FAST Forward:
A way ahead in Breast Irradiation

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Disclosures

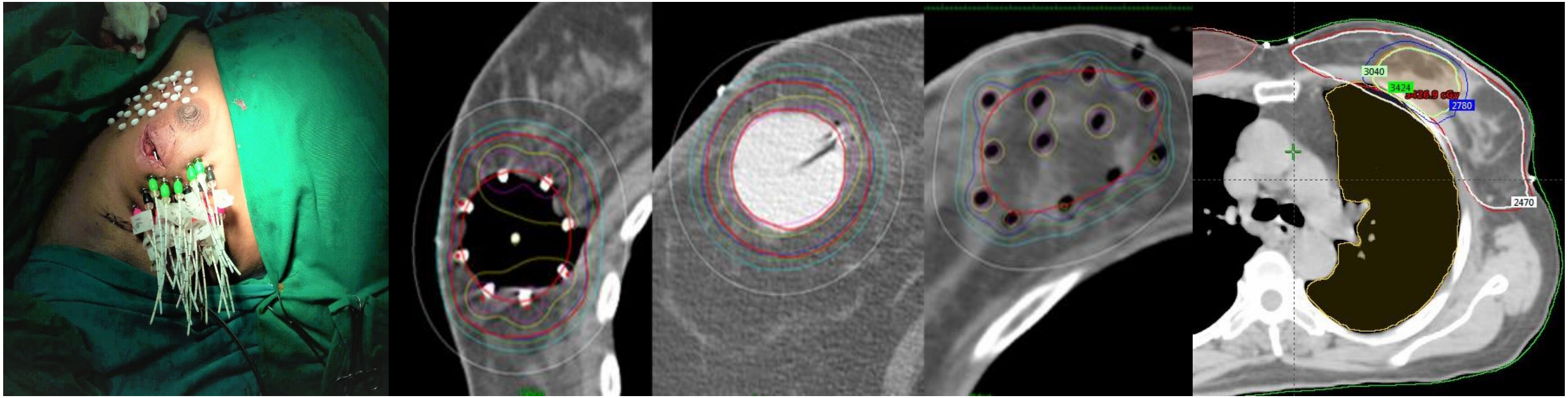
- None

Flow of the Presentation

- Introduction
- Evidence in support of moderate hypofractionation
- FAST Forward Study
- Possible future of FAST-Forward
- Applicability to Indian patients
- TMC Experience
- Cost-Effectiveness
- Summary

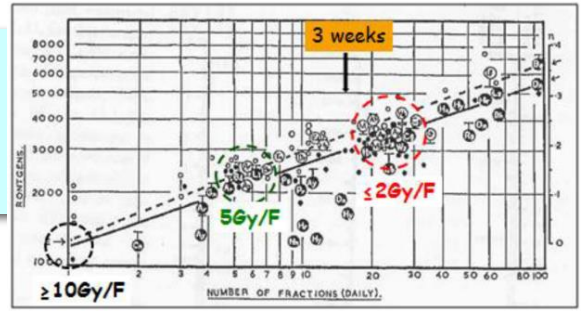
Hypofractionation & Breast Cancer

- Various Forms of Hypofractionation practiced



What about Hypofractionation for the whole breast with EBRT?

Hypofractionation & Breast Cancer



- Cohen et. al. 1952 Inop Breast cancer→ Initial reports of α/β =3.8
- Manchester Fractionation
- 4 main Prospective RCTs (n=7095; 1986 - 2001)

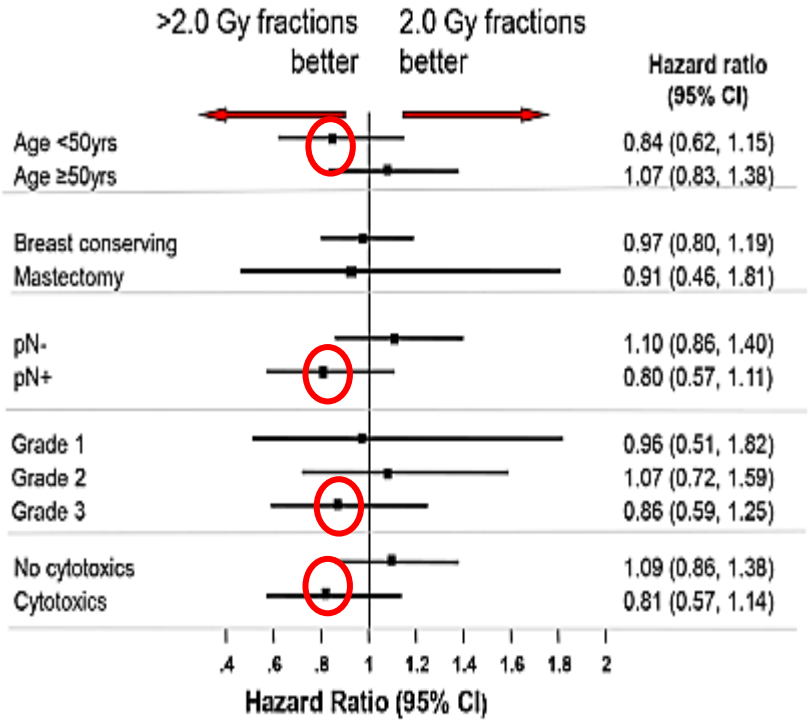
	START-P[8]	START-A[10]	START-B[11]	Ontario[7]
Years accrual	1986–1998	1998–2002	1999–2001	1993–1996
Total number of patients	1410	2236	2215	1234
Standard arm (Gy/fr/weeks)	50/25/5	50/25/5	50/25/5	50/25/5
Test arm A (Gy/fr/weeks)	42.9/13/5	41.6/13/5	40.0/15/5	42.5/16/3.1
Test arm B (Gy/fr/weeks)	39/13/5	39/13/5	n/a	n/a
Mean age (years)	54.5	57.2	57.4	Not reported
Node+ (%)	32.7	28.8	22.8	0
Mastectomy (%)	0	15	8	0
Tumour size ≥ T_2 (%)	42.5[a]	48.6[b]	35.9[b]	20.0[b]
Boost (%)	74.5	60.6	42.6	0
Chemotherapy (%)	13.9	35.5	22.2	11
Regional radiotherapy (%)	20.6	14.2	7.3	0

Yarnold J. BJR 2019

Efficacy of Hypofractionation

- Excellent Local Control; Numerically superior to conventional Fractionation

Trial	Randomisation (Gy/fraction)	% 5 year local relapse (95% CI)	% 10 year local relapse (95% CI)
START-P[9,13]	50.0/25	7.9 (5.4–10.4)	12.1 (8.8–15.5)
	42.9/13	7.1 (5.4–10.4)	9.6 (6.7–12.6)
	39.0/13	9.1 (6.4–11.7)	14.8 (11.2–18.3)
START-A[10,13]	50.0/25	3.4 (2.3–5.1)	6.7 (4.9–9.2)
	41.6/13	3.1 (2.0–4.7)	5.6 (4.1–7.8)
	39.0/13	4.4 (3.1–6.2)	8.1 (6.1–10.7)
START-B[11,13]	50.0/25	3.3 (2.4–4.6)	5.2 (2.7–5.2)
	40.0/15	1.9 (1.2–3.0)	3.8 (2.7–5.2)
Ontario[12]	50.0/25	3.2[a]	6.7[b]
	42.5/16	2.8[a]	6.2[b]



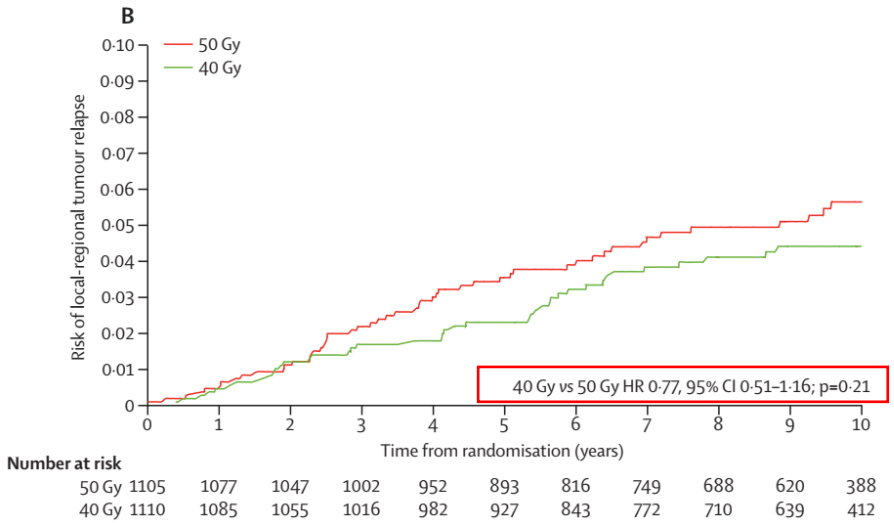
UK-START Studies

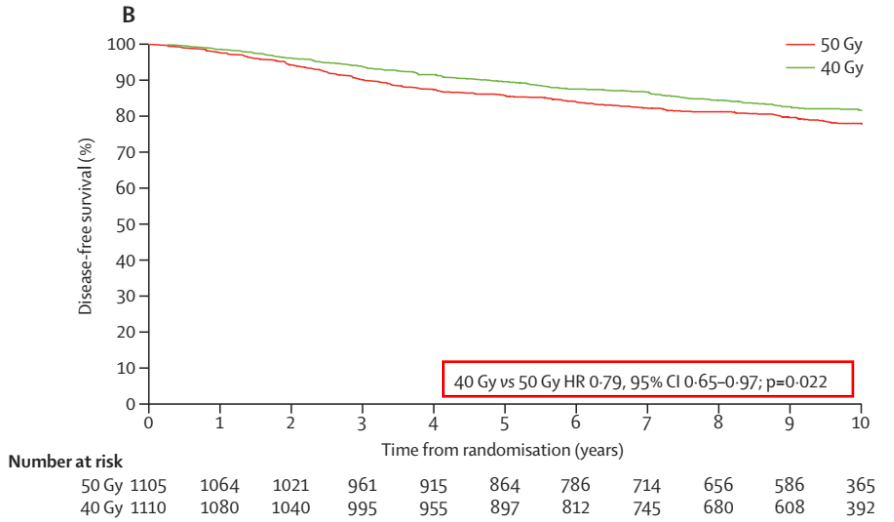
- Diverse patient populations
  - Younger
  - Post Mastectomy
  - Grade III
  - Receipt of CT
  - Regional Nodal RT (mostly SCF & upper Axilla n=470)
- Diverse End-points
  - Radiation sensitivity
  - LRC
  - Toxicity
  - DFS/ OS

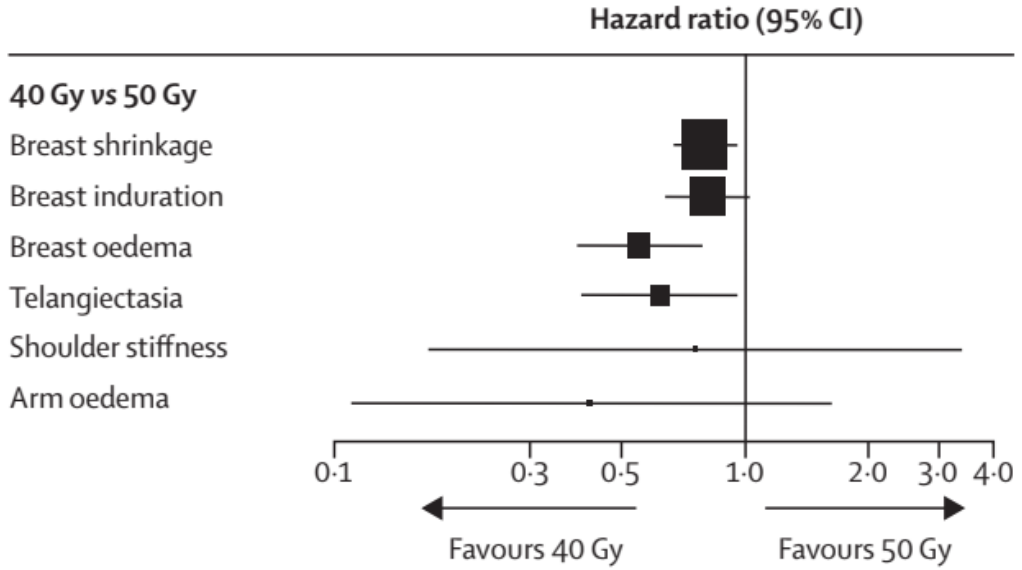
Table 5. START pilot, A & B (*n* = 5861): patient and treatment characteristics[13]

	Number patients
Age <50 years	1389
Age = 50 years	4472
Breast conserving	5348
Mastectomy	513
pN–	4318
pN+	1421
Grade 1	1213
Grade 2	2398
Grade 3	1271
No cytotoxics	4346
Cytotoxics	1480

UK-START B: Efficacy & Toxicity







Any breast cancer-related event†					
50 Gy	222/1105 (20·1%)	14·3% (12·3–16·5)	22·2% (19·7–25·0)	1·00	..
40 Gy	182/1110 (16·4%)	10·4% (8·7–12·4)	18·3% (16·0–20·9)	0·79 (0·65–0·97)	0·022
All-cause mortality					
50 Gy	192/1105 (17·4%)	10·9% (9·1–12·9)	19·2% (16·8–21·9)	1·00	..
40 Gy	159/1110 (14·3%)	7·9% (6·4–9·6)	15·9% (13·7–18·4)	0·80 (0·65–0·99)	0·042

- **Excellent Local Control, DFS, OS & Toxicity profile**
- **MRM/ DCIS/ Recon not well represented**

Haviland et. al 2013 Lancet Oncol

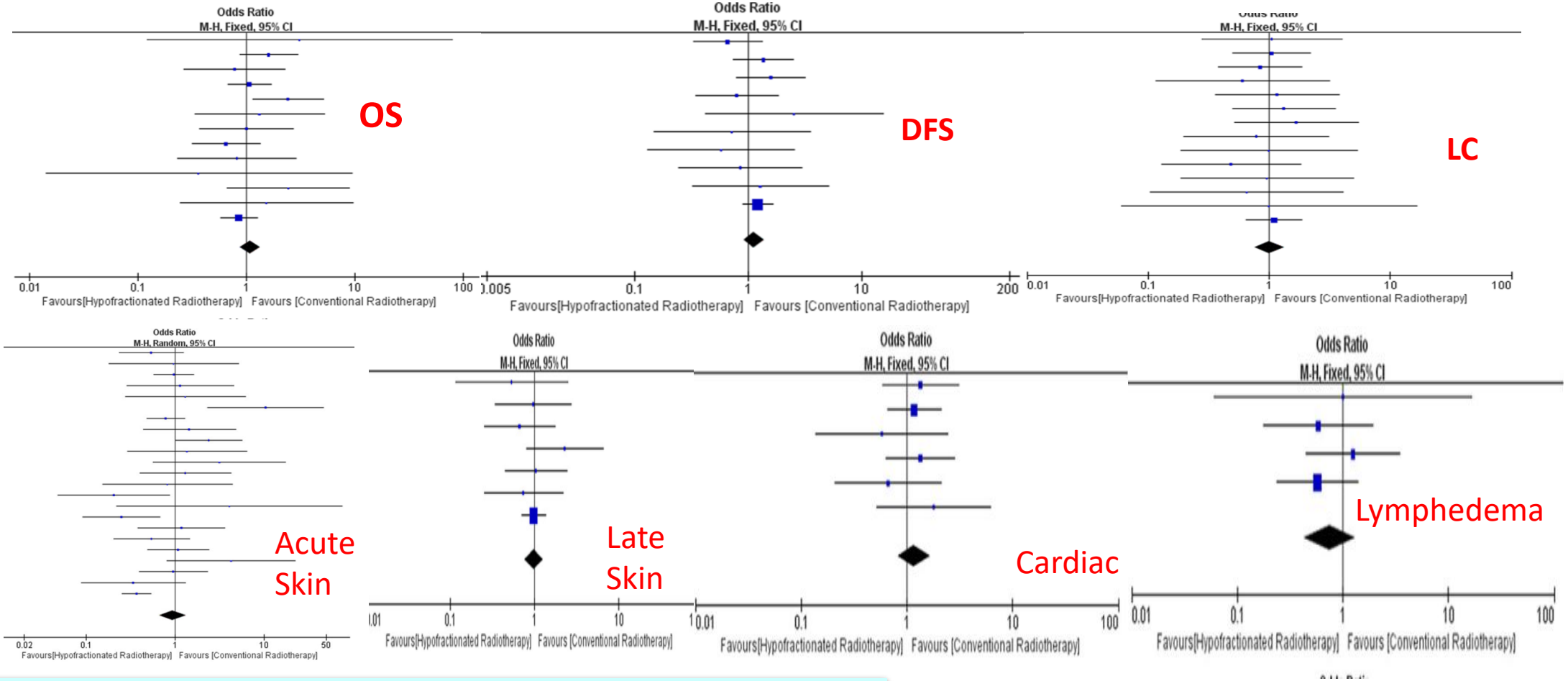
Mastectomy & Hypofractionation

	Ko et. al.	Wang et. al.	Chitapanarux et. al	Khan et. al.
Hypofractionation (n)	133	406	980	744
Dose	40Gy/16 fr	43·5 Gy in 15	42.4- 56Gy/16-20 fr	40-44Gy/16 fr
Median FU	5.03 yrs	~5 yrs	~6 yrs	~3yrs
Gr III toxicity	None	Acute Skin: 8 Vs 3% (SS)	Gr ≥II Skin & Subcut Significantly better	Implant loss 24%
5 yr LRFS	97.5%	5yr LRFS =91.7% NS	5yr LRFS=96% NS	3 yr LRFS=89.2%

- Clearly established the safety and the efficacy of hypofractionation in PMRT as expected
- Consistently better rates of toxicity

Mastectomy & Hypofractionation

- Meta-analysis; 25 controlled studies (n=3871)



NS different with respect to efficacy/ toxicity postmastectomy

Liu et al. 2020 Radiation Oncology

DCIS & Hypofractionation

	Lalani et. al.	Hathout et. al.	Wai et. al.	Rakovitch et. al.	Nilsson C et. al.
n=	638	440	371	744	2534
Dose	42.5Gy/16 fr	42.5Gy/ 16 fr	40-44Gy/16 fr	40-44Gy/16 fr	40-44Gy/16 fr
Median FU	9.2 yrs	4.4 yrs	9.3	14 yrs	5-14 yrs
TBB	324	125		399	2534
10 yr LRFS	86 Vs 89% (NS)	5yr LRFS =97%	NS	10 yr LRFS=91%	NS
MVA	Age< 45yrs, Int/ High nuclear grade & +ve margins	+ve margins, premenopausal status, & nuclear grade 3	comedo histology, high nuclear grade, and close, +ve margin	Age< 45yrs, Int/ High nuclear grade & +ve margins	+ve margins

TROG 07.01 A randomized phase III study of radiation doses and fractionation schedules in non-low risk ductal carcinoma in situ (DCIS) of the breast. → 2yr QoL no difference between Conv vs mod Hypofrac (42.5/16fr)

Reconstructed breast & Hypofractionation

- Ph-II prospective of Stage II/III
- N=69, 2010-2014
- 36.63Gy/11 fr @ 3.33Gy/fr +
- 13.32Gy/4fr e- scar boost (~60Gy BED)
- ~60% recon breast (88% TE, 7% Immediate, 5% augmentation)
- 28% Gr-II skin tox
- No Gr-III or more acute/late tox
- 6 patients implant failure (<10% vs 18-30% in literature)
- Alliance A221505 (RT CHARM) → RCT 42.5Gy/16fr

Table 4 Treatment-related toxicities

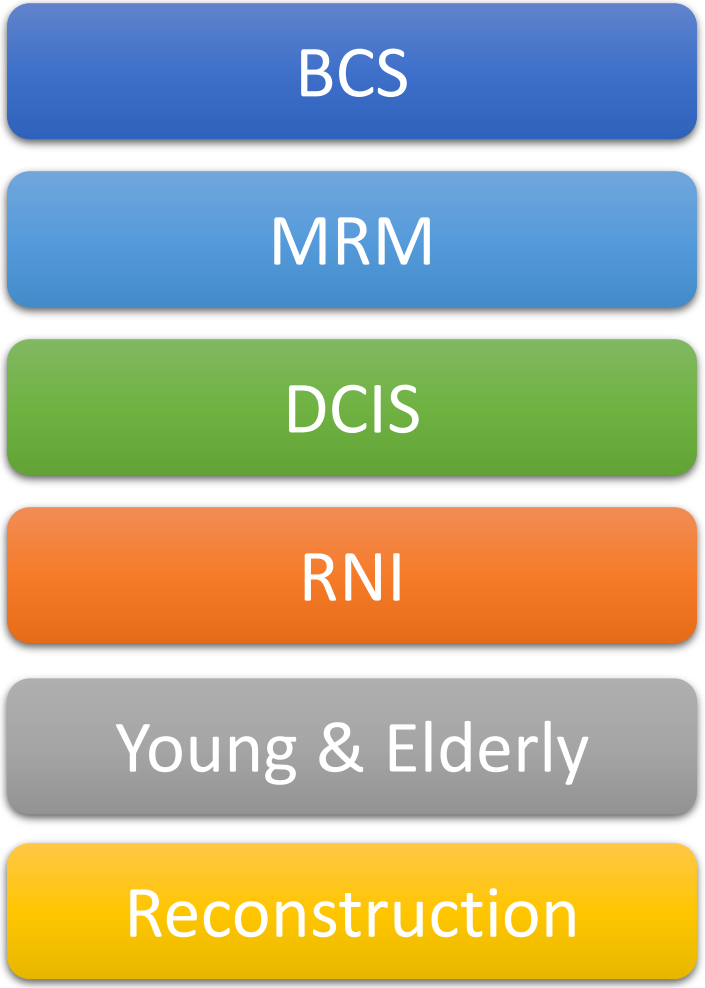
	Grade 1 toxicities		Grade 2 toxicities	
	Acute, n (%)	Late, n (%)	Acute, n (%)	Late, n (%)
Skin	37 (55)	20 (30)	19 (28)	0
Fatigue	15 (22)	12 (18)	8 (12)	2 (3)
Pain	13 (19)	9 (13)	2 (3)	5 (8)
Lymphedema	1 (2)	1 (2)	2 (3)	1 (2)
Subcutaneous	0	11 (17)	1 (2)	0
Telangiectasia	0	11 (17)	0	0
Other*	2 (3)	0	1 (2)	0

* Bronchospasm (wheezing), shoulder stiffness.

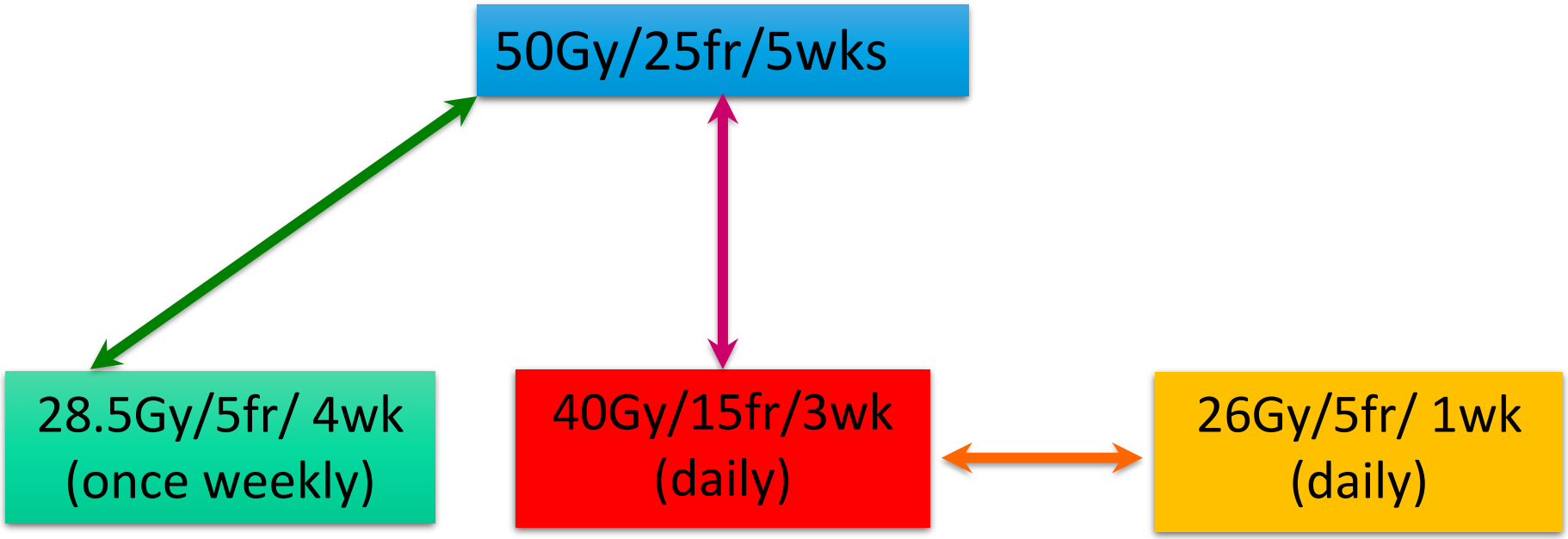
Poppe et al. IJROBP 2020

Moderate Hypofractionation

- Similar efficacy & toxicity across patients populations



Intercomparison of different fractionation regimen



UK FAST RCT
10-yr Toxicity & LRC same

UK START-B RCT LRC Same;
40GY/15fr Less Acute / Late Toxicity

UK FAST Forward RCT
5-yr LRC & Tox same

R Sarin, TMC

Randomized Groups

FAST (2004-2007; n=915)

- Standard: (n=302)
  - **50Gy/ 25 fr; 5 weeks**
- Experimental Arm 1: (n=308)
  - **30Gy/ 5 fr; once a week, 5 weeks**
  - α/β =4 for late toxicity
- Experimental Arm 2: (n=305)
  - **28.5Gy/ 5 fr; once a week, 5 weeks**
  - α/β =3 for late toxicity

FAST FORWARD (2011-2014; n=4110)

- Pilot testing: (n=30)
  - 30Gy/5 fr; 3 weeks
- Standard: (n=1368)
  - **40Gy/ 15 fr; 3 weeks**
- Experimental Arm 1: (n=1370)
  - **27Gy/ 5 fr; 1 week, α/β =3**
  - Assuming No TT compensation
- Experimental Arm 2: (n=1372)
  - **26Gy/ 5 fr; 1 week, α/β =3**
  - Assuming TT compensation
- Stratified by risk groups
- 10 or 16 Gy TBB with e-

Study Inclusions

FAST

- ≥ 50 years
- Invasive carcinoma,
- **BCS only**
- margin –ve, pT<3.0 cm,
- pN0
- ER +ve allowed HT

Exclusion

- MRM
- Need for RNI/ TBB
- Neoadjuvant or adjuvant cytotoxic therapy

FAST FORWARD

- ≥ 18 years
- Invasive carcinoma,
- Any Sx, Negative margins
- pT1-3 pN0-1 (1-2)* M0
- ER +ve allowed HT
- Her2-Neu +ve → Trastuzumab

Exclusion

- ≥65yrs, pT1 G1/2, ER+ve/Her2 -ve Microinvasive disease
- Concurrent CT
- Previous Malignancy/ RT to chest
- ≥10 nodes +ve/ SCF nodes/ IMN Nodes

Outcome Measures

FAST

- **Primary:**
- Change in photographic breast appearance (baseline, 2 & 5 years)
- **Secondary:**
- Local tumor control
- Radiation-induced changes in the breast and other later responding tissues

FAST FORWARD

- **Acute Toxicity pilot**
- **Primary:**
- 5-yr Local Relapse rates
- **Secondary:**
- Prevalence of late breast toxicities at 5 years
- PROM
- Health Economics study

RT planning

FAST

- Supine on a BB
- Reproducibility → orthogonal laser
- CTV: whole breast up to deep fascia, not include underlying muscle and ribcage (ESTRO)
- PTV: 1cm 3D expansion limits: midline & mid-axillary line
- Max Lung: 2cm on CT/ conv simulator.
- Cardiac shielding
- Prescription: ICRU point
- Central plane Max- min dose ≤ 10%
- No Cobalt RT

FAST FORWARD

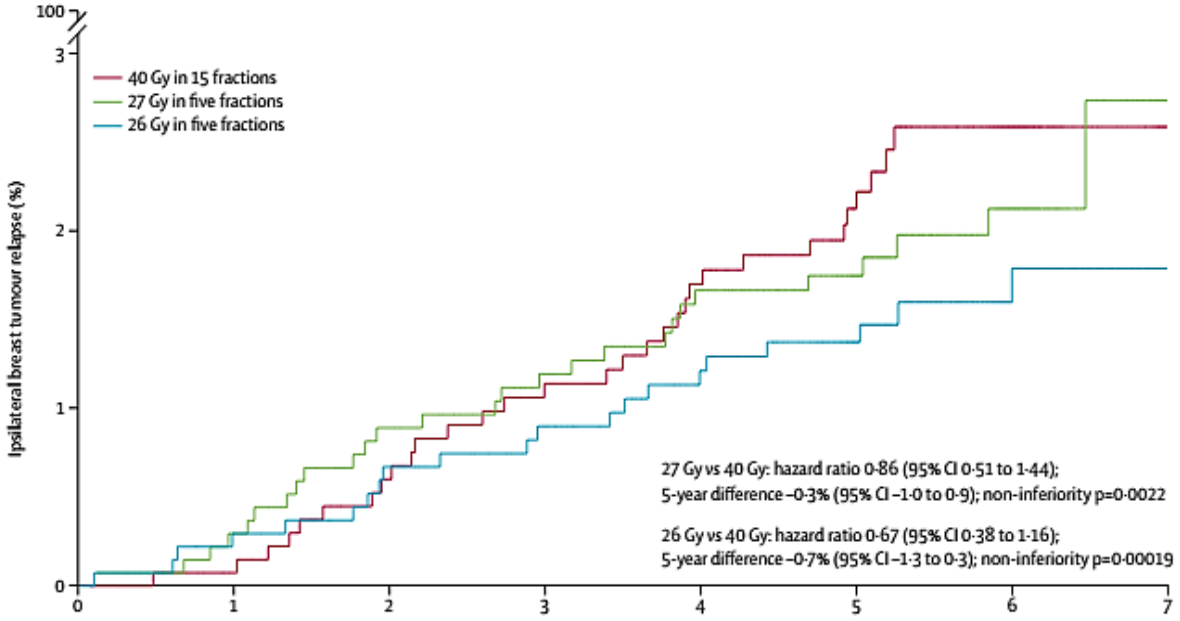
- Supine on BB or Vacuum Bag
- **Only 3D CT based planning**
- **Planning was similar in most ways**
- TBB delineation was mandatory and was strongly advised to use clips/ gold markers
- Field based PTV may be used for dosimetric reporting
- **Mandatory contouring of I/l Lung, Heart**
- Lymphatic arm→ Brachial Plexus
- **Bitangential RT/ FiF-IMRT**
- **Tissue heterogeneity correction applied**

Set-up Verification & QA requirements

- **Daily imaging using EPID (KV/ MV)**
- **All displacements are corrected at each fraction**
- After correction → > 5mm difference → repeat set-up/ re-sim
- **Similar verification for all the fractions of conformal photon boost**
- For e- boost → Visual verification with skin marking
- **QA and credentialing of the contouring, treatment technique assessment, homogeneity, prescription points, IMRT technique**
- **Assessment of Daily QC protocols**, measurement of phantom* readings
- **QC Image verification protocol**
- Complete verification of the 1st 3 patients treated incl CT dataset quality
- In-vivo dosimetry on the 1st day of test arm and within 1 week of control arm

Study Results

Brunt et. al. Lancet Oncol 2020



Estimated cumulative incidence **of IBTR 5 years was 2·1%** (95% CI 1·4 to 3·1) for 40 Gy (expected incidence 2%),
1·7% (1·2 to 2·6) for 27 Gy &
1·4% (0·9 to 2·2) for 26 Gy
Estimated absolute differences in IBTR versus 40 Gy
–0·3% (–1·0 to 0·9) for 27 Gy &
–0·7% (–1·3 to 0·3) for 26 Gy

	Cumulative number of events	Estimated cumulative incidence by 5 years (95% CI)	Hazard ratio (95% CI); p value	Estimated absolute difference vs 40 Gy at 5 years (95% CI)
Ipsilateral breast tumour (local) relapse*				
40 Gy (n=1361)	31 (2·3%)	2·1% (1·4 to 3·1)	1 (ref)	..
27 Gy (n=1367)	27 (2·0%)	1·7% (1·2 to 2·6)	0·86 (0·51 to 1·44); 0·56	−0·3% (−1·0 to 0·9)
26 Gy (n=1368)	21 (1·5%)	1·4% (0·9 to 2·2)	0·67 (0·38 to 1·16); 0·15	−0·7% (−1·3 to 0·3)
Locoregional relapse†				
40 Gy (n=1361)	43 (3·2%)	2·8% (2·0 to 3·9)	1 (ref)	..
27 Gy (n=1367)	35 (2·6%)	2·3% (1·6 to 3·3)	0·80 (0·51 to 1·25); 0·33	−0·5% (−1·4 to 0·7)
26 Gy (n=1368)	29 (2·1%)	1·8% (1·2 to 2·7)	0·66 (0·41 to 1·06); 0·083	−0·9% (−1·6 to 0·2)
Distant relapse				
40 Gy (n=1361)	59 (4·3%)	3·8% (2·9 to 5·0)	1 (ref)	..
27 Gy (n=1367)	69 (5·0%)	4·7% (3·7 to 6·0)	1·16 (0·82 to 1·64); 0·41	0·6% (−0·7 to 2·3)
26 Gy (n=1368)	76 (5·6%)	5·1% (4·0 to 6·4)	1·27 (0·90 to 1·79); 0·17	1·0% (−0·4 to 2·9)
Any breast cancer-related event‡				
40 Gy (n=1361)	119 (8·7%)	7·8% (6·5 to 9·4)	1 (ref)	..
27 Gy (n=1367)	112 (8·2%)	7·2% (5·9 to 8·7)	0·93 (0·71 to 1·20); 0·56	−0·6% (−2·2 to 1·5)
26 Gy (n=1368)	114 (8·3%)	7·5% (6·2 to 9·0)	0·94 (0·73 to 1·22); 0·65	−0·4% (−2·1 to 1·6)
All-cause mortality				
40 Gy (n=1361)	92 (6·8%)	5·4% (4·3 to 6·8)	1 (ref)	..
27 Gy (n=1367)	105 (7·7%)	6·9% (5·7 to 8·4)	1·12 (0·85 to 1·48); 0·42	0·6% (−0·8 to 2·5)
26 Gy (n=1368)	90 (6·6%)	5·6% (4·5 to 7·0)	0·96 (0·72 to 1·28); 0·78	−0·2% (−1·5 to 1·5)

Physician reported NTEs

Brunt et. al. Lancet Oncol 2020

- Similar between Standard and 26Gy arm
- Significantly higher for all the NTEs for the 27Gy arm except Breast/ CW discomfort
- 26Gy arm appears to equally safe as the 40Gy/15 fr

	Number of moderate or marked events/total number of assessments over follow-up	Odds ratio for schedule (95% CI)	p value for comparison with 40 Gy
Any adverse event in the breast or chest wall*	--	--	--
40 Gy	651/6121 (10·6%)	1 (ref)	--
27 Gy	1004/6303 (15·9%)	1·55 (1·32–1·83)	<0·0001
26 Gy	774/6327 (12·2%)	1·12 (0·94–1·34)	0·20
Breast distortion†	--	--	--
40 Gy	232/5724 (4·0%)	1 (ref)	--
27 Gy	363/5953 (6·1%)	1·51 (1·15–1·97)	0·0028
26 Gy	299/5945 (5·0%)	1·20 (0·91–1·60)	0·19
Breast shrinkage†	--	--	--
40 Gy	330/5728 (5·8%)	1 (ref)	--
27 Gy	503/5944 (8·5%)	1·50 (1·20–1·88)	0·0004
26 Gy	369/5943 (6·2%)	1·05 (0·82–1·33)	0·71
Breast induration (tumour bed)†	--	--	--
40 Gy	185/5713 (3·2%)	1 (ref)	--
27 Gy	304/5948 (5·1%)	1·56 (1·19–2·05)	0·0013
26 Gy	236/5937 (4·0%)	1·19 (0·90–1·59)	0·23
Breast induration (outside tumour bed)†	--	--	--
40 Gy	45/5712 (0·8%)	1 (ref)	--
27 Gy	137/5943 (2·3%)	2·79 (1·74–4·50)	<0·0001
26 Gy	97/5930 (1·6%)	1·90 (1·15–3·14)	0·013
Telangiectasia	--	--	--
26 Gy	155/6318 (2·4%)	1·47 (1·03–2·09)	0·032
Breast or chest wall discomfort	--	--	--
40 Gy	234/6086 (3·8%)	1 (ref)	--
27 Gy	269/6285 (4·3%)	1·10 (0·86–1·40)	0·44
26 Gy	250/6309 (4·0%)	0·98 (0·76–1·26)	0·86

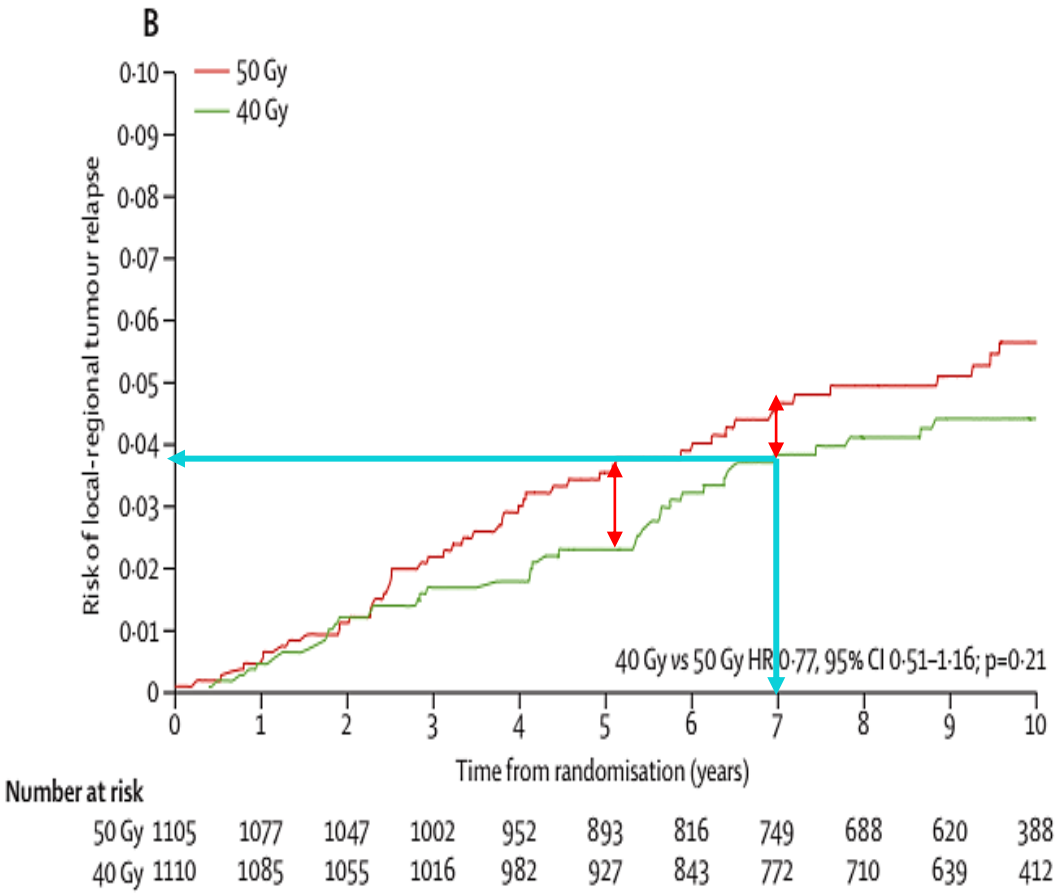
Interpretation **26 Gy in five fractions over 1 week is non-inferior to the standard of 40 Gy in 15 fractions** over 3 weeks for local tumour control, and is as safe in terms of normal tissue effects up to 5 years for patients prescribed adjuvant local radiotherapy after primary surgery for early-stage breast cancer.

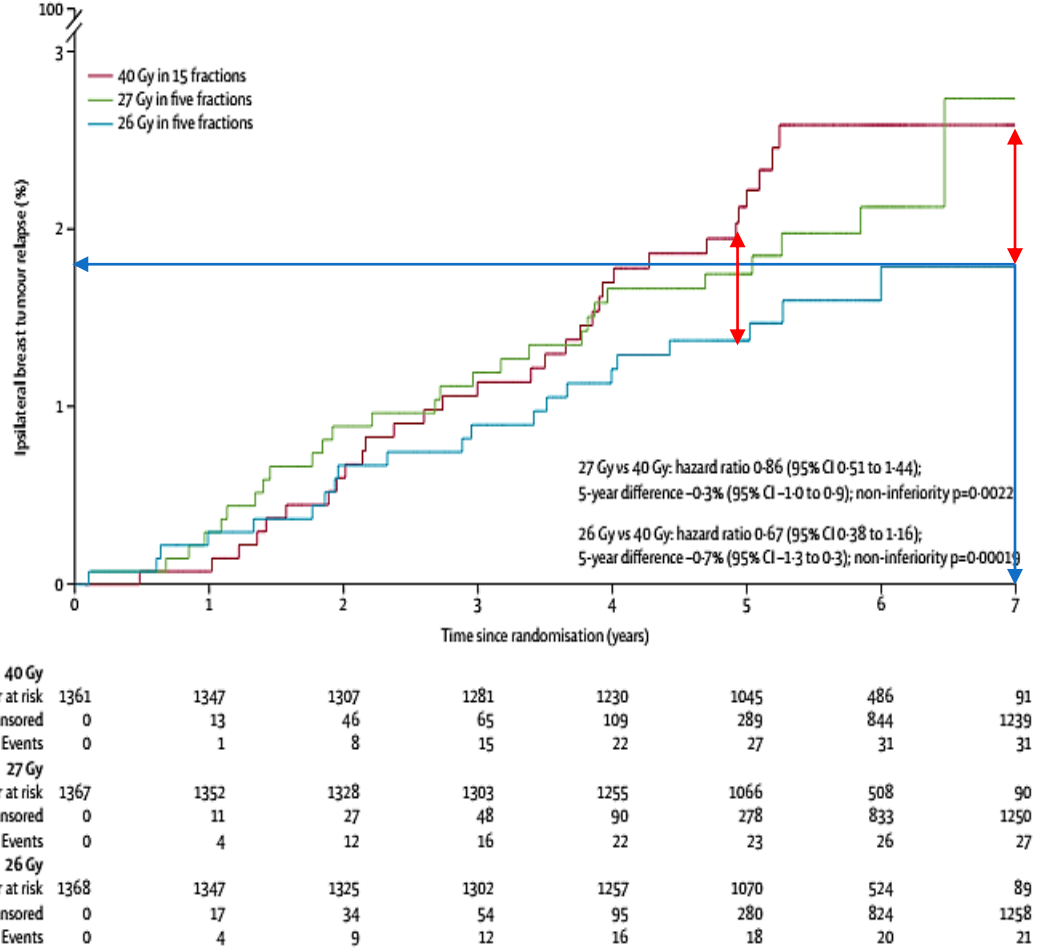
Comparison of START-B with FAST-Forward

Haviland et. al 2013 Lancet Oncol

Brunt et. al. Lancet Oncol 2020

Lower Event rates & Continued separation





Late Toxicity & Hypofractionation

- Cardiac toxicity is dose dependent
- Assuming an α/β as low as 1.5
- The regimen is itself safer

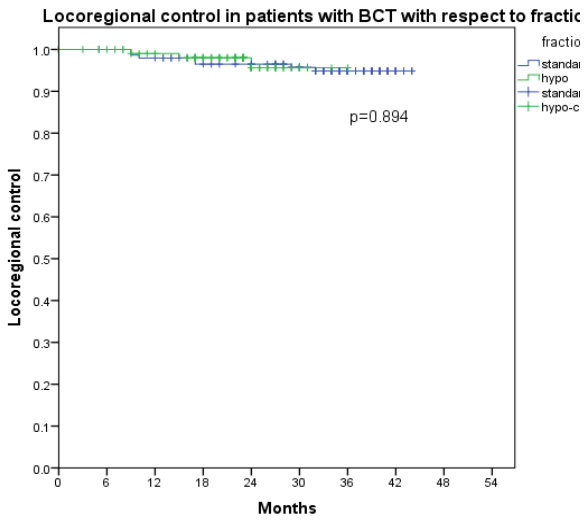
α/β	EQD2		
	50Gy/25fr	40Gy/15fr	26Gy/5fr
3	50	45.5	42.64
2	50	46.7	46.8
1.5	50	48	49.7

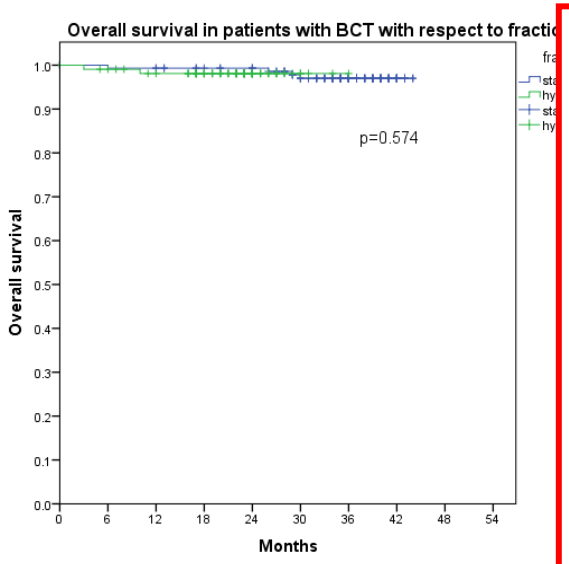
- Cardiac safety→ Treatment planning & adopting DIBH/ Prone breast RT
- Long term data from UK-START → no excess mortality
- Breast Shrinkage START-B: 10 yrs 31.2% Vs 26.2%
- Long-term results will mostly be similar to 5 year results but in the absence of retrospective evidence → Not standard

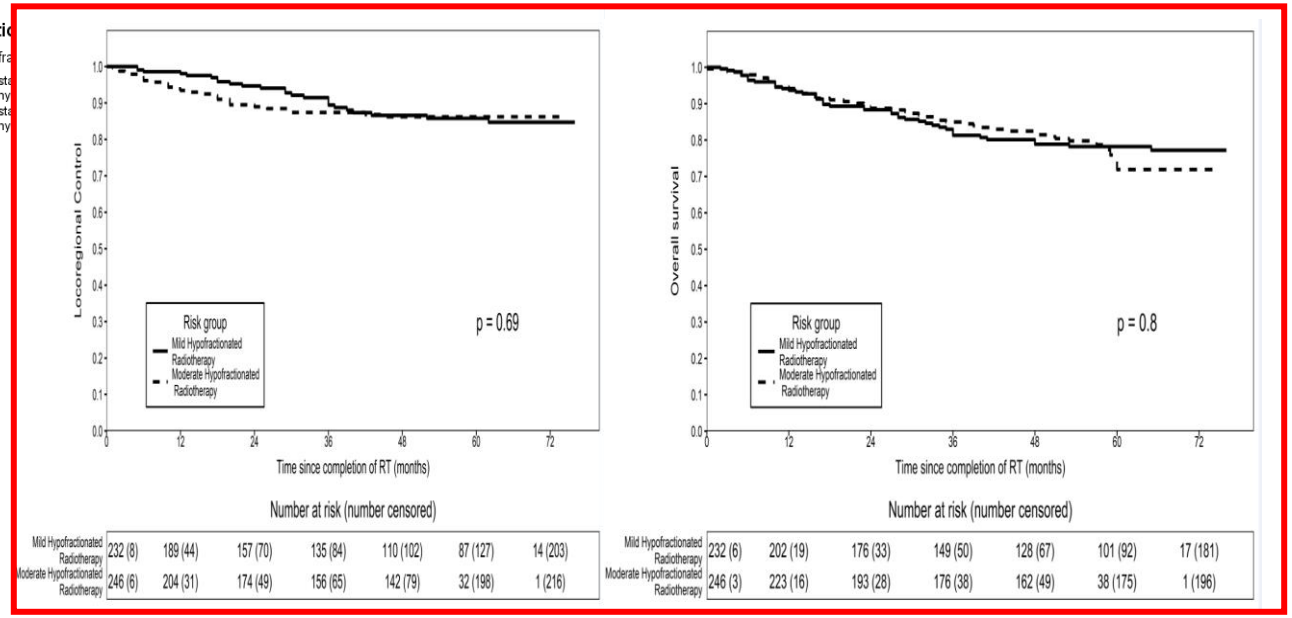
	START B (n=1110)	FAST (n=613)	FAST-Forward (n=2735)	TMH (n=1721)
Median Age (yrs)	61	62	61	50
T1	709 (63.8%)	496 (80.9%)	1859 (67.9%)	279 (16.2%)
T2	>2cm:288 (25.9%)	117 (19%)	813 (29.7%)	1013 (58.8%)
T3	NK	0	55 (2%)	429 (24.9%)
Gr-I/ II	843 (75.9%)	542 (88.4%)	1968 (71.9%)	283 (16.4%)
Gr-III	267 (24%)	69 (11.2%)	767 (28%)	1438 (83.5%)
HR+/Her2-ve	976* (87.9%)	613 (100%)	2227 (81.4%)	782 (45.5%)
HR+/-/Her2+ve	~5-7%	0	196 (7%)	281 (16.3%)
TNBC	~7% (No HT)	0	224 (8.2%)	301 (17.5%)
BCS *	1018 (91.7%)	613 (100%)	2637 (96.4%)	927 (53.8%)
MRM	92 (8.2%)	0	209 (7.6%)	794 (46.1%)
pN0	804 (72.4%)	613 (100%)	2234 (81.6%)	866 (50.3%)
pN+	266 (24%)	0	499 (18.2%)	855 (49.6%)
Boost	446 (43.8%)	0	669 (24.4%)	883 (95%)
No Boost	565 (55.5%)	613 (100%)	2058 (75.2%)	44 (5%)
NACT	0 (491 adj 44.2%)	0	99(3.6%)adj 694: 25.3%	763 (44.4%)
No NACT	1110 (100%)	613 (100%)	2634 (96.3%)	958 (55.6%)

Hypofractionation: TMH Experience

- Adopted as a policy since 2014 for all patients receiving RT to breast/ chestwall +/- SCF
- Unpublished data Courtesy Dr. Ashwini Budrukkar & Dr. Niranjan Dash
- Conventional Vs Hypofractionated RT → no significant differences in LFS, LRFS and OS
  Fewer Hospitalizations from RT induced Gr-III toxicity increased throughput/ quality Rx



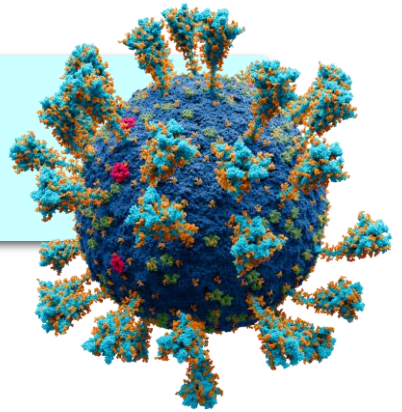




3 year LFS for BCT (n=268) 97 & 97.6%; OS: 97 & 98.1%

5 year LFS for MRM (n=478) 85.8 & 86.2%; OS: 78.2 & 71.9%

Pandemic Blues: Opportunity in adversity



50Gy/25fr/5wks

28.5Gy/5fr/ 4wk (once weekly)

40Gy/15fr/3wk (daily)

26Gy/5fr/ 1wk (daily)

UK FAST RCT
10-yr Toxicity & LRC same

UK START-B RCT LRC Same;
40GY/15fr Less Acute / Late Toxicity

UK FAST Forward RCT
5-yr LRC & Tox same

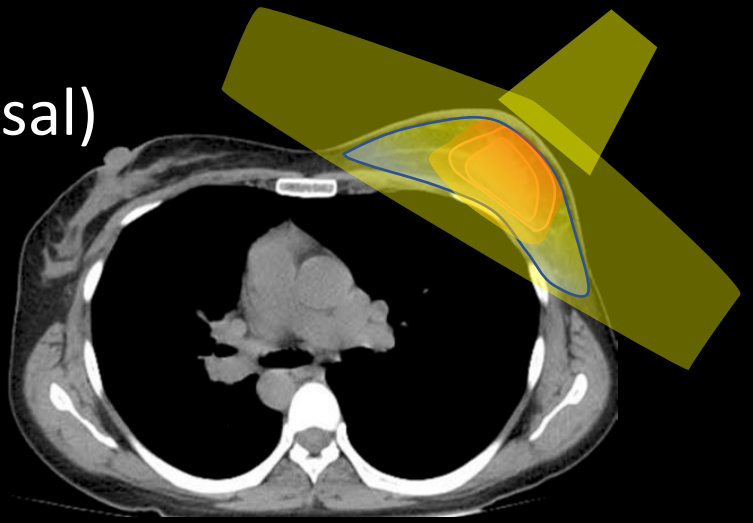
33Gy/5fr Tumour Bed ***48Gy/15fr tumour bed*** ***32Gy/5fr tumour bed***

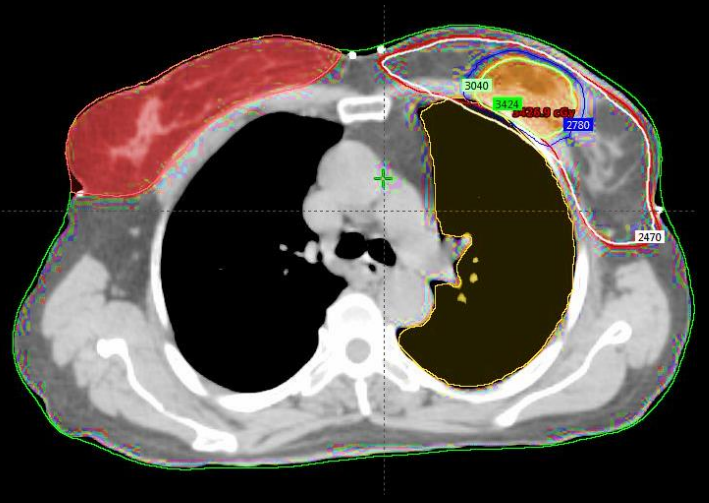
Radio-biologically equivalent SIB dose used in TMH for cases requiring boost

R Sarin, TMC

TMH Experience

- >1100 women (median age 49yrs; ~40% postmenopausal)
  - ER/PR +ve/ Her2 -ve ~50%
  - Triple +ve ~15%
  - Her2 enriched ~10%
  - TNBC ~20%
- ~50% recd NACT; 68% recd Adj CT; >95% recd CT
- Nearly all Her2 +ve patients recd. at least conc Trastuzumab
- ~50% MRM; Oncoplasty in 8% cases,
- 70% FF/ 30% F
- RNI → ~75%; TBB among pts with BCS: ~85%
- 60-70% → with Fif-IMRT, DIBH <5%, Inv IMRT ~25%
- TBB → SIB ; PMRT → Bolus all fr, no scar boost





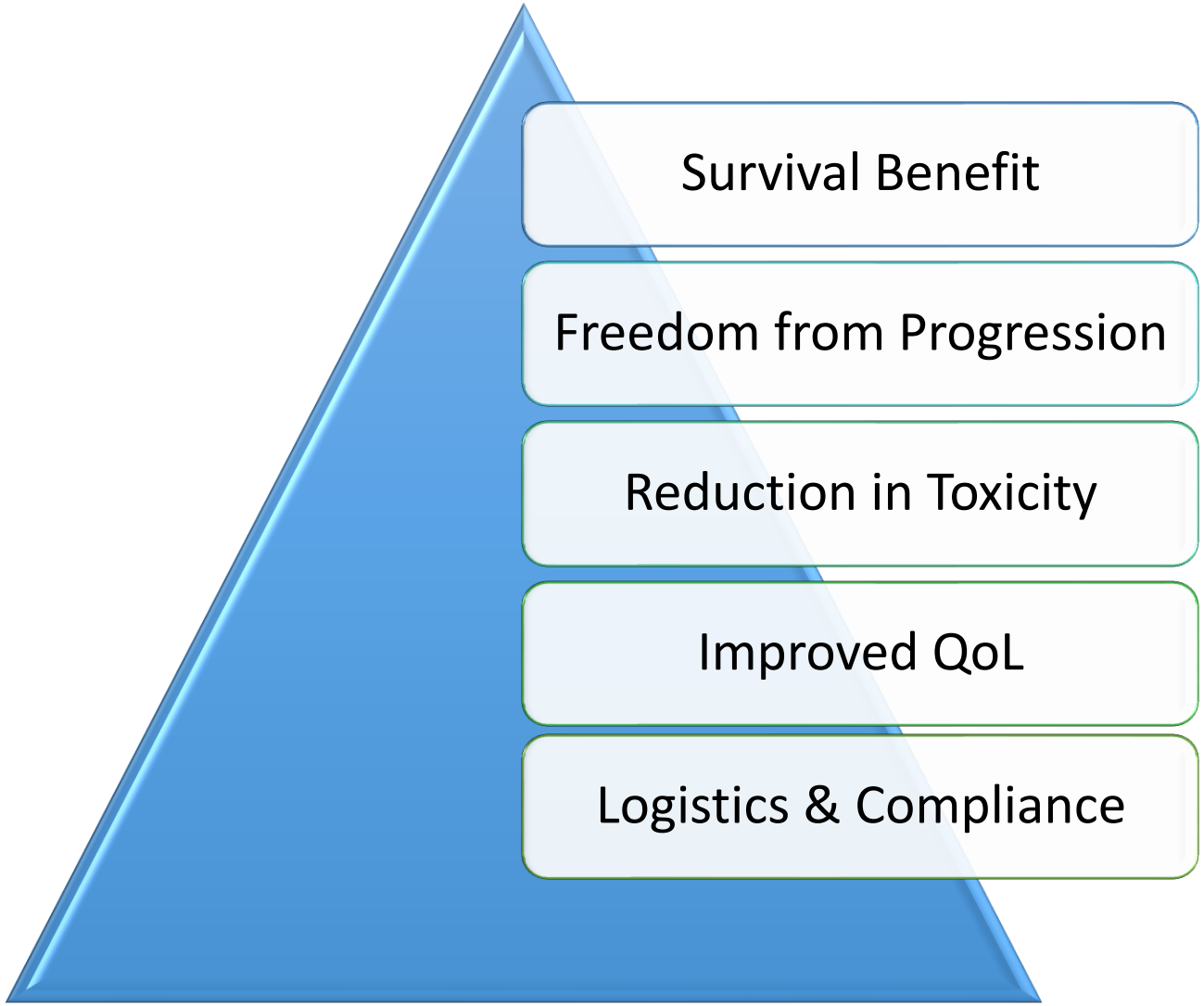
Unpublished work from the TMC Mumbai Unconventional Fractionation Registry

Acute Toxicity

- Skin
  - Gr 0 15%
  - Gr 1 80%
  - Gr 2 4%
  - Gr 3 0.1%
- Odynophagia
  - Gr 0 60%
  - Gr 1 33%
  - Gr 2 5%
  - Gr 3 0.1%
- No Brachial Plexopathy
- No excess acute toxicity
- Toxicity for FF peaks by 2nd -3rd week

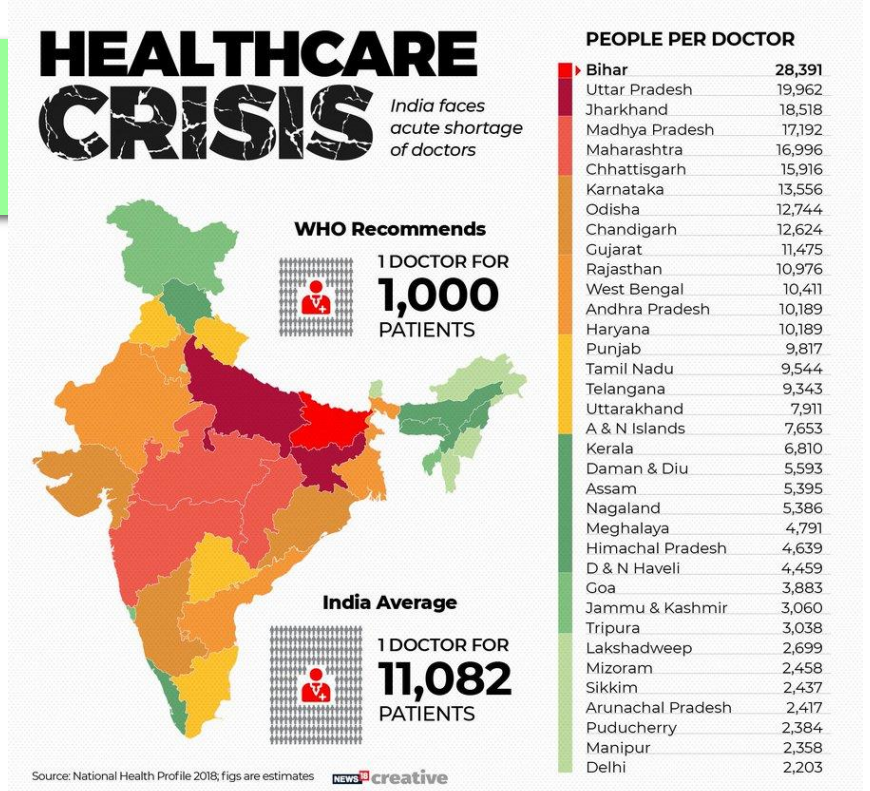
Unpublished work from the TMC Mumbai Unconventional Fractionation Registry

Pyramid of Priority



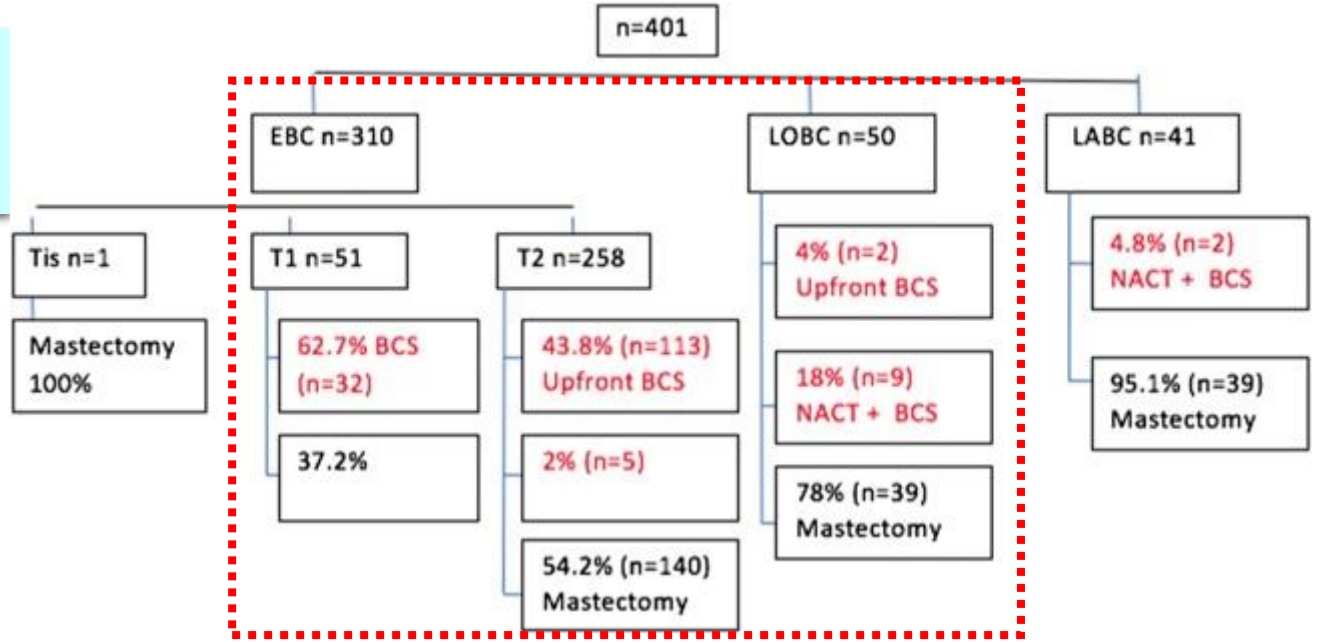
Challenges in LMICs (India)

- Large population and country with Cultural/ Regional Diversity
- Heterogenous practices across oncologists (Medical/ Surgical& Radiation)
- Poor access to specialized healthcare and oncological training (Medical/ Paramedical)
- Poor penetration of breast conservation → Lack of RT services/ Additional expenses/ Lack of awareness
- Healthcare→ Low priority reflected in budget allocation→ Essentially Self paid
- Govt aided centres → Lack of state-of-the-art facilities



Breast Conservation Gap

- Eligible patients
- Refuse conservation
  - Non-availability if RT centre
  - Avoid RT
  - RT Unaffordable
  - Fear of recurrence



Hassan Ali et al. 2019 IJC

Region	Population of each region (%)	Area of each region (%)	Number of machines available in each region (%)							
			Simulator	CT-Sim	Telecobalt	Linacs	RAL Brachy	Tomo	Cyber Knife	Gamma Knife
Central	8.10	13.6	1 (2.5)	2 (4)	15 (8.3)	12 (3.3)	13 (5.2)	0 (0)	0 (0)	0 (0)
East	22.33	12.8	4 (10)	1 (2)	20 (11.1)	22 (6)	16 (6.4)	1 (12.5)	0 (0)	0 (0)
North	24.82	20.5	15 (37.5)	13 (26)	42 (23.3)	85 (23.3)	65 (26)	1 (12.5)	3 (42.9)	5 (71.4)
North-East	3.57	7.8	1 (2.5)	3 (6)	10 (5.6)	6 (1.6)	6 (2.4)	0 (0)	0 (0)	0 (0)
South	21.09	19.4	12 (30)	18 (36)	50 (27.8)	150 (41.1)	88 (35.2)	3 (37.5)	4 (57.1)	1 (14.3)
West	20.09	26.0	7 (17.5)	13 (26)	43 (23.9)	90 (24.7)	62 (24.8)	3 (37.5)	0 (0)	1 (14.3)
Total	100	100	40 (100)	50 (100)	180 (100)	365 (100)	250 (100)	8 (100)	7 (100)	7 (100)

States included in each region: Central: Chhattisgarh, Madhya Pradesh, East: Bihar, Jharkhand, Orissa, West Bengal, North: Chandigarh, Delhi, Haryana, Himachal Pradesh, Jammu and Kashmir, Punjab, Uttar Pradesh, Uttarakhand, North-East: Arunachal Pradesh, Assam, Manipur, Meghalaya, Mizoram, Nagaland, Tripura, South: Andhra Pradesh, Karnataka, Kerala, Puduchery, Tamilnadu, Telengana, West: Goa, Gujarat, Maharashtra, Rajasthan, States not included: Andaman & Nicobar Islands, Sikkim, D & N Haveli, Daman & Diu, Lakshadweep; CT: Computed tomography, RAL: Remote after-loading

Munshi et al. 2019 IJC

Mitigation Strategies

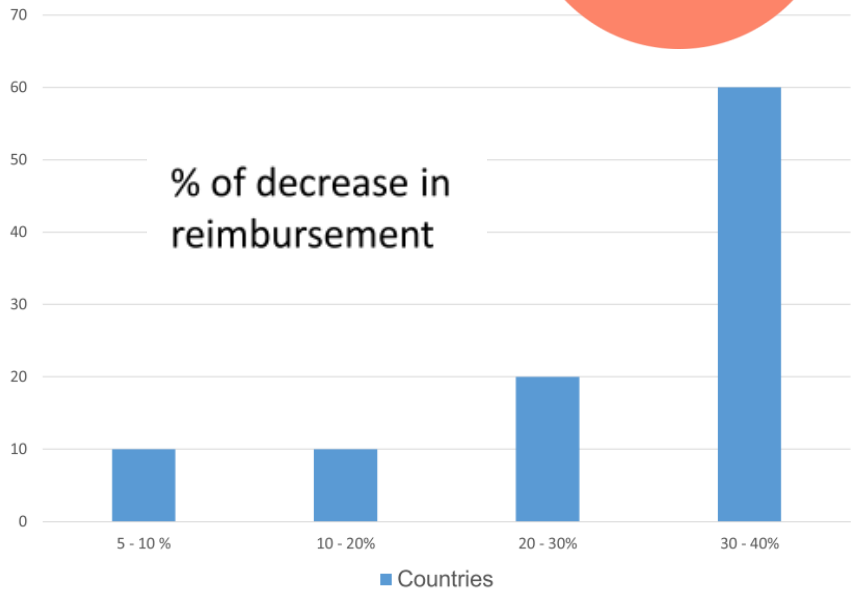
- Increase the RO to Patient Ratio
- Improve the patient to machine ratio
- Reduce the direct + indirect cost of RT
- Improve Awareness of breast conservation safety

Cost of RT

- Cost of healthcare→ rising due to rapid technological advancement
- Misconception → Costs of RT driven by cost of equipment
- Labour-intensive planning & delivery → **Wages drive costs**
- Misconception for complex plans → **RT planning** will become more significant **driver of cost than delivery**
- Planning 1 time process << Time for delivery remains high and adds cost of QA
- Cost of RT essentially driven by total treatment time
- 25% case load breast ca → Major impact

Impact of Hypofractionation on Cost

- Physician
  - US/Europe Remuneration structure→ Fixed fee / Fee-for-service
  - ROs in 77% countries → 10 to ~40% reduction in revenue due to adoption of hypofractionation
- Loss of revenue from Medicare reimbursement
  - OZ→ ~$2000/ pt , USA→ $4300
- Indirect cost:
  - Transportation (average number of miles/ day, the average reimbursement rate per mile)
  - Parking costs,
  - Loss of hourly wages by hours spent during treatment & displacement



Marta et al. Clinical Oncology 2020

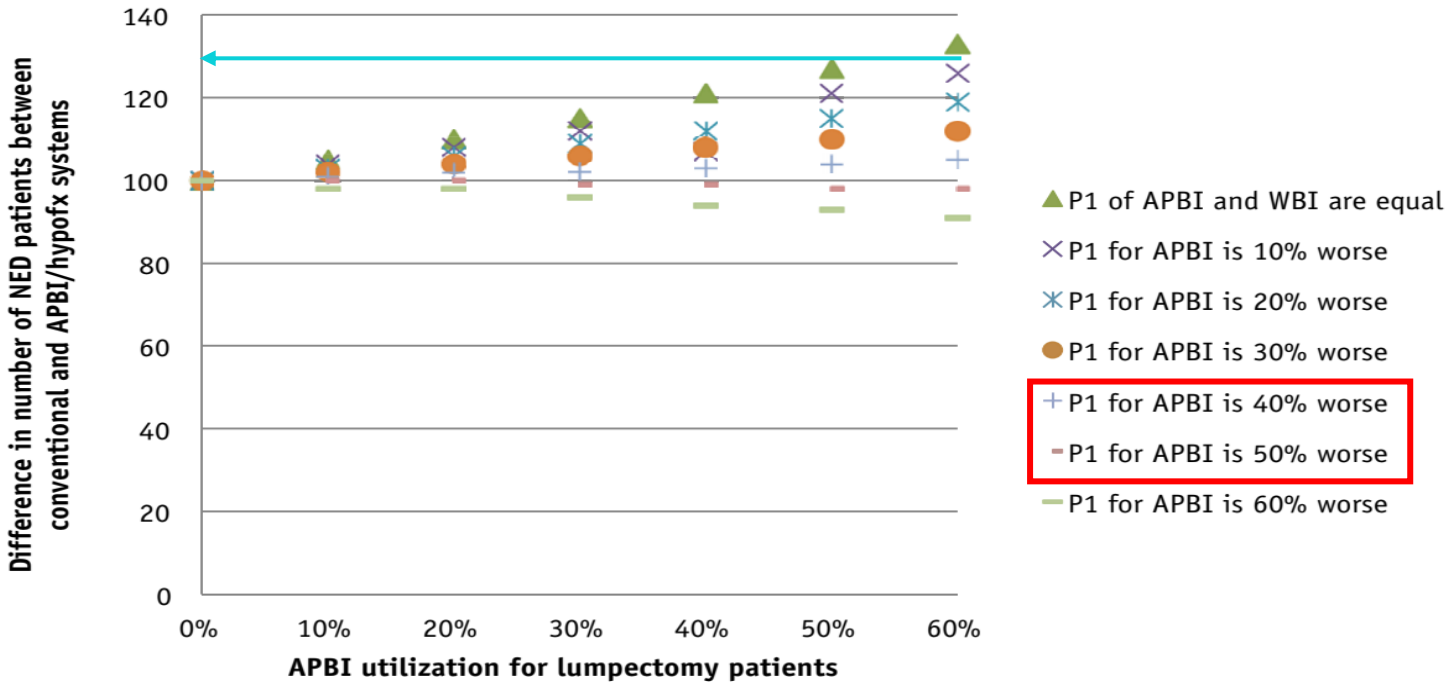
Cost Effectiveness of 5 fr for LMIC?

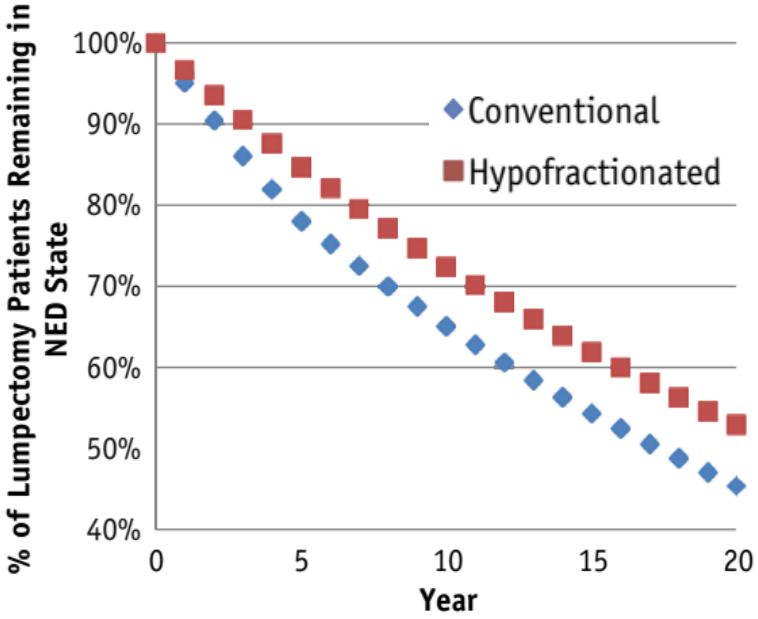
- Boscoe et al. → >75 km for treatment are ~ 1.4 times more likely to choose mastectomy
- Geographic & logistic barriers → precluded from BCS
- Markov Chain modelling using data from SKMCH Pakistan (APBI eligible)
- Simulate the real-life implications of a major change in treatment strategy

- External validity of the model → 15-yr OS results from EBCTCG/Oxford meta-analyses

Khan et al. IJROBP 2017

Impact on OS (Society)





- Absolute gain in OS ~4% and DFS ~7% at 15 years
- OS after BCS improved from 54% to 62%
- Improvement in OS at population level → Limited access
- Future studies should evaluate this for common malignancies

Khan et al. IJROBP 2017

Benefits of Ultra-hypofractionated RT

Patient

- Reduced hospital visits → Reduce infection risk
- Reduced expenditure on stay and travel to the hospital
- Lower toxicity → Lower expenses
- Improved access to RT without compromising outcomes → Increased acceptance to BCS
- Reduced treatment interruptions
- Improved QOL → Priceless

Hospital

- Reduced hospital visits → Reduce infection risk & PPE use
- Improved access to care: number of patients that can be treated in limited hours & resources
- Reduced working hours of the machine & its running cost (Electricity/ Water/ HR)
- Improvement in quality of the treatment → lower rates of toxicities & higher patient satisfaction
- Early Breakeven

Summary

- Pre-requisite for Hypofractionated RT → Strict QA → Uniform treatment policies & standard planning & treatment techniques
- FAST- Forward RT arm 26Gy/5 fr → safe and effective as 40Gy/15 fr
- Planned with techniques routinely used in most centres (Fif-IMRT/ 3DCRT)
- Like START studies → Like FAST Forward studies
- TMC Mumbai experience of UHF-RT → Unique aspect SIB further reducing the TT
- Early results suggest : ISO-EFFECTIVE, ISO-TOXIC, & COST-EFFECTIVE
- Beyond pandemic currently: Highly select population
- FAST → Favorable patient population (Low risk)
- FAST FORWARD → EBC, Node negative, No NACT, Favorable biology
- In future → 5 or fewer fractions may be the way forward!

Acknowledgements

- Dr. JP Agarwal
- Dr. Rajiv Sarin, Dr. Tabassum Wadasadawala & Dr. Revathy Krishnamurthy
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- Ms. Ashwini Khandavalli (Research Associate)
- Patients