Factors correlating with reexcision after breast-conserving therapy

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Accepted 24 April 2008
Available online 9 June 2008

Abstract

Aim: The aim of this study was to evaluate factors affecting the risk for reexcision following breast-conserving surgery. Positive tumor margins are critical for local disease control following surgery for breast cancer. Several factors, including tumor size, multifocality, and an extensive in situ component, may be associated with a higher rate of repeat operations due to positive margins. This study included mammographic density in the analysis.

Methods: A total of 565 breast cancer patients were considered eligible for breast-conserving therapy after a core biopsy had confirmed malignancy. The patients' mammographic findings were reviewed, and mammographic density was documented in addition to the histopathological features of the lesions. Associations between these factors and the risk for a second operation were analyzed using the chi-squared test, and a model was developed for multivariate analysis.

Results: At least one repeat operation was necessary in 121 patients (21.4%), and mastectomy was ultimately necessary in 54 patients (9.6%). Tumor size, multifocality, and the presence of an in situ component were identified as risk factors. A mammographic density of category 4 was associated with a need for further surgery (OR 3.2; 95% CI, 1.2–11).

Conclusions: Mammographic density is an additional risk factor for a second operation following breast-conserving procedures, and it may make radiographic and intraoperative localization of the tumor technically difficult. Using mammographic density to define a group of patients with a higher risk of reexcision might allow these patients to benefit from more sophisticated methods of localization and margin assessment.

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Keywords: Tumor margins; Reexcision; Second operation; Breast-conserving surgery; Mammographic density

Introduction

Surgical standard of care

Whether or not a breast tumor has been adequately removed is established by assessing the lesion margins. Breast-conserving therapy with adjuvant radiotherapy should be regarded as the treatment of first choice if it is feasible. Eligibility for breast-conserving therapy is assessed by the breast surgeon on the basis of tumor size, the ratio of tumor size to breast size, and the location of the tumor.

A tumor-free margin of at least 1 mm is considered to be safe enough for the surgical treatment of invasive breast cancer, and 5 mm for intraductal breast cancer. The long-term risk for local recurrences, which mostly develop in the vicinity of the initial tumor, indicates that local recurrences derive from residual tumor cells.

Reexcision due to positive margins

Narrow margins or positive margins require subsequent operations, which may result in mastectomy, a poor cosmetic outcome, and additional costs. Intraoperative assessment of tumor-free margins is based on the sense of touch and optical assessment of the excised specimen by the surgeon, radiographer, and pathologist. The surgeon’s preoperative...
assessment is routinely based on mammography, breast ultrasonography, and the clinical examination, with each of these diagnostic methods having different levels of accuracy. The reported rates of repeat surgery range from 10% to 57%.12–17

**Risk factors for reexcision**

Several factors have been associated with a higher probability for positive margins after the first operation. One study, including 283 patients, showed that a large tumor size was associated with a positive margin status, whereas age, grading, estrogen or progesterone receptor status, lymphatic invasion, axillary lymph-node status, and an extensive intraductal component were not associated with positive margins.18 No differences in the reexcision rate were observed between preoperatively or postoperatively administered chemotherapy procedures.16 Another study reported an association between nodal status and reexcision, identified in a multivariate analysis, with an odds ratio of 1.1 (95% CI, 1.1–1.3).15 One study concerned with the preoperative bracket localization of breast tumors reported a reexcision rate of more than 90% (10 of 11 patients) in women with dense breasts.19 Another study did not find any association between mammographic density and the risk for a second operation.20 In summary, the data are inconsistent, and their value in deciding on treatment for the individual patient is limited. Some of the published studies have included patients who were initially considered for breast-conserving surgery in addition to those who were considered for mastectomy as the initial operation. In other studies, the numbers of patients are too small for the analysis of multiple confounding factors to be capable of detecting risk factors for reexcision.

**Study aim**

The aim of the present study was to analyze prospectively documented data from our specialist breast unit in relation to factors that may be associated with a higher rate of reexcision, with special regard to mammographic density. Mammographic density plays a pivotal role in the sensitivity of breast cancer detection and in the accuracy of preoperative staging.21–23 It was hypothesized that mammographic density has an effect on the feasibility of breast-conserving therapy, affecting the procedure either through poorer preoperative staging or poorer intraoperative and postoperative assessment of the tumor location.

**Patients and methods**

**Patients and study design**

A retrospective analysis was carried out of 565 patients who were diagnosed with breast cancer between January 2002 and June 2005. The patients’ data were documented prospectively in the context of the documentation for specialist breast units conducted by the German Cancer Society (www.onkozert.de). The data collected are broadly consistent with the documentation criteria established by the European Society of Mastology (EUSOMA).24 The 565 patients were selected from a total of 1241 patients who were diagnosed with primary unilateral invasive breast cancer at the University Breast Center in Franconia, Germany, between January 2002 and April 2006. A total of 355 of these patients (29%) were not eligible for analysis, as the primary treatment they received was mastectomy. These patients were excluded to ensure that the clinical setting was defined as precisely as possible; reexcision rates in patients who undergo primary mastectomy are quite low. In 221 of the remaining patients (18%), the diagnosis was confirmed by open biopsy on the basis of Breast Imaging Reporting and Data System (BI-RADS™) grade 4 findings on mammography. These patients were also excluded from the analysis, as the surgical strategy was presumably different. A further 100 patients (8%) were excluded because the initial mammography had not been carried out at the University Breast Center and standardized reviewing of their mammograms was not possible.

**Surgical procedure**

Local disease affecting the breast was assessed using mammography, breast ultrasonography, and clinical examination. The axilla was assessed using clinical examination and ultrasonography. All of the patients underwent wide local tumor excision, with the ventral excision extending to the skin and the dorsal excision extending to the pectoralis fascia. The aim was to achieve margins of more than 1 cm. The tumor specimen was marked three-dimensionally and assessed radiographically. When necessary, the radiographer recommended reexcision in order to confirm the radiographic completeness of the resection. In addition, the pathologist assessed the tumor margins macroscopically and recommended reexcision if the specimen margins were not clear of tumor. These margins were excised if feasible. Frozen sections of the surgical specimen margins were not taken routinely, in accordance with the EUSOMA recommendations,25,26 and were therefore not part of the analysis. Only five of the patients were assessed using intraoperative frozen sections of the specimen.

**Measurements**

The tumor specimens were examined for tumor type, estrogen-receptor status, progesterone-receptor status, proliferation as defined by immunohistochemistry for MIB-1, HER2/neu expression as defined by the DAKO score (DAKO, Glostrup, Denmark), and grading. Mammographic density was documented in accordance with the BI-RADS classification published by the American College of Radiology (ACR),27 in which breast density
is categorized into four groups: 1, almost entirely fat; 2, scattered fibroglandular tissue; 3, heterogeneously dense; and 4, extremely dense. All of the mammographic findings were reviewed by K.H. and R.S.W. for this study.

**Statistical considerations**

To assess the association between the documented variables and the need for reexcision or mastectomy, each parameter was tested using the chi-squared test in the bivariate analysis. In addition, a stepwise reverse (α = 0.05; β = 0.1) logistic regression model was built to assess the association in a multivariate model. The dependent variable was the need for a second operation (no/yes). Independent variables were age (<45 years; 45–54 years; 55–64 years; and ≥65 years), tumor type (invasive ductal; invasive lobular; other), tumor size (<2 cm; ≥2 cm), multifocality (no/yes), in situ component (not present/present), axillary lymph node status (negative/positive), mammographic density (ACR categories 1–4), vascular invasion (no/yes), neoadjuvant chemotherapy (no/yes), estrogen-receptor status, progesterone-receptor status, and HER2/neu status (all three variables: negative/positive), grading (1/2/3), proliferation status assessed by Ki-67 (<20% staining; ≥20% staining). All of the statistical analyses were carried out using the Statistics Program for the Social Sciences (SPSS) program, version 14.0 (SPSS Inc., Chicago, IL, USA).

**Results**

Of the 565 patients included, sufficient treatment was possible with one operation in 444 (79%). A total of 21% had to undergo at least one more operation, up to a maximum of four operations, due to positive margin status after the first breast operation. In 54 patients (10%), mastectomy was ultimately necessary. The mean age of the patients was 56 years, and the mean tumor size was 1.7 cm, with 159 tumors (28%) being larger than 2 cm. Most of the tumors (n = 408; 72%) were invasive ductal lesions. The mammographic density was distributed over the four categories, with 8% (n = 45) in ACR category 4 and 45.8% (n = 259) in ACR category 3. Other tumor characteristics, such as multifocality, the presence of an in situ component, axillary node status, vascular invasion, and histopathological parameters are summarized in Table 1.

**Univariate analysis/significant associations**

Patients who required a second operation were more likely to be older (56.4 vs. 53.6 years; p = 0.022) and to have larger tumors (2.15 cm vs. 1.54 cm; p < 0.001). Patients with a multifocal tumor had to undergo a second operation in 40% of cases, in comparison with only 18% of those without multifocal lesions (p < 0.001). If there was an in situ component in the lesion, the reexcision rate was 29% in comparison with 10.0% in patients who had a tumor without an in situ component (p = 0.02). In this analysis, a positive axillary lymph node status was associated with a significantly higher rate of repeat surgery (28% in N1 patients vs. 19% in N0 patients; p = 0.022). In addition, a higher ACR category of mammographic density was associated with higher reoperation rates: 18%, 18%, 22%, and 42% for categories 1, 2, 3, and 4, respectively.

**Univariate analysis/no associations**

Common histopathological parameters were analyzed in relation to their association with the excision rate. None of the characteristics tumor type (p = 0.14), vessel invasion (p = 0.14), estrogen receptor status (p = 0.99), progesterone receptor status (p = 0.72), HER2/neu status (0.99), grading (p = 0.46), proliferation status as assessed by Ki-67 testing (p = 0.44), and undergoing neoadjuvant chemotherapy (p = 0.99) showed a significant association with repeat surgery.

**Multivariate analysis**

For the multivariate analysis (Table 2), we constructed a reverse stepwise logistic regression model. None of the variables found to be nonsignificant in the univariate analysis achieved significance in the multivariate model, and age and nodal status were excluded by the model as not being independent predictors of the rate of second operations. Mammographic density, tumor size, multifocality, and the presence of an in situ component were the variables shown by the multivariate analysis to be associated with the reexcision rate. Patients with a dense breast (ACR category 4) had an adjusted odds ratio (OR) of 3.6 (95% confidence interval [CI], 1.2–11.0). A tumor size of more than 2 cm resulted in an OR of 3.0 (95% CI, 1.8–4.9). Multifocality was also highly significant, with an OR of 3.2 (95% CI, 2.0–5.4); and the contributing factor, the presence of an in situ component, showed an OR of 3.1 (95% CI, 1.8–5.4).

**Discussion**

**Definition of positive margins**

The rate of repeat surgery depends on the definition of the width of the tumor margin used, and the rates reported in literature consequently vary, ranging from 10% to 57%. The margin status is one of the most important predictive factors for local recurrence, even in patients in whom radiation treatment of the primary tumor bed is carried out; however, the correct surgical margin is still a matter of debate. Evidence has been obtained from retrospective and prospective trials, using subgroup analyses with arbitrarily established definitions of clear margins. The value used to define clear margins needs to be confirmed as being useful for achieving long-term local control.
of the disease. Most studies have used cut-off points of more than 1 mm or more than 2 mm as defining tumor-free margins. A summary of these studies is provided by Singletary.10 However, there does not appear to be relationship in the published studies between the width of the negative margin and the rate of local recurrence, which ranges from 0% to 10% and is a clear function of the follow-up time. However, there is some evidence that the subgroup of lobular breast cancers may not necessarily be compromised by positive margins in relation to the local recurrence rate.29 The cut-off point of 1 mm for margin assessment used in the present study therefore appears to be sufficient.

Comparison with similar studies

The present study analyzed a highly selected group of patients to assess the rate at which repeat breast operations became necessary due to positive tumor margins. The analysis only included patients who had had an invasive breast cancer diagnosed by a preoperative core biopsy and who were considered by the breast surgeon to be candidates for breast-conserving procedures. For the surgical procedure, mammographic guidance and intraoperative assessment of the surgical specimen by radiography was the standard practice. Frozen sections were not performed routinely. In these patients, the rate of reexcision was 21%. Some factors appear to be independent predictors of the impossibility of carrying out breast-conserving therapy.14,15,18,30 The study by Mullenix et al.20 included patients who had undergone mastectomy and breast-conserving therapy as the primary surgical treatment, and identified the type of surgery initially carried out as being the main risk factor for a second operation (OR 11.9; 95% CI, 2.5–57.8). The type of surgery used is thus the main confounding factor in this group. Keskek et al.23 focused on patients who were candidates for breast-conserving therapy. In the multivariate analysis, tumor type and tumor size were found to be significant predictive factors. However, the present study did not confirm any influence of the tumor type on the need for repeat surgery, as reported in three previous studies.18,31,32

### Table 1
Patient characteristics and univariate analysis of the association between tumor and patient characteristics with the risk for reexcision

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>One operation</th>
<th>At least one reexcision</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td>565 (100)</td>
<td>444 (78.6)</td>
<td>121 (21.4)</td>
<td>0.022*</td>
</tr>
<tr>
<td>Mean age</td>
<td>55.8 (SD = 11.6)</td>
<td>53.6 (SD = 11.6)</td>
<td>56.4 (SD = 11.6)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mean tumor size (SD)</td>
<td>1.67 (SD = 1.13)</td>
<td>1.54 (SD = 0.88)</td>
<td>2.15 (SD = 1.70)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2 cm (%)</td>
<td>403 (100)</td>
<td>338 (84)</td>
<td>65 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;2 cm (%)</td>
<td>159 (100)</td>
<td>105 (66)</td>
<td>54 (34)</td>
<td></td>
</tr>
<tr>
<td>Missing data (%)</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Multifocality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (%)</td>
<td>401 (100)</td>
<td>331 (82)</td>
<td>70 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes (%)</td>
<td>114 (100)</td>
<td>68 (60)</td>
<td>46 (40)</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>50</td>
<td>45</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>In situ component</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not present (%)</td>
<td>240 (100)</td>
<td>216 (90)</td>
<td>24 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Present (%)</td>
<td>305 (100)</td>
<td>217 (71)</td>
<td>88 (29)</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>20</td>
<td>11</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Axillary node status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (%)</td>
<td>145 (100)</td>
<td>105 (72)</td>
<td>40 (28)</td>
<td>0.020</td>
</tr>
<tr>
<td>Negative (%)</td>
<td>412 (100)</td>
<td>334 (81)</td>
<td>78 (19)</td>
<td></td>
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<tr>
<td>Missing data</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Mammographic density</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR category 1 (%)</td>
<td>51 (100)</td>
<td>42 (82)</td>
<td>9 (18)</td>
<td>0.003</td>
</tr>
<tr>
<td>ACR category 2 (%)</td>
<td>210 (100)</td>
<td>173 (82)</td>
<td>37 (18)</td>
<td></td>
</tr>
<tr>
<td>ACR category 3 (%)</td>
<td>259 (100)</td>
<td>203 (78)</td>
<td>56 (22)</td>
<td></td>
</tr>
<tr>
<td>ACR category 4 (%)</td>
<td>45 (100)</td>
<td>26 (58)</td>
<td>19 (42)</td>
<td></td>
</tr>
</tbody>
</table>

*Paired t-test; †two-sided chi-squared test. Reexcision rates are highlighted in bold. Characteristics with no association are mentioned in the Results section.

### Table 2
Multivariate analysis of factors associated with the risk of reexcision

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjusted odds ratio</th>
<th>95% confidence intervals</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammographic density</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR category 1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR category 2</td>
<td>1.1</td>
<td>0.4</td>
<td>2.7</td>
</tr>
<tr>
<td>ACR category 3</td>
<td>1.4</td>
<td>0.6</td>
<td>3.5</td>
</tr>
<tr>
<td>ACR category 4</td>
<td>3.6</td>
<td>1.2</td>
<td>11.0</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2 cm</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2 cm</td>
<td>3.0</td>
<td>1.8</td>
<td>4.9</td>
</tr>
<tr>
<td>Multifocal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.2</td>
<td>2.0</td>
<td>5.4</td>
</tr>
<tr>
<td>In situ component</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not present</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>3.1</td>
<td>1.8</td>
<td>5.4</td>
</tr>
</tbody>
</table>

ACR, American College of Radiology (classification).
Mammographic density

In the present study, mammographic density was found to be associated with a higher risk of positive tumor margins after the first operation. In all, 42% of patients with an ACR density category of 4 had to undergo a second operation, in comparison with 17.6% of patients in categories 1 and 2. The negative findings reported by Malik et al. might be explained by a smaller sample size.

Clinical impact

The implication for clinical practice is that patients who have a higher risk for a second operation after an attempt at breast-conserving therapy may be able to benefit from improved preoperative tumor localization or from better intraoperative margin assessment. Some of the risk factors described reflect the technical feasibility of tumor localization—such as mammographic density, multifocality, and in situ components. Tumor size affects the technical practicability of breast-conserving surgery, assuming that the surgeon’s aim is to achieve good cosmetic results—as should always be the case. As it was possible to treat most of the patients in whom breast-conserving therapy was planned without mastectomy (90%), no change in the principles used to select the surgical method is needed.

With regard to preoperative localization, bracket wire localization could be used to assist the surgeon in achieving complete excision of calcifications. Magnetic resonance imaging-guided bracket wire localization has also been described in relation to invasive cancers. These methods could be taken into consideration when designing a future interventional study on risk factors for repeat surgery.

Intraoperative ultrasonography has also been considered as a method of reducing the need for a second operation due to positive margins. Most nonpalpable lesions can be located using mammography, and the surgeon can then assess the margins in relation to the location in the breast. Some small comparative studies have evaluated the feasibility of this technique and confirmed that it is useful. The procedure could also be considered as a further option for use in a larger interventional study in high-risk patients in the effort to reduce the numbers of second operations required.

In the present study, intraoperative morphological assessment of the tumor margins was routinely carried out using radiography of the excised specimen. This procedure should be the standard of care, and was used in all of the patients included in the study. The strength of this approach is that the margins can be assessed not only for the visible tumor mass, but also in relation to ductal carcinoma in situ. The method is capable of identifying positive margins intraoperatively and can reduce the need for a second operation, as it allows immediate reexcision.

Finally, frozen-section analysis of tumor margins can also be taken into consideration in the effort to reduce the need for a second operation. In comparison with the final histopathological findings, this method has been reported to provide a false-positive rate of between 0% and 1.1% and false-negative rates of 0.1% and 4.4%. The costs of the procedure and its accuracy, particularly in smaller tumors, need to be taken into consideration.

Conclusion

Several risk factors, including mammographic density, were identified by this study as relevant for planning the best approach to ensure tumor-free margins in patients who are candidates for breast-conserving therapy. Greater mammographic density is associated with increased difficulty in preoperative and intraoperative localization and excision of the whole tumor. It may be possible to use this characteristic to identify patients in whom more accurate localization of the tumor is needed, using the methods mentioned above, or to establish a need for additional assessment of the tumor cavity and specimen to detect residual tumor during the initial operation and thereby reduce the need for repeat surgery in these patients.

Conflict of interest

None of the authors has any financial and personal relationships with other people or organizations to disclose that could inappropriately influence their work. This includes employment relationships, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.


