

Title: FAST-Forward phase 3 RCT of 1-week hypofractionated breast radiotherapy: 3-year normal tissue effects

Authors: Brunt AM, Haviland JS, Sydenham MA, Alhasso A, Bloomfield D, Chan C, Churn M, Cleator S, Coles CE, Emson M, Goodman A, Griffin C, Harnett A, Hopwood P, Kirby A, Kirwan C, Morris C, Sawyer E, Somaiah N, Syndikus I, Wilcox M, Wheatley D, Zotova R, Bliss JM, Yarnold JR.

Purpose/Objective

FAST-Forward aims to identify a 5-fraction schedule of adjuvant radiotherapy delivered in 1 week that is at least as effective and safe as the UK standard 15-fraction regimen after primary surgery for early breast cancer. The primary endpoint is local-regional relapse at 5 years, with normal tissue effects (NTE) important secondary endpoints. Previous breast radiotherapy trials have shown that NTE rates at 3 years predict 5 and 10-year comparisons; NTE results up to 3 years are reported here.

Material/methods

The FAST-Forward trial (ISRCTN19906132) randomised patients with invasive carcinoma of the breast (pT1-3 pN0-1 M0) following breast conservation surgery or mastectomy (immediate reconstruction was allowed) to 40Gy in 15 fractions over 3 weeks (control), 27Gy or 26Gy in 5 fractions over 1 week (1:1:1) to whole breast or chest wall. A tumour bed boost of 16Gy in 8 fractions or 10Gy in 5 fractions was given where indicated. NTEs were assessed annually by clinicians, at baseline, 3, 6, 12 and 24 months by patients and from photographs at 2 years compared with a pre-radiotherapy baseline. Clinician and patient assessments used a 4-point scale corresponding to none, mild, moderate, marked; photographic assessments of change in breast appearance were scored as none, mild or marked. Schedules were compared using cross-sectional analyses at specific time-points and survival analysis. Due to multiple testing a significance level of 0.005 was used. A lymphatic sub-study is ongoing.

Results

From November 2011 to June 2014, 4096 consenting patients were recruited (1361 40Gy, 1367 27Gy, 1368 26Gy). Median follow-up is 48 months (IQR 37-50), with 98% of year 3 visit forms returned. Levels of marked NTEs at 2 or 3 years were very low (Table). Clinician assessments of individual NTEs at 3 years and patient assessments at 2 years were similar between schedules. Prevalence of change in photographic breast appearance at 2 years was statistically significantly higher for 27Gy compared with 40Gy, but similar for 26Gy with 40Gy. The composite endpoint of any clinician-assessed NTE in the breast showed statistically significantly higher levels at 3 years for 27Gy compared with 40Gy (excess of moderate/marked effects +4.4%, 95%CI 1.6-7.2); 26Gy was similar to 40Gy (+1.4%, -1.2 – 4.0). Cumulative incidence rates of any clinician-assessed moderate/marked NTE in the breast up to 3 years were 40Gy: 20.8% (95%CI 18.6-23.2), 27Gy: 28.8% (26.4-31.4), 26Gy: 21.8% (19.6-24.2).

Conclusion

Levels of marked NTEs were low for all schedules. Late effects after 26Gy in 5 fractions over 1 week appear to be similar to 40Gy in 15 fractions over 3 weeks.

Funding

National Institute for Health Research Health Technology Assessment Programme - HTA (UK) (09/01/47)

Table: Cross-sectional results for clinician, photographic and patient assessments of normal tissue effects

Normal tissue effect	Grade	40Gy in 15 fractions (3 weeks) n (%)	27Gy in 5 fractions (1 week) n (%)	26Gy in 5 fractions (1 week) n (%)
Clinician assessments at 3 years:		N=1076¹	N=1120¹	N=1109¹
Worst grade of any normal tissue effect in the breast ²	None	586 (54)	542 (48)	573 (52)
	Mild	379 (35)	414 (37)	406 (37)
	Moderate	104 (10)	139 (12)	106 (10)
	Marked	7 (<1)	25 (2)	24 (2)
<i>P-value</i> ³	-	<0.001	0.06	
Breast induration (maximum score in & outside tumour bed)	None	814 (80)	807 (76)	839 (79)
	Mild	165 (16)	209 (20)	181 (17)
	Moderate	35 (3)	41 (4)	32 (3)
	Marked	4 (<1)	10 (<1)	9 (<1)
<i>P-value</i> ³	-	0.01	0.53	
Breast shrinkage	None	727 (71)	773 (72)	776 (73)
	Mild	236 (23)	207 (19)	218 (21)
	Moderate	57 (6)	79 (7)	58 (5)
	Marked	4 (<1)	9 (<1)	9 (<1)
<i>P-value</i> ³	-	0.60	0.65	
Breast distortion	None	781 (76)	787 (73)	817 (77)
	Mild	197 (19)	229 (21)	198 (19)
	Moderate	43 (4)	46 (4)	35 (3)
	Marked	2 (<1)	9 (<1)	11 (1)
<i>P-value</i> ³	-	0.08	0.93	
Photographs at 2 years:		N=400	N=410	N=414
Change in breast appearance (compared with pre-radiotherapy baseline)	None	370 (92)	345 (84)	370 (89)
	Mild	28 (7)	45 (11)	32 (8)
	Marked	2 (1)	20 (5)	12 (3)
<i>P-value</i> ³	-	<0.001	0.02	
Patient assessments at 2 years:		N=491	N=509	N=505
Overall breast appearance (compared with contralateral breast)	None	75 (15)	83 (16)	105 (21)
	Mild	264 (54)	240 (47)	261 (52)
	Moderate	99 (20)	108 (21)	83 (16)
	Marked	53 (11)	78 (15)	56 (11)
<i>P-value</i> ³	-	0.10	0.12	

¹ Number of clinical assessments overall (denominators for individual NTEs vary); ² Any NTE includes breast distortion, breast shrinkage, breast induration (in & outside tumour bed), telangiectasia, breast/chest wall oedema; ³ χ^2 test for trend; comparison with 40Gy in 15 fractions (control)