Prognosis After Ipsilateral Breast Tumor Recurrence and Locoregional Recurrences in Patients Treated by Breast-Conserving Therapy in Five National Surgical Adjuvant Breast and Bowel Project Protocols of Node-Negative Breast Cancer

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A B S T R A C T

Purpose

Locoregional failure (LRF) after breast-conserving therapy (BCT) is associated with increased risk of distant disease and death. The magnitude of this risk has not been adequately characterized in patients with lymph node-negative disease.

Patients and Methods

Our study population included 3,799 women randomly assigned to five National Surgical Adjuvant Breast and Bowel Project protocols of node-negative disease (ie, B-13, B-14, B-19, B-20, and B-23) who underwent lumpectomy and whole breast irradiation with or without adjuvant systemic therapy. Cumulative incidences of ipsilateral breast tumor recurrence (IBTR) and other locoregional recurrence (oLRR) were calculated, along with distant-disease-free interval (DDFI) and overall survival (OS) after these events. Cox models were employed to model mortality by using clinical and pathologic factors jointly with these events.

Results

Four hundred nineteen patients (11.0%) experienced LRF; 342 (9.0%) experienced IBTR, and 77 (2.0%) experienced oLRR. The 12-year cumulative incidences of IBTR and oLRR in patients treated with adjuvant systemic therapy were 6.6% and 1.8%, respectively. Overall, 37.1% of IBTRs and 72.7% of oLRRs occurred within 5 years of diagnosis. Older age, black race, higher body mass index (BMI), larger tumors, and occurrence of IBTR or oLRR were significantly associated with increased mortality. The 5-year OS after IBTR and oLRR were 76.6% and 34.9%, respectively. Adjusted hazard ratios for mortality associated with IBTR and oLRR were significantly higher in estrogen receptor (ER)-negative patients than in ER-positive patients ($P = .002$ and $P < .0001$, respectively). Patients with early LRF had worse OS and DDFI than those with later-occurring LRF.

Conclusion

Although LRF is uncommon in patients with node-negative breast cancer who are treated with lumpectomy, radiation, and adjuvant systemic therapy, those who do develop LRF have substantially worse OS and DDFI.

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INTRODUCTION

Locoregional failure (LRF) is associated with an elevated risk of developing distant disease and of death in patients treated either by mastectomy or lumpectomy.¹⁻⁹ The use of adjuvant breast radiation and systemic treatments influence the incidence of LRF; for example, a lower incidence of ipsilateral breast tumor recurrence (IBTR) was observed in National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-06 when both

treatment modalities were employed in patients with node-positive disease.¹⁰⁻¹² The incidence of LRF in patients with node-positive disease has remained remarkably constant in subsequent trials, as reflected in our analysis of patients who participated in five NSABP trials of node-positive disease, in which the 10-year cumulative incidences of IBTR and other locoregional recurrences (oLRR) were 8.7% and 6%, respectively.⁹

In protocol B-06, the relative hazard of distant disease after IBTR was 3.41 (95% CI, 2.70 to

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4.30); more recently, in a cohort of 2,669 lumpectomy-treated patients in five protocols of node-positive disease (ie, NSABP protocols B-15, B-16, B-18, B-22, and B-25), that relative hazard was 2.72 (95% CI, 2.23 to 3.33).^{1,9} In the latter report, we noted adjusted relative hazards for mortality of 2.58 (95% CI, 2.11 to 3.15) and 5.85 (95% CI, 4.80 to 7.13) associated with IBTR and oLRR, respectively.

Because the risk of developing metastatic disease in the absence of LRF is lower in patients with node-negative breast cancer than in those with node-positive breast cancer, there is a question of whether the biologic significance of LRF is different in the two populations. Moreover, because patients with node-negative disease have different initial therapies, the long-term outcomes of those who also experience LRF cannot be extrapolated from previous studies.^{1,9} In this report, we examine the cumulative incidences of IBTR and oLRR according to clinical and pathologic variables, and we assess their effects on the risk of distant disease and mortality in patients treated with breast-conserving therapy (BCT; ie, lumpectomy and radiation therapy) with or without adjuvant systemic therapy in five NSABP adjuvant trials of node-negative disease. We also examine how the timing of LRF influences prognosis.

PATIENTS AND METHODS

Study Population

Patients examined in this analysis were selected from those who were randomly assigned into NSABP protocols B-13, B-14, B-19, B-20, or B-23.¹³⁻²⁰ These studies were approved by institutional review committees; assurances were approved by the Department of Health and Human Services; and the studies are in accordance with the Helsinki Declaration. Informed consent was required for participation. B-13 and B-14 each had a registration arm; because there were differences in the follow-up times between randomly assigned and registered patients, only the randomly assigned patients were considered for these analyses. The study population for this report includes all patients randomly assigned to these five studies who met eligibility criteria, had follow-up information, and were treated by lumpectomy plus levels 1 to 2 axillary node dissection. Node-negative lymph node status, tumor-free lumpectomy margins, and the administration of postoperative radiotherapy that consisted of 50 Gy to the whole breast was required. Only patients with estrogen-receptor (ER)-negative tumors were eligible for protocols B-13, B-19, and B-23. Con-

versely, only patients whose tumors were ER positive were eligible for protocols B-14 and B-20.

No adjuvant therapy was administered in one arm of B-13; placebo was administered in one arm of B-14 (Table 1). Chemotherapy alone was administered in one of the two randomly assigned arms in B-13, in both arms in B-19, and in two arms of B-23. Tamoxifen alone was administered in one arm of B-14 and in one arm of B-20. The combination of tamoxifen and chemotherapy was administered in two of the B-20 arms and in two of the B-23 arms.

Definitions of End Points

An IBTR was defined as a recurrent invasive carcinoma that occurred after lumpectomy and breast irradiation in either the skin or parenchyma of the ipsilateral breast without clinical-radiologic evidence of regional or distant disease. All other local or regional recurrences, namely in the ipsilateral internal mammary, supraclavicular, infraclavicular, axillary nodes, or nonbreast skin of the ipsilateral chest wall, were classified as oLRR. LRFs (IBTR or oLRR) were included only if they were first events. Clinical, radiologic, and pathologic reports were used to document treatment failures. Distant failures were defined as all cancers that occurred at sites other than local or regional sites. Event times for the calculation of DDFI were censored in instances when patients died as a result of other causes but not when patients experienced LRF. The overall survival (OS) end point included all deaths.

Statistical Methods

For this report, we first characterized the occurrence of the site-specific first events, IBTR and oLRR, by using cumulative incidence curves²¹ with potential prognostic factors (eg, age, menopausal status, race, body mass index [BMI], nodal status, clinical and pathologic tumor size, and ER and progesterone receptor [PR] status). Times to LRF were calculated from the date of surgery. Formal inferences for times to LRF were achieved by using the method described by Gray.²²

Second, we used multivariate analyses to characterize the influences of IBTR; oLRR; and other clinical, pathologic, and demographic factors on mortality or on the occurrence of distant disease. The candidate clinical, pathologic, and demographic variables used in these latter analyses were the same as those used in the characterization of IBTR and oLRR. Stepwise procedures were employed to determine the final models by using variables associated with *P* values less than .05.²³ The Kaplan-Meier method²⁴ was used to estimate OS and DDFI after the occurrence of IBTR or oLRR by using the times from first clinical failure event until death or distant disease, respectively. We report 5-year results for these end points to minimize bias associated with the decreased time at risk for mortality and distant disease for those who experienced later LRF compared with those who experienced earlier LRF. Finally, LRF was modeled as a time-dependent predictor of mortality.^{1,9,23,25} ER status by LRF status interactions were tested and were accounted for in the final models if the

Table 1. Summary of Five Node-Negative NSABP Protocols

Protocol	Treatment Comparison	Tumor Status	Assessment Date		No. of Patients		
			Study Initiation	Follow-Up Closure	Accrued (n = 10,709)	Randomly Assigned (n = 9,118)	Eligible and Randomly Assigned With Follow-Up (n = 8,873)
B-13	No adjuvant tx v M→F + LV	N0, ER–	8/1/1981	5/31/2004	1,116	760	731
B-14	Placebo v TAM	N0, ER+	1/4/1982	5/1/2007	4,127	2,892	2,817
B-19	M→F + LV v CMF	N0, ER–	10/17/1988	3/17/2006	1,095	1,095	1,074
B-20	TAM v M→F + TAM v CMF + TAM	N0, ER+	10/17/1988	3/17/2006	2,363	2,363	2,299
B-23	CMF × 6 + placebo v CMF × 6 + TAM v AC × 4 + placebo v AC × 4 + TAM	N0, ER–	5/21/1991	3/17/2006	2,008	2,008	1,952

Abbreviations: NSABP, National Surgical Adjuvant Breast and Bowel Project; tx, treatment; M, methotrexate; F, fluorouracil; LV, leucovorin; TAM, tamoxifen; CMF, cyclophosphamide-methotrexate-fluorouracil; AC, adriamycin-cyclophosphamide; ER, estrogen receptor.

resulting *P* values were less than .01. Statistical analyses were carried out by using SAS (SAS Inst, Cary, NC) and S-plus (Statistical Sciences, Seattle, WA; and Insightful Corp, Palo Alto, CA) software. The findings presented in this study were based on information received at the NSABP Biostatistical Center as of the closure date of each study (Table 1).

RESULTS

A total of 10,709 women were enrolled onto the five studies: 9,118 were randomly assigned, and 1,591 were registered. Among the 9,118 randomly assigned patients, 3,799 (42.8%) underwent lumpectomy, had follow-up information, and were eligible for this analysis. This group, which had a median time on study of 16.1 years, constituted our population at risk for LRF.

Patient characteristics of the cohort treated by lumpectomy in these trials are listed in Appendix Table A1 (online only). The rates of lumpectomy were lower in earlier trials than in later trials. Overall at entry, 49.3% of the women were aged 49 years or younger, and 27.7% were aged 60 years or older. More than half of the patients in the ER-negative cohort were younger than 50 years at entry. In contrast, there were proportionately older patients in the ER-positive cohort.

The majority of tumors (67%) measured clinically were 2 cm or less. The distribution of patients by race varied considerably among the trials, and black patients were in lower proportions in ER-positive lumpectomy trials (2.7% in B-14 and 5.5% in B-20) and in higher proportions in ER-negative trials (6.4% to 14.9%).

As of March 2006, 342 (9.0%) of the 3,799 patients developed IBTR, and 77 (2.0%) developed oLRR (Table 2). Of the 342 who developed IBTR, 127 (37.1%) occurred within 5 years, and 233 (68.1%) occurred within 10 years, of the initial surgery. Of the 77 oLRRs, 56 (72.7%) occurred within 5 years, and 71 (92.2%) occurred

within 10 years, of the initial surgery. The pooled 12-year cumulative incidences were 7.6% for IBTR and 2.0% for oLRR.

Cumulative Incidence of LRF by Patient Characteristics

Cumulative incidences of LRF by patient characteristics are summarized in Appendix Figures A1 and A2 (online only), respectively. Younger women had a significantly higher cumulative incidence of IBTR than did older women ($P < .0001$; Fig A1A). The 12-year incidences of IBTR for women aged 49 years or younger, 50 to 59 years, and 60 years or older were 9.6%, 5.8%, and 5.6%, respectively (Fig A2A).

Race had marginal significance associated with IBTR univariately ($P = .04$; Fig A1B) but was not significant when adjusted for age, tumor size, and BMI. In contrast, race was highly significantly associated with oLRR ($P = .001$; Fig A2B). For both outcomes, black women fared more poorly than did white women. BMI was not significantly associated with IBTR or oLRR.

Clinical tumor size was not significantly associated with IBTR ($P = .26$) but was significantly associated with oLRR ($P = .006$; Figs A1C and A2C), whereas pathologic tumor size was a significant predictor of IBTR ($P = .003$) but not of oLRR ($P = .07$; Figs A1D and A2D). As expected, patients with larger tumors fared more poorly than did those with smaller tumors.

ER status was not significantly associated with either the incidence of IBTR ($P = .81$; Fig A1E) or oLRR ($P = .95$; Fig A2E). However, ER-negative patients appeared to have an increased incidence of early IBTR and oLRR events, which leveled off over time, whereas ER-positive patients had a fairly constant incidence of both IBTR and oLRR. PR status was not significantly associated with either

Table 2. Rates of IBTR and oLRR After Lumpectomy

Variable	Treatment Protocol							Overall
	B-13		B-14		B-19	B-20	B-23	
	No Rx	M→F	Placebo	TAM				
No. at risk*	119	116	534	530	389	1,027	1,084	3,799
Median time on study, years	18.2	18.2	19.9	19.9	16.5	15.3	12.1	16.1
With IBTR								
No.	23	6	90	45	34	77	67	342
%	19.3	5.2	16.9	8.5	8.7	7.5	6.2	9.0
Cumulative IBTR incidence, %								
3-year	7.6	0.9	3.8	1.7	3.1	1.2	2.5	2.4
5-year	11.0	1.7	5.1	2.1	3.6	2.1	3.6	3.4
10-year	15.3	2.6	11.0	3.6	6.5	4.8	6.2	6.4
12-year	15.3	5.4	11.6	5.0	7.9	6.5	6.9	7.6
With oLRR								
No.	1	3	17	10	10	17	19	77
%	0.8	2.6	3.2	1.9	2.6	1.7	1.8	2.0
Cumulative oLRR incidence, %								
3 year	0.8	1.7	1.7	0.6	1.8	1.0	1.4	1.2
5 year	0.8	1.7	2.1	0.8	2.1	1.3	1.6	1.5
10 year	0.8	2.6	3.2	1.1	2.6	1.5	1.8	1.9
12 year	0.8	2.6	3.2	1.3	2.6	1.6	1.8	2.0

Abbreviations: IBTR, ipsilateral breast tumor recurrence; oLRR, other locoregional recurrence; Rx, adjuvant therapy; M, methotrexate; F, fluorouracil; TAM, tamoxifen.

*Includes all eligible, node-negative patients with follow-up information who underwent lumpectomy and postoperative radiation therapy.

the incidence of IBTR or oLRR ($P = .83$ and $P = .19$, respectively; analyses not shown).

Adjuvant therapy had great influence on the incidence of IBTR ($P < .0001$; Fig A1F) but not on oLRR ($P = 0.21$; Fig A2F). For patients who were assigned to the arms with no adjuvant therapy, the pooled 12-year incidence of IBTR was 12.3%. In contrast, those assigned to tamoxifen alone, chemotherapy alone, and tamoxifen plus chemotherapy had 12-year incidences of 6.7%, 6.4%, and 6.8%, respectively (pooled value, 6.6%).

DDFI and OS After LRF

As shown in Figure 1, 5-year DDFI and OS after IBTR were 66.9% and 76.6%, respectively. Patients who experienced oLRR had worse outcomes (ie, 27.8% 5-year DDFI after oLRR, and 34.9% 5-year OS after oLRR). Overall, the risk of developing distant disease and mortality were consistently greater after oLRR than after IBTR, irrespective of the original treatment.

A model of OS that used IBTR and other significant factors is listed in Table 3. There was significant interaction between ER status and IBTR ($P = .002$), and IBTR had greater impact on mortality in ER-negative than in ER-positive patients. The adjusted hazard ratio (HR) for mortality after development of IBTR was 4.49 (95% CI, 3.29 to 6.13) in ER-negative patients and 2.32 (95% CI, 1.72 to 3.14) in ER-positive patients. Other significant multivariate predictors of mortality included age at entry, race, BMI, and clinical and pathologic tumor sizes. Older women and those with larger tumors (> 2.0 cm) had significantly higher mortality than did younger women and those

with smaller tumors. BMI was also highly significantly associated with mortality ($P = .0089$). Black women experienced an elevated mortality even after analyses were adjusted for BMI and other factors.

The effect of oLRR on mortality (Table 4) was magnified compared with that of IBTR, but a similar interaction with ER status was observed ($P < .0001$); oLRR had a greater impact on mortality in ER-negative patients than in ER-positive patients. The adjusted HR for mortality after development of oLRR was 19.84 (95% CI, 13.33 to 29.74) in ER-negative patients versus 6.43 (95% CI, 4.29 to 9.64) in ER-positive patients. All the other clinical factors mentioned for IBTR were significantly associated with mortality in patients who experienced oLRR with similar HRs. For the occurrence of distant disease after LRF, somewhat higher risks were observed with similar patterns, but the differential effects by ER status were nonsignificant.

Timing of LRF As Predictor of OS and DDFI

By using different time cutoffs, we observed substantial and significant decreases in death at 5 years for patients who experienced late LRF versus early LRF (Table 5). OS and DDFI after oLRR were much worse than after IBTR at every time interval. The 5-year OS after LRF for those whose oLRR occurred within 2 years of their original diagnosis of cancer was only 19.5%.

DISCUSSION

This retrospective analysis of patients treated by BCT for node-negative breast cancer in five randomized trials indicates that the

Fig 1. Outcomes after ipsilateral breast tumor recurrence (IBTR) and other locoregional recurrence (oLRR) by estrogen receptor (ER) status. (A) Distant-disease-free interval (DDFI) and (B) overall survival (OS) for the first 5 years after IBTR by ER status; and (C) DDFI and (D) OS for the first 5 years after oLRR by ER status. The total numbers of events and deaths are measured during all follow-up time after the diagnosis of IBTR or oLRR.

Table 3. Multivariate Cox Model of Mortality Using IBTR and Other Factors

Variable	Multivariate Analysis			
	Hazard Ratio*	95% CI	df	P
IBTR status†				
ER-negative patients (no, yes)‡	4.49	3.29 to 6.13	2	< .0001
ER-positive patients (no, yes)	2.33	1.72 to 3.14		
Age at entry, years				
≤ 49, 50-59	1.14	0.95 to 1.37	2	< .0001
≤ 49, ≥ 60	1.72	1.44 to 2.04		
Race				
White, black	1.51	1.18 to 1.93	2	.0007
White, other	0.68	0.44 to 1.07		
BMI quartile				
First, second quartile	0.93	0.75 to 1.44	3	.0089
First, third	1.10	0.89 to 1.36		
First, fourth	1.30	1.05 to 1.60		
Clinical tumor size, cm				
≤ 2, > 2.1	1.27	1.07 to 1.51	1	.0062
Pathologic tumor size, cm				
≤ 2, > 2.1	1.44	1.22 to 1.71	1	< .0001

NOTE. Analysis was based on a cohort of 3,348 patients who had known values for all of the listed factors. In each variable comparison, the first listed value was considered the baseline level for each analysis.

Abbreviations: IBTR, ipsilateral breast tumor recurrence; ER, estrogen receptor; BMI, body mass index.

*Hazard ratio was based on average mortality of the second category of each variable compared with the baseline category.

†Analyzed as a time-varying covariate.

‡Test for ER status × IBTR status interaction yielded $P = .002$.

Table 4. Multivariate Cox Model of Mortality Using oLRR and Other Factors

Variable	Multivariate Analysis			
	Hazard Ratio*	95% CI	df	P
oLRR status†				
ER-negative patients (no, yes)‡	19.84	13.33 to 29.54	2	< .0001
ER-positive patients (no, yes)	6.43	4.29 to 9.64		
Age at entry, years				
≤ 49, 50-59	1.10	0.92 to 1.32	2	< .0001
≤ 49, ≥ 60	1.74	1.46 to 2.08		
Race				
White, black	1.33	1.04 to 1.70	2	.036
White, other	0.77	0.49 to 1.20		
BMI quartile				
First, second	0.91	0.73 to 1.14	3	.0044
First, third	1.07	0.87 to 1.32		
First, fourth	1.31	1.06 to 1.61		
Clinical tumor size, cm				
≤ 2, > 2.1	1.20	1.02 to 1.43	1	.032
Pathologic tumor size, cm				
≤ 2, > 2.1	1.52	1.28 to 1.80	1	< .0001

NOTE. Analysis was based on a cohort of 3,348 patients who had known values for all of the above factors. In each variable comparison, the first listed value was considered the baseline level.

Abbreviations: oLRR, other locoregional recurrence; ER, estrogen receptor; BMI, body mass index.

*Hazard ratio was based on average mortality of the second category of each variable compared with the baseline category.

†Analyzed as a time-varying covariate.

‡Test for ER status × oLRR status interaction yielded $P < .0001$.

10-year incidence of IBTR and oLRR was lower for women with node-negative disease (ie, 6.4% and 1.9%, respectively) than we previously reported for node-positive disease (ie, 8.7% and 6.0%, respectively).⁹ Moreover, if only patients who received adjuvant systemic therapies were considered, then the 10-year incidences for IBTR and oLRR in these node-negative trials were even lower (ie, 5.2% and 1.7%, respectively). The reduction in the 10-year incidence of IBTR by greater than 50% in patients who received systemic therapy compared with those who were treated by surgery and radiation alone is indicative of the effectiveness of adjuvant chemotherapy and adjuvant hormonal therapy in the control of locoregional disease. In addition, patients with node-negative disease who received these systemic therapies benefited from reduced incidence of distant metastases and mortality.^{16,26,27}

The adjusted HR for IBTR associated with death in our present cohort disregarding ER status (HR, 3.04; 95% CI, 2.42 to 3.81; data not shown) was similar to that in our previous report of patients with node-positive breast cancer (HR, 2.58; 95% CI, 2.11 to 3.15),⁹ as indicated by the overlapping confidence intervals. Subsequent mortality was substantially greater if the first event was an oLRR rather than an IBTR. In addition, the mortality HR after oLRR was greater in these women with node-negative disease than in those with node-positive disease who were more likely to die or to have a distant failure event than were patients with node-negative disease in the absence of LRF. Interestingly, LRF had a significantly larger effect on mortality and distant disease in ER-negative women than in ER-positive

women. At 5 years after the occurrence of IBTR, 76.6% of patients were alive, and 67.1% had no distant disease. Among those ER-positive patients who were treated with systemic tamoxifen and/or chemotherapy and who developed IBTR, 83.0% were alive, and 72.7% were free of distant cancer 5 years after the occurrence of IBTR (data not shown). Among those who received chemotherapy in the ER-negative trials, 67.0% were alive and 61.5% were free of distant cancer 5 years after the occurrence of IBTR (data not shown). Voogd et al²⁸ reported a survival after LRF of 39% at 10 years. Most of the distant failures in that study occurred within the first 5 years of local recurrences. Moreover, only 4% of their patients received any systemic therapy for the LRF, which may better reflect the natural history of the disease.

The occurrence of oLRR confers an even poorer prognosis. Five years after oLRR, only 27.8% (95% CI, 18.5% to 41.9%) of patients remained free of distant disease, and only 34.9% (95% CI, 25.3% to 48.3%) were alive (Fig 1). Although these estimates have broad CIs, they are similar to values noted in patients with node-positive disease.⁹ The relative benefit of a later time to recurrence was less striking for oLRR (compared with IBTR), as the event itself confers a much greater eventual risk for metastatic disease and death than does an IBTR.

Age at entry was a stronger predictor of survival in this node-negative cohort than for women with node-positive disease.⁹ This may partially be explained by the lower baseline levels of mortality in our node-negative cohort. Galper et al²⁹ reported similar relative risks associated with distant cancers or death in women older than 60 years.

Table 5. Comparison of OS and DDFI After IBTR and oLRR for Early Versus Late Event Occurrences in Lumpectomy Patients From NSABP Protocols

Time of Event by Event Type, Months	No. of Patients	No. of Deaths*	OS (%)†	No. of Distant Events‡	DDFI (%)§
IBTR					
≤ 24	54	41	38.9	37	39.6
> 24	288	67	84.9	90	72.1
≤ 36	90	56	51.3	51	51.1
> 36	252	52	87.5	76	72.9
≤ 48	109	63	57.8	62	55.2
> 48	233	45	87.3	65	72.7
≤ 60	127	73	61.4	72	54.2
> 60	215	35	87.7	55	75.1
oLRR					
≤ 24	36	30	19.5	30	12.5
> 24	41	27	48.3	25	41.5
≤ 36	47	38	30.7	38	16.6
> 36	30	19	41.8	17	48.0
≤ 48	54	44	30.3	43	19.4
> 48	23	13	46.3	12	49.2
≤ 60	56	45	29.7	44	18.9
> 60	21	12	49.1	11	53.2

NOTE. National Surgical Adjuvant Breast and Bowel Project protocols are B-13, B-14, B-19, B-20 and B-23.

Abbreviations: OS, overall survival; DDFI, distant disease-free interval; IBTR, ipsilateral breast tumor recurrence; oLRR, other locoregional recurrence; NSABP, National Surgical Adjuvant Breast and Bowel Project.

*Total No. of deaths after IBTR or oLRR during all follow-up time.

†Reported as 5-year OS after event.

‡Total No. of distant events after IBTR or oLRR during all follow-up time.

§Reported as 5-year DDFI after event.

Race and obesity also were considered in this analysis. In both models (Tables 3 and 4), black patients had an at least 33% higher adjusted risk of death than white patients, whereas the risks for these events were lowest for patients in the “other or unknown” race category. Although previous studies have found breast conservation to be an effective option in black women,³⁰ other studies have shown a greater rate of local failure³¹ and less frequent completion of radiotherapy outside of clinical trials.³² Black patients have derived similar benefit from systemic chemotherapy in ER-positive and -negative trials when compared with white patients, but black patients have less favorable OS as a result of non-breast cancer–related death.³³ Women in the highest BMI quartile had a 30% higher risk of death than those in the lowest quartile. Our analysis and previous analyses of NSABP protocols of ER-negative, node-negative disease showed no significant effect of increased weight on LRF but significant increases in mortality.^{34,35}

Time intervals between the treatment of primary breast cancer and IBTR greatly affect survival.^{1,9,36} IBTRs that occur later have consistently been associated with better prognosis than those that occur earlier. For example, in a population-based study,³⁷ the 5-year distant-recurrence-free survival among 173 patients with invasive local recurrence at ≤ 5 years compared with 85 patients whose recurrences occurred more than 5 years after diagnosis was 41% versus 68%. Two possible reasons for this difference are that recurrences proximate to initial treatments may indicate persistent chemotherapy-insensitive or radiotherapy-resistant disease and that later recurrences may be more likely than early recurrences to represent new primary tumors in the ipsilateral breast.^{38,39}

The NSABP has now analyzed the prognosis of 6,468 women treated in five prospective, randomized trials of node-positive disease and five of node-negative disease, among whom 843 had LRFs (ie, 601

IBTRs and 242 oLRRs). Our combined results indicate that patients who experienced IBTR and who were originally diagnosed with stage I disease had prognoses similar to those with stage II disease; likewise, patients who experienced IBTR and who were originally diagnosed with stage II disease had similar prognoses to patients with stage III disease. An oLRR forecasts a much greater risk of distant failure and death for patients than does an IBTR. Because the 5-year OS and DDFI in patients who experienced oLRR are similar for patients with both node-negative and node-positive disease, oLRR may be a harbinger of metastatic disease regardless of the original stage at diagnosis.

There are no standard guidelines for treatment strategies after LRF. Salvage mastectomy has been the predominant local treatment modality for operable IBTR; however, approaches that use repeat lumpectomy and partial breast repeat radiation are emerging.^{40–43} The role of chemotherapy in the management of patients who have experienced LRF, regardless of the nature of the original surgical or adjuvant treatment, has not been established for patients who were originally diagnosed with stage I or II disease. An ongoing multicenter trial by the International Breast Cancer Study Group (IBCSG; <http://www.ibcsg.org>) and by the NSABP (<http://www.nsabp.pitt.edu>) is addressing this issue.⁴⁴ Given the poor prognoses of patients who have experienced oLRR or IBTR, even when they were originally diagnosed as having node-negative disease, it is important that new therapeutic strategies be developed for their management.

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