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The Management of Locally Advanced Breast Cancer: a Combined Modality Approach

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Abstract—*The prognosis for patients who have locally advanced breast cancer and are treated with conventional locoregional therapy is poor. Between* 1974 *and* 1981, 93 *evaluable patients with stages III (nine patients) and IV* (84 *patients) disease who had received no prior therapy were placed on a combined regimen of* 5-*fluorouracil,* 500 mg/m^2 *on days* 1 *and* 8, *doxorubicin (adriamycin),* 50 mg/m^2, *and cyclophosphamide,* 500 mg/m^2 *on day* 1 *(FAC) every* 3 weeks *for three cycles or until maximum tumor reduction occurred. This treatment was followed by mastectomy, local irradiation or both. FAC chemotherapy was then resumed until a total of* 450 mg/m^2 *of adriamycin had been given. At this time adriamycin was discontinued and replaced with methotrexate,* 30 mg/m^2 *on days* 1 *and* 8 *(CMF), in* 3-*week cycles until the patient had received therapy for a total of* 24 months. *The complete and partial response rate to initial FAC chemotherapy was* 86%, *allowing* 89 *of* 93 *patients who had tumors considered to be technically unresectable to become free of clinically detectable disease with subsequent local therapy. After a median follow-up of* 53 months *disease recurred in* 47 *patients, six of whom had attained a second disease-free status following local therapy. The estimated median length of survival for the whole group was* 66 months, *and the median disease-free interval (DFI) was* 30 months. *Age, race, menopausal status and the presence of supraclavicular lymphadenopathy had no effect on prognosis. In patients with stage III disease DFI and survival duration were increased, as was true also for patients with residual tumors of* ≤1 cm *in their mastectomy specimens. Patients in whom the tumors were estrogen receptor (ER)-positive also had longer DFI than those with ER-negative tumors. In spite of the encouraging results obtained with the combined modality approach to treating locally advanced breast cancer, future improvement should be pursued through additional hormonal therapy, optimal local radiation therapy timing and early resumption of intensive chemotherapy following locoregional treatment.*

INTRODUCTION

THE TERM 'locally advanced' (T_{3b}, T_4, N_2, N_3) breast cancer refers to tumors larger than 5 cm, the presence of supraclavicular or fixed axillary lymphadenopathy, invasion of the chest wall by tumor, skin edema, ulcerations or satellite lesions—all without evidence of distant metastasis [1]. Despite the technical feasibility of complete resection by radical mastectomy in many instances, tumors in this category are considered unresectable due to a high local recurrence rate of more than 50% with no lasting clinical remissions and only occasional survivors at 5 yr [2].

The poor results obtained with surgery alone prompted the use of radiation therapy, alone or in conjunction with surgery, as the primary mode of treatment [3–5]. This form of combined therapy resulted in better local control in 50–75% of the patients, at the expense of an increased rate of complications (lymphedema, fibrosis and necrosis) from supervoltage high-dose radiotherapy in excess of 60 Gy [3].

The benefits obtained with locoregional therapy are limited. In patients who undergo

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surgical resection following radiation therapy, the incidence of residual disease is high in the resected breast (75%) and in the axilla (68%), with only 10% complete tumor sterilization [6]; significant side-effects result from the use of supervoltage radiotherapy [3]; and despite a reasonable level of local control, most patients still succumb to distant metastasis, the median survival duration being 30 months [5, 6]. These results indicate that in a high proportion of patients early micrometastases are present, and additional systemic therapy is necessary to control disseminated disease.

The increased effectiveness of combination chemotherapy in treating patients with breast cancer prompted this investigation [7, 8], adding systemic chemotherapy to radiation therapy or surgery, or both, in an effort to maintain both systemic and regional control of locally advanced breast cancer. This approach was aimed at decreasing the need for radical surgery and 'radical' radiotherapy doses and at improving remission duration and prognosis.

The findings discussed in this report were obtained from a study of 93 evaluable patients treated at The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston between January 1974 and November 1981; these data update the experience and results reported from this institution [9].

MATERIALS AND METHODS

Between January 1974 and November 1981, 102 previously untreated patients with locally advanced breast cancer proved by biopsy were entered in the study. Tumors were classified as T_3, T_4, N_2, N_3 and were graded according to the American Joint Commission modification of the TNM classification. All patients were examined by a multidisciplinary tumor board, consisting of a medical oncologist, a surgical oncologist and a radiotherapist, who made the decisions concerning inclusion in the study and the sequencing of locoregional therapy. Patients who had advanced primary tumors amenable to complete surgical resection or who had inflammatory carcinoma were not entered in this study. Patients in whom distant metastasis, overt congestive heart failure or uncontrolled hypertension were diagnosed were also not included. Age or performance status were not considered criteria for excluding the patient from the study.

All patients had a history and physical examination, complete blood count and serum chemistry, urinalysis, electrocardiogram, chest roentgenograms, carcinoembryonic antigen levels, bone surveys or bone scans, or both, for determining metastatic disease, liver–spleen scan and bilateral xeromammograms. Prior to 1978 bone marrow aspiration and brain scans were performed as indicated, but thereafter they were done routinely as part of the patient profile. Complete blood counts were obtained weekly during treatment, and the doses of chemotherapy were adjusted to the degree of myelosuppression. Tumor measurements were made every 3 weeks until a disease-free status was reached. Surveys were done for metastatic involvement every 3–4 months during therapy and every 4–6 months thereafter. Adriamycin cardiotoxicity was monitored, as indicated, by follow-up electrocardiograms and radionuclide cardiac scanning.

The initial treatment program consisted of chemotherapy with 5-fluorouracil, doxorubicin (adriamycin), and cyclophosphamide (FAC) for three cycles (52 patients treated between 1974 and 1977) or until a maximal response was obtained (41 patients treated between 1977 and 1981). In the latter group stability of the disease after three courses or lack of substantial further tumor reductions $\geqslant$25% with each subsequent treatment following three courses compared to the size of the tumor prior to the course was an indication for locoregional therapy. Bacillus–Calmette–Guerin (BCG) non-specific immunotherapy was administered to the initial 52 patients only (Table 1). Upon completion of this therapy, patients were re-evaluated by the tumor board and local therapy was planned according to their response status, as follows: (1) in patients in whom a complete remission (CR) or tumor reduction to less than 2 cm was achieved after initial FAC therapy, radiation therapy was administered to the breast and lymph nodes. Some patients with large breasts also underwent simple mastectomy to facilitate radiotherapy delivery; (2) in patients with partial regression but persistent tumor, a simple or extended simple mastectomy was performed followed by radiation therapy to the chest wall and peripheral lymph nodes; and (3) in patients with no substantial tumor reduction and in whom the tumor remained technically unresectable, treatment with only local radiotherapy to the tumor and peripheral lymph nodes was attempted in twice-daily fractions, as described later.

Surgery was performed 3 weeks after the third cycle of FAC, and radiotherapy was started either 2–3 weeks after surgery or 3 weeks after the last dose of chemotherapy. Chemotherapy and radiotherapy were not given simultaneously. 60-Cobalt radiation after surgery or complete remission following chemotherapy consisted of 50 Gy to the chest wall or breast and to the internal mammary, supraclavicular and axillary lymph nodes. The area of residual tumor or scar was

Table 1. *Locally advanced primary breast cancer treatment program*

FAC × 3 (1974–1977), or Until maximal response → surgery, radiotherapy → FAC* → CMF (1977–1981) (total duration of therapy: 2 yr)	
FAC	
5-Fluorouracil	500 mg/m² i.c. days 1 + 8
Adriamycin	50 mg/m² i.v. day 1
Cyclophosphamide	500 mg/m² i.v. day 1
BCG immunotherapy†	6×10^8 units by scarification on days 9, 13 and 17
CMF	
Cyclophosphamide	500 mg/m² p.o. day 2
Methotrexate	30 mg/m² i.m. days 1 + 8
5-Fluorouracil	500 mg/m² p.o. days 1 + 8
Immunotherapy† as with FAC	

Duration of cycles, FAC of CMF: 21 days.
*Until a total dose of 450 mg/m² of adriamycin is reached.
†Given to the inital 52 patients.

given an additional 15–20 Gy to a restricted field, as described by Brown *et al.* [10]. When no substantial tumor reduction was obtained after initial chemotherapy, patients were treated with twice-daily fractions of radiotherapy to the breast for a total dose of 55 Gy/5 weeks (50 fractions), with a boost to the areas of residual disease. Whenever possible, internal mammary nodes were treated with the electron beam to decrease the risk of additive cardiotoxicity from adriamycin and irradiation.

Three weeks after completion of radiotherapy or 2 weeks after surgery, chemotherapy with FAC-BCG was reinstituted until a total cumulative dose of 450 mg/m² of adriamycin had been given. Then adriamycin was discontinued and maintenance chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) plus BCG was started (Table 1). The planned total treatment duration was 24 months.

In the group treated between 1977 and 1981, eight patients with estrogen receptor (ER)-positive tumors received additional hormonal therapy with tamoxifen, 10 mg orally twice daily. Twelve patients were treated for shorter periods (between 12 and 18 months), five of whom received additional tamoxifen maintenance therapy.

Complete remission (CR) was defined as disappearance of all subjective or objective evidence of tumor. Partial remission (PR) represented a 50% or more reduction of the sum of the products of the largest perpendicular diameters of measurable lesions without the development of new lesions. Patients with less than 50% decrease to 25% or less increase in tumor measurements were considered to have stable disease (SD). All other patients had progressive disease. Both palpation and mammographic measurements were used to determine responses.

Patients in whom disease recurred following combined modality therapy were treated by means of various hormonal manipulations, chemotherapy or local salvage therapy (surgery or radiotherapy).

The disease-free interval (DFI) was calculated from the date of mastectomy or the date of CR. Survival was calculated from the time chemotherapy was started. The Kaplan and Meier method was used to calculate DFI and survival curves [11], and the generalized Wilcoxon test was employed to determine differences between survival curves [12].

RESULTS

One hundred and two eligible patients were entered in this study. Nine patients were considered inevaluable: five had received no local therapy, two had evidence of bone metastasis at the start of therapy and two were lost to follow-up after the initial course of chemotherapy.

Ninety-three patients who completed the initial therapeutic regimen as planned were considered evaluable for analysis, and their distribution is shown in Table 2. The median age for evaluable patients was 56 yr (range 28–79 yr). Thirty-four patients were premenopausal and 59 were postmenopausal. Seventy-seven patients were white. The ER status of the primary tumor was available for 47 patients: 25 (53%) were positive and 22 (47%) were negative. Age, menopausal status, race and stage of disease were comparable in patients treated between 1974 and 1977 and between 1977 and 1981.

Table 2. Locally advanced breast cancer—clinical stage by TNM classification (93 patients)

Clinical stage-grouping	TNM classification	No. of patients
Stage III	T_2N_2	3
	T_3N_1	1
	T_3N_2	5
Stage IV	T_2N_3	5
	T_3N_3	5
	T_4N_{0-1}	31
	T_4N_2	24
	T_4N_3	19
Total		93

Reponse, disease-free interval and survival

The overall response rate (CR + PR) after initial chemotherapy was 86%. The rate was slightly higher in patients who were treated with chemotherapeutic agents until a maximum response was achieved (90 vs 82%). Thus sufficient tumor reduction was obtained in 89 of the 93 patients (96%) whose tumors were initially considered technically unresectable to render them free of clinical disease with subsequent local therapy. After a median follow-up period of 53 months, 42 of the 89 patients (47%) remained free of disease after being treated with the combined modality approach while 53% have since suffered relapses. The median overall duration of remission in these patients was 30 months (Fig. 1). Six were disease-free after surgical resection of the locally recurring lesion and five remained disease-free after being followed for 5–32 months in the second recurrence after local therapy. The estimated length of survival was 66 months, with 3- and 5-yr survival rates of 64 and 52%.

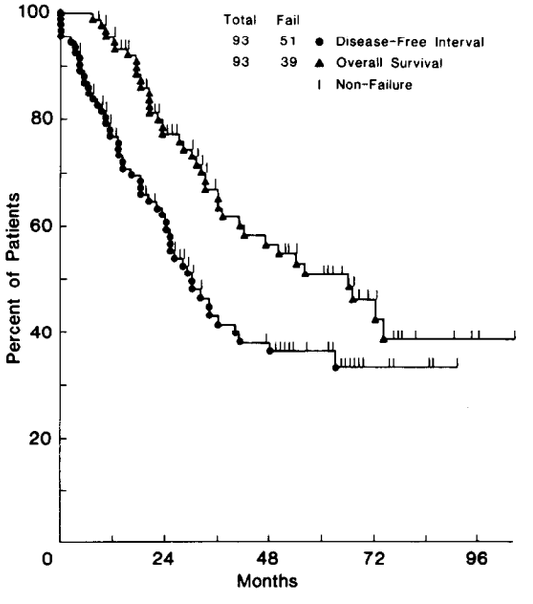

Fig. 1. Disease-free interval (DFI) and survival of patients with locally advanced breast cancer treated with the combined modality approach.

Importance of host and treatment variables

After the initial cytoreductive chemotherapy with FAC, 17 patients (18%) achieved CR, 63 patients (68%) achieved PR and 12 patients (13%) had SD. Only one patient had progressive disease after two cycles of chemotherapy. The median time to achieve PR was 6 weeks. Four percent of patients treated between 1974 and 1977 and 44% of patients treated between 1977 and 1981 received more than three cycles of chemotherapy before local therapy. This resulted in a slightly higher response rate in the latter group (90 vs 82%). There was no significant difference in the degree of nodal involvement or residual tumor size in the patients who underwent surgery in either group. DFI and survival rates were also similar.

In 51 patients local therapy consisted of surgery and radiotherapy, while 40 patients were treated either with surgery or radiotherapy (Table 3). Seventeen patients did not receive radiotherapy for the following reasons: no evidence of tumor in the mastectomy specimen (4); medical contra-indications (6); bilateral advanced primary breast cancer (2); early death (1); patient refusal (2); and relapse prior to scheduling radiotherapy (2).

DFI and survival of patients were analyzed in relationship to various prognostic factors. Age, race and menopausal status had no significant effect on DFI or survival. Of the 22 patients with ER-negative tumors, recurrent disease has developed in 17 (77%), and in these the median DFI was 24 months. In the group of patients with ER-positive tumors, 12 (48%) had recurrent disease, and the median DFI was 30 months ($P = 0.3$). Despite the impressively longer survival rate of patients with ER-positive tumors (median of 66 vs 33 months), the difference was not statistically significant.

Table 3. Locally advanced breast cancer—locoregional therapy

Response to FAC	Type of local treatment	No. of patients	No NED	%
Stable	RT	1	-	
(12 patients)	surgery + RT	11	6	(55)
Partial remission	surgery	14	4	(28)
(63 patients)	RT	14	5	(36)
	surgery + RT	35	16	(46)
Complete remission	surgery	4	3	(75)
(17 patients)	RT	7	5	(71)
	surgery + RT	6	3	(50)

The patient with progressive disease had two courses of FAC but no local therapy.

Supraclavicular lymphadenopathy had no adverse effect on prognosis. The median DFI in these patients was 32 months, compared with 30 months for those with no supraclavicular involvement.

The effect of initial response to chemotherapy on DFI and survival also was evaluated. A definite trend toward prolongation of DFI was noted in patients in whom CR was achieved (63 months) when compared with those who had PR (29 months, $P = 0.09$) or SD (18 months, $P = 0.06$). However, this finding did not translate into increased survival in the three subgroups (66 vs 56 vs 54 months).

Although only a few patients with stage III disease were included in this study, their outcome was better than those with stage IV disease. The median DFI in those with stage III disease exceeded 45 months, compared with 26 months ($P = 0.07$) in patients with stage IV tumors.

The size of residual tumor in the mastectomy specimen also had a bearing on prognosis. The DFI was 42 months for patients in whom the tumor in the mastectomy specimen measured $\leqslant$1 cm compared with 23 months ($P = 0.06$) for those with larger residual tumors.

A major concern during the study was the interruption of chemotherapy and systemic treatment during the administration of locoregional therapy. To determine the significance of such delays, patients were divided into two subgroups: (1) those in whom systemic chemotherapy was resumed within 7 weeks from the time of surgery or end of radiotherapy; and (2) those in whom it was delayed beyond this period. Early resumption of chemotherapy was associated with a better median DFI (41 vs 28 months) and survival (72 vs 56 months), although this difference did not reach statistical significance.

Another issue difficult to assess was the duration of maintenance chemotherapy required to obtain optimal results. We compared the outcome of patients who had completed 24 months of therapy with that of patients who received shorter courses of chemotherapy and remained disease-free at 24 months. Patients who suffered relapses before 24 months were not included in the analysis. The second group consisted of the 12 patients in whom the total duration of therapy was shortened to 9–18 months and six additional patients who refused further chemotherapy after being treated for 4–14 months. No significant difference in median DFI and survival was noted between the two groups.

Patterns of relapse and toxicity

At the time of the analysis, 47 patients have relapsed. The following analysis is confined to the initial manifestation of relapse, initial relapse censoring later relapses. Distant metastasis occurred in 33 patients (37%) and locoregional recurrence in 17 patients (18%). Three patients had simultaneous relapse at both local and distant sites. Distant metastasis involved the lungs in seven patients, liver in eight, pleura in 11, bone in 13 and other sites in three. A second primary breast cancer developed in two patients (2.1%). Locoregional recurrence as a first sign of relapse developed in five of 18 patients who did not receive radiation therapy (28%) and in 12 of 74 patients who did receive radiation therapy (16%). There was no significant difference in the incidence of local or distant metastasis when chemotherapy was given with surgery alone, with radiotherapy alone or with both forms of treatment. These patients tolerated treatment well, although all of them had nausea, vomiting and alopecia. Myelosuppression was the dose-limiting toxicity and was similar in degree and duration to that encountered in other FAC programs [7]. Following completion of radiotherapy, a substantial proportion of patients required moderate dose reductions of 20% during subsequent courses of chemotherapy. Major complications consisted of seven infectious conditions (four pneumonias, one sepsis, two urinary tract infections) and six febrile episodes during neutropenia. Congestive heart failure

developed in seven patients, but it was mild and easily controlled in six of them. In one, however, the condition was severe and resulted in the only treatment-related death. All seven patients were elderly, with a median age of 64 yr (range 52–73 yr); five received XRT in addition to chemotherapy, and in two of these it was delivered to the left breast area. Severe mucositis, methotrexate liver dysfunction and radiation recall occurred in one patient each.

DISCUSSION

Our study demonstrates the effectiveness of a combined modality approach using preoperative cytoreductive chemotherapy and surgery or radiotherapy, or both, in the treatment of patients with locally advanced breast cancer. Despite the large initial tumor burden, in 86% of the patients chemotherapy produced objective regression of tumors. In 89 of 93 patients sufficient tumor reduction was achieved to make them technically resectable. Subsequent locoregional therapy produced a disease-free state in these patients; in fact, a substantial number (25%) did not require surgery. Locoregional therapy was feasible with less radical procedures, such as simple or extended simple mastectomies, and radiotherapy doses of 45–50 Gy, thus avoiding the serious local complications occurring in previous studies using radical mastectomy or high-dose protracted radiotherapy [3].

The influence of various prognostic factors on outcome was analyzed. Among the 47 patients in whom ER information was available, 25 (53%) had ER-positive tumors, an incidence similar to that of primary tumors and metastatic disease [13]. Thus local progression of disease in the absence of systemic dissemination cannot be explained on the basis of ER characteristics. The ER status correlated with prognosis: patients with ER-positive tumors had longer intervals of remission and survival than those with ER-negative tumors, although the difference was not statistically significant. This finding concurs with the information available for other categories of breast cancer [13]. The limited number of patients in our study precludes making conclusions concerning additional hormonal therapy in ER-positive tumors. However, a large amount of information has been accumulated about metastatic breast cancer that suggests a 50–60% response rate following hormonal therapy for ER-positive tumors compared with less than 10% in patients with ER-negative tumors [14, 15]. These circumstances, together with the favorable results obtained with combined hormonal therapy and chemotherapy [13–16], encourage the addition of hormonal therapy in patients with locally advanced breast cancer.

Age, race and menopausal status had no effect on the results. Similarly, supraclavicular lymphadenopathy had no effect on prognosis. Although the number of patients was small, those with stage III disease seemed to fare better than those with stage IV disease ($P = 0.07$). Our study did not establish the value of administering chemotherapy until maximal tumor response over the results of a three-cycle fixed schedule before locoregional therapy was started. In spite of a slightly higher response rate and lower incidence of axillary nodal involvement, the DFI and survival were not significantly different. This is not surprising since the majority of responses usually take place within the period of three cycles. Also, a considerable number of patients are necessary to detect improvements in the range of 20% if statistical significance is to be reached.

Of note is the fact that no residual tumor was found in four mastectomy specimens, and in seven patients only microscopic disease was seen. A more interesting finding was the correlation of the size of residual tumor with outcome: both DFI and survival were longer ($P = 0.06$) in patients with tumors of $\leqslant 1$ cm in their mastectomy specimens. In view of these results, the use of preoperative cytoreductive chemotherapy until maximal tumor response occurs prior to starting local therapy seems appropriate.

The timing of local radiotherapy needs to be critically evaluated. Although radiotherapy does decrease the postoperative local recurrence rate, it does not increase length of survival [17] and may compromise the chemotherapy doses. In our study a substantial proportion of patients who received radiotherapy later experienced decreased tolerance to chemotherapy, and subsequent 20% dose reductions were necessary. Evidence is accumulating in support of a dose–response curve for chemosensitive tumors such as breast cancer; even small reductions in doses may drastically decrease the response rate [18, 19]. Moreover, our study suggests that a delay in resumption of systemic chemotherapy after locoregional treatment may worsen the prognosis. Nissen–Meyer *et al.* [20] also reported that patients who were given systemic cyclophosphamide immediately after surgery remained in remission for significantly longer periods than those in whom chemotherapy was delayed for 3 weeks. Bearing these facts in mind, one might conclude that local radiotherapy is best started after completion of the chemotherapy treatment program to allow the delivery of maximally tolerable doses, to avoid treatment delays after surgery and, at the same time, to decrease the high incidence of local relapses in

patients treated with surgery as the sole locoregional modality.

Worsening of prognosis was not apparent in patients in whom treatment of short duration was undertaken. Tancini *et al.* [21] reported equivalent results in patients with stages II and III tumors who were given adjuvant chemotherapy for six or 12 cycles. Thus it is possible that locally advanced breast cancer may respond to shorter courses of maintenance chemotherapy as effectively as to treatments of longer duration.

The rationale for the combined modality approach in treating locally advanced breast cancer is based on several important facts. The success of systemic combination chemotherapy in both metastatic disease [22] and in the adjuvant setting [23] favors its use in locally advanced disease. In the majority of patients treated with locoregional therapy, relapse occurs in the form of distant metastasis in spite of good local control. In such cases early micrometastatic disease may be present that would require a systemic approach [5, 6]. Finally, preoperative cytoreductive chemotherapy would provide sufficient 'medical tumor debulking', thereby permitting less radical forms of surgery and radiotherapy to be employed. This principle has already been applied, with favorable results, in treating other types of tumors such as sarcomas and head and neck cancers.

Table 4 lists the major studies conducted to investigate the effect of various treatment regimens on locally advanced breast cancer. A significant trend toward improved prognosis is seen following the addition of systemic combination chemotherapy. The median survival of 66 months in our population is impressive when compared with the reported 20–30 months median survival from previous studies using locoregional therapy as the sole treatment modality.

Rubens *et al.* [24] reported 24 patients with locally advanced breast cancer who received four courses of adriamycin and vincristine (AV) followed by radiotherapy, eight courses of AV and then eight courses of CMF. The median duration of response was 33 months, which is significantly longer than that of the historical control group treated with radiotherapy alone (10.5 months; $P = 0.02$). Chauvergne *et al.* [25], using only four cycles of adriamycin, vincristine and methotrexate before radiotherapy, reported a similar improvement in prognosis and a median DFI longer than 31 months.

Bruckman *et al.* [5] reviewed the Harvard experience with 116 patients with locally advanced breast cancer and noted a 51% 4-yr DFI in 26 patients who received some form of adjuvant chemotherapy, which was an improvement over the 29% DFI ($P = 0.02$) in a matched group of patients treated with radiotherapy alone. De Lena *et al.* [26, 27], who used a similar multimodal treatment program, reported a longer duration of remission (19 months) in patients treated with additional adriamycin-containing chemotherapy than in those treated with locoregional therapy only (11 months). Although it is very difficult to compare patient populations treated at different institutions, the improved median DFI (30 vs 19 months) and survival (66 vs 50 months) in our series compared to the study of De Lena *et al.* [27] suggest a possible benefit from more intensive chemotherapy regimens. Similar results were also

Table 4. Comparison of locoregional to combined therapy approaches in locally advanced breast cancer

Reference	No. of patients	Treatment modality	Remission duration Median (months)	Remission duration 5-yr%	Survival duration Median (months)	Survival duration 5-yr%
[4]	455	RT	N.A.	20	N.A.	32
[6]	454	RT ± surgery	24	N.A.	30	30
[29]	266	RT + surgery	N.A.	N.A.	N.A.	28
[5]	116	RT	13	22	36	25
	41	RT + CT	36	N.A.	N.A.	N.A.
[24]	24	RT + CT (AV-CMF)	33 (10.5 in historical control)	T.E.	36 (25 in historical control)	T.E.
[25]	54	CT + RT ± surgery	>31	T.E.	>31	T.E.
[26, 27]	110	RT + CT (AV)	19 (11 in control)	53 (3 yr)	50	50 (4 yr)
Present study	93	CT + surgery + RT	30	37	66	53

RT = Radiation therapy; CT = chemotherapy; A = adriamycin; V = vincristine; C = cyclophosphamide; M = methotrexate; F = 5-fluorouracil; N.A. = not available; T.E. = too early.

reported by Sponzo *et al.* [28] and Rubens [13].

In conclusion, the use of a combined treatment modality consisting of initial cytoreductive chemotherapy and late maintenance chemotherapy in addition to the locoregional treatment improved the prognosis in patients with locally advanced breast cancer. Less radical forms of surgery and radiotherapy were possible, and the disease-free interval and survival were significantly lengthened.

Treatment of breast cancer patients may be further enhanced by the addition of hormonal therapy, optimal timing of local radiotherapy and, finally, more intensive chemotherapy, starting immediately after surgical resection or, even, intraoperatively.

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