

THE INFLUENCE OF MARGIN WIDTH ON LOCAL CONTROL OF DUCTAL CARCINOMA IN SITU OF THE BREAST

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ABSTRACT

Background Ductal carcinoma in situ is a non-invasive carcinoma that is unlikely to recur if completely excised. Margin width, the distance between the boundary of the lesion and the edge of the excised specimen, may be an important determinant of local recurrence.

Methods Margin widths, determined by direct measurement or ocular micrometry, and standardized evaluation of the tumor for nuclear grade, comedonecrosis, and size were performed on 469 specimens of ductal carcinoma in situ from patients who had been treated with breast-conserving surgery with or without postoperative radiation therapy, according to the choice of the patient or her physician. We analyzed the results in relation to margin width and whether the patient received postoperative radiation therapy.

Results The mean (\pm SE) estimated probability of recurrence at eight years was 0.04 ± 0.02 among 133 patients whose excised lesions had margin widths of 10 mm or more in every direction. Among these patients there was no benefit from postoperative radiation therapy. There was also no statistically significant benefit from postoperative radiation therapy among patients with margin widths of 1 to <10 mm. In contrast, there was a statistically significant benefit from radiation among patients in whom margin widths were less than 1 mm.

Conclusions Postoperative radiation therapy did not lower the recurrence rate among patients with ductal carcinoma in situ that was excised with margins of 10 mm or more. Patients in whom the margin width is less than 1 mm can benefit from postoperative radiation therapy. (N Engl J Med 1999;340:1455-61.)

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THE use of postoperative radiation therapy in patients with ductal carcinoma in situ of the breast is controversial. The National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-17, a prospective, randomized trial, showed that the actuarial local-recurrence rate of ductal carcinoma in situ at eight years is 12 percent among patients treated with excision plus radiation therapy and 27 percent among patients treated with excision alone.¹ In 1993, these data led the NSABP to recommend postoperative irradiation of the breast for all patients with ductal carcinoma in situ who receive conservative surgical treatment.²

This recommendation was questioned because the initial NSABP study lacked subgroup analyses, making it impossible to identify subgroups of patients who did not benefit from radiation therapy.^{3,4} Work by numerous groups,⁵⁻¹⁶ including the NSABP investigators,^{1,17} indicated that pathological evaluation of the excised tumor for nuclear grade, comedonecrosis, size, and margin width is important in predicting recurrence and in identifying which patients are likely to benefit from postoperative radiation therapy. Preventing local recurrence is important because about one half of such recurrences are invasive cancers with the potential to metastasize.

A quantitative algorithm based on three factors (tumor size, margin width, and histologic classification) was developed as a prognostic index to aid decision making about the treatment of ductal carcinoma in situ.¹⁸ However, the reproducibility of accurate measurements of tumor size by three-dimensional reconstruction has been questioned.¹⁹ The reproducibility of histologic classification may also be difficult,²⁰ although in recent studies with defined criteria there was a high degree of concordance between observers.²¹⁻²⁴

We investigated whether the margin width of tumors that are stratified according to nuclear grade, the presence or absence of comedonecrosis, and size could predict the likelihood of local recurrence in patients who did or did not receive postoperative radiation therapy. We aimed to identify a subgroup of patients with such a low risk of local recurrence that postoperative radiation therapy is not needed.

METHODS**Patients**

We studied 469 patients with ductal carcinoma in situ: 390 were treated with breast-conserving therapy at the Breast Center in Van Nuys, California, from September 1979 through February 1998, and 79 patients were treated at Children's Hospital, San Francisco, from November 1972 through October 1987. All patients with ductal carcinoma in situ were included. Treatment was not randomized, and the study was retrospective. The Children's

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TABLE 1. ASSOCIATION OF RECURRENCE AND MARGIN WIDTH IN PATIENTS WITH DUCTAL CARCINOMA IN SITU.*

MARGIN WIDTH (mm)	NO RADIATION THERAPY			RADIATION THERAPY			RELATIVE RISK (95% CI)†	P VALUE‡
	NO. OF PATIENTS	NO. WITH LOCAL RECURRENCE	PROBABILITY OF RECURRENCE WITHIN 8 YR	NO. OF PATIENTS	NO. WITH LOCAL RECURRENCE	PROBABILITY OF RECURRENCE WITHIN 8 YR		
≥10	93	2	0.03±0.02	40	1	0.04±0.04	1.14 (0.10–12.64)	0.92
1 to <10	124	23	0.20±0.04	100	15	0.12±0.04	1.49 (0.76–2.90)	0.24
<1	39	13	0.58±0.13	73	21	0.30±0.06	2.54 (1.25–5.18)	0.01

*Plus-minus values are means ±SE.

†Values shown are the relative risks of recurrence in the group that did not receive radiation as compared with the group that did. CI denotes confidence interval.

‡P values were calculated with the likelihood-ratio test of the Cox proportional-hazards model.

Hospital series^{7,15} was a pilot series to evaluate excision alone for a small group of patients who met a set of strict criteria: the lesion was not palpable, was detected by mammography, and was 25 mm or less in diameter; all margins were at least 1 mm wide; and microcalcifications were absent on postoperative mammography. The Van Nuys series^{5,18} did not have a set of rigid criteria, and the patient's preference was important in selecting treatment. In general, patients who had lesions of 40 mm or less and final margins at least 1 mm in width were treated with breast preservation; patients with larger lesions or with persistently positive margins after repeated excision were generally treated with mastectomy, usually followed immediately by reconstruction. These guidelines were not absolute: some patients who could have been treated with breast preservation elected mastectomy, and vice versa.

Until 1989, radiation therapy was routinely added to the treatment of most patients after breast-conserving surgery; thereafter, most of these patients were treated with excision alone. External-beam irradiation of the whole breast (dose, 40 to 50 Gy) was performed with a 4- or 6-MeV linear accelerator, and a boost of 16 to 20 Gy was delivered to the tumor bed by iridium-192 implant or external beam.

Every effort was made to excise all the suspect lesions completely and to examine microscopically all the excised tissue. Localization by needle, intraoperative radiography of the specimen, and correlation with the preoperative mammogram were performed in every case involving a nonpalpable tumor. Margins were marked with ink or dye, and the specimens were serially sectioned at 2-to-3-mm intervals.

Pathological Evaluation

Tissue sections were arranged and prepared for evaluation in sequence. Pathological evaluation included determination of the histologic subtype, the nuclear grade, the presence or absence of comedonecrosis, the maximal diameter of the lesion, and the margin width. The size of small lesions was determined by direct measurement or by ocular micrometry of specimens stained on slides. The size of large lesions was determined by a combination of direct measurement and estimation according to three-dimensional reconstruction with a sequential series of slides. For example, a lesion that measured 5 mm on a single slide but that extended across 10 sequential sections was estimated to be 25 mm in size, since the average size of each block was 2.5 mm. Tumors were divided into two groups according to size: small (diameter, ≤10 mm) and large (>10 mm). Size was also analyzed as a continuous variable.

Margin width was determined by direct measurement or ocular

micrometry. The smallest single distance between the edge of the tumor and an inked line delineating the margin of normal tissue was reported. Tumors were divided into three groups according to margin width: close or involved (width, <1 mm), intermediate (1 to <10 mm), and wide (≥10 mm). Margins in patients who underwent repeated excision and in whom no additional ductal carcinoma in situ was found were reported as being at least 10 mm in width.

Tumors were divided into three groups according to nuclear grade, as follows: grade 1, low; 2, intermediate; and 3, high. Our grading method has been described previously.¹¹

Comedonecrosis was considered present if there was any architectural pattern of ductal carcinoma in situ in which a central zone of necrotic debris with karyorrhexis was identified, no matter how limited. Tumors were divided into two groups according to the presence or absence of comedonecrosis.

Statistical Analysis

The outcome measure we used was time to local recurrence, calculated as the time from tumor excision to the date of local recurrence. Seventy-five ipsilateral breast-cancer lesions were detected after initial treatment; 69 of them (92 percent) were at or near the site of the original lesion. Since it was impossible to determine which lesions were true local recurrences and which were new cancers, all 75 were scored as local recurrences. Data from patients who did not have a local recurrence were censored at the date of last follow-up. Five patients died of metastatic breast cancer after local invasive recurrence; 31 patients died from causes not related to breast cancer.

Kaplan-Meier plots²⁵ were used to estimate the probability of remaining free of local recurrence at eight years; standard errors were calculated with Greenwood's formula.²⁶ The Cox proportional-hazards model²⁶ was used to evaluate the association of radiation, margin width, comedonecrosis, tumor size, and nuclear grade (each alone and then jointly) with time to local recurrence. The likelihood-ratio test based on the Cox model was used to calculate two-sided P values; standard errors, calculated from Cox models, were used to construct confidence intervals. Plots of the log-transformed Kaplan-Meier estimates were used to assess visually the assumption of proportional hazards. Within the strata formed by the three margin-width groups, the assumption of proportional hazards was not unreasonable.

The relative risk based on the Cox model was defined as the ratio of the hazard of recurrence among patients who did not receive radiation divided by the hazard of recurrence among the patients who did receive radiation.

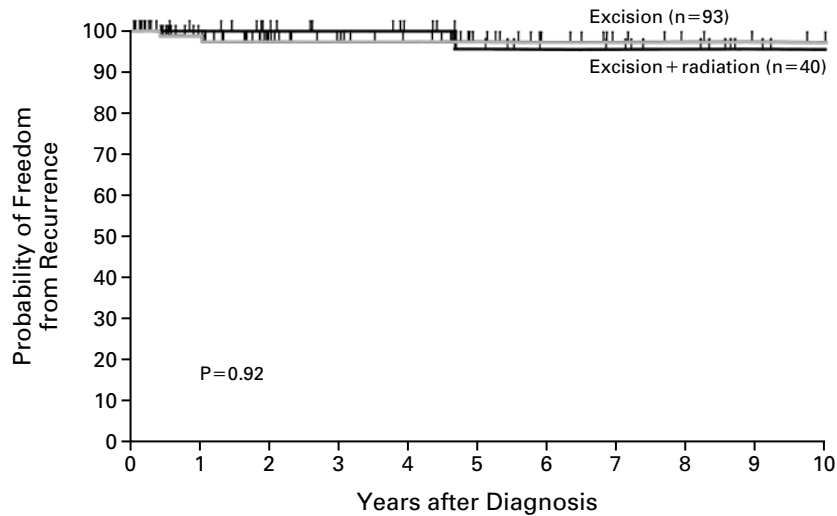


Figure 1. Recurrences in 133 Patients with Ductal Carcinoma in Situ and Excision Margins at Least 10 mm Wide.

Data were analyzed according to treatment. There was no benefit from the addition of radiation therapy after excision ($P=0.92$ by the log-rank test). The tick marks indicate patients whose data were censored.

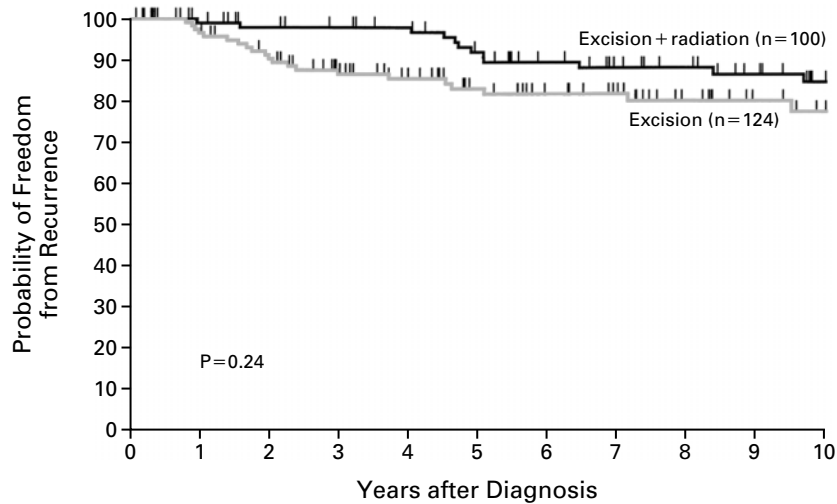


Figure 2. Recurrences in 224 Patients with Ductal Carcinoma in Situ and Excision Margins 1 to <10 mm Wide.

Data were analyzed according to treatment. The benefit from the addition of radiation therapy was not statistically significant ($P=0.24$ by the log-rank test). The tick marks indicate patients whose data were censored.

RESULTS

Of the 469 patients who were treated with local excision, 213 also received postoperative radiation therapy. There were 75 local recurrences: 38 in patients who underwent only excision (16 with invasive carcinoma and 22 with ductal carcinoma in situ) and 37 in patients treated with excision plus postoperative radiation therapy (19 with invasive carcinoma

and 18 with ductal carcinoma in situ). The mean follow-up was 81 months for all patients, 92 months for patients who received radiation therapy, and 72 months for patients treated with excision only.

Table 1 shows the probability of local recurrence when lesions were stratified according to treatment and margin width. Figures 1, 2, and 3 show these data graphically. Only 3 of the 133 patients with mar-

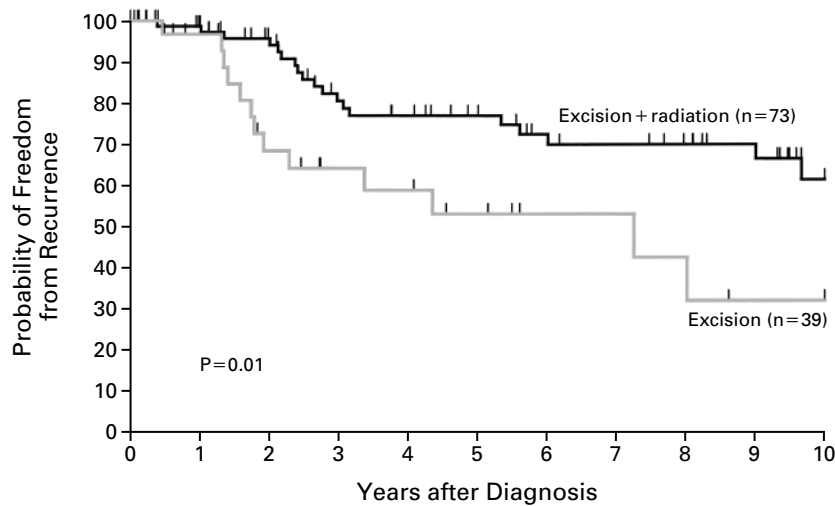


Figure 3. Recurrences in 112 Patients with Ductal Carcinoma in Situ and Excision Margins Less Than 1 mm Wide.

Data were analyzed according to treatment. The benefit from the addition of radiation therapy was significant ($P=0.01$ by the log-rank test). The tick marks indicate patients whose data were censored.

gins 10 mm wide or wider had a local recurrence, and there was no reduction in the probability of local recurrence with the addition of postoperative radiation therapy. Among patients with margins of 1 to <10 mm who did not receive radiation therapy as compared with those who did receive radiation therapy, the relative risk of local recurrence was 1.49. This value was not significant ($P=0.24$). In contrast, among patients with margins less than 1 mm wide who did not receive radiation, as compared with those who did, the relative risk of recurrence was 2.54 ($P=0.01$).

TABLE 2. BASE-LINE CHARACTERISTICS OF THE LESIONS ACCORDING TO TREATMENT GROUP AND MARGIN WIDTH.

MARGIN WIDTH	NO RADIATION THERAPY	RADIATION THERAPY	P VALUE
≥10 mm (n=133)	93	40	
Median size of tumor (mm)	9	12.5	0.04
Mean nuclear grade	2.24	2.08	0.29
Nuclear grade 3 (% of patients)	46	35	0.23
Comedonecrosis (% of patients)	23	28	0.30
1 to <10 mm (n=224)	124	100	
Median size of tumor (mm)	8	14.5	<0.001
Mean nuclear grade	1.98	2.15	0.10
Nuclear grade 3 (% of patients)	32	32	0.96
Comedonecrosis (% of patients)	48	67	0.004
<1 mm (n=112)	39	73	
Median size of tumor (mm)	19	18	0.10
Mean nuclear grade	2.62	2.38	0.07
Nuclear grade 3 (% of patients)	67	48	0.06
Comedonecrosis (% of patients)	74	79	0.53

Since whether to treat with radiation therapy was decided by the physician and patient rather than as part of a randomized trial, the data were further examined to see whether the benefit of radiation therapy in patients with margins narrower than 1 mm and the lack of benefit in patients with margins of 10 mm or more could be explained by an imbalance in prognostic factors. Table 2 summarizes base-line pathological characteristics according to treatment group and margin width. Among patients with margins of 10 mm or more, there were no statistically significant differences between the two treatment groups in nuclear grade or the presence or absence of comedonecrosis, but the patients who received radiation therapy tended to have larger tumors. Among patients with margins of 1 to <10 mm who received radiation therapy, tumors tended to be larger and were more likely to have comedonecrosis than those of patients treated only with excision. Among patients with margins narrower than 1 mm, there were no significant differences in base-line variables between the two treatment groups.

Table 3 shows the relative risks of recurrence after stratification according to tumor size, nuclear grade, and the presence or absence of comedonecrosis. In all cases, the relative risks did not change substantially after these adjustments. Regardless of the pathological findings, the probability of local recurrence was low if the margins were wide, and the incidence of local recurrence was not reduced by the addition of radiation therapy. With margins of 1 to <10 mm, the difference between excision only and excision plus radiation was not significant. With margins narrower than 1 mm, there was a significant decrease in

TABLE 3. ASSOCIATION OF RADIATION THERAPY WITH RECURRENCE AFTER STRATIFICATION ACCORDING TO THE PRESENCE OR ABSENCE OF COMEDONECROSIS, NUCLEAR GRADE, AND TUMOR SIZE.

MARGIN WIDTH (mm)	UNADJUSTED ANALYSIS		VARIABLE	ADJUSTED ANALYSIS	
	RELATIVE RISK (95% CI)*	P VALUE†		RELATIVE RISK (95% CI)*	P VALUE‡
≥10	1.14 (0.10–12.64)	0.92	Comedonecrosis	1.22 (0.11–13.93)	0.87
			Nuclear grade	1.08 (0.09–12.70)	0.95
			Size	1.69 (0.15–18.79)	0.66
1 to <10	1.49 (0.76–2.90)	0.24	Comedonecrosis	1.84 (0.93–3.61)	0.08
			Nuclear grade	1.75 (0.87–3.56)	0.11
			Size	1.87 (0.93–3.78)	0.08
<1	2.54 (1.25–5.18)	0.01	Comedonecrosis	2.56 (1.25–5.26)	0.01
			Nuclear grade	2.30 (1.12–4.76)	0.03
			Size	2.52 (1.23–5.14)	0.02

*Values shown are the relative risks of recurrence in the group that did not receive radiation therapy as compared with the group that did. CI denotes confidence interval.

†P values for the unadjusted analysis were calculated with the likelihood-ratio test of the Cox proportional-hazards model.

‡P values for the adjusted analysis were calculated with the likelihood-ratio test of the Cox proportional-hazards model with stratification according to necrosis (present or absent), nuclear grade (1, 2, or 3), and tumor size (≤10 mm or >10 mm).

the probability of local recurrence when radiation therapy was added.

DISCUSSION

There are three major approaches to the treatment of ductal carcinoma in situ: mastectomy, excision with radiation therapy, and excision alone. After mastectomy, there is little risk of local recurrence (either of invasive cancer or of ductal carcinoma in situ).^{5,27-30} Breast preservation, with or without radiation therapy, yields a better cosmetic result and the breast remains sensate, but there is an increased probability of local failure.^{5-11,31-34} Approximately one half of all local recurrences are invasive and therefore a threat to life.^{14,15,31,35}

The results of NSABP protocol B-17 showed a significant decrease in the rate of local recurrence, particularly invasive local recurrence, among patients treated with excision followed by postoperative radiation.¹⁻³ More than 800 patients with ductal carcinoma in situ in whom the tumor was excised with clear surgical margins (defined as no tumor at the line of resection) were randomly assigned to either excision only or excision plus radiation therapy. After five to eight years of follow-up,^{1,2} there was a significant decrease in the rates of local recurrence of ductal carcinoma in situ and invasive breast cancer among patients treated with radiation therapy. This result led the NSABP to recommend postoperative radiation therapy for all patients with ductal carcinoma in situ who choose breast-conserving surgery.

The NSABP protocol did not require the marking of margins, complete tissue processing, radiography

of tissue specimens, or measurement of margin width. In the initial NSABP report, more than 40 percent of the tumors were not measured.² For these reasons, the NSABP study was unable to identify subgroups of patients who might not need radiation therapy. In other series, patients who are not likely to benefit from radiation therapy have been identified, such as those with small, well-excised, non-comedo lesions¹⁰ or well-differentiated lesions.¹⁴ These subgroups may account for more than 30 percent of all patients with ductal carcinoma in situ.^{10,12,14-16}

The data presented here suggest that margin width is an excellent predictor of local recurrence and the likelihood of residual ductal carcinoma in situ. If our results are confirmed, margin width might be used as the sole determinant of the need for postoperative radiation therapy. However, the evaluation of margin widths requires complete tissue processing, without which involved margins and invasive foci may go unrecognized. Standardized and reproducible methods of margin evaluation must be developed and prospectively tested.

Since most local recurrences are at or near the primary lesion and therefore probably result from an inadequate initial excision, completely excised lesions should require no additional treatment, such as radiation. Some evidence suggests that complete excision is possible. Ductal carcinoma in situ is almost always unicentric (involving a single ductal unit) but is commonly multifocal (with multiple foci of disease in a single ductal unit).³⁶⁻³⁸ Holland et al.³⁷ showed that 118 of 119 patients with ductal carcinoma in situ had lesions that were confined to a single segment of the

breast. The lesions were often larger than expected and extended beyond mammographically identified microcalcifications, and skipped areas (segments of disease-free, normal-appearing epithelium) were common. Although the lesions are often large, ductal carcinoma in situ is a local disease lacking two important components of the fully expressed, malignant phenotype: stromal invasion and distant metastasis. This characteristic and the almost always unicentric distribution of the disease make complete excision, and therefore surgical cure, theoretically possible.

Our data reveal a significant benefit when radiation therapy is given to patients with margins narrower than 1 mm. The rate of local recurrence at eight years is cut nearly in half, from 58 to 30 percent, but this reduction is insufficient. In many patients with margins this narrow, radiation therapy, though highly effective, simply cannot compensate for inadequate surgery. By contrast, with margin widths of at least 10 mm, there is little likelihood of residual ductal carcinoma in situ.³⁵⁻³⁷

The preliminary results of NSABP protocol B-24 were released recently.³⁹ In this trial, more than 1800 patients with ductal carcinoma in situ were randomly assigned to treatment with excision plus radiation therapy and either tamoxifen or placebo. At five years, the local-recurrence rate was 6.4 percent for the tamoxifen group and 8.6 percent for the placebo group. Our patients with margin widths of 10 mm or more who underwent only excision had a similarly low rate of local recurrence (3 ± 2 percent at eight years) without either radiation therapy or tamoxifen. This result suggests that in patients with wide, clear margins (≥ 10 mm, as measured with complete and sequential tissue processing), additional therapy is unlikely to be of benefit.

Radiation therapy markedly improved the outcome of patients with close or involved margins (< 1 mm) and, to a lesser (but not statistically significant) degree, the outcome of patients with margins of intermediate size (1 to < 10 mm). These data were collected carefully and prospectively; their weakness is that they are not the results of a randomized clinical trial. Our findings need to be confirmed by a study that uses thorough mammographic correlation and standardized pathological assessment, as described here.

In summary, our data suggest that excellent local control can be achieved without radiation therapy when margin widths of at least 10 mm are obtained, regardless of nuclear grade, the presence or absence of comedonecrosis, or tumor size.

Supported by a grant (5 P30 CA14089) from the National Cancer Institute.

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