Influence of Resection Volume on Locoregional Recurrence of Breast Cancer after Breast-conserving Surgery

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Abstract. Background: The goals of breast-conserving surgery are to provide the survival equivalent of mastectomy, a cosmetically acceptable breast and a low rate of locoregional recurrence in the treated breast. This retrospective study investigated the impact of the resection volume on locoregional recurrence after breast-conserving therapy in patients with early-stage invasive breast cancer. Patients and Methods: Retrospective data from 185 women who were treated for operable breast tumours by breast-conserving surgery between 1995-1999 at the Martin-Luther-University in Halle/Germany were included in our study. Extent of total resection volume (TRV), tumour volume (V) and difference volume (DV) was compared for the influence on locoregional recurrence. Results: Our data showed no significant correlation between the risk of locoregional recurrence and the extent of resection volume. Predictors of an increased risk of locoregional recurrence after breast-conserving surgery were large primary tumour, grading, lymphatic vascular invasion, hormone receptor status and lack of radiotherapy or hormonal therapy. Conclusion: According to the accuracy of locoregional disease control and maintenance of the breast’s shape, our results support conservative surgery in early-stage breast cancer followed by radiotherapy and adjuvant systemic therapy.

Breast cancer surgery has changed over the past decades and continues to evolve. With the emergence of breast-conserving surgery (BCS), women with invasive breast cancer may now preserve their breast without sacrificing the oncological outcome. BCS refers to surgical removal of the tumour (with negative surgical margins) followed by moderate-dose radiotherapy to eradicate any residual disease. The goals of BCS are to provide the survival equivalent of mastectomy, a cosmetically acceptable breast and a low rate of recurrence in the treated breast. Several clinical trials directly comparing BCS with mastectomy have shown equivalent survival between the two treatment approaches (1-3). Despite the equivalence in overall survival with modified radical mastectomy and BCS, breast conservation would have limited appeal if high locoregional recurrence rates were to result in a significant number of subsequent mastectomies. Accordingly radiotherapy is an essential component of BCS in order to provide adequate control of microscopically residual disease and improve survival (4-6). In comparing the results of BCS with mastectomy and assessing the probability and impact of locoregional recurrence, it is important to identify predictive factors that may increase the risk of locoregional recurrence. Microscopic resection margins are the major selection factor for breast-conserving surgery because of their impact on locoregional recurrence. Women with negative excision margins have low rates of locoregional recurrence following BCS, while positive resection margins are associated with a higher risk of recurrence (7-10). Presence of an extensive intraductal component (EIC) that had previously been considered a contraindication for BCS is only a risk factor for locoregional recurrence when the margins of resection are not evaluated (11-13). Other factors that may help predict for locoregional recurrence include young age at diagnosis, hormone receptor status and the presence of lymphovascular invasion (LVI) (14-18). In addition to locoregional recurrence, a major goal of BCS is the preservation of a cosmetically acceptable breast. Several surgical factors play a role in the cosmetic appearance of the breast such as size and placement of the incision or management of the lumpectomy cavity in which careful attention to detail will improve the aesthetic results. However the amount of resected breast tissue is the major determinant of appearance following BCS (19, 20). The appropriate margin of grossly normal breast tissue around

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the tumour for women undergoing BCS is still uncertain (1-3, 21). Larger resections may be necessary for invasive carcinomas with an extensive intraductal component, or for infiltrating lobular carcinomas (11, 12, 22, 23). The relation between the resection volume and the risk of locoregional recurrence in patients with invasive breast cancer treated with BCS and radiotherapy has not been previously analyzed in detail. In an attempt to assess the impact of optimal extent of resection volumes on locoregional recurrence (LRR) in patients given breast-conserving surgery, we reviewed the database of the Department of Obstetrics and Gynecology at the Martin Luther University in Halle, Germany.

**Patients and Methods**

**Patient characteristics.** For this retrospective study, the records of 185 patients with primary invasive breast cancer treated between January 1995 and December 1999 were reviewed. Data regarding a subset of these patients were published in an earlier study (24). Patients with positive microscopic resection margins after BCS were not included. Clinical and histopathological data were obtained from clinical files and pathology reports at the Department of Obstetrics and Gynecology, Martin Luther University Halle-Wittenberg Medical School, Germany.

The standard surgical treatment for all patients consisted of BCS with removal of sufficient normal breast tissue to ensure both tumour-free specimen margins and a satisfactory cosmetic result and axillary dissection. The tumours were clinically classified as described by the American Joint Committee on Cancer (25). Hormone receptor status was determined immunohistochemically (26). Radiotherapy was individually planned and was initiated after proper wound healing. It was given by tangential beams from a linear accelerator (4-6 MV) to the breast parenchyma including 1 cm of the surrounding tissue. The standard dose given was 50 Gy in 2-Gy daily fractions, five fractions per week. In some patients, a boost was recommended. Combination chemotherapy consisted of either intravenous cyclophosphamide 600 mg/m², methotrexate 40 mg/m² and fluorouracil 600 mg/m² (CMF) administered on days 1 and 8, or intravenous epirubicin 90 mg/m² and cyclophosphamide 600 mg/m² (EC), or a combination of CMF and EC; a few patients were treated with taxane-containing regimens. Hormone receptor-positive patients received 20 mg Tamoxifen daily for five consecutive years of history, physical examination and haematological tests including tumour markers (CEA and CA 15-3). Mammography and chest X-rays were performed on an annual basis. Ultrasonography of the upper abdomen and a bone scintigram were performed if tumour recurrence was suspected. All available pathology reports were reviewed for tumour size, histological subtype, histological grade, microscopic margin involvement, lymphatic vessel invasion, extensive intraductal component, nodal status and hormone receptor status. The dimensions of the excised specimens were obtained from the original pathology reports. The total resection volume (TRV) was estimated by length x height x width (cm³) of the resected tissue including the tumour. Re-excision volumes also were calculated, and the total TRV was comprised of the sum of total resection volumes for all excisions. The tumour volume (V) was determined using the calculation for an ellipsoid figure: \( V = \frac{4}{3} \pi (l \times h \times w) \text{ cm}^3 \). Subtraction of the tumour volume from TRV was performed to assess the volume of tumour-free tissue termed the difference volume (DV).

**Statistical analysis.** The primary study end-point was LRR, an event of ipsilateral breast tumour recurrence, or if no such event occurred date of follow-up. The resection volumes were expressed as the mean±standard deviation (SD). The Pearson product-moment correlation coefficient \( r \) measured the tendency of the different volumes to increase or decrease together. The Chi-square distribution \( \chi^2 \), Mann-Whitney U-test and Student’s t distribution were used to assess the effects of resection volumes and prognostic factors on locoregional recurrence. A \( p \)-value \( \leq 0.05 \) was considered statistically significant. The SPSS statistical software system (SPSS 10.0; SPSS Inc. Chicago, IL, USA) was used to perform all calculations.

**Results**

For this study an overall collective of 185 women with primary breast cancer was analyzed. Ten patients (5.4%) developed LRR of the tumour in the treated breast during follow-up. No patient had died due to underlying disease. The surviving patients were followed up for a median of 52.3 months (range 0.3-102.9 months) from the time of primary surgery. Detailed clinicopathologic patient characteristics are given in Table I. The mean TRV was 244.74 cm³ (range 6.02 cm³-1834 cm³). Analysis concerning the coherence of TRV with prognosis showed smaller TRVs in patients with LRR (76.37 cm³ vs. 271.93 cm³) but the results failed to retain significant correlation \( p=0.144 \). The mean tumour-free DV was 242.24 cm³ (range 6.72 cm³-1828.43 cm³). Pearson’s correlation coefficient showed a strong relationship between DV and TRV \( (r=1.0) \), a smaller volume of tumour-free tissue was associated with higher risk of LRR \( (70.014 \text{ cm}^3 \text{ vs. } 269.48 \text{ cm}^3) \). But the association between DV and LRR did not approach statistical significance \( p=0.184 \). The mean tumour volume as defined was 1.77 cm³ (range 0.01 cm³-47.69 cm³). There was no linear correlation between V and TRV \( (r=0.183) \) or DV \( (r=0.161) \). With respect to the risk of LRR, \( V \) \( (p=0.020) \) had a significant influence \( (3.09 \text{ cm}^3 \text{ vs. } 13.39 \text{ cm}^3) \) (see Table II). The presence of lymphovascular invasion (LVI) was identified in 8 specimens (4.3%) and significantly correlated with the risk of LRR \( (p=0.018) \). LVI did not influence the size of TRV \( (p=0.648) \) or DV \( (p=0.613) \). Higher DV \( (379.9 \text{ cm}^3 \text{ vs. } 138.6 \text{ cm}^3) \) had no significant impact on LRR \( (p=0.317) \) in patients with LVI. An EIC was seen in 23 specimens (12.4%). The association between the LRR rate and EIC \( (p=0.268) \) failed to retain significance. Proof of EIC had no significant impact on the TRV \( (p=0.720) \) or DV \( (p=0.720) \). Three patients omitted adjuvant radiotherapy (1.6%). All these patients were seen in the group with LRR \( (p=0.0001) \). With respect to the risk...
of LRR more prognostic factors were analyzed: only positive hormone receptor status ($p=0.023$), tumour grading ($p=0.049$), adjuvant hormone therapy ($p=0.006$), and radiotherapy ($p<0.0001$) is associated with a significant influence. Age, menopause status, nodal status, histopathology and adjuvant chemotherapy failed to show significance in the risk of LRR (see Table III).

**Discussion**

Since the early 1990s, breast-conservation therapy has been accepted as an equivalent to mastectomy for the surgical treatment of early-stage breast cancer. In this study, the overall LRR rate after BCS was 5.4%. In large prospective randomized trials, local recurrence rates for patients treated with BCS ranged from 5% to 20%. The broad range of follow-up times in these studies may account for the range of recurrence rates (1, 3, 6). This study provides information with a shorter follow-up time for a median of 52.3 months, which could explain the lower rate of LRR than that of other published series. Risk factors for LRR reported in the literature have included patient age, tumour histology, high grade, large tumour size, positive resection margins, multifocality, multiple tumours, EIC, positive nodal status, negative hormone receptor status and LVI (14-16, 27-30). Although we could not assess all of these factors, we found that large tumour volume, high grade, lymphatic vascular invasion, negative hormone receptor status and the lack of radiotherapy or hormonal therapy were independent predictors of LRR in early-stage invasive breast cancer. Macroscopic tumour size ($pT$) has been found to be a risk factor for LRR among patients with early-stage breast cancer treated with breast-conserving surgery. In some studies, patients with tumours larger than 2 cm on histological examination were at increased risk of developing local recurrence, particularly those who were not given radiotherapy (31, 32). We found tumour volume to be an independent risk factor for the development of LRR (13.39 cm$^3$ vs. 3.09 cm$^3$). Risk factors for the development of local recurrence have been described, including a high extent of intraductal component, lymphatic vascular invasion and positive tumour margins (9, 12-18, 27, 29, 33-35). A relationship among TRV, EIC and local recurrence has been suggested by Vicini et al. (11). They looked at resection volumes in 507 patients with invasive carcinoma treated with conservative surgery and radiotherapy between 1968 and 1982. They calculated resection volume by multiplying height $\times$ width $\times$ length and found that in patients with tumours which were EIC-..
negative, smaller excision volumes were able to establish good local control. In the EIC-positive tumours, however, only large excision volumes provided acceptable local recurrence rates. The present study shows that in our group of 185 patients, the presence of EIC had no significant impact on the TRV ($p=0.720$) or DV ($p=0.720$). Our analyzed resection volumes (TRV and DV) as described were not significantly associated with the risk of LRR. In consideration of the low rate of LRR (5.4%) and limited time of follow-up, a trend for smaller DV and TRV with a higher risk of locoregional-recurrence can be seen. Although LVI status is increasingly used to specify indications for adjuvant systemic therapy in patients with early-stage breast cancer, the association of LVI with locoregional control and its role in guiding locoregional therapy decisions are less well defined (15, 18, 19).

The present study demonstrates that patients with LVI have high LRR risks. LVI status was a significant prognostic factor of LRR ($p=0.018$). Despite higher DVs (379.9 cm$^3$ vs. 138.6 cm$^3$) patients with LVI had no significantly lower risk of LRR ($p=0.317$). Other reported risk factors for the development of local recurrence have been described, including age, nodal status and adjuvant chemotherapy (2, 3, 14, 17, 35). Because our study was retrospective in nature, data on these factors were not available for sufficient numbers of patients to draw meaningful conclusions. In conclusion, the goals of BCS are to provide the survival equivalent of mastectomy, a cosmetically acceptable breast and a low rate of recurrence in the treated breast. Independent predictors of an increased risk of LRR after BCS are large primary tumour, negative hormone receptor status, positive margin status, high grade, lymphatic vascular invasion, and lack of radiotherapy or hormonal therapy. Our findings support conservative surgery in early stage breast cancer followed by adjuvant systemic therapy and radiotherapy.

References


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