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

2 Ian H Kunkler, MB, BChir¹, Linda J Williams, PhD¹, Wilma JL Jack, MB, ChB², David A

3 Cameron, MD¹, J Michael Dixon, MD¹

4 University of Edinburgh¹, Western General Hospital, Edinburgh²

5 Corresponding author:

6 Professor Ian Kunkler,

7 Professor of Clinical Oncology,

8 Institute of Genetics and Cancer,

9 University of Edinburgh,

10 Crewe Road,

11 Edinburgh, United Kingdom

12 EH4 2XR

13 Contact Tel +44 7841414504

14 Email: i.kunkler@ed.ac.uk

15

16 **Abstract**

17 Background

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

21 Methods

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

27 Results

28 658 women were randomized to whole breast irradiation and 668 to no irradiation
29 and the median follow up was 9.1 years. Cumulative incidences of ipsilateral breast
30 cancer recurrence to 10 years were 0.9% (95% CI 0.1-1.7%) for irradiation and 9.5%
31 (95% 6.8-12.3%) for no irradiation [HR 10.4 (95% CI 4.1-26.1.) $p < 0.0001$]. Although
32 the local recurrence was higher in the no irradiation group, distant recurrences at 10
33 years were not increased in this group and were 3.0% (95%CI 1.4%, 4.5%) with
34 irradiation and 1.6% (95%CI 0.4, 2.8%), without irradiation. Overall survival at 10
35 years was almost identical, at 80.8% (95% CI 77.2-84.3%) with irradiation vs 80.7%
36 (95% CI 76.9, 84.3%) with no irradiation. Regional recurrence and breast cancer
37 specific survival also did not differ between the two groups.

38 Conclusion

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

42 **Introduction**

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

59

60 **Methods**

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

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

70

71 Patient selection

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

84

85 Treatment

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

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

96

97 Study endpoints

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

104

105 Statistical analysis

106 Our null hypothesis was no difference between the irradiated and non-irradiated
107 groups in terms of local recurrence at 5 years. PRIME II was originally powered to
108 detect a difference at five years of at least 5% (5% with radiotherapy, 10% without
109 radiotherapy), with 80% power and 5% significance level with a target of recruiting
110 1000 patients. Ethical approval was granted on November 14, 2008 to increase the
111 sample size to 1294 because both randomized and non-randomized studies (14)
112 suggested that our initial estimate of local recurrence rate was excessive. Our
113 revised estimates enabled the detection of a difference of at least 3% (2% with

114 radiotherapy and 5% without radiotherapy) at five years with 80% power, 5%
115 significance level with 10% allowance for loss to follow up. Our planned statistical
116 analysis of primary and secondary outcomes of PRIME II was documented on
117 20/3/20 before analysis. Compliance with adjuvant endocrine therapy was included
118 as an additional secondary endpoint.

119

120 Data were analysed with Kaplan-Meier plots and by log rank testing (Mantel-Cox
121 statistic for the equality of survival distributions between levels of treatment).
122 Hazard ratios and 95% CI were estimated with the Cox proportional hazards model,
123 with the proportional hazards assumption tested for each model using the graphical
124 and numerical methods described by Lin et al (15). All analyses are by intention to
125 treat and are two-tailed tests. Since no procedure for type 1 error control was
126 implemented for secondary outcomes, results for these outcomes are reported as
127 point estimates and confidence intervals only, without hypothesis testing.

128 Confidence interval widths have not been adjusted for multiple testing and may not
129 be used in place of hypothesis testing. Pre-defined exploratory endpoints were
130 impact of duration of endocrine therapy and level of tumor ER on outcomes.

131 Clinicians were asked to note on the annual clinical research form whether a patient
132 was still taking adjuvant endocrine therapy, and if not, when they stopped. This
133 allowed an analysis of the data with adjuvant endocrine therapy as a time-varying
134 covariate, where the risk of local recurrence at time t for patients taking adjuvant
135 endocrine therapy compared to the risk of patients not taking adjuvant endocrine
136 therapy at time t .

137

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

144

145 **Results**

146 1326 patients were randomly allocated to either postoperative irradiation (n=658) or
147 not (n=668) from 16/4/2003 to 22/12/2009 (Fig 1). Patients were recruited from the
148 UK (1263), Greece (22), Australia (16) and Serbia (25). Table 1 shows the baseline
149 characteristics of the trial population which are similar between the treatment
150 groups. The median age of patients at study entry was 70 years (IQR 67-74) and
151 <10% of patients had ER poor tumors. Of 584 patients for whom radiotherapy data
152 were available, 91 (16%) received a tumor bed boost after whole breast irradiation.
153 After 10 years follow up, the cumulative incidence of local recurrence was 0.9% (95%
154 CI 0.1-1.7%) in women allocated to radiotherapy, and 9.5% (95% 6.8-12.3%) for
155 those allocated to no radiotherapy (Fig 2a). The hazard ratio comparing patients
156 allocated to no radiotherapy vs radiotherapy was 10.4 (95% CI 4.1-26.1), $p < 0.0001$
157 (full data, not censored at 10 years).

158 51 patients allocated to no radiotherapy and five who were allocated to
159 radiotherapy developed local recurrences. In the no radiotherapy arm, 48/51 local
160 recurrences occurred as the first event, including 37 who had only local recurrence.
161 Overall survival at 10 years was 80.8% in the no radiotherapy group (95% CI, 77.2-

162 84.3%) and 80.7% in the radiotherapy group (95% CI,76.9-84.3%)[fig 2d]. Cumulative
163 incidence of 10-year distant recurrences was 3.0% (95%CI 1.4%, 4.5%) with
164 irradiation and 1.6% (95%CI 0.4, 2.8%) without. No differences at 10 years in distant
165 recurrence (fig 2b), regional recurrence, contralateral breast cancer (not shown) or
166 new non breast cancers were noted (Supplementary table S1). The 10-year disease-
167 free survival was 68.9% in the no radiotherapy group (95% CI, 64.7-73.0%) and 76.3%
168 (95% CI 72.5-80.2%), (fig S1) in those who received radiotherapy. The 10-year breast
169 cancer-specific survival was 97.4% (95% CI 96.0-98.8) in patients allocated to no
170 radiotherapy and 97.9% (95% CI 96.5-99.2) in patients allocated to radiotherapy (fig
171 2c). Sixteen deaths were due to breast cancer in the no radiotherapy group and 15 in
172 the irradiated group (Supplementary table S2). Most causes of death were not due
173 to breast cancer. 25% of all deaths (59/231) were due to cancer other than breast.
174
175 In a subgroup analysis of local recurrence by ER status, it was lower in patients with
176 ER rich cancers compared to the whole population (fig 3).
177 The 10-year local recurrence rates for ER rich tumors were 1.0% (95% CI 0.1-1.9%)
178 for the radiotherapy group and 8.6% (95% CI, 5.7-11.4) in patients who did not
179 receive radiotherapy [HR 8.23, 95% CI 3.24-20.85, reference group ER rich with
180 radiotherapy]. For patients with ER poor tumors, 10-year local recurrence rates were
181 19.1% (95% CI 8.2-29.9%) in the no radiotherapy group [HR =23.93 95% CI 8.43-
182 67.93, compared with reference group ER rich with radiotherapy]. No local
183 recurrence events were observed in ER poor tumors randomized to radiotherapy,
184 but the sample size was very small (n=53). As data were collected on length of time
185 adjuvant endocrine therapy was taken, the time dependent analysis found an

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

192

193 A multivariate Cox proportional hazards analysis of risk factors for local recurrence
194 (Supplementary table S3) showed that only ER status was significant with
195 radiotherapy in the model, and other risk factors had little effect on the impact of RT
196 radiotherapy (univariate HR=0.10, 95% CI 0.04-0.24; multivariate HR=0.10, 95% CI
197 0.04-0.25).

198 No model failed the proportional hazards assumption test.

199

200 **Discussion**

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

210 and irradiation fits with the results of the earlier CALGB 9343 trial in T1, NO HR+
211 patients ≥ 70 years treated by breast-conserving surgery and tamoxifen (8), with a 7%
212 absolute reduction in local recurrence from irradiation at 10 years . Our observations
213 in a higher risk population show a similar reduction in the rate of local recurrence.
214 Earlier trials of irradiation after breast-conserving surgery (17-23) apart from the
215 Italian trial (23) were not exclusive to older patients, limiting their generalizability to
216 an older population.

217

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

230

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

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

244

245 The risk/benefit ratio of irradiation and endocrine therapy in low risk ER+ older
246 patients has become more nuanced (32) with hypofractionated dose schedules (33),
247 accelerated partial breast irradiation (34) and improved delivery techniques (35).

248 Given the limitations of partial breast irradiation (demanding localization of
249 treatment site and quality assurance) compared to whole breast irradiation, we
250 concur with the view (36) that adjuvant endocrine therapy without irradiation is the
251 principal competitor to whole breast irradiation. For non-irradiated patients who do
252 develop local recurrence, the option of further breast-conserving therapy and
253 irradiation are available, so recurrence does not necessarily mean loss of the breast.

254

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

257 and clinicians can balance the harms and benefits of irradiation knowing that
258 avoiding it does not increase breast cancer deaths.
259
260 Few patients in the study had grade 3 cancers (n=36) or lymphovascular invasion
261 (n=39) and so whether radiotherapy can be avoided in these patients is not clear.
262 From studies of neoadjuvant endocrine therapy (in preparation) ER rich grade 3
263 tumors do not respond less well than lower grade tumors. However, our study was
264 underpowered to detect any difference in local recurrence between grade 3 and
265 grade 1 and 2 tumors. For grade 3 tumors and lymphovascular invasion, our
266 estimates of effect size are not very precise due to low numbers, and we can
267 speculate that in selecting suitable patients for the trial, clinicians were cautious in
268 enrolling patients with grade 3 tumors or lymphovascular invasion because the risk
269 of local recurrence is raised twofold in patients with grade 3 histology or
270 lymphovascular invasion (37,38), though their relevance as risk factors in older
271 patients is unclear. Confining the option of omission of irradiation to grade 1 and 2
272 tumors is also in line with current European guidelines (24,25). No grade 3 tumors
273 were included in the CALGB 9343 trial (8).

274

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

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

285

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

290

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

293

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

301

302

303

304 **Acknowledgements**

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306 Government and the Breast Cancer Institute, Western General Hospital, Edinburgh.
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308 patients who participated and investigators (listed in the Supplementary Appendix).

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310

311 Figure 1: CONSORT diagram of recruitment and follow up

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

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

316 Figure 3: Local recurrence by ER status and radiotherapy

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

319

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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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* Protocol specified adequate margins (≥ 1 mm) after re-excision, the actual size was not requested.

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‡ Defined as, ER ≥ 7 Allred score, fmoI ≥ 20 , $\geq 50\%$, +++, strongly positive, or ER +ve (where no other information available). In 12 patients, ER was not reported.

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¶ The majority of patients who were outside the 40-50Gy guidance were from countries other than the UK

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‡ Only 584 copies of the post-radiotherapy form were returned. Only one patient failed to complete RT once started, one patient had their boost dose altered once begun.

439

440 Figure 1