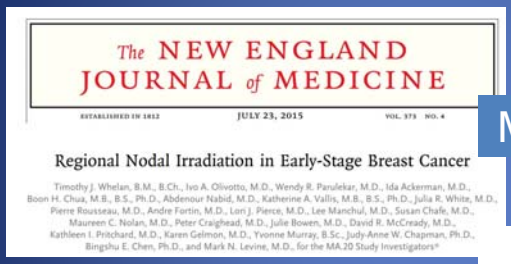
EBCTCG Meta-Analysis 2014



DFS
5.6% at 10 yrs
7.9% at 20 yrs

EBCTCG, Lancet 2014

Recent Publications: Regional Nodal Irradiation

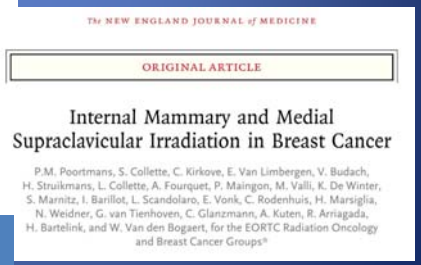

The NEW ENGLAND JOURNAL of MEDICINE

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., Boon H. Chua, M.B., B.S., Ph.D., Abdenour Nabid, M.D., Katherine A. Vallis, M.B., B.S., Ph.D., Julia R. White, M.D., Pierre Rousseau, M.D., Andre Fortin, M.D., Lori J. Pierce, M.D., Lee Manchul, M.D., Susan Chafe, M.D., Maureen C. Nolan, M.D., Peter Craighead, M.D., Julie Bowen, M.D., David R. McCready, M.D., Kathleen I. Pritchard, M.D., Karen Gelmon, M.D., Yvonne Murray, B.Sc., Judy-Anne W. Chapman, Ph.D., Bingshu E. Chen, Ph.D., and Mark N. Levine, M.D., for the MA.20 Study Investigators*

MA.20


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*

EORTC 22922

Whelan et al, NEJM 2015

Poortmans et al, NEJM 2015

Regional Nodal Irradiation

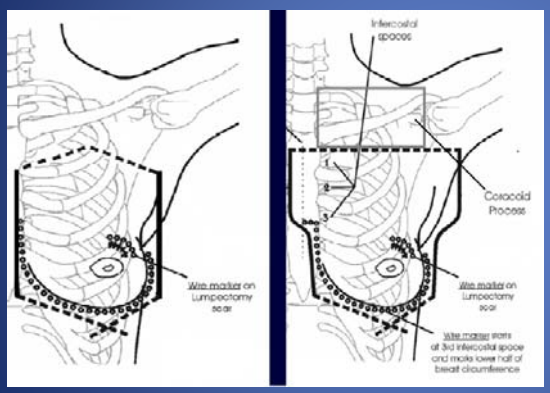
- MA.20:
  - 1832 pN+ (85% N1) or high risk N- pts (10%)
  - BCS and ALND, adjuvant systemic tx
  - WBI ± RNI
    - RNI = IMNs, SCV, ICV, ± Ax
- EORTC 22922:
  - 4000 pN+ (44% N1) or high risk N- pts (43%)
  - BCS (76%) or M and ALND, adjuvant systemic tx
  - WBI or CW ± RNI
    - RNI = IMNs, SCV, ICV, ± Ax

* definitions of high risk N- differed as types did use of chemotherapy/endocrine therapy

Whelan et al, NEJM 2015

Poortmans et al, NEJM 2015

MA.20 Radiation



- WBI
  - 50/25
  - +/- 10 Gy boost
- WBI + RNI (45/25)
  - IMNs
  - SCV/Level III

Whelan et al, NEJM 2015

Regional Nodal Irradiation

- Results from MA 20 and EORTC 22922:
  - 10 yr median follow up
  - Primary endpoint was OS
  - RNI improved locoregional DFS, distant DFS, and death from breast cancer, but did not improve OS

Whelan et al, NEJM 2015

Poortmans et al, NEJM 2015

MA.20 Results

OS
82.8% vs 81.8%
p=0.38

ER-
81.3% vs 73.9%
p=0.05

DFS
5% at 10 yrs
82% vs 77%
p=0.01

Isolated LR DFS
95.2% vs 92.2%
p=0.009

Distant DFS
86.3% vs 82.1%
p=0.03

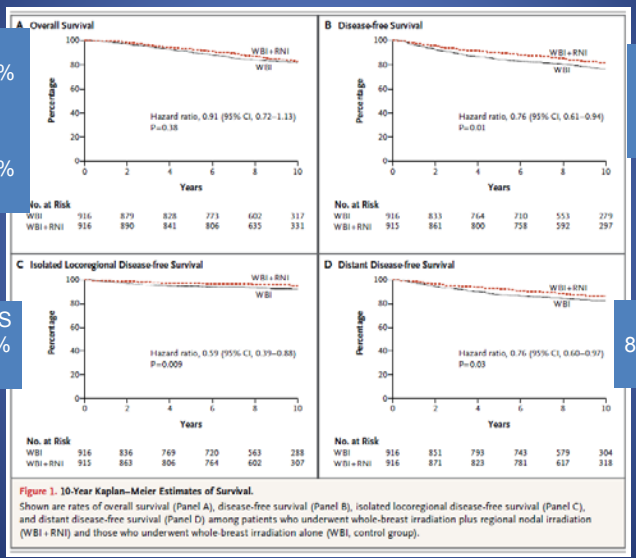


Figure 1. 10-Year Kaplan–Meier Estimates of Survival.
Shown are rates of overall survival (Panel A), disease-free survival (Panel B), isolated locoregional disease-free survival (Panel C), and distant disease-free survival (Panel D) among patients who underwent whole-breast irradiation plus regional nodal irradiation (WBI + RNI) and those who underwent whole-breast irradiation alone (WBI, control group).

Whelan et al, NEJM 2015

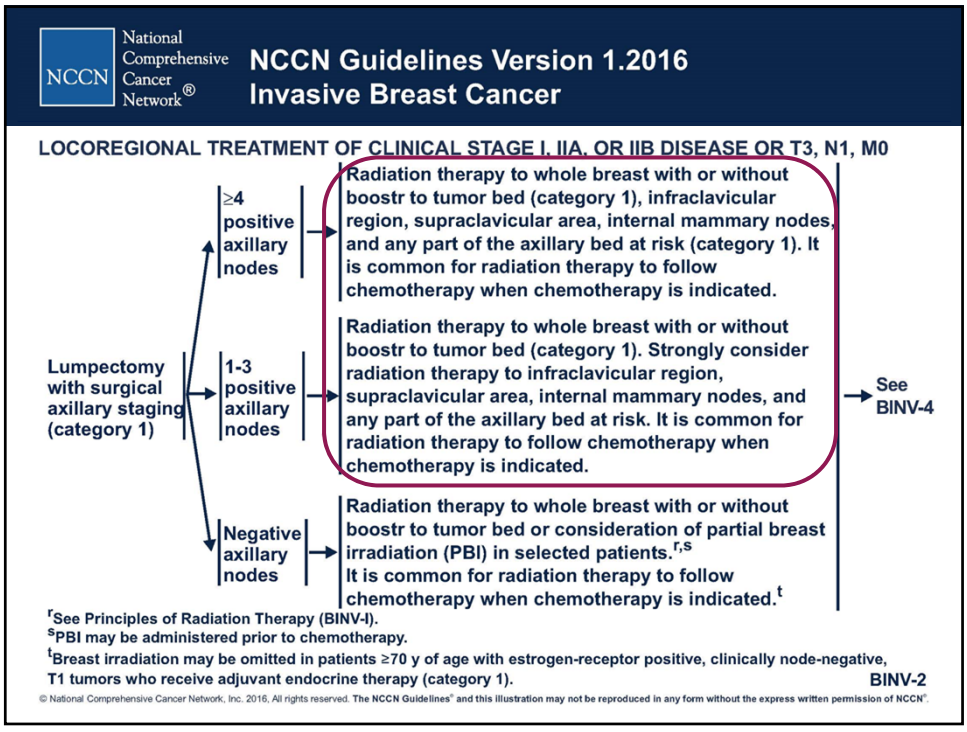
How do we interpret and reconcile the differences between these studies in determining the role for regional nodal irradiation?

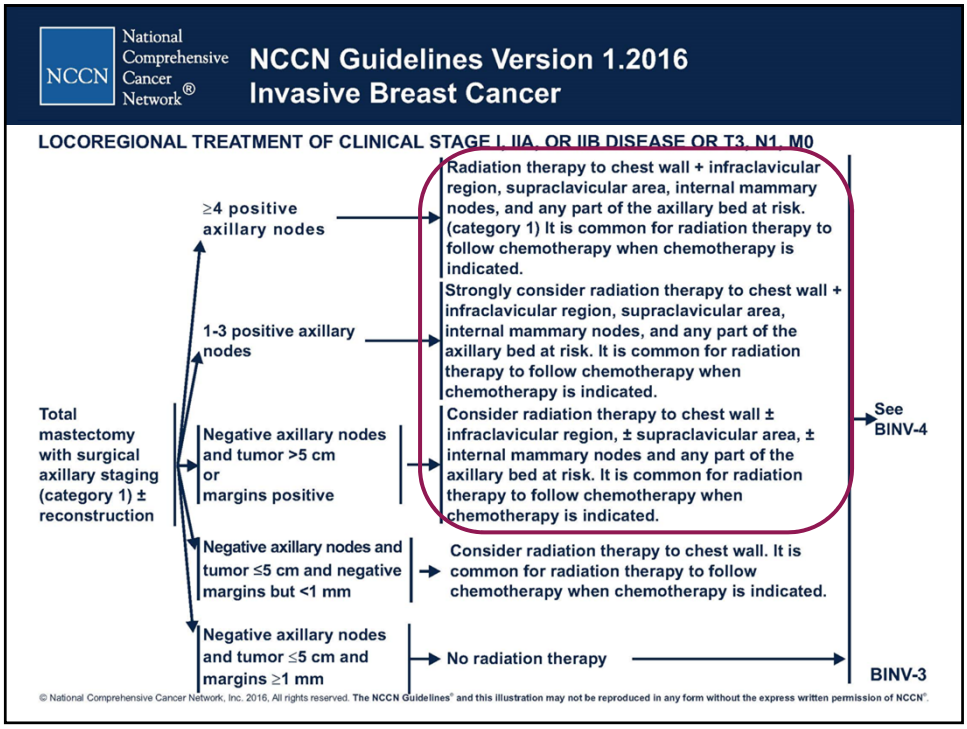
Which patients need regional nodal irradiation (or not)?

- Consider whether a given study is applicable and whether an individual patient met the study eligibility.
- Assess individual risk for recurrence.
- Nomograms may be helpful.
  - MDACC and MSKCC
  - Prediction of additional positive non SLNs
  - T stage, histology, grade, # positive LNs, # LNs, size of LN met, ECE, LVSI, multifocality, ER status

Which patients need regional nodal irradiation (or not)?

Questions and answers regarding the extent of lymph node surgery (SLN Bx vs Ax LND) are not the same as question and answers regarding the need for, type of, and extent of regional nodal radiation.





Regional Nodal Irradiation

- Which nodal volumes treated?
  - SCV
  - ICV
  - Axillary bed at risk
  - IMNs
- Attention to normal tissue dose constraints
  - In particular heart and lung

Areas of Ongoing Study

- Concominant boost with hypofractionation
  - RTOG 1005
- cN+ disease receiving neoadjuvant chemotherapy
  - Extent of axillary surgery and/or radiation
  - SLN bx negative→ NSABP B51
  - SLN bx positive → Alliance A011202
- Hypofractionation for nodal RT / PMRT
- Use of biologic parameters to guide local therapy options

Adjuvant Radiation Therapy in Early Stage Breast Cancer

- Learning objectives:
  - To describe various adjuvant radiation treatment options in early stage breast cancer
    - Many radiation treatment options
    - Optimize individual treatment

Adjuvant Radiation Therapy in Early Stage Breast Cancer

- Learning objectives:
  - To recognize patient and clinical factors that influence adjuvant radiation treatment selection
    - Multiple variables and factors
      - Patient factors
      - Treatment factors
      - Disease burden
      - Biology
    - Not one single method to assess risk
    - Increasingly biology will be used to tailor therapies

Adjuvant Radiation Therapy in Early Stage Breast Cancer

- Future Directions
  - To be better able to assess risk and treat accordingly
  - Define greater role for hypofractionation
  - Define more groups for omission of RT
  - Define in whom to treat or not treat with RNI
  - Define radiation treatment selection following neoadjuvant therapy