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CLINICAL INVESTIGATION **Breast**

PREDICTORS OF REEXCISION FINDINGS AND RECURRENCE AFTER BREAST CONSERVATION

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Purpose: To identify predictors of reexcision findings and local recurrence in the setting of breast-conserving therapy with radiation.
Methods: The records of 535 patients who underwent breast-conserving surgery followed by radiation for Stage I or II cancer between 1972 and 1996 were reviewed. The mean follow-up period for surviving patients without evidence of recurrence is 6 years. Various clinical and pathologic prognostic factors were examined for significance with regard to reexcision findings and recurrence rates. Pathologic margin status was classified as negative, close (≤2 mm), positive, or indeterminate.
Results: The pathologic margin status was the most important predictor of local recurrence. The freedom from local relapse (FFLR) at 6 years was 97% for patients with negative pathologic margins and 86% for all others ($p < 0.0001$). There was no significant difference in recurrence rates among patients with close, positive, or indeterminate margins. However, the use and sequencing of systemic therapy affected recurrence rates among these patients. For patients with close, positive, or indeterminate margins, the crude risk of local recurrence was 4% among patients who received tamoxifen or received chemotherapy integrated with or after radiation. The risk of local recurrence was 16–29% among the patients with close, positive, or indeterminate margins who did not receive systemic therapy or who received radiation after completion of chemotherapy. Local recurrence rates were low in patients with negative margins (2–8%) regardless of the use of systemic therapy or its timing. The presence or absence of residual disease at reexcision did not predict recurrence as long as the final margins were negative. Among patients who underwent reexcision before radiation, extensive intraductal component (EIC) ($p = 0.0001$) and young patient age ($p = 0.03$) were predictive of residual disease in the specimen. Patients with initially close margins and no EIC had a low risk of residual disease at the time of reexcision, as did patients older than age 65 without EIC.
Conclusion: Pathologic margin status is the most important predictor of local recurrence after breast conservation with radiation. Patient age and EIC were significant predictors of residual disease at reexcision. The use and timing of systemic therapy appear to influence the risk of local recurrence in patients who do not have negative lumpectomy margins. © 2003 Elsevier Inc.

Breast, Radiotherapy, Margins.

INTRODUCTION

Several randomized trials have established the efficacy of breast-conserving surgery followed by radiation for Stage I and II breast cancer (1). However, outcome predictors for patients treated with breast conservation are important in defining optimal patient selection and surgical management. Various clinical and pathologic criteria have been proposed to have prognostic import for local recurrence, including patient age (5) margin status (6), extensive intraductal component (EIC) (10, 11), and lymphovascular invasion (3). The impact of systemic therapy (12, 13) and radiation dose (14, 15) has also been described.

In earlier work, we found margin status to be the most important predictor of local recurrence after breast conservation (16). However, many patients in that series had indeterminate margin status because of prevailing pathologic and surgical practices. This review updates results for previously reported patients and includes a larger number of patients with defined margin status using uniform criteria. The predictors of findings at reexcision are also examined.

METHODS AND MATERIALS

The records of 535 patients treated with breast-conserving radiotherapy (RT) at Stanford University or the Wash-

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Table 1. Characteristics of the 535 patients

Age	
<50	197
≥50	338
Pathologic T stage	
T1	399
T2	108
Pathologic N stage	
N0	350
N1	117
NX	13
Reexcision	
Yes	262
No residual	168
Residual	91
No	273
Final margin status	
Negative	342
Indeterminate	110
Close	55
Positive	28
Extensive intraductal component	
Present	60
Absent	308
Not available	166
Estrogen receptor status	
Positive	227
Negative	89
Not available	219
Total radiation dose	
<60 Gy	232
≥60 Gy	303
Systemic therapy	
None	242
Chemotherapy	142
Tamoxifen	140

ington-Stanford Radiation Oncology Center between 1972 and 1996 for Stage I or II breast cancer were reviewed with Institutional Review Board approval. Clinical and pathologic data were recorded as previously described (16). Margin status was classified on the initial and reexcision specimens as positive when invasive or *in situ* disease was seen at an inked surgical margin, close when tumor cells were ≤2 mm from the ink, negative if tumor was >2 mm from the inked margin, or indeterminate when the specimen was removed in pieces without orientation or not inked. Pathologic specimens were routinely reviewed at Stanford before treatment. All available pathologic material until 1992 on patients with close, positive, or indeterminate margins (non-negative margins) was re-reviewed by a single pathologist (K.N.) for margin status and other histologic features, such as EIC, lymphovascular invasion (LVI), grade, and histologic type (approximately 146 cases). Uniform criteria were subsequently established, and data were abstracted directly from the pathology reports for patients treated between 1993 and 1996. The mean follow-up for surviving patients without local or distant recurrence is 6 years (median 5 years). The mean follow-up for the patients with non-negative margins is 7.5 years. Characteristics of the patients are given in Table 1.

Radiation treatment policies varied over the years of the study. Most commonly, patients received 50.40 Gy prescribed to the isocenter in 1.8-Gy fractions followed by a 10-Gy electron boost to the tumor bed using ultrasound guidance. In earlier years, patients received Ir 192 implant boosts (107 patients), reduced photon fields (14 patients), or no boost (189 patients). Fourteen percent of patients with non-negative margins did not receive a boost, as compared with 47% of patients with negative margins. Adjuvant systemic therapy recommendations also changed over the years of the study. One hundred forty-two patients received systemic chemotherapy; approximately 30% of patients during the early (pre-1985) and later (1986–1996) years of the study received chemotherapy. Most commonly, patients received cyclophosphamide, methotrexate, and fluorouracil concurrent with radiation (112 patients). Thirty patients received chemotherapy before (19) or after RT (11); 27 patients received anthracycline-based chemotherapy. One hundred forty patients received tamoxifen; the use of adjuvant tamoxifen increased from 8% to 46% of all patients from the earlier (pre-1985) to the later (1986–1996) years of the study. Two hundred forty-two patients received no systemic therapy.

The actuarial probability of freedom from local recurrence as a first failure was calculated using the Kaplan-Meier method. Analysis of potential prognostic factors was performed using Cox regression analysis (SPSS, Inc., Chicago, IL). Factors were included in the forward conditional Cox multivariate analysis if the univariate p value was ≤.05. For variables found to have independent prognostic value ($p < 0.05$) by multivariate analysis, the hazard ratio (HR) with the 95% confidence interval (CI) was calculated. Association between patient characteristics was determined with the chi-square test, and significance of correlations was assessed with Pearson's coefficient. Factors included in the regression analysis for local recurrence were: patient age (<50, ≥50 years), pathologic tumor size, pathologic nodal status (N0/N1), EIC (present/absent), estrogen receptor status (positive/negative), reexcision findings (residual disease/no residual), margin status (negative/non-negative), use of systemic adjuvant therapy (yes/no), and total radiation dose (<60 Gy, ≥60 Gy). For the patients who underwent reexcision, variables in the analysis for the finding of residual tumor included: patient age, tumor size, nodal status, EIC, estrogen receptor status, and LVI.

RESULTS

Local recurrence

For the entire group of patients, the actuarial freedom from local recurrence (FFLR) at 6 years for patients with negative margins was 97% vs. 86% for close, positive, or indeterminate (non-negative) margins ($p < 0.0001$, Fig. 1). Excluding patients with indeterminate margin status, the FFLR was 97% vs. 87%, respectively. There was no significant difference in local recurrence rates among non-negative margins by type (Table 2). The actuarial FFLR for

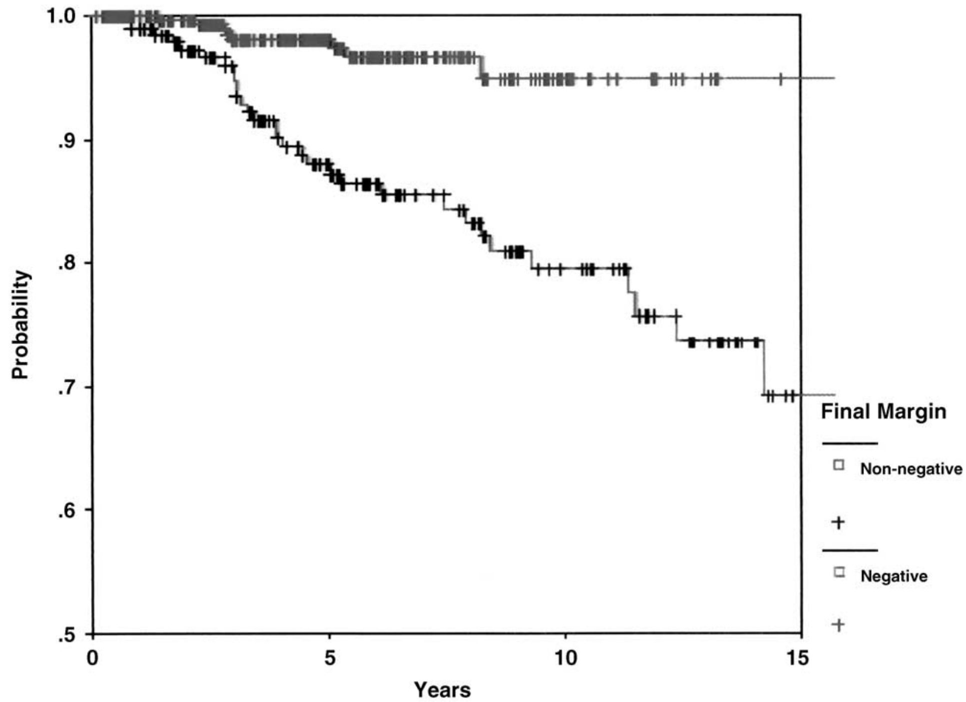

Fig. 1. Freedom from local recurrence by margin status ($p < 0.0001$).

close margins was 78%, for indeterminate margins was 85%, and for positive margins was 83%. However, because our general policy included reexcision for positive margins, only 28 patients were in the positive margin category. Aside from margin status, a borderline predictor of recurrence in the multivariate analysis was total radiation dose ($p = 0.08$), favoring doses ≥60 Gy (Table 3). Among patients who underwent reexcision, the presence or absence of residual disease in the specimen was not a predictor of outcome, as long as final margins were negative (Fig. 2).

Regression analysis for the patients with non-negative margins did not identify other prognostic factors for local recurrence. However, the use and timing of systemic therapy appeared to influence recurrence rates in these patients ($p = 0.033$, Table 4, Fig. 3). The crude risk of local recurrence was 4% for patients who received chemotherapy concurrent with RT, received chemotherapy after RT, or received tamoxifen. The crude risk of local recurrence was 16% for patients who did not receive systemic therapy and 29% for those who received RT after completion of chemotherapy. In contrast, for patients with negative margins, the risk of local recurrence was between 0% and 10%, regardless of the use or timing of systemic treatment.

Table 2. Local recurrence rates by final margin status (6-year actuarial)

Margin	Patients (no.)	Recurrence (%) 6-year actuarial	Recurrence (%) crude
Negative	342	3	3
Close	55	22	13
Positive	28	17	18
Indeterminate	110	15	17

Reexcision findings

For patients who underwent reexcision, predictors of finding residual disease in the specimen were presence of EIC ($p = 0.0001$) and patient age ($p = 0.03$). The absolute probability of finding residual tumor at the time of reexcision relative to age, EIC, and initial margin status is shown in Tables 5 and 6. Patients with initial close margins and without EIC had a low likelihood (11%) of finding residual carcinoma at reexcision, as did patients older than age 65 without EIC (10%). All other groups of patients with non-negative margins had a significant (≥32%) likelihood of finding residual disease at reexcision.

DISCUSSION

Breast-conserving surgery with radiation is an established treatment for early-stage breast cancer. The final pathologic margin status of the lumpectomy specimen is the most important factor determining local recurrence rates in the majority of reports. Although a “negative” inked surgical margin is advised, variation exists in general surgical practice and among cooperative group studies in terms of what is considered an acceptable margin in the setting of breast conservation.

Few studies have reported results separately for patients with negative or close margins, and the definition of a close margin is not uniform among these reports (Tables 7 and 8). With the exception of the Park report,

Table 3. Univariate and multivariate analysis for local recurrence

Factor	Univariate p	Multivariate p	Hazard ratio	CI 95%
Age (older or younger than 50)	0.070			
T size	0.638			
Path N	0.808			
Final margin	<0.0001	<0.0001	9.771	2.818–33.877
Estrogen receptor status	0.731			
Extensive intraductal component	0.331			
Radiotherapy dose	0.012	0.079		
Systemic therapy	0.072			
Reexcision finding	0.016	0.819		

close margins (≤2 mm) appear to increase the relative risk for local recurrence. In several reports, the recurrence rates for close margins are similar to those reported for focally positive margins (Table 9). Our data also show an increased risk of local recurrence for patients with close margins. However, all of these reports contain a relatively limited number of patients with close margins and there is potential for significant variability in other factors, such as age, EIC, degree of closeness (focal/extensive), radiation dose, and systemic therapy details among these small groups of patients. For example, Wazer found that patients younger than 45 with close margins had the same risk of recurrence as patients with positive margins; however, older patients with close margins had the same recurrence rates as those with negative margins (8). Freedman reported that patients with close margins after initial excision had a 7% risk of local recurrence and a 21% risk if close margins were present after reexcision (9). Receipt of systemic therapy appeared to delay recurrence for close/positive margins. The Joint Center for Radiation Therapy in Boston found no local recurrences in patients with close margins who received RT before chemotherapy and a 23% recurrence rate in patients whose radiation was delayed by administration of systemic therapy (17). Although reexcision is sometimes inconvenient and may have negative cosmetic consequences, the risks of local recurrence must be carefully considered. Among patients with close margins, those who are young, have an EIC present, have already had reexcision, or are expected to have a significant delay in

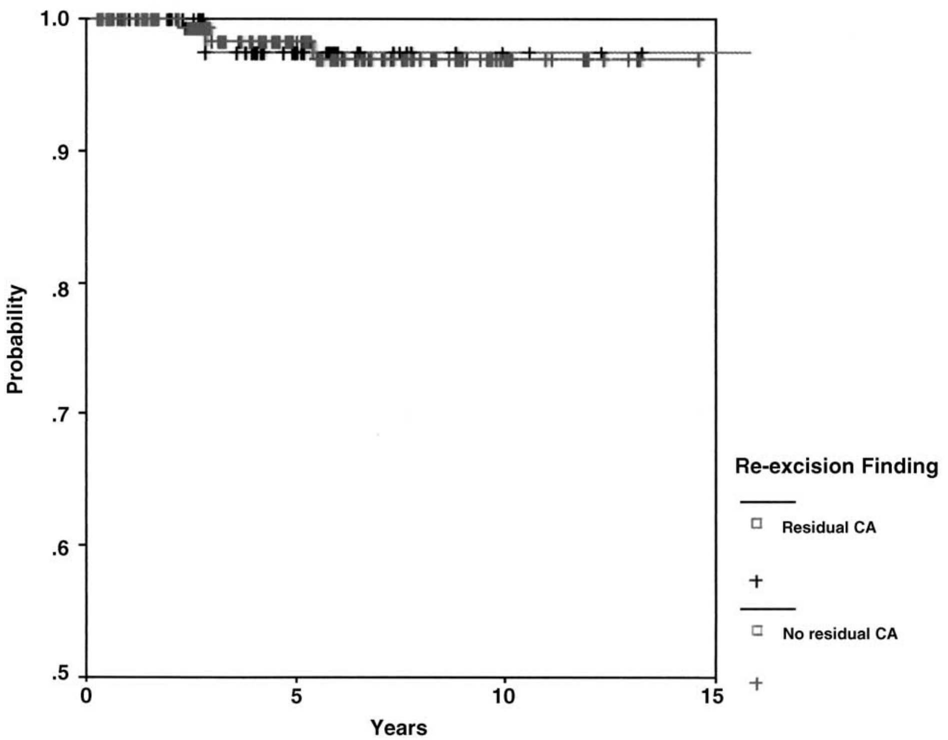

Fig. 2. Freedom from local recurrence for patients with negative margins by reexcision findings (residual vs. no residual carcinoma).

Table 4. Crude risk of local recurrence by margin status, systemic therapy, and radiotherapy timing

	Early RT	Late RT (after chemotherapy)
Close, positive, indeterminate margins		
Chemotherapy	2/48 (4%)	2/7 (29%)
Tamoxifen	1/28 (4%)	
No systemic therapy	17/109 (16%)	
Negative margins		
Chemotherapy	3/75 (4%)	1/12 (8%)
Tamoxifen	2/113 (2%)	
No systemic therapy	1/133 (2%)	

initiation of radiation, further surgical excision should be strongly considered.

In our series, we found that patients with close, positive, or indeterminate margins fared better when they received systemic therapy that did not entail a substantial delay in the timing of breast radiation. However, the number of patients in any specific subgroup of margin status and systemic therapy/timing is quite small. Also, the exact surgery-RT interval was not recorded. Nonetheless, this finding is consistent with the limited information available on the impact of systemic therapy and its timing on local recurrence in the breast. The Joint Center "upfront-outback" randomized trial of chemotherapy preceding or after RT for breast preservation found an increased risk of local failure in patients with close or unknown margins who received chemotherapy first (32%) as compared with RT first (4%) (18). That trial, as well as data from the International Breast Cancer Study Group trials, did not show any impact of chemotherapy timing on local recurrence for patients with negative margins (19). Both chemotherapy and tamoxifen reduced local recurrence in breast preservation patients in the NSABP B-13 and B-14 studies (12 13), as well as in the M.D. Anderson experience (20). Tamoxifen also appeared to reduce the local recurrence risk of patients with close, positive, or indeterminate margins in our study.

The role of prognostic factors other than margin status in local recurrence is less clear. Young patients (<40–45) have been reported to have an increased risk of recurrence independent of margin status. In our series, age did not have

Table 5. Probability of residual carcinoma at reexcision (%)

	Initial margins			
	Close	Focal +	Positive NOS	Extensive +
EIC				
Present	38	100	66	89
Absent	11	32	33	50

Abbreviations: NOS = not otherwise specified; Focal + = less than 3 low-power fields involved; EIC = extensive intraductal component.

Table 6. Probability of finding residual carcinoma at reexcision (%)

	Age		
	<50	50–65	>65
Extensive intraductal component			
Present	79	66	40
Absent	27	28	10

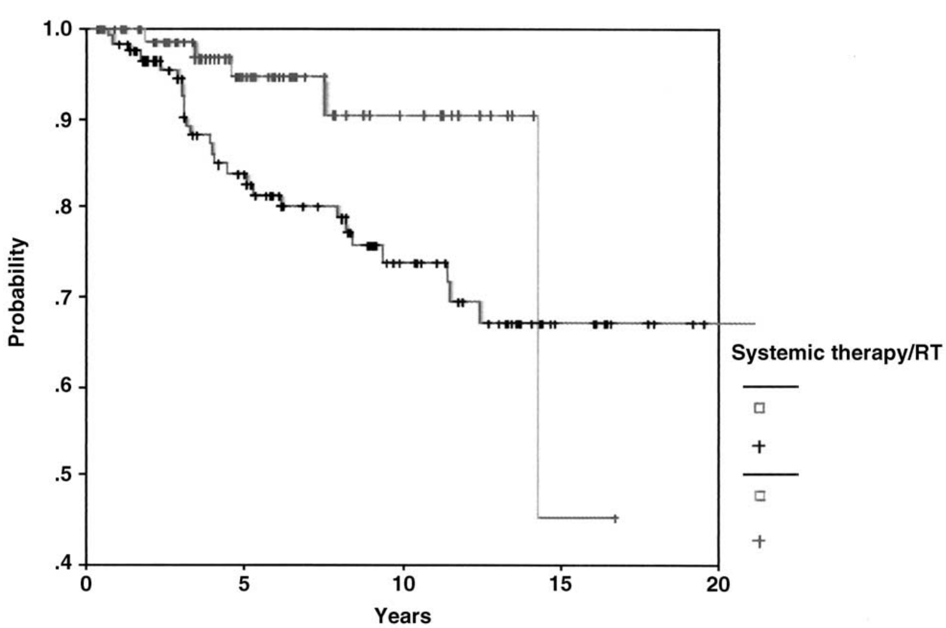

Fig. 3. Freedom from local recurrence for patients with close, positive, or indeterminate margins according to use of systemic therapy and radiotherapy (RT) timing (p = 0.033 for systemic therapy with early radiation vs. no systemic therapy or chemotherapy with delayed RT).

Table 7. Local recurrence rates for negative margins

Series	Patients (no.)	Definition	Follow-up years (method)	Local recurrence (%)
Park (6)	341	>1 mm	8 (C)	7
Park (6)	101	No residual	8 (C)	8
Petersen (7)	518	>2 mm	8 (A)	8
Wazer (8)	290	>2 mm	8 (A)	3
Freedman (9)	968	>2 mm	10 (CI)	7
Touboul (21)	417	>2 mm	5 (A)	6
Present	342	>2 mm	6 (A)	3

Abbreviations: A = actuarial; C = crude; CI = cumulative incidence.

Table 8. Local recurrence rates for close margins

Series	Patients (no.)	Definition	Follow-up years (method)	Local recurrence %
Park (6)	94	≤1 mm	8 (C)	7
Petersen (7)	96	≤2 mm	8 (A)	17
Freedman (9)	142	≤2 mm	10 (CI)	14
Wazer (8)	99	≤2 mm	6 (median)	RR 1.69
Present	55	≤2 mm	6 (A)	22

Abbreviations: A = actuarial; C = crude; CI = cumulative incidence; RR = relative risk.

an impact on local recurrence rates among patients with negative margins, and the absolute local recurrence rate among younger patients was clearly acceptable. This may reflect the relatively small number of younger patients in this series. However, it may also reflect the more strict criteria for negative margins (>2 mm) that we used. Most of the reports in which young age was prognostic did not distinguish close from negative margins. Some data indicate that young patients more often have closer margins of excision, as well as an increased incidence of EIC and LVI (24). Younger patients also benefit more from higher doses of tumor bed radiation (14), and attention to margin status may be of special importance for them. Young age was a predictor of finding residual carcinoma at the time of reexcision in this report.

Several limitations exist in the findings of this retrospective study. First, institutional criteria for and application of breast conservation undoubtedly varied over the 24 years of the study. In addition, wide variation in radiation and chemotherapy practices occurred over this time, and pathologic practices changed as well. Although we attempted to standardize the definition of various pathologic features, not all material was reviewed by a single pathologist. Because patients with non-negative margins were generally treated in the earlier time frame, the mean follow-up time for margin categories also differs; the reported 6 year follow-up interval represents the mean for the entire group. In addition, the small number of patients in various subgroups limits the number of analyses that can be performed with any expectation of

Table 9. Local recurrence rates for positive margins

			Local	Recurrence	(%)
Series	Patients (no.)	Follow-up	Focal +	Extensive +	All +
Park (6)	192	8 (C)	14	27	18
Petersen (7)	124	8 (A)	10		
Wazer (8)	105	6 (med)			RR 3.88
Freedman (9)	152	10 (CI)			12
Cowan (22)	152	5 (C)	14	31	20
DiBasie (23)	86	5 (A)	9	26	14

Note: the definition of focally positive margins varied in each of these reports. Definitions included a single positive margin, one or two positive margins, ≤3 low-power fields of involvement, involvement of a single shave margin.

Abbreviations: A = actuarial; C = crude; CI = cumulative incidence; med = median; RR = relative risk.

statistical significance. Ideally the findings, particularly regarding the timing of systemic therapy, would be reexamined by merging data with other large institutions, which would then permit further analyses to be performed.

In summary, close, positive, or indeterminate margin status conferred a substantially increased risk of local recurrence in this study. The use of systemic therapy and its timing appear to influence the risk of recurrence in these patients.

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