

Boost radiotherapy in young women with ductal carcinoma in situ: a multicentre, retrospective study of the Rare Cancer Network



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Summary

Background Outcome data in young women with ductal carcinoma in situ (DCIS) are rare. The benefits of boost radiotherapy in this group are also unknown. We aimed to assess the effect of boost radiotherapy in young patients with DCIS.

Methods We included 373 women from 18 institutions who met the following inclusion criteria: having tumour status Tis and nodal status (N)0, age 45 years or younger at diagnosis, and having had breast-conserving surgery. 57 (15%) patients had no radiotherapy after surgery, 166 (45%) had radiotherapy without boost (median dose 50 Gy [range 40–60]), and 150 (40%) had radiotherapy with boost (60 Gy [53–76]). The primary outcome was local relapse-free survival.

Findings Median follow-up was 72 months (range 1–281). 55 (15%) patients had local relapse. Local relapse-free survival at 10 years was 46% (95% CI 24–67) for patients given no radiotherapy, 72% (61–83) for those given radiotherapy without boost, and 86% (78–93) for those given radiotherapy and boost (difference between all three groups, $p < 0.0001$). Age, margin status, and radiotherapy dose were significant predictors of local relapse-free survival. Compared with patients who had no radiotherapy, those who had radiotherapy had a decreased risk of local relapse (without boost, hazard ratio 0.33 [95% CI 0.16–0.71], $p = 0.004$; with boost, 0.15 [0.06–0.36], $p < 0.0001$).

Interpretation In the absence of randomised trials, boost radiotherapy should be considered in addition to surgery for breast-conserving treatment for DCIS.

Introduction

Incidence of ductal carcinoma in situ (DCIS) of the breast has increased greatly since the introduction of mammography screening.¹ Treatment is given mainly to prevent local relapse, especially the progression to invasive disease. Death from breast cancer is rare in patients with DCIS, irrespective of whether mastectomy or breast-conserving surgery is done.²

In three randomised trials^{3–5} investigating the role of radiotherapy after breast-conserving surgery for DCIS, the risk of recurrence in the ipsilateral breast for patients assigned to radiotherapy was about half that of those assigned to no radiotherapy. In the NSABP (National Surgical Adjuvant Breast Project) B-17 trial ($n = 828$),³ patients assigned excision plus whole-breast radiotherapy at 50 Gy had a lower risk of local recurrence than those assigned excision only, at 8 years of follow-up (hazard ratio 0.39 [95% CI 0.27–0.56]; $p < 0.0001$). In the EORTC (European Organisation for Research and Treatment of Cancer) 10853 trial ($n = 1010$),⁴ patients were allocated treatment in a similar design. At 4 years of follow-up, the hazard ratio of local recurrence was 0.62 (0.44–0.87) for patients assigned additional radiotherapy versus those assigned excision only ($p = 0.005$). In the UKCCR (UK Coordinating Committee on Cancer Research) trial,⁵ 1694 patients were randomly assigned in a 2×2 design: 544 received excision only, 567 excision plus tamoxifen,

267 excision plus radiotherapy, and 316 excision plus radiotherapy and tamoxifen. Similar to the NSABP and the EORTC trials, the UKCCR trial showed a significant reduction in local recurrence in patients who were assigned radiotherapy compared with those who were not, at 5 years of follow-up (0.38 [0.25–0.59]; $p < 0.0001$).

Young age has been reported as an independent risk factor for local recurrence after breast-conserving surgery in 705 patients with DCIS (aged ≤ 40 years)⁶ and in 1360 patients with invasive breast cancer (aged ≤ 45 years).⁷ This finding was also confirmed in randomised trials.^{4,8,9} A boost of 16 Gy to the primary tumour site after 50 Gy of whole-breast radiotherapy reduced the risk of local recurrence in patients with invasive breast cancer, which was greatest in those aged 40 years or younger.^{8,9}

The total radiotherapy dose used in the randomised studies of DCIS was 50 Gy to the whole breast. Whether patients with DCIS, especially young patients, will benefit from boost radiotherapy has not been investigated so far. In a retrospective study, we aimed to estimate the effect of boost radiotherapy on local relapse-free survival in patients with DCIS aged 45 years or younger.

Methods

Patients

Records of 373 patients taken from February, 1978, to August, 2004, were analysed retrospectively in a study by

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the Rare Cancer Network. Patients were from 18 institutions in Australia, Belgium, France, the UK, Israel, Italy, the Netherlands, Spain, Switzerland, Turkey, and the USA. All 373 available patients met the following eligibility criteria: having pure DCIS (tumour status Tis, nodal status [N]0), age 45 years or younger at diagnosis, and having had breast-conserving surgery. The upper age limit was fixed at 45 years because about 20% of patients with DCIS meet this criterion, and to allow adequate numbers of patients for analysis.¹⁰

Median age was 41 years (range 23–45). Surgery consisted of local excision in all 373 patients, of whom 230 (62%) underwent a re-excision. 57 (15%) were not given radiotherapy after surgery, 166 (45%) received whole-breast radiotherapy without boost (median dose 50 Gy [range 40–60]), and 150 (40%) received whole-breast radiotherapy with a boost. The decision about

radiation boost was made at the discretion of the radiation oncologist. Total boost dose was 10 Gy for 98 patients, more than 10 Gy for 41, and less than 10 Gy for 11. The boost was given with orthovoltage photons in 40 patients, with electrons in 101, and with interstitial implants in nine. The median total dose for all patients given whole-breast radiotherapy and boost was 60 Gy (range 53–76).

Adjuvant tamoxifen was given to 26 patients (7%): two of 57 who received no radiotherapy, 17 of 166 who received radiotherapy without boost, and seven (5%) of 150 who received radiotherapy with a boost.

Statistical analysis

The primary outcome was local relapse and local relapse-free survival. Secondary outcomes were regional relapse, distant relapse, contralateral relapse, and death. Local relapse was defined as any recurrence of breast cancer (either invasive or in-situ) in the operated breast. Contralateral relapse was defined as any recurrence of breast cancer (either invasive or in-situ) in the contralateral breast. Regional relapse was defined as invasive breast cancer in the axillary, periclavicular, and internal mammary lymph nodes. Distant relapse was any recurrence of invasive breast cancer in the body apart from operated or contralateral breast, or regional lymph nodes. Local relapse-free survival was defined as the time from the date of surgery to local relapse as a first event (with or without simultaneous regional or distant relapse). We defined overall survival as the time from surgery to death from any cause. Kaplan-Meier analysis was used to calculate survival curves.

Data were obtained from a review of medical records by the principal investigator of every centre according to a structured questionnaire. Baseline characteristics were compared across the treatment groups with Fisher's exact test. The product-limit method was used to estimate local relapse-free survival and overall survival for all three treatment groups. We used the log-rank test (unstratified) to compare the survival estimates. Proportional hazards regression analysis was used to estimate the effect of radiotherapy (with and without boost) after adjustment for age (≤ 39 years vs 40–45 years), method of detection (clinical, mammography, unknown), tumour size (largest diameter ≤ 20 mm vs > 20 mm), necrosis (presence or absence), tumour grade (grade 1, 2, 3, unknown), tumour margin status (clear, positive, unknown), and oestrogen-receptor status (oestrogen-receptor negative, positive, unknown). Indicator variables for all the baseline prognostic factors (including unknown categories) were simultaneously included in the regression model along with indicator variables for radiotherapy. With the regression results, we calculated hazard ratios, along with p values and 95% CIs. The p value for every prognostic factor was obtained from a Wald test. We regarded $p < 0.05$ (two-sided) as significant. For prognostic factors significantly associated with local relapse-free

	No radiotherapy (n=57)	Radiotherapy without boost (n=166)	Radiotherapy with boost (n=150)	p*
Age (years)				
≤ 39	19 (33%)	46 (28%)	43 (29%)	0.72
40–45	38 (67%)	120 (72%)	107 (71%)	
Detection method				
Clinical	24 (42%)	39 (23%)	26 (17%)	0.001
Mammography only	31 (54%)	122 (73%)	110 (73%)	
Unknown	2 (4%)	5 (3%)	14 (9%)	
Tumour size				
≤ 20 mm	34 (60%)	85 (51%)	54 (36%)	0.002
> 20 mm	10 (18%)	30 (18%)	23 (15%)	
Unknown	13 (23%)	51 (31%)	73 (49%)	
Necrosis				
Yes	21 (37%)	68 (41%)	48 (32%)	0.25
None reported	36 (63%)	98 (59%)	102 (68%)	
Tumour grade				
1	22 (39%)	31 (19%)	32 (21%)	0.04
2	11 (19%)	28 (17%)	27 (18%)	
3	15 (26%)	51 (31%)	39 (26%)	
Unknown	9 (16%)	56 (34%)	52 (35%)	
Margin status				
Clear	53 (93%)	117 (70%)	74 (49%)	< 0.0001
Positive	2 (4%)	7 (4%)	11 (7%)	
Unknown	2 (4%)	42 (25%)	65 (43%)	
Oestrogen-receptor status				
Negative	1 (2%)	5 (3%)	5 (3%)	0.06
Positive	6 (11%)	45 (27%)	41 (27%)	
Unknown	50 (88%)	116 (70%)	104 (69%)	

Data are number of patients (%). *Based on two-sided Fisher's exact tests.

Table 1: Baseline characteristics of patients

Rare Cancer Network is an organisation founded in Switzerland, which brings together information from different countries about diagnosis and treatment of rare cancers. For more information, see <http://www.rarecancer.net>

survival in the regression analysis, the product-limit method was used to estimate 10-year overall survival and local relapse-free survival, according to treatment group. Statistical analysis was done by use of SAS version 9.1.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study, and had final responsibility to submit the paper for publication.

Results

Table 1 summarises the baseline characteristics of patients by treatment group. After median follow-up of 72 months (range 1–281), 55 (15%) patients had local relapse, of whom 28 had invasive breast cancer, 26 had DCIS, and one was not specified as invasive or DCIS breast cancer. Relapse was regional in eight (2%) patients and contralateral in 23 (6%) patients and distant in nine (2%) patients, all of whom had subsequent invasive local relapse; and one of whom also had previous contralateral breast cancer. Seven (2%) patients died, five because of invasive breast cancer. One patient had malignant melanoma about 2 years after diagnosis of DCIS and died 1 year later without signs of breast-cancer recurrence. The remaining patient died for unknown reasons.

The 10-year overall survival for all patients was 97% (95% CI 95–100), with no significant difference between the three treatment groups ($p=0.96$). Local relapse-free survival at 10 years was 46% (24–67) in patients given no radiotherapy, 72% (61–83) in those given radiotherapy without boost, and 86% (78–93%) in those given radiotherapy with boost (figure).

Table 2 shows the analysis results from multivariable proportional hazards regression. Compared with no radiotherapy, radiotherapy without boost was associated with a reduced risk of local relapse ($p=0.004$), as was radiotherapy with boost ($p<0.0001$). Compared with radiotherapy without boost, radiotherapy with boost had a significant advantage (hazard ratio 0.45 [0.23–0.90], $p=0.024$).

Analyses unadjusted for baseline characteristics showed that local relapse-free survival was 63% (49–76) for patients aged 39 years or younger and 81% (74–88) for those aged 40–45 years, and 77% (68–86) in patients with clear margins and 43% (16–71) in those with positive margins. Adjusted analyses showed that age 40–45 years, clear margin status, and use of radiotherapy were significant predictors of local relapse-free survival (table 2).

Discussion

Our study showed that local relapse-free survival at 10 years rises progressively for patients with DCIS given breast-conserving surgery only, those given additional radiotherapy without boost, and those given additional

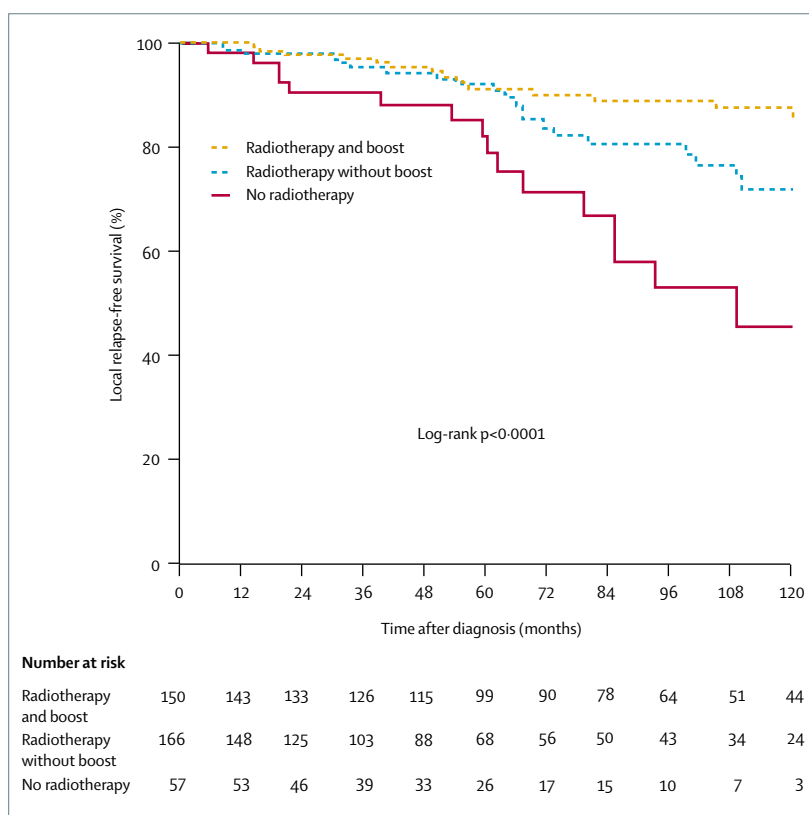


Figure: Local relapse-free survival by treatment group

radiotherapy and boost. Age, margin status, and use of radiotherapy were significant predictors of local relapse-free survival, and boost radiotherapy offers a significant advantage over radiotherapy without boost for young women with DCIS.

Despite a substantial increase in newly diagnosed DCIS because of the introduction of mammography screening, little is known about the best treatment in young patients with DCIS, who are a minority of the cohort of DCIS patients. Only 51 (6%) of 863 patients in the EORTC study were aged 40 years or younger,¹¹ and only 31 (21%) of 148 in a retrospective analysis of the William Beaumont Hospital (Royal Oak, MI, USA) were younger than 45 years.¹⁰ No firm treatment recommendation can be given for young women, because of their under-representation in study groups.

Three large randomised trials of DCIS^{3–5} have shown a highly significant risk reduction of about 50% for ipsilateral breast relapse in patients who received excision plus adjuvant radiotherapy, by comparison with those who received local excision only. The EORTC trial has been updated;¹² the hazard ratio for local relapse-free survival was 0.53 (95% CI 0.40–0.70, $p<0.0001$) for patients assigned to local excision only versus those assigned additional radiotherapy, and young age (≤ 40 years) was a leading risk factor for local relapse in the multivariable analysis (1.89 [1.18–2.90]). Young

	Hazard ratio (95% CI)	p*
Age (years)		
≤39	1.00	0.010
40–45	0.46 (0.25–0.83)	
Detection method		
Mammography only	1.00	0.5
Clinical	0.75 (0.37–1.52)	
Unknown	1.63 (0.54–4.91)	
Tumour size		
≤20 mm	1.00	0.1
>20 mm	1.16 (0.50–2.68)	
Unknown	1.95 (1.02–3.72)	
Necrosis		
Yes	1.00	0.4
None reported	0.78 (0.43–1.44)	
Tumour grade		
1	1.00	0.8
2	1.01 (0.36–2.79)	
3	1.46 (0.56–3.80)	
Unknown	1.23 (0.50–3.01)	
Margin status		
Clear	1.00	0.02
Positive	3.53 (1.48–8.43)	
Unknown	1.13 (0.54–2.34)	
Oestrogen-receptor status		
Negative	1.00	0.9
Positive	0.71 (0.17–2.96)	
Unknown	0.68 (0.18–2.59)	
Treatment		
No radiotherapy	1.00	<0.0001
Radiotherapy without boost	0.33 (0.16–0.71)	
Radiotherapy with boost	0.15 (0.06–0.36)	

*p values are based on two-sided Wald tests.

Table 2: Hazard ratio estimates for local relapse-free survival

patients assigned to excision plus radiotherapy had 26% local recurrence,¹² which was similar to the 28% value estimated in patients from our study (age ≤45 years) at 10 years. In a retrospective analysis¹¹ of 148 patients with DCIS, of whom 94% received a boost (median total dose 60.4 Gy), 18% of patients younger than 45 years, 5% of those aged 45–65 years, and 4% of those older than 65 years had a relapse in the ipsilateral breast.¹¹

Only a few studies, all of which had a small sample size, have investigated the relation between young age and outcome in patients with DCIS;^{6,10,13} these studies showed that, similar to invasive breast cancer, young age is a risk factor for local recurrence. The underlying reason is not clear; however, young patients with DCIS might have increased risk of local relapse because smaller

volumes of the breast tissue are excised, or because more patients have a high nuclear grade, central necrosis,¹⁴ and *ERBB2* overexpression.¹⁵ Salvage treatment might have differed between groups, potentially affecting our results, but this was not assessed in our study. For patients in our study, an unacceptably high number of those who did not receive radiotherapy had relapse (54% at 10 years). This number was reduced by use of radiotherapy without boost (28% local relapse at 10 years), although this value was still unsatisfactorily high.

Particularly, young patients have shown benefit from boost radiotherapy, with a fall in local relapse from 20% to 10% in 449 patients aged 40 years ($p=0.002$), and a fall from 10% to 6% for 1334 patients aged 41–50 years ($p=0.02$).^{8,9} Although several links between age and factors related to patients, treatments, and tumours were identified, only age and boost treatment were independently related to local control in a multivariable analysis.⁹

In the available randomised trials, no boost irradiation was used for DCIS. We recorded a significant advantage from the addition of a boost compared with radiotherapy only. In particular, radiotherapy with boost was associated with a reduction in the risk of local relapse compared with radiotherapy only, which is very similar to the effect of boost irradiation in invasive breast cancer.

About half the local recurrences in our study were invasive, which is similar to the proportion in the randomised trials. Of patients who had local relapse that was invasive, 12% (seven of 57) had no radiotherapy, 8% (14 of 166) had radiotherapy without boost, and 5% (seven of 150) had radiotherapy with boost. Prevention of invasive breast-cancer recurrence is especially important because of the effect that invasive recurrence might have on survival.

Our study had weaknesses typical of retrospective designs. In particular, patients were included over more than 26 years, during which treatment preferences might have changed. We tried to investigate this effect by dividing patients into three groups: treatment up to 1990, 1991–99, and 2000 onwards. However, we saw no difference in univariate analysis between these groups for local relapse-free survival (log-rank, $p=0.35$). We could not investigate the effect of tamoxifen treatment on the outcome in younger patients with DCIS, because only 26 patients received adjuvant hormonal treatment. The value of tamoxifen is still controversial; unlike the NSABP B-24 trial,¹⁶ no significant benefit was seen in the reduction of local recurrence for those who received tamoxifen in the UK trial.⁵ Furthermore, we did not do a central review of pathology records, and important variables were often not reported, such as tumour size, margin width, grade; or hormonal-receptor status. However, prospective randomised trials in DCIS have had similar issues—eg, in the EORTC,¹¹ the exact measurement of margin width was present in only 5% of

the pathology reports, and more than 40% of patients had no tumour size measurement in the initial NSABP report.¹⁷ We cannot exclude the idea that use of an additional boost was driven by adverse prognostic factors. Baseline characteristics were often not all reported, although we did not find large imbalances for the other significant factors (young age and positive margins) in patients with or without a boost (table 1). Most participating departments probably had a fixed treatment protocol, and the addition of a boost probably depended more on the departments' protocol than on the characteristics of the patient and tumour. Furthermore, the inclusion of missing data in the multivariable analysis did not reduce the positive effect of radiotherapy. The high frequency of lesions detected by mammography in our study is noteworthy because young patients do not usually participate in population-based screening programmes. This finding might have been because these young patients were at high risk of breast cancer, although we did not assess these characteristics.

Apart from radiotherapy and age, and in accordance with published work,^{6,12,18} positive margin status was a significant predictor of local relapse-free survival in the multivariable analysis. Although a large excised breast volume might have been beneficial with respect to local relapse, such information was seldom available, and the excision volume could not be analysed.

According to guidelines and recent overviews, new studies to answer the boost question also in DCIS are encouraged.^{19–21} Our findings clearly suggest that the radiation dose is very important for local tumour control for patients with DCIS aged 45 years or younger. However, because of our study's limitations, our results can only generate hypotheses, and data from large randomised trials should answer the boost question, especially in patients with DCIS who are at high risk for local relapse.

Therefore, in the absence of randomised trials, whole-breast radiotherapy followed by a boost should be considered for breast-conserving treatment in young patients with DCIS.

Contributors

G Gruber and A Omlin thought of the original idea for the study and planned its design. A Omlin, M Amichetti, D Azria, P Fournier, P Poortmans, D Naehrig, R C Miller, M Krengli, C Gutierrez Miguelez, D Morgan, H Goldberg, L Scandolaro, P Gastelblum, M Ozsahin, D Dohr, D Christie, U Oppitz, U Abacioglu, and G Gruber participated in the data collection. B F Cole and G Gruber did the statistical analyses. G Gruber, A Omlin, and B F Cole were responsible for the final draft of the report. All authors participated in critical revision of the report.

Conflicts of interest

We declare no conflicts of interest.

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