External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial

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Summary

Background Whole breast irradiation delivered once per day over 3–5 weeks after breast conserving surgery reduces local recurrence with good cosmetic results. Accelerated partial breast irradiation (APBI) delivered over 1 week to the tumour bed was developed to provide a more convenient treatment. In this trial, we investigated if external beam APBI was non-inferior to whole breast irradiation.

Methods We did this multicentre, randomised, non-inferiority trial in 33 cancer centres in Canada, Australia and New Zealand. Women aged 40 years or older with ductal carcinoma in situ or node-negative breast cancer treated by breast conserving surgery were randomly assigned (1:1) to receive either external beam APBI (38·5 Gy in ten fractions delivered twice per day over 5–8 days) or whole breast irradiation (42·5 Gy in 16 fractions once per day over 21 days, or 50 Gy in 25 fractions once per day over 35 days). Patients and clinicans were not masked to treatment assignment. The primary outcome was ipsilateral breast tumour recurrence (IBTR), analysed by intention to treat. The trial was designed on the basis of an expected 5 year IBTR rate of 1·5% in the whole breast irradiation group with 85% power to exclude a 1·5% increase in the APBI group; non-inferiority was shown if the upper limit of the two-sided 90% CI for the IBTR hazard ratio (HR) was less than 2·02. This trial is registered with ClinicalTrials.gov, NCT00282035.

Findings Between Feb 7, 2006, and July 15, 2011, we enrolled 2135 women. 1070 were randomly assigned to receive APBI and 1065 were assigned to receive whole breast irradiation. Six patients in the APBI group withdrew before treatment, four more did not receive radiotherapy, and 16 patients received whole breast irradiation. In the whole breast irradiation group, 16 patients withdrew, and two more did not receive radiotherapy. In the APBI group, a further 14 patients were lost to follow-up and nine patients withdrew during the follow-up period. In the whole breast irradiation group, 20 patients were lost to follow-up and 35 withdrew during follow-up. Median follow-up was 8·6 years (IQR 7·3–9·9). The 8-year cumulative rates of IBTR were 3·0% (95% CI 1·9–4·0) in the APBI group and 2·8% (1·8–3·9) in the whole breast irradiation group. The HR for APBI versus whole breast radiation was 1·27 (90% CI 0·84–1·91). Acute radiation toxicity (grade ≥2, within 3 months of radiotherapy start) occurred less frequently in patients treated with APBI (300 [28%] of 1070 patients) than whole breast irradiation (484 [45%] of 1065 patients, p<0·0001). Late radiation toxicity (grade ≥2, later than 3 months) was more common in patients treated with APBI (346 [32%] of 1070 patients) than whole breast irradiation (142 [13%] of 1065 patients; p<0·0001). Adverse cosmesis (defined as fair or poor) was more common in patients treated with APBI than in those treated by whole breast irradiation at 3 years (absolute difference, 11·3%, 95% CI 7·5–15·0), 5 years (16·5%, 12·5–20·4), and 7 years (17·7%, 12·9–22·3).

Interpretation External beam APBI was non-inferior to whole breast irradiation in preventing IBTR. Although less acute toxicity was observed, the regimen used was associated with an increase in moderate late toxicity and adverse cosmesis, which might be related to the twice per day treatment. Other approaches, such as treatment once per day, might not adversely affect cosmesis and should be studied.

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Introduction

Whole breast irradiation after breast conserving surgery reduces local recurrence, improves survival, and provides good cosmetic results for women with early-stage breast cancer.[1–4] Whole breast irradiation is usually delivered once per day over 3–5 weeks, and so accelerated partial breast irradiation (APBI), delivered over 1 week or less to the tumour bed, was developed to provide a more convenient treatment.[5] After breast conserving surgery, most local recurrences occur at or near the primary site of the cancer,[6–8]

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See Online for appendix

Research in context

Evidence before this study

Radiotherapy to the whole breast for 3–5 weeks duration has been the standard treatment after breast conserving surgery. Accelerated partial breast irradiation (APBI) techniques were developed to reduce treatment time. An underlying premise of APBI was that the smaller volume of breast tissue could be treated with larger fractions over a shorter period with acceptable toxicity. The limiting of treatment to the primary tumour site was on the basis of previous studies that had shown that this was where most local recurrences occurred.

Before initiating the trial, we did a systematic review of breast irradiation using MEDLINE from Jan 1, 1966, to Jan 31, 2005. Search terms included: "breast neoplasms", "lumpectomy", "breast conservation", "radiotherapy", "partial breast irradiation", "clinical trials", "practice guidelines", and "meta-analysis". We identified 20 prospective, phase 1–2 trials evaluating different techniques for partial breast radiotherapy including single or multicatheter brachytherapy, intraoperative therapy, and external beam radiotherapy using 3D conformal or intensity modulated techniques. All techniques were promising, with little local failure or toxicity. We chose to evaluate CT-guided, external beam radiotherapy in our trial because it was non-invasive and was not resource intensive as it used existing widely available radiotherapy technology.

Added value of this study

Several randomised trials of different techniques of partial breast irradiation have been published with conflicting results. Two trials of intraoperative radiotherapy reported higher rates of local recurrence compared with conventional whole breast irradiation. A trial of interstitial brachytherapy and another of non-accelerated (over 3 weeks) external beam partial breast radiotherapy reported similar rates of local recurrence compared with whole breast irradiation, but median follow-up was 6–6·6 years and few events were observed. This report of the RAPID trial provides longer-term outcomes (8·6 years median follow-up) and more events for an accelerated (twice daily for 5 days) partial breast external beam technique compared with whole breast irradiation for women with ductal carcinoma in situ and node-negative breast cancer. The results show similar rates of local recurrence and reduced acute toxicity (within 3 months of treatment) for APBI compared with whole breast irradiation. The twice per day dose prescription regimen caused more grade 2 or higher late toxic effects and worse cosmetic outcomes.

Implications of all the available evidence

Our results show that although the APBI regimen in RAPID was non-inferior to whole breast irradiation in terms of local recurrence, it was associated with increased late toxicity and adverse cosmesis. Hence, we are not able to recommend the twice per day regimen used in RAPID for routine clinical practice. This study in conjunction with previous trials supports the importance of radiotherapy technique, dose, and fractionation on outcomes after breast conserving surgery. Accelerated external beam partial breast irradiation given once per day might not be associated with increased toxicity and is a subject of ongoing investigation.

which could be treated effectively with partial breast radiotherapy. Moreover, the smaller breast volume could be treated with larger radiotherapy fractions in a shorter period with similar toxicity to whole breast irradiation.[9]

Several different techniques for APBI have been developed, including single or multicatheter brachytherapy; intraoperative therapy with electrons or photons, and external beam radiotherapy using 3-dimensional conformal radiotherapy (3DCRT) or intensity modulated radiotherapy (IMRT). External beam radiotherapy is non-invasive and uses modern CT planning systems and linear accelerators that are widely available, whereas other methods are invasive and resource intensive, requiring surgical procedures and specialised radiotherapy delivery systems. We did a pilot study[10] of external beam APBI in 104 women with early-stage breast cancer. At a median follow-up of 37 months, only one local recurrence and one grade 3 toxicity were observed.

On the basis of these results, we initiated a randomised controlled trial (RAPID) in February 2006. The primary objective of the trial was to find out if external beam APBI delivered in 1 week was non-inferior to whole breast irradiation with respect to preventing local recurrence after breast conserving surgery. An important secondary objective was to evaluate the late radiation toxicity associated with APBI compared with whole breast irradiation. At a planned interim analysis after a median follow-up of 2·5 years, we observed an increase in adverse cosmesis associated with APBI.[11] The results of the planned primary efficacy and long-term toxicity analyses are now reported.

Methods

Study design and participants

We did this multicentre, randomised, non-inferiority trial in 33 cancer centres in Canada, Australia, and New Zealand (appendix pp 2–4). Eligible patients were women aged 40 years or older with ductal carcinoma in situ (DCIS) or invasive ductal carcinoma who had undergone breast conserving surgery. Eligible patients had microscopically clear margins and negative axillary lymph nodes, measured by sentinel node biopsy or axillary dissection for those with invasive disease, and by clinical examination for those with DCIS alone. Patients with isolated tumour cells or micrometastases 2 mm or smaller in the lymph nodes were eligible. Exclusion criteria included tumour size larger than 3 cm, lobular carcinoma, more than one primary tumour in different

quadrants of the breast, or a radiotherapy plan that did not meet protocol-defined dose volume constraints for APBI (appendix p 5). Ethics approval was obtained by the institutional review board of each participating centre, and written informed consent was obtained from all patients.

Randomisation and masking

At random assignment, patients were stratified for age (<50 years, ≥50 years), histology (DCIS alone or invasive breast cancer), tumour size (<1·5 cm, ≥1·5 cm), oestrogen receptor (positive, negative) if invasive disease, and treatment centre. Eligible patients were randomly allocated (1:1) by the Ontario Clinical Oncology Group coordinating centre in Hamilton, ON, Canada, using a centralised minimisation procedure, to whole breast irradiation (control arm) or APBI. Due to treatment administration, patients and clinicians could not be masked to treatment assignment.

Procedures

All patients were CT-planned and treated with external beam radiotherapy in the supine position. Patients assigned to whole breast irradiation were treated with 42·5 Gy in 16 fractions once per day or 50 Gy in 25 fractions once per day using a pair of opposed fields tangentially arranged across the chest. The longer fractionation was permitted for large breast size at the discretion of the treating radiation oncologist. Wedges or limited forward planning with IMRT (field-in-field technique) were permitted. Other radiotherapy planning details are provided in the appendix (p 6). Additional boost radiation to the primary site of 10 Gy in 4–5 fractions once per day was permitted for patients deemed at moderate to high risk of local recurrence as per local centre policy.

Patients allocated to APBI were treated with 3–5 non-coplanar, conformal fields. The clinical target volume was the tumour bed including surgical clips, plus a 1 cm margin excluding chest wall, pectoralis major, and 5 mm from skin. The planning target volume was the clinical target volume plus an additional 1 cm expansion. 3DCRT or IMRT was permitted. The prescribed dose was 38·5 Gy in 10 fractions administered twice per day, separated by 6–8 h over 5–8 days. Boost radiation was not permitted. Other radiotherapy planning details are provided in the appendix (p 6). Adjuvant chemotherapy, if used, was given before radiotherapy. Endocrine therapy was initiated either concurrently or after radiotherapy. Trastuzumab was recommended for patients with human epidermal growth factor receptor 2 positive disease. There was a comprehensive radiotherapy quality assurance (RTQA) programme to ensure radiotherapy was administered according to protocol. Before a study site was opened for accrual, physicians' contouring of the tumour bed and each centre's APBI planning were credentialled. After opening, each centre completed a pretreatment review of at least ten patients who received APBI (appendix p 6). A final RTQA review was done on all randomised patients. Patients were followed up according to a prescribed schedule (appendix p 6).

Outcomes

The primary outcome was ipsilateral breast tumour recurrence (IBTR), defined as histological evidence of invasive or in situ disease in the ipsilateral breast. IBTR was described as a true or marginal recurrence if it recurred within 2 cm of the tumour bed, or as an elsewhere recurrence. Secondary outcomes were disease-free survival (defined as time from random assignment to documented recurrence in the ipsilateral breast, regional lymph nodes, or distant sites), event-free survival (defined as time from random assignment to documented recurrence, contralateral breast cancer, second cancer, or death), overall survival, radiation toxicity, adverse cosmesis, and quality of life. All events (recurrences, second cancers, and deaths) were adjudicated by two physicians unaware of treatment allocation. If there was disagreement, a third physician reviewed the event.

Toxicity was assessed with the National Cancer Institute Common Terminology Criteria for Adverse Events v3. Adverse cosmesis was defined as the proportion of patients with a fair or poor global cosmetic score using the European Organisation for Research and Treatment of Cancer Breast Cancer Cosmetic Rating System.[12] Nurses compared the treated breast with the untreated breast and graded characteristics including the size and shape of the breast, location of the areola and nipple, presence of telangiectasia, appearance of the surgical scar, and global cosmetic score. Characteristics were graded on a four-point scale: 0=excellent or no difference, 1=good or small difference, 2=fair or moderate difference,

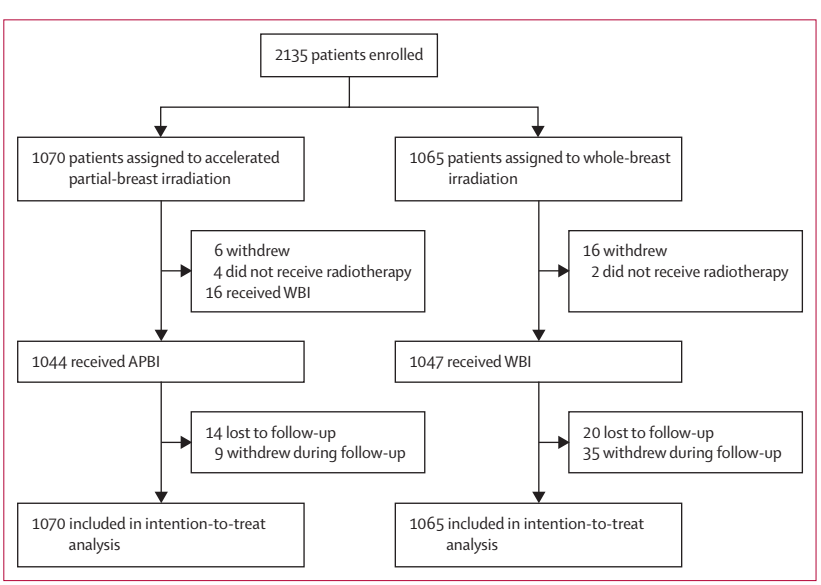

Figure 1: **Trial profile**

and 3=poor or large difference. Only the global cosmetic outcome is reported. Nurses were trained with an online guide and standardised photographs. Patients were also asked to provide a self-assessment of cosmetic outcome using a similar questionnaire.

	APBI	WBI
All patients		
n	1070	1065
Age at entry, years; median (IQR)	61 (54–68)	61 (54–68)
Histology		
Invasive disease	879 (82%)	875 (82%)
DCIS only	191 (18%)	190 (18%)
Tumour size		
<1·5 cm	758 (71%)	734 (69%)
≥1·5 cm	312 (29%)	331 (31%)
Patients with invasive disease		
n	879	875
Age at entry, years; median (IQR)	62 (55–68)	62 (54–68)
Tumour size		
<1·5 cm	613 (70%)	587 (67%)
≥1·5 cm	266 (30%)	288 (33%)
Oestrogen receptor		
Positive	803 (91%)	779 (89%)
Negative	76 (9%)	96 (11%)
Her2neu status		
Positive	56 (6%)	44 (5%)
Negative	794 (90%)	802 (92%)
Unknown	29 (3%)	29 (3%)
Nodal status		
pN0	874 (99%)	865 (99%)
pN0(i+), pN1mi	5 (<1%)	10 (1%)
Nodal assessment		
Sentinel node biopsy	643 (73%)	651 (74%)
Axillary node dissection	229 (26%)	224 (26%)
Unknown	7 (1%)	0
Overall grade		
1	387 (44%)	362 (41%)
2	353 (40%)	361 (41%)
3	133 (15%)	143 (16%)
Unknown	6 (1%)	9 (1%)
Lymphovascular invasion		
Present	60 (7%)	51 (6%)
Not present	819 (93%)	824 (94%)
Adjuvant therapy		
Endocrine therapy	540 (61%)*	510 (58%)*
Chemotherapy	109 (12%)*	115 (13%)*
No adjuvant therapy	300 (34%)	319 (36%)

Data are n (%) unless otherwise specified. APBI=accelerated partial breast irradiation. WBI=whole breast irradiation. DCIS=ductal carcinoma in situ. pN0=no regional node metastasis identified histologically. pN0(i+)=malignant cells identified in regional nodes no larger than 0·2 mm. pN1mi=micrometastasis larger than 0·2 mm and no larger than 2 mm. *70 APBI and 69 WBI patients received both endocrine and chemotherapy.

Table 1: **Patient characteristics by treatment**

Statistical analysis

The study was designed to assess the non-inferiority of APBI relative to whole breast irradiation. Originally, we estimated an IBTR risk of 4% at 5 years on the basis of our previous trial of hypofractionated whole breast irradiation in node-negative breast cancer.[13] Based on a non-inferiority margin of 2·75% (HR <1·71), one-sided α 5% and power 90%, 124 events were required in 2128 patients. By September, 2010, less than half of the IBTR events expected had occurred and we did not consider it practical or cost-effective to extend follow-up or accrue more patients. Blinded to treatment allocation, we adjusted the sample size on the basis of an expected 5-year IBTR rate of 1·5%, a revised non-inferiority margin of 1·5% (HR <2·02), and 85% power, which required 64 events in a similar number of patients. The inferiority margin was small clinically and was deemed acceptable. Two interim analyses for efficacy were done after 30 and 50 events using the Peto-Haybittle rule.

The two radiotherapy regimens were compared using the estimate of the HR from a Cox proportional hazards model with treatment as the single predictor, and stratified on age, tumour size, histology, and oestrogen receptor status (for invasive disease only). Non-inferiority was declared if the upper bound of the two-sided 90% CI for HR was less than 2·02. The Kaplan-Meier method was used to describe the IBTR rates. Disease free survival, event-free survival, and overall survival were analysed similarly. For these, HRs with 95% CIs were calculated and non-inferiority tests were not considered. Data censoring details are provided (appendix p 6). The number of IBTRs that were a true or marginal recurrence, or an elsewhere recurrence, were reported for each treatment group. Heterogeneity of the treatment effect according to prespecified subgroups were examined using Cox modelling (including only treatment with each factor and their interaction) for each of the following categorical variables: the stratification factors (age, histology, tumour size, oestrogen receptor), tumour grade for invasive disease patients (grade 3 *vs* other), adjuvant therapy (yes *vs* no), and the American Society of Radiation Oncology APBI Suitability Criteria (suitable *vs* not suitable).[14] All analyses were based on the intention-to-treat principle. A per protocol analysis including only patients who received study treatment as allocated was done for IBTR as a sensitivity analysis.

The proportion of patients with radiation-related toxic effects in each treatment group were compared by grade using Fisher's exact test. The proportion of patients in each treatment group with an adverse (fair or poor) cosmetic outcome based on the nurse assessments was compared at 3, 5, and 7 years using the Fisher's exact test. For these multiple comparisons, statistical significance was defined as p<0·01. A similar approach was used for patient self-assessments of cosmetic outcome. All analyses were done with the use of SAS software, version 9.4. This trial was registered with ClinicalTrials.gov, NCT00282035.

Role of the funding source

The funders of the trial had no role in the study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the study data and had final responsibility for the decision to submit for publication. JAJ and MNL also had full access to the study data.

Results

Study participants

Between Feb 7, 2006, and July 15, 2011, 2135 patients were enrolled in the trial, with 1070 patients assigned to APBI and 1065 to whole breast irradiation. 26 APBI patients did not receive the assigned treatment: 16 received whole breast irradiation, six withdrew from the study, and four did not receive radiotherapy. In the whole breast irradiation group, 18 patients did not receive the assigned treatment: 16 withdrew, and two did not receive radiotherapy (figure 1). 23 patients receiving APBI and 55 patients receiving whole breast irradiation had incomplete follow-up due to withdrawal or loss to follow-up.

Baseline characteristics were similar between treatment groups (table 1). Median age was 61 years (IQR 54–68); 82% had invasive cancer and 18% had DCIS only. For invasive cancers, 68% of tumours were <1·5 cm, 90% were oestrogen receptor positive, 60% received endocrine therapy, and 13% received chemotherapy. APBI was delivered using 3DCRT in 934 (87%) of 1070 patients and IMRT in 110 (10%). Whole breast irradiation was delivered as 42·5 Gy in 16 fractions in 873 (82%) of 1065 patients, and 224 (21%) of 1065 patients received boost radiation. On final radiotherapy review, protocol deviations were observed in 44 (4·1%) of 1070 patients treated with APBI and in nine (0·8%) of 1065 patients treated with whole breast irradiation. Median follow-up was 8·6 years (IQR 7·3–9·9).

65 IBTRs were observed, 37 in the APBI group, and 28 in the whole breast irradiation group. In patients treated with APBI, the 5 year cumulative rate of IBTR was 2·3% (95% CI 1·4–3·2) and the 8 year cumulative rate was 3·0% (1·9–4·0). In patients treated with whole breast irradiation, the 5 year cumulative rate of IBTR was 1·7% (0·9–2·5) and the 8 year cumulative rate was 2·8% (1·8–3·9; figure 2). The HR for APBI versus whole breast irradiation was 1·27 (90% CI 0·84–1·91). Thus, the upper bound of the estimated 90% CI did not exceed the non-inferiority margin of 2·02. A per protocol analysis provided similar results (appendix p 7). 37 (57%) of 65 IBTRs were at or near the primary site (17 in the APBI group, 20 in the whole breast irradiation group) and 28 (43%) occurred elsewhere in the breast (20 in the APBI group, eight in the whole breast irradiation group). The treatment effect was homogeneous across different subgroups (appendix p 10).

Cancer outcomes as a first event are shown in table 2. No statistical differences were observed between

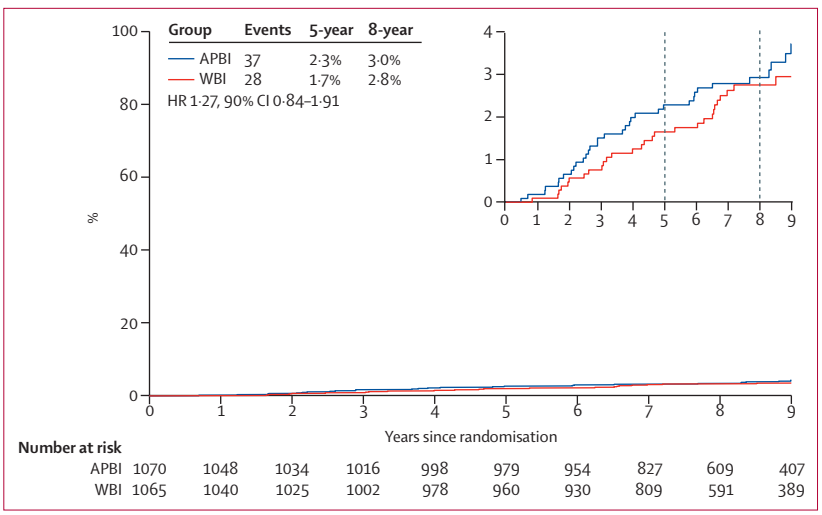

Figure 2: **Rates of IBTR over time**

1 minus Kaplan-Meier estimates for IBTR. The insert shows the same graph but with the y-axis truncated at 4%. IBTR=ipsilateral breast tumour recurrence. APBI=accelerated partial breast irradiation. WBI=whole breast irradiation. HR=hazard ratio.

	APBI	WBI
Total patients	1070	1065
Ipsilateral breast tumour recurrence	37 (3·5%)	28 (2·6%)
Regional recurrence	4 (0·4%)	2 (0·2%)
Distant recurrence	20 (1·9%)	18 (1·7%)
Contralateral breast cancer	29 (2·7%)	38 (3·6%)
Non-breast second cancer*	84 (7·9%)	57 (5·4%)
Death	25 (2·3%)	27 (2·5%)
Any event	199 (19%)	170 (16%)

Data are n (%) unless otherwise specified. APBI=accelerated partial breast irradiation. WBI=whole breast irradiation. *Site of second cancers are provided in the appendix (p 8).

Table 2: **Event types as a first event by treatment group**

treatment groups for disease free survival (HR 1·20, 95% CI 0·83–1·76; appendix p 11) or for event-free survival (1·16, 0·95–1·43; appendix p 12). There were 140 deaths in total (76 in the APBI group, 64 in the whole breast irradiation group) and no differences were detected in overall survival (1·18, 0·84–1·64; appendix p 13). In the APBI group, 24% of deaths were due to breast cancer, 42% to other cancers, and 8% to cardiac disease; in the whole breast irradiation group, 25% of deaths were due to breast cancer, 27% to other cancers, and 14% to cardiac disease (appendix p 9).

Acute radiation toxicity (within 3 months of radiotherapy start) was less in patients treated with APBI than whole breast irradiation (grade ≥2: 300 [28%] of 1070 APBI *vs* 484 [45%] of 1065 whole breast irradiation, p<0·0001; grade 3: 19 [1·8%] APBI *vs* 18 [1·7%] whole breast irradiation, p=0·99). The difference was largely due to a decrease in radiation dermatitis and breast swelling with APBI (table 3). Late radiation toxicity

	APBI (n=1070)			WBI (n=1065)		
	Grade 2	Grade 3	Total	Grade 2	Grade 3	Total
Acute period						
Radiation dermatitis	101 (9·4%)	1 (<0·5%)	102 (9·5%)	322 (30·2%)	6 (0·6%)	328 (30·8%)
Fatigue	130 (12·1%)	9 (0·8%)	139 (13·0%)	146 (13·7%)	5 (0·5%)	151 (14·0%)
Breast swelling	63 (5·9%)	1 (<0·5%)	64 (6·0%)	90 (8·5%)	1 (<0·5%)	91 (8·5%)
Breast pain	69 (6·4%)	2 (<0·5%)	71 (6·6%)	78 (7·3%)	4 (<0·5%)	82 (7·7%)
Pneumonitis	2 (<0·5%)	0	2 (<0·5%)	7 (0·7%)	1 (<0·5%)	8 (0·8%)
Any acute toxicity	281 (26·3%)	19 (1·8%)	300 (28·0%)	466 (43·8%)	18 (1·7%)	484 (45·4%)
Late period						
Induration or fibrosis	214 (20·0%)	31 (2·9%)	245 (22·9%)	48 (4·5%)	1 (<0·5%)	49 (4·6%)
Telangiectasia	86 (8·0%)	13 (1·2%)	99 (9·3%)	39 (3·7%)	0	39 (3·7%)
Breast pain	48 (4·5%)	3 (<0·5%)	51 (4·8%)	19 (1·8%)	1 (<0·5%)	20 (1·9%)
Chest wall pain	26 (2·4%)	4 (<0·5%)	30 (2·8%)	3 (<0·5%)	0	3 (<0·5%)
Fatty necrosis	24 (2·2%)	5 (0·5%)	29 (2·7%)	2 (<0·5%)	2 (<0·5%)	4 (<0·5%)
Any late toxicity	298 (27·9%)	48 (4·5%)	346 (32·3%)	131 (12·3%)	11 (1·0%)	142 (13·3%)

Data are n (%) unless otherwise specified. APBI=accelerated partial breast irradiation. WBI=whole breast irradiation. *Worst grade experienced by patients in the acute period (within 3 months from start of radiotherapy), and in the late period (beyond 3 months).

Table 3: **Radiation toxicity* by treatment and period**

	Baseline	3 years	5 years	7 years
Nurse assessment APBI				
Excellent	354	275	231	148
Good	484	413	360	291
Fair	180	240	225	196
Poor	16	35	57	55
Fair + poor	196 (19%)	275 (29%)	282 (32%)	251 (36%)
Total	1034	963	873	690
Nurse assessment WBI				
Excellent	373	389	335	246
Good	474	377	363	263
Fair	161	149	115	101
Poor	12	11	16	16
Fair + poor	173 (17%)	160 (17%)	131 (16%)	117 (19%)
Total	1020	926	829	626
Patient self-assessment APBI				
Excellent	314	313	244	175
Good	469	387	358	294
Fair	203	188	189	158
Poor	42	64	66	56
Fair + poor	245 (24%)	252 (27%)	255 (30%)	214 (31%)
Total	1034	963	873	690
Patient self-assessment WBI				
Excellent	289	370	329	250
Good	518	378	343	279
Fair	184	131	119	71
Poor	37	31	25	21
Fair + poor	221 (22%)	162 (18%)	114 (18%)	92 (15%)
Total	1028	910	816	621

Data are n or n (%). APBI=accelerated partial breast irradiation. WBI=whole breast irradiation. *Global cosmetic outcome assessed by the nurse and by the patient using the European Organisation for Research and Treatment of Cancer Breast Cancer Cosmetic Rating System.

Table 4: **Cosmesis outcome rating* by treatment over time**

(beyond 3 months) was greater in patients treated with APBI (grade ≥2: 346 [32%] APBI *vs* 142 [13%] whole breast irradiation, p<0·0001; grade 3: 48 [4·5%] APBI *vs* 11 [1·0%] whole breast irradiation, p<0·0001). The observed differences were primarily due to an increase in breast induration and skin telangiectasia with APBI (table 3).

Table 4 shows the cosmetic outcome assessed by trial nurses at baseline, 3, 5, and 7 years. Patients treated by APBI had similar cosmetic scores at baseline but a higher proportion of APBI patients had adverse cosmesis (defined as fair or poor) than did those treated by whole breast irradiation at 3 years (absolute difference, 11·3%, 95% CI 7·5–15·0), 5 years (16·5%, 12·5–20·4), and 7 years (17·7%, 12·9–22·3). The comparison of cosmesis between groups was similar when measured by patient self-assessment (table 4). There was a trend for cosmesis in the APBI group to worsen over time (appendix p 14).

Discussion

In the RAPID trial, external beam APBI was non-inferior to whole breast irradiation in preventing IBTR in women with DCIS or node-negative breast cancer. The risk of local recurrence was low in both treatment groups and the absolute differences over 8 years were small. The risk of local recurrence in the RAPID trial was lower than observed in our previous trials of whole breast irradiation, probably as a result of the inclusion of patients with smaller cancers, better imaging and surgical techniques, and improved adjuvant systemic therapy.[3,14]

Partial breast irradiation represents a new paradigm for the local treatment of breast cancer, and our extended follow-up enabled us to look at the impact of this approach. Partial breast irradiation was based on the observation that most recurrences in the treated breast occurred at the site of the primary tumour.[6–8] Although the rates of IBTR were relatively similar between treatment arms, the distribution of events in the ipsilateral breast were different. In patients treated with whole breast irradiation, the majority of recurrences occurred in the area of the primary surgical site (a true/marginal recurrence). By contrast, in the APBI group, more of the in-breast events were away from the primary surgical site (deemed an elsewhere recurrence). This observation is unexpected and needs to be confirmed in other trials. We are mindful of the limitations in identifying the site of recurrence in an irradiated breast. Nonetheless, this result challenges the previously held belief that following local treatment, most ipsilateral breast cancer events will occur at or near the primary

surgical site. The inference is that the part of the breast not radiated is at a higher risk of developing either recurrence or a new cancer. Molecular clonality studies may also help in determining what is a true local recurrence versus a new ipsilateral primary cancer.

The number of distant metastases and breast cancer deaths were similar between treatment groups. This is reassuring and suggests that there was little negative effect of APBI with respect to systemic recurrence in this patient population. APBI results in less radiation exposure to surrounding organs and it has been hypothesised that the radiation-induced second cancer risk would be reduced.[15] We observed fewer contralateral breast cancers with APBI compared with whole breast irradiation, and an increase in other second cancers, but event-free survival was not statistically different between groups. The increased incidence of second cancers included lung and other non-thoracic cancers not normally attributable to thoracic radiotherapy (melanoma, colorectal, and gynaecological). We used strict criteria to reduce radiation exposure to the underlying lung[16] and no relationship was observed between sidedness of the breast cancer treated and lung cancers observed. We postulate that the observed increase in second cancers is probably related to chance.

Acute radiation toxicity, which is more dependent on the total dose received rather than fraction size, was less in patients treated with APBI compared to whole breast irradiation. In keeping with the results of the interim analysis,[10] we observed an increase in late subcutaneous tissue fibrosis and skin telangiectasia in patients treated with APBI compared with whole breast irradiation. This increase was largely due to an increase in grade 2 toxic effects. These toxic effects contributed to a deterioration in the appearance of the breast that worsened over time, which was consistent with a late effect of radiotherapy. Cosmetic deterioration was observed by both nurse and patient self-assessment and was due primarily to an increase in fair rather than poor cosmesis. Late radiation toxicity may be related to the volume of breast treated, fraction size, or interval between fractions. Radiobiological models suggest that the dose per fraction used in this trial is less likely to contribute to the toxicity observed[17] as the total dose was reduced, and we were unable to show a major effect of treatment volume on the toxicity observed in the trial.[18] Studies now suggest that an interval between external beam fractions of 6 h is not adequate for repair of radiation injury to healthy tissues[19] and studies of external beam partial breast irradiation report less late toxicity when inter-fraction intervals are 24 h or more.[20–22]

Several randomised trials of different techniques of partial breast irradiation have been published with conflicting results.[22–25] Two trials of intraoperative radiotherapy reported higher rates of local recurrence compared with conventional whole breast irradiation,[23,24] which might reflect therapy that was too targeted or conformal, leading to geographic miss of the area at risk or an increase in elsewhere recurrences. A trial of interstitial brachytherapy[25] and another of non-accelerated external beam partial breast irradiation[22] reported similar rates of local recurrence compared with whole breast irradiation, but median follow-up was 6–6·6 years and few events were observed. Late toxicity associated with partial breast irradiation was not increased in those trials. In the brachytherapy trial, radiotherapy was delivered twice per day for 4 days. The insertion of active sources in the breast results in a smaller volume of tissue treated to a higher dose, which could explain why less toxicity was observed. In the trial of non-accelerated external beam radiotherapy,[26] treatment was given once per day over 3 weeks, which reduced the risk for late toxicity. Recently, results of NSABP B-39/RTOG 0413,[27] which compared APBI using external beam (3DCRT) or brachytherapy (single or multicatheter) techniques to whole breast irradiation in 4216 women with DCIS, node-negative, or 1–3 node-positive disease were reported at a median follow-up of 10 years. Investigators were unable to show the non-inferiority of APBI compared with whole breast irradiation, which might be related to the inclusion of higher risk node-positive patients or the use of multiple APBI techniques.

We identified a number of potential limitations of our trial. During the conduct of the study, the overall IBTR event rate was lower than expected. Constrained by the predetermined sample size, we decided to increase the non-inferior boundary for the tolerable HR and lower the power slightly. This increase was justified because the absolute event rate of IBTR was very low, and fewer events were needed to ensure that the final analysis was adequately powered. In the trial, it was not practical to mask nurses and patients to the type of study radiation treatment, which could have led to a bias in the assessment of cosmesis. Cosmetic assessments were performed independently by patients and nurses, and physicians unaware of treatment allocation performed a cosmetic assessment using photographs of the treated and untreated breasts.[11] There was a high degree of agreement between the three approaches that cosmesis was worse with APBI. Another potential limitation relates to the generalisability of the study findings. In the whole breast irradiation group, additional boost radiation to the primary site was optional and used in only 21% of patients. This was appropriate, as most patients were low risk. Whole breast irradiation without boost radiation is increasingly used for low risk patients.[28]

RAPID is one of the largest APBI trials to date with mature follow-up. We focused on a broad group of DCIS and node-negative patients and evaluated external beam radiotherapy techniques that are less invasive and resource intensive than other techniques. We incorporated an extensive RTQA programme assuring high compliance with the protocol. The APBI regimen used was shown to be non-inferior to whole breast irradiation in preventing local recurrence supporting external beam

radiotherapy for partial breast treatment. Although less acute toxicity was observed, the regimen was associated with an increase in moderate late toxicity and adverse cosmesis, which might be related to the twice per day regimen used. As such, it is difficult to recommend the twice per day regimen for routine use. It is possible that once per day APBI treatment with a longer interval between fractions would not adversely affect cosmesis, and this is a subject of ongoing investigation.[29]

Contributors
TJW and IAO were the coprincipal investigators. JAJ was the senior statistician and MNL as scientific lead of OCOG provided guidance for trial management. TJW, IAO, JAJ, MNL, AF, IG, CSG, FEP, and WAB contributed to the design of the study. MA, SB, TSB, SC, BHC, AF, FG, IG, D-HK, SL, TMc, TMu, AMN, IAO, FEP, TT, and TJW recruited patients and collected data. JAJ and CSG did the statistical analyses. TJW, MNL, JAJ, and IAO wrote the first draft of the manuscript. All authors contributed to interpretation of the data, revision of the report, and approved the final manuscript. TJW was supported by a Tier 1 Canada Research Chair.

Declaration of interests
The authors declare no competing interests.

Data sharing
A complete de-identified patient-level dataset can be made available to researchers for the purpose of meta-analysis or a newly proposed study. Any requests should be accompanied by a 2 page proposal. The trial Steering Committee will review and, if acceptable, provide approval of the request. A signed data sharing access agreement will be required. The data will be provided as SAS datasets (as a CPT or XPT file). Any other format requests might incur costs to the requestor. Data will be available for 15–36 months after publication of the initial study results. Data requests should be sent to Dr Mark N Levine at mlevine@mcmaster.ca.

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