Breast-conserving therapy for ductal carcinoma in situ

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Chapter 2

Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853

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Abstract

Background  Ductal carcinoma in situ (DCIS) of the breast is a disorder that has become more common since it may manifest as microcalcifications that can be detected by screening mammography. Since selected women with invasive cancer can be treated safely with breast-conservation therapy it is paradoxical that total mastectomy has remained the standard treatment for DCIS. We did a randomised phase III clinical trial to investigate the role of radiotherapy after complete local excision of DCIS.

Methods  Between 1986 and 1996, women with clinically or mammographically detected DCIS measuring less than or equal to 5 cm were treated by complete local excision of the lesion and then randomly assigned to either no further treatment (N=503) or to radiotherapy (N=507, 50 Gy in five weeks to the whole breast). The median duration of follow-up was 4.25 years (maximum 12.0). All analyses were by intention to treat.

Results  502 patients were followed up in the no further treatment group and 502 in the radiotherapy group. In the no further treatment group 83 women had local recurrences (44 recurrences of DCIS, and 40 invasive breast cancer). In the radiotherapy group 53 women had local recurrences (29 recurrences of DCIS, and 24 invasive breast cancer). The 4-year local relapse-free rate was 84% in the group treated with local excision alone compared with 91% in the women treated by local excision plus radiotherapy (logrank \( P=0.005 \), Hazard Ratio=0.62). Similar reductions in the risk of invasive (40%, \( P=0.04 \)) and non-invasive (35%, \( P=0.06 \)) local recurrence were seen.

Conclusions  Radiotherapy after local excision for DCIS, as compared to local excision alone, reduced the overall number of both invasive and non-invasive recurrences in the ipsilateral breast at a median follow-up of 4.25 years.
Introduction

Breast-conserving treatment for patients with ductal carcinoma in situ (DCIS) is a relatively new treatment option. Until a decade ago total mastectomy was the standard treatment for women with DCIS. At that time DCIS was a rare disease, comprising only 2 to 5% of all breast cancers presenting clinically as a palpable mass, bloody nipple discharge, or Paget's disease of the nipple. An almost 100% cure rate could be achieved with ablative treatment. Rare exceptions were cases labelled as DCIS but with histologically undetected microinvasion from which tumour emboli emerged and gave rise to distant metastases.

With the widespread use of mammographic screening, the incidence of DCIS has increased, such that these lesions now comprise 15 to 20% of all breast cancers detected in population screening programs. Most of these cases are clinically occult and detected because of microcalcifications on mammograms.

For selected women with invasive breast carcinoma, breast-conserving therapy has already proved to be as effective as mastectomy. Hence it is paradoxical that DCIS, a non-invasive lesion, is generally treated by more extensive surgery than is invasive breast cancer. But whereas mastectomy for DCIS can almost invariably achieve cure, breast-conserving treatment in DCIS could increase the risk of residual disease, which might recur and progress into invasive carcinoma, thereby increasing the risk of dying from metastatic disease.

In the mid-eighties several randomised clinical trials were started to find out what is the best breast-conserving treatment for patients with DCIS. We report the initial results of a phase III randomised study done between 1986 and 1996 to examine the effect of radiotherapy after local excision of DCIS.

Methods

Participants

Women with DCIS of the breast were randomly assigned radiotherapy, or no further treatment after histological confirmation that the lesion had been completely excised. Extent of free margins was not specified other than that DCIS should not be present at the margin of the sample. Patients gave informed consent according to the institute's regulations.

Patients with lesions with a diameter up to 5 cm, without evidence of invasive carcinoma or Paget's disease of the nipple, were eligible for the study. Size was determined by either clinical measurement or from the extent of microcalcifications on the mammograms. Axillary dissection was not required nor advised but, if done, the axillary lymph nodes had to be free of metastases. Patients were excluded who were more than 70 years of age, were pregnant, or had a past or concomitant malignant disease other than adequately treated basal-cell carcinoma of the skin or cone-biopsied carcinoma in situ of the cervix. Those with a performance status of greater than or equal
to 2 according to the WHO criteria, or with a mental condition or social situation precluding long-term follow-up, were also excluded.

Study design
Patients were centrally randomised at the EORTC Data Center. Randomisation was done by minimisation and was stratified for institution. The primary endpoints were invasive and non-invasive recurrence in the treated breast. Secondary endpoints included regional recurrence, metastasis, death, and contralateral breast cancer. Recurrence-free intervals were defined as the time between the date of randomisation and the date of recurrence of the disease. All analyses were by intent to treat. All randomised patients for whom information was available were included. The time-to-recurrence curves were calculated with the Kaplan-Meier analysis and compared by means of a two-sided logrank test. Size of the treatment difference was calculated on the basis of the hazards ratio and its 95% CI.

All patients underwent wide resection of the portion of the mammary gland harbouring the lesion. The resection was intended to remove the whole lesion or the entire area with microcalcifications. The cutaneous incision, depending on the tumour site and size, was radial or curvilinear to obtain the best cosmetic result. The surgical samples were sent to the pathologist to have the margins inked and to get information on histology and margin status. If the DCIS was incompletely excised at the first attempt, a second operation was done.

External-beam radiotherapy had to be started within 12 weeks after surgery. The patient was irradiated in the supine position with immobilisation of the ipsilateral arm. The target area had to encompass the chest wall. The breast was irradiated by means of medial and tangential portals. The medial border was drawn at the midline, the upper border was drawn between the first and second intercostal spaces and laterally to the soft tissue of the central axilla. The dorsal border was at the midaxillary line or 1-2 cm beyond, depending on breast tissue. The lower border was 1 cm below the inframammary sulcus. In addition, the margin had to be at least 2 cm clear of any incision. Correction for divergence had to be made by a slight angulation of the beam to obtain a flat dorsal plane. In this way, unnecessary irradiation of lung tissue could be reduced. The second measure to limit the irradiation of unnecessary lung tissue was the adaptation of the dorsal planes of the treatment portals to the angle of the chest wall. The patient had to be irradiated each day through both tangential portals. To achieve a homogeneous dose distribution over the whole breast, a compensatory filter or wedge was used for each individual patient. The maximum allowable difference in dose distribution over the target volume in the central plane was 10%.

The prescribed irradiation dose was 50 Gy in 25 fractions (2 Gy per fraction) to be given in 5 weeks. This dose was directed at the intersection of the central axis of the beams (according to the International Commission on Radiation Units and Measurements definition), or, if this intersection was outside the target volume because of correction for divergence, the dose had to be directed in the centre of the target volume. No boost was advised nor were the adjacent lymph-node stations irradiated.
Patients were followed at 6-monthly intervals until the 10th postoperative year, and then at annually intervals. Bilateral mammograms had to be done every year. Follow-up data were sent yearly at the EORTC Data Center. Suspected local or regional recurrences had to be confirmed histologically.

In 1996 patients' medical files were reviewed during site visits. 843 (84%) of the medical files were available for review. The remaining 167 files were not reviewed because the hospitals were too far away in 82 cases. 18 files were not available at time of the visit, and 67 patients were randomised after the visit.

At the review further information was collected about patient, treatment and tumour characteristics. Eligibility was checked and, if an event had occurred, detailed information was collected on methods of detection and treatment at that time. The analysis described in this paper is based on data collected during the review. In cases for which no review data were available, detailed data were requested from the local trial investigator. If there was no response to this request, the original data reported to the EORTC Data Center were used for the analysis.

Data on the original diagnosis of DCIS, tumour size, and completeness of excision were derived from the report of the local pathologist.

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**Figure 1 Trial profile**
Results

Between March 1986 and July 1996, 1010 women were randomly assigned to no further treatment (503 patients) or to radiotherapy (507 patients) by 46 institutes from 13 different countries (Figure 1). The number of randomised patients per institute varied from one to 151. The four main institutes together entered 48% of the patients. For two patients no information was available, and no follow-up data were available on another six patients. These eight patients were excluded from the analysis.

41 patients were randomised although they did not meet the criteria for entry (25 in the local excision alone group and 16 in the radiotherapy group). 11 patients were older than 70 years, eight women had had a previous malignant disease before the diagnosis of DCIS was made, two had a histologically confirmed Paget’s disease of the nipple, and 11 had lesions larger than 5 cm. There were four cases of microinvasion (according to the local pathologist), and in seven cases the margins were affected. One patient was randomised after having undergone a mastectomy. Three patients had more than one reason for ineligibility. 11 patients who were randomised to the no further treatment

Table 1 Characteristics of patients and treatment received

<table>
<thead>
<tr>
<th></th>
<th>No further treatment (N=503)</th>
<th>Radiotherapy (N=507)</th>
<th>Total (N=1010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) age (years)</td>
<td>53 (25-76)</td>
<td>53 (27-94)</td>
<td>53 (25-76)</td>
</tr>
<tr>
<td><strong>Clinical signs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpable lesion</td>
<td>109 (22%)</td>
<td>99 (19%)</td>
<td>208 (21%)</td>
</tr>
<tr>
<td>Mean diameter palpable lesion (mm)</td>
<td>22</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Nipple discharge</td>
<td>40 (8%)</td>
<td>34 (7%)</td>
<td>74 (7%)</td>
</tr>
<tr>
<td>Mammographic lesion only</td>
<td>350 (70%)</td>
<td>372 (73%)</td>
<td>722 (71%)</td>
</tr>
<tr>
<td>Mean diameter mammographic abnormality (mm)</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of operations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>321 (64%)</td>
<td>336 (66%)</td>
<td>657 (65%)</td>
</tr>
<tr>
<td>2</td>
<td>178 (35%)</td>
<td>158 (31%)</td>
<td>336 (33%)</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>6 (1%)</td>
<td>7 (1%)</td>
</tr>
<tr>
<td>Axillary dissection performed</td>
<td>98 (19%)</td>
<td>104 (21%)</td>
<td>202 (20%)</td>
</tr>
<tr>
<td><strong>Radiotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boost received*</td>
<td>98 (19%)</td>
<td>104 (21%)</td>
<td>202 (20%)</td>
</tr>
</tbody>
</table>

All data are number of patients (%) unless where indicated.

* Median dose 10 Gy.
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group received radiotherapy, and 19 patients randomised to radiotherapy did not receive radiotherapy. Five patients assigned radiotherapy received it more than 12 weeks following the last date of surgery.
The analyses were conducted twice, once including all randomised patients and once excluding the ineligible cases. Because the two analyses yielded the same conclusions (data not shown), the results presented here include all randomised patients. Analysis on the basis of the treatment actually given also yielded similar results (data not shown). Characteristics of patient according to treatment group are listed in Table 1. All factors are well balanced between the two groups. The cut-off date for this analysis was July 1998, when the median duration of follow-up was 4.25 years (maximum 12.0 years).
There were 136 patients with local recurrences, 83 in the no further treatment group and 53 in the radiotherapy group. The local recurrence free interval was significantly longer in the radiotherapy than in the no further treatment group (P=0.005). The 4-year local

### Table 2 Recurrence-free intervals and hazard ratios according to treatment

<table>
<thead>
<tr>
<th>Event Category</th>
<th>No further treatment</th>
<th>Radiotherapy</th>
<th>Hazard ratio (95% CI)</th>
<th>Logrank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All local recurrence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No further treatment</td>
<td>83</td>
<td>53</td>
<td>0.62 (0.44-0.87)</td>
<td>0.005</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DCIS recurrence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No further treatment</td>
<td>44</td>
<td>29</td>
<td>0.65 (0.41-1.03)</td>
<td>0.06</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Invasive recurrence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No further treatment</td>
<td>40</td>
<td>24</td>
<td>0.60 (0.37-0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Distant metastasis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No further treatment</td>
<td>12</td>
<td>12</td>
<td>0.98 (0.44-2.18)</td>
<td>NS</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No further treatment</td>
<td>12</td>
<td>12</td>
<td>0.97 (0.44-2.16)</td>
<td>NS</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Contralateral breast cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No further treatment</td>
<td>8</td>
<td>21</td>
<td>2.57 (1.24-5.33)</td>
<td>0.01</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Event-free survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No further treatment</td>
<td>93</td>
<td>78</td>
<td>0.82 (0.61-1.10)</td>
<td>0.20</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* 1 patient with recurrence of DCIS had a second recurrence that was invasive.
Logrank $P = 0.005$

Figure 2a Time to local recurrence by treatment group

Logrank $P = 0.06$

Figure 2b Time to DCIS recurrence by treatment group
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recurrence-free rates were 91% and 84%, respectively (Table 2). 73 patients (44 in the no further treatment group, 29 in the radiotherapy group) had recurrences of DCIS, and 64 patients (40 vs 24) developed invasive breast cancer. Figure 2a shows the local, 2b the DCIS, and 2c the invasive recurrence-free intervals.

There were 24 patients who developed distant metastases. Figure 3 shows the time to distant metastasis. The 4-year metastasis-free rate was similar in the two groups: 98% in the no further treatment, and 99% in the radiotherapy group. Three patients developed distant metastasis without a prior local or contralateral event, three patients following a contralateral event, one after a bilateral invasive recurrence and 16 because of an invasive local recurrence. Only one patient in the no further treatment group had an isolated axillary lymph-node metastasis without evidence of local recurrence; she developed distant metastasis as well.

There were 24 deaths. 11 patients died from ipsilateral breast recurrence (seven in the no further treatment group and four in the radiotherapy group), one patient in the no further treatment group died after an invasive contralateral breast cancer, four because of another malignant disease (one patient in the no further treatment group had bladder cancer, three in the radiotherapy group had mediastinal lymphoma, carcinoma of the sinus ethmoidalis region, or acute myeloid leukaemia). Two patients died of cardiovascular disease (one in the radiotherapy group and one in the no further treatment group), one from postoperative bleeding for another surgery (in the radiotherapy group), and three from metastases as first event (one in the no further treatment group, two in the radiotherapy group). For two patients the cause of death is
Figure 3 *Time to metastasis by treatment group*

Figure 4 *Survival by treatment group*
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Figure 5 Time to contralateral breast cancer by treatment group

Figure 6 Time to first event by treatment group
unknown (without evidence of recurrent disease, one in no further treatment group and one in radiotherapy group). The 4-year overall survival rate was 99%. Overall, the number of deaths was the same in the two groups (log rank P=0.94, Figure 4).

29 patients developed a contralateral breast cancer (21 (4%) of 507 in the radiotherapy group and 8 (2%) of 503 in the no further treatment group). Eight contralateral breast tumours were DCIS (three in the no further treatment group and five in the radiotherapy group), and 21 were invasive carcinomas (five vs 16). The 4-year contralateral recurrence-free interval was 99% in the no further treatment group versus 97% in the radiotherapy group (table 2). There was a significant difference in time to contralateral recurrence (log rank P=0.01; Figure 5).

171 patients had at least one event. The first events were 133 local recurrences, 26 contralateral breast cancers, one isolated regional recurrence, three distant metastases without evidence of local recurrence and eight deaths due to other causes (Figure 6). The 4-year event-free survival rate is 82% in the no further treatment group versus 86% in the radiotherapy group (Table 2).

Six patients had both an ipsilateral and contralateral relapse. One patient had a simultaneous bilateral recurrence of DCIS, one patient developed an ipsilateral invasive carcinoma at the same time as a contralateral DCIS, one patient had an ipsilateral DCIS 3 years after a contralateral DCIS, one had an ipsilateral DCIS recurrence 4 years after a contralateral invasive breast cancer, and two developed contralateral invasive breast cancer after having had an invasive local recurrence. Three patients with a local recurrence of DCIS (two in the no further treatment group and one in the radiotherapy group) developed a second local recurrence after breast-conserving therapy for this local recurrence; one recurrence progressed to an invasive recurrence, one patient developed Paget’s disease of the nipple, and one had a second recurrence of DCIS.

**Discussion**

At a median follow-up of 4.25 years the results of this randomised clinical trial show that radiotherapy after local excision of DCIS of the breast gives a longer local recurrence-free interval than local excision alone.

The design of our trial is similar to the National Surgical Adjuvant Breast and Bowel Project (NSABP) Trial B-17, which also showed a beneficial effect of radiotherapy on local control. The findings of the NSABP were unchanged in an update based on a median follow-up of 8 years. We compared our data with those of the NSABP B-17 data published in 1993, in view of the comparable duration of follow-up. At a median follow-up of 3.6 years, the NSABP study showed 92 local recurrences in 790 patients, a rate of 12%, with 16% in the no further treatment group and 7% in the radiotherapy group. At a median follow-up of 4.25 years in our study there are 137 local recurrences in 1002 patients, a rate of 14%, with 17% in the no further treatment group and 11% in the radiotherapy group. When the local relapses are classified as DCIS and invasive
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carcinomas, our study shows approximately equal reductions by radiotherapy: a reduction of DCIS recurrence from 8% to 5% (hazard ratio=0.65, 95% CI 0.41-1.03) and a reduction from 8% to 4% (0.60, 0.37-0.97) of invasive breast cancer. The NSABP showed a much higher reduction of invasive local recurrence after radiotherapy with a relative risk of 0.20 compared with local excision alone. Although the overall local-recurrence rates do not seem to differ much in the two studies, our study does not confirm a similar magnitude of reduction of invasive local recurrence due to radiotherapy as found in the NSABP B-17; after 4 years, even with radiotherapy, 4% of the patients developed invasive breast cancer in our study after a relatively short follow-up period. In two other large, non-randomised studies, half of the reported local relapses after local excision plus radiotherapy were invasive breast cancers\textsuperscript{10,11}. The results of our study accord with these findings.

When all first events are included, there was no significant difference in event free survival rates for the radiotherapy group (86%) compared with the no further treatment group (82%; P=0.20). This is caused by a significantly higher rate of contralateral breast cancers in the radiotherapy group. We have no adequate explanation for this phenomenon. Studies investigating the induction of breast cancer after radiotherapy for Hodgkin’s disease have shown intervals of at least 8 years between the primary treatment and presentation of subsequent breast cancer. The first analysis of the NSABP B-17 did not report a difference in the occurrence of contralateral breast cancer, although in their 8-year update a higher, but non-significant rate of contralateral breast cancer in the radiotherapy group was found when only those contralateral breast cancers occurring as first event (13 in the no further treatment group vs 19 in the radiotherapy group) were included. However, when all contralateral breast cancers were included in the analysis, this difference disappeared (18 vs 20)\textsuperscript{9}. Studies investigating breast-conserving therapy for invasive breast cancer have never reported an increased rate of contralateral breast cancer. Although our results may have occurred by chance we will monitor this finding, because if the increase is due to radiation therapy, it will decrease the overall value of this form of therapy for DCIS patients.

Silverstein and colleagues\textsuperscript{12} reported a large non-randomised study of 333 patients with DCIS treated with breast-conserving treatment and examined factors associated with the development of a local recurrence. Three factors - DCIS classification (based on nuclear grade and presence of necrosis), size and margin status- were combined in a prognostic index. Based on the score of this prognostic index a treatment recommendation was made. It was suggested that lesions with a low score (that is, low grade, small lesions excised with a wide free margin) could be treated conservatively without radiotherapy, with a very low risk of local recurrence. Recently, the same investigators argued that in the same group of patients the margin width is the most important prognostic factor for local recurrence in breast-conserving treatment for DCIS\textsuperscript{13}. Lesions that were excised with a margin of 10 mm or more had an excellent local recurrence-free survival rate, and postoperative radiotherapy did not lower the recurrence rate in this group. However, our study has not confirmed the theory of subgroups requiring different treatments. The number of events is still too small in our study for identification of subgroups of
patients who will benefit to different degrees from radiotherapy. The results of a centrally coordinated histology review are forthcoming.

At a median follow-up of 4.25 years, similar rates of distant metastases and death were observed in the two groups. However, these numbers are (fortunately) still very small. The risk of eventually dying from breast cancer when DCIS is treated with breast-conserving treatment is still not clear. In the this study 15 patients died from breast cancer. Although this does not seem a high rate, the follow-up time was relatively short. A few of these deaths would probably have occurred even if the patients had initially had a mastectomy. However, given the number of invasive local recurrences, a significant number will probably die from metastatic disease. Longer follow-up is needed to investigate whether the beneficial effect of radiotherapy on local control will improve survival rates.

Although mastectomy for DCIS results in a virtually 100% cure rate, the disease can occasionally recur. Also, missed invasive foci in mastectomy samples possibly account for a few deaths from breast cancer. Although a randomised study comparing mastectomy with breast-conserving treatment for DCIS has never been done, several non-randomised studies have shown that survival rates after mastectomy do not reach 100%.

Other options, apart from ablative treatment followed by reconstruction, include the use of hormonal therapy such as tamoxifen. The results of the NASBP B-24 showed a significant decrease in the risk of breast cancer events in patients treated with local excision, radiotherapy, and tamoxifen, compared with local excision and radiotherapy alone.

Patients with an unacceptably high risk of local recurrence despite breast-conserving surgery plus radiotherapy (and tamoxifen) need to be identified so that they can be offered mastectomy. Also, patients should be identified who have a very low risk of local recurrence, and whose benefit from adjuvant therapy is so small that they may be offered the option of local excision alone.

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