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CLINICAL INVESTIGATION **Breast**

LOCOREGIONAL TREATMENT OUTCOMES FOR INOPERABLE ANTHRACYCLINE-RESISTANT BREAST CANCER

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Purpose: To assess the therapeutic outcomes and treatment-related morbidity of patients treated with radiation for inoperable breast cancer resistant to anthracycline-containing primary chemotherapy.

Methods and Materials: We analyzed the medical records of breast cancer patients treated on five consecutive institutional trials who had been designated as having inoperable locoregional disease after completion of primary chemotherapy, without evidence of distant metastases at diagnosis. The cohort for this analysis was 38 (4.4%) of 867 patients enrolled in these trials. Kaplan–Meier statistics were used for survival analysis, and prognostic factors were compared using log–rank tests. The median follow-up of surviving patients was 6.1 years.

Results: Thirty-two (84%) of the 38 patients were able to undergo mastectomy after radiotherapy. For the whole group, the overall survival rate at 5 years was 46%, with a distant disease-free survival rate of 32%. The 5-year survival rate for patients who were inoperable because of primary disease extent was 64% compared with 30% for those who were inoperable because of nodal disease extent ($p = 0.0266$). The 5-year rate of locoregional control was 73% for the surgically treated patients and 64% for the overall group. Of the 32 who underwent mastectomy, the 5-year rate of significant postoperative complications was 53%, with 4 (13%) requiring subsequent hospitalization and additional surgical revision. Preoperative radiation doses of ≥54 Gy were significantly associated with the development of complications requiring surgical treatment (70% vs. 9% for doses <54 Gy, $p = 0.0257$).

Conclusion: Despite the poorer prognosis of patients with inoperable disease after primary chemotherapy, almost one-half remained alive at 5 years and one-third were free of distant disease after multidisciplinary locoregional management. These patients have high rates of locoregional recurrence after preoperative radiotherapy and mastectomy, and the morbidity associated with this approach may limit dose-escalation strategies. Alternative therapeutic strategies such as novel systemic agents, use of planned myocutaneous repair for closure, or radiation combined with radiosensitizing agents, should be considered in this class of patients. © 2002 Elsevier Science Inc.

Preoperative radiotherapy, Breast cancer, Inoperable disease.

INTRODUCTION

Primary (neoadjuvant) systemic chemotherapy is a vital component of the management of locoregionally advanced breast cancer. Prospective and retrospective analyses have reported that approximately 80% of patients treated with primary chemotherapy achieve a partial or complete response (1–8). Correspondingly, for patients who present with disease that is initially inoperable, most are able to undergo surgical resection after primary chemotherapy.

Many series, including our own, have indicated that the tumors that fail to respond to primary chemotherapy have higher metastatic rates compared with those that respond (1, 7, 9–18). We recently reported our experience treating 177 patients with disease refractory to primary chemotherapy and found that these patients had high rates of both locoregional and distant recurrence. Most of those who did not achieve a partial response to chemotherapy continued to have operable disease, and we found that surgery was critically important for both achieving locoregional control and minimizing the risk of death from breast cancer (9).

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For the patients whose tumors remain inoperable after chemotherapy, the optimal management strategy is less clear. Historically, we have considered inoperable disease as either gross residual disease in the axilla or supraclavicular fossa that could not be completely resected without excessive morbidity or significant residual disease in the breast that could not be completely resected using primary skin closure. Our management approach for these patients has been to use preoperative radiotherapy (RT) in the hope that a modified radical mastectomy will become possible. Currently, little or no published data are available regarding the success and toxicity of preoperative RT for patients with inoperable breast cancer after primary chemotherapy. These data are needed to provide information about the selection of the radiation dose and the determination of factors that are predictive of outcome.

In this paper, we reviewed the data from patients treated on consecutive institutional trials involving the use of primary chemotherapy for breast cancer. We analyzed the clinical outcome and postoperative morbidity for the patients who had inoperable disease after primary chemotherapy and subsequently received RT.

METHODS AND MATERIALS

We retrospectively analyzed the data from 5 consecutive prospective clinical trials conducted at The University of Texas M. D. Anderson Cancer Center that investigated the role of primary chemotherapy for patients with nonmetastatic breast cancer. Between 1985 and 1998, 867 patients were enrolled into these trials. The eligibility criteria for these trials changed over the course of time. However, all trials required that patients have T3 primary disease or Stage III–IV disease. Patients with Stage IV disease were eligible only if they had ipsilateral involvement of supraclavicular lymph nodes without additional evidence of metastatic disease. A total of 186 patients (21%) were prospectively judged to have less than a partial response to the primary chemotherapy. Of these, only 38 patients (4.4% of the total population of the 5 studies) make up the population of this current report because they had disease characteristics that required RT for inoperable disease after failure of anthracycline-containing primary chemotherapy. The other 148 patients underwent surgery followed by RT or palliative care if distant disease developed during primary chemotherapy. These patients were assessed jointly by a medical oncologist, surgeon, radiologist, and radiation oncologist after completion of primary chemotherapy and determined to be inoperable. Twenty patients were thought to have inoperable disease because of unresectable adenopathy (fixed axillary disease and/or supraclavicular disease), and 18 patients were thought to have inoperable disease because the primary disease extent precluded a primary skin closure.

Table 1 shows the clinical, disease, and treatment characteristics of the 38 patients in this study. The multidisciplinary team prospectively assigned the clinical stages according to the American Joint Committee on Cancer Staging and End Results Reporting guidelines (19) after physical examination, mammography, chest radiography, bone scan, and liver evaluation (liver scan, ultrasonography, or CT). Patients who had systemic metastases or inflammatory carcinoma were treated on different protocols and were not included in this study. Twenty-nine of the patients (76%) in this series had Stage IIIB or greater disease at diagnosis. The 2 patients with Stage IIB disease had primary tumor sizes >5 cm without nodal involvement. The 9 patients with Stage IV disease had ipsilateral supraclavicular node involvement without other systemic metastases (regional Stage IV).

Table 2 describes the primary chemotherapy regimens the patients received. All patients were treated with doxorubicin-containing combinations; 6 patients also received taxane-based chemotherapy. The details regarding these regimens have been published in earlier reports (1, 20, 21). In

Table 1. Patient characteristics

Median follow-up* (y)	6.1
Age (y)	
Mean	47.3 ± 8.9
≤40	7 (18)
Clinical stage	
IIB	2 (5)
IIIA	7 (18)
IIIB	20 (53)
IV†	9 (24)
T stage	
T0	1 (3)
T1	0
T2	3 (8)
T3	8 (21)
T4	26 (68)
N stage	
N0	6 (16)
N1	10 (26)
N2	19 (50)
N3	3 (8)
Adjuvant chemotherapy	
None	16 (42)
VM	14 (37)
VMF	7 (18)
FAC + VM	1 (3)
Adjuvant tamoxifen	
Yes	12 (32)
No	26 (68)
Estrogen receptor status	
Positive	10 (26)
Negative	21 (55)
Unknown	7 (19)
Progesterone receptor status	
Positive	11 (29)
Negative	18 (47)
Unknown	9 (24)

Data in parentheses are percentages.

* Of surviving patients.

† Indicates ipsilateral supraclavicular lymph node involvement without systemic metastases.

Abbreviations: VM = vinblastine, methotrexate; VMF = vinblastine, methotrexate, 5-fluorouracil; FAC = 5-fluorouracil, doxorubicin, cyclophosphamide.

Table 2. Primary chemotherapy treatment

Protocol	Years of study	Primary chemotherapy	Cycles (*n*)	Patients/total population (*n*)
85-01	1985–1989	VACP	3	11/200
89-007	1989–1991	FAC	4	11/203
91-015		FAC or dose-		
	1991–1994	escalated FAC	4	9/202
94-002	1994–1998	FAC	4	1/174
97-099	1998–2000	AT	6	6/88

Abbreviations: FAC = 5-fluorouracil, doxorubicin, cyclophosphamide; VACP = vincristine, doxorubicin, cyclophosphamide, and prednisone; AT = doxorubicin, docetaxel.

summary, FAC chemotherapy consisted of 500 mg/m^2 5-fluorouracil given on Days 1 and 4 or 8, 50 mg/m^2 doxorubicin given as a Day 1 bolus or as a 72-h continuous infusion, and 500 mg/m^2 cyclophosphamide given on Day 1. For those patients receiving dose-escalated FAC, the doses of these drugs were increased to 600, 60, and 1000 mg/m^2, respectively. The VACP regimen consisted of 1.5 mg/m^2 vincristine, 60–75 mg/m^2 doxorubicin, 600–750 mg/m^2 cyclophosphamide, and 40 mg prednisone. Finally, the AT regimen consisted of 60 mg/m^2 doxorubicin and 60 mg/m^2 docetaxel given as i.v. boluses.

After chemotherapy, the medical team prospectively determined the clinical response of the primary tumor and regional lymph nodes according to standard response categories: (*1*) complete response (CR)—total resolution as assessed by physical or radiologic examination; (*2*) partial response (PR)—≥50% reduction of the product of the 2 largest perpendicular dimensions of the mass; (*3*) minor response—<50% reduction; (*4*) no change; and (*5*) progressive disease. Response was evaluated by a combination of physical examination, serial mammograms, and more recently, serial sonograms.

All 38 patients received RT (Table 3) to the breast and surrounding lymphatic regions immediately after primary chemotherapy. The involved breast was treated with conventional tangential fields to a median dose of 50 Gy (range 30–65) using a beam energy of 6 MV in 21 patients and ^{60}Co γ rays in the remaining 17 patients. An anterior field treating the supraclavicular fossa and axillary apex to a median dose of 50 Gy (range 30–64) was prescribed for all patients. Additionally, the midplane axilla was boosted to a median dose of 45 Gy (range 26–50) using a posterior axillary field. The internal mammary chain was treated to a median dose of 50 Gy (range 30–66) in 25 patients, with 22 receiving electron beam treatments to minimize the dose to the underlying thoracic structures. Six patients received a boost to the primary tumor bed using external beam RT (range 4–14 Gy), and 2 received interstitial brachytherapy boosts of 15 Gy. Five patients received 5-fluorouracil concurrently with RT. One patient received palliative RT consisting of 30 Gy to both breasts because locally progressive disease had extended to the contralateral breast during primary chemotherapy.

Table 3. Radiotherapy

Site	Patients (*n*)	Median dose (Gy)
Breast	38	50 (30–65)
SCV	38	50 (30–64)
Axilla (midplane)	38	45 (26–50)
IMC	25	50 (30–66)
Tumor bed boost	8	10 (4–15)

Data in parentheses are the range.

Abbreviations: SCV = supraclavicular fossa/axillary apex; IMC = internal mammary chain.

After completion of RT, 32 patients (84%) underwent mastectomy. Surgery was generally performed 4–6 weeks after RT completion. Postoperatively, 22 patients (58%) received additional chemotherapy. These regimens changed during the period of the clinical trials and included the use of vinblastine and methotrexate, vinblastine, methotrexate, and 5-fluorouracil, and FAC (similar to the preoperative regimen). Twelve patients (32%) received tamoxifen postoperatively.

The Kaplan–Meier method (22) was used to calculate the actuarial statistics for overall survival (OS), distant disease-free survival (DDFS), locoregional control, locoregional recurrence (LRR), and postoperative morbidity. OS and DDFS were measured from the date of diagnosis. Locoregional control, LRR, and postoperative morbidity were measured from the date of mastectomy. Two-sided log–rank tests (23) were used to detect differences in OS, DDFS, LRR, and postoperative morbidity associated with independent clinical or pathologic variables. Cases with unknown values were excluded from the univariate analyses.

Locoregional control was defined as clinically free of disease after completion of surgery and/or RT. LRR was defined as having a recurrence (only after achieving locoregional control) in the ipsilateral chest wall, skin, or regional nodes, with or without prior, simultaneous, or subsequent distant metastases. Distant disease was defined as visceral metastatic disease, not including the ipsilateral supraclavicular nodes. For DDFS calculations, distant disease recurrence was scored as an event, and nonbreast cancer deaths were censored. The postoperative complications analyzed included wound infection, wound dehiscence, wound/flap

Table 4. Inoperable breast cancer after primary chemotherapy: clinical response assessed after chemotherapy and RT

	Response to CT (%)	Response to RT (%)
Primary		
CR	0 (0)	5 (13)
PR	7 (18)	5 (13)
MR	11 (29)	18 (47)
NC	12 (32)	4 (11)
PD	7 (18)	3 (8)
No primary at diagnosis	1 (3)	1 (3)
Unclear	—	2 (5)
Nodes		
CR	2 (5)	14 (37)
PR	7 (18)	8 (21)
MR	4 (11)	3 (8)
NC	13 (34)	4 (11)
PD	9 (24)	5 (13)
No nodes at diagnosis	3 (8)	3 (8)
Unclear	—	1 (3)

Abbreviations: CT = chemotherapy; RT = radiotherapy; CR = complete response; PR = partial response; MR = minor response; NC = no change; PD = progressive disease.

necrosis, lymphedema, brachial plexopathy, rib fracture, and chronic pain requiring long-term pain management.

RESULTS

From a total population of 867 breast cancer patients treated with primary anthracycline-containing chemotherapy, 38 patients (4.4%) had inoperable residual disease after chemotherapy and subsequently received RT in attempt to make mastectomy possible. These patients were considered to be inoperable because they had either gross residual disease in the axilla or supraclavicular fossa that could not be completely resected without excessive morbidity or residual disease in the breast that could not be completely resected using primary skin closure.

The clinical response rates to primary chemotherapy and RT are shown in Table 4. In these patients, primary chemotherapy resulted in an overall clinical tumor response of 18% (0% CR, 18% PR) and an overall nodal response of 23% (5% CR, 18% PR). RT resulted in an overall tumor response of an additional 26% (13% CR, 13% PR) and an overall nodal response of an additional 58% (37% CR, 21% PR).

Thirty-two patients (84%) underwent surgery consisting of a modified radical mastectomy, radical mastectomy, or a simple mastectomy. Thirty patients (79%) underwent axillary dissection. Ten patients (31%) required myocutaneous reconstruction: 3 had trans-rectus abdominis myocutaneous flaps, 6 had latissimus dorsi flaps, and 1 had a gluteal flap. Two of the patients underwent mastectomy for palliative reasons after the development of distant disease during and after RT. All 5 patients who were treated with concurrent 5-fluorouracil and RT were able to undergo mastectomy. Of the 6 patients who did not undergo surgery, 1 patient no longer had any detectable disease and 5 patients experienced progressive disease during RT (1 had locally progressive disease in the axilla and 4 developed distant metastases).

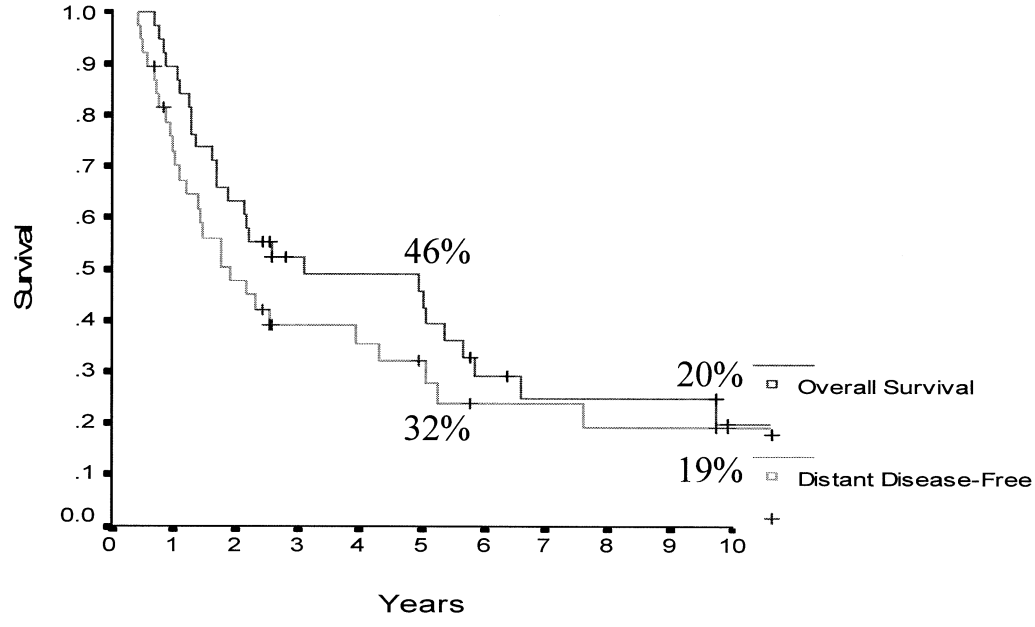
The median clinical tumor size at diagnosis was 8 cm (range 0–17). On completion of chemotherapy before RT, the median clinical tumor size was 7 cm (range 0–15). Of those who had mastectomy after RT, the median pathologic tumor size was 3.4 cm (range 0–13.0). Eight patients (25%) had residual primary tumors of $\leq$2 cm, 14 patients (44%) had tumors $>$2 cm but $\leq$5 cm, and 7 patients (22%) had tumors $>$5 cm. No residual primary disease could be identified in 3 patients (9%). The median number of positive lymph nodes was 2 (range 0–17). Of those who underwent axillary dissection, 13 patients (43%) had 1–3 positive nodes, 6 (20%) had 4–9 positive nodes, and 3 (10%) had $\geq$10 positive nodes. No positive nodes were identified in 8 patients (27%). In this series of patients, only 2 (5%) had a complete pathologic response; their clinical stage at diagnosis was IIIB (T4N2M0) and IV (T4N1M1). The surgical margins were $>$2 mm in 24 (75%), $\leq$2 mm in 4 (13%), and positive in 4 (13%) patients. Pathologic skin involvement was present in 8 patients (25%), and lymphvascular invasion was present in 15 patients (47%).

Thirty-one patients (82%) were initially rendered disease free after RT and mastectomy. Of the 7 patients with residual disease, 5 did not undergo surgery because of progressive disease, and 2 underwent palliative mastectomy after distant disease developed during and after RT.

Clinical outcomes and prognostic factors

After a median follow-up of 6.1 years among surviving patients, 29 patients (76%) experienced progressive disease after completion of all therapies. As a component of their first failure, 5 (13%) had LRR alone, 21 (55%) developed distant metastatic disease alone, and 3 (8%) developed both. Of the 9 patients (24%) who remained disease free, 3 died of other causes (motor vehicle accident, pneumonia, and congestive heart failure).

The OS and DDFS rates for all patients were 46% and 32% at 5 years and 20% and 19% at 10 years, respectively (Fig. 1). Table 5 lists the 10-year rates of OS and DDFS categorized according to the clinical and pathologic characteristics. When clinically assessed after primary chemotherapy, patients who were inoperable because of nodal disease extent had significantly worse OS and DDFS than did those who were inoperable only because of primary breast disease extent (Fig. 2). Also, having advanced nodal stage (N2 or N3) or poor nodal response (minor response, no change, or progressive disease) after chemotherapy was associated with significantly worse OS and DDFS (data in Table 5). Although not statistically significant, patients with $\geq$4 pathologically positive nodes had a lower rate of DDFS (0% vs. 33%, $p = 0.0576$). A tumor size $>$5 cm correlated with significantly worse DDFS and showed a trend toward worse OS (data in Table 5). OS and DDFS were not associated



Patients at Risk:			
Overall Survival	38	14	3
Distant Disease-Free	38	8	2

Fig. 1. OS and DDFS for all patients measured from the date of diagnosis.

with clinical stage, T stage or N stage at diagnosis, primary response to chemotherapy, primary or nodal response to RT, or radiation dose to the breast ($p > 0.2$ for all comparisons).

Locoregional control was initially achieved in 33 patients (87%), with 5- and 10-year rates of 64%. For those who achieved locoregional control, the 5- and 10-year rate of LRR was 27%. Of the 7 patients who had LRR, recurrence was an isolated first event in 3, an event simultaneous with distant disease in 3, and an event subsequent to distant disease in 1. The sites of locoregional failure were as follows: 4 patients had recurrences in the chest wall, 1 had recurrence in the axilla, and 2 had recurrences at both sites. At last follow-up, 6 patients had died of distant disease, and 1 was alive with locoregional disease.

Although not statistically significant, 2 factors were found to be associated with LRR. Patients with nodal disease that did not respond to RT (minor response, no change, or progressive disease) had a higher rate of LRR (82% vs. 29%, $p = 0.0526$). In addition, a trend was noted for a higher rate of LRR in the patients who received radiation doses to the breast of ≤50 Gy (80% vs. 49%, $p = 0.0726$), although in this analysis, we included the 1 patient treated palliatively to 30 Gy. LRR was not associated with clinical stage, T stage or N stage at diagnosis, primary or nodal response to chemotherapy, primary or nodal response to RT, pathologic tumor size, or the number of pathologically positive nodes ($p > 0.2$ for all comparisons). All 7 patients with LRR had negative margins.

Postoperative morbidity

For the 32 patients who underwent mastectomy, the 5-year rate of significant postoperative morbidity was 53% (Fig. 3). The complications were wound infection in 4 patients, wound dehiscence in 2, flap necrosis in 2, significant lymphedema in 3, brachial plexopathy in 1, rib fracture in 1, and chronic pain requiring pain medications in 7. Four of these patients (13%) required hospital admission and additional surgery: 2 for wound dehiscence, 1 for flap necrosis, and 1 for rib fracture.

The rate of postoperative complications requiring surgical revision was significantly associated with radiation doses of ≥54 Gy to the involved breast (70% vs. 9%, $p = 0.0257$). Although not statistically significant, patients receiving doses >50 Gy also had a higher overall rate of postoperative complications (85% vs. 43%, $p = 0.0983$). Factors that were not significant included radiation dose to the midplane axilla, use of photon beams vs. ^{60}Co γ rays, use of 5-fluorouracil concurrently with RT, use of myocutaneous flap closure vs. primary closure, clinical T stage, tumor size by physical examination, pathologic tumor size, clinical N stage, and the number of pathologically positive lymph nodes ($p > 0.1$ for all comparisons). Of the 2 patients who had brachytherapy boosts, 1 had a rib fracture and the other remained complication free.

DISCUSSION

We present data regarding the clinical outcomes and toxicity of RT for patients with inoperable disease after primary chemotherapy. It is generally expected that these patients have very poor prognoses. Numerous studies investigating the role of neoadjuvant chemotherapy have established that patients who do not achieve at least a PR have

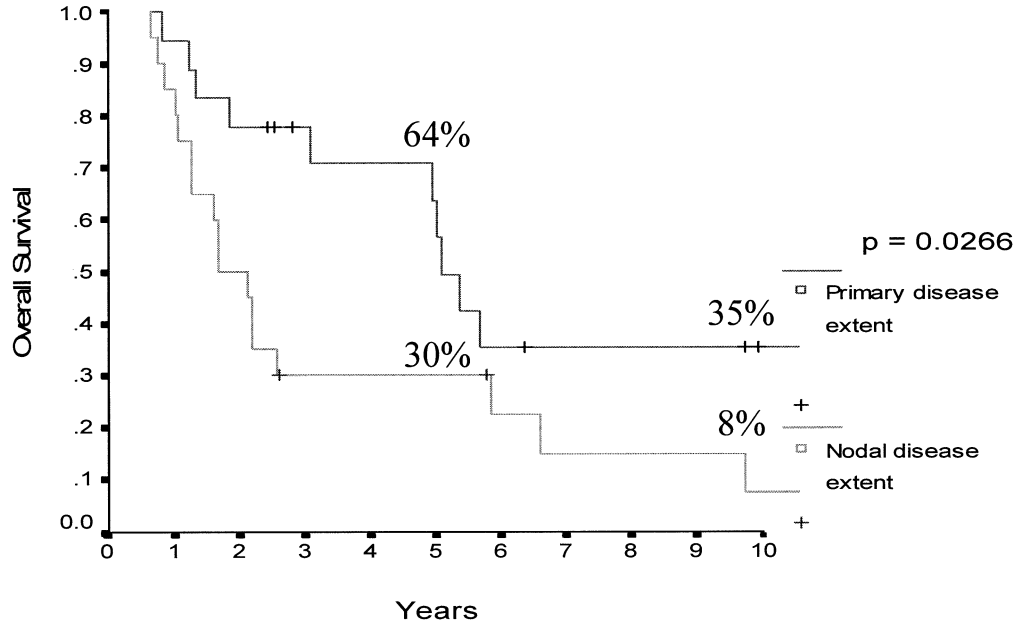
Table 5. Inoperable breast cancer after primary chemotherapy: 10-year rates of survival according to single prognostic variables

		Distant disease-free survival		Overall survival	
Factor	Patients (*n*)	10-y rate	*p*	10-y rate	*p*
Clinical stage at diagnosis					
IIB-IIIA	9	13	0.0585	28	0.4699
IIIB	20	29		17	
IV	9	22		33	
T stage at diagnosis					
≤T2	4	25	0.6215	0	0.8637
T3	8	19		31	
T4	26	20		20	
N stage at diagnosis					
N0-1	16	15	0.8097	31	0.3693
N2-3	22	27		14	
T stage after CHT					
≤T2	6	33	0.1562	0	0.4624
T3	5	33		40	
T4	27	18		18	
N stage after CHT					
N0-1	19	27	0.0130	37	0.0276
N2-3	19	11		7	
Inoperable after CHT					
Primary disease extent only	18	26	0.0174	35	0.0266
Nodal disease extent	20	14		8	
Pathologic primary size (cm)					
≤2	11	56	0.0172	16	0.0687
>2–5	14	17		21	
>5	7	0		0	
Pathologic node status					
0-3 +LN	21	33	0.0576	22	0.5962
>4 +LN	9	0		21	
Primary response to CHT					
Yes	7	57	0.1829	48	0.2403
No	30	13		16	
Nodal response to CHT					
Yes	9	65	0.0041	40	0.0178
No	26	4		6	
Primary response to RT					
Yes	10	15	0.8124	0	0.8344
No	25	17		21	
Nodal response to RT					
Yes	22	13	0.3883	15	0.9893
No	12	8		10	
RT Dose to breast (Gy)					
≤50	27	16	0.6367	14	0.9361
>50	11	44		44	

Abbreviations: CHT = chemotherapy; RT = radiotherapy; LN = lymph node; Response = clinically assessed as complete or partial response.

significantly higher metastatic rates than do those who do respond (1, 7, 10–18), with 5-year survival rates of 0–24% (1, 10). Because of their guarded outcome, the patients who remain inoperable after chemotherapy are often considered for Phase I studies exploring new chemotherapy regimens as a last resort.

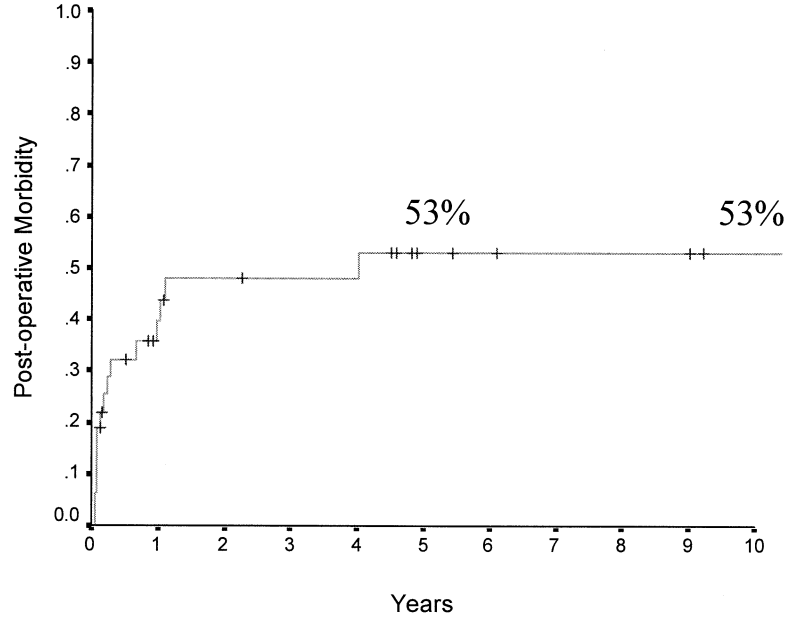
Our approach for these patients has been to use aggressive locoregional management, initiating preoperative RT in the hope of proceeding with mastectomy. This strategy is considered superior because the combination of both RT and surgery after primary chemotherapy has been shown to decrease locoregional failure and increase survival compared with RT alone after chemotherapy (16, 24–28). Using this approach, almost one-half of the patients in this series remained alive at 5 years, and one-third were free of distant disease. These outcomes (5-year OS rate 48%) are not significantly worse than those (5-year OS rate 36–65%) for the overall population of women treated for locally advanced breast cancer reported by a number of investigators (1, 10, 12, 29–31). Our retrospective data therefore suggest that having inoperable disease after primary chemotherapy, by itself, is not predictive of significantly worse survival, and multidisciplinary locoregional treatment may be able to achieve a chance of prolonged survival.



Patients at Risk:			
Primary disease extent	18	9	2
Nodal disease extent	20	5	1

Fig. 2. OS for patients who were inoperable because of nodal disease extent compared with those who were inoperable only because of primary disease extent.

Unfortunately, but not totally unexpectedly, our series of patients had a high rate of LRR after RT and mastectomy (5-year rate 27%). Furthermore, the high probability of treatment-related morbidity precluded investigating whether radiation dose escalation could improve locoregional control. Of those who underwent mastectomy, more than one-



Patients at Risk:	32	6	2

Fig. 3. Postoperative morbidity of the 32 patients who underwent mastectomy measured from the time of surgery.

half had a significant postoperative complication, and several patients required additional surgical revision. The complication rates were highest in those who received a dose of ≥54 Gy. Similar complication rates of 40–65% have been published by other institutions investigating preoperative RT and mastectomy for locally advanced breast cancer (32–35). These data collectively support the need to develop novel treatment strategies such as RT combined with radiosensitizing agents. Alternatively, we are also investigating whether patients with extensive inoperable primary disease after chemotherapy could be better treated with surgical procedures using myocutaneous repair for closure followed by postmastectomy RT.

The possibility of long-term survival, combined with the high risk of postoperative morbidity, has important implications regarding treatment recommendations for this class of patients. Because they are inoperable after primary chemotherapy, the crucial therapeutic decision is whether to proceed with locoregional treatment despite the poor response to initial therapy. In our analysis, patients who were inoperable after chemotherapy only because of primary disease extent (tumor size precluding a primary skin closure), rather than nodal disease extent (N2–3 or M1 disease), had significantly more favorable OS and DDFS. Similarly, having a less advanced nodal stage (N0 or N1) or a clinical nodal response (CR or PR) after chemotherapy was associated with better outcomes. Our data indicate that these patients should proceed with definitive locoregional treatments. In contrast, for those patients who are inoperable because of advanced nodal disease extent, quality-of-life issues regarding the high risk of treatment-related morbidity should be weighed very carefully given their poor prognosis, and it may be appropriate to consider these patients for Phase I clinical trials.

The sample size of this series was relatively small because primary chemotherapy is effective at achieving disease response. More than 95% of patients who were treated with chemotherapy in our institutional protocols were able to proceed with surgery as the initial form of local therapy. Our limited sample size may not have had enough power to detect other prognostic factors that could be incorporated into treatment recommendations.

CONCLUSION

Despite the poor prognosis of having inoperable disease that persists after primary chemotherapy, aggressive locoregional management using preoperative RT and mastectomy offers these patients long-term survival that is surprisingly better than expected. Using this approach, almost one-half of the patients remained alive at 5 years. Our data indicate that patients who are inoperable only because of primary disease extent have significantly better outcomes than those who are inoperable because of nodal disease extent. These clinical prognostic factors, combined with the high risk of LRR and postoperative morbidity, should be carefully considered when making therapeutic decisions after primary chemotherapy. These concerns emphasize the need to develop novel treatment strategies such as RT combined with radiosensitizing agents, more extensive surgical procedures combined with myocutaneous repair for closure, or new effective systemic agents.

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