ASSOCIATION OF RADIATION ONCOLOGISTS OF INDIA

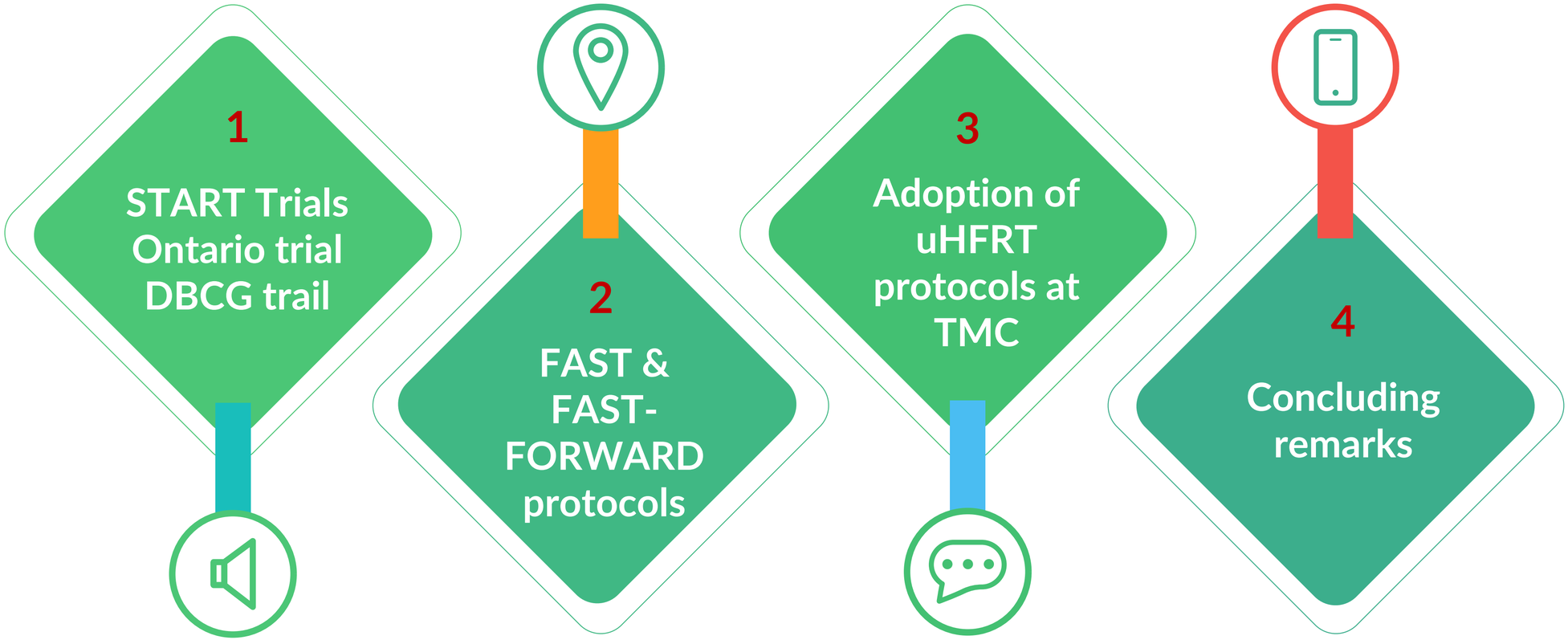
टाटा स्मारक केंद्र
Tata Memorial Centre

Hypofractionation trials for breast cancer beyond START

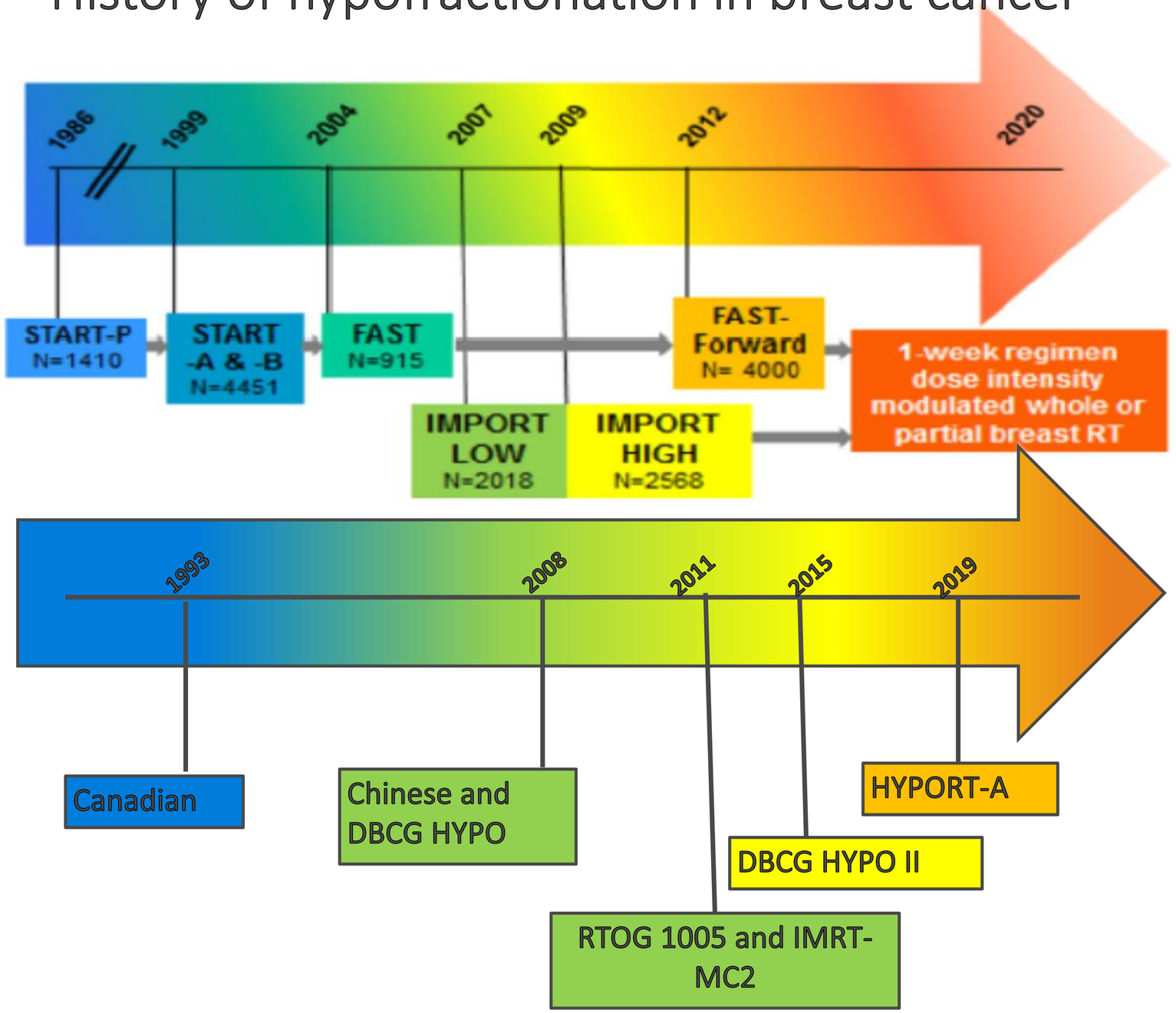
Are we ready now for FAST & FAST-F?

- Tabassum Wadasadawala, MD, DNB
- Professor Radiation Oncology & Convenor Breast DMG
- ACTREC, Tata Memorial Centre, Mumbai

Flow of presentation



History of hypofractionation in breast cancer



Benefits of HFRT

- Improved **access** (10% to 100%)
- Reduce number of treatment **machines** (Datta et al, Adv Radiat Oncol 6:100565, 2021)
- Improved **survival** (Khan et al, Int J Radiat Oncol Biol Phys 97:287-295, 2017)
- Reduced treatment **interruptions** (Rudat et al, Strahlenther Onkol 193:375-384, 2017)
- Higher **completion** rates (Lamm et al, Surgery 72:31-40, 2022)
- **Cost** saving (Irabor et al, JCO Glob Oncol 6:667-678, 2020)

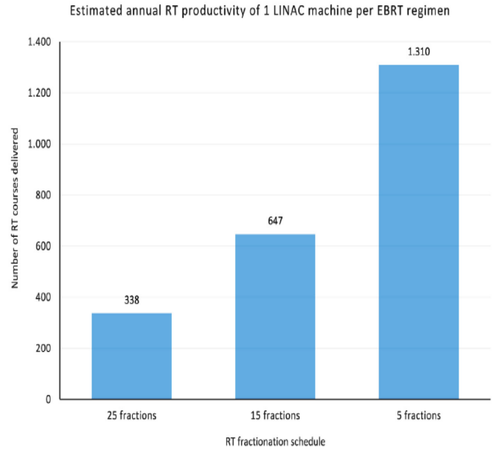


Figure 2. Estimated Annual EBRT Productivity of 1 LINAC machine per RT regimen, in terms of number of EBRT courses delivered (1 EBRT course = 1 patient).

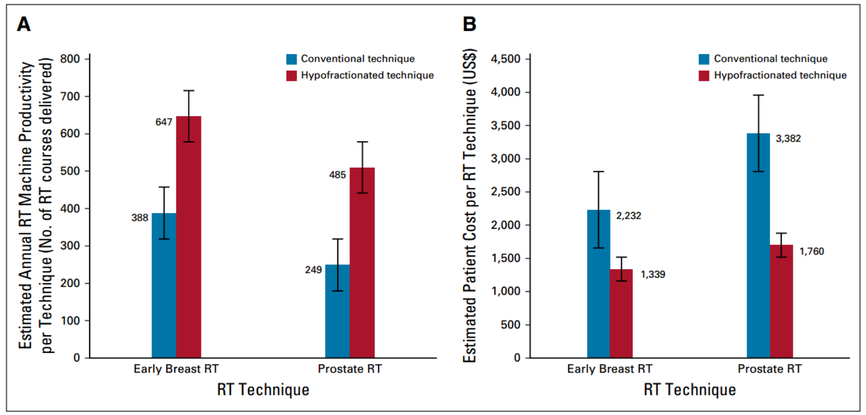


FIG 1. Bar graphs of (A) the estimated annual output of a department with a single linear accelerator, assuming the machine was used solely to deliver the specified radiation therapy (RT) technique; and (B) the estimated differences in cost with changes in RT fractions.

Irabor et al, JCO Global Oncol 6:667-678. © 2020 b

MODERATE HYPOFRACTIONATION TRIALS

Summary of Pivotal UK trials

Regimen	Treatment schedule over the course of 5 weeks	$EQD_{2\,Gy}$ ($\alpha/\beta = 3.5$)
Conventional 25 × 2 Gy		50 Gy
START A 13 × 3.0/3.2 Gy		46.1 Gy/50.4 Gy
START B 15 × 2.67 Gy		44.9 Gy

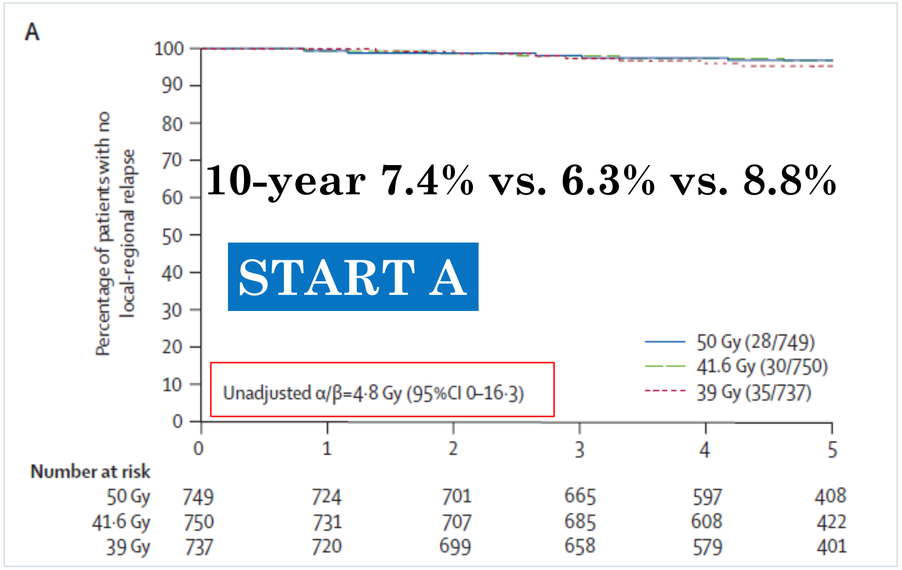
No ↓ in OTT

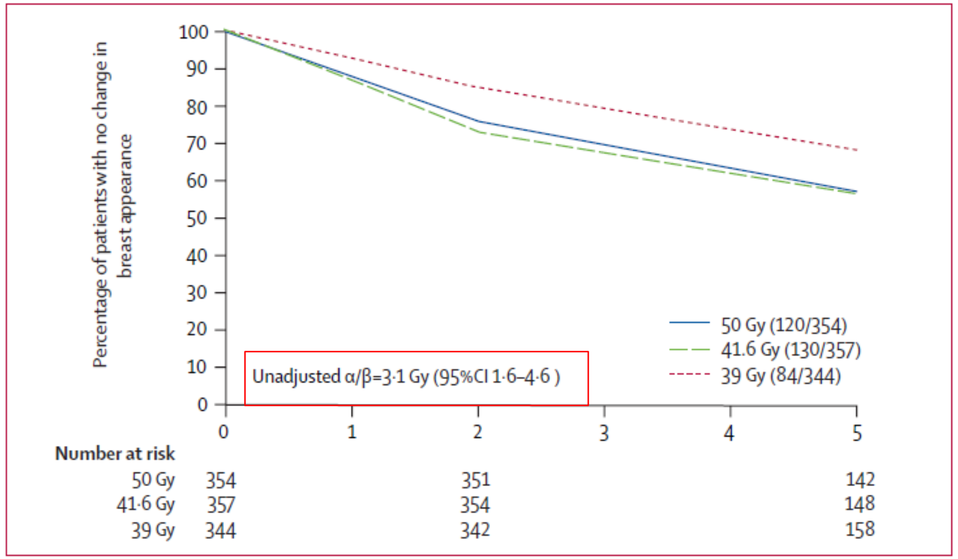
↓ in OTT

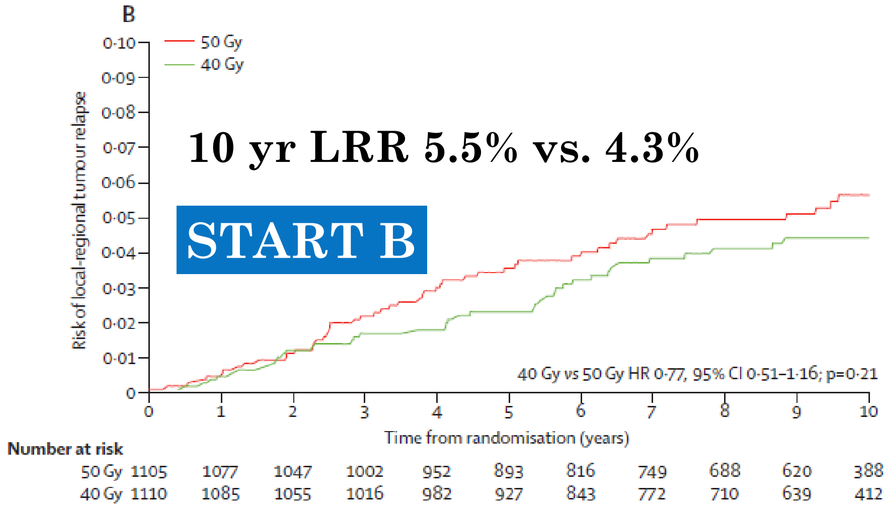
Krug et al, Strah Onko 2021

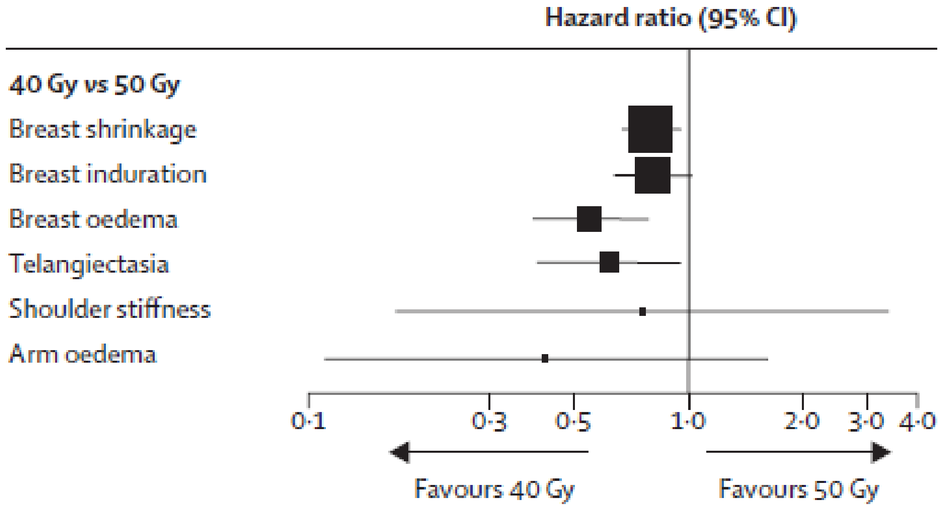
Trial	Sample size	Endpoint	Median FU	LC control	Late normal tissue effect
START A	2236	LRC	9.3 years	10-yr 7.4% vs. 6.3% vs. 8.8%	Shrinkage 26.8% vs. 26.8% vs. 22.7%
START B	2215	LRC	9.9 years	10-yr 5.5 vs 4.3%	Shrinkage 25.5% vs 22%

START trials

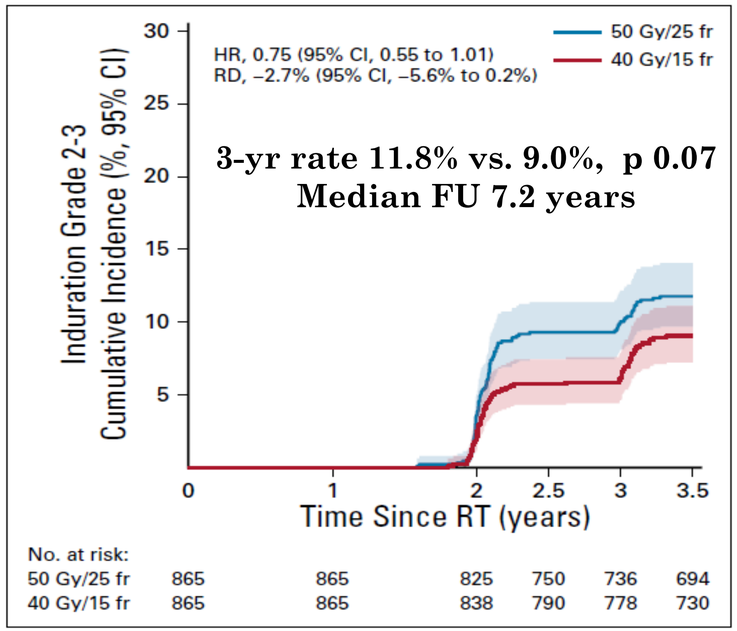






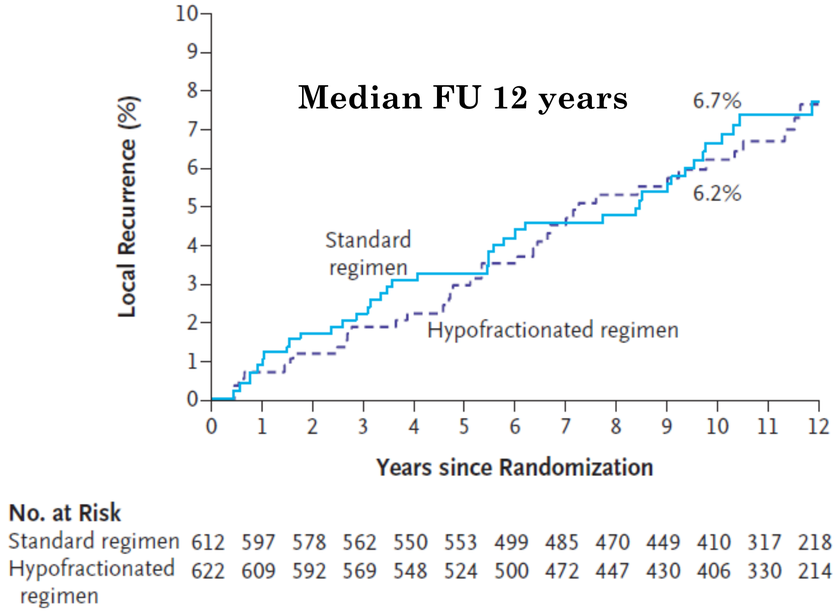


Lancet Oncol 2008 and 2013



VARIABLE	P value	RR	95% CI
UNIVARIATE			
Hypo (40 Gy vs 50 Gy)	0.74	0.95	(0.72-1.27)
Breast size (S vs L)	*0.003*	*1.56*	*(1.16-2.09)*
Chemotherapy (no vs yes)	0.70	1.06	(0.79-1.42)
Boost (no vs yes)	0.59	1.10	(0.79-1.52)
MULTIVARIATE			
Hypo (40 Gy vs 50 Gy)	0.74	0.95	(0.72-1.27)
Breast size (S vs L)	*0.003*	*1.56*	*(1.16-2.09)*
Chemotherapy (yes vs no)	NS		
Boost (yes vs no)	NS		

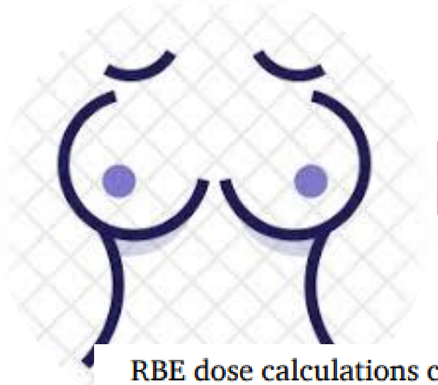
DBCG HYPO TRIAL



10 yr estimate	Std (50 Gy)	Hypo (42.5 Gy)
Skin grade 3	2.7%	2.5%
Subcut fibrosis	3.6%	2.5%
Excellent or good cosmesis	71.3%	69.8%

ONTARIO TRIAL

Lancet Oncol 2013, NEJM 2010, Offerson JCO, 2020



HFRT delivers radio biologically safe dose

https://doi.org/10.1016/j.critrevonc.2020.103090

RBE dose calculations considering different α/β values for normal tissue and breast cancer for the fractionation schedules compared in the START-B trial[10]. The RBE calculations are shown at dose levels of 107 %, 105 %, 100 %, 70 % and 50 % for 3 different scenarios.

Realistic scenario α/β 2 for Normal Tissue and 3.5 for Tumour					
Schedule and dose level	Numerical dose	EQD2 α/β = 2	BED α/β = 2	EQD2 α/β = 3.5	BED α/β = 3.5
50/25 Dose level 107 %	25*2.14 = 53.5 Gy	55.37Gy	110.75Gy	54.86Gy	86.21Gy
40/15	15*2.85 = 42.8 Gy	51.90 Gy	103.70 Gy	49.41Gy	77.65Gy

Optimistic scenario α/β 3 for both Normal Tissue and Tumour			
Schedule and dose level	Numerical dose	EQD2 α/β = 3	BED α/β = 3
50/25 Dose level 107 %	25*2.14 = 53.5 Gy	55Gy	91.66Gy
40/15	15*2.85 = 42.8 Gy	50.08Gy	83.46Gy

Worst case scenario α/β 1 for Normal Tissue and 5 for Tumour					
Schedule and dose level	Numerical dose	EQD2 α/β = 1	BED α/β = 1	EQD2 α/β = 5	BED α/β = 5
50/25 Dose level 107 %	25*2.14 = 53.5 Gy	56.00 Gy	167.99Gy	54.57Gy	76.40 Gy
40/15	15*2.85 = 42.8 Gy	54.93Gy	164.78Gy	48Gy	67.2 Gy

Late effects

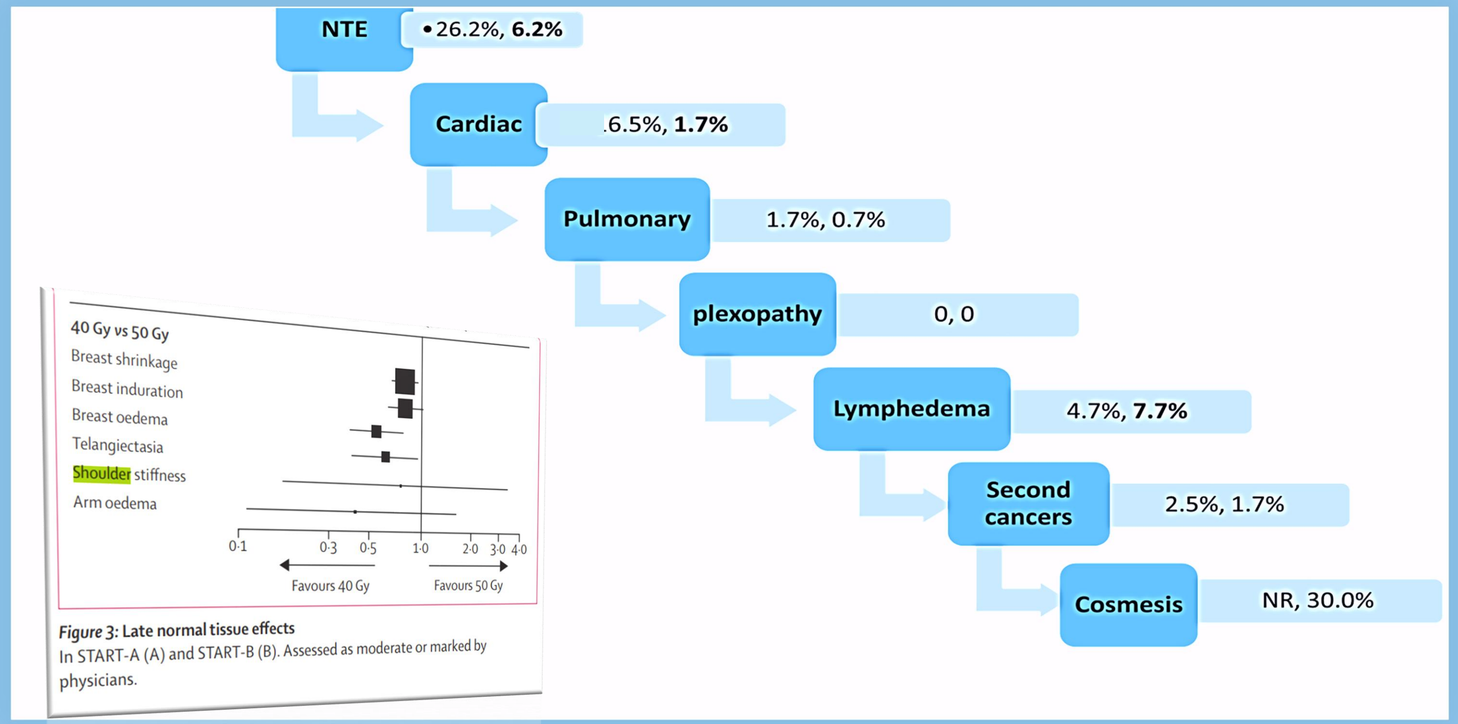


Figure 3: **Late normal tissue effects**
In START-A (A) and START-B (B). Assessed as moderate or marked by physicians.

- HFRT delivers radio-biologically **safer dose** to the normal tissues
- Forest plots favor HFRT
- Normal tissue effects are either same or fewer

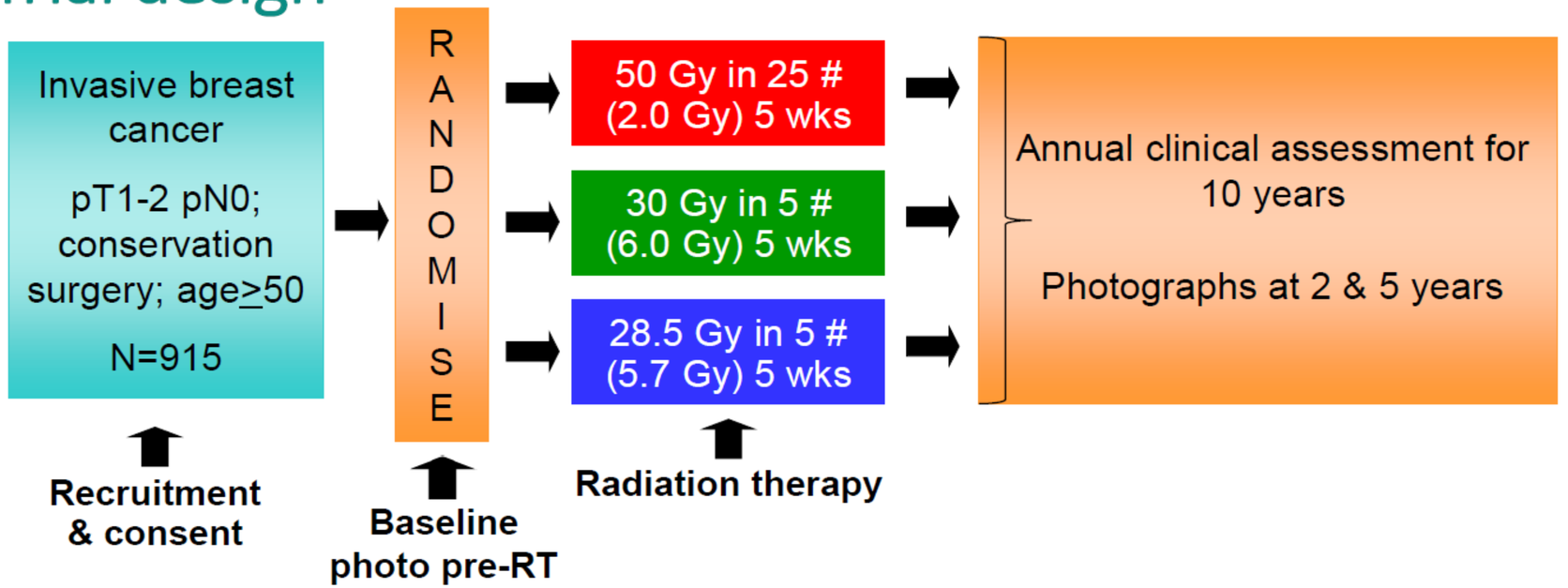
ULTRA
HYPOFRACTIONATION TRIALS

Phase III randomised trial

First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015)

The FAST Trialists group [1]

Trial design



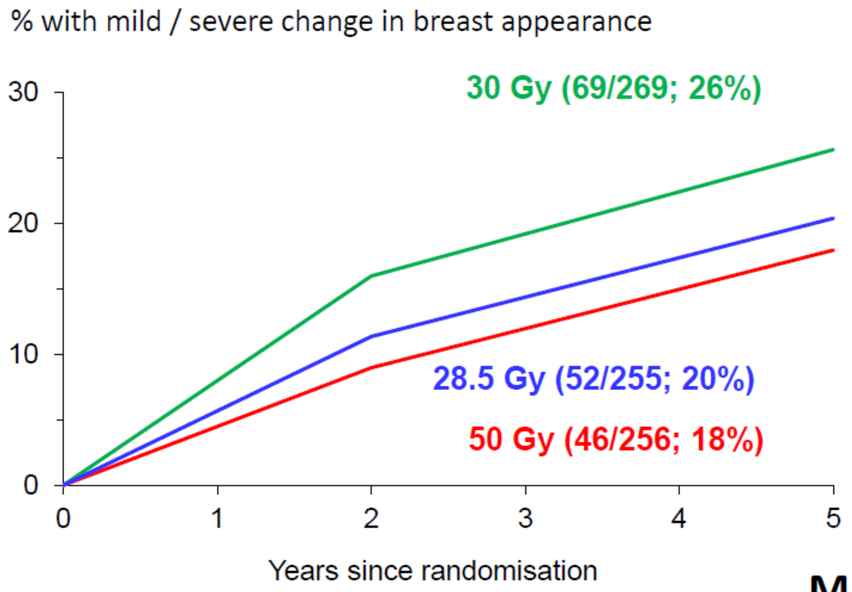
Primary endpoint:
2-year change in photographic breast appearance

Secondary endpoints:
5-year change in photographic breast appearance
clinical assessments of late adverse events
ipsilateral local tumour control

- 64% were >60 years
- 72% post SNB/sampling
- 81% pTsize ≤ 2 cm
- 88.5% grade 1-2 tumors
- 84% small to medium size breast
- 89.5% received hormone therapy

#ASTRO18

Photographic assessment of overall change in breast appearance by 5 years



	Difference (95%CI)
30Gy vs **50Gy**	+7.4% (0.3, 16.7) p=0.03
28.5Gy vs **50Gy**	+2.4% (-3.8, 10.8) p=0.47

Marked changes: 2%, 4%, 2%

#ASTRO18

Fractionation Sensitivity (α/β estimates)

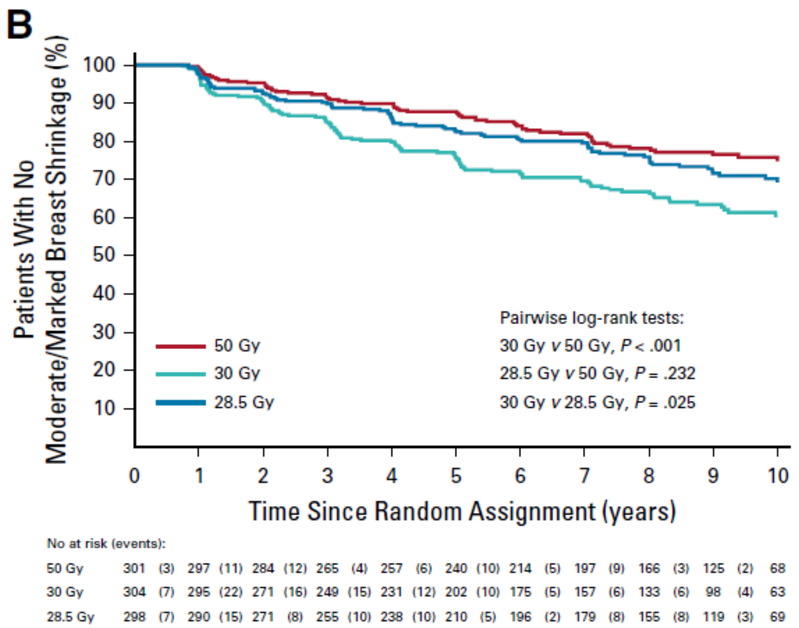
α/β 2.4Gy (95% CI 0.4-4.3 for photographic change and 1.3-3.5 for clinical assessment)

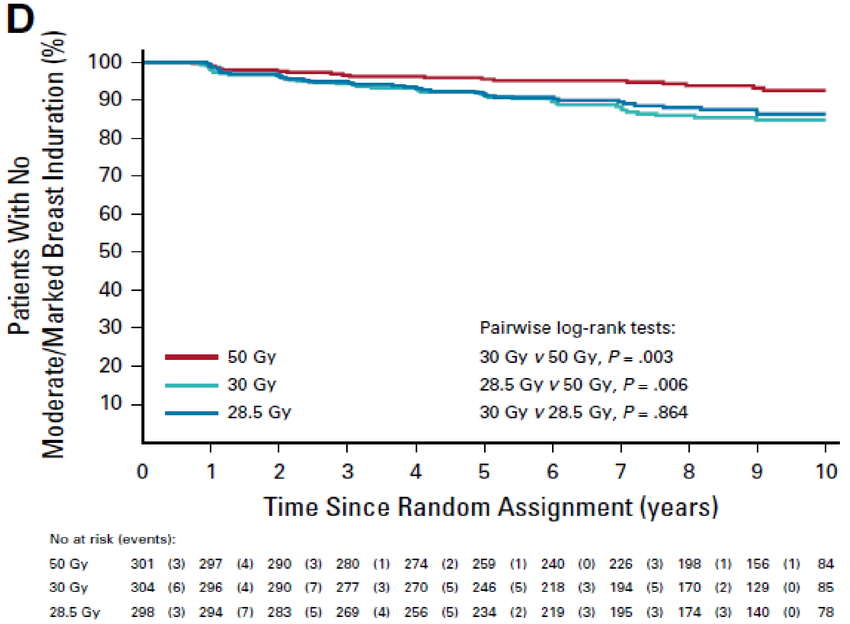
28.5 Gy in 5 # = 52.5 Gy in 2 Gy #

30.0 Gy in 5 # = 57.3 Gy in 2 Gy #

Brunt et al, JCO, 2020

Clinical assessment of late AE in breast





Incidence: 22.9% vs. 26.5% vs 34.2%
KM estimates: 28.5% vs. 33.4% vs 40.5%

Incidence: 6.3% vs. 12.7% vs 13.2%
KM estimates: 7.4% vs. 18.6% vs 15.2%

Estimate of 10-year local relapse rate: 1.3% (95%CI 0.7, 2.3%)

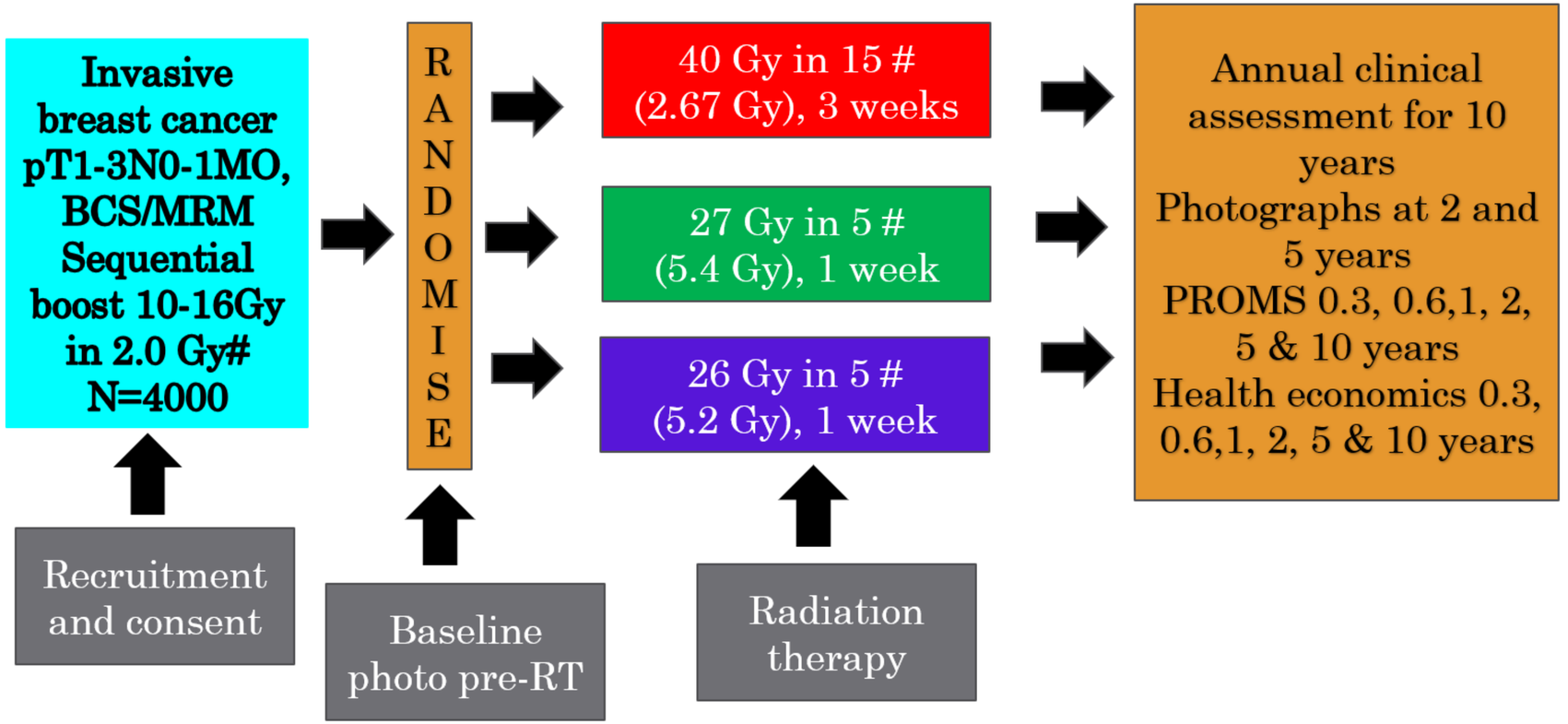
#ASTRO18

Brunt et al, JCO, 2020

update

Radiotherapy and Oncology 120 (2016) 114–118

Acute skin toxicity associated with a 1-week schedule of whole breast radiotherapy compared with a standard 3-week regimen delivered in the UK FAST-Forward Trial



- 14.6% were <50 years
- 93.3% BCS, 85% Ax sampling
- 81% node negative
- 71.6% grade 1-2 tumors
- 98.3% T1-2 (median 1.6 cm)
- 89% hormone positive
- 24% boost given (10Gy in 80%)

Primary endpoint: Ipsilateral local tumor control

Secondary endpoint: Acute effects, late effects, health economics, other disease related endpoints

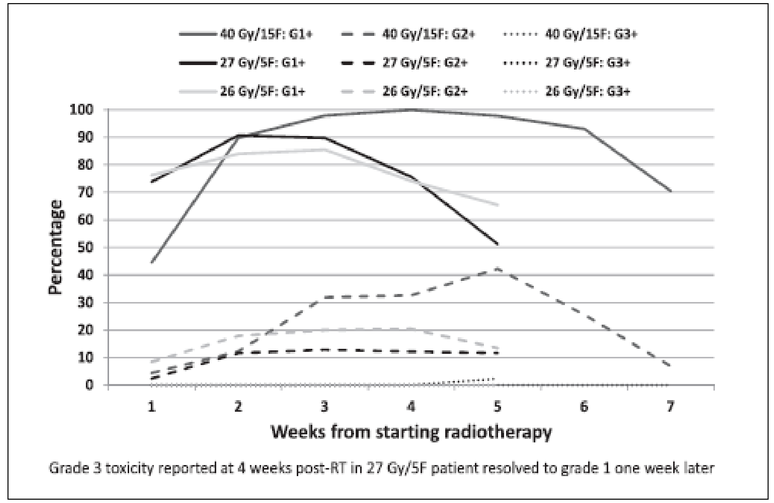
Lymphatic sub-study: 2015 (results awaited this year)

FAST-Forward
5 × 5.2/5.4 Gy

41.1 Gy/43.7 Gy

Acute toxicity

RTOG (%)	40 in 15	27 in 5	26 in 5
N	44	51	52
Grade 0-1	32	51	68
Grade 2	55	39	27
Grade 3-4	**13.6**	**9.8**	**5.8**
CTCAE (%)	40 in 15	27 in 5	26 in 5
N	43	41	53
Grade 0-1	49	63	64
Grade 2	51	27	36
Grade 3-4	**0**	**2.4**	**0**

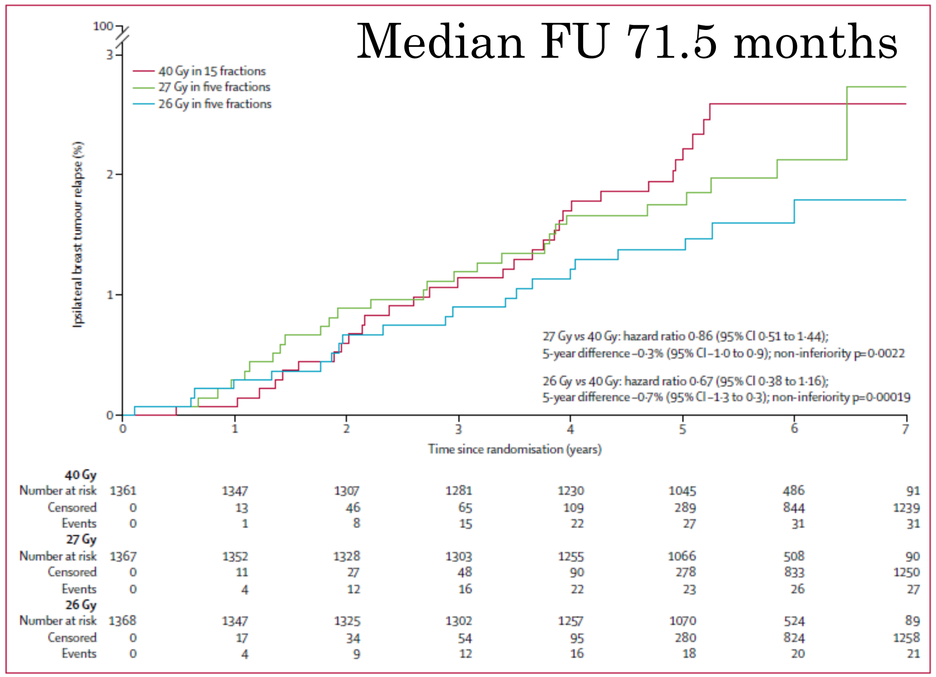


Grade 3 toxicity reported at 4 weeks post-RT in 27 Gy/5F patient resolved to grade 1 one week later

- Grade 2 toxicity was largely due to moderate to brisk erythema
- Erythema after the 1-week schedule is less intense and settles about 2 weeks earlier than after the 3-week schedule.

Primary endpoint

Comparison	HR	Difference
40 Gy vs 27 Gy	0 · 86 (95% CI 0 · 51 to 1 · 44)	-0.3%
40 Gy vs 26 Gy	0 · 67 (95% CI 0 · 38 to 1 · 16)	-0.7%



The unadjusted α/β estimate for IBTR was 3 · 7 Gy (0 · 3 to 7 · 1)

EQD2 estimates of without time correction

- 44 · 7 Gy for 40 Gy,
- 43 · 1 Gy for 27 Gy,
- 40 · 6 Gy for 26 Gy

Brunt, Lancet Oncol 2020

Late toxicity: physician assessed

Endpoint	40 in 15	27 in 5	26 in 5	OR to 40	P value 40 & others	P value 26 & 27
Any adverse event	10.6%	15.9%	12.2%	**1.55** **1.12**	**<0.0001** **0.20**	0.0001
Breast distortion	4.0%	6.1%	5.0%	**1.51** **1.20**	**0.0028** **0.19**	0.083
Breast shrinkage	5.8%	8.5%	6.2%	**1.50** **1.05**	**0.0004** **0.71**	0.0018
Breast induration TB	3.2%	5.1%	4.0%	1.56 **1.19**	**0.0013** **0.23**	0.047
Breast induration non-TB	0.8%	2.3%	1.6%	**2.79** **1.90**	**<0.0001** **0.013**	0.059
Telengiectasia	1.0%	1.6%	1.6%	**1.68** **1.53**	**0.025** **0.070**	0.65
Breast edema	1.5%	3.4%	2.4%	**2.18** **1.47**	**<0.0001** **0.032**	0.0097
Breast discomfort	3.8%	4.3%	4.0%	**1.10** **0.98**	**0.44** **0.86**	0.35

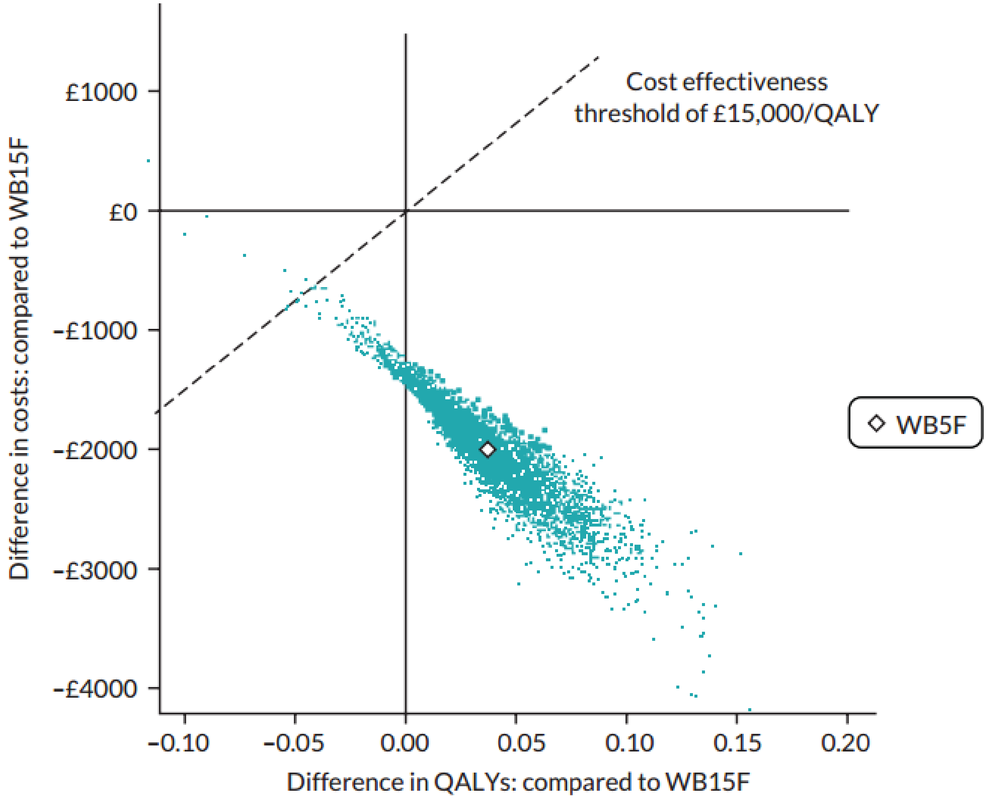
KM estimates for 5 yr: 26.8% vs. 35.1% vs. 28.5%

Late toxicity: PROMS

Endpoint at 60 months	40 in 15	27 in 5	26 in 5	OR to 40	P value 40 & others	P value 26 & 27
Change in breast appearance	31.4%	36.4%	30.0%	**1.22** **0.91**	**0.033** **0.33**	0.0018
Change in photo-graphic appearance (5 yr)	12.0%	26.9%	13.1%	**2.29** **1.26**	**<0.0001** **0.24**	0.0006
Breast harder or firmer	20.4%	27.5%	24.7%	**1.42** **1.22**	**0.0003** **0.048**	0.1007
Breast swollen	4.8%	9.1%	7.4%	**1.46** **1.27**	**0.0080** **0.11**	0.22

- The unadjusted α/β estimate for NTE was 1 · 7 Gy (95% CI 1 · 2 to 2 · 3)
- EQD2 estimates of without time correction
  - 47 · 1 Gy for 40 Gy,
  - 51 · 6 Gy for 27 Gy,
  - 48 · 3 Gy for 26 Gy

FAST-F Health Technology Assessment



WB15F = whole breast 15 fractions; WB5F = whole breast 5 fractions; QALYs = quality adjusted life years.

FIGURE 17 Base case cost-effectiveness plane comparing 5 fractions to 15 fractions.

	40 in 15 fractions	26 Gy / 27 Gy in 5 fractions
Cost	£31,640	£29,638
QALYs	11.08 QALYs	11.12 QALYs

- **5 fractions is associated with lower costs and greater QALYs and found to be cost-effective**
- **The ICER was below the cost-effectiveness plan**

Largest Real-world Data of Regional Nodal Irradiation using UltraHypoFractionated 5-fraction adjuvant Radiation therapy (UHFRT) for breast Cancer from a single Institute In India

R. Pathak, **R. Sarin**, T. Wadasadawala, R. Krishnamurthy,

S. Karmakar, A. Khandavalli, N. Abbas & Breast Disease Management Group

Dept of Radiation Oncology & Medical Physics, Tata Memorial Hospital & ACTREC,

***Tata Memorial Centre (TMC),* Mumbai, INDIA**

Funding: Intramural TMC, Dept. of Atomic Energy (DAE), India

@RajivSarin5 @RadOncTMC

TMC Breast UHFRT Registry

Largest RNI UHFRT Cohort of 1024 patients

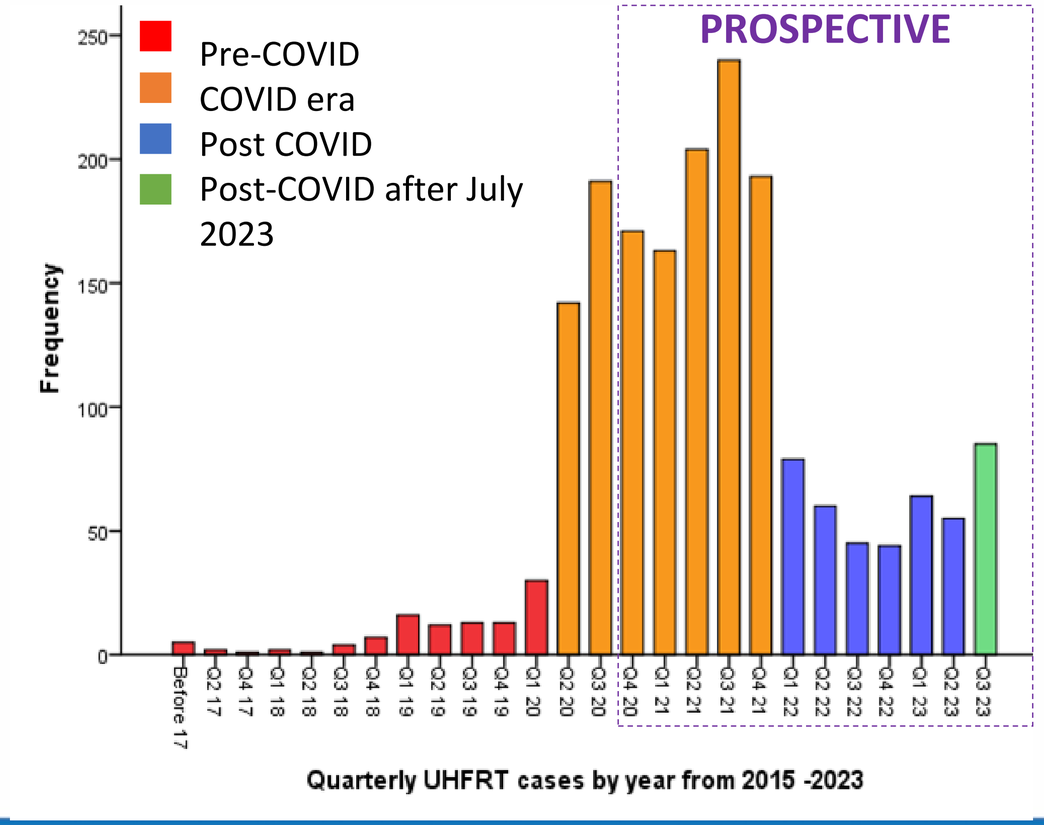
FAST (265 patients); FAST-Forward (759 patients)

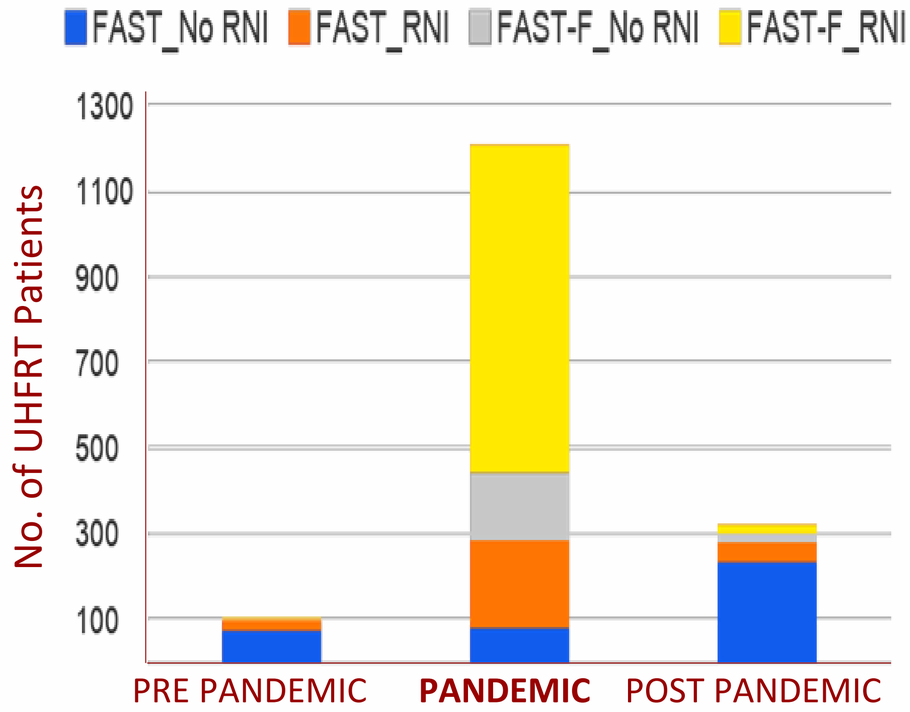
Pre pandemic: UHFRT (FAST) for highly selected early breast cancers

Pandemic: UHFRT (mostly FAST-Forward) for all, including RNI cases

Post Pandemic : UHFRT use continued, but for selected cases

- **IEC approved- Ambispective Registry. Retrospective (2017-Sept 2020) -- -- Prospective after Sept 2020**
- Of the 1616 New Stage 1-3 Breast Cancer cases, 1024 who have received RNI included in this report





UHFRT RNI Cohort (1039 breasts in 1024 patients)

PATIENT CHARACTERISTICS (n=1024) 1008 Females; 16 Males	
Median Age (IQR) yrs	49 (42-56) yrs
<50 yrs*	536 (52%)
50-59 yrs	293 (29%)
≥60 yrs	195 (19%)
Postmenopausal	481 (47%)

Age <50 yrs at diagnosis
56% FAST-Forward group vs 42% FAST group (p<0.001)

TUMOUR CHARACTERISTICS (1039 breasts in 1024 patients)		
Histology	**IDC**	1005 (96%)
Grade	**III**	921 (88.6%)
Receptor Status	**HR +/ Her2 -**	510 (49.1%)
	HR+/ Her2 +	184 (17.7%)
	HR-/ Her2+	112 (10.8%)
	TNBC	230 (22.1%)
T stage	**T0-T2**	565 (54.3%)
	T3- T4	474 (45.6%)
N Stage	**N0** **N1**	80 (7.7%) 429 (41.3%)
	N2 **N3**	246 (23.7%) 285 (27.4%)
Stage	**OBC**	355 (34.2%)
	LABC	684 (65.8%)

SYSTEMIC THERAPY given to 1021/1024 (99.7%) patients	
NACT → Surgery	159 (15.5%)
NACT → Surgery → Adjuvant CT	442 (43.2%)
Surgery → Adjuv CT	364 (35.5%)
Hormone Therapy in ER/PR +ve cases	690/694 cases
Trastuzumab in Her2 +ve cases	295/296 cases

SURGERY (n=1039 Breasts)	
BCS Upfront BCS After NACT	387 (37.3%) 173 214
MRM	647 (62.2%)

Max Acute Skin Toxicity may appear 1-2 weeks after end of UHFRT in 5% cases

Median FU from end of RT	25.1 months (95% CI 24.3- 25.9 m)
Median FU from Diagnosis	34.2 months (95% CI 33.3- 35.1 m)

FULL COMPLIANCE TO RT in 1024 UHFRT RNI COHORT

(3/592 cases in the Non RNI UHFRT cohort could not complete RT or had a long or unplanned interruptions)

Patients were reviewed weekly in the FAST regime and once or more in the FF regimen and again 2 weeks after completion of RT

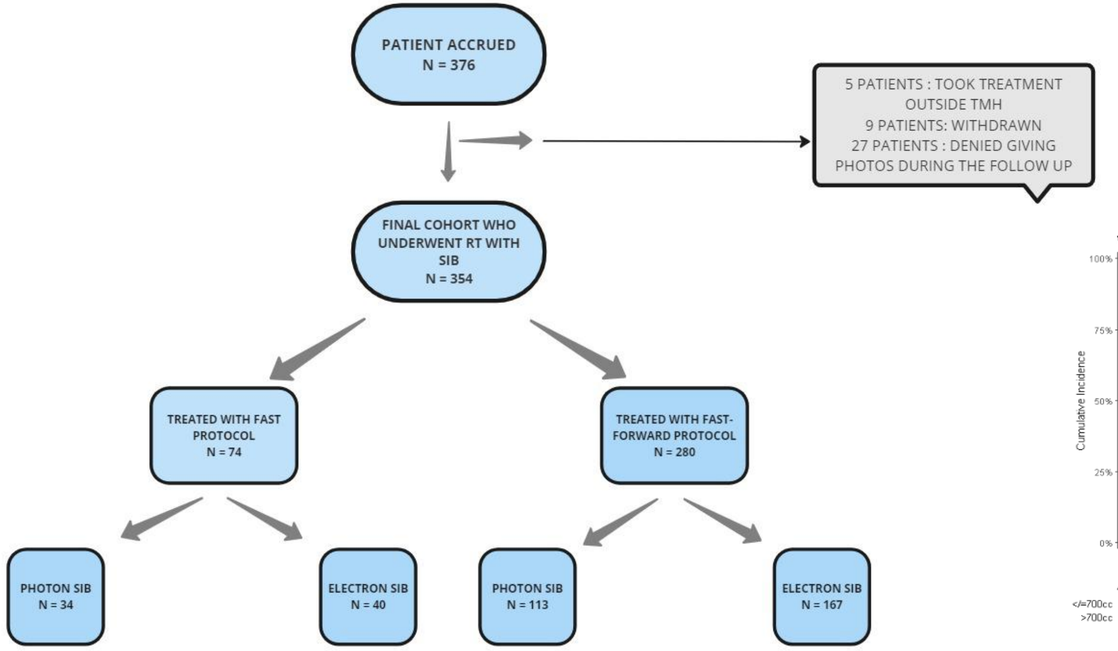
Maximum ACUTE Toxicity (RTOG) *(at RT conclusion or within 2 weeks)*	
Skin Toxicity (in 1039 breasts)	
Gr 0	99 (9.5%)
Gr 1	859 (82.6%)
Gr 2	77 (7.5%)
Gr 3	1 (0.1%)
Pharyngeal Toxicity (in 1024 cases)	
Gr 0	599 (57.7%)
Gr 1	356 (34.2%)
Gr 2	76 (7.3%)
Gr 3	4 (0.4%)

Late toxicity from Nodal Irradiation (CTCAE v5)

- Arm edema (Maximum Grade at any time point after RT)
  - Full cohort: Any grade: 238 (22.9%), Grade II/III: 38 (3.7%)
  - FAST: Any grade: 54 (20.1%), Grade II/III: 7 (2.6%)
  - FAST-Forward: Any grade: 184 (23.8%), Grade II/III: 31 (4%)

- No Radiation induced Cardiomyopathy / Pneumonitis/Brachial plexopathy

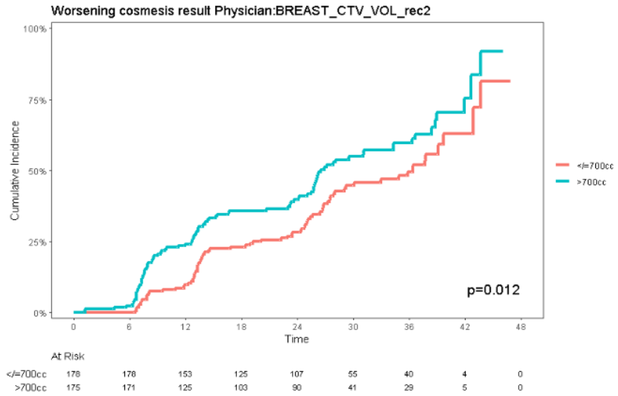
- Tumour laterality & cardiac doses evaluated for patients who died of unknown or cardiac causes to rule out Radiation Induced Cardiac death

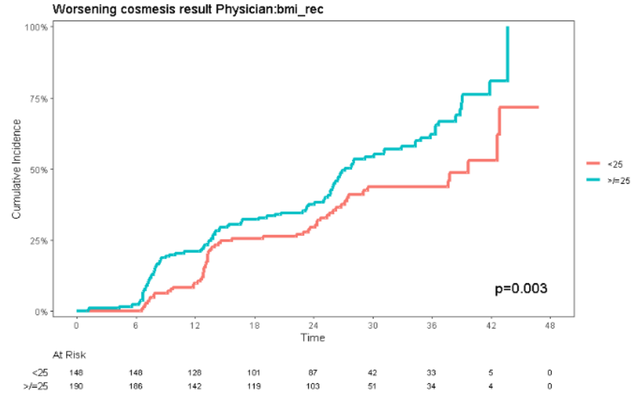


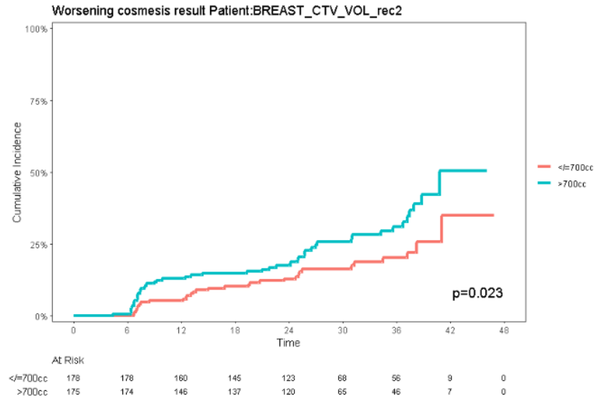
- The median follow up was 31.31 months.
- The mean age of the patient's cohort was 46 years.

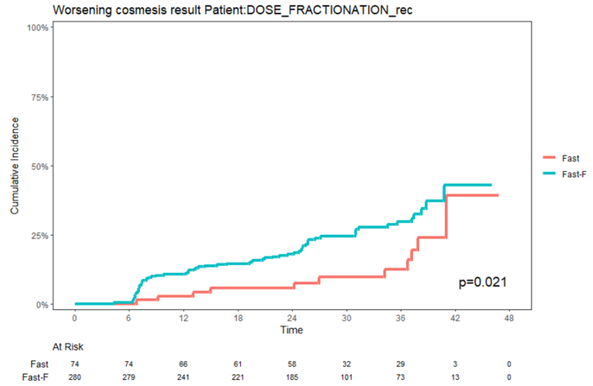
METHOD OF ASSESSMENT	N=354. number of patients with events	12 months	24 months
Physician	**177**	17% (13%,21%)	34% (29%,39%)
Patient	81	9% (6.3%,12%)	15% (12%,19%)
BCCT.core	173	17% (13%,22%)	33% (28%,38%)

PHYSICIAN REPORTED WORSENING









PATIENT REPORTED WORSENING

Is FAST FORWARD the way forward in radiotherapy for locally advanced breast cancer – Learnings from the COVID pandemic

Prashanth Giridhar , Satyajit Pradhan , Lincoln Pujari , Prarabdh Singh , Abhishek Shinghal , Chaturbhaj Khandelwal , Chandrima Mukherjee , Mayank Tripathi , Varun Shukla , Manikandan M V , Zacchariah Choudary , Anuj Gupta

PII: S1526-8209(23)00287-2
DOI: https://doi.org/10.1016/j.clbc.2023.11.003
Reference: CLBC 1703

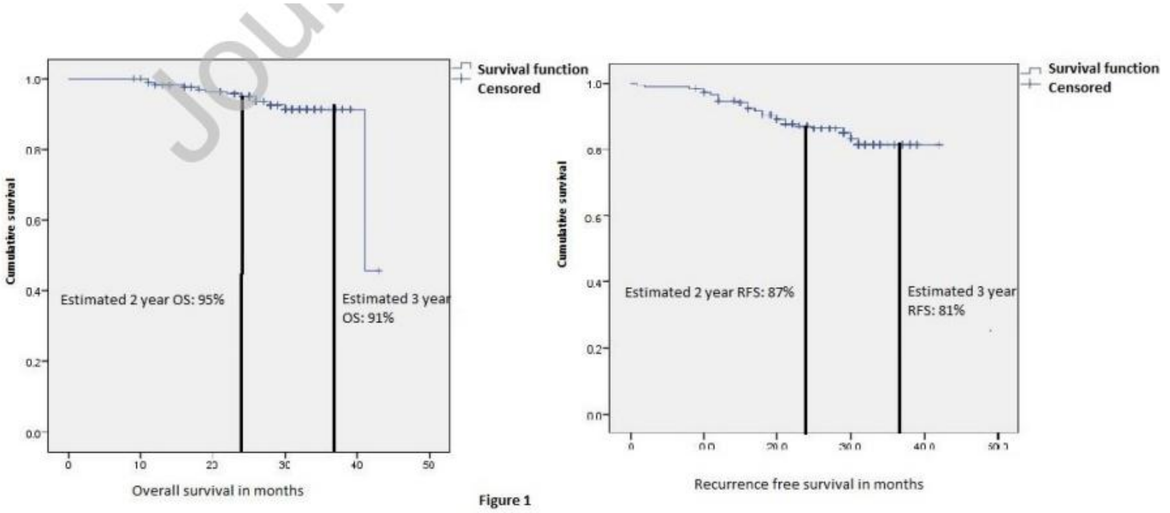


Figure 1. Overall and recurrence free survival in patients receiving ultra-hypofractionated radiotherapy

- A total of 172 LABC patients received ultra-hypofractionated RT.
- The median age of presentation was 49 years (Range: 29 – 76 years).
- Median follow up of the cohort was 27 months (Range: 9 – 42 months).
- Median of mean lung dose was 1.69 Gy (L) and 0.33 Gy (R)
- Median lung dose 4.95 Gy

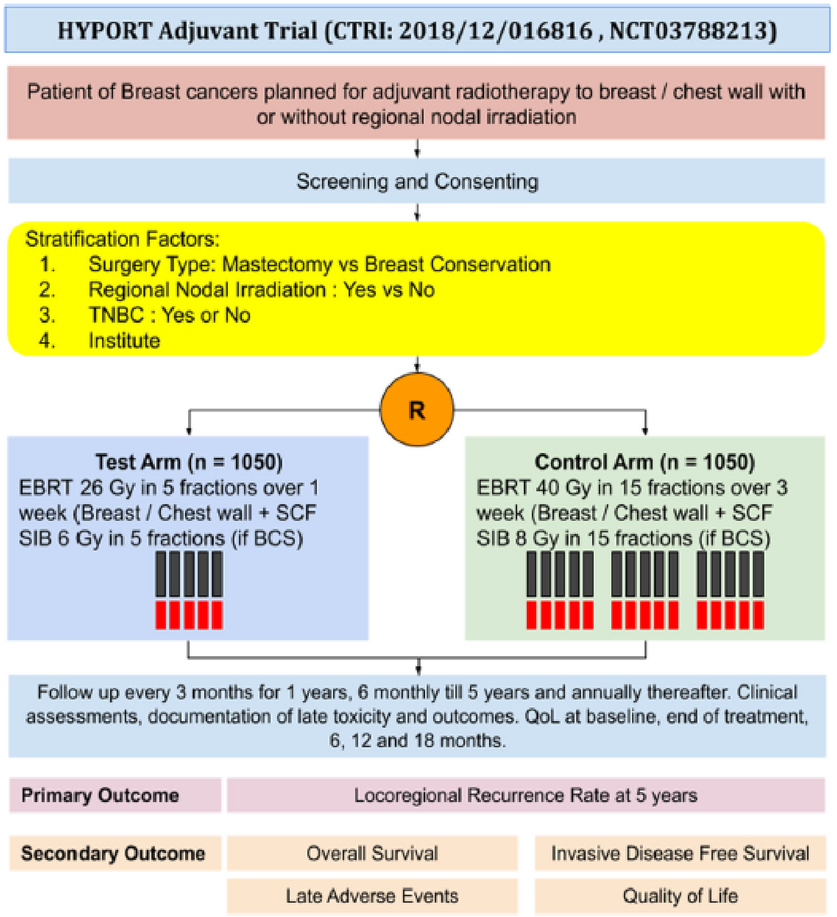
Table 5: Prognostic Factors Affecting RFS and LRRFS.

Parameters	Mean RFS				Mean LRRFS			
	Months	95% CI	P value		Months	95% CI	P value	
			Univariate	Multivariate			Univariate	Multivariate
NACT								
Yes	NR	-	**0.045**	NS	NR	-	0.199	NS
No	NR	-			NR	-		
Pathological stage								
T2N1 (After NACT) or lower	**37.32**	35.89 – 38.75	**0.013**	NS	37.92	36.72 – 39.12	0.118	NS
T3N2 or higher	**35.71**	33.11 – 38.32			38.86	36.91 – 40.82		
ENE								
No	**39.14**	37.64 – 40.64	**0.001**	**0.028**	40.65	39.58 -41.71	**0.017**	NS
Yes	**33.02**	28.91 – 37.13			30.97	34.22 – 40.75		
Receptor status								
Hormone positive	**38.49**	36.76 – 40.23	**0.091**	NS	40.46	39.26 – 41.67	0.142	NS
Triple negative	32.36	28.55 – 36.18			35.27	32.22 – 38.32		
Her 2 neu enriched	**31.13**	28.63 – 33.62			32.24	30.78 – 33. 69		
Type of surgery								
MRM	37.48	35.77 – 39.20	0.38	NS	39.85	38.62 – 41.07	0.52	NS
BCS	39.21	35.61 – 42.81			40.43	37.58 – 43.28		
LVI								
No	38.39	36.54 – 40.25	0.333	NS	39.62	38.01 – 41.23	0.699	NS
Yes	36.75	33.92 – 39.44			40.29	38.67 – 41.91		
Pathological CR								
No	37.29	35.56 – 39.04	0.182	NS	NR	-	0.186	NS
Yes	40.87	38.72 – 43.01			NR	-		
Gap from Last Dose CT to RT								
< 6 weeks	36.988	33.49 - 40.48	0.411	NS	40.78	39.14 – 42.43	0.140	NS
6 – 12 weeks	36.153	34.46 - 37.85			37.85	36.76 – 38.96		
>12 weeks	36.874	33.49 - 40.26			38.10	34.94 – 41.27		

BCS -Breast Conservation Surgery; CR -Complete Response; CT - Chemotherapy; ENE - Extra-nodal Extension; LRRFS - Loco-regional Recurrence Free Survival; LVI - Lymphovascular Invasion; MRM -Modified Radical Mastectomy; NACT -Neo-adjuvant Chemotherapy; RFS - Recurrence Free Survival; RT- Radiotherapy

- Objective: Test the safety of 1-week course of RT with SIB in a trial population having relatively advanced cancers, younger patients with triple-negative cancers and majority requiring a tumour bed boost
- Non-inferiority trial **with 5-yr LRC** as primary endpoint

HYPORT ADJUVANT



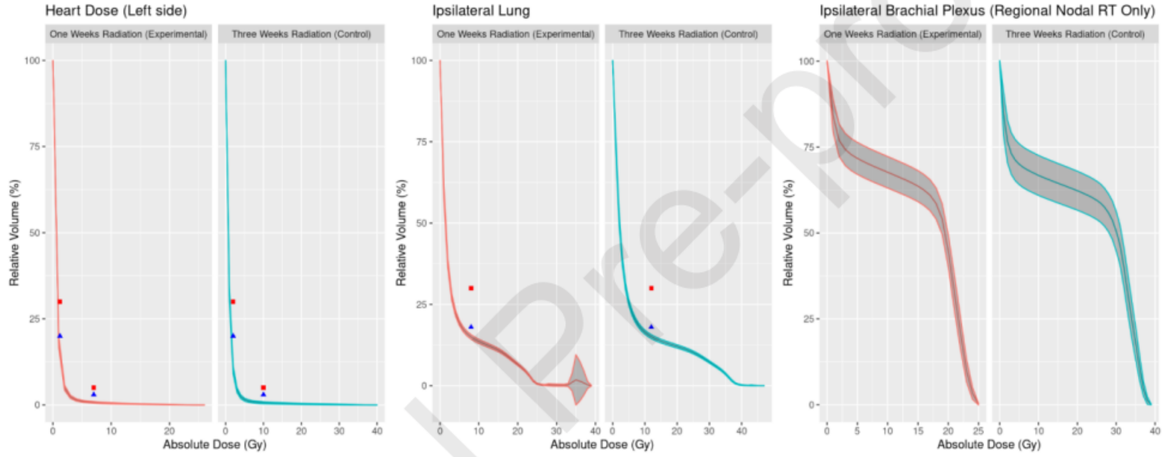
Chatterjee et al, Trials 2022

Variable	N = 135 (test arm)	N= = 136 (STD arm)
Laterality Left	58.1%	49.2%
Surgery BCS MRM	43.7% 55.8%	41.1% 58.7%
Chemotherapy NACT	38.9%	30.8%
T4	20.7%	19.2%
Grade 3	75%	73.5%
ER negative	25.6%	27.9%
Her2 positive	28.6%	27.9%
SCF irradiation	72.0%	69.1%
IMN irradiation	4.4%	2.2%
Tangential technique	95.5%	97.7%

Overall, three patients (1.1%) experienced grade 3 radiation dermatitis (none received SIB), no other Grade 3 or higher toxicities reported.

Fig 3: Prevalence of radiation dermatitis in entire and SIB population at different time points

Fig 2: Mean and 95% confidence intervals of the mean at each dose bin for heart (left sided), ipsilateral lung and ipsilateral brachial plexus plotted as histograms for patients treated with tangential fields. The red and blue points in the heart and ipsilateral lung doses represent the mandatory and optimal dose constraints respectively.



HYPORT Adjuvant Acute toxicity and patient dosimetry quality assurance results- Interim Analysis, Chakraborty et al, RO July 2022

Ongoing trials

HYPORT

- 26 in 5 for Br/CW
- 32 in 5 for SIB

RTOG 1005

- 42.7 in 16 for WBI
- 48 in 15 for SIB

DBCG HYPO II

- 40 in 15 for WBI
- 45.75 in 15 for SIB

- HFRT has revolutionized adjuvant radiotherapy in breast cancer
- Moderate HFRT is the current gold standard
- Results from RCTs of ultra HFRT and registry data demonstrate safety
- Ultra HFRT is likely to replace moderate HFRT
- Just a matter of TIME!

Contact

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