Australian Government
Cancer Australia

Recommendations for use of

Hypofractionated radiotheraphy for early (operable) breast cancer

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A CLINICAL PRACTICE GUIDELINE DEVELOPED BY CANCER AUSTRALIA*

This guideline supplements guideline recommendations 10 on the use of radiotherapy (page 8) and information about radiotherapy (pages 67-75) in the *Clinical practice guidelines for the management of early breast cancer*, 2nd edition 2001.[1]

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Purpose

This guideline includes statements and recommendations based on available, high-level evidence about the use of hypofractionated *radiotherapy* for the treatment of women with early (operable) breast cancer. The guideline aims to provide health professionals with information designed to assist in making management recommendations for patient outcomes. These guidelines will inform the development of information specifically for consumers about *early breast cancer*, including treatment options.

Endorsed by:

The Royal Australian and New Zealand College of Radiologists
The Faculty of Radiation Oncology

* In 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.

Background

Early breast cancer is defined as tumours not more than five centimetres in diameter, with either impalpable or palpable but not fixed *lymph* nodes and with no evidence of distant metastases.[1] Primary treatment of early breast cancer usually involves surgery to remove the tumour (breast conserving surgery or mastectomy) and management of the *axilla*.[1] Complete pathology reporting following surgery will inform the *adjuvant* treatment options for individual women.

Several trials have shown that *breast conserving surgery* followed by whole breast *radiotherapy* is effective in reducing the risk of *local recurrence* and improving the long-term outcomes of appropriately selected patients with early breast cancer.[2]

Conventional adjuvant whole breast radiotherapy is typically delivered over a period of 5 weeks using a standard dose of 2 Gray (Gy) per treatment episode (fraction) in 25 fractions to a total dose of 50 Gy.[3] A tumour bed boost of 10-16 Gy in 2 Gy fractions[4,5] is sometimes delivered after whole breast radiotherapy.

Hypofractionated whole breast radiotherapy involves fewer fractions; however each fraction contains a larger daily dose of radiation than the conventional 2 Gy per fraction. The total dose of radiation used in a course of hypofractionated radiotherapy is reduced to compensate for the increased toxicity effect of larger daily fractions.

Compared to conventional radiotherapy regimens, the duration of a hypofractionated radiation treatment course is shorter by several days or weeks, as fewer fractions are required. A hypofractionated regimen may be more convenient for patients and less-resource intensive than a conventionally fractionated regimen.[6]

Conventional radiotherapy and hypofractionated radiotherapy can be hypothesised to have a similar effect, based on radiobiological principles. The aim of hypofractionated radiotherapy is to balance as high a daily dose as possible in order to kill tumour cells, against a dose low enough to minimise the side-effects of treatment.

Sensitivity of tissues to radiation fraction size is described by the α/β ratio. Low α/β values indicate greater sensitivity to fraction size than higher α/β values. It has been hypothesised that breast cancer is as sensitive to fraction size as normal breast tissue with a low α/β value, and confirmation would indicate that fewer, larger fractions are as effective as conventional 2 Gy fractions.[7]

Clinical Practice Recommendations

Please see the statements of evidence on which the recommendations are based.

Recommendations to individual women should be based on their circumstances, the absolute benefits and harms of treatment, and their personal preferences. These factors should be discussed with individual women. Women treated with conventional or hypofractionated *radiotherapy* should be reviewed regularly and monitored for side effects and adverse events.

It is important to note that research on hypofractionated whole breast radiotherapy for *early breast cancer* is continuing. Clinical judgement should be applied in the context of the currently available evidence and emerging findings from the continuing body of research.

RECOMMENDATIONS	LEVEL OF EVIDENCE[13]	REFERENCE
In women with early breast cancer who require post-operative whole breast radiotherapy and for whom hypofractionated radiotherapy is being considered:		
Women should be informed of the potential benefits and risks, and potential side effects and adverse events of hypofractionated radiotherapy and conventionally fractionated radiotherapy.	I	NBCC & NCCI[14]
Patient and tumour characteristics		
Hypofractionated radiotherapy can be offered as a suitable alternative to conventionally fractionated radiotherapy for women: • aged 50 years and over • with pathological *stage* T1-2, N0, M0 • with low or intermediate histologic *grade* breast cancer • who have undergone breast conserving surgery • with clear surgical margins	I	Cancer Australia systematic review[15] ASTRO guidelines[16]
There is insufficient evidence to make a recommendation for or against the use of hypofractionated radiotherapy for women: • aged less than 50 years • with pathologic stage T3+ and/or N1+ tumour • with high histologic grade breast cancer • who are treated with total mastectomy • who receive *chemotherapy* and/or targeted biological therapies Refer to patient characteristics table for characteristics of trial populations to inform clinical judgement on the suitability of hypofractionated radiotherapy for women within or outside the above criteria.		Cancer Australia systematic review[15] ASTRO guidelines[16]
Optimal schedule		
Recommended hypofractionated schedules for whole breast radiotherapy, based on current evidence are: • 42.5 Gy in 16 fractions given at the rate of one fraction per day, 5 fractions per week over 22 days	II	Canadian[6, 11]

RECOMMENDATIONS	LEVEL OF EVIDENCE[13]	REFERENCE
• 40 Gy in 15 fractions given at the rate of one fraction per day, 5 fractions per week over 21 days		START B[12]
Adverse events and toxicity		
When selecting an appropriate radiotherapy schedule, consideration should be given to the possibility of adverse events including early acute reactions and late toxic effects.	I	Cancer Australia systematic review[15]

Statements of evidence

Below are the statements of evidence on which the clinical practice recommendations are based.

STATEMENTS	LEVEL OF EVIDENCE[13]	REFERENCE
In women with early (operable) breast cancer who have undergone total mastectomy:		
There is insufficient evidence to inform the safety and efficacy of hypofractionated chest wall irradiation in women who have undergone *mastectomy*.		Cancer Australia systematic review[15]
In women with early (operable) breast cancer who have undergone breast conserving surgery:		
Patient and tumour characteristics		
Hypofractionated *radiotherapy* is equivalent to conventional fractionated regimens* of radiotherapy in women aged over 50 years, with pathological *stage* T1-2, N0, M0 and low to intermediate histologic *grade* tumours.	I	Cancer Australia systematic review[15]
Due to the relatively small numbers of patients in sub-group analyses of randomised trials, there is insufficient evidence to inform the safety and efficacy of hypofractionated radiotherapy for women: • aged less than 50 years • with locally advanced breast cancer • with a high histologic grade (grade 3) tumour • with node positive disease • who receive chemotherapy and/or targeted *biological therapies*. Refer to patient characteristics table.		Cancer Australia systematic review[15]
Local recurrence		
There are similar rates of local *recurrence* for women treated with hypofractionated radiotherapy and conventionally fractionated radiotherapy at 5-12 years follow-up.	I	Cancer Australia systematic review[15]
A hypofractionated radiotherapy regimen of 39 Gy in 13 fractions over 35 days is associated with a statistically significant higher rate of local recurrence compared with a hypofractionated radiotherapy regimen of 42.9 Gy in 13 fractions over 35 days at 10 years follow-up.	II	RMH/GOC, 2006[7]
Subgroup analysis of a randomised controlled trial showed that for patients with high grade tumours, the hypofractionated radiotherapy regimen of 42.5 Gy in 16 fractions over 22 days was associated with a higher local recurrence rate compared with conventionally fractionated radiotherapy regimens at 12 years follow-up. This finding has not been confirmed in the START A or START B trials.	II III	Canadian[6] Haviland[17]
Loco-regional recurrence		

STATEMENTS	LEVEL OF EVIDENCE[13]	REFERENCE
There are similar rates of loco-regional recurrence for women treated with hypofractionated radiotherapy and conventionally fractionated radiotherapy regimens at 5 years follow-up.	I	Cancer Australia systematic review[15]
Distant recurrence		
One randomised controlled trial reported that a hypofractionated radiotherapy regimen of 40 Gy in 15 fractions over 21 days is associated with a statistically significant lower rate of distant relapse than the conventionally fractionated regimen at 6 years median follow- up.	II	START B[12]
Overall survival		
There are similar overall survival rates reported for women treated with hypofractionated radiotherapy compared with patients treated with conventionally fractionated radiotherapy at 5-12 years follow-up.	I	Cancer Australia systematic review[15]
One randomised controlled trial reported that a hypofractionated radiotherapy regimen of 40 Gy in 15 fractions over 21 days was associated with a statistically significant lower all-cause mortality at 6 years median follow-up compared with the conventionally fractionated regimen.	II	START B[12]
Adverse events and cosmetic outcomes		
One randomised controlled trial reported that global cosmetic outcome worsened over time for women treated with either hypofractionated radiotherapy or conventionally fractionated radiotherapy, however there were no significant differences observed over 10 years between the hypofractionated regimen of 42.5 Gy in 16 fractions over 22 days and the conventionally fractionated regimen	II	Canadian[6]
One randomised controlled trial reported that the hypofractionated radiotherapy regimen of 39 Gy in 13 fractions over 35 days was associated with a lower risk of developing any late radiation effect than a conventionally fractionated radiotherapy regimen at 10 years follow-up. However, the hypofractionated regimen of 42.9 Gy in 13 fractions over 35 days was associated with a higher risk of developing any late radiation effect than a conventionally fractionated radiotherapy regimen at 10 years follow-up.	II II	RMH/GOC[9] RMH/GOC[9]
At 5 years follow-up, measuring changes in skin appearance, there was a statistically significant difference favouring the hypofractionated regimens of 39 Gy in 13 fractions over 35 days (START A) and 40 Gy in 15 fractions over 21 days (START B) compared to the conventionally fractionated regimen.	II	START A[10] START B[12] Hopwood[18]
Cardiac toxicity		
Evidence was insufficient or inconclusive about cardiac toxicity related to hypofractionated radiotherapy in comparison with		START A[10] START B[12]

STATEMENTS	LEVEL OF EVIDENCE[13]	REFERENCE
conventionally fractionated radiotherapy. However, the heart was protected from exposure to radiation in randomised controlled trials.		
Quality of life		
No statistically significant differences in quality of life scores were found in women undergoing radiotherapy after surgery between hypofractionated and conventionally fractionated radiotherapy regimens at 5 years follow-up.	II	START A[10] START B[12]
Regional nodal radiotherapy		
There is insufficient evidence to support the use of hypofractionated regional nodal radiotherapy.		Cancer Australia systematic review[15]
Tumor bed boost		
There is insufficient evidence to determine the safety and efficacy of a tumour bed boost administered in sequence after hypofractionated whole breast radiotherapy		Cancer Australia systematic review[15]
Chemotherapy/Targeted therapies		
There is insufficient evidence to determine the safety and efficacy of hypofractionated radiotherapy for women who receive chemotherapy and/or targeted biological therapies		Cancer Australia systematic review[15]

*Conventional regimens of radiotherapy usually involve a dose of 50 Gy in 25 fractions over 5 weeks.

Summary of evidence

The statements and recommendations about the use of hypofractionated radiotherapy for women with *early breast cancer* are based on a Cancer Australia systematic literature review including available evidence from 2001 to March 2010 from randomised controlled trials. The literature review was undertaken using a systematic method of searching and selection. Searches for full-length publications and abstracts were conducted in EMBASE, Medline and the Cochrane Database of Systematic Reviews. A search of conference websites was also conducted, including 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. Following application of the exclusion criteria, a total of 10 citations were identified as eligible for the review. Of the included citations there were two systematic reviews and five randomised controlled trials (some trials were reported by multiple citations).

Five randomised controlled trials, including one conference abstract[8] with limited information available, compared the use of one or more hypofractionated radiotherapy regimens to a conventional radiotherapy regimen for women with early *invasive breast cancer*. The United Kingdom's Royal Marsden Hospital/ Gloucestershire Oncology Centre[7, 9] (RMH/GOC) and the Standardisation of Breast *Radiotherapy* Trial A[10] (START A) tested two hypofractionated radiotherapy regimens. A Canadian trial[6, 11] and the Standardisation of Breast Radiotherapy Trial B[12] (START B) each tested one hypofractionated radiotherapy regimen. In all trials, the conventional radiotherapy regimen used as a comparator was 50 Gy in 25 fractions, delivered over 5 weeks.

A range of hypofractionated radiotherapy regimens were examined, including

- 39 Gy in 13 fractions over 35 days[7, 9-10]
- 40 Gy in 15 fractions over 21 days[12]
- 40 Gy in 15 daily fractions[8]
- 41.6 Gy in 13 fractions over 35 days[10]
- 42.5 Gy in 16 fractions over 22 days[6, 11]
- 42.9 Gy in 13 fractions over 35 days[7,9]

Two trials included women who had undergone *breast conserving surgery* only.[6-7, 9, 11] Three trials included women who had undergone breast conserving surgery or *mastectomy*.[8, 10, 12]

In patients who had breast conserving surgery, hypofractionated and conventional radiotherapy regimens were delivered to the whole breast in all five randomised controlled trials.

Median follow-up ranged from 5.1 years (4.4 - 6.0 years) in the START A[10] trial to 16.9 years (15.4 - 18.8 years) in the trial by Spooner et al.[8]

Summary of Trial Results

Trial and patient characteristics

Recommendations and statements of evidence have been made on the basis of the patient populations of the randomised trials. In some instances, patient populations included in sub-group analysis including age, tumour size and *grade*, use of tumour bed boost and use of adjuvant systemic therapies were smaller than required to infer broad clinical recommendations.

Table 1 identifies trial populations and primary outcomes measured. Of note:

- Five trials identified the patient population characteristics as early *invasive breast cancer* T1-3, N0-1, M0.[6-12]
- RMH/GOC and the Canadian trial limited the trial populations to those who had *breast conserving surgery* only.[6-7, 9, 11]
- Women participating in the Spooner, START A or START B trials had breast conserving surgery or *mastectomy*.[8, 10, 12]

Table 1: Trial characteristics

Trial	Population	Median follow-up (range) years	Intervention	Comparator	Outcomes measured
Post breast conserving surgery					
RMH/GOC[7, 9]	T1-3, N0-1, M0 <75 years	9.7 (7.8-11.8)	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[6,11]	Invasive *carcinoma* with negative axillary nodes	12 (range not reported)	42.5 Gy in 16 fractions over 22 days (n=622)	50 Gy in 25 fractions over 35 days (n=612)	Local recurrence Overall survival Adverse events and toxicity Cosmetic outcome
Post breast conserving surgery or mastectomy					
START A[10]	T1-3a, N0-1, M0	5.1 (4.4-6.0)	39 Gy in 13 fractions over 5 weeks (n=737) 41.6 Gy in 13 fractions over 5 weeks	50 Gy in 25 fractions over 5 weeks (n=749)	Local recurrence Overall survival

Trial	Population	Median follow-up (range) years	Intervention	Comparator	Outcomes measured
			(n=750)		Adverse events and toxicity Cosmetic outcome Quality of life
START B[12]	T1-3a, N0-1, M0	6.0 (5.0-6.2)	40 Gy in 15 fractions over 3 weeks (n=1110)	50 Gy in 25 fractions over 5 weeks (n=1105)	Local recurrence Overall survival Adverse events and toxicity Cosmetic outcome Quality of life
Spooner[8] Note: Conference abstract only, limited information available.	Stage 1 and 2 Median tumour size 2.0cms	16.9 (15.4-18.8)	40 Gy in 15 daily fractions or 50 Gy in 25 daily fractions	Delayed salvage treatment	Time to first relapse
			n=707		

Table 2 identifies key characteristics of patients involved in four of the randomised controlled trials

Table 2: Patient characteristics

	RMH/GOC n=1410 Yarnold[9]		Canadian n=1234 Whelan[11]		START A n=2236 Bentzen[10]		START B n=2215 Bentzen[12]	
	n	%	n	%	n	%	n	%
Treated with breast conserving surgery	1410	100%	1234	100%	1900	85%	2038	92%
Age >50 years	987	70%	929	75%	1727	77%	1758	79%
T0-2	1383	98%	994	81%	1741	78%	1987	90%
N0	564	40%	1234	100%[16]	1547	69%	1635	74%
Adjuvant treatment								
None	289	21%	593	48%	172	8%	84	4%
Tamoxifen only	918	65%	505	41%	1210	54%	1592	72%

	RMH/GOC n=1410 Yarnold[9]		Canadian n=1234 Whelan[11]		START A n=2236 Bentzen[10]		START B n=2215 Bentzen[12]	
Chemotherapy only	40	3%	136	11%	245	11%	155	7%
Tamoxifen + chemotherapy	156	11%	0	0%	548	25%	336	15%
Other	7	1%	0	0%	47	2%	27	1%
High tumour grade	NR	NR	233	19%	629	28%	509	23%

NR=Not Reported

Local Recurrence

Four trials reported on local recurrence.[6-7, 10-12] There was no evidence that hypofractionated *radiotherapy* regimens were associated with a statistically significant difference in local recurrence rate when compared with the control arms of 50 Gy in 25 fractions over 5 weeks.[6-7, 10, 12]RMH/GOC noted a statistically significant difference in recurrence rates between the two hypofractionated regimens (42.9 Gy vs 39 Gy: 9.6% vs 14.8%, p=0.027) but not when either of the hypofractionated regimens was compared to 50 Gy in 25 fractions.[7]

Subgroup analyses

Table 3 includes the local tumour recurrence rates reported by the randomised trials. Subgroup analyses for local recurrence were performed in one trial.[6] Analyses showed that treatment effect was similar regardless of age, tumour size, oestrogen-receptor status, and use of systemic therapy.

The Canadian, START A and START B trials included 19%, 28% and 23% of patients with high-grade tumours respectively. Among these women at 12 years follow-up, the Canadian trial reported a 10-year local recurrence rate of 15.6% for patients treated with hypofractionated radiotherapy compared to 4.7% for patients who received conventionally fractionated radiotherapy.[6] Results of the START A and START B trials at 8 years follow-up concluded that hypofractionated radiotherapy was equally effective for high and non-high grade breast cancers.[16]

In addition, a retrospective cohort study of patients with grade 3 tumours reported no evidence for inferiority in local control for hypofractionated radiotherapy (42.5-44 Gy in 16 fractions). The 10-year cumulative incidence of local relapse was 6.9% (95% CI 5.4-8.5%) for the hypofractionated group (n=1083) and 6.2% (95% CI 3.6-9.8%) for the conventional fractionation group (n=252) (p=0.99).[19]

Table 3: Five year rates for local recurrence[20]

Trial	Median follow-up (range) years	Treatment group	Five year local tumour recurrence rate (%)
RMH/GOC[7, 9]	9.7 (7.8-11.8)	50 Gy in 25 fractions over 5 weeks	12.1

Trial	Median follow-up (range) years	Treatment group	Five year local tumour recurrence rate (%)
		42.9 Gy in 13 fractions over 5 weeks	9.6
		39 Gy in 13 fractions over 5 weeks	14.8
Canadian[6, 11]	12 (not reported)	50 Gy in 25 fractions over 5 weeks	3.2^
		42.5 Gy in 16 fractions over 22 days	2.8^
START A[10]	5.1 (4.4-6.0)	50 Gy in 25 fractions over 5 weeks	3.2
		41.6 Gy in 13 fractions over 5 weeks	3.2
		39 Gy in 13 fractions over 5 weeks	4.6
START B[12]	6.0 (5.0-6.2)	50 Gy in 25 fractions over 5 weeks	3.3
		40 Gy in 15 fractions over 3 weeks	2.0

^ 6.7% and 6.2% at 10 years

Loco-regional recurrence

Two trials reported on loco-regional recurrence rates.[10, 12] There was no evidence that any hypofractionated regimen was associated with a statistically significant difference in local-regional recurrence rate when compared with the control arms of 50 Gy in 25 fractions over 5 weeks.[10, 12]

Distant recurrence

Two trials reported on distant recurrence.[10, 12] START B reported that the hypofractionated regimen of 40 Gy in 15 fractions over 3 weeks had a statistically significantly lower rate of distant relapse when compared with the conventional regimen of 50 Gy in 25 fractions over 5 weeks (HR 0.69 95% CI 0.53-0.91 p=0.01).[12] START A found no statistical difference between hypofractionated radiotherapy and the conventionally fractionated regimen (41.6 Gy arm, HR 0.92 95% CI 0.66-1.28, p=0.64; 39 Gy arm, HR 1.29 95% CI 0.95-1.76, p=0.10).[10]

Overall survival

Four trials reported on overall survival.[6, 8, 10, 12] START B found that 40 Gy in 15 fractions over three weeks was associated with a statistically significantly lower all-cause mortality when compared to 50 Gy in 25 fractions over five weeks (HR 0.76 95% CI 0.59-0.98, p=0.03).[12] The three other trials found no statistically significant difference in overall survival between hypofractionated and conventional regimens. Therefore, there was no evidence that hypofractionated radiotherapy was associated with worse overall survival in comparison to conventionally fractionated radiotherapy.

Adverse events and cosmetic outcomes

Four trials reported on adverse events and cosmetic outcomes.[6, 9-10, 12] Across the four trials and radiotherapy regimens tested, 30-55% of women experienced some change in breast appearance.

Canadian trial results

The Canadian trial reported on toxic effects of irradiation on the skin and subcutaneous tissue five and ten years after randomisation.[6] The incidence of reported effects increased over the follow-up period, although the proportion of women with grade 3 radiation-associated skin and subcutaneous tissue morbidity was 4% or less, with no reports of grade 4 morbidity. At 10 years, there were no skin toxic effects for 70.5% of women in the conventional radiotherapy group, compared to 69.8% of women in the hypofractionated radiotherapy group. There were no toxic effects in subcutaneous tissue in 45.3% of women in the conventional radiotherapy group, compared with 48.1% of women in the hypofractionated radiotherapy group.[6]

Following assessments at baseline, three, five and ten years after randomisation, the global cosmetic outcome worsened over time, however there were no significant differences observed between the 42.5 Gy group and the 50 Gy group at any time.[6] At ten years follow-up, 71.3% of women in the 50 Gy group compared to 69.8% of women in the hypofractionated radiotherapy treatment group had an excellent or good cosmetic outcome.[6] Cosmetic outcome was shown to be affected by time from randomisation, patient's age and tumour size but there was no interaction with the treatment.[6]

RMH/GOC trial results

After a minimum follow-up of five years, the proportion of patients who recorded any change in breast appearance after 50 Gy in 25 fractions, 39 Gy in 13 fractions and 42 Gy in 13 fractions was 39.6%, 30.3% and 45.7% respectively.[9]

For photographically assessed changes in breast appearance, the trial found a higher risk of developing any radiation effect for patients allocated to 42.9 Gy in 13 fractions, compared to those allocated to 39 Gy in 13 fractions or 50 Gy in 25 fractions (p=<0.001 for comparison of three fractionation schedules).[9]

Clinical assessment of patients also indicated significant differences between the three fractionation schedules, with the 42.9 Gy group experiencing the highest incidence of events for overall breast cosmesis (p=<0.001), breast shrinkage (p=0.026), breast distortion (p=0.005), breast oedema (p=0.004), induration (p=0.001) and shoulder stiffness (p=0.001).[9]

START A and START B trial results

START A found that according to patient self-assessments of five normal tissue effects on the breast or breast area* the rates of moderate or marked effects at five years were similar for 41.6 Gy and 50 Gy.[10] Rates of moderate or marked normal tissue effects tended to be lower after treatment in the 39 Gy group compared to the 50 Gy group, with a significantly lower rate of change in skin appearance (p=0.004). Changes in breast appearance and breast hardness were the most common changes reported.[10]

START A also measured change in breast appearance using photographic assessment; the hazard ratios for any change in breast appearance compared to the 50 Gy arm was 1.09 (p=0.62) after 41.6 Gy and 0.69 (p=0.01) after 39 Gy.[10]

Although mostly not statistically significant, the patient quality of life self-assessments of normal tissue effects in START B suggested that cosmetic outcomes were favourable in the 40 Gy group in most of the assessed normal tissue effects, with a significantly lower rate of change in skin appearance compared to the 50 Gy treatment arm (p=0.02).[12] Changes in breast appearance and breast hardness were the most common changes reported. Photographic assessments also showed that change in breast appearance was less likely after treatment in the 40 Gy arm than the 50 Gy arm with a hazard ratio of 0.83 (p=0.06).[12]

Combined results of the START A and START B trials found that any change in skin appearance occurred significantly less often in the 39 Gy and 40 Gy arms when compared with the control arms of 50 Gy in 25 fractions over five weeks (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).[18]

Other adverse events

Three trials investigated the incidence of symptomatic lung fibrosis and symptomatic rib fracture.[10-12] The reported rates were low at 5 years follow-up, and balanced between the regimens. One woman in the 41.6 Gy arm of the START A trial developed *pneumonitis* nine months after treatment; another developed mild signs of brachial plexopathy two years following treatment.[10] The Canadian trial reported four cases of pneumonitis (two women in the 42.5 Gy group, and two women in the 50 Gy treatment group).[11] One woman in the 50 Gy treatment group experienced rib fracture attributed to radiation therapy.[11]

While damage to the pectoral muscle has been highlighted as a possible concern,[20] none of the trials reported this outcome.

Cardiac toxicity

No trials reported the long-term effects of radiotherapy on cardiac tissues; however the START A authors noted the need to protect the heart from exposure to radiotherapy as a priority.[10] The Canadian trial identified no significant difference in overall survival between the conventional and hypofractionated radiotherapy regimens; at a median follow-up of 12 years, few cardiac-related deaths were observed, and no increase occurred in patients who received the hypofractionated schedule.[6]

The START A and START B trials report that the incidence of ischaemic heart disease was low at five years follow-up; however, the authors noted that 15-20 years of follow-up would be required to reliably measure the late normal tissue effects including cardiac damage.[10, 12]

Quality of life

Two trials reported quality of life outcomes using the European Organisation for Research and Treatment of Cancer (EORTC) breast cancer module.[10, 12] Three subscales were used in the analysis: breast symptoms (pain, swelling, oversensitivity, and skin problems in the breast); arm or shoulder symptoms subscale (swelling in the arm or hand, arm or shoulder pain, and difficulty moving the arm); and body image subscale. Based on these measures, there was no evidence that a hypofractionated radiotherapy regimen was associated with a statistically significant difference in quality of life scores.[18] Subgroup analysis by surgery type was performed. The small numbers of patients and events in some subgroups limited the statistical power of these analyses. There were no statistically significant differences in outcomes based on trial groups; nor were any interaction tests significant overall.[10, 12]

No other assessment of patient quality of life was available. Authors of the Canadian trial suggested that the inconvenience of a prolonged course of daily treatment made a substantial contribution to the decreased

quality of life experienced by women treated with radiotherapy for breast cancer.[11] A shorter fractionation schedule lessens the practical burden of treatment for women, and will have important quality of life benefits with respect to convenience and less time away from home and work.

Regional nodal radiotherapy

Three trials included women undergoing regional nodal radiotherapy.[9-10, 12] RMH/GOC trial reported that 20.6% of patients underwent regional nodal radiotherapy to the *axilla* and/or supraclavicular fossa.[9] There were no recorded cases of brachial plexopathy among these women.

START A reported that the decision to administer regional nodal radiotherapy was made pre-randomisation and was used in approximately 14% of patients.[10] One patient developed mild symptoms of brachial plexopathy but it was not reported if the patient received regional nodal radiotherapy. In two patients randomised to the 41.6 Gy arm and prescribed radiotherapy to the breast and supraclavicular fossa, the total dose was reduced to 39 Gy because of concerns regarding sensitivity of brachial plexus to fraction size.[10]

START B reported that 7.3% of patients received regional nodal radiotherapy.[12] No cases of brachial plexopathy were reported among the women given radiotherapy to the supraclavicular fossa, axilla or both.[12]

Use of tumour bed boost

Tumour bed boost was used in three of the randomised trials.[9-10, 12] Between January 1986 and July 1997, patients in the RMH/GOC trial were randomly assigned to receive a boost or not. Subsequently, all patients were offered an elective boost. The proportion of women who received a tumour bed boost was similar among the treatment groups.[10] There was a statistically significant reduced risk of induration (p=0.001) and telangiectasia (p=0.026) in patients randomised to no boost.[9]

The proportion of women who received a tumour bed boost was similar among the treatment groups in the START A and START B trials. However, sub-group analysis on tumour bed boost was not reported.[10, 12]

Use of adjuvant systemic therapies

Four trials included women who received adjuvant systemic therapies.[6-7, 10, 12] In the Canadian trial, 11% of women received chemotherapy in both the conventional and hypofractionated radiotherapy regimens; and 41% received tamoxifen in both the conventional and hypofractionated radiotherapy regimens.[6] Sub-group analysis of the rates of local recurrence showed no statistically significant difference between the conventional and hypofractionated regimens at five years and ten years.[6]

No sub-group analysis on the use of systemic therapies was reported in the RMH/GOC, START A or START B trials.[7, 9-10, 12] In each trial, the proportions of women who received systemic therapies including tamoxifen and/or chemotherapy were similar among the study groups. The START trials required a two week gap between exposure to chemotherapy and radiotherapy.[10, 12]

No trials specifically assessed the use of hypofractionated radiotherapy in conjunction with chemotherapy or other *biological therapies*.

Delivery of radiotherapy

Four trials provided information on the radiotherapy techniques used. Patients in all four trials were treated in a supine position. The RMH/GOC and Canadian trials specified that patients were treated with one or both arms raised above the shoulder.

In all four trials, 6-megavoltage *x-rays* were used for most patients but higher energy megavoltage x-rays or cobalt x-rays were also used. Where regional radiotherapy was indicated, the target volume included the supraclavicular nodes with or without the axillary nodes.[7, 10, 12]

Four trials reported that the maximum dose to the breast on the central axis was no less than 93% to 95% and no more than 105% to 107% of the prescribed dose.[6-7, 9-12] The Canadian trial excluded patients whose separation along the central axis exceeded 25cm; however the other trials used higher energy x-rays for patients with larger breasts to achieve acceptable dose homogeneity.[6-7, 10-12] RMH/GOC and Canadian trials reported the use of wedge tissue compensators to ensure a uniform dose distribution throughout the target volume.[7, 9, 11]

Three trials included women allocated to receive a tumour bed boost.[9-10, 12]Women allocated to receive a boost in RMH/GOC received a dose of 14 Gy to the 90% isodose (15.5 Gy to 100%) in 7 daily fractions.[9] Ten Gy in 5 daily fractions to the 100% isodose was delivered after whole breast radiotherapy to women allocated to receive a boost in the START A and START B trials.[10, 12]

*Patient quality of life self-assessments include the following changes since radiotherapy - breast shrinkage; breast hardness; change in skin appearance; swelling in area of affected breast; change in breast appearance.

Strengths and weaknesses of evidence

Overall the evidence included in the systematic review was of high quality.[15] One trial, Spooner[8], was rated as low quality evidence, as results were limited to one conference abstract. All trials included populations of over 700 women.[15]

All reported outcomes need to be considered in the context of the range of hypofractionated *radiotherapy* regimens that were evaluated. Although 50 Gy in 25 fractions was used as a control arm in all trials, six different hypofractionated radiotherapy regimens were investigated.

Not all trials were powered to detect a difference in all outcomes. RMH/GOC and the Canadian trial were powered to detect a difference in local tumour *recurrence* rates. START A and START B were powered to detect a difference in local-regional tumour relapse rate. The included trials had a follow-up period of 5-17 years.[15]

Unanswered questions

Important unanswered questions about the use of hypofractionated *radiotherapy* in *early breast cancer* are outlined below. Some of these questions may be addressed in ongoing trials:

- Treatment outcomes for patients who received hypofractionated radiotherapy in relation to age, tumour size and histologic grade
- Optimal hypofractionated radiotherapy schedule
- Safety and efficacy of tumour bed boost administered after hypofractionated radiotherapy
- Safety and efficacy of hypofractionated regional nodal radiotherapy
- Hypofractionated radiotherapy for DCIS
- Potential interactions between *adjuvant* systemic therapies and hypofractionated radiotherapy
- Long-term effects of hypofractionation on cardiac toxicity
- Long-term effects of hypofractionation on rib morbidity
- Psychosocial outcomes for women receiving hypofractionated radiotherapy, including impact of hypofractionated radiotherapy on quality of life, such as side-effects and practical implications of a shorter treatment schedule
- Health economic considerations of hypofractionated radiotherapy

Ongoing Trials

One randomised controlled trial investigating the use of hypofractionated *radiotherapy* for *early breast cancer* is ongoing:

- FAST Trial** (UK) compares 28.5 Gy or 30 Gy in five once-weekly fractions of 5.7 Gy or 6.0 Gy respectively, with a control dose of 50Gy in 25 fractions over 5 weeks, delivered with three dimensional dose-compensated whole-breast radiotherapy.

**First results of the FAST Trial have indicated the 28.5 Gy in 5 fractions schedule was comparable to the schedule 50 Gy in 25 fractions, and milder than the 30 Gy in 5 fractions schedule, for adverse effects on breast appearance.[21]

International Guidelines

- The American Society for Radiation Oncology (ASTRO) guidelines on fractionation for whole breast irradiation 2010[16]
- The New Zealand Ministry of Health Guidelines for Management of Early Breast Cancer 2009
- NICE 2009 Guidelines for early and locally advanced breast cancer

Conclusion

Overall, there was no evidence that any of the hypofractionated *radiotherapy* regimens investigated in the randomised controlled trials was associated with a statistically significant difference in *local recurrence* rate or a significantly worse overall survival rate when compared to a conventionally fractionated regimen. However, subgroup analysis of one randomised controlled trial[6] showed adverse local control outcomes for patients with a high *grade* tumour treated with hypofractionated radiotherapy after *breast conserving surgery*. This has not been confirmed in other trials. There were some differences in adverse events, toxicity and cosmetic outcomes, although they were not consistent across the hypofractionated radiotherapy protocols.

These results should be considered in the context of the included patient populations, statistical power of the trials, variations in the hypofractionated radiotherapy regimens used and lengths of follow-up. There were insufficient patient numbers in the trials to make a definitive recommendation about the integration of systemic therapy, regional nodal radiotherapy and tumour bed boost in patients who receive hypofractionated radiotherapy. Adverse events including cosmetic outcomes are important considerations for women receiving radiotherapy. Clinicians should consider and discuss with women the absolute benefits and harms when considering a hypofractionated radiotherapy regimen.

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External Review

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Topic-specific guideline development process

Priority topic areas for guideline development are determined in consultation with key stakeholders including experts in relevant disciplines and consumer representatives. A specific multidisciplinary Working Group, including consumers, is established for each topic identified and is involved in all aspects of guideline development. A systematic evidence review is undertaken for each guideline. All members are asked to declare any conflicts of interest and these declarations are recorded. The content of the guideline is not influenced by any external funding body. The guideline is reviewed externally by key stakeholders and the wider community and endorsement is sought from relevant professional colleges and groups in Australia.

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