Breast-conserving therapy for ductal carcinoma in situ

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Chapter 8

Breast-conserving therapy for Paget’s disease of the nipple; a prospective EORTC study of 61 patients

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Submitted
Abstract

*Background* The purpose of this study was to assess the outcome of breast-conserving therapy by means of a cone excision and radiotherapy for patients with Paget’s disease of the nipple without associated invasive breast cancer.

*Methods* Between 1987 and 1998, 61 eligible patients were registered in the EORTC study 10873. Most patients (97%) presented without an associated palpable mass. At histological examination, the majority (93%) had an underlying ductal carcinoma in situ (DCIS); in 7% only Paget’s disease was found. Treatment consisted of a complete excision of the nipple-areolar complex including the underlying breast tissue with tumour-free margins, followed by external irradiation to the whole breast. 50 Gy in 25 fraction. The primary endpoint was local recurrence.

*Results* At a median follow-up of 6.4 years, four of the 61 patients developed a recurrence in the treated breast. one DCIS and three invasive. One patient with an invasive local recurrence died from disseminated breast cancer. The 5-year local recurrence rate was 5.2% (95% CI 1.8-14.1%).

*Conclusions* Breast-conserving therapy is a feasible alternative for patients with Paget’s disease and limited extent of underlying DCIS. To achieve good local control, the treatment should consist of a complete excision of the nipple-areolar-complex including the underlying disease, followed by irradiation to the whole breast.
Introduction

Paget’s disease of the nipple is a rare manifestation of breast cancer, representing approximately 1-3% of all cases. Patients present clinically with eczematous changes of the nipple, sometimes associated with itching, ulceration and bleeding. Histologically, Paget’s disease is characterised by intraepidermal spread of large round or ovoid tumour cells with abundant pale cytoplasm and large pleomorphic and hyperchromatic nuclei with prominent nucleoli. There has been much debate about the exact origin of these Paget’s cells, but nowadays most authors postulate the epidermotropic theory, which assumes that Paget’s cells are ductal carcinoma cells that have migrated from the underlying mammary ducts to the epidermis of the nipple. The theory is supported by the presence of underlying ductal carcinoma in situ or invasive breast cancer in almost all patients. The prognosis of the disease is highly dependent on the stage of the associated carcinoma.

To achieve adequate local control, standard treatment has been mastectomy. In recent years, few studies have suggested a role for breast-conserving therapy (BCT) in selected groups of patients with Paget’s disease. Those cases with a limited extent of underlying breast malignancy would be especially suitable for this type of treatment. The available data are however limited, with small numbers of patients and various types of BCT.

In 1987, the European Organization for Research and Treatment of Cancer (EORTC) started a multi-centre registration study to assess the feasibility of BCT for patients with Paget’s disease of the nipple without associated invasive breast cancer. All patients were treated with a cone excision and radiotherapy to the whole breast. The results of this study are presented.

Patients and Methods

Patients

Women with histologically-proven Paget’s disease of the nipple with or without an underlying ductal carcinoma in situ (DCIS) were eligible to enter the study. A preoperative bilateral mammogram was required for all patients. Patients with a palpable lesion were allowed to enter the study; however, histological examination should not reveal invasive carcinoma. Furthermore, underlying DCIS should not extend more than 5 cm from the nipple, and the Paget and DCIS had to be excised with histologically-confirmed tumour-free margins.

Excluded were patients over 75 years of age, pregnant patients, those with a previous or concomitant malignancy except either adequately-treated basal cell carcinoma of the skin or cone-biopsied carcinoma in situ of the cervix, and those with a mental condition or social situation precluding long-term follow-up.
Surgery
The excision had to be performed within six weeks of the nipple biopsy. Surgery consisted of a cone excision including the skin with nipple-areolar complex and the subareolar breast tissue. If the cone showed DCIS extending into the surgical margin a wider excision was recommended, but the size of the cone and re-excision should not exceed 5 cm width and depth. An axillary dissection was not recommended.

Pathology
It was recommended to ink all surgical margins, to section the cone in 3 to 5 mm intervals and radiograph all serial sections, and then to sample the nipple and the remaining tissue completely. Any DCIS transected at inked margins had to be considered as margin involvement.

Radiotherapy
External beam radiotherapy to the whole breast had to be given to all patients, and had to start within eight weeks of the final surgery. The prescribed dose was 50 gray in 25 fractions. No boost was advised. A detailed description of the applied technique has been given elsewhere.

Follow-up
Patients are followed up until death. Patients had to be examined one month post-operatively, at three months, and thereafter at three-monthly intervals for three years, at six-monthly intervals until the tenth post-operative year, and then at yearly intervals. A bilateral mammogram had to be made six weeks post-operatively, and thereafter annually.

Study endpoints/statistical considerations
After informed consent was obtained, patients were centrally registered at the EORTC Data Center. The primary study endpoint was local recurrence. Secondary endpoints were distant metastasis and death due to breast cancer. All local recurrences had to be confirmed histologically. Time to local recurrence was defined as time between the cone excision and date of recurrence. Two patients died before experiencing a local recurrence and were censored at the date of death. The time-to-local-recurrence curve was calculated using the Kaplan-Meier technique. A 95% confidence interval of the recurrence rate was calculated using the technique described by Rothman.

Results
Between 1987 and 1998, 61 patients were registered as eligible at the EORTC Data Center. The median age of the patients was 58 years (range, 31-74 years).
Table 1 Patient, treatment and tumour characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpable mass</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>59 (97)</td>
</tr>
<tr>
<td>yes</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Mammography</td>
<td></td>
</tr>
<tr>
<td>no abnormality</td>
<td>51 (84)</td>
</tr>
<tr>
<td>microcalcifications</td>
<td>8 (13)</td>
</tr>
<tr>
<td>unknown</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Areola completely excised at cone</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>5 (8)</td>
</tr>
<tr>
<td>yes</td>
<td>56 (92)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Paget without DCIS</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Paget with DCIS limited to the ducts just behind the nipple</td>
<td>49 (80)</td>
</tr>
<tr>
<td>Paget with more extensive DCIS (&lt;5cm)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>extent DCIS unknown (&lt;5 cm)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

Patient, treatment and tumour characteristics are summarised in Table 1. Most patients presented without a palpable mass and the majority of the mammograms showed no abnormality. At histological examination most lesions were accompanied by DCIS, which was generally limited to the major underlying ducts. All excision margins were reported free.

The median time from the nipple biopsy to the cone excision was 22 days (range, 0-212 days). Ten patients underwent the cone excision more than six weeks post-biopsy. Radiotherapy delivery started with a median of 41 days after the final excision (range, 17-140 days). In 15 patients the radiotherapy started more than eight weeks after surgery. The median dose of the delivered irradiation was 50 Gy (range, 50-60), in a median of 25 fractions (range 18-33). In one patient the number of Gy/fractions was unknown, and in one patient the number of fractions was not reported.

Outcome
The median follow-up was 6.4 years (maximum 12.5 years). Thirty-five patients were followed longer than five years. Four of the 61 patients developed a local recurrence, one DCIS and three invasive. Details about these patients are given in Table 2. One patient with an invasive recurrence developed signs of distant metastases eight years after the recurrence. She died a few months later. Two other patients died; one died of a cerebro-vascular accident without evidence of recurrent disease, and one died of another malignancy 2.5 years after the diagnosis of the Paget, without a local recurrence.

Figure 1 shows the Kaplan-Meier curve of the time to local recurrence. At 5 years, the
Table 2 Characteristics of patients with recurrence

<table>
<thead>
<tr>
<th>Original Paget</th>
<th>Local recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpable mass</td>
<td>Time to recurrence (months)</td>
</tr>
<tr>
<td>Palpable mass</td>
<td>Underlying DCIS</td>
</tr>
<tr>
<td>Palpable mass</td>
<td></td>
</tr>
<tr>
<td>Palpable mass</td>
<td></td>
</tr>
<tr>
<td>Palpable mass</td>
<td></td>
</tr>
</tbody>
</table>

N- = axillary lymph-node negative, LR = local recurrence

local recurrence rate is estimated to be 5.2% (95% confidence interval 1.8-14.1%). Three patients developed a local recurrence within five years, two of them having an invasive local recurrence.

Discussion

The results of this study show that breast-conserving therapy by a cone excision and radiotherapy can be an acceptable treatment alternative for patients with Paget’s disease of the nipple and a limited extent of underlying DCIS. The 5-years local recurrence rate is estimated to be only 5.2%. With 61 patients, our series is currently the largest of BCT for Paget’s disease. Only a few other studies have evaluated BCT in patients with Paget’s disease 10-13, of which the results are summarised in Table 3. Due to the small numbers of patients included, and the large variation in patient selection, treatment applied and duration of follow-up, the results of these studies are inconclusive and often contradictory. Our results cannot be directly compared with the other available studies, since the selection and treatment applied differs considerably from most other studies. There, surgery often consisted of a diagnostic nipple biopsy only, and in some studies radiotherapy was not given or only to the central area of the breast.

An underlying invasive or non-invasive breast cancer is present in almost 100% of the cases with Paget’s disease, and the prognosis for Paget’s disease is a direct reflection of the stage of the underlying carcinoma7. The present study was restricted to those cases
Breast-conserving therapy for Paget’s disease of the nipple

Figure 1 Time to local recurrence of 61 patients treated with breast-conserving therapy for Paget’s disease of the nipple with or without underlying DCIS

with an underlying DCIS only, to enable comparison of outcome with the 100% cure rate that can be assumed if these patients were treated with mastectomy. Although it seemed appropriate to study the possibility of BCT for Paget’s disease in a randomised setting, the extremely low incidence of the disease and the different natural history of those cases accompanied by DCIS or invasive carcinoma, precludes a proper randomised comparison between mastectomy and BCT.

Stockdale showed that all three patients with an underlying mass and treated with a nipple biopsy only and radiotherapy, recurred and died from metastatic disease⁹, which can easily be explained by the fact that a palpable mass is often associated with the presence of an underlying invasive carcinoma¹².⁵.

Local excision plus radiotherapy has been performed increasingly for patients with DCIS. However, even with the application of radiotherapy, local recurrence rates of 10% at 5 years have been observed¹⁴,¹⁷, which is higher than the estimated recurrence rate in the present study. For our study, a strong selection of patients with Paget’s disease suitable for BCT has been made. Most cases showed no microcalcifications on the mammogram, and although in almost every case an underlying DCIS was found at histology, the extent was mostly limited. A complete excision by a central cone excision is probably easier to achieve, compared to the technically-difficult surgical procedure of a wire-guided local excision for a non-palpable, and peripherally-located DCIS. In BCT
<table>
<thead>
<tr>
<th>Author</th>
<th>Period</th>
<th>N patients</th>
<th>Clinical presentation</th>
<th>Mammogram</th>
<th>Surgery</th>
<th>RT</th>
<th>Median FUP (months)</th>
<th>Local recurrence</th>
<th>Metastasis</th>
</tr>
</thead>
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<tr>
<td>Paone⁶</td>
<td>49-79</td>
<td>5</td>
<td>no mass</td>
<td>UK</td>
<td>cone</td>
<td>no RT</td>
<td>UK</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lagios³</td>
<td>UK</td>
<td>5</td>
<td>no mass</td>
<td>negative</td>
<td>4 TNAC</td>
<td>no RT</td>
<td>50</td>
<td>1 Paget</td>
<td>0</td>
</tr>
<tr>
<td>el-Sharkawi¹⁰</td>
<td>UK</td>
<td>3</td>
<td>no mass</td>
<td>2 negative 1 not done</td>
<td>biopsy</td>
<td>central area breast, variable dose</td>
<td>3-5.5 years</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Kollmorgen¹¹</td>
<td>63-96</td>
<td>10</td>
<td>UK</td>
<td>UK</td>
<td>5 cone 5 biopsy</td>
<td>UK</td>
<td>61</td>
<td>2 (unknown histology)</td>
<td>2</td>
</tr>
<tr>
<td>Fourquet⁸</td>
<td>60-84</td>
<td>20</td>
<td>no mass</td>
<td>6 calcifications 14 negative</td>
<td>17 biopsy 2 TNAC 1 PNAC</td>
<td>57 Gy whole breast</td>
<td>90</td>
<td>3 Paget</td>
<td>0</td>
</tr>
<tr>
<td>Bulens¹¹</td>
<td>71-84</td>
<td>13</td>
<td>no mass</td>
<td>9 negative 2 calcifications 2 skin thickening</td>
<td>biopsy</td>
<td>30-65 Gy whole breast 8/13 boost</td>
<td>52</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stockdale³</td>
<td>72-88</td>
<td>28</td>
<td>25 no mass</td>
<td>19 negative 2 not done 4 positive 3 with mass</td>
<td>3 mass</td>
<td>biopsy</td>
<td>variable; mostly limited to central area breast</td>
<td>UK no mass:</td>
<td>2 Paget</td>
</tr>
<tr>
<td>Dixon³</td>
<td>73-89</td>
<td>10</td>
<td>no mass</td>
<td>calcifications under nipple</td>
<td>cone</td>
<td>no RT</td>
<td>56</td>
<td>1 Paget</td>
<td>3</td>
</tr>
<tr>
<td>Pierce¹⁵</td>
<td>80-94</td>
<td>30</td>
<td>no mass</td>
<td>24 negative 5 calcifications 1 not done</td>
<td>variable (73% TNAC)</td>
<td>50 Gy whole breast</td>
<td>62</td>
<td>2 DCIS</td>
<td>3 invasive</td>
</tr>
<tr>
<td>Bijker</td>
<td>86-98</td>
<td>61</td>
<td>59 no mass</td>
<td>51 negative 7 calcifications</td>
<td>cone</td>
<td>50 Gy whole breast</td>
<td>77</td>
<td>1 DCIS</td>
<td>3 invasive</td>
</tr>
</tbody>
</table>

TNAC = total nipple-areolar complex, PNAC = partial nipple areolar complex, UK = unknown
for DCIS, the width of the tumour-free margin is reported as one of the major prognostic factors for recurrence\textsuperscript{15}.

The small number of events in our series precluded the identification of factors that are associated with an increased risk of recurrence. However, the prognosis of patients with Paget’s disease and DCIS is not essentially different from those patients presenting with a non-symptomatic DCIS, and risk factors for recurrence will be similar for the two lesions. Thus, obtaining a complete excision will also be one of the prerequisites for the success of BCT for Paget’s disease.

We were not able to evaluate the cosmetic results in this series. Although preservation of the affected nipple by performing a small biopsy only is reported to give good cosmetic outcome, it is our opinion that all patients should undergo a cone excision including the removal of the complete nipple areola complex, to maximally reduce the risk of residual disease. In patients treated with a cone excision, nipple reconstruction or nipple tattoo is an acceptable alternative for obtaining good cosmesis\textsuperscript{19,20}.

In Paget’s disease, the underlying DCIS is almost exclusively of the large cell, “comedo” type\textsuperscript{21,22}. Also, a high rate of the lesions is HER2/Neu positive\textsuperscript{21-23}, which is associated with a more aggressive behaviour and a poor prognosis in invasive breast cancer. It is likely that, when progression to invasion occurs, the invasive breast cancer will be of the high grade III type, which is associated with a high risk of regional and distant metastasis. It should be kept in mind that one of the three patients with an invasive recurrence in this series died from metastatic breast cancer.

Breast-conserving therapy has been proven to be an acceptable alternative for patients with invasive and non-invasive breast cancer. Although long-term follow-up will be required, the first results of this study suggest that there is also a place for the conservative management of patients with Paget’s disease of the nipple and limited underlying breast malignancy.

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Appendix

The following institutions, listed with their principal investigators, participated in this study:

The Netherlands Cancer Institute, Amsterdam, the Netherlands (EJT Rutgers), University of Florence, Department of Medical and Surgical Critical Care: Section of General and Oncological Surgery, Italy (L. Cataliotti), Centre Henri Becquerel, Rouen.
France (J-P Julien), Odense University Hospital, Odense, Denmark (C Rose), Rotterdam's Radiotherapeutisch Instituut, the Netherlands (A van Geel), Academisch Ziekenhuis Utrecht, the Netherlands (H Struikmans), Leiden University Medical Centre, the Netherlands (EM Noordijk), Radiotherapeutisch Instituut Limburg, Heerlen, the Netherlands (JJ Jager), Hopital Cantonal Universitaire de Geneve, Geneve, Switzerland (J Kurtz), Center Eugène Marquis, Rennes, France (C Chenal), St Savas Hospital, Athens, Greece (I Karydas), Academisch Medisch Centrum, Amsterdam, the Netherlands (CW Taat), Diakonessenhuis, Utrecht, the Netherlands (C Perre), Innsbruck Universitaetsklinik, Innsbruck, Austria (Margreiter).

References


