Combined Chemotherapy and Radiotherapy for Patients With Breast Cancer and Extensive Nodal Involvement

By Owen Ung, Allan O. Langlands, Bruce Barraclough, and John Boyages

Purpose: **This retrospective review examines local control, freedom from distant failure, and survival for patients with nonmetastatic breast cancer with extensive nodal disease (> 10 nodes, 45 patients; or ≥ 70% involved nodes if < 10 nodes found, 19 patients). All patients received chemotherapy and radiotherapy following mastectomy.**

Patients and Methods: **Sixty-four patients were treated between January 1980 and December 1988 at Westmead Hospital, Westmead, NSW Australia. The median follow-up duration for surviving patients was 91.5 months (range, 56 to 121). The median age was 51 years, and the median number of positive nodes was 11. Four successive protocols evolved, each with three phases, as follows: induction chemotherapy (doxorubicin or mitoxantrone, plus cyclophosphamide; three cycles), radiotherapy (50 Gy in 25 fractions to chest wall and regional nodes), then chemotherapy (cyclophosphamide, methotrexate, and fluorouracil [CMF]) of progressively shorter duration. Radiotherapy and chemotherapy were concurrent in the fourth regimen.**

Results: **One patient (1.5%) developed local recurrence before distant relapse, and seven patients (11%) developed local and/or regional recurrence simultaneously or after distant relapse. The 5-year actuarial freedom from distant relapse and overall survival rates were 45% and 65%, respectively. Overall survival did not vary significantly by menopausal status, nodal subgroup, or dose-intensity. There were no treatment-related deaths.**

Conclusion: **Combined chemotherapy and radiotherapy in standard dosage is an acceptable approach following mastectomy for patients with extensive nodal involvement at high risk for local recurrence and distant relapse. This approach should be considered standard best therapy for any randomized trials that examine high-dose chemotherapy or bone marrow transplantation for this subgroup of patients.**

J Clin Oncol 13:435-443. © 1995 by American Society of Clinical Oncology.

THE OPTIMUM management of patients with extensive nodal involvement following total mastectomy is undefined and has evolved with the recognition that such patients are at high risk not only for local recurrence, but also for distant relapse and death. The definition of patients with extensive nodal involvement has varied from a high absolute number (usually ≥ 10) to a high percentage of the number of nodes dissected being positive.[1] However, the extent of histologic involvement of the axillary nodes is dependent on the type of surgery performed and the extent of the pathologic analysis of the axillary specimen. Most clinicians define patients with ≥ 10 involved nodes to be at high risk, but it is unclear what constitutes extensive involvement if fewer than 10 nodes are dissected and/or fewer than 10 nodes are identified by the pathologist.

Data on the natural history of 24,136 women with extensive nodal involvement who were treated before 1972 with mastectomy with or without adjuvant radiation therapy is available from a national survey by the American College of Surgeons.[2] The risk of locoregional recurrence and death increased as the number of positive nodes increased. There was no clear dividing point by the absolute number of involved nodes. Patients with more than 10 positive nodes constituted 14% of all patients with positive nodes. The 5-year absolute survival rate in this group was 18.5%. Donegan and Lewis[3] also found that the number of positive nodes represented a continuum of increasing risk for treatment failure. In their study of 801 cases of breast cancer treated by radical mastectomy, patients with more than 10 involved nodes had a local recurrence rate of approximately 50% and a 10-year survival rate of less than 10%.

During the mid-1970s, the first results of adjuvant multiagent chemotherapy following mastectomy began to show significant improvements in disease-free survival. The recognition that adjuvant radiotherapy increased morbidity without an improvement of overall survival resulted in a diminution of its use, even in cases considered at high risk of local recurrence.[4] Several subsequent randomized studies showed a benefit for the addition of radiotherapy to chemotherapy after mastectomy.[5-13] Most of these studies reported a reduction in the risk of local recurrence and an improvement in disease-free survival. The largest study also found a survival advantage for adjuvant radiation and chemotherapy.[14]

The poor prognosis of patients with extensive nodal

From the Departments of Radiation Oncology and Surgery, Westmead Hospital, Westmead, Australia.

Submitted April 19, 1994; accepted September 20, 1994.

Address reprint requests to John Boyages, PhD, Department of Radiation Oncology, Westmead Hospital, Westmead, NSW 2145, Australia.

0732-183X/95/1302-0019$3.00/0

disease has promoted the use of adjuvant dose-intensive chemotherapy[15,16] or the use of high-dose chemotherapy with autologous bone marrow transplant.[15,17,18] Initial results have demonstrated a possible improvement in disease-free survival. However, there are a number of caveats, including small numbers of patients, short follow-up periods, and selection of younger and fitter premenopausal patients for these studies. Extensive pretreatment staging in the most recent trials of adjuvant chemotherapy or autologous bone marrow transplantation may explain the improvement of results with time. Any improvement in disease-free survival and possible overall survival from newer approaches must be balanced against increased morbidity, mortality, and cost.

In this report, we update the results of a series of patients with extensive nodal disease treated at Westmead Hospital with combined chemotherapy and radiotherapy in standard doses after total mastectomy and axillary dissection. Isolated local recurrence was rare, and acceptable rates of 5-year distant disease-free survival and overall survival were achieved for both premenopausal and postmenopausal patients. Our results are comparable to less mature results of high-dose chemotherapy with or without bone marrow transplantation and were achieved with minimal morbidity and no treatment-related mortality. This approach should be considered standard best therapy for randomized trials investigating high-dose chemotherapy or bone marrow transplantation for this subgroup of patients.

PATIENTS AND METHODS

Patient/Tumor Characteristics

Between January 1980 and December 1988, 64 patients with nonmetastatic breast cancer with extensive nodal involvement were treated with combined chemotherapy and radiotherapy following total mastectomy at the Department of Radiation Oncology, Westmead Hospital, Westmead, Australia. The median age for the patient group was 51 years (range, 24 to 72) and 49% of patients were premenopausal or perimenopausal.

Extensive nodal disease was defined as T1, T2, or T3 tumor (1978 International Union Against Cancer [UICC] staging system) without evidence of metastatic disease in a patient with ≥ 10 axillary lymph nodes involved (45 patients) or ≥ 70% involvement if fewer than 10 nodes were identified following an axillary dissection (19 patients). The median tumor size was 4 cm (range, 2 to 10). The number of nodes dissected ranged from four to 36 (median, 17) and the median number of positive nodes was 11 (range, three to 26). All patients underwent a metastatic evaluation that consisted of a blood count, routine blood chemistries, a chest x-ray, and bone scan and/or liver ultrasound if indicated by abnormalities in serum alkaline phosphatase or liver renal enzymes. Patients were excluded if they had significant cardiac or respiratory comorbidity (two patients) or if they were older than 75 years of age.

Treatment

All patients had undergone total mastectomy and axillary dissection. Treatment consisted of three cycles of induction chemotherapy, followed by locoregional radiotherapy then progressively shorter courses of additional chemotherapy. Four regimens evolved over the study period, with the aim to reduce the overall treatment time and treatment morbidity.

Phase 1 consisted of three cycles of either doxorubicin (50 mg/m^2; regimens 1 and 2) or since mid-1987, mitoxantrone (12 mg/m^2) combined with cyclophosphamide (750 mg/m^2; regimens 3 and 4) administered intravenously on day 1 of a 21-day cycle.

Phase 2 of treatment involved radiotherapy, of which all patients received 6-MV photons to the chest wall, supraclavicular fossa, and axilla. Typically, 50 Gy was delivered in 2-Gy fractions to the breast by medial and lateral tangential fields, using wedges to correct for inhomogeneity over 5½ weeks. The ipsilateral supraclavicular fossa and axilla were treated by an anterior field, prescribing 50 Gy in 25 fractions at 1.5 cm depth to the supraclavicular fossa. A posterior axillary boost was used to prescribe 50 Gy in 25 fractions to the midplane of the axilla. The internal mammary nodes were not routinely irradiated. One centimeter of bolus to the skin of the chest wall was used on a daily or second-daily basis for 70% of patients.

Phase 3 consisted of progressively shorter courses of cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2), and fluorouracil (600 mg/m^2) (CMF), usually administered intravenously on a 3-week cycle. Eleven patients who received regimen 1 were given oral cyclophosphamide (100 mg/m^2 on days 1 to 14), methotrexate (40 mg/m^2 on days 1 and 8), and fluorouracil (600 mg/m^2 on days 1 and 8) on a 4-week cycle for 12 courses as previously reported.[1] A reduction to six cycles of intravenous CMF (regimen 2, 20 patients; regimen 3, 13 patients) was based on an Italian study[19] that examined CMF in the adjuvant setting. Our results of intravenous versus oral CMF are published elsewhere.[20] The reduction to three cycles, given synchronously with radiotherapy (regimen 4, 20 patients), was empirical. The overall treatment time was reduced from a minimum of 50 weeks (regimen 1) to 18 weeks (regimen 4). Tamoxifen 20 mg/d was given for 2 years starting with the first cycle of chemotherapy to patients whose tumors were estrogen receptor-positive. Blood counts were performed before each course of chemotherapy and weekly during radiotherapy.

Follow-Up Evaluation

Follow-up data were obtained to June 1993. The median follow-up duration for surviving patients was 91.5 months (range, 56 to 121 m). Twenty-seven of 32 surviving patients (84%) had a follow-up duration ≥ 60 months and all patients were monitored for at least 56 months. Two patients with documented metastatic disease were lost to follow-up at 9 and 29 months, respectively. Patients who remained disease-free were reviewed every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Apart from yearly mammograms for the contralateral breast, investigations were not performed routinely, but on the basis of symptoms.

Statistical Methods

Local recurrence was defined as recurrent disease in the ipsilateral chest wall or regional lymph nodes. Local recurrence was scored even when it occurred after a distant relapse. Crude and actuarial

rates of local recurrence were calculated. Differences in rates of local recurrence were compared using the combined binomial exact test (CBET).[21] Local recurrence was scored as occurring concurrently with distant relapse if it was detected within 2 months of distant relapse. Actuarial rates of freedom from distant failure (FDF) and overall survival were calculated using the method of Kaplan and Meier.[22] Differences were compared using the log-rank test.[23] The most common sites of distant relapse were bone (45%), lung and pleura (29%), and liver (11%). Three patients with contralateral breast cancer and two patients with contralateral axillary disease were scored as having a distant relapse. The probability of distant relapse was examined by nodal subgroup (> 10 nodes $v \geq 70\%$ involvement if < 10 nodes identified) and by menopausal status. Postmenopausal patients were defined as those ≥ 50 years of age at diagnosis. Death from all causes was scored as an event for survival analysis. Two patients died from causes other than breast cancer while disease-free. Subgroup analyses of the risk of distant relapse and survival were calculated separately by age at diagnosis (< 50 years $v \geq 50$ years) and nodal status (≥ 10 positive nodes or ≥ 70% involved nodes). P values ≤ .05 were considered statistically significant. Time to recurrence and follow-up times were calculated from the date of mastectomy. The influence of dose-intensity was examined using total doses of cyclophosphamide, as this was given in both phases of chemotherapy using the method reported by Hryniuk and Levine.[24] However, dose-intensity was not associated with the risk of distant relapse (results not shown). Toxicity for each phase of treatment was evaluated for all patients according to the World Health Organization (WHO) classification.

Complications of treatment were abstracted from the radiotherapy and chemotherapy records. Data collected included information on leukopenia, alopecia, symptomatic pneumonitis, and arm edema. Minimal, moderate, or severe arm edema was arbitrarily set at a difference of 0.5 to 2 cm, 2.1 to 4.0 cm, and greater than 4.0 cm in girth between the treated and untreated side, usually measured 10 cm above the olecranon.

RESULTS

After a median follow-up duration of 91.5 months, eight patients (12.5%) have developed local recurrence. Seventy-five percent of local recurrences occurred within 30 months and all occurred within 48 months after mastectomy. Concurrent local recurrence and distant relapse occurred in four patients, distant first then local in three patients, and local followed by distant in only one patient (1.5%). For six of eight patients, local recurrence was minor and asymptomatic. Local recurrence generally occurred in the scar or chest wall and consisted of small nodules. One patient was noted to have small axillary nodules and three patients had supraclavicular masses. All of these nodules were controlled by local excision and/or hormonal treatment. Two patients developed uncontrolled local recurrence. A 54-year-old woman, who developed metastatic disease concurrently, died with a supraclavicular mass and carcinoma en curraise. The other patient, who is still alive, has progressive local recurrence.

Table 1 lists the number of patients who have developed distant relapse by nodal subgroup. After a median follow-up duration of 91.5 months, the crude rate of freedom from distant relapse was 39%. The proportion of patients who were free from distant relapse at 5 years (ie, excluding three patients who relapsed after 5 years) was 45%. Thirty-two patients (50%) are alive, 22 in the group of 45 patients (49%) with ≥ 10 involved lymph nodes and 10 of 19 patients (53%) with ≥ 70% involvement and fewer than 10 nodes identified (nonsignificant difference). The 5-year actuarial rate of freedom from distant relapse was 45% and the 10-year rate was 35% (Fig 1). The 5-year overall survival rate was 65% and the 10-year rate was 48% (Fig 1). Nine patients (14%) were alive and free of disease for ≥ 8 years. The crude rate of survival was not significantly different by nodal group (Table 1 and Fig 2).

Table 2 lists the results of an analysis of the effect of age at diagnosis on the risk of distant relapse and survival. Patients were divided into two groups: age ≥ 50 years (predominantly postmenopausal) or less than 50 years (predominantly premenopausal). Of note, 52% of the study group were older than 50 years. There were no significant differences in freedom from distant relapse or survival (Fig 3).

The postsurgical treatment regimen was reasonably well tolerated. During phase 1, minor delays in treatment due to toxicity occurred in 19% of patients. Only three of 64 patients failed to complete the three planned cycles. Leukopenia was the most common toxicity, but total WBC counts decreased less than 2.0/μL in only two patients. Fifty-three patients (83%) received ≥ 85% of the planned dose of cyclophosphamide. Approximately 60% of patients experienced some nausea during this phase, but this was severe for only two women. There were no severe reactions to radiotherapy. Moist desquamation occurred in 20 women (31%), and it was localized and responded to topical local treatments. The risk of moist

Table 1. Crude Rates of Distant Relapse and Overall Survival by Nodal Subgroup

Group	No.	Freedom From Distant Failure		Surviving Patients	
		No.	%	No.	%
≥ 10 positive nodes	45	16	36	22	49
≥ 70% nodes positive (if < 10 nodes dissected)	19	9	47	10	53
P		NS		NS	
Total	64	25	39	32	50

Abbreviation: NS, not significant.

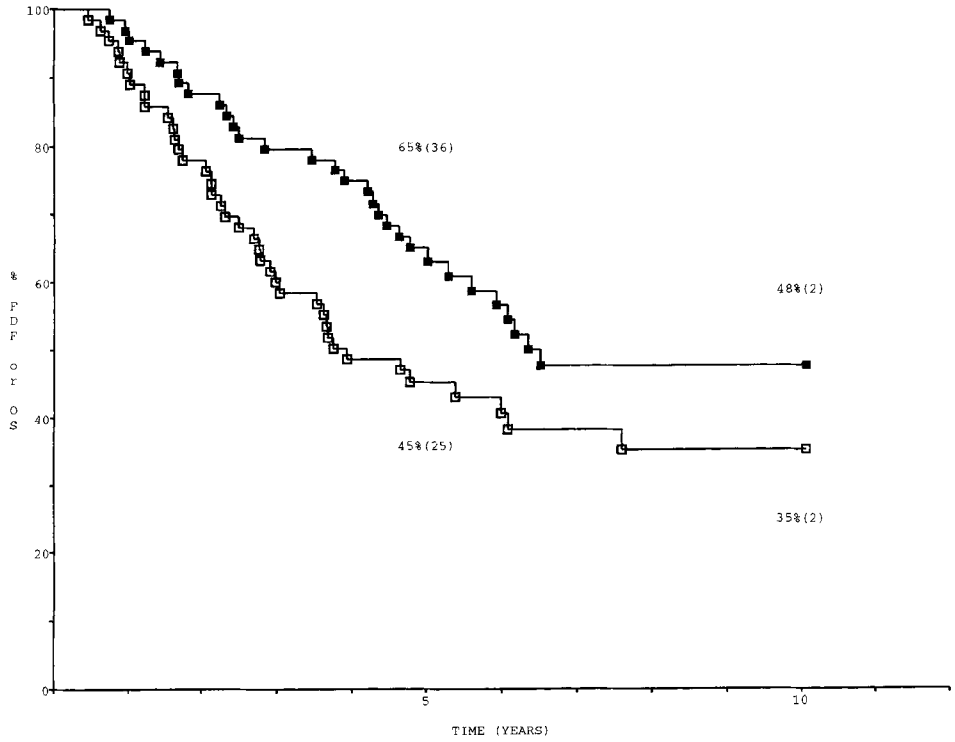

Fig 1. Freedom from distant failure (□, FDF) survival and overall survival (■, OS) for all patients. The 5- and 10-year rates of FDF were 45% (25 patients at risk) and 35% (2 patients at risk), and of OS were 65% (36 patients at risk) and 48% (2 patients at risk).

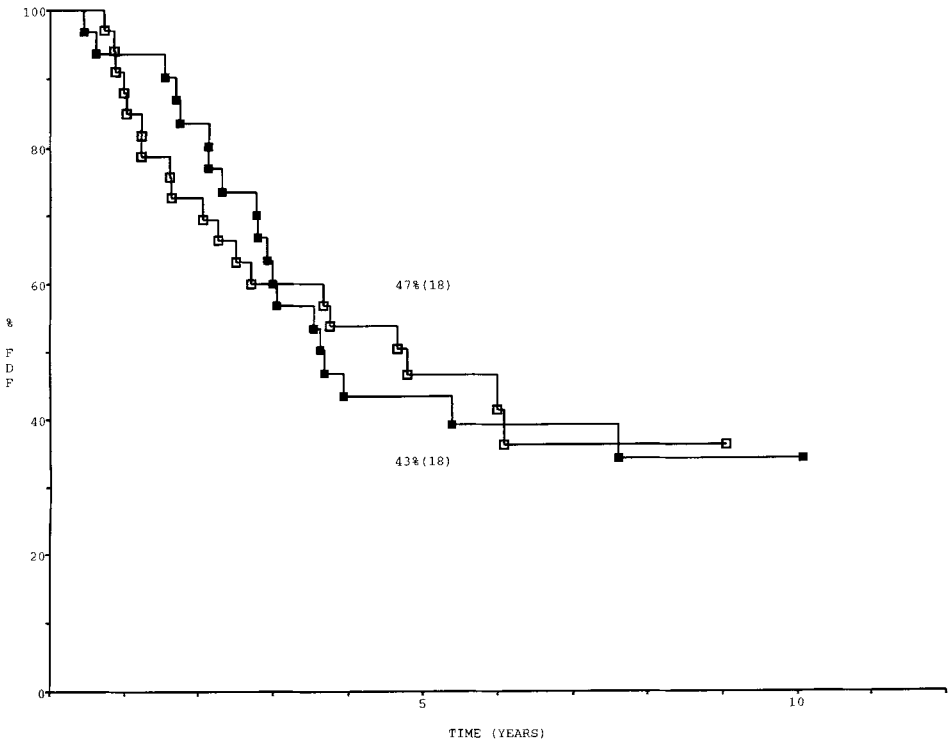

Fig 2. FDF for patients with ≥ 10 positive nodes (45 patients, □) and < 10 positive nodes (but ≥ 70% or more involved by carcinoma; 19 patients, ■). The 5-year rate of FDF was 42% for group 1 (16 patients at risk) and 53% for group 2 (10 patients at risk) (not significant).

Table 2. Crude Rates of Distant Relapse and Overall Survival by Age at Diagnosis

		FDF		Surviving Patients	
Group	No.	No.	%	No.	%
< 50 years	31	11	36	16	52
≥ 50 years	33	14	42	16	48
P		NS		NS	

desquamation was unaffected by treatment protocol. Fifty-two patients (81%) completed the planned number of cycles of chemotherapy for phase 3 of the treatment course. Seven patients (11%) received less than 50% of the planned dose. Forty women (63%) received ≥ 85% and 24 women (38%) received 100% of the planned dose of cyclophosphamide. Concurrent CMF and radiotherapy as given in protocol 4 did not influence the risk of marrow suppression. The percentages of cyclophosphamide given compared with that planned were 77%, 88%, 92%, and 100% for protocols 1 to 4, respectively. Minor delays due to toxicity occurred for 19 women during phase 3. Leukopenia was common, but WBC counts of less than 2.0/μL occurred on only four occasions. Sixty-two percent of patients experienced no nausea during this phase and severe vomiting was rare. Moderate nausea and vomiting occurred in 18% of women. Symptomatic pulmonary pneumonitis occurred in four patients (6%). Arm edema was documented in 17 patients (27%) and was severe for eight (13%).

DISCUSSION

In this report, we have updated our experience on the management of patients with nonmetastatic breast carcinoma with extensive nodal involvement treated with combined chemotherapy and radiotherapy following mastectomy.[1] We report high local control rates and moderate rates of freedom from distant relapse and survival using a protocol that is associated with acceptable toxicity and no treatment-related mortality.

There is a consensus that patients found to have ≥ 10 positive nodes following total mastectomy and axillary dissection have extensive nodal involvement and a poor prognosis.[2,3,25] However, there is no clear definition of what constitutes extensive nodal involvement if fewer than 10 nodes are found after an axillary dissection. Warren and Tompkins[26] found that patients with greater than 50% involvement of identified nodes had a 38% 5-year disease-free survival rate compared with 19% if all nodes identified were involved. In this report, we defined extensive nodal disease as ≥ 10 involved nodes or ≥ 70%

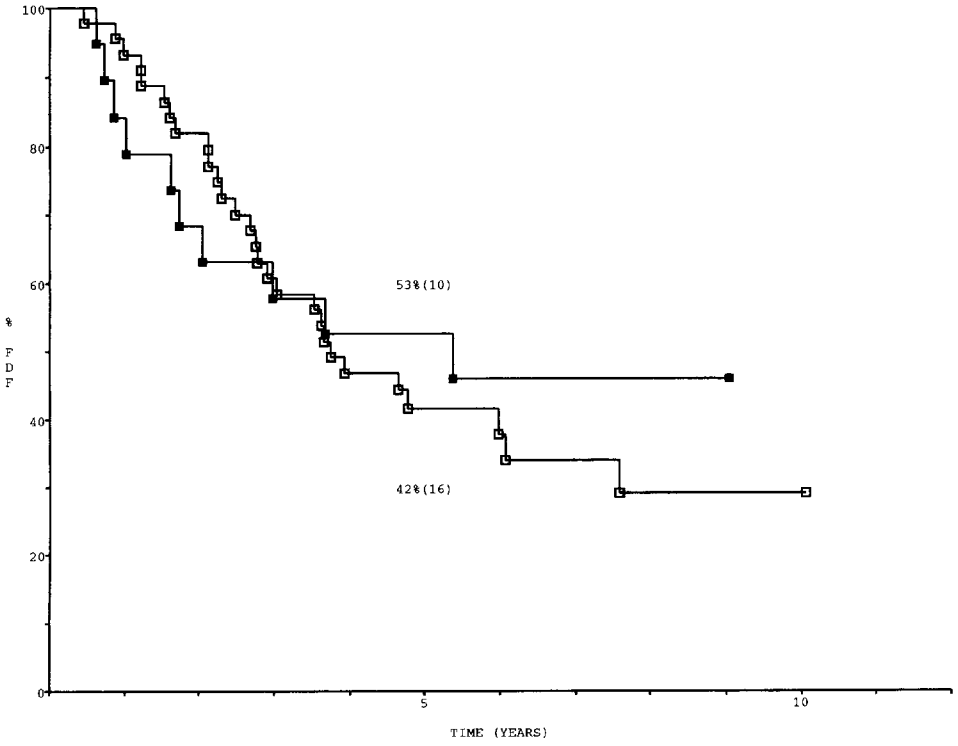

Fig 3. FDF for patients aged < 50 years (n = 31, ■) and ≥ 50 years (n = 33, □). The 5-year rate of FDF was 43% for younger patients and 47% for older patients (not significant).

involvement if fewer than 10 nodes were identified.[1] Of note, there was no significant difference in the risk of distant relapse or overall survival between these two subgroups (Table 1).

Adjuvant chemotherapy in standard doses has improved disease-free survival and possibly overall survival compared with historic and randomized controls. In the randomized trial of adjuvant CMF chemotherapy following mastectomy reported by Bonadonna et al,[25] fewer patients had ≥ 10 or positive nodes (7%) than would have been predicted from the American College of Surgeon's survey (14%). This may indicate selective referral of lower-risk patients to a trial of adjuvant chemotherapy without radiation therapy. The probability of local recurrence was not reported, but patients in both the control and treated arms had a very poor prognosis, with a 7-year relapse free survival rate of 11%. A recent nonrandomized study of 564 patients treated with mastectomy and adjuvant chemotherapy reported local recurrence rates by nodal status.[27] At 3 years, patients had an isolated locoregional recurrence rate of 22% (> seven nodes positive) compared with 14% (four to seven nodes positive) and 8% (< three nodes positive) ($P < .001$). The reported rates of local recurrence may be low because of short follow-up times and because local recurrences were not scored after distant relapse. Of note, the majority of patients in our study developed local recurrence either concurrently or after distant relapse. For six of eight patients, local recurrences were localized, and for two patients, carcinoma en curaisse was present at last follow-up evaluation or death.

The use of chemotherapy and radiotherapy versus chemotherapy alone following mastectomy has been studied in eight randomized trials.[5-7,10-14] Most studies are small, with a median of approximately 200 patients (range, 159 to 1,473). Also, most studies use a cutoff of more or less than four positive nodes to define extensive nodal involvement. The small number of patients could mean that a small, but clinically important difference in survival may be undetected. All seven studies that reported patterns of relapse showed an increase in disease-free survival for patients who received adjuvant radiotherapy. A statistically significant reduction in local recurrence was found in five studies.[5,11-14] Four studies[7,10,13,14] showed a significant improvement in disease-free survival by using a combined modality approach, and the largest study from Denmark of 1,473 patients also found a significant 5-year survival advantage.[14] Follow-up times ranged from less than 1 year to 9 years. The 5-year actuarial survival rate was 68% for patients who received adjuvant chemotherapy and radiotherapy, compared with 63% for patients who received adjuvant chemotherapy ($P = .03$). In our series, most surviving patients were monitored for at least 5 years and the 5-year actuarial rate of overall survival was 63%.

Limited data are available from randomized trials of adjuvant chemotherapy for patients with extensive nodal disease also treated with radiotherapy. One study found, by subgroup analysis, a significant improvement in 5-year overall survival for patients with four or more positive nodes who received postmastectomy chemotherapy and radiotherapy (54%) compared with patients who received adjuvant radiotherapy (35%) or adjuvant chemotherapy (46%) ($P = 0.01$).[10] A study from the Southeastern Cancer Study Group also separately analyzed patients with four or more positive nodes treated with mastectomy and adjuvant treatment. After a median follow-up duration of 10 years, patients who received postmastectomy radiotherapy and chemotherapy had a survival rate of 55% compared with 46% for patients who received adjuvant chemotherapy alone (nonsignificant difference).[13] Table 3 lists previous reports that have published data for patients with extensive nodal involvement, generally defined as ≥ 10 involved lymph nodes. Of note, our results, at a median follow-up time of 91.5 months, are comparable to those of more recent studies using more intensive chemotherapy dose regimens with or without autologous bone marrow transplantation.

Radiotherapy and chemotherapy can be given without a reduction in hematologic tolerance.[5,28,29] Our study compares favorably with other reports, in which 83% of patients received ≥ 85% of the planned dose of cyclophosphamide for phase 1 and 63% for phase 2. Symptomatic pneumonitis occurred in 4% of patients. The combined modality approach has been well tolerated, with an acceptable degree of toxicity and no treatment-related mortality. Treatment was well tolerated irrespective of menopausal status.

The concept that more chemotherapy is necessarily better has not been clearly established. There is evidence that a threshold may exist whereby increased toxicity associated with higher doses of chemotherapy will not be rewarded by improved tumor outcome.[30,31] However, in an attempt to improve the results of treatment for this group of patients, a number of investigators have explored more dose-intensive chemotherapy regimens.[15,16] Hudis et al,[15] at the Memorial Sloan-Kettering Cancer Center, have accrued 45 patients with more than four positive

Table 3. Previous Studies Including Patients With Extensive Nodal Involvement

First Author	Year	No. of Patients	% ≥10 Nodes Positive	Time of Results	Nodal Subgroup	Adjuvant Treatment	% Local Recurrence	Disease-Free Survival (%)	Overall Survival (%)
Nemoto[2]	1980	1,088	14.3	60 months	> 10	± RT	?	26	28
Donegan[3]	1978	801	?	5-24 years	> 10	Nil	~50	~10	~5
Bonadonna[4]	1976	9	5.0	10 years act.	≥ 10	CMF	?	11	44
Bonadonna[25]	1985	58	100	72 months, med	≥ 10	A/CMF	?	60	84
Pisansky[27]	1993	96	17.0	112 months, med	> 7	CFp	22	50†	?
Buzdar[34]	1992	283	100	5 years, act	≥ 10	A, C, ± M ± V ± RT	5 (+ RT), 11 (no RT)	41	56
Uematsu[35]	1993	39	17	60 months, act	≥ 10	A +/or CMF ± RT	7.7	14	?
Fowble[36]	1988	30	40	28 months, med	> 8	CMF + RT	3.3	27	?
Davidson[37]	1992	62	100	40 months	≥ 10	High-dose CAMV	?	53	81
Peters[17]	1993	102 (85)*	100	40 months, med	≥ 10	FAC, CPA, cDDP, BCNU + ABMT + TAM	6	72	77
Gianni[33]	1992	85 (48)*	100	21 months, med	≥ 10	High-dose CMV, CPA, L-PAM + ABMT	?	93	92
Current study	1994	64	100	60 months, act	≥ 10	NC or AC-RT-CMF	12.5	45	65

Abbreviations: C, cyclophosphamide; M, methotrexate; F, fluorouracil; A, doxorubicin; V, vincristine; RT, radiotherapy; CPA, cisplatin; cDDP, carmustine; ABMT, autologous bone marrow transplant; TAM, tamoxifen; N, mitoxantrone; p, prednisone; med, median; act, actuarial; BCNU, carmustine.

*Number eligible.

nodes to a dose-intensive chemotherapeutic regimen of cyclophosphamide with granulocyte colony-stimulating factor after doxorubicin. After less than 12 months of follow-up evaluation, half have completed chemotherapy and remain relapse-free. Twenty separate hospital admissions were required for 11 patients because of complications, but there were no treatment-related deaths. A study from the Johns Hopkins University examined the value of a 16-week dose-intensive regimen for 53 patients with ≥ 10 positive nodes. At a median follow-up time of 21 months, there were 13 relapses with a projected 3-year actuarial disease-free survival rate of 61%. Seven patients (13%) required hospitalization, but there were no treatment-related deaths.[16] In our study, only two patients required hospitalization during treatment, and the 3-year disease-free survival rate was 60%. This is comparable given that all surviving patients were monitored for a minimum of almost 5 years and the median follow-up duration was 91.5 months.

High-dose chemotherapy and autologous bone marrow transplantation has also been examined for this group of patients. However, it is important to note that patients are highly selected for this approach, often on the basis of general fitness and younger age.[32] The Milan group offered this treatment to 85 patients, but 37 (44%) either refused treatment or could not undergo treatment for logistic reasons. All patients were aged ≤ 55 years, compared with 70% in this age group in our study. Forty-eight patients with ≥ 10 positive nodes were treated. The 2-year actuarial relapse-free survival rate was 93% with one (2%) treatment-related death.[33] Peters et al[18] at Duke University treated a similar group of high-risk patients with high-dose cyclophosphamide, cisplatin, and carmustine with autologous bone marrow transplantation as consolidation after standard-dose adjuvant chemotherapy. Of note, 95% of patients were ≤ 50 years of age. Furthermore, patients were highly selected. Investigations included computed tomography of the head, chest, abdomen, and pelvis; bone scans and bilateral bone marrow aspirations; and biopsies. With a median follow-up duration of 3.3 years, the disease-free survival rate was 72% and overall survival rate 77%. Treatment-related mortality was high at 12%. Our study showed comparable results at similar follow-up times, without treatment-related mortality, and was used for both premenopausal and postmenopausal women.

We conclude that patients with extensive nodal disease after mastectomy treated with postmastectomy chemotherapy and radiotherapy achieve comparable high local control, disease-free, and overall survival rates to more intensive chemotherapy regimens with or without bone marrow transplantation. As such, there has to be a reasonable prediction from efficacy and cost-effective analysis of current studies that higher survival rates will be ob-

tained using these high-dose chemotherapy approaches given their high cost, significant morbidity, and risk of treatment-related mortality before the commencement of new trials using this approach. Randomized trials of bone-marrow transplantation for this subset of patients with extensive nodal disease should include a standard best-treatment control arm in which patients are treated with adjuvant chemotherapy and radiotherapy similar to that used in our study.

ACKNOWLEDGMENT

We acknowledge the assistance of Karen Nemic and Jenny Harding for data management, Val Gebski for statistics, and Dott Smith for secretarial support. We also thank the surgeons and oncologists who were involved in the care of these patients.

REFERENCES

1. Boyages J, Langlands AO: The efficacy of combined chemotherapy and radiotherapy in advanced non-metastatic breast cancer. Int J Radiat Oncol Biol Phys 14:71-78, 1988

2. Nemoto T, Vana J, Bedwani RN, et al: Management and survival of female breast cancer—Results of a national survey by the American College of Surgeons. Cancer 45:2917-2924, 1980

3. Donegan WL, Lewis JD: Clinical diagnosis and staging of breast cancer. Semin Oncol 5:373-384, 1978

4. Bonadonna G, Brusamolino E, Valagussa P, et al: Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 294:405-410, 1976

5. Griem KL, Henderson IC, Gelman R, et al: The 5-year results of a randomized trial of adjuvant radiation therapy after chemotherapy in breast cancer patients treated with mastectomy. J Clin Oncol 5:1546-1555, 1987

6. Blomqvist C, Tiusanen K, Elomaa I, et al: The combination of radiotherapy, adjuvant chemotherapy (cyclophosphamide-doxorubicin-ftorfur) and tamoxifen in stage II breast cancer. Long term follow-up results of a randomised trial. Br J Cancer 66:1171-1176, 1992

7. Ragaz J, Jackson S, Plenderleith I, et al: Randomized study of adjuvant chemotherapy versus chemotherapy and locoregional radiation in breast cancer—10 year results of the British Columbia trial. Proc Am Soc Clin Oncol 31:183, 1990 (abstr)

8. Buzdar AU, Blumenschein GR, Smith TL, et al: Adjuvant chemotherapy with fluorouracil, doxorubicin, and cyclophosphamide, with or without bacillus Calmette-Guérin and with or without irradiation in operable breast cancer. A prospective randomized trial. Cancer 53:384-389, 1984

9. Dewar JA, Benhamou E, Benhamou S, et al: Predictors of distant metastatic relapse in conservatively treated breast cancer. Proc Eur Soc Ther Radiol Oncol 1987 (abstr)

10. McArdle CS, Crawford D, Dykes EH, et al: Adjuvant radiotherapy and chemotherapy in breast cancer. Br J Surg 73:264-266, 1986

11. Muss HB, Cooper MR, Brockshmidt JK, et al: A randomized trial of chemotherapy (L-PAM vs CMF) and irradiation for node positive breast cancer. Eleven year follow-up of a Peidmont Oncology Association trial. Breast Cancer Res Treat 19:77-84, 1991

12. Ahmann DL, O'Fallon JR, Scanlon PW, et al: A preliminary assessment of factors associated with recurrent disease in a surgical adjuvant clinical trial for patients with breast cancer with special emphasis on the aggressiveness of therapy. Am J Clin Oncol 5:371-381, 1982

13. Velez-Garcia E, Carpenter JT, Moore M, et al: Postsurgical adjuvant chemotherapy with or without radiotherapy in women with breast cancer and positive axillary nodes: A Southeastern Cancer Study Group (SEG) trial. Eur J Cancer 28A:1833-1837, 1992

14. Overgaard M, Juul Christensen J, Johansen H, et al: Evaluation of radiotherapy in high-risk breast cancer patients: Report from the Danish Breast Cancer Cooperative Group (DBCG 82) trial. Int J Radiat Oncol Biol Phys 19:1121-1124, 1990

15. Hudis C, Lebwohl D, Crown J, et al: Feasibility of adjuvant dose-intensive cyclophosphamide (C) with G-CSF after doxorubicin (A) in women (pts) with high risk stage II/III resectable breast cancer (BC). Proc Am Soc Clin Oncol 111:55, 1992 (abstr)

16. Abeloff MD, Beveridge RA, Donehower RC, et al: Sixteen-week dose-intense chemotherapy in the adjuvant treatment of breast cancer. J Natl Cancer Inst 82:570-574, 1990

17. Peters WP: High-dose chemotherapy and autologous bone marrow support in the treatment of metastatic and primary breast cancer. Breast 2:110-114, 1993

18. Peters WP, Ross M, Vredenburgh JJ, et al: High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary breast cancer. J Clin Oncol 11:1132-1143, 1993

19. Tancini G, Bonadonna G, Valagussa P, et al: Adjuvant CMF in breast cancer: Comparative 5-year results of 12 versus 6 cycles. J Clin Oncol 1:2-9, 1983

20. Lindeman GJ, Boyages J, Driessen C, et al: Intravenous or oral adjuvant CMF for node-positive breast cancer. Aust NZJ Surg 62:556-562, 1992

21. Rice WR: A new probability model for determining exact *P*-values for 2×2 contingency tables when comparing binomial proportions. Biometrics 2:1-22, 1988

22. Kaplan EL, Meier P: Nonparametric estimation for complete observations. J R Stat Soc A 135:185-207, 1972

23. Mantel N, Haenszel W: Chi-square tests with one degree of freedom: Extensions of the Mantel-Haenszel procedure. J Am Stat Soc 58:690-700, 1963

24. Hryniuk W, Levine MN: Analysis of dose intensity for adjuvant chemotherapy trials in stage II breast cancer. J Clin Oncol 4:1162-1170, 1986

25. Bonadonna G, Rossi A, Valagussa P: Adjuvant CMF chemotherapy in operable breast cancer: Ten years later. World J Surg 9:707-713, 1985

26. Warren S, Tompkins VN: Significance of the extent of axillary metastases in carcinoma of the female breast. Surg Gynecol Obstet 76:327-330, 1943

27. Pisansky TM, Ingle JN, Schaid DJ, et al: Patterns of tumor relapse following mastectomy and adjuvant systemic therapy in patients with axillary lymph node-positive breast cancer. Cancer 72:1247-1260, 1993

28. Lippman ME, Lichter AS, Edwards BK, et al: The impact of primary irradiation treatment of localized breast cancer on the ability to administer systemic adjuvant chemotherapy. J Clin Oncol 2:21-27, 1984

29. Harris JR, Hellman S: Adjuvant chemotherapy in breast can-

cer patients treated by primary radiation therapy: Editorial. Int J Radiat Oncol Biol Phys 9:1757-1758, 1983

30. Gurney H, Dodwell D, Thatcher N, et al: Escalating drug delivery in cancer chemotherapy: A review of concepts and practice—Part 1. Ann Oncol 4:23-34, 1993

31. Gurney H, Dodwell D, Thatcher N, et al: Escalating drug delivery in cancer chemotherapy: A review of concepts and practice—Part 2. Ann Oncol 4:103-115, 1993

32. Hillner BE, Smith TJ, Desch CE: Efficacy and cost-effectiveness of autologous bone marrow transplantation in metastatic breast cancer. JAMA 267:2055-2061, 1992

33. Gianni AM, Siena S, Bregni M, et al: Growth factor-supported high-dose sequential (HDS) adjuvant chemotherapy in breast cancer with ≥ 10 positive nodes. Proc Am Soc Clin Oncol 11:60, 1992 (abstr)

34. Buzdar AU, Shu-Wan Kau, Hortobagyi GN, et al: Clinical course of patients with breast cancer with ten or more positive nodes who were treated with doxorubicin-containing adjuvant therapy. Cancer 69:448-452, 1992

35. Uematsu M, Bornstein BA, Recht A, et al: Long-term results of post-operative radiation therapy following mastectomy with or without chemotherapy in stage I-III breast cancer. Int J Radiat Oncol Biol Phys 25:765-770, 1993

36. Fowble B, Glick J, Goodman R: Radiotherapy for the prevention of local-regional recurrence in high risk patients post mastectomy receiving adjuvant chemotherapy. Int J Radiat Oncol Biol Phys 15:627-631, 1988

37. Davidson NE, Abeloff MD: Adjuvant systemic therapy in women with early-stage breast cancer at high risk for relapse. J Natl Cancer Inst 84:301-305, 1992