6th Annual Breast Cancer Symposium Hudson NY

De-escalation of RT

Beryl McCormick MD October 18, 2024

"Short Course" Breast Radiation : decrease in treatment number

Less than Whole Breast or PBI: Decrease in volume of tissue

NSABP B-51:Identifying patients who DON"T need regional node RT

Recent trials for Low-risk Breast Caner evaluating NO RT

What is hypofraction?

- A method of prescribing a course of external beam radiation, with higher doses per day or per fraction, and fewer total treatment visits than “Standard Radiation”
- Standard Radiation = 200 cGy per day, five days per week
- Total doses with hypofractionation will be a lower numeric sum than with standard radiation, but the “radiation biology” equivalent dose

Radiation Biology Hypothesis

- α/β ratio thought for many years to be about 10 for breast cancer, similar to skin, mucosa, and squamous cell cancer of the H & N.
- Newer evidence suggests α/β ratio for adenocarcinoma, (breast and prostate) is much lower and closer to late-reacting healthy tissue
- This supports using fewer but larger fractions for breast tissue and breast cancers

Breast Radiotherapy

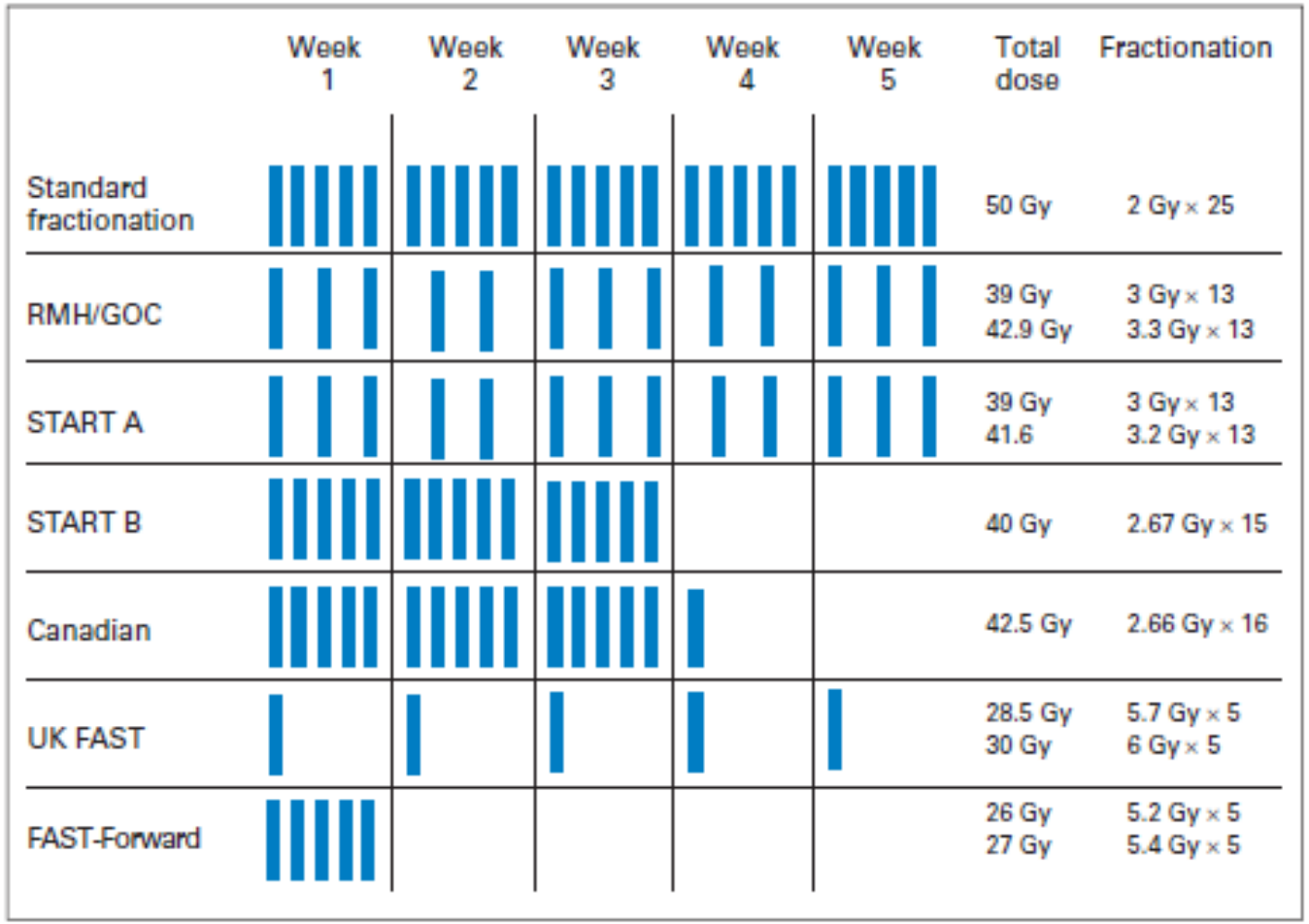
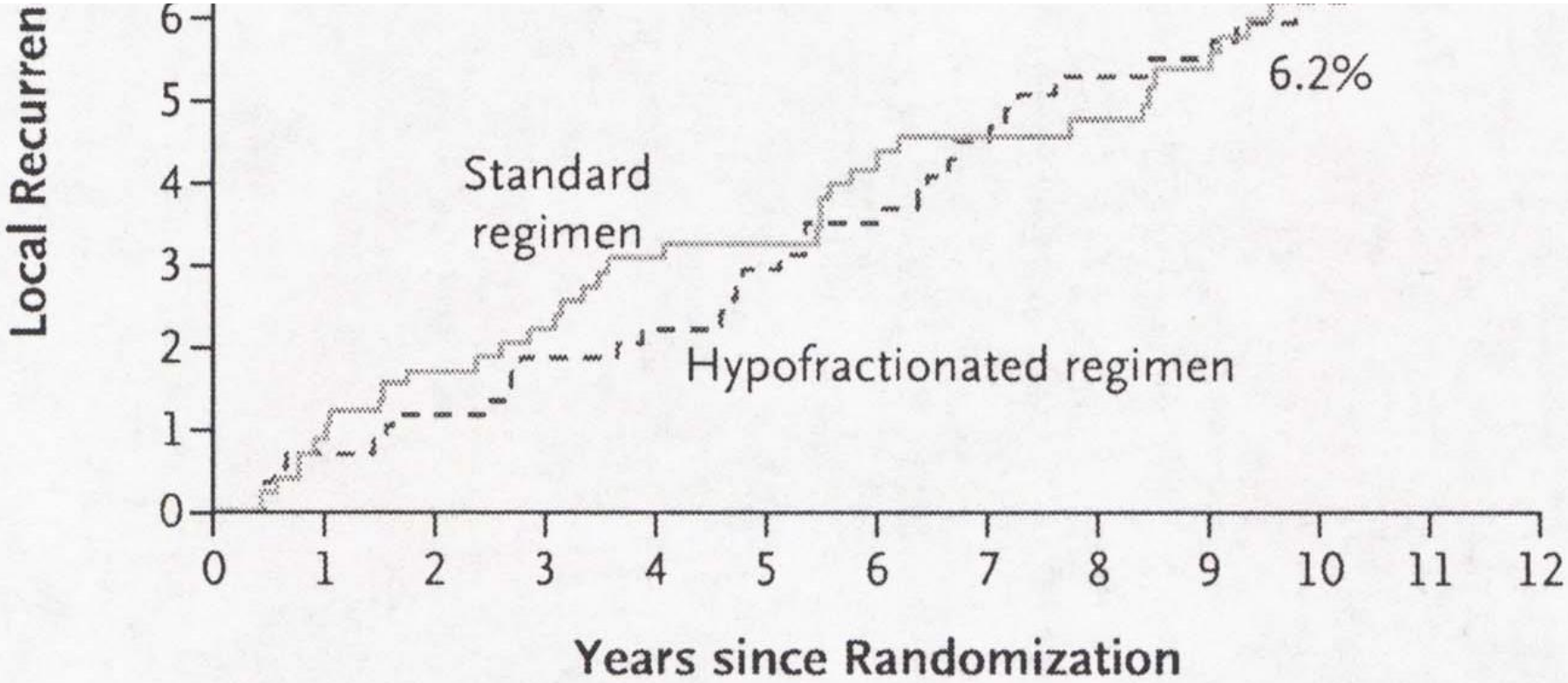


Fig 1. Summary of fractionation schedules tested in randomized trials. RMH/GOC, Royal Marsden Hospital/Gloucester Oncology Center; START A, Standardization of Breast Radiotherapy Trial A; START B, Standardization of Breast Radiotherapy Trial B; Canadian, Randomized Trial of Breast Irradiation Schedules After Lumpectomy for Women With Lymph Node–Negative Breast Cancer; UK FAST, United Kingdom FAST Trial (Radiation Therapy in Treating Women With Localized Breast Cancer); FAST-Forward, Randomized Clinical Trial Testing a One Week Course of Curative Whole Breast Radiotherapy Against a Standard Three Week Schedule in Terms of Local Cancer Control and Late Adverse Effects in Patients With Early Breast Cancer.

Hypofractionated BCS Canadian Trial

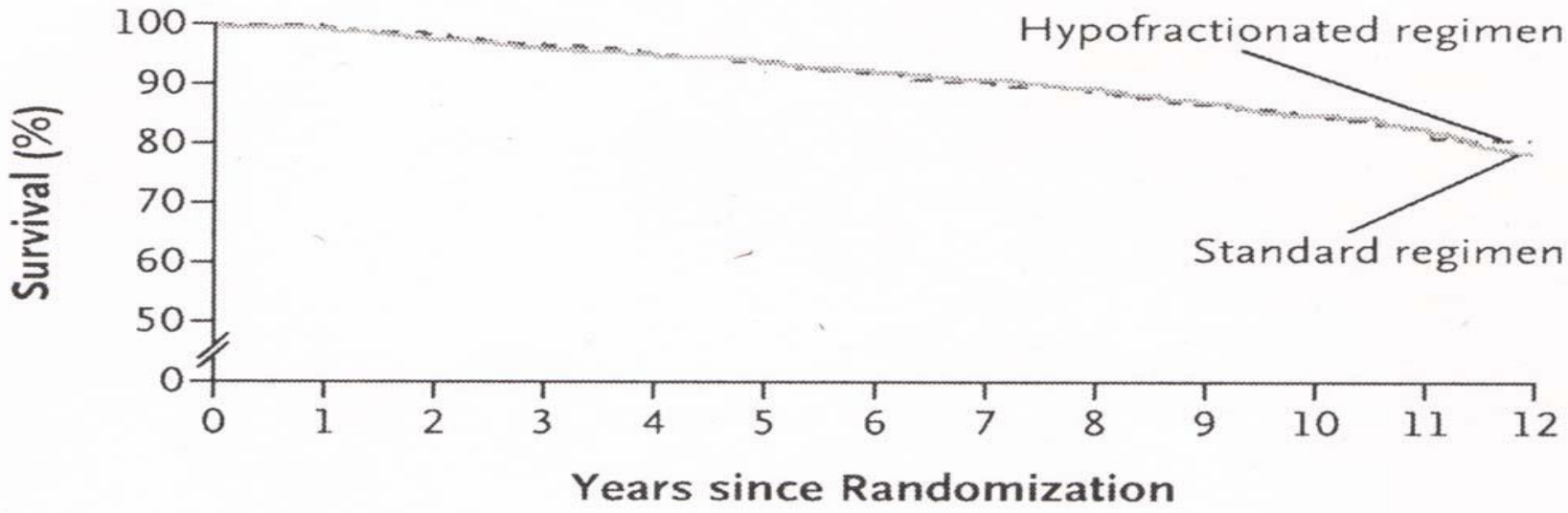
1234 women	ALL Node Negative
Stratified by age, T size, adjuvant tx and center	41 % received tam, 11 % chemo
50 Gy in 25 fx over 5 weeks vs. 42.5 Gy in 16 fx over 22 days	No boost



No. at Risk

Standard regimen	612	597	578	562	550	553	499	485	470	449	410	317	218
Hypofractionated regimen	622	609	592	569	548	524	500	472	447	430	406	330	214

B



No. at Risk

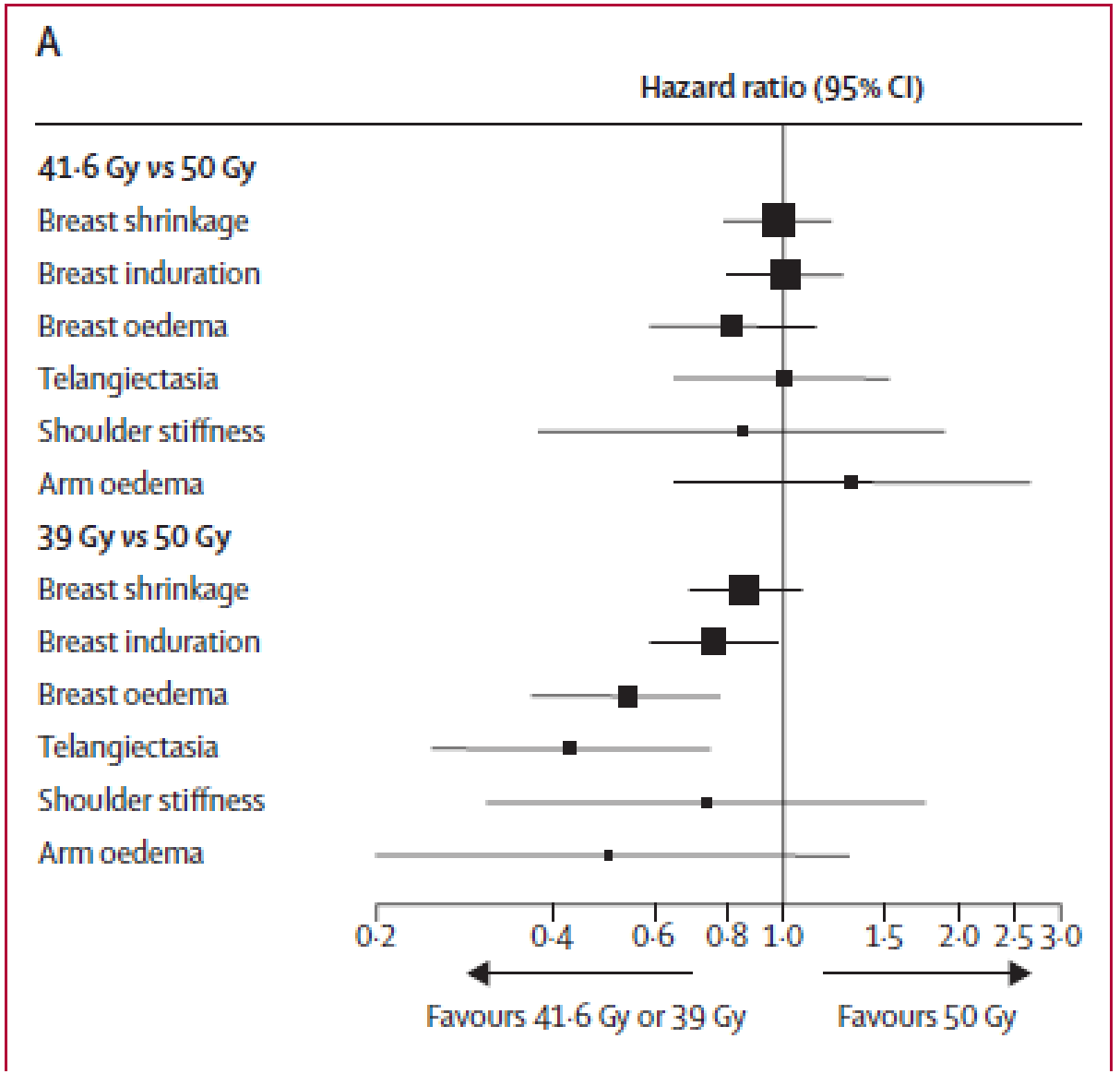
Standard regimen	612	606	594	583	573	559	535	519	505	487	453	355	242
Hypofractionated regimen	622	617	605	592	576	562	539	517	495	482	455	369	241

Figure 1. **Outcomes in Patients with Breast Cancer Who Received a Hypofractionated Regimen of Radiation Therapy as Compared with Patients Who Received the Standard Regimen.**

Panel A shows Kaplan–Meier estimates for local recurrence ($P<0.001$ for noninferiority), and Panel B shows Kaplan–Meier estimates for overall survival ($P=0.79$).

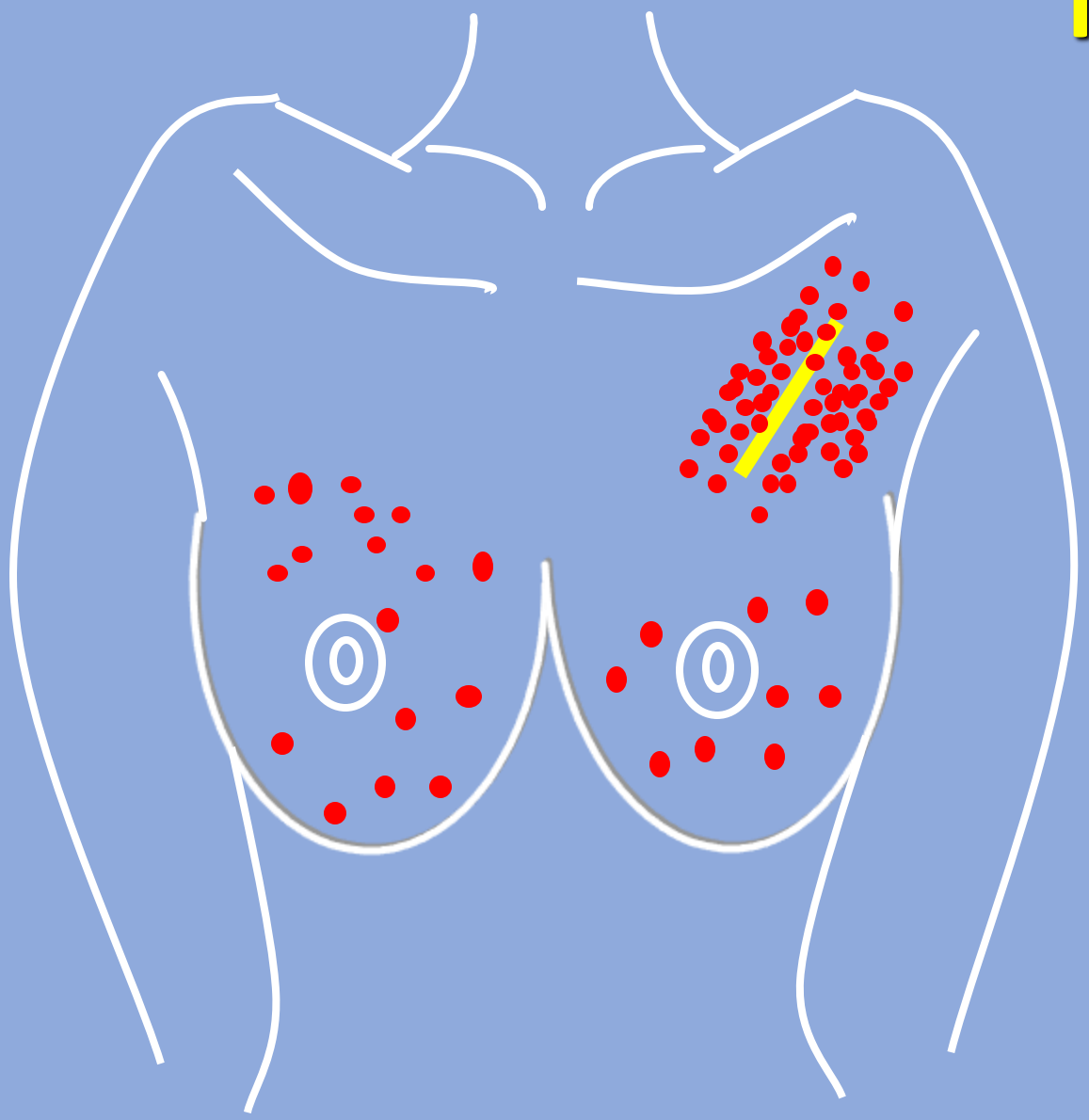
Late effects: Start A

Cosmetic Outcome; standard vs moderate hypofractions



Brachytherapy and External Beam PBI after breast surgery

PBI is also hypofractionated, short course radiation, but only the lumpectomy bed or cavity is treated, not the entire breast



Milan 3 (567 cases)

12 years follow-up

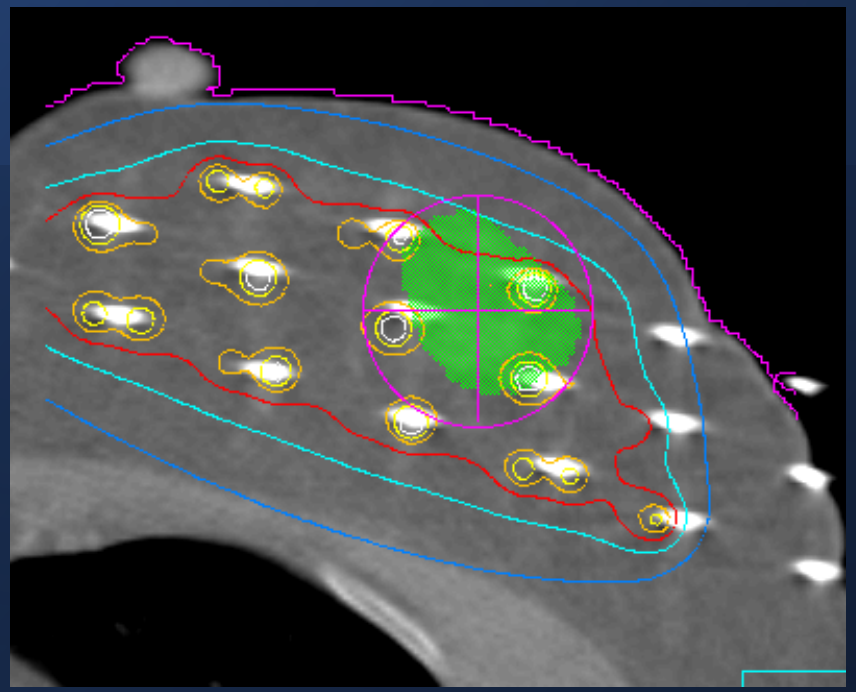
67 Recurreces

58 in the operative area

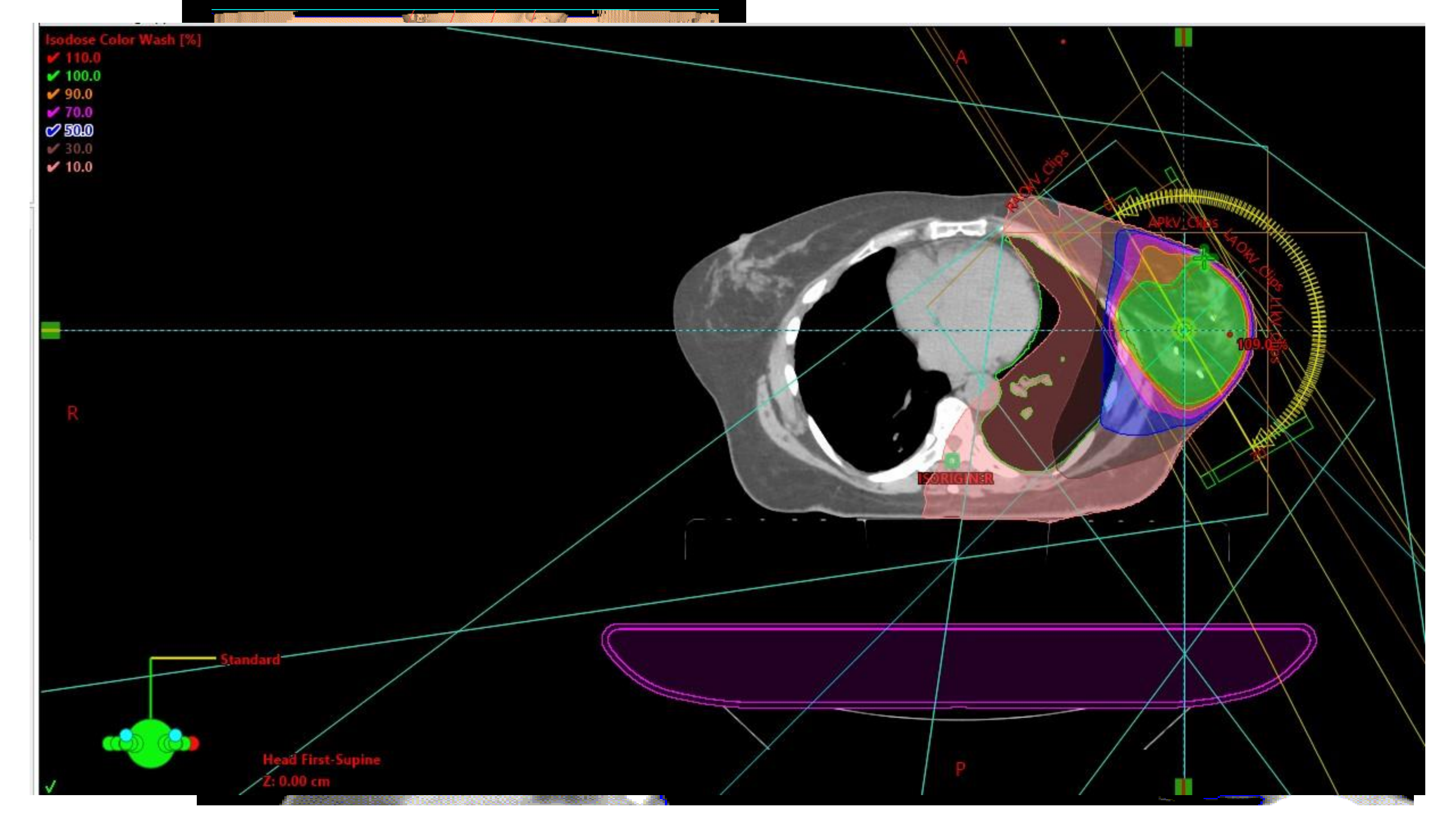
9 in other quadrants

13 Contralateral breast carcinomas

Breast Brachytherapy:
Multi-plane catheter-based Radiotherapy



Elliptical Balloons

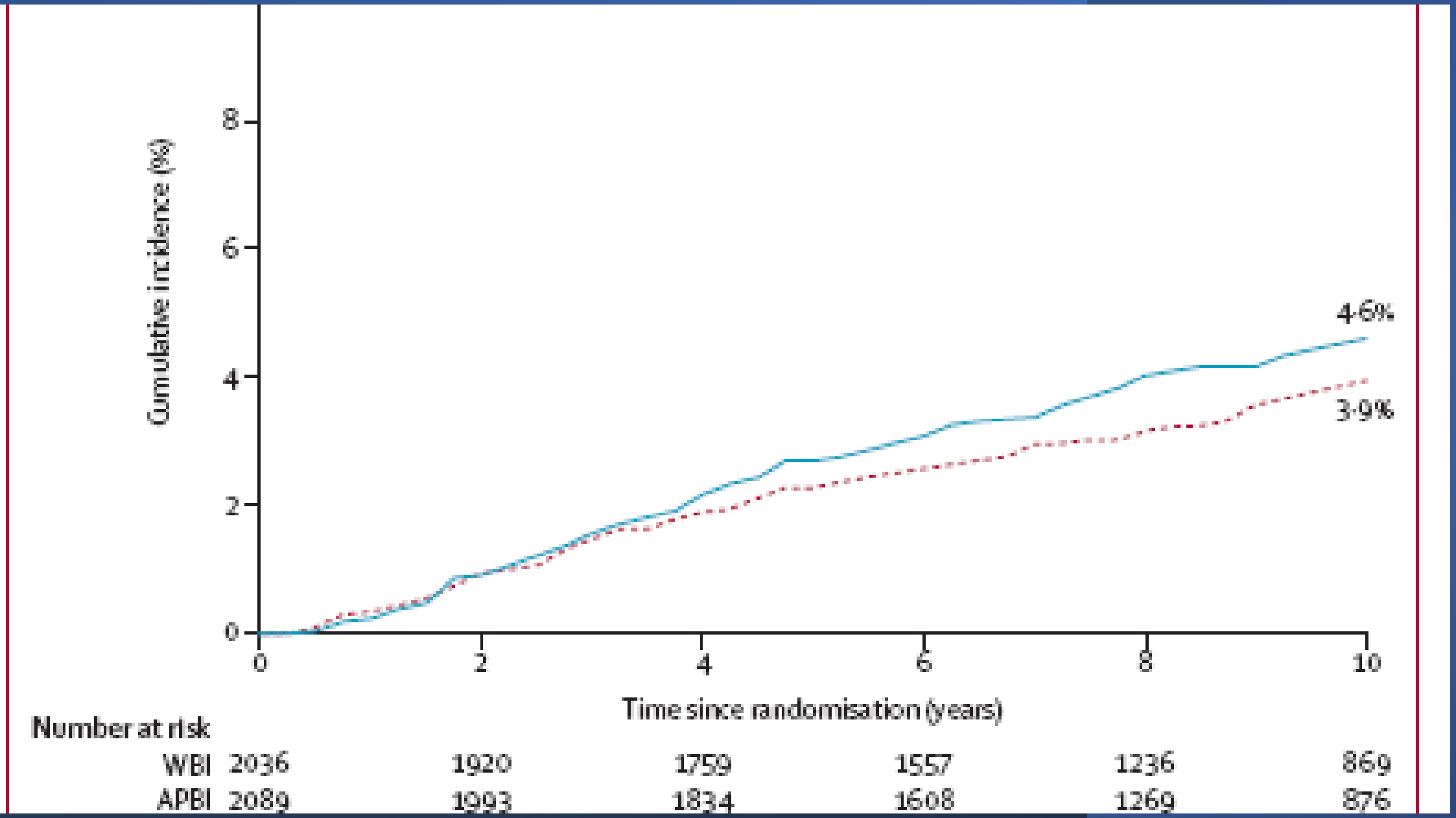

Isodose Color Wash [%]
110.0
100.0
90.0
70.0
50.0
30.0
10.0
A
R
P
RAOkV_clips
APkV_clips
LAOkV_clips
109.0
ISORIGINER
Standard
Head First-Supine
Z: 0.00 cm

RTOG 0413-NSABP B-39

Prospective Phase III trial comparing 1 week of BID Partial Breast RT (PBI) to standard 6 week whole breast RT after lumpectomy

Includes 4216 patients: DCIS (25 %), Stage I (65 %), and Stage II (10 %) Breast Cancer

At 10 years, local control in the treated breast was 95.2 % in PBI Group and 95.9 % in standard arm, which was significant (Trial set up as non-inferiority)


Cumulative incidence (%)
8
6
4
2
0
4·6%
3·9%
0
2
4
6
8
10
Time since randomisation (years)
Number at risk
WBI 2036 1920 1759 1557 1236 869
APBI 2089 1993 1834 1608 1269 876

PBI at MSK

- The BID treatment regimen over 5 days was dropped
- Thru a dose escalation trial (Powell et al), a dose of 40 Gy given once per day over 2 weeks became the standard.
- Other shorter fractionation: Florence Trial , 6 Gy per day, given in 5 non-consecutive days. THIS fractionation has become the most widely used RT schedule in our department over the last year.
- MSK trial which recently met accrual: (19-300) used 3 fractions only.

PBI Conclusions

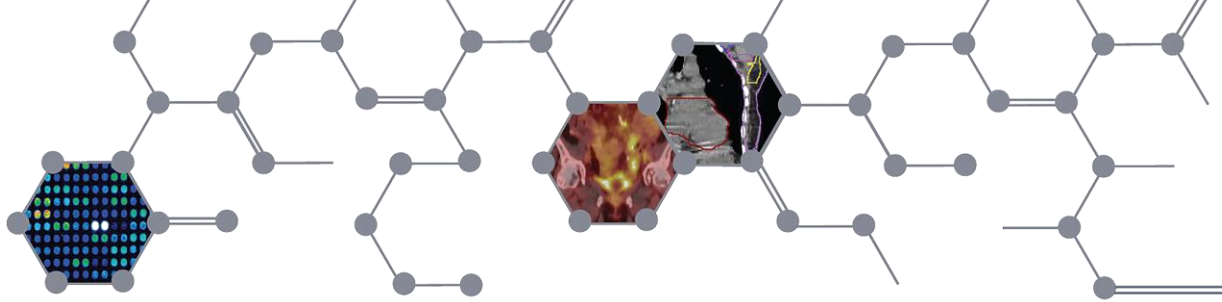
- A good choice after breast conserving surgery for older patients who are more interested in a short course of radiation
- Patients need to have a cavity to whole breast volume ration of no more than 25 %, to avoid treating a large part of the breast (in a small breasted patient with a large cavity) to the higher doses.
- Prefer standard whole breast in those under 50, or with multi-focal cancers, aggressive cancers (such as triple negative), or family history for higher risk of cancer

Hypofractionation Summary

- Hypofractionation schedule of 15-16 treatments over 3 weeks and a day most commonly used
- Shorter schedules of as little as 1 week of treatment used if patient is frail and cosmesis not major concern (or in Pandemic)
- A recent RTOG study demonstrated that the “boost” dose could be incorporated into the daily whole breast treatment in many patients, resulting in no need for the extra “boost” week of treatment

NRG ONCOLOGY

Advancing Research. Improving Lives.™



DEC 5-9, 2023
SAN ANTONIO BREAST CANCER SYMPOSIUM®

Loco-regional Irradiation in Patients with Biopsy-proven Axillary Node Involvement at Presentation Who Become Pathologically Node-negative After Neoadjuvant Chemotherapy: Primary Outcomes of NRG Oncology/NSABP B-51/RTOG 1304

Eleftherios P. Mamounas[1*], Hanna Bandos[2], Julia R. White[3*], Thomas B. Julian[4], Atif J. Khan[5], Simona F. Shaitelman[6], Mylin A. Torres[7], Frank A. Vicini[8], Patricia A. Ganz[9], Susan A. McCloskey[10], Peter C. Lucas[11,12], Nilendu Gupta[3], X. Allen Li[13], Beryl McCormick[5], Saumil Gandhi[6], Rahul D. Tendulkar[14], Vivek S. Kavadi,[15], Masahiko Okamoto[16], Samantha Andrews Seaward[17], William J. Irvin, Jr.[18], Jolinta Lin [7], Robert Mutter[19], Thierry M. Muanza[20], Andrew A. Muskovitz[21], Reshma Jagsi[22], Anna C. Weiss[23,24], Walter J. Curran, Jr.[7], and Norman Wolmark[12]

*These authors contributed equally.

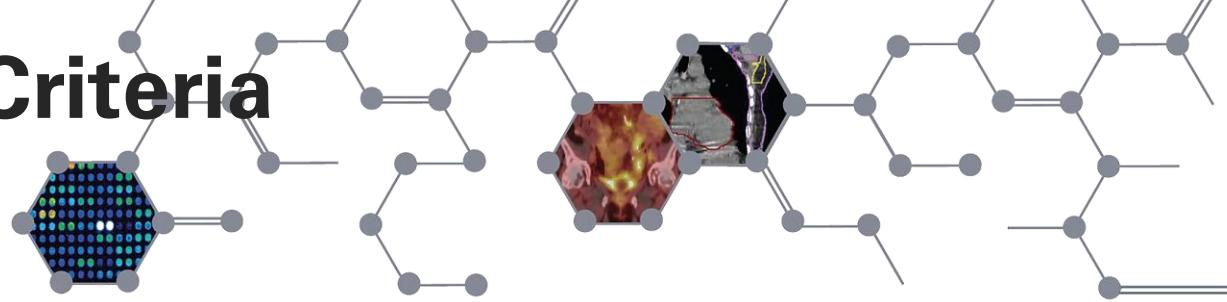
Background/Rationale

- For patients who undergo upfront surgery and are found to have pathologically positive axillary lymph nodes, the benefit of adjuvant regional nodal irradiation including the chest wall after mastectomy (CWI+RNI) or when added to whole breast irradiation after lumpectomy (WBI+RNI) is well established.[1]
- Patients who present with axillary lymph node involvement, receive neoadjuvant chemotherapy (NAC), and are found to be pathologically node-negative at surgery (ypN0), have lower loco-regional recurrence rates compared to those who remain pathologically node-positive (ypN+).[2]
- In this phase III, randomized trial we evaluated whether CWI+RNI after mastectomy or WBI+RNI after lumpectomy significantly improves invasive breast cancer recurrence-free interval in clinically node (+) patients who are found to be ypN0 after NAC.

1. McGale, P, et al: Lancet 383(9935): 2127-2135. 2. Mamounas EP, et al: J Clin Oncol 2012; 30(32):3960-3966

Eligibility Criteria

NRG ONCOLOGY
Advancing Research. Improving Lives.™



DEC 5-9, 2023
SAN ANTONIO BREAST CANCER SYMPOSIUM®

- **Eligible Patients:**
  - Clinical cT1-3, N1, M0 invasive breast cancer
  - Biopsy-proven N+ by FNA/core needle biopsy
  - Complete ≥8 weeks of neoadjuvant chemotherapy (with anti-HER2 therapy if HER2+)
  - Axillary nodes histologically negative after NAC (ypN0) by sentinel lymph node biopsy (with ≥2 nodes removed), axillary lymph node dissection, or both
  - Mastectomy or lumpectomy
  - Known ER/PR and HER-2 status at presentation

Study Schema

NRG ONCOLOGY
Advancing Research. Improving Lives.™

DEC 5-9, 2023
SAN ANTONIO BREAST CANCER SYMPOSIUM®

Clinical T1-3, N1, M0 BC

Axillary Lymph Node (+) (FNA or Core Needle Biopsy)

Neoadjuvant Chemo (+ Anti-HER2 Therapy for HER2 neu + Pts)
Path Negative Axillary Nodes at Surgery (ALND or SLNB ± ALND)

Stratification
Type of Surgery (Mastectomy, Lumpectomy); **HR-status** (+/–);
HER2 status (+/–); **Adjuvant Chemo** (yes/no); **Breast pCR** (yes/no)

Randomization

No Regional Nodal Irradiation ("No RNI")	**Regional Nodal Irradiation ("RNI")**
Breast XRT if BCS	Breast XRT if BCS
No Chest Wall XRT if Mastectomy	Chest Wall XRT if Mastectomy

FNA: Fine Needle Aspiration; ALND: Axillary Lymph Node Dissection; SLNB: Sentinel Lymph Node Biopsy; XRT: Radiation; BCS: Breast Conserving Surgery

NSAPB B 51 Randomization

- Patients enrolled in the study and found to have a complete response in the lymph nodes after neo-adjuvant chemotherapy at surgery were randomized
- For mastectomy patients , one cohort received standard 5 week radiation to the chest wall and nodes, and the other cohort had no radiation
- For lumpectomy patients, one cohort received standard radiation to the breast and the nodes, and the other cohort received breast radiation only

Baseline Characteristics (1)

NRG ONCOLOGY
Advancing Research. Improving Lives.™

DEC 5-9, 2023
SAN ANTONIO BREAST CANCER SYMPOSIUM®

Characteristic		No RNI (%) n=821	RNI (%) n=820
Age	**Median**	52 years	52 years
	≤ 49 yrs	40	41
	50-59 yrs	32	33
	≥ 60 yrs	28	26
Race	Asian	8	6
	Black/African American	17	18
	White	69	69
	Unknown/Other	6	6
Ethnicity	Hispanic or Latino	14	14
	Not Hispanic or Latino	83	82
	Unknown	3	3
Clinical Tumor Size	T1	21	21
	T2	59	61
	T3	20	18

Baseline Characteristics (2)

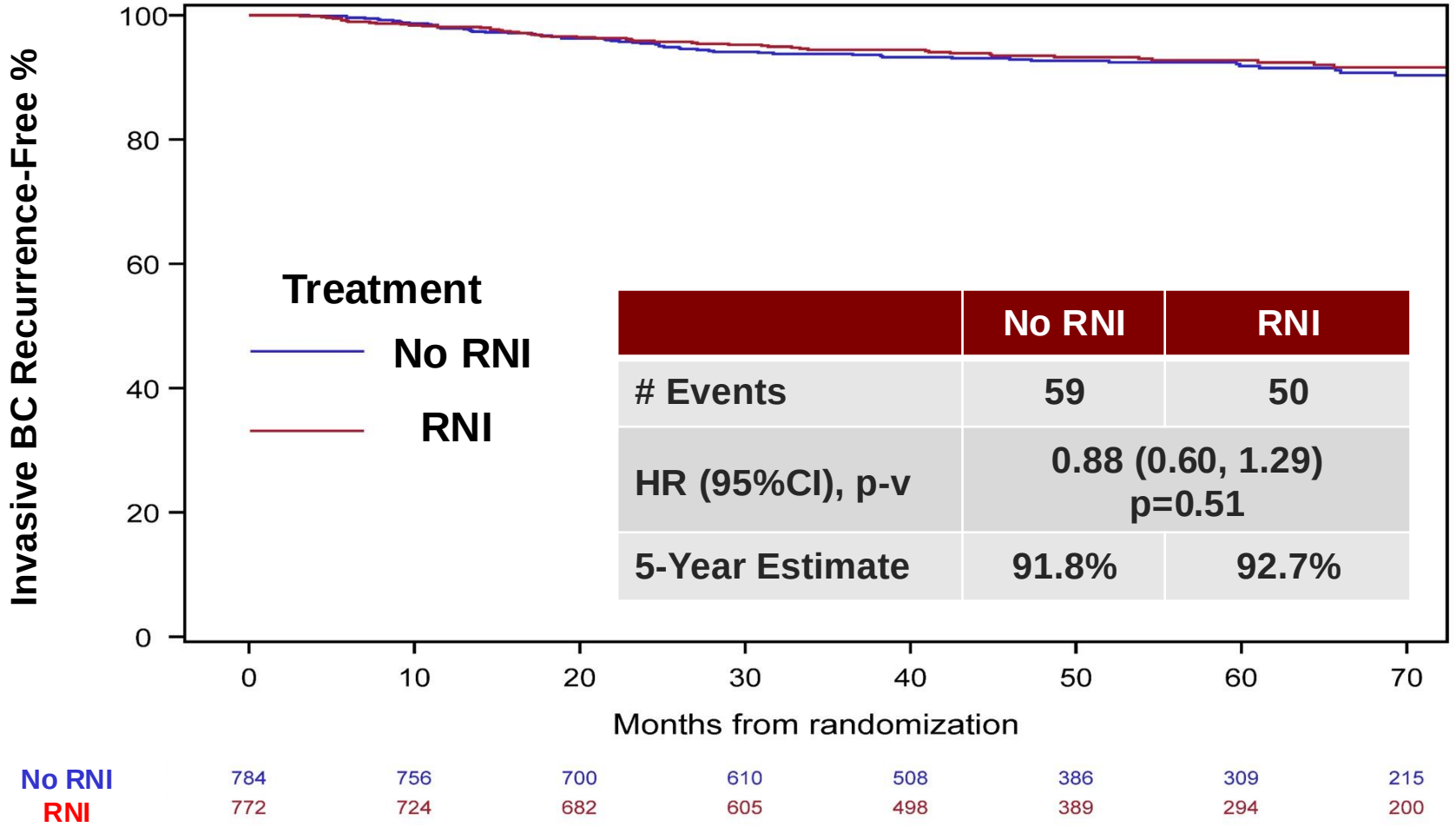
NRG ONCOLOGY
Advancing Research. Improving Lives.™

DEC 5-9, 2023
SAN ANTONIO BREAST CANCER SYMPOSIUM®

Characteristic		No RNI (%) n=821	RNI (%) n=820
Tumor Subtype	Triple-negative ER+ and/or PR+/HER2- ER- and PR-/HER2+ ER+ and/or PR+/HER2+	21 22 25 31	23 20 24 33
Breast Surgery	Lumpectomy Mastectomy	58 42	58 42
Axillary Surgery	SLNB ALND (+/-SLNB)	55 45	56 44
pCR in Breast	No Yes	22 78	21 79
Adjuvant Chemotherapy	No Yes	100 <1	99 1

Primary Endpoint

Invasive Breast Cancer Recurrence-free Interval (IBCRFI)



	No RNI	RNI
# Events	59	50
HR (95%CI), p-v	0.88 (0.60, 1.29) p=0.51	
5-Year Estimate	91.8%	92.7%

At MSK, the results of this trial were adopted as outlined below

- For patients with a ypT0N0, or ypTisN0, or ypT1N0 response, regional nodal radiation was omitted, per the results of NSAPB B51 trial
- For patients who had ypT2 residual disease in the breast, but were N0, regional node radiation is considered optional
- Standard regional nodal RT if the patient had residual disease in the nodes, including just mic residual.

Total De-escalation: No RT for patients with low risk invasive cancer

Well known trials with long follow up

- CALGB 9343 “Elderly” trial: T1N0 Invasive Cancer, ER (+), randomized to Standard Whole Breast RT and 5 years Tamoxifen, or just 5 years Tamoxifen. Age 70 or above
- Prime II Trial: Same trial but for Age 65 and above
- Results showed no differences in survival, DFS, need for mastectomy
- The risk of Local Recurrence was 10 % without radiation, and 2 % with radiation, at 10 years.
- This result was statistically significant

Recent and ongoing trials for pT1 Cancers

- Single arm Studies include:
- Idea for ER, PR (+) cancers with an Oncotype score of 18 or less,
- Lumina for ER, PR (+), Her 2 (-) and Ki67 of 13.25 or less,
- Precision, for PAM 50 score and otherwise same criteria
- Minimum age for entry is 50 or 55 years.
- All enrolled patients get endocrine therapy only

Early Results : IDEA Trial

- 186 patients enrolled, and followed at least 56 months.
- Ipsilateral Breast recurrence: 3.3% in the 50-59 y/o group and 3.6 % in the 60-69 y/o group
- Caveat: These are all ER (+), highly favorable cancers which tend to recur many years from diagnosis
- Caveat: Many patients do not like taking ET for 5 years

Early Results: Lumina Trial

- 740 patients enrolled, with a median age of 67 years, and 11.6 % older than 75
- Follow up was 5 years
- 10 patients recurred, for a cumulative incidence of 2.3 % . Of those 6 were true local recurrences and 4 were elsewhere
- Caveats: Short follow-up and patient profile very favorable

Ongoing Randomized Trials for pT1 Cancer

- EXPERT for luminal A using Pam -50, comparing Endocrine Therapy (ET) to Breast RT plus ET
- Natural Study using IHC, comparing ET to ET plus Partial Breast RT (APBI)
- EUROPA using IHC and Ki-67 20 and under, comparing ET to APBI plus ET
- DEBRA using Oncotype score of 18 or less, comparing ET to ET and Breast RT

Thank you and Questions?