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ORIGINAL REPORT

Patterns of Locoregional Failure in Patients With Operable Breast Cancer Treated by Mastectomy and Adjuvant Chemotherapy With or Without Tamoxifen and Without Radiotherapy: Results From Five National Surgical Adjuvant Breast and Bowel Project Randomized Clinical Trials

Alphonse Taghian, Jong-Hyeon Jeong, Eleftherios Mamounas, Stewart Anderson, John Bryant, Melvin Deutsch, and Norman Wolmark

From the National Surgical Adjuvant Breast and Bowel Project Operations and Biostatistical Centers, National Surgical Adjuvant Breast and Bowel Project; Department of Biostatistics, University of Pittsburgh, Graduate School of Public Health; and Department of Radiation Oncology, University of Pittsburgh Medical Center Presbyterian, Pittsburgh, PA; Department of Radiation Oncology, Massachusetts General Hospital/Boston Medical Center, Boston, MA; and Aultman Cancer Center, Canton, OH.

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Address reprint requests to Alphonse Taghian, MD, PhD, Department of Radiation Oncology, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114; e-mail: ataghian@partners.org.

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ABSTRACT

Purpose
To assess patterns of locoregional failure (LRF) in lymph node–positive (LN+) breast cancer patients treated with mastectomy and adjuvant chemotherapy (± tamoxifen) and without postmastectomy radiotherapy (PMRT) in five National Surgical Adjuvant Breast and Bowel Project trials.

Patients and Methods
We examined 5,758 patients enrolled onto the B-15, B-16, B-18, B-22, and B-25 trials. Median follow-up time was 11.1 years. Distribution of pathologic tumor size was ≤ 2 cm, 2.1 to 5 cm, and more than 5 cm in 30%, 52%, and 11% of patients, respectively. Distribution of the number of LN+ was one to three, four to nine, and ≥ 10 in 51%, 32%, and 16% of patients, respectively. Ninety percent of patients received doxorubicin-based chemotherapy.

Results
The overall 10-year cumulative incidences of isolated LRF, LRF with or without distant failure (DF), and DF alone as first event were 12.2%, 19.8%, and 43.3%, respectively. Cumulative incidences for LRF as first event with or without DF for patients with one to three, four to nine, and ≥ 10 LN+ were 13.0%, 24.4%, and 31.9%, respectively ($P < .0001$). For patients with a tumor size of ≤ 2 cm, 2.1 to 5.0 cm, and more than 5.0 cm, these incidences were 14.9%, 21.3%, and 24.6%, respectively ($P < .0001$). Multivariate analysis showed age, tumor size, premenopausal status, number of LN+, and number of dissected LN as significant predictors for LRF as first event.

Conclusion
In patients with large tumors and four or more LN+, LRF as first event remains a significant problem. Although PMRT is currently recommended for patients with four or more LN+, it may also have value in selected patients with one to three LN+. However, in the absence of a randomized trial examining the worth of radiotherapy in this group of patients, the value of PMRT remains unknown.

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INTRODUCTION

During the last 50 years, a number of randomized clinical trials have been carried out to test the merit of postmastectomy radiotherapy (PMRT) in patients with breast cancer.[1,2] The great majority of these trials did not include adjuvant chemotherapy and

were not confined to high-risk patients.[2-4] These studies showed that the addition of radiotherapy (RT) resulted in a significant reduction in locoregional failure (LRF) but no improvement in overall survival.[1] However, in patients with a higher risk of local failure who have undergone adjuvant chemotherapy as well as modern RT, locoregional RT after surgery has been found to reduce mortality.[2]

Recent randomized trials of PMRT in node-positive patients[5-7] have stimulated discussion about the generalizability of their findings to current practice, particularly because the benefit in survival demonstrated in these studies has been found in patients with one to three and with four or more positive lymph nodes (LN+). However, in those studies, cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy was used in node-positive patients. In the United States and Canada, the great majority of patients with LN+ would be treated with doxorubicin-based chemotherapy.[8] In the Danish trials, axillary lymph node (LN) dissection was considered substandard because only an average of seven LNs were removed[6,7] compared with 15 to 17 LNs removed in other studies.[9-11] Furthermore, the rate of total LRF in patients with one to three LN+ who did not receive PMRT in these trials was higher than the rate in these series[9-11] (30% to 31%[5-7] *v* 13% to 19.7%,[9-11] respectively). Thus, the applicability of findings from these trials to current practice in the United States regarding the use of PMRT in patients treated by doxorubicin-based chemotherapy and with adequate axillary LN dissection has been questioned.

Recently, three large studies[9-11] reported a pattern of LRF after modified radical mastectomy (MRM) in patients receiving adjuvant chemotherapy. Recht et al[9] reported the pattern of failure in more than 2,000 patients in Eastern Cooperative Oncology Group (ECOG) trials who received CMF chemotherapy. Katz et al[10] reported it in the M.D. Anderson Cancer Center (MDA) experience with 1,031 patients who received doxorubicin-based chemotherapy, and Wallgren et al[11] reported it in patients enrolled onto the International Breast Cancer Study Group (IBCSG). In the present study, we examine the pattern of LRF in 5,758 patients enrolled onto the following five randomized clinical trials of the National Surgical Adjuvant Breast and Bowel Project (NSABP): trials B-15, B-16, B-18, B-22, and B-25.[12-16] Only patients who were treated by MRM, had at least one LN+ removed, and received adjuvant chemotherapy with or without tamoxifen and no PMRT were included in this analysis.

PATIENTS AND METHODS

Study Population

Patients included in this report were treated in five NSABP studies (B-15, B-16, B-18, B-22, and B-25) evaluating adjuvant chemotherapy but not allowing adjuvant PMRT. To be included in this analysis, patients must have had follow-up information, satisfied the eligibility requirements for the studies, undergone MRM, and had at least one pathologically positive axillary LN but did not receive PMRT. A brief summary of each of the five trials is provided in Table 1. Also, treatment details, outcome, and other aspects of each trial are explained in the previous publications.[12-16]

Statistical Methods

In NSABP studies, local failure (LF) is defined as any recurrence of tumor in the ipsilateral chest wall or in mastectomy scars. Regional failure (RF) is defined as any recurrence of tumor in the ipsilateral supraclavicular, infraclavicular, axillary, or internal mammary nodes. Recurrence in any other site in this study was

Table 1. Summary of NSABP Treatment Protocols and Number of Patients Included in the Present Report

Trial	No. of Patients	Period	Regimen
B-15[12]	1,671	1984-1988	4 AC* *v* 4 AC + 3 CMF† *v* 6 CMF‡
B-16[13]	605	1984-1988	Tam *v* ACT§ *v* PFT‖ → PAFT
B-18[14]	215	1988-1993	4 AC → surgery *v* surgery → 4 AC
B-22[15]	1,658	1989-1991	4 AC (4 × 600)¶ *v* 4 AC (2 × 1200)** *v* 4 AC (4 × 1200)††
B-25[16]	1,609	1992-1994	4 AC (4 × 1200) *v* 4 AC (2 × 2400)‡‡ *v* 4 AC (4 × 2400)§§
Total	5,758	1984-1994	

Abbreviations: NSABP, National Surgical Adjuvant Breast and Bowel Project; AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and fluorouracil; Tam, tamoxifen; ACT, doxorubicin, cyclophosphamide, and tamoxifen; PFT, phenylaline mustard, fluorouracil, and tamoxifen; PAFT, phenylaline mustard, fluorouracil, tamoxifen, and doxorubicin; IV, intravenous.

*Doxorubicin 60 mg/m^2 IV and cyclophosphamide 600 mg/m^2 IV.

†Cyclophosphamide 750 mg/m^2 IV, methotrexate 40 mg/m^2 IV, and fluorouracil 600 mg/m^2 IV.

‡Cyclophosphamide 100 mg/m^2 by mouth, methotrexate 40 mg/m^2 IV, and fluorouracil 600 mg/m^2 IV.

§Four cycles of AC and tamoxifen for 5 years.

‖Seventeen cycles of melphalan 4 mg/m^2 by mouth and fluorouracil 300 mg/m^2 IV and tamoxifen for 5 years. In 1985, the PFT arm of the protocol was modified to PAFT to include doxorubicin 30 mg/m^2.

¶Doxorubicin 60 mg/m^2 IV and cyclophosphamide 600 mg/m^2 IV for 4 cycles.

**Doxorubicin 60 mg/m^2 IV for four cycles and cyclophosphamide 1,200 mg/m^2 for the first two cycles.

††Doxorubicin 60 mg/m^2 IV and cyclophosphamide 1,200 mg/m^2 for four cycles.

‡‡Doxorubicin 60 mg/m^2 IV for four cycles and cyclophosphamide 2,400 mg/m^2 for the first two cycles.

§§Doxorubicin 60 mg/m^2 IV and cyclophosphamide 2,400 mg/m^2 for four cycles.

considered as distant failure (DF). For our study, isolated LF (ILF) was defined as any first LF without evidence of simultaneous DF. Here, simultaneous DF is defined as any subsequent DF that occurred within 4 months after the diagnosis of the first LF. Isolated RF (IRF) was defined similarly as any RF as a first event without evidence of simultaneous DF. Isolated LRF (ILRF) was defined as any first LF or RF without evidence of simultaneous DF. The occurrence of contralateral events and other second primary cancers was ignored in the determination of (isolated) local, regional, or locoregional recurrences. LRF with or without DF (LRF ± DF) was defined as any first LRF with or without any subsequent DF.

Time to ILF was defined as time from definitive surgery to the first diagnosis of an ILF. Time to other LF with a simultaneous DF was also defined as time from surgery to the first LF, not time to a subsequent DF. Time to a RF or LRF with or without simultaneous DF was similarly defined. Time to DF and death were defined as time from surgery to the first DF and death, respectively. If LF or RF occurred without a subsequent DF but with the additional follow-up time being less than 4 months, we counted this event as an isolated event.

The nonparametric method[17] was used to estimate 10-year cumulative incidence for ILF, IRF, ILRF, LRF ± DF, and DF alone. For the analysis of cumulative incidence for each end point, competing events were defined as any first isolated recurrence, any first other recurrence followed by a DF within 4 months, any first DF, and any death without evidence of previous recurrence. Gray's K-sample statistic was used to test whether any statistical significance of differences existed in cumulative incidence among groups stratified by protocols (univariate analysis).[18] The proportional hazard model[19] was used to test the association between cause-specific hazard functions and selected patient and tumor characteristics and to estimate the magnitude of such association, stratified by protocols. All P values were two-tailed, and a $P \leq .05$ was considered significant. Analyses were based on all follow-up information received at the NSABP Biostatistical Center as of December 31, 2002.

RESULTS

Study Population and Patient and Tumor Characteristics

A total of 5,758 patients from the five studies met the predetermined criteria and are included in this analysis (Table 1). All patients were treated between 1984 and 1994. Patient and tumor characteristics are listed in Table 2.

Table 2. Patient, Tumor, and Treatment Characteristics in the Study Population

Characteristic	No. of Patients	%
Age, years		
Median	48	
Range	21-75	
20-29	117	2.0
30-39	1,013	17.6
40-49	2,050	35.6
50-59	1,600	27.8
60-69	903	15.7
≥ 70	75	1.3
Menopausal status		
Premenopausal	2,612	45.4
Perimenopausal	423	7.3
Postmenopausal	2,699	46.9
Unknown	24	0.4
ER status		
Negative	2,123	36.9
Positive	3,354	58.2
Unknown	281	4.9
Pathologic tumor size, cm		
Median	2.8	
Range	0-20	
≤ 2 cm	1,744	30.3
2.1-5 cm	2,971	51.6
≥ 5.1 cm	615	10.7
Unknown	428	7.4
No. of positive LN		
Median	3	
Range	1-43	
1-3	2,957	51.4
4-9	1,854	32.2
10	930	16.1
Unknown	17	0.3
No. of axillary LN dissected		
Median	16	
Range	1-62	
1-5	108	1.9
6-9	580	10.1
≥ 10	4,848	84.2
Unknown	222	3.8
Chemotherapy regimen		
Doxorubicin based	5,199	90.3
CMF*	559	9.7

Abbreviations: ER, estrogen receptor; LN, lymph node; CMF, cyclophosphamide, methotrexate, and fluorouracil.
*National Surgical Adjuvant Breast and Bowel Project B-15 trial.[13]

Rates of LRF ± DF

The median follow-up time without any first recurrence for all patients was 11.1 years (range, 0.003 to 18.0 years). The median follow-up time for patients who were alive was 11.9 years (range 0.43 to 18.0 years). The numbers of patients at risk for any first recurrence at 5 and 10 years were 3,188 and 1,674, respectively. Of the 5,758 patients, 715 (12.4%) presented with ILRF as first event. An additional 442 patients (7.7%) presented with LRF followed by a subsequent DF within 4 months, and 1,673 patients (29.1%) presented with DF as a first event. The overall cumulative incidence of LRF ± DF at 10 years was 19.8%, stratified by protocol. The 10-year cumulative incidence of DF alone as a first event was 43.3%. The median times to develop ILRF and DF were 2.0 and 2.9 years, respectively. The majority (71%) of LRF occurred within the first 4 years, and 21.4%, 6.5%, and 1.0% of LRF occurred at 4 to 8, 8 to 12, and more than 12 years of follow-up, respectively.

Rates of LRF According to Patient and Tumor Characteristics: Univariate Analysis

The rates of ILRF and LRF ± DF according to different patient and tumor characteristics are listed in Table 3. Results from univariate analyses indicated that age, pathologic tumor size, and number of LN+ were significant

Table 3. Ten-Year Cumulative Incidence Rates and Estimates of Isolated Locoregional Failure (LRF) and LRF with or without Simultaneous Distant Failure (+/− DF)

	Isolated LRF				LRF ± DF			
	%	SE	No. of Events/ No. of Patients	*P*	%	SE	No. of Events/ No. of Patients	*P*
Age*								
20-39 years	15.1	1.1	170/1,130		26.1	1.3	293/1,130	
40-49 years	13.2	0.8	271/2,050		21.1	0.9	438/2,050	
50-59 years	10.5	0.8	175/1,600		17.3	1.0	285/1,600	
≥ 60 years	9.9	1.0	99/978	.013†	14.1	1.1	141/978	< .0001
Menopausal status*								
Premenopausal	12.8	0.7	335/2,612		21.5	0.8	564/2,612	
Perimenopausal	13.1	1.6	57/423		20.9	2.0	92/423	
Postmenopausal	11.6	0.6	322/2,699	.77	18.1	0.8	500/2,699	.22
ER status*								
Negative	13.3	0.7	281/2,123		22.0	0.9	469/2,123	
Positive	11.8	0.6	408/3,354	.28	18.7	0.7	645/3,354	.011
Pathologic tumor size, cm*								
2	9.0	0.7	161/1,744		14.9	0.9	268/1,744	
2.1-5.0	13.2	0.6	401/2,971		21.3	0.8	640/2,971	
> 5.0	15.3	1.5	94/615	< .0001	24.6	1.8	151/615	< .0001
No. of positive lymph nodes*								
1-3	8.1	0.5	247/2,957		13.0	0.6	397/2,957	
4-9	15.5	0.9	290/1,854		24.4	1.0	459/1,854	
10	18.8	1.3	174/930	< .0001	31.9	1.5	295/930	< .0001
No. of axillary lymph nodes dissected*								
1-5	19.7	3.9	21/108		27.1	4.3	30/108	
6-9	12.9	1.4	77/580		19.3	1.7	116/580	
≥ 10	11.9	0.5	584/4,848	.050	19.5	0.6	956/4,848	.11

Abbreviations: LRF, locoregional failure; ER, estrogen receptor.
*Unknowns, if any, were omitted from each analysis.
†*P* values compare overall cumulative incidence during the entire follow-up period.

predictors for both ILRF and for LRF ± DF. Estrogen receptor (ER) status was a significant predictor only for LRF ± DF. The number of resected axillary LNs was a significant predictor for ILRF but not for LRF ± DF. Table 4 lists the 10-year cumulative incidences of ILF, IRF, ILRF, LRF ± DF, and DF alone, according to various combinations of tumor size and number of LN+ groupings.

Frequency Distribution of Sites of LRF As First Events

The majority of recurrences occurred in the chest wall and around the mastectomy scar (56.9% of patients). Supraclavicular LN recurrence represented 22.6% of all LRF, and axillary failure represented 11.7%. Both of parasternal and subclavicular failures were less than 1% of the total LRF.

Rates of LRF According to Patient and Tumor Characteristics: Multivariate Analysis

The cause-specific hazard analyses through the Cox proportional hazards model[19] were performed to evaluate the statistical significance of effects of the prognostic factors of age, tumor size, number of LN+, number of LNs dissected, ER status, and menopausal status on the end points of ILF, IRF, LRF ± DF, and DF as a first event. Results

Table 4. Ten-Year Cumulative Incidence Rates for Treatment Failure for the Study Population Distributed by Tumor Size and Number of Positive Axillary Lymph Nodes

	1-3 LN+			4-9 LN+			≥ 10 LN+		
	≤ 2	2.1-5	> 5	≤ 2	2.1-5	> 5	≤ 2	2.1-5	> 5
No. of patients	1,045	1,489	229	512	982	220	187	500	165
Isolated LF, %	4.3	7.2	5.2	7.3	11.5	14.3	10.8	12.5	15.9
Isolated RF, %	2.4	3.5	2.3	7.7	5.4	8.7	8.1	10.9	6.7
Isolated LRF, %	6.0	9.7	7.5	13.4	15.0	20.3	14.0	20.4	19.6
LRF with or without DF, %	10.6	15.3	11.4	19.6	24.3	31.3	25.9	33.2	34.3
DF, %	24.6	35.7	40.5	41.0	51.6	53.9	63.1	69.1	75.0

NOTE. Subcolumn headings indicate tumor size (in centimeters).
Abbreviations: LN+, positive lymph nodes; LF, local failure; RF, regional failure; LRF, locoregional failure; DF, distant failure.

showed that age, number of LN+, and number of dissected LNs were statistically significant independent predictors for ILF, IRF, LRF ± DF, and DF. Pathologic tumor size was an independent predictor for ILF, LRF ± DF, and DF but not for IRF. Both menopausal and ER status were independent predictors of LRF ± DF. Table 5 lists the 10-year cumulative incidence rates for treatment failure for 2,403 patients with one to three LN+ who had a known tumor size of less than 5 cm according to their ER status, tumor size, and age.

DISCUSSION

Three other large studies evaluating patterns of LRF in patients treated with mastectomy and adjuvant systemic therapy but without RT have been published recently.[9-11] In the ECOG[9]and the IBCSG[11] studies, patients received adjuvant CMF, but in the MDA study, [10] anthracycline-based adjuvant chemotherapy was used. In our study, 90.3% of patients received anthracycline-based chemotherapy, and 9.7% received CMF (NSABP B-15).[12] Although similar patterns of LRF were observed in our study and in these three other studies with regard to the effect of tumor size and number of involved LNs, the rate of LRF in the group of patients with greater than 5-cm tumors who had one to three LN+ seemed somewhat lower in our study (11.4% *v* 16% to 31.4%, respectively). Certainly, patient selection and differences in eligibility criteria in the various adjuvant trials included in these reports can account for the differences. However, in the three previous reports[9-11] and in the present study, rates of LRF were lower than those reported in the three randomized trials of PMRT[5-7] (Table 6). The average number of axillary LNs dissected in the four series (ECOG,[9] MDA,[10] IBCSG,[11] and this current study) was fairly similar (between 15 and 17 LNs removed). However, in the Danish[6,7] and Canadian trials,[5] the average number of LNs removed was seven and 11, respectively. This difference in the number of removed LNs could explain, at least in part, the higher rates of LRF observed in the randomized trials.[5-7]

The value of locoregional PMRT has been the subject of long-standing intense controversy for more than a quarter of a century, and the controversy has evolved significantly over the past several years as results from new randomized trials have become available.[5-7] Although the majority of randomized trials conducted to date consistently show a reduction in local recurrence rates with the addition of RT to surgery or to surgery plus systemic therapy,[1,2,4] it was not until recently that a survival benefit was demonstrated as well.[5-7] This benefit was shown in two studies in which PMRT was added to surgery plus systemic adjuvant chemotherapy.[5,6] Because adjuvant chemotherapy has been shown to improve survival,[20] the great majority of node-positive patients would currently be treated with adjuvant chemotherapy. Therefore, extrapolation on the value of PMRT from trials that did not use adjuvant chemotherapy would not necessarily be applicable to current practice. However, there are also significant differences between the recently disclosed randomized trials of PMRT[5-7] and other studies[3,9,10,13,21,22] that have dictated standards of care in the United States, particularly as these differences relate to the extent of axillary LN dissection, the type of chemotherapy used, and the rates of LRF observed in patients who did not receive PMRT. These differences make the generalizability of the results from those trials somewhat questionable for patients treated today.

Even more controversial than the role of PMRT in node-positive patients is the role of this intervention in patients with one to three LN+. In a survey addressed to radiation oncologists in the United States, Ceilley et al[23] showed that only 58% of responders would use PMRT in this group of patients. In the NSABP currently ongoing LN+ trials (B-30 and B-31), in which the use of PMRT is left to the discretion of the treating physician, 39% to 44% of patients with one to three LN+ are receiving PMRT

Table 5. Ten-Year Cumulative Incidence Rates for Treatment Failure for 2,403 Patients With One to Three Positive Lymph Nodes Who Had Known Tumor Size of ≤ 5 cm and Estrogen Receptor Status Distributed by Age

Age	Tumor Size (cm)	ER Status	No. of Patients	Isolated LRF		LRF ± DF		DF	
				%	SE	%	SE	%	SE
< 50 years	≤ 2.0	Negative	185	9.2	2.2	14.2	2.6	28.9	3.4
		Positive	334	9.0	1.6	14.2	1.9	27.3	2.5
	2.1-5.0	Negative	390	11.7	1.6	19.0	2.0	37.2	2.5
		Positive	448	12.1	1.6	19.1	1.9	38.1	2.3
≥ 50 years	≤ 2.0	Negative	143	3.5	1.6	9.1	2.4	25.2	3.7
		Positive	308	2.7	0.9	6.4	1.4	21.2	2.4
	2.1-5.0	Negative	210	7.2	1.8	12.0	2.3	35.6	3.3
		Positive	385	7.0	1.3	10.2	1.6	32.0	2.4

Abbreviations: ER, estrogen receptor; LRF, locoregional failure; LRF ± DF, locoregional failure with or without distant failure; DF, distant failure.

Table 6. Ten-Year Cumulative Rates of Locoregional Failure With or Without Distant Failure According to Number of Positive Lymph Nodes (LN+)

Number LN+	1-3 LN+ (%)	≥ 4 LN+ (%)	Median No. of LN Dissected	Chemotherapy Used
Danish trial 82b[6]	30	42	7	CMF
Danish trial 82c[7]	31	46	7	CMF
Canadian[5]*	33	46	11	CMF
ECOG[9]†	13	29	15	CMF
MDA[10]‡	14	25-34‖	17	Doxorubicin based
IBCSG,[11]† premenopausal	19.7§	30-38§‖	≈15¶	CMF**
IBCSG,[11]† postmenopausal	16§	29-35§‖	≈15¶	CMF or tamoxifen††
NSABP†	13	24-32‖	16	Doxorubicin/CMF‡‡

Abbreviations: LN, lymph nodes; LN+, positive lymph nodes; CMF, cyclophosphamide, methotrexate, and fluorouracil; ECOG, Eastern Cooperative Oncology Group; MDA, M.D. Anderson Cancer Center; IBCSG, International Breast Cancer Study Group; NSABP, National Surgical Adjuvant Breast and Bowel Project.

*Fifteen-year actuarial rate.

†Ten-year cumulative incidence.

‡Ten-year actuarial rate.

§Rate of LRF ± DF calculated from Table 5 from Wallgren et al.[11]

‖Rate of LRF ± DF for patients with four to nine LN+ and ≥ 10 LN+, respectively.

¶Forty-seven percent of patients had 15 or more lymph nodes removed.

**All patients received at least three courses of CMF chemotherapy.

††All patients received at least three courses of CMF chemotherapy or tamoxifen for 1 to 5 years.

‡‡The percentage of patients who received doxorubicin-based chemotherapy was 90.3%.

(unpublished data). In the randomized trials,[5-7] the 10-year rate of LRF in patients with one to three LN+ who did not receive RT varied between 30% and 33% (the Canadian study[5] presented 15-year rates). In the three series from ECOG,[22] MDA,[10] and IBCSG[11] and in our series, these rates were substantially lower and varied between 13% and 19.7% (Table 6). The reasons for this discrepancy are unclear, although the differences in surgical techniques and the possible inadequacy of the LN dissection in the Danish study have been put forward as plausible explanations. The proportion of LRF that occurred in the axilla in the Danish study was 45% compared with 14% and 11.8% in the MDA and NSABP studies, respectively. The number of LNs dissected could not fully explain this discrepancy because, in the Danish study, the rate of LRF remained high (27%) in the group of patients who had more than nine LNs removed and who did not receive RT. However, the number of patients in this group was relatively small (only 25% of patients had > nine LNs removed). Other explanations have been also discussed by Recht et al,[9] such as differences in the scoring of LRF between trials or in the type of statistical analysis used.

In the MDA analysis, Katz et al[10] identified a subset of patients with one to three LN+ at higher risk of LRF. This included patients with larger tumors and extranodal extension ≥ 2 mm and those who had not undergone adequate LN dissection. In the IBCSG study, Wallgren et al[11] defined patients in the one to three LN+ group with tumor grade 1, 2, or 3 and no vascular invasion (VI) as a low-risk group for LRF (14%). However, in patients with positive VI, grade 2 and 3 tumors, and tumors greater than 2 cm, the risk for LRF was considered medium to high (18% to 27%). In our study, extranodal extension, tumor grade, and VI were not reported in our database; however, in a subgroup analysis in this population, patients less than 50 years old with a tumor size of 2 to 5 cm (ER-positive or -negative) had a 19% risk of LRF ± DF (Table 5). Such groups of patients could potentially be offered a discussion of the pros and cons of PMRT. Nevertheless, the relatively overall low LRF rate in the group of patients with one to three LN+ in our study does not justify the routine use of PMRT in this group of patients. Our findings supported the Intergroup randomized trial (Southwest Oncology Group 9927), [24] which evaluated the role of PMRT in this group of patients. However, that trial closed prematurely in June 2003 because of poor accrual. Because opinion is clearly divided on this subject, the premature closure was unfortunate.

Although the LRF ± DF rates in patients with four or more LN+ were lower in the ECOG, MDA, and the IBCSG studies[9-11] compared with the randomized trials, these rates are still considerably high. The rates varied between 42% and 46% in the randomized studies and between 24% and 38% in the other series[9-11] (Table 6). In the guidelines of the American Society of Clinical Oncology,[22] PMRT was recommended for this group of patients. In the Ceilley et al[23] survey, 95% of radiation oncologists who responded to the survey would recommend PMRT for this group of patients. In the NSABP trials (B-30 and B-31), in which PMRT is left to the discretion of the investigator, 84% to 90% of patients with four or more LN+ are receiving PMRT (unpublished data). PMRT in this group of patients would have a significant effect on local control, with approximately a two-thirds reduction in local recurrence,[1] thus decreasing the LRF rate to approximately 6% to 10%, and a possible effect on survival.

One of the criticisms of the randomized trials[5,6] relates to the use of CMF in which the cyclophosphamide is administered intravenously as opposed to orally administered

cyclophosphamide in the CMF regimen[9,11,13,25] or the more commonly used anthracycline-containing regimens for patients with positive nodes.[8] The 1998 overview analysis demonstrated that anthracycline-containing regimens have superior activity when compared with nonanthracycline-containing regimens in terms of reducing recurrence and mortality.[20] In our study, the pattern of failure data from the B-15 trial[12] demonstrates that, although the LRF ± DF was slightly higher in the oral CMF group for patients with four to nine and ≥ 10 LN+, this difference was not statistically significant. Yet several studies[25] included in the overview analysis comparing six cycles of cyclophosphamide, doxorubicin, and fluorouracil or cyclophosphamide, epirubicin, and fluorouracil to six cycles of oral CMF have demonstrated statistically significant superiority for the anthracycline-containing regimens.[20] Thus, it is uncertain whether LRF ± DF could be significantly reduced in the comparison of six cycles of cyclophosphamide, doxorubicin, and fluorouracil or cyclophosphamide, epirubicin, and fluorouracil with six cycles of CMF.

The number of removed axillary LNs has been found to have an impact on the rates of LRF in several studies.[6,9,10] In the Danish study,[6] the LRF rate increased from 27% in patients who had more than nine LNs recovered to 40% in patients who had zero to three LNs recovered. In our study, the 10-year cumulative incidence of ILRF was significantly higher in patients who had one to five LNs removed; the rates were 19.7%, 12.9%, and 11.9% for patients who had one to five, six to nine, and ≥ 10 LNs dissected, respectively ($P = .05$; Table 3). The 10-year cumulative incidence of axillary failure as a first event was 9.3% in patients with one to five LNs removed compared with 2.2% and 1.5% in patients with six to nine and 10 or more LNs removed, respectively ($P < .0001$).[26] More importantly, the number of removed LNs remained an independent prognostic factor for ILF, IRF, LRF ± DF, and DF as first event.

In the majority of studies, RF is reported as part of LRF.[5-7,10,11] To potentially identify subgroups of patients with a low risk for RF who might not benefit from regional radiation, we reported the rates of ILF and IRF as first event separately. The 10-year cumulative incidence of IRF for patients with one to three LN+ varied between 2.3% and 3.5% for various tumor sizes (Table 4). The most common approach of PMRT includes the area of the chest wall and regional LNs. The risk of radiation pneumonitis increases with the increase in the lung volume irradiated as well as with the use of chemotherapy.[27,28] In addition, the risk for arm lymphedema increases when RT includes the axilla.[29] All these facts together raise the question of the need for regional radiation in the absence of survival benefit. Should radiation be used in this group of patients? In patients with four to nine LN+, the 10-year cumulative incidence of IRF as a first event varied between 5.4% and 8.7%. This risk increased up to 10.9% in patients with ≥ 10 LN+ (Table 4).

In a study including 1,703 premenopausal patients, de la Rochefordiere et al[30] showed that younger age was an independent significant prognostic factor in disease-free survival and overall survival. However, the authors did not report information about LRF. In the Recht et al[9] (629 patients < 44 years old) and Katz et al[10] (226 patients < 40 years old) studies, age was not found to be a significant predictor of LRF. In contrast, in our study (1,131 patients < 40 years old), the LRF ± DF was significantly higher in patients 20 to 39 years of age (26.1%) compared with patients more than 60 years old (14.1%; Table 3). This difference was highly statistically significant ($P < .0001$). In fact, in our study, age was also found to be an independent prognostic factor for ILF and IRF, LRF ± DF, and DF as a first event. However, it should be noted that, in our trials, women older than 50 years received tamoxifen independent of their ER status.

In conclusion, our study of 5,758 patients demonstrates that the incidence and pattern of failure in patients with LN+ treated with mastectomy and adjuvant chemotherapy with or without tamoxifen and without PMRT are similar to those found in the ECOG,[9] MDA,[10] and IBCSG studies[11] but are different from those found in the Danish and Canadian randomized trials.[5-7] The 10-year cumulative incidence of LRF ± DF in patients in our study who had four or more LN+ is substantial enough to warrant the consideration of adjuvant PMRT for these patients. On the basis of the tumor size, the group with one to three LN+ in our study had an incidence of LRF ± DF varying between 10.6% and 15.3%, which was much lower than the 30% to 33% rates reported in the Danish and Canadian randomized trials. The overall lower rates found in the ECOG, MDA, and IBCSG series, as well as in our study, do not justify the routine use of PMRT in this group of patients, and only the results of future randomized trials will eventually settle the question.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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