Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial

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Summary

Background For most older women with early breast cancer, standard treatment after breast-conserving surgery is adjuvant whole-breast radiotherapy and adjuvant endocrine treatment. We aimed to assess the effect omission of whole-breast radiotherapy would have on local control in older women at low risk of local recurrence at 5 years.

Methods Between April 16, 2003, and Dec 22, 2009, 1326 women aged 65 years or older with early breast cancer judged low-risk (ie, hormone receptor-positive, axillary node-negative, T1–T2 up to 3 cm at the longest dimension, and clear margins; grade 3 tumour histology or lymphovascular invasion, but not both, were permitted), who had had breast-conserving surgery and were receiving adjuvant endocrine treatment, were recruited into a phase 3 randomised controlled trial at 76 centres in four countries. Eligible patients were randomly assigned to either whole-breast radiotherapy (40–50 Gy in 15–25 fractions) or no radiotherapy by computer-generated permuted block randomisation, stratified by centre, with a block size of four. The primary endpoint was ipsilateral breast tumour recurrence. Follow-up continues and will end at the 10-year anniversary of the last randomised patient. Analyses were done by intention to treat. The trial is registered on ISRCTN.com, number ISRCTN95889329.

Findings 658 women who had undergone breast-conserving surgery and who were receiving adjuvant endocrine treatment were randomly assigned to receive whole-breast irradiation and 668 were allocated to no further treatment. After median follow-up of 5 years (IQR 3·84–6·05), ipsilateral breast tumour recurrence was 1·3% (95% CI 0·2–2·3; n=5) in women assigned to whole-breast radiotherapy and 4·1% (2·4–5·7; n=26) in those assigned no radiotherapy (p=0·0002). Compared with women allocated to whole-breast radiotherapy, the univariate hazard ratio for ipsilateral breast tumour recurrence in women assigned to no radiotherapy was 5·19 (95% CI 1·99–13·52; p=0·0007). No differences in regional recurrence, distant metastases, contralateral breast cancers, or new breast cancers were noted between groups. 5-year overall survival was 93·9% (95% CI 91·8–96·0) in both groups (p=0·34). 89 women died; eight of 49 patients allocated to no radiotherapy and four of 40 assigned to radiotherapy died from breast cancer.

Interpretation Postoperative whole-breast radiotherapy after breast-conserving surgery and adjuvant endocrine treatment resulted in a significant but modest reduction in local recurrence for women aged 65 years or older with early breast cancer 5 years after randomisation. However, the 5-year rate of ipsilateral breast tumour recurrence is probably low enough for omission of radiotherapy to be considered for some patients.

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Introduction

Breast cancer is a growing global health care issue in older women. The incidence of breast cancer has risen steadily in most European countries between 1990 and 2002 in women aged 70 years or older.[1] In several clinical trials, low-risk patients have been identified in whom the effect of postoperative whole-breast irradiation is modest,[2–4] although these studies have been done mainly in younger patient populations. However, in older patients, the biology of breast cancer might be less aggressive, in view of the increased proportion of hormone receptor-positive tumours in this age group.

Postoperative whole-breast radiotherapy remains the standard of care for most patients treated by breast-conserving surgery, irrespective of age and other risk factors.[5] However, little evidence exists for the role of postoperative radiotherapy in older patients after breast-conserving surgery and adjuvant endocrine treatment because many trials, historically, excluded patients older than age 70 years. Extrapolation of the results of trials in younger patients to older patients might not be valid, particularly because of the competing risks of comorbidities in older patients. Data for the effect of age on local recurrence after breast-conserving surgery have been conflicting. In some trials, ipsilateral breast tumour recurrence falls with increasing age[6] or no effect is seen.[7,8] However, patients older than 65 years (and particularly those older than 75 years) were not well represented in any of these trials. Since tamoxifen with or without[9,10] adjuvant radiotherapy reduces the risk of tumour recurrence, we designed a randomised controlled trial in a group of older, low-risk, node-negative women with invasive breast cancer after breast-conserving surgery and adjuvant endocrine treatment to

assess the effect omission of whole-breast irradiation has on local control.

Methods

Participants

We did a phase 3 randomised controlled trial at 76 specialist cancer centres and district or regional hospitals in four countries (the UK, Greece, Australia, and Serbia; appendix pp 5–6). We recruited women aged 65 years or older with breast cancer who had undergone breast-conserving surgery and pathological axillary staging (ipsilateral four-node lower axillary node sample, sentinel node biopsy, or axillary node clearance). Eligibility criteria were: T1–T2 (up to 3 cm, longest dimension); N0; M0; hormone receptor-positive (oestrogen receptor, progesterone receptor, or both); clear excision margins (≥1 mm); no axillary involvement on histological examination (pN0); and receiving adjuvant hormone treatment (we permitted neoadjuvant hormonal treatment). Staging investigations included full blood count, liver function tests, and chest radiography. We required re-excision margins to be 1 mm or greater, but we did not request the actual final measurement because this value can be difficult for the pathologist to estimate. All patients had to be fit for treatment and follow-up (as assessed by the participating centre) and able and willing to give informed consent. We did not request details of specific performance status nor formal documentation of comorbidities. Patients' tumours could have grade 3 histological features or lymphovascular invasion, but not both.

We excluded patients if they were younger than 65 years at the time pathological results were issued or if they had a history of previous in-situ or invasive breast cancer of either breast. We also excluded women with current or previous malignant disease within the past 5 years, other than non-melanomatous skin cancer or carcinoma in situ of the cervix. We did not record HER2 status in these patients because this marker was not routinely assessed at the start of the trial.

The PRIME II study protocol received UK national ethics (MREC) approval on Sept 24, 2001. All patients gave written informed consent before randomisation. Follow-up is ongoing and will end at the 10-year anniversary of the last randomised patient.

Randomisation and masking

We randomly allocated patients to either whole-breast radiotherapy or no radiotherapy in a 1:1 ratio using a computerised randomisation service. Randomisation was by block permutation, stratified by centre, with a block size of four. Once a patient had provided informed consent, a research nurse familiar with the trial contacted the central independent randomisation service (Information Services Division Scotland, Edinburgh, UK) by telephone; a trial identifier was generated and treatment was assigned. The assignment was confirmed by a fax sent to both the registering centre and the trial manager. We could not mask participants to the treatment being given. However, no evidence was present in the trial identifier to indicate to which treatment the patient had been allocated; therefore, during follow-up and data analysis, researchers were unaware of patients' allocation unless they specifically looked for it.

Procedures

See Online for appendix

The total radiotherapy dose, number of fractions, and overall treatment time was administered according to local practice in every centre. However, we provided a guideline for dose fractionation of 40–50 Gy (2·66–2·00 Gy per fraction in 15–25 fractions) over 3–5 weeks at megavoltage irradiation to the breast. We permitted a breast boost with electrons of 10–15 Gy at appropriate energy or an iridium implant (eg, 20 Gy to 85% reference isodose). Guidelines on radiotherapy included some form of immobilisation, a planned target volume of the whole breast (margin of 1 cm), and all patients being simulated to establish the volume of lung irradiated (maximum

For the **protocol** see http://homepages.ed.ac.uk/prime/PRIME2/protocol.pdf

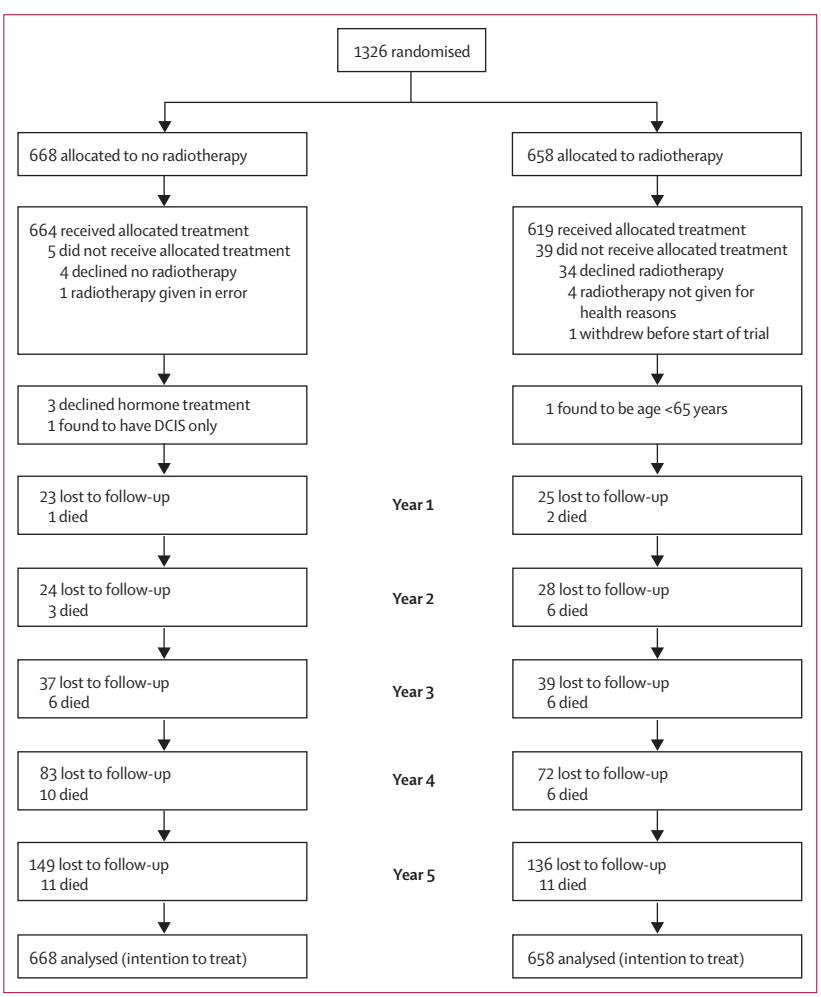

Figure 1: **Trial profile**
DCIS=ductal carcinoma in situ.

	No radiotherapy (n=668)	Radiotherapy (n=658)
Age (years)	70 (67–74)	69 (67–73)
Tumour size (mm)		
0–10	258 (39%)	265 (40%)
10·1–20	326 (49%)	319 (48%)
20·1–30	84 (13%)	74 (11%)
Margins		
<1 mm	10 (1%)	9 (1%)
1–5 mm	315 (47%)	296 (45%)
>5 mm	227 (34%)	239 (36%)
Re-excision*	112 (17%)	110 (17%)
Unknown	4 (<1%)	4 (<1%)
Grade		
1	271 (41%)	292 (44%)
2	368 (55%)	352 (53%)
3	23 (3%)	13 (2%)
Unknown	6 (<1%)	1 (<1%)
Side		
Left	359 (54%)	345 (52%)
Right	302 (45%)	305 (46%)
Unknown	7 (1%)	8 (1%)
Lymphovascular invasion		
No	631 (94%)	628 (95%)
Yes	32 (5%)	27 (4%)
Unknown	5 (<1%)	3 (<1%)
Axillary surgery		
Sentinel node biopsy only	223 (33%)	198 (30%)
Sample only	174 (26%)	211 (32%)
Sample with sentinel node biopsy	105 (16%)	107 (16%)
Clearance I/II	129 (19%)	101 (15%)
Clearance III	29 (4%)	34 (5%)
Unknown	8 (1%)	7 (1%)
Preoperative endocrine treatment		
No	608 (91%)	598 (91%)
Yes	60 (9%)	54 (8%)
Unknown	0	6 (<1%)
Oestrogen receptor status		
Rich†	593 (89%)	601 (91%)
Poor	65 (10%)	55 (8%)
Unknown	10 (1%)	2 (<1%)
Radiotherapy‡		
Within 40–50 Gy§	..	573/584 (98%)
Boost	..	91/584 (16%)

Data are median (IQR) or number of patients (%). *Protocol-specified adequate margins (≥1 mm) after re-excision, the actual size was not requested. †Defined as either an Allred score of 7 or 8, ≥20 fmol/mg protein, ≥50%, +++, strongly positive, or oestrogen receptor-positive (if no other information available). ‡584 copies of the post-radiotherapy form were returned. Only one patient failed to complete radiotherapy once started; one patient had their boost dose altered once begun. §Most patients who were outside the 40–50 Gy guidance were from countries other than the UK.

Table 1: **Patients' characteristics**

lung thickness no greater than 3 cm). We specified that the peripheral lymphatic system was not to be irradiated. We stated that a minimum of one transverse outline, taken at the central axis of the tangential fields, was to be taken. All fields were to be treated with megavoltage irradiation, with wedged fields so that dose homogeneity did not vary by more than 10%. We indicated that doses were to be prescribed to the reference point at or close to the centre of the target volume (ICRU-50). For the boost volume, we specified the tumour bed with lateral margins of 2 cm and a deep margin extending down to the underlying muscle.

We indicated tamoxifen (20 mg daily for 5 years) as the standard adjuvant endocrine treatment, but we allowed other forms of adjuvant and neoadjuvant endocrine treatment. Follow-up was for 10 years and consisted of annual clinic visits, examination and mammography for at least 5 years, and, beyond this time, either a clinic visit or a phone call to the patients' primary health care doctor to ascertain their health status, in addition to follow-up mammography.

Outcomes

The primary endpoint was ipsilateral breast tumour recurrence. Secondary endpoints were regional recurrence, contralateral breast cancer, distant metastases, disease-free survival, and overall survival. We defined ipsilateral breast tumour recurrence as any cancer in the scar, the adjacent area in the same breast, or in a different quadrant of the same breast. We defined regional recurrence as disease in the ipsilateral axillary or supraclavicular lymph nodes. The endpoints were not centrally assessed but based on local investigator review.

Statistical analysis

The null hypothesis of the PRIME II study was to show no difference between the radiotherapy and no radiotherapy groups in terms of local recurrence at 5 years. We surveyed UK oncologists to ascertain what they regarded as acceptable local recurrence; with the results of this survey, we powered the PRIME II study to detect a difference at 5 years in breast tumour recurrence of at least 5% (5% with radiotherapy and 10% without radiotherapy), with 80% power and 5% level of significance, with a target for recruitment of 1000 patients. However, subsequent randomised and non-randomised studies of breast-conserving treatment[11] indicated that our initial estimates of ipsilateral breast tumour recurrence were too high. We obtained ethics approval to amend the protocol to increase the sample size. The amendment would allow us to detect a difference in ipsilateral breast tumour recurrence of at least 3% (2% with radiotherapy and 5% without radiotherapy) at 5 years (80% power, 5% level of significance); we calculated we would need a sample size of 588 per group (1176 in total), which was increased by 10% to allow for loss to follow-up (n=1294). We rounded this number up to 1300 for convenience.

We analysed data with Kaplan-Meier plots and by log-rank testing (Mantel-Cox statistic for the equality of survival distributions between levels of treatment). We estimated hazard ratios and 95% CI with the Cox proportional hazards model. Time zero was the date of randomisation. We calculated the absolute risk reduction as the difference in local recurrence in the two study groups at 5 years, with the SE of the absolute risk reduction calculated from the pooled SEs of the individual recurrences; the absolute risk reduction was also calculated with the methods described by Altman and Andersen.[12] All analyses are by intention to treat and are two-tailed tests.

We did a hypothesis-generating unplanned subgroup analysis of local recurrence by oestrogen receptor score, dividing patients into either rich or poor oestrogen receptor status (defined according to the local reporting laboratory). A patient was defined before analysis with rich oestrogen receptor status if they were either oestrogen receptor-positive, had an Allred score of 7 or 8, had more than 20 fmol/mg protein, had more than 50% of stained cells, or were designated +++; otherwise the patient was judged to have poor oestrogen receptor status. This division was conservative, because only patients who definitely had poor oestrogen receptor status were categorised as such.

We analysed data with SPSS (release 2010, version 19.0; IBM, Armonk, NY, USA) and SAS (version 9.3, SAS Institute, Cary, NC, USA). The PRIME II study is registered with ISRCTN.com, number ISRCTN95889329.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. IHK and LJW had full access to raw data and IHK had final responsibility for the decision to submit for publication.

Results

Between April 16, 2003, and Dec 22, 2009, 1326 patients were randomly allocated to either no radiotherapy (n=668) or whole-breast radiotherapy (n=658; figure 1). Of these, 39 did not receive radiotherapy after randomisation and five received radiotherapy when they had been randomly allocated to the no radiotherapy group. Another three patients did not begin endocrine treatment after randomisation or stopped taking it shortly after starting. 1263 patients were recruited from the UK, 22 were from Greece, 16 were from Australia, and 25 were from Serbia. Table 1 shows the baseline characteristics of the trial population, which are similar between treatment groups. Patients' median age was 70 years (IQR 67–74). Fewer than 10% of patients had tumours with poor oestrogen receptor status. 91 (16%) of 584 patients for whom radiotherapy treatment data were available received a tumour bed boost after whole-breast radiotherapy.

At median follow-up of 5 years (IQR 3·84–6·05), actuarial ipsilateral breast tumour recurrence was 1·3% (95% C1 0·2–2·3) in women allocated whole-breast radiotherapy and 4·1% (2·4–5·7) in those assigned no radiotherapy (log-rank p=0·0002; figure 2). The hazard ratio for ipsilateral breast tumour recurrence in patients allocated to no radiotherapy was 5·19 (95% CI 1·99–13·52; p=0·0007; full data, not truncated at 5 years). The absolute risk reduction in ipsilateral breast tumour recurrence at 5 years was 2·9% (95% CI 1·1–4·8). The number needed to treat was calculated to be 31·8 (95% CI 27·4–55·0), which equates to an adjusted absolute risk reduction of 3·1% (95% CI 1·8–3·6) by the Altman and Andersen methodology.[12]

26 (4%) patients assigned to no radiotherapy and five (1%) women allocated to whole-breast radiotherapy had local recurrences. Of the 26 local recurrences in the no radiotherapy group, 18 women had a local recurrence only, six had both local and regional recurrence, and two had a local recurrence with distant spread. In the radiotherapy group, four patients had local recurrence only and one had local and regional recurrence. Table 2 presents post-hoc subgroup analyses of local recurrences, according to clinical and pathological factors.

Table 3 shows treatments received by patients after local recurrence. Data are insufficient for any formal tests of association, but it is noteworthy that about half the patients in each treatment group had a further wide local excision, rather than mastectomy.

We did a multivariate Cox proportional hazards analysis of local recurrence according to known risk factors for local recurrence, including pathological tumour size,

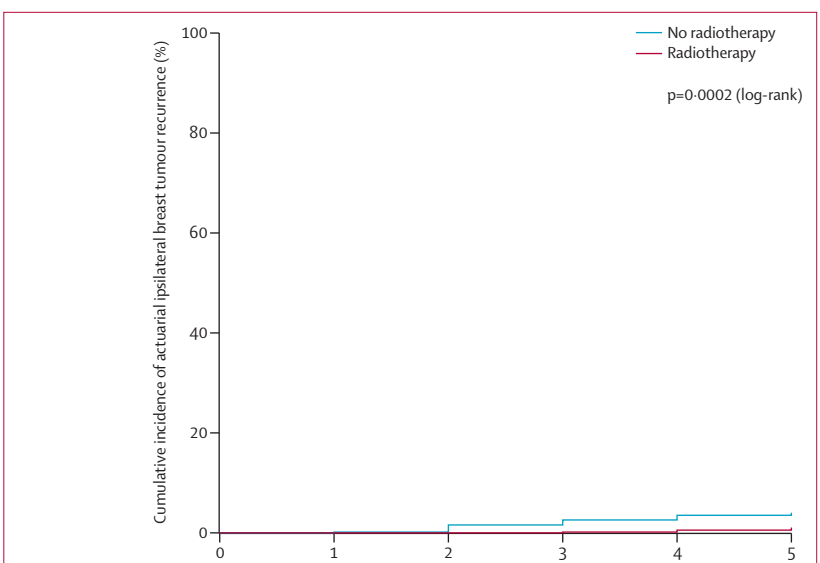

Figure 2: **Time to actuarial ipsilateral breast tumour recurrence**

	No radiotherapy (n=668)	Radiotherapy (n=658)	p value
Local recurrence	26 (4%)	5 (<1%)	
Tumour size (mm)			
0–10	10/258 (4%)	3/265 (1%)	0·04
10·1–20	10/326 (3%)	1/319 (<1%)	0·008
20·1–30	6/84 (7%)	1/74 (1%)	0·08
Margins			
<1 mm	1/10 (10%)	0/9 (0%)	0·32
1–5 mm	10/315 (3%)	4/296 (1%)	0·15
>5 mm	9/227 (4%)	1/239 (<1%)	0·01
Re-excision	6/112 (5%)	0/110 (0%)	0·01
Grade			
1	8/271 (3%)	2/292 (<1%)	0·04
2	15/368 (4%)	3/352 (<1%)	0·006
3	3/23 (13%)	0/13 (0%)	0·21
Age (years)			
65–69	8/308 (3%)	2/331 (<1%)	0·05
≥70	18/360 (5%)	3/327 (1%)	0·002
Lymphovascular involvement			
No	24/631 (4%)	5/628 (<1%)	0·0004
Yes	2/32 (6%)	0/27 (0%)	0·29
Oestrogen receptor status			
Rich	20/593 (3%)	5/601 (<1%)	0·002
Poor	6/65 (9%)	0/55 (0%)	0·03

Data are number of patients with local recurrence (%). P values calculated by χ^2 or Fisher's exact test. Data are for the full study period and have not been truncated to 5 years of follow-up. No adjustment was made for multiple testing and these results should be viewed as hypothesis-generating. No subgroup analyses were prespecified in the protocol.

Table 2: **Local recurrences, analysed by subgroup**

	No radiotherapy (n=26)	Radiotherapy (n=5)
Patients with data available	23	4
Total undergoing mastectomy	12	2
Mastectomy	5	0
Mastectomy and endocrine treatment	4	2
Mastectomy, radiotherapy, and endocrine treatment	3	0
Total undergoing wide local excision	11	2
Wide local excision	0	1
Wide local excision and endocrine treatment	2	1
Wide local excision and radiotherapy	3	0
Wide local excision, radiotherapy, and endocrine treatment	6	0

Data are number of patients.

Table 3: **Treatment received after local recurrence**

	No radiotherapy (n=668)	Radiotherapy (n=658)
Regional recurrence	1·5% (0·5–2·4) (8)	0·5% (0–1·0) (3)
Distant recurrence	1·0% (0·1–1·7) (4)	0·5% (0–1·0) (5)
Contralateral breast cancer	0·7% (0·01–1·2) (4)	1·5% (0·4–2·5) (7)
New (non-breast) cancer	4·3% (2·6–5·7) (29)	3·7% (2·1–5·0) (26)

Data are Kaplan-Meier estimates of survival (95% CI) (number of events).

Table 4: **Other recurrences (as first event) or new cancers after 5 years**

margin status, tumour grade, age, presence of lymphovascular invasion, oestrogen receptor status, and use of radiotherapy (appendix p 1). Progesterone receptor status was excluded from analyses because roughly 30% of data were missing in each treatment group. The only factor that predicted local recurrence was omission of radiotherapy (hazard ratio 4·87, 95% CI 1·86–12·74; p=0·0013), although poor oestrogen receptor status and grade 3 tumours were of borderline significance (p=0·06). However, very few women had either of these factors (36 [3%] patients had grade 3 tumours and 120 [9%] had poor oestrogen receptor status).

Overall survival at 5 years was identical in the two treatment groups (93·9%, 95% CI 91·8–96·0; p=0·34; appendix p 2). At 5 years, no differences between treatment groups were noted in regional recurrences, distant metastases, contralateral breast cancers, or new cancers (table 4). Breast cancer-free survival at 5 years was 94·5% (95% CI 92·5–96·5) in women allocated to no radiotherapy and 97·6% (96·2–99·0) in those assigned to whole-breast radiotherapy; the difference was attributable mainly to ipsilateral breast tumour recurrence. Only 12 (13%) of 89 deaths recorded by the time of analysis were due to breast cancer, eight (16%) of 49 women assigned to no radiotherapy and four (10%) of 40 allocated to whole-breast radiotherapy (appendix p 3).

In a hypothesis-generating unplanned subgroup analysis of local recurrence by oestrogen receptor score, local recurrence at 5 years for women in the rich oestrogen receptor subgroup was lower than in the whole population; for patients assigned no radiotherapy, 20 (3%) of 593 patients had a local recurrence compared with five (<1%) of 601 women allocated whole-breast radiotherapy (5-year ipsilateral breast tumour recurrence was 3·3% [95% CI 1·7–4·8] and 1·2% [0·1–2·2], respectively; p=0·002). In women with poor oestrogen receptor status, six (9%) of 65 women allocated no radiotherapy had local recurrence compared with none of 55 women allocated to whole-breast radiotherapy (ipsilateral breast tumour recurrence at 5 years was 10·3% [95% CI 2·5–18·2] and 0%, respectively; p=0·026); however, the number of patients in this analysis is small.

Discussion

The null hypothesis of the PRIME II study was that there was no difference between the radiotherapy and no radiotherapy groups in terms of local recurrence at 5 years, with an alternative hypothesis of a 3% difference between groups (2% with radiotherapy *vs* 5% with no

radiotherapy). On the basis of the results of this trial, we can reject the null hypothesis (p=0·0002, log-rank test). At median follow-up of 5 years, the absolute risk reduction in ipsilateral breast tumour recurrence at 5 years was 2·9% (95% CI 1·1–4·8) with addition of adjuvant whole-breast radiotherapy after breast-conserving surgery in a low-risk older population. Thus, at most, 4·8% of women who would not have developed a local recurrence if they had received radiotherapy would develop a local recurrence if radiotherapy were omitted. With Altman and Andersen's method,[12] the difference at 5 years is slightly larger (3·1%, 95% CI 1·8–3·6), but the upper limit of the CI is smaller. No survival benefit from radiotherapy was recorded, and most deaths within this trial were from causes other than breast cancer.

High-grade tumours,[13,14] positive margins,[15] and axillary involvement are all important factors that increase the risk of ipsilateral breast tumour recurrence. In our study, clear margins were defined as 1 mm or greater and all patients had no axillary involvement (pN0). Women with grade 3 cancers could be included in the trial as long as they had no lymphovascular invasion, but in practice only 36 (3%) patients with grade 3 cancers were randomised. Of note, in this subgroup, more patients assigned to no radiotherapy had local recurrence (three [13%] of 23) than did those allocated to whole-breast radiotherapy (none of 13), although the small numbers mean this finding should be interpreted with caution. We are confident our findings are applicable to patients with grade 1–2, T1–T2 tumours up to 3 cm, but we are cautious about their generalisability to grade 3 tumours because of the small numbers.

Our finding of a very low risk of local recurrence after breast-conserving surgery and adjuvant endocrine treatment in women allocated to whole-breast radiotherapy (1·3% at 5 years) accords with findings of other trials (appendix p 4; panel). The Cancer and Leukaemia Group (CALGB) 9343 trial[17] is the most analogous to our own; researchers tested omission of adjuvant whole-breast radiotherapy in an even lower risk and older population than was studied in PRIME II, namely small T1 tumours up to 2 cm (longest dimension) in women aged 70 years or older receiving adjuvant tamoxifen after breast-conserving surgery. A 3% gain in locoregional control from radiotherapy was recorded at 5 years (1% *vs* 4%) and a 7% gain in locoregional control was noted at 10 years (2% *vs* 9%).[18] In the British Association of Surgical Oncology II trial[3] of invasive breast cancers (<2 cm longest dimension, grade 1, or of special type [such as tubular carcinoma]), at a median follow-up of 167 months, annual local recurrence was 0·8% for women receiving tamoxifen alone and 0% when tamoxifen was given with postoperative whole-breast radiotherapy. Mean age at trial entry was 57 years. The low ipsilateral breast tumour recurrence largely reflects a lower risk group compared with the population in our trial. The German Breast Cancer Group[14] recorded ipsilateral breast tumour recurrence of 6% in women receiving adjuvant endocrine treatment alone and 2% when adjuvant endocrine treatment was combined with radiotherapy. Of note, women aged 45 years and older were included. In an Italian trial,[19] patients aged 55–75 years receiving systemic treatment were randomised to either radiotherapy or no radiotherapy. Ipsilateral breast tumour recurrence was 1% with radiotherapy or 3% without, a finding very similar to ours but not significant (p=0·07). Hughes and colleagues[18] point out that differences in local control (appendix p 4) might be accounted for largely by variations in eligibility criteria.

A hypothesis-generating observation in our study was lower breast cancer recurrence at 5 years in patients with oestrogen receptor-rich tumours compared with the total study population (1·2% *vs* 1·3% in women assigned radiotherapy; 3·3% *vs* 4·1% in women assigned no radiotherapy). By contrast, 5-year ipsilateral breast tumour recurrence in women with poor oestrogen receptor status was higher than the total study population (10·3% *vs* 4·1% in women assigned no radiotherapy). We are cautious in the interpretation of this finding because of the small numbers of patients, but these data accord with findings of the Scottish Breast Conservation trial in tumours up to 4 cm (longest dimension), in which radiotherapy conferred a four-fold reduction in local recurrence and relapse was high in women with oestrogen receptor-poor tumours in whom radiotherapy was omitted.[8] Nevertheless, our findings should at least advise caution when considering omission of radiotherapy for women with hormone receptor-poor tumours after breast-conserving surgery. Further research will be needed. We plan in future analyses of the PRIME II trial to adopt a new endpoint used by the Early Breast Cancer Trialists' Collaborative Group, of first recurrence (whether locoregional or metastatic).

In the Oxford overview of trials of adjuvant radiotherapy after breast-conserving surgery,[20] a benefit is noted from radiotherapy in reducing first recurrences (most of which are local) in all risk groups. However, the absolute benefit in the low-risk older group is very small, which accords with our findings.

Is 5-year local recurrence of 4·1% at median follow-up of 5 years sufficiently low enough for clinicians to discuss omission of radiotherapy? We believe it is. Such a policy would be practice-changing in the UK, where radiotherapy remains the standard of care for all patients after breast-conserving surgery and endocrine treatment, irrespective of age.[5] However, no international consensus exists on what level of local recurrence in this population would be acceptable to clinicians and patients if radiotherapy were omitted. Clinicians and patients must decide whether a 2·9% absolute risk reduction in local recurrence with addition of radiotherapy in this low-risk older population continues to justify radiotherapy.

Panel: **Research in context**

Systematic review

When PRIME II was being designed, in 2001, few trials included patients older than 70 years, and even fewer selected older patients specifically. To investigate the research area, we searched the Web of Science database with the terms "radiotherapy", "older", "elderly", "local recurrence", and "survival". We retrieved few suitable articles from this first search; therefore, we repeated the search with "older" and "elderly" excluded. Abstracts were checked manually. Articles that included patients older than 65 years, even if a younger cohort was also included, were examined in more detail, and we defined a cohort of low-risk patients with the evidence gathered. Existing research was scant in the age group in which we were interested, but findings did suggest that older women had lower risks of recurrence than did younger women.[16] Larger tumours, a higher grade, and involved margins were judged risk factors for recurrence, although most evidence was extrapolated from trials in younger women. The importance of these factors for older patients was poorly defined, as was the absolute effect of radiotherapy in the older age group. This dearth of evidence provided the rationale to do the trial.

Interpretation

Postoperative whole-breast radiotherapy achieved a significant but relatively small reduction in local breast recurrence at 5 years in a population of low-risk older patients with early breast cancer after breast-conserving surgery and adjuvant endocrine treatment. The only other trial in which omission of radiotherapy was investigated in a low-risk population was the CALGB trial,[17,18] in which a similar 3% reduction in local recurrence at 5 years was noted with addition of radiotherapy. Our findings add to existing evidence of the safety of omitting radiotherapy after breast-conserving surgery in older patients, in whom the benefits of adjuvant radiotherapy have been controversial, and they might encourage clinicians to consider omission of radiotherapy in all or selected older women with low-risk breast cancer after breast-conserving surgery depending on the weight they and the patient give to local recurrence.

It is noteworthy that 5-year results of the CALGB 9343 trial had little apparent effect on clinical practice in the USA,[21] despite use of radiotherapy being questioned.[22] As a result of the study, National Comprehensive Cancer Network breast cancer guidelines were changed to allow omission of radiotherapy in older patients with hormone receptor-positive cancer after breast-conserving surgery.[23] However, an analysis of Medicare data in the USA in 2007 among patients who would have met the eligibility criteria showed that the CALGB trial findings had only reduced use of adjuvant radiotherapy by 3%.[21] The reasons for this low effect are not clear and could include patient and clinician preference, diminished effect of a trial in which omission of treatment is tested, and factors specific to the US health-care system.

After longer term follow-up of the CALGB 9343 trial,[18] at 10 years, 98% of patients treated by lumpectomy, tamoxifen, and postoperative radiotherapy remained free of locoregional recurrence compared with 90% of patients in whom radiotherapy was omitted. The researchers argue that, depending on the value put on local recurrence, tamoxifen alone in oestrogen receptor-positive patients is still a reasonable option. We acknowledge, therefore, that a continuing risk of local recurrence exists beyond 5 years. Implementation of follow-up policies aimed at early detection of salvageable recurrence will be important.

Different conclusions can be drawn from our findings depending on the perspective of the clinician. Some argue that the fitness of women aged 70 years and older varies substantially. A fit 70-year-old woman has a high chance of living for more than 10 years and will have a 10% risk of relapse if radiotherapy is omitted, compared with 2% if radiotherapy is given,[24] although at the moment we have restricted our analysis to 5 years. Furthermore, radiation is, arguably, well tolerated, as shown by findings of our earlier PRIME I trial,[25,26] and with modern technology, radiotherapy confers a low risk of morbidity.[27] Moreover, availability of well-validated, hypofractionated, dose-fractionation regimens (in 15 or 16 fractions) provides convenient alternatives to the previous international standard of 25 daily fractions.

We also must account for the risks of radiation-induced cardiac morbidity and mortality[28] and radiation-induced second malignant disease,[29] and we should consider the inconvenience to patients of several weeks of treatment and high costs of limited radiotherapy resources. In the PRIME I trial,[25,26] in which we showed no effect on global quality of life from omission of postoperative radiotherapy in a similar population to that of the PRIME II trial, we concluded that radiotherapy is only cost effective if at least a 5·5% increase in local recurrence takes place after omitting radiotherapy, at the £30 000 threshold. We are cautious about extrapolating the PRIME I health economic assessment to the results of PRIME II, in which we did not undertake a formal health economic analysis, particularly in view of widespread adoption of shorter, cheaper, 3-week hypofractionated dose and fractionation schedules, compared with the previous international standard of 50 Gy in 2 Gy fractions over 5 weeks.

Similar to findings of the study by Hughes and colleagues,[17,18] we recorded no difference in overall survival or in distant metastasis-free survival, and we noted that patients were more likely to die of comorbidity than breast cancer. Only 12 (13%) of 89 deaths among the 1326 patients in our study were due to breast cancer. Other researchers[30] have argued that since the main aim of radiotherapy is to sterilise local disease, local recurrence should take precedence over overall survival (since death is a late event).

Better selection of patients at very low risk of recurrence could be assisted by biomarkers, including immunochemical compounds (eg, oestrogen receptor, progesterone receptor, and HER2). Biomarkers are currently under investigation in the Canadian LUMINA study (NCT01791829). Molecular subtype might also be important for selection, with a recent report based on a small set of immunohistochemical markers showing that molecular subtype was the only significant predictor for local recurrence after breast-conserving surgery.[31]

Limitations of our study are the absence of detailed information on comorbidities and on adherence to

endocrine treatment. However, we feel that, because of randomisation, major differences are unlikely to exist between the two treatment groups that would have affected outcomes. A further limitation of our study was the few patients we included with grade 3 tumours. Our results are really only applicable to patients aged 65 years or older with grade 1 and 2, node-negative, oestrogen receptor-positive tumours, up to 3 cm in size.

In summary, for women aged 65 years or older with early hormone receptor-positive node-negative breast cancer (≤3 cm at the longest dimension) after breast-conserving surgery, adjuvant endocrine treatment alone is a reasonable therapeutic option for some women. We must stress that every patient should be assessed individually, with tumour characteristics, comorbidity, and patient's choice as determining factors, along with an assessment of benefits and risks of treatment.

Contributors

IHK, LJW, and WJLJ contributed to study design and implementation of the trial. IHK was the principal investigator and wrote the report. LJW obtained and analysed data and wrote the report. WJLJ advised on the trial and wrote the report. DAC and JMD wrote the report. All authors contributed to interpretation of data.

Declaration of interests

We declare no competing interests.

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