

Case Conference: Post-Mastectomy Radiotherapy

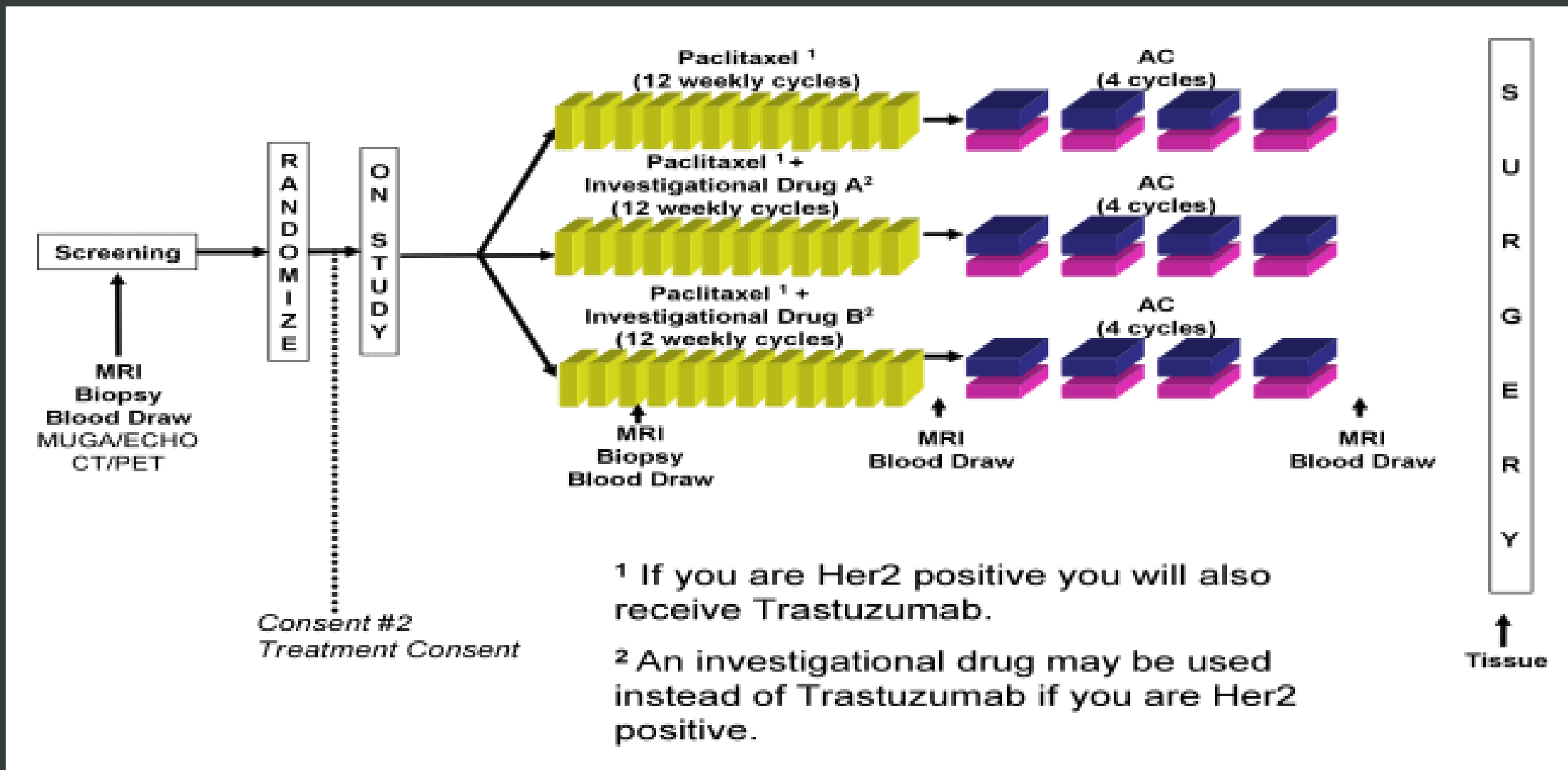
Outline

- Case
- Intro to PMRT
- Guidelines
- Studies
- Case conclusion
- Summary

Clinical Case

- 36F self-palpated a left breast mass 6/2011. Mammogram revealed suspicious mass at the 10:00 position. US-guided core biopsy showed IDC, grade 3, triple negative.
- MRI: 7.9cm area of non-masslike enhancement in the left breast and also several enlarged axillary LNs on the left level 1-2 up to 2.3cm in size.
- PET CT: Hypermetabolic left breast tumor, subpectoral LN and left axillary LNs:
 - Clinical stage: cT3N1M0 stg IIIA breast cancer.
- ISPY2 trial: randomized to standard therapy with AC+T.
- 1/3/12 – Bilateral mastectomies, left ALND and tissue expander placement. The right breast was benign. The left breast showed IDC, 8.2cm, grade 3. Her axillary dissection showed 6/6 LNs positive with large areas of extracapsular extension. LVI was widely present. Margins were clear >1cm.
 - Pathologic stage: ypT3N2a

Clinical Case



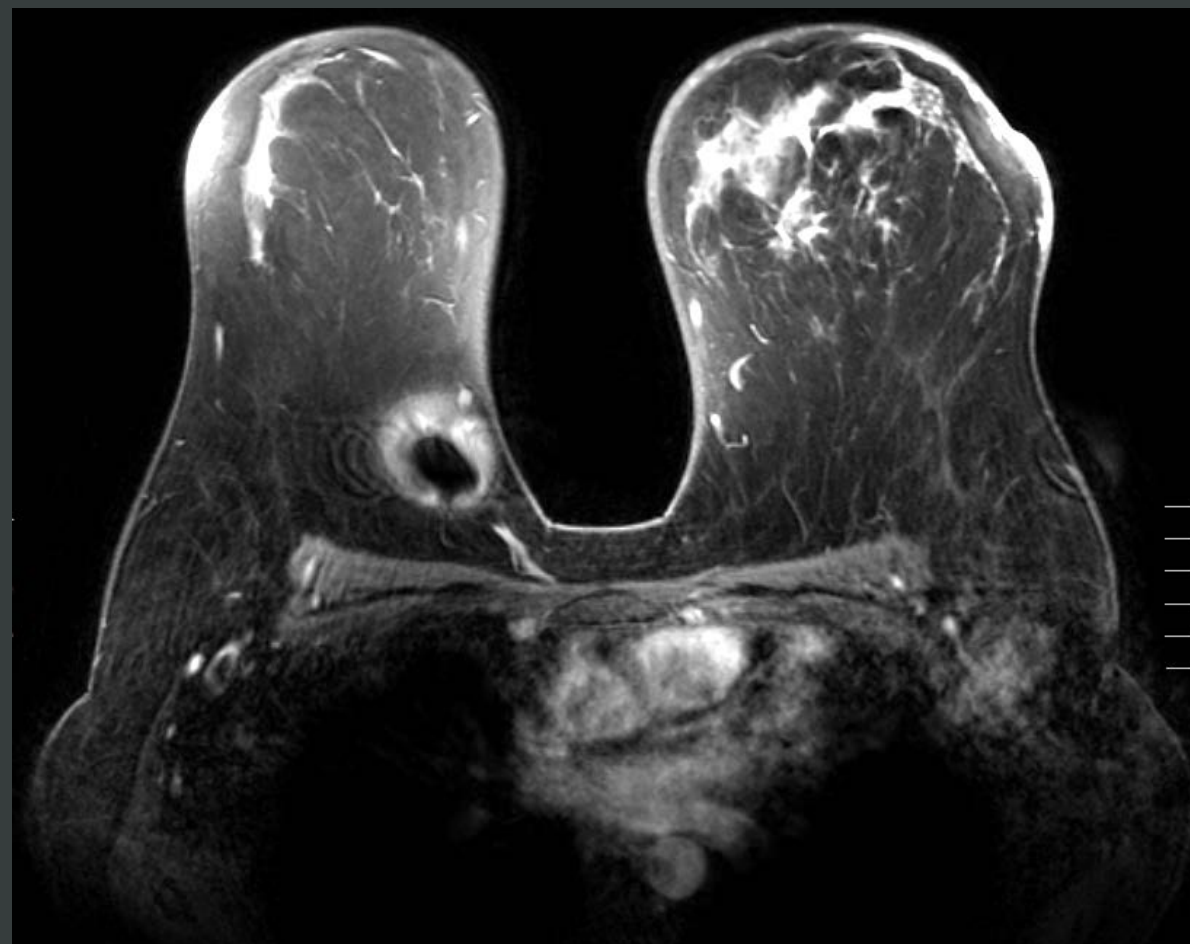
Clinical Case

- PMH: Depression, Anxiety
- Meds: MVI
- ALL: NKDA
- SH: She does not use tobacco or alcohol
- FH: grandfather with colon CA, aunt with breast CA
- PE: BREAST: She is s/p bilateral mastectomy with tissue expanders in place. The skin is healing well. There are no palpable masses on the chest wall or axilla bilaterally.

MRI

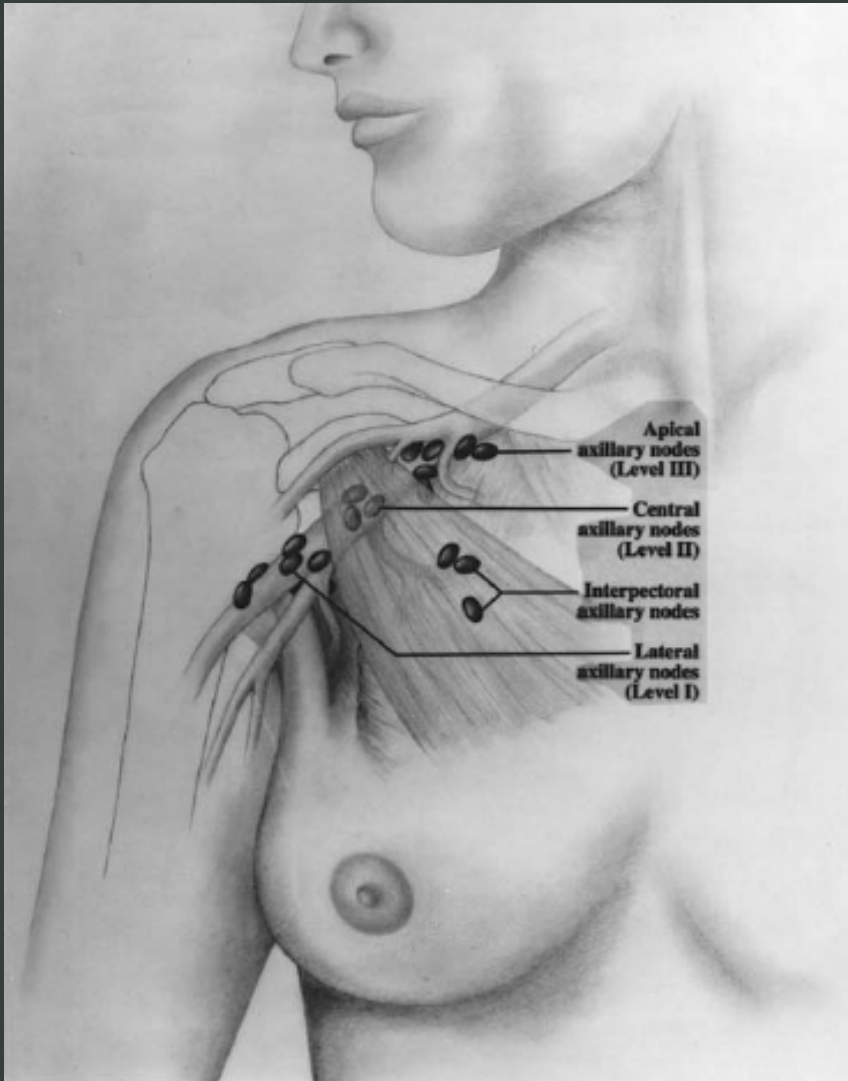


T1 Sagittal oblique level 1 lymph node 2.3 x 1.7 cm, level 2 lymph node 2.0 x 1.7 cm



T2 Axial T2 non-masslike reticular enhancement involving the upper and lower inner quadrants

Intro to PMRT



- Breast Cancer Statistics 2015 ACS

New Diagnoses: 234,190

Deaths: 40,730

- Significant risk of loco-regional failure following mastectomy:

- 15-35% for 4+ positive LN (pN2)

- 20-30% for T3 tumor (>5cm)

- PMRT reduces LRF in these high risk groups by ~5-10%

Intro to PMRT

Primary tumor (T)* ^{1Δ}	
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 (Paget 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 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)
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 [§]
<p>Posttreatment ypT.[‡] The use of neoadjuvant therapy does not change the clinical (pretreatment) stage. Clinical (pretreatment) T will be defined by clinical and radiographic findings, while y pathologic (posttreatment) T will be determined by pathologic size and extension. The ypT will be measured as the largest single focus of invasive tumor, with the modifier "m" indicating multiple foci. The measurement of the largest tumor focus should not include areas of fibrosis within the tumor bed.</p>	

Intro to PMRT

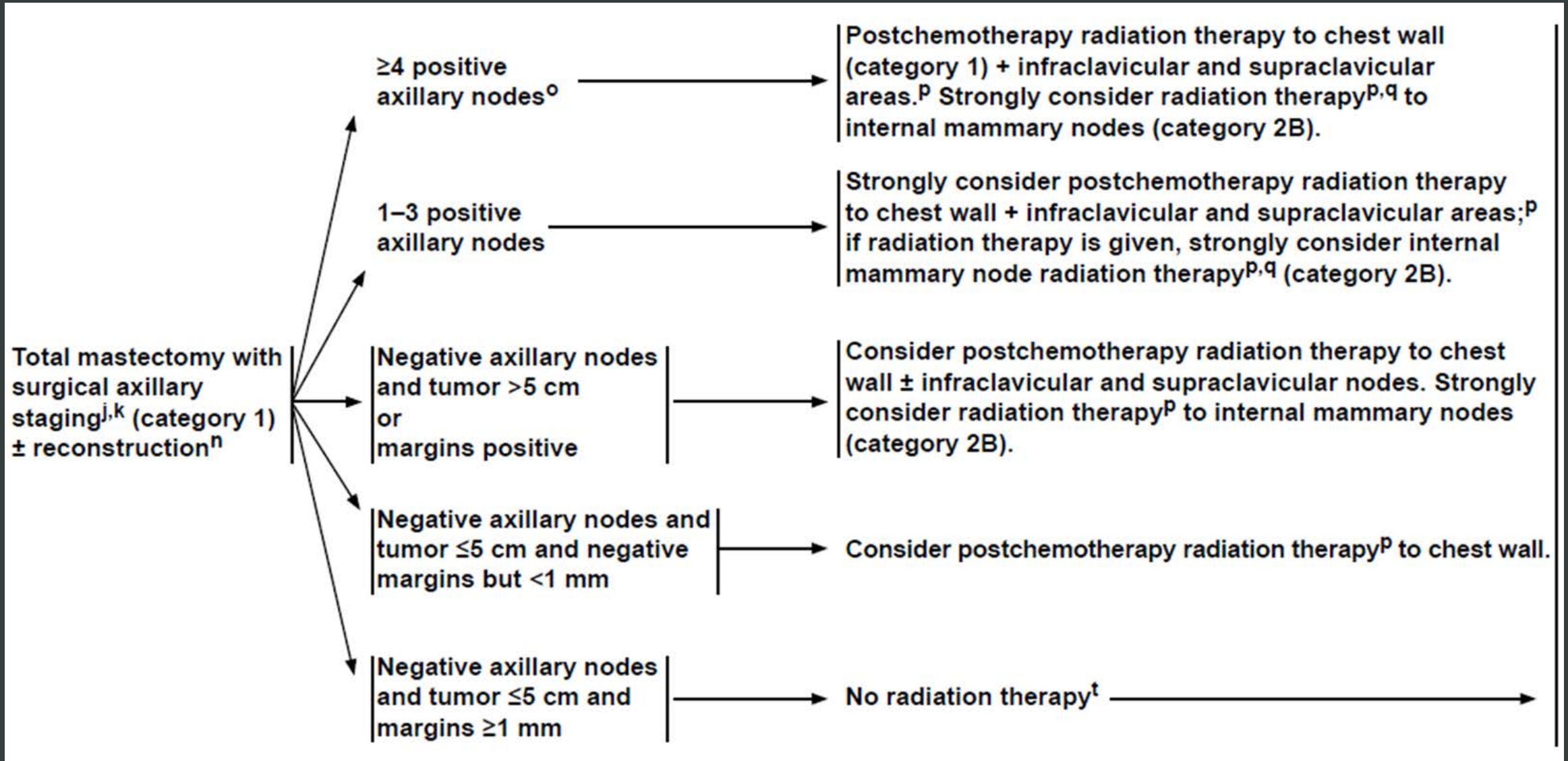
Pathologic (pN) ^{†**}	
pNX	Regional lymph nodes cannot be assessed (eg, previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis identified histologically
pN0(i-)	No regional lymph node metastases histologically, negative immunohistochemistry (IHC)
pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including isolated tumor cell clusters (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
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 ^{ΔΔ}
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 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected ^{ΔΔ}
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 <i>absence</i> 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 <i>absence</i> 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 <i>presence</i> 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 ^{ΔΔ} ; 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 <i>presence</i> 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 ^{ΔΔ}
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Guidelines: NCCN 2015 (paraphrased)

1. PMRT is RECOMMENDED when >3 positive nodes (to CW, SC, IC, STRONGLY CONSIDER IM)
2. PMRT should be STRONGLY CONSIDERED when 1-3 +N AND >5cm tumor or +margin (if given: CW, SC, IC, STRONGLY CONSIDER IM)
3. PMRT should be STRONGLY CONSIDERED* when 1-3 +N (if given: CW, SC, IC, STRONGLY CONSIDER IM)
4. PMRT should be CONSIDERED for node-negative patients with >5cm primary or +margin (if given: CW +/- SC and IC, STRONGLY CONSIDER IM)
5. PMRT usually not given for node-negative/clear margin/ <5cm, but CONSIDER (if given: CW only) if high risk of recurrence via:
Close margins <1mm, >2cm tumor, premenopausal, LVI, triple negative

*Divided NCCN panel on this rec, some think PMRT should be mandatory, others think it should only be considered

Guidelines: NCCN 2015 (paraphrased)



Notable Studies of PMRT

Should we PMRT?

- Danish 82b (CMF +/- PMRT to CW, SC, IM)
- Danish 82c (Tamoxifen x1y +/- PMRT to CW, SC, IM)
- British Columbia (CMF +/- PMRT-cobalt60 to CW, SC+PAB, IM)

A closer look at N1 (1-3 +Nodes)

- EBCTCG Meta-analysis (4 v 16% LRF)
- Harvard/MGH (10y DFS 75% vs 93%)

A closer look at T3 (Tumor >5cm)

- MGH/MDACC/Yale (PMRT warranted for T3 with LVI: 4 v 21% LRF)

A closer look at T2 (Tumor <5cm) with adverse features

- China (Triple negative T1/2N0/1 Chemo +/- PMRT 5y OS 90 v 80% favoring RT)

A closer look at fields

- Korean Supraclavicular (N1 without PMRT. Rate of isolated SC recurrence 2.7%)
- French Internal mammary (N1 or medial tumor, +/- IMN RT, No OS/DFS difference)
- EORTC (+/- Regional nodal irradiation, trend for OS, sig. benefit for DFS, CSS)
- MA20 (+/- Regional nodal irradiation, no OS benefit, sig. benefit for DFS)

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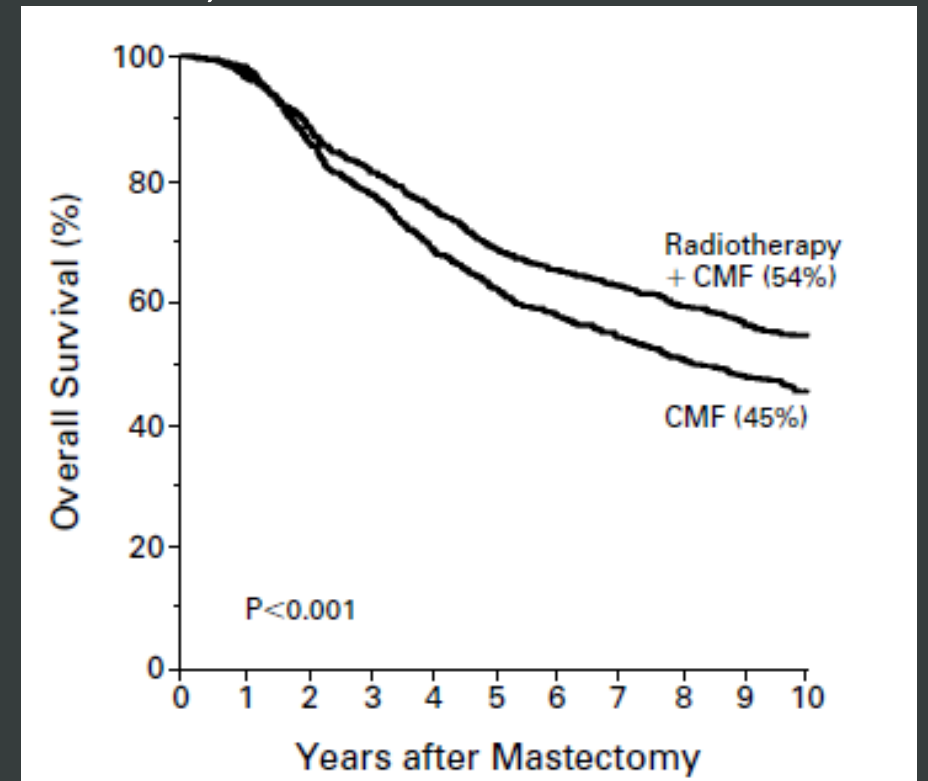
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Notable Studies of PMRT: Should we PMRT?

Danish 82b

- Prospective RCT (1982-1989)
- 1708 premenopausal women s/p mastectomy & ALND (median of 7 LNs removed)
- With one or more risk factors including positive axillary LN, tumor > 5 cm, invasion of skin or pectoral fascia.
- Randomized to CMF +/- PMRT (CW, SCV, IMNs)
- 50Gy/25fx or 48Gy/22fx
- 10-yr LRR 9% vs 32% in favor of PMRT
- 10-yr OS 54% vs 45% in favor of PMRT

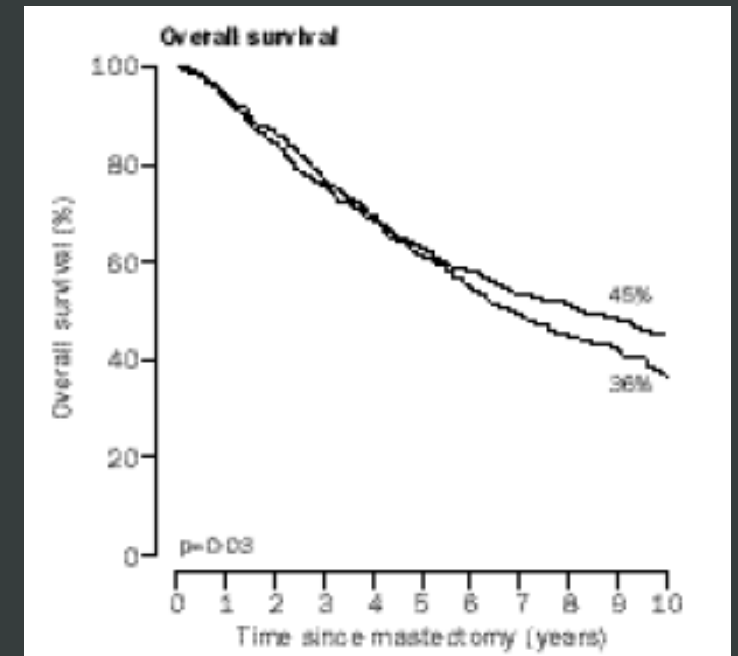


Overgaard M et al. N Engl J Med. 1997 Oct 2;337(14):949-55

Notable Studies of PMRT: Should we PMRT?

Danish 82c

- Prospective RCT (1982-1990)
- 1375 postmenopausal women s/p mastectomy & ALND
- With one or more risk factors including positive axillary LN, tumor > 5 cm, invasion of skin or pectoral fascia.
- Randomized to Tamoxifen (1 yr) +/- PMRT (CW, SCV, IMNs)
- 50Gy/25fx or 48Gy/22fx
- 10-yr LRR 8% vs 35% in favor of PMRT
- 10-yr OS 45% vs 36% in favor of PMRT

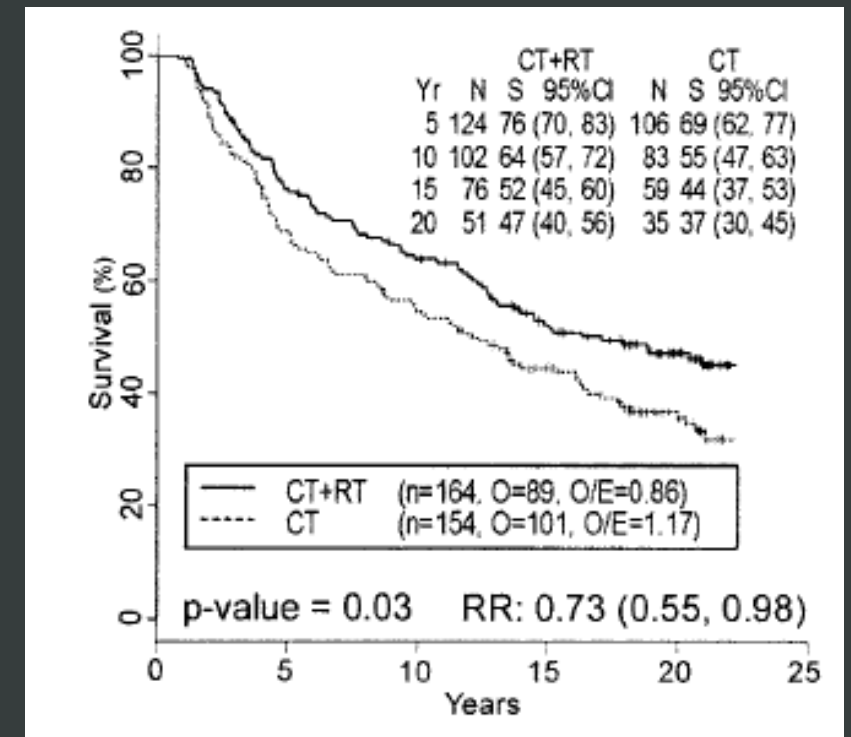


Overgaard M et al. Lancet. 1999 May 15;353(9165):1641-8

Notable Studies of PMRT: **Should we PMRT?**

British Columbia

- Prospective RCT (1979-1986)
- 318 premenopausal women s/p mastectomy & ALND with positive axillary LN
- Randomized to CMF) +/- PMRT (cobalt-60)
 - CW = 37.5Gy/16 fx w/ tangents
 - SCV (w/ PAB), 35 Gy/16 fx
 - Bilat. IM, 37.5 Gy/16fx
- 20yr LRR 10% vs 28% in favor of PMRT
- 20yr OS 37% vs 47% in favor of PMRT



Ragaz J et al. N Engl J Med. 1997 Oct 2;337(14):956-62

Ragaz J et al. J Natl Cancer Inst. 2005 Jan 19;97(2):116-26

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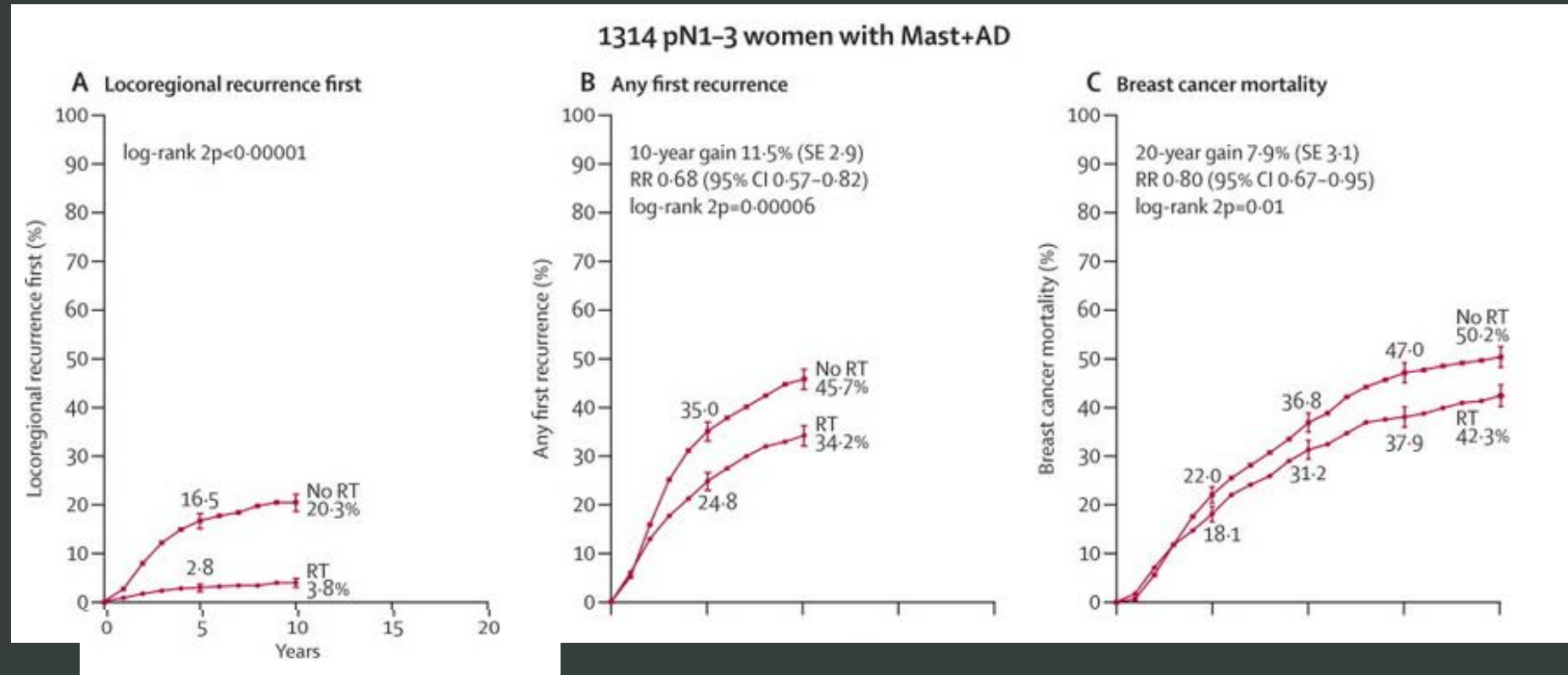
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Notable Studies of PMRT: A closer look at N1 (1-3 +Nodes)

EBCTCG Meta-analysis 2014

- Meta-analysis of 22 randomized trials
- N= 8100 randomized +/- PMRT
- Median follow-up 9.4 years per woman ~1300 had 1-3 positive nodes
- PMRT reduced locoregional recurrence (2p<0.00001), overall recurrence (RR 0.68, 95% CI 0.57–0.82, 2p=0.00006), and breast cancer mortality (RR 0.80, 95% CI 0.67–0.95, 2p=0.01).
- pN1–3=one to three pathologically positive nodes

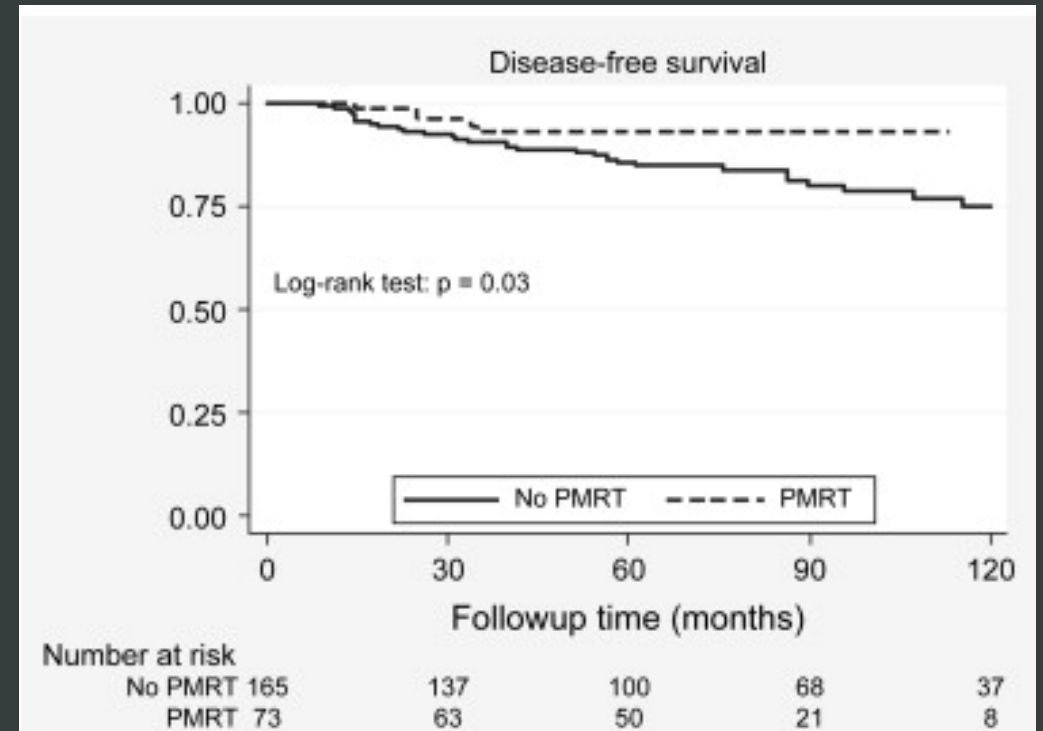


Lancet 2014;383:2127-2135

Notable Studies of PMRT: A closer look at N1 (1-3 +Nodes)

Harvard (MGH)

- Retrospective data from Harvard (1990-2004)
- 230 pts pT1/2 N1 treated with mastectomy
- Compared outcomes for those who did/didn't receive PMRT
- 10-yr DFS was 75% without PMRT vs. 93% with PMRT



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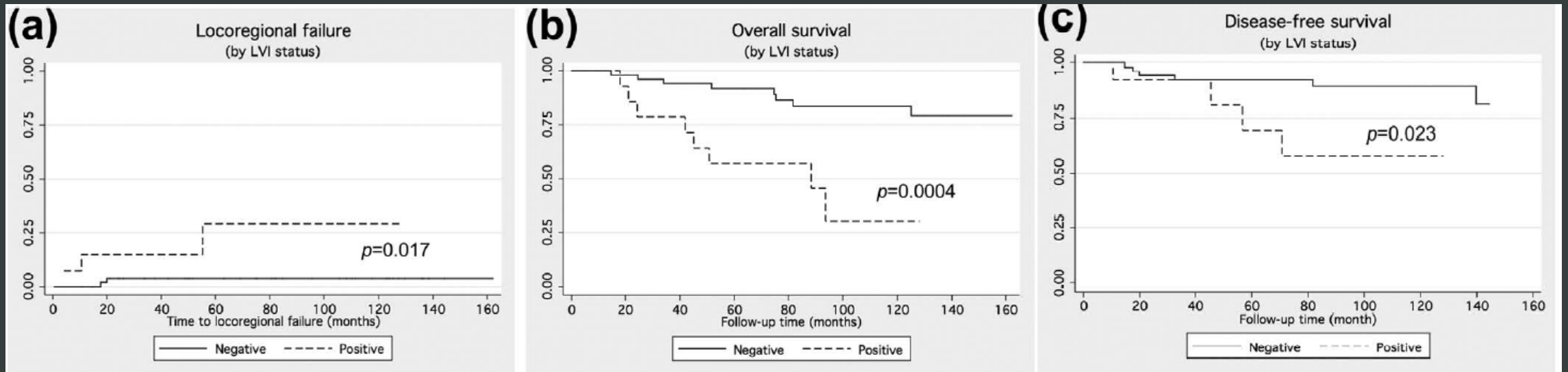
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Notable Studies of PMRT: T3 (Tumor >5cm)

MGH/MDACC/Yale (1981-2002)

- Retrospective: 70 pts T3N0 treated with mastectomy + chemo, but no RT
- Median f/u of 7yrs
- 5-yr LRF was 7.6% overall (with 4/5 occurring at chest wall)
- LVI was a/w worse LRF (21% vs. 4%), DFS and OS
- Conclusion: T3 N0 alone may not need RT, but if LVI+ then it is warranted.



Floyd SR, Int J Radiat Oncol Biol Phys. 2006 Oct 1;66(2):358-64.

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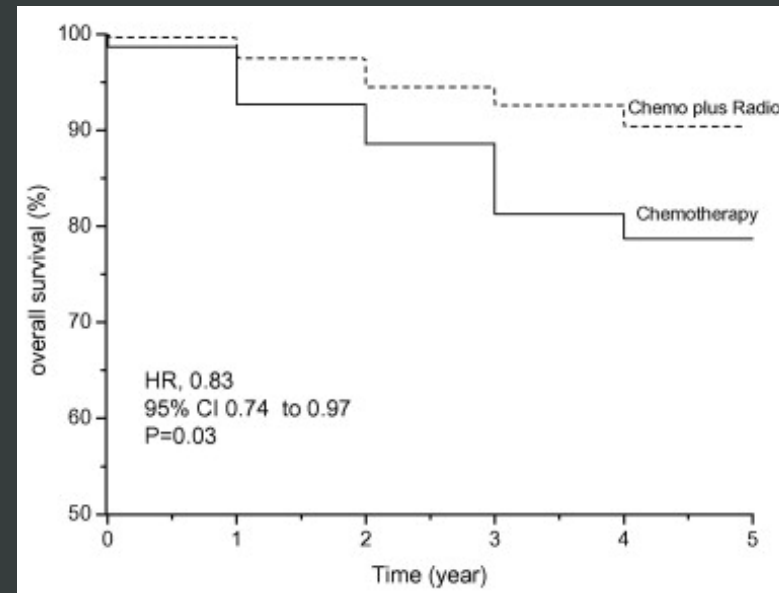
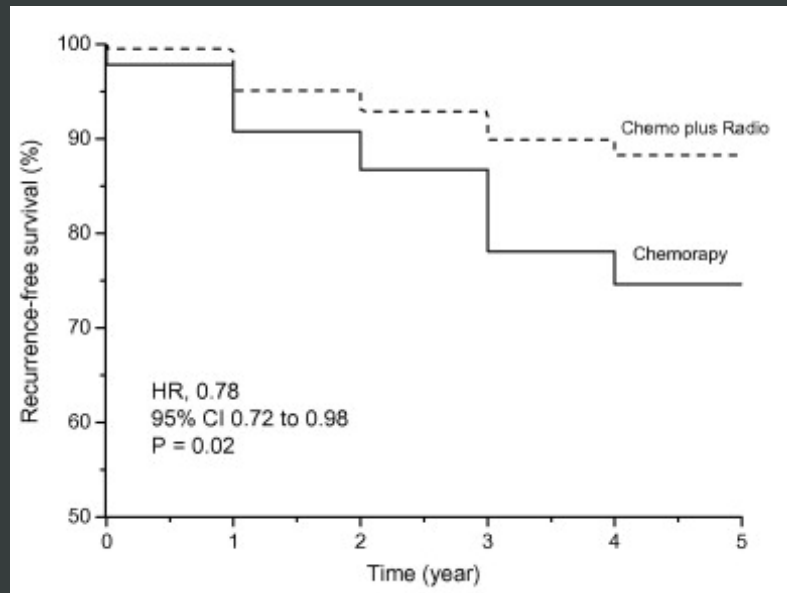
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Notable Studies of PMRT: T2 (Tumor <5cm) with adverse features

CHINA

- Conversely there are studies suggesting that T2 N0 tumors with risk factors (Grade 3, LVI, close margin) can have recurrence rates as high as 20-40%
- A phase III RCT from China of stage II triple negative pts (T1/2 N0/1) s/p mastectomy showed a RFS and OS benefit to PMRT & chemo vs. chemo alone.



- Therefore T/N stage should not be used alone when making treatment decisions about PMRT

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Notable Studies of PMRT: **A Closer Look at Fields**

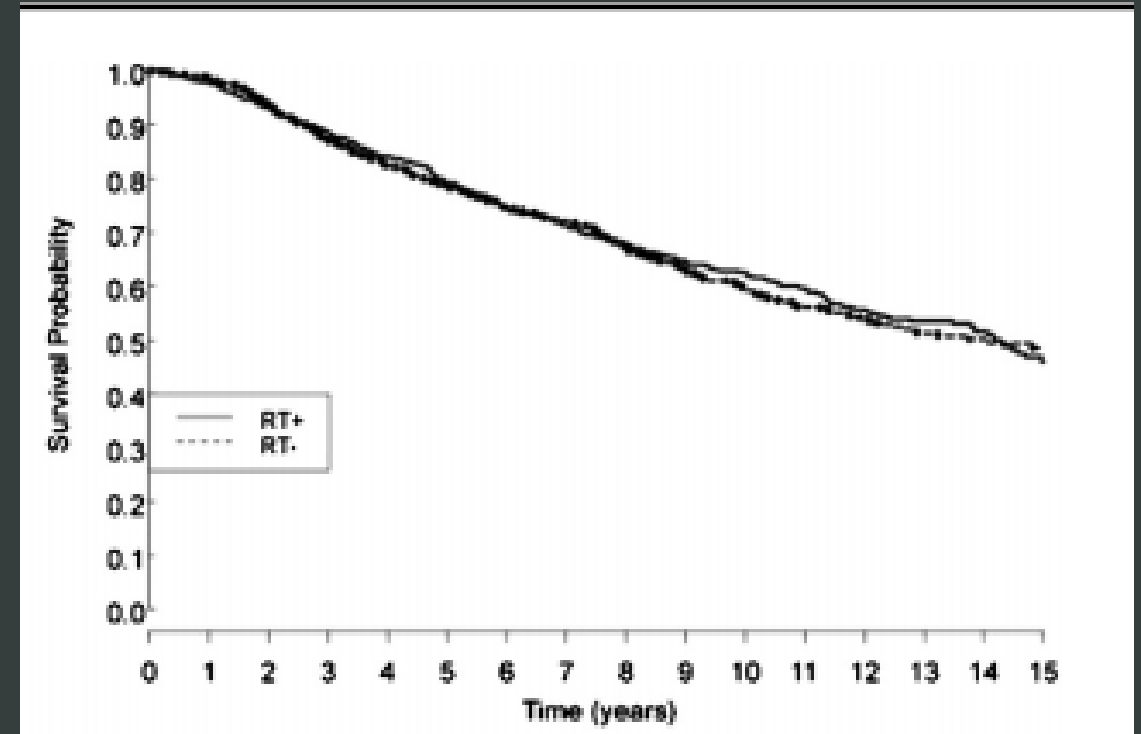
Korean Supraclavicular

- Retrospective study from Korea (1994-2003)
- 302 patients with pN1 breast cancer s/p mastectomy without chest wall or supraclavicular RT
- Median 17 axillary LNs removed
- Rate of SCV recurrence was 8.9%, but rate of SCV recurrence without distant recurrence was 2.7%
- Predictors for SCV recurrence were:
 - LVI, ECE, 2-3 + LNs (vs 1), involved level II/III axilla, $\geq 20\%$ + LNs
- If ≥ 2 risk factors then SCV RFS was 73% vs. 97%

Notable Studies of PMRT: **A Closer Look at Fields**

French Internal Mammary

- Prospective RCT from France (1991-1997)
- 1334 patients with pN1 breast cancer or medial tumors s/p mastectomy treated with RT to chest wall and SCV
- Randomized to +/- IMN RT (50Gy)
- Median follow-up of 8.6 years
- No difference in DFS or OS



Notable Studies of PMRT: A Closer Look at Fields

EORTC Regional Nodes

Phase III RCT, 1996-2004

N=4004 with early stage BC (76% BCT)

All had central/medial tumor or externally located tumor with axillary involvement.

All with whole breast/chestwall XRT but randomized to +/- IM and SCV node irradiation (50/25)

Primary Endpoint: OS

Secondary Endpoints: DFS, SFDD, CSM

Median F/U 10.9 years

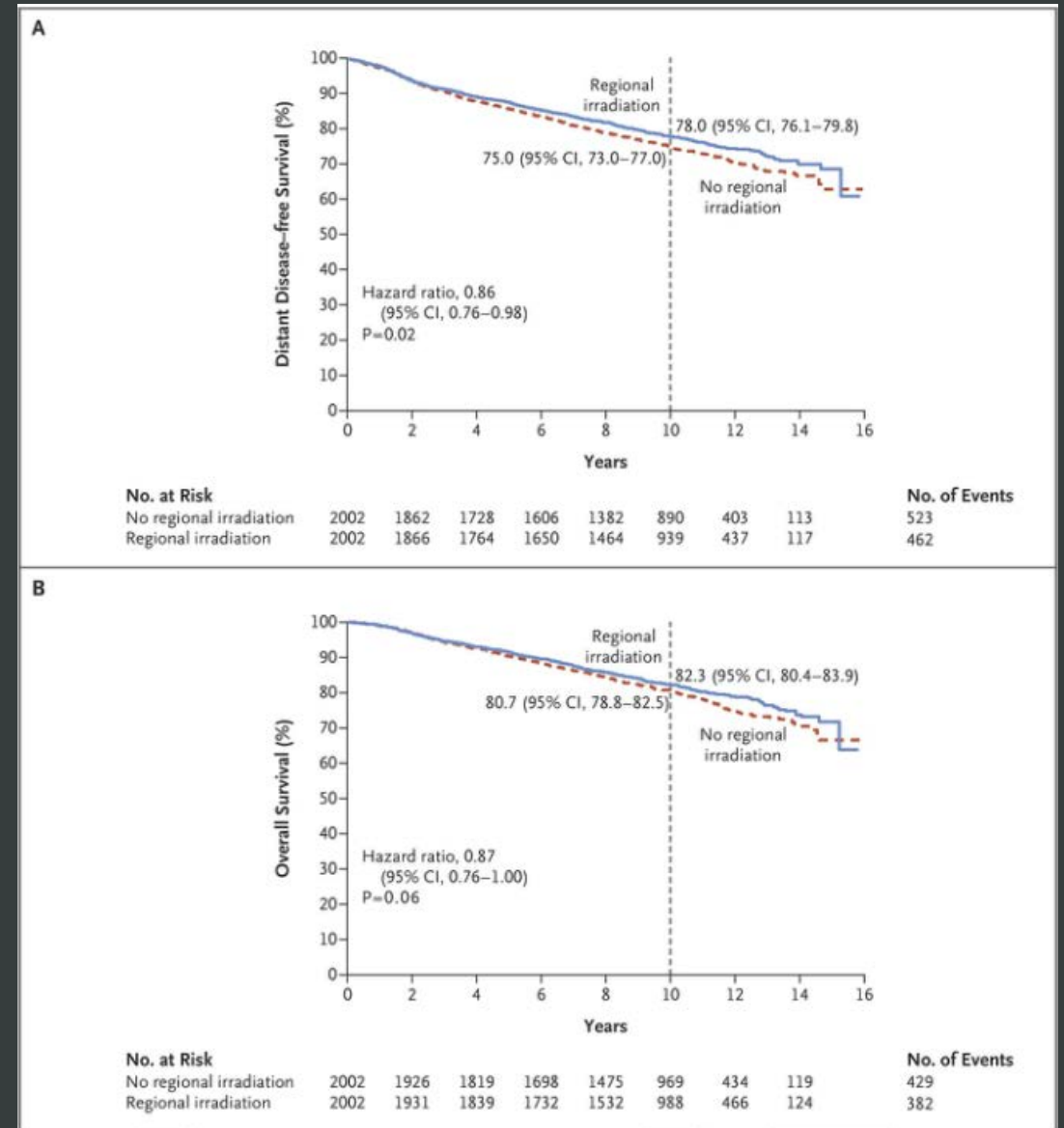
OS 82.3 vs 80.7% (p=0.06)

DFS 72.1 vs 69.1 (p= 0.04)

SFDD 78 vs 75% (p=0.02)

CSM 12.5 v 14.4% (P=0.02)

Poortmans, N Engl J Med 2015; 373:317-327 July 23, 2015



Notable Studies of (PMRT): **A Closer Look at Fields**

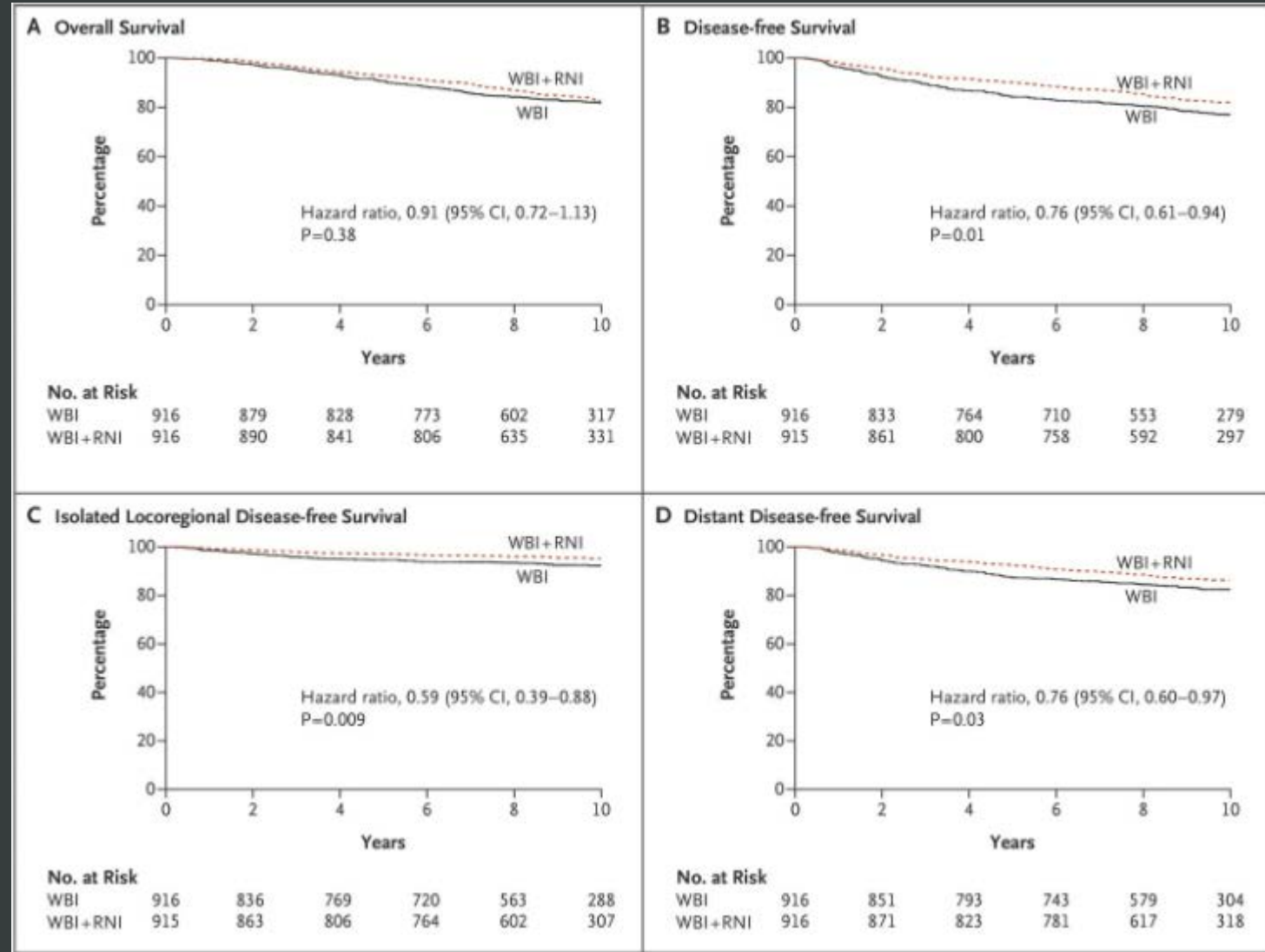
MA20 Regional Nodes

Not PMRT (all had breast conserving surgery)
 N= 1832, whole breast +/- regional nodal
 Regional nodal XRT: IM, SCV, Axillary (50/25)
 Median f/u 9.5y
 All had node+ or high risk node- (>5cm primary,
 <10 nodes with at least 1 grade 3 histology ER-, LVI)

Primary outcome: OS
 Secondary outcomes: DFS, LRDFS, DDFS

OS: 82.8 v. 81.8% P=0.38
 DFS: 82 v 77 % P=0.01
 LRDFS: 95.2 v 92.2% P=0.009
 DDFS: 86.3 v 82.4% P=0.03

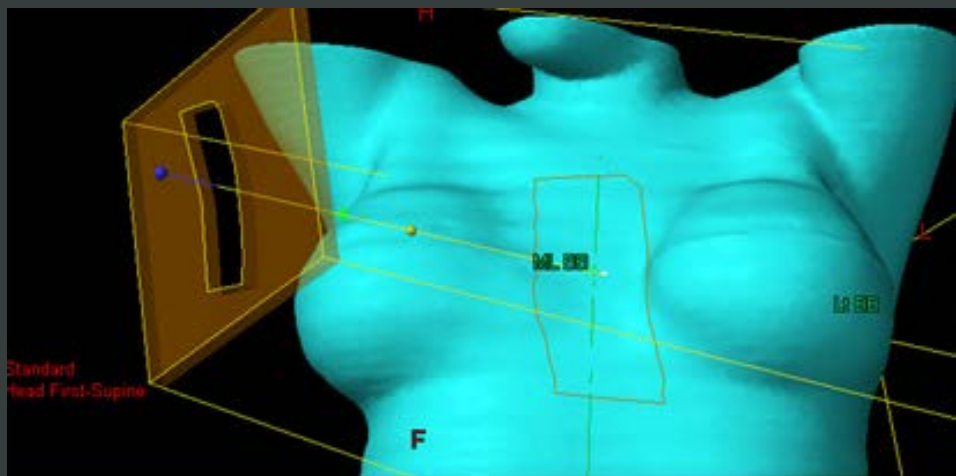
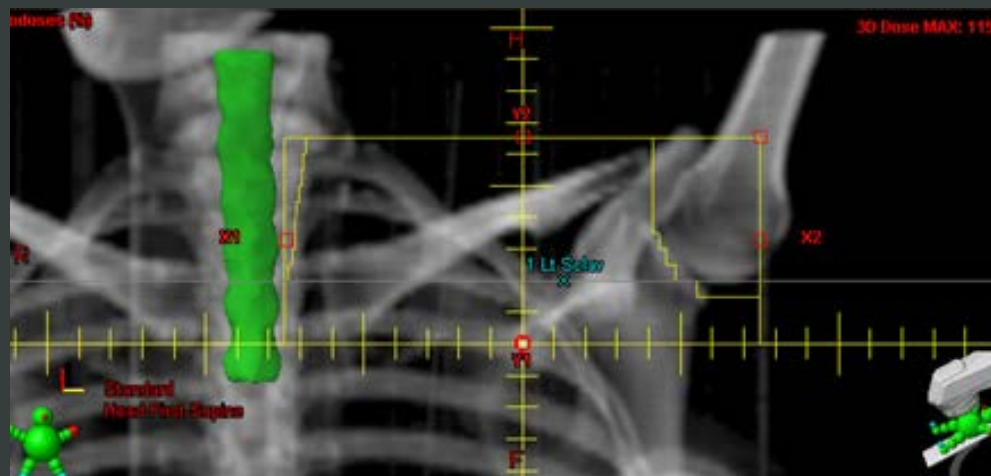
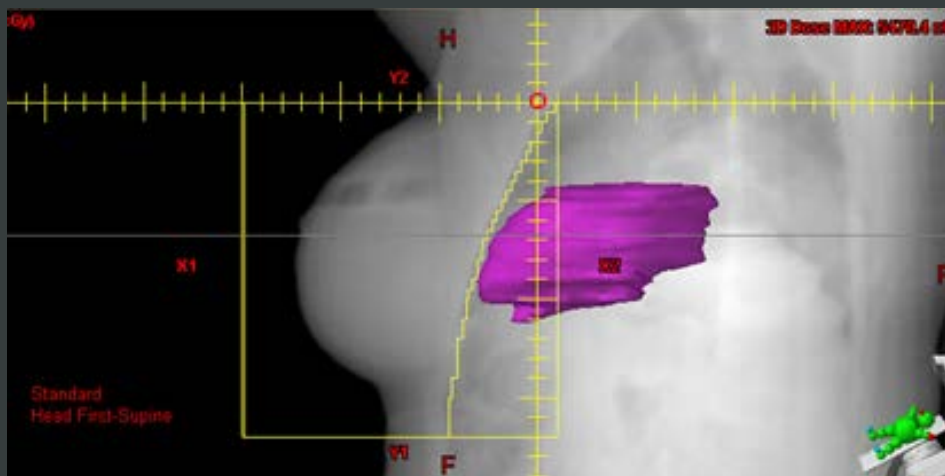
Lymphedema 8.4 v 4.5% P= 0.001
 Whelan, N Engl J Med 2015; 373: 307-316 July 23, 2015



Case Conclusion

- 36 y/o woman with cT3N1M0 stg IIIa left breast IDC s/p neoadjuvant AC+T f/b bilateral mastectomies and left ALND (pT3N2aM0 stg IIIA)
- She was treated with tangent photon fields (w/ bolus), a medial electron field, a supraclavicular field, and a posterior axillary boost.
- Prescribed dose was 50.4Gy in 28fx

Case Conclusion: Fields and Borders



Summary

- Case: PMRT was clearly indicated
- Intro to PMRT: Can reduce LRF in high risk groups by ~5-10%
- Guidelines: Treat >3 +N, most +M, >5cm
- Studies: Danish/Canadian (+/- PMRT), EORTC/MA20* (+/- regional nodes)
- Case conclusion: Pt unfortunately had distant failure, passed as inpatient in 2013