Radiation Therapy after Neoadjuvant Chemotherapy for Breast Cancer

Outline

- Case presentation
- Why neoadjuvant chemo in breast cancer?
- Diagnosis and work-up
- Surgical management of breast and axilla
- Impact of subtype (ER/PR/HER2)
- RT indications
- Case discussion

Case

- 53 yo F presented in March 2013 when she palpated a “golfball-sized lump” in her right upper outer breast.
- Diagnostic mammogram and US on 3/21/13 demonstrated a 3.8 cm oval lesion with a microlobulated margin at the 10:00 position in the R UOQ. US-guided core needle biopsy revealed infiltrating ductal carcinoma, grade 3, ER/PR/Her-2 negative with no LVI.
- Patient was referred to surgeon Dr. Parsons on 4/3/13 for consultation.
- Staging work-up with MRI brain (4/13/13) for visual changes, MRI cervical spine (4/13/13) for neck pain, and PET (4/15/2013) confirmed only a hypermetabolic 2.7 x 2.5 cm right breast mass without evidence of nodal or metastatic disease.
- SLNB done on 4/17/2013, however, revealed 1/3 nodes positive for micrometastatic disease.
- Patient referred to med onc and underwent neoadjuvant chemo with adriamycin/cytoxan (4 cycles) followed by taxotere (completed 10/3/13).
- She is currently scheduled to undergo bilateral mastectomies with axillary lymph node dissection and tissue expander placement on 11/4/2013.
- She is here for discussion of potential PMRT.

Rationale for Neoadjuvant Chemotherapy

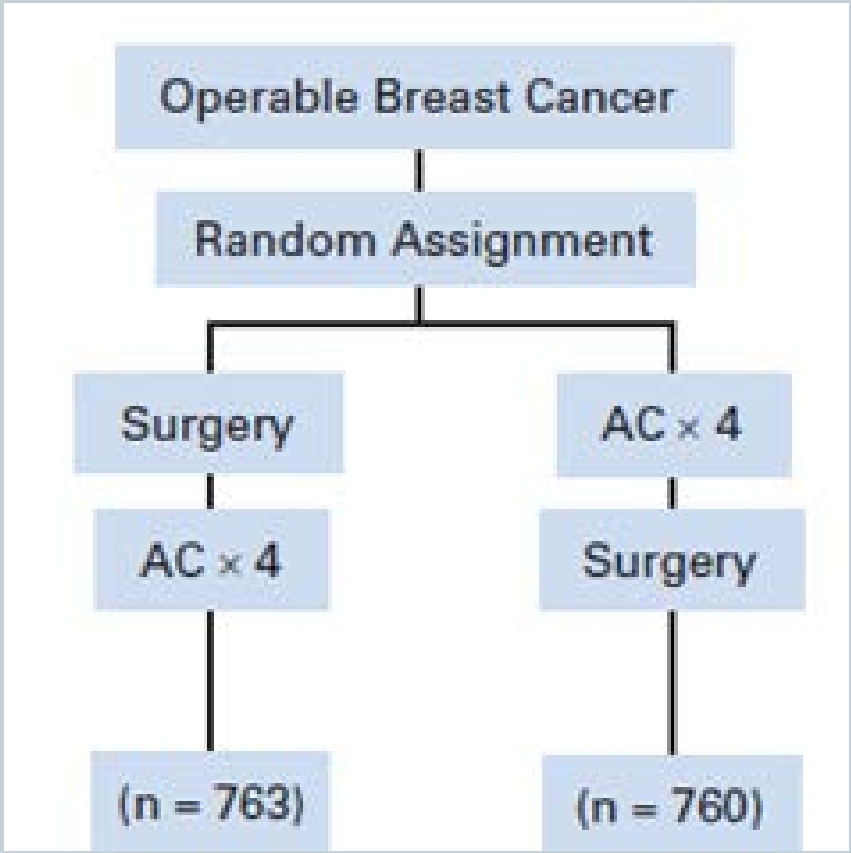
- Reduces tumor volume → facilitate BCS
- Early systemic therapy (avoid post-op delay)
- In vivo assessment of systemic therapy effectiveness
- Improved tumor vascularity before surgery may allow for improved bioavailability..?

Randomized Trials - NSABP

- B-18 = Does AC administered pre-op improve DFS or OS (vs. post-op AC)?
- B-27 = Does adding Taxol pre-op to AC improve DFS or OS (vs. pre-op AC alone)?

NSABP B-18

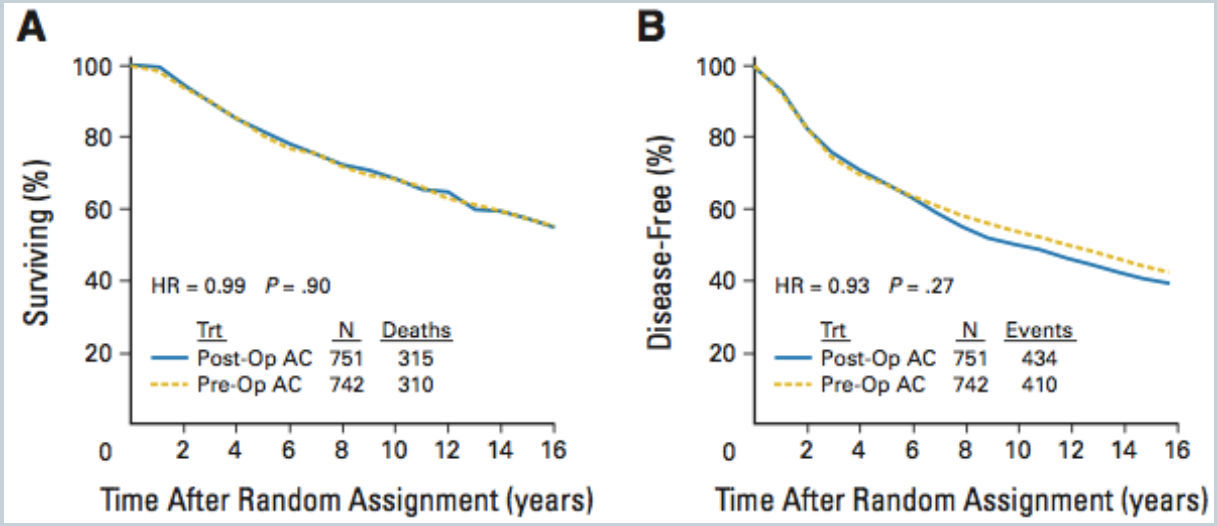
- 1988-1993
- 1523 patients with T1-3N0-1 "operable, palpable, non-fixed"
- Surgery = lumpectomy + ALND or mastectomy
  - Had to disclose surgery choice before chemo
- AC = q 3wk
- All BCS got breast RT
- No PMRT allowed
- Tamoxifen for all ≥50yo, and none <50 (no ER status)

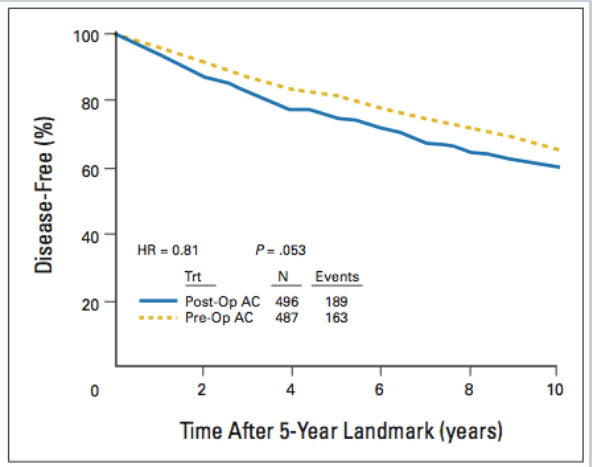


Fisher B, JCO 1997; Wolmark N JNCI 2001; Rastogi P, JCO 2008

NSABP B-18

- pCR rate 13%
- 16-yr DFS 42% vs. 39% (NS)
  - DFS "conditional on being event free for 5 yrs" trend favored NEO (p=0.053)
- 16-yr OS both 55%





Rastogi P JCO 2008

Breast Conservation in B-18

- NEO had a greater frequency of lumpectomy
  - 67% vs 60%
  - "12% improvement"
- Largest benefit seen for **tumors >5 cm**
  - 22% vs. 8%
  - "175% improvement"

Table 7. Comparison Between Postoperative and Preoperative Therapy Groups Relative to Frequency of Lumpectomy Proposed and Performed According to Nodal Status and Tumor Size

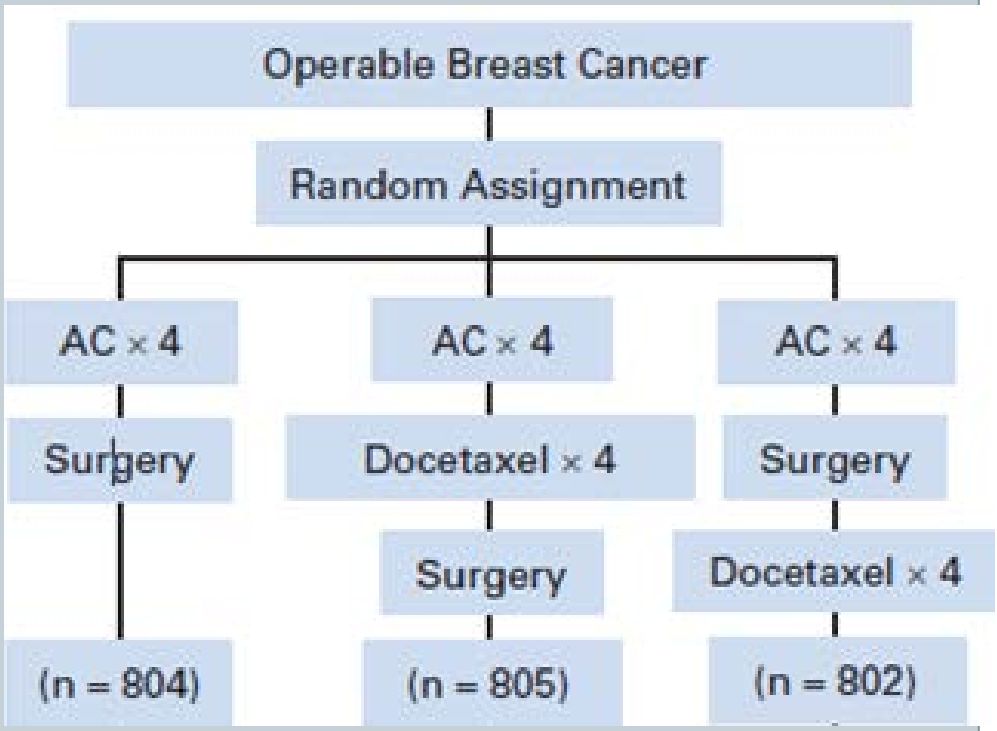
Clinical Nodal Status and Tumor Size (cm)*	Lumpectomy Proposed* (%)		Lumpectomy Performed (%)	
	Postop	Preop	Postop	Preop
All patients	66	65	60	67
≤ 2.0	83	89	79	81
2.1-5.0	71	68	63	71
≥ 5.1	3	3	8	22
Negative	70	71	64	70
≤ 2.0	85	90	80	83
2.1-5.0	73	73	65	73
≥ 5.1	4	4	8	14
Positive	53	49	48	59
≤ 2.0	74	82	76	68
2.1-5.0	67	57	56	66
≥ 5.1	2	2	9	33

*At time of patient entry and before randomization.

Fisher B et al. JCO 1997

NSABP B-27

- 1995-2000
- 2353 women, only palpable disease allowed (breast or axilla); T1-3N0-1
  - Except <2cm with N0
- 3-arms →
- Surgery = lumpectomy + ALDN or mastectomy
  - ~50% underwent mastectomy
- PMRT again not permitted.
- All pts (regardless of age) received tamoxifen x 5 yrs regardless of ER/PR status.

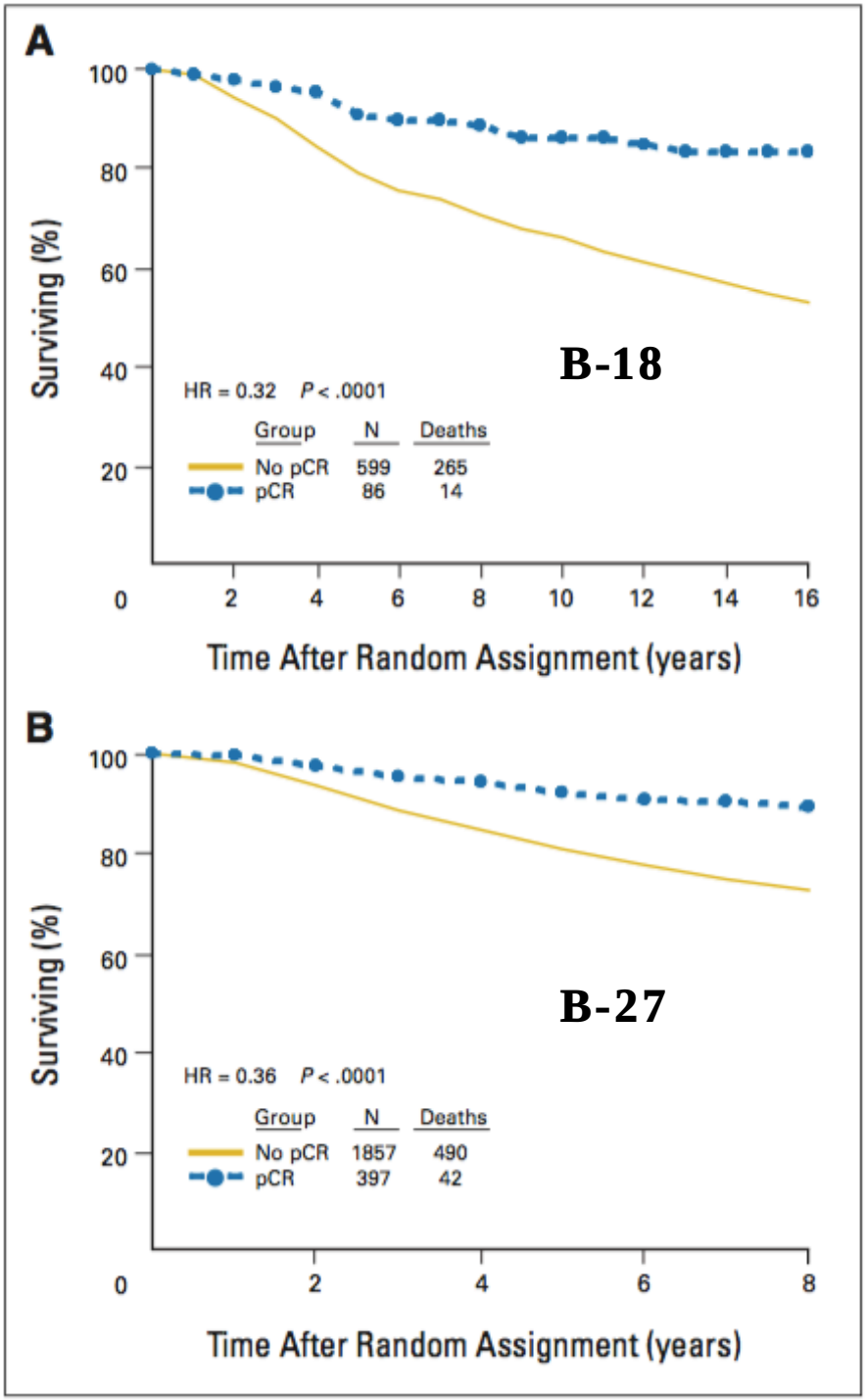


Rastogi P, JCO 2008; Bear HD, JCO 2003, 2006

NSABP B-27

- pCR rate AC* 13% vs. ACT 26% (SS)
  - *AC→S and AC→S→T
  - Having pCR significant predictor for DFS and OS
- DFS 5-year 68-71% (NS); 8-year 59-62% (NS)
- OS 5-year 82-83% (NS); 8-year 74-75% (NS)

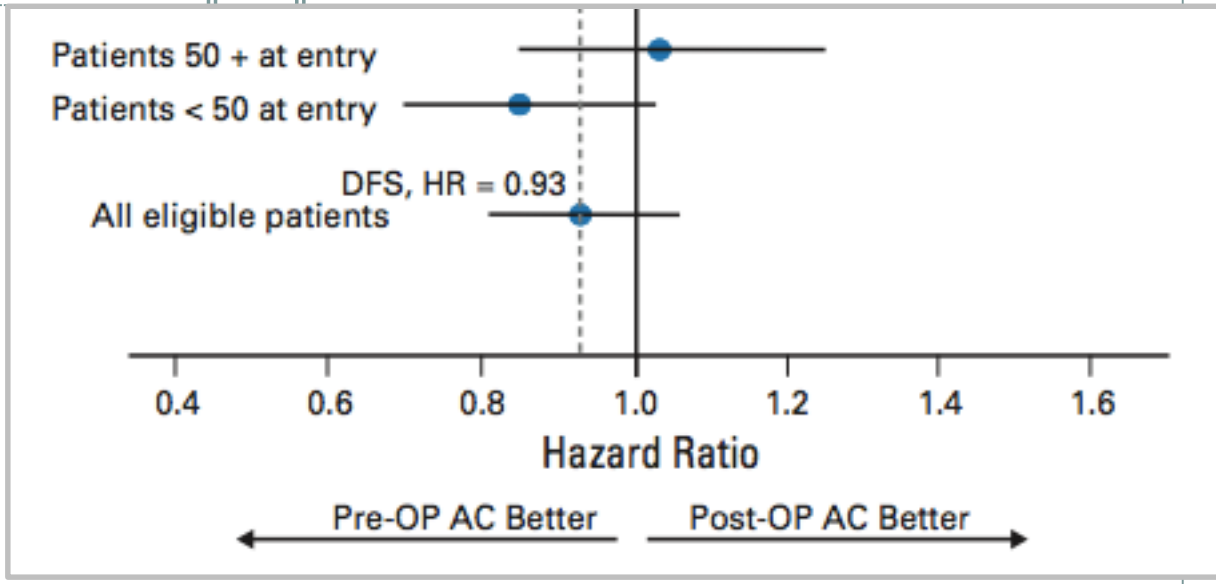
Rastogi P, JCO 2008



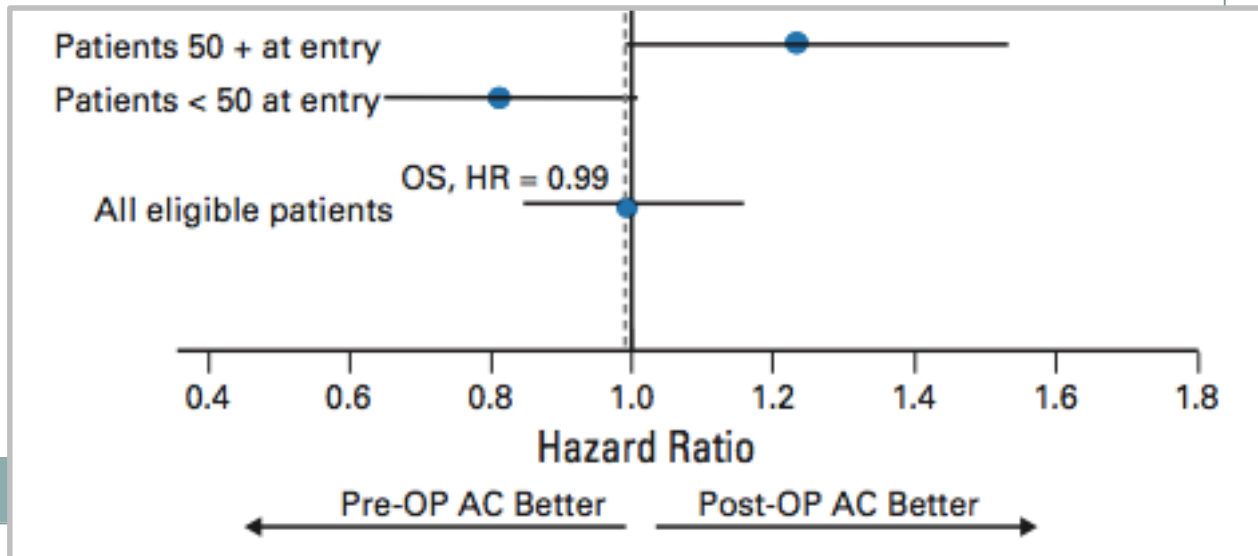
Women <50yo

Trends favored preop in women <50yo:

DFS:
HR = 0.85, P = .09 →



OS:
HR = 0.81, P = .06 →



Rastogi P, JCO 2008

Work-up per NCCN (3.2015)

Preoperative Systemic Therapy Guideline

CLINICAL STAGE

Stage IIA
T2, N0, M0

Stage IIB
T2, N1, M0
T3, N0, M0

Stage IIIA
T3, N1, M0

and

Fulfills criteria for breast-conserving surgery except for tumor size[dd]

→

WORKUP

- **History and physical exam**
- **CBC, platelets**
- **Liver function tests and alkaline phosphatase**
- **Diagnostic bilateral mammogram; ultrasound as necessary**
- **Pathology review[a]**
- **Determination of tumor ER/PR status and HER2 status[b]**
- **Genetic counseling if patient is high risk for hereditary breast cancer[c]**
- **Breast MRI[d] (optional), with special consideration for mammographically occult tumors**
- **Fertility counseling if premenopausal[e]**

Consider systemic staging (particularly if signs and symptoms are present):[f]

- **Chest diagnostic CT**
- **Abdominal ± pelvic diagnostic CT or MRI**
- **Bone scan or sodium fluoride PET/CT[g] (category 2B)**
- **FDG PET/CT[h,i] (optional, category 2B)**

→ See Preoperative Systemic Therapy Breast and Axillary Evaluation (BINV-11)

[a]The panel endorses the College of American Pathologists Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast. http://www.cap.org.

[b]See Principles of HER2 Testing (BINV-A).

[c]See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.

[d]See Principles of Dedicated Breast MRI Testing (BINV-B).

[e]See Fertility and Birth Control (BINV-C).

[f]Routine systemic staging is not indicated for early breast cancer in the absence of symptoms.

[g]If FDG PET/CT is performed and clearly indicates bone metastasis, on both the PET and CT component, bone scan or sodium fluoride PET/CT may not be needed.

[h]FDG PET/CT can be performed at the same time as diagnostic CT. The use of PET or PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III breast cancer. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.

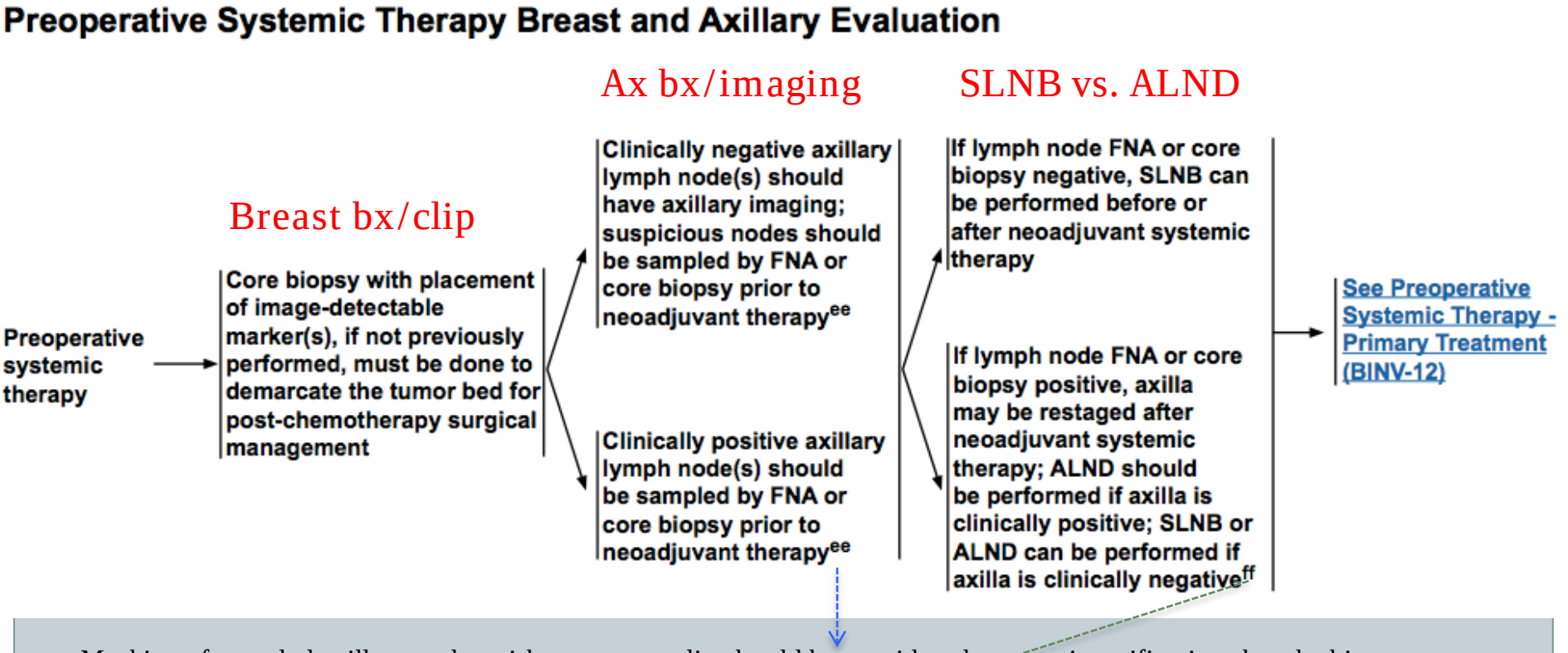
[i]FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to standard staging studies.

[dd]In cases where breast-conserving surgery may not be possible but patient will need chemotherapy, neoadjuvant treatment remains an acceptable option.

Nodal Evaluation

- For patients with clinically or radiographically positive lymph nodes, biopsy is indicated
- If biopsy+, ALND is recommended
- If biopsy-, SLN is acceptable

Work-up per NCCN (cont)



ee Marking of sampled axillary nodes with a tattoo or clip should be considered to permit verification that the biopsy-positive lymph node has been removed at the time of **ff** definitive surgery.

Among patients shown to be node-positive prior to neoadjuvant systemic therapy, SLNB has a >10% false-negative rate when performed after neoadjuvant systemic therapy. This rate can be improved by marking biopsied lymph nodes to document their removal, using dual tracer, and by removing more than 2 sentinel nodes.

NCCN 3.2015

Is ALND really needed for all cN+?

- Rationale:
  - >40% of cN1 become ypN0 (properly selected by tumor subtype and era of targeted therapy)
  - ALND is morbid
  - B-27 retrospectively calculated FNR 10.7% in cN0-1 with SLNB

- ACOSOG Z1070 enrolled…687 patients with cT0-4**N1-2**M0 with biopsy-proven nodal disease
- *Prospective observational* phase II to evaluate accuracy of SLNB (≥2 nodes) after NAC in patients with cN+

- pCR in NODES → 39%
- For cN1, false negative rate on SLNB was 12.6%

Boughey et al JAMA 2013; Boughey et al JCO 2015

Axillary ultrasound post-chemo

- Pre-specified **secondary endpoint** in ACOSOG Z1070
  - Images taken in all patients, archived, reviewed by central radiologist blinded to other imaging and final path
  - FNR for ultrasound alone was 15%

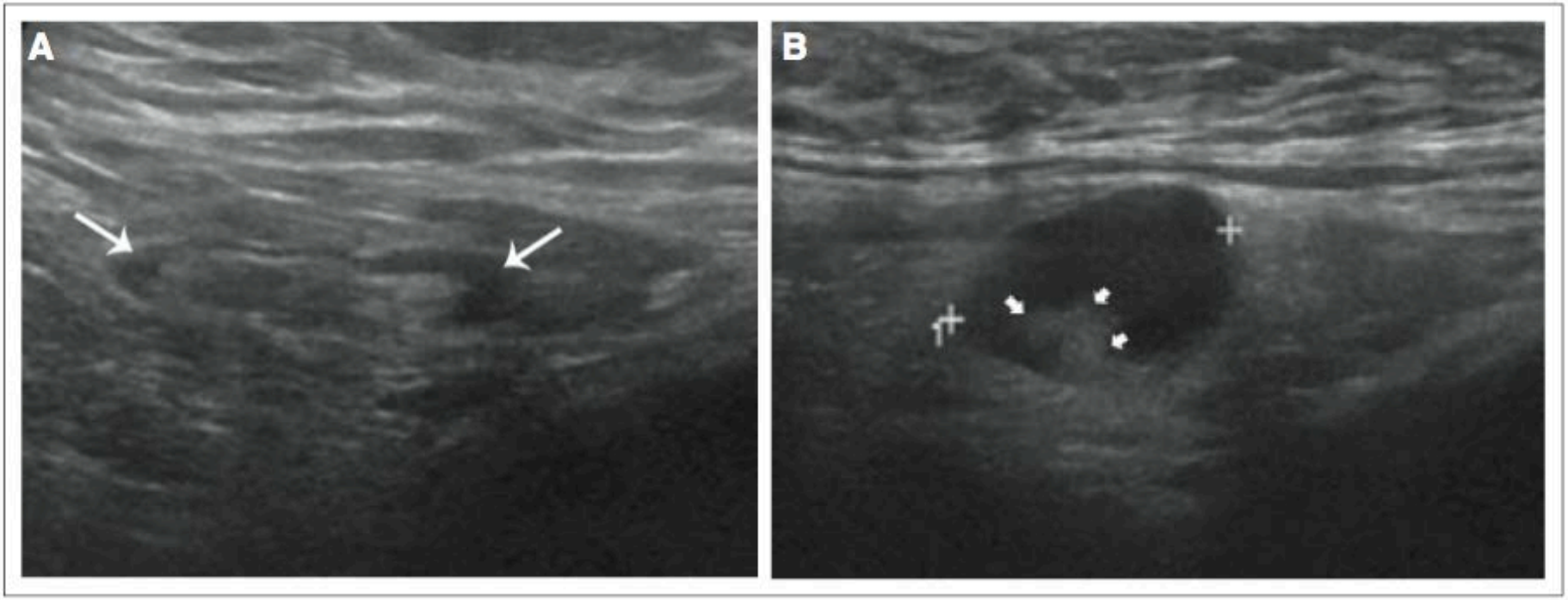
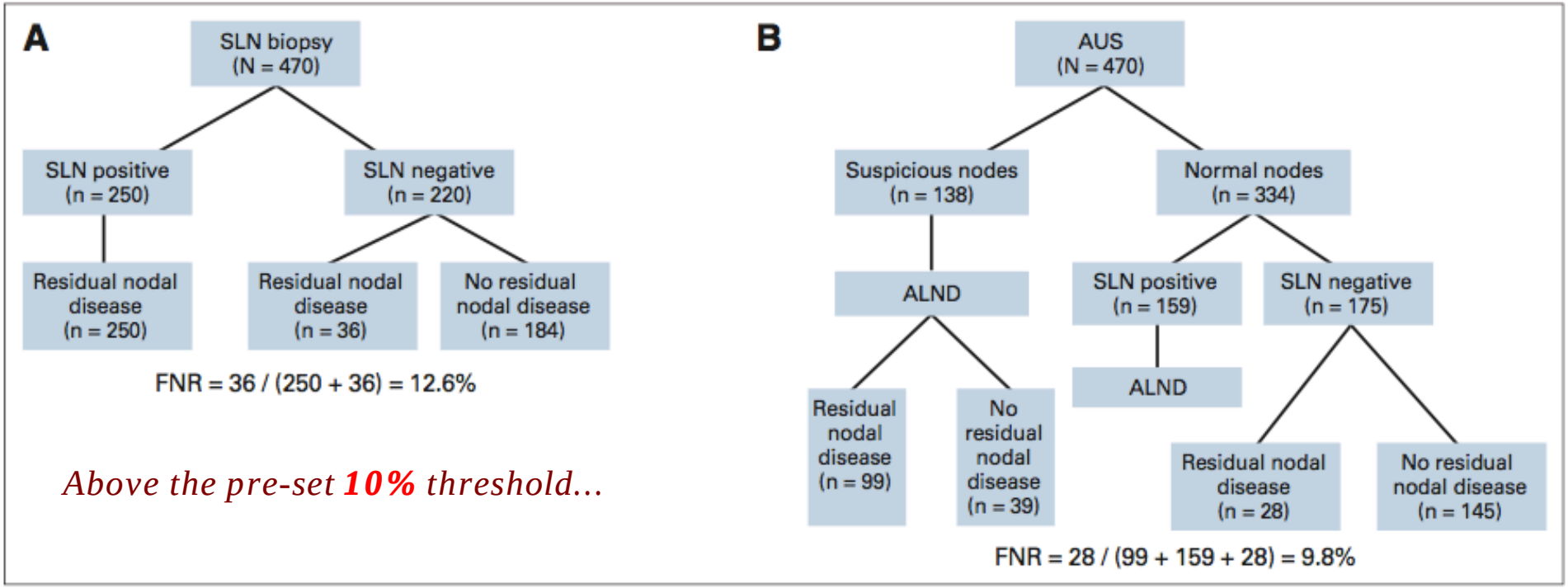


Fig 1. (A) Illustration of normal lymph nodes on ultrasound. Ultrasound image of a morphologically normal lymph node with uniform thin hypoechoic cortex (white arrows) less than 3 mm in thickness. (B) Illustration of abnormal lymph nodes on ultrasound. Ultrasound image of a metastatic axillary lymph node with diffuse hypoechoic cortical thickness and deformity of the echogenic fatty hilum (small white arrowheads).

Boughey et al JCO 2015

Combining axillary US and SLNB post-chemo

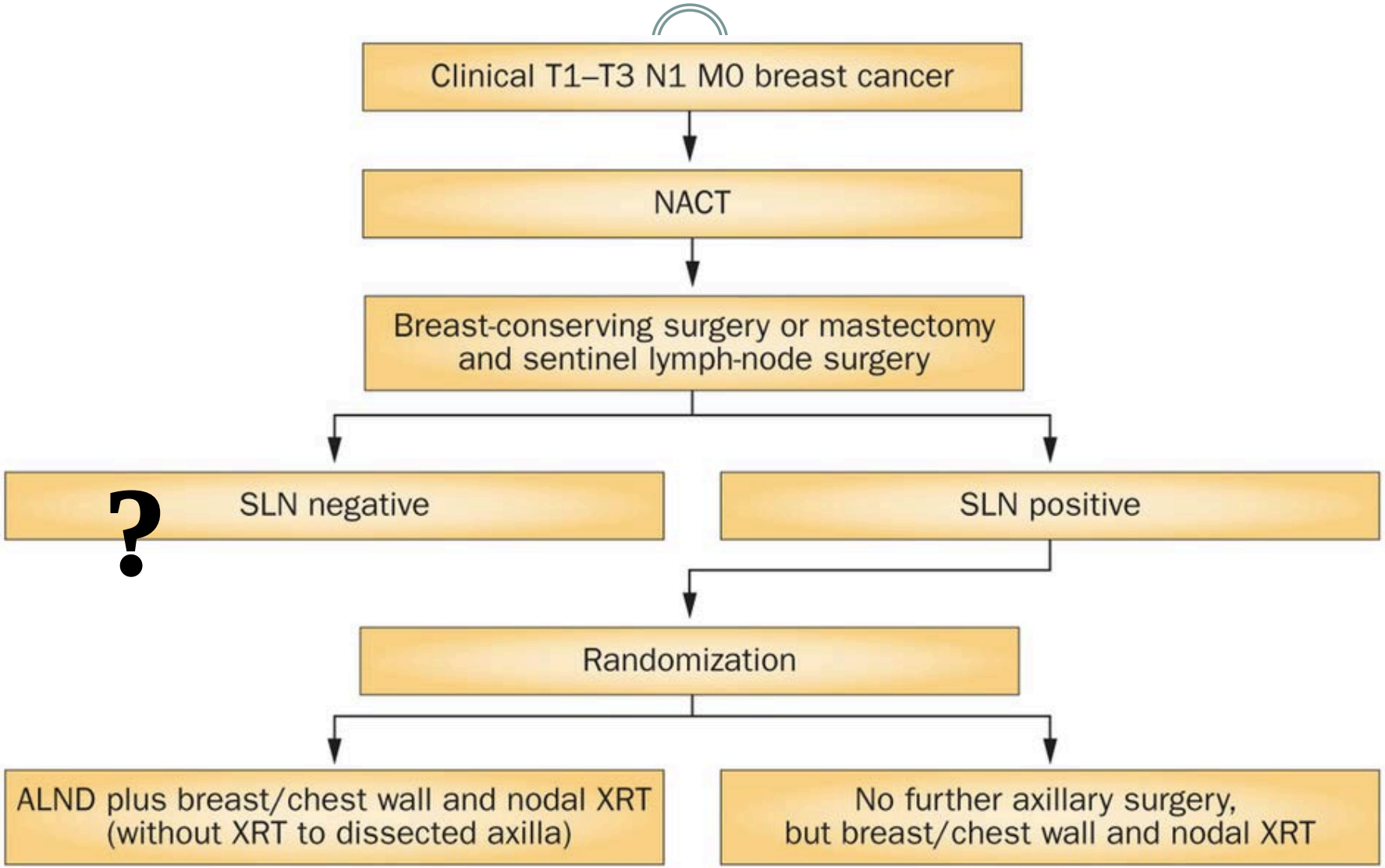


*Above the pre-set **10%** threshold…*

Fig 2. Comparison of false-negative rates (FNRs) when using (A) sentinel lymph node (SLN) surgery irrespective of axillary ultrasound (AUS) imaging findings or (B) using AUS imaging results for selective use of SLN surgery. The study participants from the American College of Surgeons Oncology Group Z1071 trial were used with the observed rates in our study. ALND, axillary lymph node dissection.

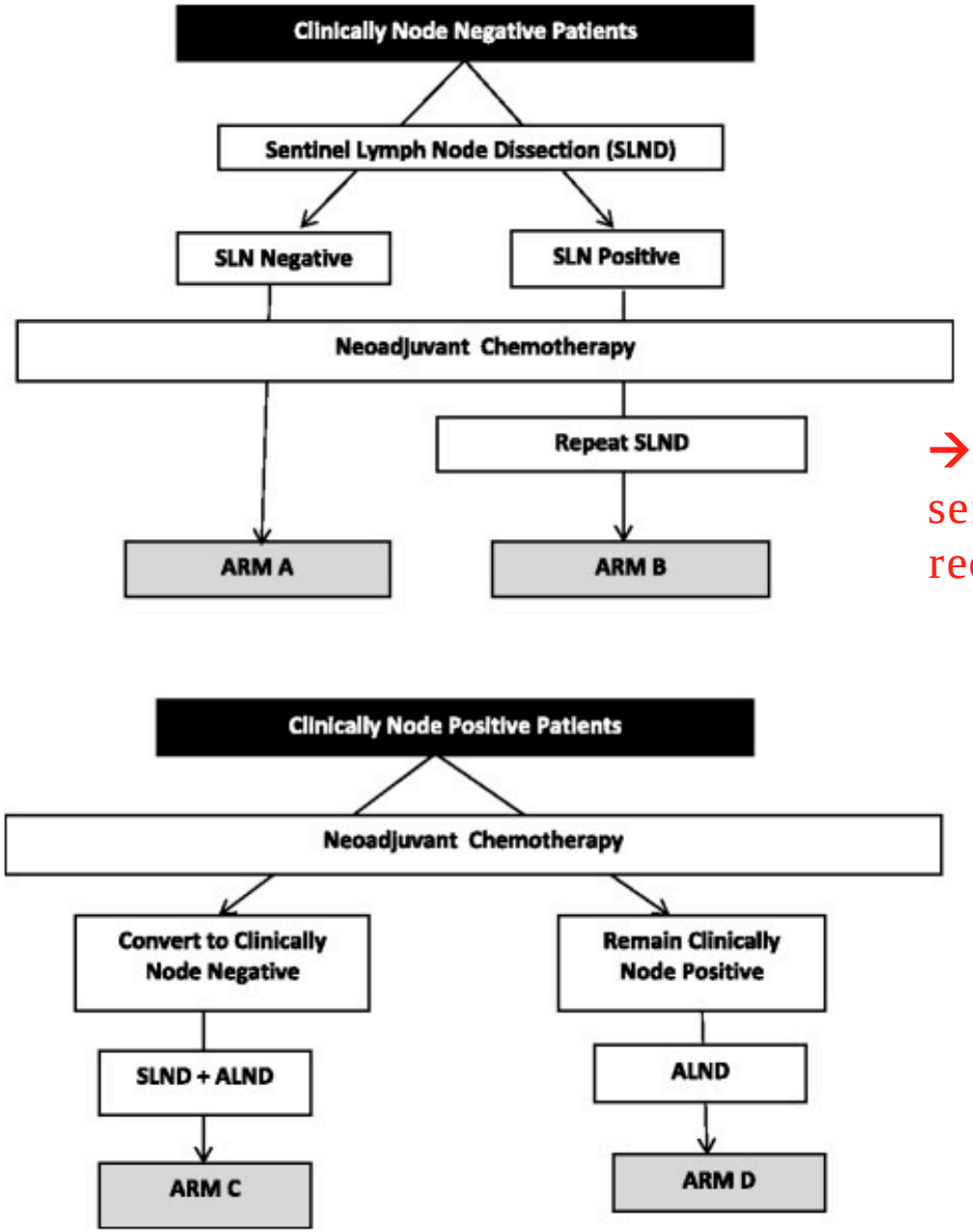
Boughey et al JCO 2015

Ongoing Alliance A11202 trial



Nature Reviews | Clinical Oncology

SENTINA Trial



→ **Repeat SLNB** only 60% sensitive, so this is not recommended.

SENTINA Trial [9]. The SENTINA trial was designed to evaluate the relationship of sentinel lymph node dissection in patients who received neoadjuvant chemotherapy; the study arms are depicted below

Biological heterogeneity!

Tumor Subtypes

- Luminal A: **ER+** and/or PR+, HER2-, **grade 1-2**
- Luminal B/HER2-: **ER+** and/or PR+, HER2-, **grade 3**

- Luminal B/HER2+: **ER+** and/or PR+, **HER2+**, all grades
- HER2+ (non-luminal): ER-/PR-/**HER2+**, all grades

- **Triple negative** (TNBC) = ER-/PR-/HER2-, all grades

Von Minckwitz et al. JCO 2012.

Impact of subtype on pCR rate

- Meta-analysis of 30 studies including 11,695
  - IQR 2001-2005
- pCR correlated with tumor subtype:
  - 8.3% ER+/HER2-
  - 18.7% ER+/HER2+
  - 38.9% ER-/HER2+ → significantly greater than TNBC, though very similar when HER2 directed therapy excluded
  - 31.1% TNBC
- Conclusion:
  - independent association between subtype and pCR
  - TNBC and HER2+/ER- highest pCR rates

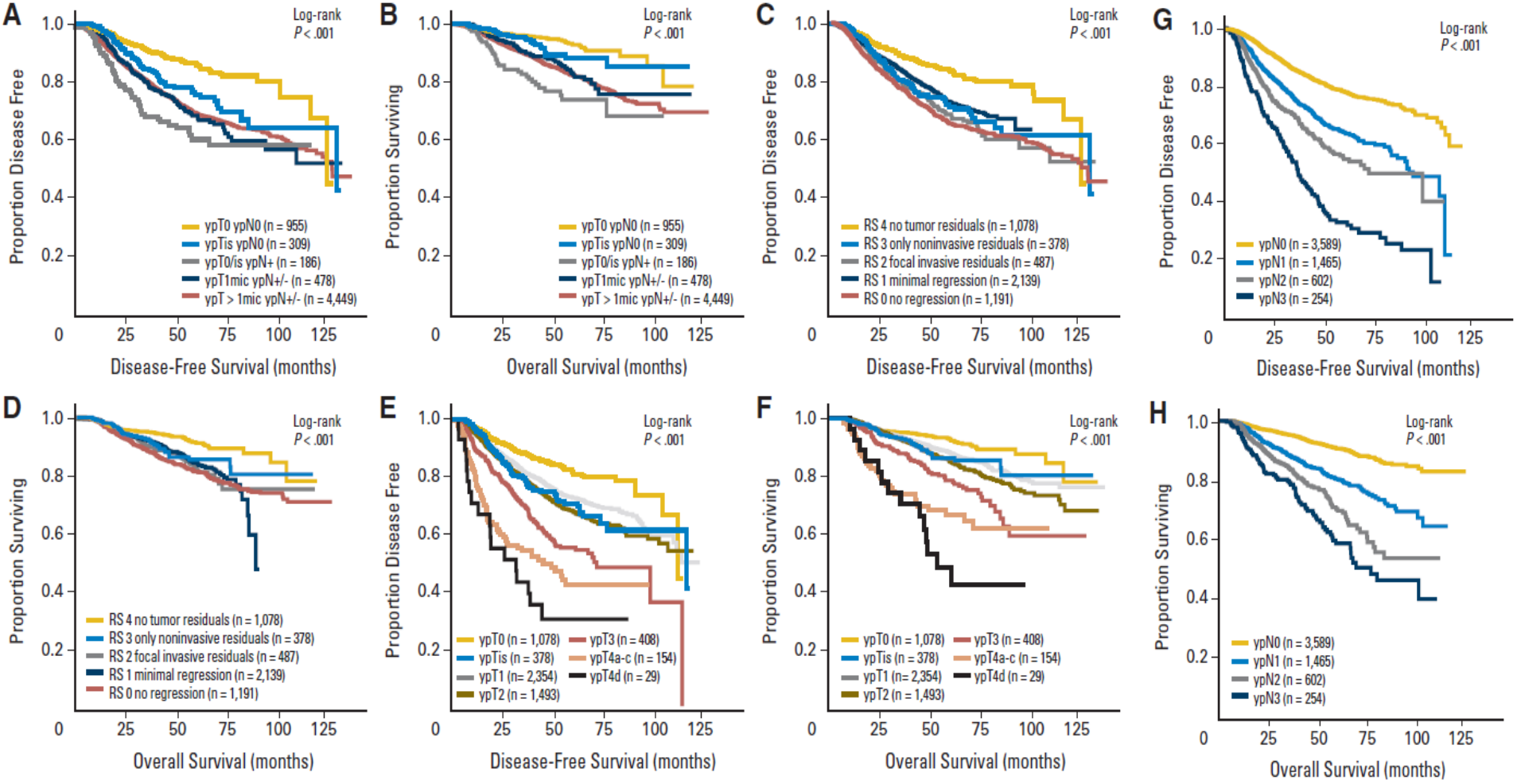
Houssami N et al. European Journal of Cancer 2012.

Impact of pCR on DFS by subtype

- Pooled analysis of 7 German RCTs that treated 6,377 patients with neoadj chemo* 1998-2006
- RT given to all patients after BCS and for mastectomy patients with stage ≥ cT3 or cN2**
- Median age 50 yrs
- Median f/u 4 yrs
- pCR was associated with improved DFS in:
  - luminal B/HER2-
  - HER2+/non-luminal***
  - Triple negative (TNBC)***
  - but **not luminal A** or **luminal B/HER2+**
- Patients with ypN+ had the worst DFS and OS

Von Minckwitz et al. JCO 2012.

How define pCR?



Von Minckwitz et al. JCO 2012

pCR improves DFS in select subtypes

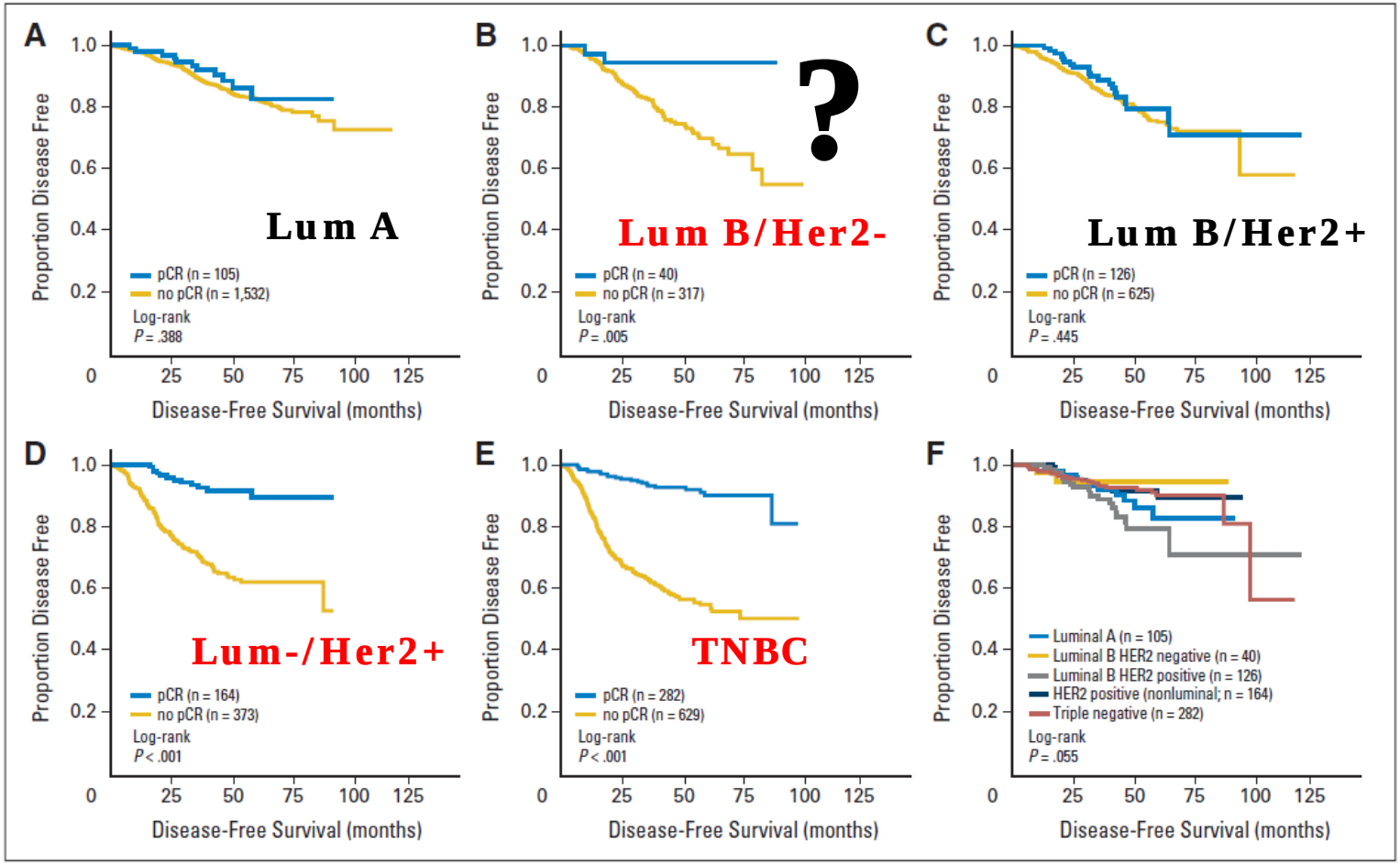


Fig 2. Prognostic impact of pathologic complete response (pCR) on disease-free survival (DFS) in 4,193 patients according to breast cancer intrinsic subtype. (A) Patients with luminal A–like tumors, (B) luminal B/human epidermal growth factor receptor 2 (HER2) –negative–like tumors, (C) luminal B/HER2-positive–like tumors, (D) HER2-positive (nonluminal) –like tumors, and (E) triple-negative tumors; (F) comparison of DFS in 717 patients achieving pCR according to breast cancer intrinsic subtype.

Von Minckwitz et al. JCO 2012

Evidence for PMRT in the Neoadjuvant Setting

NO RCTS!

In fact, NSABP B-18 and B-27 prohibited PMRT

But MDACC has a long history of using neoadjuvant chemo

NSABP B-18 and B-27

- What we CAN learn from these trials is …

PATTERNS OF FAILURE!

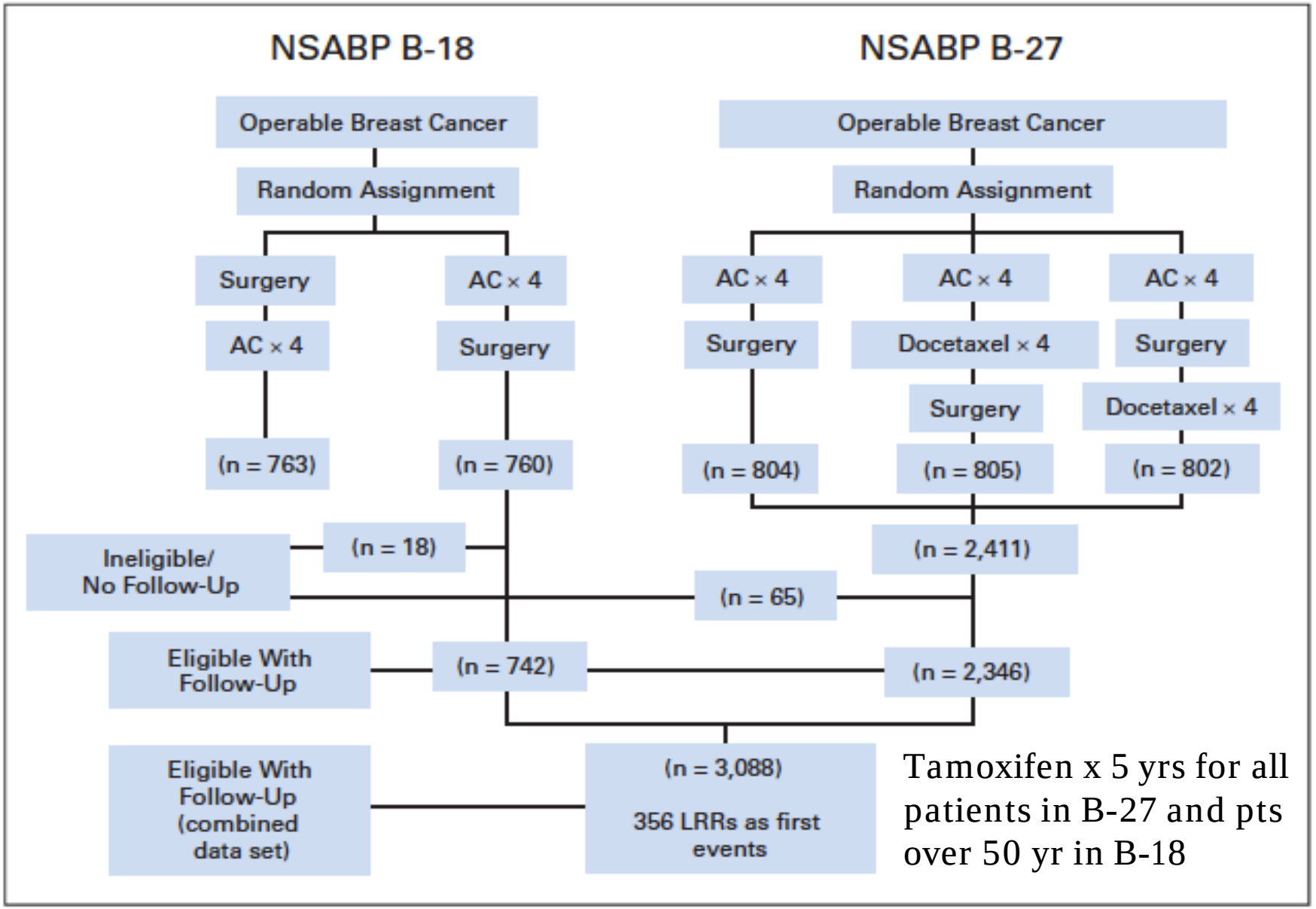
- Caveats…
  - no ER/PR/HER2 status
  - no N2

Table 1. Distribution of Selected Patient and Tumor Characteristics in NSABP B-18 and B-27 at Random Assignment (before neoadjuvant chemotherapy)

Characteristic	NSABP Trial (%)	
	B-18 (neoadjuvant AC arm) (n = 742)	B-27 (all three arms) (n = 2,346)
Patient age at random assignment, years		
< 50	51	57
≥ 50	49	43
Clinical tumor size at random assignment, cm		
cT1 (≤ 2.0)	28	14
cT2 (2.1-5.0)	59	57
cT3 (> 5)	13	29
Clinical nodal status at random assignment		
cN0	73	70
cN1	27	30
Combined clinical stage at random assignment		
cT1-2N0	65	51
cT1-2N1	22	20
cT3N0	8	19
cT3N1	5	10

Abbreviations: AC, doxorubicin/cyclophosphamide; NSABP, National Surgical Adjuvant Breast and Bowel Project.

Mamounas et al. JCO 2012



Mamounas et al. JCO 2012

LRR incidence on NSABP

- 12.6% among 1,947 patients treated with mastectomy
  - 9.0% local
  - 3.6% regional
- 10.3% among 1,100 patients treated with lumpectomy plus breast XRT
  - 8.1% local
  - 2.2% regional

Mamounas et al. JCO 2012

MVA for LRR in NSABP

Table 3. Multivariate Analysis of Independent Predictors of 10-Year LRR According to Type of Surgery

Variable	No. of Patients	LRR Events	HR	95% CI	*P*
Patients treated with mastectomy*	1,071	131			
Clinical tumor size > 5 *v* ≤ 5 cm†			1.58	1.12 to 2.23	.0095
Clinical nodal status cN(+) *v* cN(−)†			1.53	1.08 to 2.18	.017
Nodal/breast pathologic status					< .001
ypN(−)/no breast pCR *v* ypN(−)/breast pCR†			2.21	0.77 to 6.30	
ypN(+) *v* ypN(−)/breast pCR†			4.48	1.64 to 12.21	
Patients treated with lumpectomy plus breast XRT*	1,890	189			
Age ≥ 50 *v* < 50 years†			0.71	0.53 to 0.96	.025
Clinical nodal status cN(+) *v* cN(−)†			1.70	1.26 to 2.31	< .001
Nodal/breast pathologic status					< .001
ypN(−)/no breast pCR *v* ypN(−)/breast pCR†			1.44	0.90 to 2.33	
ypN(+) *v* ypN(−)/breast pCR†			2.25	1.41 to 3.59	

Abbreviations: HR, hazard ratio; LRR, locoregional recurrence; pCR, pathologic complete response; XRT, external radiation therapy.
*Includes only patients for whom all covariates are known.
†Category used as baseline for comparison of risk.

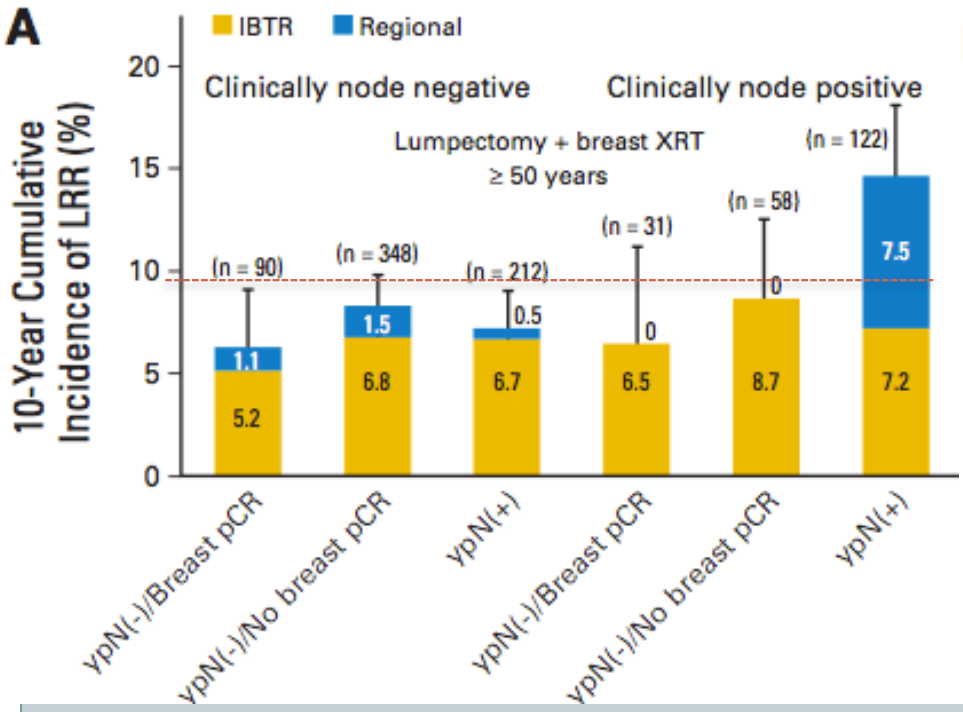
- Mastectomy: cT3+, cN+, ypT+, **ypN+**
- BCS: same...also AGE <50

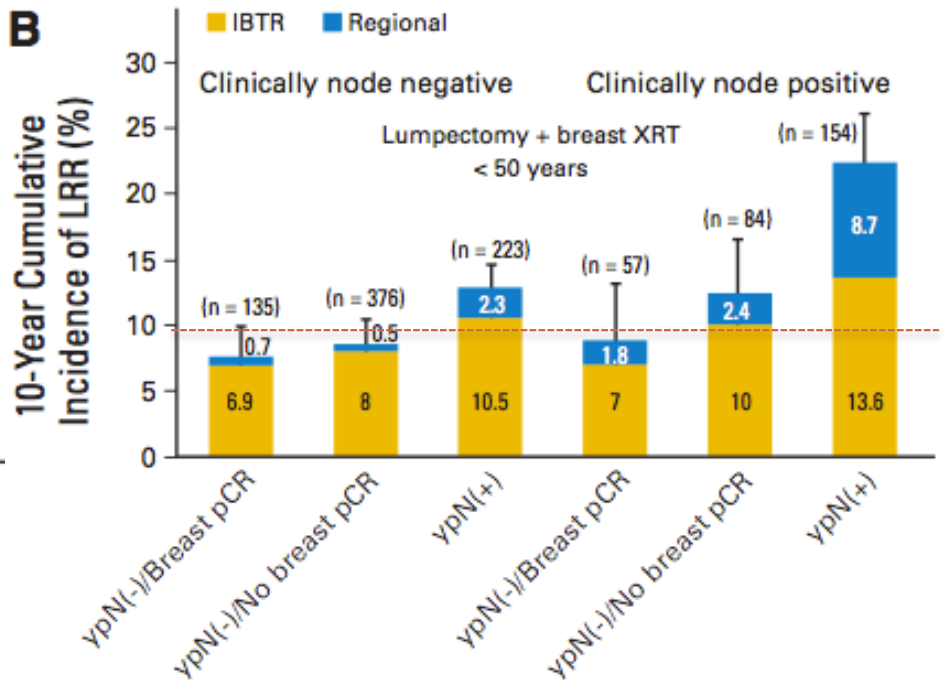
Mamounas et al. JCO 2012

LRR after **Lumpectomy** in NSABP

≥50 yo

<50 yo



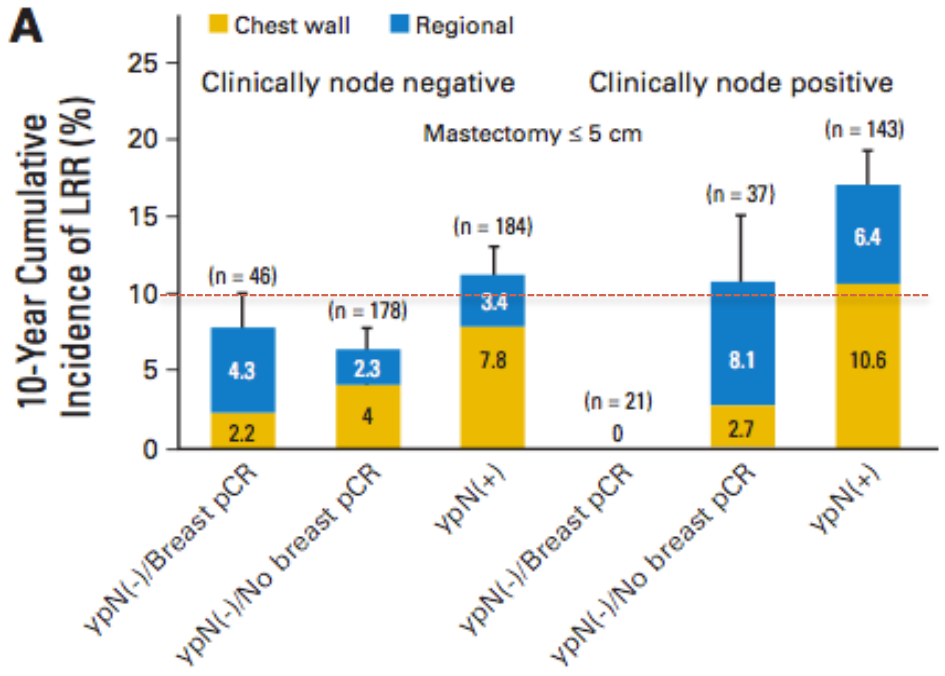


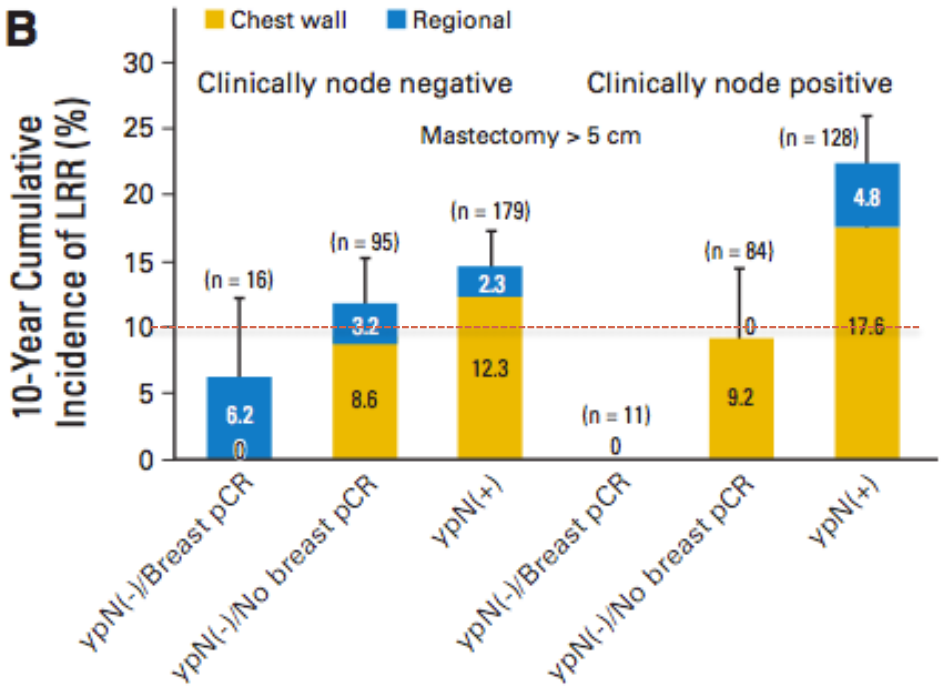
Mamounas et al. JCO 2012

LRR after **Mastectomy** in NSABP

≤5 cm

>5 cm

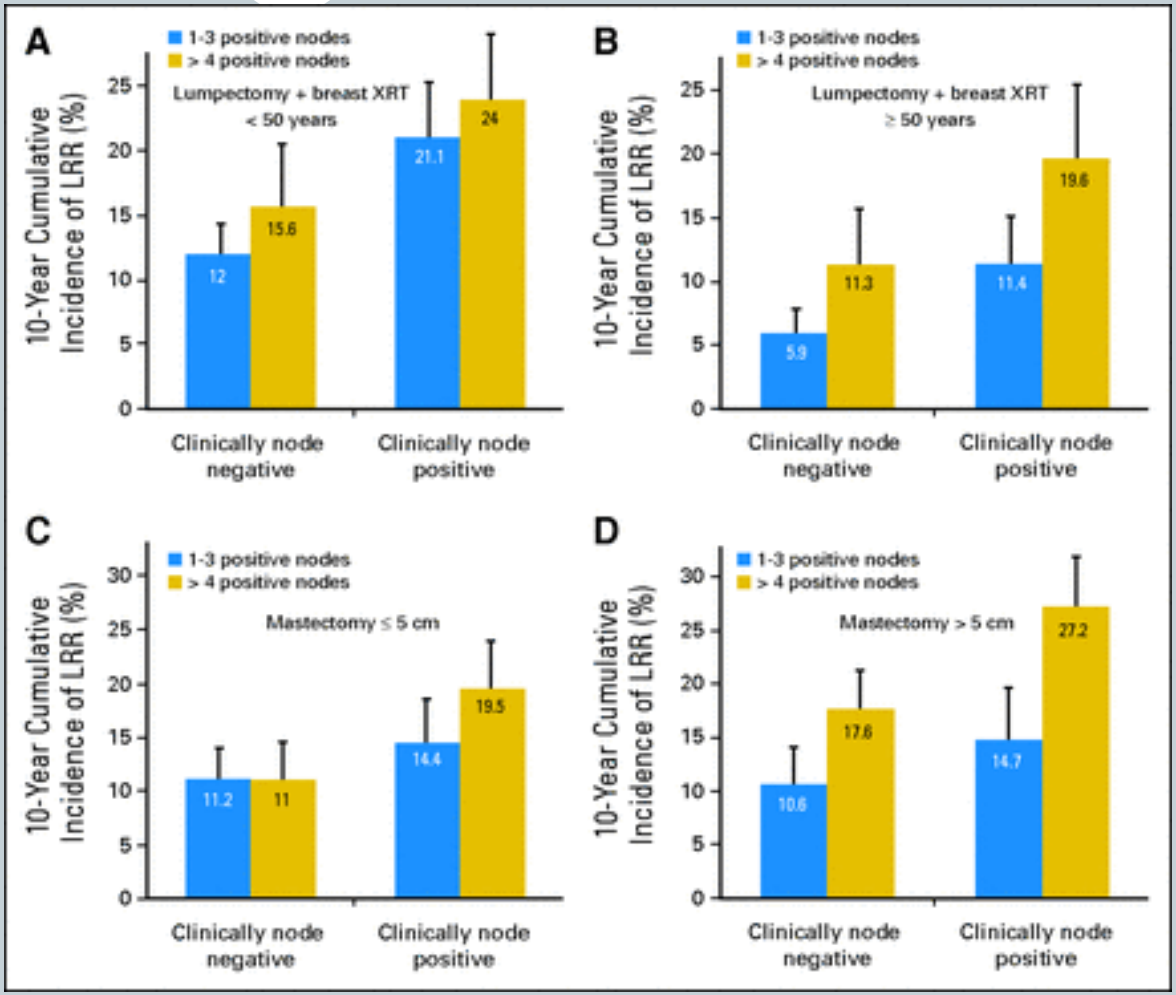




Mamounas et al. JCO 2012

LRR in ypN+ in NSABP

- LRR >10% for 1-3 positive nodes
  - (except for cN0 patients ≥50yo with BCS)



Mamounas et al. JCO 2012 (appendix)

MDACC retrospective

- Retrospective analysis of 6 prospective institutional studies at MDACC for patients with non-metastatic, non-inflammatory breast cancer 1974-2000
  - Doxorubicin-based NAC → +/- PMRT
  - 542 patients with PMRT vs. 132 patients no PMRT (non-randomized)
- PMRT associated with improved 10 yr LRR in patients with:
  - cT3 (24% without *vs* 8% with, p=0·002)
  - cT4 (46% *vs* 15%, p<0·0001)
  - cN2/3 (40% *vs* 12%, p<0·0001)
  - pT3 (31% *vs* 14%, p=0·002)
  - pT4 (52% *vs* 13%, p=0·001)
  - 4 or more +nodes on final path (59% *vs* 16%, p<0·0001)
- PMRT improved 10-year CSS for patients with:
  - Clinical stage ≥ IIIB (22% without *vs* 44% with, p=0·002)
  - cT4 (24% *vs* 45%, p=0·007)
  - cN2/3 (27% *vs* 49%, p=0·024)
  - 4 or more pN+(18% *vs* 44%, p=0·005).

Huang et al JCO 2004

MVA for LRR in MDACC study

Table 4. Multivariate Analysis of LRR

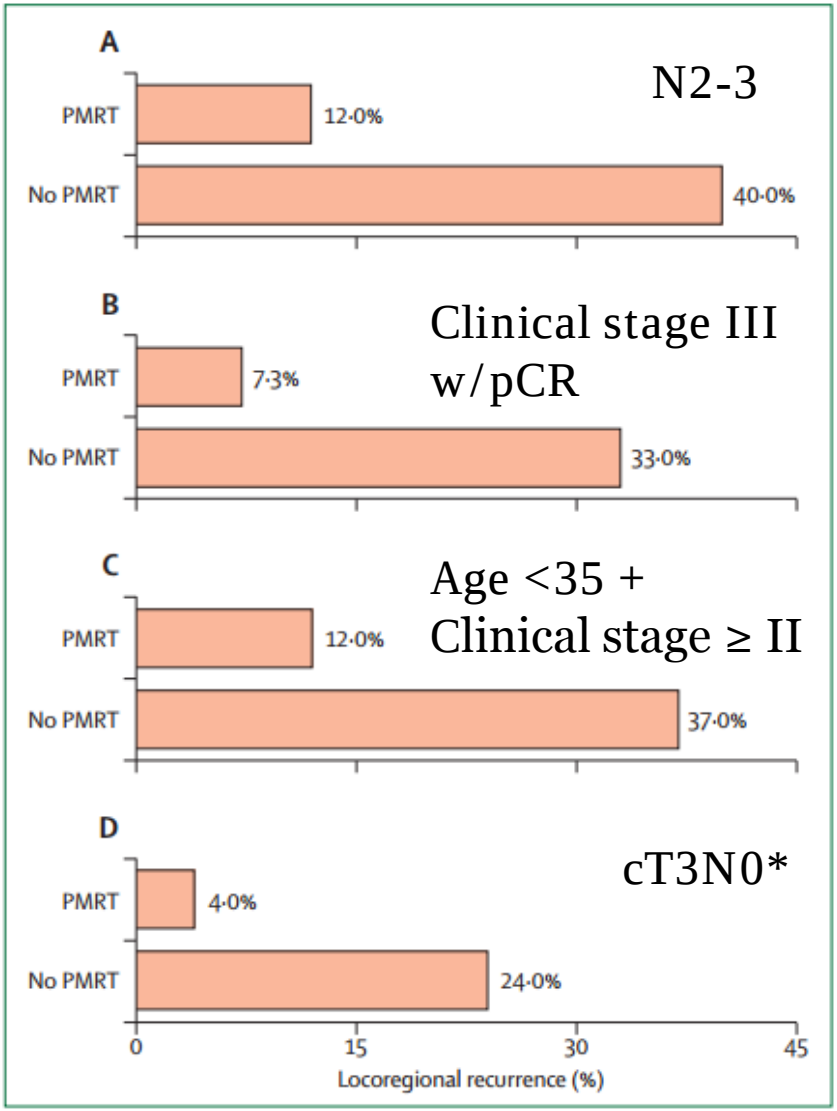
Factor	Hazard Ratio	95% CI	*P*
No radiation	4.68	2.70 to 8.13	< .0001
≥ 20% sampled nodes positive	3.58	2.11 to 6.08	< .0001
Stage ≥ IIIB	2.38	1.42 to 4.02	.001
No tamoxifen	2.19	1.19 to 4.06	.012
Minimal or worse clinical response to neoadjuvant chemotherapy	1.88	1.10 to 3.23	.021
Estrogen receptor–negative	1.69	1.04 to 2.76	.033

Abbreviation: LRR, local-regional recurrence.

Huang et al JCO 2004

MDACC Recommendations

- Recommend:
  - clinical T3–T4
  - clinical N2–N3
  - *most* with node-positive disease at resection
- *Consider:*
  - clinical stage II disease with pN+ or other high risk features including **young age (<35), ER-, poor response to chemo**



Hoffman et al, Lancet 2012

UC Athena Network Recommendations

- Based on a literature review, and 7 UC expert consensus
- "Little or no benefit" from PMRT:
  - clinical stage II (T1N0-1, T2N0), >40 yo, with ER+ disease who have a pCR or 0-3 positive axillary nodes without LVI or ECE
- high-risk features warranting consideration of PMRT:
  - <40yo
  - advanced clinical or pathologic stage and TNBC
  - presence of LVI
  - presence of ECE

Fowble et al, IJROBP 2012

Case

- 53yo post-menopausal F with triple-negative cT2N1M0 invasive ductal carcinoma of R breast now s/p bilateral mastectomies and R ALND with pCR.
- PMRT was not recommended.
- Patient proceeded with reconstruction and surveillance.

Case discussion

- What were her risk factors?
  - What if she were ER+?
- PET indicated?
- SLNB before chemo?
- Mastectomy for T2 → pCR?
  - If planned upfront, why NAC at all?
- ALND if post-NAC SLNB neg?
- (prophy bilateral mastectomies??)
- Adjuvant chemo for TNBC?
- Ongoing trials??

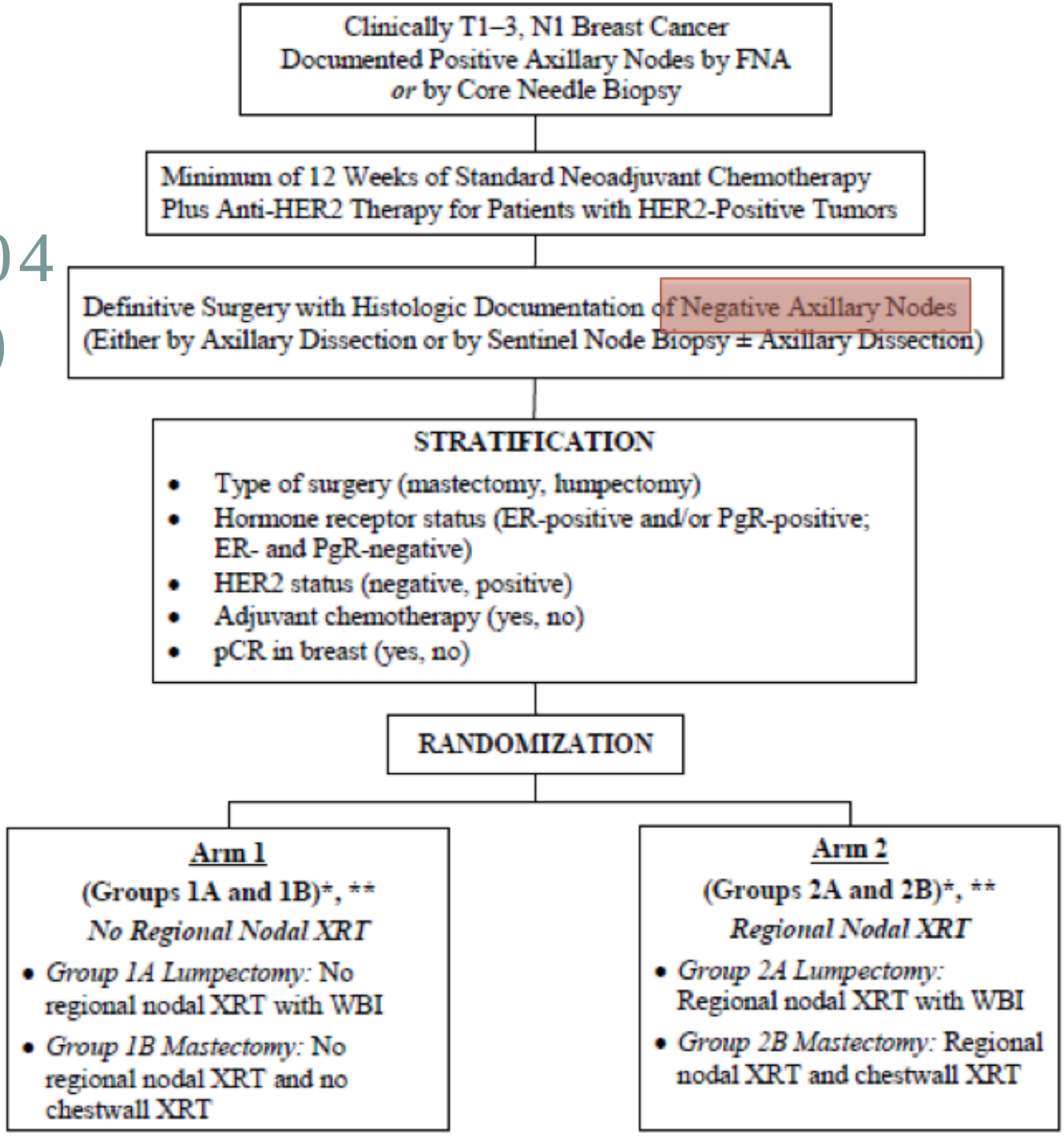
Consensus to omit PMRT after NAC

Table 1 Hypothetical clinical case scenarios

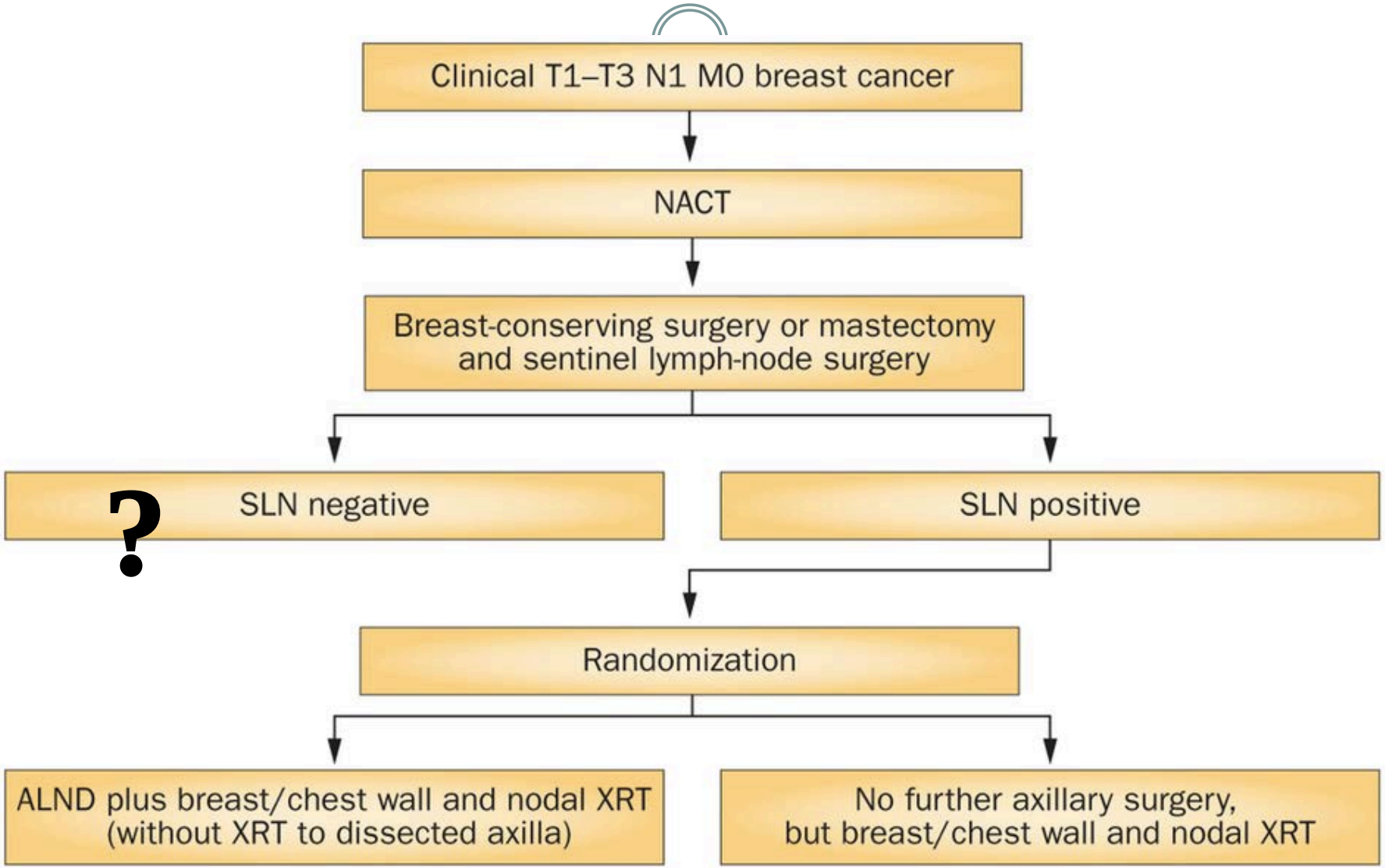
Case no.	Age (y)	Clinical stage	Location primary	Size primary (cm)	Evaluation axilla	Histology primary	Receptor	Genetic testing	Neoadjuvant chemotherapy	Mastectomy pathology
1	34	T2N0M0 IIA	Left UOQ	2.5	Clinical N0	IDC Gr 3 LVI−, Ki67 40%	ER+ PR+ Her2+	Negative	AC × 4 TH H × 1 y	pCR 2.8 cm DCIS 0/1 SN+
2	35	T2N0M0 IIA	Right UOQ	3	SNB 0/4 +	IDC Gr 3 LVI−	ER− PR− Her2−	Negative	TAC × 6	ypT2N0 2.5 cm IDC Gr 3, LVI− MIB1 60%-90%
3	40	T3N0M0 IIB	Right LOQ	5.2	Clinical N0	IDC Gr 3 LVI−	ER+ PR+ Her2−	BRCA2+	AC × 4 T × 4	ypT1N0 1 cm IDC Gr 3 0/4 SN+
4	42	T2N1M0 IIB	Left subareolar	3.5	US FNA+	IDC Gr 3 LVI−	ER− PR− Her2−	BRCA1+	AC × 4 T × 4	pCR 0/10 nodes +
5	60	T2N1M0 IIB	Left subareolar	3	US FNA+	IDC Gr 2 LVI−	ER− PR− Her2 +	NI	AC × 4 TH × 12 H × 1 y	ypT1N0 1.5 cm IDC Gr 2, LVI− 0/1 SN+, 0/8 NSN+
6	45	T2N1M0 IIB multifocal	Left UIQ	2.5 1.5	US FNA+	IDC Gr 2 LVI−	ER− PR− Her2+	Negative	AC × 4 TH × 12 H × 1 y	ypT2N0 Multifocal IDC spanning 5 cm, Gr 2, LVI−, 0/4 SN+
7	55	T2N1M0 IIB	Right UIQ	3.5	US FNA+	ILC Gr 1	ER+ PR+ Her2−	NI	AC × 4 T × 4	ypT2N1 3 cm ILC classic, Gr 1, LVI−, 1/1 SN+ (4 mm), ECE+, 0/8 NSN+
8	35	T2N1M0 IIB	Left LOQ	4.5	US FNA+	IDC Gr 2	ER+ PR+ Her2−	Negative	AC × 4 T × 4	ypT2N1 2.5 cm IDC, Gr 2, LVI− 2/2 SN+ (3 mm, 4 mm) ECE−, 0/10 NSN+
9	55	T2N1M0 IIB	Left UOQ	4	US FNA+	IDC Gr 3	ER+ PR+ Her2+	NI	AC × 4 TH × 12 H × 1 y	ypT2N1 3 cm Gr 3 IDC, LVI+, 1/1 SN+ (1.5 mm) ECE−, 0/8 NSN+
10	50	T2N1M0 IIB	Right UIQ	5	US FNA+	IDC Gr 2 LVI+	ER+ PR+	NI	AC × 4 TH	ypT2N1 4.5 cm IDC, Gr 2

Fowble B et al IJROBP 2012

Ongoing NSABP **B-51**/RTOG 1304 (NRG 9353) Trial



Ongoing Alliance A11202 trial



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THANK YOU

QUESTIONS?

UCSD Neoadjuvant chemo algorithm

- General paradigm for post-op chemo:
  - T1b+ for TNBC or HER+
  - Oncotyope to decide, even in N+
    - N0 → TCx4 (12 weeks)
    - N+ → AC*x4 → T**
      - AC prefer dose-dense AC which is q2wk + GCSF
      - T can be dose-dense (q2wk for 4 doses) or weekly x12
- Neoadjuvant
  - TNBC: AC → T → surgery → +/- carbo
    - At UCSD we do carbo concurrently with RT for ypN+
  - HER2+: PTCHx6 (q3wk)
    - Pertuzumab, taxotere, carboplatin, Herceptin (continues for 1 yr)
  - ER+/HER2-: ACx4 → T OR TC
    - AC preferred dose-dense (q2wk +GCSF) → paclitaxel (weekly or q2wk)
    - TC = docetaxel and cyclophosphamide x4 (12 weeks)

What is a pCR and when does it matter?

- Definitions of path CR across studies:

ypT0 ypN0. No invasive or noninvasive residual in breast or nodes. Used by the German study groups (German Breast Group [GBG] and Arbeitsgemeinschaft Gynäkologische Onkologie—Breast Group [AGO-B]) as part of the Sinn score.[10]

ypT0/is ypN0. No invasive residual in breast or nodes; noninvasive breast residuals allowed. Used by MD Anderson Cancer Center, Austrian Breast and Colorectal Cancer Study Group, and Neo–Breast International Group.[6,11,12]

ypT0/is ypN0/+. No invasive residual in the breast; noninvasive breast residuals and infiltrated lymph nodes allowed. Used by National Surgical Adjuvant Breast and Bowel Project.[5,13]

ypT≤1mic ypN0/+. No gross invasive residuals in the breast; focal invasive and noninvasive residuals in breast and infiltrated lymph nodes allowed. Used by French groups using the Sataloff index.[7]

Von Minckwitz et al. JCO 2012

NCCN 3.2015

Table 1

American Joint Committee on Cancer (AJCC)
TNM Staging System For Breast Cancer

Primary Tumor (T) The T classification of the primary tumor is the same regardless of whether it is based on clinical or pathologic criteria, or both. Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cutoff for a given T classification, it is recommended that the size be rounded to the millimeter reading that is closest to the cutoff. For example, a reported size of 1.1 mm is reported as 1 mm, or a size of 2.01 cm is reported as 2.0 cm. Designation should be made with the subscript "c" or "p" modifier to indicate whether the T classification was determined by clinical (physical examination or radiologic) or pathologic measurements, respectively. In general, pathologic determination should take precedence over clinical determination of T size.

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget's)	Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted
T1	Tumor ≤20 mm or less in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules).

Note: Invasion of the dermis alone does not qualify as T4

T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

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Table 1 (continued)

Regional Lymph Nodes (N)

Clinical

NX		Regional lymph nodes cannot be assessed (e.g., previously removed)
N0		No regional lymph node metastasis
N1		Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2		Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastases
	N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
	N2b	Metastases only in clinically detected* ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node metastases
N3		Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
	N3a	Metastasis in ipsilateral infraclavicular lymph node(s)
	N3b	Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
	N3c	Metastasis in ipsilateral supraclavicular lymph node(s)

**Note: Clinically detected* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration.

Pathologic (pN)*

pNX	Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis histologically

Note: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.

pN0(i-)	No regional lymph node metastasis histologically, negative IHC
pN0(I+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)
pN0(mol-)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
pN0(mol+)	Positive molecular findings (RT-PCR),** but no regional lymph node metastases detected by histology or IHC

* Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," for example, pN0(sn).

** RT-PCR: reverse transcriptase/polymerase chain reaction.

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Table 1 (continued)

Pathologic (pN) *(continued)*

pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected***
pN1mi	Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
pN1c	Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in 4–9 axillary lymph nodes; or in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastases in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN3	Metastases in ten or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected**** ipsilateral internal mammary lymph nodes in the *presence* of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected*** ; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in ten or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected**** ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes

*** "Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

**** "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.

Distant Metastasis (M)

M0	No clinical or radiographic evidence of distant metastases
cM0(I+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Staging continued on next page (ST-4)

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Table 1 (continued)

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis	N0	M0	**Stage IIIA**	T0	N2	M0
Stage IA	T1*	N0	M0		T1*	N2	M0
Stage IB	T0	N1mi	M0		T2	N2	M0
	T1*	N1mi	M0		T3	N1	M0
Stage IIA	T0	N1**	M0		T3	N2	M0
	T1*	N1**	M0	**Stage IIIB**	T4	N0	M0
	T2	N0	M0		T4	N1	M0
Stage IIB	T2	N1	M0		T4	N2	M0
	T3	N0	M0	**Stage IIIC**	Any T	N3	M0
				Stage IV	Any T	Any N	M1

* T1 includes T1mi

** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

- M0 includes M0(i+).
- The designation pM0 is not valid; any M0 should be clinical.
- If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
- Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.
- Postneoadjuvant therapy is designated with “yc” or “yp” prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

Predictors for LRR in ALL PATIENTS on NSABP

On MVA:

- Age <50
- cT3+
- cN+
- Breast pCR
- **ypN+**

Table 2. Multivariate Analysis of Independent Predictors of 10-Year LRR in the Combined Data Set*

Variable	HR	95% CI	*P*
Age ≥ 50 *v* < 50 years†	0.78	0.63 to 0.98	.03
Clinical tumor size > 5 *v* ≤ 5 cm†	1.51	1.19 to 1.91	< .001
Clinical nodal status cN(+) *v* cN(−)†	1.61	1.28 to 2.02	< .001
Nodal/breast pathologic status			< .001
ypN(−)/no breast pCR *v* ypN(−)/breast pCR†	1.55	1.01 to 2.39	
ypN(+) *v* ypN(−)/breast pCR†	2.71	1.79 to 4.09	

NOTE. The total No. of patients was 2,961, with 320 locoregional recurrence (LRR) events.

Abbreviations: HR, hazard ratio; pCR, pathologic complete response.

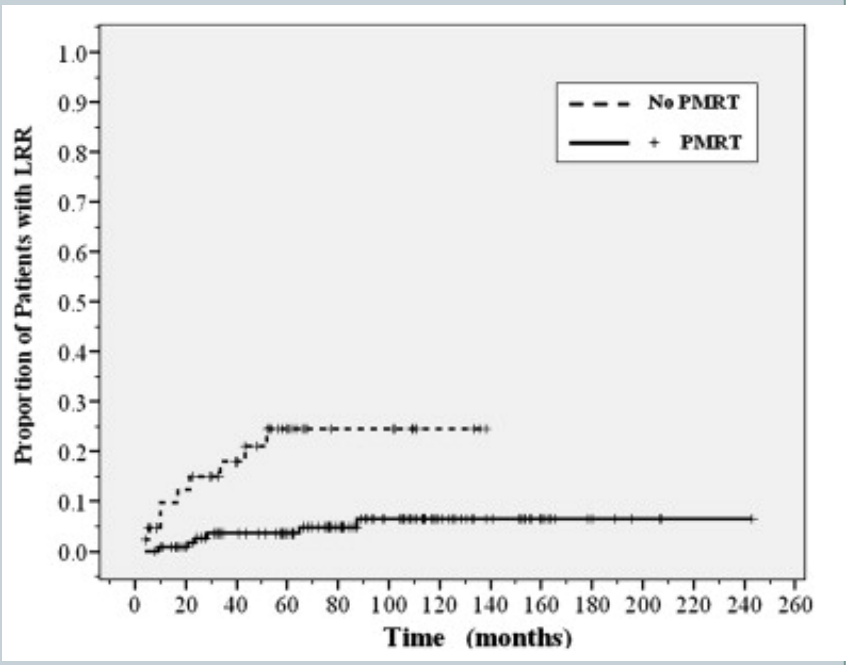
*Includes only patients for whom surgery type and all covariates are known.

†Category used as baseline for comparison of risk.

Mamounas et al. JCO 2012

cT3N0

- A retrospective analysis of 162 patients with cT3N0 disease treated at MDACC showed a benefit for PMRT for 5-yr LRR (24% to 4%; p<0·001)
- For patients with cT3N0 but pN+ disease, PMRT improved 5 –yr LRR (53% vs 5%, p<0·001)
- There was a trend towards improved 5-yr LRR with PMRT cT3N0 and pN0 (14% vs 2%, p=0·06)
  - These LRR rates are higher than reported in the NSABP studies (6.2-11.8%) depending on breast pCR



Nagar IJROBP 2011

Young Age

- 107 women < 35 yrs with clinical stage IIA–IIIC treated at MDACC with NACT and mastectomy with or without PMRT
- PMRT improved 5-year recurrence 37% without vs 12% with, p=0·001
- PMRT improved 5 yr-OS (67% vs. 48%, p = 0.03)
- No OS or LRR benefit for clinical stage IIA

Table 2. Five-year actuarial rates of LRR according to clinical and pathologic factors

Characteristic	5-y LRR rate No RT (%)	RT (%)	*p*
Clinical stage			
IIA	0	0	NA
IIB	44	0	0.003
IIIA	25	16	0.435
IIIB	33	13	0.1062
IIIC	100	17	0.276
Clinical T stage			
T1	0	0	NA
T2	32	0	0.028
T3	43	16	0.051
T4	43	13	0.015
Clinical N stage			
N0	40	0	0.045
N1	28	13	0.170
N2	50	13	0.028
N3	100	17	0.276
Positive nodes (*n*)			
0	35	15	0.079
1–3	30	11	0.164
≥4	37	12	0.001

Garg et al IJROBP 2007

Ongoing RAPCHEM trial

- The Radiotherapy After Primary CHEMotherapy for breast cancer (RAPCHEM) trial (NCT01279304) at the Netherlands Cancer Institute (Amsterdam, Netherlands) is a non-randomised prospective trial, enrolling patients with **clinical T1–T2** invasive breast cancer with **one or more pathologically proven axillary lymph nodes** who **convert to node-negative** disease after neoadjuvant chemotherapy (ypT0–2 ypN0 disease).

- Patients undergoing mastectomy do not receive postmastectomy radiation and are followed to determine 5-year locoregional recurrence.