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of New Jersey

Current Indications for Breast Radiation

Hypofractionated Whole Breast Radiation

Accelerated Partial Breast Radiation

Intraoperative Radiation

Elimination of Radiation

Proton Beam Irradiation

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Conflicts :

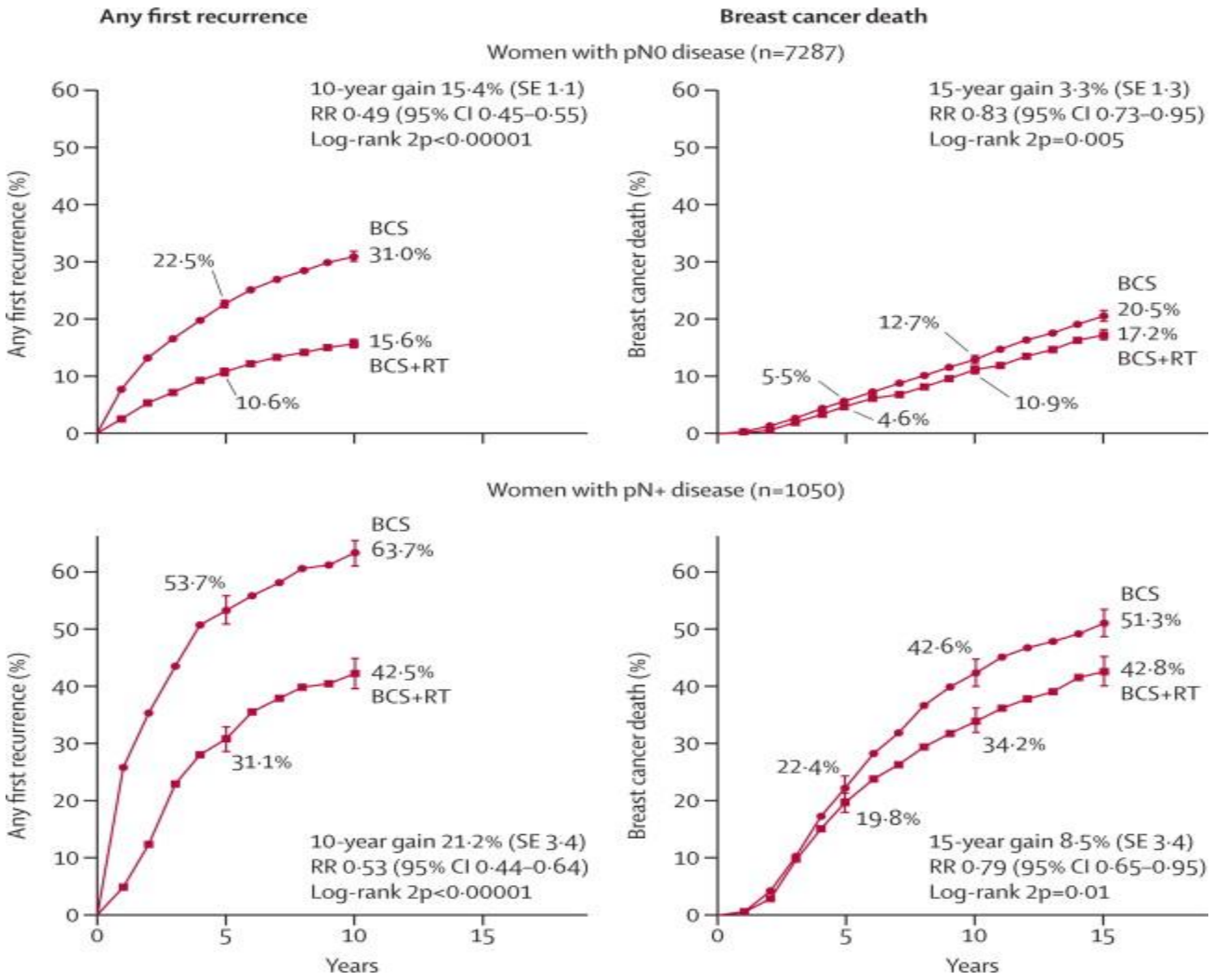
- I have no conflicts of interest to disclose

Background

- **Conventional Fractionation-Whole Breast Irradiation (CF-WBI)**
  - Whole breast: 45-50 Gy in 25-28 fractions
  - Boost: 10-16 Gy in 5-8 fractions
- Widely Embraced
- Accepted Standard of Care
- Long Term Follow-up on Efficacy and Toxicity

Local Relapse and BC Mortality Benefit: Randomized Trials of BCS compared to BCS +RT

Darby et al. Lancet 2011



Background

- **Limitations of CF-WBI**
  - Long overall treatment time
    - Patient inconvenience
    - Cost
  - Limited access in rural areas
  - Perhaps unnecessary toxicity due to irradiation of uninvolved portions of breast and normal tissue

Emerging Strategies

- **Hypofractionated Whole Breast Irradiation (HF-WBI)**
- **Accelerated Partial Breast Irradiation (APBI)**
- **Intraoperative Radiation**
- **Elimination of Radiation**

ASTRO Breast Guidelines

2009 Update 2016 to be published soon

ACCELERATED PARTIAL BREAST IRRADIATION CONSENSUS STATEMENT FROM THE AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO)

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2011 Update ongoing publication expected 2017

FRACTIONATION FOR WHOLE BREAST IRRADIATION: AN AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO) EVIDENCE-BASED GUIDELINE

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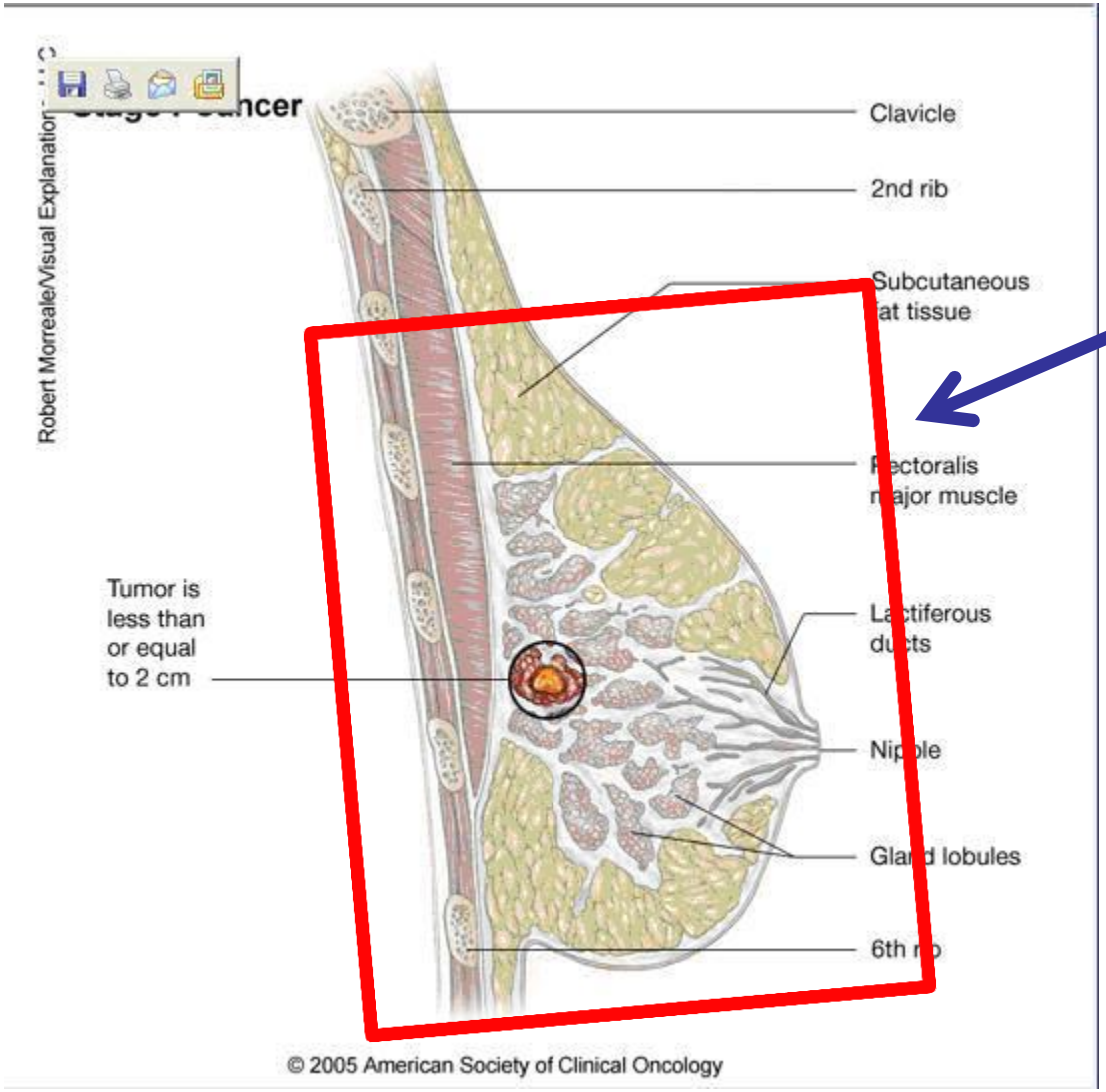
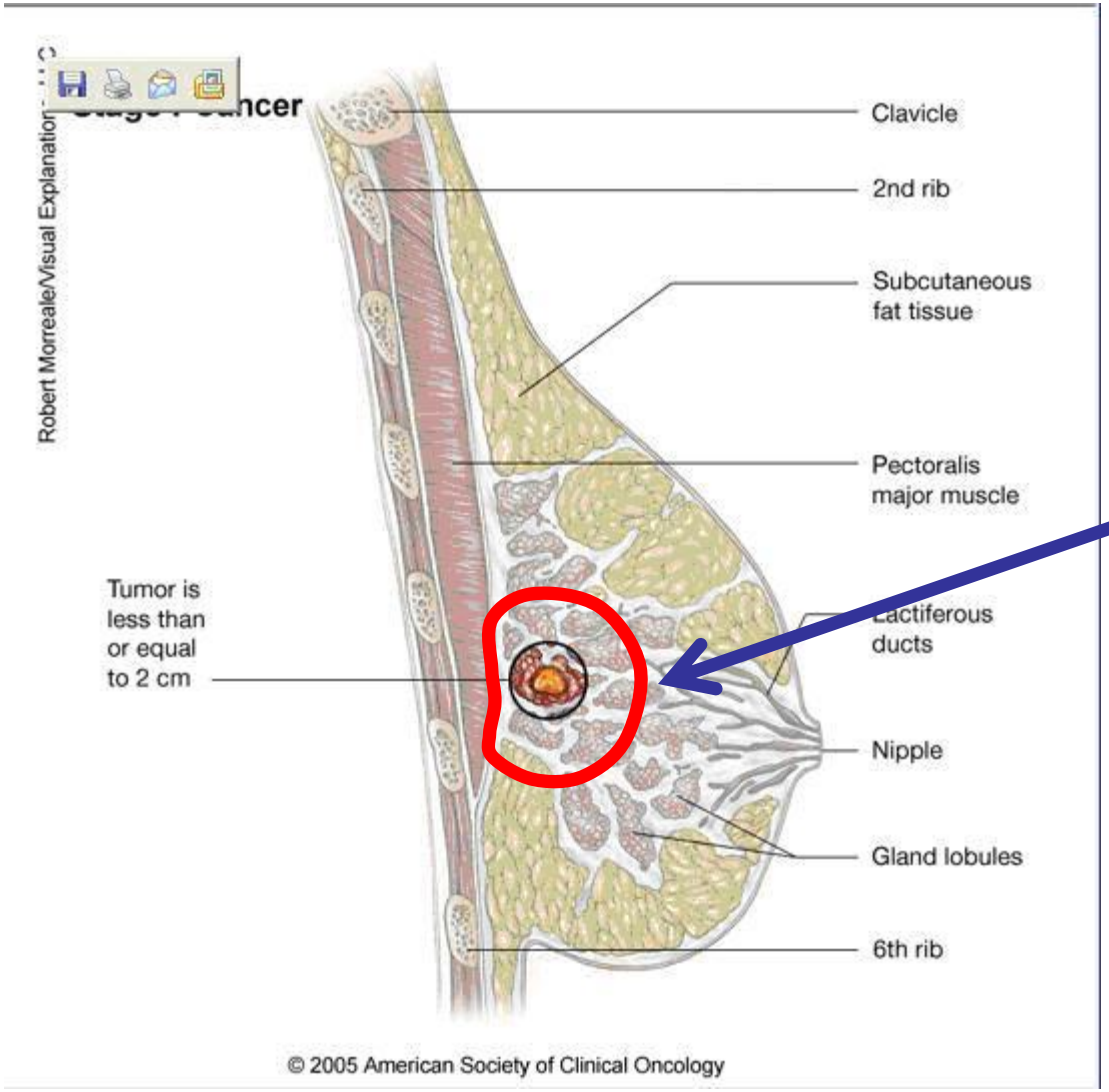
WBI vs APBI: Target Volumes



Whole Breast Target

WBI vs APBI: Target Volumes



Partial Breast Clinical Target Volume

HYPOFRACTIONATED WHOLE BREAST RT

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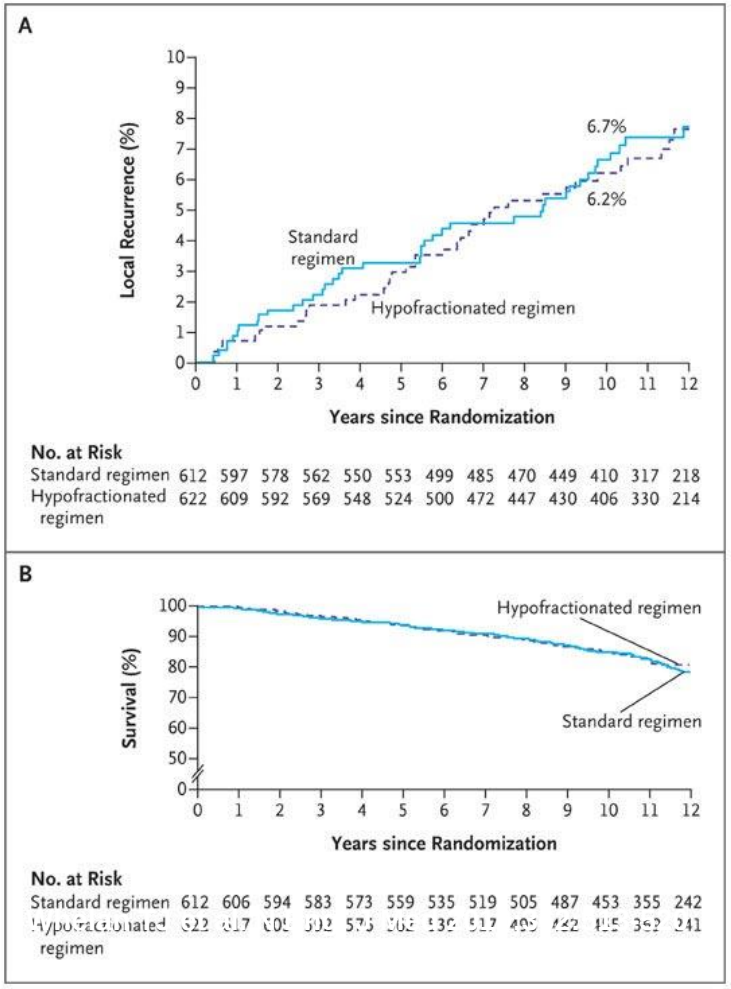
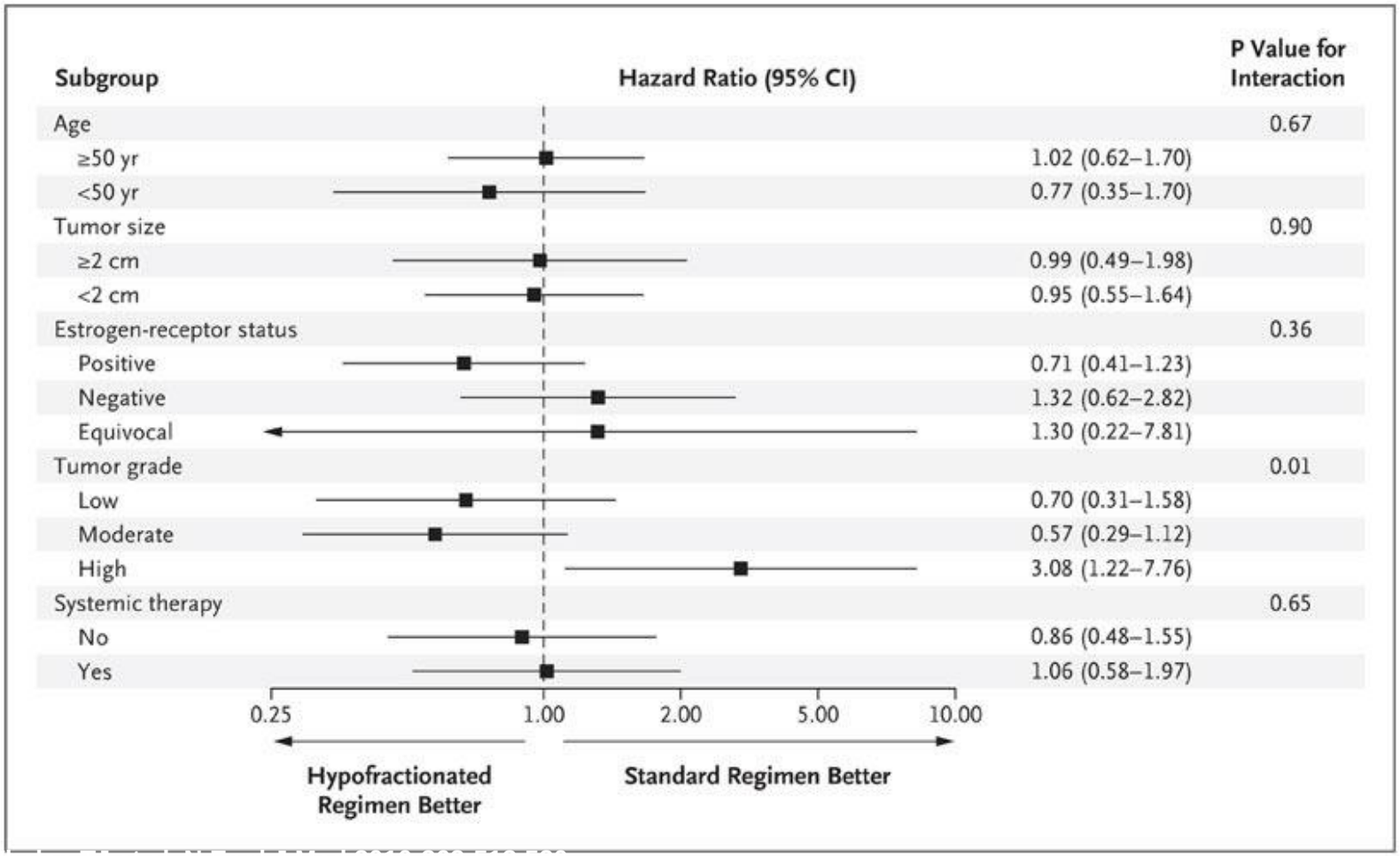
Outcomes in Patients with Breast Cancer Who Received a Hypofractionated Regimen of Radiation Therapy as Compared with Standard Regimen



The NEW ENGLAND JOURNAL of MEDICINE

Hazard Ratios for Ipsilateral Recurrence of Breast Cancer in Subgroups of Patients

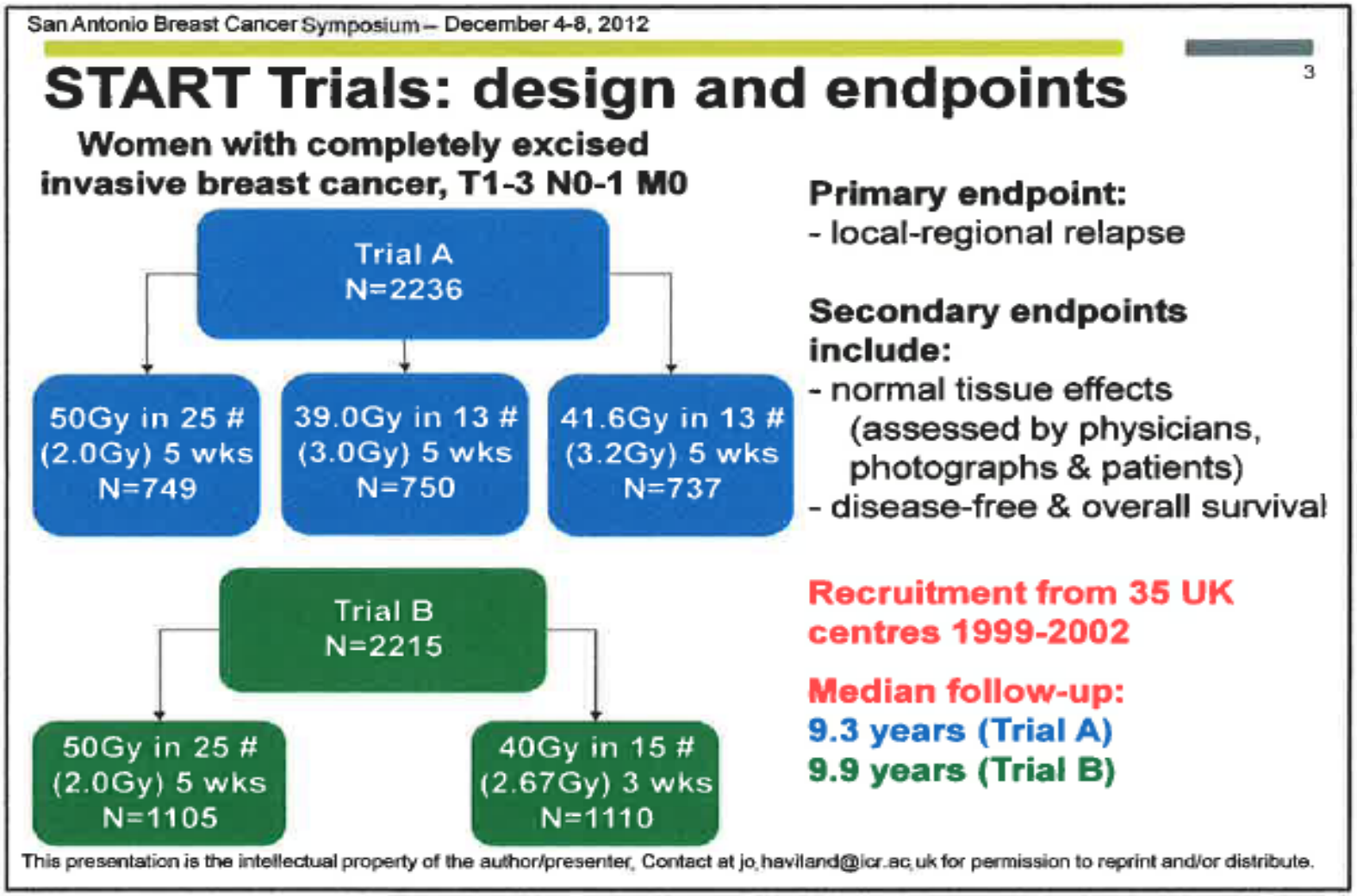


Hypofractionated whole Breast

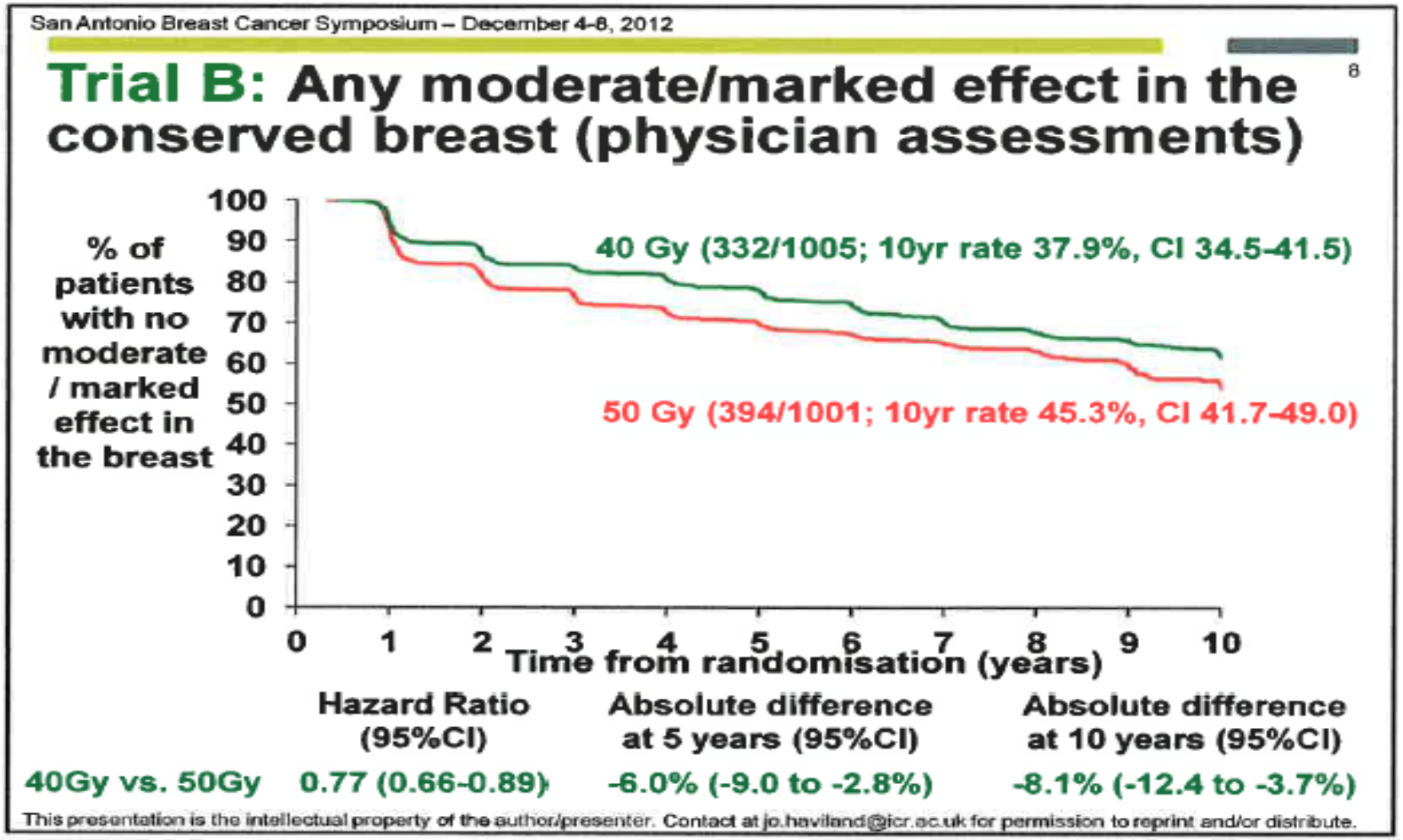
- **The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials.**
  - **Haviland et al. Lancet Oncology 2013**

- **Hypofractionated whole breast irradiation: the preferred standard of care?**
  - **Haffty and Buchholz Lancet Oncology 2013**

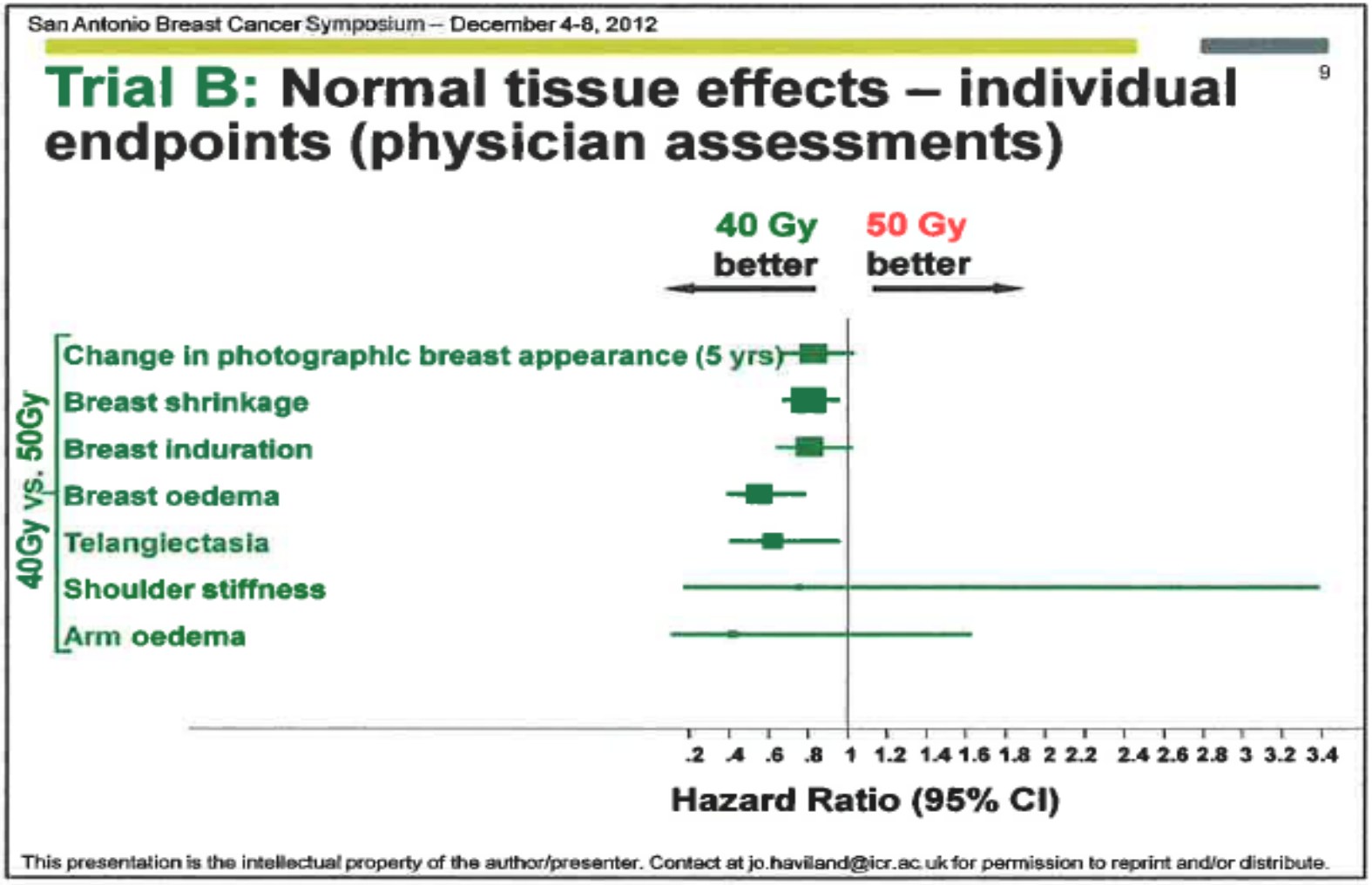
The UK START Trials



COSMETIC OUTCOME: START B



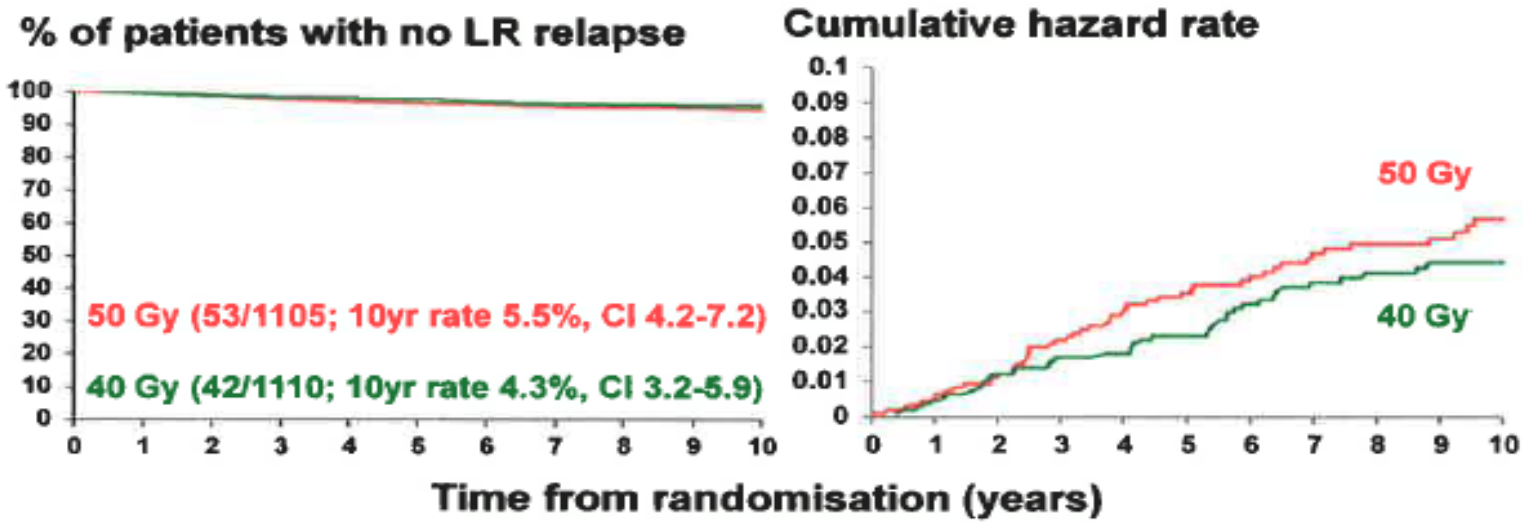
Normal Tissue Effect: START B



Local-regional Control: START B

San Antonio Breast Cancer Symposium – December 4-8, 2012

Trial B: Local-regional (LR) tumour relapse[10]

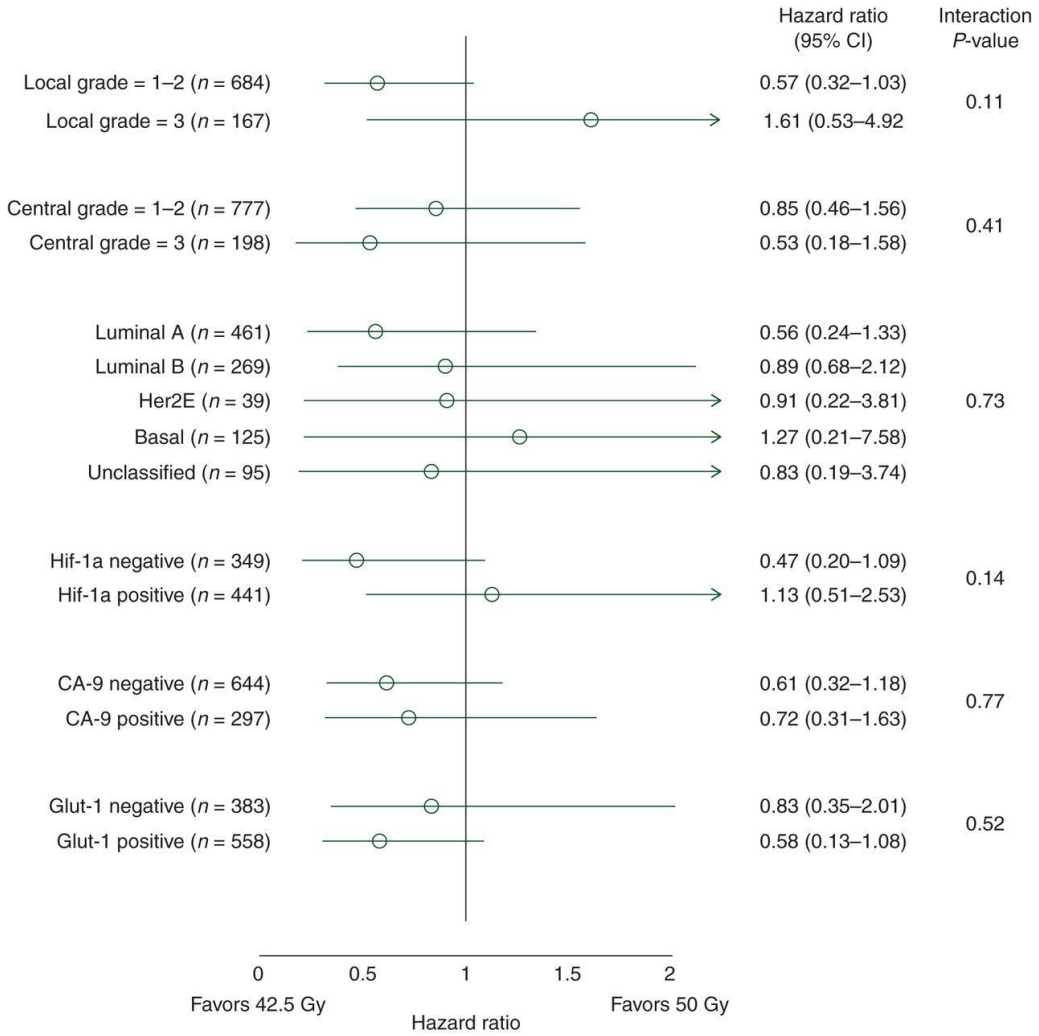


	Hazard Ratio (95%CI)	Absolute difference at 5 years (95%CI)	Absolute difference at 10 years (95%CI)
40Gy vs. 50Gy	0.77 (0.51 – 1.16)	-0.8% (-1.7 to 0.5%)	-1.2% (-2.6 to 1.0%)

Issue of High Grade and Hypofractionation

- This really should no longer be an issue.
- As previously noted in the Canadian trial for unclear reasons the local recurrence seemed higher in the hypo-fractionation arm for high grade tumors
- This was not found to be the case in the START trials
- Further analysis of the Canadian Trial Did Not Confirm that Grade was a Significant Factor upon central review

Hazard ratios for local recurrence of breast cancer in subgroups of patients.



Bane A L et al. Ann Oncol 2014;25:992-998

Annals of Oncology

HF-WBI: Clinical Data

- **Majority of patients in all trials:**
  - Treated with breast conserving surgery
  - Age ≥ 50 years
  - pT1-2 pN0
  - Chemotherapy not used
  - Homogeneity within +/- 7%

Patient group for whom data to support HF-WBI is strongest!!

However, this does not imply that this is the only group in whom HF-WBI can/should be used!!

Hypofractonated Whole Breast

- **Strong Phase III data that this is acceptable as an alternative to whole breast**
- **Remains some controversy regarding selection of higher risk patients, patients requiring a boost, younger patients, and patients who have received chemotherapy**
- **Improvements in technology, allowing more homogenous dose distribution throughout the breast, and allowing for simultaneous boost, will likely further advance and encourage the use of hypo-fractionated whole breast treatment**
- **However, long term follow-up and patient experience is still much more immature and less extensive compared to experience with conventionally fractionated whole breast treatment**

PARTIAL BREAST IRRADIATION

Rationale for Partial Breast Radiation

- The majority of all local recurrences occur within the region of initial lumpectomy
- Why do we need to radiate the whole-breast
- Early Phase I/II data on partial breast irradiation appears promising for selected patients

Potential Advantages of APBI

- All local therapy completed prior to chemotherapy
- Treatment of tissue at most increased risk of sub-clinical disease – rather than healthy breast tissue/skin may actually improve cosmesis

Potential Disadvantages

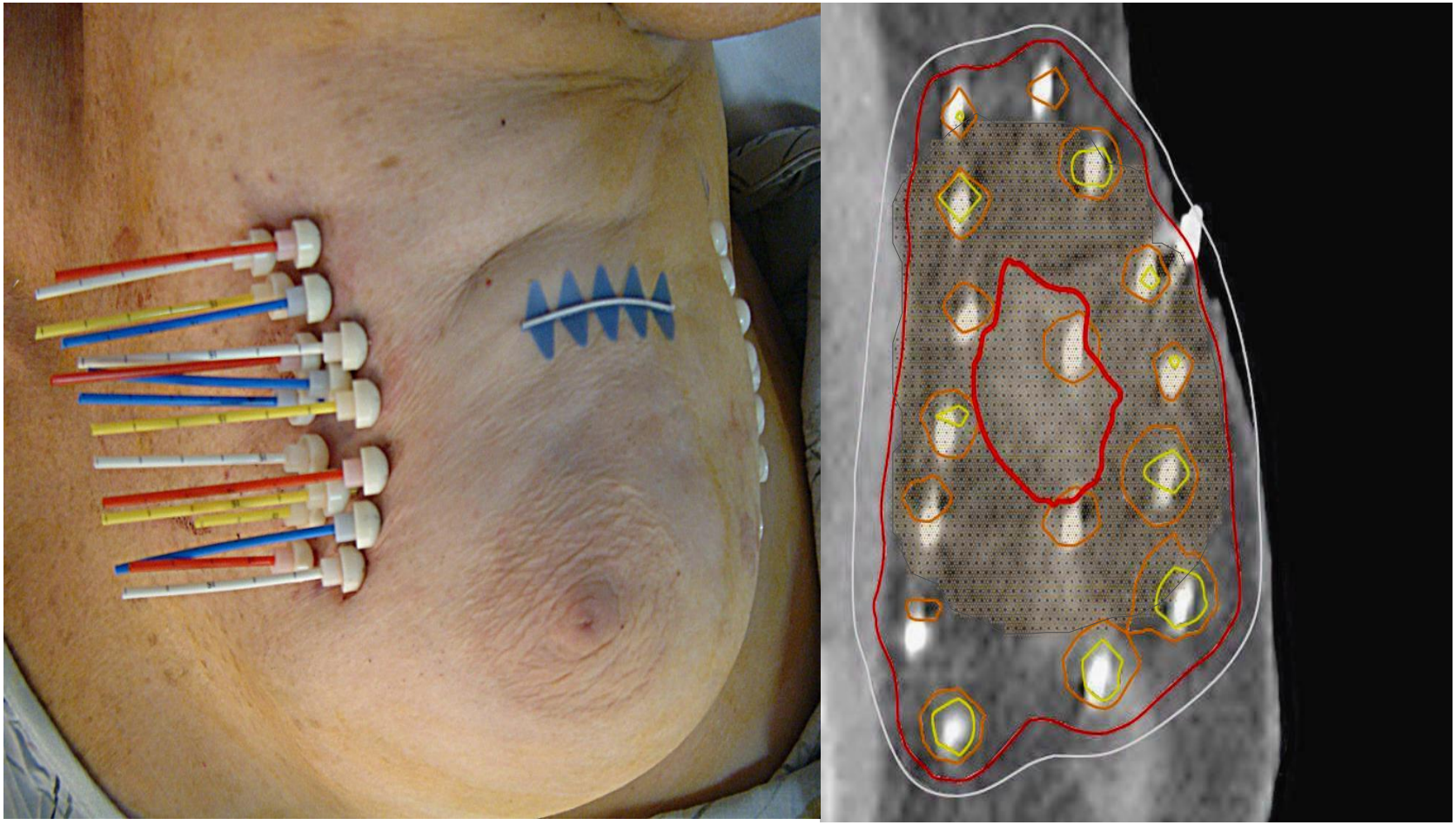
- Local relapses may be higher
- Fibrosis with larger fractions may be significant with longer follow-up
- Prospective randomized data proving its effectiveness is lacking

APBI-Treatment Approaches

- Multi-catheter Interstitial
- Single Catheter Balloon Based
- External Beam
- Intraoperative

Multi-Catheter Brachytherapy

placement – US, Stereotactic mammography, or CT guidance



APBI: Interstitial Brachytherapy

Key Study

William Beaumont

N=199

82% stage I

100% negative margins

10-yr in-breast recurrence: 3.8%

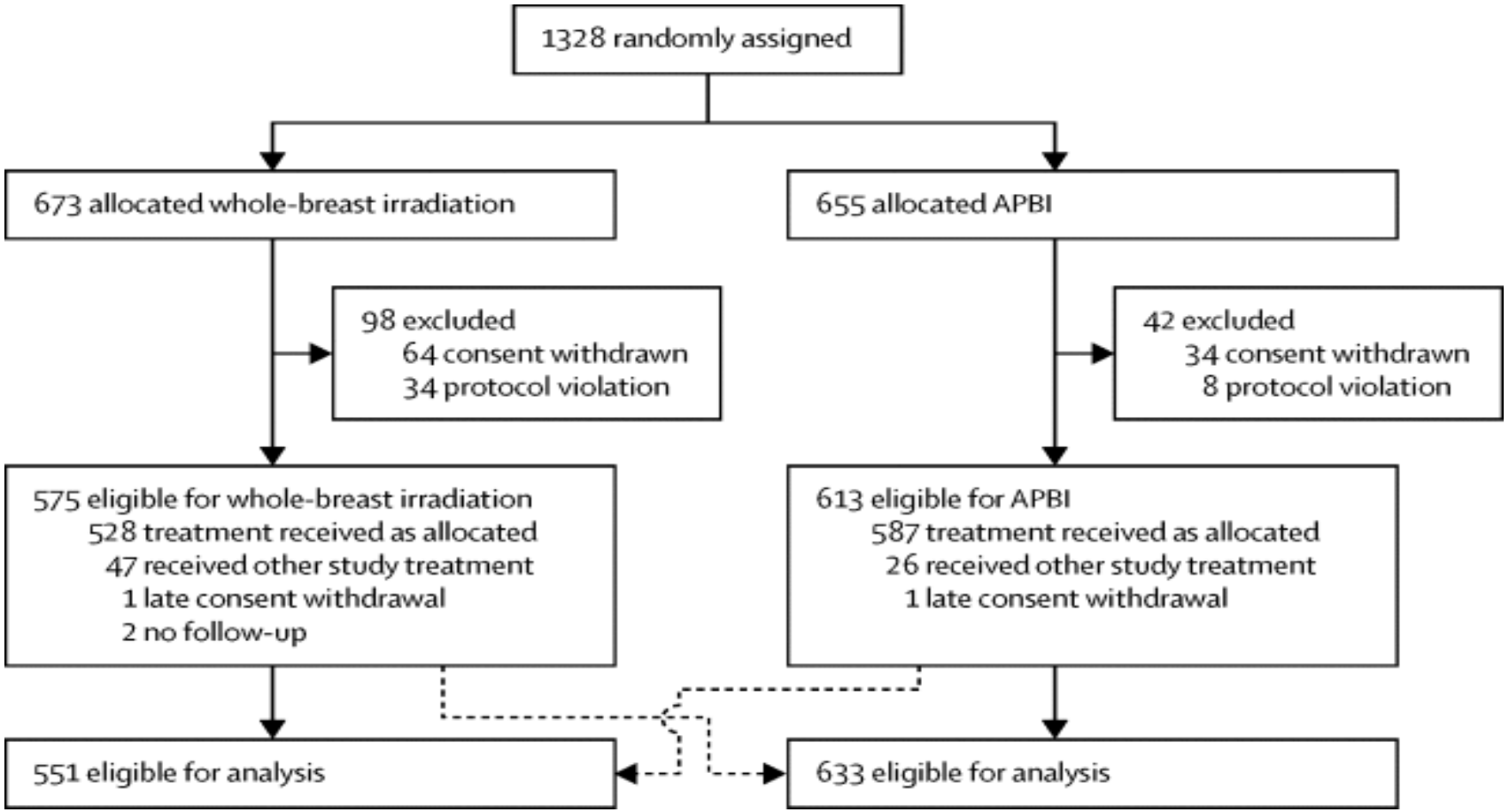
Excellent/good cosmetic outcome: 99%

Vicini et al, Int J Radiat Oncol Biol Phys 68:341-346, 2007

Interstitial Brachytherapy vs. Whole Breast

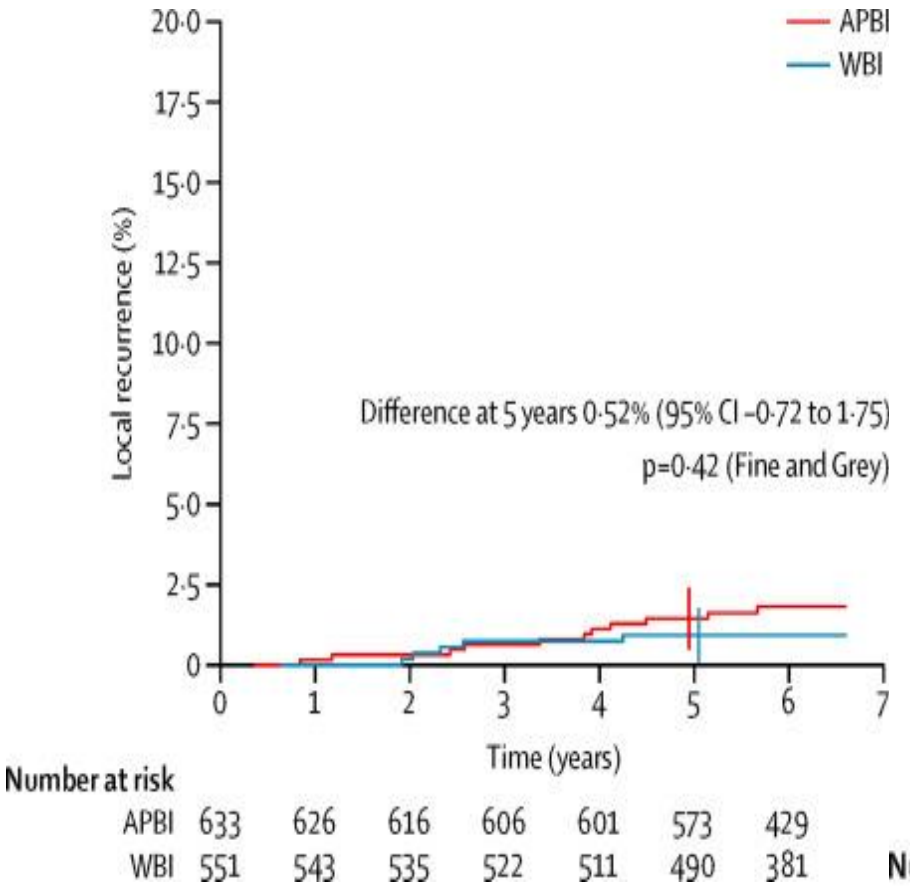
Randomized Trial (Strnad et al. Lancet, 2016)

- Randomized Trial: Whole Breast vs. Interstital Brachytherapy
- At 5 yrs, No difference in local relapse, survival, toxicity

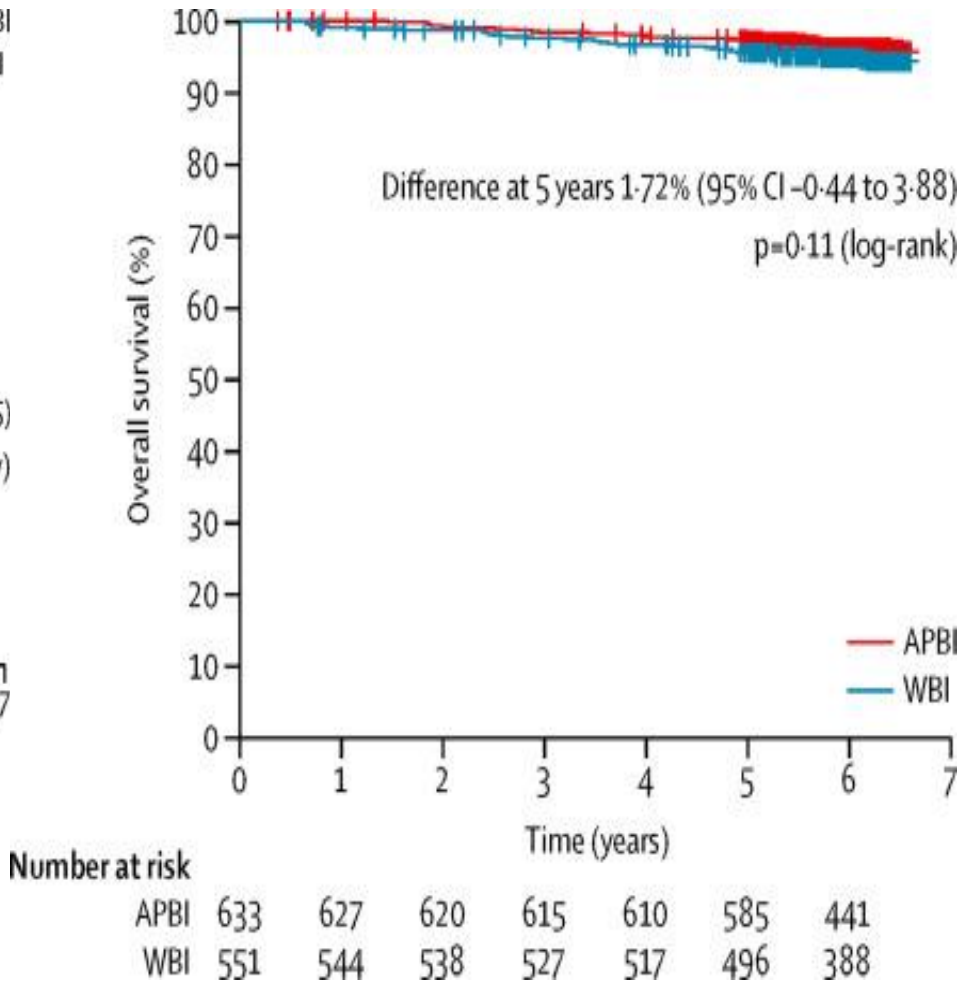


Randomized Trial: Brachy APBI vs Whole Breast

Local Relapse



Overall Survival



APBI: Interstitial Brachytherapy

Limitations

- Invasive
- Risk of infection
- Operator-dependent
- Limited diffusion
- Heterogeneous clinical outcomes

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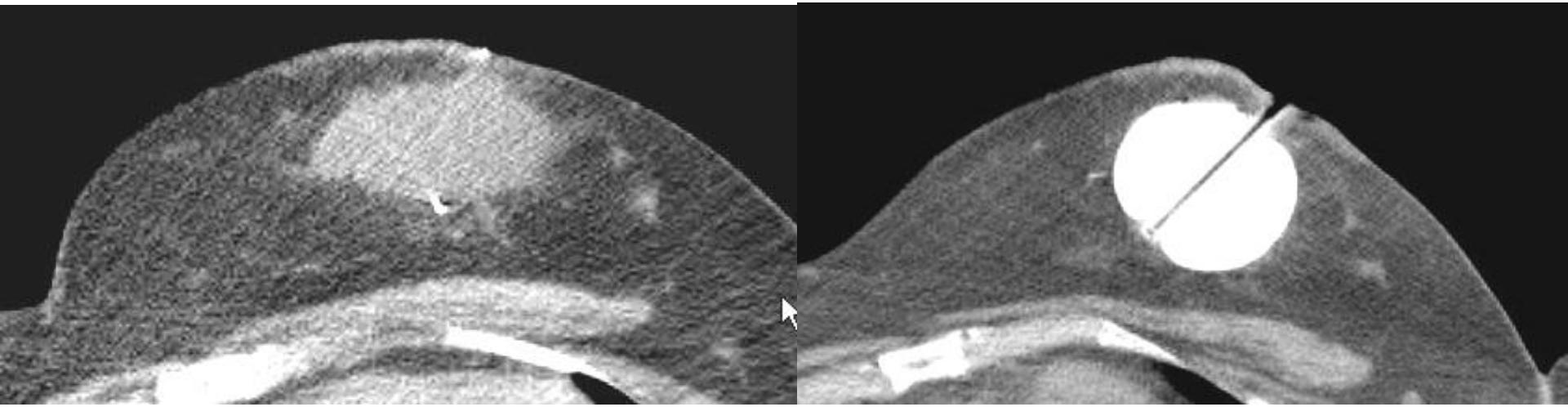
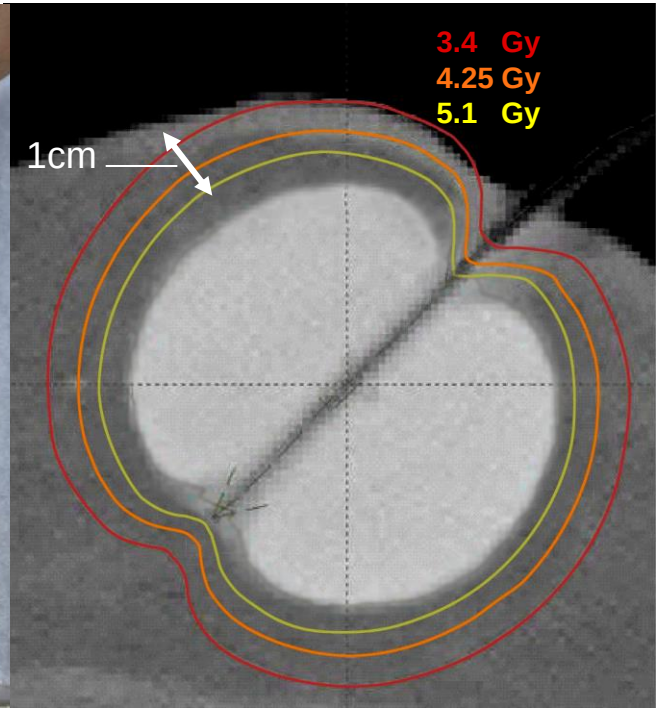
Ideal Case for Balloon Based Brachy



Placed by Surgeon or Rad Onc – at the time of lumpectomy or post lumpectomy

Target conforms to balloon surface



IntraCavitary Applicators

MammoSite
Cytyc

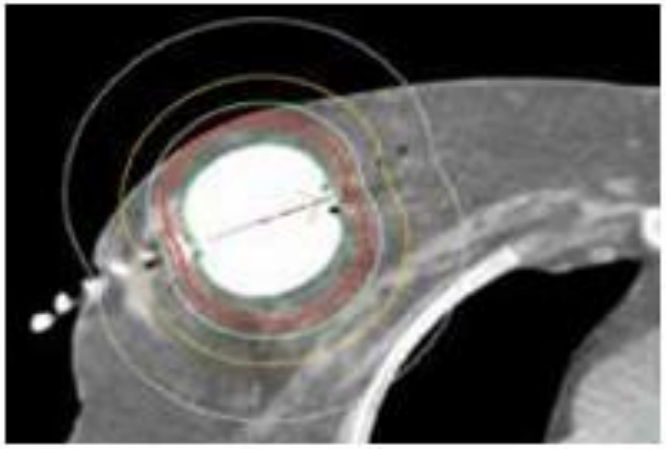
SAVI
Cianna

ClearPath
North American
Scientific

Xoft

Contura MLB
SenoRx

APBI: Balloon-based



Key Study

ASBS Mammosite Registry

N=1,449

>90% stage I

ER Negative associated with higher IBTR

5-yr in-breast recurrence: 3.8%

Excellent/good cosmetic outcome: 90.6%

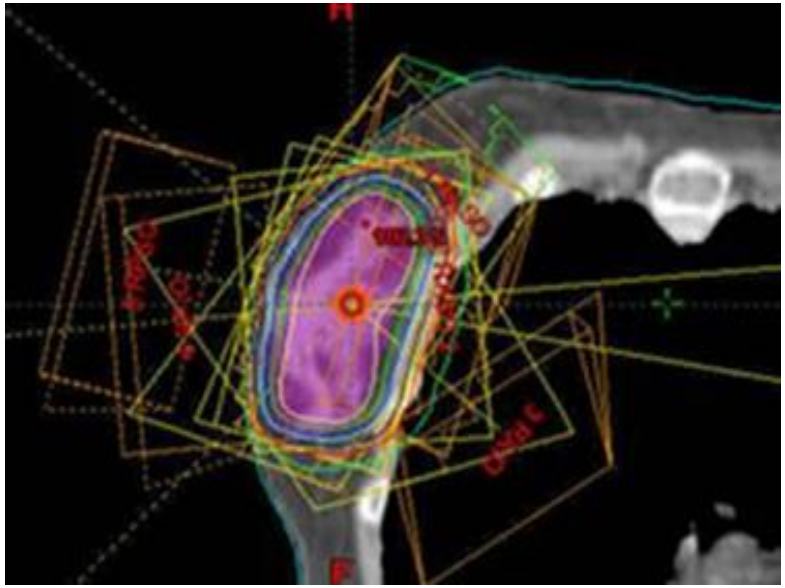
Vicini et al. Int J Radiation. Biol Phys. 2011.

APBI: Balloon-based

Limitations

- Invasive
- Risk of infection and seroma
- Short follow up
- Not appropriate for superficial lesions

APBI: External Beam



Key Study
RTOG 0319
N=53
92% stage I
100% negative margins
3-yr in-breast recurrence: 6% (95% 0-12%)

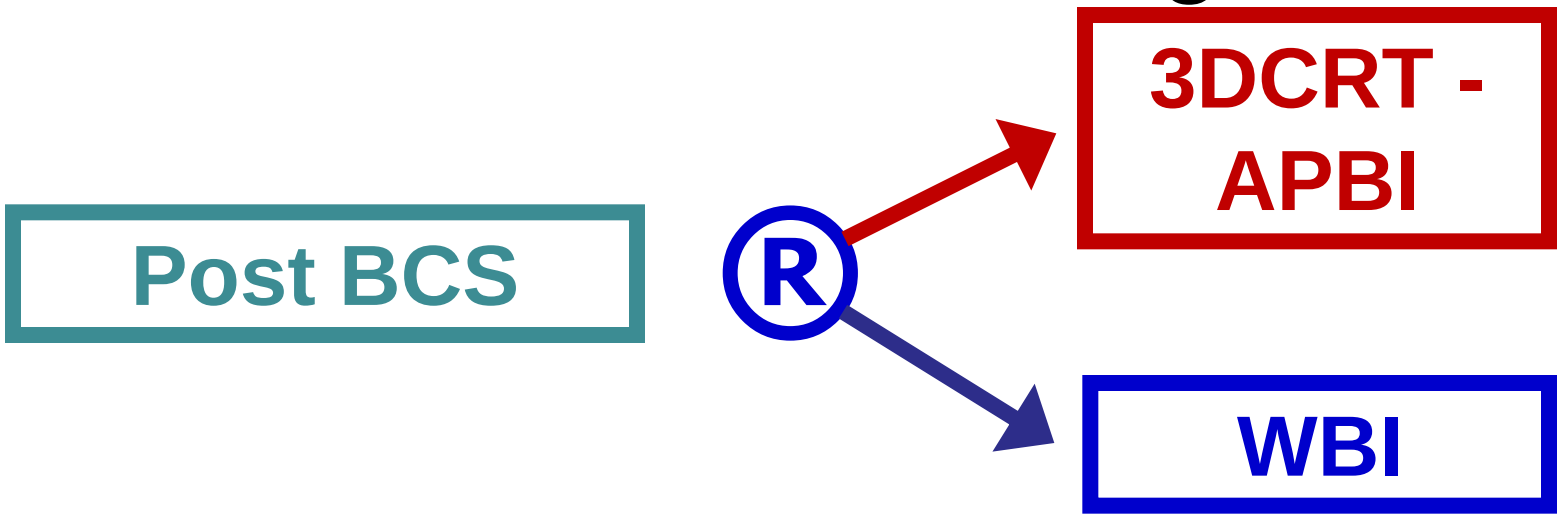
Vicini et al, Int J Radiat Oncol Biol Phys 72 (Supp 1):S3-A18, 2008

APBI: External Beam

Limitations

- Very short follow up
- Few patients treated
- Uncertainty in target delineation
- ?Uncertainty day to day setup
- Increased integral dose to breast

Canadian RAPID Trial Design



Stratification

- Age: < 50, ≥ 50
- Histology: DCIS, invasive disease
- Tumour size: < 1.5 cm, ≥ 1.5 cm
- ER status: +ve, -ve

Summary of RAPID/JCO 2014

- 2135 women randomized to WBRT vs APBI
- Whole breast (50 Gy/25 Fractions) or Canadian (42.5 Gy/16 fractions) +/- Boost
- APBI 3.85 BID to 38.5 Gy all External Beam Conformal
- Cosmesis assessed by Study Nurse and Patient:
- Cosmesis also assessed by panel of trained radiation oncologists unaware of tx arm using digital photos
- Planned interim analysis based on nurse assessment at 2.5 years
- DSMC recommended release of results based on highly significant findings

Adverse Cosmetic Assessment
3 Independent Measures

	Whole Breast	APBI	P Value
Nurse Assessment 	18.6%	31.5%	.0001
Patient Assessment 	18.4	26.2	.004
RO Panel Assessment 	16.6	35.1	.0001

ASTRO - Suitable

Variable	*Finding*
Age	≥ 60
T-stage	T1
Tumor Size	≤ 2 cm
Margins	> 2 mm
Grade	Any
LVI	No
ER Status	Positive
Multicentricity	Unifocal ≤ 2 cm
Histology	IDC or favorable
EIC	Not allowed
Pure DCIS	Not allowed
Nodes	pNO
Neoadjuvant Chemo	Not allowed

ASTRO - Cautionary

Variable	*Finding*
Age	50-59
T-stage	T0 or T2
Tumor Size	2.1-3.0 cm
Margins	Close < 2 mm
Grade	NA
LVI	Limited/focal
ER Status	Negative
Multicentricity	NA
Histology	Invasive lobular
EIC	≤ 3 cm in size
Pure DCIS	≤ 3 cm in size
Nodes	NA
Neoadjuvant Chemo	NA

ASTRO - Unsuitable

Variable	*Finding*
Age	< 50
T-stage	T3 or T4
Tumor Size	> 3 cm
Margins	Positive
Grade	NA
LVI	Extensive
ER Status	NA
Multicentricity	Present
Histology	NA
EIC	If > 3 cm in size
Pure DCIS	If > 3 cm in size
Nodes	pN1, pN2, pN3
Neoadjuvant Chemo	If used

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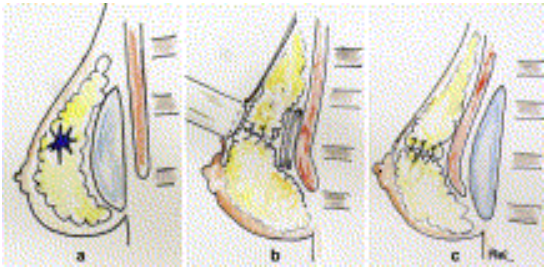
Future Directions in APBI: Exploring Ultra-short Fractionation

Update on Data from Intraoperative Trials

- Europeans accumulating large body of maturing data with **intraoperative single fraction treatment.**
  - **TARGIT**

  - **ELIOT**



TARGIT: radiobiological considerations

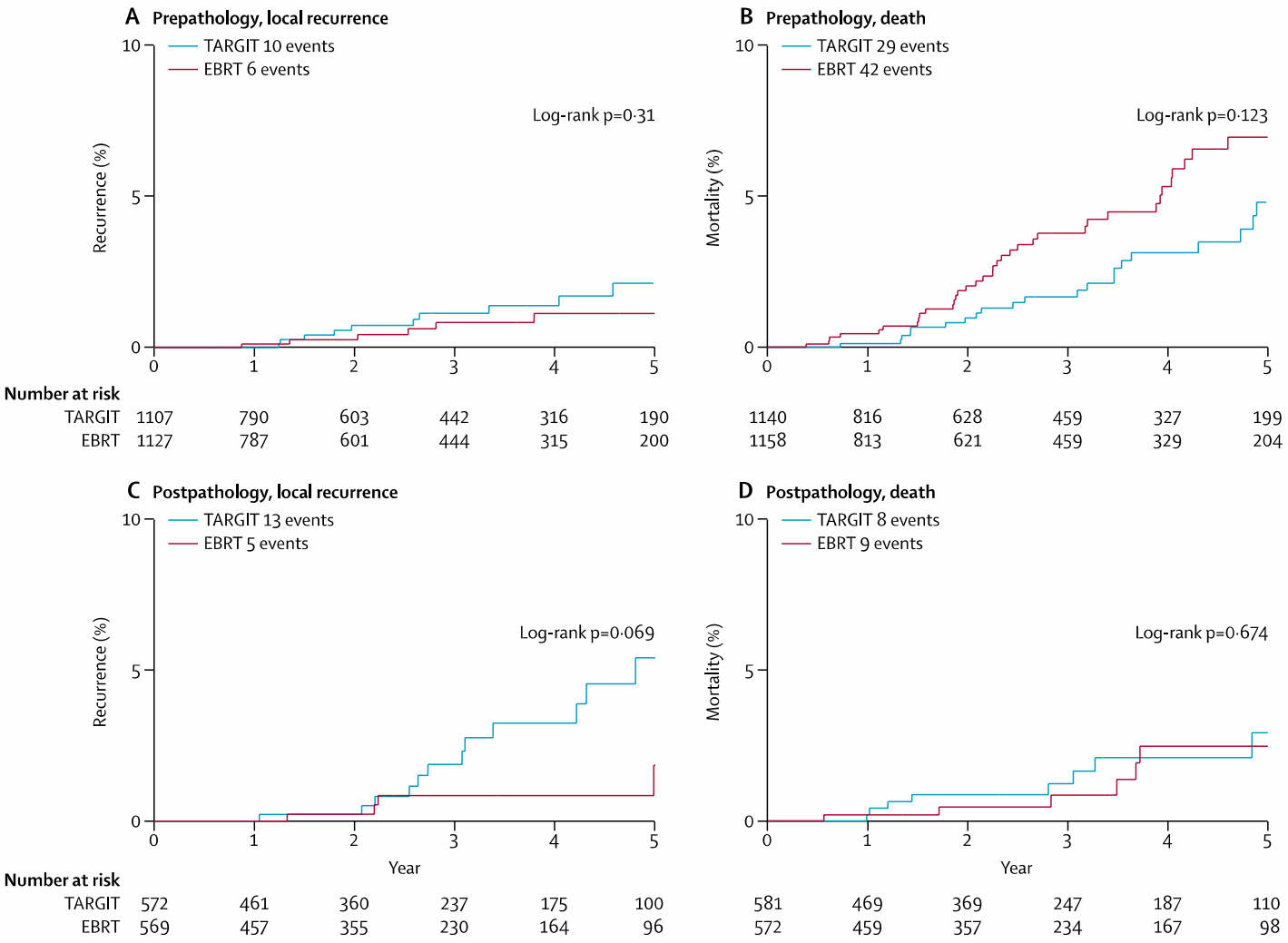
- 5 Gy at 1 cm distance?
- 50 kV source increases RBE (1.5 at 1 cm), but still low.
- Intraoperative alters lumpectomy microenvironment?

Update on the TARGIT-A trial

www.thelancet.com Vol 382 Published online November 11, 2013 http://dx.doi.org/10.1016/S0140-6736(13)61950-9

- 3451 randomized patients, median fup 2.5 years; 2020 with 4 yr fup, 1222 with 5 yr fup
- Pre vs post-pathology strata (pre-path: 21% recd whole breast RT)
- **5-year ipsilateral breast recurrence: 3.3 vs 1.3% (p=0.042).**

Update on the TARGIT-A trial



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Update on the ELIOT trial

www.thelancet.com/oncology **Published online November 11, 2013** **http://dx.doi.org/10.1016/S1470-2045(13)70497-2**

- 1184 randomized women, median fup 6 yrs
- No "remedial" whole breast RT
- **5-year ipsilateral breast recurrence: 4.4 vs 0.4% (p<0.0001)**
- Fat necrosis rate: 14.5% (versus 2-3% with device- based 5 day APBI)
- Only 23% of patients "suitable" for APBI, 33% (387/1184) "unsuitable".

Limitations of intraoperative APBI

Ultrashort Courses of Adjuvant Breast Radiotherapy

Wave of the Future or a Fool's Errand?

Atif J. Khan, MD[1]; Roger G. Dale, PhD[2]; Douglas W. Arthur, MD[3]; Bruce G. Haffty, MD[1]; Dorin A. Todor, PhD[3]; and Frank A. Vicini, MD[4]

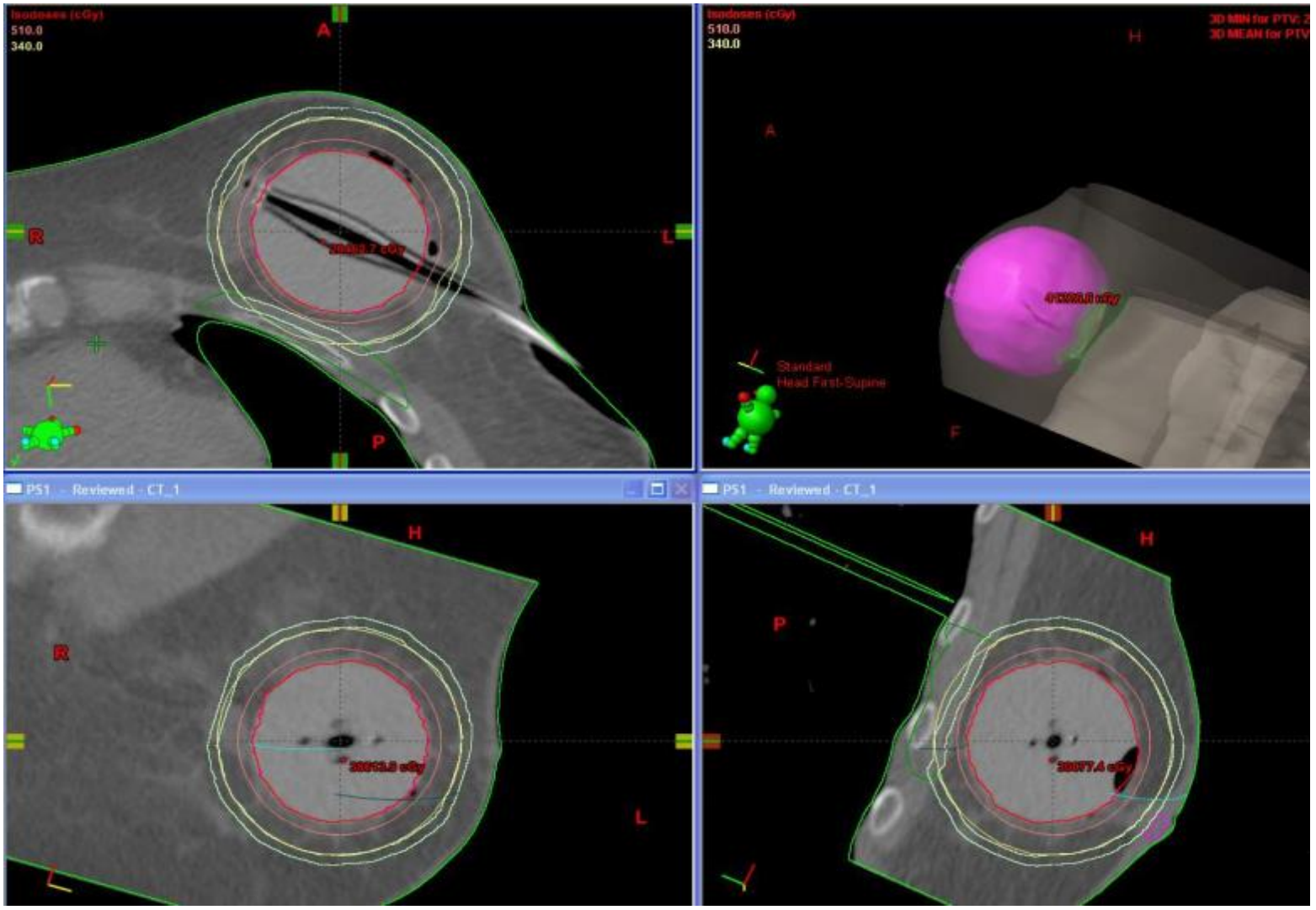
In accelerated partial breast irradiation (APBI), the most commonly used fractionation schemes include 340 or 385 centigrays delivered in a twice daily administration. A further progression of the APBI literature has been the recent interest in extremely short courses of adjuvant radiotherapy, usually delivered by intraoperative radiotherapy techniques. This newer area of single-fraction radiotherapy approaches remains highly contentious. In particular, the recently reported TARGIT trial has been the subject of both praise and scorn, and a critical examination of the trial data and the underlying hypotheses is warranted. Short-term outcomes of the related Italian ELIOT approach have also been reported. Although the assumptions of linear quadratic formalism are likely to hold true in the range of 2 to 8 grays, equating different schedules beyond this range is problematic. A major problem of current single-fraction approaches is that the treatment doses are chosen empirically, or are based on tolerability, or on the physical dose delivery characteristics of the chosen technology rather than radiobiological rationale. This review article summarizes the current data on ultrashort courses of adjuvant breast radiotherapy and highlights both the promise and the potential pitfalls of the abbreviated treatment. **Cancer 2011;000:000–000.** © 2011 American Cancer Society

- Treatment triage occurs before permanent path review (no margin/LN eval)
- 20% of patients selected for intraop got additional WBI (TARGIT-A, but not ELIOT)
- Logistics (increase OR time, coordinate schedules (surgeon/rad onc/dedicated path to do intraop assessment)
- Treatment planning is NOT image based
- Dosimetry/radiobiology not validated

Fraction-escalating "Overnight" study (short-course 2 Day APBI)

- Concept: women with early stage, low risk breast cancer can receive adjuvant RT in 2 days; women living remote from treatment center can stay "overnight" close to facility and return home on day 2
- Eligible women:
  - age ≥ 50 years
  - unifocal invasive or in situ tumors
  - less than 3.1 cm/+ Hormone Receptors
  - excised with negative margins
  - negative lymph nodes

Treatment planning



Treatment schedule

- 3 cohorts of 30 patients each with predefined stopping criteria for toxicity and a 6 month observation period between cohorts
- Radiobiology modeling by Prof Roger Dale (Imperial College UK)
  - 7 Gy times 4
  - 8.25 Gy times 3
  - 10.5 Gy times 2

Update on Phase II "Overnight" study : Khan, Arthur, Vicini, Haffty

Sponsor: Cianna Medical (Alisa Viejo, CA)

- 3 cohorts of 30 patients (n=90) with predefined stopping criteria for toxicity.

- 7 Gy x 4 → 8.25 Gy x 3 → 10.25 Gy x 2

- 30 women on cohort 1, COMPLETE ACCRUAL.

- 30 women on cohort 2, COMPLETE ACCRUAL.

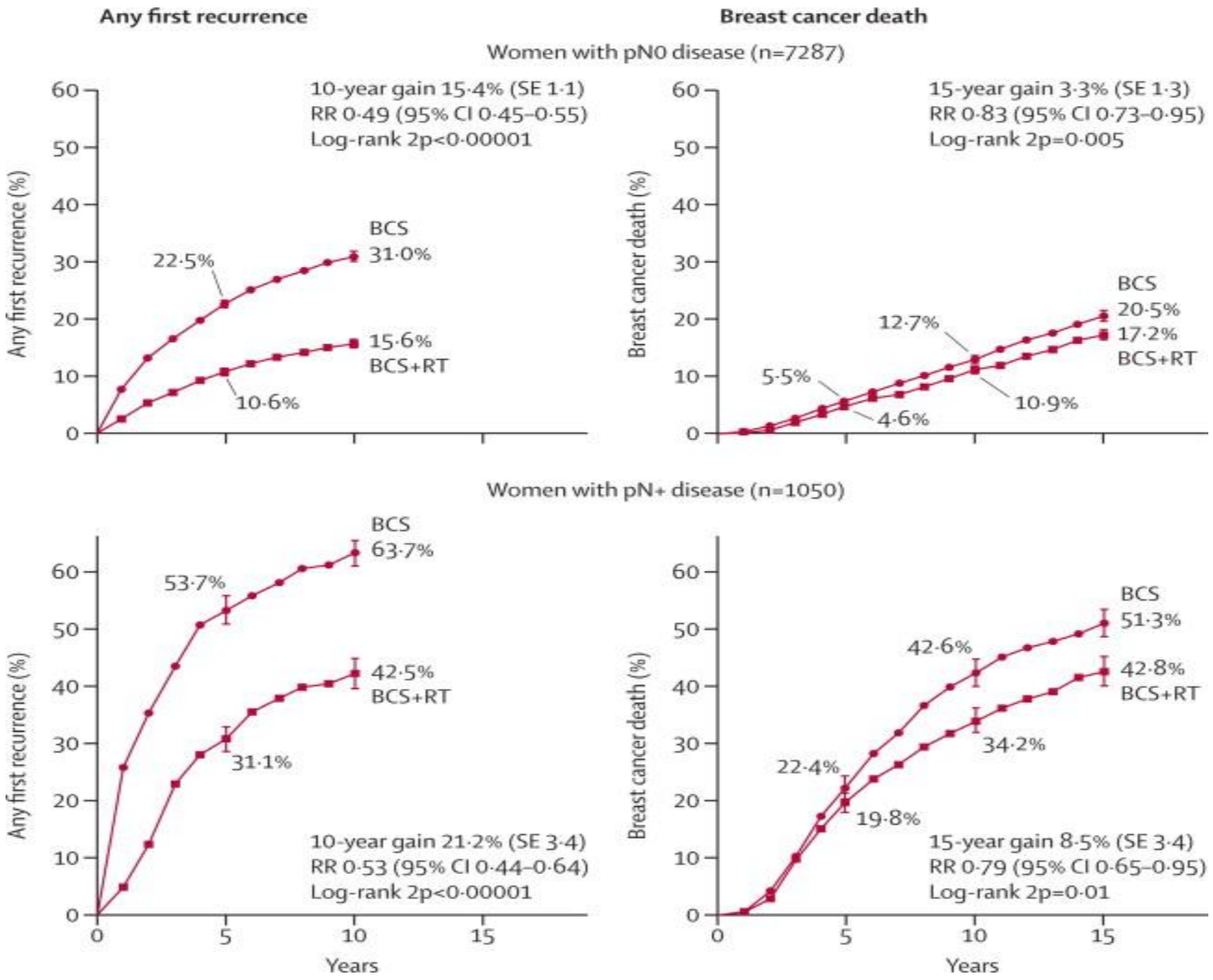
- No > grade 2 toxicity events, no safety events

What About No Radiation?

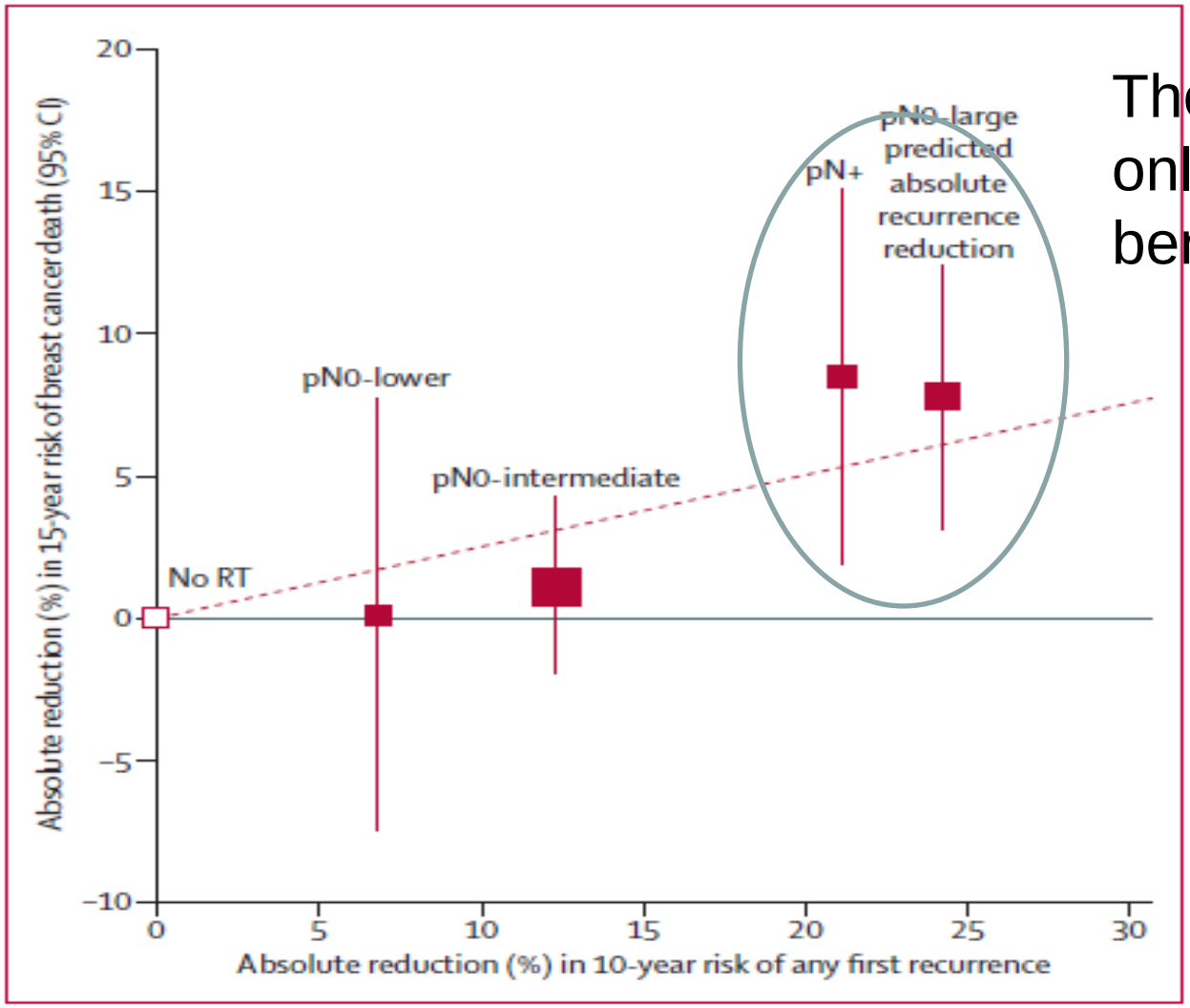
- All randomized studies show a benefit to radiation in reducing local relapse
- In some higher risk patients, this benefit translates to improvements in relapse free or even overall survival
- However, some subsets of patients are at so low risk that radiation can be avoided
- This is the subject of several trials, completed, ongoing and developing

Local Relapse and BC Mortality Benefit: Randomized Trials of BCS compared to BCS +RT

Darby et al. Lancet 2011



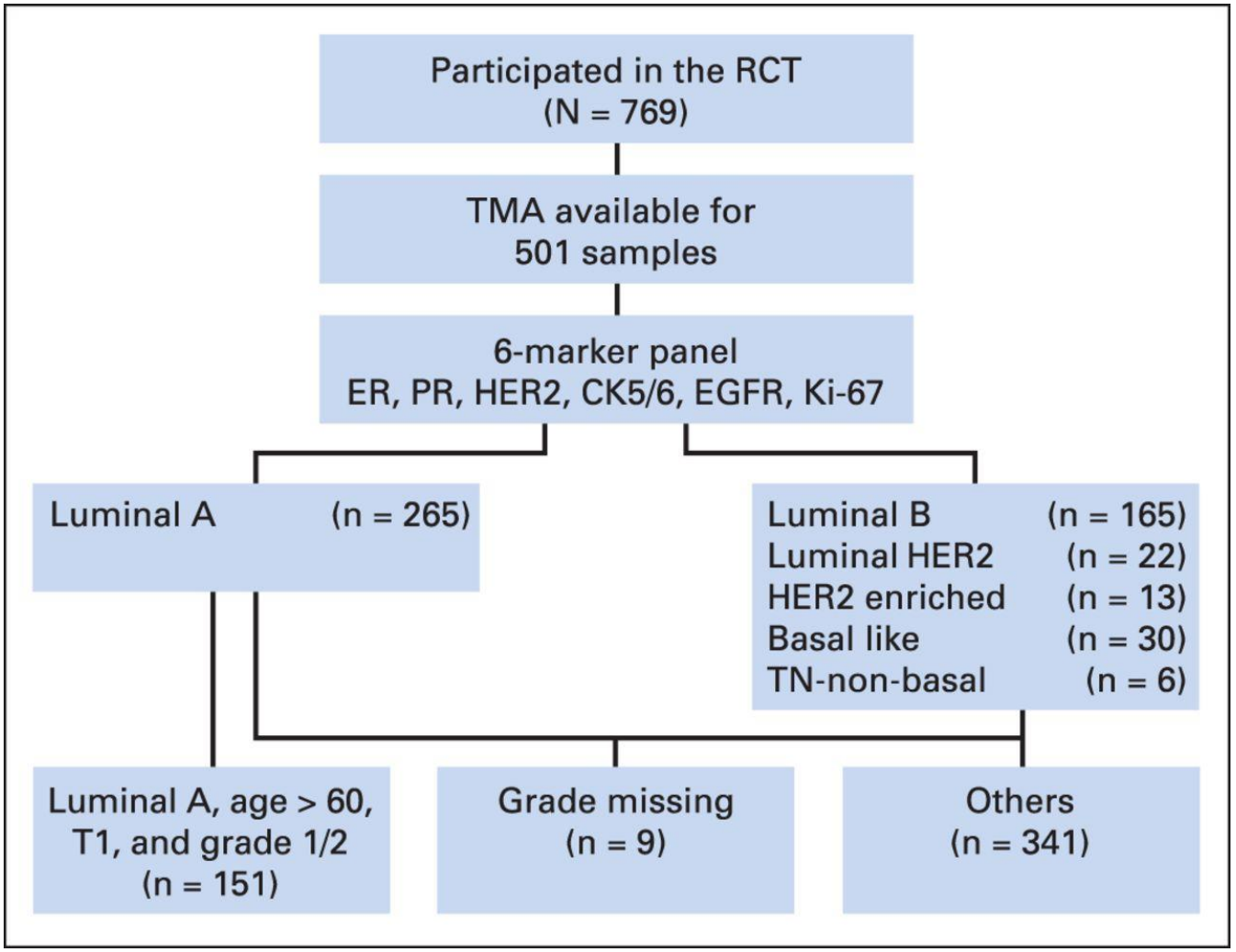
From Darby et al. Meta-analysis of BCS+/-RT



These are the only groups that benefit!

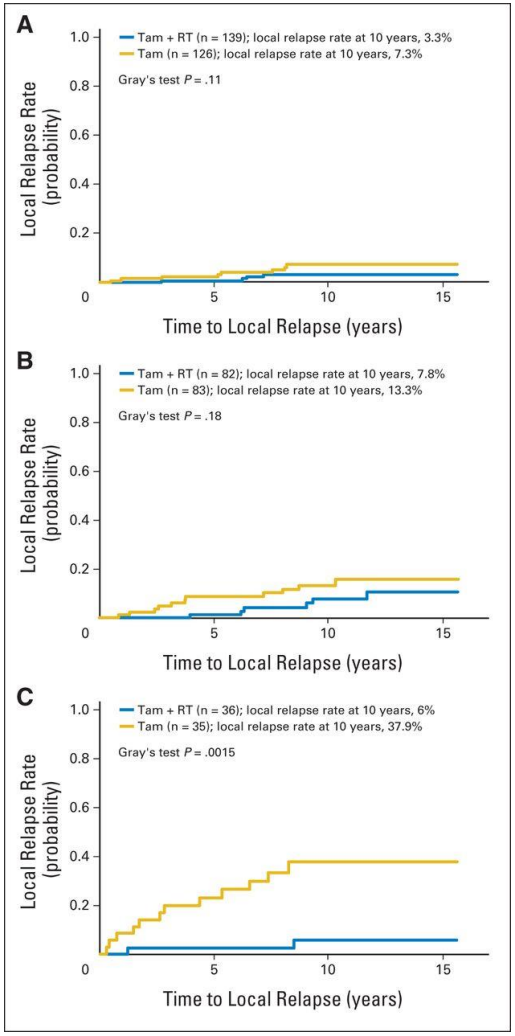
Figure 5: **Absolute reduction in 15-year risk of breast cancer death with radiotherapy (RT) after breast-conserving surgery versus absolute reduction in 10-year risk of any (locoregional or distant) recurrence**

Participant flow schema.



Fei-Fei Liu et al. JCO 2015;33:2035-2040

Cumulative incidence of ipsilateral breast relapse in the combined cohort for (A) luminal A, (B) luminal B, and (C) luminal human epidermal growth factor receptor 2 (HER2), HER2-enriched, basal-like, and triple-negative–nonbasal tumors.



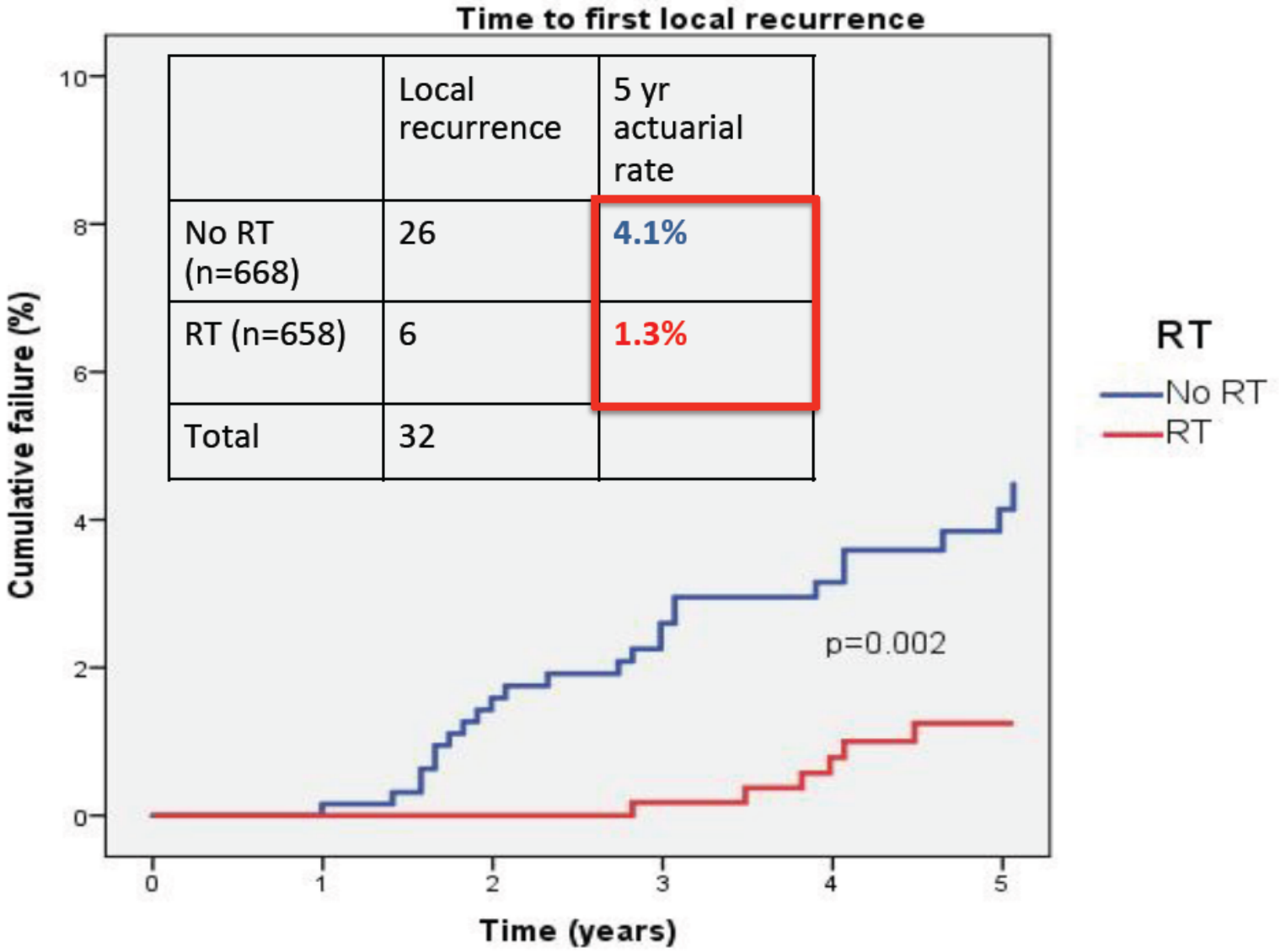
Fei-Fei Liu et al. JCO 2015;33:2035-2040

Posoperative Radiotherapy In Minimum-risk Elderly--**PRIME II**

- 1,326pts between 2003-2009 randomized to WLE and adjuvant hormonal tx +/- WBI in women ≥ 65 yrs
  - T1-2 (up to 3cm)N0M0, ER+ or PR+, clear margins (at least 1mm), N0, margins ≥ 1mm
  - Exclusion: grade 3 + LVSI
  - RT (40-50Gy in 15-25fxn)
  - 98 centers in 6 countries
  - Median f/u 5 years

Kunkler, Lancet Oncol, 2015

PRIME II



	Local recurrence	5 yr actuarial rate
No RT (n=668)	26	4.1%
RT (n=658)	6	1.3%
Total	32	

PRIME II: Unplanned Subgroup Analysis

	Local Recurrence N (%)		
ER	**No RT**	**RT**	**p-value**
High	**20/593 (3.3%)**	**5/601 (1.2%)**	**0.03**
Low	**6/65 (10%)**	**0/55 (0.0%)**	**0.026**

High ER = ER positive, ER ≥ 7, fmol >20, staining >20%, and +++

All others = Low ER

Prime II

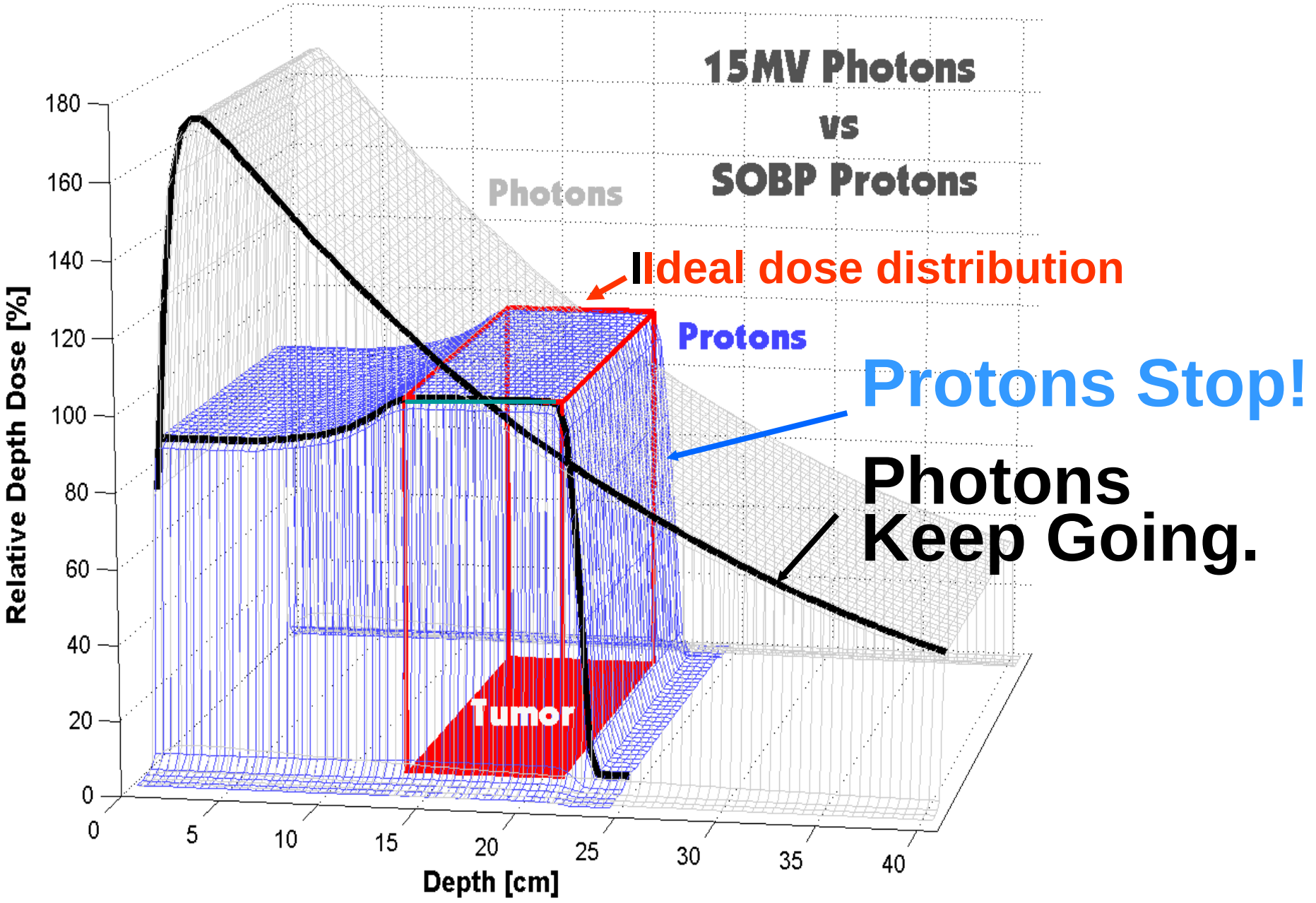
- On MVA, only factor associated with increased risk LR: omission of RT and low ER status
- NS difference RR, DM, OS, contralateral breast cancer
- Conclusions:
  - Omission of RT in women **≥ 65, pT1-T2 (up to 3cm) pN0, ER+ or PR+ breast cancer s/p BCS with endocrine therapy**: 5yr IBTR 4.1% (vs. 1.3%)
  - ***RT does reduce IBTR, but the absolute reduction is small***
  - Omission of RT does not impact OS (not surprising)

Ongoing/Planned Studies of Observation in Low Risk Breast Cancer

- Jagsi (Michigan)–Multi-institution Prospective Single Arm Study of Observation in Patients Age 50-69 with Luminal A and Low Oncotype
- Fyles et al (Canada)-Single Arm Prospective Study of Observation in Patients with Luminal A, Low Ki-67
- Bellon (Harvard)-Multi-institution Prospective Single Arm Study of Observation in Patients with Luminal A, Favorable PAM50

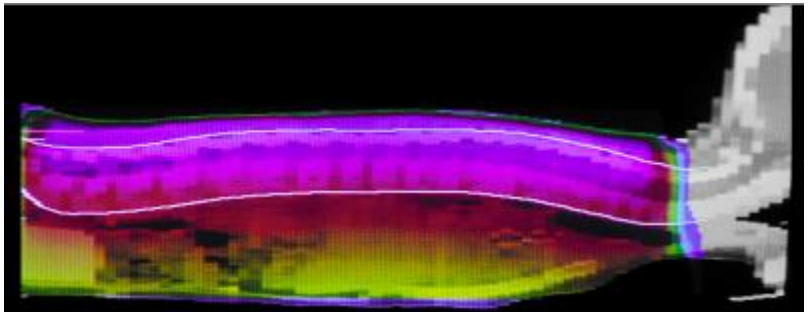
PROTON Beam for Breast Radiation

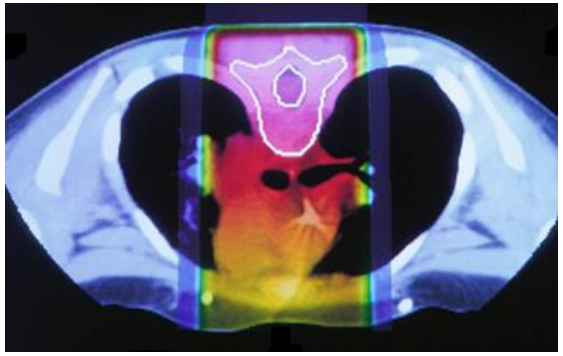
- Protons are just another way of delivering radiation
- The Beam Characteristics with no “exit” dose allow for advantages in some situations
- However, the technology is more expensive currently such that one must clearly demonstrate a benefit to justify its use to the “payers”
- A “better dosimetric plan” on paper can not always serve as justification for the use of proton beam
- While it can be used to deliver partial breast irradiation, it can be difficult currently to justify its routine use in this setting given the excellent dose distributions that can be achieved using other methods (interstitial, balloon based, external beam, intraoperative).

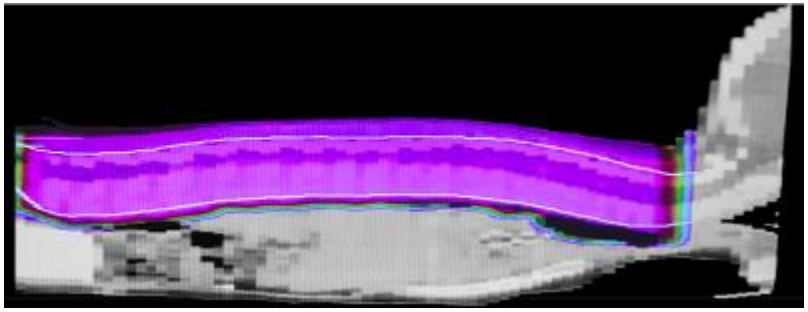

15MV Photons
vs
SOBP Protons
Photons
Ideal dose distribution
Protons
Protons Stop!
Photons
Keep Going.
Tumor
Relative Depth Dose [%]
Depth [cm]
0
20
40
60
80
100
120
140
160
180
0
5
10
15
20
25
30
35
40

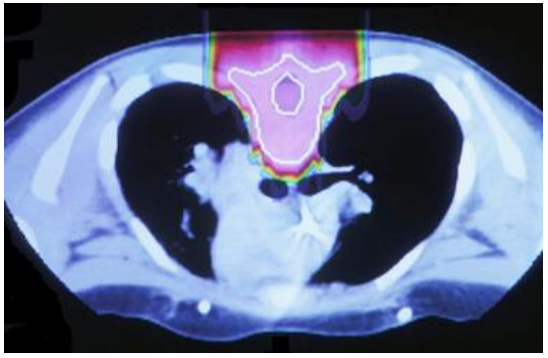
Clinical Benefit: Avoid collateral dose

Pediatric Medulloblastoma









% Dose Rec'd

Proton Beam Partial Breast Irradiation

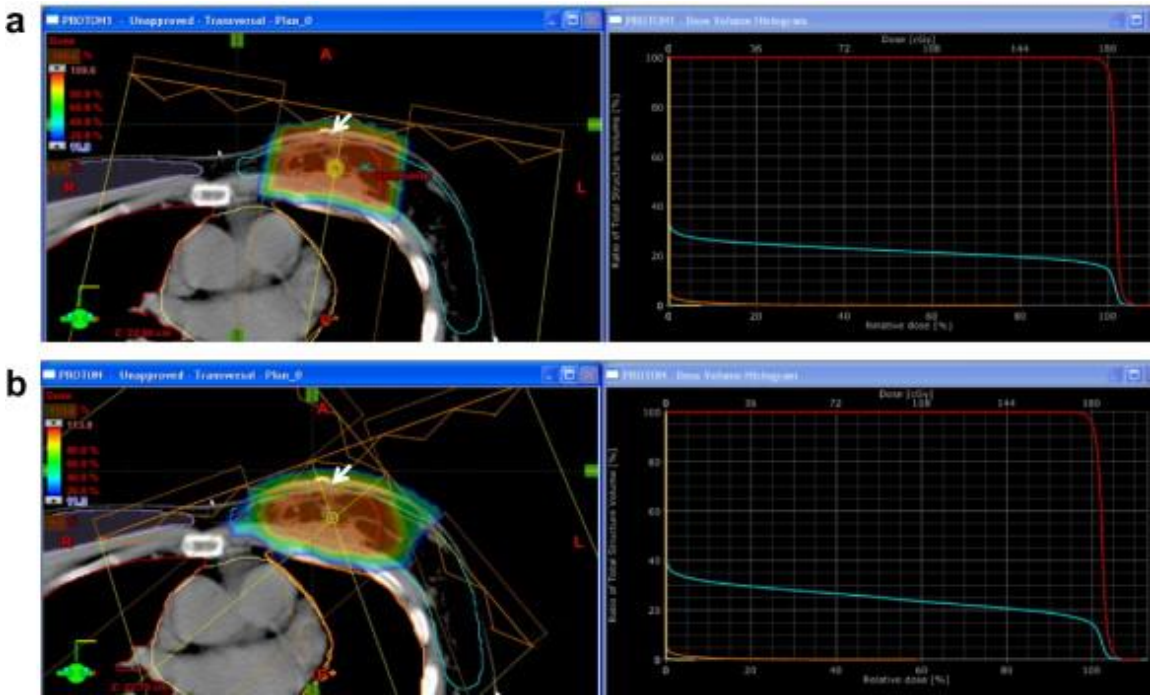


Fig. 1. Dose distribution and dose volume histogram of (a) single proton beam and (b) two field proton beam using the anterior obliqe angle in the axial plane. Lumpectomy cavity (pink); PTV (red); ipsilateral breast (cyan); lung (orange); and heart (yellow) ar...

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Phase II trial of proton beam accelerated partial breast irradiation in breast cancer

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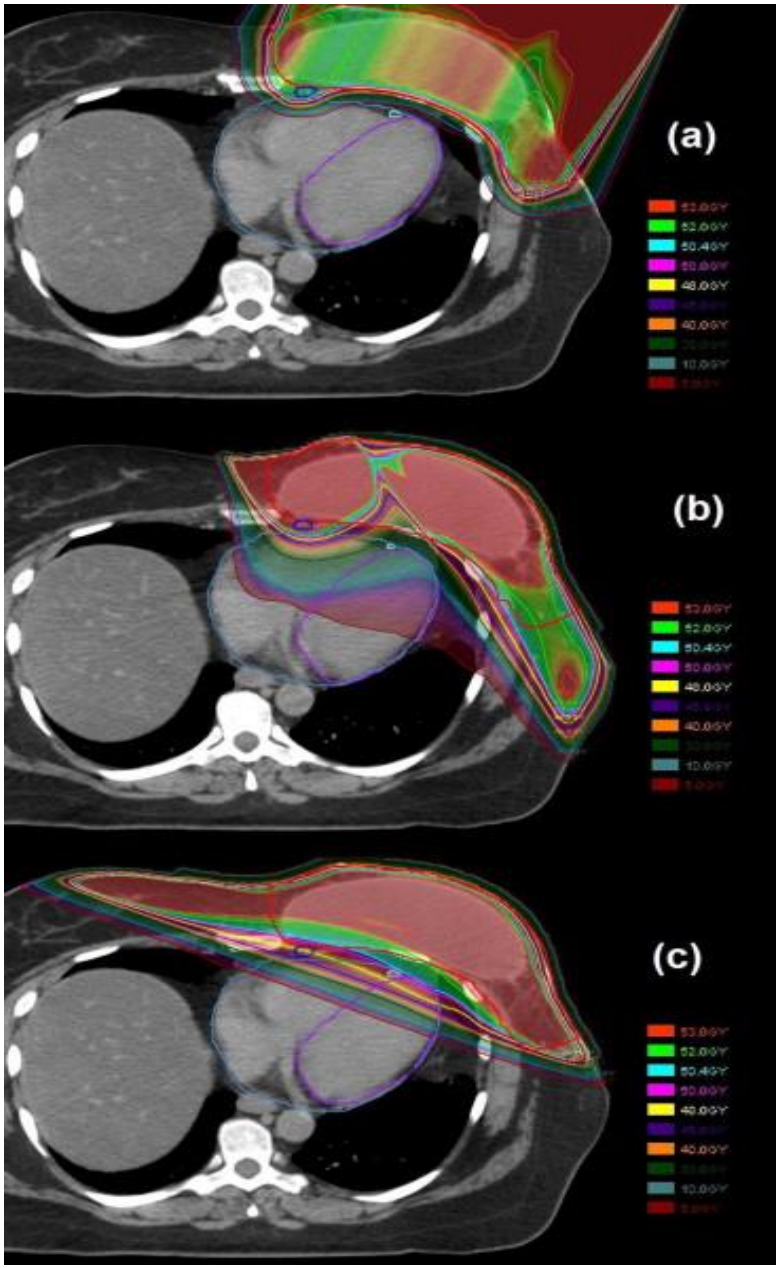
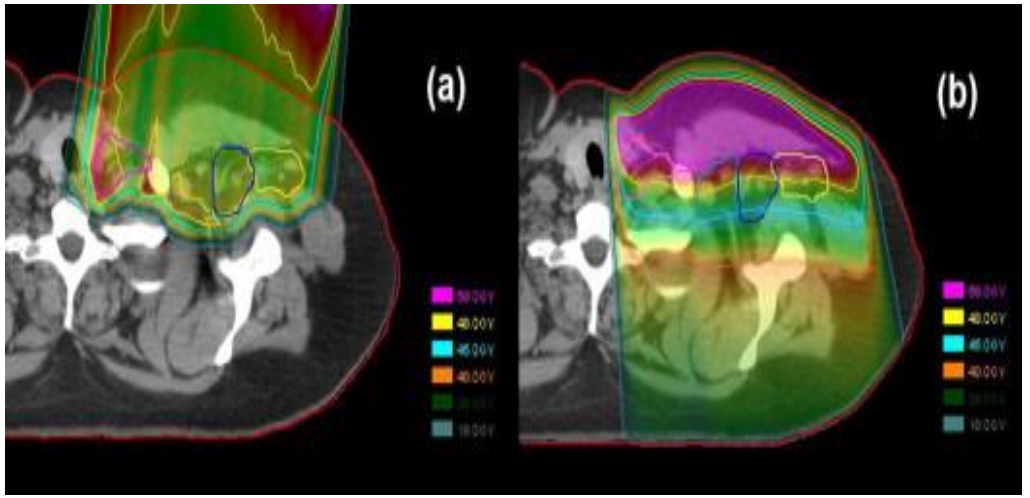
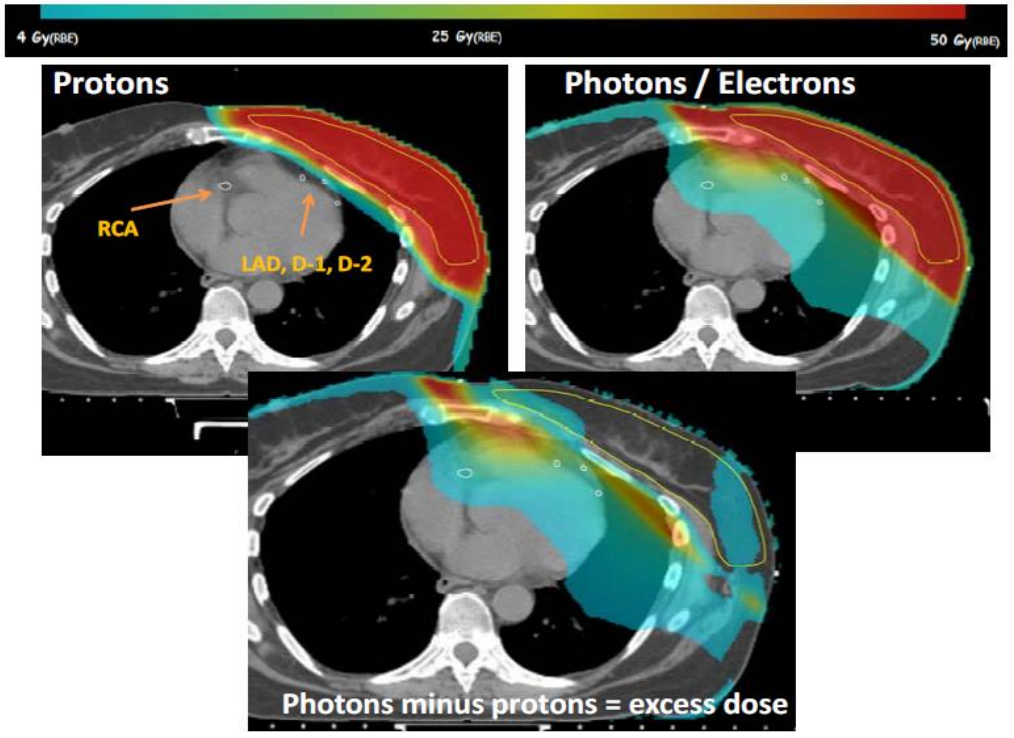
Proton Beam for regional nodal and post-mastectomy Radiation

- In certain situations where one needs to treat the breast/chest wall and regional nodes, including the internal mammary nodes there may be an advantage with protons, particularly when patient anatomy results in relatively high doses to the heart/lungs
- Currently, with conventional radiation, 3-D planning, breath holding and other technical advances, acceptable doses to normal tissues can be achieved.
- Current ongoing trial for patients in whom regional nodal irradiation is indicated: Randomized Trial of Protons vs. Photons with cardiac events/toxicity as endpoint

PROTONS vs. Photons/Electrons in PMRT







Conclusions

- Hypofractionated Whole Breast is a Reasonable Option for a majority of women with early stage breast cancer
- Partial Breast Irradiation is a reasonable option for selected patients
- Interstitial, Balloon Based or External Beam are all reasonable options when applied appropriately
- Intraoperative is also an option in selected cases, preferably on prospective trials
- Elimination of radiation is reasonable in selected cases, preferably on prospective trials
- Proton Beam may offer advantages in selected cases where regional nodal irradiation is indicated. This should be evaluated on the ongoing prospective randomized trial

Thank you for your attention!

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