

## Treatment Results and Prognostic Factors in the Management of Locoregional Recurrent Breast Carcinoma

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Between January, 1974 and December 1986, fifty eight patients with locoregional recurrent breast carcinoma who did not have evidence of distant metastasis after initial treatment of surgery with or without adjuvant chemotherapy were treated with radiation therapy. Among them, five patients were excluded from this study because of incomplete record or incomplete treatment.

The 5-year overall survival and disease free survival from the time of locoregional recurrence was 27% and 15% respectively. In univariate analysis of prognostic variables, the clinical stage at initial diagnosis, recur duration, number of recurrence sites, size of recurrences, response to the treatment, remission duration were all found to have no significant effect on survival or disease free survival. On the other hand, menopausal status at initial diagnosis, number of positive node at initial surgery, whether or not the use of adjuvant chemotherapy after initial mastectomy had definite prognostic significance. In multivariate analysis of prognostic variables, remission duration, menopausal status at diagnosis, number of axillary node at mastectomy had definite prognostic significance. On the other hand, remission duration more than 12 months, premenopausal at initial mastectomy, less than four positive axillary lymph nodes at mastectomy predicted a good prognosis.

**Key Words:** Radiotherapy, Local recurrent breast carcinoma. Prognostic factor

### INTRODUCTION

Local and/or regional recurrence of breast carcinoma is expected in about 10 to 17% of patients initially treated by radical or modified radical mastectomy, and it continues to represent a significant problem in patients with operable breast cancer undergoing mastectomy<sup>1-3</sup>). Once present, locally recurrent disease may be relatively difficult to control, and it present an ominous prognostic sign, as only a small number of such patients will remain free of disease during a sufficiently long follow-up period<sup>4-6</sup>).

This review is a retrospective analysis of patients with breast cancer who developed chest wall and/or nodal recurrence after radical or modified radical mastectomy treated at Yonsei University Hospital with either chemotherapy,

radiotherapy, or a combination of both, to evaluate the results of treatment of gross recurrences. Prognostic factors affecting patient's survival will also be reviewed and therapeutic implications are discussed.

### MATERIAL AND METHOD

Between January 4, 1974 and December 31, 1986, fifty eight patients without evidence of distant metastases were treated for locoregional recurrences of breast cancer after mastectomy. Of them, five patients were excluded because of incomplete clinical record or incomplete treatment. Therefore, 53 patients were analyzed. The patient's age ranged from 31 to 73 years (mean 49). There were 26 premenopauses and 27 postmenopauses. All of the cases were staged according to the American Joint Committee Staging System (1978). Treatment for the initial breast cancer was mastectomy alone in 31 patients (58.4%). Surgery and chemotherapy in 12 patients, surgery and radiotherapy in 8 patients,

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and two patients were received surgery and radiotherapy followed by chemotherapy. Distribution of patients by the stage, the number of positive axillary node, the treatment modalities at initial mastectomy were shown in Table 1. The locoregional area of the breast was divided into four sites: 1. Chest wall (CW) 2. Supraclavicular Area (SCL) 3. Axilla (AX) 4. Internal Mammary Node Area (IM).

Thirty two of fifty three patients (60.4%) had recurrent disease confined to only one site. the chest wall was the most common site of locoregional recurrence. Twentey one of fifty three patients (39.6%) had recurrent disease involving two or more sites (Table 2). All patients were treated with radiotherapy for their locoregional recurrent tumor. In addition, 27 patients also received chemotherapy either right before or after radiation to the chest wall either alone or in combination with other sites. Thirty-three patients had radiotherapy to the chest wall and regional lymph node bearing areas and twenty patients had radiotherapy to the involved site only. the administered tumor doses were more than 5000 cGy/25~28 fractions in all patients except for ten, who received lower doses because of previous radiotherapy.

Survival was measured from the time of first recurrence. Univariate survival distributions were estimated using the method of Kaplan and Meier<sup>7)</sup>

**Table 1.** Patient Characteristics

total No. of pts.	53
median age	52
median follow up	40 month (2 - 92)
menopausal state	
premenopause	26
postmenopause	27
initial stage	
I & II	34
III & IV	19
initial axillary node	
0 - 3	24
> 3	14
unknown	16
initial treatment	
OP	31
OP + CT	8
OP + CT + RT	2
OP + RT	12

YUMC (1974 - 1986)

and compared with the method using the log rank test<sup>9)</sup>. Potential prognostic factors were analyzed in a multivariate analysis using Cox's partially nonparametric proportional hazards model<sup>9)</sup>. Because of the small sample size all test were performed at the level of 0.05 level of significance. All analyses were performed using BMDP statistical software<sup>10)</sup>.

## RESULTS

Thirty-one of 53 patients (58.4%) obtained initial

**Table 2.** Distribution of Locoregional Recurrence Site

Sites	No. of pts (%)
Isolated single	32 (60.4%)
Chest wall	14
SCL	9
Axilla	5
Internal mammary	4
Multiple recurrence	21 (39.6%)
CW + SCL	8
SCL + IM	4
SCL + AX	3
CW + SCL + AX	3
CW + AX	2
CW + IM	1
Total	53 cases

**Table 3.** Summary of Treatment Result

<input type="checkbox"/> Response to the treatment		
CR	31/53 (58.4%)	
non-CR	22/53 (41.6%)	
<input type="checkbox"/> Locoregional failure	29/53 (54.7%)	
persistant disease	22/53	
subsequent failure	7/31	
in-field	6	
out-field	1	
<input type="checkbox"/> Distant metastasis	24/53 (39.6%)	
bone	9	
lung	7	
brain	4	
bone + brain	2	
bone + lung	2	
<input type="checkbox"/> Overall survival		
5-year survival rate		27%
5-year disease free survival rate		15%

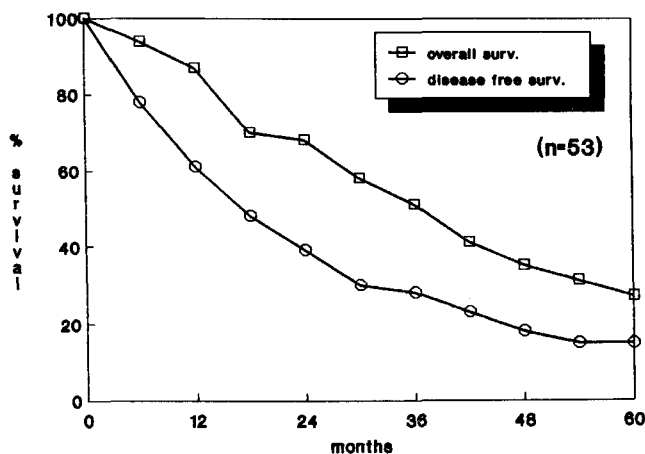
complete response of all the locoregional recurrent tumors following radiotherapy. We performed an analysis of failure among the 31 patients who had a second local failure after an initial complete clinical response. Seven of the 31 patients had a subsequent local failure. Six of these 7 patients failed within the radiation field ("in field"). Twenty-three of the 53 patients (40%) had a distant failure after radiotherapy (Table 3). The 5 year survival after treatment for locoregional recurrence was 27%, and the 5 year disease free survival was 15% (Fig. 1).

We attempted to determine factors that might influence the probability of patient's survival. The results of analyzing the potential prognostic factors one at a time are presented in Table 4. Menopausal status, the number of positive axillary nodes at diagnosis and previous chemotherapy were significantly associated with survival from first recurrence. Initial stage, disease free interval, the number of recurrence sites, recur size, response to the treatment after first recurrence, and remission duration were not significant predictors of survival. The relationship between each significant prognostic factors and survival are shown in Fig. 2, Fig. 3, and Fig. 4. Table 5 shows the results of analyzing the potential prognostic factors in a multivariate manner. Remission duration after treatment of first recurrence, menopausal status and axillary node condition at initial diagnosis, and recur size continued to correlate significantly with patients survival, but other factors no longer significant predictors of survival.

**Table 4.** Univariate Analysis of Prognostic Variables

Variables	N	5-survival	P-value
Menopausal status at Dx.			0.04
Premenopause	27	20%	
Postmenopause	26	43%	
Initial stage			0.56
I & II	34	29%	
III & IV	19	21%	
No. of positive nodes			0.006
0 - 3	24	46%	
4 or more	13	10%	
Adjuvant chemotherapy			0.008
No	39	34%	
Yes	14	7%	
Disease free interval			0.96
Within 2 year	36	32%	
Later than 2 year	17	10%	
No. of recurrence sites			0.6
Single	32	20%	
Multiple	21	25%	
Recur size			0.09
< 2 cm	17	51%	
> 2 cm	16	19%	
Response to the treatment			0.14
CR	31	34%	
non-CR	22	17%	
Remission duration			0.77
< 12 mon	25	15%	
> 12 mon	28	36%	

P-values by log rank test



**Fig. 1.** Overall and disease Free Survival.

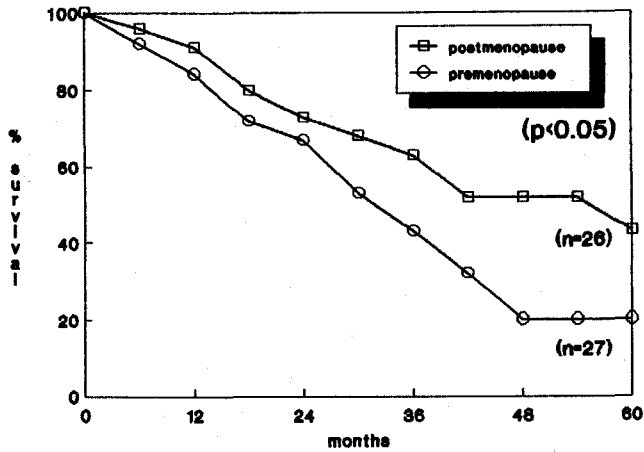


Fig. 2. Survival by menopausal status.

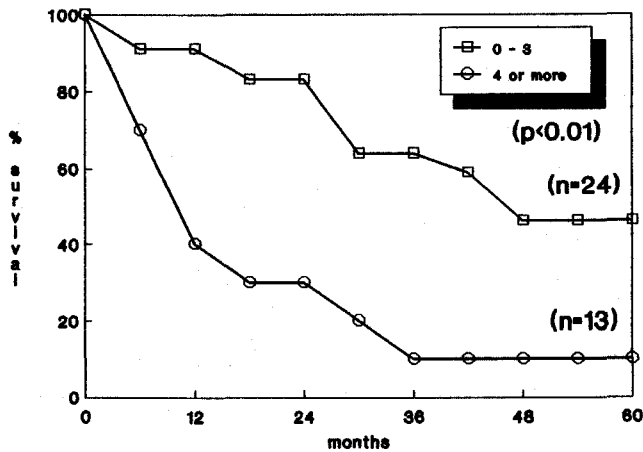


Fig. 3. Survival by nodal stage.

## DISCUSSION

In this retrospective study, we have analyzed the survival, local tumor control, failure patterns, and prognostic factors affecting survival in patients with isolated locoregional recurrence of breast cancer after mastectomy. Our results indicate that these patients have a poor prognosis similar to that noted by other investigators<sup>2,3,5,11,12</sup>. The great majority of the patients ultimately developed distant metastasis and died of disease. However, the overall 5-year survival in this study is 27%. This is rather similar to the overall 5-year survival of 21 to 31% reported by other investigators for patients with

isolated locoregional recurrent breast carcinoma<sup>13-15</sup>.

Local tumor control after treatment in this study was not found to be permanent and does not significantly influence patient's survival. Regardless of survival statistics, the importance of controlling tumor cannot be overemphasized, not only because it improves the quality of life, but also because some authors reported significantly better survival rates in patients with controlled chest wall disease than those whose disease is uncontrolled. This improvement on survival is in agreement with the report of Chu et al<sup>13</sup>, but was not reported by Bedwinek et al<sup>14</sup>. However, Bedwinek et al reported 157 cases of local recurrent breast carcinoma

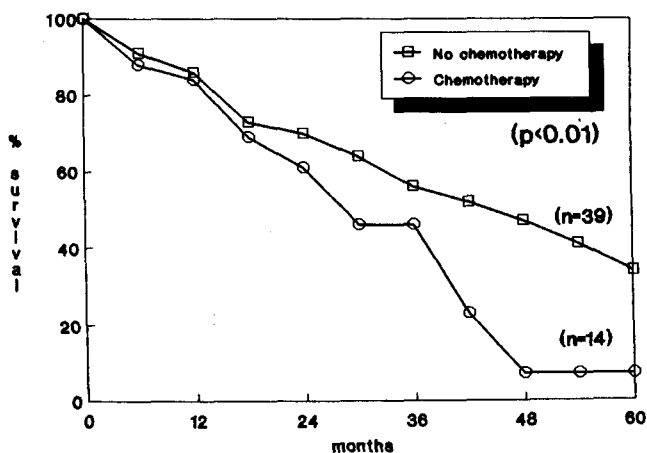


Fig. 4. Survival by previous chemotherapy.

**Table 5.** Multivariate Analysis of Prognostic Variables

Variables	P-value
Remission duration	0.000
Menopausal state	0.006
Axillary node	0.02
Recur size	0.03
Response to the treatment	0.11
Adjuvant chemotherapy	0.14
Initial stage	0.36
Treatment	0.45
Disease free interval	0.52
RT field	0.71
Recur site	0.83

By Cox's Proportional Hazards Model

about 60% of patients with uncontrolled locoregional disease develop symptoms that markedly impair the quality of life, so that benefit of controlling recurrent disease can not be stressed enough. But we believe that increased local tumor control in this situation would be unlikely to result in improved survival. Nevertheless, local tumor control should be viewed as a goal in itself since patients generally consider the presence of cancer to be highly disturbing manifestation of the disease. It is not clear that effective systemic chemotherapy will be required to improve the results of treatment in these patients. The addition of systemic chemotherapy to local therapy in the management of locoregional recurrence of breast cancer has produced variable

results. Bedwinek et al<sup>14</sup>, Toonkel et al<sup>15</sup>, Danofei et al<sup>16</sup>, and Karabali-Dalamaga et al<sup>17</sup> have noted no survival benefit with the addition of systemic therapy. Buzdar et al<sup>18</sup> reported a prolonged disease-free interval from first recurrence, a decreased incidence of re-recurrence, and a trend toward an improved two-year survival with aggressive chemotherapy given at the time of recurrence. Although there was no clear benefit to systemic therapy for recurrence in this study the systemic therapies administered varied widely and there probably were selection factors involved in determining who received systemic therapy in addition to radiotherapy. At the present time, however, it is uncertain if best results are achieved by local treatment alone, systemic treatment alone, or combined modality treatment. These various approaches will require evaluation using controlled clinical trials in order to be certain which is preferable.

The authors for the most part confirm the findings of others, that is, that the chest wall is the most common site of involvement followed by the supraclavicular region and the most important prognostic factors are the time interval to recurrence as well as the extent (single versus multiple)<sup>14</sup> and the site of recurrence (chest wall versus nodal)<sup>15</sup>. The authors also found that prognosis was related to initial treatment with those patients receiving mastectomy and chemotherapy having a decreased five-year survival compared to those treated by mastectomy with or without post-operative radiotherapy. This finding, however, may merely reflect patient selection and the likelihood that women who received initial chemotherapy had more exten-

sive nodal involvement and an overall worse prognosis. We analyzed the each prognostic variables associated with the 5-year actuarial survival rate. In univariate analysis, menopausal status at diagnosis, the number of positive axillary node at mastectomy, and adjuvant chemotherapy after mastectomy were found to affect survival statistics (Table 4). Interestingly, on univariate analysis prognostic factors affecting survival is related to initial tumor status at diagnosis. As a result, initial status at mastectomy can predict the prognosis of local recurrent breast carcinoma. In multivariate analysis, remission duration after treatment of locoregional recurrence, menopausal status and the number of positive axillary lymph node at initial mastectomy were found to affect survival statistics (Table 5). As the current results are delivered from a retrospective study, they should be interpreted with caution, these results strongly suggests that it is impossible that the natural history of patients with locoregional recurrent breast carcinoma can be altered by further local treatment, and that effective systemic chemotherapy is required to improve the results in these patients. Radiotherapy is a useful palliative procedure in patients with long disease interval. The role of radiotherapy in conjunction with systemic chemotherapy is, as yet, undefined.

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국문초록 =

### 국소재발유암의 치료성적 및 예후 인자

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유방암의 일차 치료후 흉벽이나 국소인파절에 국한된 재발은 비교적 흔하게 관찰된다. 방사선치료는 이러한 국소재발유암 환자에게 효과적인 치료법으로 사용되어 왔으나 국소병변의 관해에도 불구하고 많은 경우에서 이차개발 또는 원격전이로 인해 불량한 예후를 보이므로 최근에는 다방면 병용요법을 시도하여 환자의 수명을 연장시키고 관해율을 증가시켰다는 보고들이 있다. 이에 저자들은 국소재발유암 환자의 특성과 치료결과, 치료후 실패양상, 생존율에 영향을 미치는 예후인자를 분석하여 향후치료의 지침으로 삼고자, 1974년 부터 1986년까지 연세대학교 의과대학 치료방사선과에서 방사선치료를 받은 53명을 대상으로 후향적분석을 통해 다음과 같은 결과를 얻었다. 32예(60.4%)가 단일 병소에, 21예(39.4%)가 다발병소에 재발하였다. 방사선치료후 31예(58.4%)에서 완전관해를 보였으나 그 중 7예는 치료부위에 다시 재발하였다. 전체환자의 5년 생존율과 무병생존율은 각각 27%, 15%였다. 각각의 예후인자에 대한 단일변량분석에서는 최초 수술당시의 액와인파절전이 숫자, 보조적 화학요법의 시행 유무, 경도의 유무 등이 통계적 유의성을 보였고, 다변량분석법을 통한 분석에서는 최초수술당시의 액와인파절전이의 수, 경도의 유무, 재발시 병변의 크기, 치료후 관해기간 등이 생존율에 통계적으로 유의한 영향을 끼치는 예후인자였다.