Journal of Surgical Oncology 2009;99:99–103

Residual Disease After Re-excision Lumpectomy for Close Margins

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Introduction: While a positive margin after an attempt at breast conservation therapy (BCT) is a reason for concern, there is more controversy regarding close margins. When re-excisions are performed, there is often no residual disease in the new specimen, calling into question the need for the procedure. We sought to examine the incidence of residual disease after re-excision for close margins and to identify predictive factors that may better select patients for re-excision.

Methods: Our IRB-approved prospective breast cancer database was queried for all breast cancer patients who underwent a re-excision lumpectomy for either close or positive margins after an attempt at BCT. Close margins are defined as $\leq$2 mm for invasive carcinoma and $\leq$3 mm for DCIS. Clinicopathologic features were correlated with the presence of residual disease in the re-excision specimen.

Results: Three hundred three patients (32%) underwent re-operation for either close (173) or positive (130) margins. Overall, 33% had residual disease identified, 42% of DCIS patients and 29% of patients with invasive disease, nearly identical to patients with positive margins. For patients with DCIS, only younger age was significantly related to residual disease. For patients with invasive cancer, only multifocality was significantly associated with residual disease (OR 3.64 [1.26–10.48]). However, patients without multifocality still had a substantial risk of residual disease.

Discussion: The presence of residual disease appears equal between re-excisions for close and positive margins. No subset of patients with either DCIS or invasive cancer could be identified with a substantially lower risk of residual disease.

J. Surg. Oncol. 2009;99:99–103. © 2008 Wiley-Liss, Inc.

KEY WORDS: margins; lumpectomy; breast cancer; ductal carcinoma in situ

INTRODUCTION

While survival after breast conservation therapy (BCT) is equivalent to mastectomy, the consequences of local recurrence are not insignificant. Management of local recurrence can be both physically and psychologically demanding for patients, and when salvage mastectomy is necessary, one of the primary goals of breast conserving therapy is thwarted. Furthermore, it is possible that persistent local disease may seed (or reseed) distant metastases, with potential impact upon overall survival. Indeed, the Oxford meta-analysis has demonstrated a relationship between local control and overall survival in breast cancer, concluding that for every four local recurrences avoided by aggressive local therapy, a life may be saved [1]. It is therefore incumbent upon breast surgeons and radiation oncologists to optimize local control.

BCT consists of two components, lumpectomy and radiation therapy. While the adjuvant radiation therapy is often considered the most important factor for reducing local recurrence, the adequacy of the lumpectomy is also important, specifically obtaining clear microscopic margins. While a lumpectomy has clear advantages over mastectomy, one disadvantage is the need sometimes to return to the operating room for a re-excision lumpectomy. Re-excision rates are high, ranging from 20% to 70% in the literature, and in addition to the inconvenience and added costs, re-excision lumpectomies may result in added complications and diminish the aesthetic outcome [2–13].

While the consensus is quite clear that patients with a positive margin after lumpectomy require re-excision, there is more controversy regarding the patient with close margins, including both the definition of a close margin as well as the need to return to the operating room versus proceeding with radiation [14]. Studies examining whether local recurrence rates are increased when close margins are not re-excised have been mixed [15–23]. When re-excisions are performed, there is often no residual disease in the new specimen, calling into question the need for the procedure.

At the University of Michigan, we have maintained a strict policy of re-excision for close margins before proceeding with adjuvant radiation. At our institution, a close margin is defined by our pathologists as $\leq$2 mm for invasive cancer and $\leq$3 mm for ductal carcinoma in situ (DCIS). This approach has resulted in a low rate of local recurrence, but requires a higher rate of re-excisions [24,25]. We therefore sought to examine the incidence of residual disease after re-excision for close margins and to identify factors that may correlate with residual disease in order to better select patients for re-excision.

MATERIALS AND METHODS

All biopsy-proven breast cancer patients seen at the University of Michigan Comprehensive Cancer Center are presented at a multi-disciplinary tumor board composed of surgical, medical, radiation oncologists, radiologists, pathologists, and associated support staff. Once a patient has undergone surgical management of this cancer at the University of Michigan, data from these discussions and from the patient treatment records are entered into a prospective breast cancer database. For this study, our prospective breast cancer database was

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Received 22 April 2008; Accepted 22 October 2008

DOI 10.1002/jso.21215

Published online 8 December 2008 in Wiley InterScience (www.interscience.wiley.com).

queried for all female patients with breast cancer who underwent a re-excision lumpectomy for either close or positive margins after an initial attempt at breast conservation surgery at the University of Michigan between January 1, 2001 and December 31, 2005. Patients who proceeded to adjuvant radiation with close or positive margins were excluded. This study was approved by the Institutional Review Board at the University of Michigan.

Close margins are defined at the University of Michigan as $\leq$2 mm for invasive carcinoma and $\leq$3 mm for DCIS. The lumpectomy specimen is routinely oriented for the pathologist using three marking sutures and inked with six colors so that the involved margin can be identified. For the purpose of this study, a re-excision lumpectomy is defined as a second attempt to obtain negative margins. Therefore, a lumpectomy performed after an excisional biopsy (without a diagnosis of cancer) that had close or positive margins was not considered a re-excision. Residual disease is defined as either DCIS or invasive cancer identified within the re-excision specimen. Lobular carcinoma in situ (LCIS), atypical ductal hyperplasia (ADH), or atypical lobular hyperplasia (ALH) within the re-excision specimen were not considered residual disease. Fisher's exact test was used to determine significance between clinicopathologic features and the presence of residual disease, with a *P*-value less than .05 deemed significant. Multivariable analysis (MVA) was attempted for invasive cases using standard logistic regression. Using a backward, stepwise selection procedure, the most parsimonious model was constructed, retaining only those covariates found to have Wald-type *P*-values less than or equal to 0.1. MVA was not attempted for DCIS, as the small sample could not support multiple covariates. All statistical tests were conducted using SAS software, Version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Over this time period, 948 women were deemed eligible for BCT and had an initial attempt at a lumpectomy for either invasive breast cancer or DCIS. Of these women, 303 (32%) underwent re-operation for either close or positive margins. Positive margins prompted re-excision in 173 patients (57%) while close margins prompted re-operation in 130 patients (43%). This latter group comprises the primary population for this study. The median age for this population was 53.5 (range 31–88).

Thirty-one of the patients with close margins had DCIS, with or without microinvasion (24 and 7, respectively). All but one was diagnosed on screening mammography, with 28 having suspicious calcifications and 2 having a mass with calcifications. The final patient was discovered incidentally and had a normal mammogram. The diagnosis was made by image-guided core biopsy in 24 patients and excisional biopsy in 7 patients. Average tumor size was 1.0 cm (range 0.2–1.7 cm).

Ninety-nine of the patients with close margins had invasive cancer. Fifty of these patients were diagnosed on screening mammography while 34 discovered a mass on self-examination. Eight patients had a mass discovered on clinical examination, three patients presented with pain, and four patients initially presented with an axillary mass and were found to harbor a breast cancer. Mammographic findings for patients with invasive cancer included a mass in 69 patients (35 with calcifications, 34 without), architectural distortion or focal density (8), and calcifications alone (6). Three had missing data. Thirteen patients had a normal mammogram. The diagnosis was made by an operative biopsy in 22 patients and a percutaneous biopsy in 72 patients (5 patients had missing data). Average tumor size was 1.5 cm (range 0.2–4.6 cm). Ductal histology was present in 83 patients (7 with lobular features) and 10 patients had a lobular histology. The remaining six patients had an apocrine (1), papillary (1), medullary (1), mucinous (2), or metaplastic (1) histology.

Overall, 33% (43 patients) of those who returned for re-excision had evidence of residual DCIS or invasive carcinoma identified. The remaining 67% (87 patients) had no residual disease identified. For both DCIS and invasive cancer, these numbers were remarkably similar to the patients returning to the OR for positive margins (Fig. 1). For

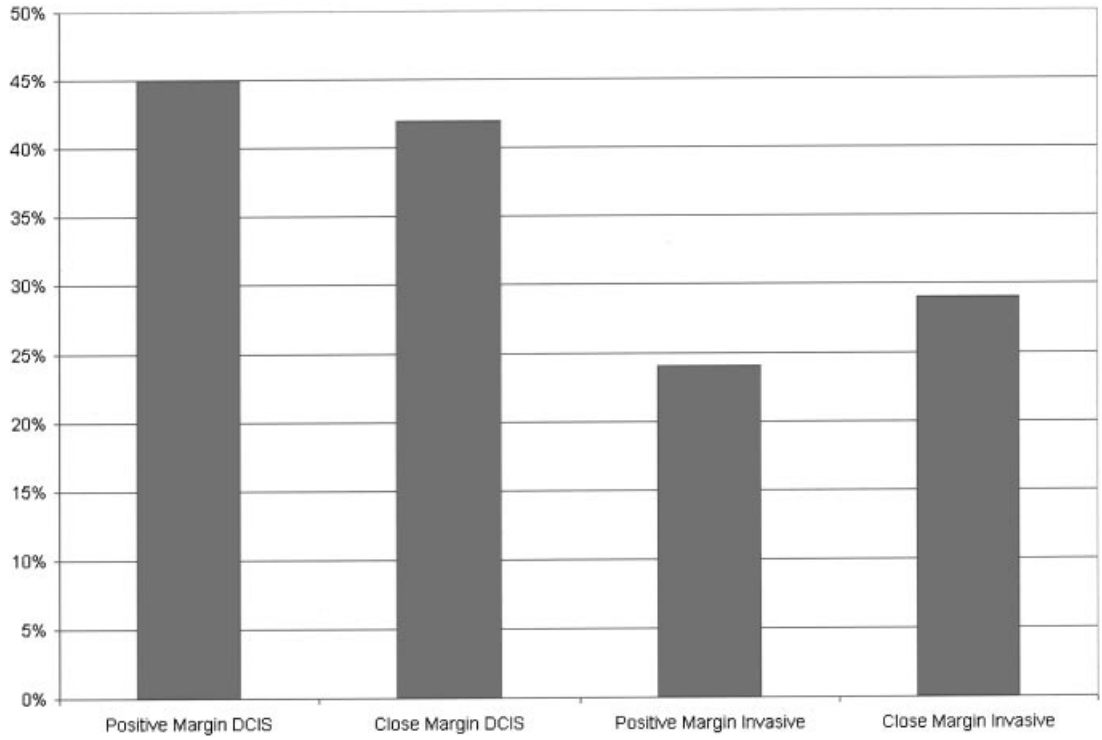

Fig. 1. Incidence of residual disease after re-excision for close or positive margins following lumpectomy for both DCIS and invasive cancer.

patients with DCIS, residual disease was found in 45% of patients with positive margins and 42% of patients with close margins. For patients with invasive disease, residual disease was identified in 24% of patients with positive margins and 29% of patients with close margins.

Risk factors predicting for residual disease upon re-excision were analyzed separately for DCIS and invasive breast cancer cases. Residual disease at the time of re-excision in patients with DCIS was not significantly associated with a patient's race, breast density on mammogram, biopsy type, tumor size, nuclear grade, estrogen receptor status, or presence of tumor necrosis (Table I). Residual disease was significantly related to a patient's age at surgery. Patients with residual disease were on average significantly younger than patients without residual disease (51.6 vs. 57.7 years, respectively).

Residual disease at re-excision for invasive disease was not significantly associated with a patient's race, age at surgery, clinical presentation or mammographic findings, breast density on mammography, biopsy type, T-stage/tumor size, positive node status, tumor histology, nuclear grade, estrogen and progesterone receptor status, HER2/Neu expression, lymphovascular invasion, or extensive intraductal component of disease (Table II). However, residual disease was significantly associated with multifocality. Patients with multifocal disease were more likely to have residual disease upon re-excision. In univariate analysis, the odds ratio estimated is 3.64 [95% CI 1.26–10.48], indicating that patients with multifocality are over 3.5 times more likely to have residual disease upon re-excision than patients without, although the validity of this association can be challenged based upon the higher proportion of missing data for this variable compared with others.

TABLE I. Distribution of Characteristics for DCIS Cases (N = 31)

Characteristics	Residual disease on re-excision: Yes N (%)	Residual disease on re-excision: No N (%)	Fisher's exact *P*-value[a]
Race			
White	11 (42.3)	15 (57.7)	0.77
Black	1 (33.3)	2 (66.7)	
Other	0	2 (100)	
Age at surgery (years)			
Mean	51.6	57.7	0.05[b]
Standard deviation	6.7	9.9	
Breast density on mammogram			
Not dense/mild	1 (33.3)	2 (66.7)	0.84
Moderate	6 (42.9)	8 (57.1)	
Very	3 (60.0)	2 (40.0)	
Unknown	2 (22.2)	7 (77.8)	
Biopsy type			0.99
Percutaneous	9 (37.5)	15 (62.5)	
Operative	3 (42.9)	4 (57.1)	
Tumor size (cm)			
Mean	1.17	0.95	0.41
Standard deviation	0.37	0.93	
Nuclear grade			
I	1 (33.3)	2 (66.7)	0.99
II	3 (42.9)	4 (57.1)	
III	8 (40.0)	12 (60.0)	
Unknown	0	1 (100)	
Estrogen receptor			
Positive	7 (38.9)	11 (61.1)	0.99
Negative	2 (40.0)	3 (60.0)	
Unknown	3 (37.5)	5 (62.5)	
Necrosis			
Present	9 (37.5)	15 (62.5)	0.99
Absent	2 (33.3)	4 (66.7)	
Unknown	1 (100)	0	

[a]Excluding the unknown category if present.
[b]Two-sample *t*-test using Satterthwaite's approximation.

TABLE II. Distribution of Characteristics for Invasive Cases (N = 99)

Characteristics	Residual disease on re-excision: Yes N (%)	Residual disease on re-excision: No N (%)	Fisher's exact *P*-value[a]
Race			
White	22 (26.5)	61 (73.5)	0.15
Black	4 (66.7)	2 (33.3)	
Other	3 (30.0)	7 (70.0)	
Age at surgery (years)			
Mean	52.5	55.4	0.32[b]
Standard deviation	13.1	13.0	
Breast density			
Not dense/mild	4 (26.7)	11 (73.3)	0.99
Moderate	15 (30.0)	35 (70.0)	
Very	1 (33.3)	2 (66.7)	
Unknown	9 (29.0)	22 (71.0)	
Biopsy type			
Percutaneous	18 (25.0)	54 (75.0)	0.24
Operative	10 (45.5)	12 (54.5)	
Other/unknown	1 (20.0)	4 (80.0)	
Tumor size (cm)			
Mean	1.67	1.42	0.30[b]
Standard deviation	1.20	0.74	
Positive nodes			
Yes	9 (25.0)	27 (75.0)	0.50
No	20 (32.3)	42 (67.7)	
Unknown	0	1 (100)	
Tumor histology			
Ductal only	23 (30.3)	53 (69.7)	0.97
Ductal and lobular	2 (28.6)	5 (71.4)	
Lobular only	3 (30.0)	7 (70.0)	
Other	1 (16.7)	5 (83.3)	
Nuclear grade			
I	5 (31.3)	11 (68.7)	0.81
II	12 (25.0)	36 (75.0)	
III	8 (30.8)	18 (69.2)	
Unknown	4 (44.4)	5 (55.6)	
Estrogen receptor			
Positive	21 (29.6)	50 (70.4)	0.99
Negative	7 (26.9)	19 (73.1)	
Unknown	1 (50.0)	1 (50.0)	
Progesterone receptor			
Positive	15 (28.9)	37 (71.1)	0.99
Negative	13 (28.9)	32 (71.1)	
Unknown	1 (50.0)	1 (50.0)	
Her2/Neu			
Positive	5 (38.5)	8 (61.5)	0.52
Negative	23 (28.1)	59 (71.9)	
Unknown	1 (25.0)	3 (75.0)	
Multifocal disease			
Yes	11 (52.4)	10 (47.6)	0.03
No	13 (23.2)	43 (76.8)	
Unknown	5 (22.7)	17 (77.3)	
Lymphovascular invasion			
Present	5 (31.3)	11 (68.8)	0.99
Absent	22 (29.0)	54 (71.0)	
Unknown	2 (28.6)	5 (71.4)	
Extensive intraductal component			
Present	7 (35.0)	13 (65.0)	0.59
Absent	20 (28.6)	50 (71.4)	
Unknown	2 (22.2)	7 (77.8)	

[a]Excluding the unknown category if present.
[b]Two-sample *t*-test using Satterthwaite's approximation.

Multivariable analyses did not reveal any significant associations between covariates and residual disease not first described on univariate analysis. The most parsimonious model included solely multifocality, and hence the model reduced to the univariate association already described.

DISCUSSION

Although all breast surgeons would agree that the presence of cancer extending to the inked margin after a lumpectomy is an indication to return to the operating room, the same cannot be said when the cancer approaches, but does not involve the margin. Some have adopted a ''negative is negative'' approach, performing re-excision lumpectomy only for positive margins. Among surgeons who will re-excise for close margins, the definition of a close margin varies, ranging anywhere from 1 to 4 mm. Even among the prospective randomized trials that demonstrated the equivalency of BCT compared with mastectomy, the definition of an ''adequate lumpectomy'' differed between studies and in some cases was not specified.

To address this issue, several institutions have retrospectively reviewed their experience with BCT, but these studies have failed to answer this question definitively. In some series, the presence of close margins was associated with an increased local recurrence rate compared to widely negative margins [15,16,18–20]. Other studies, however, failed to demonstrate this [21–23]. Interpretation of these studies is further hampered by the fact that the technology behind breast imaging and the delivery of radiation has consistently improved over the past two decades, and by a selection bias in the decision to re-excise or proceed with radiation therapy based on the location and size (focal vs. broad) of the close margin. In addition, the assessment of surgical margins is an inaccurate science as it is rarely feasible to embed the entire margin of the lumpectomy in paraffin blocks for analysis. Handling of the tissue, intraoperatively, ex vivo and particularly during specimen mammography for wire-localized lumpectomies, may compromise the margins, making clear margins appear closer. Often a re-excision performed for either a close or even positive margin fails to identify any residual disease, causing the surgeon to question whether the procedure was necessary.

If it were possible to predict which patients reliably had no residual disease in the specimen after undergoing re-excision, it might be possible to selectively apply re-excision for close margins, thereby decreasing re-excision rates and improving cosmetic outcomes without compromising local recurrence rates. To examine this, we queried our prospectively maintained database for patients who underwent a re-excision lumpectomy for any close or positive margin after a definitive lumpectomy, and assessed for the presence of residual disease. Surprisingly, the likelihood of finding residual disease after re-excising a close margin for either DCIS or invasive cancer was identical to the presence of residual cancer after re-excising a positive margin. This fact alone might suggest that there should be no difference in the approach to either a close or positive margin.

We then sought to identify those patient or primary tumor features that might correlate with the presence of residual disease, so as to identify a group of patients for whom re-excision may be avoided. We examined cases of DCIS and invasive cancer separately. For DCIS, only age was significant, with younger patients more often having residual disease (51.6 ± 6.7 vs. 57.7 ± 9.9, $P = 0.48$). The presentation, mammographic appearance, and method of biopsy for patients with DCIS were relatively uniform, precluding analysis. By Fisher's exact test, there was no significant correlation with the presence of residual disease with breast density on mammography, type of biopsy, tumor size, grade, ER expression, or presence of necrosis. It therefore seems prudent to recommend that any patients, and especially younger patients, with margins within 3 mm after lumpectomy for DCIS undergo a re-excision lumpectomy.

Examining those patients with close margins after lumpectomy for invasive cancer, there were several more factors that could be analyzed. Surprisingly, neither histology (ductal vs. lobular) nor the method of the initial biopsy (excisional vs. needle) correlated with the presence of residual disease. On univariate and multivariate analysis, only multifocality significantly correlated with the presence of residual disease. More than half the patients with multifocality harbored additional disease on re-excision, compared with less than a quarter of the patients without multifocality. While this certainly suggests a strong consideration for re-excision when multifocal disease is present, it does not mean that the absence of multifocality precludes re-excision, as over 20% of these patients still demonstrate additional disease. As no other factor showed a significant association with residual disease, a subset of patients without multifocality who can avoid re-excision could not be identified. Therefore, re-excising close margins after lumpectomy ($\leq$2 mm) for invasive cancer must be recommended.

Several caveats to this recommendation must be put forward. First, a small selection bias is in play, as some patients with focally close margins may have proceeded to radiation without re-excision based on clinical scenario. As very few patients with close margins in our database proceeded to radiation without re-excision, we are unable to use this data to examine whether re-excision for close margins has any impact on local recurrence. The presence of residual disease is not necessarily a marker of an increased risk of recurrence and as we rarely re-excise negative margins, there is no way to know the rate at which identifiable residual disease goes unrecognized, something we know does occur [26]. Although there were cases in our analysis where the volume of residual disease was quite significant, and sometimes prompted a second re-excision or mastectomy, in many cases the residual disease consisted of small foci, less than 1 mm. It is possible that this is the disease that is well managed by radiation therapy. Recent data suggest this residual disease may be further controlled through the use of a boost to the tumor bed. A large randomized trial conducted by the EORTC has demonstrated a substantial decrease in local recurrence rates among patients receiving a 16 Gy boost to the tumor bed after whole breast irradiation of 50 Gy and microscopically complete excision of early invasive breast cancer, as compared to patients not receiving boost treatment [27]. More recently, preliminary data presented from a central pathologic review of a subset of 1,724 patients with either completely resected tumors (treated on the aforementioned trial with either a 16 Gy boost or no boost) or incompletely resected disease (randomly assigned to 10 Gy vs. 26 Gy boost in a separate section of the same study), have raised the possibility that the radiation boost might compensate for inadequate surgical margins [28]. Until these data have been peer-reviewed and published, however, we continue to recommend re-excision to those patients with close or positive margins in whom further resection is technically feasible and likely to yield cosmetically acceptable results. It should be noted that the 16 Gy boost treatment in the EORTC study was associated with some detriment to cosmesis, with a significantly higher 10-year cumulative incidence of moderate to severe breast fibrosis among patients receiving the 16 Gy boost (28.1% with 66 Gy vs. 13.2% with 50 Gy).

It is important in this context to point out that an aggressive use of re-excision lumpectomy in patients with close margins does not result in an excessively high number of re-excisions nor substantially increase mastectomy rates (85% of patients with close margins in this series still underwent successful BCT). Re-excision, when done properly to assure negative margins but avoid excess breast tissue removal, may still yield cosmetically acceptable results. This is particularly true when the original specimen is properly oriented (e.g., short stitch superior, long stitch lateral, double stitch deep) so that the pathologist can properly orient the specimen and ink the margins using a 6-color system. This allows identification of the margin in question, limiting re-excision to only that area [29].

In summary, in light of the fact that the presence of residual disease appears equal between re-excisions for close margins and positive margins, it seems difficult to justify not being equally aggressive in both situations. As we could identify no subset of patients with a substantially low enough risk of harboring additional disease for either

patients with DCIS or invasive cancer, a selective approach to re-excision does not appear justified. We continue to recommend re-excision lumpectomy in all patients with margins $\leq$2 mm for invasive ductal carcinoma and $\leq$3 mm for DCIS, with the exception of a highly select group of patients, as agreed upon at a multidisciplinary breast cancer tumor board.

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