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Hypofractionated Post-Mastectomy Radiation

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Issues/Outline

- Hypfractionation-What is it?
- Adoption into Whole Breast RT
- Barriers to Adoption in Mastectomy and Regional Nodal RT
- Review of Data Using Hypofractionation PMRT and Regional Nodes
- Clinical Trials Completed and Ongoing
- Opportunities for Translational Research Evaluating Normal Tissue Complications and Future Directions

What is Hypo-fractionation in Radiation Therapy

- Radiation treatment in which the total dose of radiation is divided into large doses and treatments are given once a day or less often. **Hypofractionated** radiation therapy is given over a shorter period of time (fewer days or weeks) than standard radiation therapy.
- In breast cancer the typical hypofractionated daily dose is higher (2.5-3.3 Gy compared to 2.0 Gy), the total dose is lower (40-50 Gy compared to 50-60 Gy) and the total time is less (3-4 weeks compared to 5-6 weeks)
- Ideally the hypofractionated program should deliver a biologically equivalent dose as the standard regimen with respect to both tumor control normal tissue toxicity

Hypo-fractionated Whole Breast

- Multiple randomized trials now demonstrate equivalent cosmesis and outcome in patients treated with moderately hypo-fractionated whole breast radiation (3-4 weeks) when compared to the conventional 6-7 weeks of daily RT
- Data on randomized trials is now mature out to 10 + years
- Majority of patients on trials were treated to whole breast alone (without regional nodal radiation) and without systemic chemotherapy.
- However, chemotherapy, regional nodal radiation and young age were included in the randomized trials

ASTRO Guidelines!

- **Strong Phase III data that whole breast hypofractionation is acceptable as an alternative to standard fractionation**
  - For women with invasive breast cancer receiving WBI without regional nodal irradiation, the preferred dose-fractionation scheme is HF-WBI to a dose of 40 Gy in 15 fractions or 42.5 Gy in 16 fractions.
  - The decision to offer HF-WBI should be independent of tumor grade, hormone receptor status, HER2 receptor status, or margin status.
  - The decision to offer hypofractionation should be independent of breast cancer laterality.
  - The decision to offer HF-WBI should be independent of chemotherapy received prior to radiation and trastuzumab or endocrine therapy received prior to or during radiation.

New ASTRO Guidelines

- There is no evidence indicating deleterious effects of HF-WBI compared to CF-WBI in either younger or older patients, and thus HF-WBI may be used regardless of age. However, for patients with very long life expectancy, the panel suggests that physicians engage in discussions regarding the 10-year follow-up of existing randomized trials comparing HF-WBI to CF-WBI to ensure appropriately individualized decisions.
- HF-WBI may be used as an alternative to CF-WBI in patients with DCIS
- The decision to offer HF-WBI should be independent of breast size (including central axis separation) provided that dose-homogeneity goals, as outlined in KQ4, can be achieved.

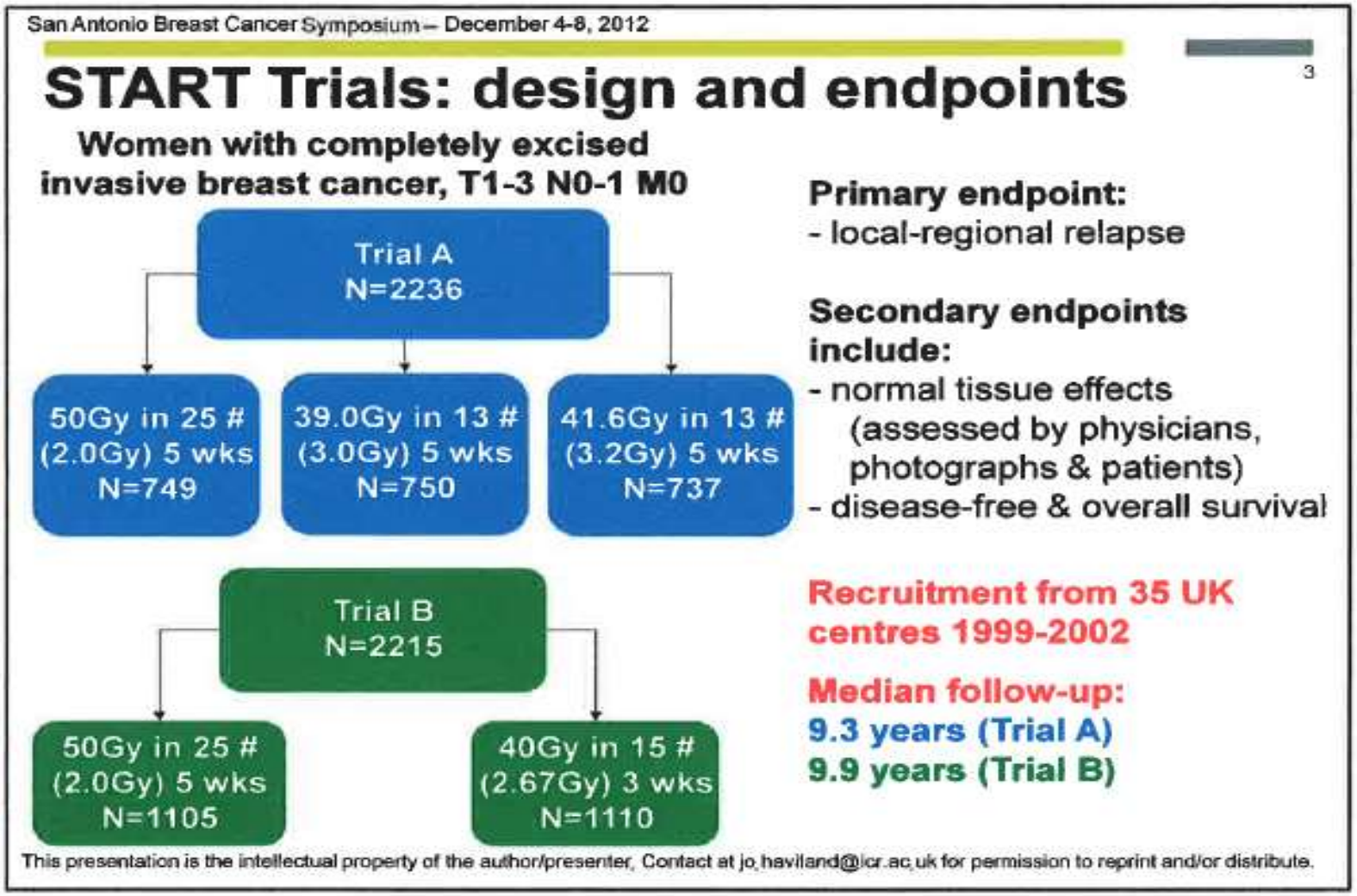
Hypofractionation in clinical radiation therapy

- Clearly shorter course of radiation have evolved as an acceptable (preferred) standard of care for the conservatively treated breast cancer patient
- Hypofractionated regimens in other disease sites including prostate, lung and other sites are evolving as acceptable alternatives
- Why not hypofractionation post mastectomy?

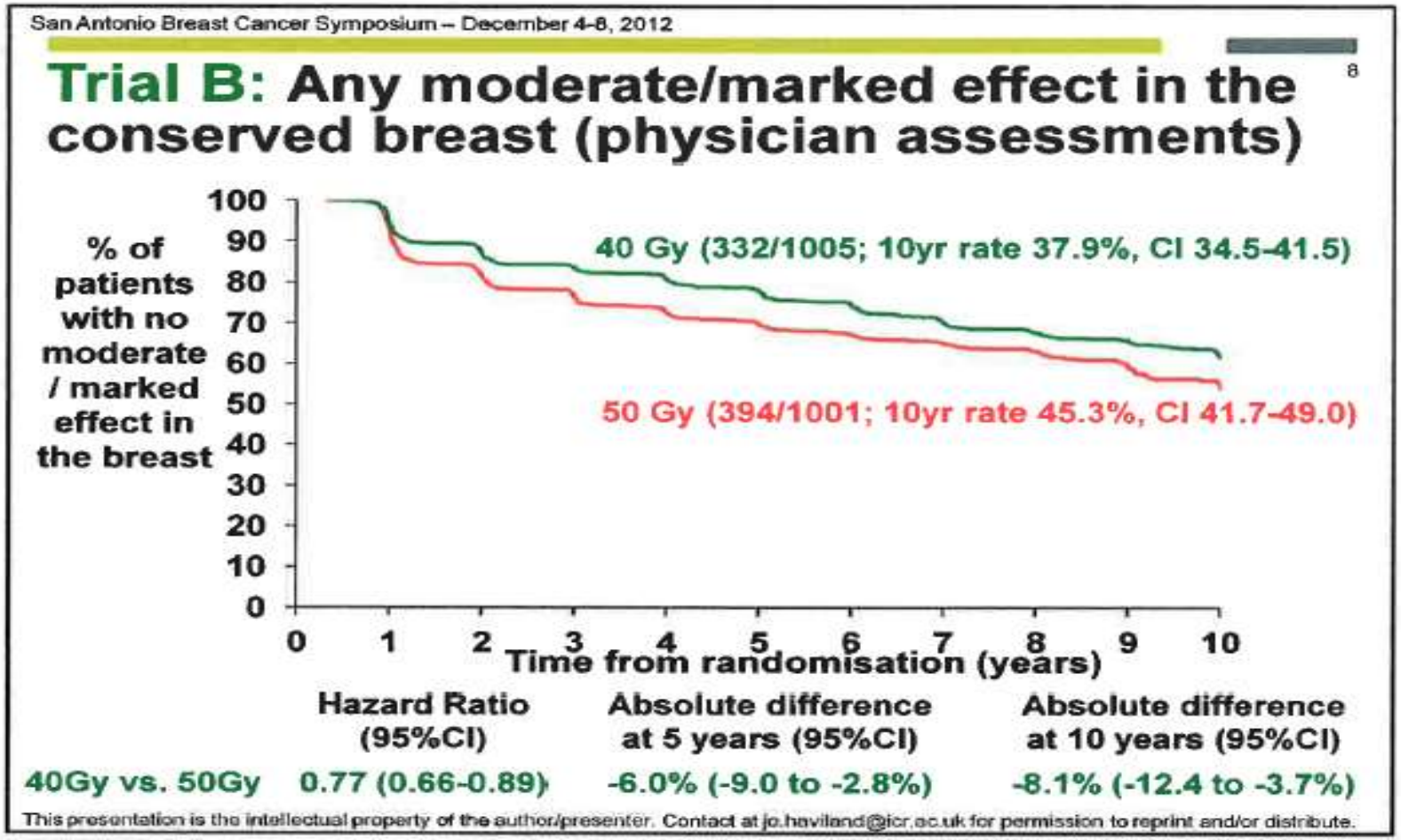
Why not hypo-fractionation post-mastectomy

- Fear that treating the supraclavicular region with hypo-fractionation will cause the dreaded brachial plexopathy
- Fear that treating the reconstructed breast with hypo-fractionation will result in higher complications
- Decades of randomized time-tested data demonstrating improved outcomes with conventionally fractionated PMRT and acceptable toxicity and long term effects-why change?
- Comfort level-Most radiation oncologists just do not feel comfortable and were trained to treat broader fields and regional nodes with the more conventional 5-6 weeks of RT at 180-200 cGy per day
- However, the long held concept that shorter courses of RT with higher daily RT doses result in more fibrosis and long term complications is simply not evident from the available data in breast cancer.

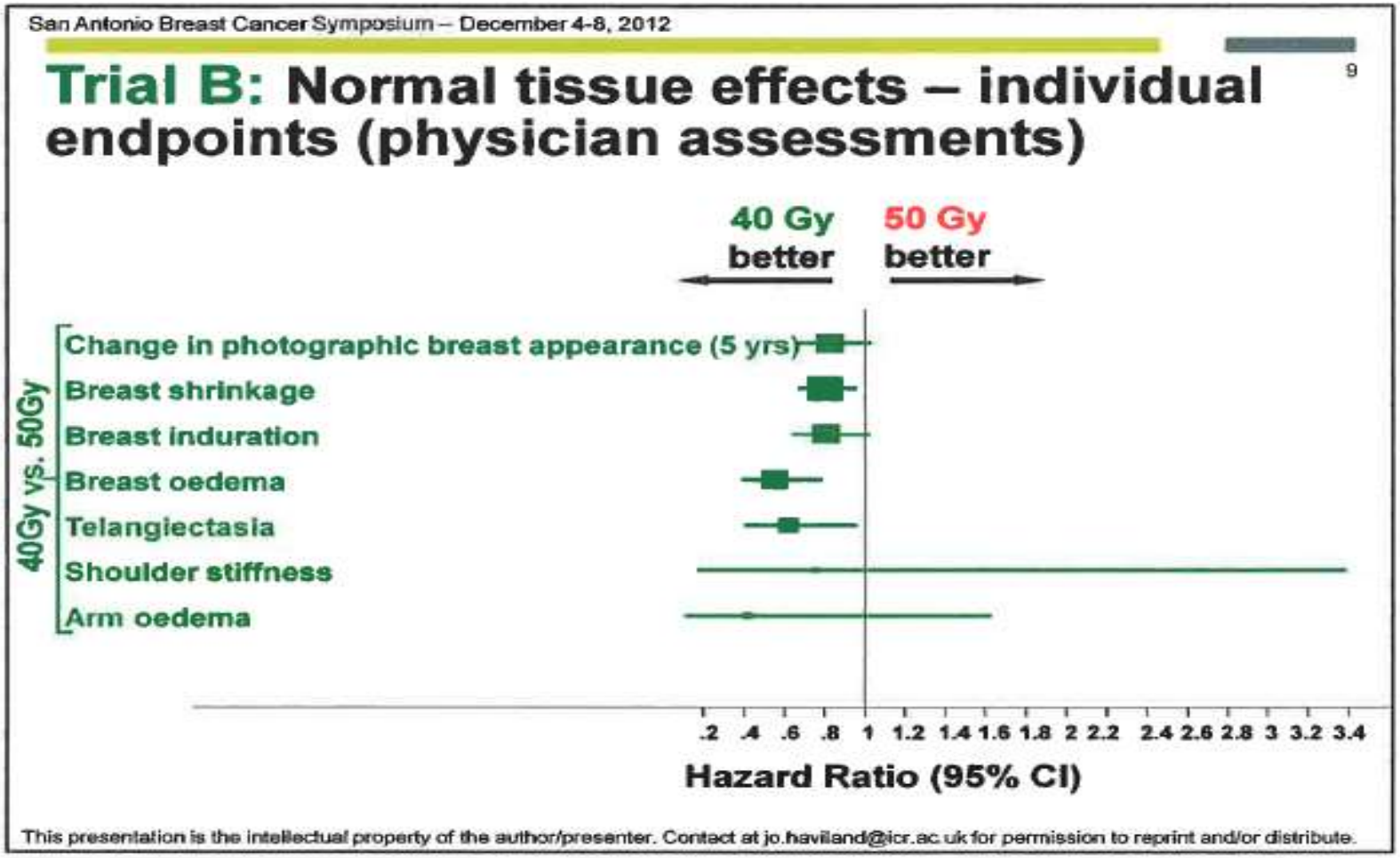
The UK START Trials



COSMETIC OUTCOME: START B



Normal Tissue Effect: START B



Hypofractionation with Regional Nodal Treatment or Post Mastectomy

- Although conventional fractionation remains the acceptable standard for treating the regional lymphatics hypo-fractionation of the regional lymphatics has been successfully done throughout the years.
- British Columbia Pre-menopausal PMRT Randomized Trial
  - 37.5 Gy in 16 Fractions of 2.34 Gy
- START A and START B-RNI Administered to 14% of Patients
  - 42.9 Gy in 3.3 Gy Fractions x13 over 5 weeks START A
  - 41.6 Gy in 3.2 Gy Fractions x 13 over 5 weeks START A
  - 40 Gy in 2.6 Gy Fractions x 15 over 3 weeks START B

Pre-existing data on hypofractionated RNI

Study	Time Period	Patients	RNI Dose (Gy)	Fractions	EQD2	Plexopathy rate	Median Follow-up
Melbourne[4]	1958-1962	117, PMRT	63	12	**114.2**	73%	**2.5 years**
Sweden[39]	1963-65	71, PMRT	57	17	**76.3**	63%	**34 years**
Hamburg, Germany[46]	1980-1993	140, SCL	52.0	20	**59.8**	14%	**8 years**
St. Thomas, London[1]	1968-1974	411, PMRT	35	6	**68.5**	NR	**10 years**
			50	12	**77.1**	NR	Lympedema 30 vs 12%
Western General Hospital, Edinburgh[41]	1979-1982	484, PMRT and RNI	42.5	10	**66.4**	1%	**10 years**
	1982-1984	289, PMRT and RNI	42.5	20	43.8	1%	

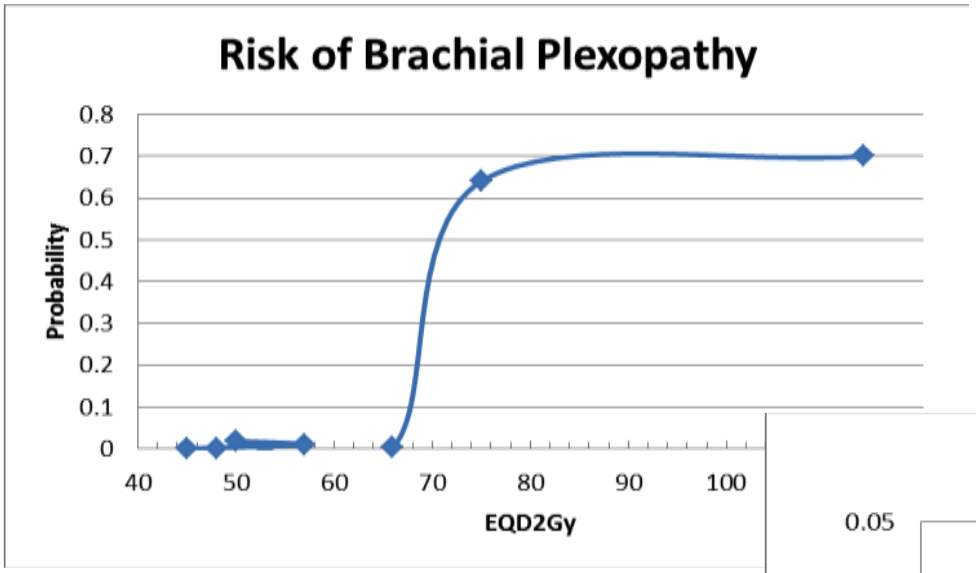
Pre-existing data on hypofractionated RNI

Study	Time Period	Patients	RNI Dose (Gy)	Fractions	EQD2	Plexopathy rate	Median follow-up
Necker, Paris	1984-1989	230, RNI use uncertain	23	4	44.6	0	4 (min)
BC PMRT	1979-1986	318 (164 PMRT)	35 Gy	16	37 Gy	0	20 years
Fairchild	1990-1996	1142	40	16	45 Gy	<1	8 years
Powell	1982-1984	1) 338 2) 111	1) 45 2) 54	1) 15 2) 30	1) 56 2) 51	6% 1%	5.5 years
RMH/GOC	1986-1998	290 (2/3rd hypofx)	42.9 Gy 39 Gy	13	47-49 Gy	0	8 years
START A/B	1998-2002	479 (278 hypofx)	40 Gy 42.9 Gy 39 Gy	13-15	47-49 Gy	1 (<1)	9.3 years

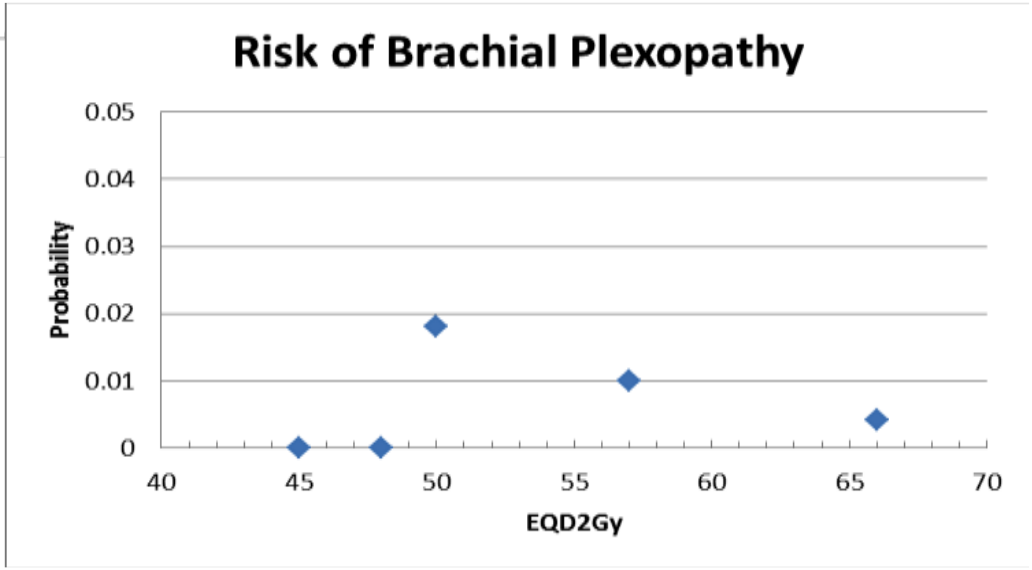
Snapshot of hypofractionation trials…

Trial	Years	Patients (N)	Arms (Gy/Fractions)	Age < 50 (%)	Boost (%)	Chemo-therapy (%)	Regional Node Irradiation (%)
RMH/GOC	1986-1998	1,410	50/25 42.9/13 39/13	30	75	14	21
OCOG	1993-1996	1,234	50/25 42.5/16	25	0	11	0
START A	1998-2002	2,236	50/25 41.6/13 39/13	23	61	36	14
START B	1999-2001	2,215	50/25 40/15	21	43	22	7

Hypo-fractioned Radiation Equivalent Dose in 2 Gy Fractionation, Incidence of Brachial Plexopathy based on published literature.



The low end of the chart magnifed…



Brachial plexopathy with hypofx:

- Exceeding known tolerance of brachial plexus will result in brachial plexopathy.
- Late neuropathy possible (but incidence plateaus at 6 yrs)
- Understanding LQ parameters and keeping EQD2 around 50 Gy is very safe
- Isoeffective schedules will behave isoeffectively on the plexus

WHAT ABOUT THE CHEST WALL/RECONSTRUCTION??

Hypofractionationation on a chest wall reconstruction:

- Not definitive, modern data.
- Data of hypo-fractionation on the intact breast suggests better normal tissue effects compared to conventional fractionation.

CINJ 041001: phase II trial

- Hypothesis: A hypofractionated course of PMRT is not more toxic than a conventionally fractionated course of PMRT.
- Patients: Stage IIA-IIIC (including clinical stage prior to NAC)
- 36.63 Gy in 11 daily fractions (3.33Gy x 11)
- Chest wall plus SCL/AX +/- IMNs
- BED equivalent to 45-50 Gy for late effects and tumor control
- Optional scar boost of 4 fractions (3.33Gy), total 15 fractions. BED ~ 60Gy.

CINJ 041001

- $$BED = nd\left(1+\frac{d}{\left(\frac{a}{b}\right)}\right)-\left(\frac{(\ln 2)T}{a(Tpot)}\right)$$

- d = dose/fraction
- n = # of identical fractions.
- T = overall treatment time after initial time lag to proliferation
- Tpot = potential tumor doubling time.

Comparison of Hypofractionation Schedules 2 Gy Equivalent Dose (Alpha/beta =4)

Target/Dose	Standard	CINJ	UK	Canadian
Whole Breast and Nodal Dose	2 Gy x 25 To 50.0 Gy **50 Gy**	3.33 Gy x 11 To 36.63 Gy **44.75 Gy**	2.66 x 15 To 40 Gy **44.4**	266 x 16 To 42.56 Gy **47.24**
Total Tumor Bed Dose with Boost	2 Gy x 30 To 60 Gy **60 Gy**	3.33 Gy x 15 To 49.95 Gy **61 Gy**	2.66 gy x 15 + 250 x 4 to 50Gy **55.5Gy**	266 x 16 (42.56) + 250 x 4 to 52.56 Gy **58 Gy**

CINJ 041001: phase II trial

- Primary Endpoint: Serious toxicity rate (chest wall pain or complications > grade 2, brachial plexopathy, pneumonitis > grade 2.)

- Sample size: Assuming background rate of toxicity at 3%, we can exclude a rate greater than 9% with 90% confidence and 80% power with 67 patients if no more than 4 serious toxicities are observed. Stopping criteria after the first 33 patients.

- Secondary endpoint: If no more than 5 LRRs in cohort of 67, the 90% CI of true LRR is between 3.7-14.5%.

Rutgers Hypo-fractionation Trial

- Prospective Phase II Trial (NCT01417286)
- 69 Patients enrolled between December 2011 and December 2014 at Rutgers CINJ and Huntsman Cancer Center at the University of Utah
- Stage II A to IIIc disease post-mastectomy with or without reconstruction (41 or 69% of patients had reconstruction)
- Treated PMRT 4995 Gy/3 Weeks (3.33 Gy/11 Fx/ to chest wall and nodes + 3.33Gy/4 Fx Boost)
- Primary Endpoint-total greater than Grade 2 Toxicity Rate below 9%
- Secondary Endpoint-Recurrence Rate between 3.7 and 14.5%
- Reconstruction Complications Attributed to Radiation -24%

Results

- Patients enrolled 12/21/2010 – 11/20/2014.
  - 69 patients enrolled, 67 evaluable patients.
  - Median follow-up = 2 years.
  - Three CTCAE grade 3 toxicities,
    - infected seroma requiring re-operation before RT (patient not evaluable),
    - one contralateral reconstruction infection,
    - one ipsilateral wound complication.
  - 2 loco-regional recurrences (4.5%)
  - 5 distant recurrences
  - 39 pre-RT reconstructions or temporary expanders (TE)
  - 32 patients with post-RT delayed or completed (TE) reconstructions
  - 6 patients with implant failure or removal
  - 7 patients with minor/elective revisions of reconstruction

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

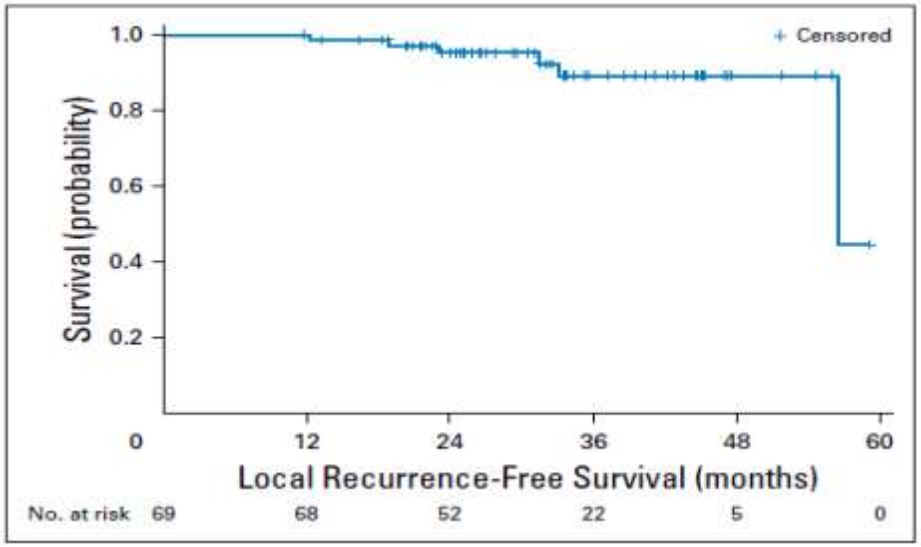
Hypofractionated Postmastectomy Radiation Therapy Is Safe and Effective: First Results From a Prospective Phase II Trial

Atif J. Khan, Matthew M. Poppe, Sharad Goyal, Kristine E. Kokeny, Thomas Kearney, Laurie Kirstein, Deborah Toppmeyer, Dirk F. Moore, Chunxia Chen, David K. Gaffney, and Bruce G. Haffty

Table 2. Treatment-Related Grade 2 Toxicities

Toxicity	No.	%
Skin	16	24.0
Fatigue	5	7.5
Pain	3	4.5
Lymphedema	3	4.5
Subcutaneous	1	1.4
Other*	1	1.4

*Hot flashes.



Hypofractionation PMRT-Moving forward

- These Phase II data **suggest** that radiation therapy delivered in 3 weeks is safe and effective post mastectomy setting treating the regional lymphatics as well as the reconstructed breast
- However, Single arm Phase II date ideally should be validated by randomized Phase III studies
- These Phase II data, along with the work of multiple individuals and cooperative groups helped to move the upcoming ALLIANCE Phase III trial forward
- The trial has been activated in Alliance.
- The trial has a Number: A221505

More Importantly the trial has a name

- **RT-CHARM**
- **R**adiation
- **T**herapy
- **C**onventional or
- **H**ypofractionated
- **A**fter
- **R**econstruction and
- **M**astectomy

Protocol development team

- Matthew Poppe, MD RadOnc, PI, U. of Utah
- Atif Khan, MD RadOnc, Co-Investigator, Rutgers CINJ
- Bruce Haffty, MD RadOnc, Co-Investigator, Rutgers CINJ
- Jamie Wagner, DO, Surgical Oncology, University Kansas
- Eric Hansen, MD, Community Oncologist, Portland, OR.
- Jay Agarwal, MD Plastic Surgery, U. of Utah
- Jared Foster, PhD Statistics, Mayo Clinic
- Jane Armer, PhD, RN, Lymphedema Outcomes, U. of Missouri
- Iwa Kong, MD, MSc, Cosmesis Assessments, McMaster U.

Intergroup Collaboration

- Tim Whelan, BM, BCh, MSc, McMaster U., NCIC-CTG
- Douglas Arthur, MD, VCU, NRG

Trial Concept

- Non-Inferiority design
  - Ensure that hypofx PMRT has acceptable reconstruction complication compared to standard fractionation
    - Primary Endpoint - Evaluate the breast reconstruction complication rate at 2 years after completion of post mastectomy radiation (Baker 3 or 4 contracture, implant removal, unplanned hospitalization or re-operation).
    - 2nd endpoint – PMRT toxicity, LC and LRC, photographic cosmetic assessment, lymphedema, PROs and cost effectiveness.

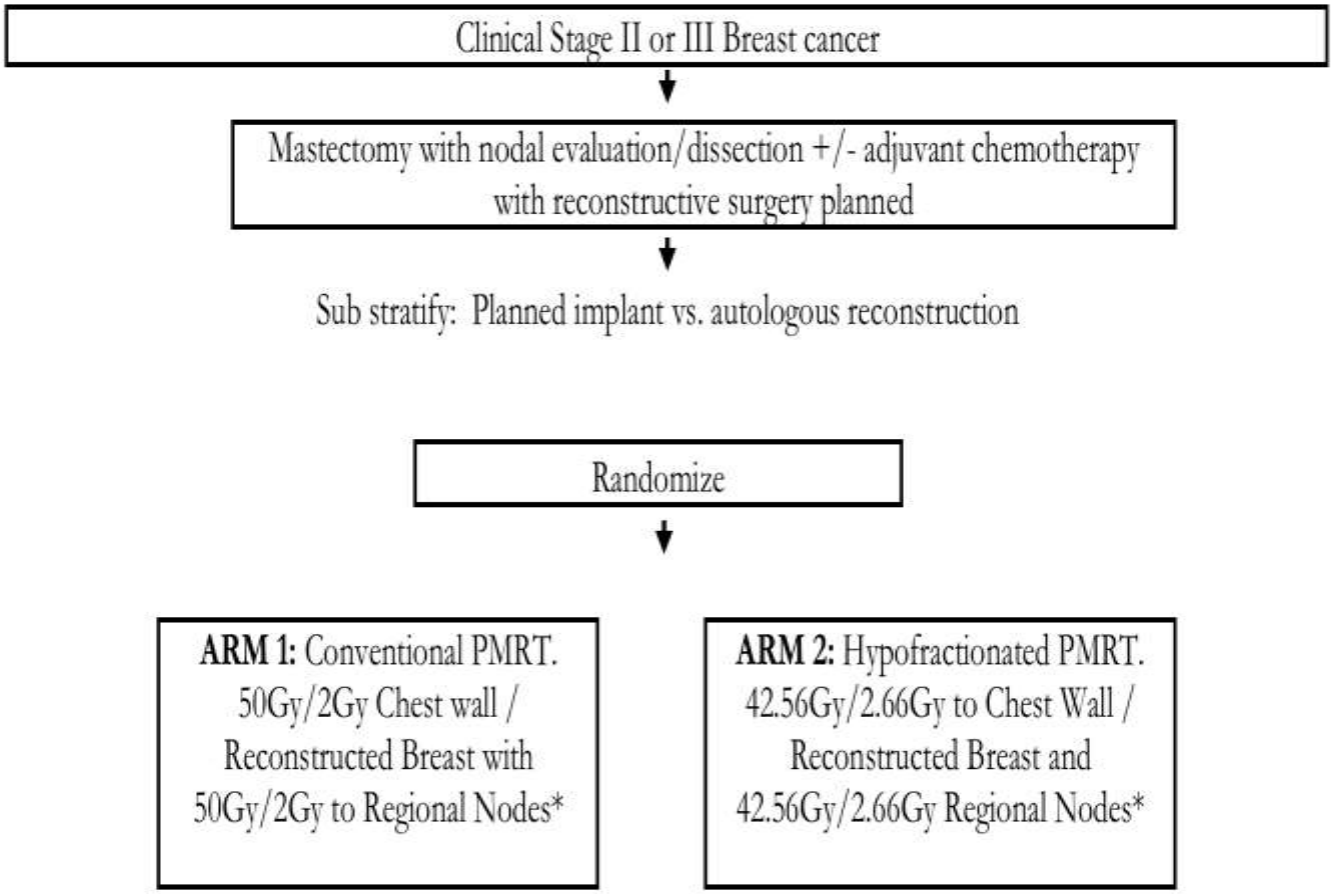
Trial Design

- 792 evaluable pts (396/arm).Target Accrual 880 Patients to allow for 10% dropout rate; Accrual estimate = 30 pts/month
- 90% power, one sided p=0.025
- Non-Inferiority Design: Hypo-fractionation is not inferior to standard fractionation with respect to the primary endpoint of reconstruction complications (Complication rate with hypofx is no greater that 10% higher than standard fx)
- Assume base reconstruction complications from PMRT 25%
  - Stats powered to exclude an increase in 10% rate of complications with hypo-fractionation or a rate of 35%
  - Baker 3 or 4 contracture, implant removal, unplanned hospitalization or re-operation

What is the background rate of reconstruction complications??

Study	Patients	Complications	Notes
Benediktsson et al. 2006	107 pts. PMRT & Immediate reconstruction, saline prosthesis	41.7% Baker 3 or 4 contracture	
Christante, et al. 2010	100 pts. PMRT & Immediate breast reconstruction	44% complications and 31% required implant removal	Delayed reconstruction patients had only a 22% complication rate
Alderman, et al. 2002	326 pts PMRT, 12 centers	52% complications in immediate reconstruction	Delayed reconstruction rate 33%
Fowble, et al. 2015	99 pts Immed TE and PMRT	18% failure rate 3.8 yrs	
Ho, et al. 2012	151 pts with implant swap and recon before RT	7-year PIRR 30%. 45% (n=17) Baker 3 or 4 contracture	17% replacement, 13% removal

A221505 RT CHARM



*Regional Nodes will include the undissected axilla, supraclavicular fossa and internal mammary nodal chain.

Enrollment to Date

- Accrual Target-880
- Sites Approved-737
- Accrual to Date-400+

Hypo-fractionation Randomized Data

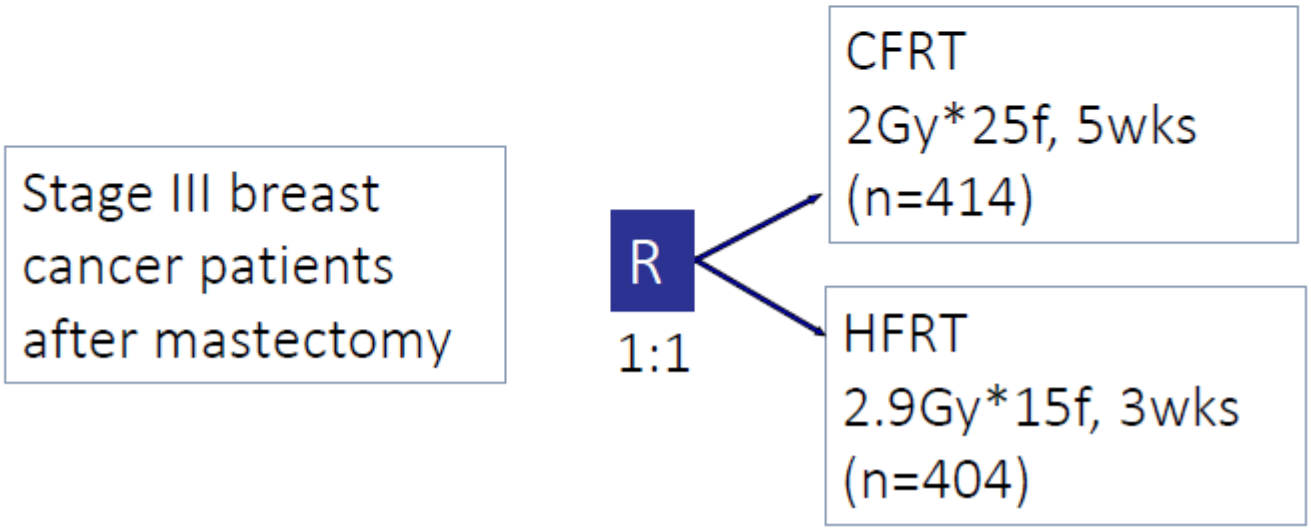
- The ALLIANCE trial is not the first randomized trial of hypo-fractionation in the post-mastectomy setting
- A recent randomized trial from China of conventional vs hypo-fractionated radiation was reported at ASTRO 2017
- All patients were treated with mastectomy, systemic therapy and randomized to conventional vs. hypo-fractionated post-mastectomy radiation to the chest wall and regional lymphatics
- However, all patients in the Chinese trial were surgically treated WITHOUT RECONSTRUCTION

Randomized Trial-Hypofractionation (43.5 gy/15Fx/3wks) vs. Standard Fractionation (50 Gy/25Fx/5Wks) Post-Mastectomy: Reported at ASTRO 2017 (Sun, Wang, et al.)

Method

A randomized phase III non-inferior trial comparing HFRT and CFRT
(Noninferority margin: 5% difference in 5-yr LRR rate)

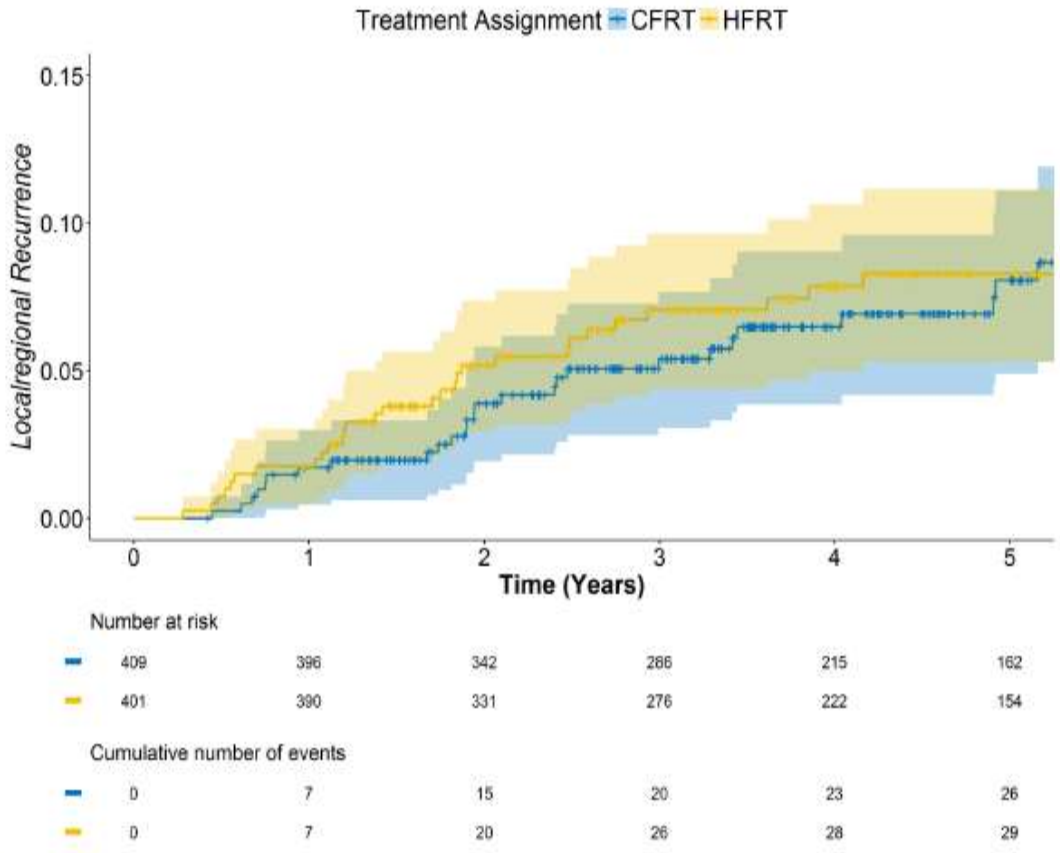
Target sample = 820 (June 2008 - June 2016)



Randomized Trial-Hypofractionation vs. Standard Fractionation Post-Mastectomy: Reported at ASTRO 2017 (Sun, Wang, et al.)

- LRR Primary Endpoint Median FU 52 Months
- No Difference in LRR (8.4% vs. 6.0%) , DM (21.3% vs. 24.3%), DFS (75.1% vs. 74.6%) or OS (84.9% vs. 87.1%) at 5 Years
- No Difference in lymphedema, shoulder disorder, pneumonitis between arms
- Fewer G3 skin reactions in hypofractionation
- No Brachial Plexopathy

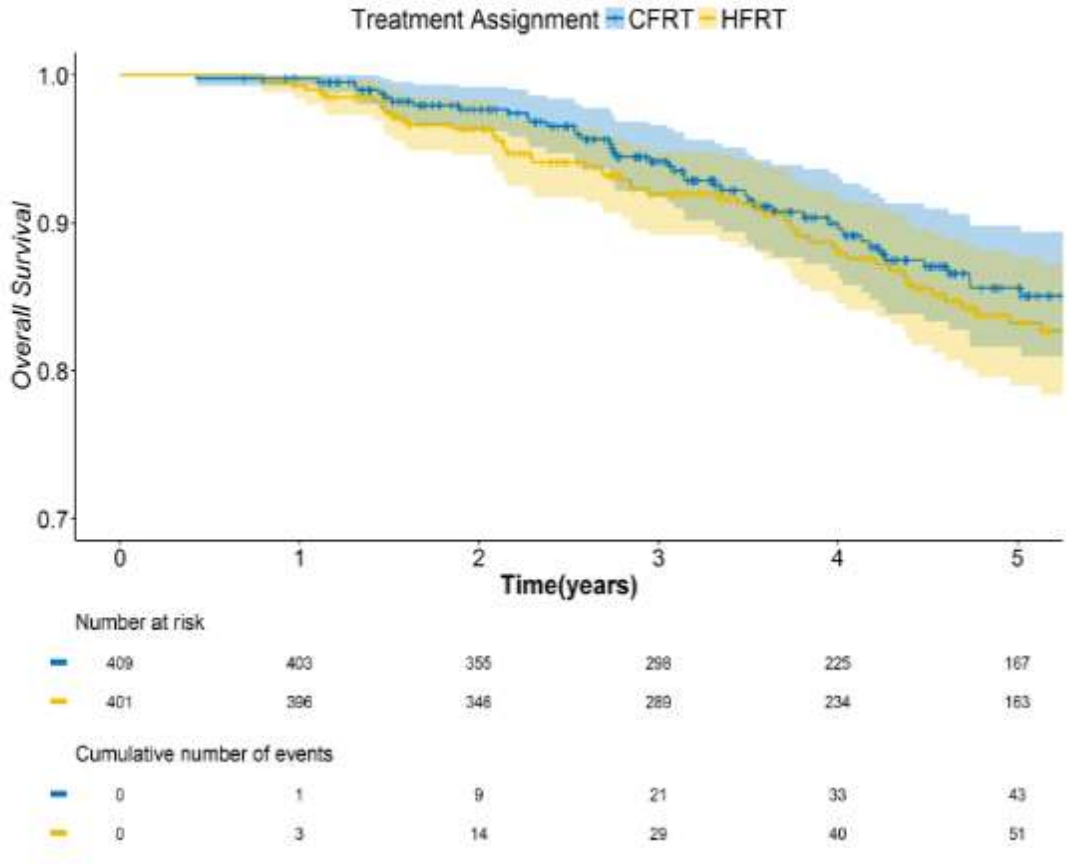
Results – Locoregional Recurrence



Median follow up time:
53 months (5-111)

5-year Actuarial Rates (95% CI)	
CFRT	8.1% (5.5, 11.8)
HFRT	8.3% (5.8, 11.8)
Difference	0.2% (-4.1, 4.5)
HR	1.10 (0.67, 1.83)

Results – Overall Survival



5-year OS Rates (95% CI)	
CFRT	85.6% (80.9, 89.2)
HFRT	83.2% (78.3, 87.1)
HR	1.13 (0.78, 1.62)

#ASTRO17

Future Directions/Translational Research

- While it is likely that hypofractionation as well as conventional fractionation will be acceptable in the vast majority of patients there clearly are some patients where toxicity, particularly longer term fibrosis and complications from radiation are more significant
- Identification of patients at higher risk of complications/fibrosis and increased reactions to radiation is an opportunity ripe for future investigation
- While still in its infancy there are a number of previous and ongoing studies evaluating single nucleotide polymorphisms to predict for increased risk of radiation complications

Polymorphisms and the Risk of Radiation Toxicity

- There are a number of genes typically associated with DNA repair processes, where variants are common in breast cancer patients. Candidates include BRCA1/2, ATM, TGF-B, CHEK2, ERCC1, PALB2, TNF-a, and others.
- Thus far, for the most part data are hypothesis generating without any clear contraindications or strong associations of adverse outcomes in patients with genetic mutations with the notable exceptions of:
  - ATM Homozygotes-Rare condition where ATM homozygotes are at increased risk of significant acute radiation toxicity
  - P53-Li-Fraumeni-where patients with this rare condition

From: **Association of Transforming Growth Factor β Polymorphism C−509T With Radiation-Induced Fibrosis Among Patients With Early-Stage Breast Cancer: A Secondary Analysis of a Randomized Clinical Trial**

JAMA Oncol. 2018;4(12):1751-1757. doi:10.1001/jamaoncol.2018.2583

Table. Multivariable Logistic Regression to Determine Grades 2 to 3 Fibrosis Among 205 Patients

Variable	Level	OR (95% CI)	*P* Value
C−509T genotype	C/C	1 [Reference]	.02
	C/T or T/T	4.47 (1.25-15.99)	
Randomization arm	CF WBI	1 [Reference]	.97
	HF WBI	1.02 (0.38-2.77)	
Panel physician-assessed cosmesis	1-2 (Excellent-good)	1 [Reference]	<.001
	3-4 (Fair-poor)	7.09 (2.41-20.90)	

Abbreviations: CF, conventionally fractionated; HF, hypofractionated; OR, odds ratio; WBI, whole-breast irradiation.

Table Title:

Multivariable Logistic Regression to Determine Grades 2 to 3 Fibrosis Among 205 Patients

Single Nucleotide Polymorphism rs1801516 in Ataxia Telangiectasia-Mutated Gene Predicts Late Fibrosis in Cancer Patients After Radiotherapy

A PRISMA-Compliant Systematic Review and Meta-Analysis

Yuyu Zhang, MD, Ziling Liu, MD, Mengmeng Wang, MD, Huimin Tian, MD, Keju Su, MD, Jiuwei Cui, MD, Lihua Dong, MD, and Fujun Han, MD

Zhang et al *Medicine* • Volume 95, Number 14, April 2016

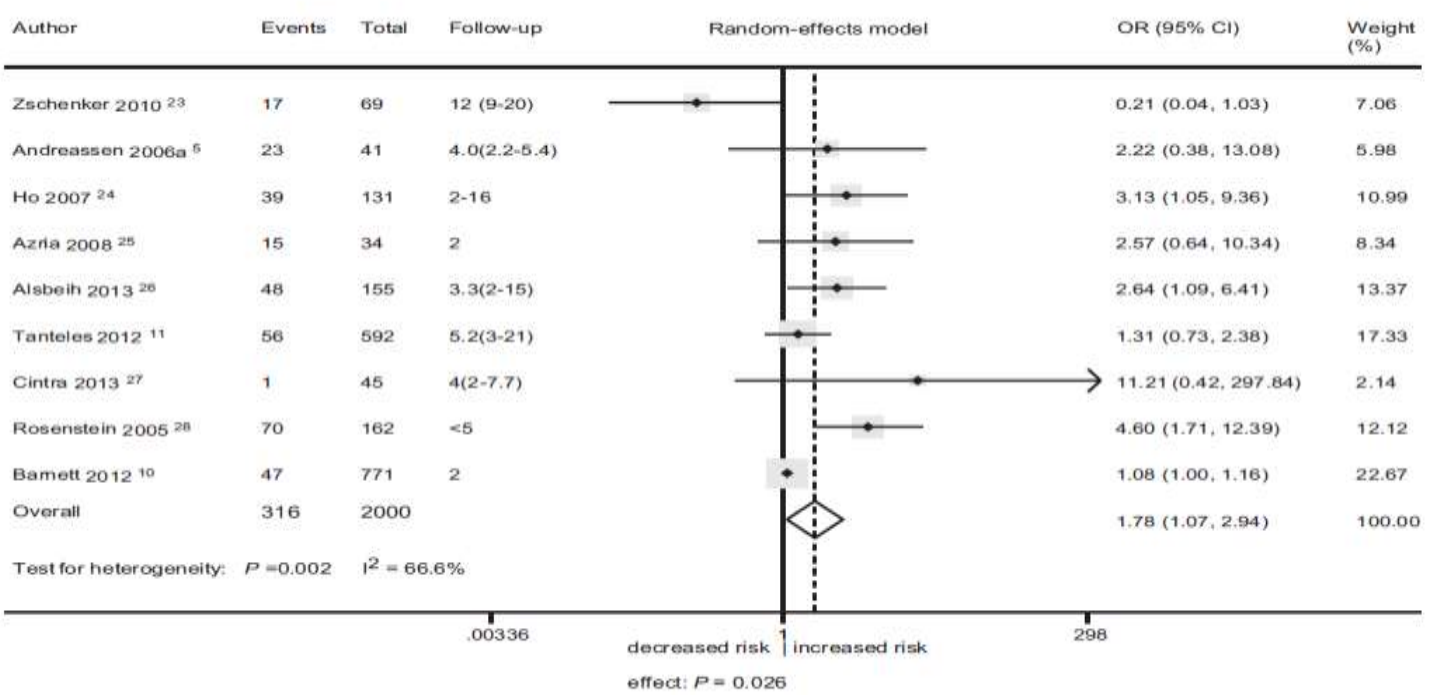


FIGURE 2. Forest plot for the association between the ataxia telangiectasia-mutated polymorphism rs1801516 and the risk of late fibrosis. CI = confidence interval, OR = odds ratio.

Current Ongoing Studies at Rutgers

- Prospectively collected blood samples on nearly 5000 breast cancer patients for analysis of single nucleotide polymorphisms
- Currently attempting to identify population of nearly 1000 treated with BCS+RT, where we will look at correlation of specific polymorphisms with outcomes including fibrosis, cosmesis and local-regional relapse.

Conclusions

- Moderate Hypo-fractionation (3-4 week courses of radiation) following mastectomy is likely highly effective and safe based on historical available clinically reliable data
- However, the bulk of data treating regional lymphatics accumulated to date has been with standard 5-6 week radiation schedules
- Fear of brachial plexopathy is a deterrent to hypo-fractionation of the regional lymphatics and supraclavicular fossa
- Fear of increased fibrosis with “more aggressive” fractionation schemes in reconstructed patients is a deterrent to hypo-fractionation in the post-mastectomy reconstructed patient
- However, available data suggest that moderate hypo-fractionation (2.6-3.3 Gy over 3-4 weeks) does not result in excess fibrosis or brachial plexopathy

Conclusion/Take Home Messages

- The current Alliance A221505 (RT_CHARM) randomized trial will address the issue of moderate hypo-fractionation in the setting of mastectomy and reconstruction
- The randomized Chinese trial (Sun, Wang et al.) and other data lend further support to the long term safety and efficacy of moderate hypo-fractionation in the post mastectomy setting
- Together these data support the potential for moderate hypofractionation in the post-mastectomy setting where radiation could be delivered in 3-4 weeks to the chest wall with or without reconstruction and the regional lympatics
- ENROLL in A221505 **RT-CHARM**
- Analysis of Genetic Variations in Specific Genes May help to identify those patients at higher risk of complications from RT

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THANK YOU!

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NCI Comprehensive Cancer Center
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