Survival in breast cancer after nipple-sparing subcutaneous mastectomy and immediate reconstruction with implants: A prospective trial with 13 years median follow-up in 216 patients

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Abstract

Aim: Validation of the oncological safety of nipple-sparing subcutaneous mastectomy and immediate reconstruction with implants (NSM) and of the outcome in patients with locoregional recurrences (LRRs) after this procedure.

Methods: Two-hundred and sixteen patients, mean age of 52.8 (29–81) years with primary unilateral breast cancer, not suitable for partial mastectomy because of large (>3 cm) or multifocal carcinoma, underwent NSM, a single procedure lasting about 1 h 30 min, between December 1988 and September 1994. Lymph node metastases were found in 40.3% of the patients, and 47 patients received radiotherapy (RT) postoperatively. All patients were monitored for at least 11.6 years or as long as they lived. Median follow-up was 13 years. The end-points were locoregional recurrence (LRR) or distant metastases (DM) as first events, disease-free survival (DFS) and overall survival (OS).

Results: Specificity at frozen section from sub-areolar tissues was 98.5%. LRR occurred in 52 patients and DM in 44 patients. DFS was 51.3% and OS was 76.4%. The frequency of LRR was 8.5% among irradiated and 28.4% among non-irradiated patients (p = 0.025). These results compare well with results after conventional mastectomy in other trials. All patients were monitored for at least 6 years after the occurrence of LRR, finding 5 years freedom from further LRR or DM of 60% and OS of 82%.

Conclusions: NSM is an oncologically safe procedure and could be offered to most patients with breast cancer unsuitable for sector resection only. RT effectively lowers the frequency of LRR. The occurrence of LRR after this operation does not significantly affect OS.

Keywords: Breast cancer; Survival; Locoregional recurrence; Nipple-sparing mastectomy; Subcutaneous mastectomy; Postoperative radiotherapy

Introduction

When this trial started, partial mastectomy (PM) had become the standard surgical treatment in Sweden for small breast cancer tumours, usually followed by radiotherapy (RT) to the affected breast. The remaining breast cancer patients (approximately 45%), who had too large or multifocal tumours, were treated with modified radical mastectomy (MRM). In a study published in 1984, Hinton et al. compared MRM with subcutaneous mastectomy and immediate reconstruction with a prosthesis and found no differences in survival. This latter procedure seemed to us a promising alternative, and we decided to evaluate it in a prospective, controlled study at the Huddinge University Hospital in Stockholm.

Skin-sparing and nipple-sparing mastectomy

Since we finished recruiting our patients, skin-sparing mastectomy has become the standard treatment for advanced breast cancer in many hospitals around the world. During the last 6 years several studies have been initiated to evaluate nipple-sparing mastectomy. As pointed out by Petit et al., this is essentially the same operation as subcutaneous mastectomy. When their surgical method is compared with ours, no essential differences are found regarding the resection of tissues before the reconstruction.

Aim

The principal aim of this study was to determine survival after nipple-sparing subcutaneous mastectomy.
and immediate reconstruction with a prosthesis (NSM) and to compare the results with those of other contemporary Scandinavian trials on breast cancer patients treated with MRM. A further aim was to examine the outcome in patients who experience locoregional recurrence (LRR) as a first event.

**Patients and methods**

**Patient groups, inclusions and exclusions**

Between December 1988 and September 1994, 272 patients underwent NSM. One hundred and three of them had undergone partial mastectomy less than 3 months earlier, after which multifocality or residual tumour was highly suspected. The other patients were selected directly for NSM because of a tumour size of 3 cm and/or verified or highly suspected multifocality. Fifty-six patients were excluded from this study for various reasons. The remaining 216 patients, with a mean age of 52.8 (29–81) years, all had primary, unilateral breast cancer, no other kind of cancer, and had not received any treatment preoperatively. They all gave their informed consent to participate in the study, which was approved by the Ethics Committee of the Karolinska Institutet, Huddinge University Hospital.

**Histopathology, axillary lymph node status, staging and oestrogen-receptor status**

Twenty-nine patients had cancer *in situ*, 72 stage I cancer, 82 stage II and 33 stage III, respectively (see Table 1). Axillary clearance (stadium II, sometimes III) was performed in all patients with invasive carcinoma and in all except 15 of the patients with cancer *in situ*. The number of removed lymph nodes varied from 4 to 20 (mean 8.8). Eighty-seven patients had metastases in 1–20 (mean 2.3) lymph nodes.

Oestrogen-receptor status (ER) was not obtained for 64 patients, of whom 29 had cancer *in situ*. It was thus recorded for 152 patients of whom 121 were ER-positive (ER > 0.04 fmol/μg DNA), but the mean ER for all 152 was 0.88 fmol/μg DNA.

**Surgical technique**

The authors performed 162 of the primary operations, but the rest were carried out by six other breast surgeons at our clinic. Silicone gel implants were used in 27 patients and placed submuscularly. In the remaining 189 patients saline-filled, textured prostheses were placed subcutaneously. A 5-mm thick plate of gland tissue with a 2 cm diameter was left beneath the nipple to preserve the blood supply of the nipple—areola complex (NAC). A biopsy specimen was taken from the gland tissue immediately adjacent to that plate and sent for frozen section. The NAC was preserved only when no malignant cells were identified at frozen section.

**Adjuvant therapy**

Adjuvant therapy was given in consensus with the oncologists of Radiumhemmet at the Karolinska University Hospital in Stockholm and following the same policy as for patients undergoing MRM during the same period at our and other hospitals in Stockholm.

**Follow-up**

All patients were monitored at our clinic, at least every 3 months for the first 5 years, and thereafter at least once a year. The date of the last assessment was 26 May 2006.

To facilitate the detection of recurrences we used mammography, slightly modified because of the presence of implants, ultrasound, and magnetic resonance imaging.

**Statistical analyses**

The primary end-point was survival. LRRs and distant metastases (DM) are reported as first site of failure and results compared by the difference test for two proportions. Disease-free survival (DFS) and overall (breast cancer-specific) survival (OS) were estimated by the Kaplan–Meier method. Indications for censoring were the occurrence of contralateral breast cancer, any other type of cancer, death by other causes than breast cancer, or emigration (two patients). The log-rank test was used to compare different groups. *p*-Values < 0.05 were accepted as significant. Statistica (version 7) was used for all analyses.
Table 2
Survival related to adjuvant therapy

<table>
<thead>
<tr>
<th>Adjuvant therapy</th>
<th>N</th>
<th>DFS (%)</th>
<th>OS (%)</th>
<th>LRR (N)</th>
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<tbody>
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<td></td>
<td></td>
<td></td>
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<td>Yes</td>
<td>47</td>
<td>51.5</td>
<td>59.5</td>
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<td>No</td>
<td>169</td>
<td>52.0</td>
<td>80.6*</td>
<td>48*</td>
</tr>
<tr>
<td>Chemotherapy</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>53</td>
<td>48.0</td>
<td>66.7</td>
<td>14</td>
</tr>
<tr>
<td>No</td>
<td>163</td>
<td>52.3</td>
<td>78.7*</td>
<td>38</td>
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<td>Hormone therapy</td>
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<td>50.0</td>
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<td>66</td>
<td>52.5</td>
<td>86.0</td>
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</table>

DFS = disease-free survival; OS = overall survival; LRR = locoregional recurrences; N = number of patients; *p < 0.05.

Results

These are summarised in Tables 1–3 and Figs. 1 and 2. The median follow-up time was 13.0 years (mean 11.3, range 0.2–17.5). For patients who were still alive at the last assessment the median follow-up time was 15.0 years. DFS, OS and the frequency of LRR were 68.0, 83.5 and 16.2%, respectively, after 5 years and 60.0, 80.5 and 20.8%, respectively, after 10 years. The most usual locations for DM were bone/marrow (54.5%), lung (18.2%), liver (11.4%) and brain (6.8%). The median time for appearance of LRR was 2.9 years (mean 4.5, range 14.2) and that of DM was 3.6 years (mean 4.9, range 0.2–14.0) after primary surgery. The LRR-rate was significantly dependent on age but not on lymph node status, tumour size, ER, histopathology or staging. Nine patients suffered LRR after the occurrence of DM.

Location and histopathology of LRR

Thirty-four of the LRRs were located in the same quadrant of the breast as the primary tumour, and four were located outside the breast (three in the axilla, one in the supraclavicular fossa). No recurrence was observed behind the prosthesis. Nineteen of the LRRs were multiple. Forty-four of the LRRs showed the same histology as the primary tumour. Invasive cancer was found in 45 and cancer in situ in seven of the LRRs. Two of the invasive cancer tumours recurred as cancer in situ, and two of the cancer in situ tumours recurred as invasive cancer.

Outcome after LRR

All the LRR patients were treated by salvage surgery (six by total mastectomy, 46 by local excision), 35 by RT, seven by chemotherapy and 20 by hormone therapy. Ten patients suffered second LRR, three of those a third LRR, and one patient had uncontrollable disease (LRR after salvage mastectomy). The 5-year rate of freedom from subsequent LRR or DM and the rate of OS after LRR as a first event were 60% and 82%, respectively. The corresponding figures after 10 years were 48.5% and 76.3%, respectively. There was no statistically significant difference in OS (from the date of primary surgery) between patients who suffered LRR as a first event and those who did not (Fig. 2). Even when the nine patients who had LRR after DM are counted in the LRR group the difference in OS is not statistically significant (80% and 70%, respectively, p = 0.123). However, OS after primary surgery was significantly worse for patients who suffered an early LRR (<3 years after primary surgery) than for those who suffered a late LRR (86% and 68%, respectively, p = 0.03).

Outcome for NAC

The NAC was removed in 11 patients at the primary operation because of a positive frozen section. Ten of these proved positive postoperatively (sensitivity 90.9%). In the 205 patients with a negative frozen section, three proved positive at the postoperative histopathological examination (specificity 98.5%). At the end of the monitoring period 184 patients had kept their NAC intact.

Table 3
Comparison with MRM in high-risk (stages II–III) breast cancer patients

<table>
<thead>
<tr>
<th>Investigators/year of publishing</th>
<th>Follow-up time (years)</th>
<th>Surgery</th>
<th>Menopausal status</th>
<th>RT</th>
<th>Systemic adjuvant therapy (N)</th>
<th>DFS (%)</th>
<th>OS (%)</th>
<th>LRR (%)</th>
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<td>Premenopausal RT+</td>
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<td>MRM</td>
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</table>

CMF = chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil; HT = hormone therapy; LRR = locoregional recurrence as a first event; DFS = distant-free survival; OS = overall survival.
Discussion

The LRR-rate in our study is high compared with the BASO guidelines. Among irradiated patients the LRR-rate was 8.5% after 13 years. Only 47 patients received RT. With today’s policy many more would be treated with RT. That none of the patients with cancer in situ and only one of the patients with stage I disease received RT can, at least in part, explain the relatively high LRR-rate in this group of patients. That most of the LRRs were situated in the same quadrant of the breast as the primary tumour may suggest inadequate surgery. However, no patient had a recurrence behind the prosthesis. The LRR-rate was significantly lower for postmenopausal than for premenopausal patients. Other investigators have found the same.

Comparison with MRM

Arriagada et al., as well as some others, have shown that lymph node positivity significantly increases the risk for LRR after MRM, and that the risk increases with an increased number of positive nodes. We were unable to confirm this after NSM. Otherwise, our results for patients with invasive cancer compare well with the results of other authors after MRM. In Table 3 our results after 10-years follow-up among patients with high-risk (stages II–III) breast cancer are compared with those of two large Scandinavian studies on patients with high-risk breast cancer operated with MRM. Our methods and doses for RT (see Patients and methods section) were about the same as those used in the other two trials. The use of other adjuvant treatment is summarised in the table. The patients in the Danish trial were recruited between 1982 and 1990 and those in the Stockholm trial during 1976–1984. In both these trials the patients were randomised to receive RT or not.

Skin-sparing and nipple-sparing mastectomy

Reports after skin-sparing mastectomy show similar results for OS as in our study but a lower frequency of LRR, at least after a median follow-up of 5 years. The results are not comparable, as all the patients in our study have been followed for exactly 5 years. The first published results after nipple-sparing mastectomy are promising, but in those studies the patient selection was narrower than in our study (e.g. no central tumours included), all patients were given RT (per- or postoperative), and the follow-up time is still much shorter.

Cosmetic results and patient satisfaction

In previous studies we found good sensibility and circulation in the operated breast after NSM and a very good patient satisfaction. Petit et al. have evaluated 64 of their patients with at least 1 year of follow-up for cosmetic result. Fifty-one of them rated it as good and only one as poor.

In our study only implants were used for reconstruction, and most often placed subcutaneously. In elderly women with ptotic breasts this gives good symmetry. In younger patients it is probably better to use autogenous tissue flaps or place the implants submuscularly.

Outcome for nipple–areola complex

The outcome reported in the Results section shows, in our opinion, that frozen section is a safe method to decide whether to preserve the NAC or not.

Outcome after (first event) LRR

In our study the occurrence of LRR did not affect OS after primary surgery (Fig. 2). This differs from the results of the Oxford-metaanalysis, which showed a 5% absolute reduction in 15-year breast cancer mortality in favour of...
the group with lower local recurrence risks. As most, if not all, of the patients in this group received RT whereas few of the women in the other group did, one can wonder how much of the reduction in mortality is due to lower LRR-rate and how much to the effect of RT.

In our study only four of the LRRs were located outside the operated breast. As reported by others, the prognosis is much worse for those than for LRRs located in the breast. This may partly explain the relatively good survival rates in our LRR patients.

In accordance with findings of other investigators, OS was significantly worse for patients who suffered early LRR than for those who suffered it late.

**Prognosis after LRR following MRM versus PM**

Nielsen et al. have found a 5-year OS rate of 43% after chest wall recurrences following MRM.

For LRR after PM, on the other hand, most authors have reported better survival rates and similar to those in our study. It has been stated before that LRRs after PM carry a considerably better prognosis than LRRs after MRM. We have found three studies comparing the outcome after LRR in patients treated initially with PM and MRM, respectively. In two of them, a significantly worse prognosis was found for chest wall recurrences than for breast recurrences after PM.

**Conclusions**

NSM, in patients with a negative frozen section from underneath the nipple, is an oncologically safe option in breast cancer unsuitable for PM. The occurrence of LRR after NSM is independent of staging and lymph node status and does not affect OS. Late LRRs (after ≥ 3 years) carry a better prognosis than early ones. The frequency of LRR can be reduced substantially by RT to the operated breast.

**Conflicts of interest**

The authors have no conflicts of interest.

**References**


