

CLOSE OR POSITIVE MARGINS AFTER MASTECTOMY FOR DCIS: PATTERN OF RELAPSE AND POTENTIAL INDICATIONS FOR RADIOTHERAPY

AFSHIN RASHTIAN, M.D.,* SHAWN IGANEJ, M.D.,* IN-LU AMY LIU, M.S.,[†]
AND SATHIMA NATARAJAN, M.D.[‡]

Departments of *Radiation Oncology and [‡]Pathology, Southern California Permanente Medical Group, Los Angeles, CA; and
[†]Research and Evaluation, Kaiser Permanente, Pasadena, CA

Purpose: Mastectomies result in very high local control rates for pure ductal carcinoma *in situ*; however, close or involved tumor margins are occasionally encountered. Data regarding the patterns of relapse in this setting are limited. **Methods and Materials:** Between 1994 and 2002, the pathology reports of 574 patients who had undergone mastectomy at our institution for pure ductal carcinoma *in situ* were retrospectively reviewed. Of the 574 patients, 84 were found to have margins of <10 mm. Of the 84 patients, 4 underwent postoperative radiotherapy and were excluded, leaving 80 patients for this analysis. Of the 80 patients, 31 had margins <2 mm and 49 had margins of 2.1–10 mm. High-grade disease was observed in 47 patients; 45 patients had comedonecrosis; and 30 had multifocal disease. Of the 80 patients, 51 were <60 years of age.

Results: With a median follow-up of 61 months, 6 (7.5%) of the 80 patients developed local recurrence. Of the 31 patients with a margin of ≤ 2 mm, 5 (16%) developed local recurrence vs. only 1 (2%) of 49 patients with a margin of 2.1–10 mm ($p = 0.0356$). Of the 6 patients with local recurrence, 5 had high-grade disease and/or comedonecrosis. All six recurrences were noted in patients <60 years old.

Conclusion: The findings of this review suggest that patients with pure ductal carcinoma *in situ* who undergo mastectomy with a margin of <2 mm have a greater-than-expected incidence of local recurrence. Patients with additional unfavorable features such as high-grade disease, comedonecrosis, and age <60 years are particularly at risk of local recurrence. These patients might benefit from postmastectomy radiotherapy. © 2008 Elsevier Inc.

Ductal carcinoma *in situ* DCIS, Margin status, Recurrence, Mastectomy.

INTRODUCTION

The management of ductal carcinoma *in situ* (DCIS) has evolved significantly during the past 30 years. Although in the 1970s mastectomy was the treatment of choice, DCIS is now often managed with breast-conserving surgery, with or without adjuvant radiotherapy (RT) (1). However, some patients still end up undergoing some form of mastectomy. Simple or total mastectomy involves removal of the breast tissue, nipple, and a small portion of overlying skin. Skin-sparing mastectomy involves removal of breast tissue with preservation of the overlying skin, nipple, and areola. Modified radical mastectomy involves simple mastectomy and axillary lymph node dissection. The management of DCIS by mastectomy cures almost all patients and remains the standard by which other treatments are measured (2). No prospective randomized trials have compared the effectiveness of mastectomy vs. breast-conserving surgery for DCIS. However, in a retrospective analysis, Silverstein *et al.* (2) demon-

strated a significant difference in disease-free survival at 10 years, in favor of those treated with mastectomy, 98% vs. 81% treated with excision and RT ($p = 0.0004$). Local recurrence developed in 2 of 167 patients in the mastectomy arm compared with 16 of 133 patients in the excision and RT arm. Several retrospective studies have reported that a margin of <1 cm predicted for an increased rate of local recurrence in patients with DCIS who underwent lumpectomy, with an even greater rate when the margin was <2 mm (3–7). However, essentially no data are available on the effect of margin status in patients who have undergone mastectomy for pure DCIS. The purpose of this study was to determine whether margin status is a predictor of local recurrence after mastectomy for pure DCIS.

METHODS AND MATERIALS

Between 1994 and 2002, the pathology reports of 574 patients who had undergone mastectomy at our institution for pure DCIS

Note—An online CME test for this article can be taken at <http://astro.astro.org> under Continuing Education.

Reprint requests to: Afshin Rashtian, M.D., Department of Radiation Oncology, 4950 Sunset Blvd., Stn. 2b, Los Angeles, CA 90028. Tel: (323) 783-5144; Fax: (323) 464-3131; E-mail:

arashtia@yahoo.com

Conflict of interest: none.

Received April 28, 2008, and in revised form June 24, 2008.
Accepted for publication June 28, 2008.

Table 1. Patient characteristics

Parameter	n (%)
Margin (mm)	
≤2	31 (38.8)
2.1–10	49 (61.2)
Grade	
1-2	30 (37.5)
3	47 (58.8)
Unknown	3 (3.7)
Comedonecrosis	
Absent	34 (42.5)
Present	45 (56.3)
Unknown	1 (1.2)
Age (y)	
0–59	29 (36.2)
≥60	51 (63.8)
Mastectomy	
Simple/total/skin sparing	55 (68.8)
Modified radical	18 (22.5)
Unknown	7 (8.7)
Multifocal	
Absent	50 (62.5)
Present	30 (37.5)

were retrospectively reviewed. Of the 574 patients, 84 were found to have a margin of <10 mm. Of the 84 patients, 4 had undergone post-operative RT and were excluded, leaving 80 patients for this analysis. The patient characteristics are listed in Table 1.

Statistical analysis was performed to determine whether a significant difference for local recurrence was present when stratified by several factors: margin <2 mm vs. 2.1–10 mm, age (<60 vs. >60 years), presence or absence of high-grade, comedonecrosis, or multifocal disease, and mastectomy type (*i.e.*, simple/skin-sparing/total mastectomy vs. modified radical mastectomy). The analysis of other factors such as hormone receptor status and multicentric disease was considered. However, with only a few pathology reports indicating the estrogen receptor status and only 3 patients with multicentric disease, a statistical analysis could not be performed on these variables. Two patients received tamoxifen as a part of adjuvant treatment.

Statistical analysis

The differences among the patient characteristics were assessed using Poisson regression analysis for a comparison of the categorical variables. Significance was evaluated using a two-sided $p < 0.05$.

Survival functions were generated using the Kaplan-Meier product limit method. The log-rank test was used to test whether the survival functions were statistically equivalent.

Statistical analyses were performed using Statistical Analysis Systems, version 9.13 (SAS Institute, Cary, NC).

RESULTS

With a median follow-up of 61 months, 6 (7.5%) of 80 patients had developed a local recurrence, of which five were noted on the chest wall and one in the axillary tail. The location of the recurrence was determined by the clinical and radiologic examination findings, when available. For these 6 patients, the median time to recurrence was 42 months from the date of mastectomy. The characteristics of these recurrences are outlined in Table 2.

Of these six recurrences, 5 recurrences (16%) were noted in the 31 patients with a margin of <2 mm compared with only one (2%) in the 49 patients with a margin of 2.1–10 mm (log-rank test, $p = 0.0356$; Fig. 1). Five recurrences (11%) developed in 47 patients with Grade 3 disease compared with one (2%) in the 30 patients with Grade 1-2 disease ($p = 0.2811$). Of the 45 patients with comedonecrosis, 5 (11%) developed a recurrence compared with 1 (2%) of the 34 patients without comedonecrosis ($p = 0.2103$). All six recurrences occurred in patients <60 years old ($n = 51$), with none of the 29 patients >60 years old developing a recurrence ($p = 0.0817$).

Of the 55 patients who had undergone simple/skin-sparing/total mastectomy, 4 (7%) developed a recurrence compared with 2 (11%) of 18 patients who had undergone modified radical mastectomy ($p = 0.9603$). Type of mastectomy was unknown in 7 patients. Of the 55 patients who had undergone simple/skin-sparing/total mastectomy, 44 underwent simple mastectomy, 9 total mastectomy, and 2 skin-sparing mastectomy.

Table 3 demonstrates the probability of local recurrence when the lesions were stratified according to all the variables analyzed.

Table 2. Characteristics of recurrences

Characteristic	Pt. No.					
	1	2	3	4	5	6
Margin (mm)	Positive	Positive	1.4	2	2	7
Margin location	Superficial	Deep	Deep	Deep	Deep/superficial	Deep
Grade	3	3	3	3	2	3
Necrosis	Yes	Yes	No	Yes	Yes	Yes
Pathologic finding	IDC/EIC	IDC	IDC/DCIS	IDC/DCIS	IDC	IDC
Recurrence site	Ax	CW	CW	CW	CW	CW
Location	Axillary tail	UOQ	Mid CW	UIQ	UIQ	Lateral CW
Size (cm)	1.8	4	4 mm	1.25	1.0	1.3
Interval to recurrence (mo)	25	48	17	72	36	60
Age at diagnosis (y)	40	55	47	41	37	58
Mastectomy	Simple	Simple	Simple	MRM	Skin sparing	MRM
Multifocal disease	Yes	No	Yes	No	Yes	No

Abbreviations: IDC = invasive ductal carcinoma; EIC = extensive intraductal component; DCIS = ductal carcinoma *in situ*; Ax = axilla; CW = chest wall; UOQ = upper outer quadrant; UIQ = upper inner quadrant; MRM = modified radical mastectomy.

Statistical analysis was also performed on the data from the 31 patients with a margin of <2 mm to determine whether the favorable and unfavorable features had an additional effect on the local recurrence rates.

As listed in Table 4, although favorable features appeared to suggest a lower absolute rate of local recurrence even when margins of ≤2 mm were noted, statistical significance could not be demonstrated, possibly because of the small number of patients in these subgroups.

The operative reports of the 6 patients with recurrence were reviewed to determine whether the fascia had been removed during mastectomy. The fascia was removed in 1 patient and left intact in 3 patients; for 2 patients, not enough information had been provided to determine with certainty whether the fascia had been removed. No patients had undergone prophylactic mastectomy.

Table 2 lists the location of the margins. The location varied in the six recurrences, although most of the margins included the deep margin.

On relapse, all 6 patients with local recurrence had an invasive component detected in their pathology specimens. Three patients developed metastatic disease, two simultaneous with local recurrence, and one 5 years after the local recurrence. One patient eventually died of her metastatic disease. The other 3 patients with local recurrence alone underwent salvage therapy and were alive with no evidence of disease at last follow-up.

The pathology slides of 4 of the 6 recurrences were available for review by a central pathologist. It was confirmed that all 4 patients had on their original mastectomy specimen with no invasive component. The margins were also reviewed and the initial findings were confirmed.

DISCUSSION

Mastectomy for pure DCIS generally results in excellent outcomes, with only 1–2% of patients developing local recurrence (2). No prospective randomized trials have compared the effectiveness of mastectomy vs. breast-conserving surgery for DCIS. The National Surgical Adjuvant Breast Project-06 was a three-arm prospective randomized trial that

Table 3. Analysis of predictors of local recurrence

Factor	Patients (n)	Recurrence (n)	p*
Margin (mm)			0.0356
≤2	31	5 (16)	
2.1–10	49	1 (2)	
Grade			0.2811
1-2	30	1 (2)	
3	47	5 (11)	
Unknown	3	0 (0)	
Comedonecrosis			0.2103
Absent	34	1 (2)	
Present	45	5 (11)	
Unknown	1	0 (0)	
Age (y)			0.0817
0–59	51	6 (12)	
≥60	29	0 (0)	
Mastectomy			0.9063
Simple/total/skin sparing	55	4 (8)	
Modified radical	18	2 (11)	
Unknown	7	0 (0)	
Multifocal			0.5549
Absent	50	3 (6)	
Present	30	3 (10)	
Margin ≤2 mm and comedonecrosis			0.0084
Present	16	4 (25)	
Absent	64	2 (3)	
Margin ≤2 mm and high grade			0.0055
Present	16	4 (25)	
Absent	64	2 (3)	
Margin ≤2 mm, comedonecrosis, and high grade			0.0528
Present	13	3 (23)	
Absent	67	3 (5)	
Margin ≤2 mm and comedonecrosis or high grade			0.0006
Present	19	5 (26)	
Absent	61	1 (2)	

Data in parentheses are percentages.

* Obtained from Poisson regression analysis.

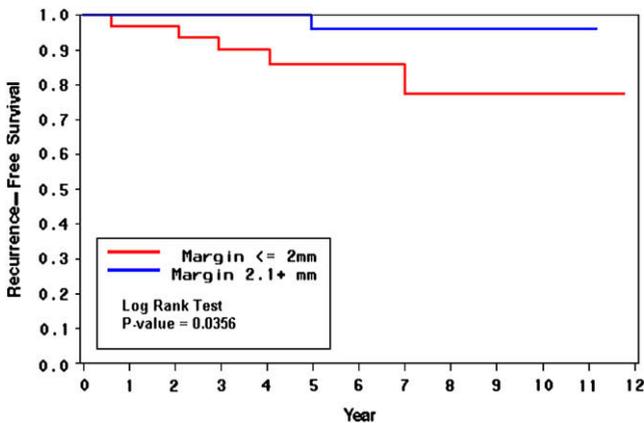


Fig. 1. Recurrence-free survival curve by margin level.

compared mastectomy vs. lumpectomy plus RT vs. lumpectomy alone in women with presumed invasive cancer. However, 78 patients were found to have pure DCIS on central pathology review. After 83 months of follow-up, no local recurrences had developed in the patients who had undergone mastectomy compared with a 7% local failure rate for those treated with lumpectomy and postoperative RT (8). Additionally, in a retrospective analysis, Silverstein *et al.* (2) showed that for patients with pure DCIS, a significant difference was found in disease-free survival at 10 years, in favor of those treated with mastectomy (98%) vs. those treated with lumpectomy and RT (81%; $p = 0.0004$). Also, a recent meta-analysis (9) of all retrospective series published up to 1998 reported only a 1.4% rate of local recurrence for those who had undergone mastectomy, providing further evidence that the recurrence risk after mastectomy for pure DCIS is very low. Nonetheless, radiation oncologists are occasionally

consulted at the discretion of the surgeons for consideration of postmastectomy RT (PMRT) when close or positive margins are encountered. Almost invariably, these consultations are requested only when close or positive margins are encountered in the mastectomy pathology specimen. Although some investigators have advised RT in this setting on the basis of anecdotal experience (10), we are unaware of any large series that have showed that close or positive margins after mastectomy for DCIS predict for an increased risk of local recurrence with statistical significance. A recently published study from The Netherlands that analyzed local recurrences after different treatment strategies for DCIS found that margin status reached statistical significance only for patients treated with breast-conserving therapies (11).

When we initially set out to perform this review, we were uncertain of how to define a close margin after mastectomy for DCIS. Because many lumpectomy studies (3–7) have suggested margins of <1 cm to be a predictor of local recurrence, we elected to review all patients with such mastectomy margins. Our study, however, revealed that only margins of ≤ 2 mm were of statistical significance in terms of carrying a greater-than-expected failure rate of 16% compared with a failure rate of around 2% for patients having wider margins ($p = 0.0356$), consistent with the failure rate reported for patients with DCIS undergoing mastectomy.

It has been demonstrated in the breast-conservation reports for DCIS that other unfavorable features, such as high-grade disease, comedonecrosis, and young age, have a significant effect on local recurrence (3–7, 12, 13). Data regarding the influence of these factors after mastectomy are scarce. Recently, a retrospective review of 223 consecutive patients with DCIS treated with mastectomy and immediate reconstruction performed at Emory University revealed an overall local recurrence rate of 3.1% that was influenced by high tumor grade ($p = 0.109$). In that study, 2 (10.5%) of 19 patients with a surgical margin <1 mm developed local failure; the difference was not statistically significant (14). Given this lack of statistical significance plus that all patients in that study were treated with skin-sparing mastectomy, it is rather difficult to draw any firm conclusions regarding the predictors of local recurrence. In our study, on multivariate analysis, margin status was the only factor to have any effect on the outcomes for the entire population. Additionally, we analyzed the subgroup of 31 patients with a margin of <2 mm to determine the risk of recurrence when other high-risk features were noted. Although the absolute risk of recurrence was greater for those patients with additional unfavorable features, we were unable to demonstrate a statistically significant difference in the local failure rate compared with those who lacked these high-risk factors. For instance, patients with margins <2 mm plus high-grade disease had a 25% recurrence rate compared with only 8% for those with a margin of <2 mm without high-grade disease ($p = 0.4140$). However, this lack of statistical significance might have been because of the small number of patients in this subgroup.

In our review, all patients with local recurrence had an invasive component on relapse despite having pure DCIS in

their initial mastectomy specimens. This finding was rather unexpected, because in the lumpectomy trials, only one-half of the patients with recurrence had evidence of invasive disease at relapse (12, 13). Kim *et al.* (15) reported on the details of the characteristics of 10 patients with chest wall relapse after mastectomy for DCIS. They found that 9 patients (90%) had an invasive component in their relapse specimen; although a number of their patients did not have pure DCIS in their original mastectomy specimens (15). Several other small case reports of chest wall recurrences after mastectomy for DCIS have also noted a very high percentage of invasive disease at relapse (15–17). These findings potentially signify that local recurrence after mastectomy carries a worse prognosis than after lumpectomy for patients with DCIS. That one-half of our patients with local recurrence also developed distant metastasis supports this argument. Therefore, it would seem beneficial to minimize the risk of local recurrence for these patients.

Lumpectomy trials for DCIS have shown that postoperative RT significantly decreases the risk of local recurrence, even in patients with close or positive margins (12, 13). The National Surgical Adjuvant Breast Project B-17 trial revealed that in patients with uncertain or involved margins, the addition of RT to lumpectomy reduced the local recurrence rate from 39% to 17% ($p < 0.05$) (13). The European Organization for Research and Treatment of Cancer 10853 also demonstrated that for patients with close or involved margins, the addition of RT to lumpectomy reduced the local recurrence rate from 32% to 16% ($p < 0.05$) (12). Extrapolating from these studies, one could conclude that a local control benefit should result from the use of PMRT when close or positive margins are obtained. No large studies of the outcomes after PMRT for DCIS are available; however, Metz *et al.* (10) reported on 3 patients who underwent PMRT for positive margins and found no locoregional recurrences or evidence of metastatic disease with a minimal follow-up of 7.1 years.

Does this mean that all patients with DCIS who have undergone mastectomy with a margin of <2 mm should undergo PMRT? We did not observe any recurrences in patients with low-grade disease or those >60 years old. Along the same lines, Kim *et al.* (15) also reported that all 10 patients with chest wall relapse after mastectomy for DCIS had

Table 4. Analysis of recurrence in patients with margin <2 mm

Factor	Patients (n)	Recurrence (n)	p^*
Grade			0.4140
1-2	12	1 (8)	
3	16	4 (25)	
Comedonecrosis			0.3330
Absent	14	1 (7)	
Present	16	4 (25)	
Age (y)			0.5601
0–59	26	5 (19)	
≥ 60	5	0 (0)	

Data in parentheses are percentages.

* Obtained from Poisson regression analysis.

intermediate to high-grade disease and only 1 of these patients was >60 years old, and that particular patient was aged 63 years. Thus, even if close margins are encountered, it would be difficult to routinely recommend RT to patients with low-grade disease or older age after mastectomy for DCIS. However, our results suggest that patients with margins of

≤2 mm who have any additional unfavorable features, such as high-grade disease, comedonecrosis, or age <60 years, are particularly at risk of local recurrence and might benefit from PMRT. We do, nonetheless, realize the limitations of a single-institutional, retrospective study and believe additional research is necessary to confirm our findings.

REFERENCES

1. Burnstein HJ, *et al.* Medical progress: Ductal carcinoma in situ of breast. *N Engl J Med* 2004;350:1430–1441.
2. Silverstein MJ, *et al.* Ten-year results comparing mastectomy to excision and radiation therapy for ductal carcinoma in situ of the breast. *Eur J Cancer* 1995;31A:1425–1427.
3. Silverstein MJ. The University of Southern California/Van Nuys prognostic index for ductal carcinoma in situ of the breast. *Am J Surg* 2003;186:337–343.
4. Vargas C, *et al.* Factors associated with local recurrence and cause-specific survival in patients with ductal carcinoma in situ of the breast treated with breast-conserving therapy or mastectomy. *Int J Radiat Oncol Biol Phys* 2005;63:1514–1521.
5. Silverstein MJ, *et al.* The influence of margin width on local control of ductal carcinoma in situ of the breast. *N Engl J Med* 1999;340:1455–1461.
6. Solin LJ, *et al.* Mammographically detected ductal carcinoma in situ of the breast treated with breast-conserving surgery and definitive breast irradiation: Long-term outcome and prognostic significance of patient age and margin status. *J Radiat Oncol Biol Phys* 2001;50:991–1002.
7. MacDonald HR, Silverstein MJ, *et al.* Local control in ductal carcinoma in situ treated by excision alone: Incremental benefit of larger margins. *Am J Surg* 2005;190:521–525.
8. Fisher ER, *et al.* Conservative management of intraductal carcinoma (DCIS) of the breast. *J Surg Oncol* 1991;47:139–147.
9. Boyages J, *et al.* Predictors of local recurrence after treatment of ductal carcinoma in situ: A meta-analysis. *Cancer* 1999;85:616–628.
10. Metz J, *et al.* Long-term outcome after postmastectomy radiation therapy for the treatment of ductal carcinoma in situ of the breast. *Am J Clin Oncol* 1999;22:215–217.
11. Schouten van der Velden AP. Local recurrences after different treatment strategies for ductal carcinoma in situ of the breast: A population-based study in the East Netherlands. *Int J of Radiat Oncol Biol Phys* 2007;69:703–710.
12. Julien JP, *et al.* Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: First results of the EORTC randomized phase III trial 10853. *J Clin Oncol* 2001;19:2263–2271.
13. Fisher ER, *et al.* Pathological findings from the National Surgical Adjuvant Breast Project (NSABP) eight-year update of protocol B-17: Intraductal carcinoma. *Cancer* 1999;86:429–438.
14. Carlson GW, *et al.* Local recurrence of ductal carcinoma in situ after skin-sparing mastectomy. *J Am Coll Surg* 2007;204:1074–1080.
15. Kim JH, *et al.* Chest wall relapse after mastectomy for ductal carcinoma in situ: A report of 10 cases with a review of the literature. *Cancer J* 2006;12:92–101.
16. De Jong E, *et al.* Recurrence after breast ablation for ductal carcinoma in situ. *Eur J Surg Oncol* 1992;12:64–66.
17. Helvie MA, *et al.* Mammographic appearance of recurrent breast carcinoma in six patients with TRAM flap breast reconstruction. *Radiology* 1998;209:711–715.