Radiation Management of Breast Cancer

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Learning Objectives:

- Identify current optimal radiation methods and suitable patient populations for breast conserving treatment in early stage invasive and non-invasive breast cancer.
- Understand rationale and indications for regional nodal irradiation post mastectomy and lumpectomy for node positive breast cancer in the setting of adjuvant and neoadjuvant systemic therapy
- Recognize radiation methods that maximize the therapeutic ratio by minimizing toxicity from breast conserving therapy in early stage disease and regional nodal irradiation in node positive disease.

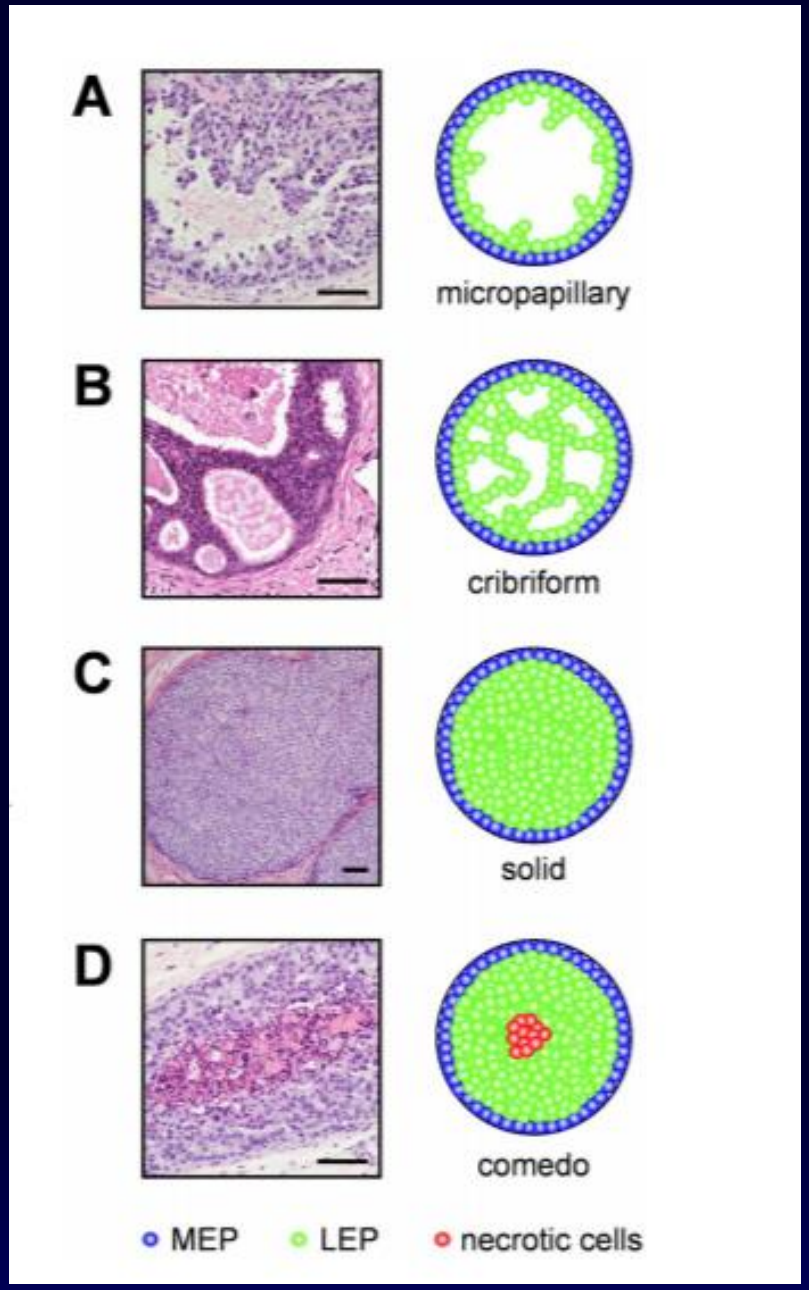
Agenda:

- DCIS: Breast Conservation (~30 minutes)
- Early Stage Invasive Breast Cancer: Breast Conservation (~30 minutes)
- Node Positive Breast Cancer: Regional nodal irradiation (~30 minutes)

DCIS

DCIS Fast Facts

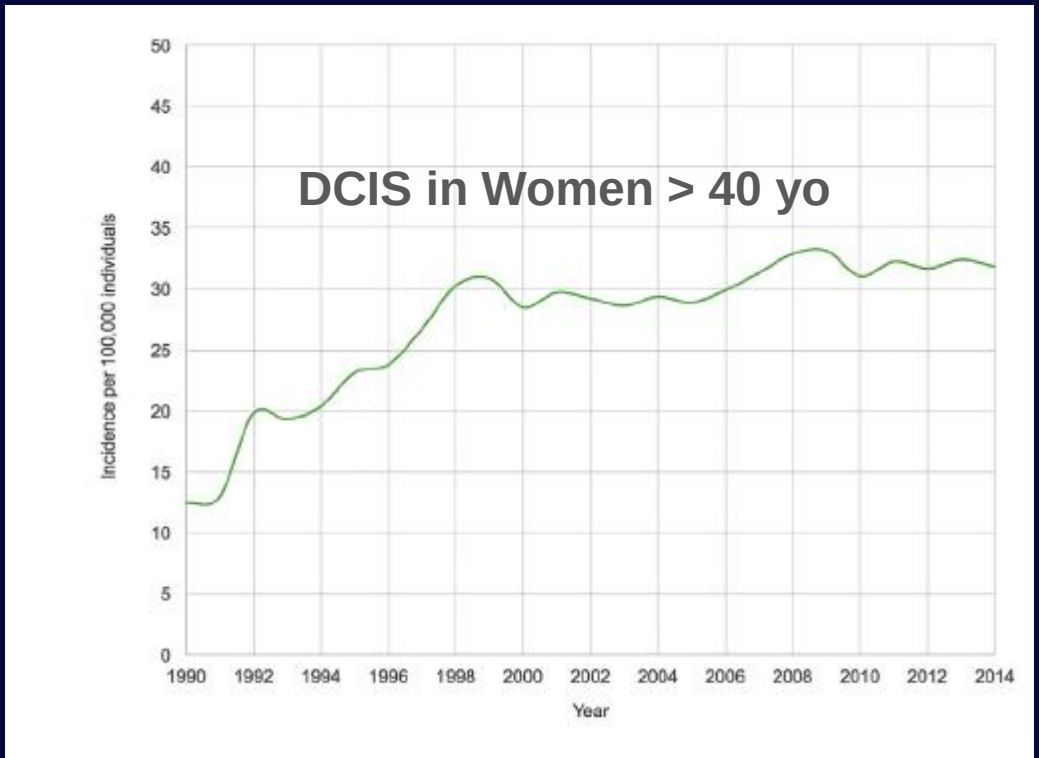
- ~ 63,000 cases diagnosed each year
- Mammographic detection most common
  - ~90% new micro-calcification
- Pathology
  - CAP guidelines*
    - Size: largest on one slide and # blocks
    - Architecture: Comedo, Paget disease (DCIS involving nipple skin) , Cribriform , Micro-papillary Papillary , Solid, Other
    - Nuclear Grade: I, II, II
    - Comedo necrosis: none, focal, central
    - Margins: specify and quantify (Min, Mod, or extensive)



* Lester et al , CAP DCIS Guidelines 2009

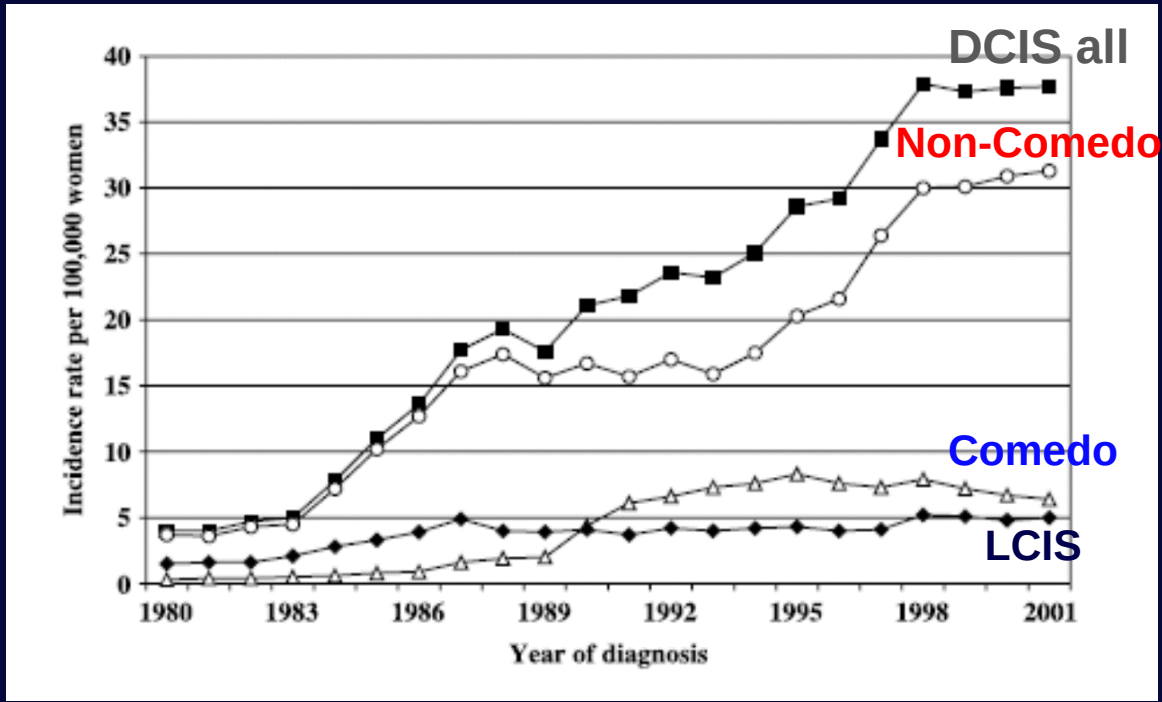
Boghaert et al. Plos one 2014

Significant Portion of the Increased Incidence of DCIS have Predominantly Lower Pathologic Risk Features



- SEER: steep rise in DCIS incidence with adoption of screening mammograms 1990-2000

Oseni et al, J Am Coll Surg 2019



- SEER: Steep rise attributable to lower risk “non-Comedo” DCIS not “Comedo” or high risk DCIS

Li et al, Cancer Epid, Biomarkers & Prev., 2005

What is the Optimal Management of DCIS Post Lumpectomy?

High vs Low Risk

Clinical Pathologic Factors

High Risk DCIS

- Palpable/ bloody nipple discharge
- Nuclear Grade 3
- Comedo, Solid
- ER and/ or PR negative
- Tumor size ≥ 25 mm
- Age < 50
- Surgical Margins positive, close (<2mm)

Low Risk DCIS

- Screen detected
- Nuclear Grade 1 or 2
- Cribriform, papillary
- ER and/ or PR positive
- Tumor size < 25 mm
- Age > 50
- Negative surgical margins (≥ 2 mm)

Case 1 “High Risk”

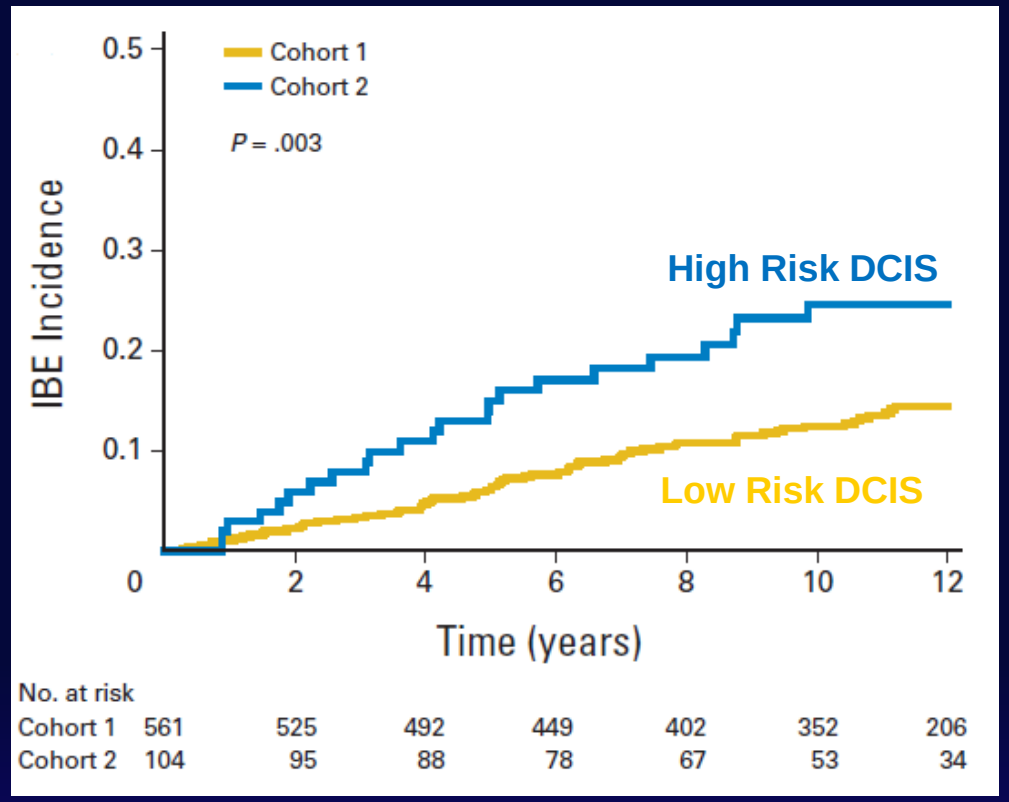
- 49 yo G0P0 post-menopausal female with new micro-calcifications LEFT breast on screening mammogram (first mammo year prior)
- Healthy, no meds, works as Administrative Assistant
- No family history
- TAH-BSO at 43 for menometrorrhagia
- Stereo core biopsy reveals 7 mm NG 3 DCIS with comedo necrosis
- ER 60%, PR 40%
- S/P Lumpectomy: 14 mm NG 3 DCIS, 4 / 16 slides, Margins all > 2 mm

Observation Post Lumpectomy for High Risk DCIS ECOG 5194 Phase II Prospective Clinical Trial

- Cohort 2:
  - Eligibility: s/p lumpectomy, < 10 mm size, NG3, negative surgical margin 3 mm
  - Population: n=104

Median Age: 58 yrs	Tumor Size (median): 7 mm
Post menopausal: 72%	Margin neg. ≥ 5 mm: 69%
Tamoxifen use: 24%	Margins Neg. ≥ 10 mm: 24%

  - Results: 12 Year outcome
    - All Ipsilateral breast event (IBE): 24.6%
    - Invasive IBE: 13.4%



Solin et al. JCO 33: 2015

Management of High Risk DCIS Post Lumpectomy

- Radiation Therapy
- Endocrine Therapy in Hormone Sensitive Cases

Goals of Breast Radiotherapy for DCIS Conservation Treatment

DCIS:

- Maximize local control
- Prevent first invasive breast cancer
- Sustain freedom from mastectomy
- Maintain sensate and acceptable cosmetic breast appearance

4 Seminal Randomized Trials Demonstrate Durable Reduction of Ipsilateral Breast Recurrence (IBR) with Post Lumpectomy Whole Breast Irradiation (WBI)

DCIS Trial	No.	F/U years	%IBR			
			LUMP alone		LUMP + RT	
			All	Invasive	All	Invasive
NSABP B-17	814	17	35	19.6	19.8	10.7
EORTC 10583	1010	15	30	16	17	10
UK ANZ	811	12.7	28	10	12	6
SweDCIS	1046	20	32	17	20	8

Wapnir, et al. JNCI, 2011
Donker et al. J Clin Oncl, 2013
Cuzick et al. Lancet Oncol, 2011
Warnberg et al. J Cin Oncol 2014

Significant Proportion of High Risk DCIS
PHASE III RCT Lumpectomy ± RT for DCIS

Trial	Years accrued	Age ≤ 50 yrs. (%)	Mam detect (%)	Tam (%)	Size (mean) mm	Neg. surg margin (%)	High grade (%)	Comedo Necr. (%)
NSABP B-17	1985-90	33	80.5	0	12.5	83	48.4	47.8
EORTC 10583	1986-96	6.5	71	0	20	78	27	38.8
UK ANZ	1990-98	9	91	0	-	85	74.5	39.5
SweDCIS	1987-99	24	78.7	3	17.8	80	-	-

Two Randomized Clinical Trials Support Tamoxifen use After Lump ± RT

Trial	Result
NSABP B24 N= 1904	• Tamoxifen reduced All, Invasive and DCIS IBR after Lump+RT • Tamoxifen reduced Contralateral Breast events
UK-ANZ N= 1694	• Tamoxifen reduced Ipsilateral DCIS events after Lump alone • Tamoxifen Reduced Contralateral breast events

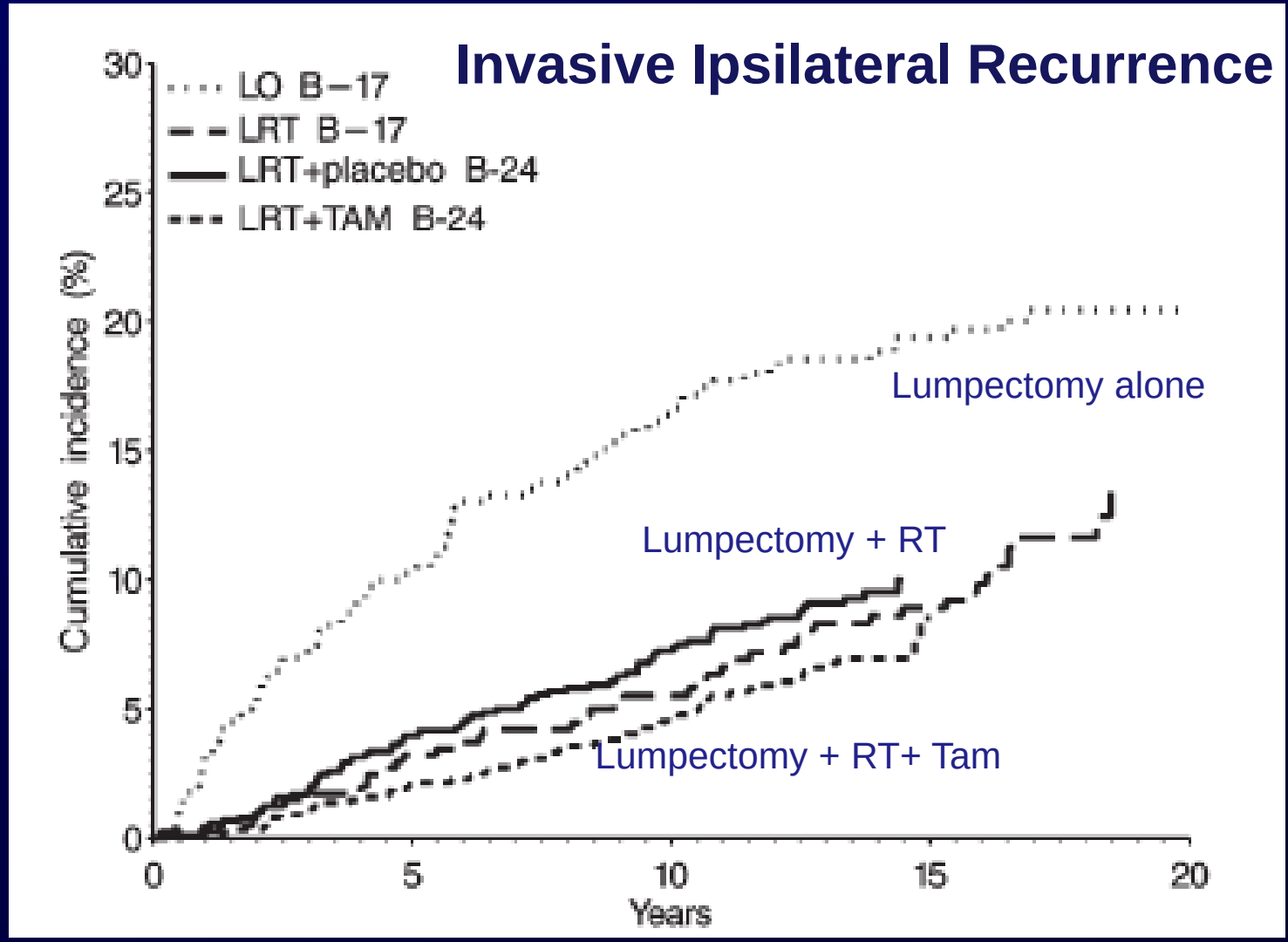
❖Hormone receptor status not required for eligibility on either trial

Fisher et al, Lancet 1999
Cusick et al, Lancet Oncol. 2011

NSABP B17, B24 Combined Analysis: RT & ET ~70% Reduction Invasive Breast Recurrence

High Risk Features
NSABP B24 Population:

- Age ≤ 49 33%
- Comedo necrosis:
  - 50% present
  - 47% “Moderate marked”
- High Nuclear Grade: 46%
- Surgical margins:
  - 16% positive
  - 44% < 1 mm



Fisher B et al, Lancet 353:1999
Fisher E et al, Am J Clin Pathol 128: 2007
Wapnir et al, JNCI 103: 2011

NSABP B24:Tamoxifen Benefits ER/ PR+ DCIS

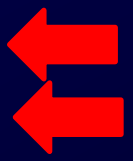
- Enrollment B24: n= 1904
- n=732 with ER / PR Status
  - 449 with sufficient tissue for central ER and PR by IHC. (76% positive)
  - 283 had ER and PR status at enrolling institution. (66% positive)
- Balanced treatment and patient variables compared to entire trial
- Median follow up 14.5 years
- No Tamoxifen effect on ER/ PR negative cases.

ER and / or PR + DCIS				
10 yr Breast Event	**Type of Recurrence**	**Placebo %**	**Tamoxifen %**	**p**
Ipsilateral	All	17	14	0.07
	Invasive	9	7	0.10
	DCIS	8	7	0.39
Contralateral	All	11	6	0.02
	Invasive	8	4	0.06
	DCIS	4	2	0.14

Allred et al, JCO 30: 2012

Two Randomized Trials Evaluated Anastrozole vs Tamoxifen for HS DCIS in Postmenopausal Women

Trial	n	Median Follow-up	Recurrence Event (Ipsilateral. + Contralateral)	Tamoxifen %	Anastrozole %	HR	p
NSABP B35	3104	9 yrs.	All	7.9	5.84	0.73	0.0234
			Invasive	4.4	2.8	0.62	0.0123
			DCIS	3.4	3.1	0.88	0.52
IBIS-II DCIS	2980	7.2 yrs.	All	5	5	0.89	0.31
			Invasive	3	3	0.8	0.16
			DCIS	2	2	0.98	0.97



NSABP B35:

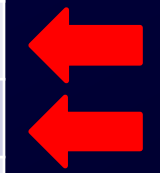
- Age interaction with Breast Cancer Free (BCFI) and Disease Free interval (DFI) events
- Women < 60 yo had improved BCFI and DFI with Anastrozole

Forbes et al, Lancet 387: 2016

Margolese, et al, Lancet 387:2016

NSABP B35
Anastrozole Reduced Contralateral Breast Events

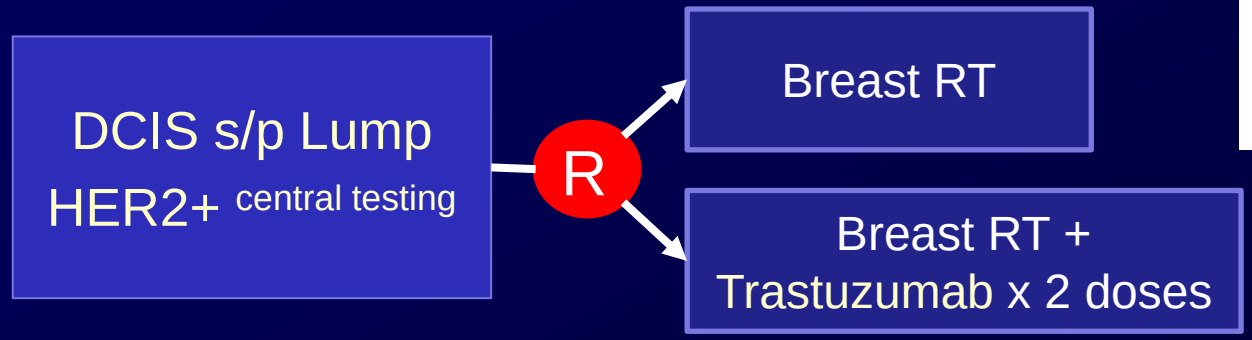
Event	Tamoxifen n=1538 # (%)	Anastrozole n=1539 # (%)	HR	p-value
Ipsilateral Breast				
Total	55 (3.57%)	46 (2.98%)	0.83	0.34
Invasive	22 (1.43%)	17 (1.1%)	0.76	0.39
DCIS	33 (2.14%)	29 (1.88%)	0.87	0.59
Contralateral Breast				
Total	60 (3.9%)	39 (2.53%)	0.64	0.032
Invasive	40 (2.6%)	21 (1.36%)	0.52	0.0148
DCIS	20 (1.3%)	18 (1.17%)	0.9	0.73
Breast Cancer at Distant Sites	7 (0.45%)	4 (0.26%)	0.57	0.37

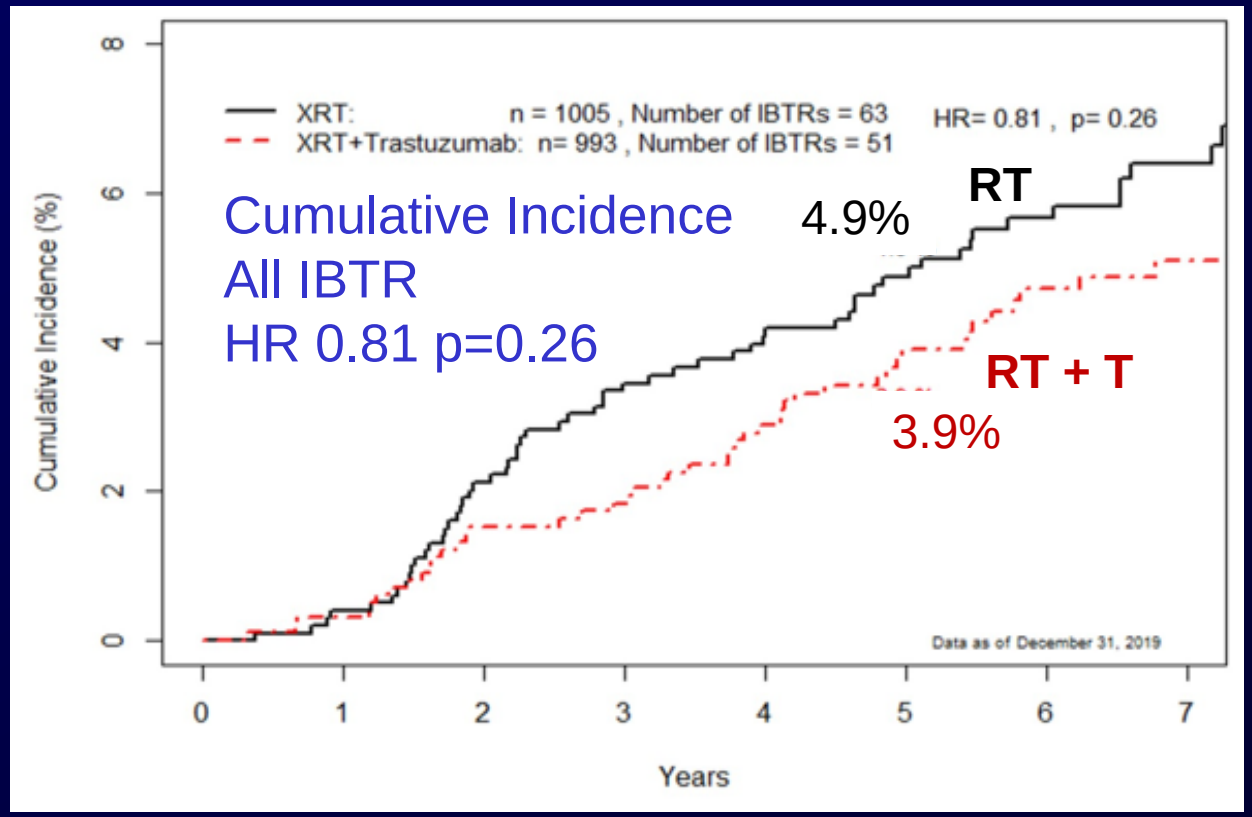


Margolese, et al, Lancet 387:2016

Should HER2 be Ordered on G3 DCIS? No
NSABP B43

- 2014 randomized 2008-2014
- Population:
  - 78% ≥ age 50
  - 74% post menopausal
  - 83% High grade DCIS
  - Hormonal therapy 57%
- Median follow up: 6.6 years





- No significant difference in All, Invasive or DCIS IBTR with Trastuzumab

Cobleigh et al, ASCO 2020

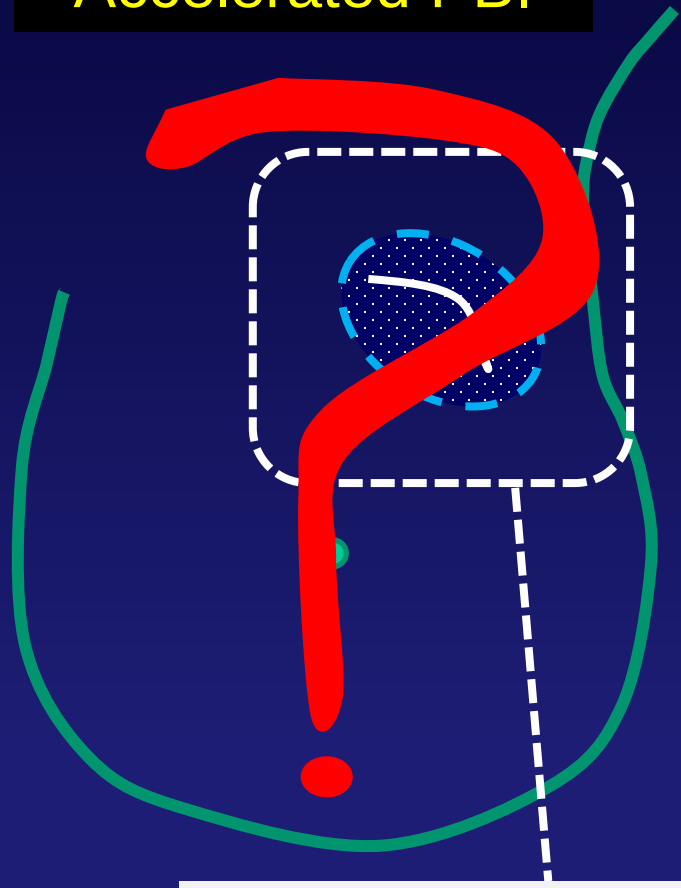
Breast Radiotherapy Methods for DCIS

High Risk DCIS

Hypofractionated WBI ± BOOST

42.56 Gy/ 2.67 Gy
16 treatment days

Accelerated PBI

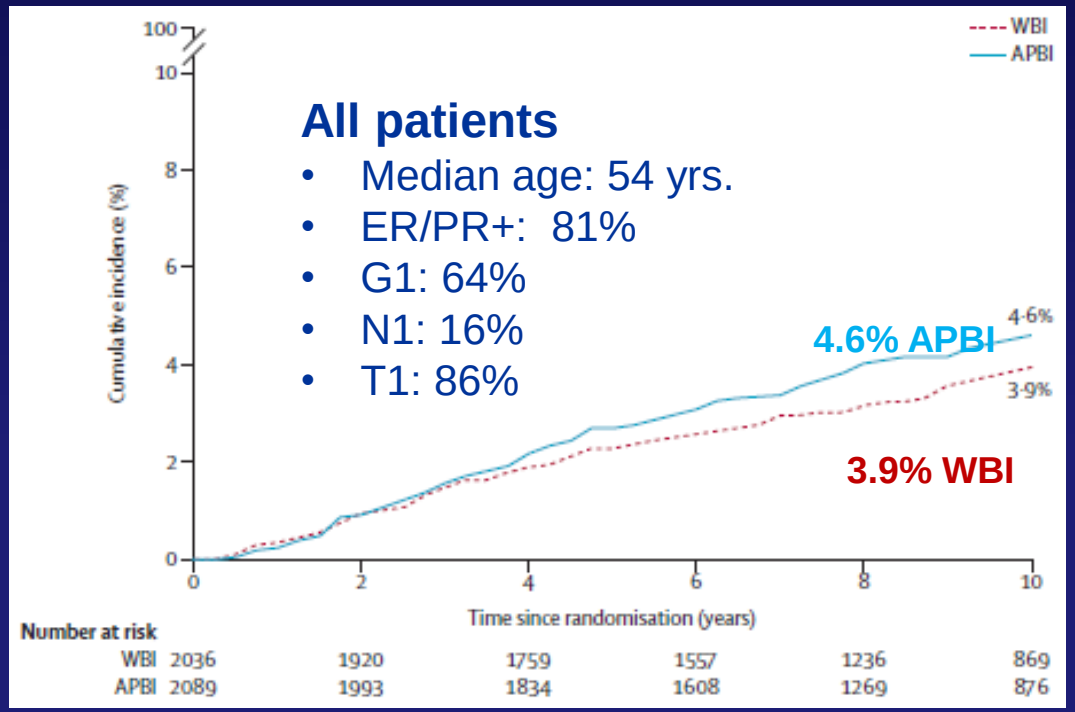


28-38 Gy/ 3.4- 5.4 Gy
5 -10 treatment days

APBI for DCIS

NRG NSABP B39 RTOG 0413 Phase III Trial

- N=4216 Total population
- 2005-2013 154 centers
- Median follow up: 10.2 yrs.
- Did not meet equivalence.



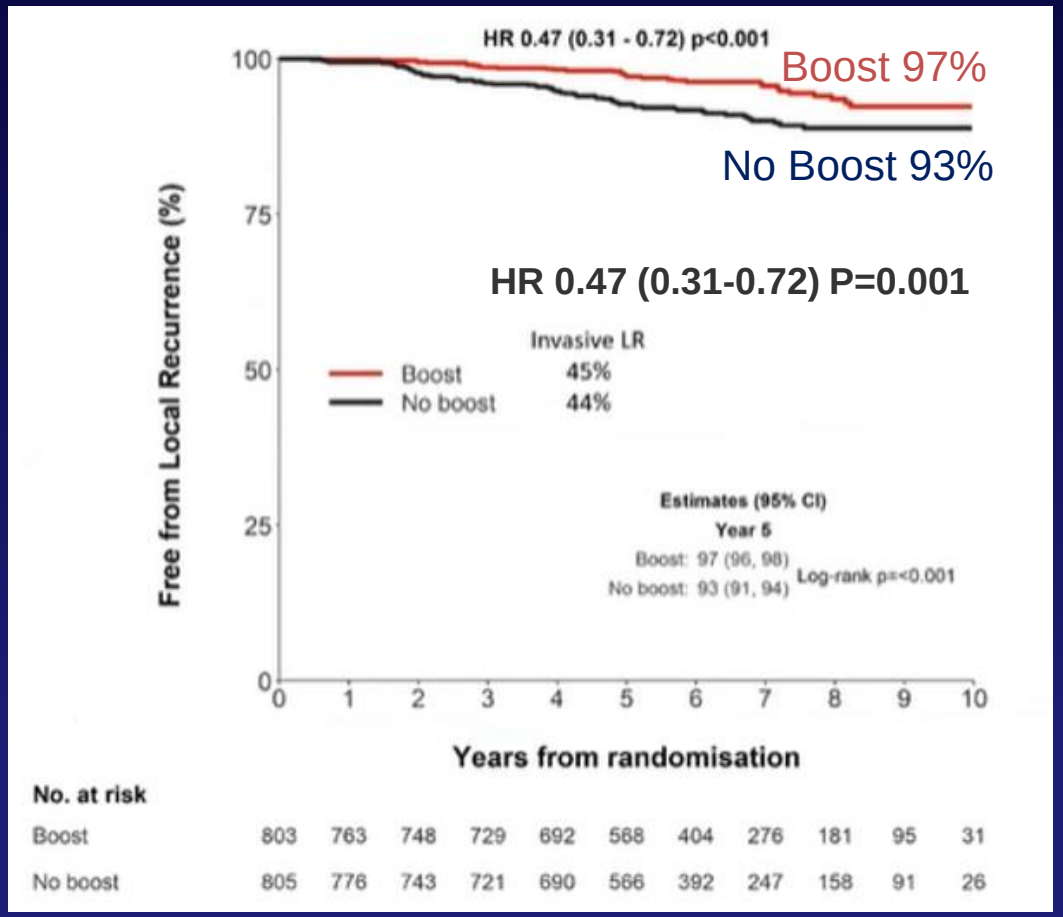
Vicini et al, Lancet 2019

- N=1031 DCIS Cases
- DCIS cohort
  - ER/PR +: 908 (88%)
  - Grade 1-2: 408 (40%)
  - Grade 3: 289 (28%)
  - Grade unknown 334 (32%)
  - Margins: negative
- 10 yr. Cumulative incidence IBTR:
  - WBI: 6.5%
  - APBI: 6.0 %
  - HR 1.01 (0.61-1.68) p=0.48
  - ★ *Not powered for subset analysis*

BIG 3-07/TROG 07.01 Radiation Boost for "Non-Low Risk" DCIS

- n=1608 2007-2014
- Multicenter, parallel RCT
  - Randomized to sequential boost 16 Gy/ 8 F vs None.
  - Second randomization to WBI of 42.56 G/ 16 F/ 2.67 Gy vs 50 Gy /25 F / 2 Gy Fractionation
- Population: "Non-Low risk"

Age ≥ 50 :	83%	Margins > 2mm:	53%
Unifocal:	91%	**Endocrine Rx:**	**12%**
DCIS < 20 mm:	64%	**Grade 3/ necrosis:**	**73%**

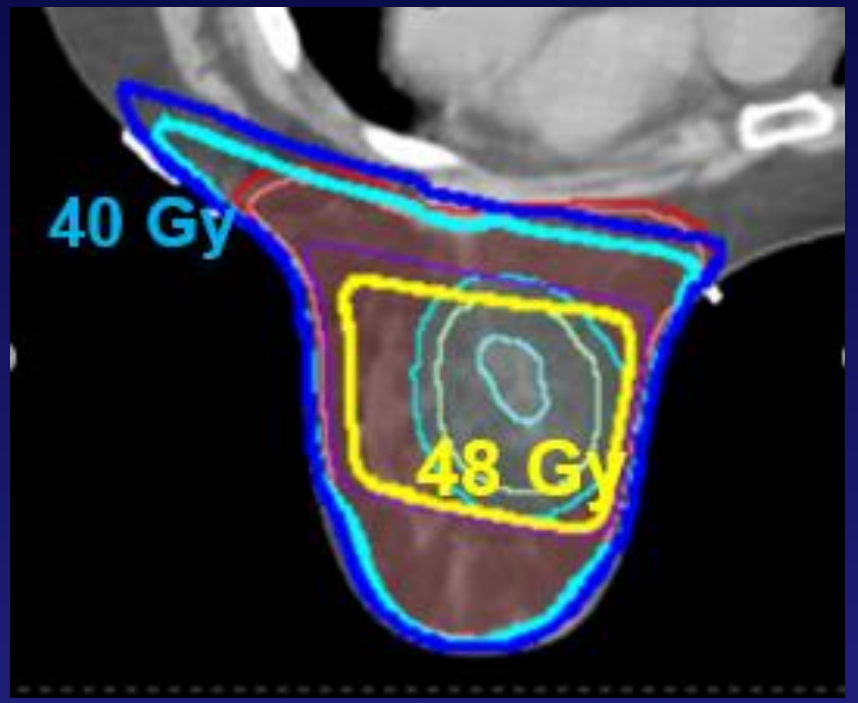


- Median Follow up: 6.6 years
- No Difference in WBI outcome by Fractionation

Chua, et al SABCS 2020

Treatment Case 1: High Risk DCIS

- Radiation therapy
  - No clip demarcating cavity so APBI problematic w/o reliable target
  - WBI with concomitant boost
    - 40 Gy/ 15 F whole breast PTVeval
    - 48 Gy/ 15 F lumpectomy PTVeval
- Endocrine Therapy
  - Tamoxifen (No uterus)
  - Patient declined Anastrozole because of personal history of osteopenia



Prone WBI w/ concomitant boost
15 Fractions 3DCRT

Case 2 “Low Risk”

- 64 yo. G4P4 female with abnormal screening mammogram, last mammogram 2 years ago.
- Overall healthy, on statin for cholesterol, has controlled HTN
- Working virtually doing billing for a trucking company.
- Mom had breast cancer diagnosed at 78 yo, died of other causes. No other family history
- Stereo core biopsy: reveals 14 mm NG 2 DCIS
- ER 95%, PR 90%
- Lumpectomy: 1.7 cm G2 DCIS, all margins > 2 mm

Management of Low Risk DCIS Post Lumpectomy

- Radiation Therapy ?
- Observation?
- Multigene signature for individual risk assessment?
- Endocrine Therapy in Hormone Sensitive Cases?

ECOG 5194: Long Term Observation after Lumpectomy for Low Risk DCIS

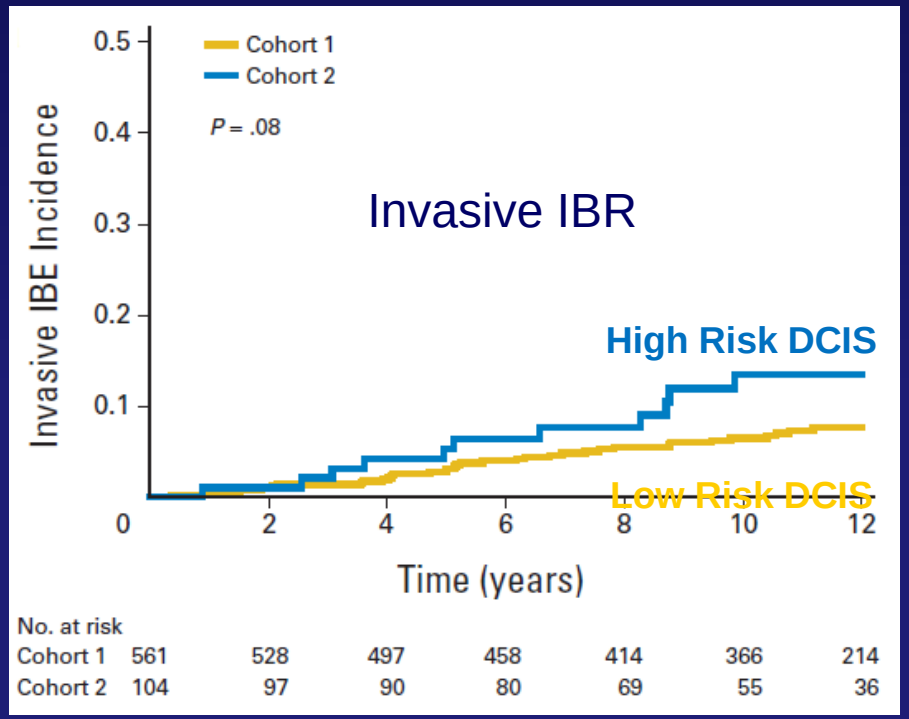
DCIS:	"Low risk"	"High Risk"
Characteristic	**Cohort 1 (n = 561)**	**Cohort 2 (n = 104)**
Patient age (median)	60 years	58 years
Postmenopausal	76%	72%
Tumor size (median)	6 mm	7 mm
Negative margins ≥ 5 mm	64%	69%
Negative margins ≥ 10 mm	21%	24%
Tamoxifen use	31%	24%

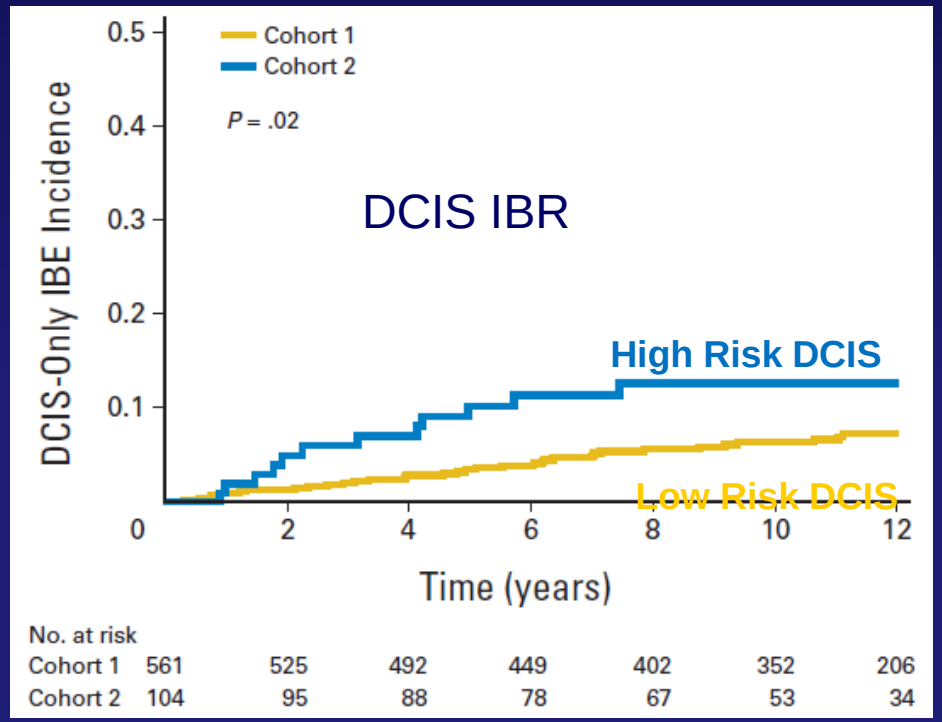
Solin et al. JCO 33:2015

E5194: Significantly Fewer All, Invasive and DCIS IBR In Low Risk DCIS Cohort

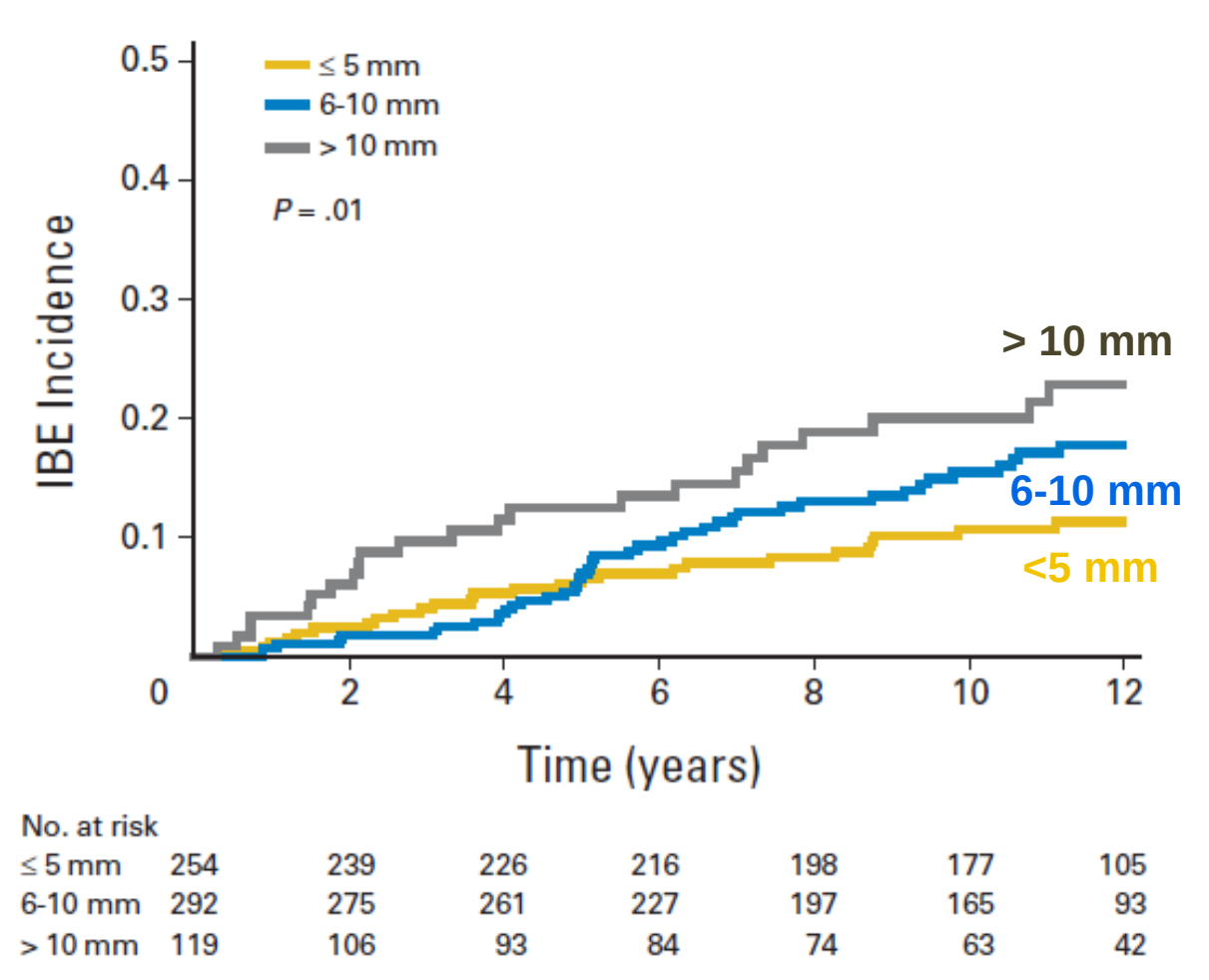
Ipsilateral recurrence	"Low risk" Cohort 1	"High risk" Cohort 2	p
ALL	**14.4%**	24.6%	**0.003**
DCIS	**7.3%**	12.6%	**0.02**
Invasive	**7.5%**	**13.4%**	**0.08**

Solin et al. JCO 33:2015





E5194: DCIS Size is the Only Factor that Correlated with IBR



Solin et al. JCO 33:2015

NRG-RTOG 9804: Phase III Randomized Trial Comparing Radiotherapy vs. Observation Post - Lumpectomy for "Good Risk" DCIS

- Mammo Detected
- DCIS NG 1-2
- ≤ 2.5 cm size
- Lumpectomy
- Negative margin, 3 mm

RANDOMIZE

Observation

Whole breast irradiation

Primary Endpoint:

- Ipsilateral breast recurrence (IBR)

- Accrual 1999 – 2006,
- 188 institutions
- Targeted accrual: 1790
- Total accrued: 626

NRG ONCOLOGY™

Comparison of Patients Enrolled on RTOG 9804 and E5194 Cohort 1

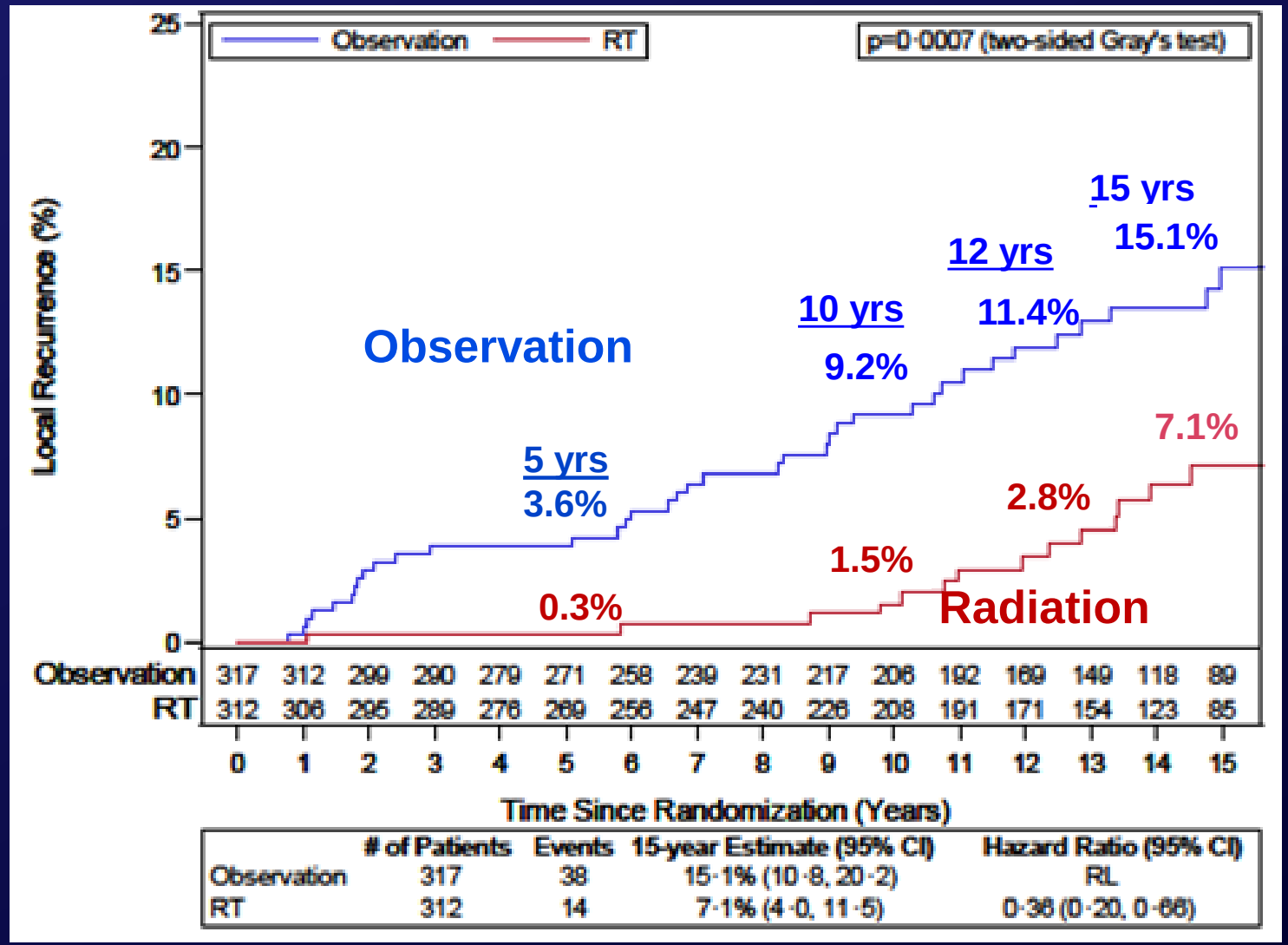
	RTOG 9804	ECOG 5194 Cohort 1 Low risk
Patient Age (median)	58	60
Age ≥ 50	80%	81%
Tumor Size (median)	5 mm	6 mm
Tumor Size ≤ 10 mm	87%	82%
Negative Margins ≥ 10 mm	64%	21%
Tamoxifen intent	69%*	31%

* Actual use: 62%

McCormick, JCO 2015
Solin, JCO 2015

RTOG 9804: Radiation Significantly Reduces All Ipsilateral Breast Recurrence for Low Risk DCIS

- Actual Tamoxifen use:
  - Observation: 66%
  - Radiation: 58%
- Median time to IBR:
  - Observation- 6.9 years
  - Radiation- 11.4 years

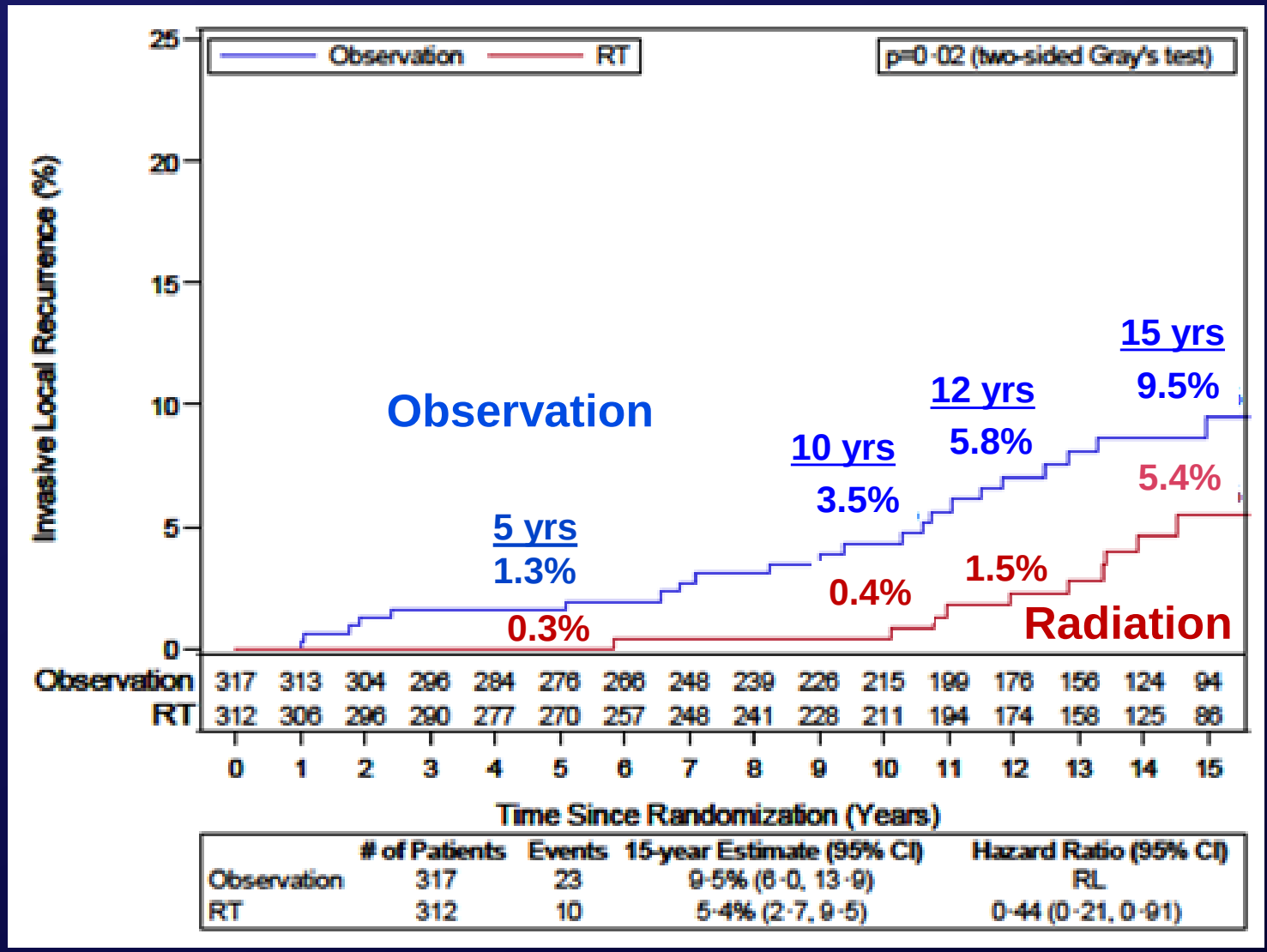


McCormick, JCO 2015
McCormick, ASTRO, 2018

RTOG 9804: Radiation Significantly Reduces Invasive Ipsilateral Breast Recurrence for Low Risk DCIS

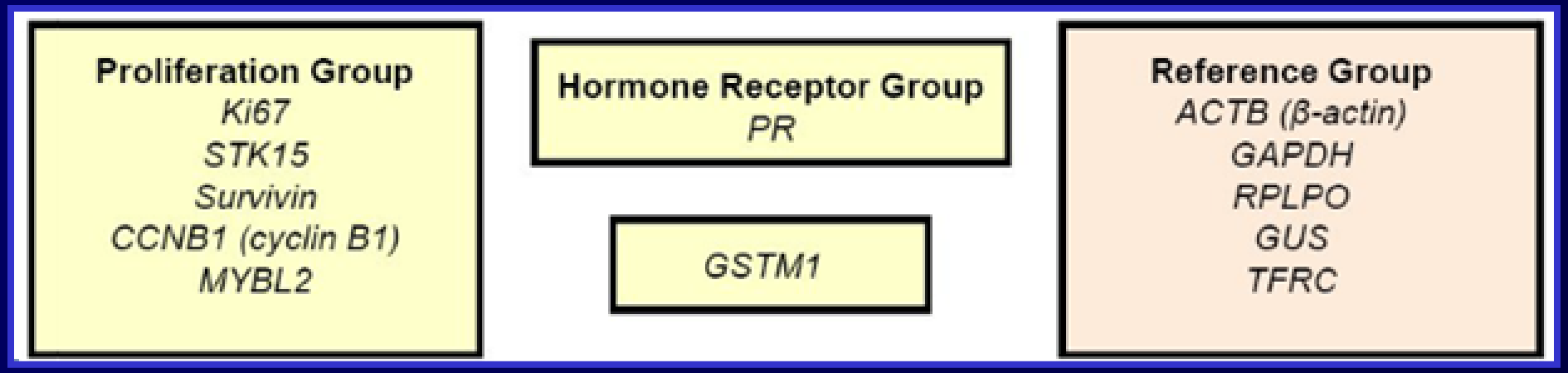
- Similar significant reduction from RT for DCIS IBR.
- No significant difference in incidence of contralateral breast cancer event.
- Multivariate Analysis:

Variable	HR	p
Radiation	0.25	0.003
Endocrine Rx	0.5	0.024



McCormick, JCO 2015
McCormick, ASTRO, 2018

DCIS Score: 12 Gene Signature

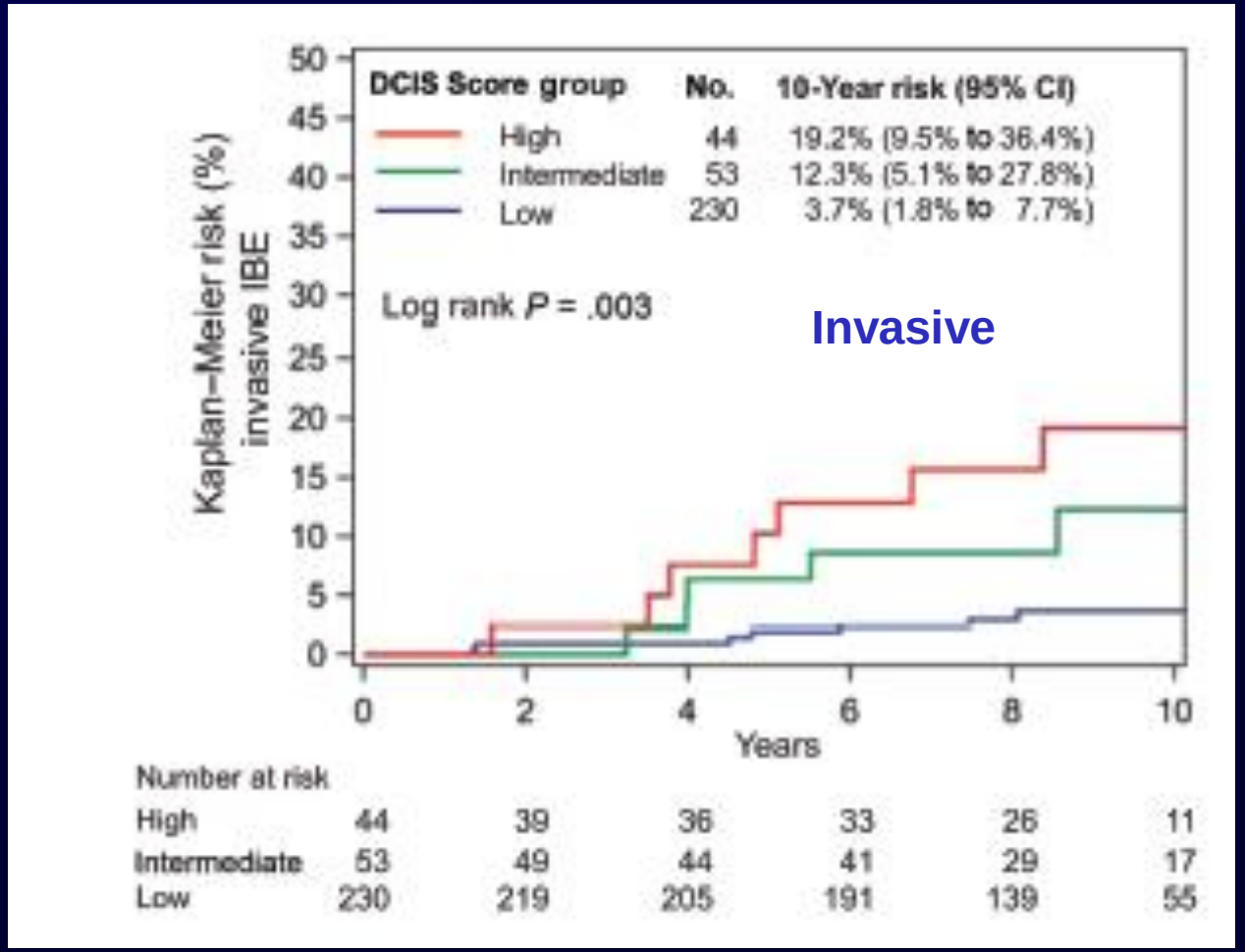


- DCIS Score: 0-100
- Three specified risk groups:
  1. Low < 39
  2. Intermediate 39-54
  3. High ≥ 54

Solin et al, JCO 2013

ECOG 5194 Cohort Studied for DCIS Recurrence Score

- No.= 327
  - 273 (83%) – G1-2
  - 54 (17%) – G3
- Median age – 61 years
- Postmenopausal – 71%
- Tamoxifen use- 29%
- **ER positive – 97%****
- 10 year outcomes



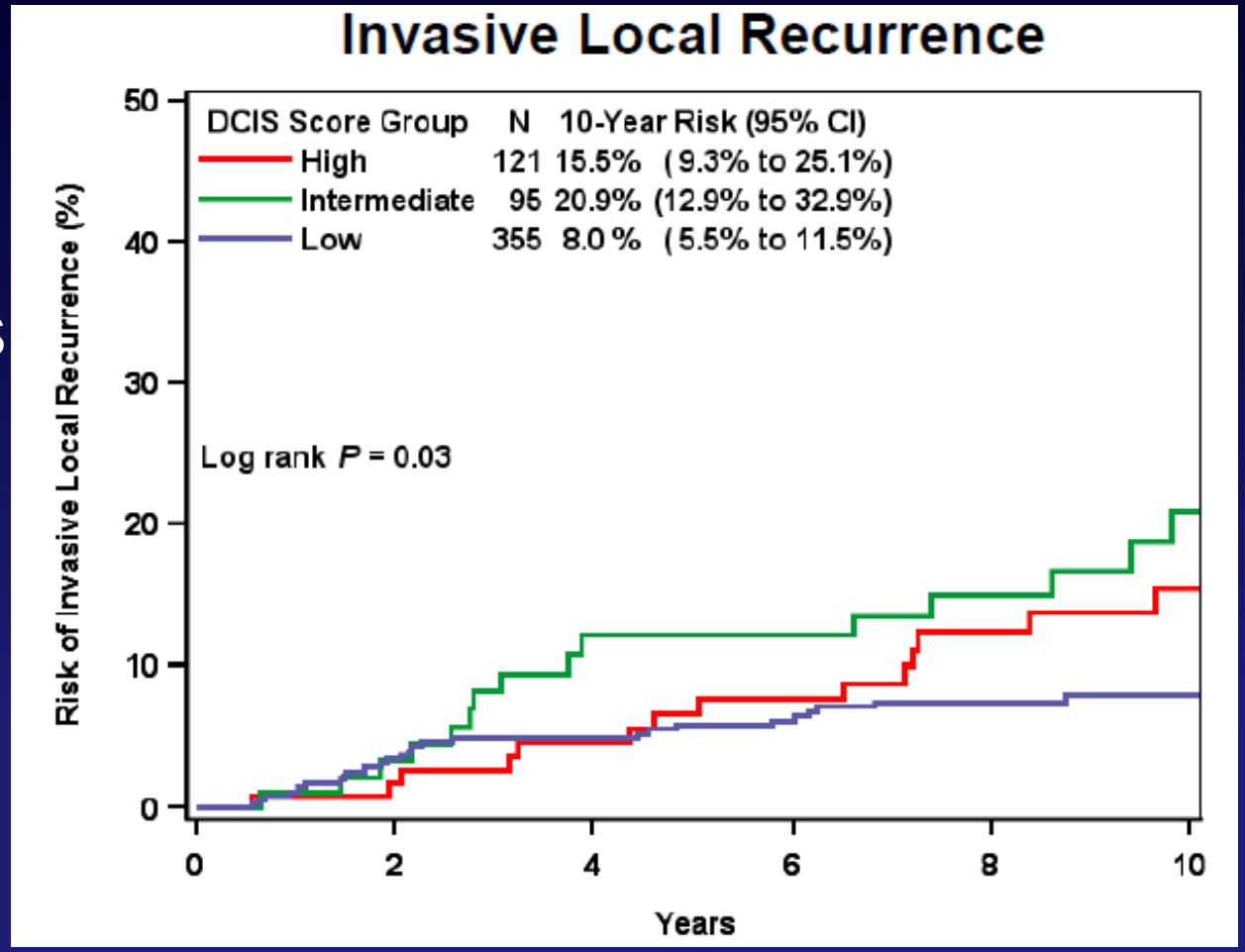
Solin et al, JNCI 2013

Validation of the 12 Gene DCIS Recurrence Score

- Ontario DCIS registry1994-2003
- Breast-conserving surgery alone
- Study Cohort: 571
  - Tissue blocks + Clinical Outcome
- Analysis: pre-specified endpoints
  - Continuous variable (0 –100)
  - 3 pre-specified risk groups
- Population:

Age ≥ 50 : 81%	Grade 3: 32%
Unifocal: 80%	ER+ 94.7%
DCIS < 10 mm: 26%	Endocrine Rx: 17%

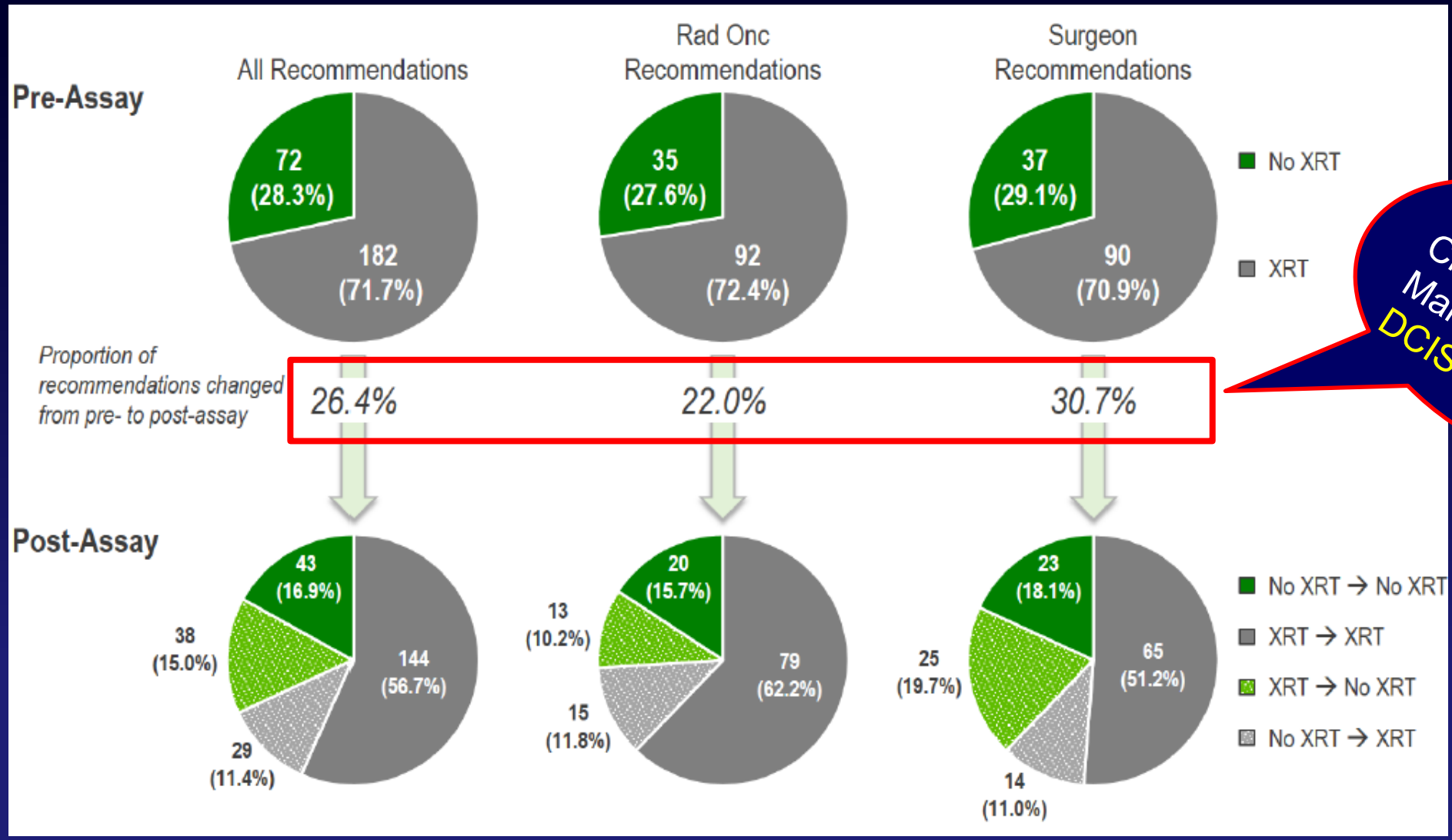
- 10 year IBR: 19.1%



Rakovich et al Breast Cancer Res Treat 2015

Clinical Utility of DCIS Recurrence Score

127 patients enrolled at 12 centers throughout the US



Change in Clinical Decision Making based on DCIS SCORE

Manders et al, Ann Surg Onc 2016

DCISionRT™ Gene Signature

Ipsilateral Breast Recurrence	Lump	Lump and RT
DS Low Risk Group (≤ 3) ALL	8%	7%
Invasive	4%	3%
DS Elevated Risk Group (>3) All	23%	11%
Invasive	15%	9%

- Consensus Continuous Score (DS): 0 – 10
- Low Risk Group: DS ≤ 3
- Elevated Risk Group: DS > 3

Bremer, et al, CCR 2018

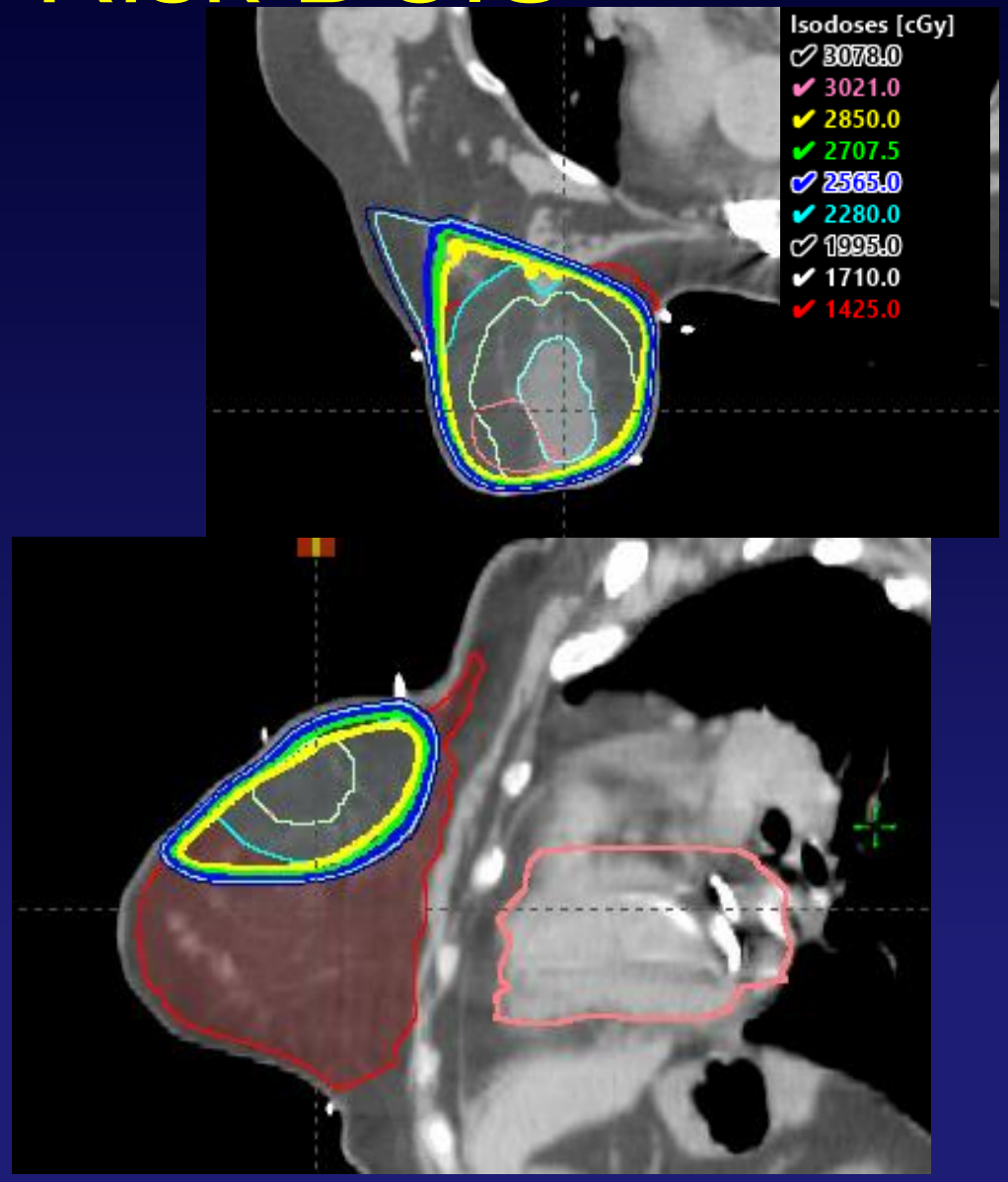
- Developed in 2 datasets:
  - Uppsala U. Hospital 1986-2004
  - U. of Mass.1999- 2008
- N = 526
  - 59% breast radiation
  - 29% endocrine Rx
- Population:

Age ≥ 50 :	72%
Grade 3:	40%
DCIS < 10 mm:	42%

- Baseline IBR
  - Lump alone: ALL 15%, inv 9%
  - Lump and RT: all 10%, inv. 7 %
- Median follow up: 9.8 years

Treatment Case 2 – Low Risk DCIS

1. Radiation:
   - Patient declined observation and multi gene assay
   - Wanted RT risk reduction
   - APBI 28.5 Gy/ 5 Fractions/ 5.4 Gy QOD
2. Endocrine Therapy
   - Anastrozole started due to patient concerns about endometrial cancer
   - Switched to Tamoxifen because of arthralgia.
   - Tamoxifen dose reduced



Prone APBI with 3DCRT

Summary:
Optimal DCIS Management after Lumpectomy

- Radiation reduces risk of recurrence in the ipsilateral breast for High and Low risk DCIS
- Endocrine therapy reduces risk some in the ipsilateral breast and mostly in the contralateral breast for HS DCIS
- Risk reduction for DCIS post lumpectomy should reflect patient's values and be a shared decision with the patient.

Breast Conservation for Invasive Breast Cancer

Invasive Breast Cancer – Fast Facts

- Roughly 200,000 new cases of invasive breast cancer diagnosed annually
- Mammogram screening widely adopted. CDC 2015: 71.6% of women aged 50-74 years had a mammogram within the past 2 years.
- 50% of breast cancer is stage 1 at diagnosis
- Subtype:
  - 65-75% - Luminal (ER and/ or PR positive)
  - 15 -17% - HER2 positive
  - 9-11% - Triple negative (ER-, PR-, HER2 -)

https://www.cdc.gov/nchs/hus/contents2018.htm#Table_033
Sareigo, Am J Surg 2008
Sinshaw, Breast Cancer Res Treat 2014

The Safety and Efficacy of Breast Conserving Therapy Established by Phase III Randomized Trials Conducted Over 30 Year ago.

Trial	*Yrs F/U*	*% Overall Survival* BCT	Mastectomy	p
Milan I	20	58	59	NS
NSABP B-06	20	46	47	NS
EORTC 1081	20	39	45	NS
DBCG-82 Tm	20	57.8	50.6	NS

Veronesi, NEJM, 2002
Fisher, NEJM, 2002
Litiere, Lancet Oncol, 2012
Blichert-Toft, Acta Oncologia 2009

Decades of Research Focused on Identifying Factors Associated with Ipsilateral Breast Recurrence (IBR)

Factor	Summary
Age	Age < 50 or 40 associated with increase LR after BCT and Mastectomy
LVI	Multiple studies supporting increased local recurrence after BCT and MRM – negative margins essential.
EIC	Negative margins largely mitigates higher risk of IBR
Tumor Size	Conflicting studies but trend for increased local recurrence with ≥ T-2 post BCT and Mastectomy
Nodal Status	More local recurrences demonstrated in higher stage disease
Lobular Histology	Conflicting studies but likely eliminated in well defined lesions on mammogram with negative margins
Systemic therapy	Appropriate chemo, endocrine, HER2 therapy reduces IBR

Surgical Margin Associated with IBR after BCT
Meta-analysis

- 33 retrospective studies, 28,162 patients, and 1,506 IBTRs.
- Median follow-up of 79.2 months (ie, 6.6 years),
- IBR: 5.3% (median, interquartile range, 2.3%- 7.6%).
- Close/positive margins vs Negative : Odds Ratio (OR) 1.96 ($p < 0.001$)
- Positive margins vs Negative: OR 2.42, ($p < 0.001$)
- Close margins vs Negative: OR 1.74 ($p < 0.001$)
- Margin Distance- no effect
  - No evidence that the odds of IBR decreased as the distance for declaring negative margins increased

Houssami N, Ann Surg Onc 2014

SSO and ASTRO Margin Guidelines

Positive Margin

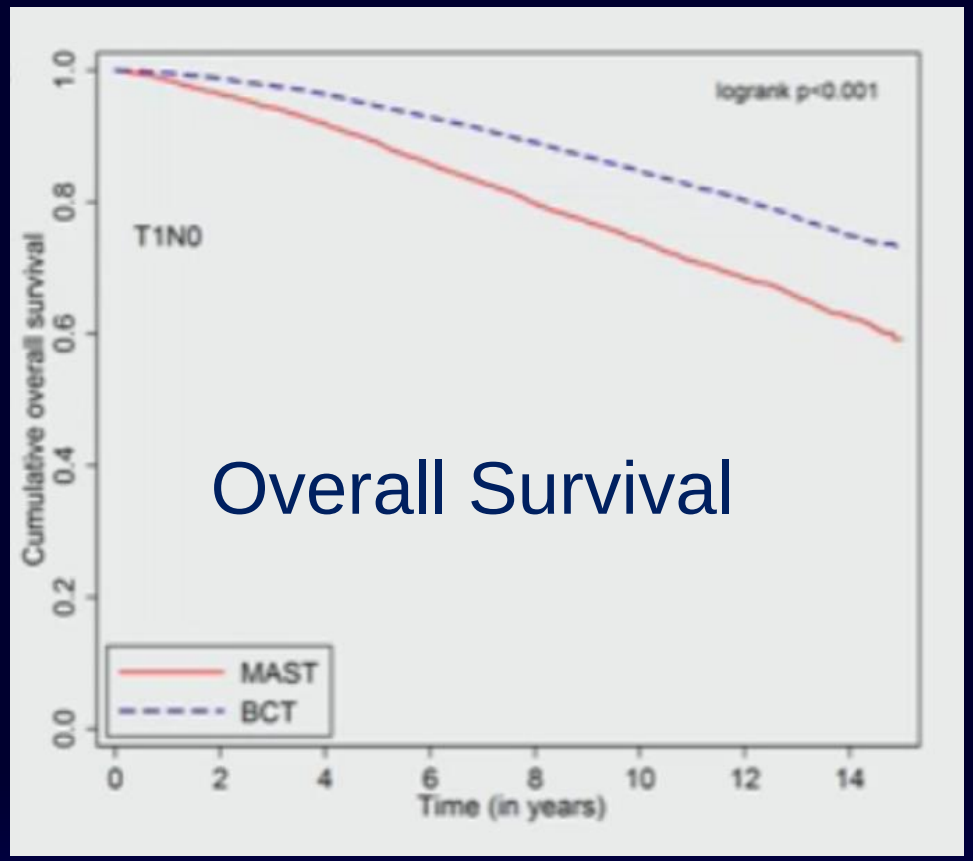
- *Defined as ink on invasive cancer or ductal carcinoma in situ (DCIS): associated with two-fold increase in IBTR.*
- *This increased risk in IBTR is not nullified by:*
  - *delivery of a RT boost dose*
  - *delivery of systemic therapy (endocrine or chemotherapy)*
  - *favorable biology*

Margin Width

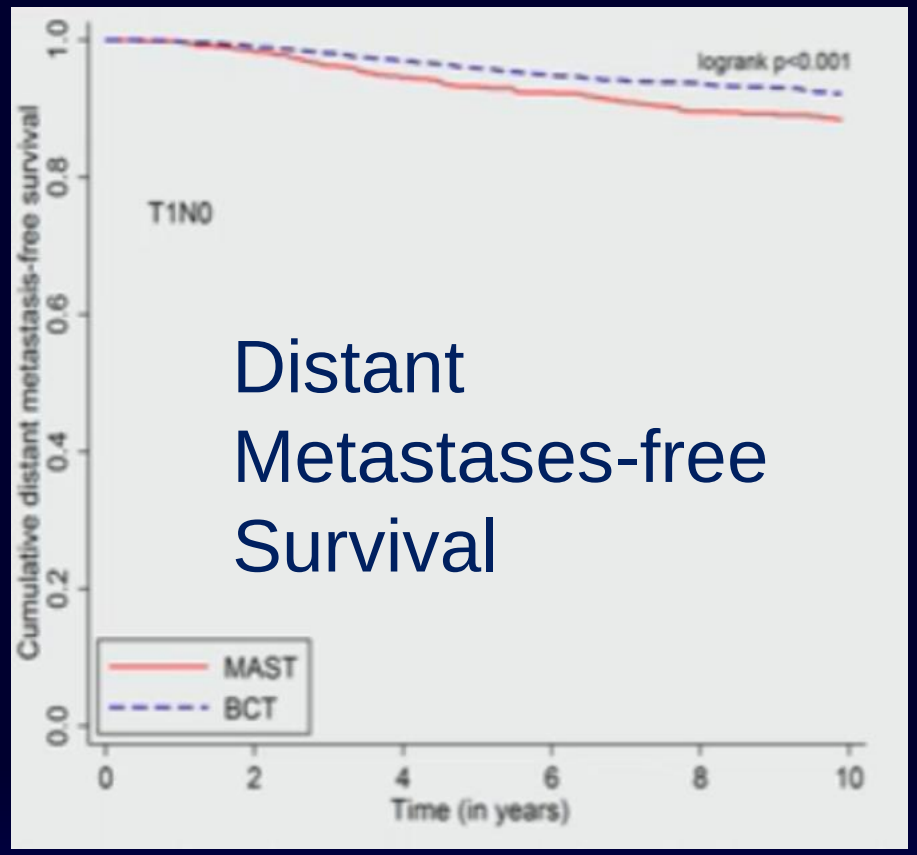
- *Negative margins (no ink on tumor) minimize the risk of IBTR.*
- *Wider margin widths do not significantly lower this risk.*
- *The routine practice to obtain wider negative margin widths than no ink on tumor is not indicated.*

Moran , J. Clin. Oncol 2014

Improved 10 year Overall Survival and Distant Metastases Free Survival with BCT



Overall Survival

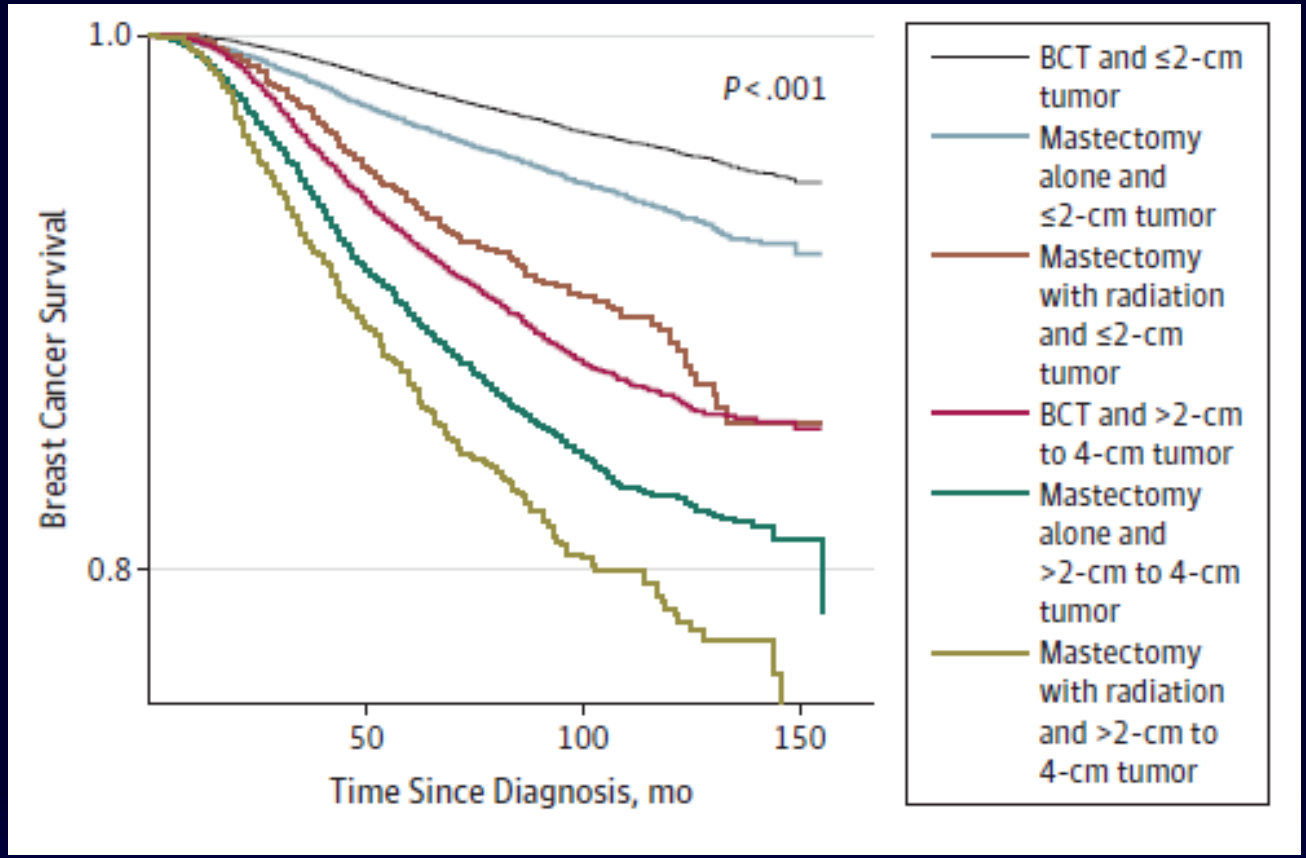


Distant Metastases-free Survival

- 2000-2004 37,200 patients, 58.4% BCT
- Median follow up time 11.3 years

van Maaren et al Lancet Oncol 2016

Breast Conservation with Lumpectomy and RT had Superior Breast Cancer Specific Survival than Mastectomy ± RT



SEER 1998-2008: 132,149 patients, BCT 92,671 (70.1%),
Mastectomy alone 34,999 (26.5%), and mastectomy with RT 4479 (3.4%).

Agarwal , JAMA Surg. 2014

Case 3

- 39 yo G2P2 premenopausal female palpates mass right breast
- Healthy, No meds, Works full time as RN
- No Family history of breast or Ovarian Cancer
- Mammogram and US confirm 2.5 cm mass.
- Axillary US negative.
- US guided core biopsy breast G2, Infiltrating ductal cancer,
- ER 60%, PR 20%, HER2 negative
- Lumpectomy and SNB: 2.8 cm G2 IDC, 0/4 SN, (T2,N0)
- Recurrence Score: 21
- S/p chemo TC x 4, OS and AI intended

Whole Breast Irradiation ± Boost!

Goals of Breast Radiotherapy for Conservation Treatment

DCIS:

- Maximize local control
- Prevent first invasive breast cancer
- Sustain freedom from mastectomy
- Maintain sensate and acceptable cosmetic breast appearance

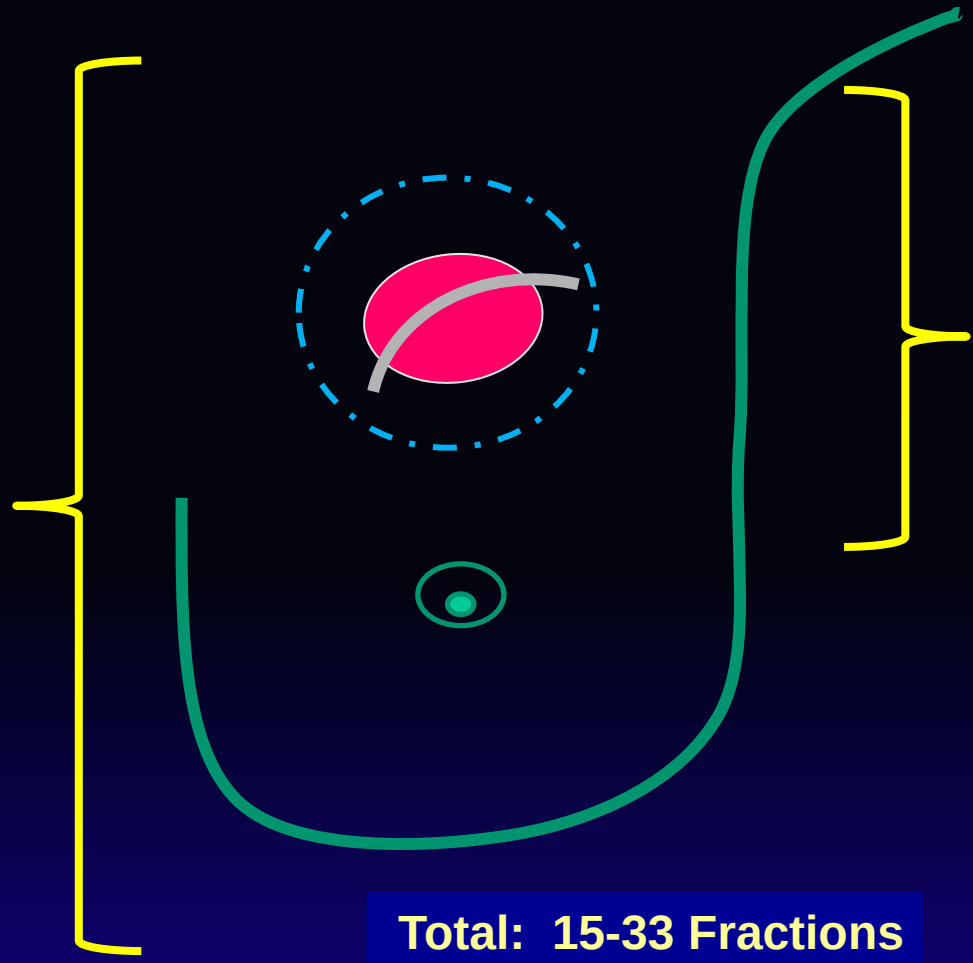
Invasive breast cancer:

- Maximize local control
- Equivalence to mastectomy
- Prevent Distant Metastases
- Optimize breast cancer/ overall survival
- Maintain sensate and acceptable cosmetic breast appearance

Whole Breast Irradiation (WBI) Post-Lumpectomy

CF: 50 Gy/ 25 Fractions
46 Gy/ 23 Fractions
50.4 Gy/ 28 Fractions

HF: 42.56 Gy/ 16 Fractions
40 Gy/ 15 Fractions



±

Boost: 10 -16 Gy
4-8 Fractions

Total: 15-33 Fractions
3-6.5 weeks

Historical Perspective of WBI Fractionation

1993–94 ACR Patterns of Care US

- US survey of Radiation Oncology facilities (randomly selected)
- n=737
- Whole breast irradiation
  - Consistent fraction size:
    - **1.8–2 Gy in 99.2%**
    - 1.8 Gy - 61.2%;
    - 2 Gy - 38.0%
  - Variable Whole breast dose:
    - 44 – 49.99 Gy - 41.8%
    - 50 - 51.99 Gy - 56.8%
- Boost: 83.8%

Shanks et al, IJROBP, 2000

1984-89 Patterns of Practice in Ontario

- N = 551 BCT patients treated with WBI
- 48 different dose/ fractionation schedules
- Most common fraction size: 2.5 or 2.67 Gy
- Boost: 85%

Whelan et al, CAN MED ASSOC J 1993

Hypo fractionation for Breast Cancer is a Patient Advocacy Achievement!

- **R.A.G.E: Radiotherapy Action Group Exposure 1991**
  - Group of UK women who experienced terrible long-term side effects as a result of radiotherapy treatment for breast cancer.
  - Late 70s and early 80s: increase in radiation-induced injuries in 29% of UK hospitals
- **UK National Health Service requests Independent Review to be commissioned by Royal College of Radiologists**
  - Identified hypofractionation regimens in use that led to > 38% rate brachial plexopathy with a latency for the onset of symptoms of 10 years
  - Genesis of the UK Breast cancer Hypofraction Trials Program that began in 1999 (e.g. START and FAST trials)

Patient voices: Living with consequences, Cancer World, 2007
Yesterday's women. The story of R.A.G.E. Macmillan Cancer Support. October 2006
Independent Review commissioned by The Royal College of Radiologists Brachial: Plexopathy from RT, 1995

WBI Fractionation Evolution

TIMELINE

1980

- Conventional Fractionation
  1.8 – 2 Gy USA/ Western Europe
- Hypo fractionation
  2.5 – 3 Gy Canada/ UK

1995

- RAGE → UK NHS Independent Review → Funded Research

2002

- OCOG Phase III 5 yr Results: 50 Gy / 25 F vs 42.5/ 16 F 2.66 Gy

2006

- START Pilot , A, B Phase III 5 yr results: 50 Gy / 25 F vs13-15 F weekly/daily 2.67-3.3 Gy

2010

- OCOG Phase III 10 yr. Results: 50 Gy / 25 F vs 42.56/ 16 F

★

2013

- START A, B Phase III 10 yr results: 50 Gy / 25 F vs 13-15 weekly or daily 2.67-3.3 Gy

★

2020

- Fast Phase III 50 Gy / 25 F vs 28.5-30 Gy / 5 F weekly 5.7 – 6 Gy
- Fast Forward Phase III 40 Gy / 15 F vs 26-27 Gy / 5 F daily 5.2 – 5.4 Gy

OCOG Phase III Randomized Trial
10-Year Update

	In-Breast Recurrence (%)		Excellent/ good Cosmesis (%)		G2-3 Toxicity Subcutaneous Tissue (%)	
	5 yr	10 yr	5 yr	10 yr	5 yr	10 yr
Hypo fractionated	2.8	6.2	79	71	6	11
Standard	3.2	6.7	78	70	5	12

Median F/U: 12 years

No differences in any endpoint

Whelan et al, NEJM 2010

Patient and Treatment Characteristics Enrolled on the START A and B Trials

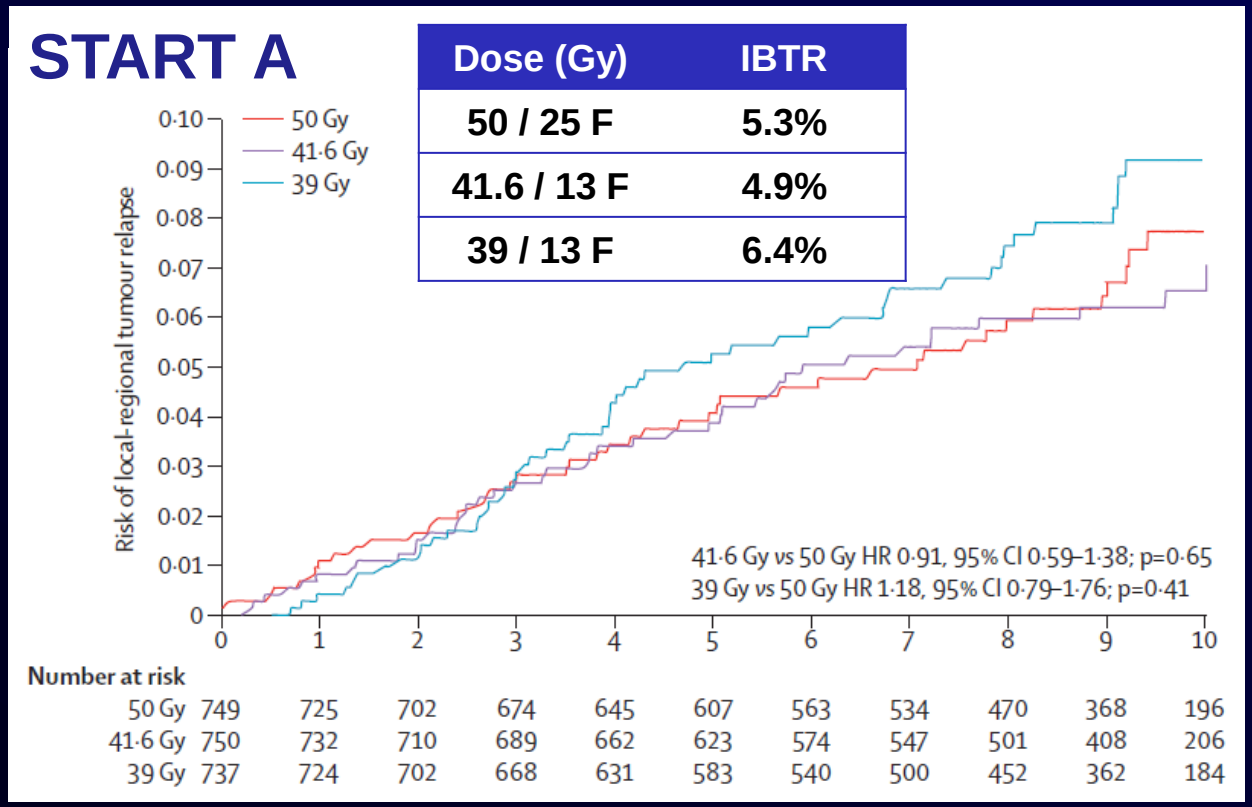
	START A	START B
Years	1999 - 2002	1999 - 2002
Median Age (yrs)	57.1	57.1
T1	51.5%	63.8%
N+	28.8%	22.8%
BCS	85%	92%
Boost	60.4%	60.6%
RNI	13.8%	13.8%
Tamoxifen	54%	72%
Tam + Chemo	24.5%	15%
Chemo	11%	7%

Haviland et al, Lancet Oncol 2013, Supplementary appendix

2013: 10-Year Follow-up Results of START A and B Randomized Trials

START A

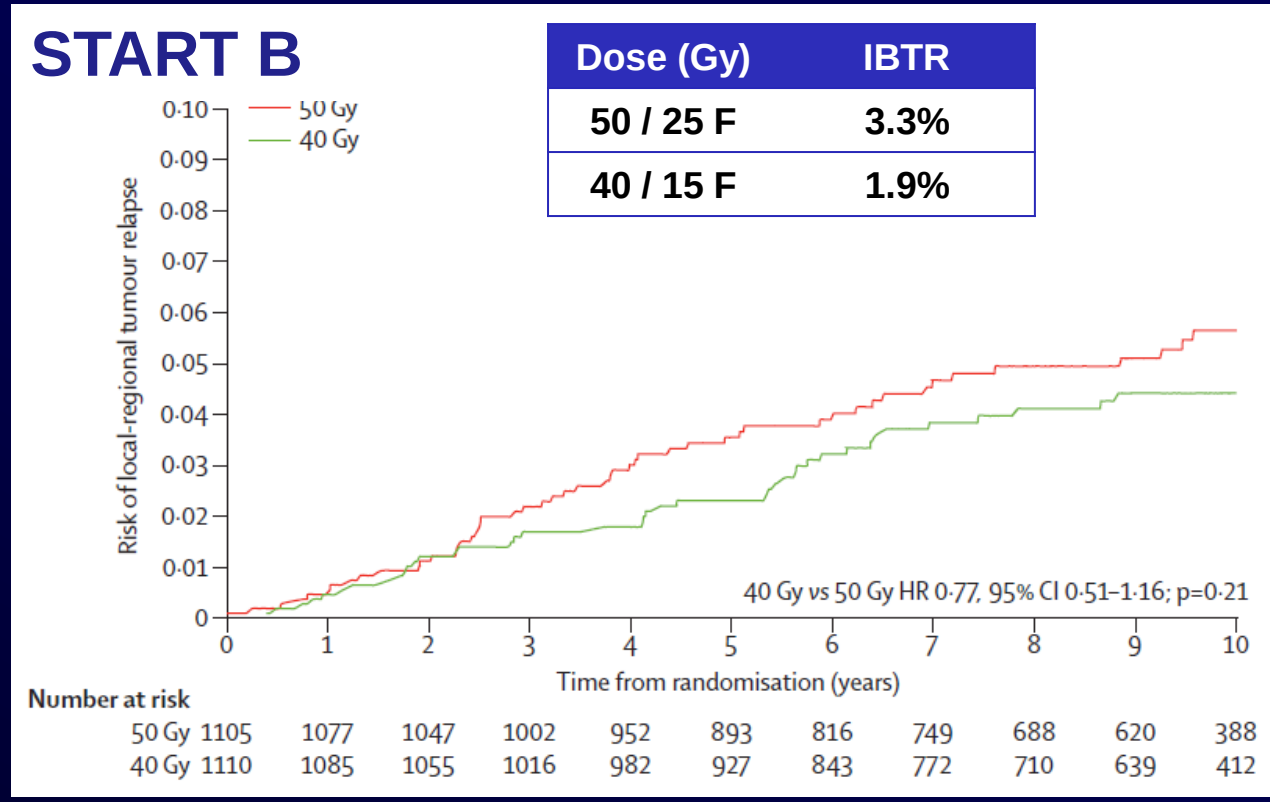
Dose (Gy)	IBTR
50 / 25 F	5.3%
41.6 / 13 F	4.9%
39 / 13 F	6.4%



Median follow-up: 9.3 years

START B

Dose (Gy)	IBTR
50 / 25 F	3.3%
40 / 15 F	1.9%

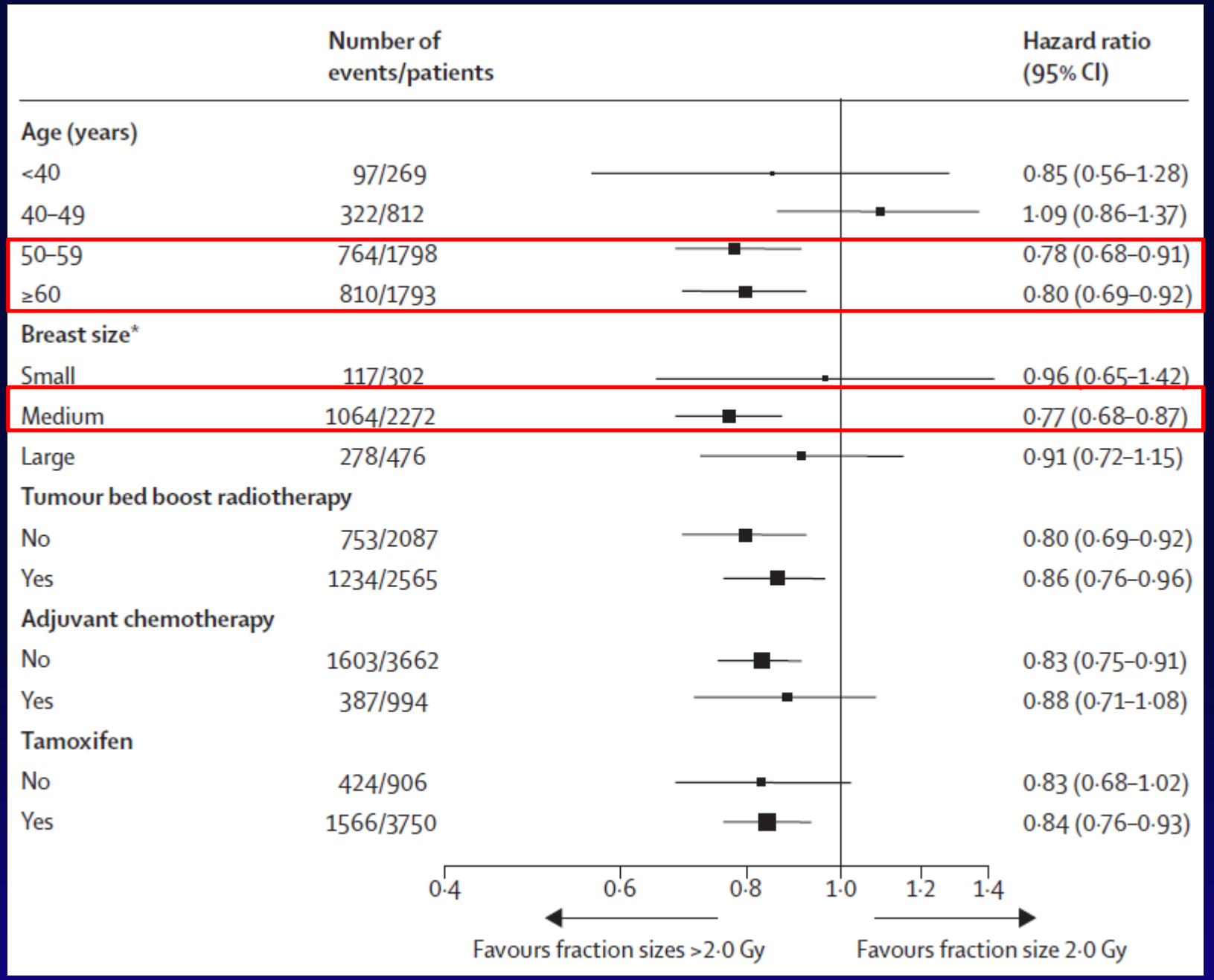


Median follow-up: 9.9 years

Haviland et al, Lancet Oncol 2013

MD Assessed Normal Tissue Effects

- Meta analysis of 3 UK trials:
  - Pilot
  - START A
  - Start B
- n= 4,660
- Normal tissue effects assessed:
  - Breast Shrinkage
  - Induration
  - Telangiectasia



Haviland et al, Lancet Oncol 2013

ASTRO Guideline Evolution for Hypo fractionated Whole Breast Irradiation

2011 Hypo fractionated WBI (42.5 Gy / 16 F)

- 50 years or older
- Stage pT1-2 pN0
- Did not receive chemotherapy

Smith et al, IJROBP 2011

2018 Hypo fractionated WBI (42.5 Gy/ 16 F or 40 Gy/ 15 F)

- Preferred WBI fractionation
- DCIS and Invasive

Smith et al, PRO 2018

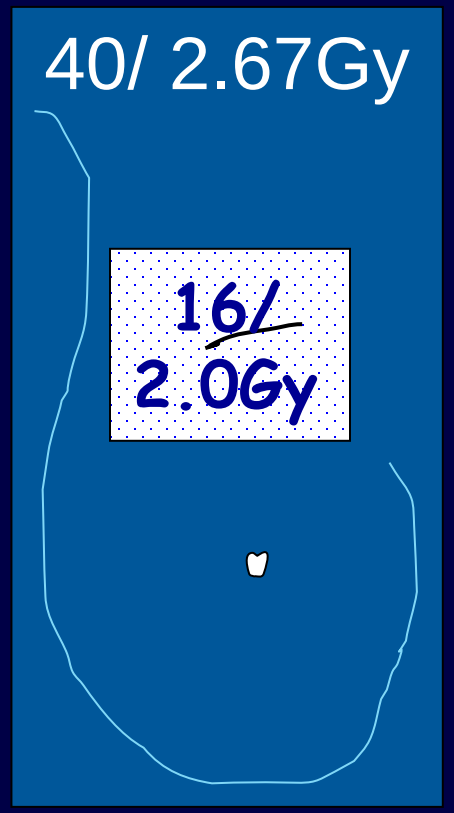
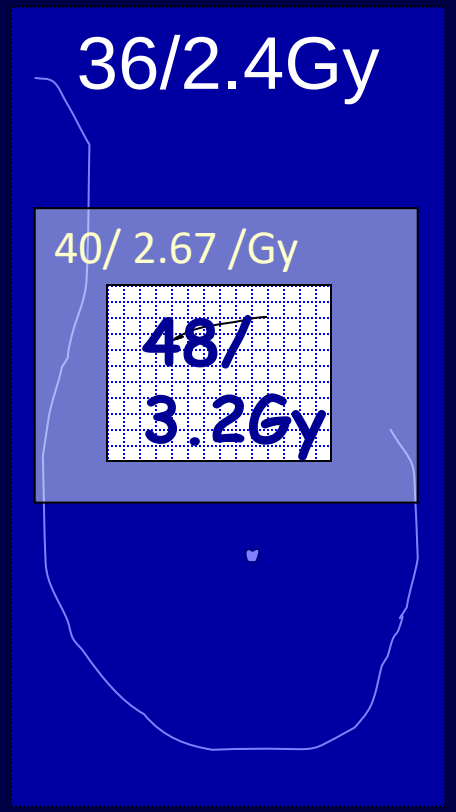
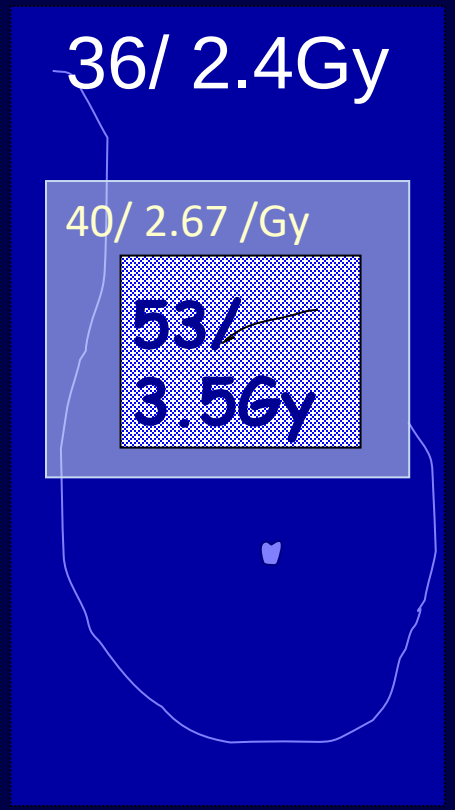
Boost Delivery in Clinical Trials Evaluating Moderate Hypo fractionation for WBI

Trial	Boost	Dose	Delivery
OCOG	None	-	-
UK Pilot	75%	14 Gy / 7 F	Sequential
START A	60.4%	10 Gy / 5 F	Sequential
START B	60.6%	10 Gy / 5 F	Sequential

UK IMPORT HIGH Trial

Normal Tissue Effects (n=840)

Primary Endpoint: Breast Appearance

Sequential boost (Control)	Concomitant Boost Test 1	Concomitant Boost Test 2
		
40/ 2.67Gy ~~16~~/ 2.0Gy	36/2.4Gy 40/ 2.67 /Gy ~~48~~/ 3.2Gy	36/ 2.4Gy 40/ 2.67 /Gy ~~53~~/ 3.5Gy
15 WBI +8 F Boost Sequential	15 Fractions	15 Fractions

Cole et al, SABCS 2018

UK IMPORT HIGH TRIAL: No Difference in Photographic Breast Appearance at 3 Years

Change in breast appearance	B: 40 Gy/ 15F L: + 16 Gy/ 8F N=218	B: 40 Gy/ 15 F L: 48 Gy/ 15 F N=210	B: 40 Gy/ 15 F L: 53 Gy/ 15 F N=213
	n (%)	n (%)	n (%)
None	183 (84)	185 (88)	177 (83)
Mild	25 (11)	23 (11)	32 (15)
Marked	10 (5)	2 (1)	4 (2)

Cole et al, SABCS 2018

NRG/ RTOG 1005 Trial

Phase III

"High Risk" Stage 0, I-II, breast cancer treated by lumpectomy

Randomization

Stratification: Age < 50 vs ≥ 50
Chemo yes vs no
Grade 1,2 vs 3
ER + vs -

Standard WBI- Sequential boost

- WBI: 50 Gy (2.0 Gy)
  42.56 Gy (2.67 Gy)
- Boost: 12-14 Gy (2 Gy)

Total : 22-33 Fractions

Hypo fractionated WBI- Concomitant boost

- WB PTV: 40 Gy/ 2.7 Gy
- Lump PTV: 48 Gy/ 3.2 Gy

Total : 15 Fractions

Targeted accrual = 2312

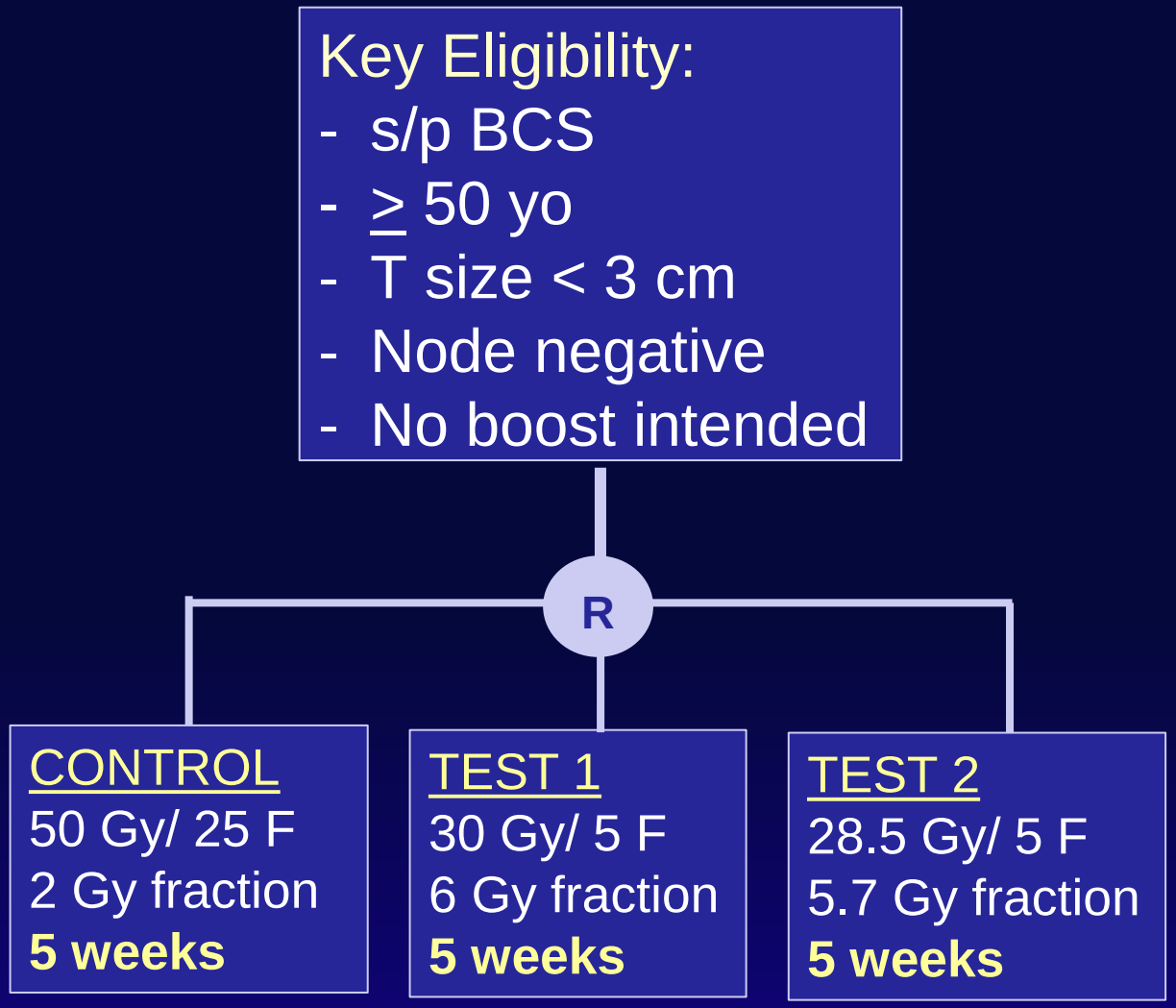
Primary Endpoint: IBTR

RTOG 1005

- Accrued 2354 2011 – 2014
- Median follow up: ~ 6 year (9-2020)
- 3DCRT 78.5% vs IMRT 21.5%
- Results pending
- Patient population:

Characteristic	%
Age < 50 years	35
G3	52.3
Close (< 2 mm) or + Margin	16.7
ER/ PR Negative	30.3
Chemotherapy	40. 9

FAST Fractionation for WBI: UK FAST Trial



- 2004 – 2007
- Accrual: 915
- Photos: baseline, 2 and 5 years
- Population:

Characteristic	
Mean Age	62.4 years
Mean T-size	1.3 cm
Grade 1-2	88.7%
Tamoxifen / AI	89.5%

CRUKE/04/015

Primary endpoint: Change in Photographic Breast Appearance

Yarnold et al, Rad & Onc, 100: 2011

Photographic Change in Breast Appearance 2 years

- **30 Gy/ 5 F/ 6 Gy q week**

  Significantly more:

  - mild to mark change in breast appearance on photos
  - Marked adverse breast effects:
    - Shrinkage
    - Induration
    - telangiectasia

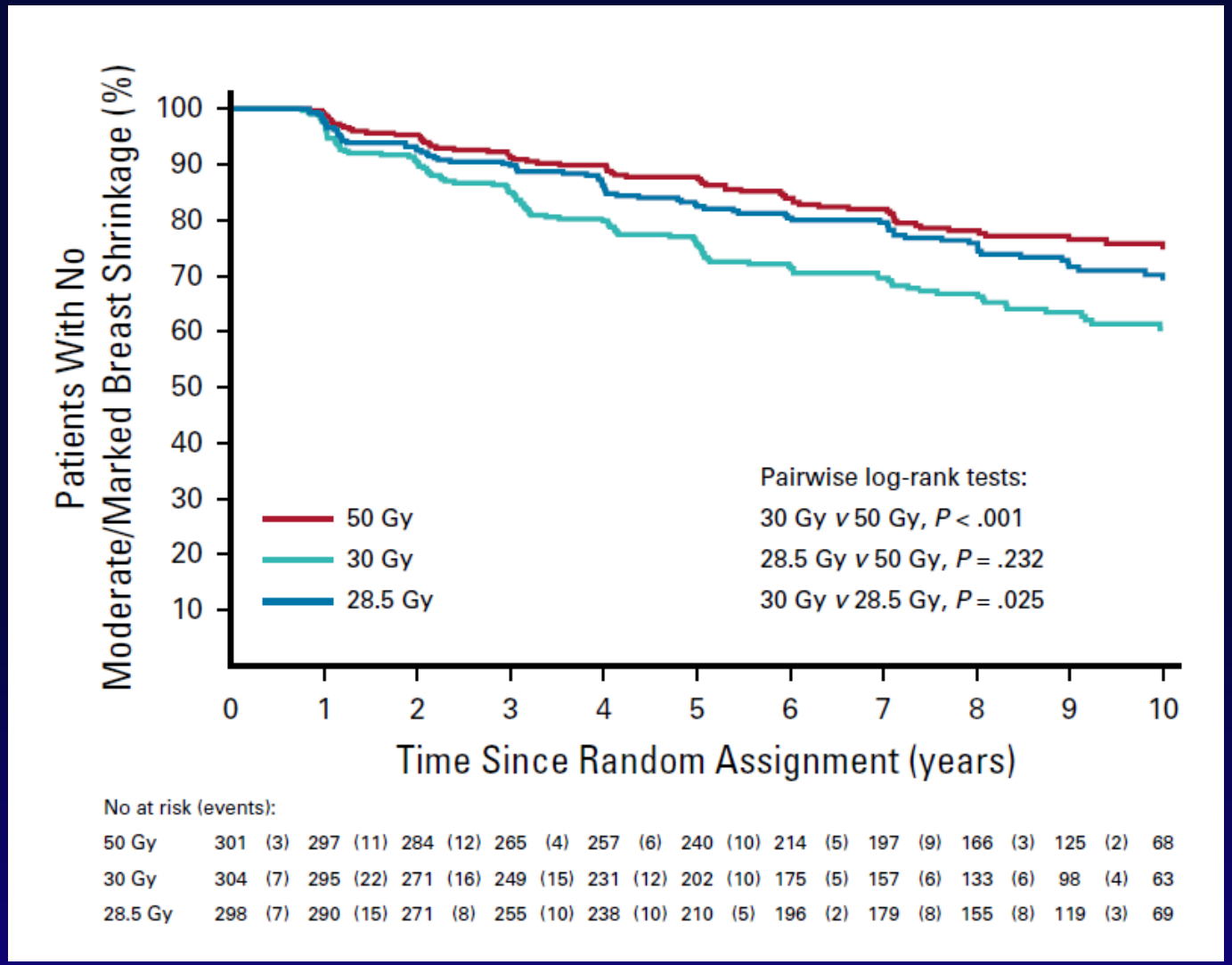
Change in Breast Appearance on Photo

	Fractionation schedule		
	50 Gy, $N = 239$ (%)	30 Gy, $N = 248$ (%)	28.5 Gy, $N = 242$ (%)
No change	189 (79.1)	160 (64.5)	184 (76.0)
Mild change	46 (19.2)	65 (26.2)	49 (20.2)
Marked change	4 (1.7)	23 (9.3)	9 (3.7)

Yarnold et al, Rad & Onc, 100: 2011

10 Year Outcome of the FAST Trial (CRUKE/04015)

- **30 Gy/ 5 F/ 6 Gy per week** significantly more:
  - mild to mark change in breast appearance on photos
  - Marked adverse breast effects.
- IBTR very low
  - 5 year: 0.7%
  - 10 year: 1.3%

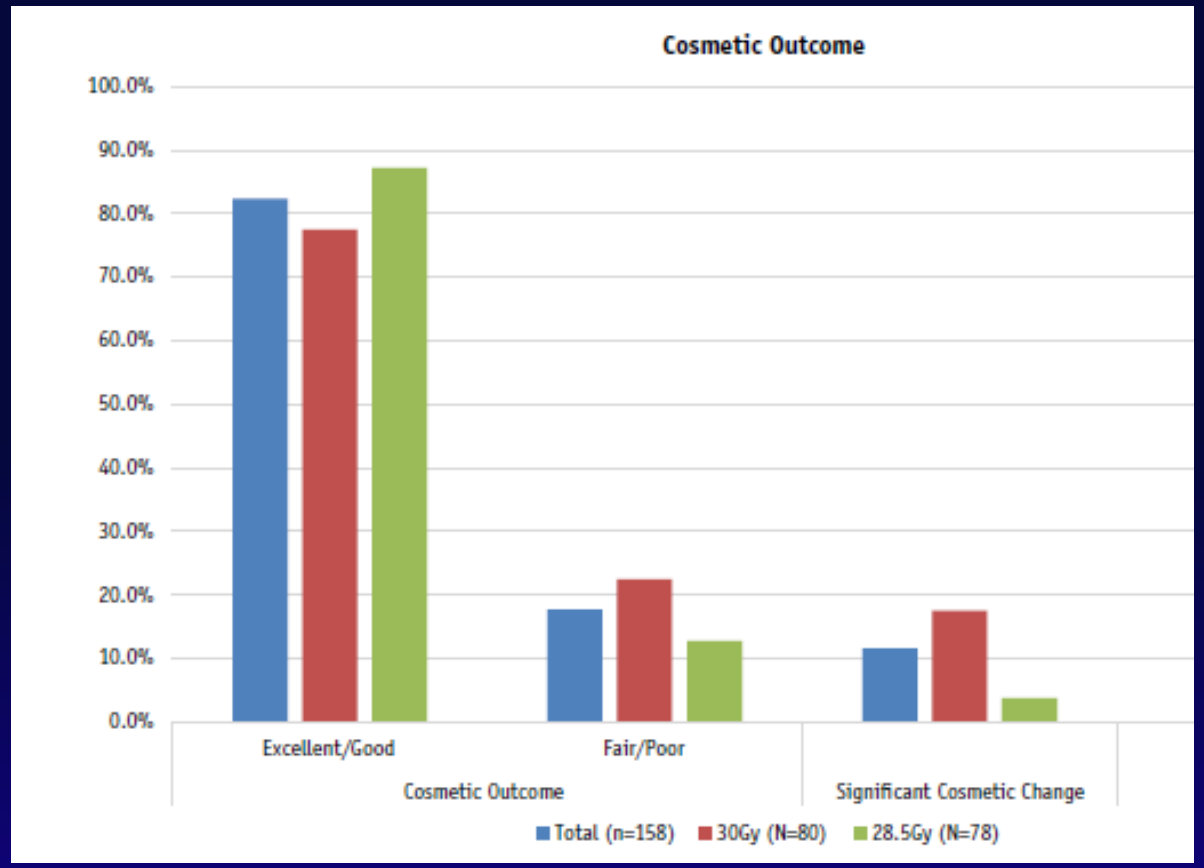


Brunt et al, JCO 2020

University of Louisville Phase II Fast Trial

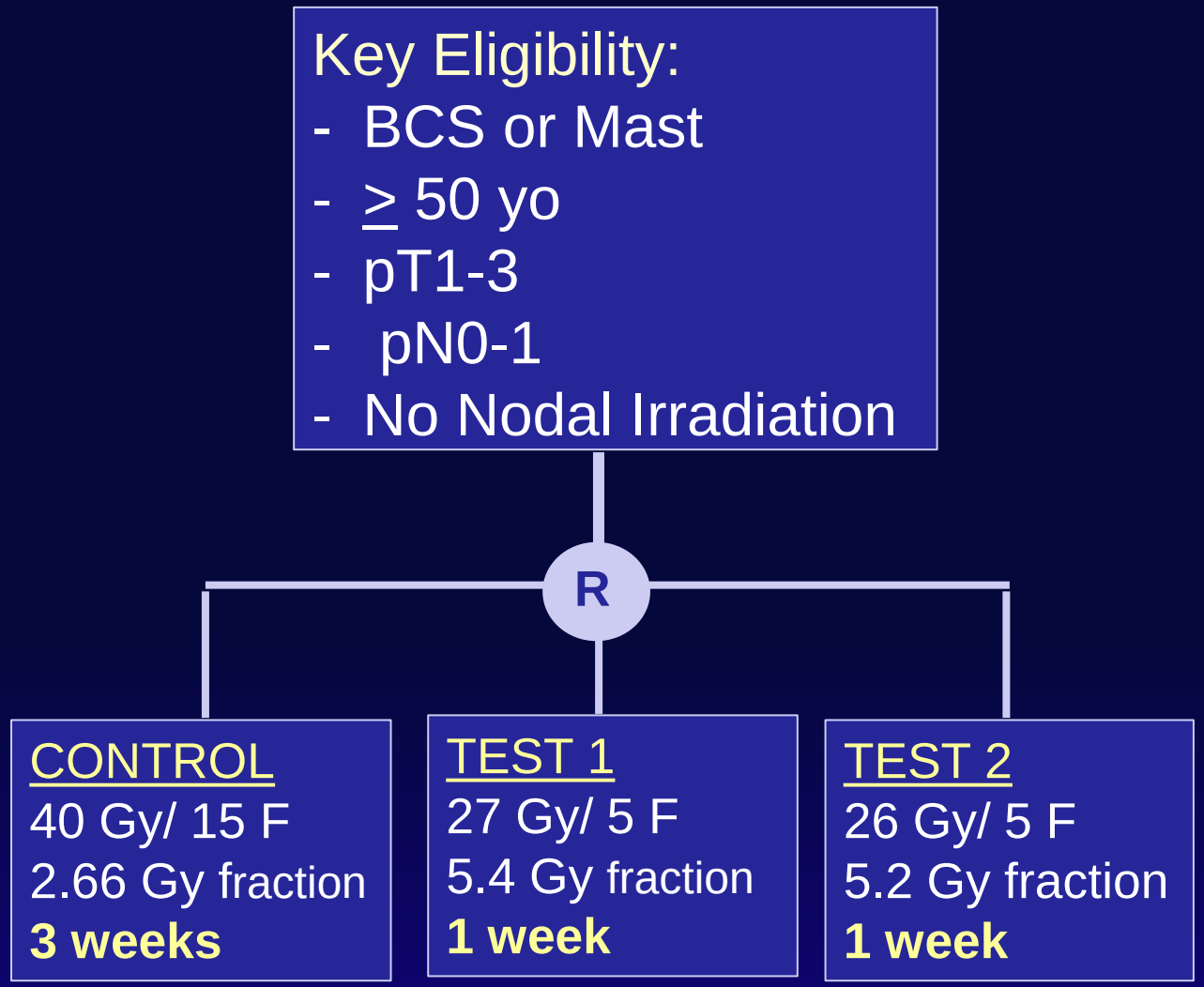
- 2011 – 2016
- N =158
- Population:
  - Median age 59
  - DCIS 21 %
  - Stage 1 60.8%
- ER/ PR +: 77%
- Whole breast irradiation:
  - 30 Gy / 5 F/ 5 weeks 82.3%
  - 28.5 Gy / 5 F/ 5 weeks 17.7%

- Median Follow up: 3.3 years
- Local recurrence: 1.3%



Dragun et al, IJRBOP 2017

UK FAST Forward Trial



Primary endpoint: Ipsilateral Breast Tumor Relapse

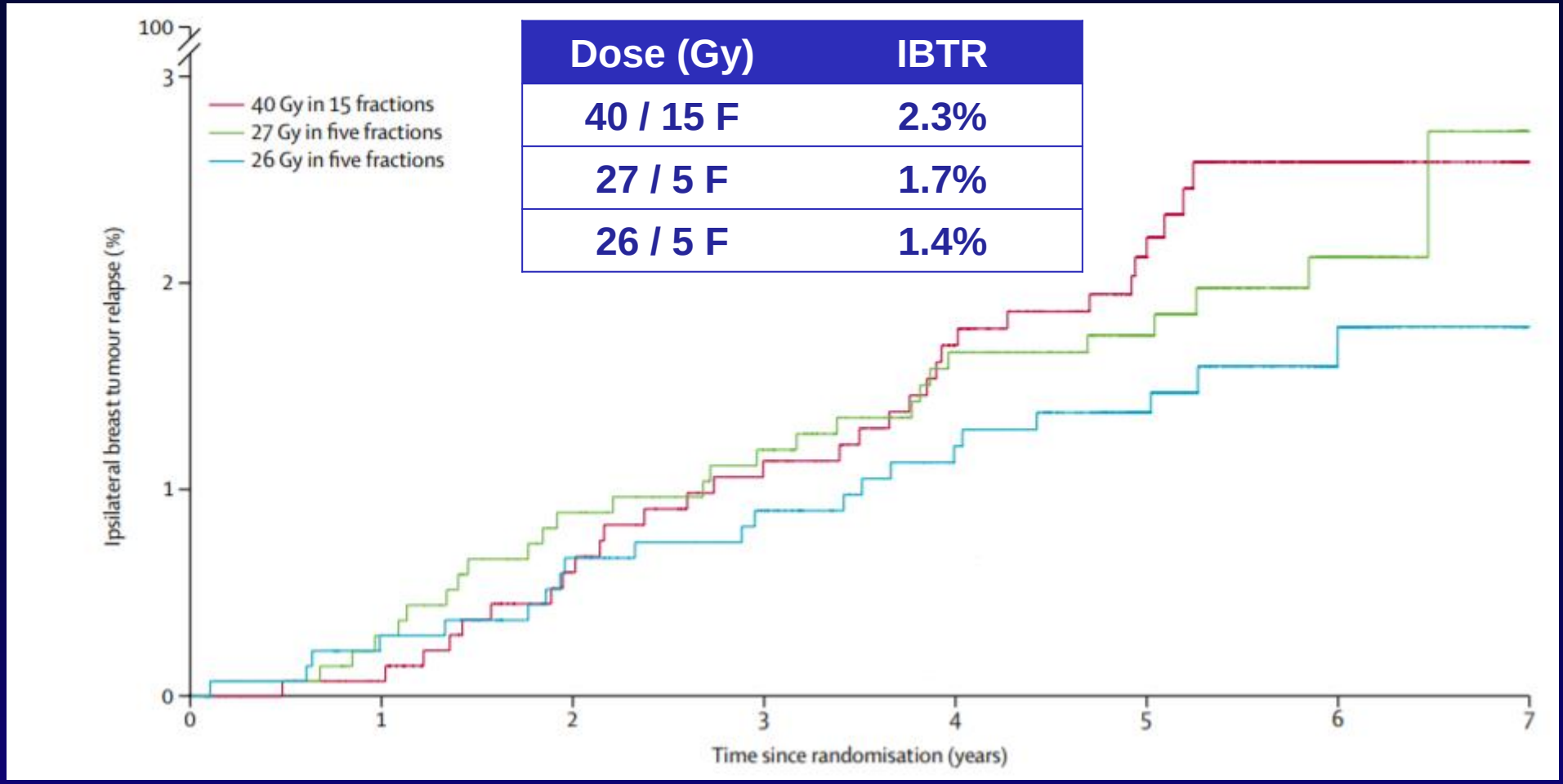
- 2011 – 2014 (97 Hospitals)
- Accrual: 4110
- Photos: baseline, 2 and 5 years
- Median Follow up: 71.5 months
- Population:

Characteristic	
Mean Age	60 years
BCS	93.5%
Median T-size	1.6 cm
Grade 1-2	71.6%
Node +	18.4%
ER+	88.6%
Boost	25%

Brunt et al, Lancet, 395: 2020

UK FAST Forward Trial
Ipsilateral Breast Tumor Relapse is Non Inferior

Dose (Gy)	IBTR
40 / 15 F	2.3%
27 / 5 F	1.7%
26 / 5 F	1.4%



Brunt et al, Lancet, 395: 2020

Toxicity and Breast Appearance Worse for 27 Gy / 5 Fraction Test Group

	MD Rated		Patient Reported Outcome	
Arm	Photo Changes Mild-Moderate	Adverse Events Breast or CW	Breast Harder or Firmer	Breast Pain
40 Gy / 15 F	12%	10.6%	20.4%	13.3%
27 Gy / 5 F	**26.9%**	**15.9%**	**27.5%**	**16.5%**
26 Gy / 5 F	13%	12.2%	24.7%	16.1%

Brunt et al, Lancet, 395: 2020

Summary: WBI Fractionation

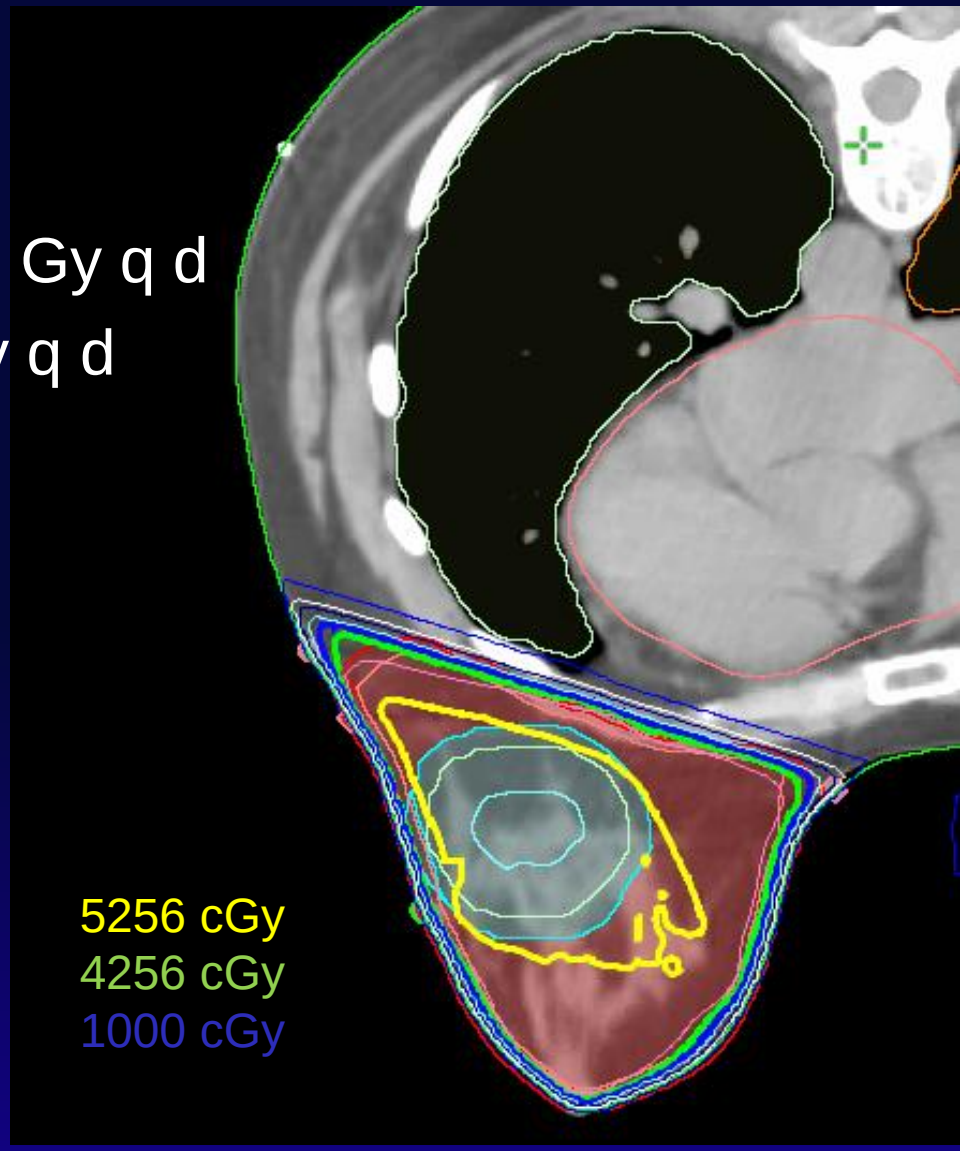
- Moderate hypo fractionation is the Standard of Care for Whole Breast Irradiation without Regional Nodal Irradiation
  - 42.56 Gy/ 16 F / 2.66 Gy per fraction (no boost)
  - 40 Gy / 15 F/ 2.67 per fraction (boost)
- Boost per standard indications:
  - Sequential: 10 Gy/ 4 or 5 Fractions
  - Concomitant: 8 Gy/ 15 F
- FAST fractionation:
  - Narrow margin for increase toxicity (27 vs 26 Gy)
  - Corroboration by another trial will solidify role in breast cancer treatment.

Case 3 Treatment

39 yo w/ pT2,N0,ER 60%, PR 20%, HER2 -, RS 21

1. Radiation:
   - Whole Breast Irradiation: 4256 cGy/ 16 F/ 2.67 Gy q d
   - Boost Lump PTVeval: 1000 cGy/ 5 F/ 200 cGy q d

2. Endocrine Therapy
   - Ovarian Suppression
   - Anastrozole started after RT



Case 4:

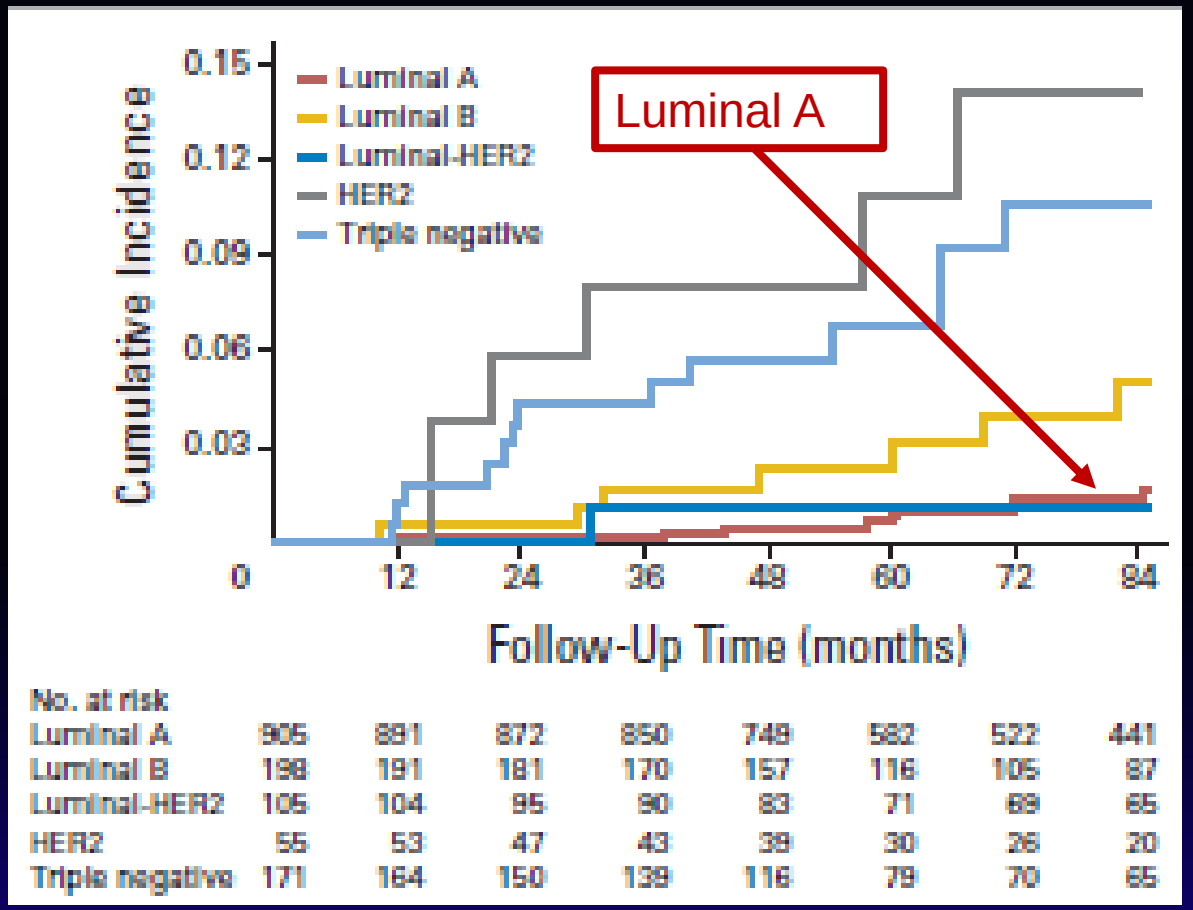
- 53-year-old post-menopausal female presented with abnormal mammogram with a stellate mass
- US Guided biopsy demonstrates a G2, IDC, ER 95%positive, PR 80%, HER2 negative
- LEFT lumpectomy and sentinel node biopsy: 1.8 cm grade 2, infiltrating ductal cancer, ER 95% positive, PR 80%, HER2 negative and all surgical margins negative, 0/2 SN
- Oncotype RS is 17.
- Endocrine therapy with Anastrozole is planned.

Breast Cancer Subtype is Associated with Local Recurrence after BCT

- n= 1434 BCT patients
- Harvard Rad Onc. Program
- Retrospectively evaluated Subtype
- 7 year median F/U

Subtype	n	7 yr IBR
Lum A	905	0.8%
Lum B	198	2.3%
Lum HER2★	105	7.4%
HER2★	55	10.8%

- Lowest Recurrence for Luminal A, ER+PR+ HER2 negative

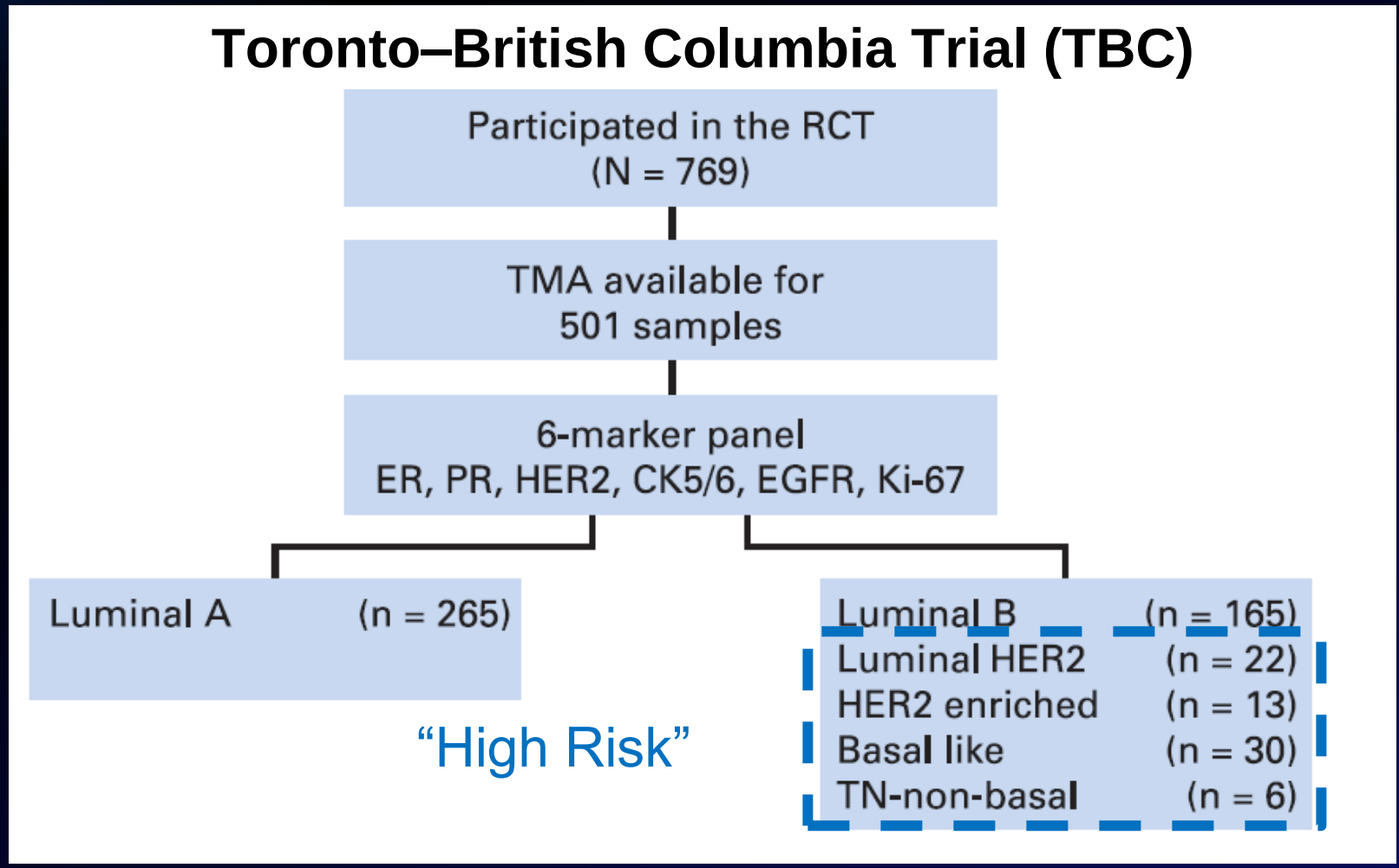


★ Did not receive Herceptin

Arvold, et al JCO 2011

Can Breast Cancer Subtype further Stratify LRR Prognosis in "Low Risk" HS Breast Cancer?

ER+, Stage 1, >50 yo



Liu et al JCO 33: 2015

TBC: Luminal A Subtype Prognostic for Reduced LRR

Variable	No.	IBR at 10 Years (%)	P
Age, years			
≤ 60	130	14.1	
Subtype			
Luminal A			
Luminal B			
Other	71	21.3	< .001

Univariate

Covariate	HR	95% CI	P
Tamoxifen + RT *v* tamoxifen	0.32	0.16 to 0.62	< .001
Subtype			
Luminal A *v* high risk	0.21	0.1 to 0.46	< .001
Luminal B *v* high risk	0.45	0.22 to 0.92	.028
Luminal A *v* luminal B	0.48	0.23 to 0.98	.045
Overall			< .001

Multivariate

- No additional benefit of RT for combination of **Luminal A** & > 60 yo & G1,2 & T1N0 (n=151)
- 10 yr Local Recurrence
  Tam and RT: 1.3%
  Tam alone: 5%
  p=.56

Liu et al JCO 33: 2015

SWEBCG91 Trial: Ipsilateral Breast Recurrence by BC Subtype w/o Systemic Rx

- 1991-1997 Phase III RCT
- Stage I- IIa Lump +/- Breast RT
- Systemic therapy: ~ 6%
- Collected tissue: n= 1,003 of 1,178
- Subtype n= 958
- "St. Galen" IHC ER, PR, HER2, Ki67
  - Lum A n=554
    (Lum a "low risk": N0, > 65 y n=180)
  - Lum B n=259
  - TN n=81
  - Her2 n=44

IBR%	RT	No RT	P
Lum A	9%	19%	.001
Lum A low risk	6%	20%	.008
Lum B	8%	24%	.001
TN	6%	21%	.08
HER2	15%	19%	.6

Median follow up: 15.2 years

Sjostrom, et al. J Clin Oncol 35:2017

What are the Implications for Luminal A Breast Cancer Treated with Endocrine Therapy for Lumpectomy and Breast Radiation?

REDUCE EXTENT OF RADIATION:

- –Accelerated Partial Breast Irradiation (APBI)
- – Intraoperative Radiation Therapy (IORT)
- – Observation

Accelerated Partial Breast Irradiation
5 Randomized Trials with Hypo fractionation:
3.4 – 6 Gy / Fraction

	n	Median Follow up	APBI Method	APBI Fractionation	Days
NIO Budapst[1]	287	10.2 yrs.	MCT	HDR 36.4 Gy / 7 F/ BID	4
U. Florence[2]	520	5 yrs.	IMRT	30 Gy/ 5 F/ QOD	10
GEC-ESTRO[3]	1184	6.6 yrs.	MCT	HDR 32 Gy / 8 F/ BID	4
OCOG Rapid[4]	2135	8.6 yrs.	3DCRT	38.5 Gy/ 3.85 Gy/ BID	5
NRG [5]			3DCRT	38.5 Gy/ 3.85 Gy/ BID	
NSABP B39/	4216	10.2 yrs.	MCT	34 Gy/ 3.4Gy/ BID	5
RTOG 0413			Balloon	34 Gy/ 3.4 Gy/ BID	

[1]Polgar et al. Rad & Onc, 2013
[2]Livi et al. Eur J Ca 2015, SABCS 2019
[3]Strnad et al. Lancet Oncol 2016
[4]Whelan, et al., Lancet, 2019
[5]Vicini et al, Lancet 2019

4 Phase III Randomized Trials:
IBR from APBI is Non-inferior to WBI

	n	Median Follow up	APBI Method	IBR		Regional Recurrence	
				APBI	WBI	APBI	WBI
NIO Budapst[1]	287	10.2 yrs.	MCT	5.5%	4.6%	2.5%	1.7%
U. Florence[2]	520	5 yrs.	IMRT	1.5%	1.4%	1.4%	1.9%
GEC-ESTRO[3]	1184	6.6 yrs.	MCT	1.4% (1.9%)*	0.92% (1.67%)*	0.49%	0.56%
OCOG Rapid[4]	2135	8.6 yrs.	3DCRT	3%	2.8%	0.4%	0.2%

[1]Polgar et al. Rad & Onc, 2013

[2] Livi et al. Eur J Ca 2015, SABCS 2019

[3]Strnad et al. Lancet Oncol 2016

[4]Whelan, et al., Lancet, 2019

*Local + 2nd Primary

All 4 APBI Phase III Non-Inferiority Trials:

Stage I Luminal Breast Cancer

	Median Age	Invasive N0	T1	Grade 1-2	ER/PR +
U. Florence[1]	62	86.2 %	93 %	89 %	96%
NIO Budapest[2]	62	94 %	100 %	100 %	89 %
GEC-ESTRO[3]	62	95 %*	89 %	90 %	95 %
OCOG Rapid[4]	61	99%	90 %	83 %	90 %

[1] Livi et al. Eur J Ca 2015

[2]Polgar et al. Rad & Onc, 2013

[3]Strnad et al. Lancet Oncol 2016

[4]Whelan, et al., Lancet, 2019

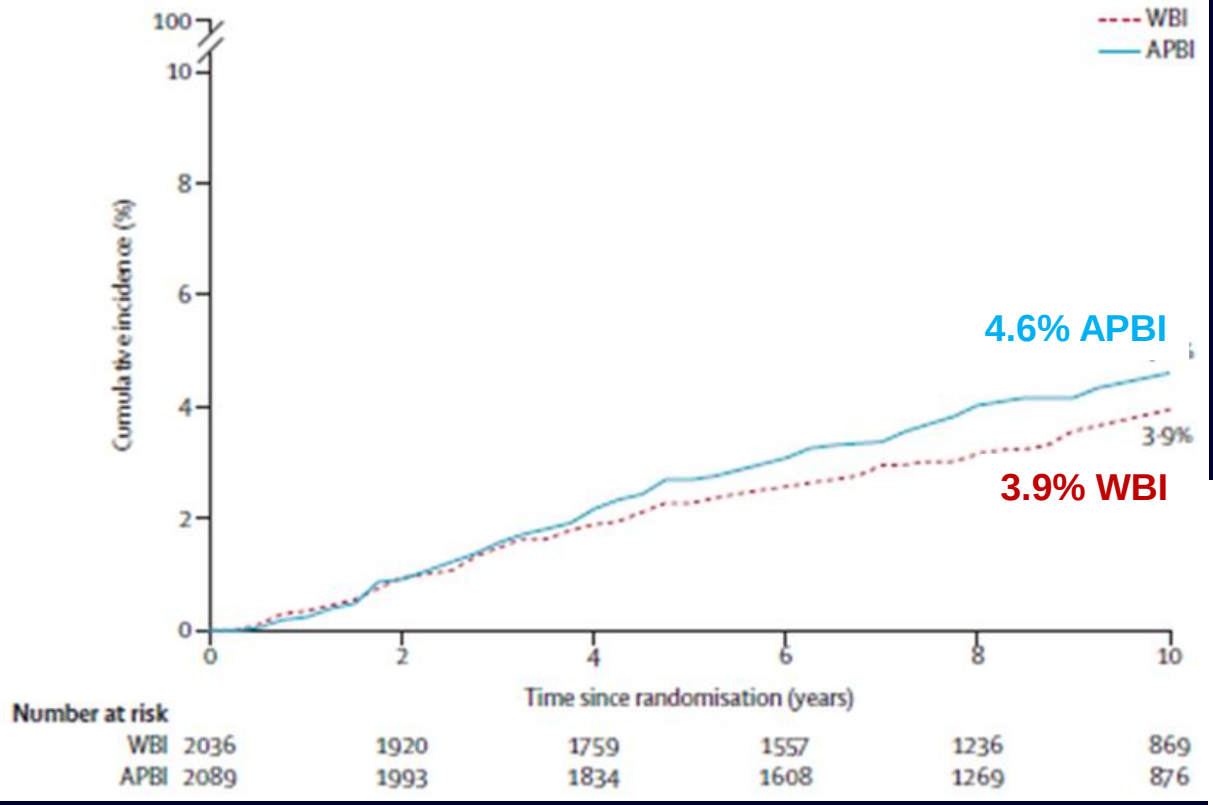
*Axillary staging was not performed in DCIS cases 4.5% (53/1185)

Median not given. ~ 95% $\leq$ 2 cm

Comparison of Patient Population Randomized APBI Trials

Clinical Trial	n	F/U Yrs.	Med. Age (yrs.)	ER+ /PR+ (%)	G1-2 (%)	TIS DCIS (%)	Invasive	
							% T1	% N0
NIO Budapest	287	10.2	-	89	100	0	100	94
U of Florence	520	5	62	96	89	11	93	86
GEC-ESTRO	1124	6.6	62	92	90	5	89	100
OCOG RAPID	2,135	8.6	61	90	83	18	-	99
NSABP B39-RTOG 0413	**4,216**	**10.2**	**54**	**81**	**64**	**24**	**86**	**84**

Ipsilateral Breast Recurrence (IBR)

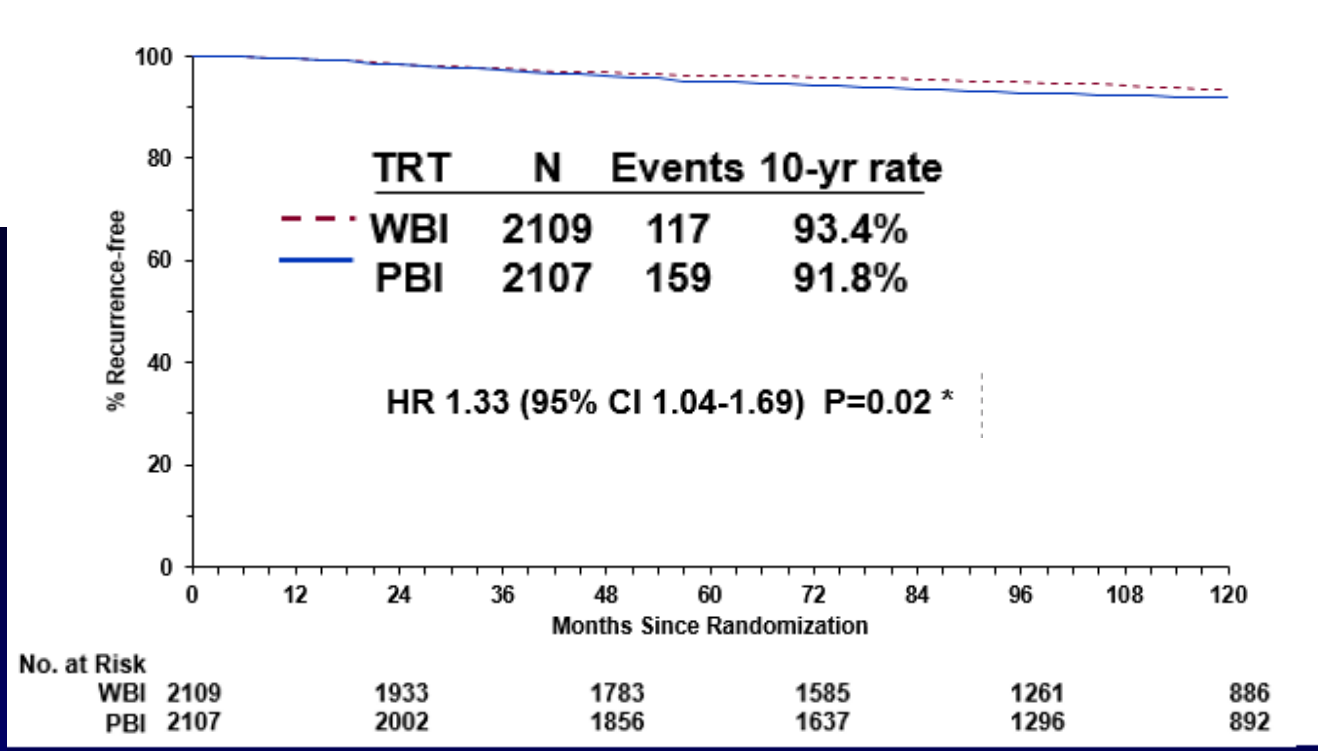


- N=4216 Total population
- 2005-2013 154 centers
- Median follow up: 10.2 yrs.

NRG ONCOLOGY™ NSABP B39-RTOG 0413

★ Did not meet equivalence criteria
- Overall favored WBI

Recurrence Free Interval



NRG ONCOLOGY™ NSABP B39-RTOG 0413

No Difference in Adverse Events

Toxicity:

- Grade 3 toxicity was 9.6% PBI *v* 7.1% WBI
- Grade 4-5 toxicity was 0.5% PBI *v* 0.3% WBI

Second Cancers:

First Site of Second Primary Cancer	WBI	PBI	Total
Contralateral breast	72	63	135
All other sites	128	129	257
Total	200	192	392

No statistically significant differences

Vicini et al, Lancet 2019

APBI Cosmetic Outcome

Phase III Trial	APBI	Excellent-Good Cosmetic Outcome
U. Florence[1]	IMRT	Favors APBI
NIO Budapest[2]	MCT Brachy	Equivalent
GEC-ESTRO[3]	MCT Brachy	Equivalent
OCOG Rapid[4]	3DCRT	Favors WBI
NRG B39-R0413[5]	3DCRT	Equivalent

[1] Livi et al. Eur J Ca 2015

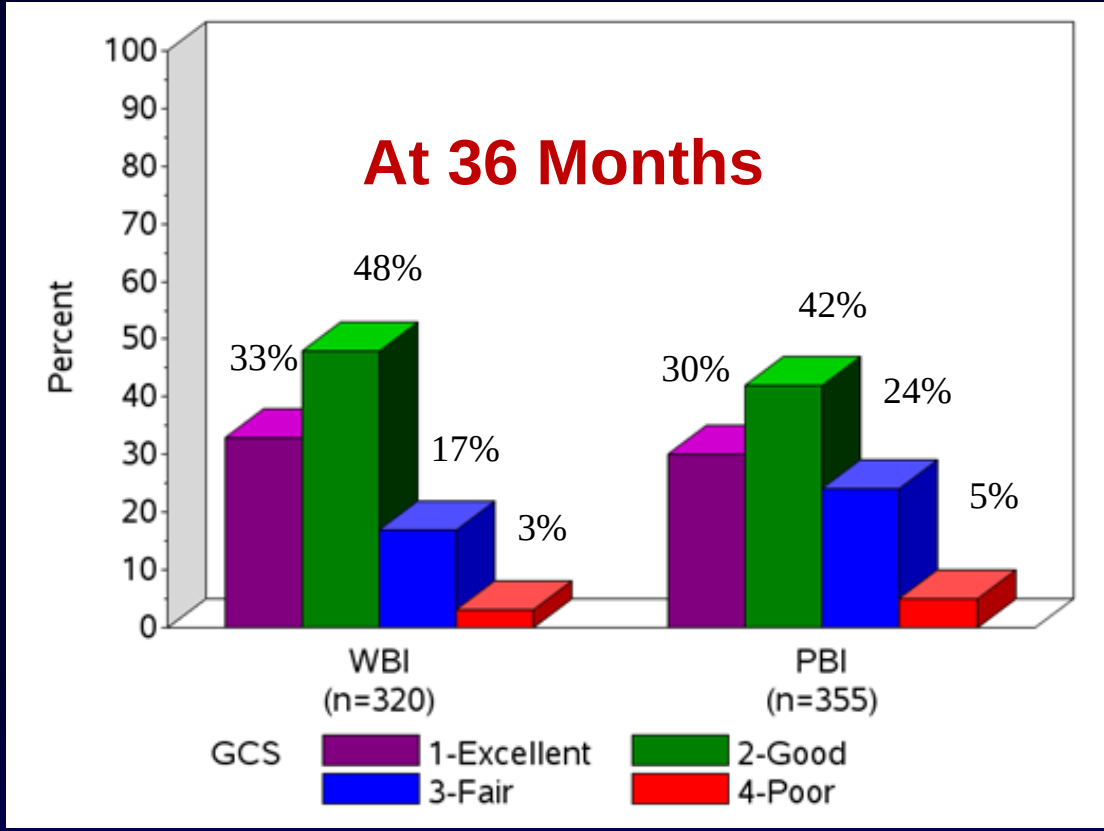
[2]Polgar et al. Rad & Onc, 2013

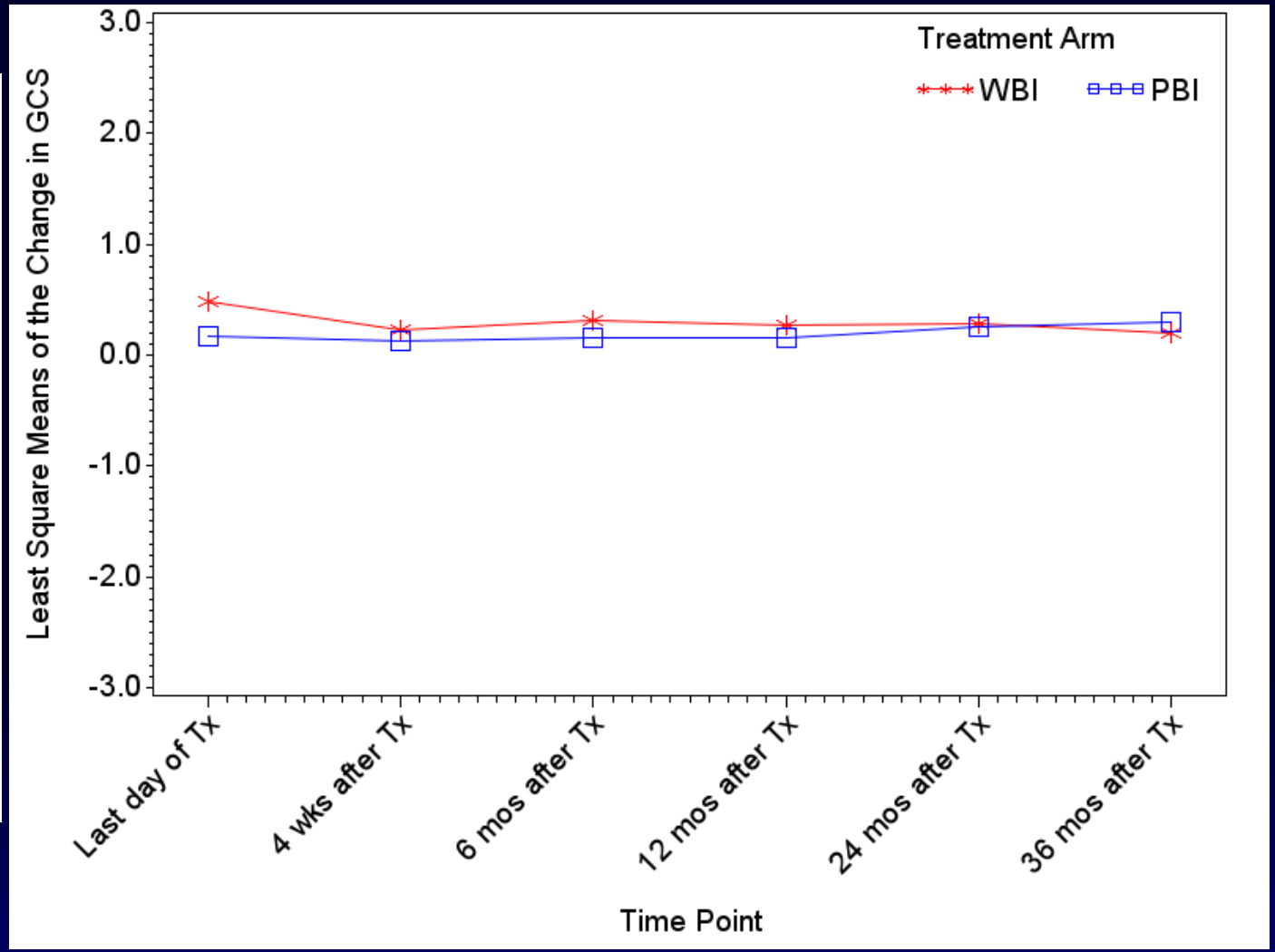
[3]Strnad et al. Lancet Oncol 2016

[4]Whelan, et al., Lancet, 2019

[5] White et al. IJROBP / ASTRO 2019

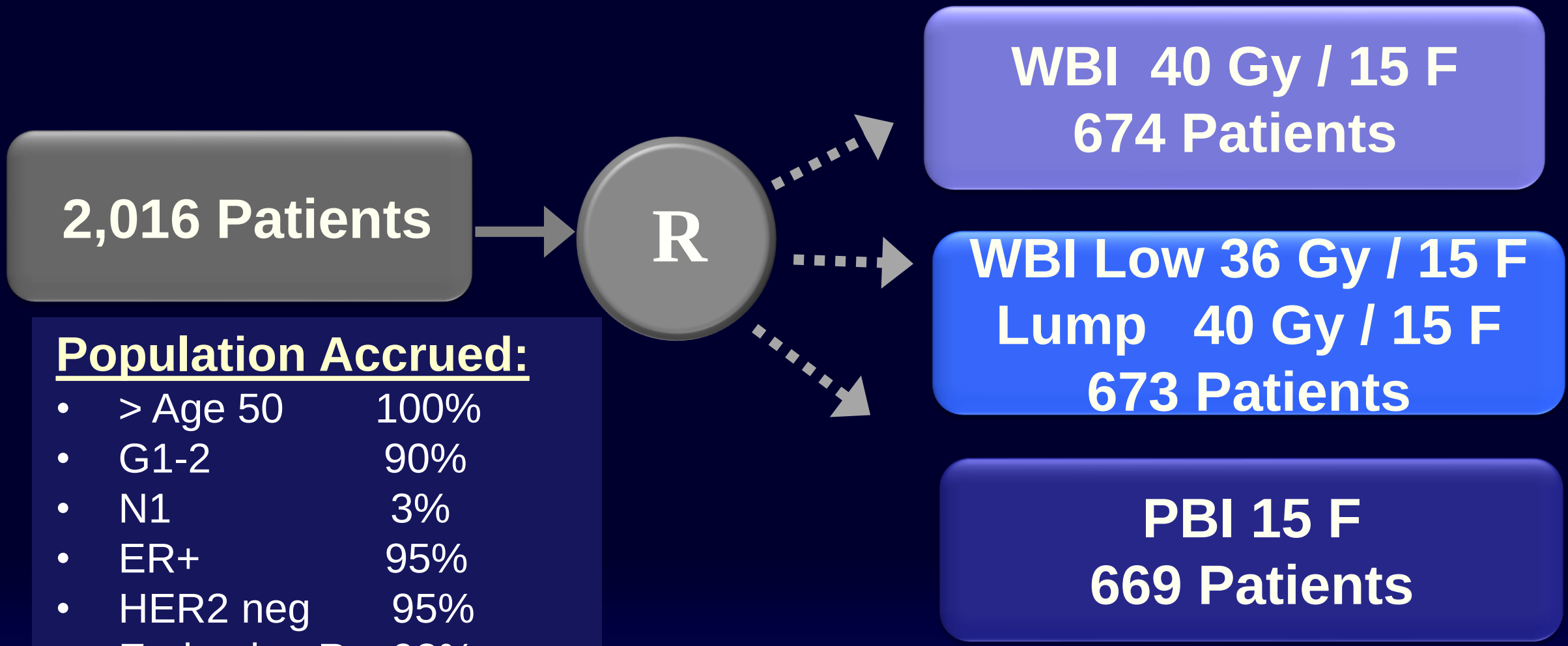
NRG NSABP B39-RTOG 0413
Global Cosmetic Score (GCS) by Patient





White et al. IJROBP / ASTRO 2019

PBI: UK Import Low Clinical Trial

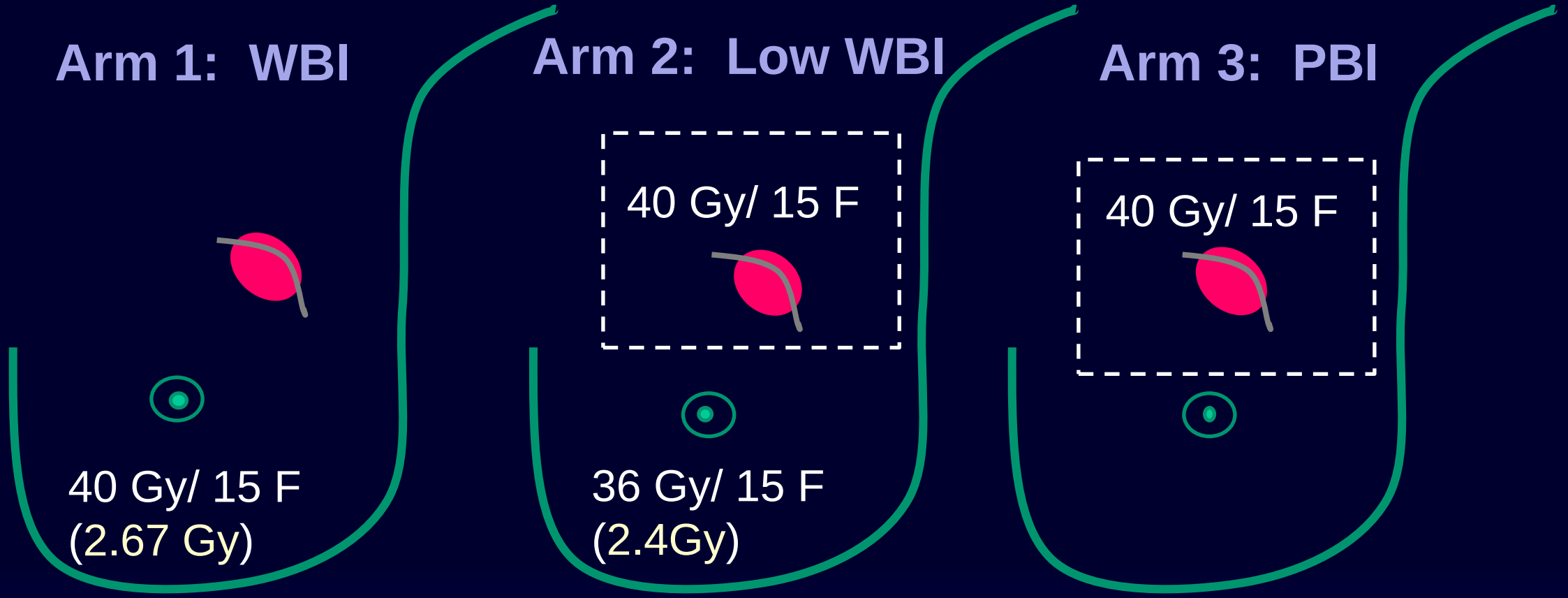


Population Accrued:

> Age 50	100%
G1-2	90%
N1	3%
ER+	95%
HER2 neg	95%
Endocrine Rx	92%
Chemo	5%

Cole et al, Lancet 2017

Import Low Clinical Trial Treatment Arms
3 Week Delivery



n = 674

n = 673

n = 669

UK Import Low Trial

5 Year Cumulative Incidence Local Regional Recurrence	
WBI	1.1%
WBI Low	0.2%
PBI	0.5%

6 year median follow up

Cole et al, Lancet 2017

"Suitable" Group

Updated ASTRO Consensus Statement for APBI

Selected Factors		**Suitable**
Patient Factors:	Age	> 50 years
Inv. Path Features:	T-size	≤ 2 cm
	T stage	T-1
	Margins	Negative (2 mm)
	ER	Positive
Nodes:	N stage	pN0 (i^{+} , $^{-}$)
DCIS :		"Low risk"

Correa et al, et al. - Practical Radiation Oncology, 2016

APBI and PBI Summary
Luminal Breast Cancer

- IBTR is low in all of the Phase III Trials evaluating APBI in comparison to WBI
- APBI is non-inferior to WBI post-lumpectomy when treating populations that are:
  - > 40-50 yo, with Stage 1 (node negative), ER+/PR+, G1-2 breast cancer
  - DCIS
- APBI is not equivalent to WBI in all populations that undergo lumpectomy
- WBI overall results in a lower event rate across all groups.

IORT

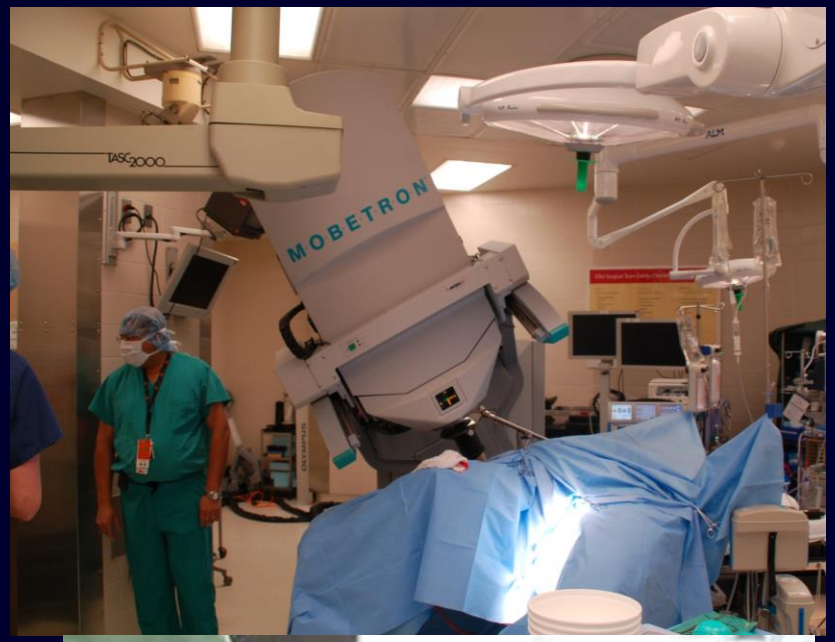
ADVANTAGES

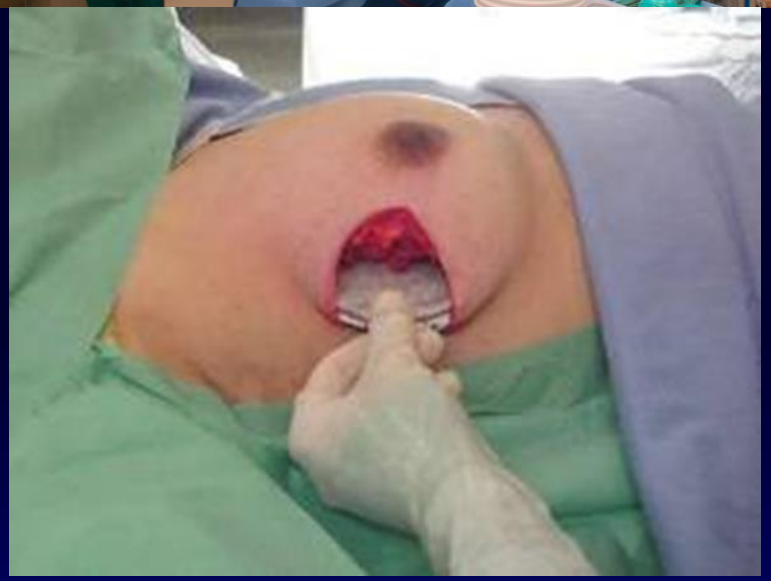
- Very localized dose
- Direct visualization of area to treat
- Reduce patient burden of care
  - Reduce travel for external beam WBI
  - Spare second procedure for brachytherapy APBI

DISADVANTAGES

- Too localized dose
- Final pathology unknown
- Patient may receive unnecessary treatment
- Evidence still evolving
- Additional O.R time

Electron IORT PBI





- Mobile linear accelerators in O.R.
- 21 Gy to 1- 2 cm around cavity
- 6-8 MeV electrons (4-15 MeV)
- 5 - 8 cm diameter cones for treatment
- ~ 1 – 3 cm depth of breast tissue

ELIOT

- Developed European Institute of Oncology, Milan, Italy
- Added lead shield under mobilized breast to protect chestwall

ELIOT Phase III Randomized Trial

Median follow-up 5.8 years

- 2000 -2007: randomized 1305 women > 48 years
- **T size < T1 85%, ER + 90%, N-1 21%**
- ~5.5% N-2 receive XRT to breast and nodes

5-year event rates	WBI 50 Gy/25 + boost	ELLIOT 21 Gy/1	p
Ipsilateral in- breast recurrence	0.7 %	5.3 %	<0.0001
In Quadrant	0.7 %	3.2 %	< 0.002
Outside quadrant	0	2.1 %	< 0.001
Regional nodal	0.4 %	1.1	< 0.02

***Increase rate of LR: T-2, G3, ER-, TNBC

Veronesi et al, Lancet Oncol 14: 2013

ELIOT PBI: by ASTRO Consensus Guidelines for APBI

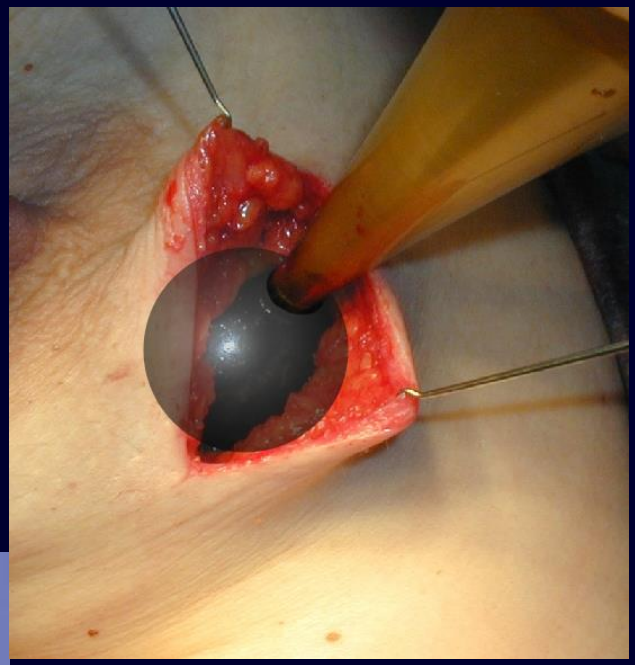
5 year rates	Suitable*	Cautionary	Unsuitable	p
n	294	698	812	
Ipsilateral in-breast recurrence	**1.5 %**	**4.4 %**	**8.8 %**	**0.003**
Regional nodal failure	1.5 %	1.9 %	1.1 %	0.55
Distant metastases	1.5 %	1.7 %	3.9 %	0.047
Cause specific survival	99.1 %	98.7 %	96.5 %	0.025

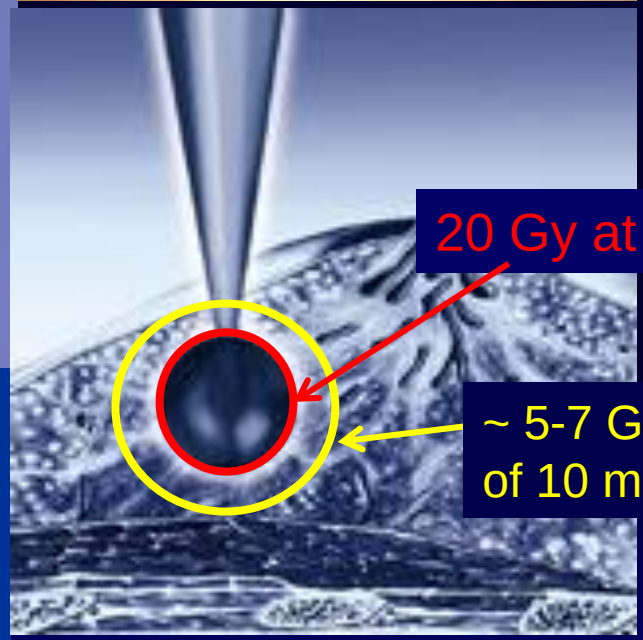
* Stage 1, ER +, > 60 yo, Margins negative

Leonardi, IJROBP, 2011

Courtesy J.Vaydia

The TARGIT Technique





INTRABEAM

- A miniature electron generator and accelerator
- A point source of 50 kV energy x-rays applicator

TARGIT-A Phase III Randomized Trial

Median follow up: 29 months

- 2000 -2012: randomized 3451 women > 45 years
- **T size ≤ T1 81.4%, ER + 90%, N-1 17%**
- ~15% randomized to TARGIT received WBI XRT to breast and nodes

5-year IBR event rates	WBI	TARGIT	p
ALL	**1.3 %**	**3.3 %**	**<0.042**
Immed. IORT (n=2298)	1.1%	2.1%	0.31
Delayed IORT (n=1153)	1.7%	5.4%	0.069
Breast Cancer Mortality	1.9%	2.6%	0.51
All Cause Mortality	5.5%	3.9%	0.099

Vaiyda, Lancet 383, 2014

Long-term Results From the Phase III TARGIT-A

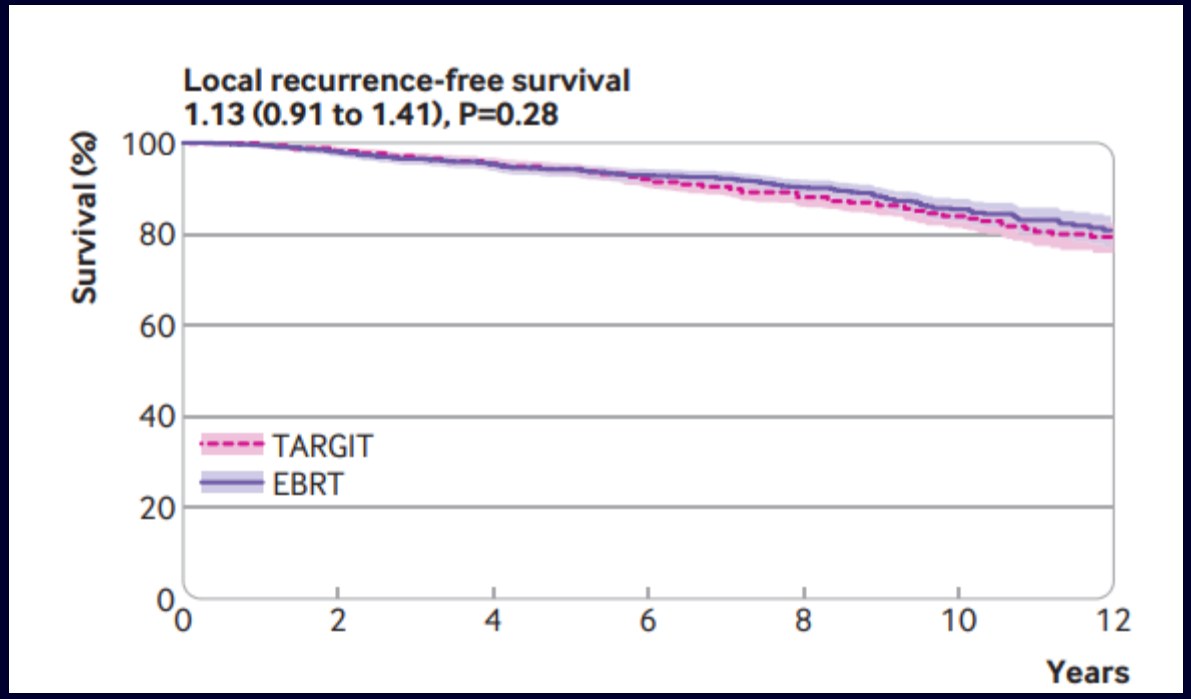
- N = 2298
- Population:

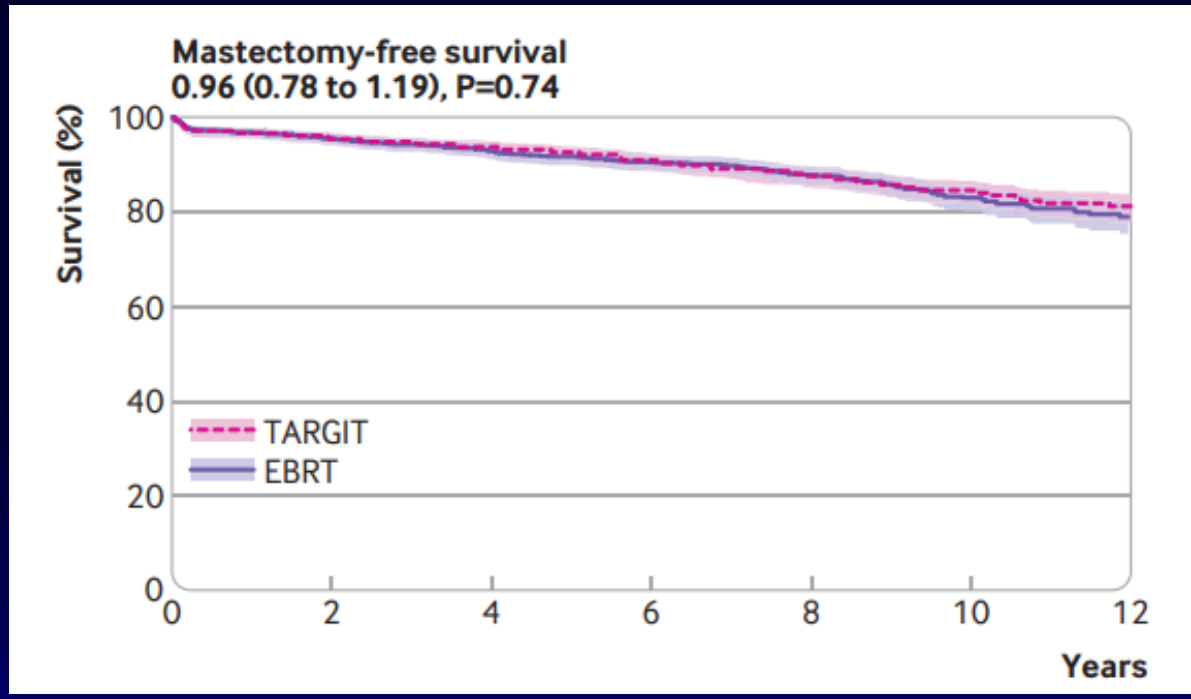
Age > 50 :	90%	Margins negative:	92%
T size < 20 mm:	84 %	**ER Positive:**	**90%**
N0:	78%	**HER2 negative:**	**85%**
G1-2:	80%	**Endocrine Rx:**	**81%**

★ IORT Arm with EBRT: 23%

- Median Follow-up: ~ 9 years (estimated)

Vaiyda et al , BMJ, 2020





Additional Course Radiotherapy after IORT PBI

- 23 % on TARGIT A underwent whole breast irradiation
- ~5.5% on ELIOT with N-2 receive XRT to breast and nodes

- Added toxicity
- Added cost

IORT PBI Summary
Luminal Breast Cancer

- One of multiple methods for treating Stage 1 HS, HER2- breast cancer in women ≥ 50
- Strength of IORT PBI: Patient Convenience!
- Optimal Patient Population: ASTRO Suitable Group
- Avoid adverse pathology: SNB FS and Wait for Results….
- Inherent challenges require thoughtful balance against potential benefits

Omission of Radiation Therapy for BCT

Post Lumpectomy Breast Radiotherapy

Advantages:

- Makes local regional recurrences and survival equivalent to mastectomy
- Avoids mastectomy

Disadvantages

- Burdensome
  - 1-4 weeks M-F 5days/ week
- Toxicity

EBCTCG 2011 Meta Analysis:

Large Gains from Radiotherapy in Cancer Control Results in Improved Breast Cancer Survival

- 10,801 BCS patients enrolled in 17 randomized clinical trials
- Median follow up 9.5 years
- Radiation therapy post-BCS:

ANY 1st Recurrence (10 yr): Breast Cancer mortality (15 yr)

19.3% BCS + RT → 21.4% BCS + RT

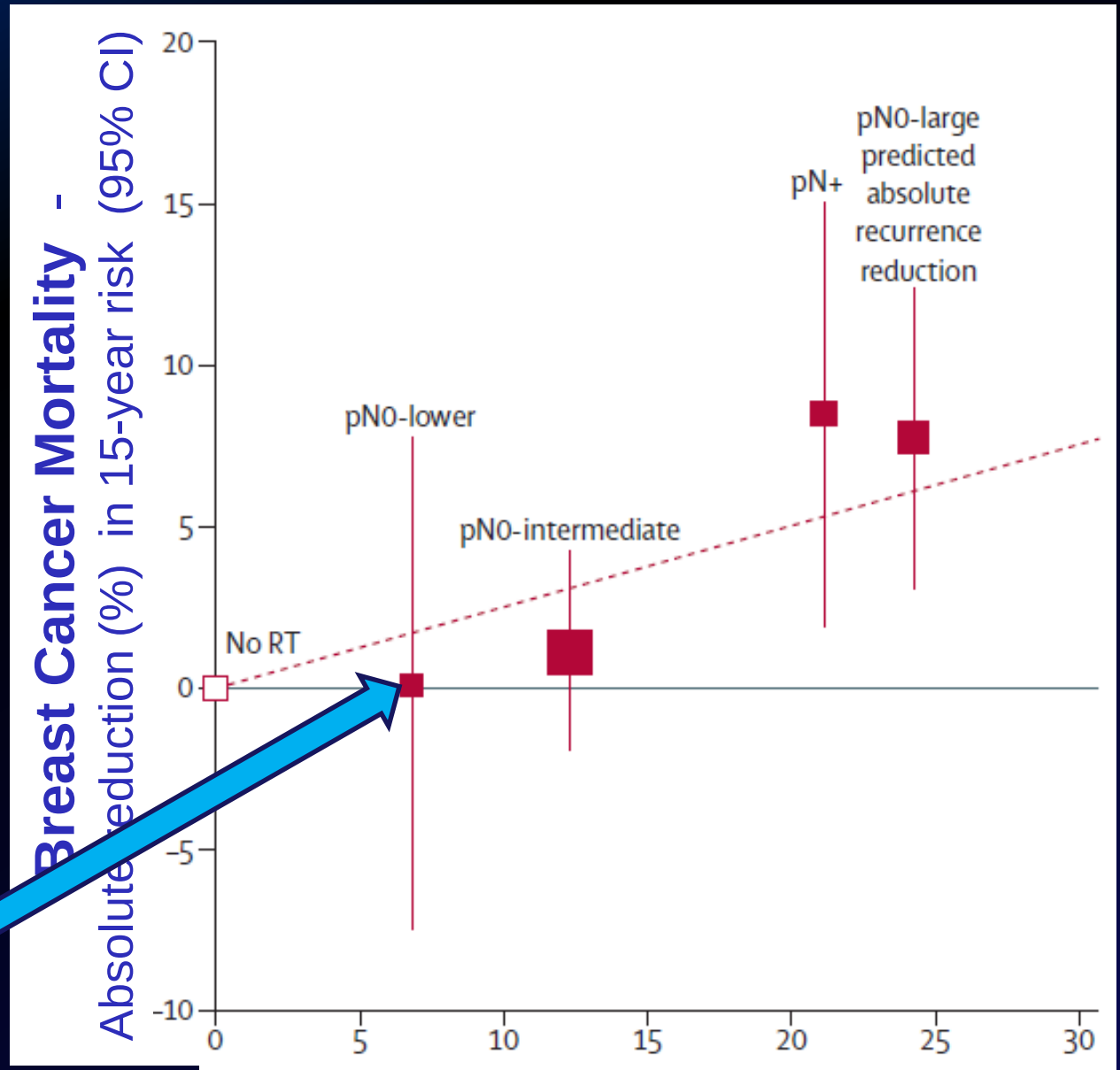
35% BCS (p<0.00001) 25.2% BCS (p=0.0005)

15.7% Gain Cancer Control **3.8% Improvement Survival**

EBCTCG Lancet 2011

Relationship of Breast Cancer Recurrence and Mortality by absolute reduction in 10 -year risk of Any 1st Recurrence

No Survival Advantage:
< 10% absolute reduction in any recurrence risk by 10 years



Lancet 378: 1707-16, 2011

Variability in Local Recurrence from Randomized Trials Omitting Radiation Therapy for "Low Risk" HS Invasive Breast Cancer ER/PR+ and Clinical Pathologic Factors

Clinical Trial	n	F/U yrs	Age > 50 y (%)	ER/PR+ (%)	Tam/AI (%)	Grade 1-2 (%)	In-breast recurrence (%) RT	In-breast recurrence (%) No RT
Tampere	264	12.1	-	100	0	85.6	11.6	27.2
GBSG-V	347	9.9	91.4	88	50	97.2	6	20
TBC	769	10.5	100	85	100	68.3	5.1	13.7
ABCSG 8a	869	4.48	99	100	100	95	0.4	5.1
CALGB 9343	626	10.5	100*	97	100	-	2	10
PRIME II	1326	7.3	100#	100	100	97	0.9	9.8

**Age ≥ 70*
 # Age ≥ 65

Holli et al Tampere, JCO 2009
Winzer et al, GBSG IV, EJC 2010
Liu et al, TBC, JCO 2015

Potter, et al ABCSG 8a, IJROBP 2007
Hughes, et al, CALGB 9343, JCO 2015
Kuncler et al, PRIME II, Lancet Onc 2015, SABCS 2020

Elderly Women with Hormone Sensitive Stage 1 Breast Cancer

	CALGB 9343 N= 626 ≥ 70 yo (median 77 yrs) 12 year follow up		PRIME2 N=1326 ≥ 65 yo (median 70 yrs) 7.3 year follow up	
	RT	No RT	RT	No RT
Local regional recurrence	1.9% (6)	10% (32)	0.9%(5)	9.8% (26)
Death From Breast Cancer	4.1% (13)	2.5% (8)	0.6%* (4)	1%* (8)
Death from all causes	52% (166)	52% (168)	6%* (40)	7.3%* (49)
Mastectomy –free rate	98% (-)	96% (-)	99.7%* (2)	98%* (12)

Hughes et al, JCO, 2013
Kunkler et al. SABCS 2020
*Kunkler et al, Lancet Oncol, 2015

PRIME2: Increase LRR with Estrogen poor tumors w/o RT ~ 18.8%

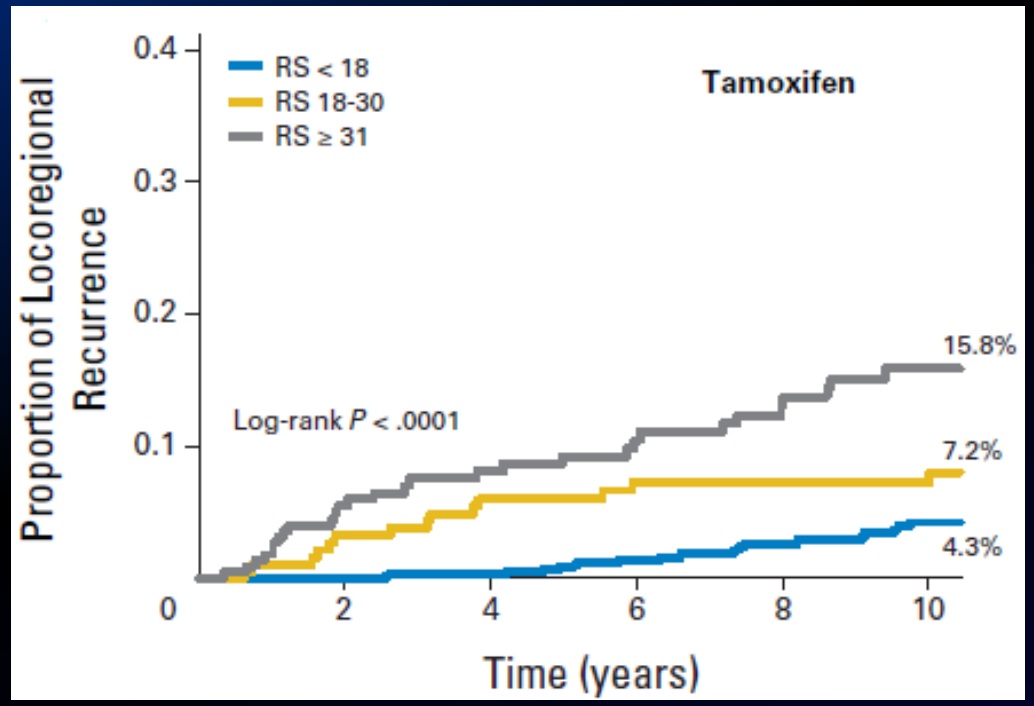
RNA Expression Assays

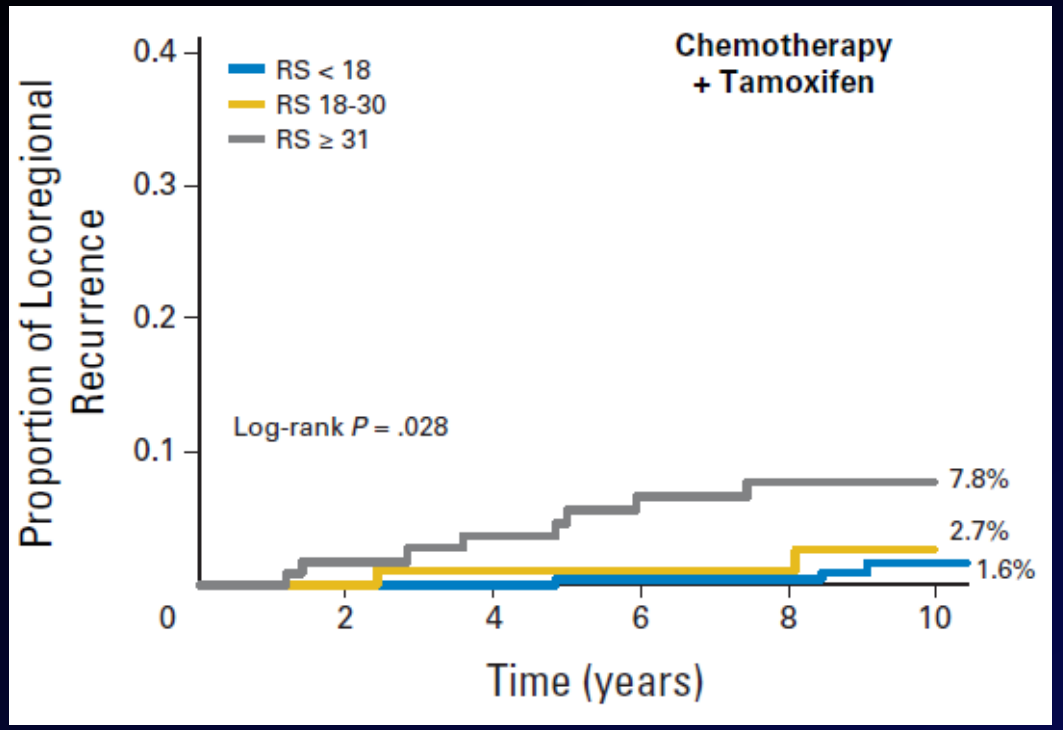
- Numerous tested, validated and further evaluated in clinical trial populations of HS breast cancer, treated with anti-endocrine therapy (Tamoxifen)
- Prognostic for DFS and OS
- Predict risk for distant relapse and benefit of systemic therapy
- *Prognostic for LRR*

*Oncotype*DX RS:	*Genomic Health*	NSABP B14, B20, B28, SWOG 8814, ATAC
EndoPredict:	*Myriad*	ABCSG 6, 8
Pam50 ROR:	*Prosigna*	NCIC MA.12, ATAC, ABCSG 8
MammaPrint	*Agendia*	Netherland Cancer Inst.

10-Year LRR Rates by RS Category

ER+, Node-Negative Patients





- NSABP B14 (+/- Tam) and B20 (Tam +/- CMF)
- 45% Lump + RT, 55% MRM
- 21-gene Onco*type*DX recurrence score (RS) n=895
- LRR was significantly associated with RS risk groups ($P < .001$).

Mamounas et al. JCO 28: 2010

RS Remains Significant on Multivariate Analysis

Variable	Hazard Ratio	95% CI	Wald Test *P*
Age (≥ 50 *v* < 50)	0.40	0.25 to 0.65	.0002
Mastectomy *v* L + XRT	0.62	0.39 to 0.99	.047
Clinical tumor size (> 2 *v* ≤ 2 cm)	0.98	0.61 to 1.59	.933
Tumor grade (moderate *v* well)	1.10	0.54 to 1.92	.113
Tumor grade (poor *v* well)	1.76	0.89 to 3.48	
Recurrence score*	2.16	1.26 to 3.68	.005

895 Tamoxifen-Treated Patients from
NSABP B-14 and B-20 Trials

Mamounas et al. JCO 28: 2010

Reduced LRR for Low Risk Stage 1 HR+, HER2- BCT Selected by Genomic Assay or Subtype

Trial Samples	Median Follow up years	Selection Criteria for "Low Risk"	10 Year LRR (%) Lumpectomy alone	10 Year LRR (%) Lumpectomy and RT
TBC Trial[1]	10	Luminal A Subtype	7.3	3.3
NSABP B14/ B20[2]	10-14	Oncotype RS $\leq$ 18	-	6.8
ECOG E2197[3]	9.7	Oncotype RS $\leq$ 18	-	3.2
ABCSG	9.5	PAM 50 ROR $\leq$ 57	-	1.9
ABCSG 8[4]	6	Endopredict Low	-	2.5
Netherlands Cancer Institute [5]	8.9	Mammaprint Low Risk	-	6.1

[1]Liu , JCO 2016
[2]Mamounas, JCO 2010
[3]Solin, Breast CA Res Treat, 2012
[4]Fitzal, Br J Ca, 2015
[5]Drukker , Breast CA Res Treat, 2014

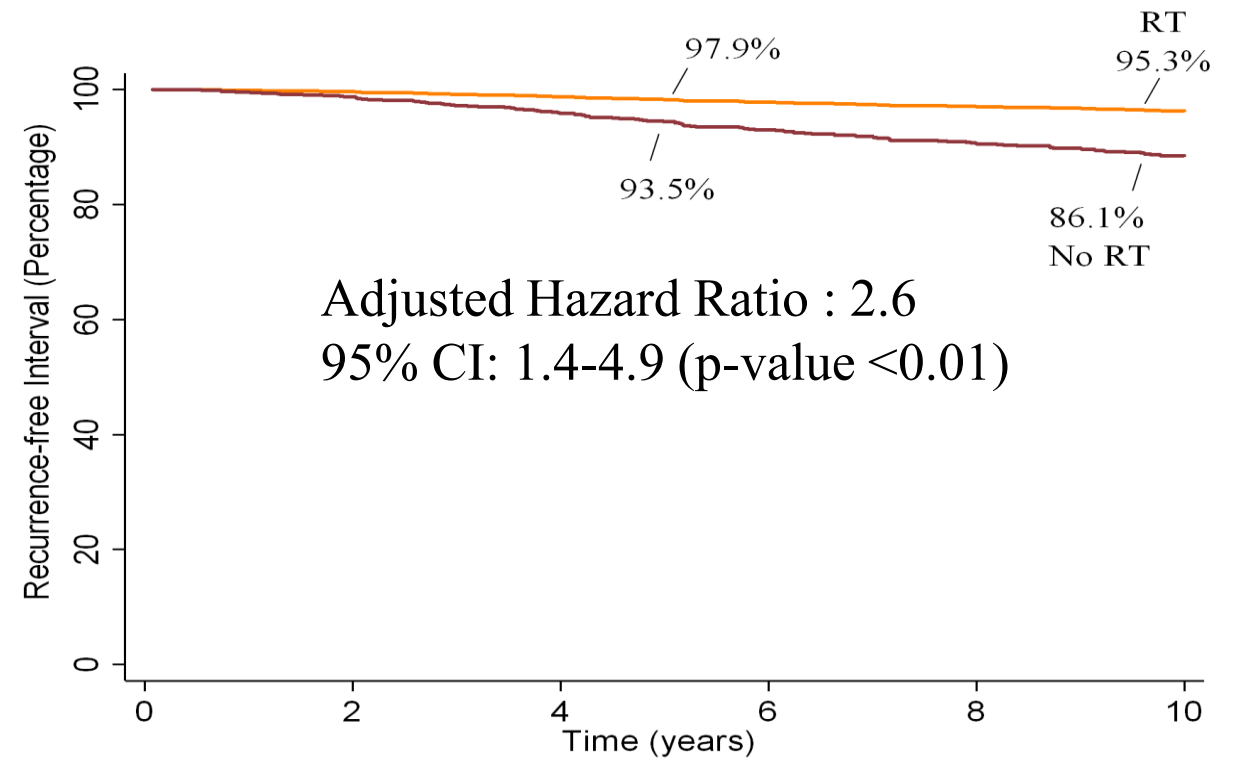
BOLD Task Force- CISNET Collaboration:

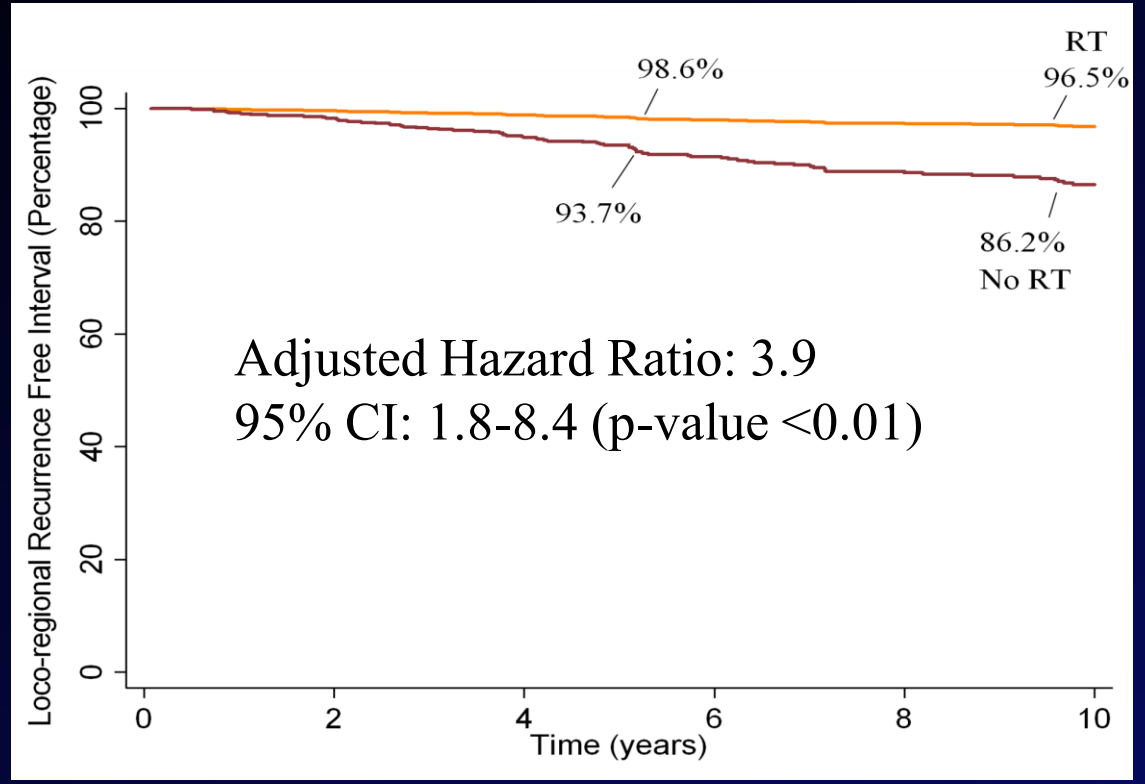
Modeling the Anticipated Outcome of an NRG Randomized Phase III Trial that Omits RT post BCS in women 50-70 yo with ER/PR + Stage 1 BC with RS ≤ 18

- NRG Oncology submitted a concept to randomize +/- RT post BCS in Stage 1, ER + RS < 18 (n= 2068)
- Worked with NCI BOLD Task Force and CISNET to model anticipated outcome
- Pooled Data Analysis :
  - 7 prior RCT Phase III stage 1 ER+PR+
  - used SEER-GHI data to impute RS

Jayasekera, et al., JNCI J Natl Cancer Inst (2018) 110(12)

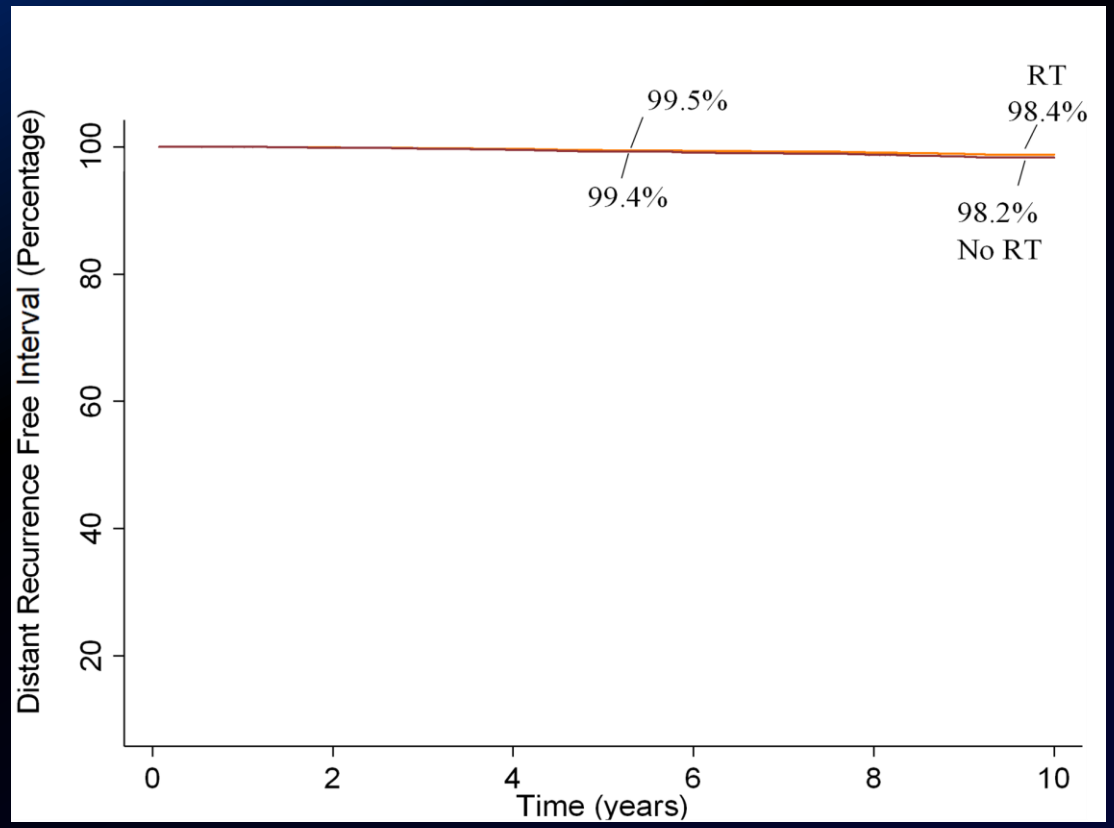
Omission of RT Increases Any First Events and Local Regional Recurrences

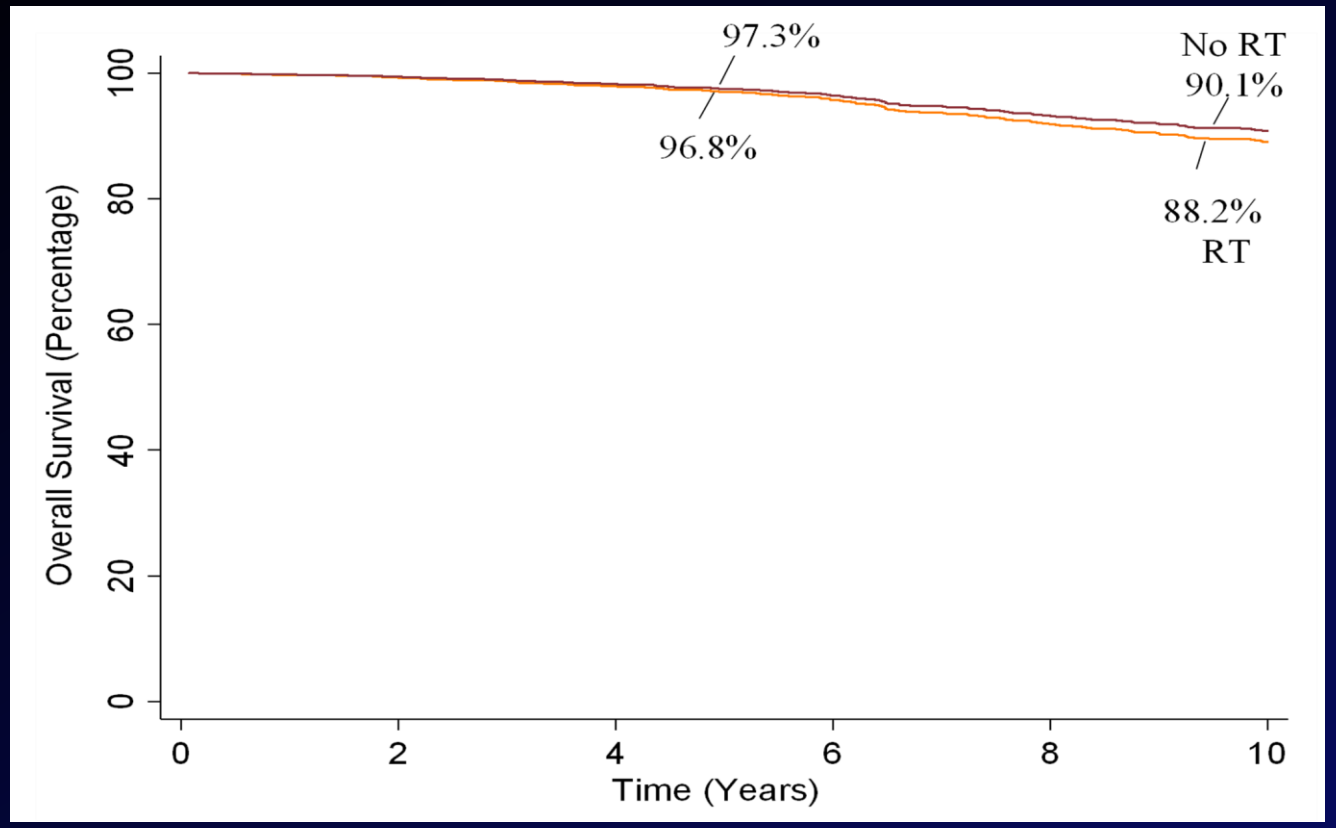




Jayasekera et al, JNCI 2018

No Difference in Distant Recurrences and Overall Survival

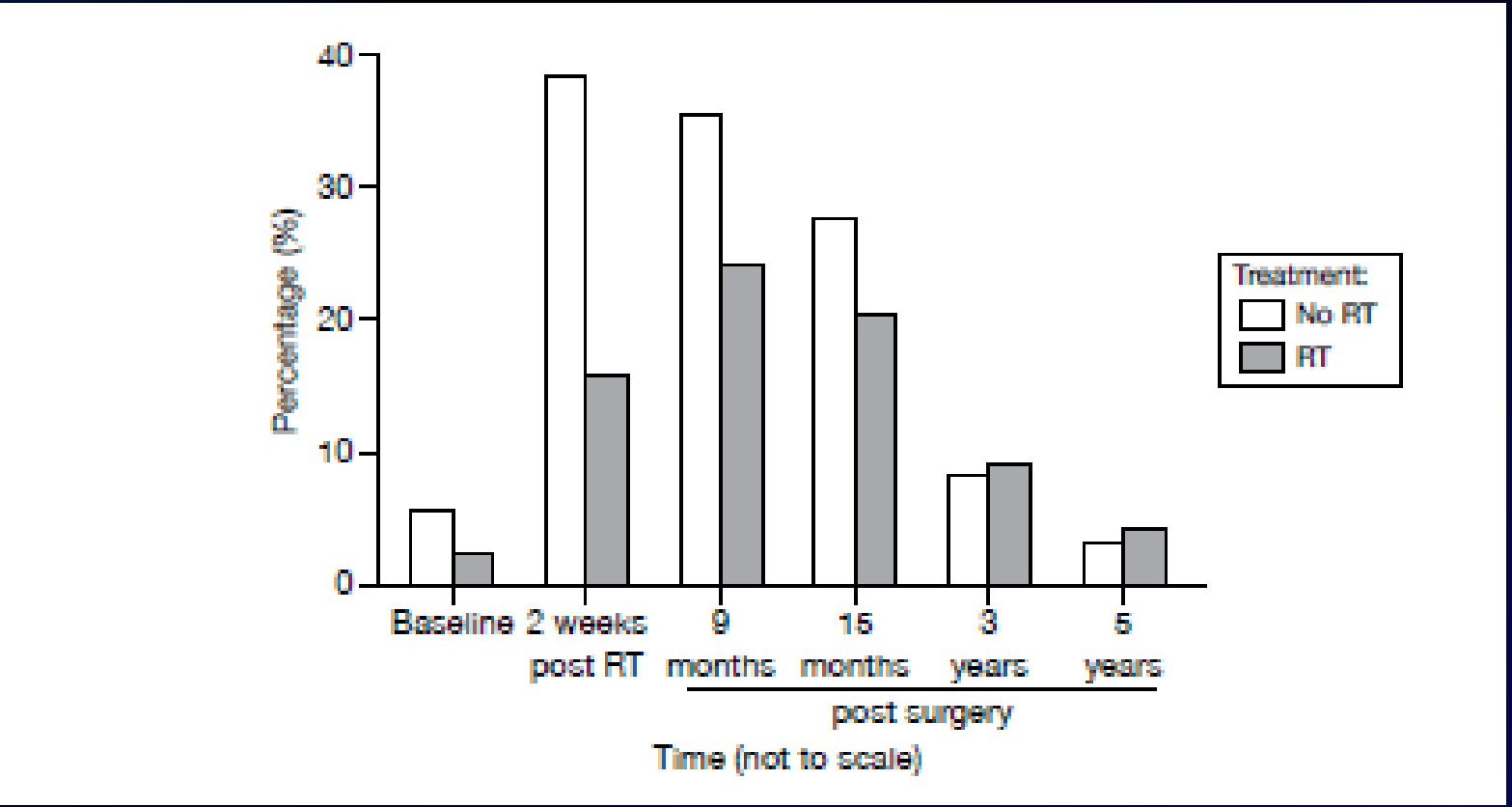




Jayasekera et al, JNCI 2018

De-escalating Radiotherapy for Breast Conservation: What are the challenges?

PRIME QOL: Concern About Recurrence High First 2 Years post Lumpectomy w/o RT

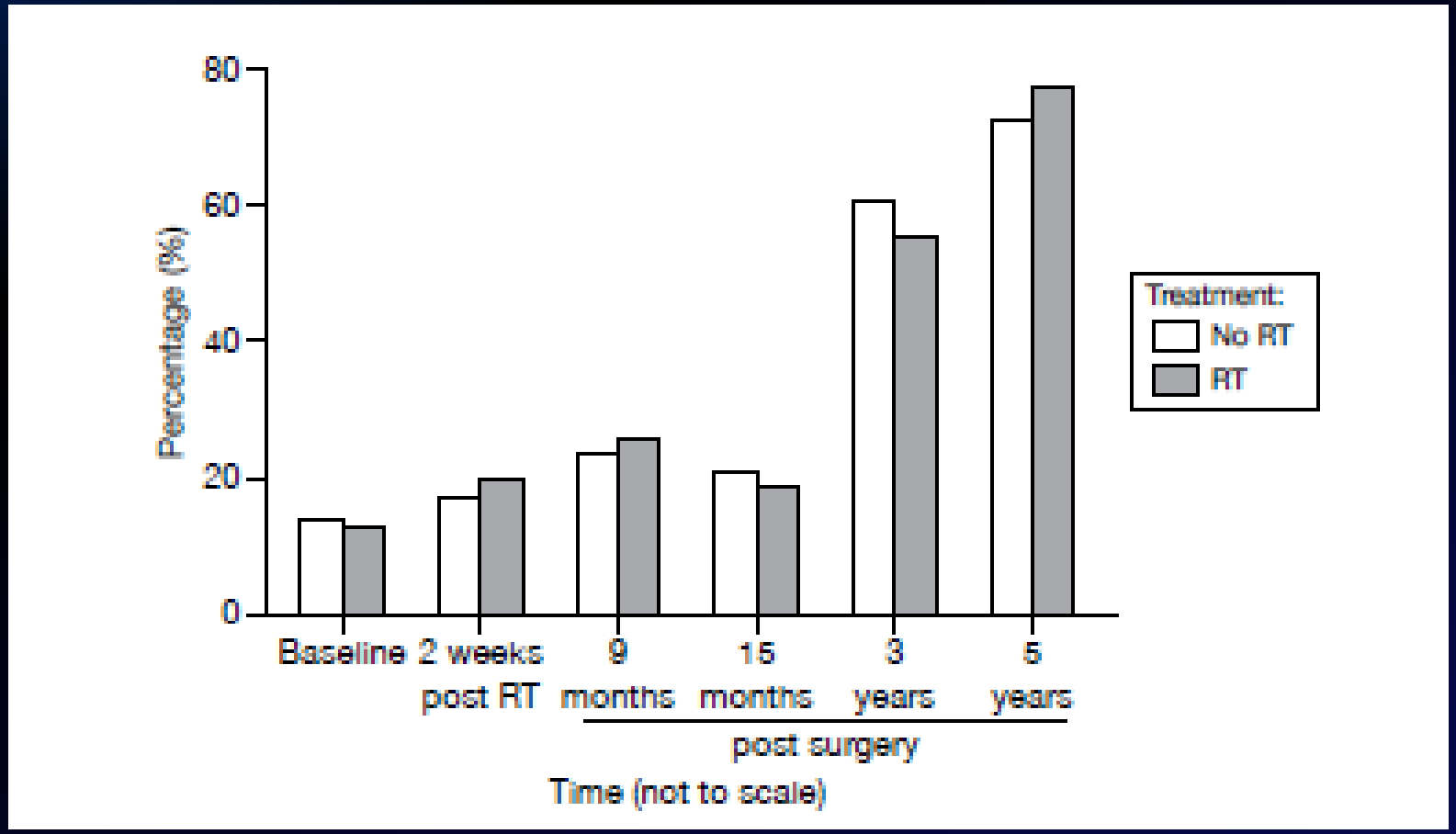


-Gradually resolved by 3 and 5 years

-No significant difference between the groups was found

Williams et al. Health Technology Assessment 2011

PRIME QOL: Patient Reported Long Term Effects From Treatment



- Endocrine therapy side effects were the most frequently mentioned
- RT effects not mentioned

Williams et al. Health Technology Assessment 2011

Likelihood of Breast Preservation is Unknown with Omission of RT

- Radiation Therapy effective at reducing LRR
  - 97-99% Local control in the breast at 6-10 years
- Mastectomy considered standard treatment of in-breast recurrence following lumpectomy with or without RT
- PRIME 2: in-breast recurrence without RT➔ 50% Mast.
- Omission of RT could result in in less breast conservation

Clinical Enthusiasm for MGA / Subtype to De-escalate RT
Multiple Ongoing Clinical Trials

Trial	CA. Gov Identifier	Design	Biological selection	Eligible patient age	Targeted Accrual
LUMINA	NCT01791829	Phase II, single arm observation	Luminal A by IHC	≥ 50 years	500
IDEA	NCT02400190	Phase II, single arm observation	RS ≤ 18	50-69 years	250
PRECISION	NCT0265375	Phase II, single arm observation	PAM 50 ROR ≤ 40	55-65 years	1380
EXPERT	NCT02889874	Phase III randomized RT vs Observation	PAM 50 Luminal A ROR ≤ 60	≥ 50 years	1167

BR007 Evaluating De-escalation of Breast Radiation (DEBRA) for BCT of Stage 1, HR+, HER2-, RS ≤ 18 Breast Cancer

Women with pT1N0M0, HER2- NEG.
ER and/or PgR-Positive Breast Cancer
Resected by Lumpectomy and
Oncotype-DX RS ≤ 18

STRATIFICATION

- Tumor size (≤ 1 cm; > 1–2 cm)
- Endocrine therapy (tamoxifen, AI)
- RS < 11, RS 11-18

RANDOMIZATION

Arm 1
Breast radiation therapy
+
Endocrine therapy

Arm 2
Observation
+
Endocrine therapy

Eligibility (Select)

- Stage 1: pT1 (≤ 2 cm), pN0
- Age ≥ 50 and < 70 years of age
- negative margins (no tumor on ink)
- pN0 (SNB or AND)
- ER and/ or PR ,HER2-negative
- Recurrence Score of ≤ 18.
- Intends to take endocrine therapy for 5 years

Primary Endpoint: IBR

Targeted Accrual: 1714

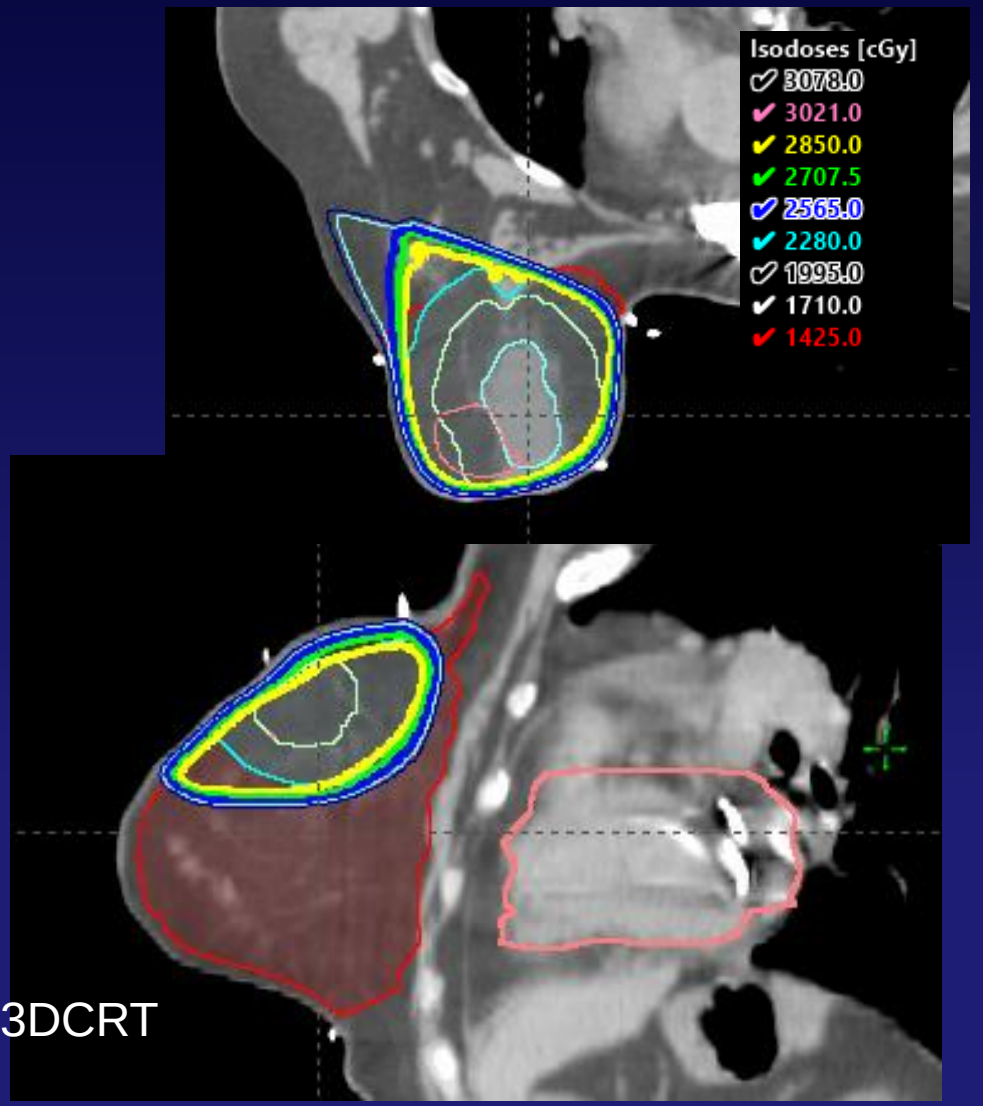
Anticipated to Open June 2021

Treatment Case 4

53 yo s/ Lump and SNB for a T1cN0, ER95%, PR 80 %, HER2 -, RS 17

1. Radiation:
   - APBI 28.5 Gy/ 5 Fractions/ 5.4 Gy QOD

2. Endocrine Therapy
   - Letrozole started after RT



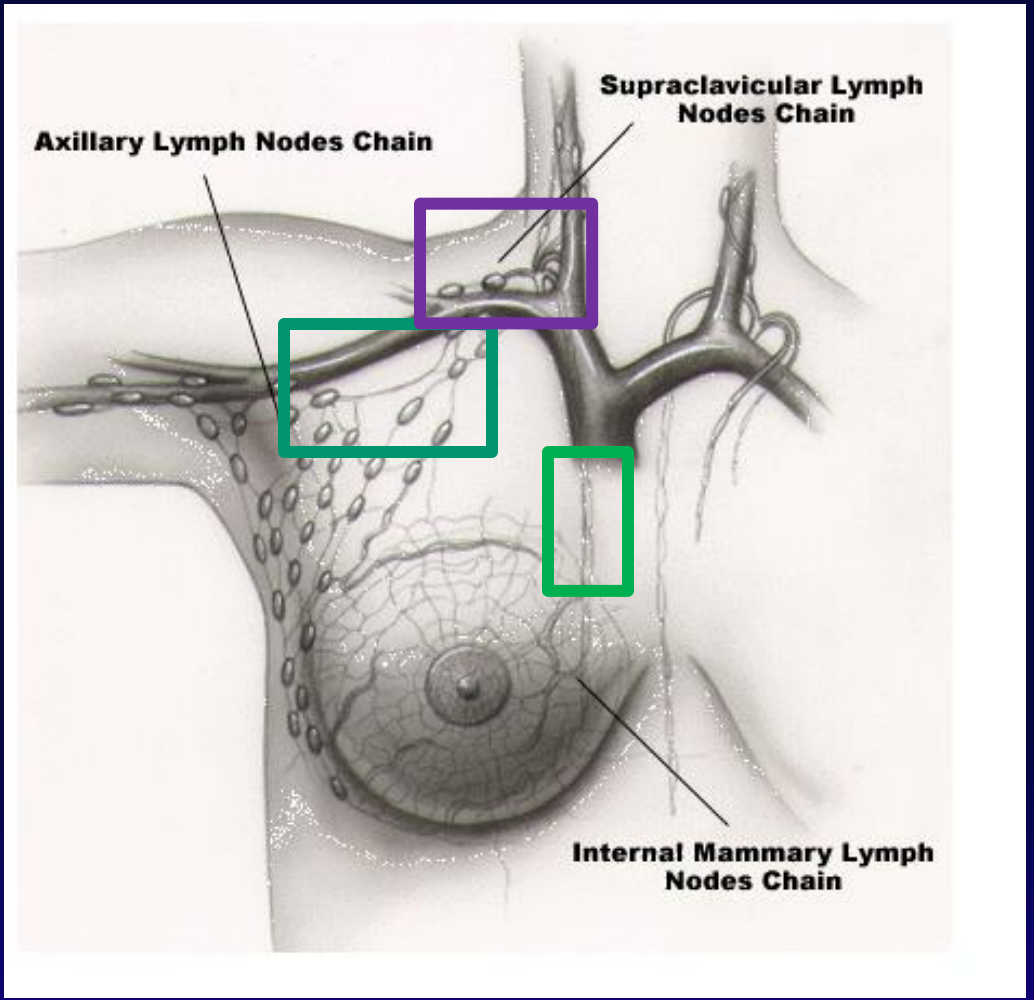
Prone APBI with 3DCRT

Regional Nodal Irradiation

“Regional Nodal Irradiation”
What is it?

Regional nodes:

- Axilla: what did not get removed with SN biopsy or dissection,“undissected or retained axilla”
- Supraclavicular
- Internal mammary: first three intercostal spaces



Regional Nodal Irradiation (RNI)

Can be delivered Post mastectomy or Post lumpectomy

- ➔ Post mastectomy and axillary surgery:
  - – Chestwall and RNI (“PMRT”)
- ➔ Post lumpectomy and axillary surgery:
  - – Breast and RNI

Case 5

- 43 yo female presented with new left breast 3 cm palpable mass and axillary node.
- Core biopsy of breast and axillary node demonstrated G3 Infiltrating ductal carcinoma, ER-PR-HER2+.
- Completed neoadjuvant TCHP x 6 cycles.
- Good partial clinical response in the breast and axillary node is no longer palpable.
- Undergoes lumpectomy and SNB with dual tracer: Residual 1.2 cm G3 IDC, ER-PR-HER2+ and 0/3 SN.
- TDM1 is planned.

Indications for RNI Established in the Adjuvant Setting

- Two seminal trials, the Danish Breast Cancer Group (DBCG) 82b and British Columbia (BC) Trials, in premenopausal women who received CMF chemotherapy demonstrated 10% absolute improvement in 10 yr. DFS with RNI-PMRT.
- Third trial, DBCG 82c, in postmenopausal who received tamoxifen demonstrated absolute improvement of 12% DFS and 5% OS with RNI-PMRT
- N1 or 1-3 positive axillary nodes comprised 60% of DBCG 82B, 58% of DBCG 82c, and 58% of the BC trial populations
- All patients on the RNI arms had radiation to the: Axilla, SCL, & IM nodes
- ASCO PMRT/ RNI Guidelines 2001 *(Recht et al, JCO 2001)*
  - 4 of more axillary lymph nodes with metastases (N2)
  - Tumor > 5 cm and 1 or more nodes with metastases (T3, N1)
  - RNI: SCL, Axilla and significant debate without consensus for IMM

Whelan et al. *NEJM* 2015;373(19):1878-1879

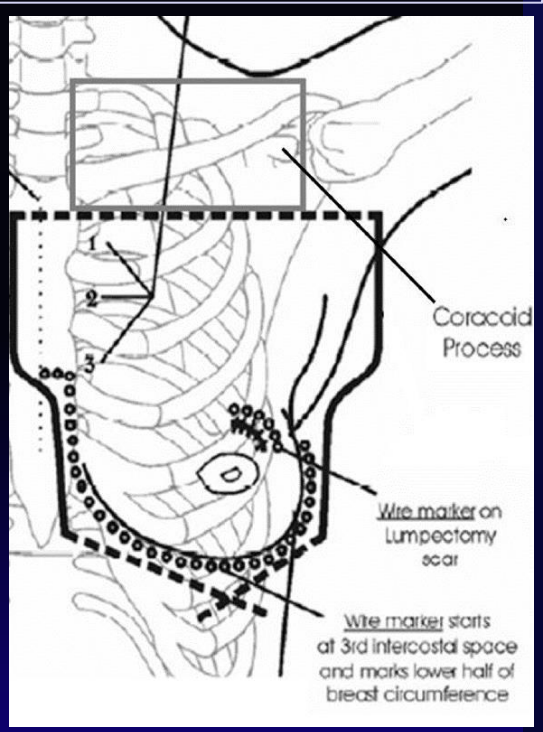
NCIC MA.20:

Node positive **Post lumpectomy**

R

WBI	WBI + RNI

- Accrued 2000-2007
- N =1832
- Median follow up: 10 years



Whelan et al. NEJM 373(19): 2015

Poortmans et al, NEJM 373: (4):317-327 *2015*

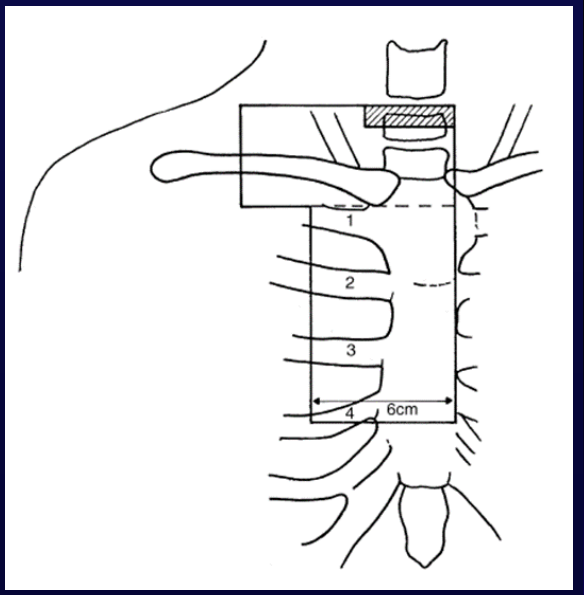
EORTC trial 22922/10925

- pN+ axillary nodes or
- pN- central or medial tumor

R

No IM-MS XRT	IM-MS XRT

- Accrued 1996-2004
- N= 4004
- 76% BCT; 24% Mast.
- Median Follow up: 10.9 years



Poortmans et al, NEJM 373: (4) *2015*

Modern Regional Nodal Irradiation (RNI) Trials Improved 10 yr. Local Regional Control, Distant DFS, DFS

			Local Reg. Recurrence			Distant Disease Free			Disease Free Surv.		
Trial	**n**	**% N1**	**No RNI**	**RNI**	**p**	**No RNI**	**RNI**	**p**	**No RNI**	**RNI**	**p**
NCIC MA.20	1832	85	6.8%	4.3%	.009	82.4%	86.3%	.03	77%	82%	.01
EORTC 22922[10y]	4004	43	9.5%	8.3%		75%	78%	.02	69.1%	72.1%	.04

⬇ 1.9% ⬆ 3.4 % ⬆ 4 %

Whelan et al. NEJM 2015;373(19):1878-1879

Poortmans et al, NEJM 373: (4):317-327 *2015*

Grade 2 -3 Toxicity on MA.20 Clinical Trial

	WBI n (%)	WBI + RNI n (%)	p
Acute:			
Pneumonitis	2 (0.2%)	11 (1.2%)	< 0.01
RT Dermatitis	372 (40.1%)	442 (49.5%)	< 0.001
Delayed:			
Lymphedema	42 (4.5%)	75 (8.4%)	0.001
Skin Changes	40 (4.3%)	62 (6.9%)	0.02
Subcutaneous Tissue	19 (2%)	37 (4.1 %)	0.01

*** Only 1 Grade 4 Toxicity “transient motor neuropathy ipsilateral arm” in the WBI + RNI group
*** No Grade 5 Toxicity

Whelan et al. NEJM 373(19): 2015

DBCG IMN Prospective Study

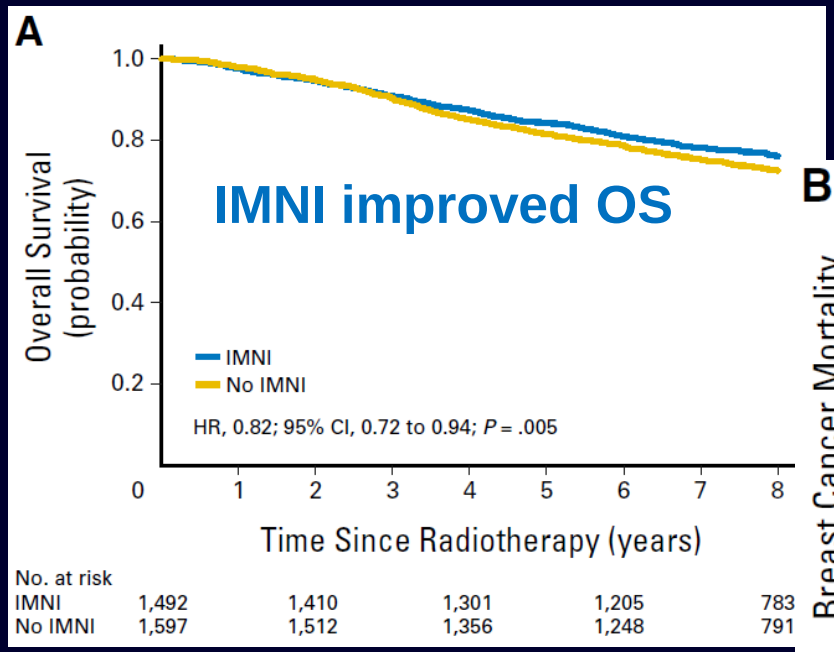
- **3,089** node-positive BC.
- All: RT to Breast/CW, SCL, AX.
- **Right**: IMN RT1-4 IC spaces and
- **Left:** No IMN RT
- Median follow-up time 8.9 years

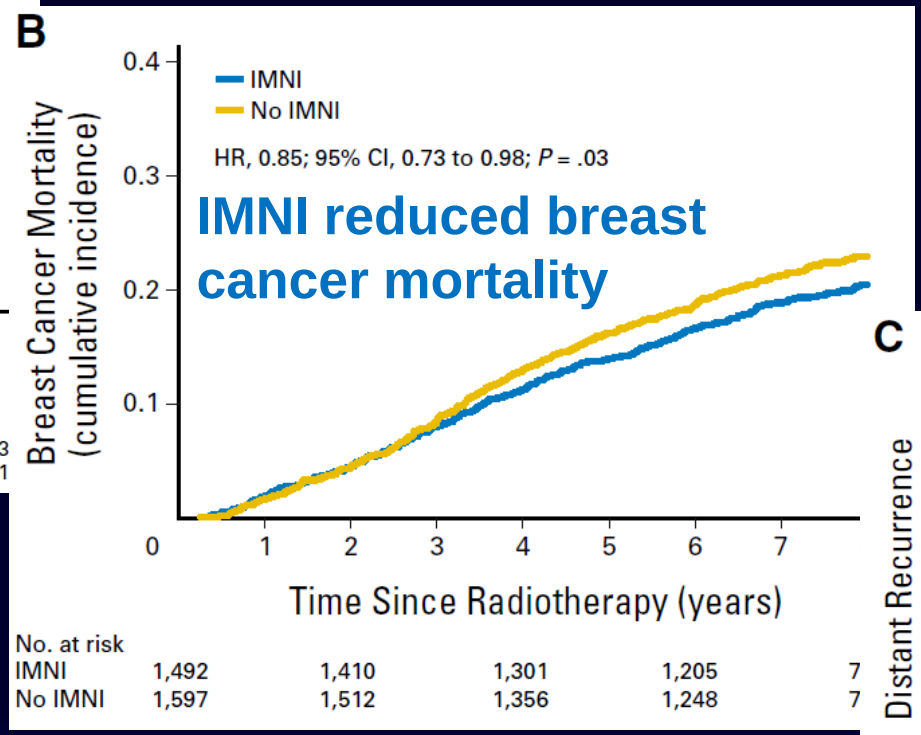
8-Yr Outcome	R-IMN RT	L-No IMN RT	HR	p- value
Distant Mets	27.4%	29.7%	0.89	.07
Breast Cancer Mortality	20.9%	23.4%	0.85	.03
Overall Survival	72.2%	75.9%	0.82	.005

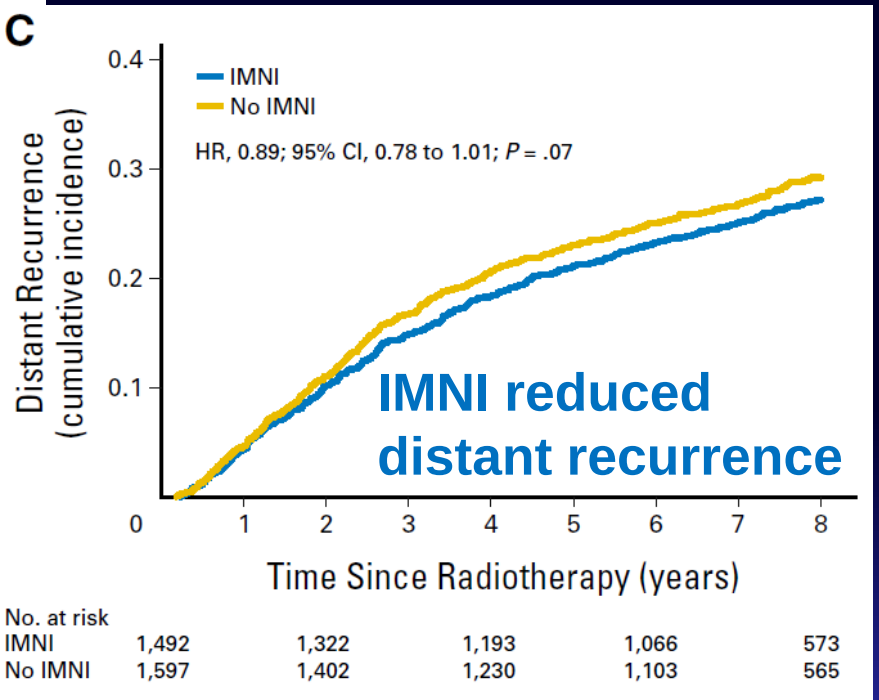
Similar number of ischemic heart disease deaths in the two groups

Thorsen et al JCO 34: 2016

Effect of Internal Mammary Node Irradiation (IMNI) in Node-Positive Breast Cancer







Median follow-up time 8.9 years

Thorsen et al JCO 34: 2016

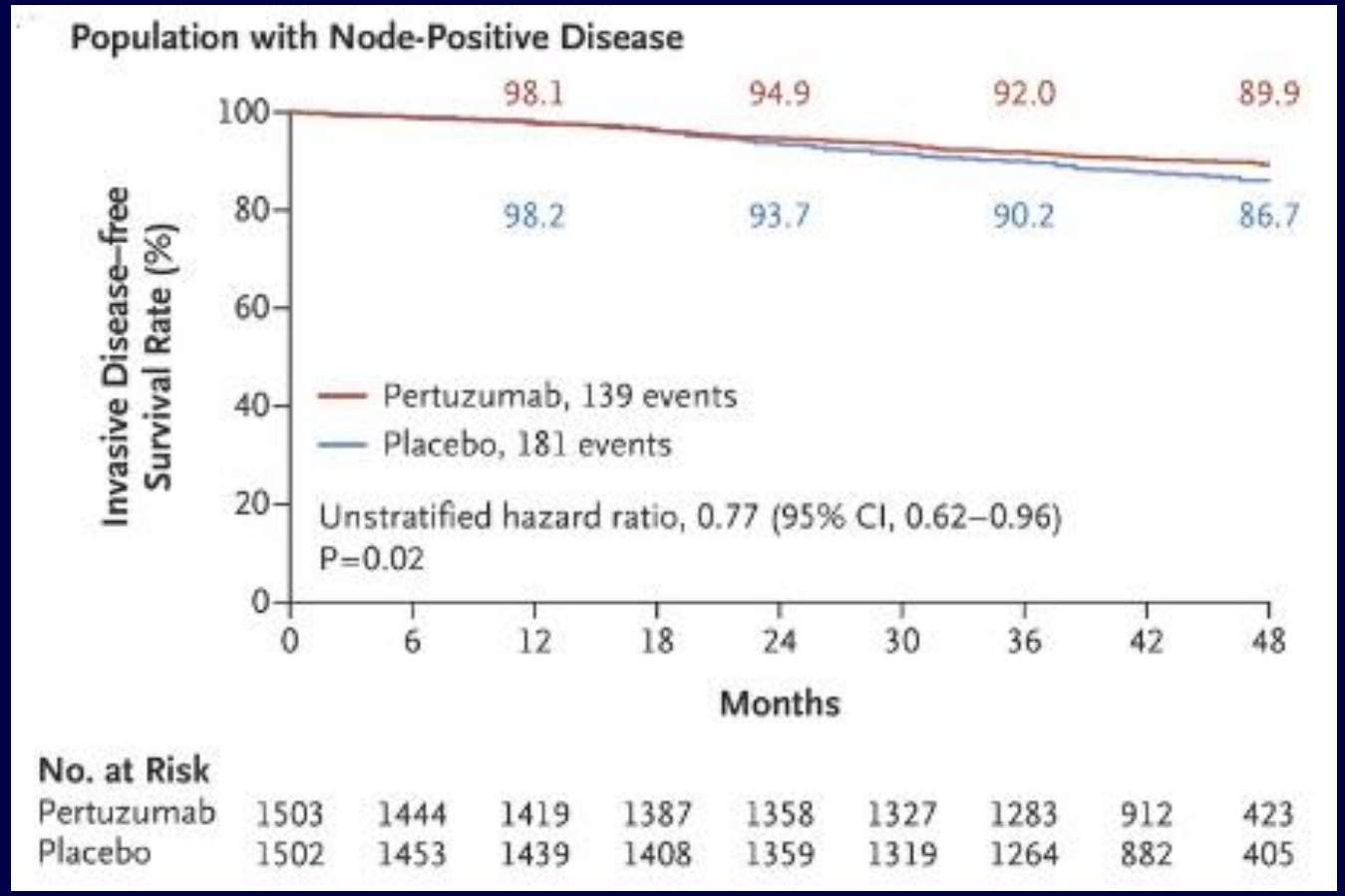
Considerations from Recent Clinical Trials for Axillary Node Positive Breast Cancer

Regional Nodal Irradiation:

- ~ 2- 4% consistent reduction in distant metastases and improvement in DFS
- Gains in local control proportional to the reduction in distant metastases

Effect of RNI is systemic

APHINITY: Difference in Invasive Disease Free Survival Rate is 3.2 %



Time to Local, regional, distant recurrence, contralateral invasive BC or death from any cause in HER2- positive patients

von Minckwitz, et al N Engl J Med 2017

Guideline Evolution for Post Mastectomy RNI Radiotherapy (PMRT)

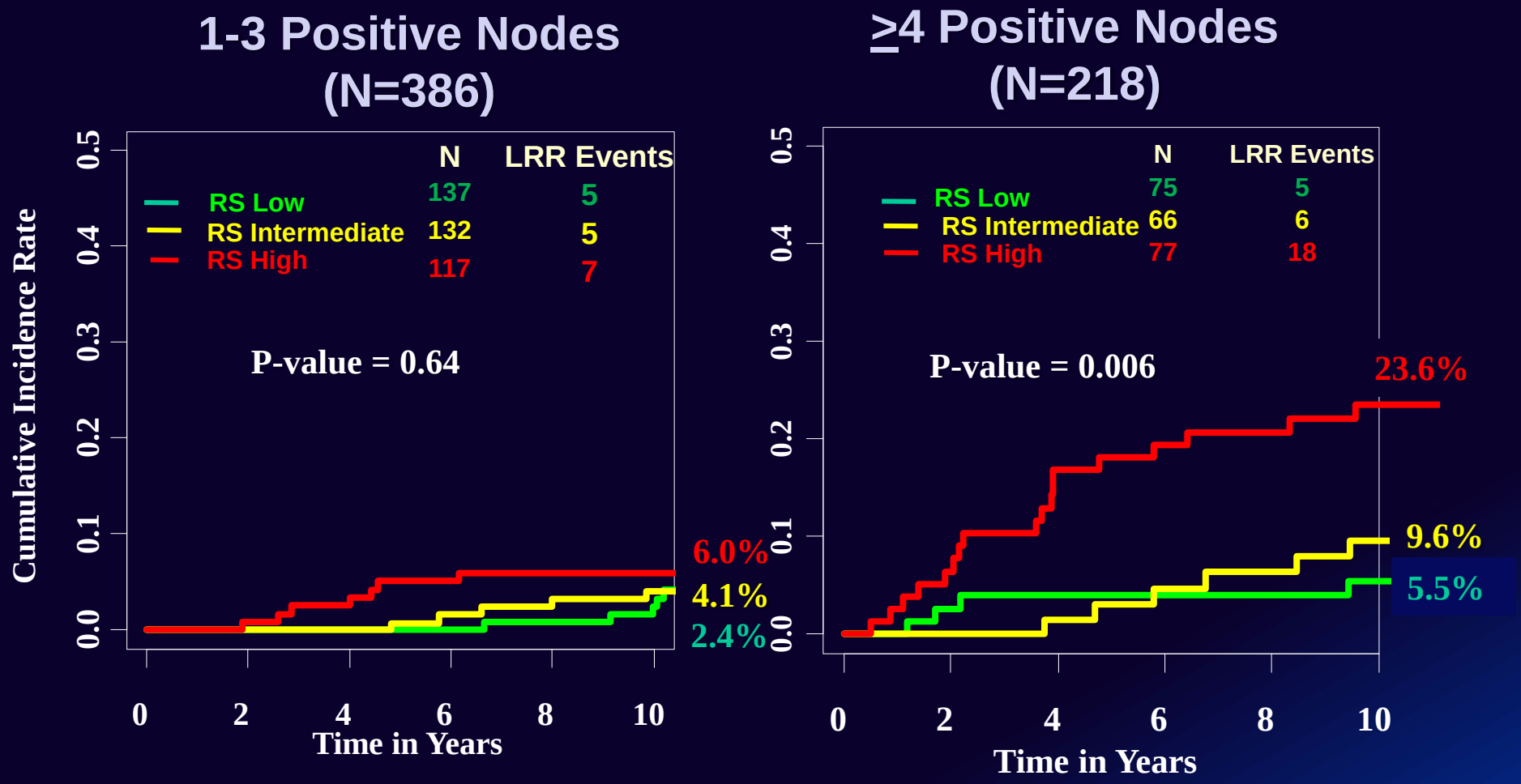
- 2001 ASCO Guideline for PMRT RNI
  - Recommended for: ≥ 4 positive axillary nodes, Stage 3
  - Insufficient evidence: 1-3 positive nodes
  - Include SCL, AX, and controversy about IMN

- 2016 ASCO Guideline for PMRT RNI
  - Recommended for: 1-3 positive axillary nodes
  - Include SCL, AX, and internal mammary nodes

Recht et al, ASCO PMRT Guidelines JCO 2001
Recht et al, ASCO PMRT Guidelines PRO 2016

Oncotype RS Multigene Assay Predicts LRR Post Mastectomy for ER/PR+ Breast Cancer

NSABP B28: ER+, Node positive



median follow-up of 11.2 years

Mamounas EP, et al. *JNCI 2017*

CCTG MA39 "Tailor RT" Phase III Trial

Women > 50 with 1-3 + axillary metastases
ER+ and/or PR+, HER2-Negative,
,Oncotype-DX RS ≤ 18,

STRATIFICATION

- SNB vs Axillary dissection
- Surgery – mastectomy vs BCT
- Adjuvant chemo – yes/ no
- Oncotype RS (0-10, 11-17)

RANDOMIZATION

Arm 1

Regional nodal irradiation
+
Endocrine therapy

Arm 2

Endocrine therapy

Targeted Accrual: 2140

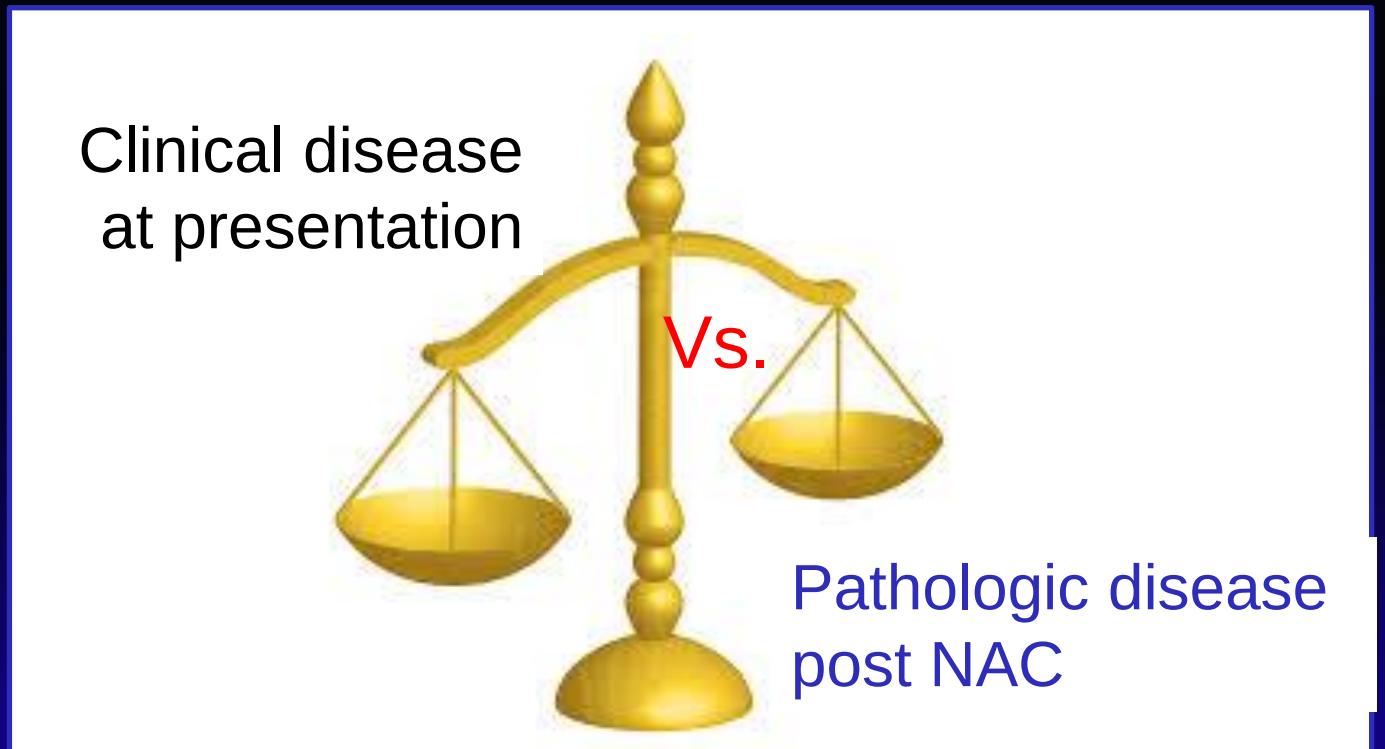
PI: Dr. Tim Whelan

Regional Nodal Irradiation for Node Positive Breast Cancer in the Adjuvant Setting

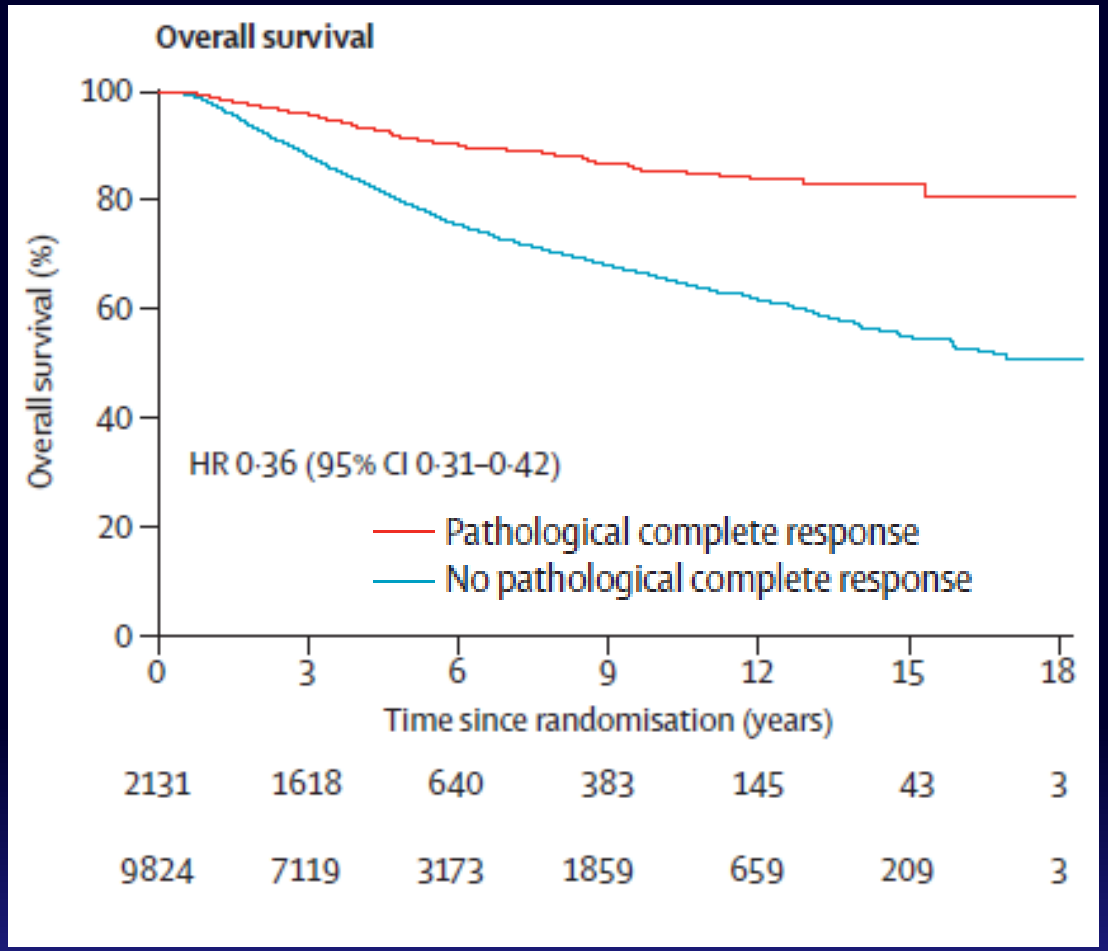
- Regional Nodal Irradiation post mastectomy and with breast conservation is indicated for breast cancer with involvement of four or more nodes (N2) and many with 1-3 nodes (N1).
- Effective regional nodal irradiation treats the retained axillary, supraclavicular and internal mammary nodes.

RNI after Neoadjuvant Chemotherapy: Ongoing Dilemma

- Current evidence for clinical decision making for RNI after NAC is informed by retrospective data.
- Unknown how to weight which factors should drive indication for RNI:



Complete Pathologic Response to Neoadjuvant Chemotherapy Prognostic for Improved Overall Survival



- Strongest association in patients with triple-negative and Her2-positive breast cancer

Cortazar et al, ***Lancet*** **2014**

Combined Analysis of NSABP B18 and B27: Examined LRR post NAC without RNI: 10-year Cumulative Incidence of LRR

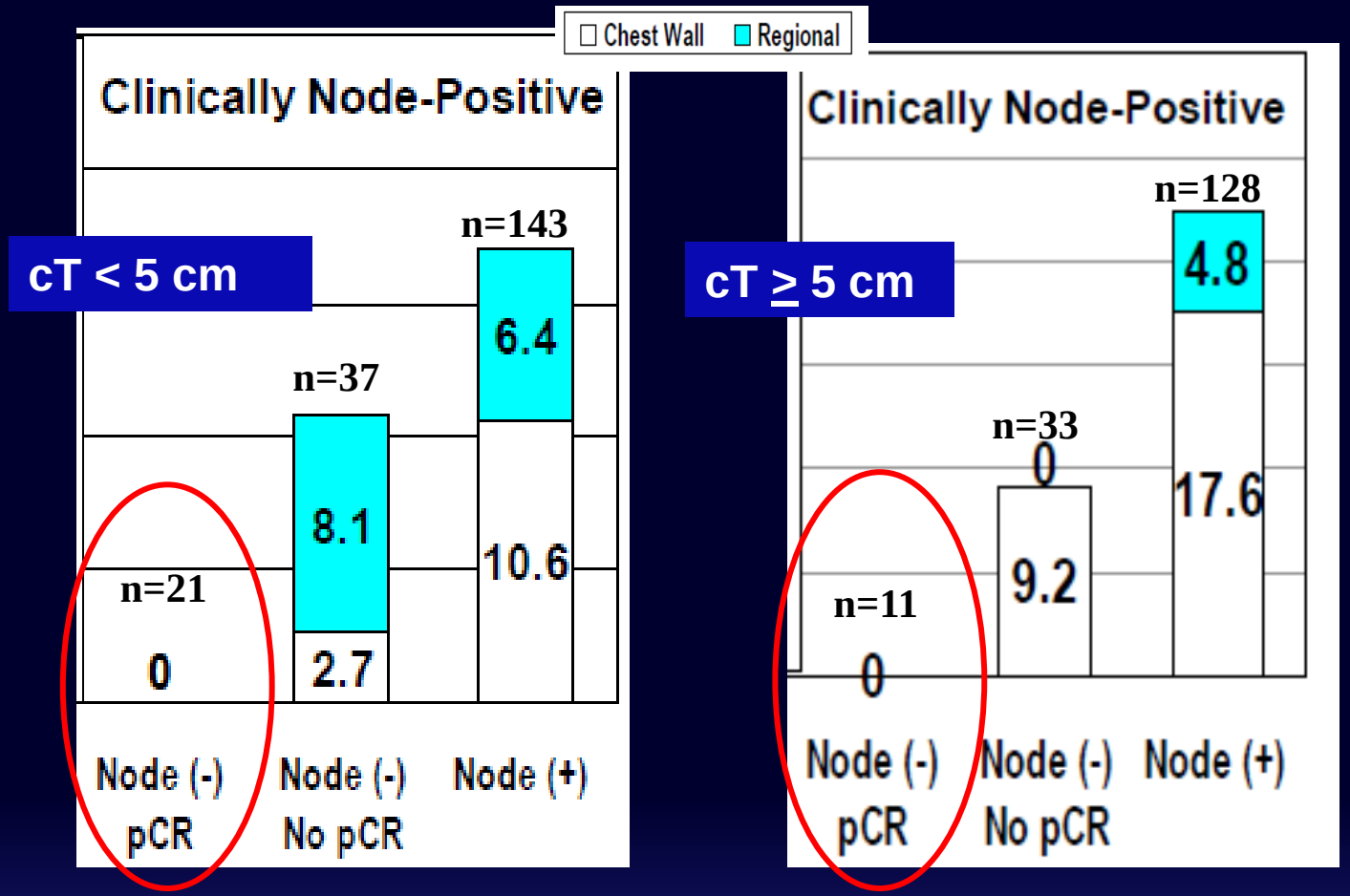
- Entire cohort (n=3,088): 11.1% (8.4% local; 2.7% regional).
- Mastectomy (n= 1947): 12.6 % (9.0% local; 3.6% regional)
- BCT (n= 1,100): 10.3 % (8.1% local; 2.2% regional).
- Multivariate analysis: 5 factors associated with LRR after NAC

Variable	HR	95% CI	p
Age (**≥ 50 yrs** *v.* < 50 yrs)	0.78	0.63-0.98	0.03
Clinical T-Size (**> 5 cm** *v* ≤ 5 cm)	1.51	1.19-1.91	0.001
Clinical N+ *v.* Clinical N-negative	1.61	1.28-2.02	0.001
ypN0/ no breast pCR *v. ypN0/ breast pCR*	1.55	1.01- 2.39	0.001
ypN+ *v.* ypN0 /breast pCR	2.71	1.79- 4.09	0.001

Median follow up: 11.8 years

Mamounas et al, JCO 2012

Combined Analysis NSABP B18 and B27: Reduced LRR with Complete Response in the Axillary Nodes



Median follow up: 15.4 years B18 and 10.7 years B27

Adapted from Mamounas et al, JCO 2012

LRR on the Phase III EORTC 10994/ BIG 1-00

- 2001-2007: 1856 randomized All NAC w / FEC or Taxane based
- Clinical stage II-III, 45% cN0 and 55% cN+
- Subtype: LumA/B ~ 42%, HER2+ 23% (Traz 7%), TN 14%, Unk 21%
- Radiation:
  - BCS: Breast/ CW RT 50 Gy/ 25 Fractions (F), boost 16 Gy/ 8 F
  - Mast: CW, Supraclav/ Infraclav. , ***IMN optional,*** 50 Gy/ 25
- Response: pCR (ypT0-TIS, ypN0): 19%
- Median follow up: 4.4 years
- Total LRR at 5 years: 4.9%
- LRR as first site of failure: 1%

Gillon et al, Eur J Ca 2017

EORTC 10994/ BIG 1-00 Multivariate Analysis: *Subtype and Response* Associated with LRR Following NAC

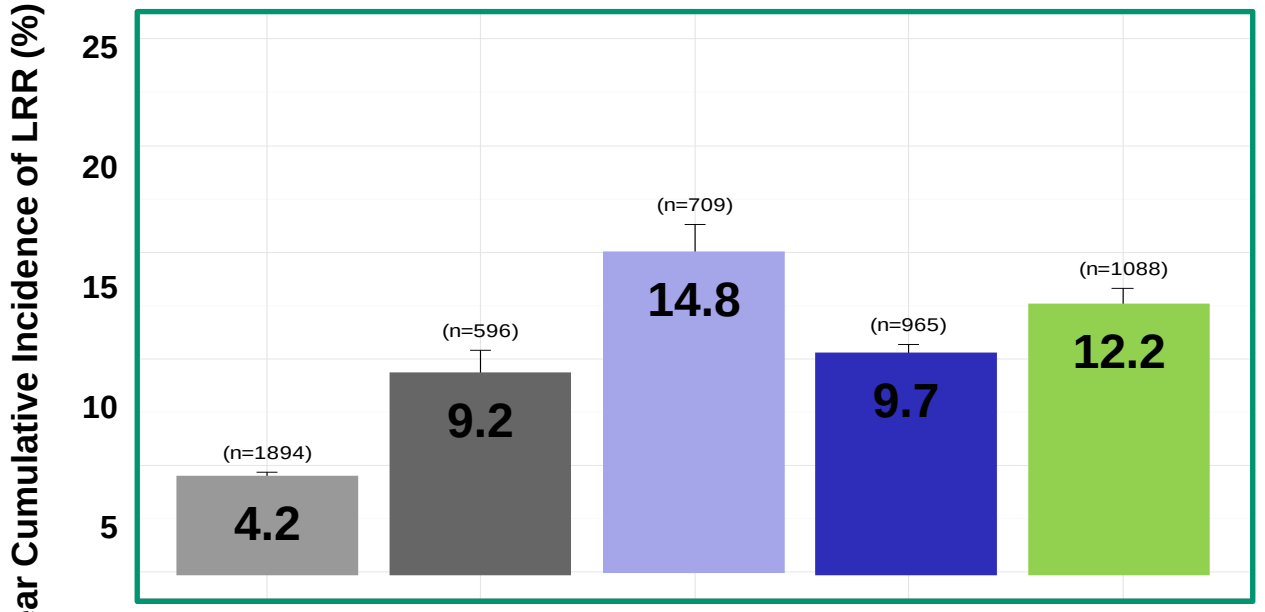
Variable	n	LRR n (%)	HR (CI)	p
Breast cancer subtype/trastuzumab				
Luminal A	491 (32.6)	8 (10.8)	1.00	< 0.0001
Luminal B (HER2−)	143 (9.5)	5 (6.8)	2.29 (0.76−6.97)	
HER2+ Trastu−	245 (16.3)	25 (33.8)	6.26 (2.81−13.93)	
HER2+ Trastu+	105 (7.0)	5 (6.8)	3.37 (1.10−10.34)	
Triple negative	219 (14.6)	20 (27.0)	6.44 (2.83−14.69)	
Unknown	302 (20.1)	11 (14.9)	2.28 (0.93−5.63)	
Pathological response				
ypT0/is ypN0	278 (18.5)	16 (21.6)	1.00	< 0.0001
ypT + ypN0	420 (27.9)	10 (13.5)	0.58 (0.26−1.28)	
ypT + ypN+ 1−3 nodes	450 (29.9)	14 (18.9)	0.74 (0.36−1.52)	
ypT + ypN+ ≥4 nodes	357 (23.7)	34 (45.9)	2.43 (1.34−4.40)	

median follow-up: 4.4 years

Gillon et al, Eur J Ca 2017

CTNeoBC Multivariate Analysis: Tumor Subtype and Pathologic Response are Independent Predictors of LRR

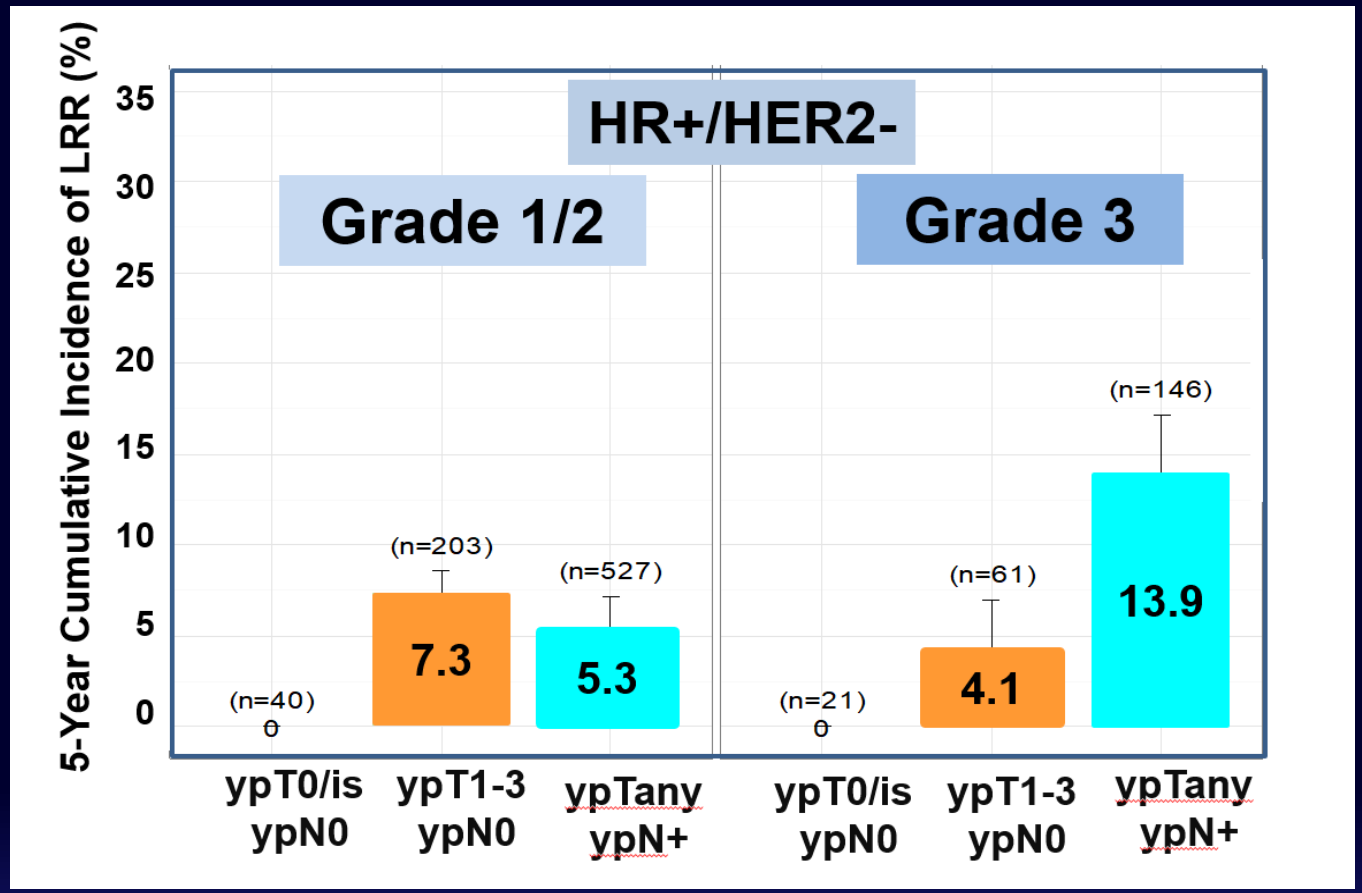
- 12 NAC trials
- 1195 pts w/ pCR info and LRR, EFS, OS
- ~ 1/3 PRMT
- Median F/Up 42 mo.
- Primary analysis: LRR



HR = Hormone Receptor (ER/PR)

Mamounas et al, Oral Abstract Session A, Breast Cancer Symposium , 2014

CTNeoBC Multivariate Analysis
HR Positive/HER-2 Negative/Mastectomy:
LRR by Breast pCR and Pathologic Nodal Status



HR = Hormone Receptor (ER/PR)

Mamounas et al, Oral Abstract Session A, Breast Cancer Symposium , 2014

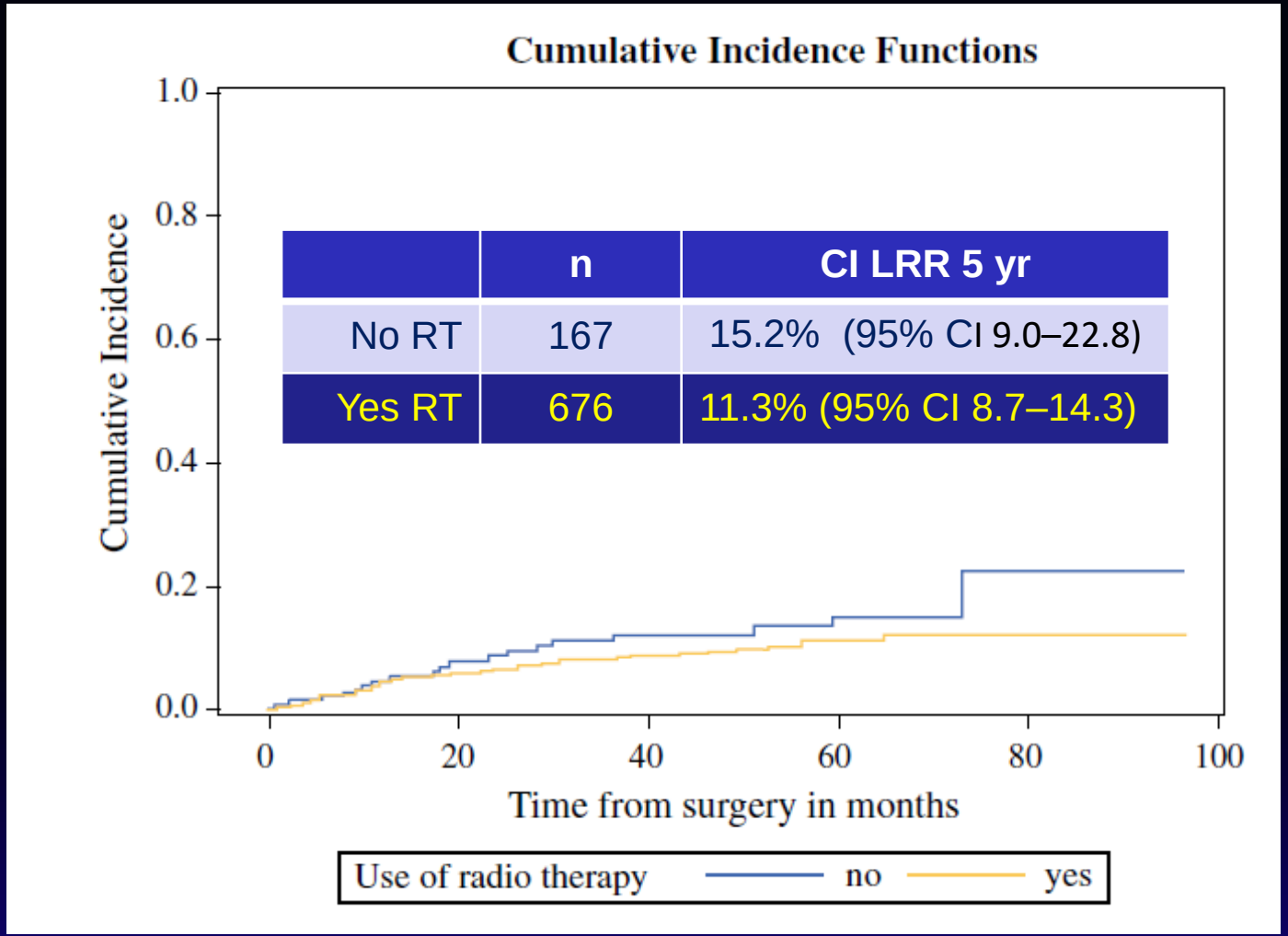
PMRT ± RNI Post NAC: Retrospective Analysis of 3 GBG Randomized Trials

- 6139 patients were treated September 2002 to July 2010:
  - GeparTrio, GeparQuattro, and GeparQuinto
- 1569 Mastectomy – 817 with clinical data and follow up.
- 676 (82.7%) received adjuvant radiation
- Radiation data available for 318 (46.4%)
  - RT to chestwall 98.7%, SCL 74.5%, IMN 15.4%, Axilla 18.2%
- cN+ 61%, ypT0/Tis ypN0 11.6%
- Subtype: HR+ 66.3%, HER2 25.2%, TN 15.7%
- Evaluated Cumulative Incidence LRR

Krug et al., Ann Surg Oncol 26: 2019

Cumulative Incidence of LRR
No Difference with PMRT ± RNI

- LRR
  - No difference overall
  - On MVA, PMRT **reduced LRR** with:
    - cT3/4 tumors p = 0.04
    - cN+ p= 0.05
    - ypN0 p = 0.06
    - **cN+/ypN0** p= 0.05



	n	CI LRR 5 yr
No RT	167	15.2% (95% CI 9.0–22.8)
Yes RT	676	11.3% (95% CI 8.7–14.3)

Median Follow up: 51 months

Krug et al., Ann Surg Oncol 26: 2019

NRG NSABP B-51/RTOG 1304 Trial Phase III

- Clinical T1-3**N1**M0 breast cancer
- Pathology positive axillary node (**FNA/Core**)
- Neoadjuvant CT ± anti HER2

ypN0 at definitive Breast Surgery + AND or SNB

Randomization

Arm 1

No Regional Nodal XRT

A. Lumpectomy: Breast XRT
B. Mastectomy: Observation

Arm 2

Regional Nodal XRT

A. Lump.: Breast/Nodal XRT
B. Mast: Chestwall/ Nodal XRT

Targeted accrual = 1636

Stratification: Type of Surgery (Mast v. Lump) , ER-Status (+ v. –), HER2 Status (+ v. –), pCR in Breast (yes v. no)

NRG ONCOLOGY™

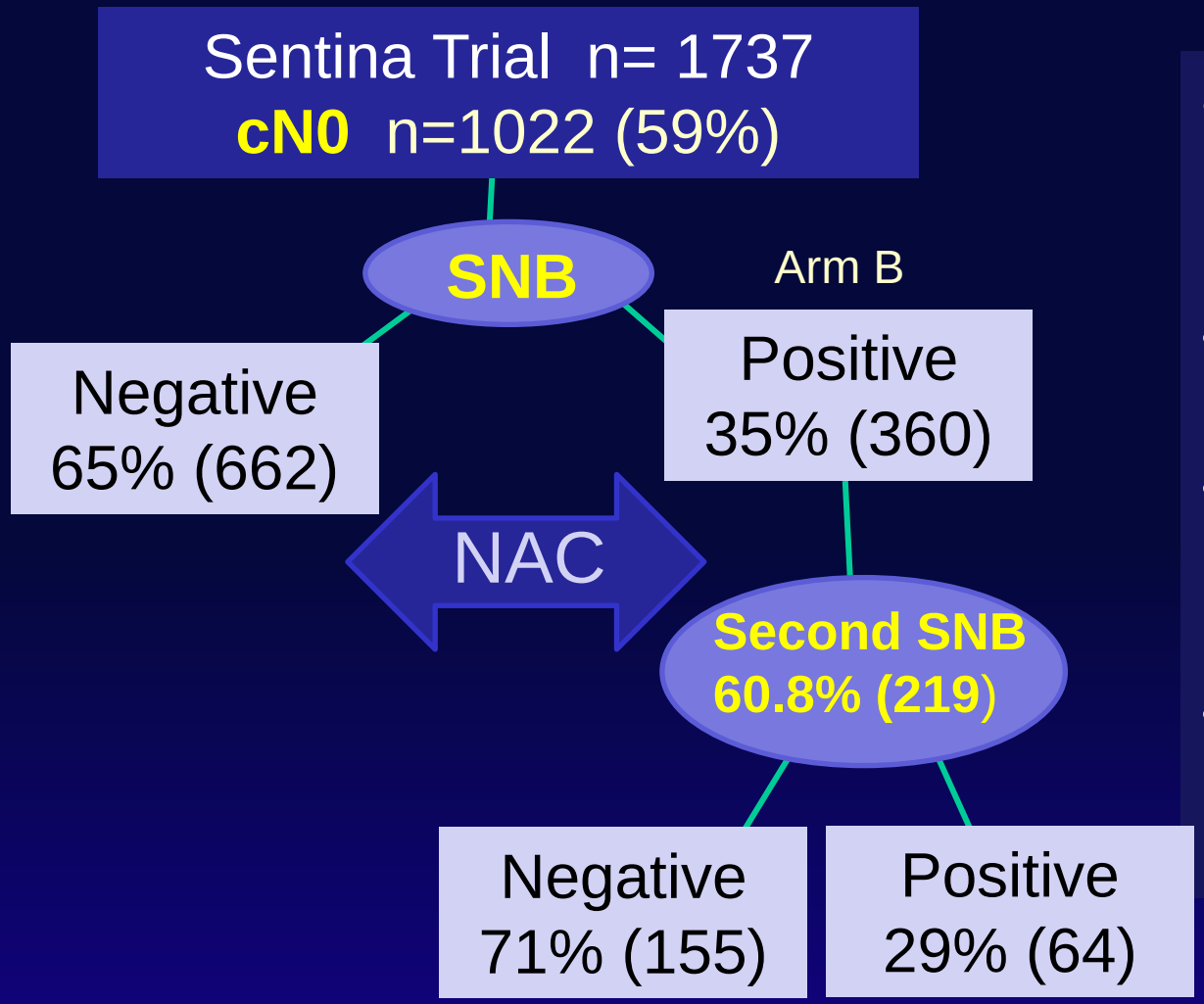
NRG NSABP B51/ RTOG 1304
Patient Characteristics (12/28/2020)

Characteristic		%
Receptor Status	TN	22.7
	HR+,HER2-	21.1
	HER2+	**56.2**
pCR Breast	yes	78.2
	No	21.8
Surgery	Mastectomy	42.3
	Lumpectomy	57.7

Accrual met 12/28/2020!!

NRG ONCOLOGY™

Presentation with cN0 Axilla: Less Regional Nodal Irradiation after NAC



- Sentina Trial (Arm B):
  - SNB Positive: 35% pre NAC
  - Second SNB post NAC 71% Negative
- cN0 ⇨ ypN0 Regional Nodal Irradiation is not indicated
- When surgery is first, RNI is recommended for many patients with 1-3 positive axillary nodes
- When NAC is first, roughly 25% cN0 spared RNI with NAC

Kuehn et al, Lancet Oncol 14:2013

ALLIANCE A011202: RNI ± ALND for SN+ after NAC

- Clinical T1-3**N1**M0 breast cancer
- Pathology positive axillary node (**FNA/Core**)
- Neoadjuvant CT ± anti HER2

cN0 after NAC

SNB and Breast Surgery

Intraop. SN + Identified

Intraop. SN negative / Final Path: SN +

Intra-op Registration and RANDOMIZATION

R

Registration and RANDOMIZATION

Open for Accrual!!

ARM 1: ALND + RNI

ARM 2: RNI

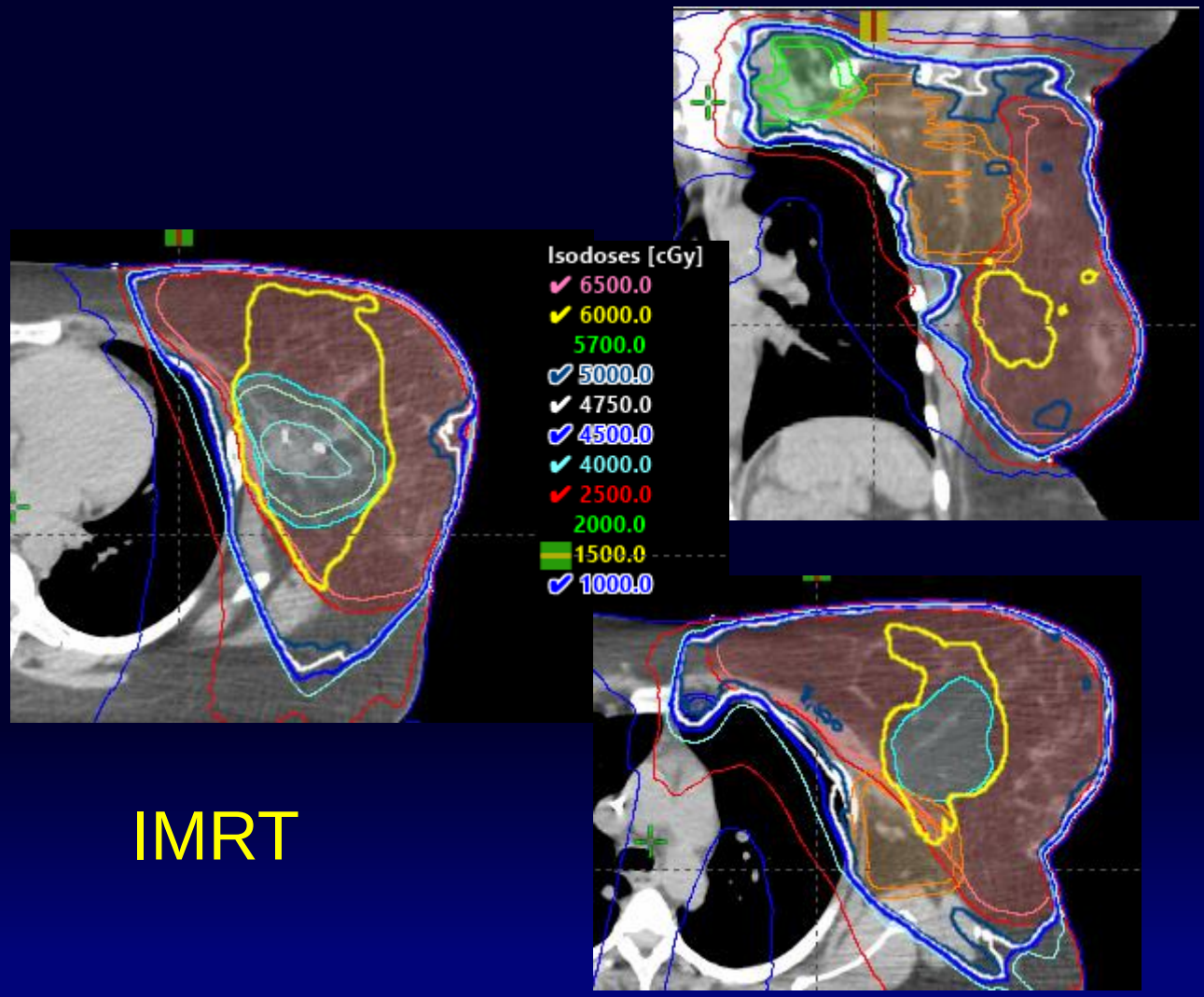
Recommendations: RNI Post Neoadjuvant Chemotherapy

- Clinical cN0/ yp N0: observation (Will avoid RNI in cN0 → SN+ with surgery 1st)
- Clinical cN+ / ypN+: regional nodal irradiation (Consider enrolling to A011202)
- Clinical cN2-3/ ypN0: regional nodal irradiation (Locally advanced disease!)
- Clinical cN1/ ypN0: (Await findings from NRG B51-RTOG1304)
  - Regional nodal irradiation in most
  - Observation – Clinical T1, "small" cN1 pre NAC → ypT0,N0; cT1, N1→ ypT0 or T1 older age, ER+/PR+/HER2-

Case 5 Treatment

43 yo with cT2N1/ ypT1cN0 G3 IDC ER-PR-HER2+

- Breast and Regional nodal RT (SCL, Ax, IMC)
  - 50 Gy/ 25 F/ 2 Gy q d
- Boost:
  - 10 Gy/ 5 F/ 2 Gy qd



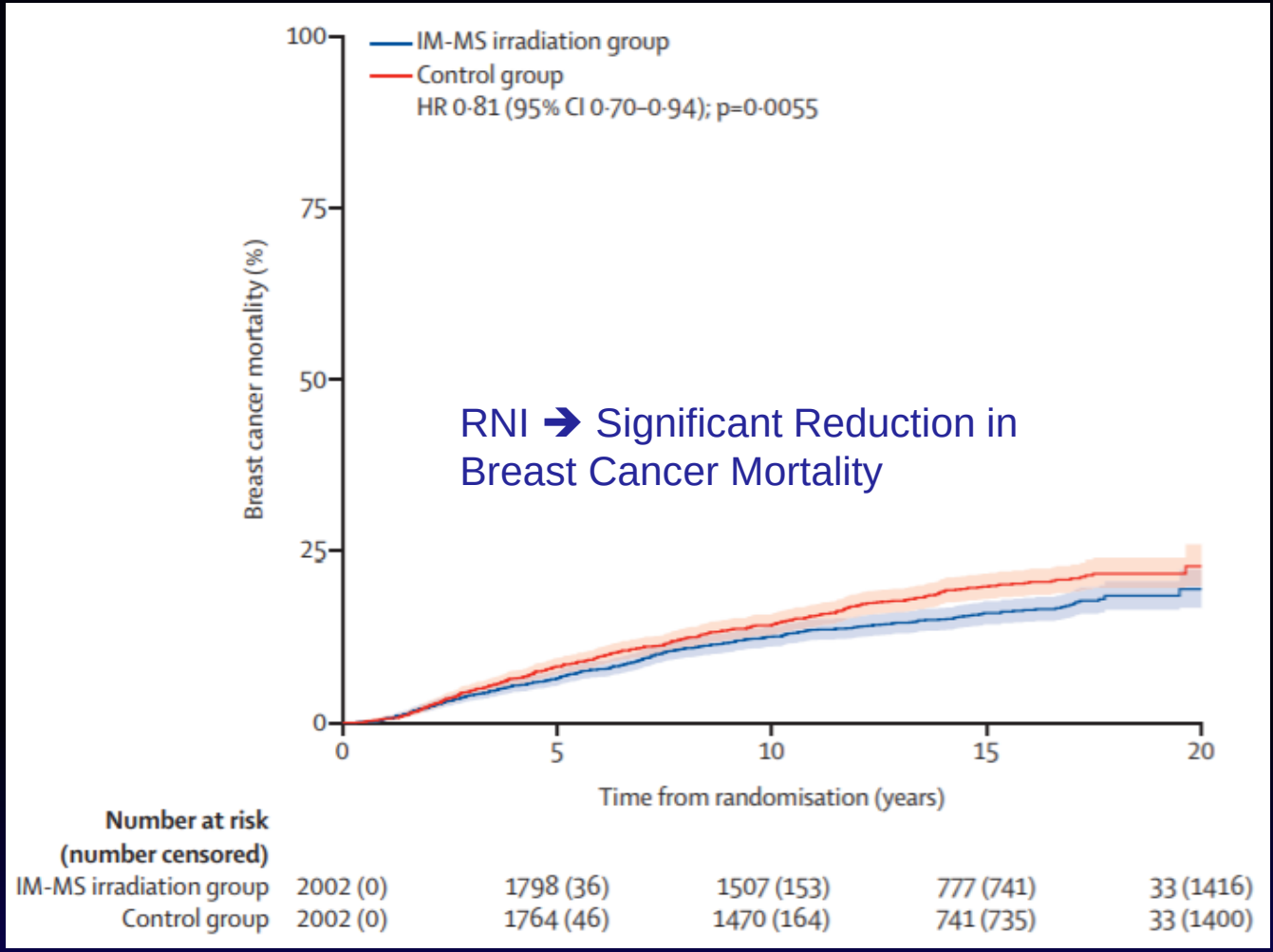
IMRT

Delivery of RNI

EORTC trial 22922/10925
15 year update

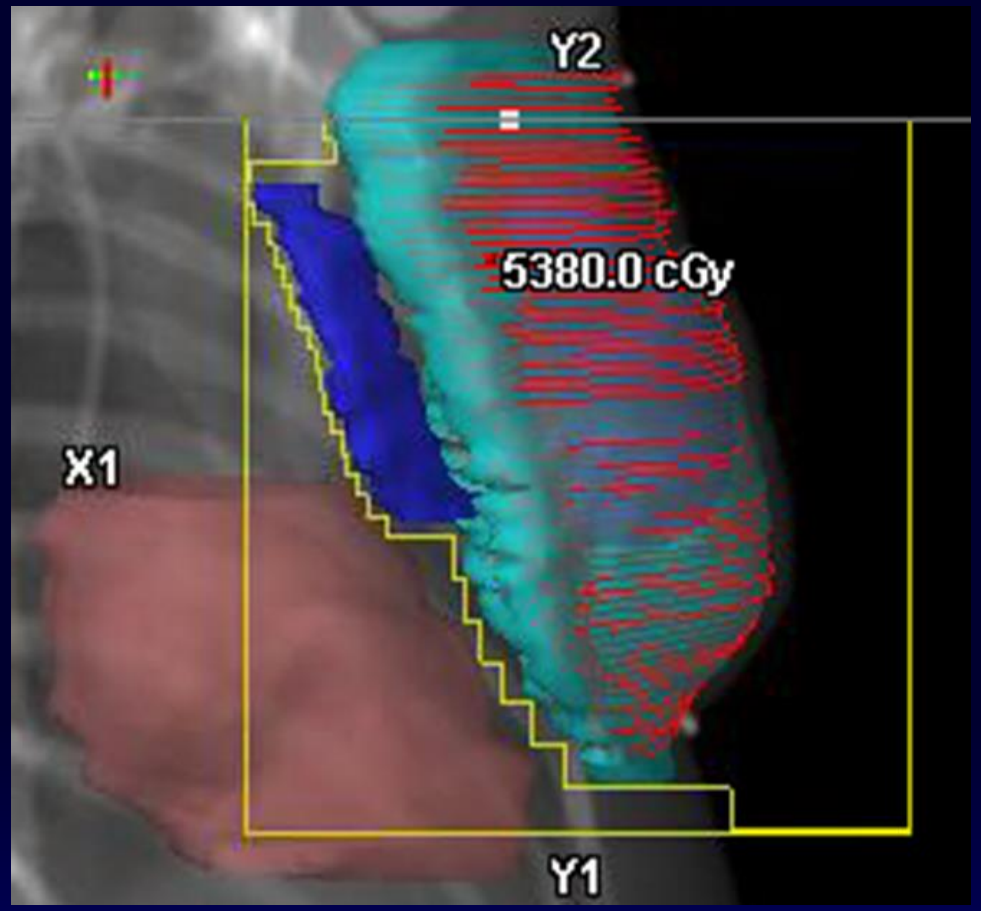
- Significant reduction of breast cancer mortality at 15 years with RNI
- No difference in 15 yr DFS, OS
- Increase # of non-BC deaths with RNI

Cause of Death	RNI	No RNI
Breast Cancer	56.7%	66.4%
Non-Breast Cancer	30.9%	26.4%
Unknown	12.5%	7.2%



Poortmans et. al., Lancet Oncol 2020

Modern Radiation Treatment Planning Allows Safe Inclusion of IMN



- 202 Women Treated with RNI:
  - 33 BCT - 169 PMRT
- Radiation methods:
  - 3DCRT 81%,
  - IMRT 18%,
  - Left sided 52% (DIBH 42%)
- Multivariate analysis: Association with unacceptable heart and lung dose
  - IMN radiation vs not p = 0.350

Bazan et al, PRO, 2017

The James
The Ohio State University
Comprehensive Cancer Center

Clinical Outcome from Adaptive Treatment Planning 3DCRT vs. IMRT for RNI

- N= 240 Node positive (Mean+: 4)
  - HR+ 60%, TN 19%, HER2 21%
  - Mastectomy 74%, BCT 26%,
  - DIBH 42% (All left sided)
  - Post NAC: 38%
- Radiation delivery:
  - Contoured for Treatment Planning:
    - Targets: CW, Breast, SCL, Ax, IMN
    - OARs : Heart, Lungs, Esophagus, Thyroid, SC
  - 3DCRT: 168
  - IMRT if OARS ***Not Met***: 72 (30%)
- 50 Gy/ 25 F/ 2 Gy (95% target/ 95% dose)
  - Bolus: Scar + 2cm
  - Boost 10-14 Gy/ 2 Gy (Lump 91%, Mast 49%
- Median f/u 51 mo.

OAR Dose (cGy)	3DCRT	IMRT
MHD	169	385
Left	259	428
Right	88	299
Ips. Lung V20 (median %)	30 (28-34)	24 (19-27)
Ips. Mean Lung dose	848	804

Pattern of Recurrences	n (%)
Isolated CW/ Breast	0
Isolated Regional Nodal	3 (1.25%)
LRR + Distant	4 (1.67%)
Distant	37 (16%)

Bazan et al, IJROBP, 2020

The James
The Ohio State University
Comprehensive Cancer Center

British Columbia PHASE III Trial of PMRT in Pre-menopausal Women with LN+ Breast Cancer used Hypo fractionation.

- 1979-86
- 318 premenopausal
- s/p MRM with ≥ 1 + Ax LN
- Nodes: 57% 1-3+, 35.3% 4+
- Randomized to: CT alone vs. CT+ RT
- CT: CMF q 21 days 6-12 mo.s
- RT: Target CW, Ax, Scl, IMC
  - DOSE: 37.5 Gy/ 15 F/ 2.5 Gy

Ragaz et al. NEJM 337: 1997 JNCI 97:2005

Phase II Trial of Hypo fractionated PMRT

- Rutgers Cancer Institute 2010-2014
- N= 69
- CW, Ax and SCL nodes. No IMN
- Dose: 36.33/ 11 F/ 3.3 Gy fraction
- Boost: 13.32 Gy/ 4 F/ 3.3 Gy fraction
- Population:
  - Median age 54 yrs
  - Stage II 91%
  - ER+ 76%
  - Reconstructed 52%
- Median follow up: 2.6 yrs

Measure	%
G2 Skin Toxicity	24
G2 Pain	4.5
Lymphedema	4.5
Implant loss	24
Local recurrence	3

Khan et al, JCO 2017

Phase III Trial Hypo fractionated PMRT to Chestwall, Level 3 Axilla, and SCL (No IMC)

ELIGIBLITY
- 18-75 yo.
- Mastectomy+ AxND
- ≥ 4 Axillary nodes +

Standard PMRT:
50 Gy / 25 F
2.0 Gy

Hypo fractionated PMRT:
43.5 Gy /16F
2.9 Gy

- 2008-2006
- n= 820
- Chestwall – 6-9 MeV, nodes 2D RT
- Median age: 49 years
- Median Tsz: 2.5 cm
- Median + nodes: 6 (4 – 11)
- ER positive: 75%
- Median follow up: 4.8 years

5 year	50 Gy/ 25 F	43.5 Gy/ 15 F
Local Regional Recurrence	8.3%	8.1%

Primary Endpoint: Local regional recurrence

Wang et al., Lancet Oncol 20: 2019

Late Toxicity

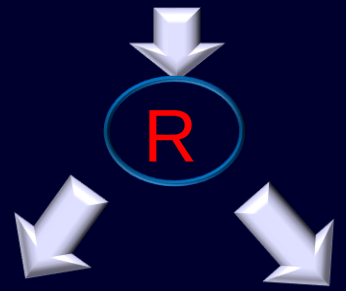
- Similar incidence

Late toxicity	50 Gy/ 25 F	43.5 Gy/ 16 F	
Skin toxicity	..	..	0·669
Grade 1–2	90 (22%)	86 (21%)	..
Grade 3	0	1 (<1%)	..
Lymphoedema	..	..	0·961
Grade 1–2	81 (20%)	78 (19%)	..
Grade 3	3 (1%)	3 (1%)	..
Shoulder dysfunction	..	..	0·734
Grade 1–2	13 (3%)	7 (2%)	..
Grade 3	1 (<1%)	1 (<1%)	..
Lung fibrosis	..	..	0·081
Grade 1–2	42 (10%)	62 (15%)	..
Grade 3	0	0	..
Ischaemic heart disease	..	..	0·569
Grade 1–2	1 (<1%)	3 (1%)	..
Grade 3	3 (1%)	4 (1%)	..

Wang et al., Lancet Oncol 20: 2019

Alliance A221505: RT CHARM

ELIGIBLITY
- Stage IIa-IIIa
- Mastectomy+ SN or AxND
- Breast reconstruction present or planned



Standard PMRT:
50 Gy / 25 F
2.0 Gy

Hypo fractionated PMRT:
42.56 Gy /16F
2.66 Gy

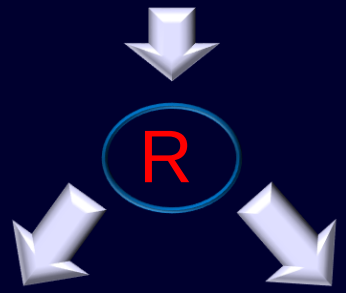
- Opened: 2017
- Targeted Accrual: 880
- Radiation targets:
  - CW/ reconstructed breast
  - Axilla
  - SCL
  - IMC

Primary Endpoint: Reconstruction Complication Rate

PI: Matthew Poppe MD

Dana Farber FABREC Clinical Trial

ELIGIBLITY
- Stage I-III
- Mastectomy+ SN or AxND
- Immediate Breast reconstruction



- Opened: 2018
- Targeted Accrual: 440
- PMRT includes:
  - CW/ reconstructed breast
  - SCL
  - Axilla (optional)
  - IMC (optional)

Standard PMRT:
CW: 50 Gy / 25 F
Nodes: 46-50/ 23-25 F

Hypo fractionated PMRT:
CW:42.56 Gy /16F
Nodes: 39.9 Gy/ 15 F

Primary Endpoint: FACT-B Physical Well Being at 6 months

PI: Rinaa Punglia MD

Summary: Regional Nodal Irradiation Fractionation

- Standard regional nodal irradiation treats SCL, Axillary and IMC nodal basins
- Conventional fractionation of 50 Gy / 25 F is still common and acceptable
- Long term effects on cardiac and brachial plexus outcomes from hypo fractionation are pending
- I use hypo fractionation of 42.56 Gy/ 16 F for RNI or PMRT for breast cancer patients $\geq$ 70 yo.
- Enroll post mastectomy reconstruction on the ALLIANCE 221505 RT Charm trial.

Thank you!