THE UK STANDARDISATION OF BREAST RADIOTHERAPY (START) TRIALS OF RADIOTHERAPY HYPOFRACTIONATION FOR TREATMENT OF EARLY BREAST CANCER

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- CONVENTIONAL FRACTIONATION : 50 Gy in 25 fractions of 2 Gy over 5 weeks- standard regimen.

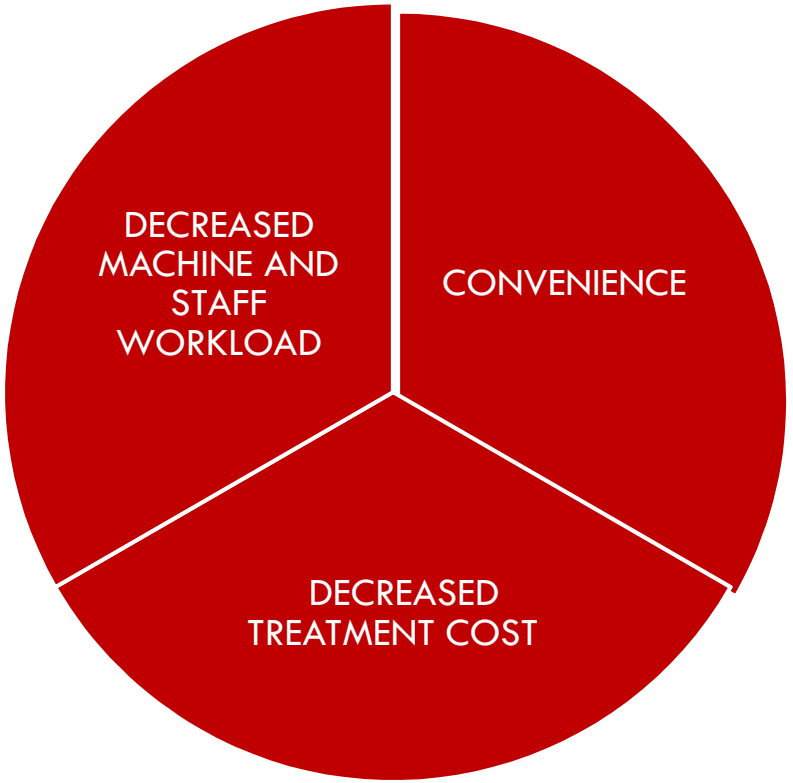
Why hypofractionate ?

- RADIOBIOLOGY
- Alpha/beta ratio of tumor is less than the normal tissue - large dose per fraction is preferred eg : PROSTATE, BREAST

IS HYPOFRACTIONATION BETTER ???

BENEFITS

started as an empirical practice in government run health care systems of UK and Canada



CONCERNS

- Cancer cure ???
- Normal tissue effects !!!

TRIALS – HYPOFRACTIONATION

- UK pilot trial (n=1410) begun in 1986, Two doses (39 Gy and 42·9 Gy) of a 13 fraction regimen delivered over 5 weeks compared with 50 Gy in 25 fractions.
- Canadian trial (n=1234) begun in 1993
- UK FAST trial

Study design and participants

- UK radiotherapy centres—17 centres for START-A and 23 for START-B.
- Patients were recruited after complete excision of primary invasive breast cancer (pT1–3a, pN0–1, M0)
- When adjuvant chemotherapy, a 2-week interval was required before the start of radiotherapy.
- Exclusion criteria – immediate breast reconstruction

START A trial

13 fraction regimen

5 weeks

- 5 week overall treatment time
- two doses of a 13 fraction regimen
- 1998-2002
- 2236 women
- 5 treatment per fortnight

START A

LR 5 YEARS

50 Gy : 3.6%

41.6 : 3.5%

39 Gy: 5.2%

- 5-year results for local tumour control and late-occurring normal tissue effects assessed by patients and from photographs were consistent with the hypothesis that breast cancer tissue and the dose limiting normal tissues are similarly sensitive to fraction size

START-B :

- pragmatic design
- 1999 – 2001
- 2215 women
- 40 Gy/15 (2.67 per fraction, 3 weeks) compared with conventional.

5 years LR

50 Gy : 3.3%

40 Gy : 2.2%

- 5-year results suggesting that local tumour control and safety of normal tissue effects are as good after 40 Gy in 15 fractions over 3 weeks as with 50 Gy in 25 fractions over 5 weeks

- Both START trials permitted prescription of a sequential tumour bed boost dose of 10 Gy in five fractions

Endpoint

- **PRINCIPAL** : **local-regional relapse**— defined as relapse in breast or chest wall, ipsilateral axilla, or supraclavicular fossa within an irradiated target volume and late normal tissue effects
- **SECONDARY** : local relapse (relapse in breast or chest wall), distant relapse (relapse in nonirradiated organs), disease-free survival (survival from any breast cancer-related event including local, regional, or distant relapse, breast cancer death, or contralateral breast cancer), and overall survival.

- Length of follow-up was calculated as time from randomisation until time of first event or last follow-up assessment, whichever occurred first

Statistical analysis

- 2236 women were recruited into START-A between Jan 20, 1999, and Dec 20, 2002
- median age was 57 years (range 25–85)
- 1900 (85%) BCS
- 1138 (51%) had tumours smaller than 2 cm, 643 (29%) had positive lymph nodes, 1572 (70%) had grade 1 or 2 disease, 793 (35%) received adjuvant chemotherapy, 1758 (79%) received tamoxifen, and 318 (14%) received lymphatic radiotherapy.
- 1152 of 1900 (61%) patients who had breast-conserving surgery had tumour bed boost radiotherapy.

- At a median follow-up in survivors of 9·3 years (8·0–10·0, maximum 12·4 years), 1700 of 2236 patients (76·0%) were alive and without relapse
- 57 (2·5%) were alive with local-regional relapse (without distant relapse)
- 78 (3·5%) were alive with distant relapse (including 16 with local-regional relapse), 392 (17·5%) had died (including 66 with local-regional relapse)
- nine (0·4%) no follow-up.
- **At the time of analysis (Feb 20, 2012), 139 of 2236 (6·2%) patients in START-A had local-regional tumour relapse**

HRs for local-regional relapse relative to the 50 Gy schedule were 0·91 (95% CI 0·59–1·38) for the 41·6 Gy schedule and 1·18 (0·79–1·76) for the 39 Gy schedule

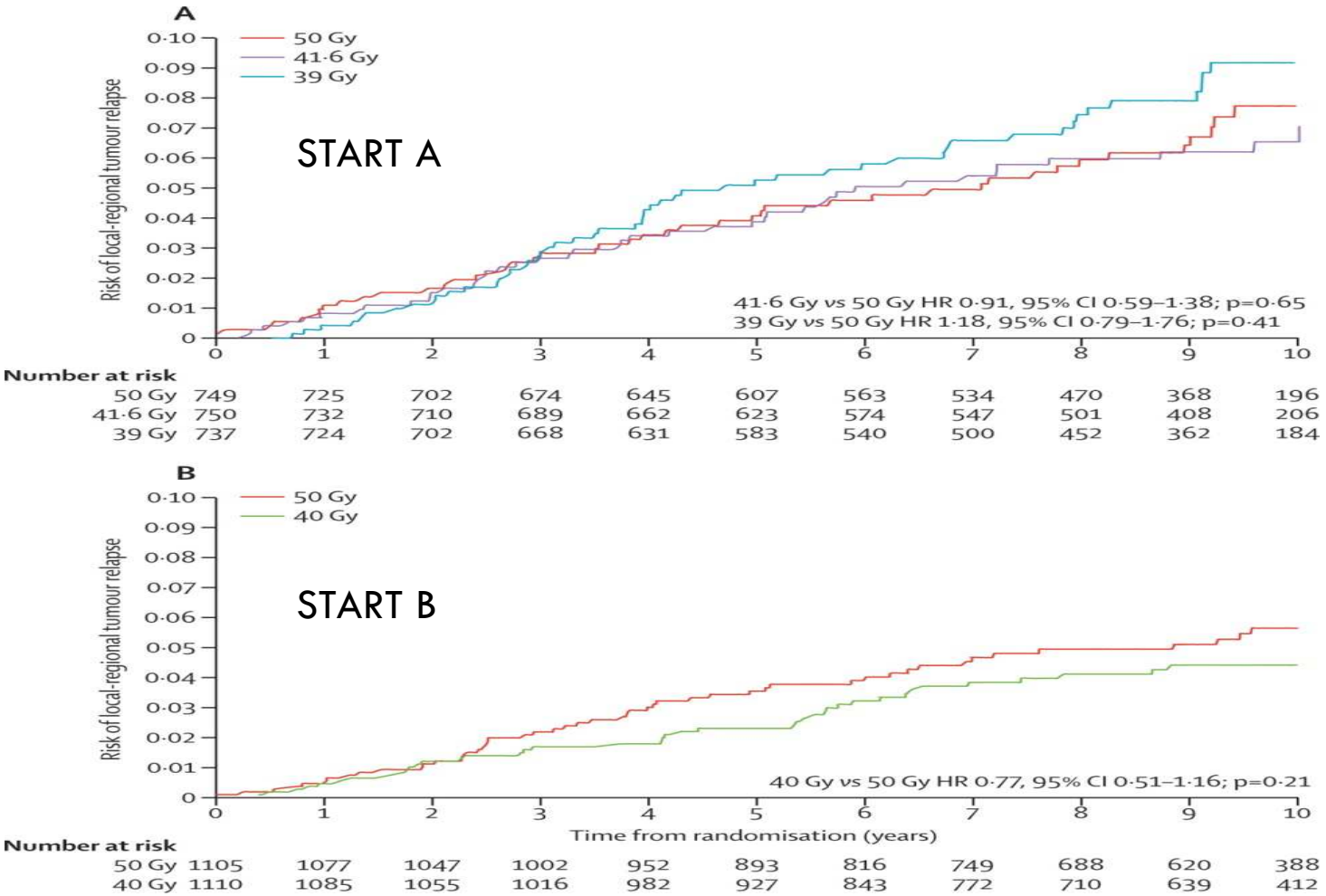
	Events (n/patients; %)	Estimated proportion of patients with event by 5 years (%; 95% CI)	Estimated proportion of patients with event by 10 years (%; 95% CI)	Crude hazard ratio (95% CI)	p value*
Local relapse					
50 Gy	40/749 (5·3%)	3·4% (2·3–5·1)	6·7% (4·9–9·2)	1·00	..
41·6 Gy	37/750 (4·9%)	3·1% (2·0–4·7)	5·6% (4·1–7·8)	0·90 (0·57–1·40)	0·63
39 Gy	47/737 (6·4%)	4·4% (3·1–6·2)	8·1% (6·1–10·7)	1·20 (0·79–1·83)	0·39
Local-regional relapse					
50 Gy	45/749 (6·0%)	4·0% (2·8–5·7)	7·4% (5·5–10·0)	1·00	..
41·6 Gy	42/750 (5·6%)	3·8% (2·6–5·5)	6·3% (4·7–8·5)	0·91 (0·59–1·38)	0·65
39 Gy	52/737 (7·1%)	5·1% (3·7–7·1)	8·8% (6·7–11·4)	1·18 (0·79–1·76)	0·41
Distant relapse					
50 Gy	100/749 (13·3%)	9·8% (7·9–12·3)	14·7% (12·2–17·7)	1·00	..
41·6 Gy	110/750 (14·7%)	9·5% (7·6–11·9)	16·8% (14·0–20·0)	1·08 (0·82–1·41)	0·58
39 Gy	121/737 (16·4%)	11·8% (9·7–14·4)	18·0% (15·1–21·2)	1·24 (0·95–1·61)	0·11
Any breast cancer-related event†					
50 Gy	154/749 (20·6%)	14·0% (11·6–16·7)	22·6% (19·5–26·1)	1·00	..
41·6 Gy	149/750 (19·9%)	11·7% (9·5–14·2)	22·7% (19·5–26·3)	0·94 (0·75–1·17)	0·57
39 Gy	163/737 (22·1%)	15·5% (13·0–18·3)	24·3% (21·1–28·0)	1·08 (0·87–1·35)	0·48
All-cause mortality					
50 Gy	130/749 (17·4%)	10·5% (8·5–13·0)	19·8% (16·8–23·2)	1·00	..
41·6 Gy	128/750 (17·1%)	10·7% (8·7–13·2)	18·4% (15·7–21·6)	0·96 (0·75–1·22)	0·74
39 Gy	134/737 (18·2%)	9·9% (8·0–12·4)	20·3% (17·3–23·7)	1·05 (0·82–1·34)	0·69

*Assessed with Wald test comparing each schedule with 50 Gy. †Local, regional, or distant relapse, breast cancer death, contralateral breast cancer.

Table 1: **Relapse and mortality according to fractionation schedule in START-A**

- estimated absolute differences in the proportion of patients with local-regional relapses at 10 years compared with 50 Gy were 0·6% (95% CI –3·0 to 2·7) for 41·6 Gy and 1·3% (–1·5 to 5·2) for 39 Gy.
- Estimated maximum 2·0% excess risk with 41·6 Gy and 4·5% with 39 Gy compared with 50 Gy

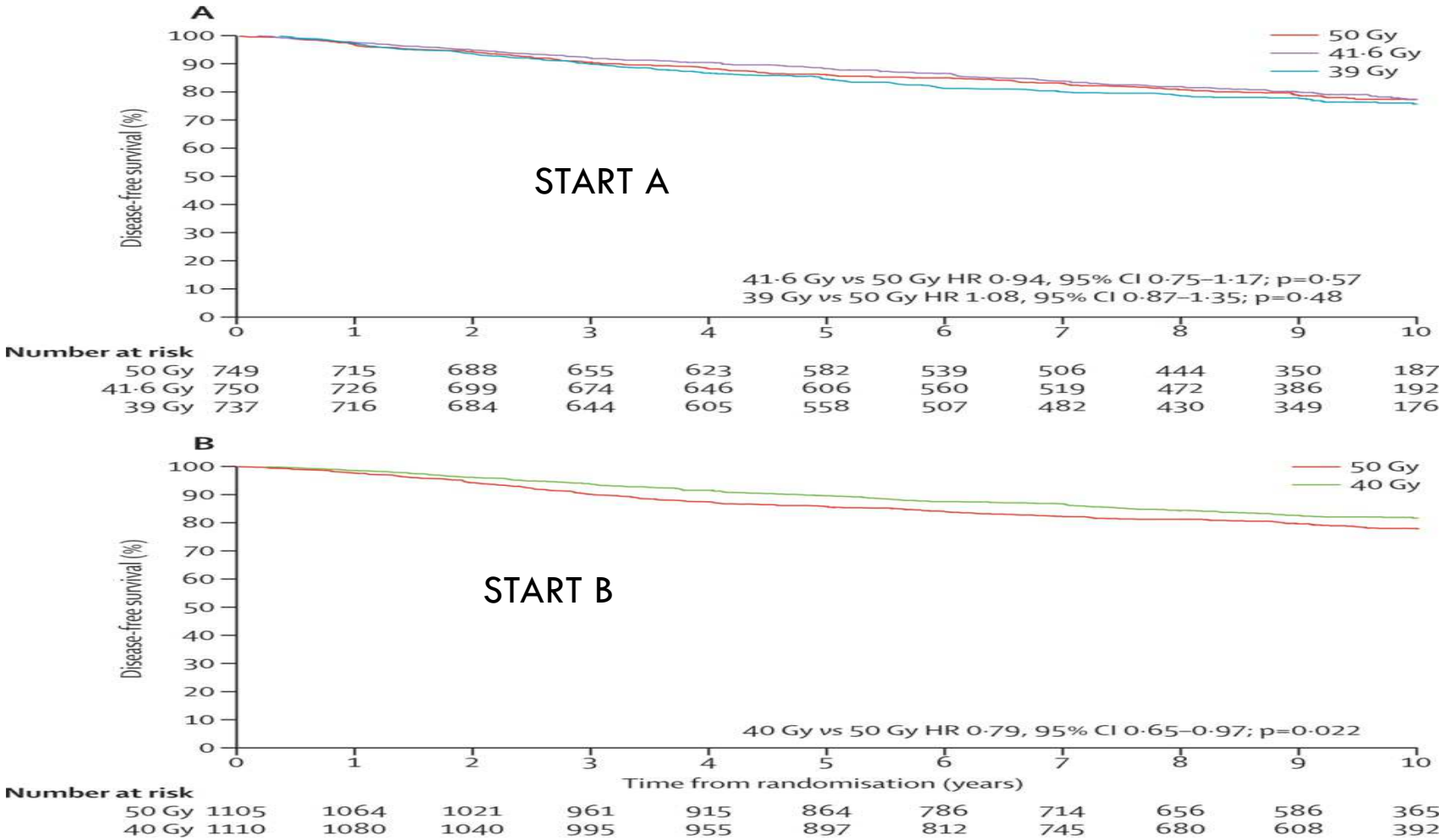
Cumulative risk of local-regional tumour relapse In START-A (A) and START-B (B).



- Estimated α/β value for local-regional relapse in START-A was 4 Gy (95% CI 0·0–8·9), adjusting for age, tumour size, type of primary surgery, use of adjuvant chemotherapy, use of tamoxifen, lymphatic radiotherapy, and tumour bed boost radiotherapy.
- Metaanalysis of START-A and the START pilot trial (349 events, 3646 women), provided an adjusted α/β value for localregional relapse of 3·5 Gy (95% CI 1·2–5·7)

- 273 of 392 deaths (69·6%) in START-A were from breast cancer (92 with 50 Gy, 86 with 41.6 Gy, and 95 with 39 Gy),
- 26 (6·6%) were related to cardiac disease only (seven with 50 Gy, 13 with 41·6 Gy, and six with 39 Gy),
- 34 (8·7%) were from other cancers (nine with 50 Gy, ten with 41·6 Gy, and 15 with 39 Gy),
- 44 (11·2%) were from other non-cancer causes (16 with 50 Gy, 16 with 41·6 Gy, and 12 with 39 Gy), and 15 (3·8%) were from unknown cause (six with 50 Gy, three with 41·6 Gy, and six with 39 Gy).
- **15 (57·7%) of the 26 deaths from cardiac disease in START-A were in women with left-sided primary tumours (four of seven with 50 Gy, ten of 13 with 41·6 Gy, and one of six with 39 Gy).**

Distant relapses, disease-free survival, and overall survival were not significantly different between schedules in START-A, START B



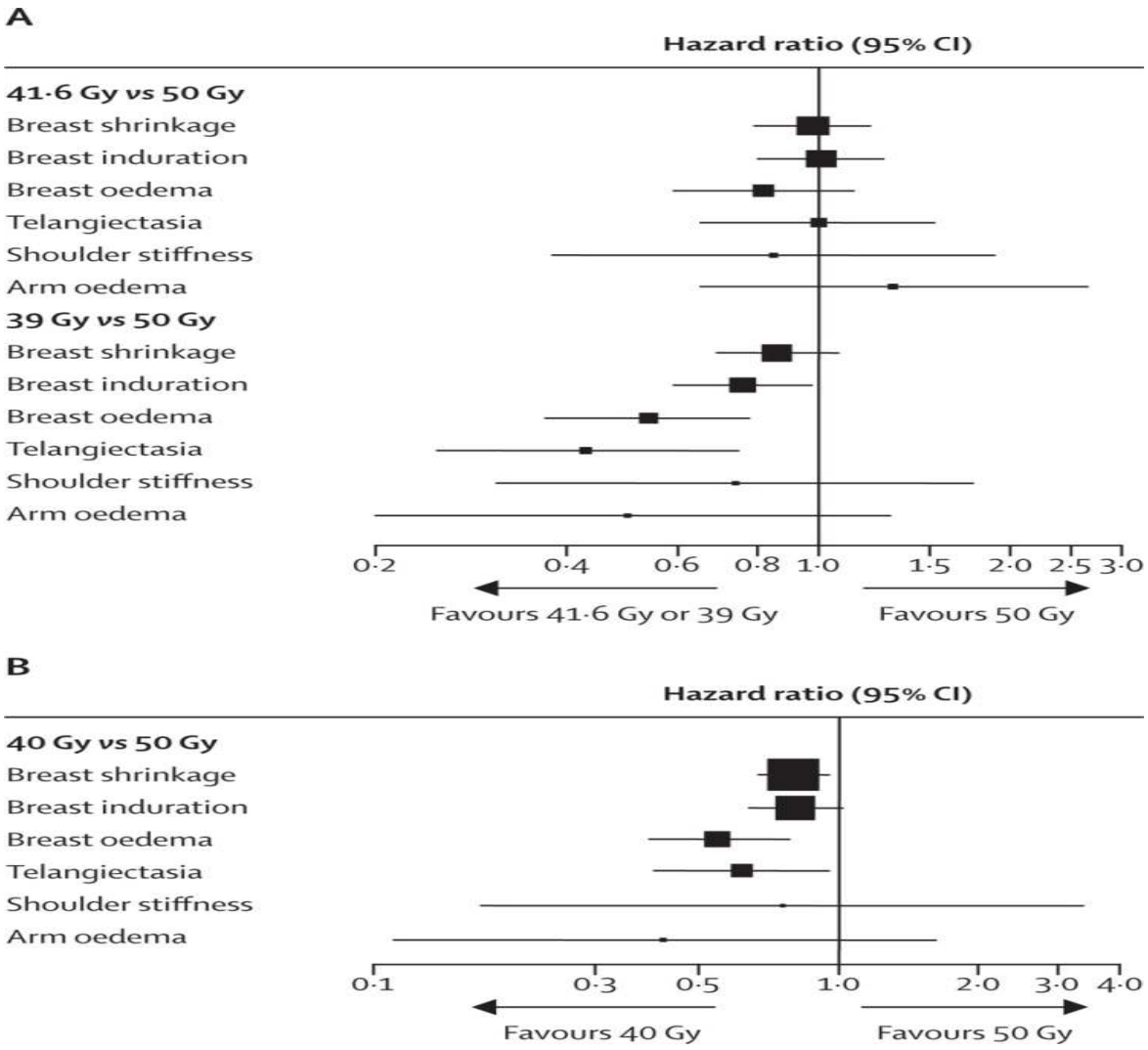
- Breast shrinkage and induration were the most common normal tissue effects at 10 years in START-A
- Moderate or marked breast induration, telangiectasia, and breast oedema were significantly less common in the 39 Gy regimen patients group than in the 50 Gy regimen group

Physician-assessed normal tissue effects by fractionation schedule START-A

	Moderate or marked events (n/patients; %)	Estimated proportion of patients with event by 5 years (%; 95% CI)	Estimated proportion of patients with event by 10 years (%; 95% CI)	Crude hazard ratio (95% CI)	p value*
Breast shrinkage†					
50 Gy	165/616 (26·8%)	14·1% (11·5–17·2)	34·2% (29·8–39·2)	1·00	..
41·6 Gy	168/627 (26·8%)	17·8% (14·9–21·1)	31·4% (27·2–36·0)	0·98 (0·79–1·21)	0·83
39 Gy	140/617 (22·7%)	14·7% (12·0–18·0)	30·0% (25·7–34·8)	0·86 (0·69–1·08)	0·19
Breast induration (tumour bed)†					
50 Gy	142/616 (23·0%)	18·5% (15·6–21·9)	27·1% (23·3–31·3)	1·00	..
41·6 Gy	150/627 (23·9%)	18·9% (16·0–22·3)	28·2% (24·2–32·7)	1·01 (0·80–1·27)	0·95
39 Gy	110/617 (17·8%)	15·0% (12·3–18·3)	21·6% (18·1–25·7)	0·76 (0·59–0·98)	0·034
Telangiectasia					
50 Gy	42/730 (5·7%)	4·3% (3·0–6·1)	7·2% (5·2–9·8)	1·00	..
41·6 Gy	43/733 (5·9%)	4·9% (3·5–6·8)	7·1% (5·2–9·5)	1·00 (0·65–1·53)	0·99
39 Gy	18/723 (2·5%)	1·3% (0·6–2·5)	3·0% (1·8–5·0)	0·43 (0·25–0·75)	0·003
Breast oedema†					
50 Gy	78/616 (12·7%)	12·1% (9·7–15·0)	13·5% (10·9–16·6)	1·00	..
41·6 Gy	67/627 (10·7%)	9·2% (7·1–11·7)	11·8% (9·3–14·8)	0·82 (0·59–1·14)	0·24
39 Gy	43/617 (7·0%)	7·3% (5·5–9·7)	7·3% (5·5–9·7)	0·54 (0·37–0·78)	0·001
Shoulder stiffness‡					
50 Gy	14/117 (12·0%)	8·8% (4·7–16·4)	17·5% (10·2–29·1)	1·00	..
41·6 Gy	10/95 (10·5%)	7·1% (3·3–15·2)	14·8% (8·0–26·6)	0·85 (0·38–1·90)	0·69
39 Gy	8/92 (8·7%)	7·5% (3·4–16·0)	11·0% (5·6–21·0)	0·74 (0·31–1·76)	0·49
Arm oedema‡					
50 Gy	15/117 (12·8%)	12·8% (7·6–21·2)	16·3% (9·9–26·2)	1·00	..
41·6 Gy	16/95 (16·8%)	11·9% (6·6–21·0)	22·5% (14·1–34·7)	1·31 (0·65–2·66)	0·45
39 Gy	6/92 (6·5%)	6·4% (2·7–14·7)	8·2% (3·7–17·6)	0·50 (0·20–1·30)	0·16
Other					
50 Gy	18/729 (2·5%)	1·3% (0·7–2·6)	3·4% (2·1–5·4)	1·00	..
41·6 Gy	20/733 (2·7%)	2·0% (1·2–3·4)	3·7% (2·3–6·1)	1·09 (0·58–2·06)	0·79
39 Gy	24/724 (3·3%)	2·3% (1·4–3·8)	3·9% (2·6–5·9)	1·37 (0·74–2·52)	0·31

*Assessed by Wald test, comparing each schedule with 50 Gy. †Only assessed in women who had breast-conserving surgery. ‡Restricted to women who received lymphatic radiotherapy (to axilla or supraclavicular fossa).

Table 2: **Physician-assessed normal tissue effects by fractionation schedule in START-A**



Moderate or marked normal tissue effects did not differ significantly between 41·6 Gy and 50 Gy groups

α/β

- α/β estimates for normal tissue endpoints in START-A (adjusting for age, breast size, surgical deficit, lymphatic radiotherapy, and tumour bed boost radiotherapy) were 3·5 Gy (95% CI 0·7–6·4) for breast shrinkage
- 4 Gy (2·3–5·6) for breast induration
- 3·8 Gy (1·8–5·7) for telangiectasia
- 4·7 Gy (2·4–7·0) for breast oedema.

	START-A				START-B		
	50 Gy (n=749)	41·6 Gy (n=750)	39 Gy (n=737)	Total (n=2236)	50 Gy (n=1105)	40 Gy (n=1110)	Total (n=2215)
Symptomatic rib fracture*							
Reported	5 (0·7%)	8 (1·1%)	9 (1·2%)	22 (1·0%)	17 (1·5%)	24 (2·2%)	41 (1·9%)
Confirmed†	0	0	1 (0·1%)	1 (<0·1%)	3 (0·3%)	3 (0·3%)	6 (0·3%)
Symptomatic lung fibrosis							
Reported	6 (0·8%)	9 (1·2%)	8 (1·1%)	23 (1·0%)	19 (1·7%)	19 (1·7%)	38 (1·7%)
Confirmed†	0	2 (0·3%)	1 (0·1%)	3 (0·1%)	2 (0·2%)	8 (0·7%)	10 (0·5%)
Ischaemic heart disease‡							
Reported	14 (1·9%)	11 (1·5%)	8 (1·1%)	33 (1·5%)	23 (2·1%)	17 (1·5%)	40 (1·8%)
Confirmed†							
Total	7 (0·9%)	5 (0·7%)	6 (0·8%)	18 (0·8%)	16 (1·4%)	8 (0·7%)	24 (1·1%)
Left sided	4 (0·5%)	1 (0·1%)	4 (0·5%)	9 (0·4%)	5 (0·5%)	4 (0·4%)	9 (0·4%)
Brachial plexopathy	0	1 (0·1%)	0	1 (<0·1%)	0	0	0

Data are n (%). *Reported cases include seven after trauma (five in START-A, two in START-B), and ten after metastases (five in START- A and five in START-B). †After imaging and further investigations. ‡26 patients in START-A and 22 in START-B had pre-existing heart disease at enrolment and were excluded.

***Table 3*: Incidence of other late adverse effects according to fractionation schedule**

Ischaemic heart disease, symptomatic rib fracture, and symptomatic lung fibrosis were rare at 10 years

START-B

- 2215 women were recruited into START-B between Jan 4, 1999, and Oct 12, 2001
- Median age was 57 years (range 23–86).
- 2038 of 2215 (92%) - BCS
- 1412 (64%) had tumours smaller than 2 cm, 504 (23%) had positive lymph nodes, 1667 (75%) had grade 1 or 2 disease, 491 (22%) received adjuvant chemotherapy, 1928 (87%) received tamoxifen, and 161 (7%) received lymphatic radiotherapy.
- 868 of 2038 (43%) tumour bed boost radiotherapy.

STATISTICS – START B

- At a median follow-up in survivors of 9·9 years (IQR 7·5–10·1, maximum 12·5 years), 1732 of 2215 (78·2%) patients were alive and without relapse
- 50 (2·3%) were alive with local-regional relapse (without distant relapse)
- 63 (2·8%) were alive with distant relapse (including ten with local-regional relapse)
- 351 (15·8%) had died (including 35 with local-regional relapse)
- 19 (0·9%) had no follow-up.

- At the time of the analysis, 95 of 2215 (4·3%) patients in START-B had local-regional tumour relapse, a lower proportion than in START-A, which is probably a result of the slightly better prognosis of patients recruited into START-B compared with START-A.

	Events (n/patients; %)	Estimated proportion of patients with event by 5 years (%; 95% CI)	Estimated proportion of patients with event by 10 years (%; 95% CI)	Crude hazard ratio (95% CI)	p value*
Local relapse					
50 Gy	50/1105 (4·5%)	3·3% (2·4–4·6)	5·2% (3·9–6·9)	1·00	..
40 Gy	36/1110 (3·2%)	1·9% (1·2–3·0)	3·8% (2·7–5·2)	0·70 (0·46–1·07)	0·10
Local-regional relapse					
50 Gy	53/1105 (4·8%)	3·5% (2·5–4·8)	5·5% (4·2–7·2)	1·00	..
40 Gy	42/1110 (3·8%)	2·3% (1·5–3·4)	4·3% (3·2–5·9)	0·77 (0·51–1·16)	0·21
Distant relapse					
50 Gy	158/1105 (14·3%)	10·5% (8·8–12·5)	16·0% (13·8–18·5)	1·00	..
40 Gy	121/1110 (10·9%)	7·5% (6·0–9·2)	12·3% (10·3–14·6)	0·74 (0·59–0·94)	0·014
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

*Assessed with log-rank test compared with 50 Gy. †Local, regional, or distant relapse, breast cancer death, contralateral breast cancer.

Table 4: **Relapse and mortality according to fractionation schedule in START-B**

HR for local-regional relapse for the 40 Gy schedule compared with the 50 Gy schedule was 0·77

- The KaplanMeier and cumulative hazard rate plots for local-regional relapse according to fractionation schedule show the low number of recurrences in both randomised groups in START-B.

- 236 of 351 (67·2%) deaths in START-B were from breast cancer (130 with 50 Gy and 106 with 40 Gy)
- 17 (4·8%) were related to cardiac disease only (12 with 50 Gy and five with 40 Gy), 48 (13·7%) were from other cancers (25 with 50 Gy and 23 with 40 Gy), 40 (11·4%) were from other noncancer causes (21 with 50 Gy and 19 with 40 Gy), and ten (2·8%) were from unknown cause (four with 50 Gy and six with 40 Gy).
- 11 (64·7%) of the 17 deaths from cardiac disease were in women with left-sided primary tumours (eight of 12 with 50 Gy and three of five with 40 Gy).
- **There were significantly fewer distant relapses up to 10 years in the 40 Gy group (HR 0·74, 95% CI 0·59–0·94), which contributed to the significantly higher rates of DFS & OS**

- Breast shrinkage ,induration - most common late normal tissue effects at 10 years START B
- Moderate or marked breast shrinkage, telangiectasia, and breast oedema were significantly lower with 40 Gy than with 50 Gy
- Ischaemic heart disease, symptomatic rib fracture, and symptomatic lung fibrosis were rare and occurred in much the same proportions with each treatment schedule

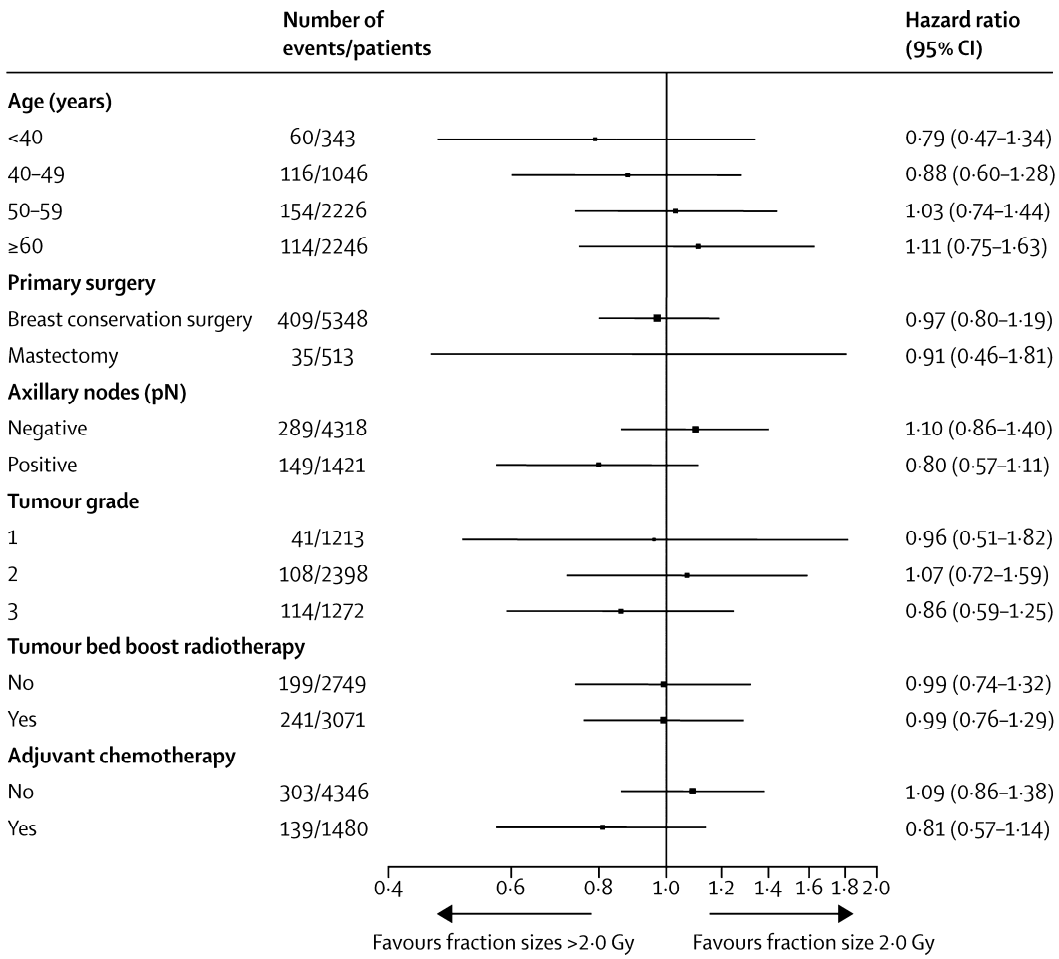
Discussion

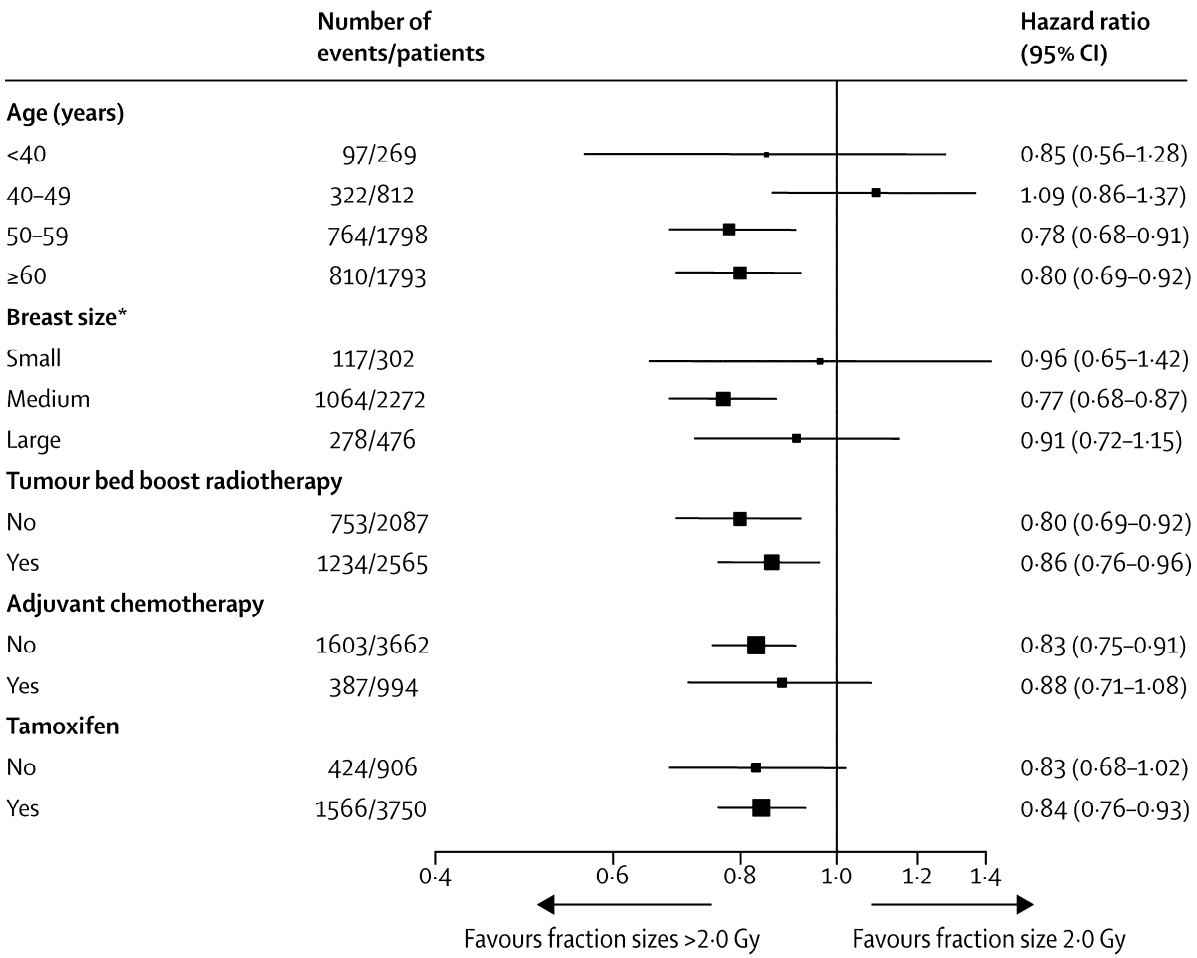
- control schedules at 10 years remain similar to those at 5 years, confirming that appropriately dosed hypofractionated radiotherapy for women with early breast cancer is safe and effective
- The 10-year results of START-B confirm that 40 Gy in 15 fractions over 3 weeks is at least as safe and effective as 50 Gy in 25 fractions over 5 weeks.

- normal tissue effects were less common after the 15 fraction regimen than the control schedule
- Application of an α/β value of 3·5 Gy for breast shrinkage as obtained from START-A and assuming no effect of treatment time on late normal tissue effects, 40 Gy in 15 fractions corresponds to 45 Gy in 2 Gy equivalents.
- The 15 fraction regimen is less harmful to normal tissues, and there is no suggestion that it is less effective in treating the cancer.

- Data from the START trials are consistent with the 10-year results of the Ontario trial, which reported that local tumour control and breast cosmesis were no worse with a regimen of 42·5 Gy in 16 fractions over 3·2 weeks compared with 50 Gy in 25 fractions over 5 weeks

- The corollary is that the continued use of small (2 Gy) fractions spares the cancer as much as the normal tissues, thereby bringing no benefit to patients.
- The unexpected survival benefit with the 40 Gy schedule at 5 years in START-B still exists at 10 years


Number of events/patients
Hazard ratio (95% CI)
Age (years)
<40
60/343
0·79 (0·47–1·34)
40–49
116/1046
0·88 (0·60–1·28)
50–59
154/2226
1·03 (0·74–1·44)
≥60
114/2246
1·11 (0·75–1·63)
Primary surgery
Breast conservation surgery
409/5348
0·97 (0·80–1·19)
Mastectomy
35/513
0·91 (0·46–1·81)
Axillary nodes (pN)
Negative
289/4318
1·10 (0·86–1·40)
Positive
149/1421
0·80 (0·57–1·11)
Tumour grade
1
41/1213
0·96 (0·51–1·82)
2
108/2398
1·07 (0·72–1·59)
3
114/1272
0·86 (0·59–1·25)
Tumour bed boost radiotherapy
No
199/2749
0·99 (0·74–1·32)
Yes
241/3071
0·99 (0·76–1·29)
Adjuvant chemotherapy
No
303/4346
1·09 (0·86–1·38)
Yes
139/1480
0·81 (0·57–1·14)
0·4
0·6
0·8
1·0
1·2
1·4
1·6
1·8
2·0
Favours fraction sizes >2·0 Gy
Favours fraction size 2·0 Gy


Number of events/patients
Hazard ratio (95% CI)
Age (years)
<40
97/269
0·85 (0·56–1·28)
40–49
322/812
1·09 (0·86–1·37)
50–59
764/1798
0·78 (0·68–0·91)
≥60
810/1793
0·80 (0·69–0·92)
Breast size*
Small
117/302
0·96 (0·65–1·42)
Medium
1064/2272
0·77 (0·68–0·87)
Large
278/476
0·91 (0·72–1·15)
Tumour bed boost radiotherapy
No
753/2087
0·80 (0·69–0·92)
Yes
1234/2565
0·86 (0·76–0·96)
Adjuvant chemotherapy
No
1603/3662
0·83 (0·75–0·91)
Yes
387/994
0·88 (0·71–1·08)
Tamoxifen
No
424/906
0·83 (0·68–1·02)
Yes
1566/3750
0·84 (0·76–0·93)
0·4
0·6
0·8
1·0
1·2
1·4
Favours fraction sizes >2·0 Gy
Favours fraction size 2·0 Gy

- **UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer**
- At 3years median follow-up, 28.5Gy in 5 fractions is comparable to 50Gy in 25 fractions, and significantly milder than 30Gy in 5 fractions, in terms of adverse effects in the breast.

- The **START pilot trial, Ontario trial, and START-A and START-B trials,** considered together, present robust evidence that hypofractionation is a safe and effective approach to breast cancer radiotherapy

Controversy

- Whether or not a **tumour bed boost** radiotherapy was given did not alter the eff ect of hypofractionation on risk of late normal tissue eff ects, and tumour bed boost radiotherapy could not have a confounding effect because it was prescribed before randomisation and was given to similar proportions of patients in each treatment schedule group
- concerns have been raised about doses to the heart with hypofractionated schedules.

- Treatment of the SCF & axilla is another aspect that is often approached conservatively, despite the fact that even a dose of 40 Gy in 15 fractions at the level of the brachial plexus delivers the equivalent of 46·7 Gy, 47·6 Gy, and 48·9 Gy in 2·0 Gy equivalents, assuming α/β values of 2·0 Gy, 1·5 Gy, and 1.0 Gy, respectively
- In other words, 40 Gy in 15 fractions is less damaging to the brachial plexus than is 50 Gy in 25 fractions, even under extreme assumptions about the fractionation sensitivity of the nervous system.

THANK YOU