Hypofractionation: what clinical trials in patients with early breast cancer tell us

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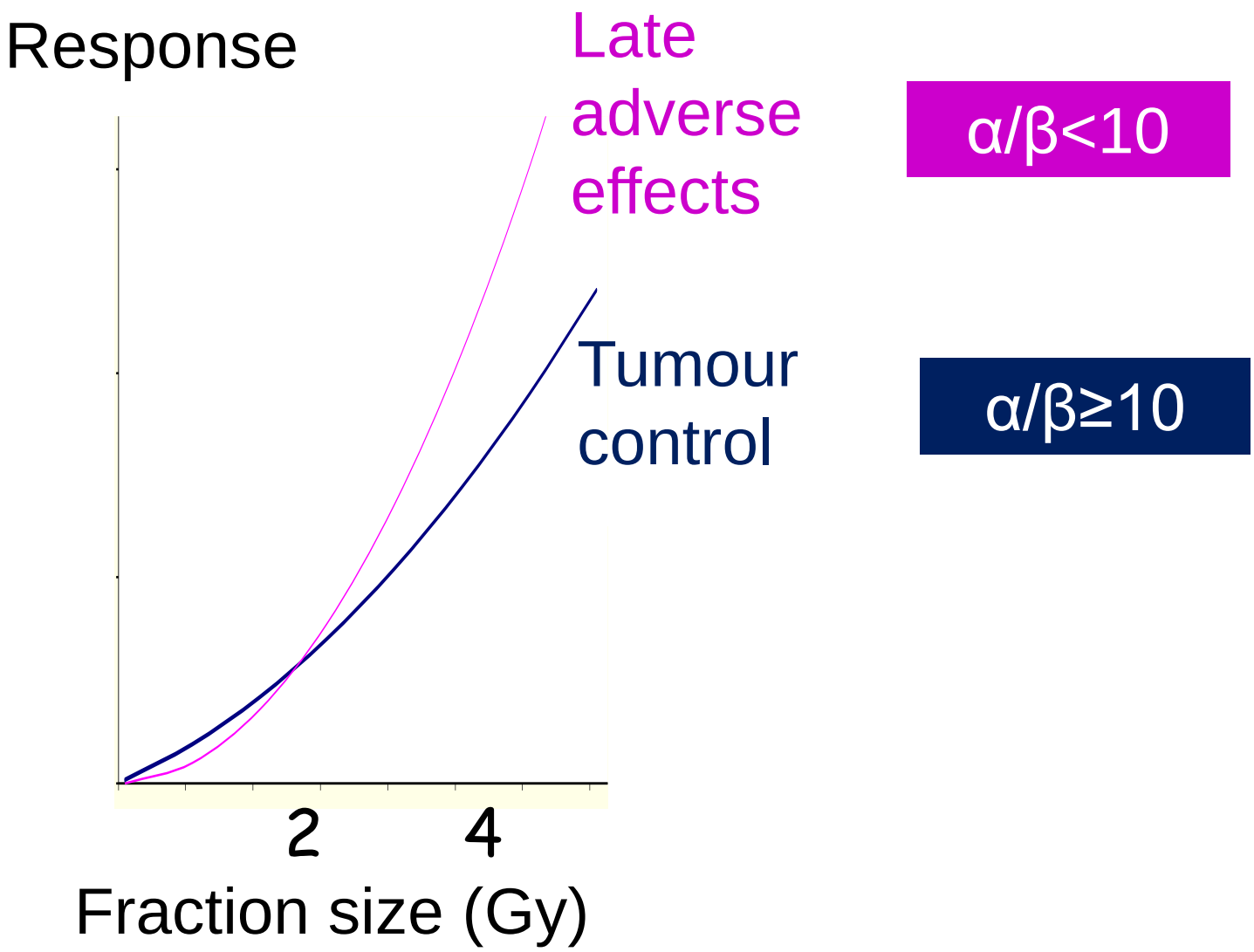
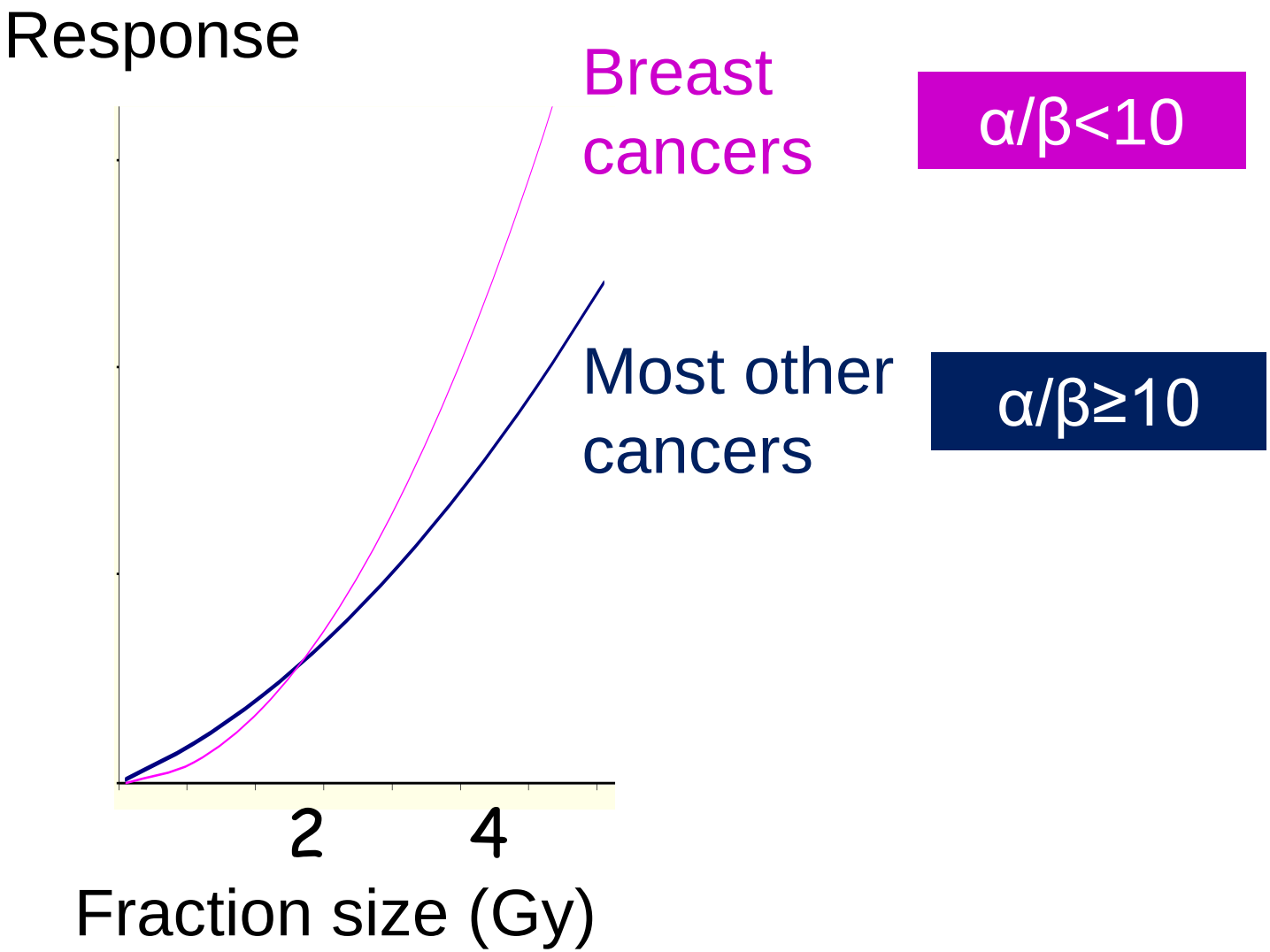
Traditional Model of Fractionation



Current Model of Breast Cancer Fractionation



Hypofractionation for patients with breast cancer: Hypothesis

Fraction sizes >2.0 Gy are as safe and effective as 2.0 Gy fractions provided an appropriate downward adjustment in total dose is introduced

Randomised Trials have Tested Hypofractionated RT after Primary Surgery for early Breast Cancer (N>14,000)

Trial	Comparison (Dose/Fraction/Week)	RT Breast (Br). Chest Wall (CW)	RT Nodal (N)	Sample size (N)
Ontario	50/25 v 42.5/16/3.2	Br		1234
START-P	50/25 v 42.9/13/5 39.0/135	Br, CW	N	1410
START-A	50/25 v 41.6/13/5 39.0/13/5	Br, CW	N	2236
START-B	50/25 v 40.0/15/3	Br, CW	N	2215
FAST	50/25 v 30.0/5/5 27.0/5/5	Br	-	915
China I	50/25 v 43.5/15/3	CW	N	820
China II	50/25 v 43.5/16/3	Br	-	734
HYPORT	50/25 v 40.0/15/3	Br	N	1854
FAST-Forward	40/15 v 27.0/5/1 26.0/5/1	Br, CW	-	4096

START-A Hypofractionation Trial Schema

Trial group	Fraction size	Total dose (Gy)	Fractions (N)	Time (weeks)
Control	2.0	50	25	5
Test 1	3.2	41.6	13	5
Test 2	3.0	39.0	13	5

Un-confounded estimates of α/β: START-Pilot & START-A Trials

Adverse effects (815 events/2263 pts):
α/β = 3.1 (95%CI 2.0-4.2)

Tumour relapse (349 events/3646 pts):
α/β = 3.5 (95%CI 1.2-5.7)

Conclusion: 2Gy fractions spare breast cancer as much as the healthy tissues (no advantage to patients!)

Haviland, Lanc Oncol,. 2013 Oct;14,1086-94

FAST Forward trial: 5 Fractions in 5 days

Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial

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Summary

Background We aimed to identify a five-fraction schedule of adjuvant radiotherapy (radiation therapy) delivered in 1 week that is non-inferior in terms of local cancer control and is as safe as an international standard 15-fraction regimen after primary surgery for early breast cancer. Here, we present 5-year results of the FAST-Forward trial.

Methods FAST-Forward is a multicentre, phase 3, randomised, non-inferiority trial done at 97 hospitals (47 radiotherapy centres and 50 referring hospitals) in the UK. Patients aged at least 18 years with invasive carcinoma of the breast (pT1–3, pN0–1, M0) after breast conservation surgery or mastectomy were eligible. We randomly allocated patients to either 40 Gy in 15 fractions (over 3 weeks), 27 Gy in five fractions (over 1 week), or 26 Gy in five fractions (over 1 week)

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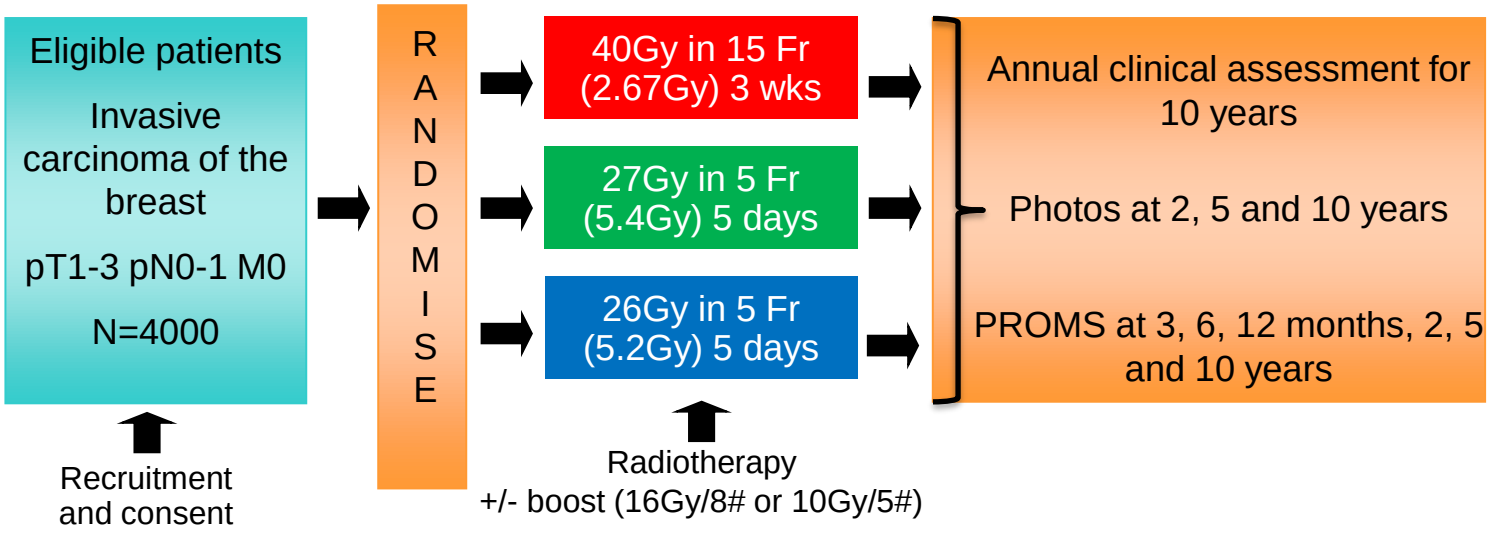
FAST-Forward: Aim

To test a 1-week course of local (breast/chest wall) adjuvant RT against 40 Gy in 15 fractions in patients with early breast cancer in terms of local cancer control and adverse effects

FAST Forward Trial design



Primary endpoint:

- Ipsilateral breast tumour relapse (IBTR)

Median follow-up: 6 years

Secondary endpoints:

- early & late adverse effects
- quality of life
- contralateral primary tumours
- regional & distant metastases
- survival

Sample size

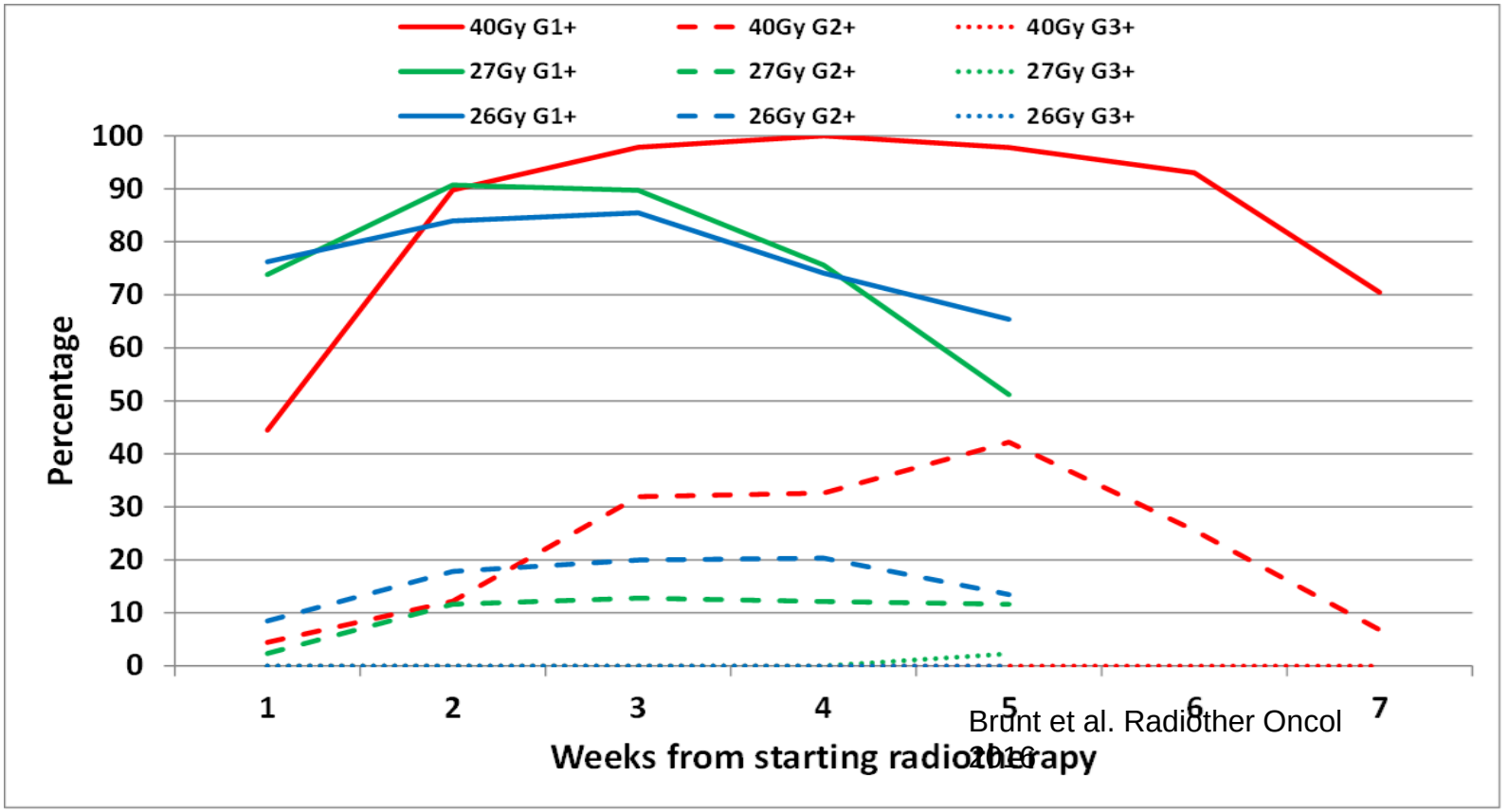
- Target sample size = 4000
- 80% power
- 1-sided α = 0.025, allowing for non-inferiority of tumour control & Bonferroni correction for comparison between each test schedule vs control
- Non-inferiority margin = absolute 1.6% increase in 5-year IBTR for 5fr schedule vs control
- Assuming 2% 5-year local relapse in 40 Gy group
- Critical hazard ratio for non-inferiority = 1.80

Baseline & treatment characteristics

		40Gy in 15# N=1361 (%)	27Gy in 5# N=1367 (%)	26Gy in 5# N=1368 (%)
Age (years)	**Median (range)**	60 (29-89)	61 (25-90)	61 (25-89)
Grade	**1**	23	23	22
	2	49	49	50
	3	28	28	28
Risk group	**Low (age≥50 & G1 or 2)**	62	63	62
	High (age<50 or G3)	38	37	38
Primary surgery	**Breast conservation**	93	94	94
	Mastectomy	7	6	6
Pathological	**Positive**	19	18	19
node status	**Negative**	81	82	81
ER / HER2 status	**ER+ / HER2+**	8	8	7
	ER+ / HER2-	82	83	81
	ER- / HER2+	2	2	3
	ER- / HER2-	8	7	9
Tumour bed boost	**Yes**	25	25	24
Boost dose	**10Gy in 5#**	76	81	77
	16Gy in 8#	24	19	23

Acute skin toxicity study

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



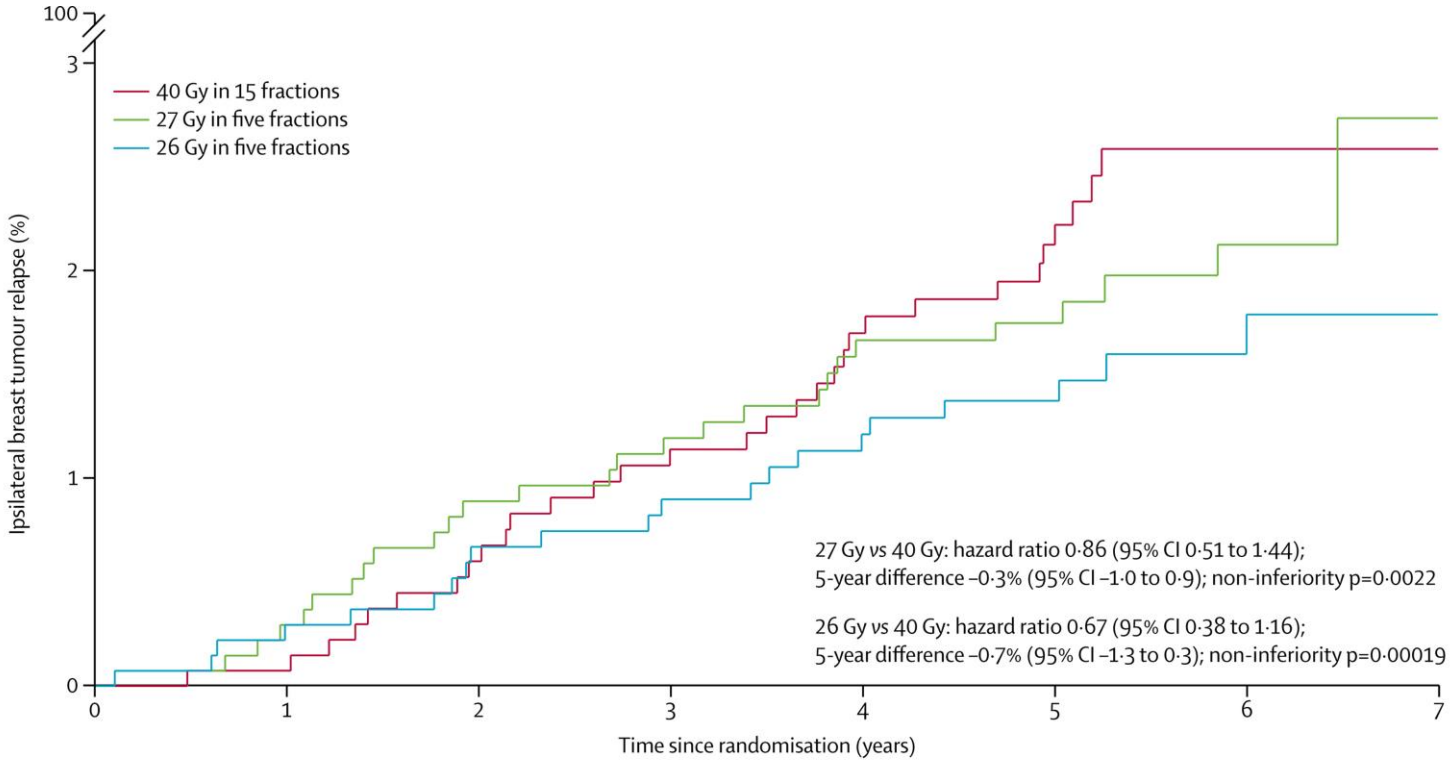
Brunt et al. Radiother Oncol 2016

Relapse & Survival

Relapse: time-to-event analysis (n=4096)

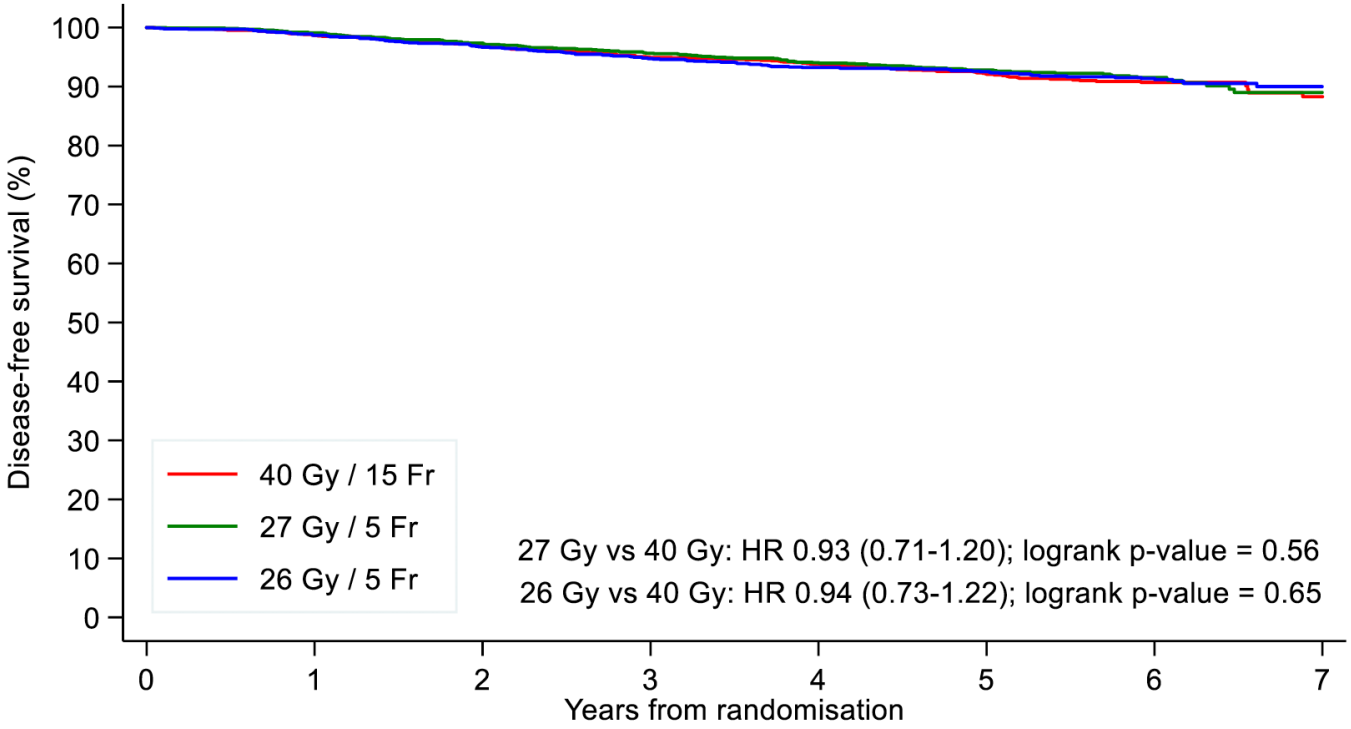
	Cumulative number of events	Estimated cumulative incidence by 5 years (95% CI)	Hazard ratio (95% CI); p value	Estimated absolute difference *vs* 40 Gy at 5 years (95% CI)
Ipsilateral breast tumour (local) relapse*				
40 Gy (n=1361)	31 (2·3%)	2·1% (1·4 to 3·1)	1 (ref)	..
27 Gy (n=1367)	27 (2·0%)	1·7% (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)

Ipsilateral breast tumour relapse



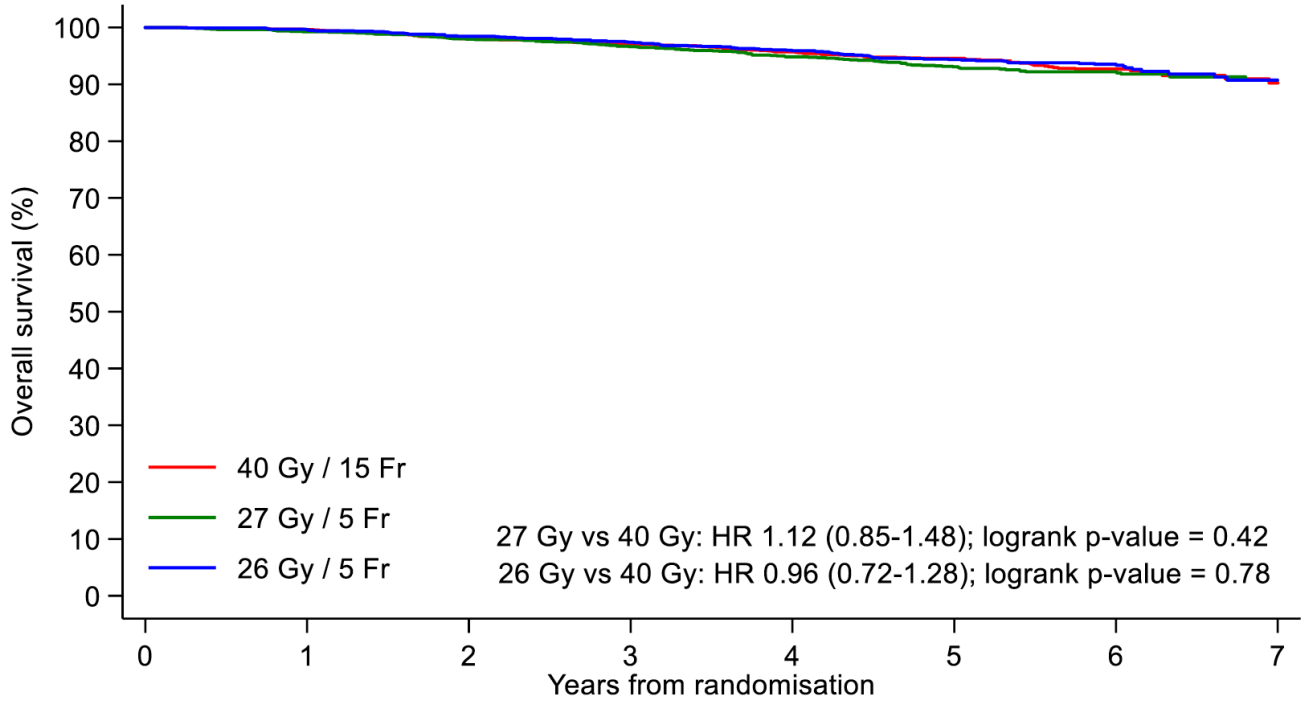
40 Gy								
Number at risk	1361	1347	1307	1281	1230	1045	486	91
Censored	0	13	46	65	109	289	844	1239
Events	0	1	8	15	22	27	31	31
27 Gy								
Number at risk	1367	1352	1328	1303	1255	1066	508	90
Censored	0	11	27	48	90	278	833	1250
Events	0	4	12	16	22	23	26	27
26 Gy								
Number at risk	1368	1347	1325	1302	1257	1070	524	89
Censored	0	17	34	54	95	280	824	1258
Events	0	4	9	12	16	18	20	21

Disease-free survival



No. at risk (40Gy)	1361	1335	1292	1253	1204	1016	475	87
censored	0	8	29	40	74	242	771	1155
event	0	18	40	68	83	103	115	119
No. at risk (27Gy)	1367	1348	1313	1277	1229	1038	493	88
censored	0	7	18	31	58	233	768	1167
event	0	12	36	59	80	96	106	112
No. at risk (26Gy)	1368	1336	1305	1270	1220	1044	513	89
censored	0	14	18	27	57	224	745	1165
event	0	18	45	71	91	100	110	114

Overall survival



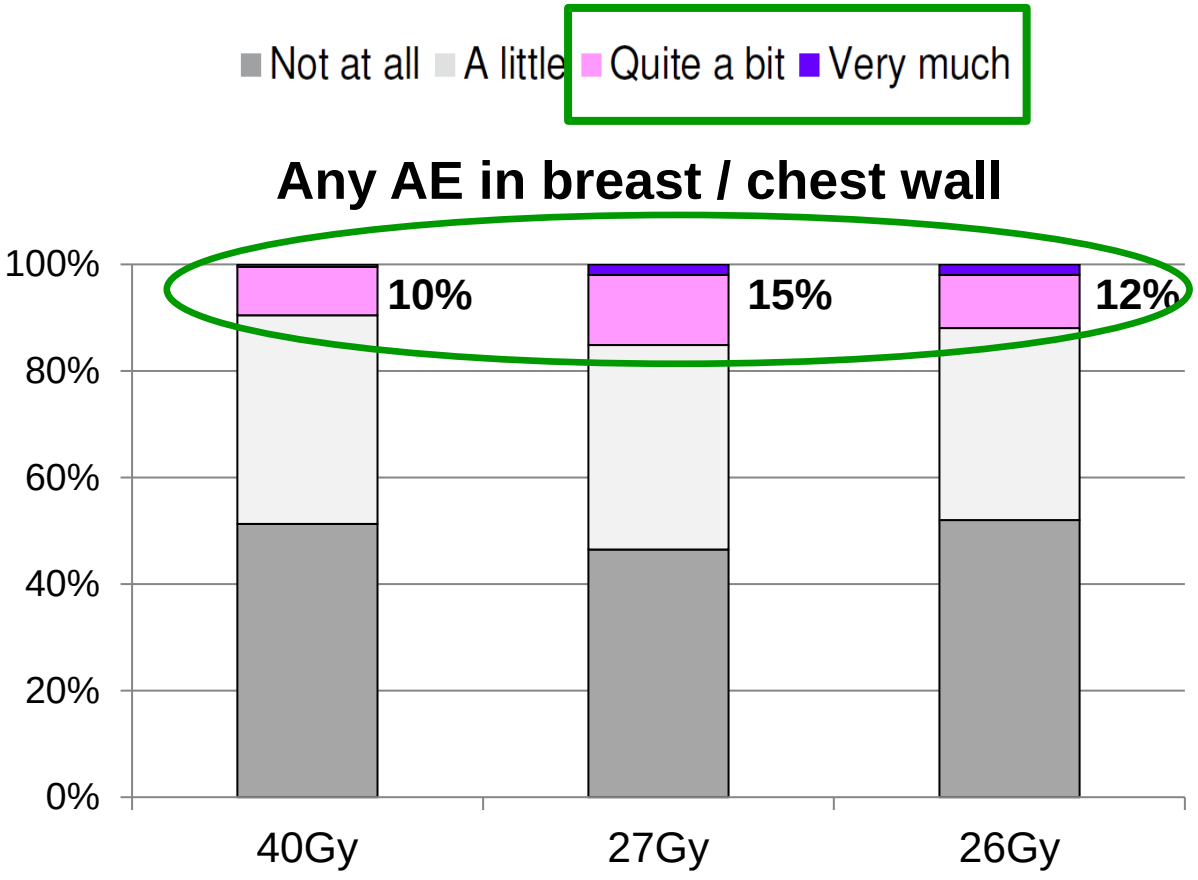
No. at risk (40Gy)	1361	1348	1312	1291	1245	1061	494	91
censored	0	8	22	31	59	228	780	1178
event	0	5	27	39	57	72	87	92
No. at risk (27Gy)	1367	1356	1337	1314	1271	1075	511	91
censored	0	1	2	7	26	199	755	1171
event	0	10	28	46	70	93	101	105
No. at risk (26Gy)	1368	1351	1332	1310	1266	1077	531	90
censored	0	12	15	23	47	216	755	1188
event	0	5	21	35	55	75	82	90

Late adverse effects (AE)

Any moderate or marked AE in the breast or post-mastectomy chest wall

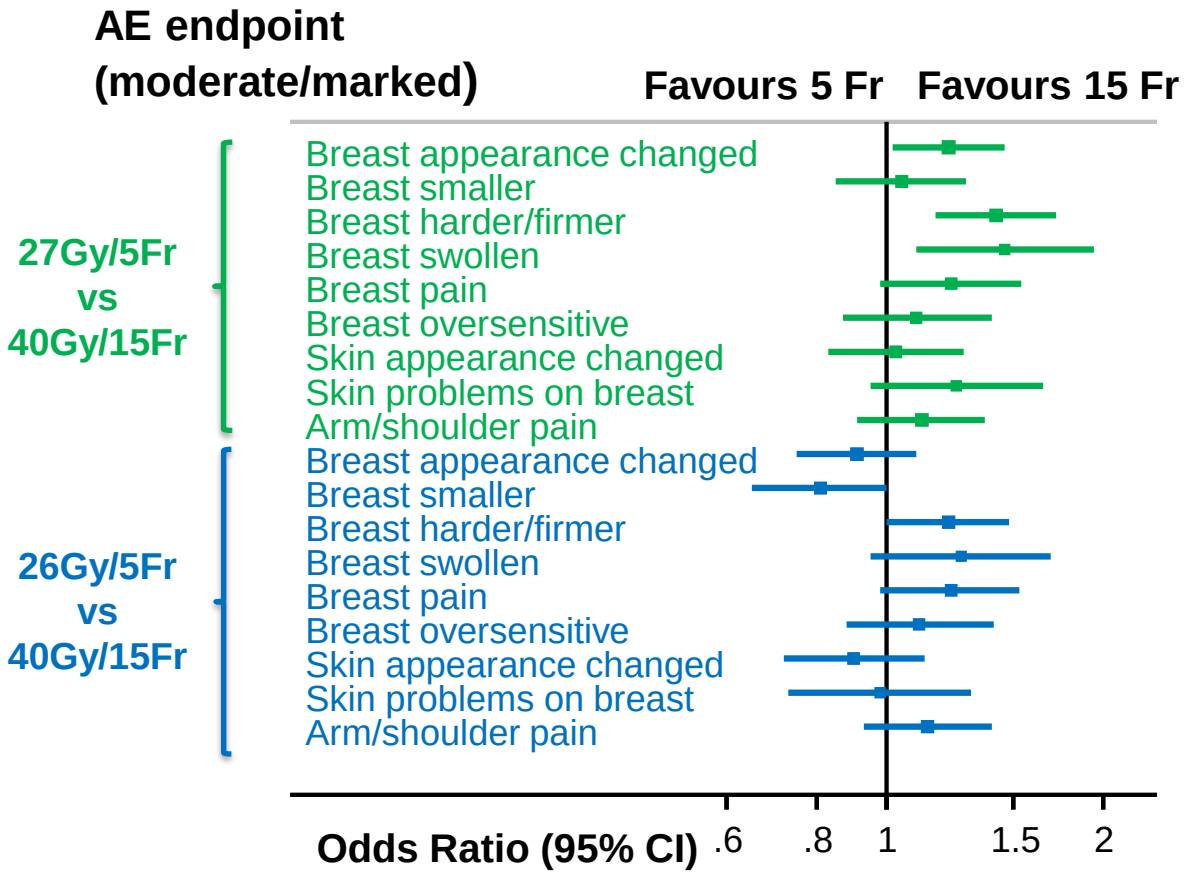
	Number of moderate or marked events/total number of assessments over follow-up	Odds ratio for schedule (95% CI)	p value for comparison with 40 Gy	p value for comparison between 27 Gy and 26 Gy	Odds ratio for years of follow-up (95% CI); p value
Any adverse event in the breast or chest wall*	..	..	..	..	0·98 (0·96–1·00); 0·055
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	0·0001	..

Clinician assessments of ‘Any AE’ in breast or chest wall at 5 years



From 1-5 years, ORs for any moderate/marked AE vs. 40Gy:
1.55 (1.32-1.84, p<0.001) for 27Gy and 1.12 (0.94-1.34, p=0.20) for 26Gy

Late adverse effects: relative treatment effects Patient assessments at 5 years (N=1774)



Fractionation sensitivity (α/β) of late adverse effects

Any clinician-reported moderate/marked AE in breast/chest wall

α/β estimate = 1.7 Gy (95% CI 1.2 – 2.3)

Photographic change in breast appearance

α/β estimate = 1.8 Gy (95% CI 1.1 – 2.4)

Patient-reported moderate/marked change in breast appearance

α/β estimate = 2.3 Gy (95% CI 1.8 – 2.9)

Late adverse effects: equivalent total doses in 2 Gy fractions (EQD2)

$\alpha/\beta \rightarrow$	**3.0**	**2.3**	**2.0**	**1.8**	**1.7**
50 Gy/25F	50	50	50	50	50
40 Gy/15F	45	46	47	47	47
27 Gy/5F	45	48	50	51	52
26 Gy/5F	43	45	47	48	49

Selected sub-groups

Absolute numbers of local relapses by patient subgroups at randomisation

Subgroup		Ipsilateral breast tumour relapse		
		40 Gy / 15 Fr N=31	27 Gy / 5 Fr N=27	26 Gy / 5 Fr N=21
Age at randomisation				
N=604	<50	3	7	4
	≥50	28	20	17
Grade				
	1	2	3	4
	2	9	9	9
N=1140	3	20	15	8
ER / HER2 status				
	ER+ / HER2+	3	4	1
	ER+ / HER2-	17	15	16
	ER- / HER2+	1	3	1
N=335	ER- / HER2-	10	5	3
	Unknown	0	0	0

Conclusions

- Moderate hypofractionation is safe & effective
- 5-Fr schedules are non-inferior to 40 Gy/15 Fr for local tumour control
- For late adverse effects:
    - 26 Gy/5 Fr similar to 40 Gy/15 Fr
    - 27 Gy/5 Fr consistent with 50 Gy/25 Fr
- UK has adopted 26 Gy/5 Fr for local adjuvant RT
- FAST Forward protocol and RT planning pack available at: https://www.icr.ac.uk/our-research/centres-and-collaborations/centres-at-the-icr/clinical-trials-and-statistics-unit/clinical-trials/fast_forward_page/

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