Improving Access to Radiotherapy Services in Breast Cancer: How Far Have We Come?

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The Road to Breast Health Equity
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MD Anderson Cancer Center Cooper
Making Cancer History®

Learning Objectives

1. Overview of access-to-care issues that require novel fractionation solutions
2. Focus on Whole-Breast Radiation ("apples-to-apples")
3. Review background, rationale and outcomes for experience with "extreme" hypofractionation (>5Gy/Fx)

Disclosures

- None

Premises to ponder

Why are we here?

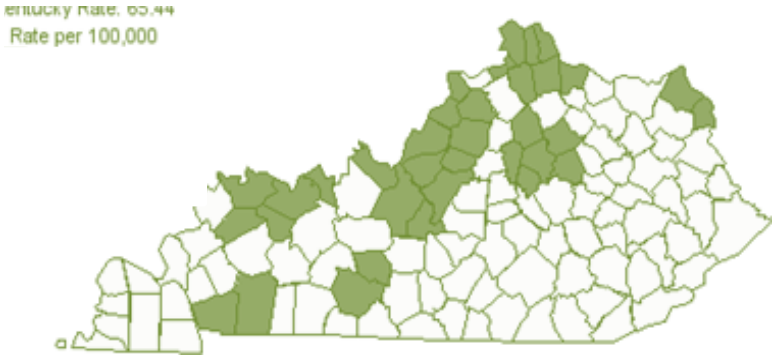
- NSABP B-06 Launched in ***August 1976***
  - 50Gy/25fx +/- boost = **<u>2Gy/day</u>**
  - "Conventional Fractionation"
  - Established "5-7 weeks of daily radiation"

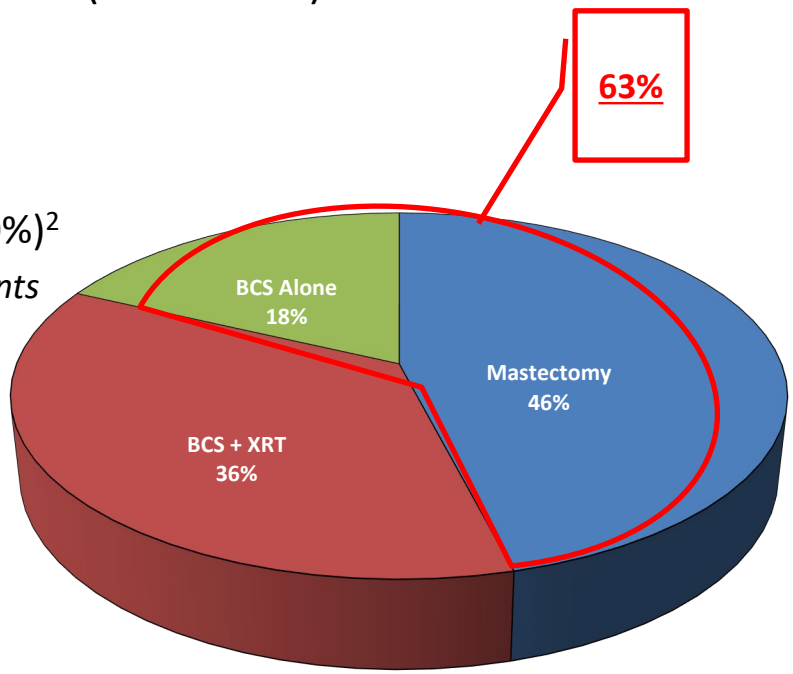
Background/Interest

- History/Interest in breast brachytherapy & Partial-breast Irradiation (PBI) as an emerging science since 2002.
  - Observed how PBI improved access to breast conservation therapy (BCT) in S. Carolina, Georgia
- Recruited to Univ. of Louisville (KY).
  - Surgical oncologists “not keen” on PBI
  - Most underserved population/worst outcomes

Observations/Groundwork

- KY is an underserved state with poor access and cancer outcomes
  - Management of Stage 0, I & II Breast Cancer (1997-2008)
  - KY SEER Data for insured patients
    - BCS Rate = 54% (range: 47-61%)[1]
      - *Lower for **rural** and **elderly** patients*
    - XRT Rate (after BCS) = 66% (range: 61-70%)[2]
      - *Lower for **rural , elderly** and **black** patients*





[1]Dragun AE, et al. Breast J. 2012 Jul-Aug;18(4):318-25
[2]Dragun AE, et al. Cancer. 2011 Jun 15;117(12):2590-8.

Survival for BCT +/- RT

Registry Type	# Patients (BCS)	Year Range	Hazard Ratio for Death (95% Confidence Interval)	RT Disparity	Reference
SEER-Medicare	49,166	1988-1999	2.02 (1.88-2.16)	SSDI-qualified patients	*McCarthy et al. 2006*[1]
NCI-CRN Audit	221	1990-1994	2.19 (1.51-3.18)	NS	*Yood et al. 2008*[2]
SEER-Medicare	7,791	1991-1999	1.32 (1.06-1.63)	AA, rural, low SES	*Gold et al. 2008*[3]
NCCR-Medicaid	230	1998-1999	1.58 (1.15-1.79)	age, comorbidity	*Foley et al. 2006*[4]
Western Australian Registry	899	1999	1.62 (1.10-2.38)	rural	*Mitchell et al. 2006*[5]
Prospective Australian Audit	1,022	1997-2006	1.84 (1.41-2.30)*	rural	*Craft et al. 2010*[6]
KCR	***11,914***	***1997-2008***	***1.67 (1.51-1.85)***	***Age, rural/Appalachia, AA, uninsured***	***Dragun et al. 2011***[7]

1.McCarthy EP, Ngo LH, Roetzheim RG, et al. Disparities in breast cancer treatment and survival for women with disabilities. Ann Intern Med 2006;145:637-45. 2.Yood MU, Owusu C, Buist DS, et al. Mortality impact of less-than-standard therapy in older breast cancer patients. J Am Coll Surg 2008;206:66-75. 3.Gold HT, Do HT, Dick AW. Correlates and effect of suboptimal radiotherapy in women with ductal carcinoma in situ or early invasive breast cancer. Cancer 2008;113:3108-15. 4. Foley KL, Kimmick G, Camacho F, Levine EA, Balkrishnan R, Anderson R. Survival disadvantage among Medicaid-insured breast cancer patients treated with breast conserving surgery without radiation therapy. Breast Cancer Res Treat 2007;101:207-14. 5. Mitchell KJ, Fritschi L, Reid A, et al. Rural-urban differences in the presentation, management and survival of breast cancer in Western Australia. Breast 2006;15:769-76. 6. Craft PS, Buckingham JM, Dahlstrom JE, et al. Variation in the management of early breast cancer in rural and metropolitan centres: Implications for the organisation of rural cancer services. Breast 2010. 7. Dragun AE, Huang B, Tucker TC, Spanos WJ. Disparities in the application of adjuvant radiotherapy after breast-conserving surgery for early stage breast cancer: Impact on overall survival. Cancer 2011;117:2590-8.

Need novel, short-course whole-breast program…

- In 2008 Hypofractionated (**HF**, aka Short-course) radiotherapy still "fringy" (>2Gy, <3Gy/fraction)
  - Canadian data not published (3-weeks, daily)
  - Only 5y data for START trials (3 weeks, daily
  - RMH trial appeared promising (still 5 weeks, every-other-day)

TABLE 1: Outcomes for selected randomized clinical trials comparing CF-RT to HF-RT.

TRIAL	MEDIAN FOLLOW-UP (YEARS)	*N*	DOSE (Gy)	# FRAC	IBTR* (%)	LRR* (%)	DFS* (%)	OS* (%)	COSMESIS* (% GOOD or EXCELLENT)	ACUTE TOXICITY* (% ≥ GRADE 3)
Canada[35]	10	612	50	25	6.7	--	--	84	71.3	3.0
		622	42.5	16	6.2	--	--	85	69.8	3.0
Royal Marsden[33]	10	470	50	25	12	--	--	--	71	--
		466	42.9	13	9.6	--	--	--	74	--
		474	39	13	15	--	--	--	58†	--
START A[37]	5	749	50	25	3.2	3.6	86	89	--	0.3
		750	41.6	13	3.2	3.5	88	89	--	0.0
		737	39	13	4.6	5.2	85	89	--	0.0
START B[27]	6	1105	50	25	3.3	3.3	86	89	--	1.2
		1110	40	15	2.0	2.2	89	92	--	0.3

Abbreviations: *N* = number of patients; FRAC = fractions; IBTR = in-breast tumor recurrence; LRR = locoregional recurrence; DFS = disease free survival; OS = overall survival.

*All statistical p-values are non-significant in the comparison of CF-RT to HF-RT, unless otherwise specified.

†Measure found to be statistically inferior to CF-RT ($p < 0.05$).

This was good but…

- No ability to “house” patients
  - Daily, slightly-shorter course not likely enough to impact trends
- Daily HFRT not really novel, somewhat pointless for a “trial”
- Institutional support for something more “dramatic”…

HF: Pushing the Limits…

- UK Pilot Study
  - Martin et al. (2008, Clin Onc.)
    - N=30; > 50y; pT1-2, N0, No Chemo
    - 30Gy/5fx, 15 days
    - Acute Tox: 13% moist desquamation
    - 2y cosmesis: 77%=no change from baseline (photo)
    - 3y PFS: 100%
- UK FAST Trial (2011, RO)
  - N=915; 2004-2007; >50y, pT1-2, N0

UK FAST Trial

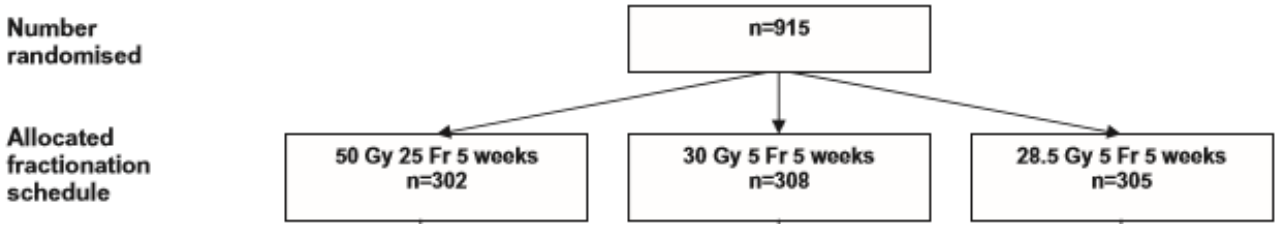


Table 2
Acute skin reactions during treatment by fractionation schedule.

RTOG grade	Fractionation schedule			Total (%)
	50 Gy (%)	30 Gy (%)	28.5 Gy (%)	
0 = No visible change	8 (7.3)	28 (25.2)	42 (39.6)	78 (23.9)
1 = Faint/dull erythema	51 (46.4)	67 (60.4)	53 (50.0)	171 (52.3)
2 = Tender/bright erythema ± dry desquamation	39 (35.5)	13 (11.7)	9 (8.5)	61 (18.7)
3 = Patchy moist desquamation, moderate oedema	12 (10.9)	3 (2.7)	2 (1.9)	17 (5.2)
4 = Confluent moist desquamation, pitting oedema	0	0	0	0
Total with known RTOG grade for acute skin reaction	110 (100)	111 (100)	106 (100)	327 (100)
Not recorded[a]	187	192	196	575
Not known	5	5	3	13
Total randomised	302	308	305	915

[a] Acute toxicity data was not collected from the beginning of the trial.

Table 3
Change in photographic breast appearance at 2 years by fractionation schedule.

	Fractionation schedule			Total, $N = 729$ (%)	Risk ratio for 30 Gy vs 50 Gy (95% CI), p-value for trend	Risk ratio for 28.5 Gy vs 50 Gy (95% CI), p-value for trend	Risk ratio for 30 Gy vs 28.5 Gy (95% CI), p-value for trend
	50 Gy, $N = 239$ (%)	30 Gy, $N = 248$ (%)	28.5 Gy, $N = 242$ (%)				
No change	189 (79.1)	160 (64.5)	184 (76.0)	533 (73.1)	1, $p < 0.001$	1, $p = 0.26$	1, $p = 0.002$
Mild change	46 (19.2)	65 (26.2)	49 (20.2)	160 (22.0)	1.48 (1.06–2.05)	1.07 (0.75–1.54)	1.37 (1.00–1.90)
Marked change	4 (1.7)	23 (9.3)	9 (3.7)	36 (4.9)	6.06 (2.14–17.20)	2.25 (0.70–7.18)	2.70 (1.28–5.67)

UK FAST Trial

Table 5
Relapses, second primary cancers and deaths by fractionation schedule.

	Fractionation schedule			Total
	50 Gy	30 Gy	28.5 Gy	
Relapses				
Local (breast skin or parenchyma)	2	0	0	2
Regional (axilla or supraclavicular fossa)	1	0	2	3
Distant	5	2	10	17
Second primary cancer	3	3	2	8
Deaths	6	5	12	23
Breast cancer	2	2	6	10
Other cause[a]	4	3	6	13

[a] Deaths from other causes included 4 cardiac-related events, 2 of which were in patients who received left-sided radiotherapy.

USA: Under-enrollment of URM

- NSABP Trials: Historically 2-3% AA Women

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Black Patients Often Never Given a Chance to Join Breast Cancer Trials

— But survey finds several actionable findings that could boost enrollment

by Ian Ingram, Managing Editor, MedPage Today May 26, 2022

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Nearly half of Black patients with metastatic breast cancer are never informed about clinical trial participation, despite the fact that most are open to the idea, according to a new survey.

Among more than 400 respondents surveyed, 40% of Black patients said they were not told about the possibility of enrolling in a clinical trial versus 33% of patients who identified as being of another race or ethnicity, reported Stephanie Walker, RN, of the Metastatic Breast Cancer Alliance in New York City.

U of L Trial: Purpose

- Pragmatic once-weekly whole-breast regimen (post BCS)
  - Improve access while avoiding controversies of APBI
  - Expand on prior experience from UK and Europe
    - 30-35Gy in 5Fx 1-2X/Wk
      - Mainly in elderly, node (-), small-breasted, biologically-favorable patients
    - UK FAST TRIAL (2004-2007)
      - N ≈ 1000; Post-menopausal, Stage I patients
        - » *Dose-reduced based on radiobiologic estimations from RMH/START Trials of HFRT*

Methods

- Phase II Trial Design (Opened 12/2010)
  - Age >21y with 0, I or II breast cancer up to 3 + LN
    - Partial mastectomy with – margins; ± SLNB
  - Dosimetry/Target definitions: standard arm of NSABP B39
  - Two regimens of 5 fx once-weekly HFRT ± boost
    - 30Gy/5fx (Dates: 12/2010-3/2013)
    - 28.5/5fx (Dates: 3/2013-1/2016)
  - Accrual: 171 (N=158 patients with ≥6mo follow-up)
  - **No restrictions on breast size or use of cytotoxic chemo.**
  - Prior publication of acute toxicity[3]
  - Endpoints: IBTR, Cosmetic outcome, Survival

[3]Dragun AE, et al. Int J Radiat Oncol Biol Phys. 2013 Mar 1;85(3):e123-8

Patient/Disease Characteristics

Table 1: Patient characteristics

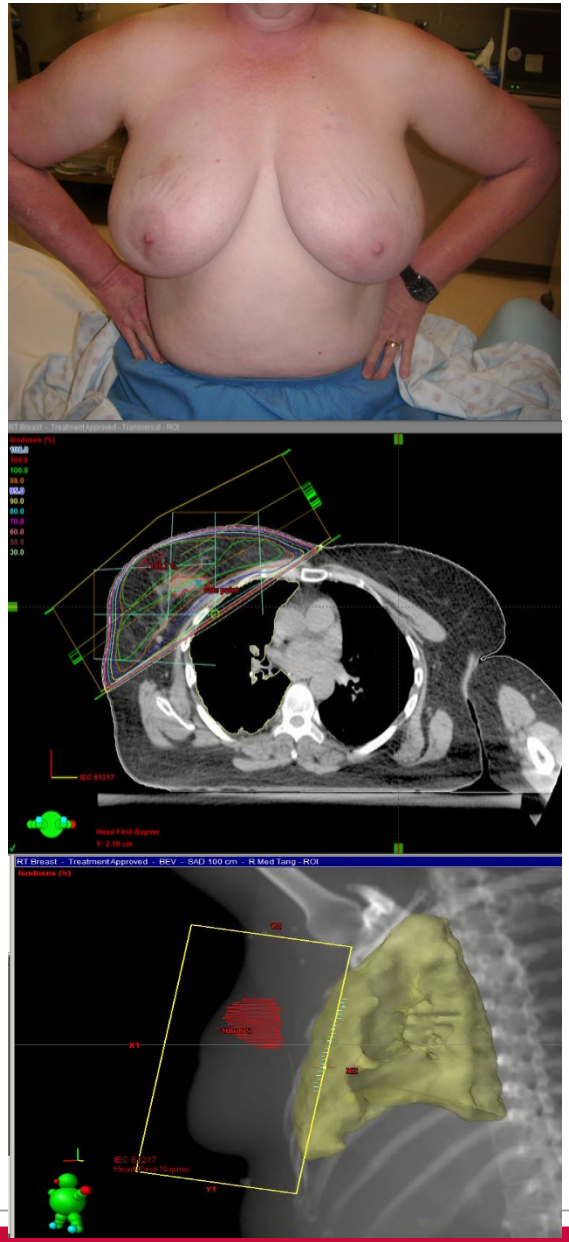
Variable	Total (N=158) N (%)	30Gy (N=80) N (%)	28.5Gy (N=78) N (%)	*p-value*
Age at Diagnosis (y)				*0.85*
Median (range)	59 (30 - 84)	59 (30 - 80)	59 (42 - 84)	
Race				*0.09*
White	125 (79.1)	59 (73.8)	66 (84.6)	
Black	33 (20.9)	21 (26.3)	12 (15.4)	
Smoking				*0.43*
No	72 (45.6)	34 (42.5)	38 (48.7)	
Yes	86 (54.4)	46 (57.5)	40 (51.3)	
Diabetes				*0.77*
No	122 (77.2)	61 (76.3)	61 (78.2)	
Yes	36 (22.8)	19 (23.8)	17 (21.8)	
Breast Size (cc)				*0.09*
Median (range)	1017 (107.6 - 2992)	1058 (107.6 - 2992)	1016 (178.2 - 2365)	
Non-large (≤ 1350)	112 (70.9)	52 (65.0)	60 (76.9)	*0.10*
Large (>1350)	46 (29.1)	28 (35.0)	18 (23.1)	

Table 2: Disease variables

Variable	Total (N=158) N (%)	30Gy (N=80) N (%)	28.5Gy (N=78) N (%)	*p-value*
AJCC Stage				*0.34*
0	33 (20.9)	13 (16.3)	20 (25.6)	
I	96 (60.8)	52 (65.0)	44 (56.4)	
II	29 (18.4)	15 (18.8)	14 (17.9)	
Node +				*0.96*
No	142 (89.9)	72 (90.0)	70 (89.7)	
Yes	16 (10.1)	8 (10.0)	8 (10.3)	
Pathology				*0.17*
DCIS	33 (20.9)	13 (16.3)	20 (25.6)	
IDC	112 (70.9)	58 (72.5)	54 (69.2)	
OTHER	13 (8.2)	9 (11.3)	4 (5.1)	
Grade				***0.05***
Low	40 (25.3)	26 (32.5)	14 (17.9)	
Intermediate	60 (38.0)	24 (30.0)	36 (46.2)	
High	58 (36.7)	30 (37.5)	28 (35.9)	
Tumor Biology				*0.50*
ER/PR +	122 (77.2)	60 (75.0)	62 (79.5)	
ER/PR -	36 (22.8)	20 (25.0)	16 (20.5)	
Side				*0.06*
Right	77 (48.7)	45 (56.3)	32 (41.0)	
Left	81 (51.3)	35 (43.8)	46 (59.0)	
Quadrant				*0.71*
Outer	106 (67.1)	53 (66.3)	53 (67.9)	
Inner	40 (25.3)	22 (27.5)	18 (23.1)	
Central	12 (7.6)	5 (6.3)	7 (9.0)	

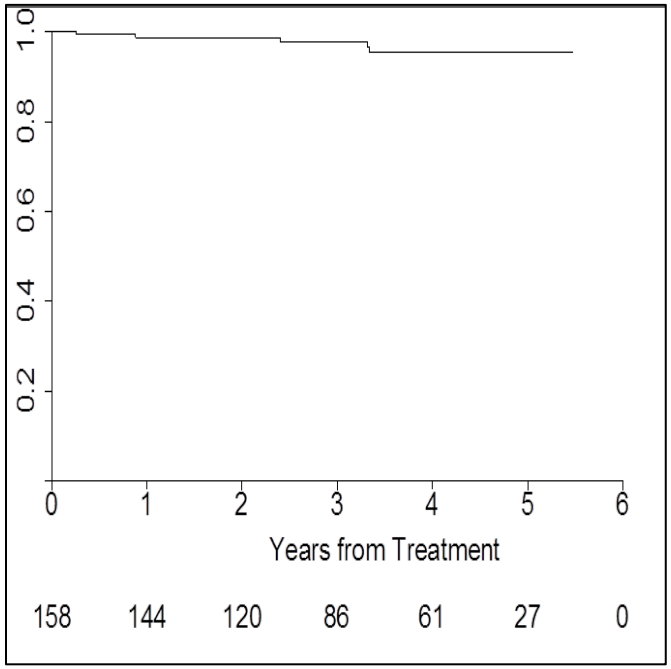
Details of Therapy

Table 3: Treatment-related variables				
Variable	**Total (N=158)** N (%)	**30Gy (N=80)** N (%)	**28.5Gy (N=78)** N (%)	***p*-value**
Seroma Volume (surgical deficit in cc)				***0.02***
Median (min - max)	11.8 (0.5 - 182.8)	15.1 (1.2 - 163.1)	7.9 (0.5 - 182.8)	
≤ 25cc	121 (76.6)	56 (70.0)	65 (83.3)	***0.05***
> 25cc	37 (23.4)	24 (30.0)	13 (16.7)	
Chemotherapy				*0.78*
No	113 (71.5)	58 (72.5)	55 (70.5)	
Yes	45 (28.5)	22 (27.5)	23 (29.5)	
Boost				*0.73*
No	130 (82.3)	65 (81.3)	65 (83.3)	
Yes	28 (17.7)	15 (18.8)	13 (16.7)	
DMAX				*0.09*
Median (min - max)	106.9 (104.7 - 110.4)	106.7 (104.7 - 110.0)	106.9 (105.0 - 110.4)	
V105				*0.49*
Median (range)	4.6% (0.0 - 28.3)	3.9% (0.0 - 28.3)	5.4% (0.0 - 24.2)	
≤ 10%	116 (75.9)	60 (80.0)	56 (71.8)	*0.08*
> 10%	38 (24.1)	16 (20.0)	22 (28.2)	



Results: IBTR

- Median follow-up: 40.1 m.
- IBTR: N=2/158 **(1.2%)**
  - Univariate analysis:
    - ***trend*** toward **ER/PR-** (*p = 0.058*)

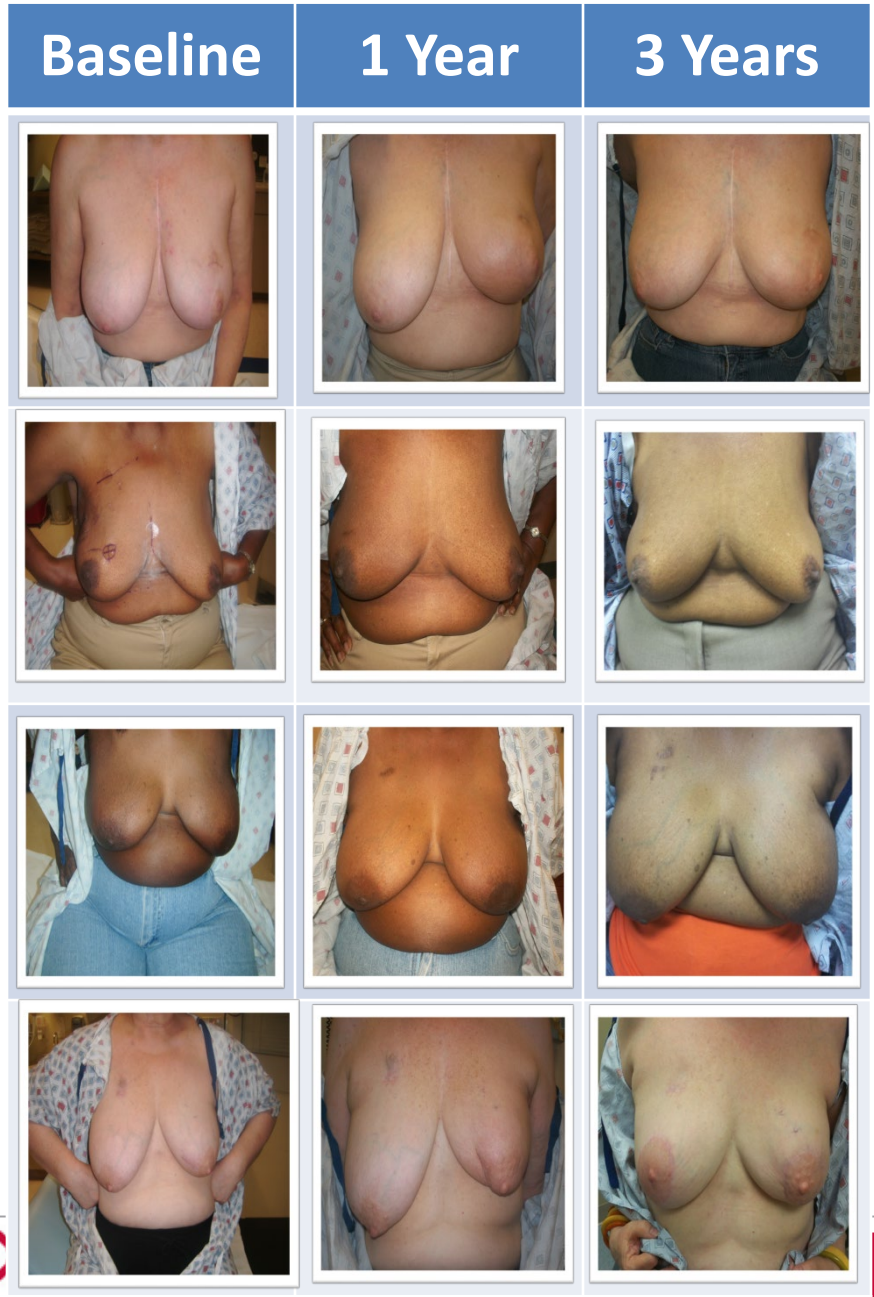


Details of Two Patients with IBTR

Age	Stage	Biology	Chemo	Cohort	Boost	First Site of Failure	Time to Failure	Disposition
61y	pT1cN0	ER/PR-, HER2-	Yes	30Gy	No	Breast, Ax LN, SCF LN	11mo	Died, Lung, Liver mets @ 23mo
84y	pT1cN1	ER/PR-, HER2-	Yes	28.5Gy	No	Inflam. Breast, Lung, pleura	3mo	Died, Lung mets@5mo

Results: Cosmesis

- **Cosmetic Outcome**
- Harvard Scale
  - Good/Excellent: **82.3%**
  - Fair/Poor: 17.7%
- "Significant photographic cosmetic change"
  - (G/E→↠F/P): **11.6%**
    - Univariate analysis: ***trend*** toward smoking (*p = 0.053*)



Similar studies

TABLE 4 : Comparative outcomes with published clinical trials of WHBI following breast surgery.

TRIAL	DESIGN	POPULATION	MEDIAN FOLLOW-UP (YEARS)	*N*	DOSE (Gy)	# FRAC	IBTR* (%)	LRR* (%)	COSMESIS* (% GOOD or EXCELLENT)	SIGNIFICANT COSMETIC CHANGE
Ortholan et al. (France)	Prospective, Single Arm	Elderly, N0-1, No CTX, PMRT (28%), RNI (30%)	5	150	32.5	5	--	2.3†	--	--
Kirova, et al. (France)	Retrospective, Non-Randomized	Elderly, N0, No CTX, No Boost	7.8	317 50	50 32.5	25 5	-- --	5‡ 6‡	88 85	-- --
Rovea, et al. (Italy)	Retrospective, Non-Randomized	Elderly, N0-2, CTX (2%), No Boost	4	298	32.5 or 30	5	2	--	86	--
Martin, et al. (UK)	Prospective, Single Arm	> 50y, Node -, No CTX, Twice-Weekly, No Boost	3	30	30	5	0†	0†	77	--
FAST Trial (UK)	Prospective, Randomized	> 50y, Node -, No CTX, No DCIS§, No Boost	3	302 308 305	50 30 28.5	25 5 5	0.7 0 0	1.0 0.0 0.7	-- -- --	10 17§§ 11
U of Louisville (USA)	**Prospective, Two Cohorts**	**≥ 30y, N0-1, DCIS (21%), CTX (29%), Boost (18%)**	**3.5**	**158**	**30 or 28.5**	**5**	**1.2**	**0**	**82**	**12**

Abbreviations: N = number of patients; FRAC = fractions; IBTR = in-breast tumor recurrence; LRR = locoregional recurrence; CTX = Chemotherapy.
*All statistical p-values are non-significant in the comparison of CF-WBI to LHF-WBI, unless otherwise specified. †At minimum of 2 year followup. ‡At minimum of 5 years followup. §Only 4 patients had pure DCIS. §§ Statistically-significant.

UK FAST Trial 10y update (*JCO* 07/2020)

(Brunt, et al.)

Acute Skin Reactions

RTOG grade	50Gy/25# N=110 (%)	30Gy/5# N=111 (%)	28.5Gy/5# N=106 (%)
0 or 1	54	85	90
2=tender/bright erythema +/- dry desquamation	35	12	8
3=patchy moist desquamation	11	3	2

No grade 4 toxicity reported (confluent moist desquamation)

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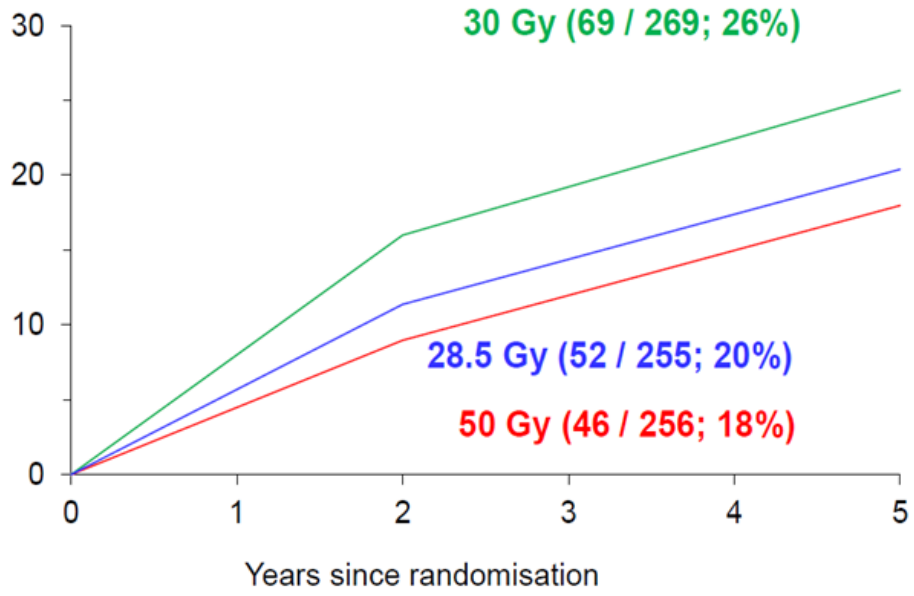
UK FAST Trial update

Photographic assessment of overall change in breast appearance by 5 years

% with mild / marked change in breast appearance



	Difference (95%CI)
30Gy vs **50Gy**	+7.7% (0.7, 14.7) p=0.04
28.5Gy vs **50Gy**	+2.4% (-4.4, 9.2) p=0.56

Marked changes: 2%, 4%, 2%

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UK FAST Trial update

Relapse and survival at median 10 years' follow-up

	50Gy/25# N=302	30Gy/5# N=308	28.5Gy/5# N=305	Total N=915
Local relapse	3	4	4	11
Regional relapse	2	0	3	5
Distant relapse	17	15	15	47
Death (breast cancer)	30 (7)	33 (8)	33 (10)	96 (25)

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

UK FAST Trial update

Fractionation Sensitivity (α/β estimates)

- Photographic change in breast appearance
  α/β = 2.4Gy (95% CI 0.4–4.3)

- Breast shrinkage (clinician assessment)
  α/β = 2.4Gy (95% CI 1.3–3.5)

If **α/β = 2.4Gy**,

- 28.5Gy in 5# ≡ 52.5Gy in 2.0Gy fractions
- 30.0Gy in 5# ≡ 57.3Gy in 2.0Gy fractions
- 27.7Gy in 5# ≡ 50.0Gy in 2.0Gy fractions (calculated)

Future Directions: WBRT

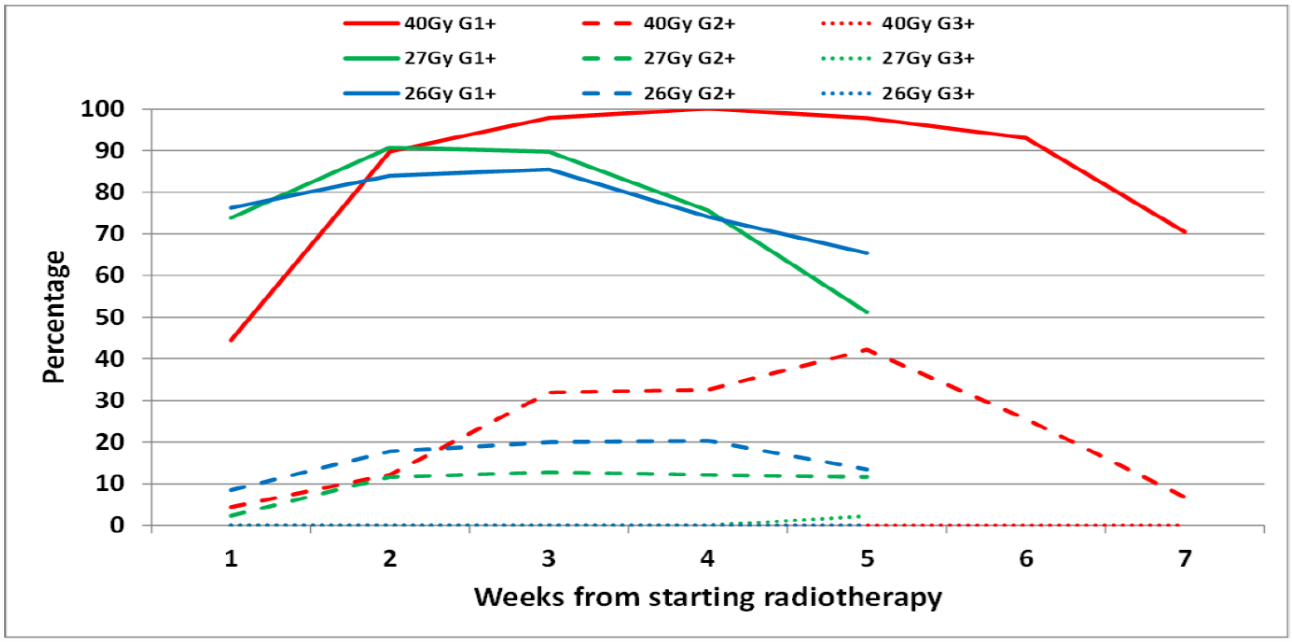
- UK FAST FORWARD Trial (Daily tx)
  - N=4100 (2011-2013); N=700 Needing RNI (2016)
  - >18y; T1-3; N0-2
  - Boost V. No Boost
  - BCT or Mastectomy
    - Control group: 40 Gy in 15 Fx of 2.7 Gy (3w)
    - Test group 1: 27 Gy in 5 Fx of 5.4 Gy (1w)
    - Test group 2: 26 Gy in 5 Fx of 5.2 Gy (1w)
  - Physician, Patient and Photographic assessments of toxicity

UK FAST FORWARD Trial @ 5y (Lancet 04/2020)

(Brunt, et al.)

Acute toxicity study

Clinical assessments of skin toxicity graded by CTCAE criteria in 150 evaluable non-boost patients (7 centres)



Brunt et al. Radiother Oncol 2016

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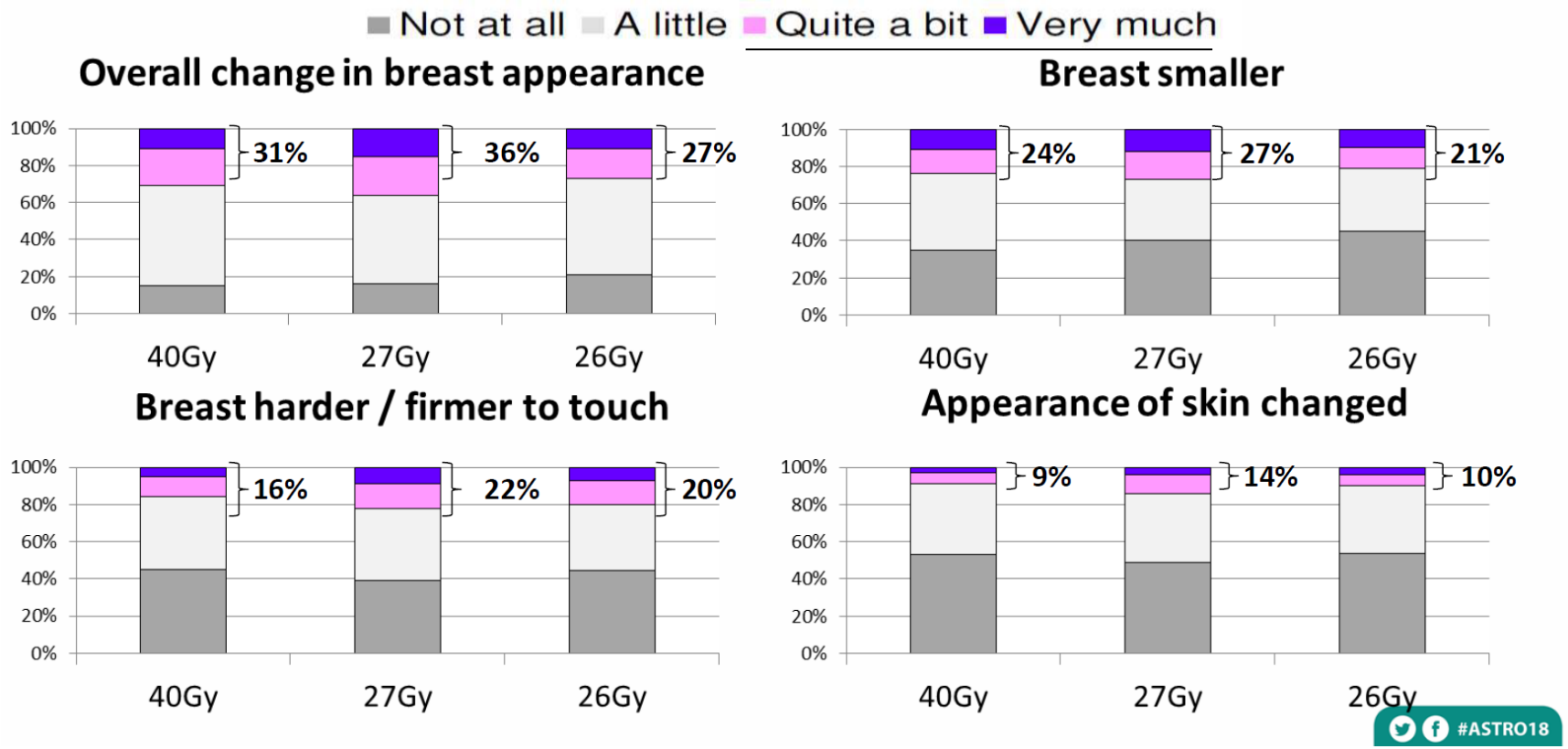
UK FAST FORWARD Trial

Patient assessments of late AE at 2 years (N=1540)



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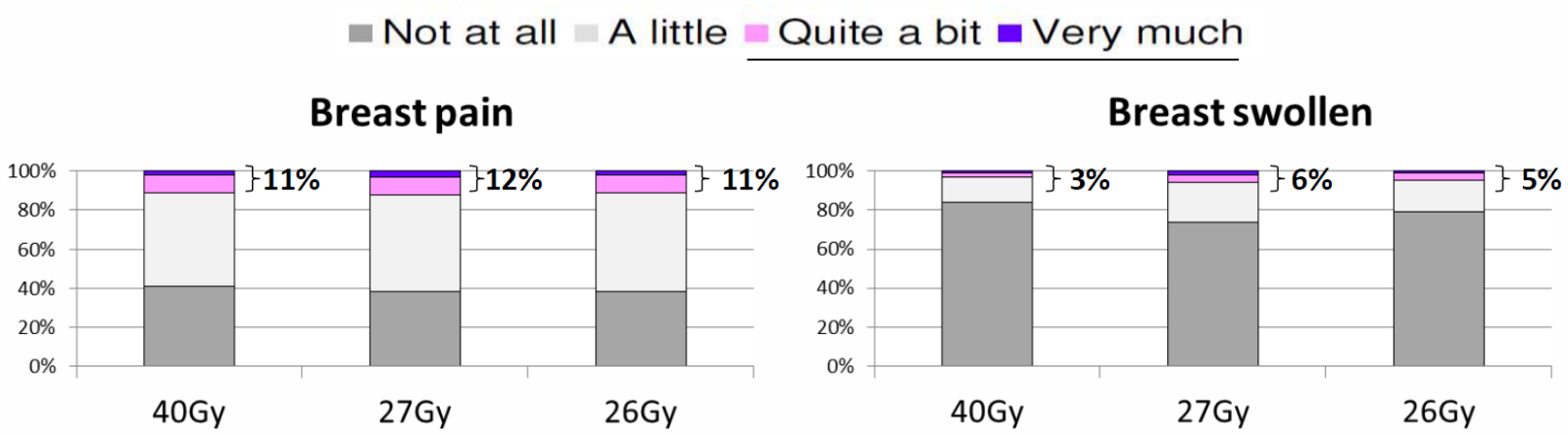
UK FAST FORWARD Trial

Patient assessments of late AE at 2 years (N=1540)



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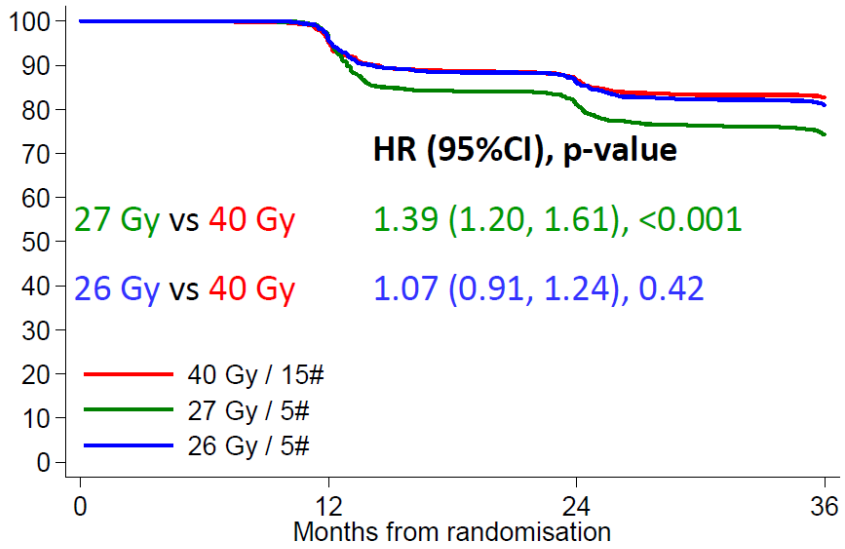
UK FAST FORWARD Trial

Any moderate/marked clinician-assessed late AE in the breast / chest wall

% with no moderate/marked breast AE



Number at risk (events)

40 Gy	1303	(63)	1230	(108)	1079	(49)	957
27 Gy	1334	(58)	1268	(192)	1031	(83)	874
26 Gy	1322	(58)	1250	(123)	1096	(63)	958

	Estimated 3-year cumulative incidence (95% CI)	Difference vs. 40 Gy (95%CI)
40 Gy	20.2% (18.1, 22.6)	-
27 Gy	28.1% (25.7, 30.6)	+6.7% (3.5, 10.3)
26 Gy	21.2% (19.0, 23.5)	+1.1% (-1.6, 4.2)

Includes distortion, shrinkage, induration, telangiectasia, oedema

UK FAST FORWARD Trial

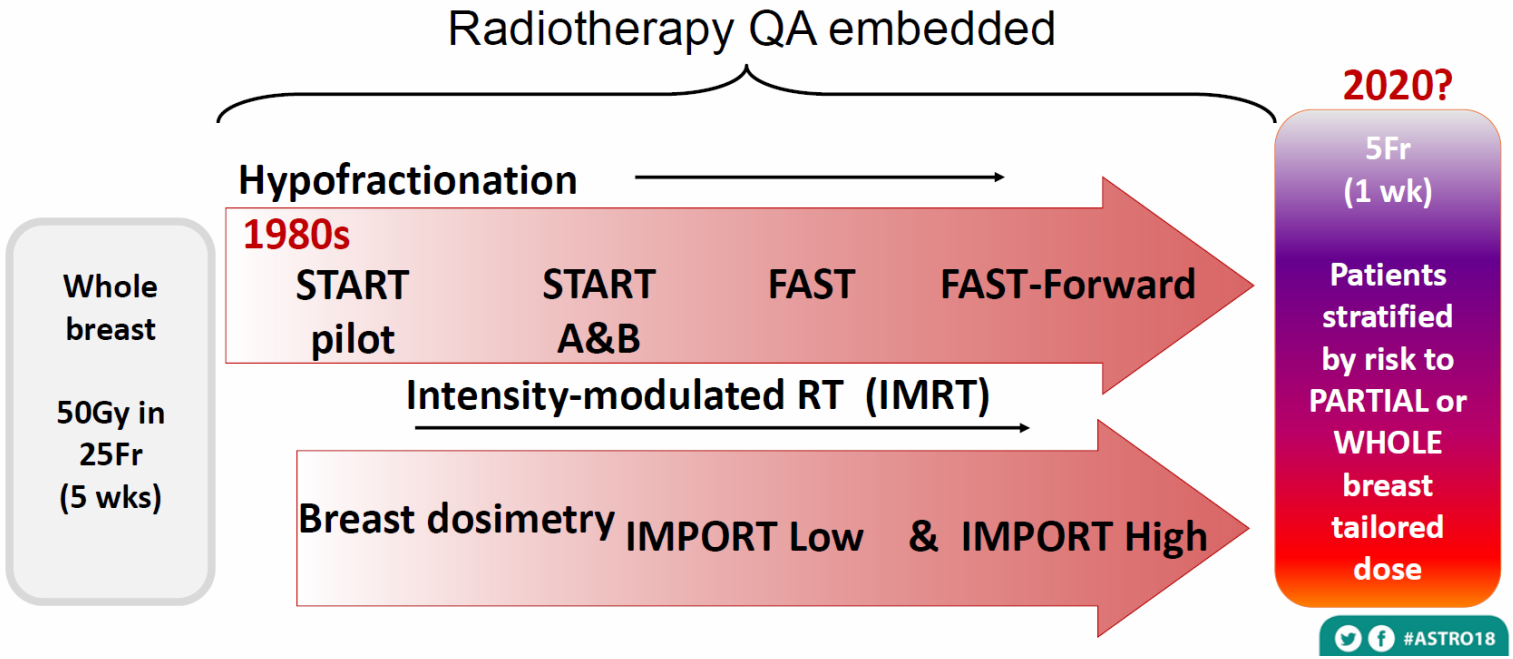
Conclusions from FAST-Forward trial

- Levels of marked late AE were low in all groups
- 27 Gy / 5# / 1 week consistent with 50 Gy / 25# / 5 weeks
- 26 Gy / 5# / 1 week similar to 40 Gy / 15# / 3 weeks
- Mature follow-up will allow interpolation to confirm equivalent 5# schedule
- Lymphatic sub-study comparing 40 Gy / 15# vs 26 Gy / 5#

#ASTRO18

Summary of WB-HFRT Evolution

Deriving a practice-changing regimen for breast external-beam RT



MDA-Cooper: OPAL-II

- 45Gy/15fx, 3 weeks
- 26Gy/5fx, 1 week
- Open to enrollment…Closing soon!
- Only trial in US
- Potential to be practice-changing and offer a more equitable solution
- High enrollment/popularity, High participation of URM women.

Conclusions

- **<u>"Extreme" HFRT is promising pragmatic alternative to daily radiotherapy</u>**
  - Potential: improve cost-efficacy, access, wide applicability
  - 10y UK Fast Trial update (Mainstream option?)
  - Part of *"all of the above"* approach to alternative breast therapies
    - HFRT, APBI, IORT, SBRT, etc..
  - **<u>Especially useful during COVID/Pandemic</u>**
    - Easy to change practice
    - Limit visits/social distancing
- MDA and Cooper will be leaders in the next decade

Thank You.

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