Congreso Chileno de Cancerologia

Early stage breast cancer: Radiotherapy perspective

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Mastectomy vs BCT

- Based on multiple phase III trials, there is equivalent long-term survival & DFS
- All trials have ≥15yrs f/u
- Outcome similar in node positive and node-negative cases and in trials that included tumors up to 4-5cm

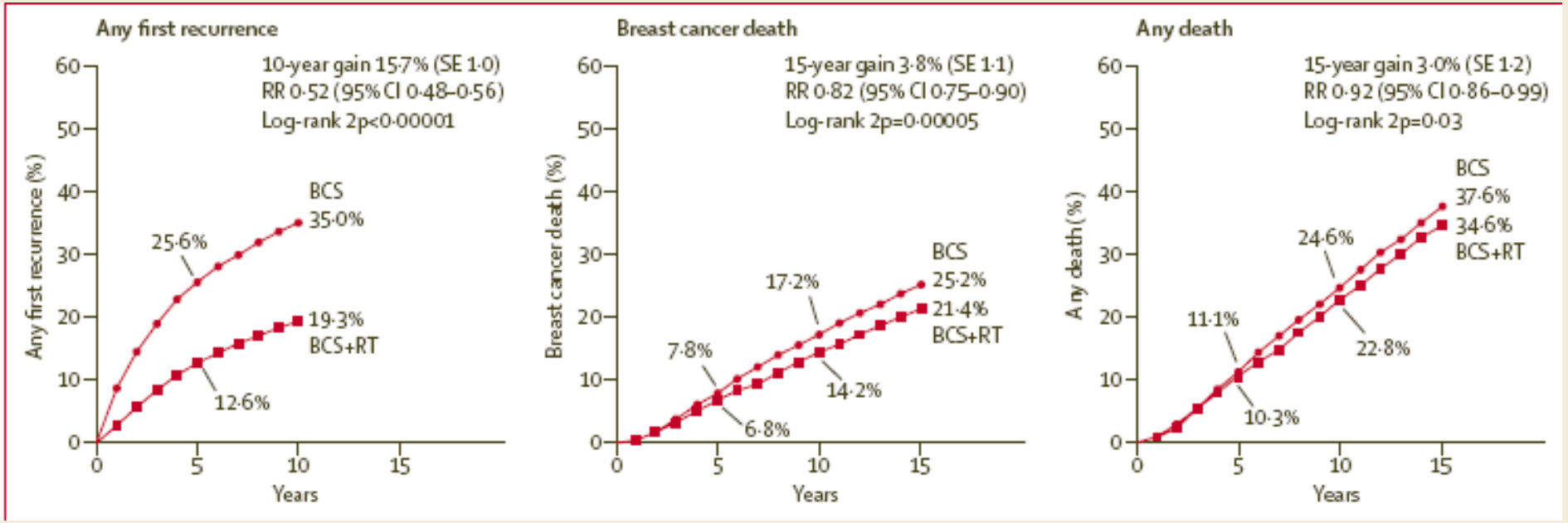
Does mastectomy provide better LRC?: EORTC 1081 & DBCG 82TM: Pooled Analysis:

- 1,772 pts (EORTC 974 + DBCG 898)
  - BCT 879
  - MRM 893
- Median f/u 9.8yrs
- Local recurrences
  - BCT: all 79/879 (10.1%) isolated 60/879 (6.8%)
  - MRM: all 80/893 (8.9%) isolated 54/893 (6%)

Outcome	BCT (n=879)				Mastectomy (n=893)				P
	At 5 yrs		At 10 yrs		At 5 yrs		At 10 yrs		
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	
Local RFS	93	91-95	90	87-92	92	90-94	91	88-92	.96
Distant RFS	76	73-79	66	62-69	76	73-80	68	65-71	.38
OS	84	81-86	67	64-71	83	80-86	67	64-70	.96

Voogd, JCO 2001

Can RT be omitted s/p surgery? EBCTCG Meta-Analysis: 2011 Update



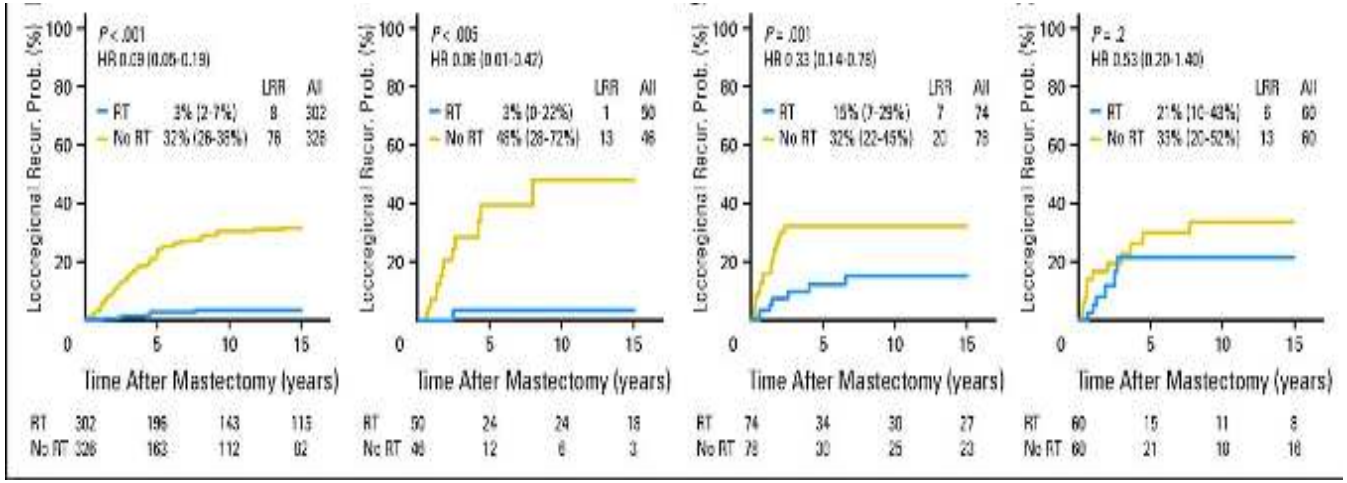
EBCTG gave us the “4:1 rule”

Greater XRT Efficacy in ER+

- Kyndi DBCG N = 1000

Rec+/H2N- Rec+/H2N+ TNBca

Rec-/H2N+



Kyndi M et al. JCO 2008;26:1419-1426

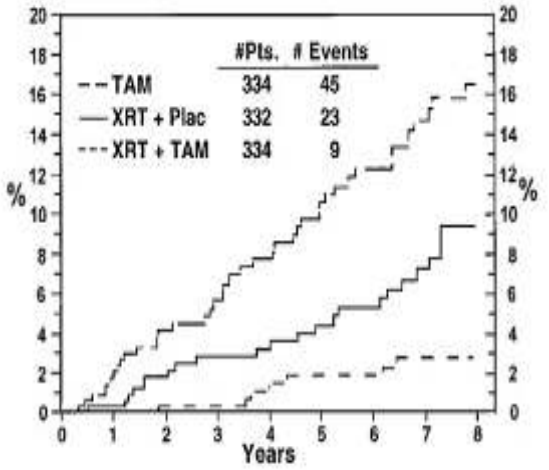
JOURNAL OF CLINICAL ONCOLOGY

Quantify Luminal LRR

Can we do less in low risk patients?

NSABP B-21

- Can tamoxifen might be utilized in lieu of RT in selected patients?
  - 1009 women T ≤1 cm post-lumpectomy randomized to tamoxifen, RT, or both
    - ER testing not required
    - 20% of patients <50
    - Negative margins no tumor on ink
  - 8-year IBTR
    - **16.5% with tam alone**
    - 9.3% with RT
    - 2.8% with both



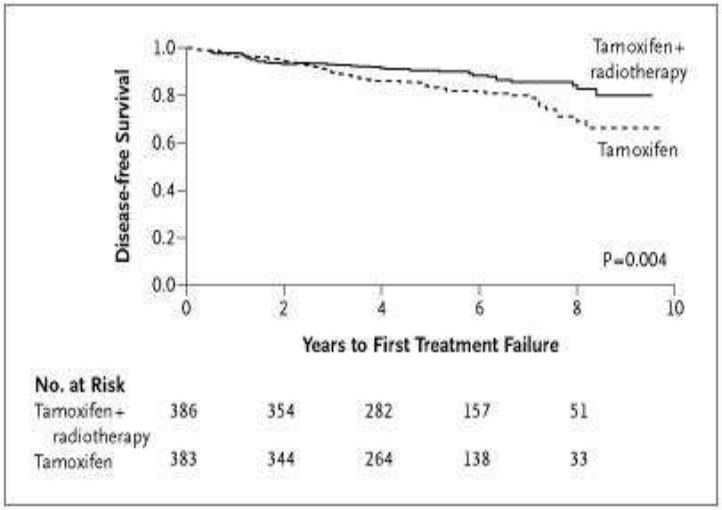
Tamoxifen, Radiation Therapy, or Both for Prevention of Ipsilateral Breast Tumor Recurrence After Lumpectomy in Women With Invasive Breast Cancers of One Centimeter or Less

By Bernard Fisher, John Bryant, James J. Dignam, D. Lawrence Wickerham, Eleftherios P. Mamounas, Edwin R. Fisher, Richard G. Margolese, Lois Nesbitt, Soonmyung Paik, Thomas M. Pisansky, and Norman Wolmark for the National Surgical Adjuvant Breast and Bowel Project

Journal of Clinical Oncology, Vol 20, No 20 (October 15), 2002: pp 4141-4149

Canadian Trial

- Patients 50+ with T1-2 node-negative breast ca randomized to observation vs RT after BCS and tamoxifen (Fyles et al. NEJM 2004)
  - IBTR 8% vs 1% at 5 years
  - At 8 years, 18% vs 4%



- Planned subgroup analysis of 611 women with T1, receptor-positive tumors: IBTR 6% vs 0.4% at 5 years and **15%** vs 4% at 8 years

CALGB 9343

- Patients
  - 636 women, age 70+
  - Clinical stage I, ER+
- Randomization
  - Tamoxifen +/- RT
- 10-yr LRR 10% vs 2% (favoring +RT), no significant difference in DMs, breast cancer-specific mortality, or all-cause mortality
- Interpretation
- Impact on practice

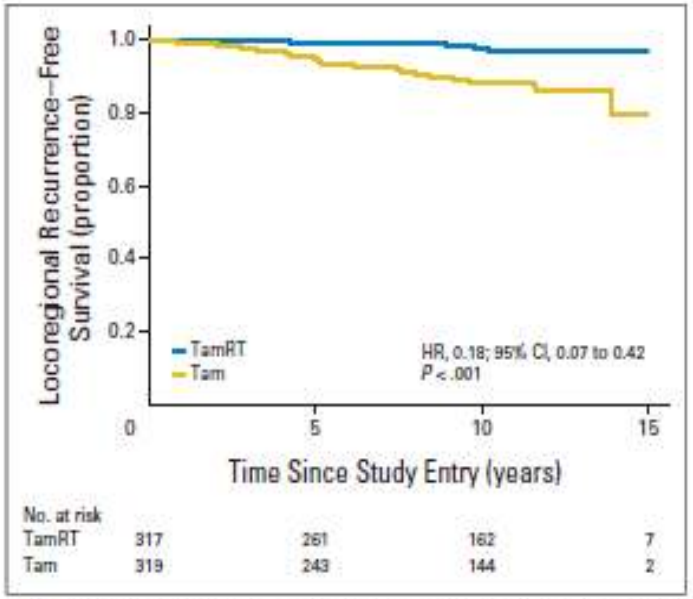


Fig 2. Time to local or regional recurrence. HR, hazard ratio; Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.

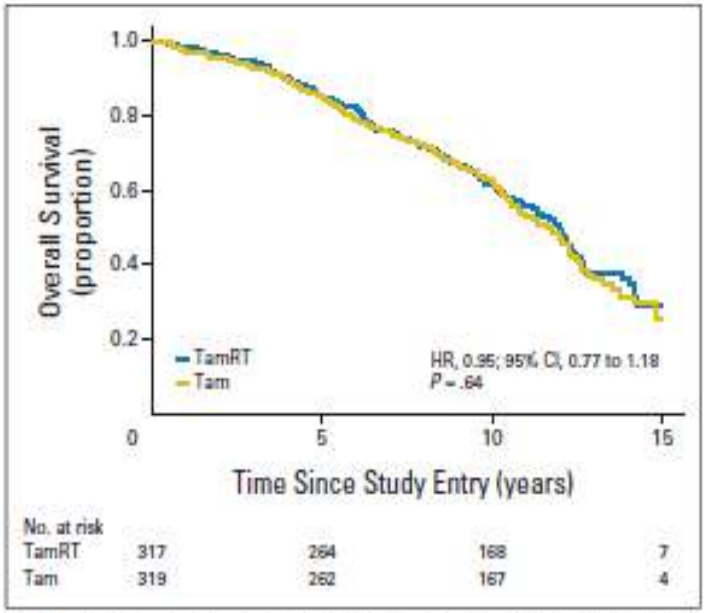
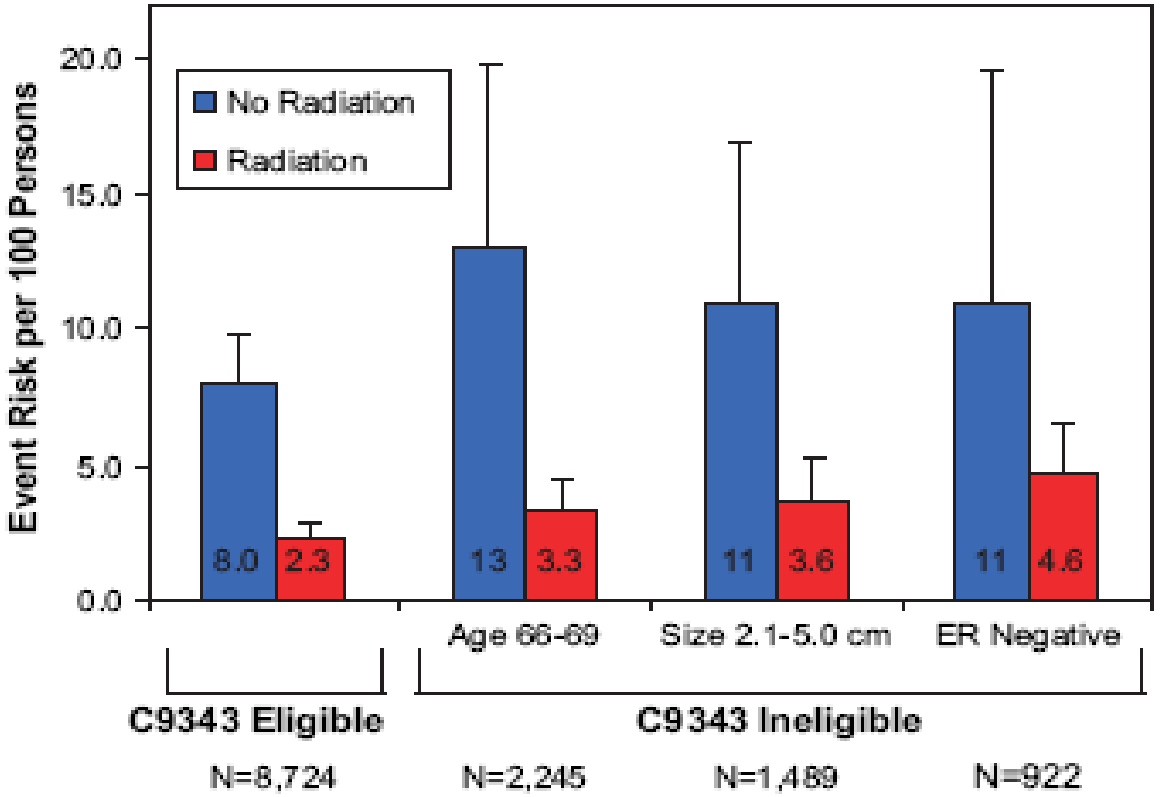


Fig 5. Overall survival. HR, hazard ratio; Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.

Off Trial?

SEER Medicare Database
CALGB 9343: Cannot be Generalized to Other Older Breast Cancer Pts



Smith JNCI 98:2006

What About When Luminal A Patients Don't Receive RT?

- 501 pts with available blocks (out of 769)
- All got tam, randomized RT or no RT
- IHC: ER. PR. HER2 (FISH), CK5/6,

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Identification of a Low-Risk Luminal A Breast Cancer Cohort That May Not Benefit From Breast Radiotherapy

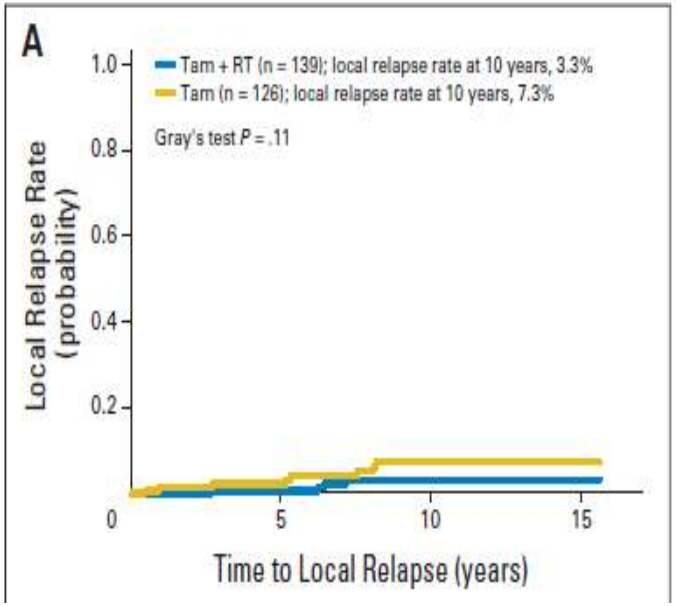


Table A5. Comparison of IBR Using the Clinical Models and Subtype Including Treatment Effects

Risk Group	No.	IBR at 10 Years (%)	95% CI	P
LR clinical luminal A	151	3.1	1.2 to 8.2	
High-risk clinical/subtype	341	11.8	8.6 to 16.1	.0063
LR clinical luminal A				
Tamoxifen + RT	77	5.0	1.6 to 15.0	
Tamoxifen	74	1.3	0.2 to 9.1	.42

Abbreviations: IBR, ipsilateral breast relapse; LR, low risk; RT, radiotherapy.

Subtype and LR after BCT

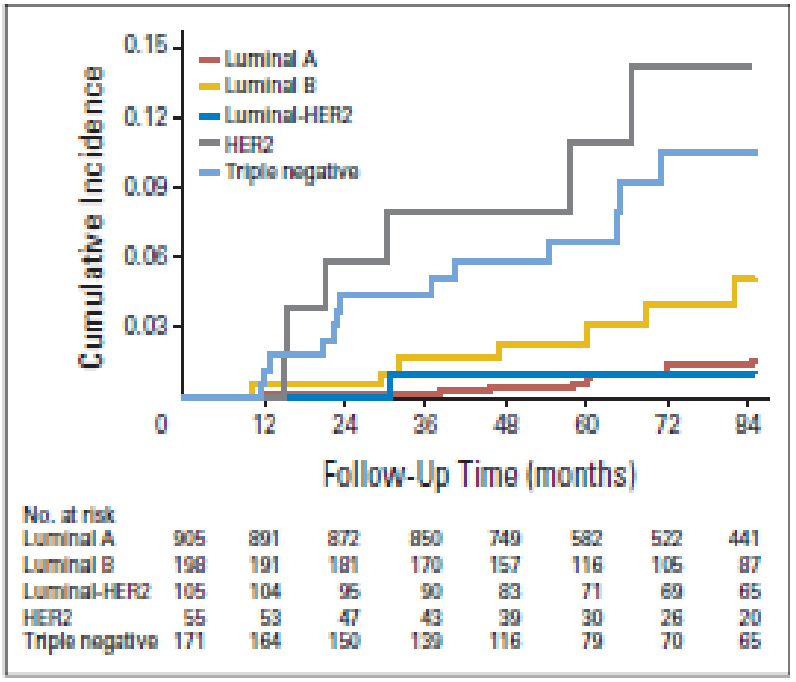
			% LR			
Study	Med FU	n	Lum A	Lum B	HER2*	TN
Nguyen	5 yr	793	0.8	1.5	8.4	**7.1**
Arvold	5 yr	1434	0.8	2.3	10.8	**6.7**
Millar	5 yr	498	1.0	4.3	7.7	**9.6**
Voduc	10 yr	1461	8	10	21	**14**

* ***No adjuvant trastuzumab***

Nguyen PL, JCO 2008. 26: 2373. Millar EK, JCO 2009. 27: 4701.
Voduc KD, JCO 2010. 28: 1684. Arvold ND, JCO 2011. 29: 3885.

Should we omit entirely? 3 Open trials = wait

- 5-year cumulative incidence of LR 0.8% in Luminal A patients (ER or PR+, Her2-, Gr 1-2) treated at Harvard (1997-2006)
- Must exercise caution—consider RTOG 9804: 0.4% and 3.2% rather than 50% RRR seen in meta-analysis

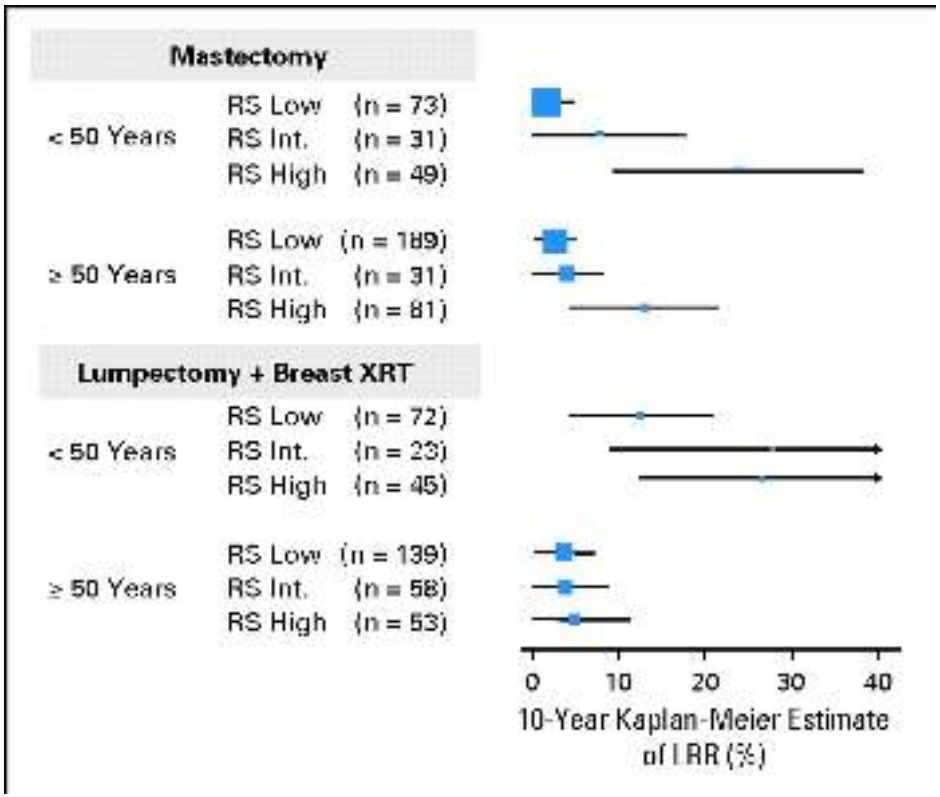


No. at risk								
Luminal A	905	891	872	850	749	582	522	441
Luminal B	198	191	181	170	157	116	105	87
Luminal-HER2	105	104	95	90	83	71	69	65
HER2	55	53	47	43	39	30	26	20
Triple negative	171	164	150	139	116	79	70	65

Fig 2. Unadjusted cumulative incidence of local recurrence by breast cancer subtype on the basis of competing risks analysis. HER2, human epidermal growth factor receptor 2.

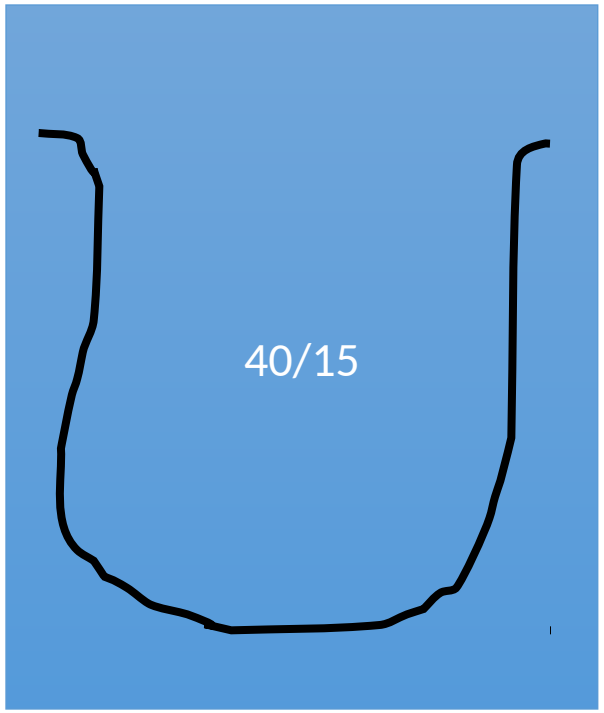
Might genomic assays allow even more sophisticated prediction of LRR?

- LRR significantly associated with RS risk groups in tamoxifen-treated patients
- Genomic profiling may discriminate better in unirradiated patients (mastectomy patients) than L+XRT

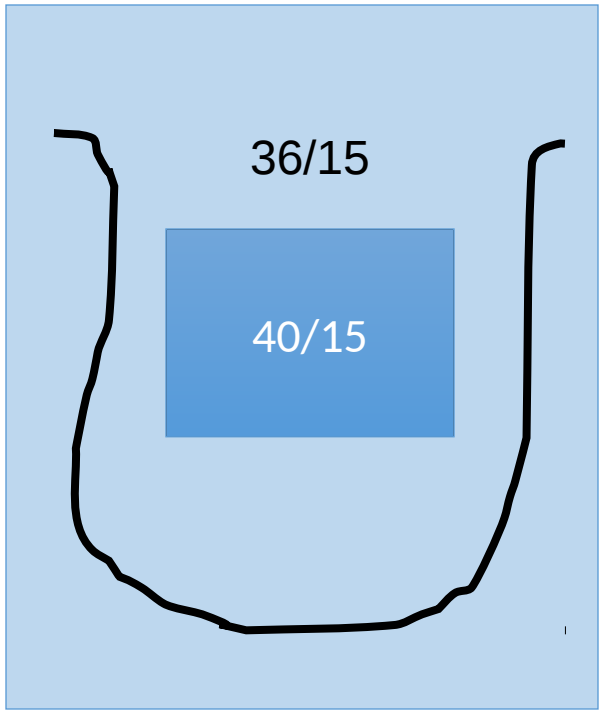


Mamounas E P et al. JCO 2010;28:1677-1683

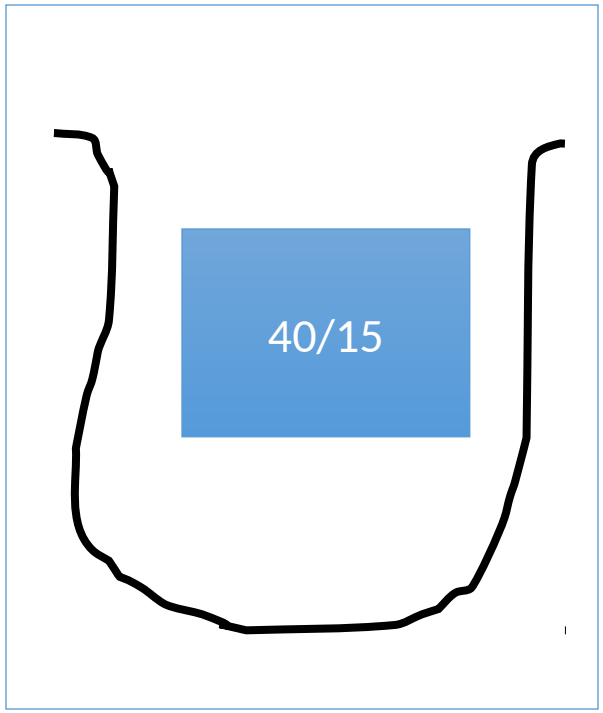
Omitting Boost in low risk biology: IMPORT LOW



1.1%



0.2



0.5

http://www.ecco-org.eu/Events/EBCC10/Abstract-search?abstractid=25356

Quantify Luminal LRR

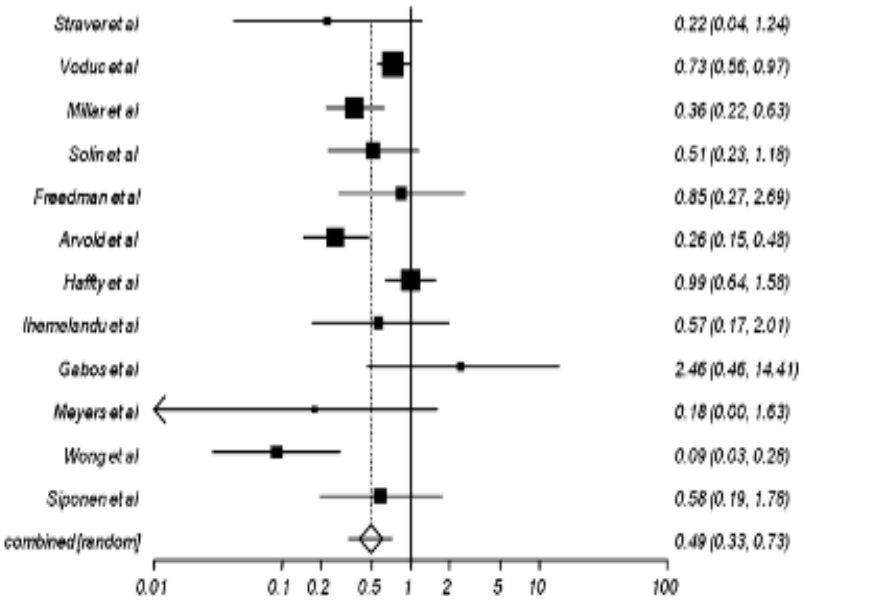
- After XRT Clinical low risk, 2-4%;
- Luminal A, < 2%.
- Omitting boost or PBI reasonable
- With high RS, consider increased boost and/or enroll on trial
- Wait on trials currently accruing to omit entirely

Quantify TNBC LRR relationship

What about early stage TNBC?

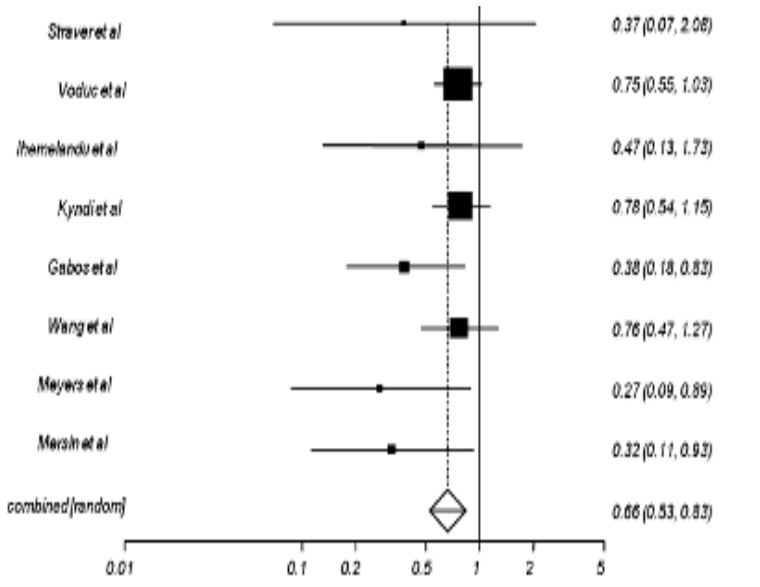
Meta-analysis: TN vs non-TN

BCT (n=7,174)



RR 0.49

Mastectomy (n=5,148)



RR 0.66

Lowery et al. *Breast Ca Res Treat* 2012

Randomized Trial of +/- PMRT in TNBC

- N=681 TNBC; 2001-2006
- Adjuvant chemotherapy: FEC or CMF
- Stage I or II; N0 82%, N1 16%
- Median follow-up: 64 months
- 1° Endpoint: Tx compliance and acute toxicity
- **2° Endpoints**:

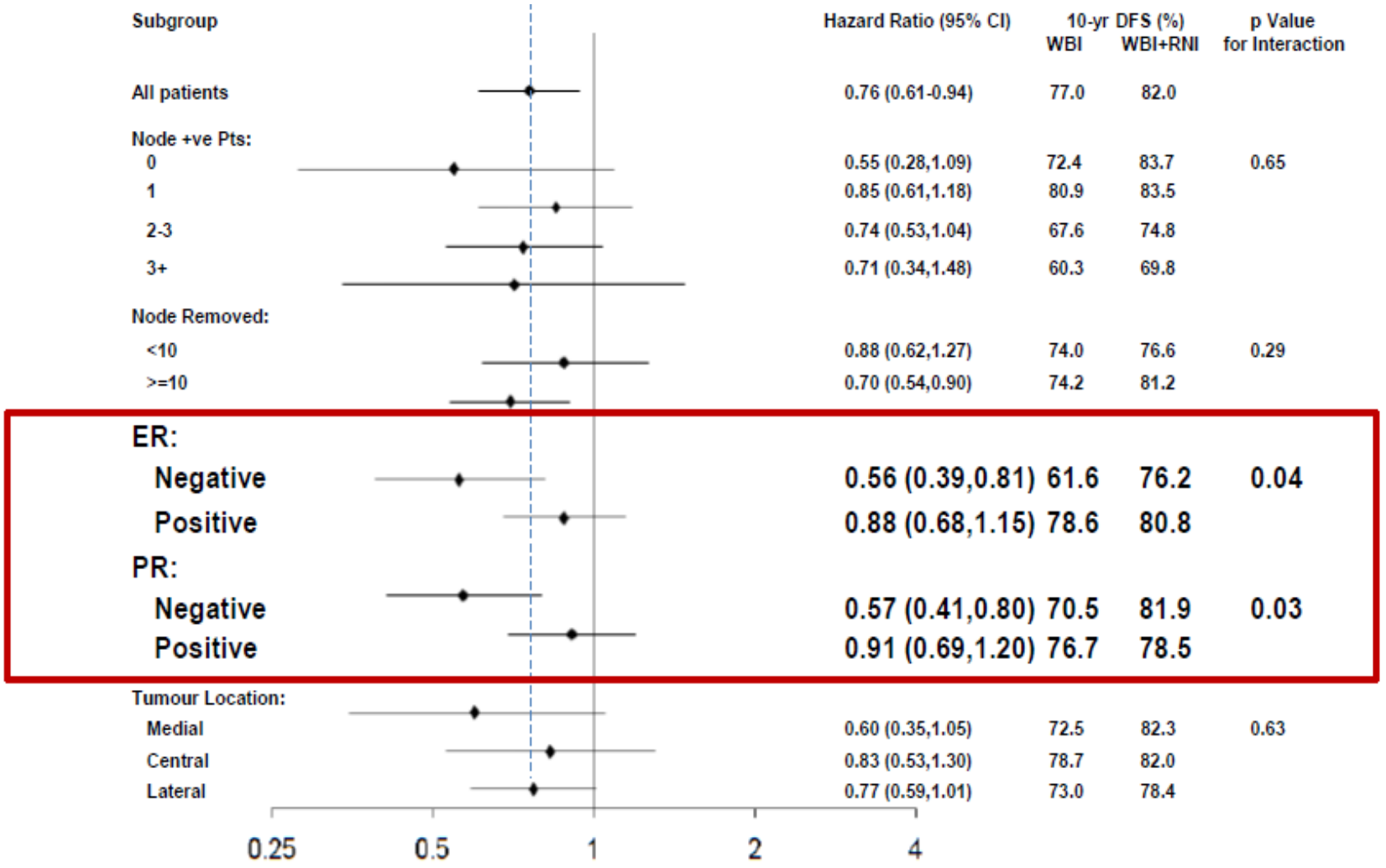
  5Y RFS: No PMRT 75% PMRT 88% p=.02
  5Y OS: No PMRT 79% PMRT 90% p=.03

Wang et al, Radiotherapy and Oncology 2011

LRF Rates in Node-Negative TNBC
No PMRT

Institution	n	Chemo	5Y LRF (%)
Shanghai	307	86%	7
U. Alberta	235	61%	10
MSKCC	198	80%	5
MGH/B.C.	172	60%	2
MDACC	78	68%	8

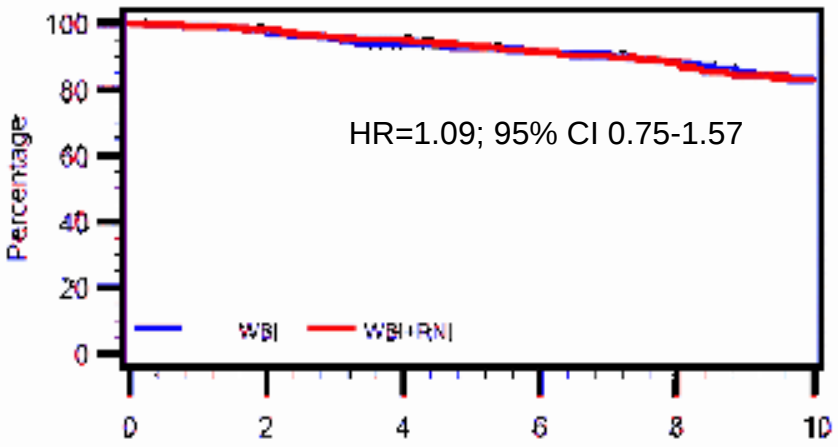
MA-20: Preplanned Subset Analysis



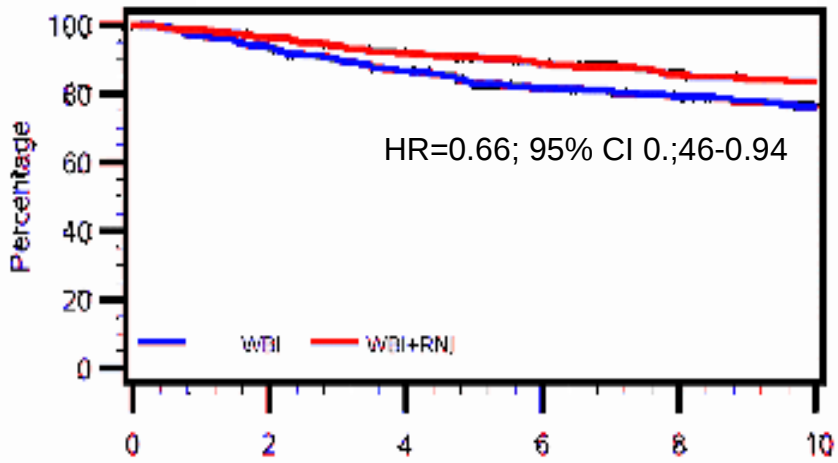
Whelan, T NEJM 2015;373:307-16

Disease-Free Survival by Subtype in MA-20

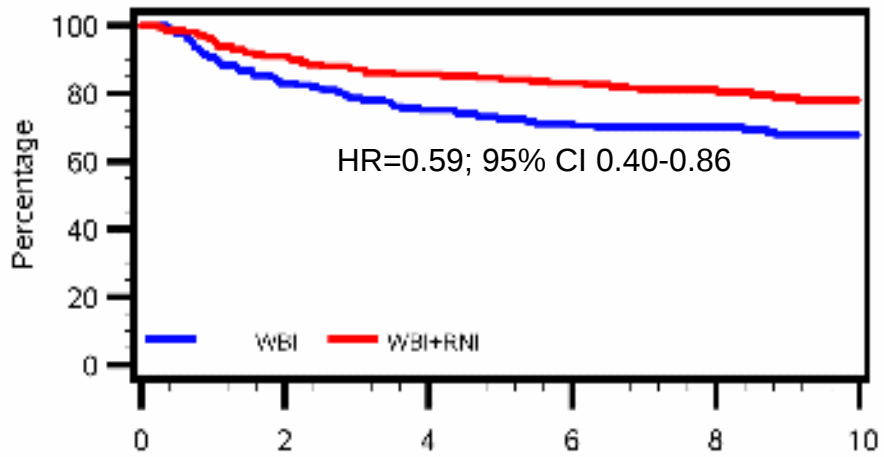
ER+: "Lum A-like"



ER+ or PR+: "Lum B-like"



ER- and PR-



***p for interaction = 0.05**

Whelan, T NEJM 2015;373:307-16

Node Negative TNBC with chemo,

- **Consider PMRT, especially if NACT and no PCR**
- LRR similar to 70 yo ER+
- RNI benefits them the most

Take-Home Points: Post-lumpectomy XRT

- Level 1 evidence: Radiation improves breast cancer survival in all but lowest risk (> 70 luminal-like)
- Local failure rates are decreasing, biology can help personalize, but local control is a life or death matter!
  - Omit cautiously

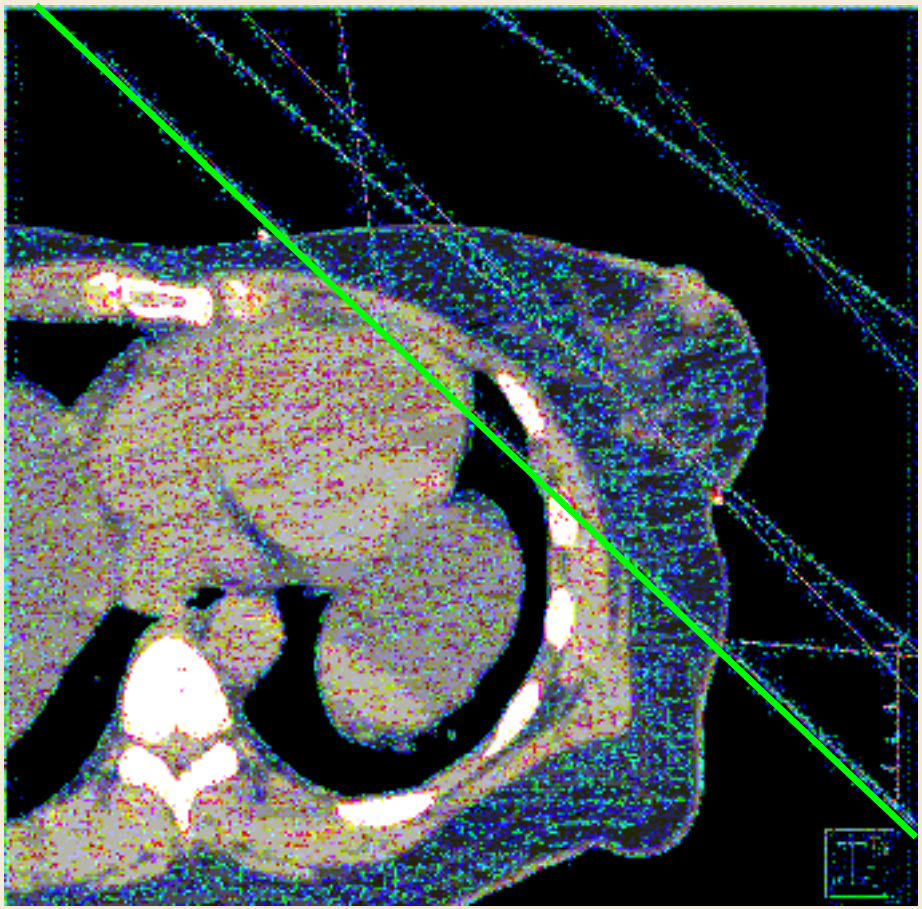
Safety and Convenience

- Heart Sparing
- HypoFx

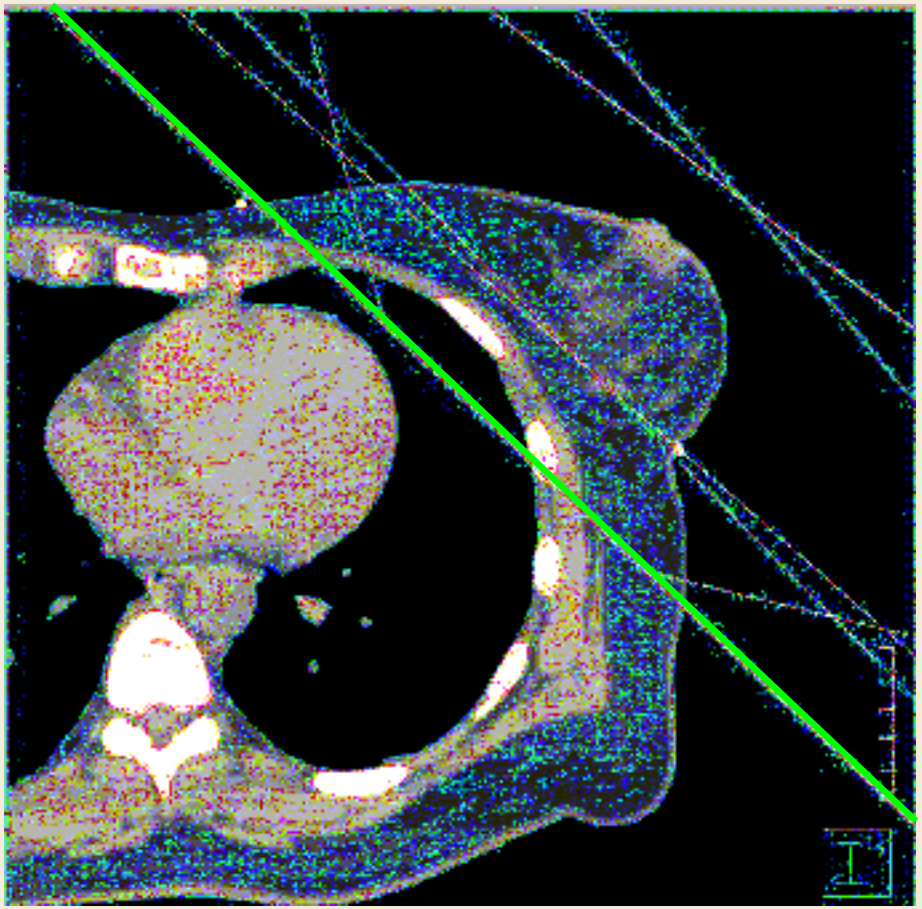
Respiratory Gating for Cardiac Protection in Breast Radiotherapy

- Deep inspiration breath hold
- Displaces heart from tangent field edge
- Useful in left breast cancer patients
- Expect ~ 50 cGy in intact left breast, 300-400 left PMRT.

DIBH Reduces Cardiac Exposure

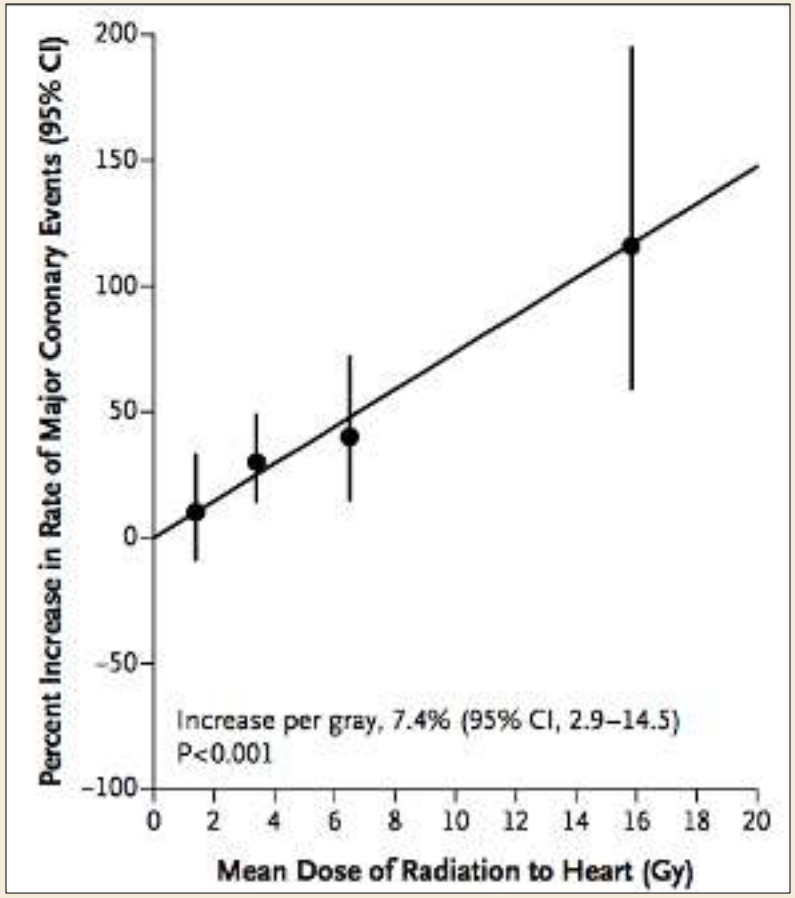


Free Breathing



Deep Inspiration Breath Hold

ASTRO 2016



7.4% increase ACE / 1 Gy MHD

- Van de Bogaard
- Cohort study – 2005-08
- Externally validated Darby et al
- Report LV-V5 superior to MHD
  - 17 vs 29 with and without events

Hypofractionation: Potential Benefits

Hypofractionation: Ontario Clinical Oncology Group

- 1,234pts pT1-2 N0
  - 69% T1N0
  - 74% ER positive (42% received tamoxifen)
  - 75% ≥ 50yo
  - 11% received systemic therapy

10 year Results:

	IBTR	OS	Gr 2-3 Skin Toxicity	Gr 2-3 SubQ Toxicity	Good-Excellent Cosmesis
50Gy/25fx	7.5%	84.4%	7.7%	10.4%	71%
42.5Gy/16fx	7.4%	84.6%	8.9%	11.9%	70%

Whelan, JNCI, 94;2002; Whelan, NEJM 2010

Hypofractionation: UK Start B Phase III Trial

- 2,215pts pT1-3 N0-1
- 23 centers in the UK
- 92% BCT
  - 42% tumor bed boost 10Gy/5fx
  - 70% tamoxifen
  - 7% chemotherapy
  - 15% tamoxifen & chemotherapy

Total Dose	# of Fxn	Wks of RT	Dose/ Fxn	10yr LRR	10yr OS
50Gy	25	5wks	2Gy	5.5%	80.8%
40Gy	15	3wks	2.67Gy	4.3%	84.1%

START Trialists' Group, Lancet, 2008; Haviland, Lancet Oncol, 2013

Hypofractionation: UK Start B Phase III Trial

	10yr Rate Mod-Severe Toxicity	p-value
Breast Shrinkage		**0.015**
50Gy	31%	
40Gy	26%	
Breast Induration		0.084
50Gy	17%	
40Gy	14%	
Telangiectasia		**0.032**
50Gy	6%	
40Gy	4%	
Breast Edema		**0.001**
50Gy	9%	
40Gy	5%	

Haviland, Lancet Oncol, 2013

ASTRO Consensus Statement on Hypofractionated WBI

Factor	ASTRO Consensus
Age	≥ 50yrs
T & N stage	pT1-2 N0
Surgery	Breast-conserving surgery
Neoadjuvant systemic chemotherapy	None
Dose heterogeneity	Dose heterogeneity ± 7%

Smith, IJROBP, 2011

EORTC 22881: 10-year Results

Outcome	No Boost	Boost	p-value
Death	81.7%	81.7%	NS
Distant Failure	16.1%	16.1%	NS
Local Failure	10.2%	6.2%	<.0001
Moderate or Severe Fibrosis	13.2%	28.8%	<.0001

Bartelink, *JCO* 2007

Benefit of a Boost by Age: EORTC 22881

- PROPORTIONAL benefit is independent of age

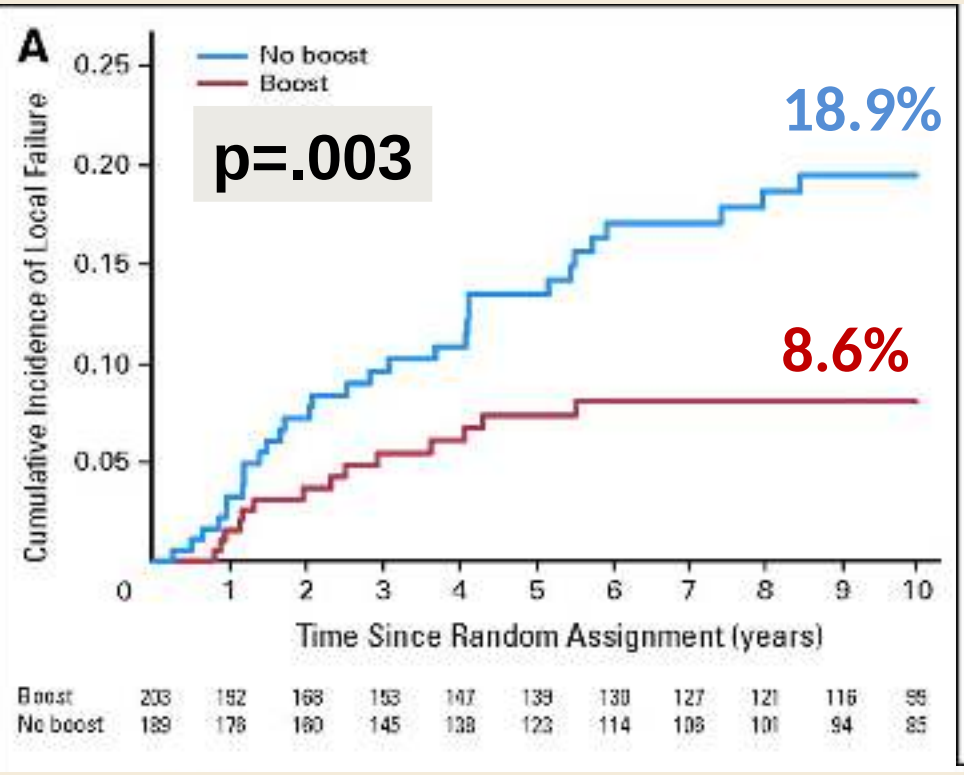
(HR 0.59 for all age subgroups)

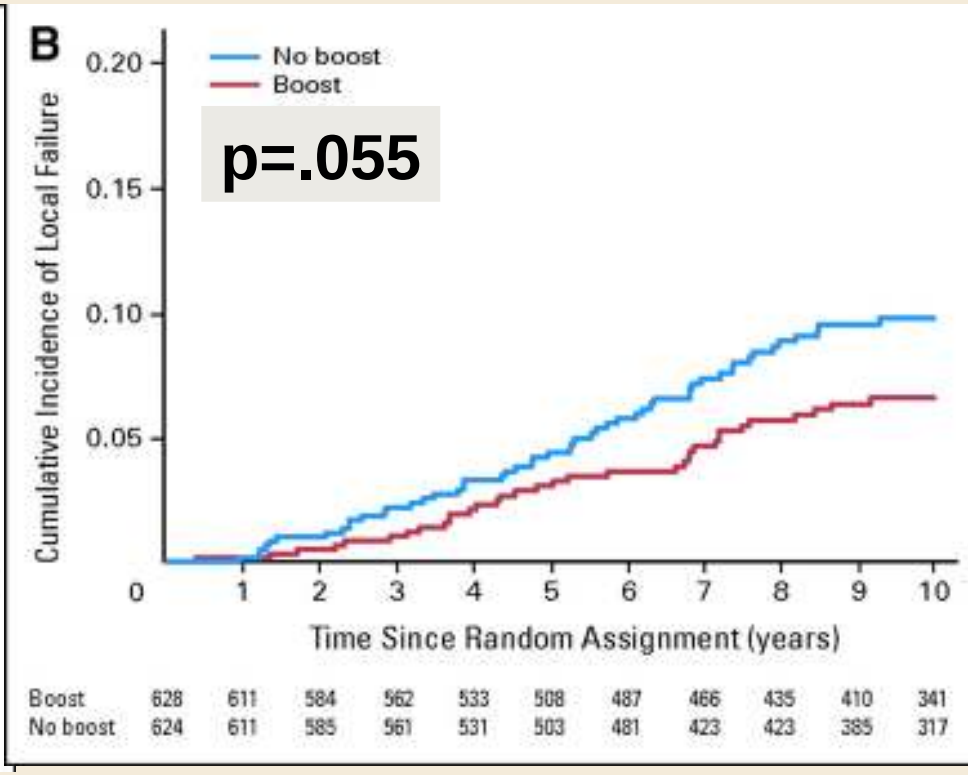
Age Group	LF	
	No Boost	Boost
≤40	23.9%	13.5%
41-50	12.5%	8.7%
51-60	7.8%	4.9%
>60	7.3%	3.8%

- ABSOLUTE local control benefit is age dependent, since young patients have higher local failure rates

Bartelink, *JCO* 2007

Benefit of a Boost by Tumor Grade: EORTC 22881





High Grade

Low – Intermediate Grade

Jones, JCO, 2009

MDA Hypofx Trial

- Randomized phase III short vs long
- Both arms included a sequential boost (40/15+ 10/5)
- PROMs no different
- Similar outcomes in > D cup, large separation, ER- disease
- We offer this to all stage I/II patients ≥ 40

- ***What is on the horizon with hypofractionation?***

UK FAST Trial

- 955 women with favorable, early stage breast cancer
- 2004-2007 at 18 centers
  - **Age ≥ 40yrs**
  - **Invasive carcinoma**
  - **BCS**
  - **Tumor Size <3.0cm**
  - **Negative margins**
  - **N0**
  - **No lymphatic RT**
  - **No systemic chemotherapy**

Total Dose	# of Fxn	Wks of RT	Fraction Dose
50Gy	25	5	2Gy
30Gy	5	5	6Gy
28.5Gy	5	5	5.7Gy

FAST Trialists' Group, Radiother Oncol, 2011

UK FAST Trial

Total Dose	# of Fxn	2yr Marked Photographic Change	3yr MD-Assessed Moderate-Marked Change
50Gy	25	1.7%	9.5%
30Gy	5	9.3%	17.3%
28.5Gy	5	4.9%	11.1%

FAST Trialists' Group, Radiother Oncol, 2011

UK FAST-Forward Trial

- **FAST-Forward**
  - **4000pts pT1-3N0-1M0 s/p BCS with negative margins**
  - **40Gy/15fxn over 15 days**
  - **27Gy/5fxn over 5 days**
  - **26Gy/5fxn over 5 days**

RTOG 10-05

- 2312 pts with early stage, high risk breast cancer
- Age ≥ 18yrs
- Stage I-II & at least one:
  - Age <50yrs
  - + axillary LN
  - LVSI
  - > 2 close margins (≤2mm)

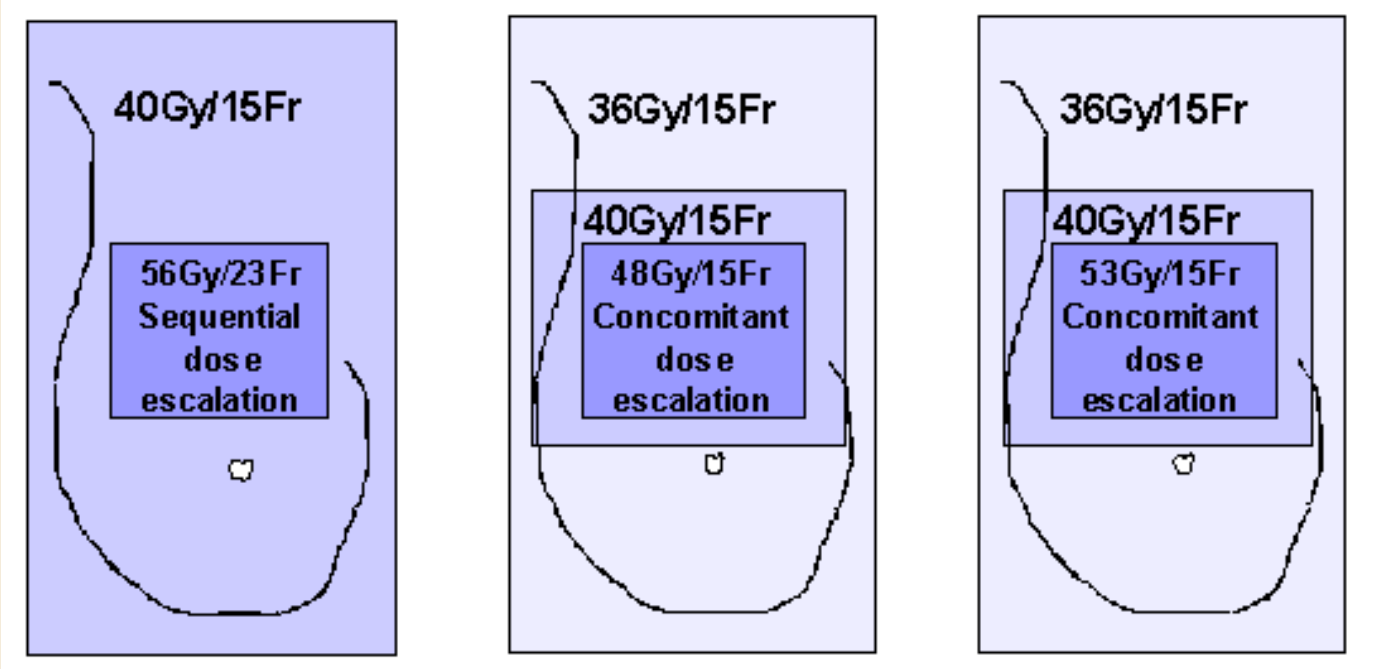
- DCIS grade 3, age <50yrs
- ypStage 0-II
  - 1 close margin & EIC

RTOG 10-05

- **Control Arm:**
  - **50Gy/25fx whole breast OR 42.7Gy/16fx**
  - **Followed by sequential boost: 12Gy/6fx OR 14Gy/7fx**
- **Test Arm:**
  - **40Gy/15fx with concurrent boost 48Gy/15fx**
- **Primary Endpoint: IBTR**
- **Secondary Endpoints: Cosmesis, breast symptoms, cardiac toxicity, feasibility, gene expression correlation to toxicity and recurrence, cost analysis, OS, DFS, DMFS**

UK IMPORT High

- **IMPORT: Intensity Modulation and Partial Organ RadioTherapy**
- **2,568 pts with early stage breast cancer with average to above average risk of recurrence**



http://www.rttrialsqa.org.uk/rttqa/?q=import-high

Conclusions

- LRR rates are decreasing
- Local Control Impacts DFS
- Consider omitting boost in luminal A patients
- Consider PMRT in TNBC N0
- Convenience is safe for many
- Avoid the heart