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Radiation Therapy following BCS: More, Less or Not at All

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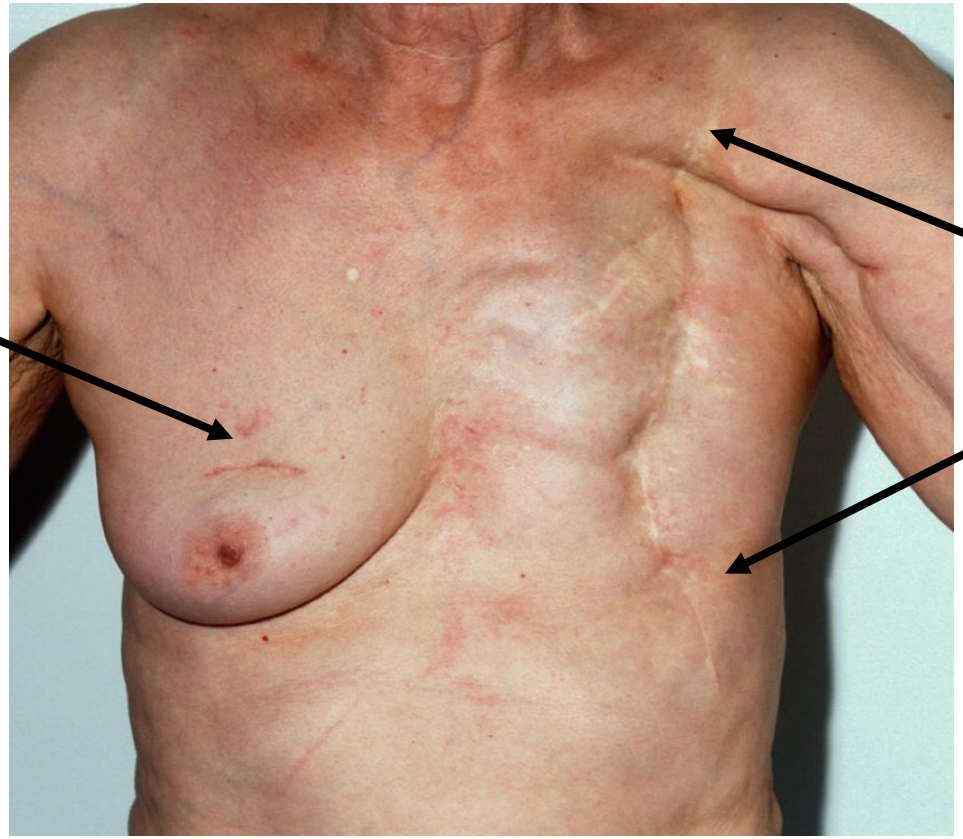
Victoria, BC

September 26, 2012

UBC

In early-stage breast cancer, Radical Mastectomy was common until mid-1970s. Today, Breast Conserving Surgery is most common.

Breast Conservation 2010 Age 74

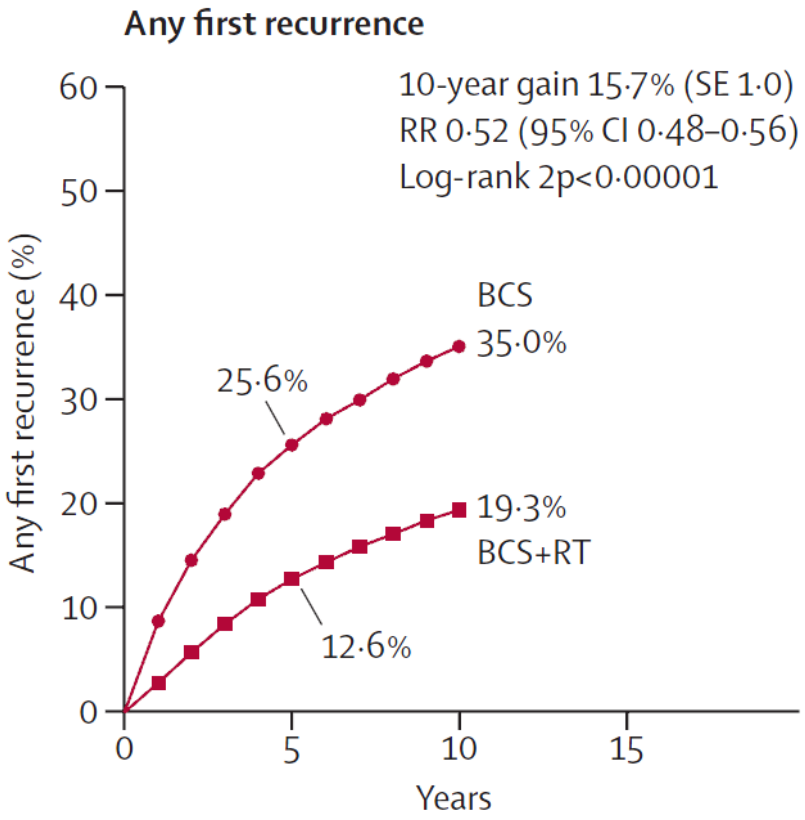


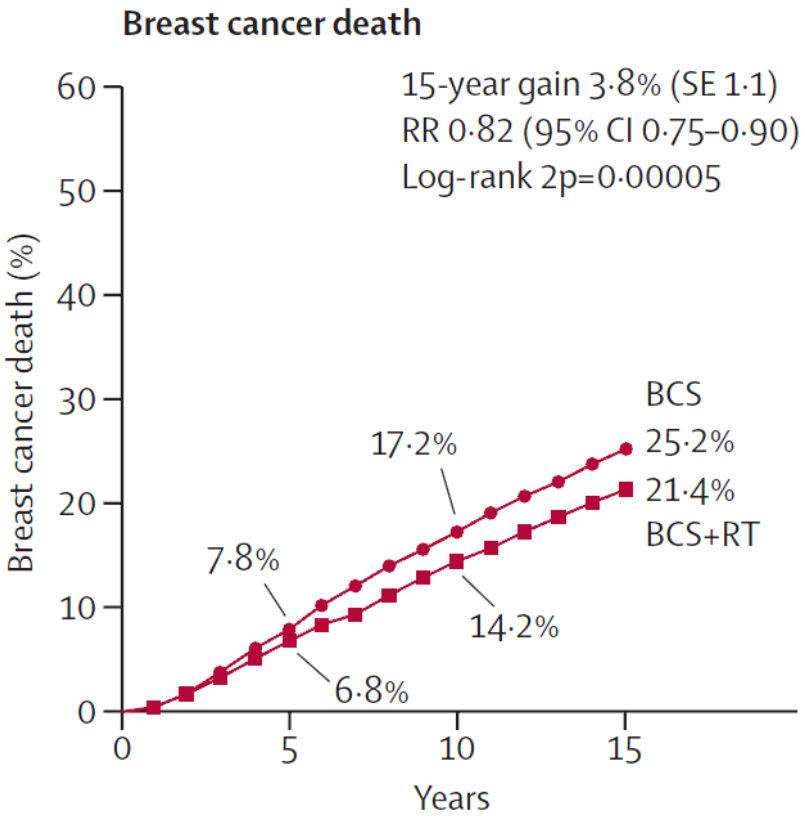
Radical Mastectomy 1968 Age 32

Early Breast Cancer Trialists' Collaborative Group

(17 randomized trials of BCS +/- RT; 1976-1999; 10,801 women)

Conclusion: RT, generally to the whole breast, after Breast Conserving Surgery reduced recurrences and improved survival





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Radiation Therapy following BCS: More, Less or Not at All

Pauline Truong: Treat the nodes too?
Tanya Berrang: Just treat part of the breast?
Sally Smith: Women who don't need RT?

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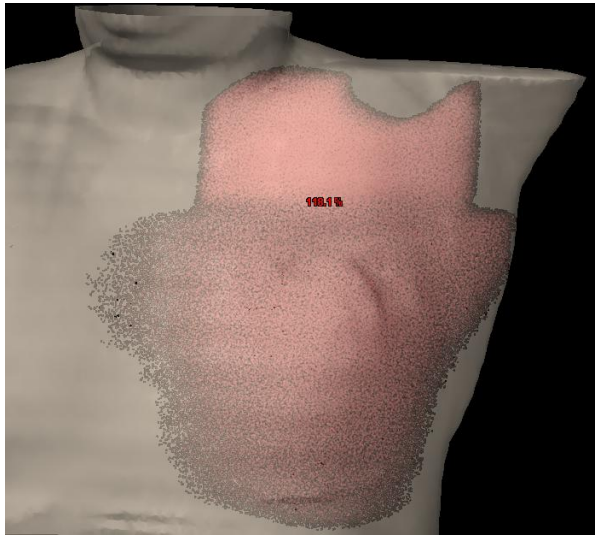
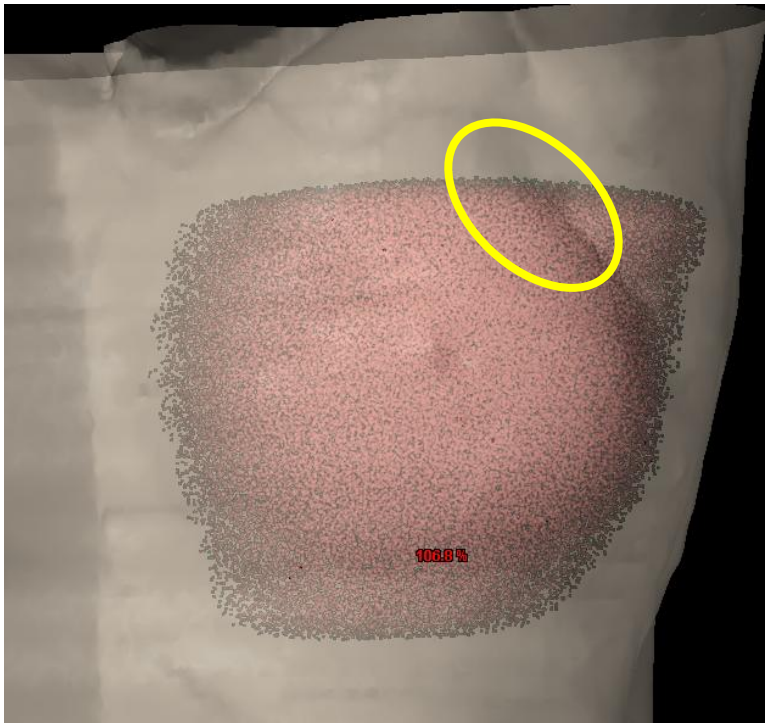
More? Nodal RT after BCS

Pauline Truong, MDCM, FRCPC
Radiation Oncologist, BCCA, Vancouver Island
Clinical Professor, UBC



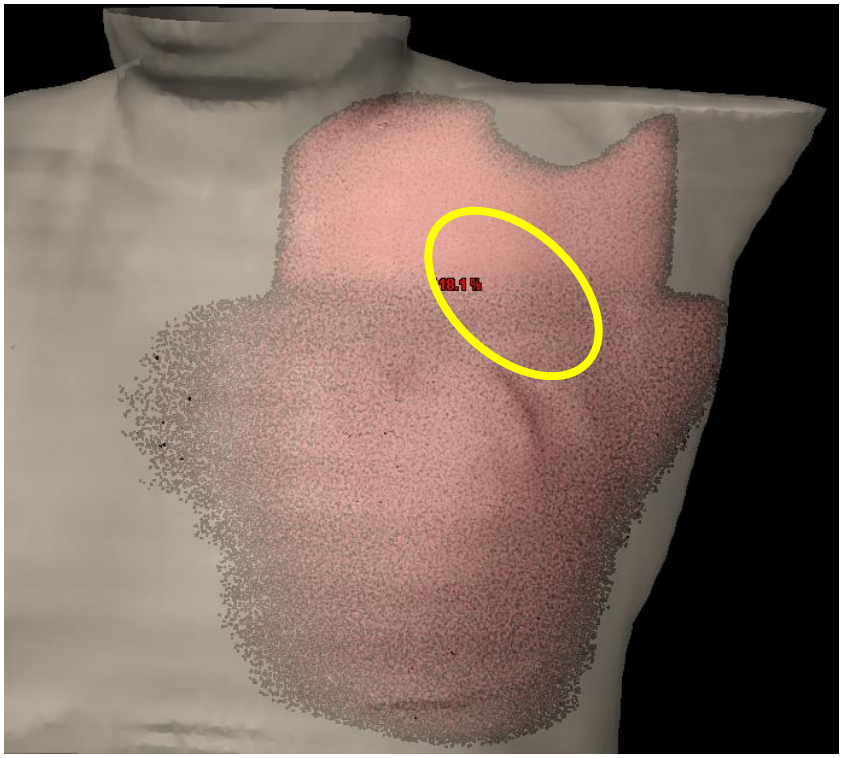
UBC

RT volume vs Level I/II AxD



RT to Breast alone

(possible inclusion of part of level I/II axilla)



RT to Breast + Nodes

(axilla, supraclavicular, internal mammary nodes)

RT Risk Benefit Ratio: Adverse Effects

Short term

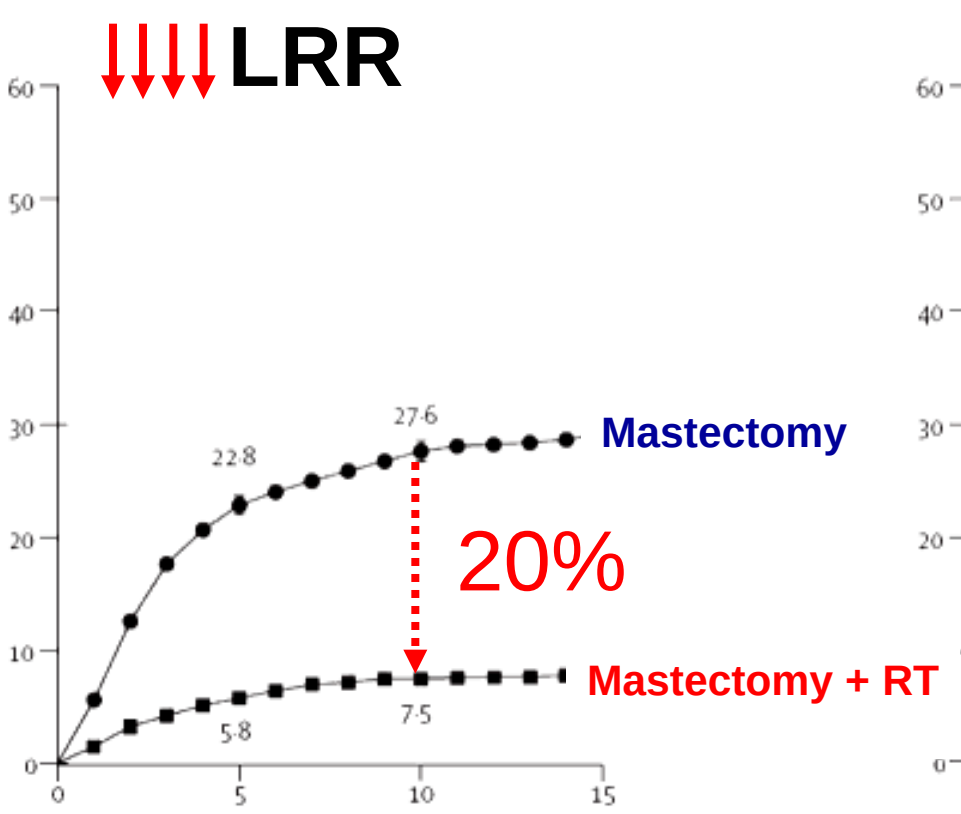
- inconvenience
- fatigue
- breast pain
- skin reaction

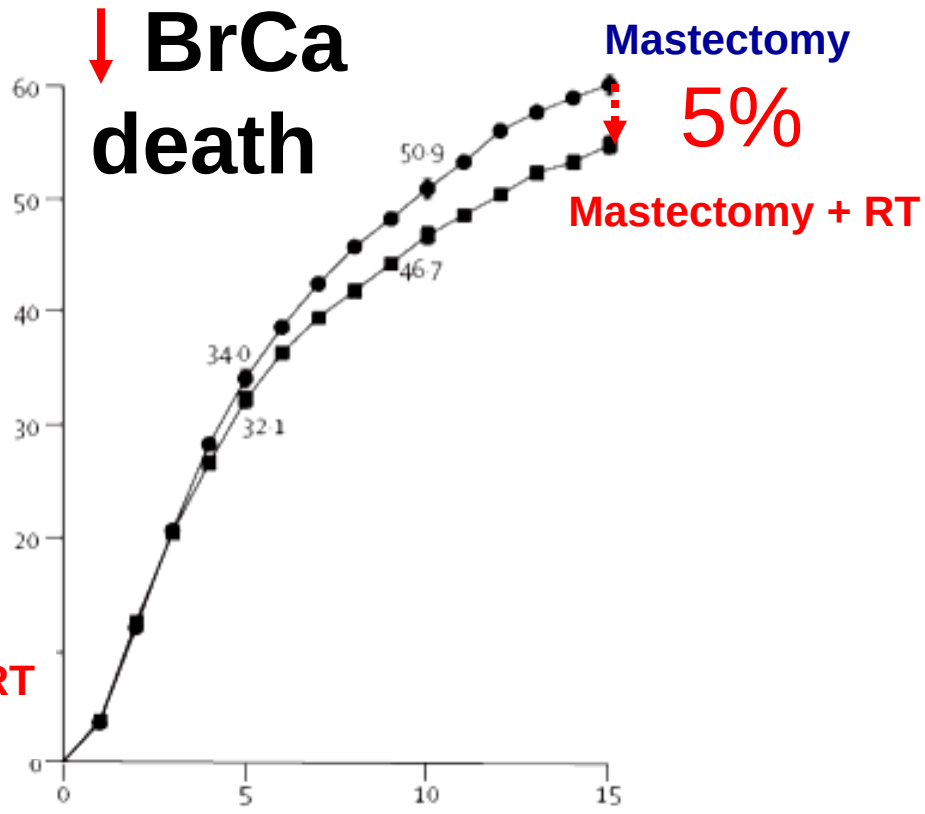
Long term

- lymphedema
- pneumonitis
- cardiac injury
- brachial plexopathy
- rib fracture
- poor cosmesis
- secondary malignancies

Why consider adding nodal RT?

Oxford Overview: 25 Trials, 8505 women, N+, Mastectomy
Chest wall + nodal RT improves local control + survival





EBCTCG Lancet 2005

Why consider adding nodal RT?

ASTRO, ASCO and Canadian Guidelines:

- Recommended postmastectomy chest wall + nodal RT for:

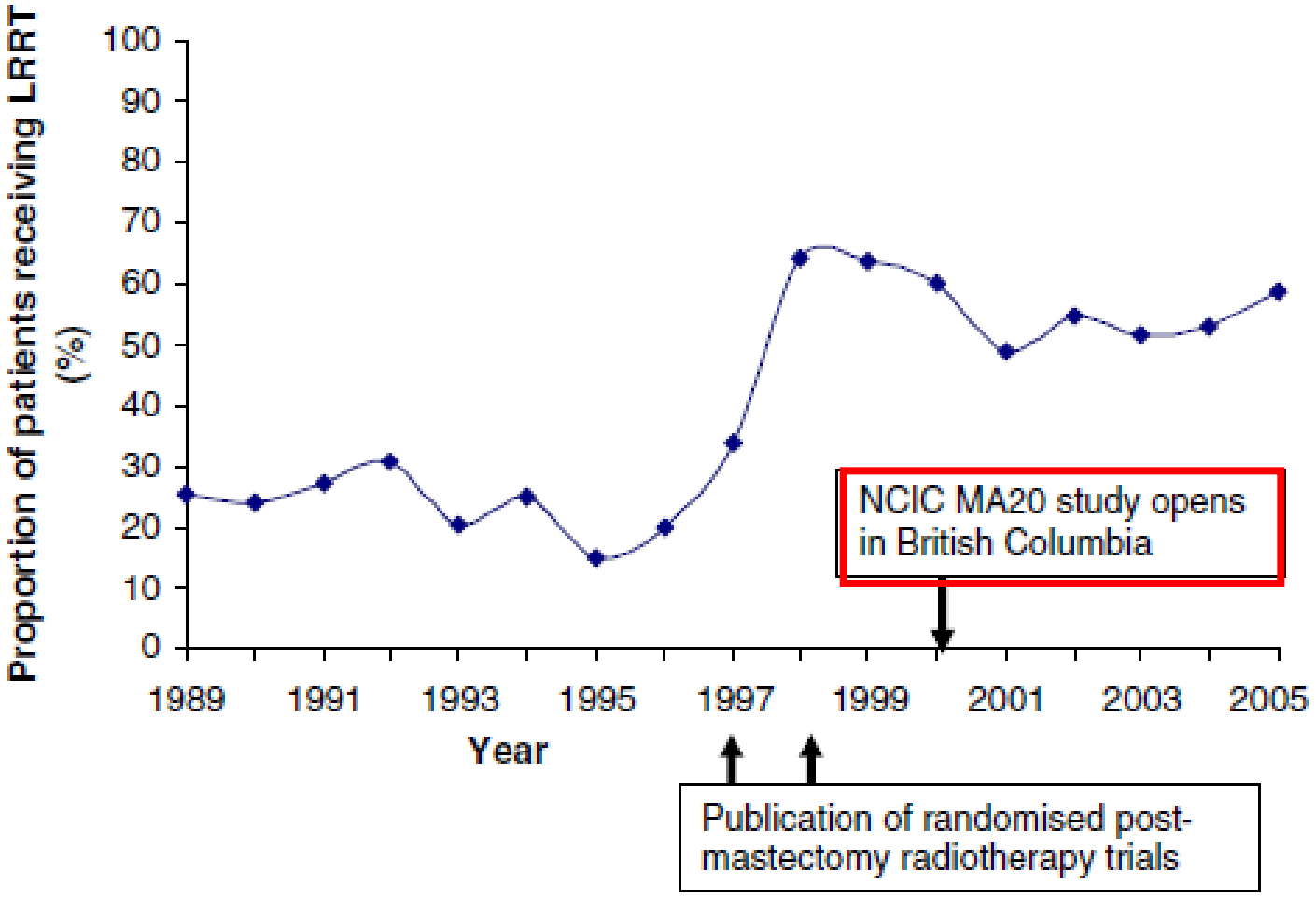
  * advanced primary tumors (T > 5 cm or invasion of skin, pectoral muscle or chest wall)

  * high volume nodal burden: ≥4 +ve nodes; large, matted nodes; extranodal extension

- Recognized controversy and need for further study among women with 1-3 +ve nodes and/or women treated with BCS

ASTRO: Harris IJROBP 2001
ASCO: Recht JCO 2003
Canadian CPG: Truong CMAJ 2004

Trial Data Impacts Practice in BC



Wai E et al. Radiother Oncol 2010

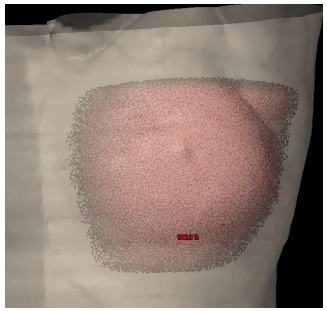
NCIC MA20 Trial

1832
Node-positive or High-risk N0 after BCS + AxD

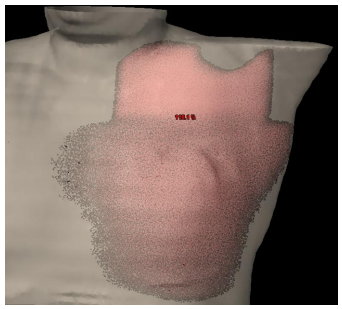
All had chemo and/or hormones

R

RT to Breast alone



RT to Breast + Nodes

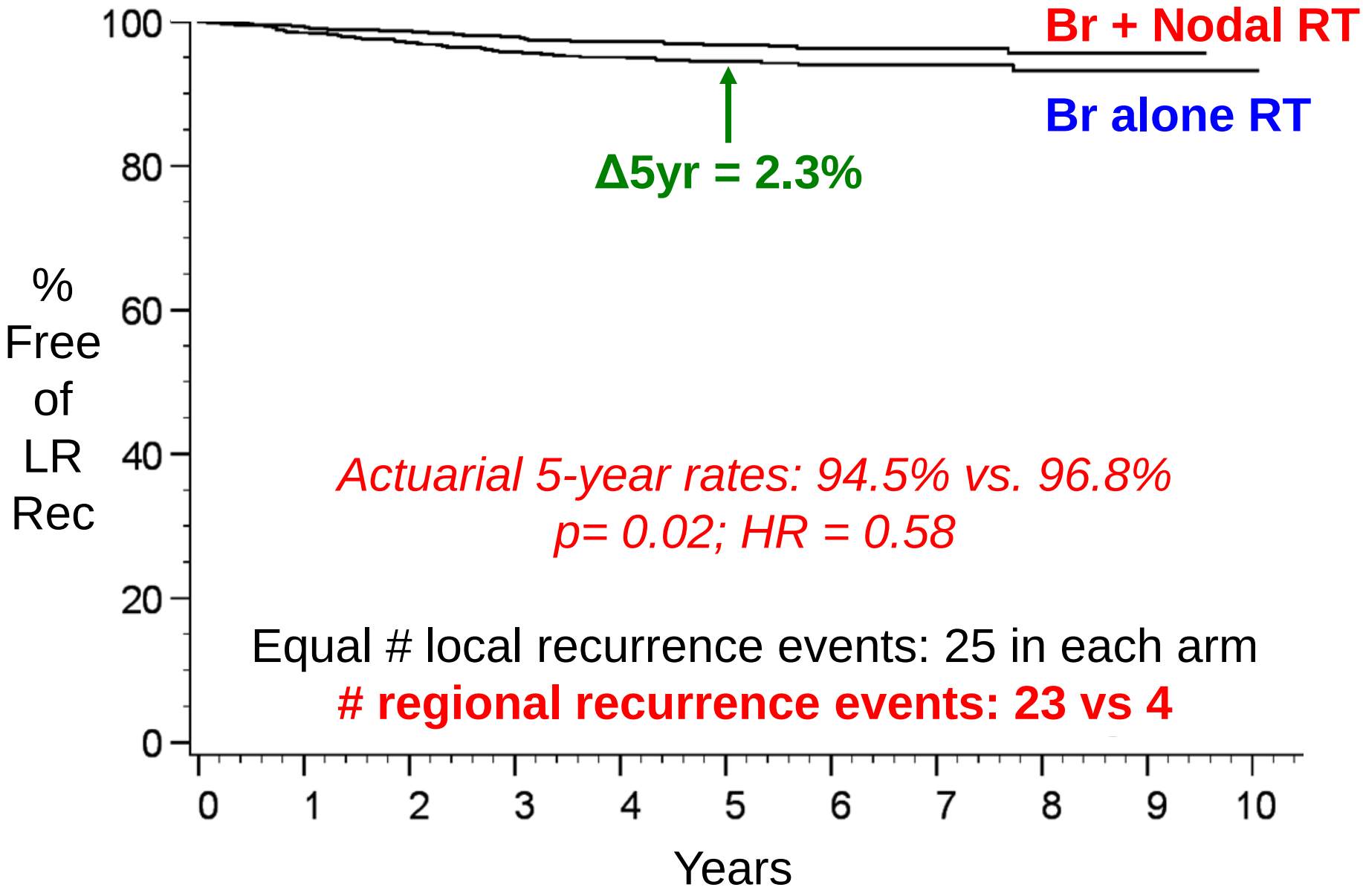


Whelan, Olivotto et al. Proc ASCO 2011; abs LB1

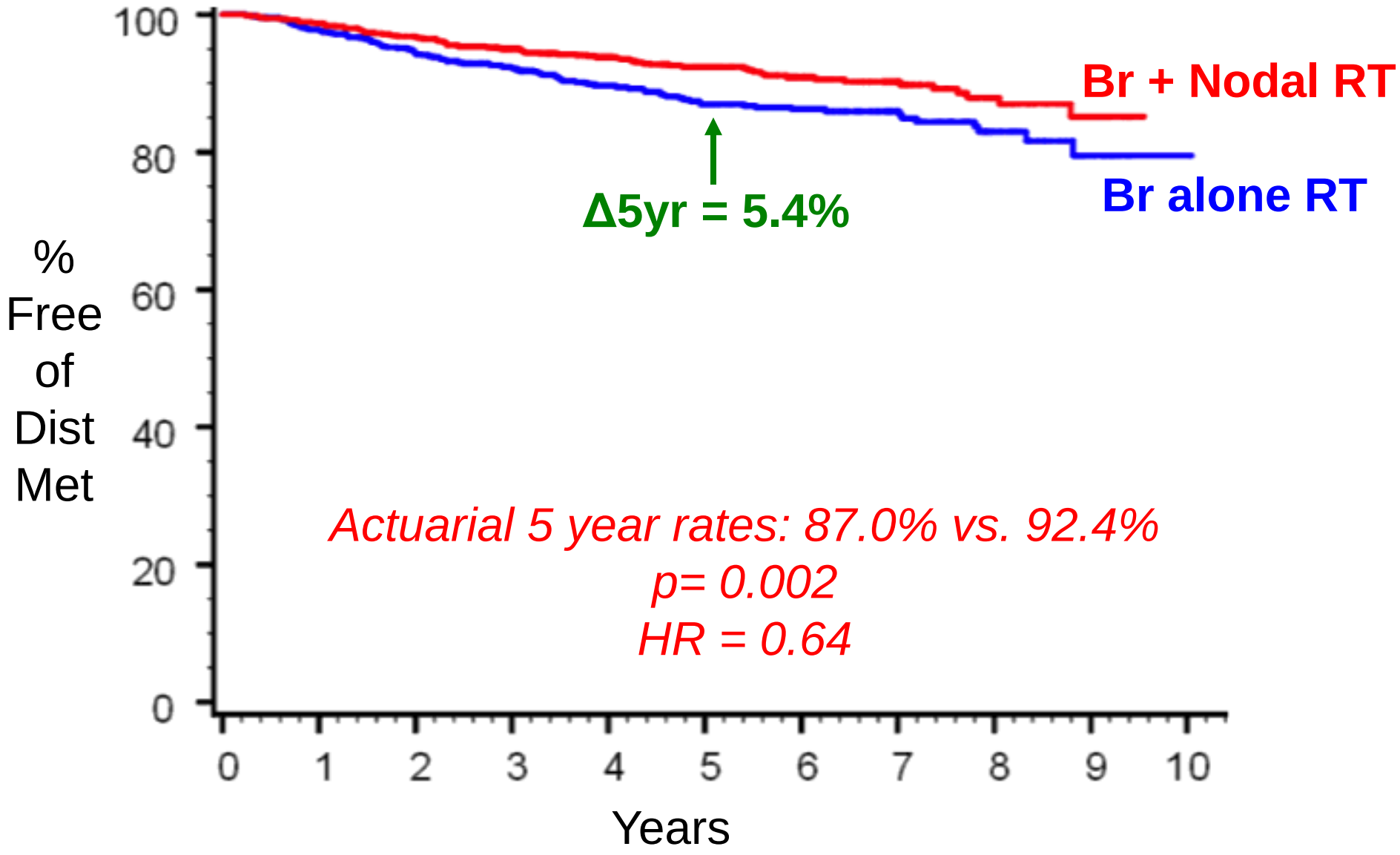
MA20 Baseline Characteristics: well balanced

	Br alone RT N=916 n (%)	Br+ Nodal RT N=916 n (%)
Age (mean yrs)	53	54
Axillary nodes removed (mean)	12	12
Node –ve	89 (10)	89 (10)
Nodes 1-3 +ve	780 (85)	776 (85)
Tumor size > 2 cm	416 (45)	457 (50)
Grade III	387 (42)	390(43)
ER –ve	235 (26)	232 (25)
Adj chemotherapy	829 (91)	830 (91)
Adj endocrine therapy	705 (77)	700 (76)
Boost RT	221 (24)	206 (22)

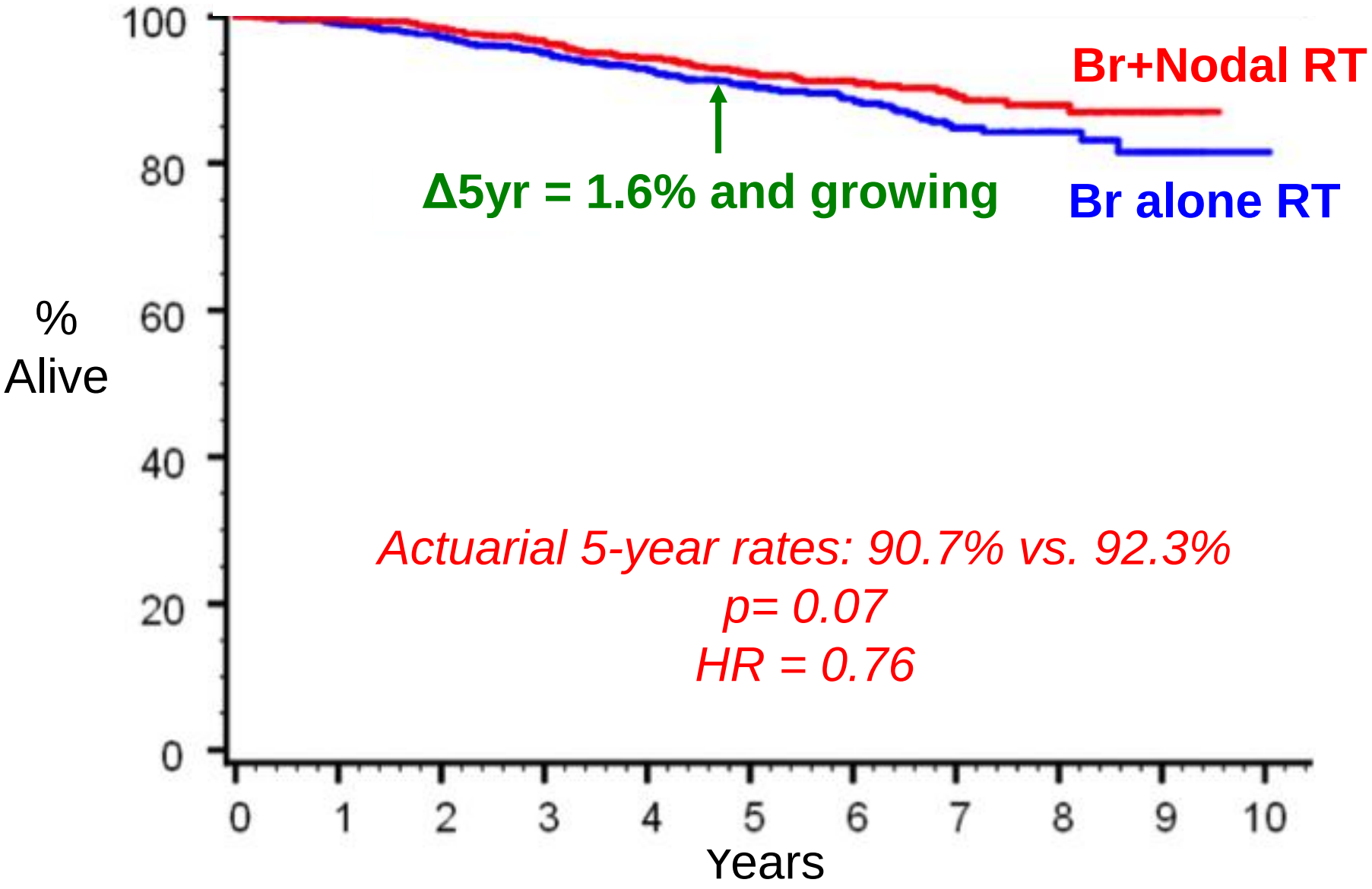
Isolated Loco-regional DFS



Distant Disease-Free Survival



Overall Survival



Adverse Events

(NCI – Common toxicity criteria v2.0, 1998)

	Br alone RT (n=927)				Br+ Nodal RT (n=893)				P Value
	Grade 2	Grade 3	Grade 4/5	Any (%)	Grade 2	Grade 3	Grade 4/5	Any (%)	
Acute									
RT dermatitis	349	23	-	372 (40)	397	45	-	442 (50)	< .001
Pneumonitis	2	-	-	2 **(0.2)**	12	-	-	12 **(1.3)**	.01
					Δ5yr = 1.1%				
Delayed									
Lymphedema	34	3	1	38 **(4.1)**	61	4	-	65 **(7.3)**	.004
					Δ5yr = 3.2%				

Patients and Assessors were not blinded to treatment allocation

MA20: Implications on Practice

- 85% of subjects were 1-3 N+ve
- Nodal RT added to Breast RT improved 5-yr
  - Loco-Regional RFS
  - Distant RFS
- Trend to improved Overall survival
- Nodal RT conferred small increased adverse effects, including pneumonitis (1%) and lymphedema (3%)

ACOSOG Z0011
Can Ax Dissection be Omitted in Selected Pts with 1-2 +ve SLN?

- Randomized 891 pts with cT1-2 tumor with H&E-positive SLNs to AxD vs no further axillary surgery
- 40% had micrometastasis or isolated tumor cells
- In AxD group, 27% had additional metastasis
- All pts received whole breast RT (possible inclusion of level I/II axilla)
- Trial closed early before reaching targeted 1900 pts
- At 6 years: no Δ in axillary recurrence, LRR, DFS and OS

Giuliano JAMA 2011

ACOSOG Z0011 has changed practice in BC

- AxD no longer routinely performed in pts who meet all criteria of:
  - T1-2 tumors
  - 1-2 positive SLNs without extranodal ext
  - acceptance of adjuvant RT

- Cases in which Z0011 results are not directly applicable (eg. T3 tumors, >2 positive SLN, extranodal disease, mastectomy) are discussed at multidisciplinary conference

What about ‘high risk N0’?

Defined in MA20 as:

– T ≥ 5 cm, or

– T ≥ 2 cm *and* < 10 nodes removed

with Gr 3 or LVI+ or ER –ve

Population-based outcomes in women with MA20-defined high-risk N0 breast cancer

- **BCCA Breast Cancer Outcomes Unit:**

- identified 11,865 women diagnosed 1989-2005, with pT1-3, 0-3 positive nodes, M0

- All had BCS + adjuvant breast RT

- Of 9201 pN0 cases, 550 (6%) met MA20-defined high-risk N0 criteria.

Truong CARO 2012

Results

- Nodal RT use
  - 1% in ‘non high risk N0’,
  - 5% in ‘MA20-defined high risk N0’
  - 44% in 1-3 N+

- Systemic therapy: 51%, 79% and 95% of the three cohorts ($p<0.001$)

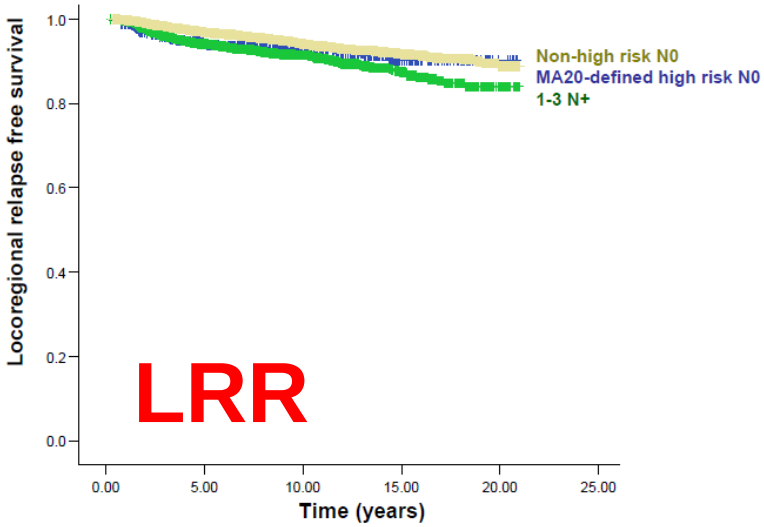
- Multivariable analysis of N0 subjects:

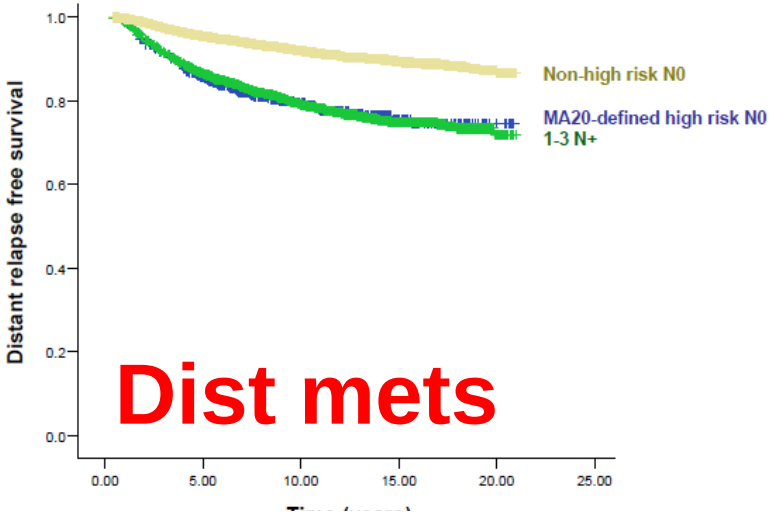
significantly increased regional and distant relapse with:

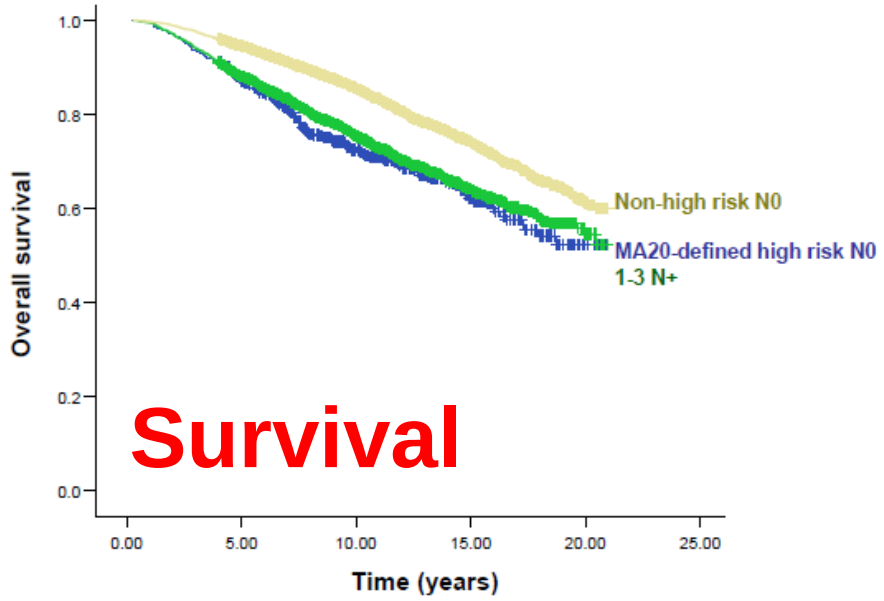
- T>2cm
- Grade 3
- LVI

Truong CARO 2012

10-year outcomes in ‘high risk N0’ similar to 1-3N+

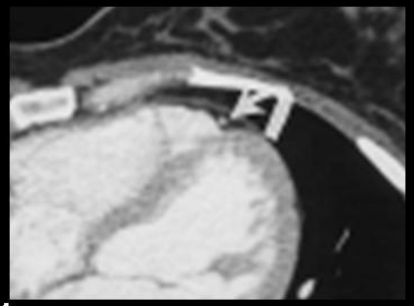




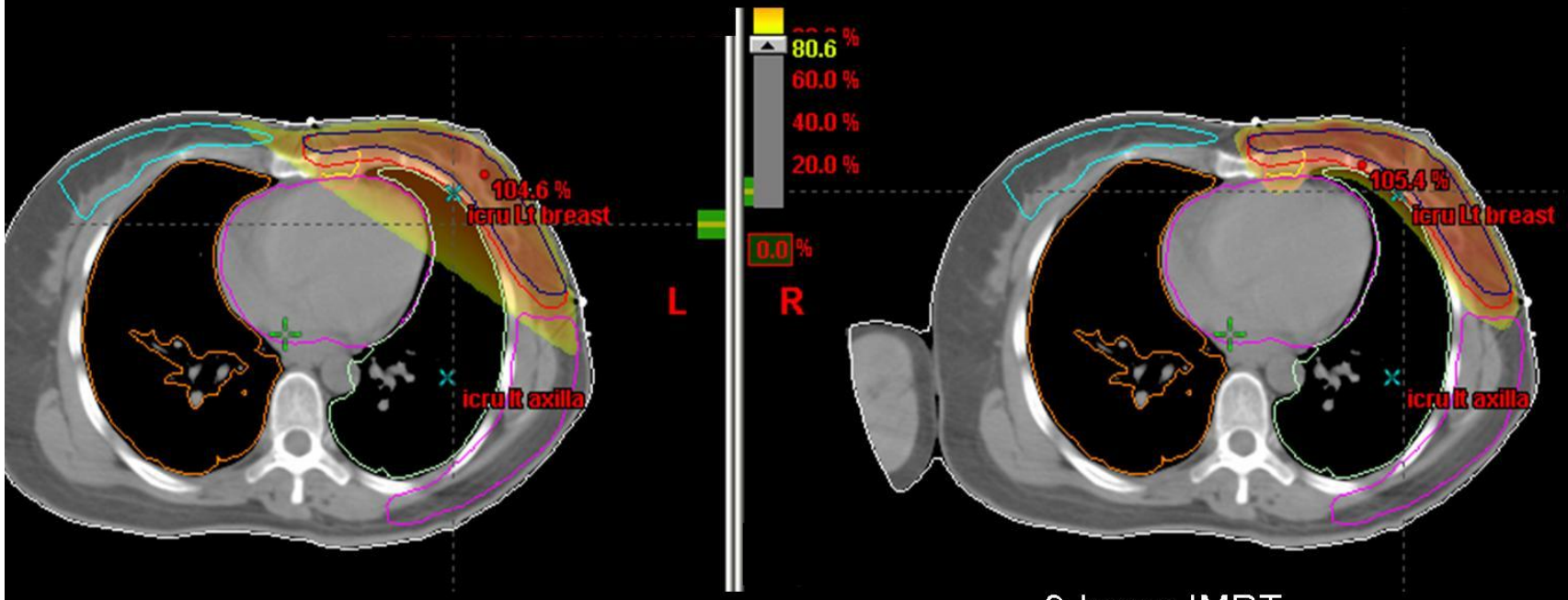


What strategies to spare heart & lung?

9-Beam IMRT reduced heart V30Gy, Lung V20 and mean dose to Healthy Tissue



Colorwash shows volume receiving ***>80%*** *of prescribed dose*

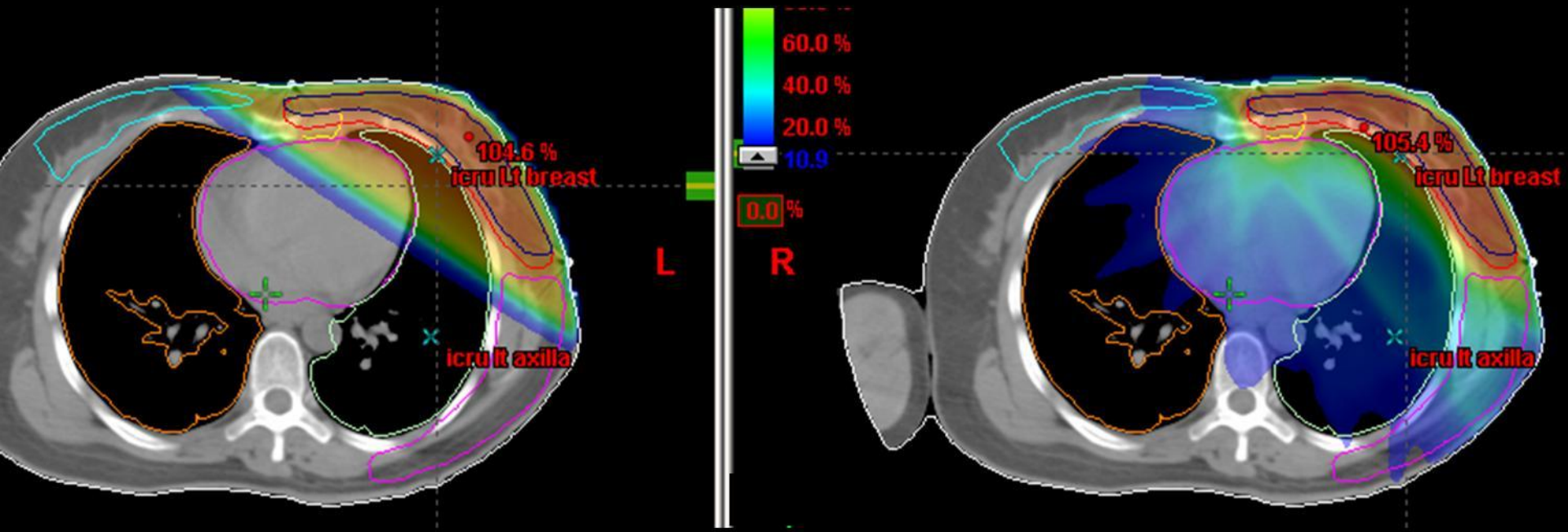


Modified-Wide Tangent

9-beam IMRT

IMRT increased volume of heart and other healthy tissues receiving 2-5Gy

Colorwash shows volume receiving >10% of prescribed dose

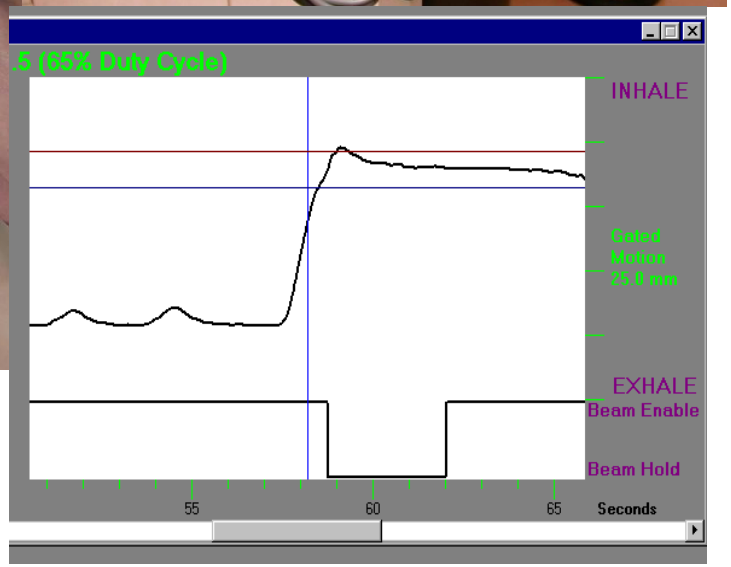


Modified-Wide Tangent

9-beam IMRT

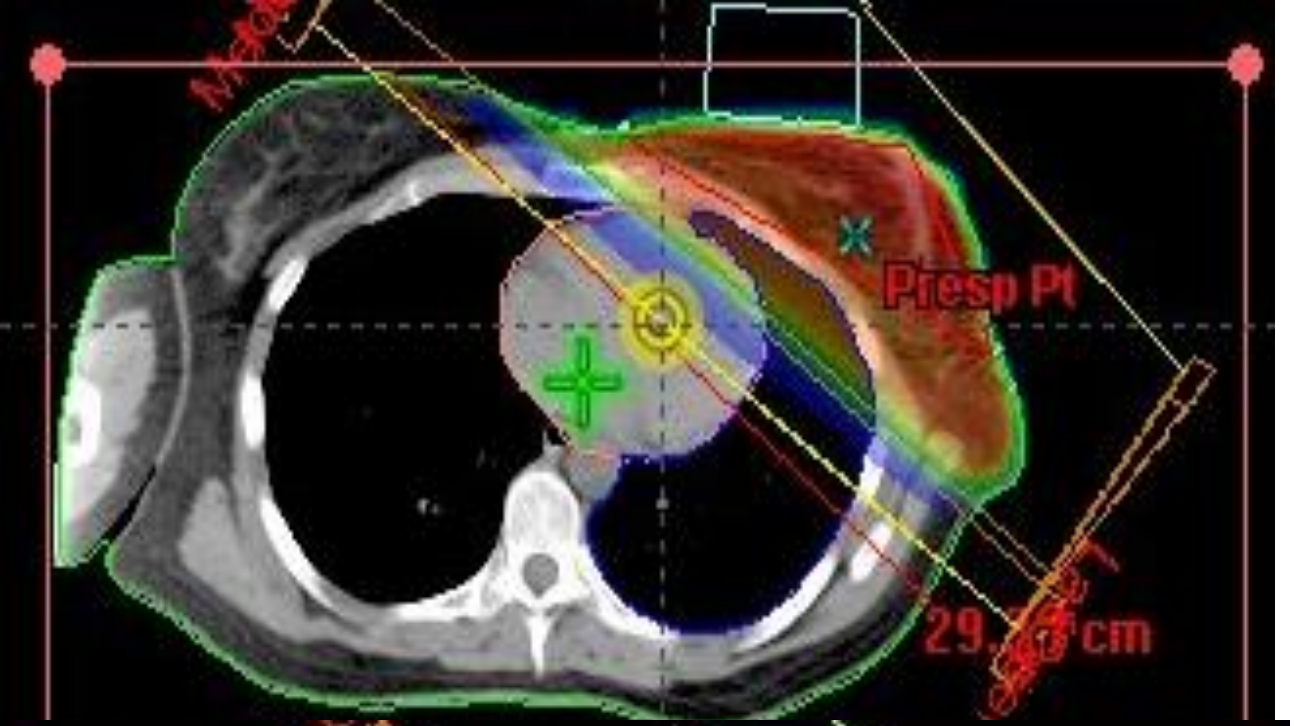
Beckham W. IJROBP 2007

Deep Inspiration Breath Hold

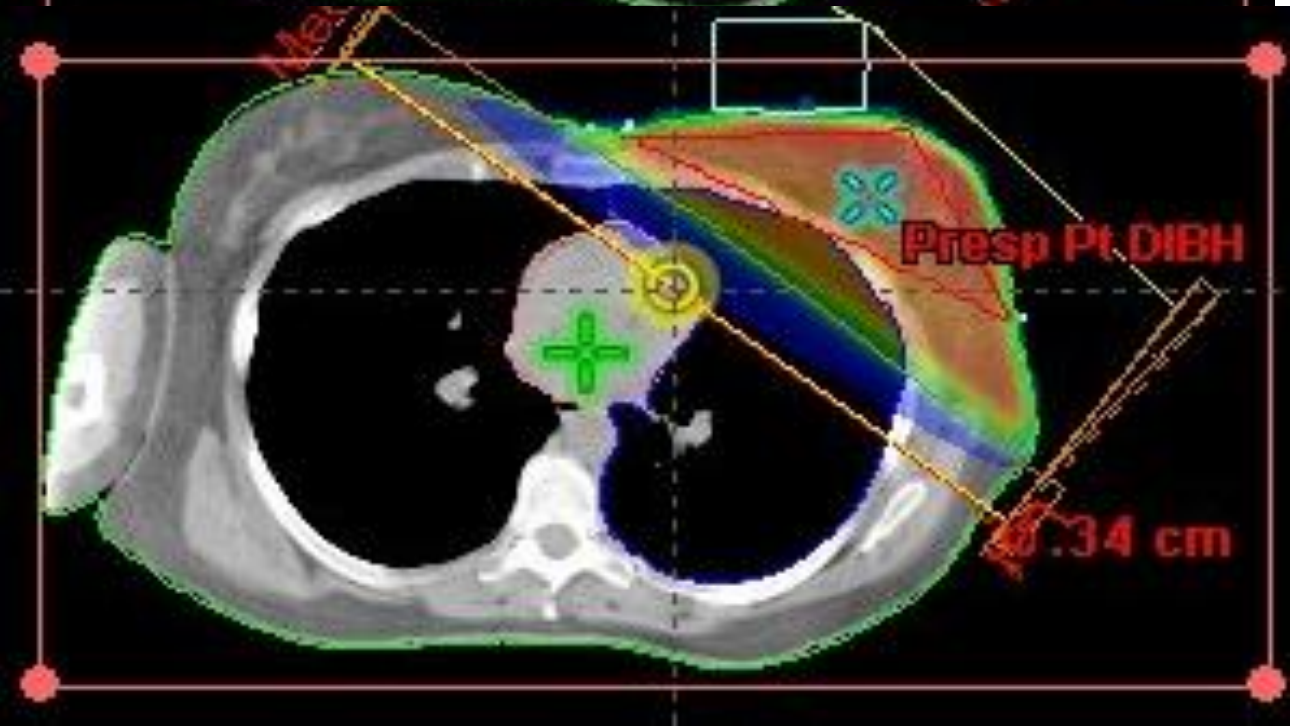


Varian RPM Gating System

Wai et al. IJROBP 2008



Free Breathing



Deep Inspiration Breath Hold

Summary
When to consider nodal RT after BCS?

- All women with node +ve disease should be offered the option of Nodal RT after BCS, especially if no AxD after positive SLNB.

- Women with node –ve disease meeting high risk criteria of T>5cm or T>2cm, <10 nodes removed, with grade 3, or LVI, or ER-ve disease are a small minority of N0 patients who warrant similar RT consideration as women with 1-3N+

Summary
When to consider nodal RT after BCS?

- Patients should be informed of the potential benefits and be willing to accept potential toxicities with added nodal RT.

- Care team should apply careful RT planning to ensure adequate coverage of regions at risk and to minimize normal tissue exposure, esp cardiac/pulmonary structures.

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‘Less’ radiation post breast conserving surgery?

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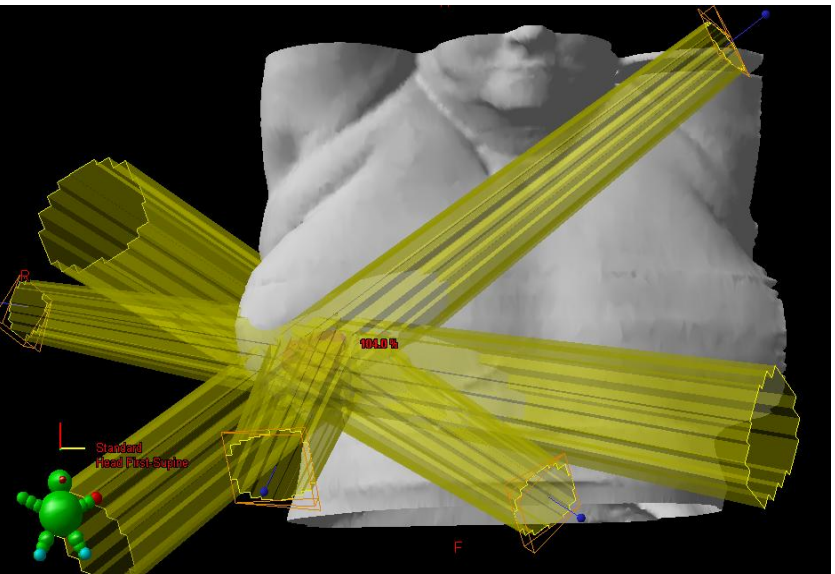
Radiation Oncologist, BCCA – Vancouver Island Centre
Clinical Assistant Professor, UBC



Goals of Breast Conservation

- Don’t compromise outcome
- Optimize cosmesis
- Optimize patient convenience/QOL

Partial Breast Irradiation (PBI)

- RT to smaller volume of breast
- Higher dose per day
- Shorter time/ more convenient

Low Risk Women Post BCS

- age >40
- ≤ 3cm tumours
- margin negative
- node negative
- LVI negative

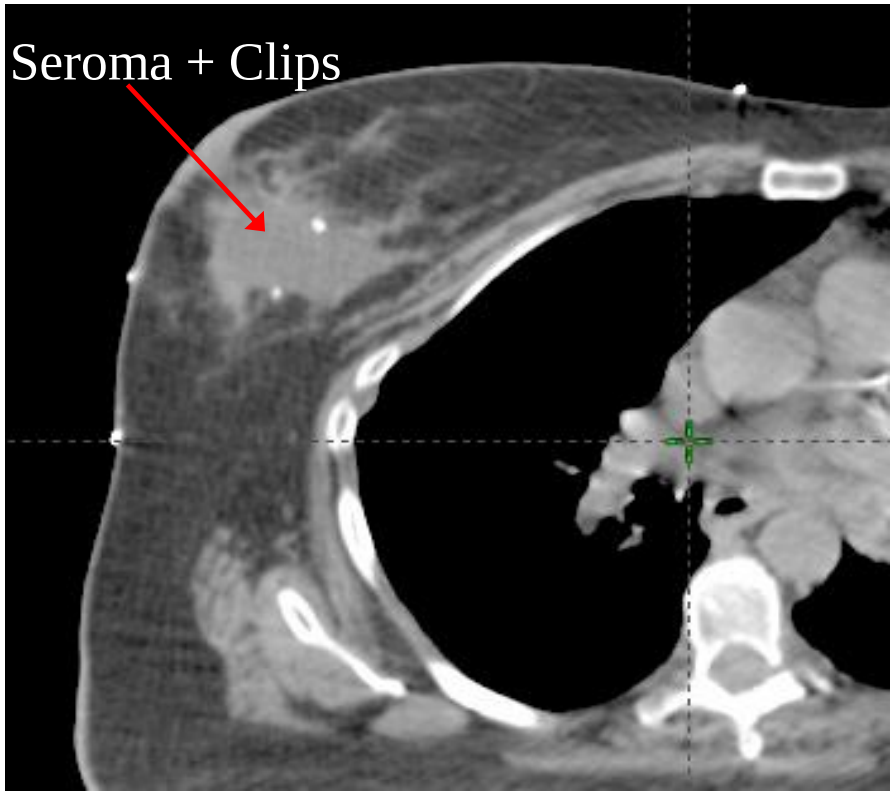
What do we need to worry about?

1. Where is the risk of recurrence?

2. Normal tissue tolerance to RT

Local Recurrence post BCS

- 70 - 80% close to the primary tumour bed or ‘seroma’
- Do we need to treat the whole breast?

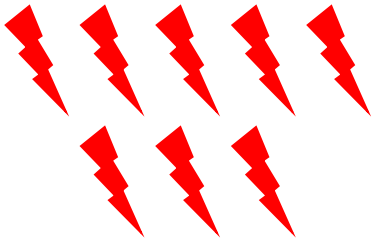


Cancer Control

- High dose/fraction

Normal Tissue Toxicity

- Low dose/fraction



Whole Breast RT

25+ fractions 

16 fractions 

Whole Breast RT

25+ fractions 

16 fractions 

<16 fractions 

Whole Breast RT

25+ fractions 

↓

16 fractions 

↓

<16 fractions 

↓

Partial Breast <16 fractions?

Whole Breast RT

25+ fractions 

↓

16 fractions 

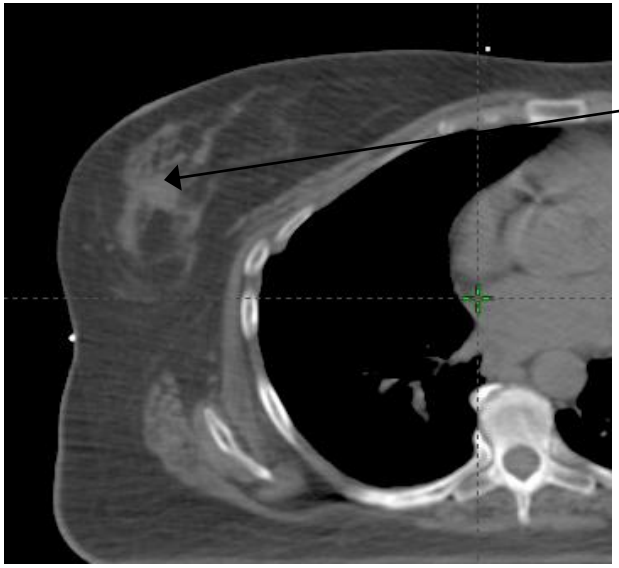
↓

<16 fractions 

↓

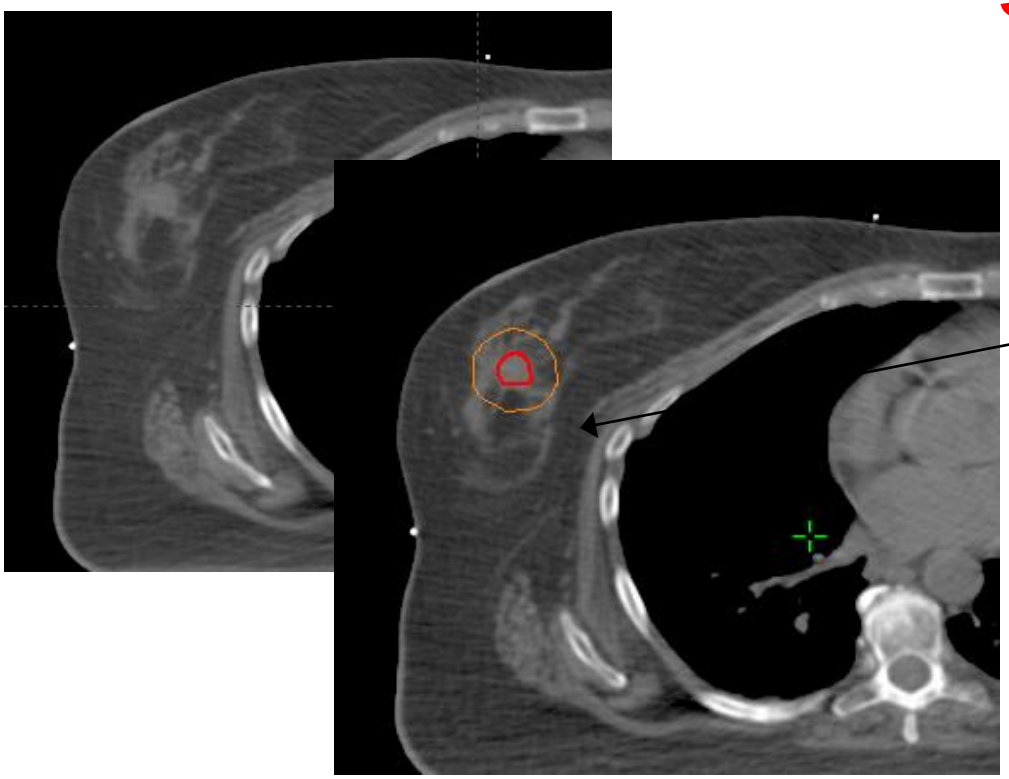
Partial Breast <16 fractions?
(10 fractions in 5 days)

What is the target for PBI?



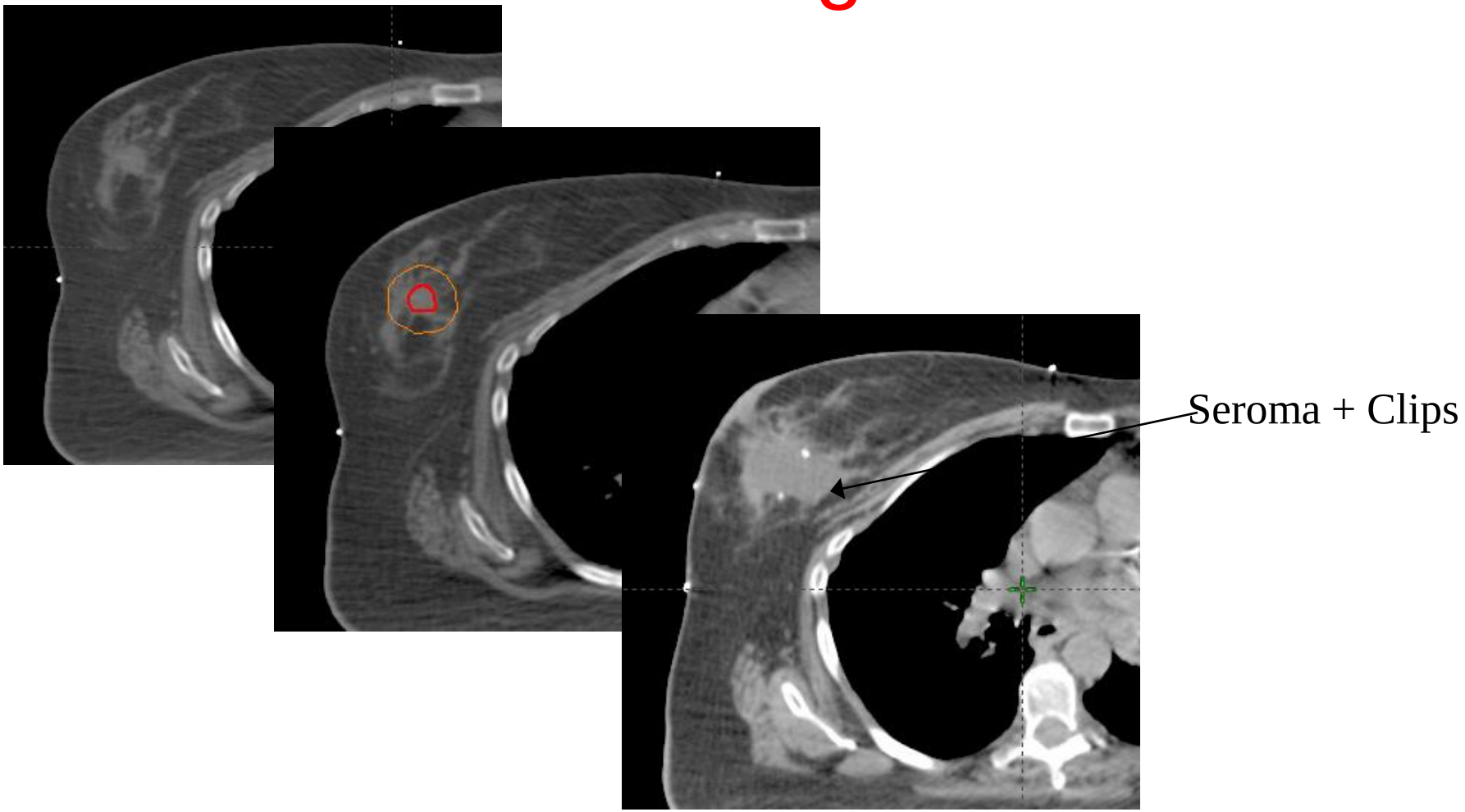
Pre-op tumour location

What is the target for PBI?

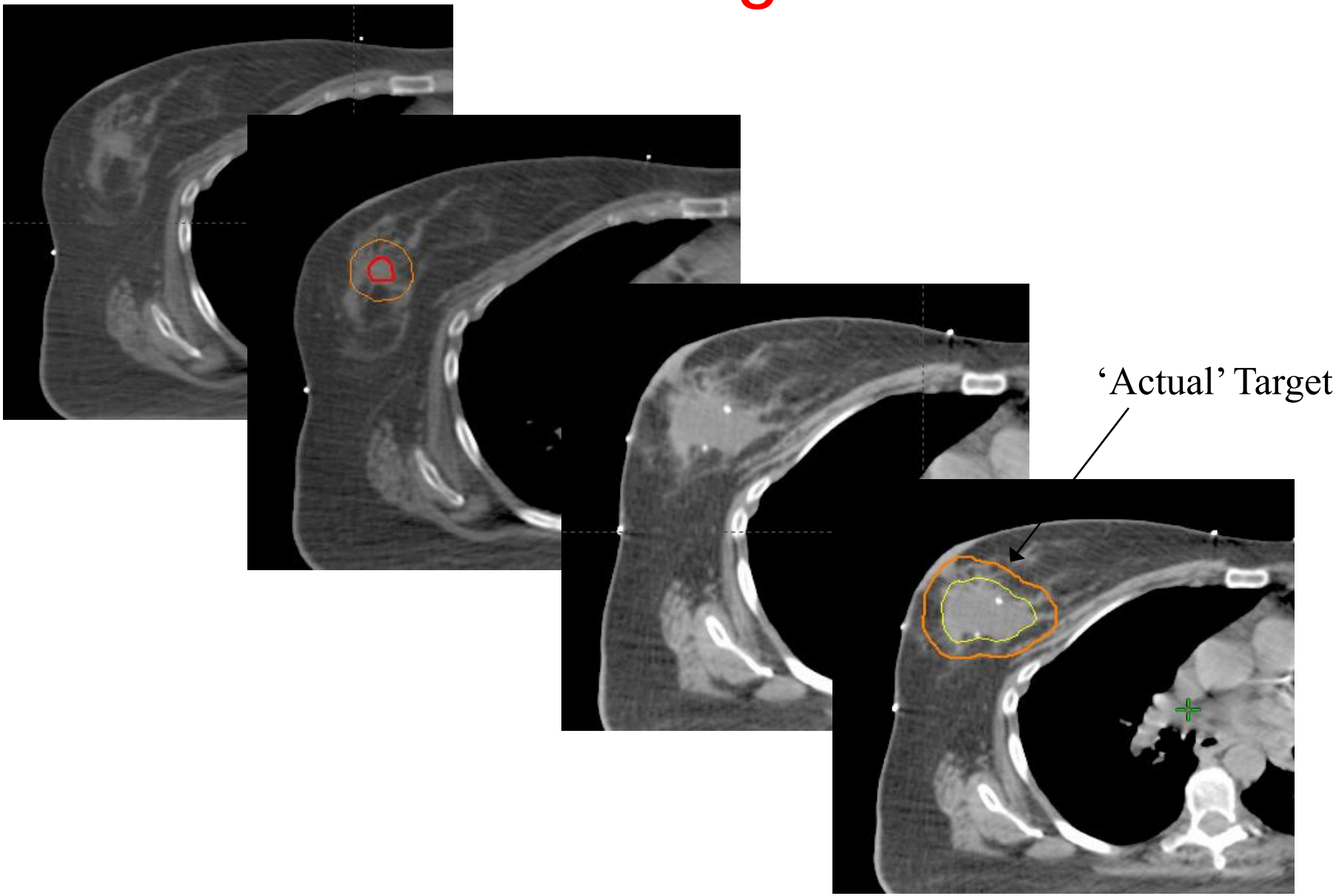


‘Ideal’ Target

What is the target for PBI?

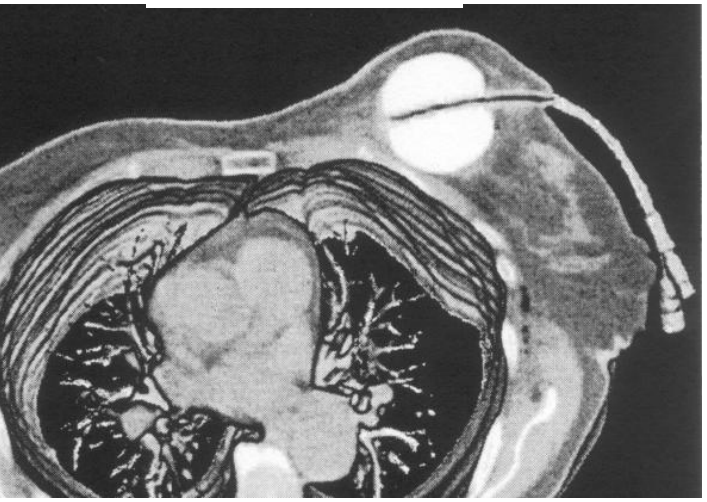


What is the target for PBI?

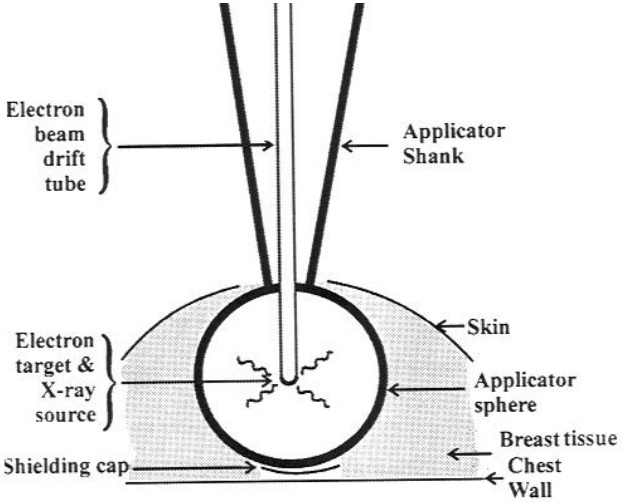


Various Techniques for PBI

Mammosite



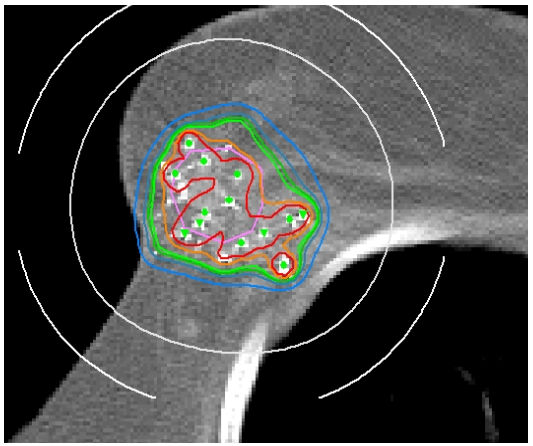
Intra-op 50Kv, *(Targit)*



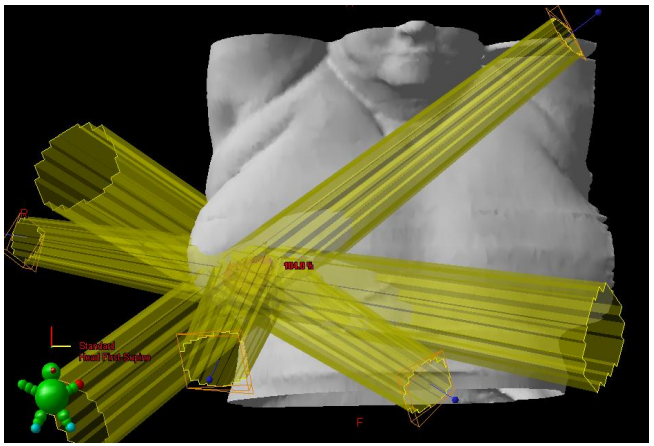
Intra-op electrons *(Milan)*

HDR Brachytherapy

Permanent Seed Brachytherapy

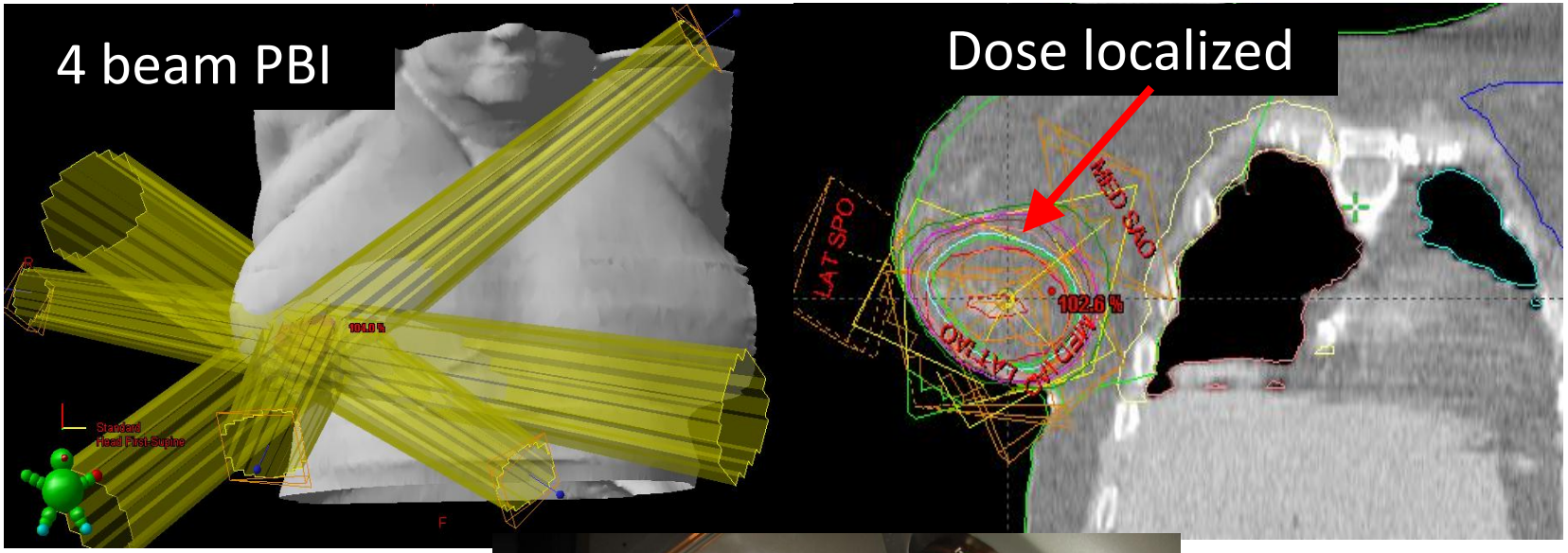


3D Conformal Photons



3D conformal Partial Breast

Most commonly used because techniques and resources are available in most RT departments



Whole vs. Partial Breast RT

- 3.5 to 5+ weeks
- 42.5-50 Gy
- Once daily treatment
- 2 beams
- Target = whole breast

- 5 to 8 days
- 38.5 Gy
- Twice a day
- 3-5 beams
- Target = seroma + margin

Canadian Pilot Study

- 120 women prospectively accrued (2005-2006)
- Low risk
  - Node negative
  - Invasive or DCIS ≤ 3cm
  - Negative margins
- 5 Canadian centres
- External Beam PBI (3-5 fields)

104 women treated with PBI
3 year follow-up

- 97% DFS
- toxicity data (84% of patients)
  - Most toxicities were Grade 1
- Cosmesis was good to excellent in 86% at baseline and 82% at 3 years

Berrang et al. IJROBP 81(5) 1220:2011

PBI Trial Eligibility

RAPID

- Age ≥40 y
- T≤ 3 cm
- pN0
- not lobular histology

Completed accrual: 2135

NSABP B39

- Age ≥18 y
- T ≤ 3 cm
- pN0 and 1-3N+
- ductal and lobular

Target accrual: 4300

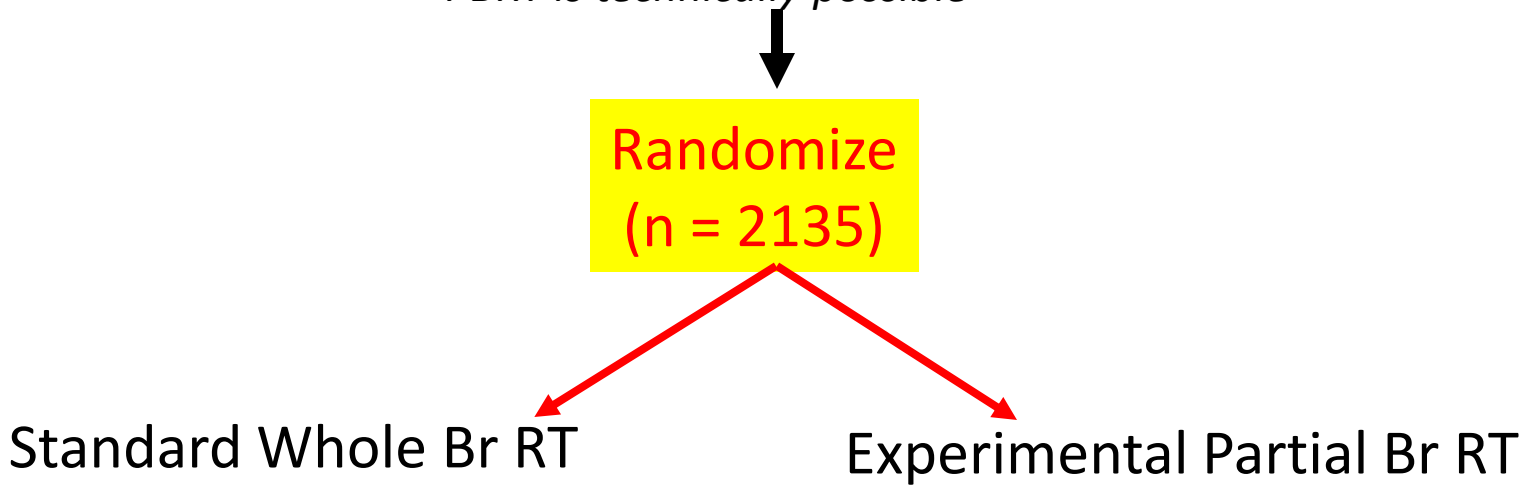
RAPID

Canadian RCT

April/06 to July/11

Eligible:

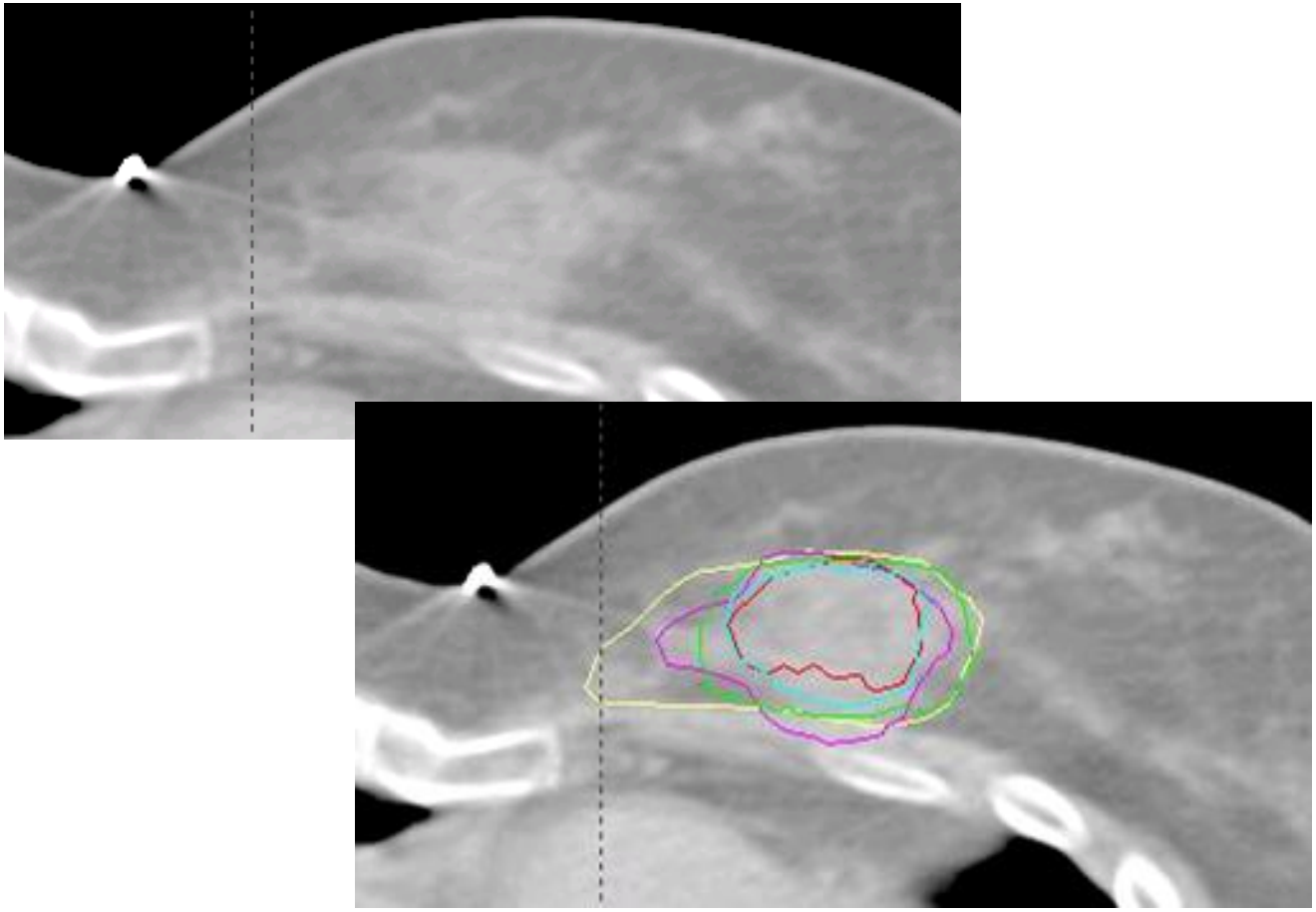
>40 years, pN0, not lobular, T<3cm, margins clear, not BRCA1-2+
PBRT is technically possible



<u>Outcomes:</u> LR, Cosmesis, Toxicity

Challenges of PBI

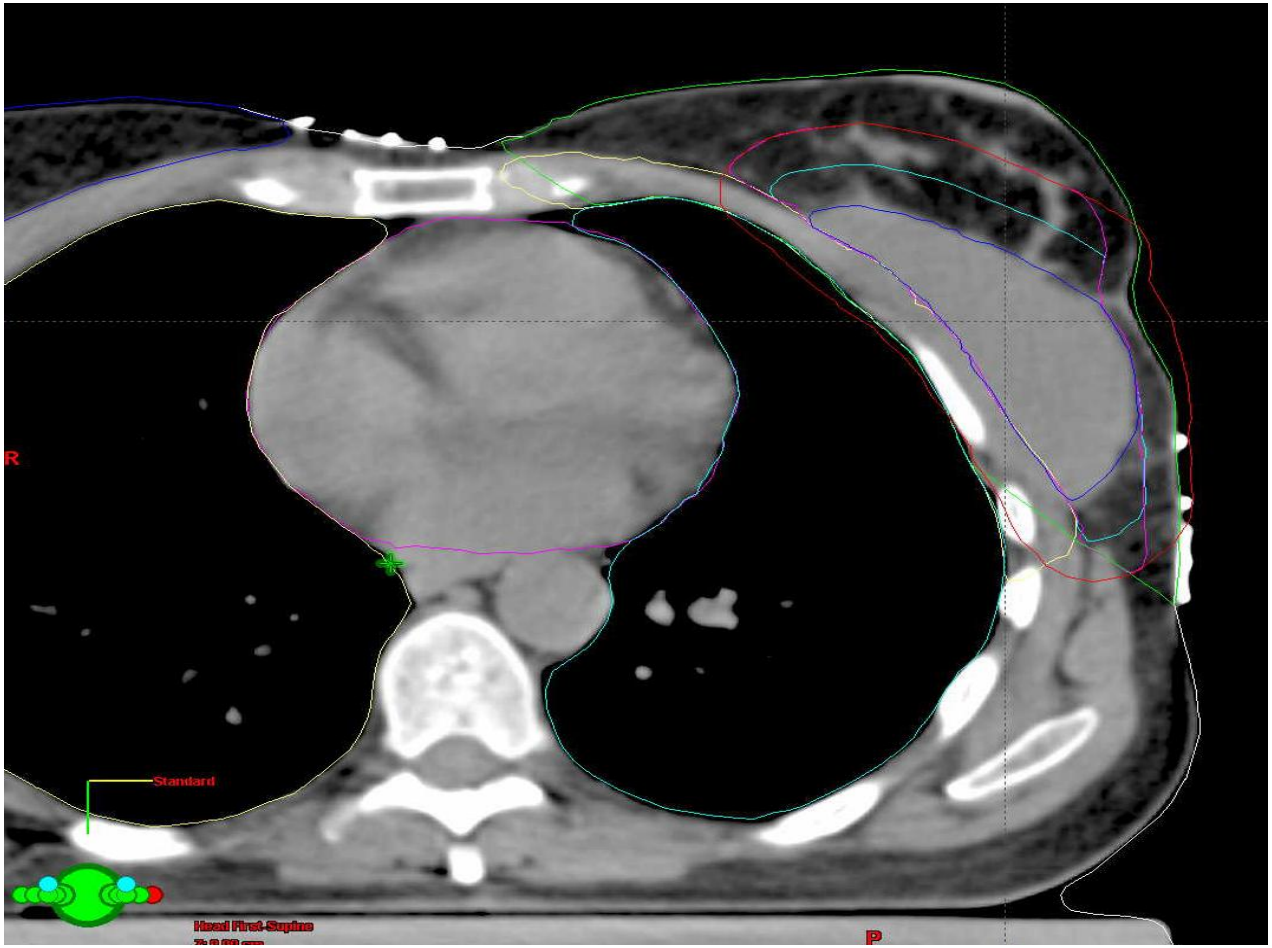
Agreeing on how to contour the Seroma



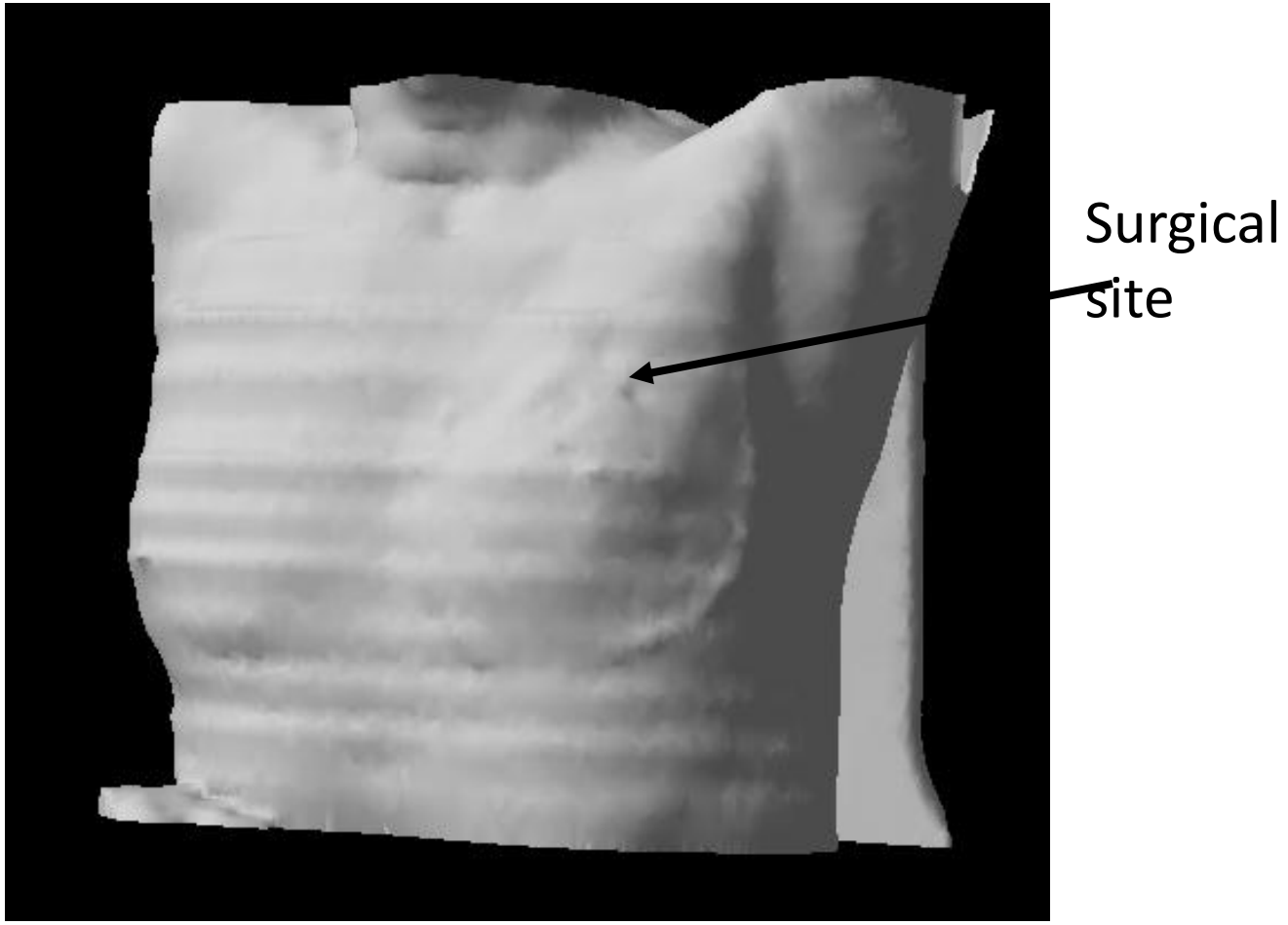
Guidelines and Training reduced inter-observer variation.

Wong E et al. IJROBP 2006:66:372-6

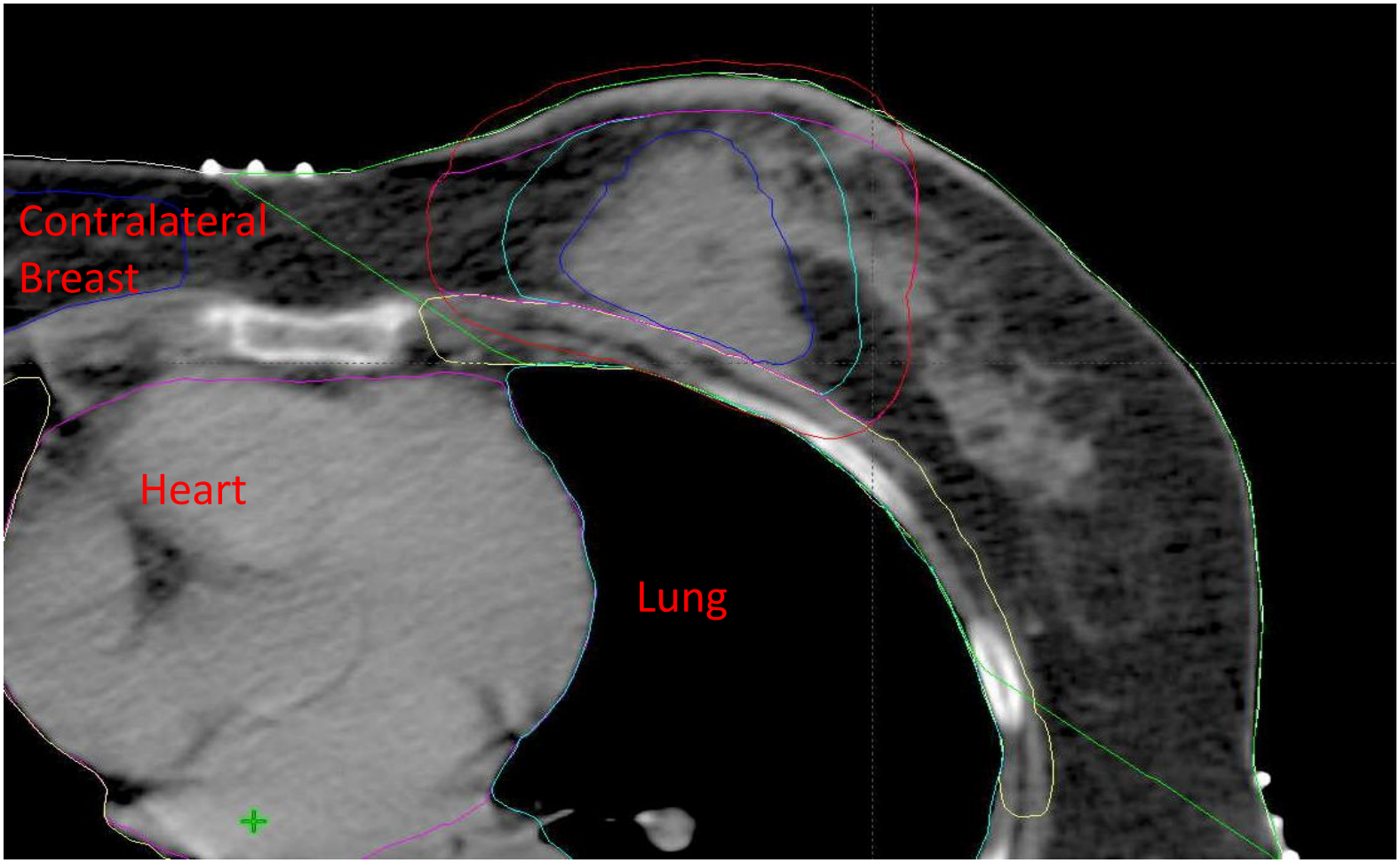
Large Seroma



Small Breast



Limiting RT to Normal Tissues



PBI Summary

- Low risk women post BCS
- Larger fraction size to part of the breast
- Complete RT in ≤ 1 week

↑ convenience

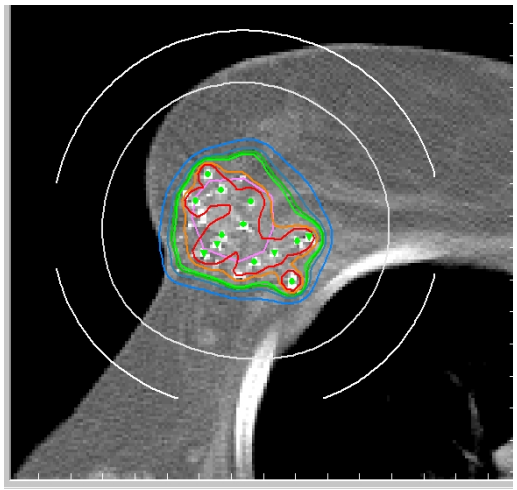
cosmesis, toxicity & recurrence?

Status of PBI in BC

- Awaiting results of RAPID
- Not generally available in BC off study
- Current pilot study

Current BCCA Study

- 2012
- Permanent seed brachy for PBI
  - CSI 3/5 patients
  - VIC 3/5 patients
  - Feasibility and resource allocation



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Not At All?

Identification of Patients at Very Low Risk of Local Recurrence after Breast Conserving Surgery

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Clinical Assistant Professor, UBC

Background

- Breast conserving surgery (BCS) + whole breast RT is current standard of care for women with early breast ca
- Consistent 2/3 reduction in local recurrence (LR) with RT
- Absolute risk reduction varies according to clinical-pathologic characteristics
- RT is inconvenient, costly, and has acute and late adverse effects, some impacting QOL (breast pain, fatigue, fibrosis, cosmesis) and some life threatening (lung/heart injury, RT-induced malignancy)

- Could some women safely avoid RT?
- Can we identify them?

RCT Data

Toronto/BC

769 women aged ≥50, pT1-2, N0 breast ca randomized to tamoxifen alone versus tamoxifen + breast RT.

5 year LR **7.7%** with tam alone vs **0.6%** with tam + RT (p=0.001)
10 year LR **13.8%** with tam alone vs **5%** with tam + RT (p=0.001)

CALGB 9343

603 women aged ≥70, pT1 (<2cm), ER+ breast ca randomized to tamoxifen alone versus tamoxifen + breast RT.

5 year LR **4%** with tam alone vs **1%** with tam + RT (p<0.001)
10 year LR **8%** with tam alone vs. **2%** with tam + RT (p<0.015)

Fyles et al. NEJM 2004
Hughes et al. NEJM 2004

Meta analysis of RT post BCS : 10 801 women in 17 randomized trials

5 yr risk of local or distant recurrence: absolute reduction with addition of breast RT after BCS in node negative women

	Absolute reduction in 5-year risk of recurrence with radiothera														
	Low grade					Intermediate grade					High grade				
	Age (years)					Age (years)					Age (years)				
	<40	40	50	60	70+	<40	40	50	60	70+	<40	40	50	60	70+
T1 (1-20mm) tumours															
Lumpectomy, ER+tam-	17	14	12	9	7	34	32	27	23	18	59	59	53	46	38
Lumpectomy, ER-poor	5	5	4	3	2	11	11	9	7	6	25	24	20	17	14
>Lumpectomy, ER+tam- or ER-poor*	6	5	4	3	3	13	13	11	9	7	29	28	24	20	16
Lumpectomy, ER+tam+	5	4	3	3	2	13	11	9	7	5	28	24	20	16	13

Why ask the question again?

New information on intrinsic subtypes

Voduc et al.

- 1271 pts treated with BCS + RT
- Identified intrinsic subtype; luminal A (ER or PR positive, Her 2 negative, Ki67 <14%) best prognosis

Ontario/BC – retrospective analysis of a prospective trial

	10yr LR	
	Tam	Tam +RT
Luminal A (n=95)	6.9%	4.5%
Luminal A ≥60	5.4%	6%
Luminal B (n=74)	24%	0%
Her 2+ (n=24)	44%	0%

Voduc JCO 2010

Fyles Cancer Res 2011

Hypothesis

- it is possible to identify groups of patients with LR risk <5% without adjuvant whole breast RT or <1.5% with RT at 5 years

Methods

- Prospective cohort study thought to be best way to identify such a population

- Who to include??

BCOU Project Objectives

- to evaluate LR and LRR risks in women aged ≥ 50 years with stage I breast cancer treated with BCS +/- RT

- to determine clinical/pathologic factors associated with ‘very low’ 5-year LR risk:

<5% without breast RT

or

<1.5% with breast RT

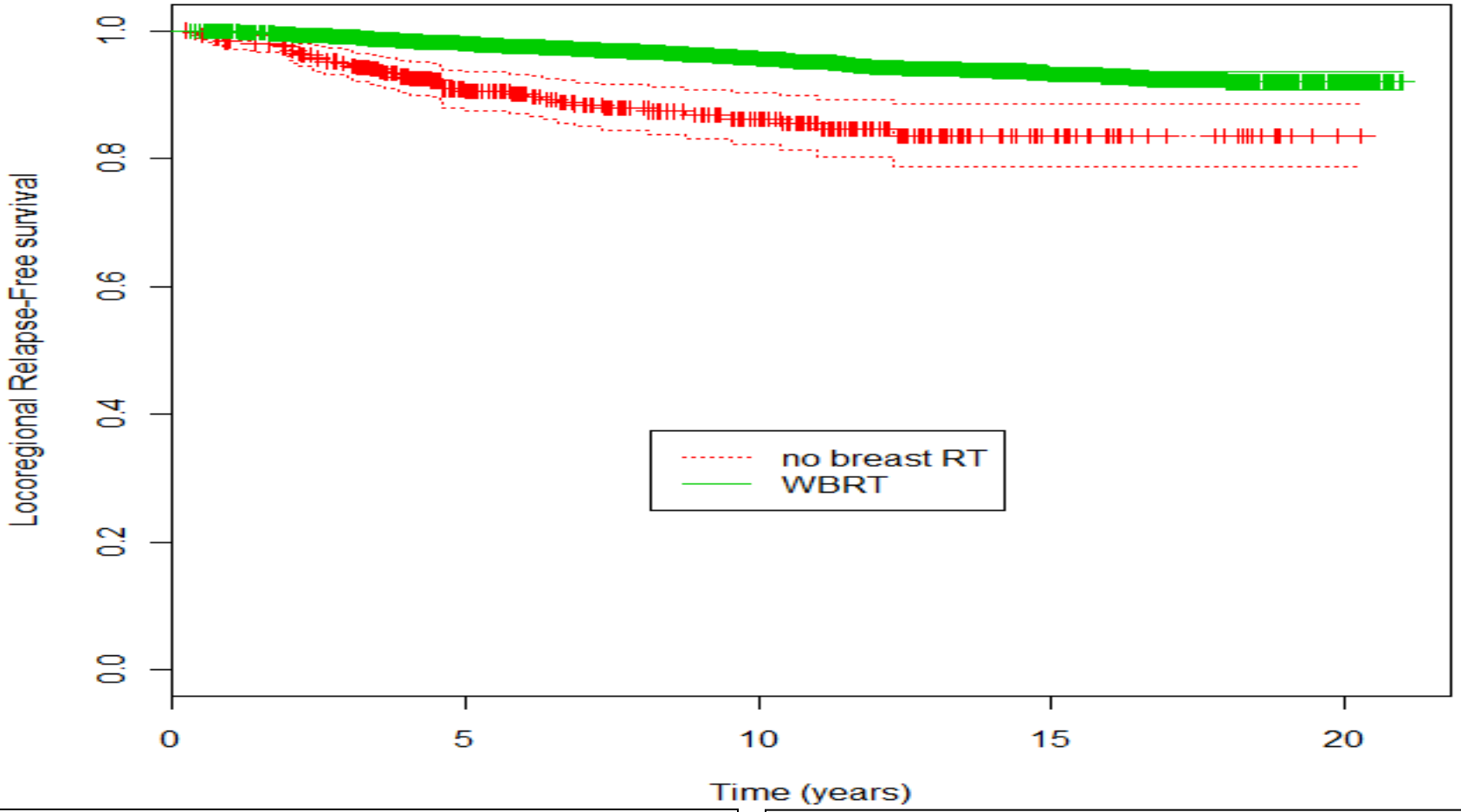
Methods

- BCCA BCOU identified women aged ≥50 yrs, referred 1989-2006, pathologic stage I (T≤2 cm, pN0) invasive breast ca
- All women had BCS +/- whole breast RT
- 5- and 10-year LR and LRR with and without RT examined using Kaplan-Meier methods
- Recursive Partitioning Analysis (RPA): to identify patients with LR risk <5% without RT or <1.5% with RT at 5 years

Clinico-pathologic Characteristics

	RT (N=5974)	No RT (N=431)	p
Median Age (yrs)	63 (50 – 91)	70 (50 – 89)	
Median T Size (cm)	1.2	1.1	
LVI	10%	7%	ns
Grade III	20%	17%	ns
Ductal Histology	92%	93%	ns
Margin Positive or close	7%	7%	ns
ER Positive	78%	81%	0.003
Endocrine Therapy	47%	44%	ns

KM LRR RT vs No RT



5-year LRR

No RT: 9.5% (n=253; 95% CI 6.5-12.5)

RT: 2.1% (n=4573; 95% CI 1.7-2.5)

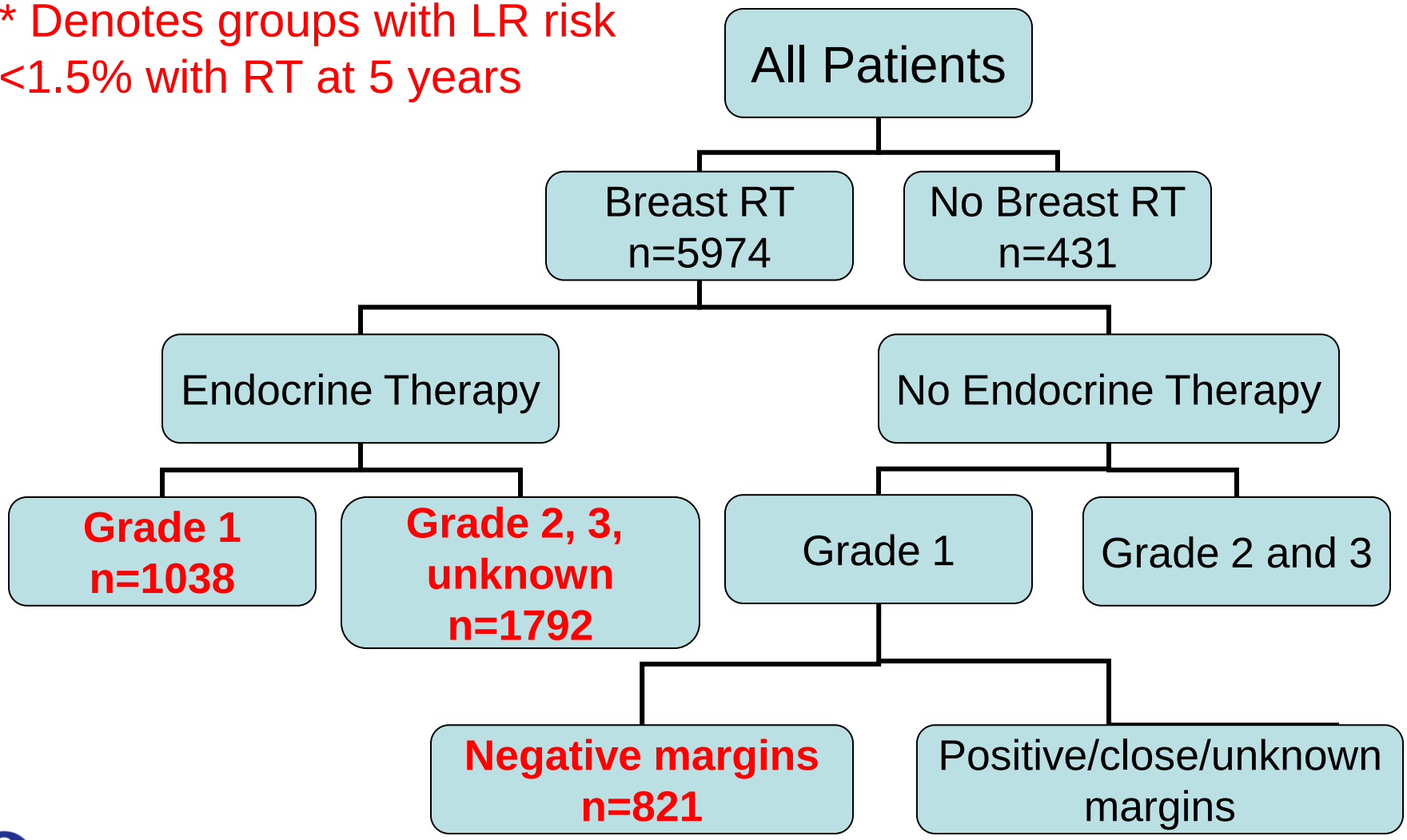
10-year LRR

No RT: 13.8% (n=133; 95% CI 9.7-17.7)

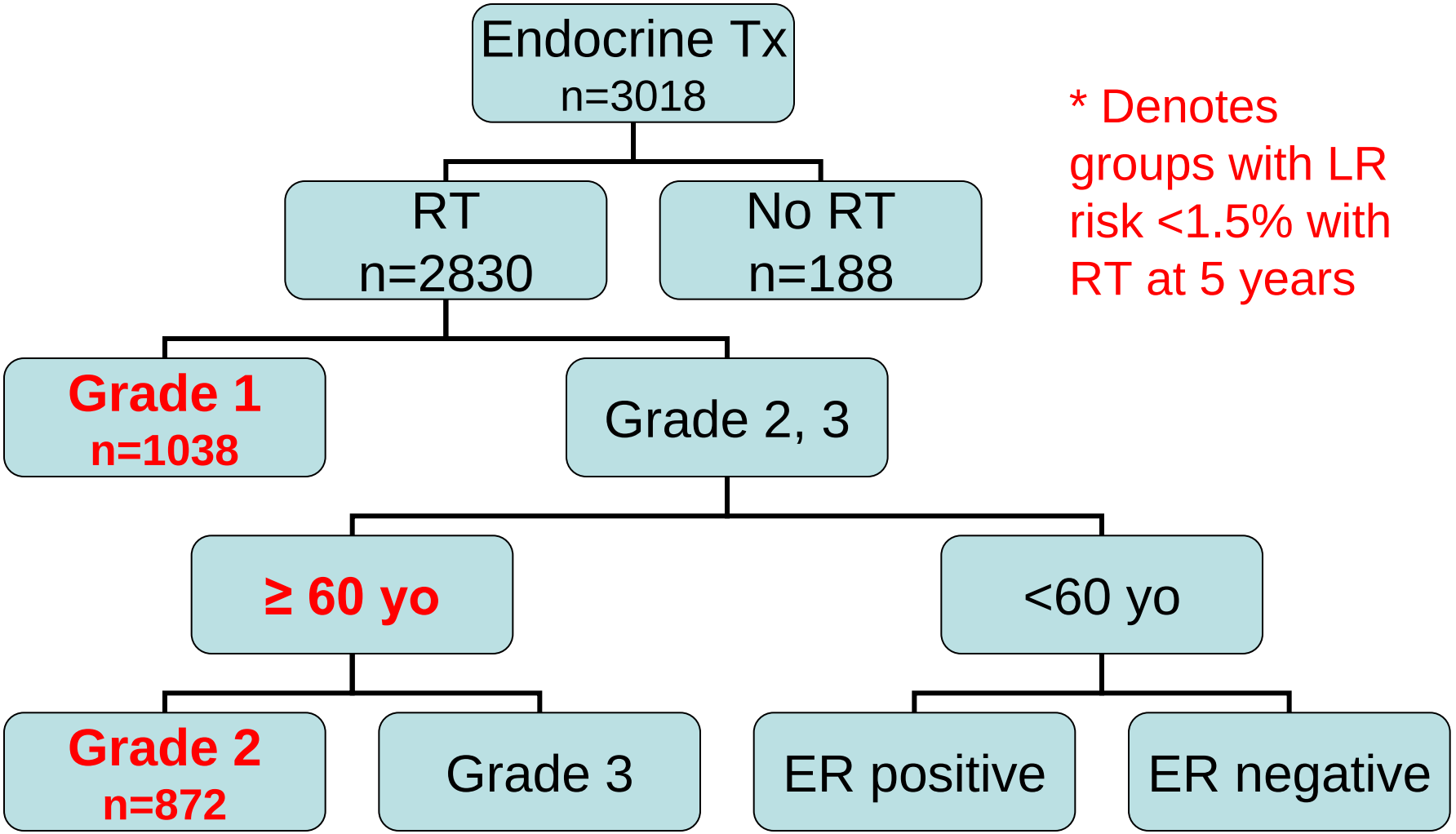
RT: 4.4% (n=2275; 95% CI 3.8-5.1)

RPA of Entire Cohort

* Denotes groups with LR risk <1.5% with RT at 5 years



RPA of LR – pts treated with endocrine tx



* Denotes groups with LR risk <1.5% with RT at 5 years

In patients treated with endocrine tx, subsets with LR ≤1.5% with RT:

- **Grade 1** (n=1038)

  LR 0.2% (95% CI 0.0-0.5) at 5 yrs

  LR 0.8% (95% CI 0.1-1.6) at 10 yrs

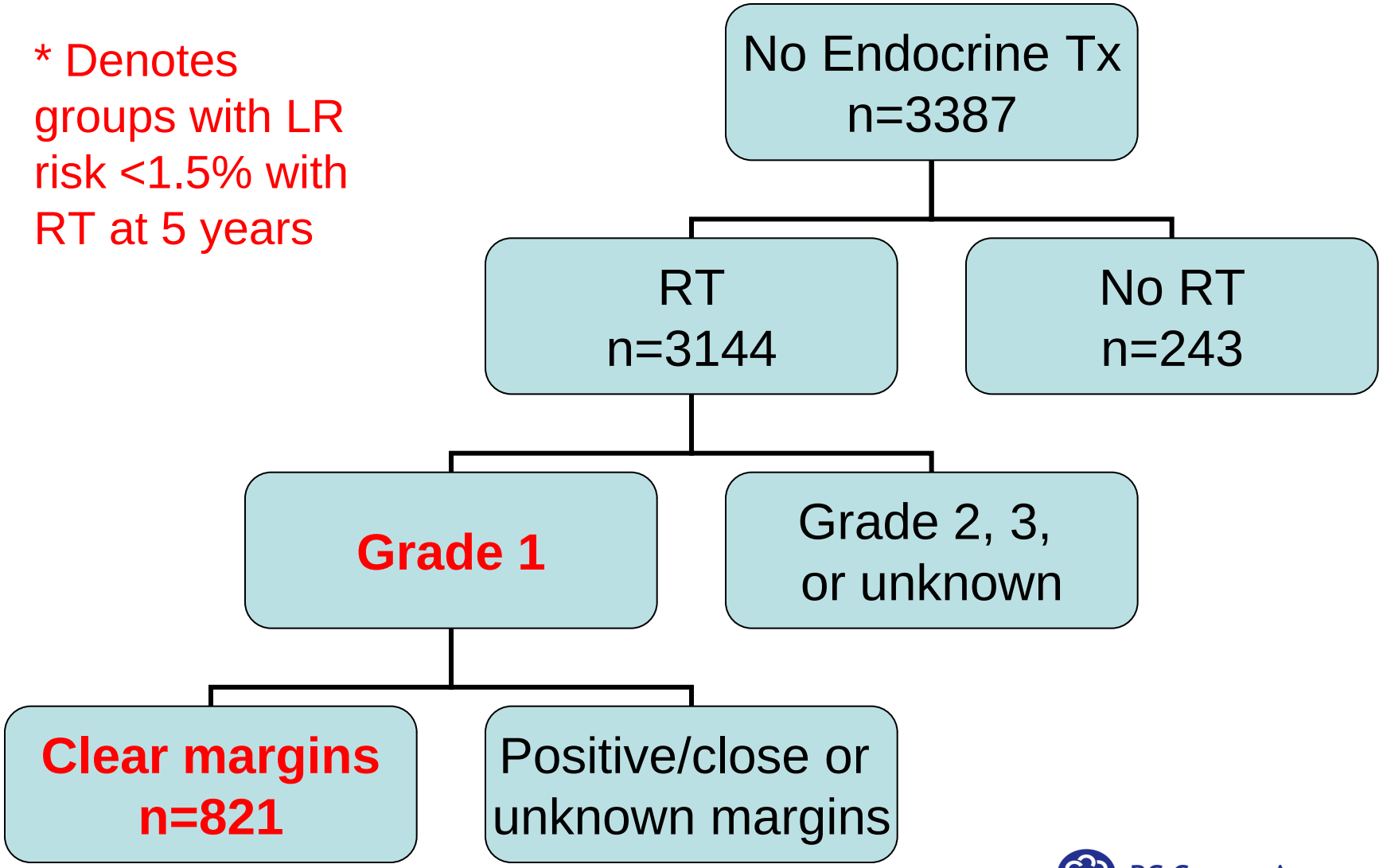
- **Over 60 plus grade 2** (n=843)

  LR 0.5% (95% CI 0-1.1) at 5 yrs

  LR 0.9% (95% CI 0.2-1.6) at 10 yrs

RPA of LR – pts treated *without* endocrine tx

* Denotes groups with LR risk <1.5% with RT at 5 years



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In patients treated without endocrine tx, subsets with LR ≤1.5% with RT:

- **Grade 1 histology plus clear margins** (n=821)
  - LR 0.6% (95% CI 0.1-1.2) at 5 yrs
  - LR 2.2% (95% CI 1.0-3.4) at 10 yrs

Conclusions

- Grade, age, margin status can be used to identify stage I patients with very low LR risk after BCS + RT
- Considering consistent two-thirds LR reduction with RT, findings *suggest* that patients with 5-year LR risk <5% without RT are:

≥50 yo, stage 1, grade 1, treated with endocrine tx
≥60 yo, stage 1, grade 2, treated with endocrine tx
≥50 yo, stage 1, grade 1, clear margins, no endocrine tx

Prospective study is critical to evaluate safety of RT omission

Lum A, No RT cohort study (Ontario/BC)

- women aged ≥60 years, treated with BCS
- unifocal pT1 pN0 invasive ductal ca
- grade 1 or 2, no LVI, clear margins
- ER and PR positive, Her 2 negative

- accepts endocrine therapy
- accessible for follow up

- send tissue block for Ki67 testing
- women with Luminal A disease (Ki67<14%) will be followed prospectively for LR risk without RT

Key Messages

- MORE? High to intermediate risk (all N+, high-risk N0): consider adding nodal to breast RT
- LESS? Non-high risk N0: whole breast RT is standard of care; partial breast RT remains investigational pending long-term follow-up
- NOT AT ALL? Very low risk N0: prospective study of no RT approach in patients with luminal A subtype who accept endocrine therapy