Breast-conserving therapy for ductal carcinoma in situ

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Chapter 7

Mammographic evaluation of adequacy of excision and detection of local recurrence in breast-conserving therapy for ductal carcinoma in situ

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Abstract

Purpose To assess the role of mammography in the evaluation of the adequacy of surgical excision and detection of local recurrence in breast-conserving therapy (BCT) for ductal carcinoma in situ (DCIS).

Materials and Methods Pre-operative and follow-up mammograms were reviewed for 53 patients who developed a local recurrence in the EORTC trial 10853 (excision with or without radiotherapy).

Results The primary DCIS was mammographically detected in 48 patients (91%). The excision appeared radiographically inadequate in 15 of them (31%): in four patients the specimen X-ray showed that the lesion was incompletely excised, in nine there was doubt about the complete presence of the lesion in the specimen and in two patients residual calcifications were present on a mammogram within four months after surgery.

In this EORTC trial, yearly mammograms were made during follow-up. Forty-five recurrences (85%) were detected mammographically. At review, the recurrent disease was earlier visible on the mammogram in 13 cases (29%): seven recurrences were visible at the previous mammogram, and six at minimally two previous mammograms.

Conclusions In these recurrent cases after BCT for DCIS, in 31% of the mammographically detected DCIS the original excision appeared inadequate by review of the mammograms. Therefore, the radiologist has an important function in the estimation of adequacy of excision of the lesion in BCT for DCIS, and in the early detection of recurrent disease. Every residual or reappearing calcifications or mass should be considered suspect.
Introduction

The widespread use of mammographic screening has led to a dramatic increase in the number of women diagnosed with ductal carcinoma in situ (DCIS). Most of these lesions are non-palpable and are mammographically detected because of calcifications. With breast-conserving therapy (BCT) being standard practice for early stages of invasive breast cancer, this treatment is increasingly employed for DCIS as well. However, excision of non-palpable lesions is a technically difficult surgical procedure, and for pathologists it is difficult to reliably assess completeness of excision. Local recurrence usually reflects failure of complete removal of the primary tumour. In only a minority of patients, the recurrence will develop in another quadrant of the breast, which can then be considered as a second primary tumour.

The radiologist plays a key role in the pre-operative estimation of extent of the disease, and in the guidance of the surgeon by wire localisation of the lesion. Furthermore, radiography of the complete and lamellated specimen serves as a basis for the evaluation of the adequacy of the excision, and as a guide for the pathologist to sample representative blocks. The success of BCT for DCIS is therefore highly dependent on the radiological assessment of the adequacy of excision.

In the European Organization for Research and Treatment of Cancer (EORTC) trial 10853, women with DCIS were randomised between radiotherapy and no further treatment after local excision of the lesion. At the time of the first analysis of the study, 136 local recurrences had occurred. The purpose of the present study was to assess whether these recurrences could be explained by review of the mammograms, and thus to identify radiological features of failure of a complete excision.

Materials and Methods

Between 1986 and 1996, 1010 women with DCIS of the breast were enrolled in the EORTC 10853 trial. Details regarding study design, eligibility criteria and endpoints have been described elsewhere. Patients were entered based on the institutional estimation of completeness of excision and extent of the lesion (maximum allowed size 5 cm). The protocol mentioned guidelines for diagnostic work-up, surgical procedures and follow-up. Pre-operative mammography of both breasts was required; the use of magnification views was not mentioned in the protocol, nor were guidelines for a needle localisation procedure and specimen radiography. Bilateral mammograms had to be performed every year during follow-up.

The 136 patients who developed a local recurrence at the time of first analysis were selected for this study. With 46 participating institutes in the trial it was difficult to collect the mammograms of all recurrent cases, mainly because in many institutes the X-rays are kept by the patients. Complete sets of pre-operative and follow-up mammograms were thus available for 53 patients. Thirty-one patients were randomised to no further treatment after local excision of the lesion, whereas 22 patients received
radiotherapy. The method of detection of the primary lesion and recurrence (mammographically, clinically, or both) and type of recurrence (DCIS or invasive) were obtained from the central database at the EORTC Data Center. The histological type of the DCIS was obtained from a central pathology review, performed for the randomised cases in the trial.

The mammograms were retrospectively reviewed by two radiologists, experienced in breast imaging (MSG and LSK). The following features were recorded: the site and type of abnormality on the pre-operative and follow-up mammograms, the shape and distribution of calcifications, the largest diameter of the primary and recurrent lesions, evaluability of completeness of excision of the primary DCIS, and the date of first appearance of the recurrence at review. Adequacy of excision was estimated by evaluation of the specimen X-ray. If a mammographic abnormality was only partially found on the specimen X-ray, and no second surgical procedure was performed, this was coded as an incomplete excision. If the lesion was found on the edge of the specimen radiogram and no surgical re-excision was performed, the adequacy of excision was estimated doubtful. If a residual abnormality was found on the first mammogram within four months after surgery, the excision was also deemed inadequate.

The kappa statistic is derived for assessing the agreement between mammographic features of the primary DCIS and recurrent lesion and between the method of detection of primary DCIS and recurrence. Values of kappa range from 0 for chance agreement only to +1 for perfect correlation\(^2\). To compare mammographic abnormalities and type of calcifications between the three histological types of DCIS the Fisher exact test is used. The distribution of calcifications is compared for the three histological types used the Chi-square test for linear trend.

**Results**

The method of detection of the primary DCIS and recurrent lesions, the distribution of type of recurrence (DCIS or invasive) and the median time to recurrence were not different for the reviewed and non-reviewed cases (data not shown).

For the 53 patients, the median time to recurrence was 35 months (range, 1 to 111 months). Thirty-one recurrences were DCIS and 22 invasive carcinoma. The median time to a DCIS recurrence was shorter (30 months) than the median time to an invasive recurrence (41 months).

The median age of the patients was 53 years (range 30 to 73).

In 14 patients (26\%) diagnostic work-up included a magnification view (Table 1).

_Mammographic features of the primary lesion_  
In 48 patients (91\%) a mammographic abnormality was found. 15 of them had associated clinical symptoms: 5 patients (9\%) had clinical symptoms without an abnormality present on the mammogram (Table 2).
Table 1 Used roentgenographic diagnostic tools in 53 patients with recurrence after breast-conserving treatment for DCIS

<table>
<thead>
<tr>
<th>Mammographic tool</th>
<th>N patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>pre-operative mammogram</td>
<td>53</td>
</tr>
<tr>
<td>magnification view</td>
<td>14</td>
</tr>
<tr>
<td>needle localisation</td>
<td>30</td>
</tr>
<tr>
<td>specimen X-ray</td>
<td>32</td>
</tr>
<tr>
<td>post-operative mammogram</td>
<td></td>
</tr>
<tr>
<td>&lt; 4 months</td>
<td>19</td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>49</td>
</tr>
</tbody>
</table>

Forty-six cases presented with calcifications on the mammogram (96%). In 12 of these an associated mass was observed, and in two cases only a mass was found (Table 3). The mean diameter of the mammographic abnormality was 24.9 mm (range, 4-70 mm). Eleven lesions were ≥ 4 cm at review. Five lesions measured more than five cm, and should therefore not have been included in the trial. Three of these were originally reported smaller than five cm. one was reported 55 mm and one did not originally give a measurement of the extent.

**Evaluation of the surgical procedure**

In 30 of the 48 mammographically detected cases a wire guided localisation procedure including specimen radiography was performed. In two cases, a specimen X-ray was made without a preceding localisation procedure. A specimen radiogram was made more often in case of a mammographically detected lesion (27 of 33 cases, 82%), compared with lesions in which associated clinical symptoms were present (five of 15 cases, 33%). The specimen X-ray of four patients showed that the lesion was incompletely excised (Table 4): in three of these four cases there was a second cluster of calcifications that originally was not recognised, and in the fourth case the area with calcifications measured more than 50 mm. On 12 of the 32 specimen radiographs there was doubt about the complete presence of the abnormality; only three of these patients had a second operation (Table 4).

**Follow-up and detection of recurrences**

The median time to the first postoperative mammogram was 6 months (range, 7 days to 2 years).

The recurrences were detected by mammography in 45 of 53 patients (85%). 13 patients had associated clinical symptoms (Table 2). Eight recurrences (15%) were detected clinically without any mammographic abnormality. Four of these eight had inflammatory breast cancer as recurrence. DCIS recurrences were more often detected by mammography only (25 of the 31, 81%) compared with the invasive recurrences, in which 7 of the 22 (32%) were detected by mammography alone.
Table 2 **Comparison of method of detection of primary DCIS with local recurrence**

<table>
<thead>
<tr>
<th>Local recurrence</th>
<th>Mammographically</th>
<th>Combination*</th>
<th>Clinically alone</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary DCIS</td>
<td>Mammographically</td>
<td>22</td>
<td>7</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Combination*</td>
<td>8</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Clinically alone</td>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>31</td>
<td>14</td>
<td>53</td>
</tr>
</tbody>
</table>

*Combination of mammographic abnormality and clinical symptoms

\[ \text{Kappa} = 0.10 \]

Table 3 **Comparison of mammographic features of primary DCIS with local recurrence**

<table>
<thead>
<tr>
<th>Local recurrence</th>
<th>Calcifications</th>
<th>Calcifications &amp; mass</th>
<th>Mass</th>
<th>No abnormality</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary DCIS</td>
<td>Calcifications</td>
<td>23</td>
<td>4</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Calcifications &amp; mass</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mass</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>No abnormality</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td>53</td>
</tr>
</tbody>
</table>

\[ \text{Kappa} = 0.15 \]

Five of 31 recurrences (16%) detected by calcifications were invasive breast cancers: four of seven with an associated mass were invasive (57%), five of seven with only a mass (71%) and all eight cases in which no mammographic abnormality was found were invasive recurrences.

Most mammographically detected recurrences were located in the same area or adjacent to that of the primary DCIS: 37 of 45 (82%). In four cases the recurrence was located in another quadrant, and in four cases the location could not be determined, since no abnormality was present on the primary mammogram.

Almost all patients (N=49) underwent their first follow-up mammogram within one year post-excision. A mammogram was made within four months after surgery in 19 patients, of which six (32%) showed residual calcifications. Three of these proved, in retrospect, incompletely excised on the specimen radiograph, and in one there was doubt about the completeness of the calcifications on the specimen X-ray. In the
remaining two no specimen X-ray was made (Table 4). Five recurrences appeared between four months and one year after the surgery. There was a delay in the mammographic recognition of recurrent disease, with 13 of the mammographically detected recurrences (29%) being visible earlier as found at the review. In seven cases an abnormality was visible on the previous mammogram; in three cases on two previous mammograms, in two cases on three previous mammograms and in one case a lesion was already visible five mammograms before the diagnosis of the recurrent disease. In all these cases, mammograms were made with yearly intervals.

The method of detection and type of abnormality of the primary DCIS related to the recurrent lesion is shown in Tables 2 and 3. Thirty-five of 46 these recurrent cases of
DCIS (76%) that were originally detected by calcifications showed again calcifications on the mammogram corresponding to the recurrence. Both cases that originally had a mass without calcifications recurred again with only a mass at mammography (Table 3). Histology of these two recurrences showed invasive carcinoma.

The mammographic findings are related to the histological type of the DCIS in Table 5. A segmental distribution of calcifications was strongly related to poorly differentiated DCIS (P=0.0006); also the linear type calcifications was significantly correlated with poorly differentiated DCIS (P=0.005).

**Discussion**

The reported rate of local recurrence in large published series varies from 9 to 26% after breast-conserving treatment for DCIS, with 16 to 26% in patients treated with local excision alone, and 9 to 16% in those treated with excision and radiotherapy.\(^1\,^2\,^3\,^4\) Approximately 50% of all recurrences are invasive carcinomas.\(^1\,^2\,^3\,^5\)

In this study we evaluated the mammographic estimation of adequacy of excision in a selected group of patients with DCIS who developed a local recurrence in the EORTC 10853 trial.\(^1\)

The multi-centre nature of this trial made it difficult to collect mammograms for all patients: we were able to review complete sets of primary and follow-up mammograms for 53 patients who developed a local recurrence. In these patients we found that in 31% with a mammographically detected DCIS, there was radiological evidence at review that the primary lesion was inadequately excised. The distribution of the type of recurrence and the median time to recurrence was not essentially different for these 53 patients, compared with the recurrences in which mammographic review was not possible. Therefore, we have not reason to assume that the present results are biased. Ipsilateral breast recurrence after BCT for DCIS is often an expression of residual disease.\(^6\,^7\) In this study, almost all recurrences occurred in the same quadrant or adjacent to the primary DCIS. In two of the four cases in which the recurrence occurred in another quadrant, the “recurrences” were at review already visible on the primary mammogram, but originally not recognised. Thus, most of the recurrences are an expression of residual disease. Others have reported a rate of 67% to 91% of all recurrences occurring at or near the site of the initial lesion.\(^3\,^4\,^8\,^9\) Truly new primary breast cancers can be expected in conservatively treated DCIS at a rate similar to the occurrence of a new primary breast cancer in the contralateral breast.

Although patients could only be randomised after a “complete local excision” of the lesion, one must conclude that many of these patients who developed a local recurrence had in fact had an incomplete excision of the primary lesion.

Not only the pathologist plays a role in the evaluation of the microscopic radicality of the excision, but the radiologist also has a key function in the measurement of the extent of the lesion, the adequacy of the surgery and hence in the assessment of the completeness of excision.
In this study several mammographic signs for recurrence risk and shortcomings in the interpretation of radiological images were found. Several times, the extent of the DCIS was underestimated on the mammogram. It has been reported that the diameter of the area of calcifications underestimates the histological extent of the DCIS, with a discrepancy greater than 2 cm in 28%\(^6\). We frequently found the calcifications located at the edge of a surgical specimen in this group of recurrent cases. When calcifications are present on the edge of a specimen, a re-excision in a second operation should always be performed, even though the histological margin status can give an impression of a complete excision. The excision should aim at a zone of radiographically-free margins surrounding the area of calcifications to ensure completeness of excision. The possibility of BCT for DCIS needs to be evaluated for each individual patient, depending on the size of the breast and the extent of the calcifications. In general, one should be very cautious in the breast-conserving approach for lesions with a mammographic diameter of more than two cm. Several studies have shown that the extent of the lesion is a predictor of residual disease\(^6,7\). The fact that many patients in this study had extensive lesions measured at mammography explains at least part of the local recurrences. Of note is the fact that in only a minority of the cases a magnification view was performed. Magnification views enhance the estimation of the extent of the lesion.

In three cases a cluster of calcifications was not recognised, and therefore not removed. A specimen X-ray was made less frequently when the DCIS presented as palpable lesion. However, it is very likely that the diameter of the palpable lesion does not predict the extent of the calcifications, since the palpable area may correspond to coincidental benign breast changes. Therefore, one might run the risk of missing the area of calcifications when the palpable lesion guides the surgical excision. We advocate performing a wire-guided localisation procedure including specimen radiography in all cases of malignant appearing calcifications. Even in the presence of a palpable lesion the area of the calcifications should be localised, to ensure the excision of the calcifications.

Glück et al have shown the value of a postoperative mammogram in the prediction of a complete excision, with a positive predictive value of 0.69 for residual calcifications\(^1\). In that study, the presence of five or more residual calcifications even had a positive predictive value of 0.90. In our series, six cases of residual disease leading to manifest recurrence were retrospectively seen on the postoperative mammogram. Post-operative mammograms should always be performed before the start of adjuvant radiotherapy.

As the majority of recurrences are detected again by mammography, mammography is of utmost importance in the follow-up of DCIS treated with breast-conservation. Yearly mammograms are a requisite for early detection of recurrences. Strikingly, at review a delay was observed in the diagnosis of recurrent disease in 29% of the mammographically detected cases, with in six cases the recurrence being visible on minimal two previous mammograms (that is, two years earlier) at review. The possibility of an observer’s bias has to be kept in mind, since the reviewers were aware of the fact that all patients in this study developed a local recurrence. Nevertheless, every residual or reappearing mammographic abnormality after BCT for DCIS is
suspect and an excision should be performed immediately in all these cases. When recurrences are (still) clinically occult, there is a higher chance of the lesion being again non-invasive, with obviously a better prognosis for these patients. Literature has reported on predicting the type of DCIS by describing the type of calcifications. Like others, we found that segmentally distributed, linear type calcifications correlate with poorly-differentiated DCIS. The pleomorphic type calcifications showed no clear correlation with the histological type, which is also in concordance with the findings of others. A wide excision with a sufficient amount of normal breast tissue must be performed in every type of calcifications. This study has shown that in BCT for DCIS, the radiologist has an important function in the estimation of the adequacy of the surgical excision, and in the early detection of recurrent disease. DCIS should be treated by a multidisciplinary breast team, in which the radiologist, surgeon and pathologist collaborate closely in the effort of obtaining a - radiologically, surgically and histologically - complete local excision.

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References


