High nuclear grade and negative estrogen receptor are significant risk factors for recurrence in DCIS

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Ductal carcinoma in situ; Nuclear grade; Hormone receptors

Summary
Introduction. Recommendations for adjuvant treatment of DCIS after breast conservation are controversial. We tried to identify further risk factors in a retrospective study of our own practice.

Patients and methods. Three hundred and thirty-two patients treated by breast conservation between 1978 and 2001 at the Department of General Surgery, University of Vienna were analysed. Tumour size, nuclear grade, hormone receptors, p53, her-2/neu, multifocality, microinvasion and post-operative therapy (irradiation, tamoxifen or combination) were analysed for their influence on breast recurrence.

Results. Overall recurrence rate was 6.1% (8/132). For patients with DCIS showing high nuclear grade or negative estrogen receptor the risk for development of ipsilateral breast recurrence is significantly higher. Newer factors like p53 and her-2/neu do not have any prognostic significance. No recurrence was observed in patients treated by post-operative irradiation and tamoxifen.

Conclusion. Nuclear grade remains the most significant factor for breast recurrence after DCIS. Hormone receptor status identifies a subset of patients with more favourable prognosis.

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Introduction

Ductal carcinoma in situ (DCIS) represents up to 15% of all breast cancer diagnosed. Treatment guidelines for this disease are controversial. Two prospective randomised trials from the NSABP have shown that irradiation reduces the number of ipsilateral breast recurrences (IBR) by about half, and tamoxifen is of further significant benefit. It remains to be seen whether all patients with DCIS need the combination treatment, for example subgroups of patients with favourable nuclear grading and adequate resection margins. In a retrospective analysis, we studied factors that might identify patients with low risk for IBR.

Patients and methods

Patient characteristics are shown in Table 1. All patients treated for DCIS in our department between 1978 and 2001 were reviewed. Patients with a history of breast or any other cancer and one
patient with DCIS and histologically positive axillary lymph nodes were excluded, leaving 190 patients. Analysis was performed in the subset of 132 patients (69.9%) treated by breast conserving surgery. The remainder underwent mastectomy.

Records were reviewed in all patients. Paraffin-embedded specimen was reviewed by a single pathologist. In 20 patients paraffin-embedded specimen were not available for further review, so data from the pathology report were used. DCIS were classified according to the recommendations of the Consensus Conference Committee. Immunochemistry for estrogen receptor (ER), progesterone receptor (PR), p53 and her-2/neu was performed on all specimens as described before. Tumours showing at least 10% positive nuclei were considered positive (more than 30% positive nuclei for her-2/neu). Tumour diameter and size of resection margin were not always recorded in the original reports.

Surgery was performed as a wide excision, if possible. Clear resection margins were determined intraoperatively by frozen section in every patient and were a pre-requisite for breast conserving surgery. Axillary dissection was routinely performed in the first part of the study period.

Guidelines for post-operative treatment changed over time. Radiotherapy was performed as external beam irradiation with a dose of 50 Gray. A boost to the tumour bed was given at a dose of 15 Gray. Tamoxifen was given at a daily dose of 20 mg orally for five years only if hormone receptors on tumour specimen were immunohistochemically positive, because of the fact that tamoxifen is beneficial only in hormone responsive invasive breast cancer.

Patients were evaluated every 3 months for the first 2 years after surgery and every 6 months thereafter. After 5 years annual examinations were performed. Mammography of both breasts was performed annually after surgery.

To determine risk of IBR univariate analysis of data were calculated using the Kaplan-Meier method. Statistical difference between curves was calculated by the log-rank test. A p-value of ≤0.05 was considered significant.

Results

Median age in the 132 patients was 56 years (range 32–85). The median follow-up was 61.6 months (11.2–244.9). Recurrence of disease was diagnosed in nine patients. In one patient recurrence was intraductal cancer 6 months after primary surgery. The patient was treated by wide excision again and is alive 6 years after local recurrence. In eight patients invasive local recurrence was diagnosed 15–162 months (median 58 months) after primary surgery. Recurrence was treated by mastectomy in all patients. In two patients axillary lymph nodes
had been removed at primary surgery. Two of the remaining six patients had positive axillary lymph nodes at surgery for recurrence. Three patients received six cycles of CMF. Two of these patients were diagnosed with distant disease 8 and 12 months after treatment of recurrence. One patient died 38 months after diagnosis of distant disease. No IBR was seen in 40 patients receiving radiotherapy and tamoxifen. Recurrence rates after tamoxifen or radiotherapy alone was 8.3 and 15% if no post-operative therapy was done. 

**Discussion**

Theoretically mastectomy is curative treatment for DCIS with recurrence rates below 1%. Most patients with DCIS are now treated with breast conserving surgery. Even with the introduction of adjuvant therapy (radiotherapy or hormonal treatment) recurrence rates are between 6 and 12% after breast conserving surgery. We have shown that BCS with careful selection criteria is a safe option for patients with DCIS. To us three factors seem important for decision on adjuvant post-operative treatment.

**Nuclear grade**

High nuclear grade has been shown to be a significant prognostic factor for the development of IBR in numerous retrospective and prospective studies. Expression of hormone receptors has also been shown to correlate with other prognostic factors. The NSABP-B24 trial tested the use of tamoxifen in patients treated by BCS and radiotherapy. In this trial tamoxifen significantly prolonged event-free survival (87.4% vs 83.3%), reduced the rate of IBR (19.6% vs 13.8%) and the number of contralateral breast cancers (8.1% vs 3.9%). While the number of invasive IBR was reduced significantly, the number of non-invasive IBR remained unchanged. However, a recent retrospective review of the data from this trial indicated, that tamoxifen is only beneficial in patients with estrogen receptor positive DCIS (RR = 0.41 for ER-positive DCIS, p = 0.0002; RR = 0.8 for ER-negative DCIS, p = ns, Table 2).

**Table 2** IBR by combined hormone receptor status and after post-operative treatment

<table>
<thead>
<tr>
<th>Estrogen receptor/progesterone receptor</th>
<th>n</th>
<th>IBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/+ or -/- or -/+</td>
<td>53</td>
<td>1</td>
</tr>
<tr>
<td>+/− or −/−</td>
<td>31</td>
<td>3</td>
</tr>
<tr>
<td>−/−</td>
<td>38</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p = ns</td>
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</table>

**Hormone receptor status and tamoxifen**

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Excision margins and radiotherapy

Careful surgery with adequate resection margins (≥ 10 mm) seems to be a pre-requisite for successful treatment of DCIS. Trials have shown that the incidence of IBR can be reduced by post-operative radiotherapy. In the EORTC trial invasive and non-invasive recurrences were reduced by post-operative radiotherapy, whereas the NSABP-B17 trial showed a significant decrease only for invasive IBR. However, in the NSABP-trial central pathologic review revealed, that margins were involved or uncertain in 21.4% of patients. Solin et al. showed, that after BCS and radiotherapy IBR rate was 29, 14 and 7% in patients with involved, unclear and free resection margins, respectively. Silverstein et al. showed that the presence of a clear resection margin is important, as is the size of the margin. Recurrence rate was low (2.3%) in patients with wide resection margins (≥ 10 mm), compared to patients with close (≥ 1 mm) margins (30.4%). Radiotherapy reduced the rate of IBR in patients with close margins, but not in patients with wide margins. Holland et al. showed that the distance between two foci of DCIS on specimen sections was < 10 mm in 92% and < 5 mm in 82% of cases. Therefore, a resection margin of 5 mm gives an 18% chance of residual disease and a resection margin of 10 mm gives an 8% chance of residual disease. In this context, the number of involved margins in the NSABP-trial seems unacceptably high and the general recommendation of the NSABP to add radiotherapy in all patients treated by BCS has often been questioned.

In conclusion, we believe that therapeutic guidelines as proposed by the NSABP cannot be recommended generally. Other important factors, including resection margin and hormone receptor status, have to be analysed further in prospective studies. At the moment we generally recommend post-operative radiotherapy for patients with unfavourable nuclear grade or negative hormone receptor status. All patients with positive hormone receptor status receive tamoxifen. In case of close resection margins reexcision should be considered, because rate of IBR is still considerable in this subset of patients, even if post-operative radiotherapy is performed.

References

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