

Hypofractionated radiotherapy for the treatment of early breast cancer: a systematic review

November 2011

Hypofractionated radiotherapy for the treatment of early breast cancer: a systematic review was developed by:

Cancer Australia
Locked Bag 3 Strawberry Hills NSW 2012 Australia
Tel: +61 2 9357 9400 Fax: +61 2 9357 9477
Website: www.canceraustralia.gov.au

© Cancer Australia 2011
ISBN Online: 978-1-74127-180-5

Recommended citation

Cancer Australia. Hypofractionated radiotherapy for the treatment of early breast cancer: a systematic review. National Breast and Ovarian Cancer Centre, Surry Hills, NSW, 2011

Copyright statements:

Paper-based publications

This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given the specific written permission from Cancer Australia to do so. Requests and inquiries concerning reproduction and rights are to be sent to the Publications and Copyright contact officer, Cancer Australia, Locked Bag 3, Strawberry Hills, NSW 2012.

Internet sites

This work is copyright. You may download, display, print and reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given the specific written permission from Cancer Australia to do so. Requests and inquiries concerning reproduction and rights are to be sent to the Publications and Copyright contact officer, Cancer Australia, Locked Bag 3, Strawberry Hills, NSW 2012

Copies of Hypofractionated radiotherapy for the treatment of early breast cancer: a systematic review can be downloaded from the Cancer Australia website: www.canceraustralia.gov.au.

Acknowledgments

This report was prepared on behalf of National Breast and Ovarian Cancer Centre (NBOCC)* by Lisa Elliott, Gregory Merlo and Adele Watson of Health Technology Analysts.

NBOCC gratefully acknowledges the contribution of the Hypofractionated Radiotherapy Working Group, chaired by Associate Professor Boon Chua (see Appendix A).

Funding

Funding for the development of this systematic review was provided by the Australian Government Department of Health and Ageing.

*On 1 July 2011, National Breast and Ovarian Cancer Centre (NBOCC) amalgamated with Cancer Australia to form a single national agency, Cancer Australia, to provide leadership in cancer control and improve outcomes for Australians affected by cancer.

Contents

Executive summary	ix
1 Introduction	1
2 Method	3
2.1 Criteria for determining study eligibility	3
2.2 Literature search methodology	3
2.3 Assessment of study eligibility	6
2.4 Included trials.....	7
2.5 Appraisal of included trials	8
2.6 Limitations of the review	10
3 Description of included studies	12
3.1 Systematic reviews	12
3.2 Primary studies	13
4 Results of included trials	23
4.1 Local recurrence	23
4.2 Local-regional recurrence	28
4.3 Distant relapse	30
4.4 Overall survival	32
4.5 Adverse events and toxicity	35
4.6 Cosmetic outcome	41
4.7 Quality of life	54
5 Guidelines	58
5.1 Guidelines search	58
5.2 Results.....	58
6 Conclusions	63
7 References	65
Appendix A Contributors	67

Tables

Table 1	Summary of key results for local recurrence.....	x
Table 2	Summary of key results for regional recurrence	xi
Table 3	Summary of key results for distant relapse	xi
Table 4	Summary of key results for overall survival	xii
Table 5	Summary of key results for adverse events and toxicity	xiii
Table 6	Summary of key results for adverse cosmetic outcomes.....	xiv
Table 7	Criteria for determining study eligibility	3
Table 8	Search strategy.....	5
Table 9	Exclusion criteria.....	6
Table 10	Included and excluded citations.....	7
Table 11	Included systematic reviews	8
Table 12	Included RCTs	8
Table 13	NHMRC Dimensions of evidence ²¹	9
Table 14	NHMRC Interim Levels of Evidence (NHMRC 2009) for evaluating interventions and diagnostic accuracy studies ²²	9
Table 15	Quality criteria for different levels of evidence ²¹	10
Table 16	Reporting biases in systematic reviews ²³	11
Table 17	Key characteristics of included studies	14
Table 18	RMH/GOC trial: Demographic and clinical characteristics of 1410 patients randomised ⁸	16
Table 19	Canadian trial: Patient characteristics ⁷	17
Table 20	START A: Patient characteristics ⁴	19
Table 21	START B: Patient characteristics ⁵	21
Table 22	RMH/GOC trial: Survival analysis of local relapse according to fractionation schedule ¹	23
Table 23	START A: Survival analyses of relapse and mortality according to fractionation schedule (Local relapse) ⁴	27
Table 24	START B: Survival analyses of relapse and mortality according to fractionation schedule (local relapse) ⁵	27
Table 25	Summary of key results for local recurrence.....	28
Table 26	START A: Survival analyses of relapse and mortality according to fractionation schedule (Local-regional relapse) ⁴	29
Table 27	START B: Survival analyses of relapse and mortality according to fractionation schedule (Local-regional Relapse) ⁵	29
Table 28	Summary of key results for local-regional recurrence ⁴⁻⁵	30
Table 29	START A: Survival analyses of relapse and mortality according to fractionation schedule (Distant relapse) ⁴	30
Table 30	START B: Survival analyses of relapse and mortality according to fractionation schedule (Distant relapse) ⁵	31

Table 31	Summary of key results for distant relapse ⁴⁻⁵	31
Table 32	Canadian trial: Cause of deaths ²	33
Table 33	START A: Survival analyses of relapse and mortality according to fractionation schedule (All-cause mortality) ⁴	33
Table 34	START B: Survival analyses of relapse and mortality according to fractionation schedule (All-cause mortality) ⁵	34
Table 35	Summary of key results for overall survival.....	34
Table 36	Canadian trial: Late toxic effects of radiation, assessed according to the RTOG-EORTC late radiation morbidity scoring scheme ^{a2}	35
Table 37	START A: Incidence of ischemic heart disease, symptomatic rib fracture, and symptomatic lung fibrosis according to fractionation schedule ⁴	36
Table 38	START A: Contralateral and other secondary cancers ⁴	36
Table 39	START B: Incidence of ischemic heart disease, symptomatic rib fracture, and symptomatic lung fibrosis according to fractionation schedule ⁵	37
Table 40	START B: Contralateral and other secondary cancers ⁵	37
Table 41	Summary of key results for adverse events and toxicity	40
Table 42	RMH/GOC trial: Survival analyses of change in breast appearance and clinical assessments of late radiation effects according to fractionation schedule ⁸	44
Table 43	START A AND B: Survival analyses of moderate or marked grade normal tissue effects from patients' self-assessments, according to fractionation schedule, type of primary surgery ⁶	46
Table 44	Canadian trial: Global cosmetic outcome assessed according to the EORTC scale ^{a2}	47
Table 45	START A AND B: Survival analyses of moderate or marked grade normal tissue effects from patients' self-assessments according to fractionation schedule, type of primary surgery ⁶	48
Table 46	START A: Mild or marked change in breast appearance ⁴	49
Table 47	START B: Mild or marked change in breast appearance ⁵	50
Table 48	Summary of key results for cosmetic outcomes.....	53
Table 49	START A AND B: Breast, arm, or shoulder symptoms and body image scale scores at 5 years ^a according to radiotherapy regimen, type of primary surgery ⁶	55
Table 50	START A AND B: Breast, arm, or shoulder symptoms and body image scale scores at 5 years ^a according to radiotherapy regimen, type of primary surgery ⁶	56
Table 51	START A AND B: Breast, arm, or shoulder symptoms and body image scale scores, according to radiotherapy regimen, over time from randomisation ⁶	57
Table 52	Search terms for guidelines websites	58

Figures

Figure 1	RMH/GOC trial: Local ipsilateral relapse in the breast according to fractionation schedule ¹	24
Figure 2	Canadian trial: Kaplan-Meier estimates for local recurrence ^{a2}	25
Figure 3	Canadian trial: Hazard ratios for Ipsilateral recurrence of breast cancer in subgroups of patients ²	26
Figure 4	Canadian trial: Kaplan-Meier estimate for overall survival ²	32
Figure 5	START A AND B: Forest plots of normal tissue effects assessed as moderate or marked by patients, according to radiotherapy regimens ⁶	39
Figure 6	RMH/GOC trial: Probability of any change in breast appearance late radiation effect ten years after radiotherapy by fractionation schedule ⁸	42
Figure 7	RMH/GOC trial: Probability of marked change in breast appearance late radiation effect ten years after radiotherapy by fractionation schedule ⁸	42
Figure 8	RMH/GOC trial: Probability of palpable breast induration ten years after radiotherapy by fractionation schedule ⁸	43
Figure 9	START A: Kaplan-Meier plot of mild/marked change in breast appearance (photographic) in 1055 patients with breast conserving surgery ⁴	49
Figure 10	START B: Kaplan-Meier plot of mild/marked change in breast appearance (photographic) in 923 patients with breast conserving surgery ⁵	50
Figure 11	START A AND B: Forest plots of normal tissue effects assessed as moderate or marked by patients, according to radiotherapy regimen ⁶	52

Executive summary

Introduction and methods

This review was commissioned by the National Breast and Ovarian Cancer Centre (NBOCC)*. The use of hypofractionated radiotherapy in early breast cancer has been identified as a topic for evidence review and guideline recommendation development. The following clinical question was selected as the focus of the systematic literature review:

What are the key outcomes associated with different dose fractionation (dosage/scheduling) for radiotherapy treatment of early (invasive) breast cancer?

A systematic method of literature searching and selection was employed in the preparation of this review. Searches were conducted in EMBASE and Medline (via EMBASE.com) and the Cochrane Database of Systematic Reviews to identify citations published between January 2001 and March 2010. A search of conference websites was also conducted. These were the American Society of Clinical Oncology, American Society of Radiation Oncology and San Antonio Breast Cancer Symposium. A total of 682 non-duplicate citations were identified. The exclusion criteria was applied to all citations, with a total of 10 publications meeting the inclusion criteria.

Key findings

Local recurrence

All five included trials reported local recurrence (RMH/GOC, Canadian, Spooner, START A and START B) (see Table 1). There was no evidence that any hypofractionated radiotherapy regimen was associated with a statistically significant difference in local recurrence rate when compared with a control arm. The Royal Marsden Hospital/Gloucester Oncology Centre (RMH/GOC) trial noted a statistically significant difference in recurrence rates when the two hypofractionated radiotherapy regimens were compared (42.9 Gy vs 39 Gy: 9.6% vs 14.8%, $p=0.027$), but not when each regimen was compared to the control arm (50 Gy in 25 fractions).¹

Subgroup analyses were performed in the Canadian trial.² There were no significant differences in any subgroup, with the exception of tumour grade. The impact of the 42.5 Gy regimen on local recurrence was less in patients with high-grade tumours compared to patients with low-grade tumours ($p=0.01$).²

* On 1 July 2011, National Breast and Ovarian Cancer Centre (NBOCC) amalgamated with Cancer Australia to form a single national agency, Cancer Australia, to provide leadership in cancer control and improve outcomes for Australians affected by cancer.

Table 1 Summary of key results for local recurrence

Study ID	Study arms	Results
Post breast conserving surgery		
RMH/GOC ¹	39 Gy in 13 fractions over 5 weeks 42.9 Gy in 13 fractions over 5 weeks 50 Gy in 25 fractions over 5 weeks*	5 year local recurrence 39 Gy vs 50 Gy: 9.1% vs 7.9%, p=NR 42.9 Gy vs 50 Gy: 7.1% vs 7.9%, p=NR 42.9 Gy vs 39 Gy: 7.1% vs 9.1%, p=NR 10 year local recurrence 39 Gy vs 50 Gy: 14.8% vs 12.1%, p=NS 42.9 Gy vs 50 Gy: 9.6% vs 12.1%, p=NS 42.9 Gy vs 39 Gy: 9.6% vs 14.8%, p=0.027 39 Gy: HR 1.33 (95% CI 0.92, 1.92), p=NS 42.9 Gy: HR 0.86 (95% CI 0.57, 1.30), p=NS
Canadian ²	42.5 Gy in 16 fractions over 22 days 50 Gy in 25 fractions over 35 days*	10 year cumulative incidence of local recurrence 42.5 Gy vs 50 Gy: 6.2% vs. 6.7%, p=NS 10 year cumulative incidence of invasive or non-invasive local recurrence 42.5 Gy vs 50 Gy: 7.4% vs. 7.5%, p=NS Subgroup analyses Patient age, tumour size, oestrogen-receptor status, tumour grade, systemic therapy, p=NS High-grade vs low grade tumours, p=0.01
Any surgery		
Spooner ³	40 Gy in 15 fractions once a day 50 Gy in 25 fractions once a day Delayed salvage treatment	17 year relapse frequency No difference, data not reported
START A ⁴	39 Gy in 13 fractions over 5 weeks 41.6 Gy in 13 fractions over 5 weeks 50 Gy in 25 fractions over 5 weeks*	5 year local relapse rate 50 Gy vs 41.6 Gy vs 39 Gy: 3.2% vs 3.2% vs 4.6%, p=NR 5 year local relapse 39 Gy: HR 1.25 (95% CI 0.74, 2.12), p=0.40 41.6 Gy: HR 1.09 (95% CI 0.64, 1.88), p=0.74
START B ⁵	40 Gy in 15 fractions over 3 weeks 50 Gy in 25 fractions over 5 weeks*	5 year local relapse rate 50 Gy vs 40 Gy: 3.3% vs 2.0%, p=NR 5 year local relapse 40 Gy: HR 0.72 (95% CI 0.43, 1.21), p=0.21

Abbreviations: CI=confidence interval, HR=hazard ratio, NR=not reported, NS=not significant

* control arm

Local-regional recurrence

The Standardisation of Breast Radiotherapy Trials A and B (START A and START B) reported regional recurrence (see Table 2).⁴⁻⁵ There was no evidence that any hypofractionated radiotherapy regimen was associated with a statistically significant difference in local recurrence rate when compared with 50 Gy in 25 fractions over 5 weeks (control).

Table 2 Summary of key results for regional recurrence

Study ID	Study arms	Results
Any surgery		
START A ⁴	39 Gy in 13 fractions over 5 weeks 41.6 Gy in 13 fractions over 5 weeks 50 Gy in 25 fractions over 5 weeks*	5 year local-regional relapse rate 50 Gy vs 41.6 Gy vs 39 Gy: 3.6% vs 3.5% vs 5.2%, p=NR 5 year local-regional relapse 39 Gy: HR 1.26 (95% CI 0.77, 2.08), p=0.35 41.6 Gy: HR 1.05 (95% CI 0.63, 1.75), p=0.86
START B ⁵	40 Gy in 15 fractions over 3 weeks 50 Gy in 25 fractions over 5 weeks*	5 year local-regional relapse rate 50 Gy vs 40 Gy: 3.3% vs 2.2%, p=NR 5 year local-regional relapse 40 Gy: HR 0.79 (95% CI 0.48, 1.29), p=0.35

Abbreviations: CI=confidence interval; HR=hazard ratio; NR=not reported
* control arm

Distant relapse

Two trials reported distant relapse (START A and START B) (see

Table 3).⁴⁻⁵ In START A, there was no statistical difference between either of the hypofractionated regimens compared with the control arm.⁴ START B reported that the 40 Gy study arm had a statistically significantly lower rate of distant relapse when compared with the control arm (HR 0.69 95% CI 0.53, 0.91, p=0.01).⁵

Table 3 Summary of key results for distant relapse

Study ID	Study arms	Results
Any surgery		
START A ⁴	39 Gy in 13 fractions over 5 weeks 41.6 Gy in 13 fractions over 5 weeks 50 Gy in 25 fractions over 5 weeks*	5 year distant relapse rate 50 Gy vs 41.6 Gy vs 39 Gy: 9.8% vs 9.5% vs 11.9%, p=NR 5 year local-regional relapse 39 Gy: HR 1.29 (95% CI 0.95, 1.76), p=0.10 41.6 Gy: HR 0.92 (95% CI 0.66, 1.28), p=0.64
START B ⁵	40 Gy in 15 fractions over 3 weeks 50 Gy in 25 fractions over 5 weeks*	5 year local-regional relapse rate 50 Gy vs 40 Gy: 10.2% vs 7.6%, p=NR 5 year local-regional relapse 40 Gy: HR 0.69 (95% CI 0.53, 0.91), p=0.01

Abbreviations: CI=confidence interval; HR=hazard ratio; NR=not reported
* control arm

Overall survival

A total of four trials reported overall survival (RMH/GOC, Spooner, START A and START B) (see Table 4).²⁻⁵ Most studies reported that there was no evidence that hypofractionated radiotherapy was associated with a statistically significantly difference in overall survival. START B found that 40 Gy in 15 fractions over three weeks was associated with a statistically significantly lower all-cause mortality rate when compared with 50 Gy in 25 fractions over five weeks (HR 0.76 95% CI

0.59, 0.98, p=0.03).⁵ Therefore, there was no evidence that any hypofractionated radiotherapy regimen was associated with a worse overall survival rate (i.e. the only study that reported a significant difference showed lower mortality for patients treated with hypofractionated radiotherapy).

Table 4 Summary of key results for overall survival

Study ID	Study arms	Results
Post breast conserving surgery		
Canadian ²	42.5 Gy in 16 fractions over 22 days 50 Gy in 25 fractions over 35 days*	10 year survival 42.5 Gy vs 50 Gy: 84.6% vs 84.4%, p=0.79
Any surgery		
Spooner ³	40 Gy in 15 fractions once a day 50 Gy in 25 fractions once a day	17 year survival No difference, data not reported
START A ⁴	39 Gy in 13 fractions over 5 weeks 41.6 Gy in 13 fractions over 5 weeks 50 Gy in 25 fractions over 5 weeks*	5 year all cause mortality 39 Gy: HR 1.00 95% CI 0.74, 1.36, p=0.99 41.6 Gy: HR 1.04 95% CI 0.77, 1.40, p=0.81
START B ⁵	40 Gy in 15 fractions over 3 weeks 50 Gy in 25 fractions over 5 weeks*	5 year all cause mortality 40 Gy: HR 0.76 95% CI 0.59, 0.98, p=0.03

Abbreviations: CI=confidence interval, HR=hazard ratio

* control arm

Adverse events and toxicity

A total of three trials reported adverse events and toxicity outcomes (Canadian, START A and START B) (see Table 5).^{2, 4-5} Most studies reported that there was no difference in adverse events and toxicity. Combined results from the START A and START B trials found that a change in skin appearance occurred significantly less often in the 39 Gy and 40 Gy arms when compared with the control arm (39 Gy HR 0.63 95% CI 0.47, 0.84, p=0.0019 and 40 Gy HR 0.76 95% CI 0.60, 0.97, p=0.0262).⁶

Table 5 Summary of key results for adverse events and toxicity

Study ID	Study arms	Results
Post breast conserving surgery		
Canadian ²	42.5 Gy in 16 fractions over 22 days 50 Gy in 25 fractions over 35 days*	Late toxic radiation effects, : NS
Any surgery		
START A ⁴	39 Gy in 13 fractions over 5 weeks 41.6 Gy in 13 fractions over 5 weeks 50 Gy in 25 fractions over 5 weeks*	Ischemic heart disease, symptomatic rib fracture, symptomatic lung fibrosis, contralateral breast cancer, other secondary primary cancers: NS
START B ⁵	40 Gy in 15 fractions over 3 weeks 50 Gy in 25 fractions over 5 weeks*	Ischemic heart disease, symptomatic rib fracture, symptomatic lung fibrosis, contralateral breast cancer, other secondary primary cancers: NS
Combined QoL data from START A and B ⁶	As for START A and START B	Tissue effects, arm and shoulder symptoms: NS Skin appearance: 39 Gy HR 0.63 (95% CI 0.47, 0.84), p=0.0019 40 Gy HR 0.76 (95% CI 0.60, 0.97), p=0.0262

Abbreviations: CI=confidence interval, HR=hazard ratio, NS=not significant

* control arm

a Assessed 3, 5, and 10 years after randomisation

Cosmetic outcome

A total of four trials reported cosmetic outcome (RMH/GOC, Canadian, START A and START B) (see Table 6).^{2, 4-5, 7-8} There was no statistically significant difference in the majority of cosmetic outcomes assessed by the included publications. RMH/GOC reported that the risk of developing any late radiation effect was statistically significantly lower for patients in the 39 Gy arm compared to the 50 Gy arm (p=0.01). For most clinically assessed breast and arm outcomes estimated at 10 years, compared to the 50 Gy arm, there were fewer events for patients in the 39 Gy arm and more in the 42.9 Gy arm.

The START A trial reported that the 39 Gy arm was associated with significantly less mild or marked change in photographic breast appearance by photographic assessment (HR 0.69 95% CI 0.52, 0.91, p=0.01),⁴ and change in skin appearance by patient self-assessment (HR 0.63 95% CI 0.47, 0.84, p=0.0019).⁶ The 40 Gy arm of the START B trial was associated with significantly less change in skin appearance by patient self assessment (40 Gy: HR 0.76 95% CI 0.60, 0.97, p=0.0262).⁶

In subgroup analyses for the START A and START B trials, the relative effects of the randomised radiation schedules on patient reported symptoms did not vary significantly according to type of primary surgery (breast conserving surgery or mastectomy).⁶

Table 6 Summary of key results for adverse cosmetic outcomes

Study ID	Study arms	Results
Post breast conserving surgery		
RMH/GOC ⁸	39 Gy in 13 fractions over 5 weeks 42.9 Gy in 13 fractions over 5 weeks 50 Gy in 25 fractions over 5 weeks*	39 Gy: adverse cosmetic outcomes were reported less frequently when compared to the 50 Gy arm (p=0.01) 42.9 Gy: Cosmetic outcomes were reported more frequently when compared to the 50 Gy arm (p=0.05)
Canadian ^{2,7}	42.5 Gy in 16 fractions over 22 days 50 Gy in 25 fractions over 35 days*	No statistically significant differences in any cosmetic outcome
Any surgery		
START A ⁴	39 Gy in 13 fractions over 5 weeks 41.6 Gy in 13 fractions over 5 weeks 50 Gy in 25 fractions over 5 weeks*	41.6 Gy: No statistically significant differences in any cosmetic outcome 39 Gy: No statistically significant differences in cosmetic outcome, with the exception of mild or marked change in breast appearance (HR 0.69 95% CI 0.52, 0.91, p=0.01)
START B ⁵	40 Gy in 15 fractions over 5 weeks 50 Gy in 25 fractions over 5 weeks*	0.77 (95% CI 0.61-0.98) p=0.02
Combined data from START A and B ⁶	As for START A and START B	Change in skin appearance 39 Gy: HR 0.63 (95% CI 0.47, 0.84), p=0.0019 40 Gy: HR 0.76 (95% CI 0.60, 0.97), p=0.0262 Subgroup analysis by breast conserving surgery and mastectomy: NS

Abbreviations: CI=confidence interval, HR=hazard ratio, NS=not significant
* control arm

Quality of life

A total of two studies reported quality of life outcomes (START A and START B).⁶ There was no evidence that any hypofractionated radiotherapy regimen was associated with a statistically significant difference in quality of life score as measured by the BR23 breast symptom subscale. Subgroup analysis was performed, with results analysed by surgery type. There were no statistically significant differences in outcomes, nor were any interaction tests significant overall.

Guidelines

In order to identify current recommendations in existing radiotherapy guidelines, a systematic search of guidelines was undertaken.

The **American Society for Radiation Oncology (ASTRO)**⁹ reported that evidence supports the equivalence of hypofractionated whole breast irradiation with conventionally fractionated whole breast irradiation for patients who satisfy all these criteria:

- Patient is 50 years or older at diagnosis.
- Pathologic stage is T1-2 N0 and patient has been treated with breast-conserving surgery.
- Patient has not been treated with systemic chemotherapy.

- Within the breast along the central axis, the minimum dose is no less than 93% and maximum dose is no greater than 107% of the prescription dose $\pm 7\%$ (as calculated with 2-dimensional treatment planning without heterogeneity corrections)

For patients who do not satisfy all of these criteria, the task force could not reach consensus and therefore chose not to render a recommendation.⁹

The **New Zealand Ministry of Health guidelines**¹⁰ made the following recommendation regarding hypofractionated radiotherapy:

Recommendation

- Radiotherapy treatment for early invasive breast cancer should use an accepted regimen such as: 50 Gy in 25 fractions over 5 weeks (Grade A[†]), 45 Gy in 20 fractions over 5 weeks (Grade B[‡]), 42.5 Gy in 16 fractions over 3.5 weeks for those with small or medium breasts, not requiring boost or nodal radiation (Grade B[†]), 40 Gy in 15 fractions over 3 weeks (Grade B²)

Good practice points

- If boost radiotherapy is used after a hypofractionated regimen it should be at the standard 2 Gy per fraction
- Women with large breasts and those with significant postoperative induration, oedema, erythema, haematoma or infection should be considered for extended fractionation, with smaller daily doses over 5–6 weeks

The **NICE 2009 guidelines**¹¹ made the following recommendation regarding dose fractionation:

Recommendation

- Use external beam radiotherapy giving 40 Gy in 15 fractions as standard practice for patients with early invasive breast cancer after breast conserving surgery or mastectomy.

Qualifying statement: This recommendation is based on RCT evidence of clinical effectiveness and the guideline development group agreeing that a regimen using fewer fractions would probably be cost effective.

The **Scottish Intercollegiate Guidelines Network (SIGN)**¹² management of breast cancer in women guidance paper was developed in 2005, prior to the publication of a number of key RCTs (such as the START trials). No formal recommendations were made.

[†] ie, body of evidence can be trusted to guide practice.

[‡] ie, body of evidence can be trusted to guide practice in most situations

1 Introduction

Aim

This review was commissioned by the National Breast and Ovarian Cancer Centre (NBOCC), Australia's national authority and source of evidence-based information on breast and ovarian cancer. In 2001, NBOCC published the second edition of the "Clinical practice guidelines for the management of early breast cancer"¹³ which replaced the first edition released in 1995. NBOCC's approach to maintaining the currency of these guidelines is to produce timely topic-specific guideline recommendations in key areas of changing evidence.

Based on input from a multidisciplinary Steering Committee and additional consultation by NBOCC, the use of hypofractionated radiotherapy in early breast cancer was identified as a topic for evidence review and guideline recommendation development. The Hypofractionated Radiotherapy Working Group selected the following clinical question as the focus of the systematic literature review:

What are the key outcomes associated with different dose fractionation (dosage/scheduling) for radiotherapy treatment of early (invasive) breast cancer?

In order to answer this clinical question, a systematic literature search was conducted. The methods and results are described in detail in the following sections.

Radiotherapy for treatment of early breast cancer

Early breast cancer has been defined as tumours of not more than five centimetres diameter, with either impalpable or palpable but not fixed lymph nodes and with no evidence of distant metastases.¹³ This corresponds to tumours that are T1-2, N0-1, M0 as currently defined by the International Union Against Cancer (UICC).⁷

Early breast cancer can be treated with a range of therapies including surgery, radiotherapy and systematic adjuvant therapy. A recent Cochrane Review noted that over the last three decades standard management practices have changed.¹⁴ Previously, most women with early breast cancer underwent removal of the whole breast (mastectomy). However, following a number of clinical studies, breast conserving surgery followed by radiotherapy has become the recommended option for women with early breast cancer.¹³⁻¹⁵

Different tissue types (including malignant tissue types) have different sensitivities to radiation and therefore respond to different radiotherapy fraction sizes. In clinical oncology a model is used in which the sensitivity to fraction size (measured by the degree of tissue damage for normal tissues, and tumour recurrence rates for malignant tumours) is represented by the constants α and β .⁴ The lower the ratio of these constants (expressed in Gy), the greater the effect of fraction size on the tissue. The most appropriate radiotherapy regimen may therefore differ between tissue types. The choice of dose in radiotherapy must balance the risk of local cancer recurrence against the harmful effects on healthy tissues.

In a “standard” whole breast radiotherapy regime, radiation is delivered over a period of 5 to 6 weeks using a standard 2 Gy radiation dose per fraction, in 25 to 30 treatment episodes, to a total dose of 50 to 60 Gy.¹⁴ Some regimens include an additional boost of radiation. In hypofractionated radiotherapy, patients receive fewer fractions, however each fraction contains a larger dose of radiation. Although the dose of each individual fraction is higher than the conventional regimen, the total dose of radiotherapy is lower. Concerns have been raised, however, as to whether shorter fractionation schedules have equivalent outcomes in terms of local tumour control, breast appearance (cosmesis), overall survival, and patient satisfaction. The concern with larger fraction sizes has been raised as radiobiological principles state that the fraction size is the dominant factor in determining late side effects.¹⁴ Higher fraction size could lead to increased scarring and retraction of breast tissue as well as skin atrophy (thinning) and telangiectasia (dilated blood vessels).

Economic considerations

One consequence of the increase in breast conserving surgery and radiotherapy is the extra demand placed on health services.^{14, 16-17} Shorter fractionation schedules have the advantages of using machine and staff time more efficiently and reducing patient inconvenience.¹⁸ Hypofractionated radiotherapy significantly reduce the amount of time that patients require radiotherapy equipment. A reduction of time per patient on the machine of about 50 minutes and 100 minutes for the patients exposed to 35 Gy over two weeks and those exposed to 27 Gy over one week respectively, compared with those exposed to 40 Gy in three weeks has been reported.¹⁸ A cohort study (n=313) conducted in Brisbane’s Princess Alexandra Hospital found that, compared to conventional radiotherapy, hypofractionated radiotherapy was associated with a 26% reduction per patient in the cost to Medicare^{*}.¹⁹

^{*} Dwyer *et al* 2009 is a conference abstract and little detail is provided of the resource utilization. The estimation for the reduction in Medicare cost appears to be based on the inference from the cohort study results that had the entire cohort received hypofractionated radiotherapy, 288 fractions per month would be ‘saved’ and available for treatment in other cancer patients.

2 Method

2.1 Criteria for determining study eligibility

The criteria for determining study eligibility are shown in Table 7. Publications were eligible for inclusion in the systematic literature review if they described a randomised controlled trial (RCT) which recruited women with early (invasive) breast cancer and patients treated by breast conserving surgery or total mastectomy.

Hypofractionated radiotherapy was defined by the Hypofractionated Radiotherapy Working Group as ‘giving larger doses of radiotherapy per fraction, but giving fewer fractions compared with standard radiotherapy’. RCTs must have compared hypofractionated radiotherapy with either standard radiotherapy, or an alternative regimen of hypofractionated radiotherapy.

The following outcomes were extracted from the publications: 1) local recurrence, 2) overall survival, 3) adverse events, 4) toxicity, 5) cosmetic outcome and 6) quality of life (assessed using a quality of life instrument). Results for subgroups were extracted where available. The pre-defined subgroups were age, breast size/width, tumour grade, nodal status, surgical margins, use in conjunction with nodal irradiation, post breast conserving surgery and total mastectomy.

Table 7 Criteria for determining study eligibility

Study design	Randomised, controlled trials
Population	Women with early (invasive) breast cancer treated with surgery
Intervention	Hypofractionated radiotherapy
Comparator	1. Standard radiotherapy 2. Other regimens of hypofractionated radiotherapy
Outcomes ^a	1. Local recurrence 2. Overall survival 3. Adverse events 4. Toxicity (including burns and blisters) 5. Cosmetic outcome 6. Quality of life (assessed using a quality of life instrument)

^a The predefined subgroups were: age, breast size/width, tumour grade, nodal status, surgical margins, use in conjunction with nodal irradiation, post breast conserving surgery and total mastectomy

2.2 Literature search methodology

A systematic method of literature searching and selection was employed in the preparation of this review. Searches for full-length publications and abstracts were conducted in EMBASE and Medline (via EMBASE.com) and the Cochrane Database of Systematic Reviews. At the request of the NBOCC and the Hypofractionated Radiotherapy Working Group, searches were restricted to English language studies published from 2001 onwards.

Search terms were approved by the NBOCC prior to searches being conducted. The reference lists of included papers were reviewed to identify any peer-reviewed evidence

that may have been missed in the literature search. Contacting of authors for unpublished research was not undertaken. The searches were conducted prior to the 31st of March, 2010. Therefore, studies published after this time were not eligible for inclusion in the systematic review.

The search strategy for the online bibliographic databases is shown in Table 8. A search of conference websites was also conducted. Three conferences were selected by the NBOCC and Hypofractionated Radiotherapy Working Group: American Society of Clinical Oncology, American Society of Radiation Oncology and San Antonio Breast Cancer Symposium. The same search terms were used for all conference abstracts. A total of 682 non-duplicate citations were identified.

Table 8 Search strategy

Database	Date searched	#	Search terms	Citations
EMBASE + Medline	<1950 – 26 Mar 2010	1	'breast cancer'/exp OR 'breast cancer' OR 'breast gland cancer'/exp OR 'breast gland cancer' OR 'breast gland neoplasm'/exp OR 'breast gland neoplasm' OR 'mammary cancer'/exp OR 'mammary cancer' OR 'mammary gland cancer'/exp OR 'mammary gland cancer' OR 'breast neoplasm'	227,592
		2	('breast' OR 'breast'/exp OR breast) AND ('cancer' OR 'cancer'/exp OR cancer OR 'carcinoma' OR 'carcinoma'/exp OR carcinoma OR 'tumour' OR 'tumour'/exp OR tumour OR 'tumour' OR 'tumour'/exp OR tumour OR 'neoplasm'/exp OR neoplasm)	288,233
		3	#1 OR #2	288,591
		4	'radiotherapy'/exp OR 'radiotherapy' OR 'irradiation therapy'/exp OR 'irradiation therapy' OR 'irradiation treatment'/exp OR 'irradiation treatment' OR 'radiation therapy'/exp OR 'radiation therapy' OR 'radiation treatment'/exp OR 'radiation treatment' OR 'therapeutic radiology'/exp OR 'therapeutic radiology' OR 'radiation; therapy' OR 'treatment, irradiation'/exp OR 'treatment, irradiation'	385,244
		5	fractionated OR hypofractionated OR fraction OR fractio*	418,274
		6	#4 AND #5	26,442
		7	'radiation dose fractionation'/exp OR 'radiation dose fractionation' OR 'dose fractionation'/exp OR 'dose fractionation' OR 'hypofractionated radiotherapy' OR 'fractionated radiotherapy'	10,331
		8	#6 OR #7	26,554
		9	#3 AND #8	2,275
		10	#9 AND [1-1-2001]/sd NOT [9-4-2010]/sd	1,336
		11	'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomised controlled trial'/exp OR 'randomised controlled trial' OR 'randomization' OR 'randomization'/exp OR randomization OR 'randomisation' OR 'randomisation'/exp OR randomisation OR 'meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review' OR 'guideline' OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo' OR 'placebo'/exp OR placebo OR randomi?ed:ab,ti OR rct:ab,ti OR 'random allocation':ab,ti OR 'randomly allocated':ab,ti OR 'allocated randomly':ab,ti OR (allocated NEAR/2 random*):ab,ti OR 'single blind':ab,ti OR 'single blinded':ab,ti OR 'double blind':ab,ti OR 'double blinded':ab,ti OR 'treble blind':ab,ti OR 'treble blinded':ab,ti OR 'triple blind':ab,ti OR 'triple blinded':ab,ti OR placebo*:ab,ti OR 'prospective study'/exp OR 'prospective study' NOT ('case study'/exp OR 'case study' OR 'case report':ab,ti OR 'abstract report'/exp OR 'abstract report' OR 'letter' OR 'letter'/exp OR letter)	1,344,424
		12	#11 AND #10	535
Cochrane Library	1800 –30 Mar 2010	1	"breast cancer" or "breast gland cancer" OR "breast gland neoplasm" OR mammary cancer" OR "mammary gland cancer" OR "breast neoplasm"	11,726
		2	breast AND (cancer OR carcinoma OR tumour OR tumour OR neoplasm)	13,831
		3	radiotherapy OR "irradiation therapy" OR "irradiation treatment" OR "radiation therapy" OR radiology OR "therapeutic radiology"	17,142
		4	fractionated OR hypofractionated OR fraction OR fractio*	11,864
		5	(#1 OR #2) AND #3 AND #4	211
ASCO	31 Mar 2010	1	"hypofractionated radiotherapy" OR "fractionated radiotherapy" OR "irradiation therapy" OR "irradiation treatment" OR "hypofractionated radiation treatment" OR "fractionated radiation treatment" OR "therapeutic radiology"	1
ASTRO			0	
SABCS			3	
Manual search				4
Total number of citations				756
Total number of non-duplicate citations				682

Abbreviations: ASCO=American Society of Clinical Oncology, ASTRO=American Society of Radiation Oncology, SABCS=San Antonio Breast Cancer Symposium

2.3 Assessment of study eligibility

Publications identified in the literature search were reviewed and the exclusion criteria shown in Table 9 applied hierarchically. As the Cochrane search was not restricted by date, the first exclusion criteria were all publications published prior to 2001 (the cut-off date for inclusion in the systematic review). Publications were excluded if they were the wrong study type (not an RCT), if they were in the wrong population (not women with early breast cancer treated with surgery), evaluated the wrong intervention (not hypofractionated radiotherapy) or the wrong comparator (not standard radiotherapy or another regimen of hypofractionated radiotherapy). Publications were excluded if they reported the wrong outcomes (as described in Table 9). Only English language publications were eligible for inclusion.

Table 9 Exclusion criteria

Wrong year	Study published prior to 2001
Wrong study type	Not randomised controlled trials
Wrong population	Not in women with early (invasive) breast cancer or patients treated with surgery
Wrong intervention	Not hypofractionated radiotherapy
Wrong comparator	Not standard radiotherapy or another regimens of hypofractionated radiotherapy
Wrong outcome	Study did not report local recurrence, overall survival, adverse events, toxicity, cosmetic outcome, quality of life or a subgroup analysis of age, breast size/width, tumour grade, nodal status, surgical margins, use in conjunction with nodal irradiation, post breast conserving surgery or total mastectomy
Insufficient follow-up	Follow-up of less than 5 years
Not in English	Not in English

The exclusion criteria was applied to all citations by reviewing the abstract and title, with 665 publications excluded (shown in Table 10). A total of 17 publications remained, and the full text version of each publication was retrieved and reviewed. The same exclusion criteria were then applied to the full text articles. A total of 10 publications met the inclusion criteria.

In Taher *et al.* 2004,²⁰ women with early breast cancer (n=30) were randomised to either i) 50 Gy in 25 fractions, followed by a boost to the tumour bed of 10 Gy in five fractions over five days or ii) 42.5 Gy in 16 fractions over 22 days with no boost. The RCT was excluded as the median follow-up was only 1.7 years. No statistical difference in acute skin reactions or cosmetic outcomes was observed between patients in the treatment arms. The study did not report local or regional recurrence, survival, or quality of life as outcomes.

Shahid *et al.* 2009¹⁸ was excluded because although it included women with early breast cancer, it was not limited to this population. For inclusion into this RCT, the primary lesion must have been T2, T3, or T4, with a nodal status of N1, N2, N3, Nx or N0. The study did not conduct subgroup analyses of women with early breast cancer.

In Shahid *et al.* 2009¹⁸, women were randomised to either i) 27 Gy in five fractions over one week or ii) 35 Gy in 10 fractions over two weeks or iii) 40 Gy in 15 fractions over three weeks (the control arm). The percentage of patients with local recurrence was 11%, 12%, and 10% for those patients in the 27 Gy, 35 Gy, and 40 Gy arms respectively (p=0.91). The five year overall survival was 87%, 83%, and 82% (p=0.89). Grade 1 skin reactions occurred significantly more often in the 40 Gy arm compared with the 27 Gy arm and the 35

Gy arm (62% vs 33% and 35%, $p < 0.05$). However, the 40 Gy arm had a significantly lower incidence of Grade 3 and 4 skin reactions compared with the 27 Gy arm, but not the 35 Gy arm (14% vs 37% and 28%, $p < 0.05$). No other adverse outcomes had a statistically significant difference in incidence rates.

Table 10 Included and excluded citations

Exclusion criteria	Number
Total citations	682
Citations excluded after review of abstract/title	
Wrong year	88
Wrong study type	186
Wrong population	57
Wrong intervention	334
Wrong comparator	0
Wrong outcome	0
Not in English	0
Total excluded citations	665
Full papers reviewed	17
Citations excluded after review of full publication	
Wrong study type	2
Wrong population	2
Wrong intervention	1
Wrong comparator	1
Wrong outcome	0
Insufficient follow-up	1
Not in English	0
Total excluded citations	7
Total included citations	10

2.4 Included trials

The literature search identified two systematic literature reviews (shown in Table 11) and eight publications describing five RCTs (shown in Table 12). Hopwood *et al.* 2010⁶ described combined results from both START A and START B and is therefore shown twice in Table 12 (i.e. there are 11 citations in the table but only 10 included publications).

For all included trials (with the exception of Spooner 2008³) there were at least two publications describing the results of the same clinical trial. In almost all instances, the first paper describes interim results (e.g. 5 years of follow-up) whereas the second paper describes the full study results (e.g. 10 years of follow-up). Throughout the report data has been taken from the most recent publication. In rare instances where this was not the case (e.g. the earlier paper reporting different outcome to the more recent paper) this has clearly been stated. Hopwood *et al.* 2010 reported combined results from both the START A and START B trials and therefore contained data not reported in the individual START A and START B publications.⁶ This has been clearly referenced throughout the report.

Table 11 Included systematic reviews

Study ID	Citation
James 2008	James ML, Lehman M, Hider PN, Jeffery M, Francis DP, Hickey BE. Fraction size in radiation treatment for breast conservation in early breast cancer. <i>Coch Data Syst Rev</i> 2008;(3).
Kalogeridi 2009	Kalogeridi MA, Kelekis N, Kouvaris J, Platoni K, Kyrias G, Pectasides D et al. Accelerated hypofractionated radiotherapy schedules in breast cancer: A review of the current literature. <i>Rev Recent Clin Trials</i> 2009; 4(3):147-151.

Table 12 Included RCTs

Study ID	Citations
Royal Marsden Hospital/Gloucester Oncology Centre (RMH/GOC)	Yarnold J, Ashton A, Bliss J, Homewood J, Harper C, Hanson J et al. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: Long-term results of a randomised trial. <i>Radiother Oncol</i> 2005; 75(1):9-17. Owen JR, Ashton A, Bliss JM, Homewood J, Harper C, Hanson J et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. <i>Lancet Oncology</i> 2006; 7(6):467-471.
Spooner (abstract only)	Spooner D, Stocken DD, Jordan S, Bathers S, Dunn JA, Jevons C, Morrison M, Oates G, Grieve R. A randomised controlled trial to evaluate both the role and optimal fractionation of radiotherapy in the conservative management of early breast cancer. <i>San Antonio Breast Cancer Symposium</i> , 2008.
Standardisation of Breast Radiotherapy Trial A (START A)	-START-Trialists'-Group, Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. <i>Lancet Oncol</i> 2008; 9:331-341. Hopwood P, Haviland JS, Sumo G, Mills J, Bliss JM, Yarnold JR. Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. <i>Lancet Oncol</i> 2010; 11(3):231-240.
Standardisation of Breast Radiotherapy Trial B (START B)	-START-Trialists'-Group, Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. <i>Lancet</i> 2008; 371:1098-1107. Hopwood P, Haviland JS, Sumo G, Mills J, Bliss JM, Yarnold JR. Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. <i>Lancet Oncol</i> 2010; 11(3):231-240.
Canadian	Whelan T, MacKenzie R, Julian J, Levine M, Shelley W, Grimard L et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. <i>J Natl Inst</i> 2002; 94(15):1143-1150. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S et al. Long-term results of hypofractionated radiation therapy for breast cancer. <i>New Engl J Med</i> 2010; 362(6):513-520.

2.5 Appraisal of included trials

Dimensions of evidence

The aim of this review was to find the highest quality evidence to answer the clinical questions being asked. In accordance with National Health and Medical Research Council (NHMRC) guidance, the following dimensions of evidence were reviewed for each of the

included studies (shown in Table 13). It is important to recognise that the value of a piece of evidence is determined by all of these dimensions, not just the level of evidence.

Table 13 NHMRC Dimensions of evidence²¹

Dimension	Reviewers definition
Strength of the evidence Level	The study design used, as an indication of the degree to which bias has been eliminated by the design alone. The levels reflect the effectiveness of the study design to answer the research question.
Quality	The methods used to minimise bias within an individual study (i.e., other than design per se)
Statistical precision	An indication of the precision of the estimate of effect reflecting the degree of certainty about the existence of a true effect, as opposed to an effect due to chance
Size of effect	Determines the magnitude of effect and whether this is of clinical importance
Relevance of evidence	Considers the relevance of the study to the specific research question and the context in which the information is likely to be applied, with regard to a) the nature of the intervention, b) the nature of the population and c) the definition of the outcomes.

Each study was also assigned a level of evidence in accordance with the NHMRC (2009) interim levels of evidence (see Table 14).²² The highest level of evidence available is a systematic review of RCTs, which is considered the study type least subject to bias. Individual RCTs also represent high-level evidence. Only systematic reviews and RCTs were eligible for inclusion in this systematic review.

Table 14 NHMRC Interim Levels of Evidence (NHMRC 2009) for evaluating interventions and diagnostic accuracy studies²²

Level	Intervention
I *	A systematic review of level II studies
II	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e., alternate allocation or some other method)
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> • Non-randomised, experimental trial ^a • Cohort study • Case-control study • Interrupted time series with a control group
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> • Historical control study • Two or more single arm studies ^b • Interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

Source: National Health and Medical Research Council (2009)²²

Note: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g., level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

* A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

^a This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (i.e., utilise A vs B and B vs C, to determine A vs C).

^b Comparing single arm studies i.e., case series from two studies.

Even within the levels of evidence stated above, there is considerable variability in the quality of evidence. In accordance with NHMRC guidelines, it was necessary to consider the quality of each of the included studies. Quality assessment was based on criteria reported by the NHMRC (2000), as shown in Table 15, with studies rated as good, fair or poor quality.²¹

Table 15 Quality criteria for different levels of evidence²¹

Study type	Quality criteria
Systematic review	<ul style="list-style-type: none"> Was an adequate search strategy used? Were the inclusion criteria appropriate and applied in an unbiased way? Was a quality assessment of included studies undertaken? Were the characteristics and results of the individual studies appropriately summarised? Were the methods for pooling the data appropriate? Were sources of heterogeneity explored?
Randomised controlled trials	<ul style="list-style-type: none"> Was allocation to treatment groups concealed from those responsible for recruiting patients? Was the study double-blinded? Were outcomes assessors blinded to treatment allocation? Were all randomised participants included in the analysis? Were treatment groups well matched at baseline? Was the study powered to detect a difference in primary outcome?

Source: Adapted from NHMRC (2000)²¹

Data synthesis

In addition to the level and quality of evidence of individual studies, the review considered the body of evidence in total. This involved consideration of the volume of evidence and its consistency.

The review presented the statistical precision of the estimated effect size, together with a discussion of its clinical significance. Finally, the review considered the relevance of the evidence, both with regard to the generalisability of the patient population and the intervention, as well as the applicability to the Australian health care setting.

2.6 Limitations of the review

This review used a structured approach to review the literature. However, there are some inherent limitations with this approach. All types of study are subject to bias, with systematic reviews, such as the one conducted here, being subject to the same biases seen in the original studies they include, as well as biases specifically related to the systematic review process. Reporting biases are a particular problem related to systematic reviews and include publication bias, time-lag bias, multiple publication bias, language bias and outcome reporting bias. A brief summary of the different types of reporting bias is shown in Table 16. Other biases can result if the methodology to be used in a review is not defined *a priori* (i.e., before the review commences). Detailed knowledge of studies performed in the area of interest may influence the eligibility criteria for inclusion of studies in the review and may therefore result in biased results. For example, studies with more positive results may be preferentially included in a review, thus biasing the results and overestimating treatment effect.

Table 16 Reporting biases in systematic reviews²³

Type of bias	Definition and effect on results of review
Publication bias	The publication or non-publication of research findings. Small, negative trials tend not to be published and this may lead to an overestimate of results of a review if only published studies are included.
Time-lag bias	The rapid or delayed publication of research findings. Studies with positive results tend to be published sooner than studies with negative findings and hence results may be overestimated until the negative studies 'catch up'.
Multiple publication bias	The multiple or singular publication of research findings. Studies with significant results tend to be published multiple times which increases the chance of duplication of the same data and may bias the results of a review.
Citation bias	The citation or non-citation of research. Citing of trials in publications is not objective so retrieving studies using this method alone may result in biased results. Unsupported studies tend to be cited often which may also bias results.
Language bias	The publication of research findings in a particular language. Significant results are more likely to be published in English so a search limited to English-language journals may result in an overestimation of effect.
Outcome reporting bias	The selective reporting of some outcomes but not others. Outcomes with favourable findings may be reported more. For example, adverse events have been found to be reported more often in unpublished studies. This may result in more favourable results for published studies.

Source: Adapted from Egger et al. (2001).²³

Some of these biases are potentially present in this review. The search was limited to English-language publications only, so language bias is a potential problem. Outcome reporting bias and inclusion criteria bias are unlikely as the reviewers had no detailed knowledge of the topic literature, and the methodology used in the review and the scope of the review were defined *a priori*.

The majority of studies included in this review were conducted outside Australia, and therefore, their generalisability to the Australian population and context needs to be considered. This review was confined to an examination of the efficacy and safety of the interventions and did not consider ethical or legal considerations associated with those interventions.

The studies were initially selected by examining the abstracts of these articles. Therefore, it is possible that some studies were inappropriately excluded prior to examination of the full text article. However, where detail was lacking, ambiguous papers were retrieved as full text to minimise this possibility. Data extraction, critical appraisal and report preparation was performed by one reviewer and double-checked by another. The review was conducted over a limited timeframe (March 2010 – June 2010).

3 Description of included studies

3.1 Systematic reviews

The literature search identified two systematic literature reviews.

3.1.1 James 2008

This Cochrane Review aimed to assess the effects of altered fraction size on women with early breast cancer who have undergone breast conserving surgery. The Cochrane Breast Cancer Group Specialised Register, MEDLINE, EMBASE, reference lists for articles and relevant conference proceeding were searched. The inclusion criteria were randomised controlled trials of unconventional versus conventional fractionation in women with early breast cancer who had undergone breast conserving surgery. Two trials were included: RMH/GOC^{1,8} and Canadian.^{2,7} Both trials were identified in the literature search conducted for this systematic literature review, and have been discussed in detail in the following sections.

There were no significant differences between the fractionation regimens in regard to cosmesis, late skin toxicity, or late radiation toxicity. For overall survival, there was no significant difference between the regimens. No data were available for costs, quality of life, or women's preference. The publication acknowledged the limitations related to assessment of subjective outcomes, such as cosmesis and breast induration.

Although both trials independently showed no difference in local control with altered fractionation, the reporting did not allow combination of data. The findings of this review provided reassurance that the practice of offering shortened radiation fractionation regimes to carefully selected groups of patients is unlikely to be detrimental in terms of breast appearance, late radiation breast toxicity, or survival.

3.1.2 Kalogeridi 2009

The authors conducted a literature search using MEDLINE, although the search strategy was not reported in the publication. Eight non-randomised trial and four randomised trials (RMH/GOC^{1,8}, Canadian^{2,7}, START A⁴ and START B⁵) were identified. All randomised studies were identified in the literature search conducted for this systematic literature review, and have been discussed in detail in the following sections.

The publication concluded that there are some significant concerns when short fractionation schedules are used for breast radiotherapy. Particularly, the authors concluded that a large dose per fraction could increase late normal tissue toxicity. However, case series, cohort studies and recently published randomised trials support the idea of hypofractionation for breast cancer, giving comparable control rates with conventional fractionation and acceptable toxicity. The authors cautioned that at least 15-20 years of follow-up was needed to assess the long-term sequelae and confirm the safety of the hypofractionated regimens.

3.2 Primary studies

The literature search identified five RCTs which met the inclusion criteria. The key characteristics are shown in Table 12. Two trials were in patients who had undergone breast conserving surgery (RMH/GOC and Canadian trials)^{1-2, 7-8} and three were in patients who had undergone any form of surgery (START A, START B and Spooner trials)³⁻⁵. All studies were considered fair quality, with the exception of Spooner which was considered poor*. Spooner 2008 is a conference abstract; no full publication of this abstract was identified in this systematic review conducted for this technical report.³ The studies evaluated a range of hypofractionated radiotherapy regimens.

The following section includes further discussion of each study design and patient population.

* The conference abstract provided insufficient study detail to rate it as either fair or good. It is unclear from the abstract whether allocation was concealed from those responsible for recruiting subjects, whether outcome assessment was blinded, and whether there was loss to follow up.

Table 17 Key characteristics of included studies

Study ID	Study type Quality	Population, median follow-up Country	Intervention	Comparator	Outcomes
Post breast conserving surgery					
RMH/GOC ^{1,8}	RCT Fair	T1-3, N0-1, M0, <75years N=1,410 9.7 years (range 7.8-11.8 years) UK	39 Gy in 13 fractions over 5 weeks (N=474) 42.9 Gy in 13 fractions over 5 weeks (N=466)	50 Gy in 25 fractions over 5 weeks (N=470)	Local recurrence Cosmetic outcomes
Canadian ^{2,7}	RCT Fair	Invasive carcinoma with negative axillary nodes, N=1,234 12 years (range not reported) Canada	42.5 Gy in 16 fractions over 22 days (N=622)	50 Gy in 25 fractions over 35 days (N=612)	Local recurrence (including subgroup analysis) Overall survival Adverse events and toxicity Cosmetic outcome
Post breast conserving surgery or mastectomy					
START A ^{4,6}	RCT Fair	T1-3a, N0-1, M0 N=2,236 5.1 years (range 4.4-6.0) UK	39 Gy in 13 fractions over 5 weeks (N=737) 41.6 Gy in 13 fractions over 5 weeks (N=750)	50 Gy in 25 fractions over 5 weeks (N=749)	Local recurrence Overall survival Adverse events and toxicity Cosmetic outcome (including subgroup analysis) Quality of life (including subgroup analysis)
START B ^{5,6}	RCT Fair	T1-3a, N0-1, M0 N=2,215 6 years (range 5.0-6.2) UK	40 Gy in 15 fractions over 3 weeks (N=1,110)	50 Gy in 25 fractions over 5 weeks (N=1,105)	Local recurrence Overall survival Adverse events and toxicity Cosmetic outcome (including subgroup analysis) Quality of life (including subgroup analysis)
Spooner ³	RCT (conference abstract) Poor ^a	Stage 1 or 2, median tumour size 2cm N=707 16.9 years (range 15.4-18.8 years) UK	40 Gy in 15 daily fractions (N=NR) 50 Gy in 25 daily fractions (N=NR)	Delayed salvage treatment	Time to first relapse

Abbreviations: NR=not reported, RCT=randomised controlled trial

a The conference abstract provided insufficient study detail to rate it as either fair or good. It is unclear from the abstract whether allocation was concealed from those responsible for recruiting subjects, whether outcome assessment was blinded, and whether there was loss to follow up.

3.2.1 Royal Marsden Hospital/Gloucester Oncology Centre trial (RMH/GOC)^{1, 8}

Patients with operable invasive breast cancer (T1–3, N0–1, M0) who needed radiotherapy were eligible for the trial. Inclusion criteria were <75 years of age, completed breast conserving surgery and complete macroscopic resection of invasive carcinoma. The study was conducted in the UK.

Patients (N=1,410) were randomised to either i) 50 Gy in 25 fractions (control group), or ii) 39 Gy in 13 fractions or iii) 42.9 Gy in 13 fractions (experimental schedules). All regimens were administered over five weeks. Patients with a complete macroscopic resection who were judged eligible by the clinician were further randomly allocated to receive a tumour bed boost or no boost. This process ended in July 1997, and all patients were offered an elective boost thereafter. The proportion of patients who received a boost was similar in all three treatment groups: 348 (74%) patients for 50 Gy, 348 (75%) for 42.9 Gy, and 351 (74%) for 39 Gy.

The trial was powered to detect a difference in tumour recurrence between each study arm, with the aim to enrol 2,250 subjects. However, recruitment was stopped prior to this number being reached as this trial was superseded by the START trials. Recruitment occurred between 1986 and 1998. The median follow-up period was 9.7 years, with a maximum of 18.4 years of follow-up. The publications did not report baseline characteristics in each study arm. Patient characteristics are shown in Table 18.

Table 18 RMH/GOC trial: Demographic and clinical characteristics of 1410 patients randomised⁸

Patient characteristic	Number (%)
Age at randomisation	
20-29	9 (0.9)
30-39	98 (7.0)
40-49	316 (22.4)
50-59	503 (35.7)
60-69	425 (30.1)
70-79	59 (4.2)
Breast size (from photographs)	
Small	186 (13.2)
Medium	952 (67.5)
Large	203 (14.4)
Not known	69 (4.9)
Surgical deficit (from photographs)	
Small	845 (59.9)
Medium	415 (29.4)
Large	76 (5.4)
Not known	74 (5.2)
cT stage	
T0	59 (4.2)
T1	749 (53.1)
T2	575 (40.8)
T3	22 (1.6)
T4	2 (0.1)
TX	3 (0.2)
cN stage	
N0	1,187 (84.7)
N1	219 (15.5)
N2	3 (0.2)
NX	1 (0.1)
Number of nodes pathologically involved	
0	564 (67.3)
1-3	202 (24.1)
4+	72 (8.6)
No axillary surgery	572 (40.6)
Adjuvant treatment	
None	289 (20.5)
Tamoxifen only	918 (65.1)
Chemotherapy only	40 (2.8)
Tamoxifen and chemotherapy	156 (11.1)
Other	7 (0.5)
Axillary supraclavicular fossa treatment	
None	337 (23.9)
Axillary supraclavicular fossa radiotherapy, no axillary surgery	231 (16.4)
Surgery, no radiotherapy	782 (55.5)
Surgery and supraclavicular fossa radiotherapy	59 (4.2)
Not known	1 (0.1)
Breast boost	
Randomised to no boost	359 (25.5)
Randomised to boost	364 (25.8)
Non-randomised boost given	687 (48.7)

Source: Yarnold 2005⁸, Table 1 page 12

3.2.2 Canadian trial^{2,7}

Patients with invasive carcinoma of the breast treated by breast conserving surgery and axillary dissection with pathologically negative axillary lymph nodes were eligible for inclusion in the trial. Key exclusion criteria were invasive disease or ductal carcinoma in situ involving the margins of excision, tumours that were larger than 5 cm in diameter, and a breast width of more than 25 cm at the posterior border of the medial and lateral tangential beams. The study was conducted in Canada.

Patients (N=1,234) were randomised to either i) 50 Gy in 25 fractions over 35 days or ii) 42.5 Gy in 16 fractions over 22 days. The 50 Gy arm was considered the control arm.

The study was designed to assess the non-inferiority of the hypofractionated regimen relative to the standard schedule for radiation therapy in terms of local recurrence. Recruitment occurred between 1993 and 1996. The study had a median follow-up of 12 years. The authors noted that the patients in each treatment arm were reasonably comparable with respect to their baseline characteristics. This is shown in Table 19.

Table 19 Canadian trial: Patient characteristics⁷

Characteristic	Number (%) 42.5 Gy N=622	Number (%) 50 Gy N=612
Age		
<50 y	157 (25)	148 (24)
50–59 y	186 (30)	155 (25)
60–69 y	181 (29)	200 (33)
≥70 y	98 (16)	109 (18)
Tumour size		
≤1 cm	183 (29)	192 (31)
>1–2 cm	317 (51)	302 (49)
>2 cm	122 (20)	118 (19)
Tumour grade		
I	215 (35)	209 (34)
II	244 (39)	236 (39)
III	117 (19)	116 (19)
Unknown	46 (7)	51 (8)
Oestrogen receptor status		
Positive	440 (71)	434 (71)
Negative	165 (27)	157 (26)
Unknown	17 (3)	21 (3)
Systemic therapy		
None	298 (48)	295 (48)
Tamoxifen	254 (41)	251 (41)
Chemotherapy	70 (11)	66 (11)

Source: Whelan 2002⁷ Table 1 page 1146

3.2.3 Standardisation of Breast Radiotherapy Trial A (START A)⁴

The START A and START B trials were conducted in parallel.⁴⁻⁵ Centres in the UK could elect to enter either Trial A (17 centres) or Trial B (23 centres). Due to earlier completion of recruitment in Trial B, those centres were invited to join Trial A after accrual to Trial B was complete. The study was conducted in the UK.

Women with operable invasive breast cancer (T1-3a, N0-1 M0) requiring radiotherapy after surgery (breast-conserving surgery or mastectomy, with clear tumour margins ≥ 1 mm) were eligible for the trial if they were aged over 18 years and did not have an immediate surgical reconstruction.

Patients (N=2,236) were randomised to either i) 50 Gy in 25 fractions (control group) or ii) 41.6 Gy in 13 fractions or iii) 39 Gy in 13 fractions (experimental schedules). All regimens were administered over five weeks to eliminate treatment time as a variable.

The trial was powered to detect a difference in local-regional tumour relapse between each 13 fraction schedule and the control group. Recruitment occurred between 1998 and 2002. The median follow-up period was 5.1 years, with a maximum of 8 years of follow-up. Demographic and clinical characteristics at randomisation were well balanced between treatment groups. This is shown in Table 20.

Table 20 START A: Patient characteristics⁴

Characteristic	Fractionation schedule			
	50 Gy n=749 (%)	41.6 Gy n=750 (%)	39 Gy n=737 (%)	Total N=2,236 (%)
Age years				
20–29	5 (0.7)	4 (0.5)	3 (0.4)	12 (0.5)
30–39	38 (5.1)	40 (5.3)	38 (5.2)	116 (5.2)
40–49	116 (15.5)	136 (18.1)	129 (17.5)	381 (17.0)
50–59	280 (37.4)	283 (37.7)	286 (38.8)	849 (38.0)
60–69	215 (28.7)	192 (25.6)	194 (26.3)	601 (26.9)
70–79	87 (11.6)	85 (11.3)	78 (10.6)	250 (11.2)
80–	8 (1.1)	10 (1.3)	9 (1.2)	27 (1.2)
Mean (SD)	57.6 (10.5)	57.0 (10.7)	57.1 (10.5)	57.2 (10.6)
Time from surgery to randomisation (weeks)				
Median time (IQR)	8.8 (5.3–20.8)	9.4 (5.9–20.2)	9.3 (5.4–21.1)	9.1 (5.4–20.7)
Range	0.4–71.3	1.0–50.3	1.1–53.6	0.4–71.3
Primary surgery				
Breast conserving surgery	631 (84.2)	641 (85.5)	628 (85.2)	1900 (85.0)
Mastectomy	118 (15.8)	109 (14.5)	109 (14.8)	336 (15.0)
Histological type				
Invasive ductal	581 (77.6)	585 (78.0)	584 (79.2)	1750 (78.3)
Invasive lobular	88 (11.7)	95 (12.7)	83 (11.3)	266 (11.9)
Mixed ductal/lobular	21 (2.8)	17 (2.3)	17 (2.3)	55 (2.5)
Other	57 (7.6)	51 (6.8)	52 (7.1)	160 (7.2)
Not known	2 (0.3)	2 (0.3)	1 (0.1)	5 (0.2)
Pathological node status				
Positive	222 (29.6)	197 (26.3)	224 (30.4)	643 (28.8)
Negative	514 (68.6)	536 (71.5)	497 (67.4)	1547 (69.2)
Not known (no axillary surgery)	12 (1.6)	17 (2.3)	15 (2.0)	44 (2.0)
Not known (missing data)	1 (0.1)	0 (0.0)	1 (0.2)	2 (0.1)
Tumour size (cm)				
<1	24 (3.2)	26 (3.5)	24 (3.3)	74 (3.3)
1–	362 (48.3)	347 (46.3)	355 (48.2)	1064 (47.6)
2–	202 (27.0)	203 (27.1)	198 (26.9)	603 (27.0)
3–	156 (20.8)	169 (22.5)	157 (21.3)	482 (21.6)
Not known	5 (0.7)	5 (0.7)	3 (0.3)	13 (0.6)
Tumour grade				
1	157 (21.0)	150 (20.0)	149 (20.2)	456 (20.4)
2	369 (49.3)	379 (50.5)	368 (49.9)	1116 (49.9)
3	212 (28.3)	207 (27.6)	210 (28.5)	629 (28.1)
Not known (not applicable) ^a	11 (1.5)	10 (1.3)	6 (0.8)	27 (1.2)
Not known	0 (0.0)	4 (0.6)	4 (0.5)	8 (0.4)
Adjuvant therapy				
None	52 (6.9)	53 (7.1)	67 (9.1)	172 (7.7)
Tamoxifen/no chemotherapy	416 (55.5)	418 (55.7)	376 (51.0)	1210 (54.1)
Chemotherapy/no tamoxifen	86 (11.5)	77 (10.3)	82 (11.1)	245 (11.0)
Tamoxifen + chemotherapy	173 (23.1)	187 (25.0)	188 (25.5)	548 (24.5)

Characteristic	Fractionation schedule			
	50 Gy n=749 (%)	41.6 Gy n=750 (%)	39 Gy n=737 (%)	Total N=2,236 (%)
Other endocrine therapy ^b	17 (2.3)	13 (1.7)	17 (2.3)	47 (2.1)
Not known	5 (0.7)	2 (0.2)	7 (0.9)	14 (0.6)
Lymphatic treatment				
None	8 (1.1)	14 (1.9)	13 (1.8)	35 (1.6)
Surgery/no radiotherapy	610 (81.4)	636 (84.8)	620 (84.1)	1866 (83.5)
Radiotherapy/no surgery	3 (0.4)	4 (0.5)	2 (0.3)	9 (0.4)
Surgery + radiotherapy	119 (15.9)	95 (12.7)	95 (12.9)	309 (13.8)
Not known	9 (1.2)	1 (0.1)	7 (0.9)	17 (0.8)
Boost (breast conserving surgery patients only)				
Number	n=631	n=641	n=628	n=1,900
Yes	381 (60.4)	391 (61.0)	380 (60.5)	1152 (60.6)
No	242 (38.3)	249 (38.8)	241 (38.4)	732 (38.5)
Not known	8 (1.3)	1 (0.2)	7 (1.1)	16 (0.8)
From Baseline photographs				
Number	n=413	n=421	n=416	n=1250
Breast size				
Small	43 (10.4)	47 (11.2)	41 (9.9)	131 (10.5)
Medium	294 (71.2)	324 (77.0)	322 (77.4)	940 (75.2)
Large	76 (18.4)	50 (11.9)	53 (12.7)	179 (14.3)
Surgical deficit				
Small	232 (56.2)	235 (55.8)	249 (59.9)	716 (57.3)
Medium	142 (34.4)	146 (34.7)	132 (31.7)	420 (33.6)
Large	39 (9.4)	40 (9.5)	35 (8.4)	114 (9.1)

Source: START A⁴ Table 1 page 332

Abbreviations: IQR=Interquartile range, SD=Standard deviation

a Lobular and other histological types.

b Other endocrine therapies include combinations of tamoxifen/anastrozole/letrozole/exemestane/goserelin, mostly within randomised trials.

3.2.4 Standardisation of Breast Radiotherapy Trial B (START B)⁵

As noted above, the START A and START B trials were conducted in parallel. Women with operable invasive breast cancer (T1-3a, N0-1, M0) requiring radiotherapy after surgery (breast-conserving surgery or mastectomy, with clear tumour margins ≥ 1 mm) were eligible for the trial if they were aged over 18 years and did not have an immediate surgical reconstruction.

Patients (N=2,215) were randomised to either i) 50 Gy in 25 fractions over five weeks or ii) 40 Gy in 15 fractions over three weeks. The 50 Gy arm was considered the control arm. The trial was powered to detect a difference in local-regional tumour relapse between each study arm. Recruitment occurred between 1998 and 2001. The median follow-up period was 6.0 years, with a maximum of 8 years of follow-up. Demographic and clinical characteristics at randomisation were well balanced between treatment groups. This is shown in Table 21.

Table 21 **START B: Patient characteristics⁵**

Characteristic	Fractionation schedule		
	50 Gy n=1,105 (%)	40 Gy n=1,110 (%)	Total N=2,215 (%)
Age years			
20–29	7 (0.6)	0 (0.0)	7 (0.3)
30–39	62 (5.6)	39 (3.5)	101 (4.6)
40–49	179 (16.2)	170 (15.3)	349 (15.8)
50–59	427 (38.6)	447 (40.3)	874 (39.5)
60–69	304 (27.5)	327 (29.5)	631 (28.5)
70–79	117 (10.6)	119 (10.7)	236 (10.7)
80–	9 (0.8)	8 (0.7)	17 (0.8)
Mean (SD)	57.0 (10.4)	57.8 (9.5)	57.4 (10.0)
Time from surgery to randomisation (weeks)			
Median time (IQR)	7.3 (4.9–12.3)	7.1 (4.9–11.9)	7.3 (4.9–12.0)
Range	0.9–45.3	0.6–49.3	0.6–49.3
Primary surgery			
Breast conserving surgery	1020 (92.3)	1018 (91.7)	2038 (92.0)
Mastectomy	85 (7.7)	92 (8.3)	177 (8.0)
Histological type			
Invasive ductal	865 (78.3)	843 (75.9)	1708 (77.1)
Invasive lobular	122 (11.0)	132 (11.9)	254 (11.5)
Mixed ductal/lobular	20 (1.8)	25 (2.3)	45 (2.0)
Other	95 (8.6)	103 (9.3)	198 (8.9)
Not known	3 (0.3)	7 (0.6)	10 (0.5)
Pathological node status			
Positive	238 (21.5)	266 (24.0)	504 (22.8)
Negative	831 (75.2)	804 (72.4)	1635 (73.8)
Not known (no axillary surgery)	36 (3.3)	39 (3.5)	75 (3.4)
Not known (missing data)	0 (0.0)	1 (0.1)	1 (0.04)
Tumour size (cm)			
<1	151 (13.7)	167 (15.0)	318 (14.4)
1–	552 (50.0)	542 (48.8)	1094 (49.4)
2–	287 (26.0)	288 (25.9)	575 (26.0)
3–	113 (10.2)	107 (9.6)	220 (9.9)
Not known	2 (0.2)	6 (0.5)	8 (0.4)
Tumour grade			
1	306 (27.7)	311 (28.0)	617 (27.9)
2	518 (46.9)	532 (47.9)	1050 (47.4)
3	261 (23.6)	248 (22.3)	509 (23.0)
Not known (not applicable) ^a	15 (1.4)	15 (1.3)	30 (1.3)
Not known	5 (0.4)	4 (0.4)	9 (0.4)
Adjuvant therapy			
None	37 (3.3)	47 (4.2)	84 (3.8)
Tamoxifen/no chemotherapy	782 (70.8)	810 (73.0)	1592 (71.9)
Chemotherapy/no tamoxifen	77 (7.0)	78 (7.0)	155 (7.0)
Tamoxifen + chemotherapy	181 (16.4)	155 (14.0)	336 (15.2)

Characteristic	Fractionation schedule		
	50 Gy n=1,105 (%)	40 Gy n=1,110 (%)	Total N=2,215 (%)
Other endocrine therapy ^b	16 (1.4)	11 (1.0)	27 (1.2)
Not known	12 (1.1)	9 (0.8)	21 (0.9)
Lymphatic treatment			
None	32 (2.9)	36 (3.2)	68 (3.1)
Surgery/no radiotherapy	980 (88.7)	984 (88.6)	1964 (88.7)
Radiotherapy/no surgery	5 (0.4)	3 (0.3)	8 (0.4)
Surgery + radiotherapy	74 (6.7)	79 (7.1)	153 (6.9)
Not known	14 (1.3)	8 (0.7)	22 (1.0)
Boost (breast conserving surgery patients only)			
Number	n=1020	n=1018	n=2038
Yes	422 (41.4)	446 (43.8)	868 (42.6)
No	584 (57.3)	565 (55.5)	1149 (56.4)
Not known	14 (1.4)	7 (0.7)	21 (1.0)
From Baseline photographs			
Number	n=522	n=514	n=1036
Breast size			
Small	49 (9.4)	42 (8.2)	91 (8.8)
Medium	377 (72.2)	390 (75.9)	767 (74.0)
Large	96 (18.4)	82 (16.0)	178 (17.2)
Surgical deficit			
Small	307 (58.8)	286 (55.6)	593 (57.2)
Medium	164 (31.4)	177 (34.4)	341 (32.9)
Large	51 (9.8)	51 (9.9)	102 (9.8)

Source: START B⁵ Table 1 page 1100

Abbreviations: IQR=Interquartile range, SD=Standard deviation

a Lobular and other histological types.

b Other endocrine therapies include combinations of tamoxifen/anastrozole/letrozole/exemestane/goserelin, mostly within randomised trials.

3.2.5 Spooner³

This citation was a conference abstract, therefore limited information was available. Patients with clinical stage 1 and 2 disease (N=707) were randomised to receive immediate postoperative radiotherapy or delayed salvage treatment (no radiotherapy). The study was conducted in the UK.

Patients receiving radiotherapy (N=NR) were further randomised to short (40 Gy in 15 daily fractions) or long (50 Gy in 25 daily fractions). The 50 Gy arm was considered the control arm. Recruitment occurred between 1985 and 1992. Patients were followed for a mean of 16.9 years. No information about patient characteristics was available.

4 Results of included trials

The results of the identified systematic reviews are not shown here as all trials that were identified in their literature searches have been described in detail below.

4.1 Local recurrence

All five included trials reported local recurrence. Two trials described patients who had undergone breast conserving surgery (RMH/GOC and Canadian)¹⁻² and three trials did not include type of surgery as an inclusion criteria (Spooner, START A and START B).³⁻⁵

4.1.1 Post breast conserving surgery

RMH/GOC trial¹

This trial compared i) 39 Gy in 13 fractions and ii) 42.9 Gy in 13 fractions with iii) 50 Gy in 25 fractions (the control arm). All fractions were administered over a five week period.

The results are shown in Table 22. Compared with the 50 Gy arm, the hazard ratio for the 42.9 Gy arm was 0.86 (95% CI 0.57, 1.30), and for the 39 Gy arm was 1.33 (95% CI 0.92, 1.92). The Kaplan-Meier estimates of local recurrence at 10 years were 12.1% (95% CI 8.8, 15.5) for the 50 Gy arm, 9.6% (95% CI 6.7, 12.6) for the 42.9 Gy arm and 14.8% (95% CI 11.2, 18.3) for the 39 Gy arm. There was a significant difference in the probability of local recurrence after 10 years between the 42.9 Gy and 39 Gy arms of the study (3·7%, 95% CI 0·3–8·3; χ^2 test, degrees of freedom [df]=1, p=0.027), with a higher rate of recurrence in the 39 Gy arm.

Table 22 RMH/GOC trial: Survival analysis of local relapse according to fractionation schedule¹

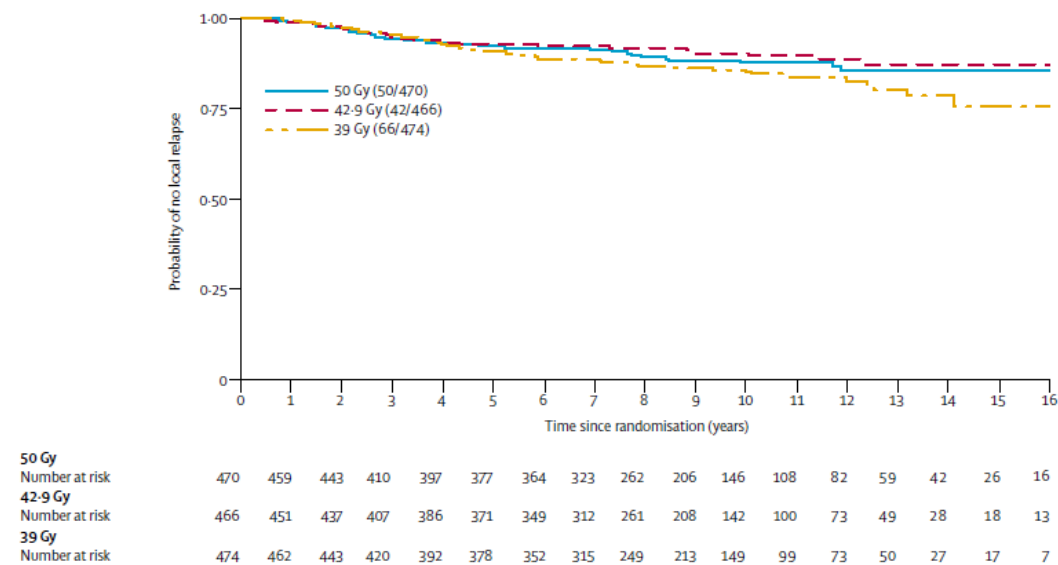
Arm	Number of local recurrence / person-years	Crude hazard ratio (95% CI) ^a	Kaplan-Meier estimates of local recurrence (95% CI)		Smoothed estimate of absolute difference (95% CI) ^a	
			5 years follow-up	10 years follow-up	5 years follow-up	10 years follow-up
50 Gy	50/3965	1	7.9% (5.4, 10.4)	12.1% (8.8, 15.5)	NR	NR
42.9 Gy	42/3840	0.86 (0.57, 1.30)	7.1% (4.6, 9.5)	9.6% (6.7, 12.6)	-1.1% (-3.3, 2.3)	-1.6% (-5.0, 3.3)
39 Gy	66/3890	1.33 (0.92, 1.92)	9.1% (6.4, 11.7)	14.8% (11.2, 18.3)	2.5% (-0.6, 6.7)	3.7% (-0.9, 9.8)

Source: Owen 2006¹, Table page 469
Abbreviations: CI=confidence interval
a Compared with 50 Gy

Figure 1 shows the recurrence-free Kaplan-Meier curves. The curves for each fractionation schedule begin to diverge after 5 years of follow-up. Hazard ratios were calculated by comparing the 42.9Gy arm and the 39 Gy arm with the 50 Gy arm. The hazard ratios for the first five years

of follow-up were 0.90 (95% CI 0.55, 1.46) for 42.9 Gy arm and 1.14 (95% CI 0.72, 1.79) for the 39 Gy arm. The hazard ratios for the period from 5 years until the end of follow-up were 0.77 (95% CI 0.36, 1.69) for the 42.9 Gy arm and 1.81 (95% CI 0.96, 3.41) for 39 Gy arm. This difference was not significant ($p=0.1$).

Figure 1 RMH/GOC trial: Local ipsilateral relapse in the breast according to fractionation schedule¹



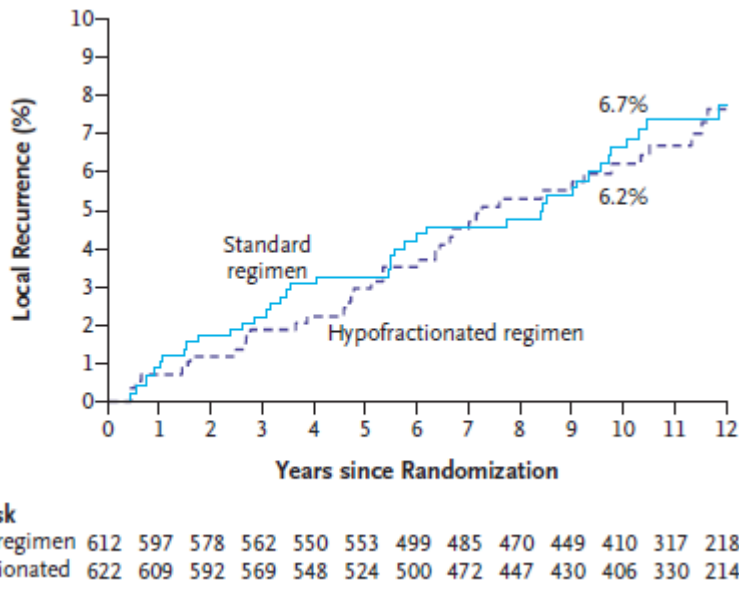
Source: Owen 2006¹, Figure 2 page 470

Canadian trial²

This trial compared i) 42.5 Gy in 16 fractions over 22 days with ii) 50 Gy in 25 fractions over 35 days (the control arm). The cumulative incidence of local invasive recurrence was similar in the two groups (as shown in Figure 2). At 10 years, the cumulative incidence of local invasive recurrence was 6.2% in the 42.5 Gy arm compared with 6.7% in the 50 Gy arm (absolute difference, 0.5 percentage points; 95% CI, -2.5, 3.5). The pre-defined criteria for non-inferiority was met (with a p value for non-inferiority of <0.001), indicating that the 42.5 Gy arm was not inferior to the 50 Gy arm.

Non-invasive recurrences occurred in six patients in the 42.5 Gy arm and seven patients in the 50 Gy arm. The 10 year cumulative incidence of invasive or non-invasive local recurrence was 7.4% in the 42.5 Gy arm as compared with 7.5% in the 50 Gy arm (absolute difference, 0.1 percentage points; 95% CI, -3.1, 3.3). A hazard ratio for the entire population was not reported.

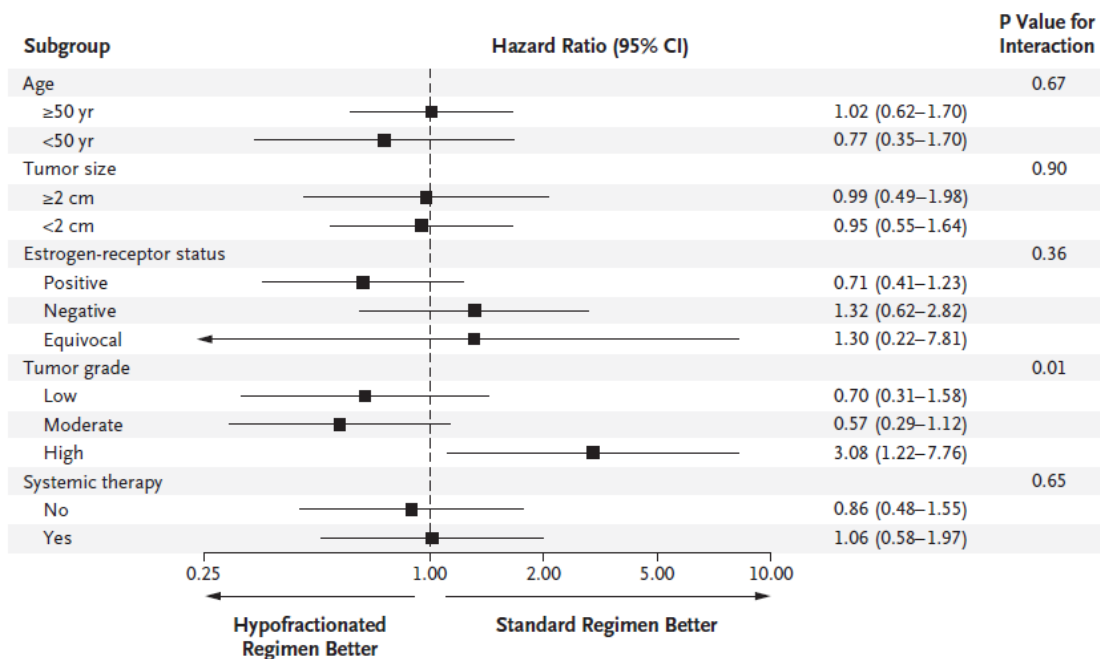
Figure 2 Canadian trial: Kaplan-Meier estimates for local recurrence^{a2}



Source: Whelan 2010² Figure 1a page 516
 a p<0.001 for non-inferiority
 Standard regimen = 50 Gy arm
 Hypofractionated regimen = 42.5 Gy arm

A subgroup analysis of local recurrence rate showed that the treatment effect of the hypofractionated protocol was similar regardless of patient age, tumour size, oestrogen-receptor status, or use of systemic therapy (shown in Figure 3). The hypofractionated regimen appeared to be less effective at preventing local recurrence in patients with high-grade tumours (p=0.01). For these patients, the 10 year cumulative incidence of local recurrence was 4.7% in the control group as compared with 15.6% in the hypofractionated-radiation group (absolute difference, -10.9; 95% CI: -19.1, -2.8). In the high grade (grade 3) patient group, the hazard ratio was 3.08 (95% CI 1.22, 7.76), compared with 0.70 (95% CI 0.31, 1.58) in the low grade patient group.

Figure 3 Canadian trial: Hazard ratios for Ipsilateral recurrence of breast cancer in subgroups of patients²



Source: Whelan 2010² Figure 2 page 517

4.1.2 Any surgery

Spooner³

This study compared i) 40 Gy in 15 fractions once a day or ii) 50 Gy in 25 fractions once a day with iii) delayed salvage treatment. The abstract stated that there was no difference in relapse frequency, or site between the two radiotherapy study arms, however no data was reported in the abstract.

START A⁴

This trial compared i) 39 Gy in 13 fractions over five weeks or ii) 41.6 Gy in 13 fractions over five weeks with iii) 50 Gy in 25 fractions over five weeks (the control arm). The relapse rates are shown in

Table 23. The crude hazard ratios for local relapse, relative to the 50 Gy arm, were 1.09 (95% CI 0.64, 1.88) for the 41.6 Gy arm and 1.25 (95% CI 0.74, 2.12) for the 39 Gy arm. These differences were not statistically significant.

Table 23 START A: Survival analyses of relapse and mortality according to fractionation schedule (Local relapse)⁴

Arm	Events/total (%)	Estimated % with event by 5 years (95% CI)	Crude hazard ratio (95% CI)	P value
50 Gy	25/749 (3.3)	3.2 (1.9, 4.6)	1	-
41.6 Gy	28/750 (3.7)	3.2 (1.9, 4.5)	1.09 (0.64, 1.88)	0.74
39 Gy	31/737 (4.2)	4.6 (3.0, 6.2)	1.25 (0.74, 2.12)	0.40

Source: Bentzen 2008⁴ Table 2 page 335
Abbreviations: CI=confidence interval

START B⁵

This trial compared i) 40 Gy in 15 fractions over three weeks with ii) 50 Gy in 25 fractions over five weeks (the control arm). The relapse rates are shown in Table 24. The crude hazard ratio for local relapse, relative to the 50 Gy arm, was 0.72 (95% CI 0.43, 1.21) for the 40 Gy arm. This was not statistically significant.

Table 24 START B: Survival analyses of relapse and mortality according to fractionation schedule (local relapse)⁵

Arm	Events/total (%)	Estimated % with event by 5 years (95% CI)	Crude hazard ratio (95% CI)	P value
50 Gy	34/1105 (3.1)	3.3 (2.2, 4.4)	1	-
40 Gy	25/1110 (2.2)	2.0 (1.1, 2.8)	0.72 (0.43, 1.21)	0.21

Source: Bentzen 2008⁵ Table 2 page 1102
Abbreviations: CI=confidence interval

4.1.3 Conclusions: Local recurrence

The results are summarised in Table 25. There was no evidence that any hypofractionated radiotherapy regimen was associated with a statistically significant difference in local recurrence rate when compared with a control arm. The RMH/GOC trial noted a statistically significant difference in recurrence rates when the two hypofractionated radiotherapy regimens were compared (42.9 Gy vs 39 Gy: 9.6% vs 14.8%, $p=0.027$), but not when each regimen was compared to the control arm.¹

Subgroup analyses were performed in one publication.² The Canadian trial analysed local recurrence by patient age, tumour size, oestrogen-receptor status, tumour grade or use of systemic therapy. There were no significant differences in any subgroup, with the exception of tumour grade. The 42.5 Gy regimen was least effective in patients with high-grade tumours compared to patients with low grade tumours ($p=0.01$).²

These results must be considered in the context of the range of hypofractionated radiotherapy regimes evaluated and different study designs used in these publications. Any imbalance between study arms in the treatments received may influence long term outcomes such as local recurrence.

Table 25 Summary of key results for local recurrence

Study ID	Study arms	Results
Post breast conserving surgery		
RMH/GOC ¹	39 Gy in 13 fractions over 5 weeks 42.9 Gy in 13 fractions over 5 weeks 50 Gy in 25 fractions over 5 weeks*	5 year local recurrence 39 Gy vs 50 Gy: 9.1% vs 7.9%, p=NR 42.9 Gy vs 50 Gy: 7.1% vs 7.9%, p=NR 42.9 Gy vs 39 Gy: 7.1% vs 9.1%, p=NR 10 year local recurrence 39 Gy vs 50 Gy: 14.8% vs 12.1%, p=NS 42.9 Gy vs 50 Gy: 9.6% vs 12.1%, p=NS 42.9 Gy vs 39 Gy: 9.6% vs 14.8%, p=0.027 39 Gy: HR 1.33 (95% CI 0.92, 1.92), p=NS 42.9 Gy: HR 0.86 (95% CI 0.57, 1.30), p=NS
Canadian ²	42.5 Gy in 16 fractions over 22 days 50 Gy in 25 fractions over 35 days*	10 year cumulative incidence of local recurrence 42.5 Gy vs 50 Gy: 6.2% vs. 6.7%, p=NS 10 year cumulative incidence of invasive or non-invasive local recurrence 42.5 Gy vs 50 Gy: 7.4% vs. 7.5%, p=NS Subgroup analyses Patient age, tumour size, oestrogen-receptor status, tumour grade, systemic therapy, p=NS High-grade vs low grade tumours, p=0.01
Any surgery		
Spooner ³	40 Gy in 15 fractions once a day 50 Gy in 25 fractions once a day Delayed salvage treatment	17 year relapse frequency No difference, data not reported
START A ⁴	39 Gy in 13 fractions over 5 weeks 41.6 Gy in 13 fractions over 5 weeks 50 Gy in 25 fractions over 5 weeks*	5 year local relapse rate 50 Gy vs 41.6 Gy vs 39 Gy: 3.2% vs 3.2% vs 4.6%, p=NR 5 year local relapse 39 Gy: HR 1.25 (95% CI 0.74, 2.12), p=0.40 41.6 Gy: HR 1.09 (95% CI 0.64, 1.88), p=0.74
START B ⁵	40 Gy in 15 fractions over 3 weeks 50 Gy in 25 fractions over 5 weeks*	5 year local relapse rate 50 Gy vs 40 Gy: 3.3% vs 2.0%, p=NR 5 year local relapse 40 Gy: HR 0.72 (95% CI 0.43, 1.21), p=0.21

Abbreviations: CI=confidence interval, HR=hazard ratio, , NR= not reported, NS=not significant

* control arm

4.2 Local-regional recurrence

Two trials reported local-regional recurrence, both in studies that did not include surgery type as an inclusion criteria (START A and START B).⁴⁻⁵

4.2.1 Any surgery

START A⁴

This trial compared i) 39 Gy in 13 fractions over five weeks and ii) 41.6 Gy in 13 fractions over five weeks with iii) 50 Gy in 25 fractions over five weeks (the control arm). The relapse rates are shown in Table 26. The hazard ratios for local-regional tumour relapse were 1.05 (95% CI 0.63, 1.75) for the 41.6 Gy arm and 1.26 (95% CI 0.77, 2.08) for the 39 Gy arm. These differences were not statistically significant.

Table 26 START A: Survival analyses of relapse and mortality according to fractionation schedule (Local-regional relapse)⁴

Arm	Events/total (%)	Estimated % with event by 5 years (95% CI)	Crude hazard ratio (95% CI)	P value
Local-regional relapse				
50 Gy	28/749 (3.7)	3.6 (2.2, 5.1)	1	–
41.6 Gy	30/750 (4.0)	3.5 (2.1, 4.3)	1.05 (0.63, 1.75)	0.86
39 Gy	35/737 (4.7)	5.2 (3.5, 6.9)	1.26 (0.77, 2.08)	0.35

Source: Bentzen *et al* 2008⁴ Table 2 page 335
Abbreviations: CI=confidence interval

START B⁵

This trial compared i) 40 Gy in 15 fractions over three weeks with ii) 50 Gy in 25 fractions over five weeks (the control arm). The relapse rates are shown in Table 27. The hazard ratios for local-regional tumour relapse was 0.79 (95% CI 0.48, 1.29) for the 40 Gy arm, which was not statistically significant.

Table 27 START B: Survival analyses of relapse and mortality according to fractionation schedule (Local-regional Relapse)⁵

Arm	Events/total (%)	Estimated % with event by 5 years (95% CI)	Crude hazard ratio (95% CI)	P value
Local-regional relapse				
50 Gy	36/1105 (3.2)	3.3 (2.2, 4.5)	1	–
40 Gy	29/1110 (2.6)	2.2 (1.3, 3.1)	0.79 (0.48, 1.29)	0.35

Source: Bentzen *et al* 2008⁵ Table 2 page 1102
Abbreviations: CI=confidence interval

4.2.2 Conclusions: Local-regional recurrence

The results are summarised in Table 28. There was no evidence that any hypofractionated radiotherapy regimen was associated with a statistically significant difference in regional recurrence rate when compared with a control arm.

These results must be considered in the context of the range of hypofractionated radiotherapy regimes evaluated and different study designs used in these publications. Any imbalance

between study arms in the treatments received may influence long term outcomes such as local-regional recurrence.

Table 28 Summary of key results for local-regional recurrence⁴⁻⁵

Study ID	Study arms	Results
Any surgery		
START A ⁴	39 Gy in 13 fractions over 5 weeks 41.6 Gy in 13 fractions over 5 weeks 50 Gy in 25 fractions over 5 weeks*	5 year local-regional relapse rate 50 Gy vs 41.6 Gy vs 39 Gy: 3.6% vs 3.5% vs 5.2%, p=NR 5 year local-regional relapse 39 Gy: HR 1.26 (95% CI 0.77, 2.08), p=0.35 41.6 Gy: HR 1.05 (95% CI 0.63, 1.75), p=0.86
START B ⁵	40 Gy in 15 fractions over 3 weeks 50 Gy in 25 fractions over 5 weeks*	5 year local-regional relapse rate 50 Gy vs 40 Gy: 3.3% vs 2.2%, p=NR 5 year local-regional relapse 40 Gy: HR 0.79 (95% CI 0.48, 1.29), p=0.35

Abbreviations: CI=confidence interval, HR=hazard ratio, NR=not reported
* control arm

4.3 Distant relapse

Two trials reported distant relapse, both in studies that did not include surgery type as an inclusion criteria (START A and START B).⁴⁻⁵

4.3.1 Any surgery

START A⁴

This trial compared i) 39 Gy in 13 fractions over five weeks and ii) 41.6 Gy in 13 fractions over five weeks with iii) 50 Gy in 25 fractions over five weeks (the control arm). The distant relapse rates are shown in Table 29. The hazard ratios for distant relapse, compared to the 50 Gy arm, were 0.92 (95% CI 0.66, 1.28) for the 41.6 Gy arm and 1.29 (95% CI 0.95, 1.76) for the 39 Gy arm. These ratios were not statistically significant.

Table 29 START A: Survival analyses of relapse and mortality according to fractionation schedule (Distant relapse)⁴

Arm	Events/total (%)	Estimated % with event by 5 years (95% CI)	Crude hazard ratio (95% CI)	P value
Distant relapse				
50 Gy	73/749 (9.7)	9.8 (7.5, 12.0)	1	–
41.6 Gy	69/750 (9.2)	9.5 (7.3, 11.7)	0.92 (0.66, 1.28)	0.64
39 Gy	93/737 (12.6)	11.9 (9.5, 14.4)	1.29 (0.95, 1.76)	0.10

Source: Bentzen *et al*/2008⁴ Table 2 page 335
Abbreviations: CI=confidence interval

START B⁵

This trial compared i) 40 Gy in 15 fractions over three weeks with ii) 50 Gy in 25 fractions over five weeks (the control arm). The distant relapse rates are shown in Table 30. The hazard ratios for distant relapse was 0.69 (95% CI 0.53, 0.91) for the 40 Gy arm. This result was statistically significant ($p=0.01$).

Table 30 START B: Survival analyses of relapse and mortality according to fractionation schedule (Distant relapse)⁵

Arm	Events/total (%)	Estimated % with event by 5 years (95% CI)	Crude hazard ratio (95% CI)	P value
Distant relapse				
50 Gy	122/1105 (11.0)	10.2 (8.4, 12.1)	1	–
40 Gy	87/1110 (7.8)	7.6 (6.0, 9.2)	0.69 (0.53, 0.91)	0.01

Source: Bentzen *et al* 2008⁵ Table 2 page 1102
Abbreviations: CI=confidence interval

4.3.2 Conclusions: Distant relapse

The results are summarised in Table 31. START A reported no statistical difference between either of the hypofractionated regimens compared with control. START B reported that the 40 Gy study arm had a significantly lower rate of distant relapse when compared with the control arm (HR 0.69 95% CI 0.53, 0.91, $p=0.01$).

These results must be considered in the context of the range of hypofractionated radiotherapy regimes evaluated and different study designs used in these publications. Any imbalance between study arms in the treatments received may influence long term outcomes such as local recurrence.

Table 31 Summary of key results for distant relapse⁴⁻⁵

Study ID	Study arms	Results
Any surgery		
START A ⁴	39 Gy in 13 fractions over 5 weeks 41.6 Gy in 13 fractions over 5 weeks 50 Gy in 25 fractions over 5 weeks*	5 year distant relapse rate 50 Gy vs 41.6 Gy vs 39 Gy: 9.8% vs 9.5% vs 11.9%, $p=NR$ 5 year local-regional relapse 39 Gy: HR 1.29 (95% CI 0.95, 1.76), $p=0.10$ 41.6 Gy: HR 0.92 (95% CI 0.66, 1.28), $p=0.64$
START B ⁵	40 Gy in 15 fractions over 3 weeks 50 Gy in 25 fractions over 5 weeks*	5 year local-regional relapse rate 50 Gy vs 40 Gy: 10.2% vs 7.6%, $p=NR$ 5 year local-regional relapse 40 Gy: HR 0.69 (95% CI 0.53, 0.91), $p=0.01$

Abbreviations: CI=confidence interval, HR=hazard ratio, NR=not reported
* control arm

4.4 Overall survival

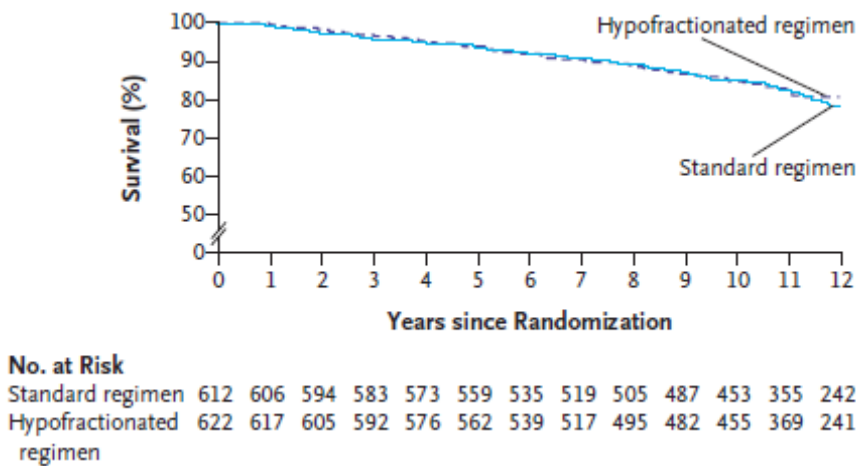
A total of four trials reported overall survival (Canadian, Spooner, START A and START B).^{2, 4-5, 7} The Canadian trial² described patients who had undergone breast conserving surgery and three publications did not include surgery type as an inclusion criteria (Spooner, START A and START B).³⁻⁵

4.4.1 Post breast conserving surgery

Canadian trial²

This trial compared i) 42.5 Gy in 16 fractions over 22 days with ii) 50 Gy in 25 fractions over 35 days (the control arm). During the study there were 126 deaths in the 50 Gy arm (20.6%) and 122 deaths in the in the 42.5 Gy arm (19.6%). At 10 years, the probability of survival was 84.4% in the 50 Gy arm compared with 84.6% in the 42.5 Gy arm (shown in Figure 4). The absolute difference was -0.2 percentage points (95% CI -4.3, 4.0). This difference was not statistically significant (p=0.79).

Figure 4 Canadian trial: Kaplan-Meier estimate for overall survival²



Source: Whelan 2010² Figure 1b page 516
p=0.79

The cause of death is shown in Table 32. In the 50 Gy arm 13.4% of deaths were related to cancer, 1.5% were related to cardiac disease and 5.7% were due to other causes. In the 42.5 Gy arm 13.2% were related to cancer, 1.9% were related to cardiac disease and 4.5% were due to other causes. None of these differences were statistically significant.

Table 32 Canadian trial: Cause of deaths²

Arm	50 Gy n (%)	42.5 Gy n (%)	P value
Deaths related to cancer	82 (13.4)	82 (13.2)	NS
Deaths related to cardiac disease	9 (1.5)	12 (1.9)	NS
Deaths related to other causes	35 (5.7)	28 (4.5)	NS

Source: Whelan 2010² page 517
Abbreviations: NS=not significant

4.4.2 Any surgery

Spooner³

This study compared i) 40 Gy in 15 fractions once a day or ii) 50 Gy in 25 fractions once a day with delayed salvage treatment. The abstract noted that there was no difference in overall survival between the two study arms, however no data was reported in the abstract.

START A⁴

This trial compared i) 39 Gy in 13 fractions over five weeks and ii) 41.6 Gy in 13 fractions over five weeks with iii) 50 Gy in 25 fractions over five weeks (the control arm). The START A trial reported all-cause mortality, rather than survival. As shown in Table 33, the hazard ratios for all-cause mortality, compared with the 50 Gy arm, were 1.04 (95% CI 0.77, 1.40) for the 41.6 Gy arm and 1.00 (95% CI 0.74, 1.36) for the 39 Gy arm. These ratios were not statistically significant.

Table 33 START A: Survival analyses of relapse and mortality according to fractionation schedule (All-cause mortality)⁴

Arm	Events/total (%)	Estimated % with event by 5 years (95% CI)	Crude hazard ratio (95% CI)	P value
50 Gy	84/749 (11.2)	11.1 (8.7, 13.4)	1	–
41.6 Gy	89/750 (11.9)	11.3 (8.9, 13.7)	1.04 (0.77, 1.40)	0.81
39 Gy	83/737 (11.3)	10.7 (8.3, 13.1)	1.00 (0.74, 1.36)	0.99

Source: Bentzen *et al* 2008⁴ Table 2 page 335
Abbreviations: CI=confidence interval

START B⁵

This trial compared i) 40 Gy in 15 fractions over three weeks with ii) 50 Gy in 25 fractions over five weeks (the control arm). The START B trial reported all-cause mortality, rather than survival. As shown in Table 34, the hazard ratio for all-cause mortality for the 40 Gy arm was 0.76 (95% CI 0.59, 0.98) compared with the 50 Gy arm. This was statistically significant (p=0.03).

Table 34 START B: Survival analyses of relapse and mortality according to fractionation schedule (All-cause mortality)⁵

Arm	Events/total (%)	Estimated % with event by 5 years (95% CI)	Crude hazard ratio (95% CI)	P value
50 Gy	138/1105 (12.5)	11.0 (9.1, 12.9)	1	–
40 Gy	107/1110 (9.6)	8.0 (6.4, 9.7)	0.76 (0.59, 0.98)	0.03

Source: Bentzen *et al*/2008⁵ Table 2 page 1102
Abbreviations: CI=confidence interval

4.4.3 Conclusions

The results are summarised in Table 35. Most studies reported that there was no evidence that hypofractionated radiotherapy was associated with a statistically significant difference in overall survival. START B found that 40 Gy in 15 fractions over three weeks was associated with a statistically significantly lower all-cause mortality rate when compared with 50 Gy in 25 fractions over five weeks (HR 0.76 95% CI 0.59, 0.98, $p=0.03$). Therefore, there was no evidence that any hypofractionated radiotherapy regimen was associated with a worse overall survival rate (i.e. the only study that reported a significant difference showed lower mortality for patients treated with hypofractionated radiotherapy).

These results must be considered in the context of the range of hypofractionated radiotherapy regimens evaluated and different study designs used in these publications. None of the publications described the treatments that patients in each study arm received after radiotherapy (e.g. chemotherapy). Any imbalance between study arms in the treatments received may influence long term outcomes such as overall survival.

Table 35 Summary of key results for overall survival

Study ID	Study arms	Results
Post breast conserving surgery		
Canadian ²	42.5 Gy in 16 fractions over 22 days 50 Gy in 25 fractions over 35 days*	10 year survival 42.5 Gy vs 50 Gy: 84.6% vs 84.4%, $p=0.79$
Any surgery		
Spooner ³	40 Gy in 15 fractions once a day 50 Gy in 25 fractions once a day	17 year survival No difference, data not reported
START A ⁴	39 Gy in 13 fractions over 5 weeks 41.6 Gy in 13 fractions over 5 weeks 50 Gy in 25 fractions over 5 weeks*	5 year all cause mortality 39 Gy: HR 1.00 (95% CI 0.74, 1.36), $p=0.99$ 41.6 Gy: HR 1.04 (95% CI 0.77, 1.40), $p=0.81$
START B ⁵	40 Gy in 15 fractions over 3 weeks 50 Gy in 25 fractions over 5 weeks*	5 year all cause mortality 40 Gy: HR 0.76 (95% CI 0.59, 0.98), $p=0.03$

Abbreviations: CI=confidence interval, HR=hazard ratio
* control arm

4.5 Adverse events and toxicity

A total of three trials reported adverse events and toxicity outcomes (Canadian, START A and START B).^{2, 4-5, 7} The Canadian trial^{2, 7} described patients who had undergone breast conserving surgery and two trials did not include surgery type as an inclusion criteria (START A⁴ and START B⁵, as well as combined data from both studies⁶).

4.5.1 Post breast conserving surgery

Canadian trial²

This trial compared i) 42.5 Gy in 16 fractions over 22 days with ii) 50 Gy in 25 fractions over 35 days (the control arm). The late toxic effects of radiation are shown in Table 36. The results were generally consistent between study arms. No grade 4 skin ulceration or soft-tissue necrosis was observed in any subjects.

Table 36 Canadian trial: Late toxic effects of radiation, assessed according to the RTOG-EORTC late radiation morbidity scoring scheme^{a2}

Site and Grade	5 year follow-up		10 year follow-up	
	50 Gy n=424 %	42.5 Gy n=449 %	50 Gy n=220 %	42.5 Gy n=235 %
Skin				
0 ^b	82.3	86.1	70.5	66.8
1	14.4	10.7	21.8	24.3
2	2.6	2.5	5.0	6.4
3	0.7	0.7	2.7	2.5
Subcutaneous tissue				
0 ^c	61.4	66.8	45.3	48.1
1	32.5	29.5	44.3	40.0
2	5.2	3.8	6.8	9.4
3	0.9	0.9	3.6	2.5

Source: Whelan 2010² Table 1 page 518

Abbreviations: CI=confidence interval, RTOG-EORTC=Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer.

a Effects of radiation therapy on skin and subcutaneous tissue were graded on a scale of 0 to 4 (with 0 indicating no toxic effects and grade 4 indicating skin ulceration or soft-tissue necrosis). RTOG-EORTC denotes the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer. b The absolute difference at 5 years was -3.8 percentage points (95% CI: -8.7, 1.0), and at 10 years the absolute difference was 3.7 percentage points (95% CI: -4.9, 12.1).

c The absolute difference at 5 years was -5.4 percentage points (95% CI: -11.9, 0.9), and at 10 years the absolute difference was -2.8 percentage points (95% CI: -11.7, 6.5).

4.5.2 Any surgery

START A⁴

This trial compared i) 39 Gy in 13 fractions over five weeks or ii) 41.6 Gy in 13 fractions over five weeks with iii) 50 Gy in 25 fractions over five weeks (the control arm). The incidence of ischemic

heart disease, symptomatic rib fracture and symptomatic lung fibrosis was low, with no differences between the study arms (shown in Table 37).

Table 37 START A: Incidence of ischemic heart disease, symptomatic rib fracture, and symptomatic lung fibrosis according to fractionation schedule⁴

Outcome	Arm	Reported n, (%)	Confirmed n, (%) ^a
Ischemic heart disease ^b	50 Gy	12 (1.6)	3 (0.4) [1] ^c
	41.6 Gy	7 (0.9)	2 (0.3) [0] ^c
	39 Gy	8 (1.1)	5 (0.7) [4] ^c
	Total	27(1.2)	10 (0.4) [5] ^c
Symptomatic rib fractures ^d	50 Gy	8 (1.1)	1 (0.1)
	41.6 Gy	9 (1.2)	2 (0.3)
	39 Gy	10 (1.4)	1 (0.1)
	Total	27 (1.2)	4 (0.2)
Symptomatic lung fibrosis	50 Gy	5 (0.7)	0 (0)
	41.6 Gy	6 (0.8)	2 (0.3)
	39 Gy	7 (0.9)	1 (0.1)
	Total	18 (0.8)	3 (0.1)

Source: Bentzen *et al*/2008⁴ Table 3 page 337

a Cases confirmed after imaging and further investigations.

b 18 patients had pre-existing heart disease at randomisation and were excluded.

c Confirmed cases of ischemic heart disease in patients with left-sided primary tumours.

d Reported cases include three with rib fracture after bone metastases and nine after trauma.

Other adverse events were discussed in the publication. In the 41.6 Gy arm, there was one case of pneumonitis which occurred nine months after treatment and one patient who developed mild symptoms and signs of brachial plexopathy two years after treatment. Two patients in the 50 Gy arm experienced an unusually marked acute skin reaction during their radiotherapy treatment, culminating in extensive moist desquamation. Neither patient had received adjuvant chemotherapy.⁴ It was assumed that no cases were reported in the other study arms, although this was not explicitly stated in the publication.

As shown in Table 38, a small number of patients had contralateral breast cancer (26 patients (1.2%)) or a secondary primary cancer (44 patients (2%)).⁴

Table 38 START A: Contralateral and other secondary cancers⁴

Outcome	Arm	n, (%)
Contralateral breast cancer	50 Gy	13 (1.7)
	41.6 Gy	5 (0.7)
	39 Gy	8 (1.1)
Other secondary primary cancers	50 Gy	15 (0.7)
	41.6 Gy	10 (0.4)
	39 Gy	19 (0.8)

Source: Bentzen *et al* 2008⁴ page 338

Patient self-assessments of late normal tissue effects are discussed in the combined START A and B publication results.⁶

START B⁵

This study compared i) 40 Gy in 15 fractions over three weeks with ii) 50 Gy in 25 fractions over five weeks (the control arm). The incidence of ischemic heart disease, symptomatic rib fracture and symptomatic lung fibrosis was low, with no differences between the study arms (shown in Table 39).

Table 39 START B: Incidence of ischemic heart disease, symptomatic rib fracture, and symptomatic lung fibrosis according to fractionation schedule⁵

Outcome	Arm	Reported (%)	Confirmed (%) ^a
Ischemic heart disease ^b	50 Gy	19 (1.7)	12 (1.1) [4] ^c
	40 Gy	15 (1.3)	7 (0.6) [3] ^c
	Total	34 (1.5)	19 (0.9) [7] ^c
Symptomatic rib fractures ^d	50 Gy	17 (1.5)	2 (0.2)
	40 Gy	16 (1.4)	2 (0.2)
	Total	33 (1.5)	4 (0.2)
Symptomatic lung fibrosis	50 Gy	15 (1.4)	1 (0.1)
	40 Gy	16 (1.4)	3 (0.3)
	Total	31 (1.4)	4 (0.2)

Source: Bentzen *et al* 2008⁵ Table 3 page 1104

a Cases confirmed after imaging and further investigations.

b 11 patients had pre-existing heart disease at randomisation and were excluded.

c Confirmed cases of ischemic heart disease in patients with left-sided primary tumours.

d Reported cases include four with rib fracture after bone metastases and three after trauma.

Other adverse events were discussed in the publication. There were no cases of brachial plexopathy in either study arm. Thirteen patients in the 50 Gy arm (1.2%) and three patients in the 40 Gy arm (0.3%) reported a marked acute reaction during radiotherapy.⁵

As shown in Table 40, a small number of patients had contralateral breast cancer (36 patients (1.6%)) or a secondary primary cancer (58 patients (2.6%)).⁵

Table 40 START B: Contralateral and other secondary cancers⁵

Outcome	Arm	n, (%)
Contralateral breast cancer	50 Gy	19 (1.7)
	40 Gy	17 (1.5)
Other secondary primary cancers	50 Gy	32 (2.9)
	40 Gy	26 (2.3)

Source: Bentzen *et al* 2008⁵ page 1103

Patient self-assessments of late normal tissue effects are discussed in the combined START A and B publication results.⁶

START A and B⁶

The START A trial compared i) 39 Gy in 13 fractions over five weeks and ii) 41.6 Gy in 13 fractions over five weeks with iii) 50 Gy in 25 fractions over five weeks (the control arm). The START B trial compared i) 40 Gy in 15 fractions over three weeks with ii) 50 Gy in 25 fractions over five weeks (the control arm). Combined patient-reported quality-of-life results from Start A and B are reported in Hopwood et al 2010.⁶

Of the 4,451 patients enrolled in either the START A or START B trials, 2,208 patients were accrued into the quality-of-life study (1,129 from START A and 1,079 from START B).⁶

Figure 5 shows the forest plot for patient reported normal tissue effects in the START A and START B trials. Two sets of outcomes were reported: breast symptoms and arm or shoulder symptoms. Many of the breast symptoms can also be considered adverse events as well as cosmetic outcomes, and have therefore been discussed here as well as in the following section on cosmetic outcomes. Breast symptom outcomes are discussed first, followed by arm or shoulder symptoms.

Breast Symptoms

In the START A trial, there were no statistically significant differences between the 41.6 Gy and 50 Gy arms. Change in breast appearance, breast hardness, breast shrinkage, pain in area of affected breast and oversensitivity in area of affected breast favoured the 50 Gy arm, while change in skin appearance and swelling in area of affected breast favoured the 41.6 Gy arm. Skin problems on or in area of affected breast had a hazard ratio of 1.01.⁶

When the 39 Gy and 50 Gy arms in the START A trial were compared, all outcomes favoured the 39 Gy arm (with the exception of breast shrinkage which had a hazard ratio of 1.00). The only outcome which statistically significantly favoured the 39 Gy arm was change in skin appearance (hazard ratio 0.63 95% CI 0.47, 0.84, p=0.0019).⁶

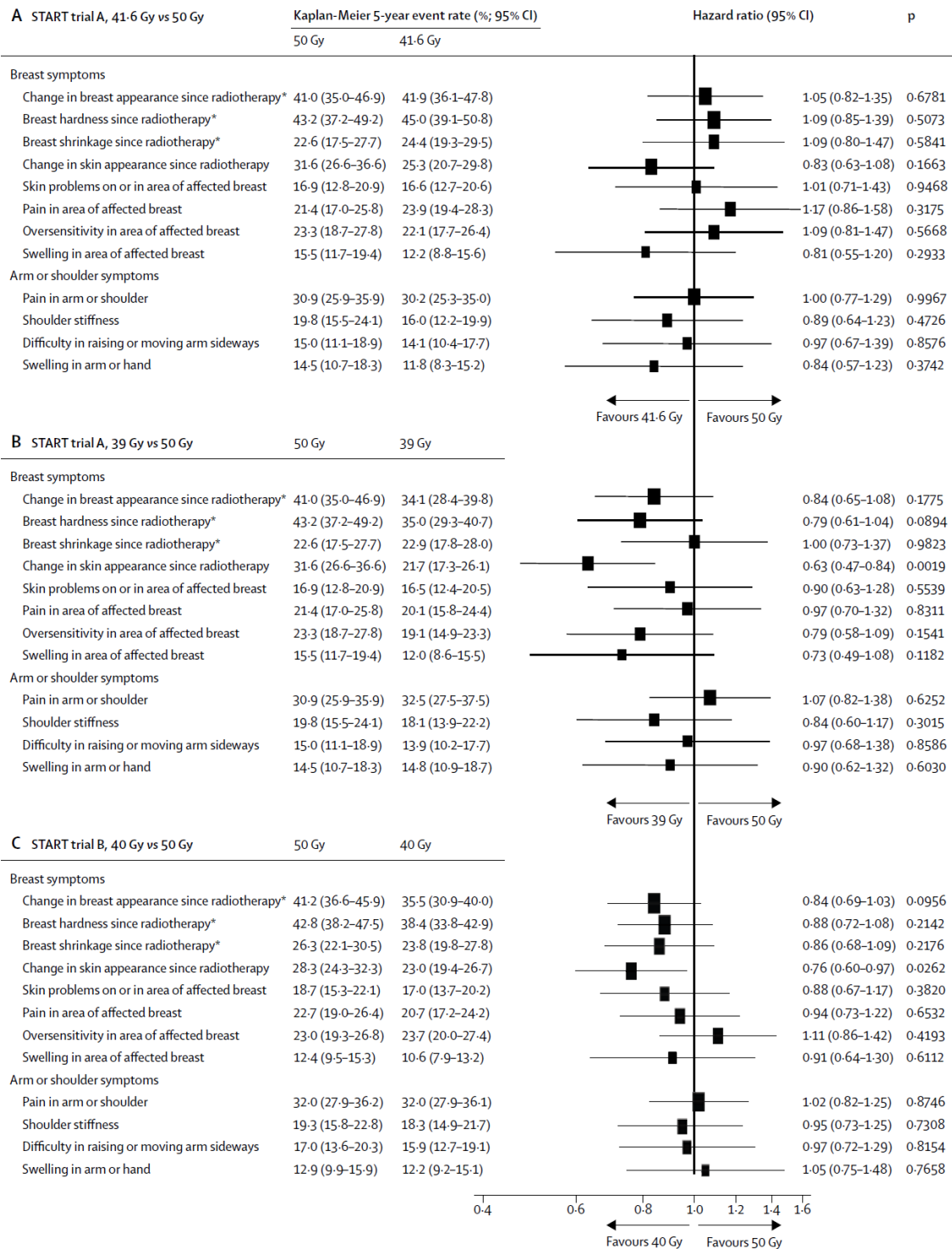
In the START B trial, all outcomes favoured the 40 Gy arm, with the exception of oversensitivity in area of affected breast. The only outcome which statistically significantly favoured the 40 Gy arm was change in skin appearance (hazard ratio 0.76 95% CI 0.60, 0.97, p=0.0262).⁶

Arm or shoulder symptoms

In the START A trial, shoulder stiffness, difficult in raising or moving arm sideways and swelling in arm or hand favoured the 41.6 Gy arm compared to the 50 Gy arm, although this was not statistically significant. Pain in arm or shoulder had a hazard ratio of 1.00. When the 39 Gy and 50 Gy arms were compared, shoulder stiffness and swelling in arm or hand favoured the 39 Gy arm, while pain in arm or shoulder favoured the 50 Gy arm, but these differences were not statically significant..⁶

In the START B trial there were no differences in arm or shoulder symptoms. The hazard ratios ranged from 0.95 to 1.05.⁶

Figure 5 START A AND B: Forest plots of normal tissue effects assessed as moderate or marked by patients, according to radiotherapy regimens⁶



Source: Hopwood *et al* 2010⁶ Figure 2 page 6

Positions of squares in the forest plot show the estimate of the hazard ratio describing relative effect of the test schedule compared with control, with the 95% CI represented by horizontal lines. Squares to the left of the vertical line indicate when rates of adverse effects are lower in the test schedule compared with control; estimates to the right of the line indicate whether rates are higher in the test schedule. Size of squares is proportional to the precision of the estimate, with larger squares indicating greater precision.

*In patients who had completed breast-conserving surgery only.

4.5.3 Conclusions

The results are summarised in Table 41. Most trials reported that there was no difference in adverse events and toxicity. Combined results from the START A and START B trials found that a change in skin appearance occurred significantly less often in the 39 Gy and 40 Gy arms when compared with the control arm (39 Gy HR 0.63 95% CI 0.47, 0.84, p=0.0019 and 40 Gy HR 0.76 95% CI 0.60, 0.97, p=0.0262).⁶

These results should be considered in the context of the difference in adverse event and toxicity outcomes assessed in each publication, and the difference in hypofractionated radiotherapy regimens evaluated.

Table 41 Summary of key results for adverse events and toxicity

Study ID	Study arms	Results
Post breast conserving surgery		
Canadian ²	42.5 Gy in 16 fractions over 22 days 50 Gy in 25 fractions over 35 days*	Late toxic radiation effects: NS
Any surgery		
START A ⁴	39 Gy in 13 fractions over 5 weeks 41.6 Gy in 13 fractions over 5 weeks 50 Gy in 25 fractions over 5 weeks*	Ischemic heart disease, symptomatic rib fracture, symptomatic lung fibrosis, contralateral breast cancer, other secondary primary cancers: NS
START B ⁵	40 Gy in 15 fractions over 3 weeks 50 Gy in 25 fractions over 5 weeks*	Ischemic heart disease, symptomatic rib fracture, symptomatic lung fibrosis, contralateral breast cancer, other secondary primary cancers: NS
Combined QoL data from START A and B ^{6^A}	As for START A and START B	Tissue effects, arm and shoulder symptoms: NS Skin appearance: 39 Gy HR 0.63 95% CI 0.47, 0.84, p=0.0019 40 Gy HR 0.76 (95% CI 0.60, 0.97), p=0.0262

Abbreviations: CI=confidence interval, HR=hazard ratio, NS=not significant, QoL=Quality-of-life

* control arm

^A Of the 4,451 patients enrolled in either the START A or START B trials, 2,208 patients were accrued into the quality-of-life study (1,129 from START A and 1,079 from START B)

4.6 Cosmetic outcome

A total of four trials reported cosmetic outcomes. Four of the trials described patients who had undergone breast conserving surgery (RMH/GOC, START A, START B and Canadian trials).^{2, 8}

⁶ Two trials described patients who had undergone mastectomy (START A and START B).⁶ The same two trials reported results for surgery types combined.⁴⁻⁵

4.6.1 Post breast conserving surgery

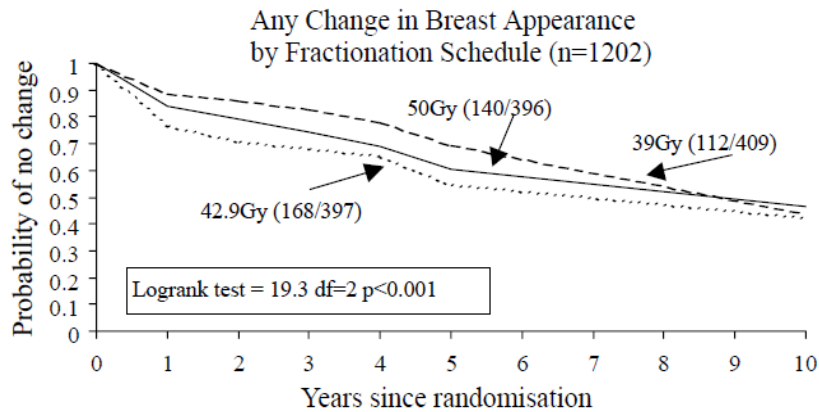
RMH/GOC trial⁸

This study compared i) 39 Gy in 13 fractions and ii) 42.9 Gy in 13 fractions with iii) 50 Gy in 25 fractions (the control arm). All fractions were administered over a five week period. Note that the cosmetic outcomes described here were all reported in Yarnold 2005⁸, but not the follow-up publication.¹ Therefore, the source for all data in this section is Yarnold 2005.⁸ A subset of 1,202 patients underwent breast appearance assessment. Change in breast appearance was assessed using photographs which were scored by blinded assessors. Clinician assessments were also performed.

The change in breast appearance, based on photographic and clinical assessment, is shown in Table 42. There was a significant difference between the three study arms in terms of any change in breast appearance, and a marked change in breast appearance ($p < 0.001$). Patients in the 39 Gy arm were the least likely to have a marked change in breast appearance at 10 years (93.4% with no event) compared with the 50 Gy arm and 42.9 Gy arm (90.2% and 84.4% with no event respectively).⁸

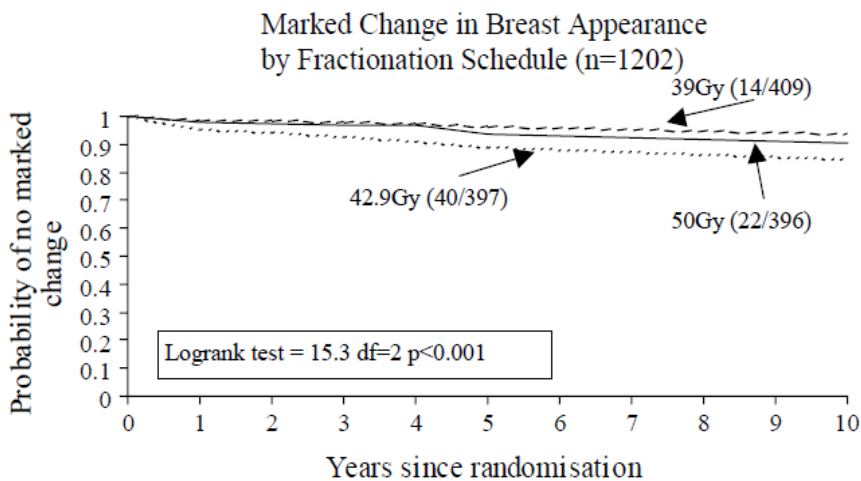
The publication noted for change in breast appearance based on photographic assessment, that there was some evidence of variation in the difference between the fractionation schedules as follow-up increased, as the 50 and 39 Gy arms appear to be converging, but analysis shows this not to be statistically significant ($p = 0.08$). The probability of any change in breast appearance ten years after radiotherapy is shown in Figure 6. The risk of developing any radiation effect was much lower for patients allocated to the 39 Gy arm compared with those allocated to the 42.9 Gy arm. There was a statistically significant difference between the 50 and 39 Gy arms of the trial over this time period ($p = 0.01$), but weaker evidence for the difference between 50 and 42.9 Gy ($p = 0.05$).⁸ Evidence was observed of a lower risk of marked change in the patients treated with 39 Gy compared to 42.9 Gy. The probability of no change was highest in the 39 Gy arm, followed by the 50 Gy arm and the 42.9 Gy arm. A similar pattern was seen for a marked change in breast appearance, as shown in Figure 7.

Figure 6 RMH/GOC trial: Probability of any change in breast appearance late radiation effect ten years after radiotherapy by fractionation schedule⁸



Source: Yarnold 2005⁸, Figure 2 page 13

Figure 7 RMH/GOC trial: Probability of marked change in breast appearance late radiation effect ten years after radiotherapy by fractionation schedule⁸

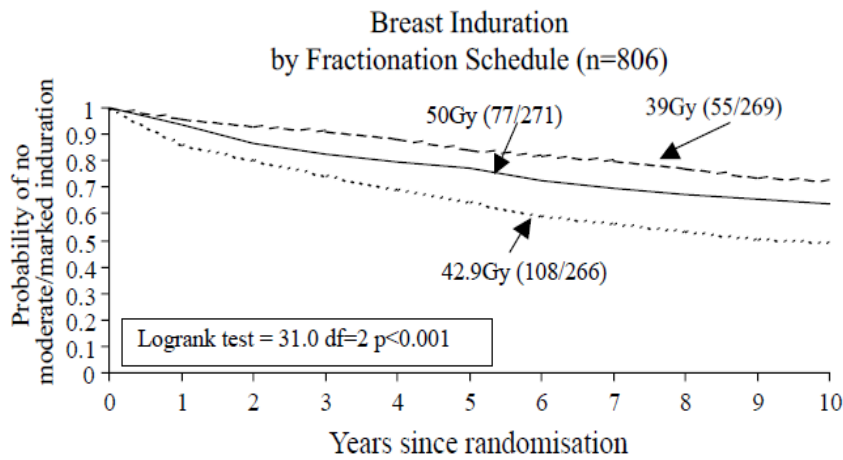


Source: Yarnold 2005⁸, Figure 3 page 14

Clinical assessments of overall breast cosmesis (involving an aesthetic judgement), breast shrinkage, breast distortion, breast oedema, induration and shoulder stiffness showed a significant difference between the treatment arms. For all outcomes (except shoulder stiffness), the estimated percent of subjects with no event at 10 years was highest in the 39 Gy arm and lowest in the 42.9 Gy arm.

The probability of palpable breast induration ten years after radiotherapy is shown in Figure 8. The 39 Gy arm had the highest probability of no change, followed by the 50 Gy arm and the 42.9 Gy arm.

Figure 8 RMH/GOC trial: Probability of palpable breast induration ten years after radiotherapy by fractionation schedule⁸



Source: Yarnold 2005⁸, Figure 4 page 14

For telangiectasia, the estimated percent of subjects with no event at 10 years was 88.0% in the 39 Gy arm, 81.9% in the 50 Gy arm, and 82.0% in the 42.9 Gy arm. The only outcome which failed to show a dose response was arm oedema (92.3% 50 Gy vs 89.5% 42.9 Gy vs 93.0% 39 Gy). The authors noted that this may be due to the small proportion (20.6%) of patients who experienced any form of lymphatic radiotherapy.

Table 42 RMH/GOC trial: Survival analyses of change in breast appearance and clinical assessments of late radiation effects according to fractionation schedule ⁸

Endpoint	Arm	Events/total (%)	Estimated % with no event at 5 years (95% CI)	Estimated % with no event at 10 years (95% CI)	P value
Photographic assessment					
Any change in breast appearance	50 Gy	140/396 (35.4)	60.4 (54.9, 65.8)	46.6 (37.2, 55.9)	<0.001
	42.9 Gy	168/397 (42.3)	54.3 (48.9, 59.7)	42.0 (33.0, 51.0)	
	39 Gy	112/409 (27.4)	69.7 (64.6, 74.8)	43.9 (30.8, 57.0)	
Marked change in breast appearance	50 Gy	22/396 (5.6)	93.6 (90.8, 96.4)	90.2 (85.0, 95.5)	<0.001
	42.9 Gy	40/397 (10.1)	88.8 (85.3, 92.2)	84.4 (77.7, 91.1)	
	39 Gy	14/409 (3.4)	96.1 (93.9, 98.2)	93.4 (87.8, 99.0)	
Clinical assessment					
Cosmesis (fair/poor)	50 Gy	165/271 (60.9)	44.1 (37.7, 50.4)	28.8 (22.3, 35.4)	<0.001
	42.9 Gy	175/266 (65.8)	37.9 (31.7, 44.1)	25.6 (19.3, 31.8)	
	39 Gy	136/269 (50.6)	54.6 (48.3, 60.9)	42.0 (34.9, 49.1)	
Breast shrinkage (moderate/marked)	50 Gy	147/271 (54.6)	49.9 (43.5, 56.3)	36.2 (29.3, 43.1)	0.026
	42.9 Gy	148/266 (55.8)	47.2 (40.8, 53.7)	34.2 (27.0, 41.5)	
	39 Gy	124/269 (46.1)	56.9 (50.6, 63.2)	44.4 (37.0, 51.7)	
Breast distortion (moderate/marked)	50 Gy	132/271 (48.9)	54.6 (48.2, 61.0)	41.5 (34.4, 48.6)	0.005
	42.9 Gy	148/266 (55.8)	45.7 (39.9, 52.1)	38.0 (31.4, 44.6)	
	39 Gy	115/269 (42.8)	59.3 (53.1, 65.4)	51.4 (44.4, 58.4)	
Breast oedema (moderate/marked)	50 Gy	34/271 (12.6)	87.6 (83.6, 91.7)	86.2 (81.8, 90.7)	0.004
	42.9 Gy	54/266 (20.3)	80.2 (75.3, 85.2)	78.5 (73.1, 83.9)	
	39 Gy	29/269 (10.8)	89.4 (85.6, 93.2)	88.5 (84.4, 92.7)	
Induration (moderate/marked)	50 Gy	77/271 (28.6)	76.9 (71.5, 82.3)	63.7 (56.6, 70.7)	<0.001
	42.9 Gy	108/266 (40.8)	64.4 (58.1, 70.6)	48.9 (41.5, 56.4)	
	39 Gy	55/269 (20.4)	84.0 (79.2, 88.8)	72.3 (65.5, 79.2)	
Telangiectasia (moderate/marked)	50 Gy	37/271 (13.8)	88.0 (83.8, 92.3)	81.9 (76.5, 87.3)	0.065
	42.9 Gy	38/266 (14.3)	87.0 (82.7, 91.4)	82.0 (76.5, 87.5)	
	39 Gy	23/269 (8.6)	94.4 (91.4, 97.4)	88.0 (83.0, 92.9)	
Arm oedema (moderate/marked)	50 Gy	17/271 (6.3)	93.8 (90.7, 97.0)	92.3 (88.6, 96.1)	0.494
	42.9 Gy	22/266 (8.3)	91.7 (88.1, 95.3)	89.5 (85.1, 93.8)	
	39 Gy	16/269 (5.9)	95.4 (92.7, 98.1)	93.0 (89.2, 96.8)	
Shoulder stiffness (moderate/marked)	50 Gy	21/271 (7.8)	94.1 (91.2, 97.0)	90.0 (85.6, 94.3)	<0.001
	42.9 Gy	48/266 (18.1)	84.0 (79.3, 88.6)	78.2 (72.3, 84.0)	
	39 Gy	19/269 (7.1)	94.2 (91.2, 97.2)	89.9 (85.3, 94.6)	

Source: Yarnold 2005⁸, Table 2 page 13

START A and B⁶

The START A trial compared i) 39 Gy in 13 fractions over five weeks and ii) 41.6 Gy in 13 fractions over five weeks with iii) 50 Gy in 25 fractions over five weeks (the control arm). The START B trial compared i) 40 Gy in 15 fractions over three weeks with ii) 50 Gy in 25 fractions over five weeks (the control arm).⁶

Of the 4,451 patients enrolled in either the START A or START B trials, 2,208 patients were accrued into the quality-of-life study (1,129 from START A and 1,079 from START B). Of these 2,208 patients, 1,831 had undergone breast-conserving surgery before radiotherapy (885 from START A and 946 from START B).⁶

Table 43 reports the self-reported cosmetic outcomes for the women who underwent breast conserving surgery before radiotherapy. These outcomes were similar between treatment arms across the two RCTs. The low numbers of patients and events in some subgroups limited the statistical power of these analyses.⁶

Table 43 START A AND B: Survival analyses of moderate or marked grade normal tissue effects from patients' self-assessments, according to fractionation schedule, type of primary surgery⁶

Study	Arm	Hazard ratio (95% CI)
Change in skin appearance since radiotherapy		
START A	50 Gy	1
	41.6 Gy	0.92 (0.68–1.25)
	39 Gy	0.63 (0.45–0.88)
START B	50 Gy	1
	40 Gy	0.80 (0.63–1.03)
Skin problems on or in area of affected breast ^a		
START A	50 Gy	1
	41.6 Gy	1.02 (0.70–1.50)
	39 Gy	0.87 (0.58–1.30)
START B	50 Gy	1
	40 Gy	0.86 (0.65–1.15)
Pain in area of affected breast ^a		
START A	50 Gy	1
	41.6 Gy	1.29 (0.92–1.82)
	39 Gy	1.01 (0.70–1.45)
START B	50 Gy	1
	40 Gy	0.97 (0.74–1.26)
Oversensitivity in area of affected breast ^a		
START A	50 Gy	1
	41.6 Gy	1.14 (0.81–1.58)
	39 Gy	0.79 (0.55–1.12)
START B	50 Gy	1
	40 Gy	1.18 (0.91–1.53)
Swelling in area of affected breast ^a		
START A	50 Gy	1
	41.6 Gy	0.87 (0.58–1.32)
	39 Gy	0.68 (0.44–1.05)
START B	50 Gy	1
	40 Gy	0.89 (0.62–1.29)
Arm or shoulder pain ^a		
START A	50 Gy	1
	41.6 Gy	1.05 (0.79–1.39)
	39 Gy	1.11 (0.83–1.48)
START B	50 Gy	1
	40 Gy	1.03 (0.83–1.29)
Shoulder stiffness ^a		
START A	50 Gy	1
	41.6 Gy	0.94 (0.65–1.37)
	39 Gy	0.98 (0.67–1.41)
START B	50 Gy	1
	40 Gy	0.94 (0.70–1.25)
Difficulty in raising or moving arm sideways ^a		
START A	50 Gy	1
	41.6 Gy	1.16 (0.76–1.77)
	39 Gy	1.15 (0.75–1.76)
START B	50 Gy	1
	40 Gy	0.99 (0.73–1.35)
Arm or hand swelling ^a		
START A	50 Gy	1
	41.6 Gy	0.77 (0.49–1.21)
	39 Gy	0.92 (0.60–1.42)
START B	50 Gy	1
	40 Gy	1.12 (0.78–1.60)

Source: Hopwood et al 2010⁶ Table 3 page 7 and Table 4 page 8

Abbreviations: CI=confidence interval

^a Results adjusted for baseline scores.

Canadian trial²

This trial compared i) 42.5 Gy in 16 fractions over 22 days with ii) 50 Gy in 25 fractions over 35 days (the control arm). Table 44 reports the cosmetic outcome at baseline, 5 years, and 10 years. Although the global cosmetic outcome worsened over time, no significant differences were observed between the groups at any time. The repeated-measures logistic-regression analysis suggested that the cosmetic outcome was affected by the time from randomisation as well as by the patient's age and tumour size, but there was no interaction with treatment.

Table 44 Canadian trial: Global cosmetic outcome assessed according to the EORTC scale^{a2}

Rating	Baseline		5-year follow-up		10-year follow-up	
	50 Gy %	42.5 Gy %	50 Gy %	42.5 Gy %	50 Gy %	42.5 Gy %
Excellent	46.3	46.8	34.3	36.4	27.8	30.6
Good	36.3	37.0	44.9	41.5	43.5	39.2
Fair	15.1	14.6	17.3	19.0	25.5	25.4
Poor	2.3	1.6	3.5	3.1	3.2	4.8
Excellent or good	82.6	83.8 ^b	79.2	77.9 ^c	71.3	69.8 ^d

Source: Whelan 2010² Table 2 page 519

Abbreviations: CI=confidence interval

a Absolute differences were calculated as the value in the group that received the standard regimen minus the value in the group that received the hypofractionated regimen.

b Absolute difference at baseline, -1.2 percentage points (95% CI: -5.4, 3.1).

c Absolute difference at 5-year follow-up, 1.3 percentage points (95% CI: -4.2, 6.7).

d Absolute difference at 10-year follow-up, 1.5 percentage points (95% CI: -6.9, 9.8).

4.6.2 Post mastectomy

START A and B⁶

The START A trial compared i) 39 Gy in 13 fractions over five weeks and ii) 41.6 Gy in 13 fractions over five weeks with iii) 50 Gy in 25 fractions over five weeks (the control arm). The START B trial compared i) 40 Gy in 15 fractions over three weeks with ii) 50 Gy in 25 fractions over five weeks (the control arm).

Of the 4,451 patients enrolled in either the START A or START B trials, 2,208 patients were accrued into the quality-of-life study (1,129 from START A and 1,079 from START B). Of these 2,208 patients, 377 had undergone a mastectomy before radiotherapy (244 from START A and 133 from START B).

Table 45 reports the self-reported cosmetic outcomes for the women who underwent mastectomy before radiotherapy. These outcomes were similar between treatment arms across the two RCTs. The low numbers of patients and events in some subgroups limited the statistical power of these analyses.

Table 45 START A AND B: Survival analyses of moderate or marked grade normal tissue effects from patients' self-assessments according to fractionation schedule, type of primary surgery⁶

Study	Arm	Hazard ratio (95% CI)
Change in skin appearance since radiotherapy		
START A	50 Gy	1
	41.6 Gy	0.53 (0.28–0.99)
	39 Gy	0.64 (0.34–1.17)
START B	50 Gy	1
	40 Gy	0.48 (0.20–1.16)
Skin problems on or in area of affected breast ^a		
START A	50 Gy	1
	41.6 Gy	0.90 (0.39–2.10)
	39 Gy	1.07 (0.48–2.38)
START B	50 Gy	1
	40 Gy	2.26 (0.43–11.80)
Pain in area of affected breast ^a		
START A	50 Gy	1
	41.6 Gy	0.82 (0.42–1.61)
	39 Gy	0.87 (0.45–1.69)
START B	50 Gy	1
	40 Gy	0.63 (0.22–1.79)
Oversensitivity in area of affected breast ^a		
START A	50 Gy	1
	41.6 Gy	0.87 (0.42–1.81)
	39 Gy	0.81 (0.39–1.68)
START B	50 Gy	1
	40 Gy	0.55 (0.19–1.54)
Swelling in area of affected breast ^a		
START A	50 Gy	1
	41.6 Gy	0.40 (0.11–1.51)
	39 Gy	0.98 (0.36–2.61)
START B	50 Gy	1
	40 Gy	4.18 (0.61–28.37)
Arm or shoulder pain ^a		
START A	50 Gy	1
	41.6 Gy	0.83 (0.47–1.47)
	39 Gy	0.97 (0.56–1.69)
START B	50 Gy	1
	40 Gy	0.92 (0.47–1.80)
Shoulder stiffness ^a		
START A	50 Gy	1
	41.6 Gy	0.74 (0.37–1.46)
	39 Gy	0.45 (0.20–0.99)
START B	50 Gy	1
	40 Gy	1.10 (0.47–2.58)
Difficulty in raising or moving arm sideways ^a		
START A	50 Gy	1
	41.6 Gy	0.61 (0.30–1.24)
	39 Gy	0.61 (0.31–1.23)
START B	50 Gy	1
	40 Gy	0.79 (0.35–1.77)
Arm or hand swelling ^a		
START A	50 Gy	1
	41.6 Gy	1.09 (0.50–2.35)
	39 Gy	0.88 (0.40–1.95)
START B	50 Gy	1
	40 Gy	0.65 (0.20–2.17)

Source: Hopwood et al 2010⁶ Table 3 page 7 and Table 4 page 8

Abbreviations: CI=confidence interval

^a Results adjusted for baseline scores.

4.6.3 Any surgery

START A⁴

This trial compared i) 39 Gy in 13 fractions over five weeks and ii) 41.6 Gy in 13 fractions over five weeks with iii) 50 Gy in 25 fractions over five weeks (the control arm). The change in breast appearance was assessed by photograph in 1,055 patients who had undergone breast conserving surgery.

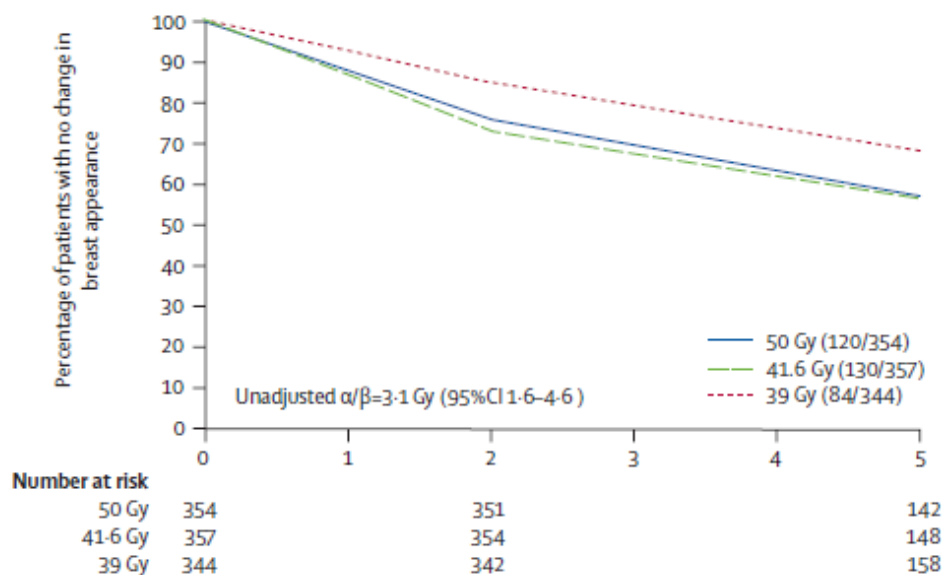
The hazard ratios for a mild or marked change in breast appearance, compared with the 50 Gy arm, were 1.09 (95% CI 0.85, 1.40) for the 41.6 Gy arm and 0.69 (95% CI 0.52, 0.91) for the 39 Gy arm. This difference was not significant for the 41.6 Gy arm ($p=0.62$), but was significant for the 39 Gy arm ($p=0.01$). This is shown in Table 46. A Kaplan-Meier plot is shown in Figure 9.

Table 46 START A: Mild or marked change in breast appearance⁴

Study arm	Crude hazard ratio (95% CI)	P value
50 Gy	1	–
41.6 Gy	1.09 (95% CI 0.85, 1.40)	0.62
39 Gy	0.69 (95% CI 0.52, 0.91)	0.01

Source: Bentzen *et al* 2008⁴ page 337
Abbreviations: CI=confidence interval

Figure 9 START A: Kaplan-Meier plot of mild/marked change in breast appearance (photographic) in 1055 patients with breast conserving surgery⁴



Source: Bentzen *et al* 2008⁴ Figure 3 page 337

Other cosmetic outcomes are discussed on page 50 as part of the combined START A and B study data.

START B⁵

This trial compared i) 40 Gy in 15 fractions over three weeks with ii) 50 Gy in 25 fractions over five weeks (the control arm). The change in breast appearance was assessed by photograph in 923 patients who had undergone breast conserving surgery.

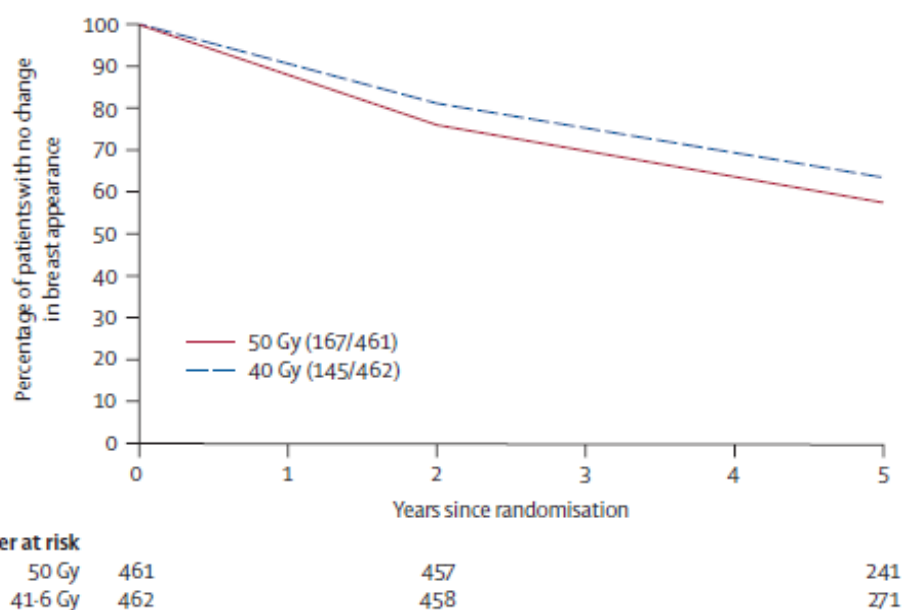
The hazard ratio for a mild or marked change in breast appearance for the 40 Gy arm (compared with the 50 Gy arm) was 0.83 (95% CI 0.66, 1.04; $p=0.06$). This is shown in Table 47. A Kaplan-Meier plot is shown in Figure 10.

Table 47 START B: Mild or marked change in breast appearance⁵

Study arm	Crude hazard ratio (95% CI)	P value
50 Gy	1	–
40 Gy	0.83 (0.66, 1.04)	0.06

Source: Bentzen *et al*/2008⁵ page 1103
Abbreviations: CI=confidence interval

Figure 10 START B: Kaplan-Meier plot of mild/marked change in breast appearance (photographic) in 923 patients with breast conserving surgery⁵



Source: Bentzen *et al*/2008⁵ Figure 4 page 1103

Other cosmetic outcomes are discussed below as part of the of the combined START A and B trials data.

START A and B⁶

The START A trial compared i) 39 Gy in 13 fractions over five weeks and ii) 41.6 Gy in 13 fractions over five weeks with iii) 50 Gy in 25 fractions over five weeks (the control arm). The

START B trial compared i) 40 Gy in 15 fractions over three weeks with ii) 50 Gy in 25 fractions over five weeks (the control arm).

Of the 4,451 patients enrolled in either the START A or START B trials, 2,208 patients were accrued into the quality-of-life study (1,129 from START A and 1,079 from START B).

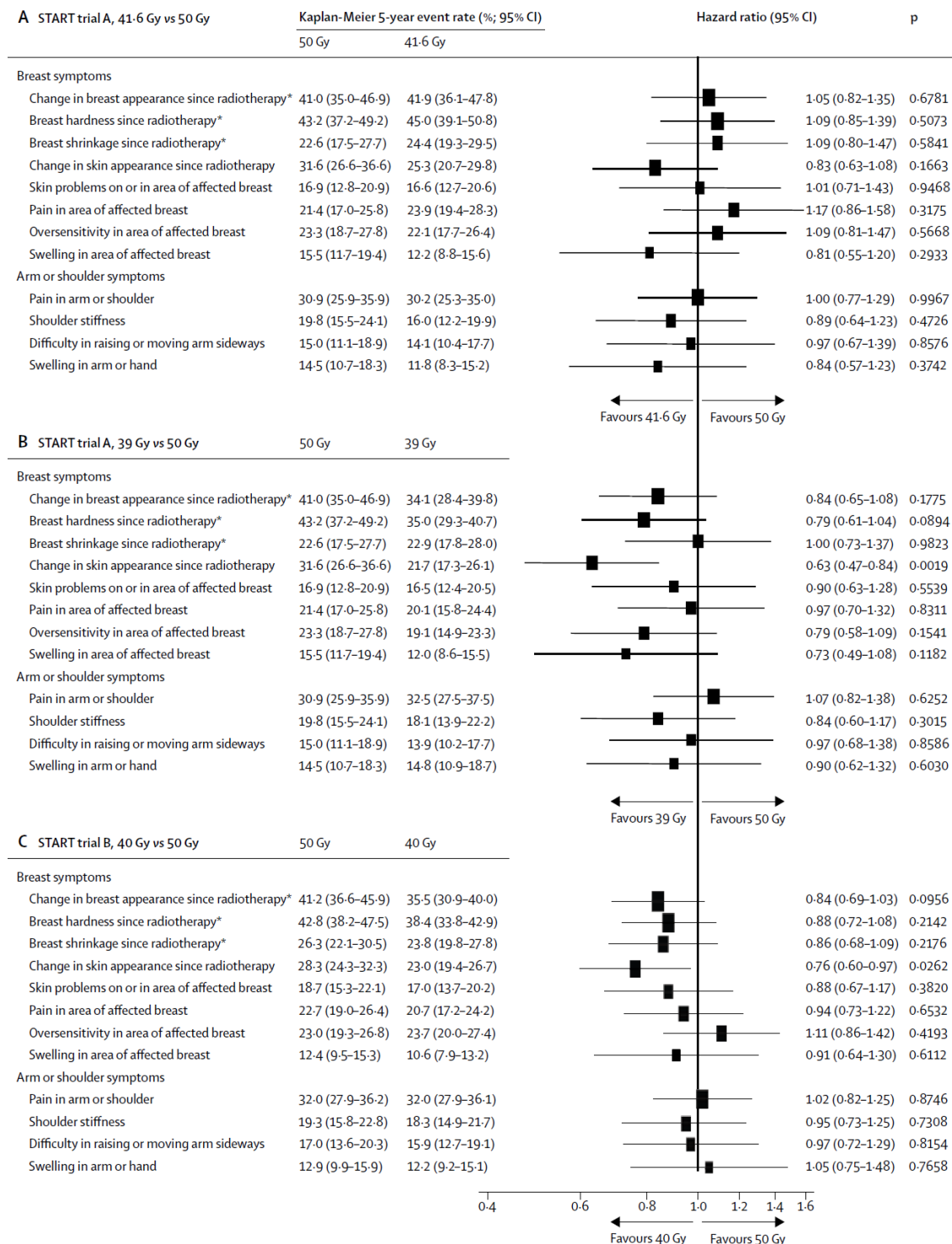
Figure 11 shows the forest plot for patient reported normal tissue effects in the START A and START B trials. Two sets of outcomes were reported: breast symptoms and arm or shoulder symptoms. Arm or shoulder symptoms have been discussed in the previous section on adverse events and toxicity.

In the START A trial, there were no statistically significant differences between the 41.6 Gy and 50 Gy arms. Change in breast appearance, breast hardness, breast shrinkage, pain in area of affected breast and oversensitivity in area of affected breast favoured the 50 Gy arm, while change in skin appearance and swelling in area of affected breast favoured the 41.6 Gy arm. Skin problems on or in area of affected breast had a hazard ratio of 1.01.

When the 39 Gy and 50 Gy arms in the START A trial were compared, all outcomes favoured the 39 Gy arm (with the exception of breast shrinkage which had a hazard ratio of 1.00). The only outcome which statistically significantly favoured the 39Gy arm was change in skin appearance (hazard ratio 0.63 95% CI 0.47, 0.84, $p=0.0019$).

In the START B trial, all outcomes favoured the 40 Gy arm, with the exception of oversensitivity in area of affected breast which favoured the 50 Gy arm. The only statistically significant difference was change in skin appearance, which favoured the 40 Gy arm (hazard ratio 0.76 95% CI 0.60, 0.97; $p=0.0262$).

Figure 11 START A AND B: Forest plots of normal tissue effects assessed as moderate or marked by patients, according to radiotherapy regimen⁶



Source: Hopwood et al 2010⁶ Figure 2 page 6

Positions of squares in the forest plot show the estimate of the hazard ratio describing relative effect of the test schedule compared with control, with the 95% CI represented by horizontal lines. Squares to the left of the vertical line indicate when rates of adverse effects are lower in the test schedule compared with control; estimates to the right of the line indicate whether rates are higher in the test schedule. Size of squares is proportional to the precision of the estimate, with larger squares indicating greater precision. *In patients who had completed breast-conserving surgery only. (A) START trial A, 41.6 Gy vs 50 Gy. (B) START trial A, 39 Gy vs 50 Gy. (C) START Trial B, 40 Gy vs 50 Gy.

4.6.4 Conclusions

The results are summarised in Table 48. There was no statistically significant difference in the majority of cosmetic outcomes assessed by the included publications.

RMH/GOC reported the risk of developing any late radiation effect was statistically significantly lower for patients in the 39 Gy arm compared to the 50 Gy arm ($p=0.01$). For most clinically assessed breast and arm outcomes estimated at 10 years, compared to the 50 Gy arm, there were fewer events for patients in the 39 Gy arm and more in the 42.9 Gy arm.⁸

The START A trial reported that the 39 Gy arm was associated with significantly less mild or marked change in photographic breast appearance (HR 0.69 95% CI 0.52, 0.91, $p=0.01$)⁴ and change in skin appearance (HR 0.63 95% CI 0.47, 0.84, $p=0.0019$).⁶ The 40 Gy arm of the START B trial was associated with significantly less change in skin appearance (40 Gy: HR 0.76 95% CI 0.60, 0.97, $p=0.0262$).⁶

In subgroup analyses for the START A and START B trials, the relative effects of the randomised radiation schedules on patients reported symptoms did not vary significantly according to type of primary surgery (breast conserving or mastectomy).⁸

These results should be considered in the context of the difference in cosmetic outcomes assessed in each publication, the methods of assessing cosmetic outcome and the difference in hypofractionated radiotherapy regimens.

Table 48 Summary of key results for cosmetic outcomes

Study ID	Study arms	Results
Post breast conserving surgery		
RMH/GOC ⁸	39 Gy in 13 fractions over 5 weeks 42.9 Gy in 13 fractions over 5 weeks 50 Gy in 25 fractions over 5 weeks*	39 Gy: adverse cosmetic outcomes were reported less frequently when compared to the 50 Gy arm ($p=0.01$)
Canadian ²	42.5 Gy in 16 fractions over 22 days 50 Gy in 25 fractions over 35 days*	No statistically significant differences in any cosmetic outcome
Any surgery		
START A ⁴	39 Gy in 13 fractions over 5 weeks 41.6 Gy in 13 fractions over 5 weeks 50 Gy in 25 fractions over 5 weeks*	41.6 Gy: No statistically significant differences in any cosmetic outcome 39 Gy: No statistically significant differences in cosmetic outcome, with the exception of mild or marked change in breast appearance (HR 0.69 95% CI 0.52, 0.91, $p=0.01$)
START B ⁵	40 Gy in 15 fractions over 5 weeks 50 Gy in 25 fractions over 5 weeks*	0.77 (95% CI 0.61-0.98), $p=0.02$
Combined data from START A and B ^{6A}	As for START A and START B	Change in skin appearance 39 Gy: HR 0.63 95% CI 0.47, 0.84, $p=0.0019$ 40 Gy: HR 0.76 95% CI 0.60, 0.97, $p=0.0262$ Subgroup analysis by breast conserving surgery and mastectomy: NS

Abbreviations: CI=confidence interval, HR=hazard ratio, NS=not significant

* control arm

^A Of the 4,451 patients enrolled in either the START A or START B trials, 2,208 patients were accrued into the quality-of-life study (1,129 from START A and 1,079 from START B)

4.7 Quality of life

The START A and START B trials reported quality of life outcomes .⁶

4.7.1 Post breast conserving surgery

START A and B⁶

The START A trial compared i) 39 Gy in 13 fractions over five weeks and ii) 41.6 Gy in 13 fractions over five weeks with iii) 50 Gy in 25 fractions over five weeks (the control arm). The START B trial compared i) 40 Gy in 15 fractions over three weeks with ii) 50 Gy in 25 fractions over five weeks (the control arm).

Of the 4,451 patients enrolled in either the START A or START B trials, 2,208 patients were accrued into the quality-of life study (1,129 from START A and 1,079 from START B). Of these 2,208 patients, 1831 had undergone breast-conserving surgery before radiotherapy (885 from START A and 946 from START B).

Table 49 shows the results of three self-reported scales assessed using the EORTC (European Organisation for Research and Treatment of Cancer) modules for subjects who underwent breast-conserving surgery: the BR23 breast symptoms subscale, the BR23 arm or shoulder symptoms subscale and the body image scale.⁶ There was no significant difference in outcomes based on study arm. The low numbers of patients and events in some subgroups limited the statistical power of these analyses.

Table 49 START A AND B: Breast, arm, or shoulder symptoms and body image scale scores at 5 years^a according to radiotherapy regimen, type of primary surgery⁶

Study	Arm	Median (IQR)
BR23 breast symptoms subscale (0–100)		
START A	50 Gy	8.3 (0–25.0)
	41.6 Gy	8.3 (0–16.7)
	39 Gy	8.3 (0–16.7)
START B	50 Gy	8.3 (0–16.7)
	40 Gy	8.3 (0–16.7)
BR23 arm or shoulder symptoms subscale (0–100)		
START A	50 Gy	11.1 (0–22.2)
	41.6 Gy	11.1 (0–22.2)
	39 Gy	11.1 (0–22.2)
START B	50 Gy	11.1 (0–22.2)
	40 Gy	11.1 (0–22.2)
Body image scale (0–30)		
START A	50 Gy	1.0 (0–5.0)
	41.6 Gy	2.0 (0–7.0)
	39 Gy	1.0 (0–5.0)
START B	50 Gy	1.0 (0–5.0)
	40 Gy	1.0 (0–5.0)

Source: Hopwood et al 2010⁶ Table 5 page 9

Higher scores indicate more symptoms or concerns.

^a Subgroup analyses undertaken with all follow-up data in generalised estimating equation models, but only 5-year data are shown for simplicity of presentation

4.7.2 Post mastectomy

START A and B⁶

The START A trial compared i) 39 Gy in 13 fractions over five weeks and ii) 41.6 Gy in 13 fractions over five weeks with iii) 50 Gy in 25 fractions over five weeks (the control arm). The START B trial compared i) 40 Gy in 15 fractions over three weeks with ii) 50 Gy in 25 fractions over five weeks (the control arm).

Of the 4,451 patients enrolled in either the START A or START B trials, 2,208 patients were accrued into the quality-of-life study (1,129 from START A and 1,079 from START B). Of these 2,208 patients, 377 had undergone a mastectomy before radiotherapy (244 from START A and 133 from START B).

Table 50 shows the results of three self-reported scales for subjects who underwent mastectomy: the BR23 breast symptoms subscale, the BR23 arm or shoulder symptoms subscale and the body image scale. There was no significant difference in outcomes based on study arm. The low numbers of patients and events in some subgroups limited the statistical power of these analyses.

Table 50 **START A AND B: Breast, arm, or shoulder symptoms and body image scale scores at 5 years^a according to radiotherapy regimen, type of primary surgery⁶**

Study	Arm	Mastectomy Median (IQR)
BR23 breast symptoms subscale (0–100)		
START A	50 Gy	8.3 (0–20.8)
	41.6 Gy	8.3 (0–25.0)
	39 Gy	8.3 (0–22.9)
START B	50 Gy	8.3 (0–16.7)
	40 Gy	8.3 (0–16.7)
BR23 arm or shoulder symptoms subscale (0–100)		
START A	50 Gy	11.1 (5.6–33.3)
	41.6 Gy	11.1 (0–33.3)
	39 Gy	11.1 (0–22.2)
START B	50 Gy	11.1 (0–22.2)
	40 Gy	11.1 (0–22.2)
Body image scale (0–30)		
START A	50 Gy	8.0 (2.2–15.5)
	41.6 Gy	3.0 (0–8.0)
	39 Gy	6.0 (1.0–11.0)
START B	50 Gy	4.0 (1.0–9.5)
	40 Gy	4.0 (0–7.0)

Source: Hopwood et al 2010⁶ Table 5 page 9

Higher scores indicate more symptoms or concerns.

^a Subgroup analyses undertaken with all follow-up data in generalised estimating equation models, but only 5-year data are shown for simplicity of presentation

4.7.3 Any surgery

START A and B⁶

The START A trial compared i) 39 Gy in 13 fractions over five weeks and ii) 41.6 Gy in 13 fractions over five weeks with iii) 50 Gy in 25 fractions over five weeks (the control arm). The START B trial compared i) 40 Gy in 15 fractions over three weeks with ii) 50 Gy in 25 fractions over five weeks (the control arm).

Of the 4,451 patients enrolled in either the START A or START B trials, 2,208 patients entered the quality-of-life study (1,129 from START A and 1,079 from START B). Quality of life was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) breast-cancer module BR23. This consists of six subscales, of which three were used in the analysis: breast symptoms subscale (pain, swelling, oversensitivity, and skin problems in the breast), arm subscale (swelling in arm or hand, arm or shoulder pain, and difficulty moving the arm), and body image (containing four items which were not reported in the publication).

Table 51 shows the results of three self-reported scales: the BR23 breast symptom subscale, the BR23 arm or shoulder symptoms subscale and the BR23 body image scale. There was no significant differences between regimens for the breast symptom subscale (START A $p=0.5558$, START B $p=0.8757$), the arm or shoulder symptoms subscale (START A $p=0.2071$, START B $p=0.3101$) or the body image scale (START A $p=0.9990$, START B $p=0.3405$). For all

radiotherapy regimens across each of the three scales, scores declined significantly indicating improved body image, between baseline and 60 months ($p < 0.0001$).

Table 51 START A AND B: Breast, arm, or shoulder symptoms and body image scale scores, according to radiotherapy regimen, over time from randomisation⁶

	0 months median (IQR)	6 months median (IQR)	12 months median (IQR)	24 months median (IQR)	60 months median (IQR)
BR23 breast symptoms subscale (0–100)					
Trial A					
50 Gy	16.7 (8.3–25.0)	16.7 (8.3–33.3)	16.7 (8.3–25.0)	8.3 (0–25.0)	8.3 (0–25.0)
41.6 Gy	16.7 (8.3–25.0)	16.7 (8.3–33.3)	16.7 (0–25.0)	8.3 (0–25.0)	8.3 (0–16.7)
39 Gy	16.7 (8.3–25.0)	16.7 (8.3–25.0)	16.7 (0–25.0)	8.3 (0–16.7)	8.3 (0–16.7)
Trial B					
50 Gy	16.7 (8.3–25.0)	16.7 (8.3–33.3)	16.7 (8.3–25.0)	8.3 (0–16.7)	8.3 (0–16.7)
40 Gy	16.7 (8.3–25.0)	16.7 (8.3–33.3)	16.7 (0–25.0)	8.3 (0–16.7)	8.3 (0–16.7)
BR23 arm or shoulder symptoms subscale (0–100)					
Trial A					
50 Gy	22.2 (0–33.3)	11.1 (0–22.2)	11.1 (0–22.2)	11.1 (0–22.2)	11.1 (0–22.2)
41.6 Gy	11.1 (0–33.3)	11.1 (0–22.2)	11.1 (0–22.2)	11.1 (0–22.2)	11.1 (0–22.2)
39 Gy	22.2 (11.1–33.3)	11.1 (0–33.3)	11.1 (0–22.2)	11.1 (0–22.2)	11.1 (0–22.2)
Trial B					
50 Gy	11.1 (11.1–33.3)	11.1 (0–22.2)	11.1 (0–22.2)	11.1 (0–22.2)	11.1 (0–22.2)
40 Gy	22.2 (11.1–33.3)	11.1 (0–33.3)	11.1 (0–22.2)	11.1 (0–22.2)	11.1 (0–22.2)
Body image scale (0–30)					
Trial A					
50 Gy	3.0 (1.0–8.0)	3.0 (0–7.0)	3.0 (0–7.0)	2.0 (0–7.0)	2.0 (0–7.0)
41.6 Gy	4.0 (1.0–8.7)	2.0 (0–6.0)	2.0 (0–6.0)	2.0 (0–6.0)	2.0 (0–7.0)
39 Gy	4.0 (1.0–9.0)	2.0 (0–7.0)	2.0 (0–7.0)	2.0 (0–7.0)	2.0 (0–6.0)
Trial B					
50 Gy	3.0 (0–8.0)	2.0 (0–6.0)	1.0 (0–5.0)	1.0 (0–5.7)	1.5 (0–6.0)
40 Gy	3.0 (0–7.0)	2.0 (0–6.0)	1.0 (0–5.0)	1.0 (0–5.0)	1.0 (0–5.0)

Source: Hopwood et al 2010⁶ Table 2 page 5

Abbreviations: IQR=interquartile range

Higher scores indicate more symptoms or concerns.

4.7.4 Conclusions

The START A and START B trials evaluated quality of life outcomes.⁶ There was no evidence that any hypofractionated radiotherapy regimen was associated with a statistically significant difference in quality of life score as measured by the BR23 breast symptom subscale.²⁴ Subgroup analysis was performed, with results analysed by surgery type. There were no statistically significant differences in outcomes, nor were any interaction tests significant overall.

These results must be considered in the context of the range of hypofractionated radiotherapy regimes and single quality of life instrument used to assess this outcome.

5 Guidelines

5.1 Guidelines search

In order to identify current recommendations in existing radiotherapy guidelines, a systematic search of guidelines was undertaken in March 2010. The nine guideline websites which were searched are shown in Table 52. The same search terms were used for all websites. Manual searching of reference lists was also performed. A total of three citations were identified. One set of guidelines⁹, that was published after the literature search date, was included *post hoc*.

Table 52 Search terms for guidelines websites

Guideline websites	Search terms	Citations
Agency for Healthcare Research and Quality	"hypofractionated radiotherapy" OR "fractionated radiotherapy" OR "irradiation therapy" OR "irradiation treatment" OR "hypofractionated radiation treatment" OR "fractionated radiation treatment" OR "therapeutic radiology" OR ("breast cancer" AND radiotherapy)	0
EuroScan		0
Australia and New Zealand Horizon Scanning Network		0
Centre for Reviews and Dissemination		0
MSAC		0
National Guideline Clearinghouse		0
NHMRC		0
NHS Evidence		2
CADTH		0
Manual		1
Total	3	

5.2 Results

The American Society for Radiation Oncology (ASTRO) guidelines on fractionation for whole breast irradiation 2010⁹

Based on the same body of evidence evaluated in this systematic review, ASTRO found that evidence supports the equivalence of hypofractionated whole breast irradiation with conventionally fractionated whole breast irradiation for patients who satisfy all these criteria:

- Patient is 50 years or older at diagnosis.
- Pathologic stage is T1-2 N0 and patient has been treated with breast-conserving surgery.
- Patient has not been treated with systemic chemotherapy.
- Within the breast along the central axis, the minimum dose is no less than 93% and maximum dose is no greater than 107% of the prescription dose ($\pm 7\%$) (as calculated with 2-dimensional treatment planning without heterogeneity corrections).

For patients who do not satisfy all of these criteria, the task force could not reach consensus and therefore chose not to render a recommendation.

There were few data to define the indications for and toxicity of a tumour bed boost in patients treated with hypofractionated radiotherapy. The task force agreed that the use of hypofractionated radiotherapy alone (without a boost) is not appropriate when a tumour bed boost is thought to be indicated. When a boost is indicated, there was lack of consensus regarding the appropriateness of hypofractionated radiotherapy. Although the majority of the task force members thought that there were sufficient data showing safety of hypofractionated radiotherapy followed by a tumour bed boost to recommend its use in otherwise suitable patients, a minority believed that conventional radiotherapy should be used instead when a tumour bed boost is indicated.

For patients not receiving a tumour-bed boost, the task force favoured a dose of 42.5 Gy in 16 fractions over approximately 22 days when hypofractionated radiotherapy was planned. The optimal hypofractionated radiotherapy regimen to use when a boost is given and the optimal tumour-bed boost dose-fractionation to use in conjunction with hypofractionated radiotherapy have not been determined.

Two-dimensional treatment planning with optimisation of dose homogeneity in the central axis is the minimum acceptable standard for hypofractionated radiotherapy treatment planning. However, CT-guided treatment planning using three-dimensional dose compensation is strongly recommended to optimise dose homogeneity throughout the entire breast. As a conservative measure, the task force recommended exclusion of the heart from the primary treatment fields provided that coverage of the primary tumour site is not compromised.

The New Zealand Ministry of Health Guidelines for Management of Early Breast Cancer 2009¹⁰

The New Zealand Ministry of Health guidelines made the following recommendation regarding hypofractionated radiotherapy:

Recommendation

• Radiotherapy treatment for early invasive breast cancer should use an accepted regimen such as:

50 Gy in 25 fractions over 5 weeks (Grade A)

45 Gy in 20 fractions over 5 weeks (Grade B)

42.5 Gy in 16 fractions over 3.5 weeks for those with small or medium breasts, not requiring boost or nodal radiation (Grade B)

40 Gy in 15 fractions over 3 weeks* (Grade B)

Good practice points

• If boost radiotherapy is used after a hypofractionated regimen it should be at the standard 2 Gy per fraction

• Women with large breasts and those with significant postoperative induration, oedema, erythema, haematoma or infection should be considered for extended fractionation, with smaller daily doses over 5–6 weeks

* It should be noted that the data for long-term follow-up in the latter three schedules of this recommendation is still awaited
Notes

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

A good practice point represents the opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available

A summary of the findings of the systematic review used to inform the guidelines is presented below.

Survival

The SIGN guideline¹² reported data from the Canadian trial that found no significant difference in overall survival rate at the five-year follow-up with a hypofractionated compared with standard regimen.⁷ The START Trialists Group reported that in the START B trial there were significant differences in disease-free and overall mortality rates in favour of the group who received the hypofractionated regimen (40 Gy in 15 fractions over 3 weeks).⁵ The authors anticipate that this effect will diminish over time, and the long-term follow-up of the trial continues.

Loco-regional recurrence

In the Canadian trial study reported in the SIGN guideline, no significant difference in local recurrence free rate at the five-year follow-up was seen (96.8% with 25 fractions vs 97.2% with 16 fractions; 95% CI 1.5–2.4).⁷ At the five-year follow-up, RMH/GOC reported hazard ratios comparing 50 Gy to 42.9 Gy of 0.90 (95% CI 0.55–1.46) and 1.14 (95% CI 0.72–1.79) for 39 Gy compared to 50 Gy.¹ After 10 years, the probability of recurrence was significantly greater in the 39 Gy than in the 42.9 Gy group (difference 3.7%, 95% CI 0.3–8.3, $p=0.027$). RMH/GOC concluded that the results were consistent with the hypothesis that fewer, larger fractions are at least as safe and as effective as 'standard' regimens but that the shorter schedule should be restricted to clinical trials.¹ At the five-year follow-up, the START Trialists Group reported of the START B trial that the absolute difference in loco-regional recurrence could be up to 1.7% better and at most 1% worse with the hypofractionated regimen. The trial authors concluded that the delivery of 40 Gy in 15 fractions appeared to result in a loco-regional recurrence rate that was at least as favourable as the 'standard' 50 Gy in 25 fractions.⁵

Other outcomes

Cosmetic results at five years were similar between fractionation schedules. However, in a 12-year update of the Canadian trial data, the incidence of moderate to severe late radiation morbidity (subcutaneous fibrosis) at 10 years doubled (8% vs 4%)^{††} in the shorter fractionation schedule.⁷ The START A trial reported in a quality of life assessment that changes in breast appearance and breast hardness were the most commonly reported side effects. These side effects were less marked in the 39 Gy group and similar in the 41.6 Gy and 50 Gy groups, in contrast to those found at 10 years by RMH/GOC. (11.2% for 42.9 Gy in 13 fractions of 3.3 Gy vs 6.4% for 50 Gy in 25 fractions of 2 Gy). Both the START A and START B trials reported that the follow-up period of five years was too short to assess potential late normal tissue effects, such as cardiac damage.⁴⁻⁵

Follow-up continues for these trials. The long-term safety of the short fractionation schedule for the nodal areas has not been established.

Conclusions

Based on a review of the published evidence it was noted that there is currently insufficient evidence to identify one optimum fractionation schedule. The results of ongoing clinical trials will

^{††} The 8% vs 4% values come directly from the text of the The New Zealand Ministry of Health Guidelines. It has been noted that these values are not consistent with the results reported in Whelan 2010, however the The New Zealand Ministry of Health Guidelines do not cite a page or table reference, or note if this data was calculated post hoc or obtained from the authors.

inform guidelines in the future. To minimise late tissue damage whilst maximising tumour control, the Guideline Development Team supported the administration of boost dose radiotherapy at 2 Gy per fraction where indicated following a hypofractionated regimen. The Guideline Development Team also noted that extended fractionation with smaller doses over five to six weeks should be considered in women with large breasts and postoperative side effects.

NICE 2009 guidelines for early and locally advanced breast cancer¹¹

The NICE 2009 guidelines made the following recommendation regarding dose fractionation:

Recommendation

- Use external beam radiotherapy giving 40 Gy in 15 fractions as standard practice for patients with early invasive breast cancer after breast conserving surgery or mastectomy.

Qualifying statement: This recommendation is based on RCT evidence of clinical effectiveness and the guideline development group agreeing that a regimen using fewer fractions would probably be cost effective.

The summary of the clinical evidence noted that rates of local recurrence were not significantly different between conventional 50 Gy fractions and hypofractionated schedules. One study (START B) found that distant relapse was lower in the hypofractionated arm which improved the rates of disease-free survival and overall survival.⁵ Assessments of cosmetic outcomes were less consistent, and depended on the comparisons made. One RCT⁷ reported no significant difference between the 50 Gy and 42.5 Gy arms, whilst another⁸ reported a significantly poorer cosmetic outcome in the 42.9 Gy arm when compared to the 39 Gy arm. The hazard ratio for no change in breast appearance was significantly improved in the 39 Gy arm of the START A trial⁴ compared to 50 Gy; whilst there was no difference between the 50 Gy and 41.6 Gy arms in START A⁴ or between 50 Gy and 40 Gy in START B⁵.

Global cosmetic outcomes were also less consistent since effects were reported at different times and between different fractionation doses. Breast oedema, fibrosis, lymphoedema and telangiectasia were reported in few studies.

The guidelines advised that careful treatment planning is required for all patients to avoid potential hotspots in the breast but this may be particularly important with hypofractionated schedules. Patients with breast reconstruction/augmentation or large breast size may have a better cosmetic result using conventional dose radiotherapy of 50 Gy in 25 fractions (lower dose per fraction), although 3D radiotherapy planning may make hypofractionated regimens equivalent.

The use of hypofractionated regimes should result in considerable saving of resources, both human and financial.

SIGN 2005¹²

The Scottish Intercollegiate Guidelines Network (SIGN) management of breast cancer in women guidance paper was developed in 2005, prior to the publication of a number of key RCTs (such as the START trials). No formal recommendations were made.

The guidelines noted that “current evidence is not able to identify an optimal dose/fractionation for post-operative radiotherapy. It is therefore reasonable to treat patients with currently accepted regimens such as 50 Gy in 25 daily fractions over five weeks, 45 Gy in 20 fractions, or 40 Gy in 15 or 16 fractions. Results of ongoing trials investigating fractionated are awaited”.

6 Conclusions

A systematic review of the literature identified five clinical trials of hypofractionated radiotherapy for the treatment of early breast cancer. Two trials were in patients who had undergone breast conserving surgery (RMH/GOC and Canadian trials)^{1-2, 7-8} and three were in patients who had undergone any form of surgery (START A, START B and Spooner)³⁻⁵. The studies evaluated a number of different hypofractionated radiotherapy regimens.

All five trials reported local recurrence rates (RMH/GOC, Canadian, Spooner, START A and START B trials). There was no evidence that any hypofractionated radiotherapy regimen was associated with a statistically significant difference in local recurrence rate when compared to a control arm. The Canadian trial reported no difference when subgroups were analysed, with the exception of tumour grade. The impact of the 42.5 Gy regimen on local recurrence was less in patients with high-grade tumours compared to patients with low-grade tumours ($p=0.01$).²

Two studies (START A and START B) reported local-regional and distant relapse. The studies found no significant difference in local-regional relapse.⁴⁻⁵ START B reported that the 40 Gy study arm had a statistically significantly lower rate of distant relapse when compared with the control arm ($p=0.01$).⁵

Four studies reported overall survival (Canadian, START A, START B and Spooner). Most studies reported that there was no evidence that hypofractionated radiotherapy was associated with a statistically significant difference in overall survival. The START B study found that 40 Gy in 15 fractions over three weeks was associated with a statistically significantly lower all-cause mortality rate when compared with 50 Gy in 25 fractions over five weeks ($p=0.03$).⁵ Therefore, there was no evidence that any hypofractionated radiotherapy regimen was associated with a worse overall survival rate (i.e. the only study that reported a significant difference showed lower mortality for patients treated with hypofractionated radiotherapy).

Three studies reported adverse events and toxicity outcomes (Canadian, START A and START B). There were generally no differences in adverse events and toxicity outcomes between the study arms. START A and START B noted a statistically significant difference in skin appearance (favouring the 39 Gy arm, $p=0.0019$ and 40 Gy arm, $p=0.0262$ when compared with the control arm).⁶

Four studies reported cosmetic outcomes (RMH/GOC, Canadian, START A and START B). Some studies reported differences in cosmetic outcomes between study arms. The RMH/GOC trial reported that the risk of developing any late radiation effect was statistically significantly lower for patients in the 39 Gy arm compared to the 50 Gy arm ($p=0.01$), but more often in the 42.9 Gy arm compared to the control ($p=0.05$).⁸ START A and START B reported that changes in skin appearance were less frequent in patients receiving 39 Gy in 13 fractions ($p=0.0019$) and patients receiving 40 Gy in 13 fractions ($p=0.0262$), when compared to 50 Gy in 25 fractions.⁶

START A and START B reported quality of life outcomes. There was no evidence that any hypofractionated radiotherapy regimen was associated with a statistically significant difference in quality of life score as measured by the BR23 breast symptom subscale. There was no difference in cosmetic outcomes or quality of life when outcomes were evaluated by surgery type.⁶

Overall, there was no evidence that the evaluated hypofractionated radiotherapy regimens were associated with an increased rate of local recurrence or reduced survival. There were some differences in adverse events and toxicity, as well as cosmetic outcomes.

All of the reported outcomes need to be considered in the context of range of hypofractionated radiotherapy regimens that were evaluated. Although 50 Gy in 25 fractions was used as a control arm in all trials, no two trials compared the same two radiotherapy regimens, making comparisons difficult. The study design should also be considered. Not all studies were powered to detect a difference in all outcomes. RMH/GOC^{1, 8} was powered to detect late change in breast appearance and the Canadian^{2, 7} trials were powered to detect a difference in local recurrence. START A⁴ and START B⁵ were powered to detect a difference in local-regional tumour relapse rate. The included studies had a follow-up period of 6 – 10 years. This length of follow-up should be sufficient to detect a difference in outcome.

The generalisability the findings must also be considered. For example, the Canadian trial excluded patients who had node-positive invasive carcinoma, or patients with a breast width of more than 25 cm.⁷ It may be that the results of this study may not apply to women with ductal carcinoma in situ only, women with node-positive cancer or women with large breasts.

The literature review did not identify any studies which specifically assessed the use of hypofractionated radiotherapy in conjunction with chemotherapy or other biological therapies. The Canadian trial assessed local recurrence by systematic therapy use, and found no difference recurrence rates.²

Overall, there was no evidence that any hypofractionated radiotherapy regimen was associated with a statistically significant difference in local recurrence rate or a significantly worse overall survival rate. There were some differences in adverse event, toxicity and cosmetic outcomes, although this was not consistent across all hypofractionated radiotherapy protocols. These results should be considered in the context of the included patient populations, statistical power of the studies, different hypofractionated radiotherapy regimens used and length of follow-up.

7 References

1. Owen JR, Ashton A, Bliss JM, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. *Lancet Oncol* 2006;7(6):467-71.
2. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010;362(6):513-20.
3. Spooner D, Stocken DD, Jordan S, et al. A randomised controlled trial to evaluate both the role and optimal fractionation of radiotherapy in the conservative management of early breast cancer. *San Antonio Breast Cancer Symposium*, 2008.
4. Bentzen SM, Agrawal RK, Aird EG, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol* 2008;9(4):331-41.
5. Bentzen SM, Agrawal RK, Aird EG, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* 2008;371(9618):1098-107.
6. Hopwood P, Haviland JS, Sumo G, et al. Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. *Lancet Oncol* 2010;11(3):231-40.
7. Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *J Natl Cancer Inst* 2002;94(15):1143-50.
8. Yarnold J, Ashton A, Bliss J, et al. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial. *Radiother Oncol* 2005;75(1):9-17.
9. Smith BD, Bentzen SM, Correa CR, et al. Fractionation for Whole Breast Irradiation: An American Society for Radiation Oncology (ASTRO) Evidence-Based Guideline. *Int J Radiat Oncol Biol Phys* 2010;July 15(Epub ahead of print):1-10.
10. New Zealand Guidelines Group (NZGG). *Management of early breast cancer*. NZGG: Wellington New Zealand, 2009.
11. National Institute for Health and Clinical Excellence (NICE). *Early and locally advanced breast cancer: diagnosis and treatment*. NICE: UK, 2009.
12. Scottish Intercollegiate Guidelines Network (SIGN) *Management of breast cancer in women: A national clinical guideline*. SIGN: Edinburgh Scotland, 2005.
13. National Breast Cancer Centre. *Clinical practice guidelines for the management of early breast cancer (2nd edition)*. Commonwealth of Australia: Canberra, 2001.
14. James ML, Lehman M, Hider PN, et al. Fraction size in radiation treatment for breast conservation in early breast cancer. *Cochrane Database Syst Rev* 2008;3):CD003860.
15. NIH consensus conference. *The treatment of early breast cancer*. *JAMA* 1991;265(3):391-5.
16. Ash D. Waiting times for cancer treatment. *Clin Oncol (R Coll Radiol)* 2000;12(3):140.
17. Mackillop WJ, Fu H, Quirt CF, et al. Waiting for radiotherapy in Ontario. *Int J Rad Oncol, Biol, Phys* 1994;30(1):221-8.
18. Shahid A, Athar MA, Asghar S, et al. Post mastectomy adjuvant radiotherapy in breast cancer: A comparison of three hypofractionated protocols. *J Pak Med Assoc* 2009;59(5):282-87.
19. Dwyer P, Hickey B and Burmeister B. Hypofractionated breast radiotherapy: impact on departmental waiting times and cost. *J Med Imag Radiat Oncol* 2009;54(3):229-34.

20. Taher AN, El-Baradie MM, Essa H, et al. Hypofractionation versus conventional fractionation radiotherapy after conservative treatment of breast cancer: early skin reactions and cosmetic results. *J Egypt Natl Canc Inst* 2004;16(3):178-187.
21. National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Canberra: Commonwealth of Australia, 2000.
22. National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Commonwealth of Australia: Canberra, 2009.
23. Egger M, Smith GD and Sterne JA. Uses and abuses of meta-analysis. *Clin Med* 2001;1(6):478-84.
24. Sprangers MA, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *J Clin Oncol* 1996;14(10):2756-2768.

Appendix A Contributors

Working group members

The following people were members of the working group:

- Associate Professor Boon Chua (Chair) Radiation oncologist
- Dr Marie-Frances Burke Radiation oncologist
- Professor Geoff Delaney Radiation oncologist
- Dr Jane O'Brien Surgeon
- Ms Jan Rice Breast care nurse
- Ms Geraldine Robertson Consumer representative
- Dr Kirsty Stuart Radiation oncologist

Cancer Australia staff

The following Cancer Australia staff were involved in the project:

- Ms Katrina Anderson Project Officer – Research
- Ms Phillipa Hastings Project Officer
- Dr Anne Nelson Evidence Review & Research Leader
- Ms Sue Sinclair General Manager
- Ms Heidi Wilcoxon Program Manager