

Predictors of Re-excision among Women Undergoing Breast-Conserving Surgery for Cancer

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Background: Up to 60% of breast cancer patients who undergo breast-conserving surgery (BCS) require re-excision to obtain clear margins, causing delays in adjuvant treatment and poor aesthetic results. However, patient and treatment-related factors associated with re-excision are not well defined.

Methods: We surveyed all women undergoing breast conserving surgery between January 2002 and May 2006 regarding their breast disease ($n = 714$, response rate = 79.5%). The medical record was reviewed to determine the receipt of re-excision lumpectomy following BCS, and obtain tumor stage, histology, and biopsy method (surgical versus needle biopsy). Patient age, breast size, tumor location in the breast, and receipt of chemotherapy were self-reported. Logistic regression was used to determine significant predictors of re-excision lumpectomy.

Results: In this sample, 51.4% of women required only one breast excision, 41.9% required two breast excisions, and 6.6% required three breast excisions. Overall, 10.8% of women required a mastectomy following initial attempt at BCS. Factors significantly correlated with re-excision lumpectomy included smaller breast size (A cup: OR = 2.7; 95%CI: 1.32–5.52; B cup: 1.63; 95%CI: 1.02–2.62), lobular histology (OR = 1.93; 95%CI: 1.15–3.25), and receipt of surgical biopsy (OR = 3.35; 95%CI: 2.24–5.02). Women who received adjuvant chemotherapy (OR = 2.49; 95%CI: 1.19–5.22) were more likely to require re-excision compared with women who received neoadjuvant chemotherapy.

Conclusions: Re-excision lumpectomy is common, and is significantly correlated with smaller breast size, lobular histology, surgical biopsy, and chemotherapy timing. Attention to these risk factors can improve the quality of care delivered to BCS patients by decreasing the cost and morbidity associated with multiple re-excision procedures.

Key Words: Breast-conserving surgery—Reoperation—Neoadjuvant chemotherapy—Diagnostic technique.

Breast conserving surgery is the preferred surgical treatment over mastectomy for women with early-stage breast cancer.^{1–3} However, successful treatment requires elimination of all gross and microscopic disease, and residual cancer in the surgical bed following lumpectomy increases the risk of future recurrence. Therefore, women who have positive

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surgical margins following BCS are advised to undergo either re-excision of the lumpectomy cavity or mastectomy prior to receiving additional adjuvant therapy.⁴⁻⁷

Of patients undergoing BCS 30–60% will require additional excision for residual cancer. Such procedures can increase the risk of wound infection, delay the initiation of adjuvant chemotherapy and radiation therapy, increase postoperative anxiety, and result in worse aesthetic outcomes.⁸⁻¹⁰ However, there are no clear guidelines for an appropriate number of excision attempts, and risk factors for re-excision are not well defined. Nonetheless, it is important to identify factors associated with re-excision lumpectomy in order for clinicians to adjust their treatment approach, and potentially reduce the burden of such procedures on the health care system due to associated cost and morbidity.

To study this, we surveyed women who underwent BCS at the University of Michigan over a 4 year period to describe the patient- and treatment-related factors associated with re-excision lumpectomy and mastectomy following initial attempt at BCS.

METHODS

Study Population

Women who underwent BCS at the University of Michigan Medical Center between January 2002 and May 2006 were identified for recruitment ($n = 898$), excluding those who underwent BCS for benign disease. BCS patients were surveyed with a mailed questionnaire using the Dillman method.¹¹ Of these patients, 714 (79.5%) responded to the survey. The study protocol was approved by the institutional review board at the University of Michigan. The mean age of nonresponders was 53.6 years (range 20–85 years), 78.9% were white, 8.8% were African American, and 12.3% were of other ethnicity, and 45.9% underwent re-excision lumpectomy.

Measures

Our dependent variables included the receipt of re-excision lumpectomy, and the receipt of mastectomy following attempted breast-conserving surgery. Information regarding re-excision was obtained from the medical record, and was defined as any further surgical breast procedure following either an excisional biopsy or lumpectomy for margin control,

excluding those procedures performed for immediate postoperative complications.

The following independent variables were obtained by patient report: patient age, body mass index (BMI), bra cup size, tumor location in the breast, method of diagnosis, and receipt of chemotherapy. Patient age was categorized into the following groups: ≤ 40 years, 41 to 50 years, 51 to 60 years, 61 to 70 years, and 71 years and older. Body mass index was calculated by patient report of height and weight on the mailed survey, and was categorized in the following way: < 25 kg/m², 25–30 kg/m², 31–35 kg/m², and ≥ 35 kg/m². Patients were asked to report their bra cup size (A cup, B cup, C cup, D cup or larger) as a measure of breast size. Finally, receipt and timing of chemotherapy administration (adjuvant or neoadjuvant) was determined by patient report. In this sample 65 (9.7%) patients received preoperative chemotherapy, 211 (31.5%) received postoperative chemotherapy, and 394 (58.8%) reported they received no chemotherapy.

Several independent variables related to the patient's disease were obtained by medical record review and by report to the University of Michigan Cancer Center Registry: the presence of microcalcifications on breast imaging or in the surgical specimen, multifocal or multicentric disease, histology, tumor grade, the presence of ductal carcinoma in situ (DCIS) in the surgical specimen, tumor size, and disease stage. Tumor size was categorized as: less than 1 cm, 1.0 to 1.9 cm, 2.0 to 2.9 cm, and 3.0cm or larger. Tumor stage was based on the 6th Edition of the American Joint Commission on Cancer Coding and Staging Manual. Pathologic stage information was available for 84% of patients. For those patients in whom pathologic stage was not available, clinical stage was used. Histology was categorized in the following groups: ductal histology, lobular or mixed ductal and lobular tumors, and other tumor histology. Tumor grade was grouped in the following way: low-grade or well-differentiated tumors, intermediate-grade or moderately differentiated tumors, and high-grade or poorly/undifferentiated tumors. Finally, method of diagnosis was obtained by review of the medical record, and categorized as needle biopsy (either core-needle biopsy or fine needle aspiration) or surgical biopsy.

Statistical Analysis

We used descriptive statistics to display the characteristics of the patient sample, and used chi-square tests to generate bivariate associations between our

TABLE 1. Characteristics of the study population

| | | n | % |
|---|-------------|-----|------|
| Age | ≤ 40 years | 60 | 8.4 |
| | 41–50 years | 184 | 25.8 |
| | 51–60 years | 235 | 32.9 |
| | 61–70 years | 127 | 17.8 |
| | ≥ 71 years | 97 | 13.6 |
| | Missing | 11 | 1.5 |
| Number of excisions performed among women undergoing BCS | 1 | 315 | 51.4 |
| | 2 | 256 | 41.9 |
| | 3 | 40 | 6.6 |
| Number of women undergoing mastectomy following attempted BCS | | 70 | 10.3 |
| Number of excisions attempted prior to mastectomy | 1 | 26 | 37.1 |
| | 2 | 32 | 45.7 |
| | 3 | 12 | 17.1 |

independent and dependent variables. We chose to collapse the category of multiple excisions to two or more excisions. Few women underwent more than two excisions, and we had limited statistical power to perform this subgroup analysis.

We tested the correlation between re-excision lumpectomy and each independent variable using multiple logistic regression. Similarly, we used multiple logistic regression to test the correlation between receipt of mastectomy following attempted BCS and each independent variable. Both bra cup size and BMI were highly correlated when testing for multicollinearity in our regression analysis. Therefore, we elected to include bra cup size in our multivariate analysis as a measure of breast size. Wald tests were used to test for differences for group variables. A *p*-value of less than 0.05 was considered statistically significant. All analysis was performed using Stata 9.0 (Statacorp, TX).

RESULTS

Table 1 details the characteristics of the study sample. In this sample of women undergoing BCS, 8.9% were aged 40 or younger, 25.9% were 41 to 50 years, 33.8% were 51 to 60 years, 17.8% were 61 to 70 years, and 13.8% were 71 years or older. Approximately half (51.4%) of women required only one breast excision, 41.9% required two breast excisions, and 6.6% required three breast excisions. Overall, 10.8% of women required a mastectomy following initial attempt at BCS, with 37.1% undergoing one excision prior to mastectomy, 45.7% undergoing two excisions prior to mastectomy, and 17.1% undergoing three excisions prior to mastectomy.

Table 2 describes the bivariate associations between each factor and the percentage of women

who underwent re-excision lumpectomy and mastectomy following BCS. With respect to patient factors, age and breast size were significantly correlated with re-excision lumpectomy. Women aged 41 to 50 years were more likely to undergo re-excision lumpectomy (64.0%), followed by women aged 40 or younger (52.5%) (*p* = 0.03). Women with smaller breasts were more likely to undergo re-excision lumpectomy compared with women with larger breasts (A cup: 70.2%, B cup: 56.8%, C cup: 52.0%, D cup or larger: 47.2%; *p* = 0.01). Age was the only patient factor significantly correlated with receipt of mastectomy, and a larger proportion of younger women underwent mastectomy compared with older women (≤ 40 years: 20.3%, 41–50 years: 11.4%, 51–60 years: 10.9%, 61–70 years: 6.6%, ≥71 years: 5.3%; *p* = 0.03).

Disease factors correlated with re-excision lumpectomy included the presence of multifocal or multicentric disease, tumor position in the breast, and tumor histology (Table 2). Women with multifocal or multicentric disease were more likely to undergo re-excision lumpectomy (presence of multifocal or multicentric disease: 74.2% versus one focus of disease 52.7%, *p* = 0.02), as well as women with lobular tumor histology (lobular: 65.4% versus ductal: 50.8% versus other: 56.9%; *p* = 0.02). Disease factors correlated with receipt of mastectomy included tumor histology, stage, and presence of multifocal or multicentric disease. Women with lobular tumors and more advanced disease stage were more likely to undergo mastectomy (lobular: 18.7%, ductal: 8.8%, other: 8.3%; *p* = 0.008. Stage 0: 7.6%, stage I: 7.6%, stage II: 15.1, stage III and IV 20.6%, *p* = 0.01). Women with multifocal or multicentric disease were more likely to undergo mastectomy than women with unifocal disease (22.6% versus 9.6%, *p* = 0.02). Among women with stage 0 disease, there was no significant difference in the rate of re-excision disease by the presence of DCIS, or by tumor size.

With respect to practice patterns, both biopsy method and timing of chemotherapy administration were correlated with re-excision lumpectomy (Table 2). Women who underwent a surgical biopsy were more likely to undergo re-excision lumpectomy compared with women who underwent a needle biopsy (74.2% versus 44.1%, *p* < 0.001). Women who received neoadjuvant chemotherapy were less likely to undergo re-excision lumpectomy (neoadjuvant chemotherapy: 31.3% versus adjuvant chemotherapy: 58.8%; *p* < 0.001).

Table 3 displays the multivariate analysis evaluating predictors of re-excision lumpectomy. Smaller breast size, surgical biopsy method, chemotherapy

TABLE 2. Univariate correlates of re-excision and mastectomy among women undergoing BCS

| | | Re-excision lumpectomy | | | Mastectomy | | |
|------------------------------------|-------------------------|------------------------|------|----------------|------------|------|----------------|
| | | n | % | <i>p</i> value | n | % | <i>p</i> value |
| Patient Factors | | | | | | | |
| Age | < 40 years | 31 | 52.5 | | 12 | 20.3 | |
| | 41–50 years | 112 | 64.0 | | 20 | 11.4 | |
| | 51–60 years | 117 | 50.9 | | 25 | 10.9 | |
| | 61–70 years | 57 | 47.1 | | 8 | 6.6 | |
| | > 71 years | 47 | 50.0 | 0.03 | 5 | 5.3 | 0.03 |
| BMI (kg/m ²) | < 25 kg/m ² | 135 | 54.9 | | 29 | 11.8 | |
| | 25–30 kg/m ² | 124 | 54.9 | | 19 | 8.4 | |
| | 31–35 kg/m ² | 55 | 56.7 | | 13 | 13.4 | |
| | > 35 kg/m ² | 30 | 41.7 | 0.19 | 5 | 6.9 | 0.34 |
| Cup size | A or smaller | 40 | 70.2 | | 8 | 14.0 | |
| | B | 113 | 56.8 | | 26 | 13.1 | |
| | C | 116 | 52.0 | | 18 | 8.1 | |
| | D or larger | 76 | 47.2 | 0.01 | 15 | 9.3 | 0.28 |
| Disease Factors | | | | | | | |
| Tumor location in breast | Upper outer | 140 | 54.1 | | 24 | 9.3 | |
| | Upper inner | 49 | 50.0 | | 14 | 14.3 | |
| | Lower inner | 16 | 38.1 | | 3 | 7.1 | |
| | Lower outer | 49 | 65.3 | | 6 | 8.0 | |
| | Central | 2 | 18.2 | 0.01 | 0 | 0.0 | 0.39 |
| Stage | 0 | 82 | 56.9 | | 11 | 7.6 | |
| | 1 | 171 | 53.8 | | 24 | 7.6 | |
| | 2 | 96 | 51.9 | | 28 | 15.1 | |
| | 3 & 4 | 17 | 50.0 | 0.79 | 7 | 20.6 | 0.01 |
| Tumor grade | Low grade | 107 | 48.2 | | 27 | 12.2 | |
| | Moderate | 164 | 55.8 | | 26 | 8.8 | |
| | High grade | 78 | 56.9 | 0.15 | 13 | 9.5 | 0.45 |
| Microcalcifications | Yes | 233 | 56.2 | | 48 | 11.6 | |
| | No | 132 | 49.4 | 0.08 | 21 | 7.9 | 0.11 |
| Multifocal or multicentric disease | Yes | 23 | 74.2 | | 7 | 22.6 | |
| | No | 342 | 52.7 | 0.02 | 62 | 9.6 | 0.02 |
| Histology | Ductal | 255 | 50.8 | | 44 | 8.8 | |
| | Lobular | 70 | 65.4 | | 20 | 18.7 | |
| | Other | 41 | 56.9 | 0.02 | 6 | 8.3 | 0.008 |
| Presence of DCIS | Yes | 79 | 56.8 | | 13 | 9.4 | |
| | No | 287 | 53.0 | 0.41 | 57 | 10.5 | 0.69 |
| Tumor size | < 1 cm | 120 | 54.6 | | 16 | 7.3 | |
| | 1–1.9 cm | 150 | 56.4 | | 31 | 11.7 | |
| | 2–2.9 cm | 66 | 55.5 | | 14 | 11.8 | |
| | > 3 cm | 25 | 39.1 | 0.09 | 9 | 14.1 | 0.27 |
| Practice patterns | | | | | | | |
| Biopsy method | Needle | 201 | 44.1 | | 48 | 10.5 | |
| | Surgical | 164 | 74.2 | 0.001 | 22 | 10.0 | 0.82 |
| Chemotherapy | Neoadjuvant | 20 | 31.3 | | 9 | 14.1 | |
| | Adjuvant | 120 | 58.8 | 0.001 | 34 | 16.7 | 0.001 |

timing, and tumor histology were significantly correlated with re-excision lumpectomy. Women with A or B cup breasts were more likely to require re-excision compared with women with D cup or larger breasts (A cup: OR = 2.7; 95%CI: 1.32–5.52; B cup: 1.63; 95%CI: 1.02–2.62). Women who underwent surgical biopsy were more likely to require re-excision lumpectomy compared with women who underwent needle biopsy (OR = 3.35; 95%CI: 2.24–5.02). Women who received adjuvant chemotherapy were more likely to require re-excision compared with women who received neoadjuvant chemotherapy (OR = 2.49; 95%CI: 1.19–5.22). Finally, women

with lobular tumors were more likely to require re-excision compared with women with ductal tumors (OR = 1.93; 95%CI: 1.15–3.25).

Table 4 displays the multivariate analysis evaluating predictors of mastectomy following BCS. Younger age, multifocal or multicentric tumors, and lobular histology were significantly correlated with receipt of mastectomy following BCS. Women aged 40 years or younger were more likely to undergo mastectomy following attempted BCS compared with women aged 51–60 (OR = 2.52; 95%CI: 1.04–6.14). Women with multifocal or multicentric disease were more likely to undergo mastectomy following

TABLE 3. Multivariate analysis of correlates of re-excision lumpectomy among women undergoing breast-conserving surgery

| | | Odds of undergoing re-excision lumpectomy (95% CI) |
|------------------------------------|--------------|--|
| Age | ≤40 years | 1.03 (0.52–2.04) |
| | 41–50 years | 1.58 (0.99–2.53) |
| | 51–60 years | – |
| | 61–70 years | 0.75 (0.45–1.25) |
| | ≥71 years | 0.64 (0.35–1.16) |
| | Wald test | 10.11 ($p < 0.039$) |
| Bra cup size | A or smaller | 2.70 (1.32–5.52) |
| | B | 1.63 (1.02–2.62) |
| | C | 1.32 (0.84–2.09) |
| | D or larger | – |
| | Wald test | 8.81 ($p < 0.032$) |
| Biopsy method | Needle | 1 |
| | Surgical | 3.35 (2.24–5.02) |
| Multifocal or multicentric disease | No | 1 |
| | Yes | 1.60 (0.62–4.12) |
| Chemotherapy | Adjuvant | 2.49 (1.19–5.22) |
| | Neoadjuvant | – |
| | None | 2.55 (1.09–6.01) |
| | Wald test | 5.97 ($p < 0.051$) |
| Histology | Ductal | 1 |
| | Lobular | 1.93 (1.15–3.25) |
| | Other | 1.35 (0.75–2.41) |
| | Wald test | 6.54 ($p < 0.038$) |
| Tumor size | < 1 cm | 1 |
| | 1–1.9 cm | 1.28 (0.83–2.00) |
| | 2–2.9 cm | 1.53 (0.78–3.00) |
| | ≥ 3 cm | 1.22 (0.53–2.78) |
| | Wald test | 2.02 ($p < 0.569$) |
| Stage | CIS | 1 |
| | I | 0.90 (0.55–1.47) |
| | II | 1.03 (0.513–2.07) |
| | III or IV | 0.89 (0.32–2.50) |
| | Wald test | 0.41 ($p < 0.94$) |

attempted BCS compared with unifocal disease (OR = 3.76; 95%CI: 1.36–10.41). Finally, women with lobular tumors were more likely to undergo mastectomy compared with women with ductal tumors (OR = 2.73; 95%CI: 1.39–5.36).

DISCUSSION

In this sample of women undergoing BCS, nearly half of women required re-excision lumpectomy, and 10% required mastectomy following initial attempt at BCS. Patient-, disease-, and treatment-related factors were associated with an increased risk of re-excision lumpectomy and mastectomy following BCS. Women with smaller breasts and lobular tumors were more likely to undergo re-excision lumpectomy compared with women with larger breasts and ductal tumors. Neoadjuvant chemotherapy and needle

biopsy techniques reduced the risk of re-excision lumpectomy. Finally, younger age, multifocal or multicentric disease, and lobular tumor histology were significantly correlated with receipt of mastectomy following attempted BCS.

Although previous authors have described a correlation between positive margins and larger tumor size, this is the first study to systematically evaluate the effect of breast size.^{12,13} Both smaller breast size and larger tumor size create a more technically challenging procedure for surgeons attempting to preserve the breast. It is possible that surgeons hesitate to remove a large volume of tissue in patients with small breasts due to concerns of poor cosmetic results, which can lead to inadequate tissue resections. However, we observed that neoadjuvant chemotherapy reduced the risk of re-excision lumpectomy. Multiple randomized controlled trials have demonstrated that neoadjuvant chemotherapy can expand the number of breast cancer patients eligible for BCS, particularly among women with locally advanced disease and large tumor size.^{14,15,16} While these findings are encouraging for women with larger tumors who desire breast conservation, it may be difficult to identify women who will respond to neoadjuvant chemotherapy, and to predict tumor size following neoadjuvant chemotherapy. Furthermore, mammography and ultrasound techniques may not accurately identify tumor shrinkage in women who have received chemotherapy.¹⁷ Nonetheless, neoadjuvant chemotherapy should be considered for women at risk for multiple re-excisions with breast conservation.

In this study, we also observed an increased risk of re-excision for women with lobular tumors. Invasive lobular disease is associated with insidious tumor biology, and it may be more difficult to appreciate the full extent of disease on physical examination or mammography.¹⁸ Additionally, lobular tumors may be more likely to be larger tumors at presentation, further increasing the risk of BCS failure.¹⁹ Finally, women who underwent surgical biopsy to diagnose breast cancer were at greater risk for subsequent re-excisions. Following pathologic confirmation of malignancy with a needle biopsy, surgeons are better equipped to perform a cancer-directed resection and obtain adequate margins compared with a diagnostic excision. Because excisional biopsies are intended only for the purpose of determining lesion pathology, surgeons may tend to be less aggressive than needed for a cancer resection in order to minimize postoperative defects.^{20,21}

TABLE 4. Multivariate analysis of correlates of mastectomy among women undergoing breast-conserving surgery

| | | Odds of undergoing mastectomy (95% CI) |
|------------------------------------|--------------|--|
| Age | ≤40 years | 2.52 (1.04–6.14) |
| | 41–50 years | 0.89 (0.43–1.82) |
| | 51–60 years | 1 |
| | 61–70 years | 0.78 (0.32–1.91) |
| | ≥71 years | 0.66 (0.21–2.06) |
| | Wald test | 7.03 ($p < 0.13$) |
| Bra cup size | A or smaller | 1.51 (0.54–4.17) |
| | B | 1.53 (0.73–3.23) |
| | C | 0.78 (0.35–1.71) |
| | D or larger | 1 |
| | Wald test | 4.38 ($p < 0.22$) |
| Biopsy method | Needle | 1 |
| | Surgical | 0.804 (0.43–1.51) |
| Multifocal or multicentric disease | No | 1 |
| | Yes | 3.76 (1.36–10.41) |
| Chemotherapy | Adjuvant | 1.45 (0.53–4.00) |
| | Neoadjuvant | 1 |
| | None | 0.63 (0.18–2.25) |
| | Wald test | 3.97 ($p < 0.14$) |
| Histology | Ductal | 1 |
| | Lobular | 2.73 (1.39–5.36) |
| | Other | 0.90 (0.33–2.48) |
| | Wald test | 9.03 ($p < 0.01$) |
| Tumor size | < 1 cm | 1 |
| | 1–1.9 cm | 1.31 (0.61–2.81) |
| | 2–2.9 cm | 0.89 (0.32–2.44) |
| | ≥ 3 cm | 1.06 (0.31–3.68) |
| | Wald test | 1.07 ($p < 0.78$) |
| Stage | CIS | 1 |
| | I | 0.57 (0.24–1.38) |
| | II | 1.01 (0.34–3.01) |
| | III or IV | 1.27 (0.31–5.16) |
| | Wald test | 3.21 ($p < 0.36$) |

Limitations

This study has several important limitations. First, the study sample was drawn from a single, tertiary referral center, and the patient characteristics and surgeon practice patterns we observed may not be generalizable to all treatment settings. Additionally, patient nonresponders were less likely to have undergone re-excision lumpectomy, and more likely to be nonwhite. Bra cup size, height, and weight were self reported, and not routinely documented in the medical record. Therefore, these findings may be subject to recall bias. Finally, we were unable to obtain an accurate measurement of specimen volume, as this was a retrospective study.

Implications

Despite these limitations, this study has identified several important patient- and treatment-related factors that may place BCS patients at an increased risk for multiple excisions. Such findings can be used

to improve the care for patients at the time of consultation, and throughout their care. Surgeons evaluating women with a breast abnormality should attempt needle biopsy techniques whenever possible. Additionally, identifying an optimal ratio between the volume of tissue resection required and the total preoperative volume of the breast tissue may be useful for surgeons planning breast cancer resections. Although future study is warranted to further explore this concept, such a ratio can guide surgical management decisions and identify women who may be better BCS candidates with neoadjuvant chemotherapy. Neoadjuvant chemotherapy reduces the risk of re-excision lumpectomy, and increases the number of women eligible for BCS. Attention to those factors that increase the risk for multiple excisions can improve the quality of care delivered to BCS patients by decreasing the cost and morbidity associated with multiple re-excision procedures.

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