Hypofractionation in Breast Cancers: When and How

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Radiotherapy after breast-conserving surgery, generally with axillary clearance (BCS±RT) in all women (node-negative or node-positive)

(7311 women, 17% with node-positive disease)

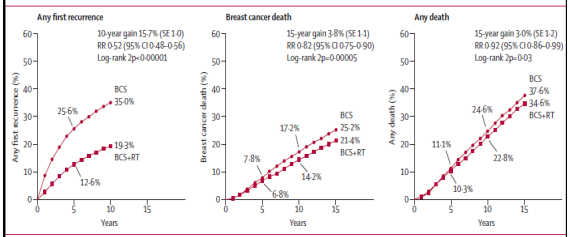

Figure 1: Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year risk of any (locoregional or distant) first recurrence and on 15-year risk of breast cancer death and death from any cause in 10 801 women (67% with pathologically node-negative disease) in 17 trials

Further details are in webappendix p 5. RR=rate ratio. Rate ratios in this figure include all available years of follow-up.

EBCTCG Lancet 2011; 378: 1707-16

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Hypothesis – START Trial

"Breast cancer is as sensitive to fraction size as late-reacting AE"

If so, small fractions spare breast cancer as much as the late-reacting AE

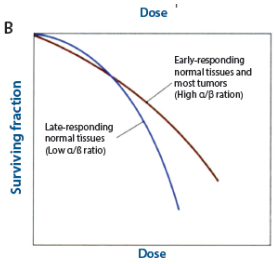
This suggests NO disadvantages

(& shorter treatment times may help tumour control)

Prof John Yarnold, ICR

Fractionation Sensitivity

Some Cancers are more sensitive to fraction size



- Ellis Isoeffect Formula: 45Gy in 15 fractions is equivalent to 50Gy in 25 fractions
- Worse Cosmesis, RAGE review
- Hypofractionation (in breast cancers) was written off

Eblan MJ et al Oncology (Williston Park) 2014 Jun;28(6):

Williams M. IRJOBP 1985;11. 1570e3P6.

Trials in Breast Cancer Hypofractionation

Trial	Ontario	START A	START B
T	1-2	1-3	1-2
N	0	0-1	0-1
Dose Comparator to 50Gy/25fr weeks	42G.5y/16fr3weeks	39Gy/13fr 41.6/13fr 5 weeks	40Gy/15fr 3 weeks
Boost	No	Yes	Yes
Local recurrence	NS	NS	NS
Cosmesis (Late changes in breast appearance)	Similar	Significantly better for 39Gy	Hypofractionation (HR 0.83 p=0.06)

What is the likely alpha/beta ratio for breast cancers?

The estimated radiobiological parameters from different clinical data (95% CL).

	α/β (Gy)	$\Delta(\alpha/\beta)$	α (Gy^{-1})	$\Delta(\alpha)$	T_d (day)	$\Delta(T_d)$
Whelan	3.21	3.86	0.16	0.10	10.4	17.1
Owen	4.39	7.45	0.05	0.04	12.2	26.2
Shelley	2.21	1.59	0.13	0.06	21.3	71.5
START A	3.91	3.47	0.02	0.06	17.1	58.5
START B	2.49	1.63	0.09	0.02	15.9	9.7
Clark	1.44	1.27	0.03	0.10	10.8	48.6
Arriagada	3.89	6.25	0.04	0.04	11.0	12.2

X. Sharon Qi et al Radiotherapy and Oncology 100 (2011) 282–288

International Guidance

- NICE Recommended 40Gy in 15 fractions for all curative adjuvant radiotherapy
- ASTRO (Guarded recommendation 2011)
  - >50yrs
  - T1-2, N0
  - No Chemotherapy
  - Dose to be kept between 93-107%

Concern 1: Age <50yrs

- EBCTCG overview- 20-35% risk of LR at 10yrs
- Boost Studies suggested age trend with LR
- Canadian study- stratified recruitment -No difference in LR
- START 10year data (1389 patients) – No difference in LR

Haviland Lancet Oncol 2013

Concern 2: Safe to treat Grade 3 tumours?

- Ontario study subgroup analysis >LR in Gr 3
  - Unplanned subgroup
  - START data does not show any difference with respect to grade
  - British Columbia 1335patients data analysis showed no difference in LR for Gr 3 patients following hypofractionation

Haviland Lancet Oncol 2013
Herbert IRJOBP 2012

Concern 3: Cardiac Toxicity

- Swedish group: Worse Cardiac outcome with hypofractionated RT
- 43Gy in 10 fr over 5 weeks had higher Ischaemic Heart disease compared to 45Gy in 20 fr over 5 weeks

Contributing factors

- Hypofractionation in 4.3Gy per fraction
- Parasternal Photon use
- (More use of PF in 4.3Gy group)
- (No difference in Left/right sided RT)

Tjessem et al IRJOBP 2012

Heart Dose: How Low is Good?

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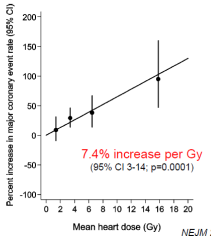
The NEW ENGLAND JOURNAL of MEDICINE

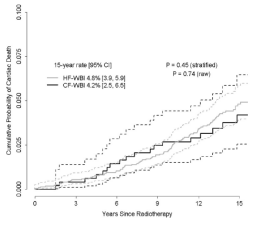
Radiation Associated Cardiac Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer
Dose-response relationship for major coronary events



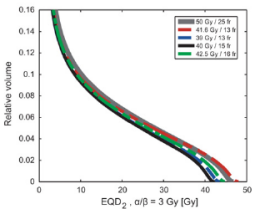
NEJM 2013; 368:987-98

Cardiac Toxicity contd..

Canadian Data (5334 patients)



Dosimetric Correlates:



Hypofractionation reduces cardiac dose and does not increase Cardiac Death

Chan et al Radiotheraapy and Oncology 2012

Appelt et al Clini Oncol (RCR) 2013

Other Toxicities

- No increase in Brachial plexopathy in the 4 RCTs
- No increase in Pulmonary fibrosis reported in the START A/B studies

Clinical Oncology 25 (2013) 127–134

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Breast Radiotherapy: Less is More?

C.E. Coles *, A.M. Brunt †, D. Wheatley ‡, M.B. Mukesh *, J.R. Yarnold §

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

Joanne S Haviland, J Roger Owen, John A Dewar, Rajiv K Agrawal, Jane Barrett, Peter J Barrett-Lee, H Jane Dobbs, Penelope Hopwood, Pat A Lawton, Brian J Magee, Judith MRL Sandra Simmons, Mark A Sydenham, Karen Venables, Judith M Bliss*, John R Yarnold*, on behalf of the START Trialists' Group†

Is it fair to generalise the data?

Clinical Oncology 24 (2012) 228

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Letter

Hypofractionation in Breast Cancer: Is it Fair to Generalise the Data?

	Grade 3	T2 and above	Node Positive	Age <50yrs	SCF treated
% of Patients in START A/ B/ START Pilot studies	up to 28.1%	up to 48.6%	up to 37%	>20%	21%

Chatterjee S et al Clin Onc (RCR) 2012

What dose volume planning requirements are mandatory for hypofractionated breast RT?

- Large Breasts could lead to more heterogeneity leading to more toxicity (double trouble)
- Ontario Study allowed patients with seperation of 25cm or less
- START A/B studies had breasts with seperation more than 25cm (17.2% START B)
- 2d Planning was required
- 95-105% dose in central axis
- Wedges and compensators used

Dose Heterogeneity and Cosmesis in hypofractionation

- Conformal Planning or IMRT Can improve cosmesis by restricting dose of 107% or less in <2cc breast volume
- Within 95-107% dose heterogeneity did not affect cosmesis on photographic changes even for more extreme hypofractionation

Coles et al Radiotherapy and Oncology 2012
Tsang et al Radiotherapy and Oncology 2012

Current Practice: National

- Increasing uptake of START B type regime
- Likely to increase throughput
- Optimise resources
- At least 2d treatment plans must be generated
- Dose homogeneity must be optimised in the breast by simple techniques

What about the Indian population?

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Article in Press

Outcomes Following a Moderately Hypofractionated Adjuvant Radiation (START B Type) Schedule for Breast Cancer in an Unscreened Non-Caucasian Population

S. Chatterjee, M. Arunsingh, S. Agrawal, D. Dabkara, A. Mahata, I. Arun, R.K. Shrimali, R. Achari, I. Mallick, R. Ahmed

Data from Tata Medical Center, Kolkata

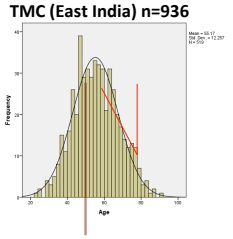
Abstract | Full Text | Images | References

Highlights

- ER/PR/HER2 status in Indian patients are similar to the reported Western literature.
- Hypofractionated radiation is safe and effective post mastectomy, BCS and for SCF RT.
- Locoregional recurrences were small and not affected by molecular type.
- Hypofractionated radiotherapy (START B type) is as safe as conventional radiotherapy.

Audit of Demographics data Eastern (Patient Charecteristics)

TMC (East India) n=936



Mean Age	NACT	Grade 3	pT2 or>	pN2/ 3
53yrs	35.5%	53%	65%	23.7 %

Audit of Changed Practice: India

- Published Early Toxicity

Table 2. Skin Toxicity (in numbers)

			RTOG GRADING			
			END RT	1 Month	3 Months	6 Months
BCS	Grade	I	45	24	10	5
		II	15	0	0	0
		III	3	0	0	0
		IV	0	0	0	0
Mastectomy	Grade	I	69	5	2	0
		II	4	0	0	0
		III	0	0	0	0
		IV	0	0	0	0

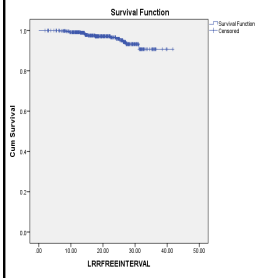
Hypofractionated Radiotherapy for Breast Cancers - Preliminary Results from a Tertiary Care Centre in Eastern India

Moujhuri Nandi[1*], Anurupa Mahata[2], Indranil Mallick[3], Rimpa Achari[4], Sanjoy Chatterjee[5]

Asian Pacific Journal of Cancer Prevention, Vol 15, 2014

Audit of Outcome Data/ Demographics

Local Control at 2yrs – projected to be 94%



Heart Dose: Comparable to published data

HEART DOSIMETRY-LEFT SIDED BREAST CANCERS				
Variable (mean)	All patients	Whole breast RT Dose in cGy	Chest Wall RT Dose in cGy	P values (CI - 95%)
Heart Dose (cGy) (MHD)	396.0 (22.8 - 858.0)	365.7 (22.8 – 744.7)	404.0 (126.4- 858.0)	0.988
V2.5(%)	20.2	21.6	19.1	0.016
V5(%)	11.9	11.1	11.8	0.492
V30 (%)	6.0	5.6	6.4	0.085
MHD-MS (in Cm)	0.6 (0 -3.1)	0.9 (0-2.8)	0.6 (0 – 3.1)	0.078
MHD-AS (in Cm)	1.9 (0.5 -3.7)	1.8 (0.5 – 3.5)	1.9 (0.7 -3.7)	0.930

Chatterjee et al ESTRO abstract 2015

Can Hypo-fractionation work post Mastectomy?

Published full text

- 133 patients fron New Zealand database
- 40Gy 16 fr
- No Gr 3 toxicity, 10% Gr 2
- 5yr LC 97.6%

Abstract ESTRO 2015

- Mastectomy 41% (206) patients with median follow up of 21 months
- LC rate same a BCS group
- Acute toxicity similar (Gr1 91%)

- Ko et al JMIRO 2014 2014 Oct 6

Does Hypofractionation work in DCIS?

Author, year	Country	No of patients	Median follow-up	Total dose/fraction (standard)	Total dose/fraction (hypofractionated)	Dose/fraction (boost)	Thresholds for margin status analysis	NOS
Hathout L, 2013	Canada	440	4.4 yrs	–	42.5 Gy/16 fr	10˚ Gy/4 fr	Positive Close < 3 mm Wide ⩾ 3 mm	7
Julian TB, 2011	USA	1569	14.2 yrs	50 Gy/25 fr	–	NR	Positive Negative	NA
Kim JH, 2014	Korea	728	82 mo	50.4˚/28 fr	–	10˚ Gy/5 fr	Close < 2 mm Negative ⩾ 2 mm	7
Lalani N, 2014	Canada	1609	9.2 yrs	50 Gy/25 fr	40–44 Gy/16 fr	NR	Positive Negative	8
Meattini I, 2013	Italy	389	7.7 yrs	50 Gy/25 fr	–	10–20 Gy/5–10 fr	Positive Negative	7
Omlin A, 2006	USA	373	72 mo	50˚ Gy/25 fr	–	10˚ Gy/5 fr	Positive Clear	6
Rakovitch E, 2013	Canada	1895	10 yrs	50 Gy/25 fr	40–44 Gy/16 fr	12˚ Gy/6 fr	Positive Negative	8
Tunon-de-Lara C, 2010	France	66	160 mo	50 Gy/25 fr	–	10 Gy/5 fr	Positive or close < 3 mm Negative ⩾ 3 mm	7
Vidali C, 2012	Italy	586	136 mo	50˚ Gy/25 fr	–	10˚ Gy/5 fr	Positive Close < 2 mm Negative ⩾ 2 mm	7
Wai ES, 2011	Canada	482	9.3 yrs	50 Gy/25 fr	44 Gy/16 fr	7.5 Gy/3 fr	Positive Close < 2 mm Negative ⩾ 2 mm	7
Williamson D, 2010	Canada	266	3.76 yrs	50 Gy/25 fr	42.4 Gy/16 fr or 40 Gy/16 fr	12.5 Gy/5 fr	Close < 1 mm 1–9 mm ⩾ 10 mm	7
Wong P, 2012	Canada	220	46 mo	50 Gy/25 fr	45 Gy/20 fr or 42.5 Gy/16 fr	7.5 Gy/3 fr to 16 Gy/8 fr	Positive or < 1 mm ⩾ 1 mm	6
Yerushalmi R, 2006	Israel	75	81.5 mo	50 Gy/25 fr	–	10 Gy/5 fr	Positive or < 1 mm ⩾ 1 mm	6

Conclusion: Hypofractionated radiotherapy seems to be a safe option in patients with DCIS after breast-conserving surgery while the addition of boost reduces the risk for local recurrence in the presence of positive margins. However, the level of evidence for these observations ranges between very low and low and the results of the ongoing randomized trials are necessary to confirm the results with higher level of evidence.

Summary: Hypofractionation

Invasive Cancer

- Robust RCT evidence exists for T1-3, N0-1 disease
- Level 2 data exists for all subgroup of patients
- India specific published data is now available
- It is as safe and as effective as conventional doses

Caution

- One must try do at least 2d planning and ensure dose homogeneity in the central axis between 95-107%
- In DCIS although evidence and use of hypofractionation is emerging Level 1 data is awaited
- It is recommended that data is adited after changes in practice

Further Hypofractionation

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- FAST Trial – FASTer radiotherapy for breast cancer patients
- *Prospective randomised clinical trial testing 5.7 Gy and 6.0 Gy fractions of whole breast radiotherapy*
- *in terms of late normal tissue responses and tumour control*
- Control arm: 50.0 Gy in 25 fractions of 2.0 Gy over 35 days
- Test arm 1: 30.0 Gy in 5 fractions of 6.0 Gy over 35 day (α/β value = 4 Gy)
- Test arm 2: 28.5 Gy in 5 fractions of 5.7 Gy over 35 days (α/β value = 3 Gy)

ICR The Institute of Cancer Research

FAST-Forward

in partnership with NHS National Institute for Health Research

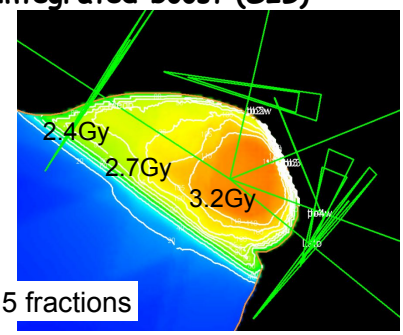
Randomised clinical trial testing a 1-week course of curative whole breast radiotherapy against a standard 3-week schedule in terms of local cancer control and late adverse effects in patients with early breast cancer

CI: Professor Murray Brunt

Simultaneous Integrated Boost: Further Hypofractionation

- Beware OAR doses

IMPORT HIGH: Simultaneous integrated boost (SIB)



15 fractions

Slide Courtesy: Dr Charlotte Coles

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HYPORT

Adjuvant

HYPOfractionated Radiation Therapy comparing a standard radiotherapy schedule (over three weeks) with a novel one week schedule in Adjuvant breast cancer: An open label randomised controlled study (HYPORT- Adjuvant)

Coordinating Center:

Tata Medical Center, 14 MAR (E-W), Newtown Action Area III, Kolkata, West Bengal, 700156

Trial management Committee:

All principal investigators (PI) from participating institutes.

Chief Investigator: Dr Sanjoy Chatterjee, Consultant Radiation Oncology, Tata Medical Center, Kolkata

Joint Chief Investigator: Dr Santam Chakraborty, Consultant Radiation Oncology, Tata Medical

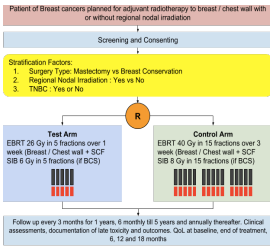
First Multi-Centre Collaborative Hypofractionation Breast Cancer Study from India with external Peer QA

Centres Collaborating

- TMC Kolkata
- CMC Vellore
- SGPGI Lucknow

- Recruited 100 cases in 3months
- 2 centres will go live within next 2 weeks (Site QA being performed and IRB Clearance received in each centre)

Schema



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Thank You