Ductal Carcinoma in Situ of the Breast

Increasing Importance of Radiotherapy as a Part of the Therapy Approach

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Background: The treatment of ductal carcinoma in situ of the breast (DCIS) has changed dramatically during the last decade.

Material and Methods: In a review article, prospective randomized and retrospective studies of different treatment options of DCIS are evaluated to define the new role of radiotherapy.

Results: Until a few years ago, total mastectomy was the standard treatment of DCIS achieving a 95−98% cure rate. Three randomized studies show that adjuvant radiotherapy following local excision significantly reduces the rate of invasive and noninvasive recurrences by 40−60%, thus making breast conservation possible. Retrospective studies evaluated prognostic factors (tumor size; age; margin width, presence of necrosis; grading) in order to define subgroups of patients whom adjuvant radiotherapy can be safely spared. Adequately excised tumors with favorable grading and not associated with necrosis are potential candidates. Further evaluation in prospective randomized studies is, however, required.

Conclusion: Radiotherapy is an essential part of breast-conserving treatment of DCIS to achieve sufficient local control.

Key Words: Ductal carcinoma in situ/DCIS · Breast cancer · Radiotherapy

Duktales Carcinoma in situ der Brust. Zunehmende Bedeutung der Bestrahlung im Rahmen der multimodalen Therapie

Hintergrund: Die Behandlung des duktales Carcinoma in situ (DCIS) hat sich im letzten Jahrzehnt deutlich geändert.

Material und Methodik: In einem Übersichtsartikel werden prospektive und retrospektive Studien ausgewertet, um die Rolle der Strahlentherapie neu zu definieren.

Ergebnisse: Bis vor wenigen Jahren war die Mastektomie die Standardbehandlung des DCIS mit Heilungsquoten von 95−98%. Drei randomisierte Studien zeigten, dass eine adjuvante Radiotherapie nach Tumorexzision die Rate an invasiven und nichtinvasiven Rezidiven signifikant um 40−60% senkt. Auf diese Weise ist eine sichere Brusterhaltung möglich. Retrospektive Untersuchungen bewerteten prognostische Faktoren (Tumorgröße; Alter; Weite des Resektionsrandes; Nekrosen; Differenzierungsgrad), um Subgruppen zu definieren, bei denen auf eine adjuvante Bestrahlung ohne Erhöhung der lokalen Rezidivrate verzichtet werden kann. Potentielle Kandidaten sind adäquat exzidierte Tumoren mit einem günstigen Differenzierungsgrad, die nicht mit Nekrosen assoziiert sind. Allerdings müssen diese Ansatzpunkte noch in prospektiv-randomisierten Studien überprüft werden.

Schlussfolgerung: Die Strahlentherapie ist ein wichtiger Bestandteil der brusterhaltenden Therapie des DCIS, um eine adäquate lokale Kontrolle zu erreichen.

Schlüsselwörter: Duktales Carcinoma in situ/DCIS · Brustkrebs · Strahlentherapie

Introduction

Ductal carcinoma in situ (DCIS) of the breast is characterized by a proliferation of malignant epithelial cells without perforation of the basal membrane in the glandular duct of the breast. Since more patients have been taking part in mammography screening, the frequency of this tumor has increased. While the percentage of DCIS contributing to the total number of mammary carcinomas recorded in the Tumor Register of Rostock until 1990 was < 1%, this has continuously increased since then to reach the present level of 5–8% of all mammary car-
In studies done in the USA, the DCIS percentage of carcinomas detected using mammography was even up to 20% [3, 22]. The optimal treatment of DCIS has been a matter of controversial discussion in recent years. Until a few years ago, mastectomy was the standard procedure [3]. Since the work done, among others, by Rolf Sauer [32–34] showed that, in the case of invasive carcinoma, breast-conserving therapy was equivalent to mastectomy in early stages and therefore more and more patients with invasive cancer were treated by breast-conserving therapy [16, 23], this method was also tested for noninvasive DCIS. In this regard, the role of radiotherapy was investigated in three randomized studies in recent years. Consequently, on the basis of the results of these studies and the current discussion in the literature, an overview of the possibilities, indications and problems of radiotherapy in the treatment of DCIS will be presented here.

**Mastectomy**

Until a few years ago, mastectomy was the standard treatment of DCIS. Retrospective studies show that in > 95% of the cases the disease can be cured [41]. The local recurrence rate is between 0% and 12% in retrospective series; in a meta-analysis by Boyages et al. [6], it amounted to 1.4%. The few recurrences after mastectomy were traced back to either the presence of an undetected invasive carcinoma, the development of a new mammary carcinoma in the glandular tissue of the breast which remained behind after mastectomy, or a residual DCIS focus.

The treatment of DCIS using mastectomy has never been compared in prospective randomized studies of breast-conserving therapy. For this reason, only retrospective data are available. According to a meta-analysis done by Boyages et al. [6] from published retrospective and prospective studies, the local recurrence rate is lowest after mastectomy at 1.4% (95% confidence interval [CI] 0.7–2.1%), and highest after tumorectomy alone at 22.5% (95% CI 16.9–28.2%). Using additional irradiation, the recurrence rate after breast-conserving therapy was able to be decreased to 8.9% (95% CI 6.8–11%); the low level after mastectomy could, however, not be achieved. Presumably, the patients’ prognosis would not be compromised by the higher local recurrence rate; in randomized studies survival rates following breast-conserving therapy of 98–99% after 5 years and 86% after 12 years were determined [12, 20, 46], and after 15 years a survival rate of 92% following operation and irradiation was found in retrospective studies [42]. Therefore, it will also be impossible in the future to conduct a suitable randomized study.

**Breast-Conserving Therapy and Radiotherapy**

The goal of radiotherapy is a reduction of the local recurrence rate, which can amount to up to 40% after excision alone. An improvement in survival rate is not possible with the primary prognosis already excellent. Meanwhile, three randomized studies on the significance of radiotherapy have been published:

- the NSABP B-17 study [10, 12],
- the EORTC 10853 study [20],
- and the UKCCCR study [46].

With these, the data of a total of 2,372 randomized patients are available. Radiotherapy was done in all three studies consistently; the residual breast was irradiated with single doses of 2 Gy up to a total dose of 50 Gy.

The studies do, however, differ in essential points (Table 1):

- **the inclusion criteria:** in the NSABP B-17 study patients with diffuse calcifications were included, as long as there was no indication of an invasive carcinoma. By contrast, in the EORTC study only patients with a tumor diameter of up to 5 cm and without evidence of an invasive carcinoma or Paget’s cancer were included. The age limit was 70 years. The UKCCCR study took in patients with a DCIS that had been detected within the framework of preventive mammography, as well as patients with a microinvasive carcinoma (< 1 mm). An age limit was not applied in the NSABP B-17 and the UKCCCR study.
- **the median follow-up period:** it ranges from 10 (NSABP B-17 study) to 4.33 (UKCCCR study) and 4.25 years (EORTC 10853 study).
- **the patients’ age:** while in the NSABP B-17 study 33% of the patients were < 50 years of age, this age group amounted

### Table 1. Treatment results of the three randomized trials of local excision (OP) versus local excision and radiotherapy (OP + RT).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients (n)</th>
<th>Follow-up (years)</th>
<th>Treatment</th>
<th>Invasive recurrences (%)</th>
<th>Noninvasive recurrences (%)</th>
<th>Overall ipsilateral recurrences (%)</th>
<th>Contralateral breast cancer (%)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher et al. 2001</td>
<td>818</td>
<td>10.7</td>
<td>OP</td>
<td>16.8 p = 0.00001</td>
<td>14.6 p = 0.001</td>
<td>31.7 p = 0.000005</td>
<td>5.8 p = 0.24</td>
<td>12-year results</td>
</tr>
<tr>
<td>Julien et al. 2000</td>
<td>1,002</td>
<td>4.25</td>
<td>OP + RT</td>
<td>7.7 p = 0.04</td>
<td>8.0 p = 0.06</td>
<td>15.7 p = 0.005</td>
<td>1 p = 0.01</td>
<td>4-year results</td>
</tr>
<tr>
<td>UKCCCR 2003 [46]</td>
<td>1,552</td>
<td>4.33</td>
<td>OP + RT</td>
<td>6 p = 0.01</td>
<td>7 p = 0.004</td>
<td>14 p = 0.001</td>
<td>3 p = 0.44–0.65</td>
<td>5-year results</td>
</tr>
</tbody>
</table>

*rate per 1,000 patients per year