Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer

Breast-conserving surgery +/- irradiation in women with early breast cancer

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Abstract

Background

Limited level 1 evidence evaluates the omission of postoperative radiotherapy after breast-conserving surgery in older women with hormone receptor positive early breast cancer receiving adjuvant endocrine therapy.

Methods

A phase 3, randomized trial of omitting irradiation was performed in 1326 women aged ≥65 years with pT1-T2 (≤3cm), pN0, hormone receptor positive breast cancer treated by breast-conserving surgery with clear margins and adjuvant endocrine therapy. Patients were randomly assigned to whole breast irradiation [40-50Gy] or no irradiation. The primary endpoint was ipsilateral breast tumor recurrence.

Results

658 women were randomized to whole breast irradiation and 668 to no irradiation and the median follow up was 9.1 years. Cumulative incidences of ipsilateral breast cancer recurrence to 10 years were 0.9% (95% CI 0.1-1.7%) for irradiation and 9.5% (95% 6.8-12.3%) for no irradiation [HR 10.4 (95% CI 4.1-26.1.) p<0.0001]. Although the local recurrence was higher in the no irradiation group, distant recurrences at 10 years were not increased in this group and were 3.0% (95%CI 1.4%, 4.5%) with irradiation and 1.6% (95%CI 0.4, 2.8%), without irradiation. Overall survival at 10 years was almost identical, at 80.8% (95% CI 77.2-84.3%) with irradiation vs 80.7% (95% CI 76.9, 84.3%) with no irradiation. Regional recurrence and breast cancer specific survival also did not differ between the two groups.

Conclusion

Omission of radiotherapy increases local recurrence but has no detrimental effect on distant recurrence and overall survival for women ≥65 years with low risk, hormone receptor positive early breast cancer.

Introduction

Twenty-six percent of USA breast cancer diagnoses are in women aged 65-74 years (1). The prevalence of breast cancer in older adults is rising (2). Under-representation of older breast cancer patients in clinical trials has led to under- and over-treatment (3). The Early Breast Cancer Trialists' Cooperative Group (EBCTCG) (4) meta-analysis showed that radiotherapy after breast-conserving therapy, while reducing the overall cumulative recurrence in node negative patients, confers only a modest survival benefit. Omission of RT after breast-conserving therapy in low risk, older patients with smaller, hormone receptor positive (HR+) tumors remains controversial (5-7) with limited long term level 1 evidence (2,8-12). The 5-year results of the PRIME II trial showed that irradiation reduced ipsilateral recurrence from 4.1% to 1.3% in women ≥65 years with pT1-2 (up to 3cm), pN0, HR+ tumors treated by breast-conserving therapy and adjuvant endocrine therapy (9). Despite guidelines supporting omitting RT in women ≥ 70 years with T1, HR+ tumors treated by breast-conserving therapy and adjuvant endocrine therapy (10-12), use of RT in the USA in this setting remains high (13). We report the 10-year outcomes of the PRIME II trial.

Methods

PRIME II, a phase 3 randomized clinical trial, was designed by the Scottish Cancer Trials Breast Group (SCTBG). Methods have been previously described (9). It was undertaken in 76 centers in the UK, Greece, Australia and Serbia. The protocol received UK ethics approval (Sept 24th, 2001). All patients gave written informed consent to participation. The trial is registered with ISRCTN.com, number

ISRCTN95889329. Ian Kunkler, Robin Prescott and Mike Dixon designed the study with the SCTBG. The authors wrote the paper, vouch for the data, and confirm adherence to the protocol. The sponsors and funders of the trial had no role in its design or conduct, no access to the data and no role in its analysis or publication.

Patient selection

Women ≥65 years were included with pT1-2 (up to 3cm in largest dimension) breast cancer treated by breast-conserving therapy + axillary staging (four node lower axillary sample, sentinel node biopsy or axillary node clearance and were pN0, estrogen receptor (ER), and/or progesterone receptor positive, had clear excision margins (≥1mm) and received adjuvant or neoadjuvant endocrine therapy. Patients were eligible with grade 3 histology or lymphovascular invasion but not both. Patients were excluded if <65 years, or had a history of in situ/invasive carcinoma of either breast, previous malignant disease within the previous five years except non-melanoma skin cancer or carcinoma in situ of the cervix. Neither HER2 status, since it was not routinely measured at initiation of the trial, nor comorbidities were recorded. All patients had to be fit for treatment and follow up. The trial CONSORT diagram is shown in Figure 1.

Treatment

At study entry, patients were randomly allocated (1:1) to receive either whole breast irradiation or no irradiation using a computerized randomization service. Guidelines were given for irradiation (40-50 Gy, 2.66-2.00 Gy per fraction in 20-25 fractions) over 3-5 weeks. A breast boost was allowed with electrons (10-15 Gy) or with an

iridium implant (e.g., 20 Gy to 85% reference isodose)(10). We recommended tamoxifen 20 mg/day for five years as standard adjuvant endocrine therapy. Follow up was by annual clinical visits for at least five years and subsequently by clinic visit or telephone call to the patient or community doctor to determine their health status. Annual bilateral mammography was recommended but mammography at the first, third and fifth anniversaries was acceptable.

Study endpoints

The primary study endpoint was ipsilateral breast tumor recurrence. Secondary endpoints were regional recurrence, contralateral breast cancer, distant metastases, disease-free survival and overall survival. Local recurrence was defined as any cancer in the scar or in the same breast. Regional recurrence was defined as disease in the ipsilateral axillary/supraclavicular lymph nodes. The endpoints were based on local investigator review and not centrally assessed.

Statistical analysis

Our null hypothesis was no difference between the irradiated and non-irradiated groups in terms of local recurrence at 5 years. PRIME II was originally powered to detect a difference at five years of at least 5% (5% with radiotherapy, 10% without radiotherapy), with 80% power and 5% significance level with a target of recruiting 1000 patients. Ethical approval was granted on November 14, 2008 to increase the sample size to 1294 because both randomized and non-randomized studies (14) suggested that our initial estimate of local recurrence rate was excessive. Our revised estimates enabled the detection of a difference of at least 3% (2% with

radiotherapy and 5% without radiotherapy) at five years with 80% power, 5% significance level with 10% allowance for loss to follow up. Our planned statistical analysis of primary and secondary outcomes of PRIME II was documented on 20/3/20 before analysis. Compliance with adjuvant endocrine therapy was included as an additional secondary endpoint.

Data were analysed with Kaplan-Meier plots and by log rank testing (Mantel-Cox statistic for the equality of survival distributions between levels of treatment). Hazard ratios and 95% CI were estimated with the Cox proportional hazards model, with the proportional hazards assumption tested for each model using the graphical and numerical methods described by Lin et al (15). All analyses are by intention to treat and are two-tailed tests. Since no procedure for type 1 error control was implemented for secondary outcomes, results for these outcomes are reported as point estimates and confidence intervals only, without hypothesis testing. Confidence interval widths have not been adjusted for multiple testing and may not be used in place of hypothesis testing. Pre-defined exploratory endpoints were impact of duration of endocrine therapy and level of tumor ER on outcomes. Clinicians were asked to note on the annual clinical research form whether a patient was still taking adjuvant endocrine therapy, and if not, when they stopped. This allowed an analysis of the data with adjuvant endocrine therapy as a time-varying covariate, where the risk of local recurrence at time t for patients taking adjuvant endocrine therapy compared to the risk of patients not taking adjuvant endocrine therapy at time t.

Post hoc subgroup analysis of local recurrence according to ER score was performed. Patients were divided into ER rich or poor categories. ER rich patients were pre-defined as having an Allred score of 7 or 8, > 20 fmol/mg protein, > 50% of stained cells or classified as +++. The remaining patients were assessed as ER poor. Data were analysed with SPSS (version v22; IBM, Armonk, NY, USA) and SAS v9.4 for Windows.

Results

1326 patients were randomly allocated to either postoperative irradiation (n=658) or not (n=668) from 16/4/2003 to 22/12/2009 (Fig 1). Patients were recruited from the UK (1263), Greece (22), Australia (16) and Serbia (25). Table 1 shows the baseline characteristics of the trial population which are similar between the treatment groups. The median age of patients at study entry was 70 years (IQR 67-74) and <10% of patients had ER poor tumors. Of 584 patients for whom radiotherapy data were available, 91 (16%) received a tumor bed boost after whole breast irradiation. After 10 years follow up, the cumulative incidence of local recurrence was 0.9% (95% CI 0.1-1.7%) in women allocated to radiotherapy, and 9.5% (95% 6.8-12.3%) for those allocated to no radiotherapy (Fig 2a). The hazard ratio comparing patients allocated to no radiotherapy vs radiotherapy was 10.4 (95% CI 4.1-26.1), p<0.0001 (full data, not censored at 10 years).

51 patients allocated to no radiotherapy and five who were allocated to radiotherapy developed local recurrences. In the no radiotherapy arm, 48/51 local recurrences occurred as the first event, including 37 who had only local recurrence. Overall survival at 10 years was 80.8% in the no radiotherapy group (95% CI, 77.2-

84.3%) and 80.7% in the radiotherapy group (95% CI,76.9-84.3%)[fig 2d]. Cumulative incidence of 10-year distant recurrences was 3.0% (95%CI 1.4%, 4.5%) with irradiation and 1.6% (95%CI 0.4, 2.8%) without. No differences at 10 years in distant recurrence (fig 2b), regional recurrence, contralateral breast cancer (not shown) or new non breast cancers were noted (Supplementary table S1). The 10-year disease-free survival was 68.9% in the no radiotherapy group (95% CI, 64.7-73.0%) and 76.3% (95% CI 72.5-80.2%), (fig S1) in those who received radiotherapy. The 10-year breast cancer-specific survival was 97.4% (95% CI 96.0-98.8) in patients allocated to no radiotherapy and 97.9% (95% CI 96.5-99.2) in patients allocated to radiotherapy (fig 2c). Sixteen deaths were due to breast cancer in the no radiotherapy group and 15 in the irradiated group (Supplementary table S2). Most causes of death were not due to breast cancer. 25% of all deaths (59/231) were due to cancer other than breast.

In a subgroup analysis of local recurrence by ER status, it was lower in patients with ER rich cancers compared to the whole population (fig 3).

The 10-year local recurrence rates for ER rich tumors were 1.0% (95% CI 0.1-1.9%) for the radiotherapy group and 8.6% (95% CI, 5.7-11.4) in patients who did not receive radiotherapy [HR 8.23, 95% CI 3.24-20.85, reference group ER rich with radiotherapy]. For patients with ER poor tumors, 10-year local recurrence rates were 19.1% (95% CI 8.2-29.9%) in the no radiotherapy group [HR =23.93 95% CI 8.43-67.93, compared with reference group ER rich with radiotherapy]. No local recurrence events were observed in ER poor tumors randomized to radiotherapy, but the sample size was very small (n=53). As data were collected on length of time adjuvant endocrine therapy was taken, the time dependent analysis found an

increased risk of local recurrence in patients no longer taking endocrine therapy [HR=4.66 (95% CI 1.77, 12.25) in the no radiotherapy group.. Other studies (16) have shown that less than 80% adherence is associated with significantly less benefit from adjuvant endocrine therapy. Figure S3 shows the local recurrence rates for patients split by whether they had taken 80% of the recommended 5 years of adjuvant endocrine therapy, equivalent to 4 or more years of treatment.

A multivariate Cox proportional hazards analysis of risk factors for local recurrence (Supplementary table S3) showed that only ER status was significant with radiotherapy in the model, and other risk factors had little effect on the impact of RT radiotherapy(univariate HR=0.10, 95% CI 0.04-0.24; multivariate HR=0.10, 95% CI 0.04-0.25).

No model failed the proportional hazards assumption test.

Discussion

This study confirms that whole breast irradiation significantly reduces the 10-year incidence of local recurrence after breast-conserving surgery in HR+, older women treated with adjuvant endocrine therapy from 9.5% without irradiation to 0.9% with irradiation. The local recurrence rate in irradiated patients up to 10 years remains low while that for non-irradiated patients continues at the same rate with no apparent plateau. However, the absolute reduction in local recurrence at 10 years was modest (8.6%). Despite this reduction, irradiation had no effect on regional or distant metastases, nor on breast cancer-specific or overall survival. Our low cumulative incidence of local recurrence at 10 years after breast-conserving surgery

and irradiation fits with the results of the earlier CALGB 9343 trial in TI, NO HR+ patients ≥70 years treated by breast-conserving surgery and tamoxifen (8), with a 7% absolute reduction in local recurrence from irradiation at 10 years . Our observations in a higher risk population show a similar reduction in the rate of local recurrence. Earlier trials of irradiation after breast-conserving surgery (17-23) apart from the Italian trial (23) were not exclusive to older patients, limiting their generalizability to an older population.

Our 9.5% local recurrence cumulative incidence in non-irradiated patients lies within The European Society of Mastology (EUSOMA) guidelines of a maximum loco-regional recurrence rate of 10% at 10 years (24). Our results also accord with the small benefit from irradiation in the low-risk older group in the meta-analysis of trials of adjuvant radiotherapy after breast-conserving surgery (4). EUSOMA guidelines recommend that patients aged >70 years receiving adjuvant endocrine therapy with low-risk tumors may be treated without irradiation (25), similar to that of the UK NICE (26) and the NCCN guidelines which allow omission of irradiation in women aged ≥65 (26) or ≥70 years (11) with stage 1, ER+ breast cancer after breast-conserving surgery. Our findings provide additional data that the higher cumulative incidence of local recurrence seen when irradiation is omitted has no impact on distant disease-free or overall survival.

The applicability of these results to clinical practice will be influenced by the balance of risks and benefits of radiation compared to those of adjuvant endocrine therapy. Irradiation has morbidity including cardiac events and second cancers (27,28). We

did not collect radiation toxicity for PRIME II. However the morbidity in the PRIME I trial, that also randomized to +/- irradiation after breast-conserving surgery, showed no difference in global quality of life (29,30). An increase in cardiovascular events has been reported both for tamoxifen and aromatase inhibitors (31]. In contemporary practice higher risk patients (T2 or grade 3 HR+ tumors) are likely to be treated with an aromatase inhibitor as endocrine therapy rather than tamoxifen. The results of PRIME II are similar to the BASO II trial (19) where local disease was controlled by tamoxifen or irradiation given alone. Viable options for patients meeting the entry criteria for PRIME II are a short course of irradiation or adjuvant endocrine therapy. The advantage of endocrine therapy is that it also reduces contralateral events.

The risk/benefit ratio of irradiation and endocrine therapy in low risk ER+ older patients has become more nuanced (32) with hypofractionated dose schedules (33), accelerated partial breast irradiation (34) and improved delivery techniques (35). Given the limitations of partial breast irradiation (demanding localization of treatment site and quality assurance) compared to whole breast irradiation, we concur with the view (36) that adjuvant endocrine therapy without irradiation is the principal competitor to whole breast irradiation. For non-irradiated patients who do develop local recurrence, the option of further breast-conserving therapy and irradiation are available, so recurrence does not necessarily mean loss of the breast.

Women in PRIME II in either arm were more likely to die from other causes than breast cancer. Of the 231 deaths only 31 (13%) were due to breast cancer. Patients

and clinicians can balance the harms and benefits of irradiation knowing that avoiding it does not increase breast cancer deaths.

Few patients in the study had grade 3 cancers (n=36) or lymphovascular invasion (n=39) and so whether radiotherapy can be avoided in these patients is not clear. From studies of neoadjuvant endocrine therapy (in preparation) ER rich grade 3 tumors do not respond less well than lower grade tumors. However, our study was underpowered to detect any difference in local recurrence between grade 3 and grade 1 and 2 tumors. For grade 3 tumors and lymphovascular invasion, our estimates of effect size are not very precise due to low numbers, and we can speculate that in selecting suitable patients for the trial, clinicians were cautious in enrolling patients with grade 3 tumors or lymphovascular invasion because the risk of local recurrence is raised twofold in patients with grade 3 histology or lymphovascular invasion (37,38), though their relevance as risk factors in older patients is unclear. Confining the option of omission of irradiation to grade 1 and 2 tumors is also in line with current European guidelines (24,25). No grade 3 tumors were included in the CALGB 9343 trial (8).

Our data are consistent with an earlier observation (9) that patients with ER rich cancers have a lower cumulative incidence of local recurrence at 10 years, than ER low cancers (Fig 3) with the new observation that longer durations of adjuvant endocrine therapy are associated with lower local recurrence in patients not having irradiation (Fig S3). The number of patients who completed 5 years of endocrine therapy was between 60-70%. Patients who are less than 80% adherent with

endocrine therapy are thought to have poorer outcomes (16,39). We did not collect data on adherence. Instead, using the reported end as a surrogate measure,we found a four-fold increased local recurrence risk for patients who were not taking endocrine therapy vs those continuing, in the no radiotherapy group.

The importance of ER poor status as a risk factor for local recurrence is underlined by our multivariate analysis (Supplementary table S3). It accords with the Scottish Conservation trial where relapse was higher in non-irradiated patients with ER poor tumors (20).

Our study has some limitations. We did not collect comorbidities or monitor compliance with endocrine therapy prospectively.

Omission of postoperative irradiation after breast-conserving surgery and adjuvant endocrine therapy for ER+ tumors varies is influenced by co-morbidities. Relatively high levels of irradiation for such patients have been reported from non randomized studies in the US (13). The PRIME II trial provides robust evidence that irradiation can be safely omitted in women with grade 1 and 2, ER rich cancers in women =/> 65 years treated by breast-conserving therapy provided they receive 5 years of adjuvant endocrine therapy.

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Figure 1: CONSORT diagram of recruitment and follow up

Figure 2: a) local recurrence; b) distant recurrence; c) breast cancer-specific survivial; d) overall survival

Note: Confidence intervals have not been adjusted for multiple testing and should not be used in place of hypothesis testing

Figure 3: Local recurrence by ER status and radiotherapy

Note: Confidence intervals have not been adjusted for multiple testing and should not be used in place of hypothesis testing

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Table 1: Demographics

Variable	Levels	No Radiotherapy (n=668)	Radiotherapy (n=658)
Age in years	Mean (sd)	71·12 (4·96)	70·78 (4·74)
	Median (IQR)	70 (67-74)	69 (67-73)
Tumor size N (%)	0-10mm	258 (38·6%)	265 (40·3%)
	10·1-20mm	326 (48·8%)	319 (48·5%)
	20·1-30mm	84 (12·6%)	74 (11·2%)
Margins N (%)	<1mm	10 (1·5%)	9 (1·4%)
	1-5mm	315 (47·2%)	296 (45·0%)
	>5mm	227 (34·0%)	239 (32·3%)
	Re-excision®	112 (16·8%)	110 (16·7%)
	Unknown	4 (<1%)	4 (<1%)
Grade N (%)	1	271 (40·9%)	292 (44·4%)
	2	368 (55·6%)	352 (54·6%)
	3	23 (3·5%)	13 (2·0%)
	Unknown	6 (<1%)	1 (<1%)
Side N (%)	Left	359 (53·7%)	345 (52·4%)
	Right	302 (45·2%)	305 (45·4%)
	Unknown	7 (1·0%)	8 (1·2%)
LVI N (%)	No	631 (95·2%)	628 (95·9%)
	Yes	32 (4·8%)	27 (4·1%)
	Unknown	5 (<1%)	3 (<1%)
Axillary surgery	SNB only	223 (33.4%)	198 (30.1%)
	Sample only	174 (26.0%)	211 (32.1%)
	Sample with SNB	105 (15.7%)	107 (16.3%)
	Clearance <10 nodes	43 (6.4%)	35 (5.3%)
	Clearance ≥10 nodes	109 (16.3%)	99 (15.0%)
	Unknown	14 (2·1%)	8 (1·2%)
Pre-operative endocrine therapy N (%)	No	608 (90·9%)	598 (91·7%)
	Yes	60 (9·1%)	54 (8·3%)
	Unknown	0	6 (<1%)
ER status N (%)	High¥	593 (88·8%)	601 (91·3%)
	Low	65 (9·7%)	55 (8·4%)
	Unknown	10 (1·5%)	2 (<1%)
Radiotherapy	within 40-50Gy	-	573¶/584‡ (98·1%)
	Boost	-	91/584 (15·6%)

Abbreviations: LVI=lymphovascular invasion; SNB=sentinel node biopsy; ER=estrogen receptor;

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434 ® Protocol specified adequate margins (≥1mm) after re-excision, the actual size was not requested.
435 ¥ Defined as, ER≥7 Allred score, fmol≥20, ≥50%, +++, strongly positive, or ER +ve (where no other information
436 available). In 12 patients, ER was not reported.
437 ¶ The majority of patients who were outside the 40-50Gy guidance were from countries other than the UK
438 ‡ Only 584 copies of the post-radiotherapy form were returned. Only one patient failed to complete RT once
439 started, one patient had their boost dose altered once begun.

440 Figure 1