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Postmastectomy Radiotherapy and Chemotherapy in Patients with Breast Cancer

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Purpose: To evaluate the treatment outcomes after postmastectomy radiotherapy (PMRT) and chemotherapy in patients with breast cancer.

Materials and Methods: The PMRT were retrospectively analyzed in 83 patients with stage II-III female breast cancer treated between 1989 and 1995. The median age was 46 years (range, 23-77); Seventy-seven patients had modified radical mastectomies, 5 radical mastectomies and 1 simple mastectomy. Three patients (4%) had pathologically negative axillae, and the remaining 80 (96%) had positive axillae. Eleven, 23, 44 and 5 patients had pathological stages IIA, IIB, IIIA, and IIIB, retrospectively. Eighty (96%) patients were treated with hockey-stick fields. The median dose of PMRT was 50.4 Gy, in 1.8 Gy fractions. Adjuvant systemic chemotherapy was given to 74 patients (89%). CMF-based or doxorubicin-containing regimens were given to 54 patients (65%). The median follow-up time was 82 months (range, 8-171) after the mastectomy.

Results: The 5 and 10-year overall survival rates for all patients were 65 and 49%, respectively. The univariate and multivariate analyses of the factors affecting the overall survival revealed the stage to be the most significant prognostic factor (p=0.002), followed by the combination of chemotherapy. Thirteen patients (16%) developed a LRF, at an interval of 4-84 months after radiotherapy, with a median of 20 months. The only significant prognostic factor affecting LRF was the combination of chemotherapy, in both the univariate and multivariate analyses. With respect to the sequence of chemoradiation, the sequence had no statistical significance (p=0.90). According to the time interval from mastectomy to the onset of radiotherapy, the LRFR of the patients group treated by RT within or after 6 month postmastectomy 6 months were 14 vs. 27%, respectively (p=0.24). One third of the patients (26/83) developed distant metastasis, in 2-92 months, after radiotherapy, with a median of 21 months. The most commonly involved site was bone in 13 cases. The pathological staging was the only significant prognostic factor in both the univariate and multivariate analyses that affected distant failure. Radiological findingof radiation pneumonitis on a simple chest x-ray was shown in 20% (17/83), with a time interval ranging from 2 to 7 months post-radiotherapy, with a median of 3 months. The stable lung fibrosis settled in 11 patients (65%).

Conclusion: It was concluded through this analysis that the combination of PMRT with in chemotherapy resulted in better overall survival and local control than PMRT alone in patients needing PMRT.

Key Words: Postmastectomy Radiotherapy, Chemotherapy, Breast cancer

Introduction

The value of postmastectomy radiotherapy (PMRT) has been increasing as the survival gain has been recognized in the prospective studies as well as retrospective studies in patients with locally advanced or axillary node metastatic breast cancer.[1~6] In addition, nowadays the radiation treatment technique has been improving and PMRT can be safely delivered

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using improved techniques to avoid radiation-induced normal tissue damage which was considered to be one of the reasonable explanation of poor survival gain in spite of improved locoregional disease control by PMRT.[7]

Over the past decade, the role of multi-agent chemotherapy has also become increasingly important in the management of patients with nonmetastatic breast cancer. Chemotherapy was considered to improve survival in patients with breast cancer.[8,9] However, there is controversial issue regarding the optimal combination of chemotherapy and radiotherapy for the best outcomes of survival and local control.[3,10~13]

Through this analysis, we hope to evaluate treatment outcomes of PMRT and chemotherapy in patients with stage II-III breast cancer.

Materials and Methods

Between 1989 and 1995, eighty-three patients without a history of prior malignancy received PMRT to the chest wall and regional lymph nodes following mastectomy for stage II-III invasive female breast cancer and their characteristics were summarized in Table 1.

The median age was 46 years (range, 23 to 77 years) and pathological finding was infiltrating ductal carcinoma in all 83 patients. Patients had a metastatic evaluation consisting of routine blood chemistries, chest X-ray and usually bone scan. Axillary dissection was performed as a part of mastectomy in all of the patients. Three patients (4%) had pathologically negative axillae, and the remaining 80 patients (96%) had positive axillae. Pathologic staging was done using TNM guideline of 1992.[14] Eleven patients had clinical stage IIA disease, 23 had Stage IIB, 44 Stage IIIA, and 5 Stage IIIB. Seventy-seven patients had a modified radical mastectomy, 5 had a radical mastectomy and one had a simple mastectomy (Table 2).

Radiation therapy was given on 6 MV x-ray combined with electron beams(Clinac 1800, Varian, USA Co.). Eighty (96%) patients were treated with hocky-stick fields, consisting of an axillary, supraclavicular, and internal mammary in x-ray field. The other chest wall and internal mammary node boost were

Table 1. Patients Characteristics (N=83)

Characteristics	No. of patients (%)
Age (yrs)	
Range	23~77
Median	46
Menopause status	
Premenopausal	53 (64)
Postmenopausal	30 (36)
Site	
Right breast	35 (42)
Left breast	48 (58)
T stage	
x	2 (2)
1	10 (12)
2	37 (45)
3	29 (35)
4	5 (6)
N stage	
0	3 (4)
1	47 (56)
2	33 (40)
No. of axillary LN metastasis	
0	3 (4)
1~3	13 (16)
4~9	31 (37)
10 or more than	28 (34)
Unknown	8 (9)
Stage	
IIA	11 (13)
IIB	23 (28)
IIIA	44 (53)
IIIB	5 (6)

Table 2. Treatment Characteristics (N=83)

Characteristics	No. of patients (%)
Operation hospital	
Inside	40 (48)
Outside	43 (52)
Operation	
Radical mastectomy	5 (6)
Modified radical mastectomy	77 (93)
Subcutaneous mastectomy	1 (1)
Chemotherapy	
No	4 (5)
Yes	74 (89)
Unknown	5 (6)
Chemotherapy regimens	
FAC	25 (34)
CMF	17 (23)
CEF	12 (16)
EP	8 (11)
Unknown	12 (16)
Combination of chemoradiation	
Neoadjuvant ChT	6 (8)
RT-ChT	11 (15)
ChT-RT	19 (26)
Concurrent	11 (15)
ChT-RT-ChT	21 (28)
Unknown	6 (8)

Abbreviation: RT: radiotherapy, ChT: chemotherapy

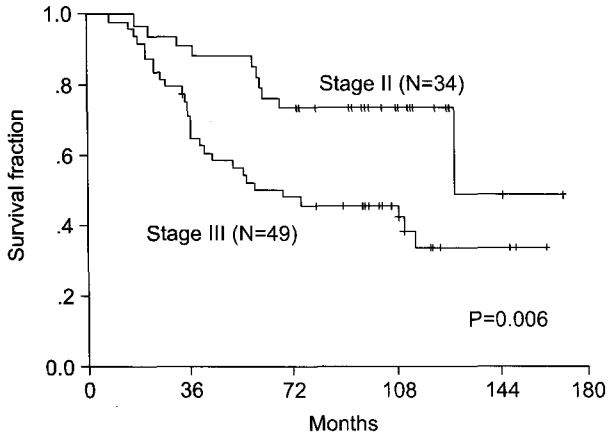

Fig. 1. The survival difference between stage II and III breast cancer patients with postmastectomy radiotherapy and chemotherapy was shown.

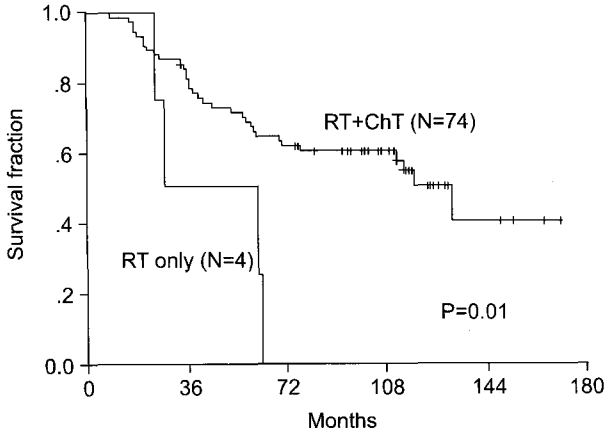

Fig. 2. The survival difference between breast cancer patients with postmastectomy chemoradiation (RT+ChT) and radiotherapy (RT) alone was shown.

treated with electron beam and the electron beam energy was dependent on the thickness of the chest wall. The median dose of radiation was 50.4 Gy to the lymphatics and chest wall. Bolus was used for all or part of the treatment of the chest wall as a compensator for the different chest wall thickness. Posterior axillary boost was used in 70 patients.

Adjuvant systemic chemotherapy was given to 74 patients (89%) at the discretion of the treating physician (Table 2). Of four patients with radiotherapy alone, 3 were postmenopausal and 1 premenopausal. Of those, 2 patients were stage II and 2 stage III. The chemotherapy regimens varied in the drugs used, the number of cycles, and the sequencing with RT. Cyclophosphamide, methotrexate, fluorouracil (CMF)-based or doxorubicin-containing regimens were given to 54 patients (65%) receiving chemotherapy.

Follow-up information was available in 79 patients (95%). Median follow-up time was 82 months (range 8~171). Local-regional failure (LRF) was defined as the appearance of the tumor on the chest wall or in the ipsilateral supraclavicular, axillary, infraclavicular, or internal mammary lymph nodes before or simultaneously with the development of distant failure. Follow-up time and time to failure were calculated from the date of operation. Actuarial overall survival, local control and distant failure rate was calculated using the Kaplan-Meier methods and statistical comparison was tested with a two-sided Log-rank test. Multivariate analyses were performed using a Cox proportional hazard model (SPSS v 11.0 for Windows).

Results

Of all 83 patients, forty patients were alive at the time of last follow-up. The 5- and 10-year overall survival rate of all patients was 65% and 49%, respectively. We included the prognostic parameters for the survival analysis such as age, menopausal status, stage, number of axillary node metastasis, time interval from operation to radiotherapy, and combination of chemotherapy. The univariate analysis of prognostic factors affecting overall survival revealed stage II and the combination of chemoradiation to be significant (Fig. 1, 2). Multivariate analysis of the factors affecting overall survival showed stage to be the most significant prognostic factor (p= 0.002) and the next was the combination of chemotherapy (Table 3).

Thirteen patients (16%) developed a LRF at an interval of 4~84 months after radiotherapy with median 20 months. Six of these patients had an isolated recurrence (five had an isolated axillary failure, one had supraclavicular involvement) and the remaining seven had simultaneous distant metastasis and LRF. There was no identifiable internal mammary node failure. The only significant prognostic factor affecting LRF was the combination of chemotherapy both in univariate and multivariate analysis (Table 4). In the analysis of sequence of chemoradiation excluding patients with neoadjuvant chemotherapy, the sequence did not have any statistical significance. According to the time interval from mastectomy to the onset of radiotherapy, LRFR of patients group treated by RT less

Table 3. Univariate and Multivariate Analysis of Prognostic Factors Affecting Overall Survival

Variable	No. of patients	Survival (%)	p-value	
			Univariate	Multivariate
Age (yr)			0.38	0.577
35 or less than	18	39		
Above 35	65	57		
Menopause			0.54	0.583
Premenopausal	53	49		
Postmenopausal	30	60		
T stage			0.53	0.265
x	2	100		
1	10	60		
2	37	57		
3	29	45		
4	5	40		
N stage			0.71	0.679
0	3	33		
1	47	34		
2	33	39		
No. of axillary LN metastases			0.45	-
0	3	100		
1~3	13	57		
4~9	31	58		
10 or more than	28	46		
Stage			0.006	0.002
II	34	71		
III	49	40		
Delayed time to RT (month)			0.90	0.879
6 or less than	72	54		
Above 6	11	45		
Chemotherapy			0.01	0.011
No	4	0		
Yes	74	55		
Combination of chemoradiation			0.45	-
RT-ChT	11	64		
ChT-RT	19	53		
Concurrent	11	36		
ChT-RT-ChT	21	67		

Abbreviation: RT; radiotherapy, ChT; chemotherapy

Table 4. Univariate and Multivariate Analysis of Prognostic Factors Affecting Locoregional Failure

Variable	No. of patients	LRF (%)	p-value	
			Univariate	Multivariate
Age (yr)			0.87	0.665
35 or less than	18	17		
above 35	65	15		
Menopause			0.27	0.088
Premenopausal	53	19		
Postmenopausal	30	10		
T stage			0.74	0.302
x	2	0		
1	10	10		
2	37	13		
3	29	21		
4	5	20		
N stage			0.61	0.406
0	3	0		
1	47	15		
2	33	18		
No. of axillary LN metastases			0.57	-
0	3	0		
1~3	13	8		
4~9	31	16		
10 or more than	28	21		
Stage			0.25	0.153
II	34	12		
III	49	18		
Delayed time to RT (month)			0.24	0.179
6 or less than	72	14		
Above 6	11	27		
Chemotherapy			0.01	0.055
No	4	50		
Yes	74	15		
Combination of chemoradiation			0.90	-
RT-ChT	11	18		
ChT-RT	19	16		
Concurrent	11	9		
ChT-RT-ChT	21	10		

than or more than postmastectomy 6 months was 14% vs. 27%, respectively (p=0.24).

One third of the patients (26/83) developed distant metastasis at an interval of 2~92 months after radiotherapy with median 21 months. The most common involved site was bone in 13 cases and lung and liver in each 3 cases, brain in 2, contralateral breast in 2 and skin in 1 case, respectively. Pathologic staging was the only significant prognostic factor both in univariate and multivariate analysis affecting distant failure (Table 5).

Moist desquamation was documented in the records in 12 of 83 patients (14%). Radiological finding of radiation pneumonitis in the simple chest x-ray was shown in 20% (17/83). RTOG grade 1 was 15 and 2 patients were grade 2. The usual site was upper lobe of each irradiated site with appositional photon field for the supraclavicular area and the appearing time was ranged from 2 months post-radiotherapy to 7 months, the median was 3 months. The stable lung fibrosis was settled in 65% patients (11/17) and the others was disappeared during follow-up period. The lymphedema was shown in one patient

Table 5. Univariate and Multivariate Analysis of Prognostic Factors affecting Distant Failure

Variable	No. of Pts.	Distant failure (%)	p-value	
			Univariate	Multivariate
Age (yr)			0.47	0.767
35 or less than	18	44		
Above 35	65	34		
Menopause			0.16	0.400
Premenopausal	53	43		
Postmenopausal	30	23		
T stage			0.45	0.311
x	2	0		
1	10	20		
2	37	35		
3	29	45		
4	5	40		
N stage			0.71	0.213
0	3	33		
1	47	34		
2	33	39		
No. of axillary LN metastases			0.51	–
0	3	33		
1~3	13	31		
4~9	31	29		
10 or more than	28	46		
Stage			0.01	0.006
II	34	21		
III	49	47		
Delayed time to RT (month)			0.75	0.853
6 or less than	72	35		
Above 6	11	45		
Chemotherapy			0.27	0.142
no	4	50		
yes	74	15		
Combination of chemoradiation			0.78	–
RT-ChT	11	36		
ChT-RT	19	36		
Concurrent	11	45		
ChT-RT-ChT	21	33		

Abbreviation: RT; radiotherapy, ChT; chemotherapy

after 1 year PMRT. There was no records on the occurrence of rib fracture or brachial plexopathy.

Discussion

Although the efficacy of PMRT in decreasing LRF has been clearly demonstrated, the larger issue concerns its effect on survival. In most randomized series, the use of postoperative radiotherapy failed to improve the survival rates after mastectomy, even when LRF were decreased.[15~19] In these many trials, PMRT was given using orthovoltage equipment and techniques that delivered considerable doses to the heart. Some of these trials showed a late increase in cardiac mortality in patients treated with RT compared with unirradiated patients.[16,17] Many of the earlier trials used techniques of irradiation which did not adequately treat the target volume to optimal doses.[20] However, a recent randomized trial with a large number of patients has demonstrated significantly better locoregional control, relapse free survival, and overall survival rates with the use of PMRT in addition of adjuvant chemotherapy.[21~24]

A substantial risk of LRF after mastectomy has been well documented when PMRT was not used.[25,26] This risk is strongly related to the presence and extent of axillary nodal involvement. LRF occurs in 4 to 8% of patients with pathologically negative axillary nodes and 25 to 27% of patients with positive nodes.[25,26] As the number of positive nodes increases, the rate of LRF increases.[26] PMRT is associated with a significant decrease in the risk of LRF.[27~29] The published data demonstrate a crude LRFR of only 6%, even in node-positive patients. However, in our analysis, the actuarial LRFR was 16% which is a rather poor compared to the results presently reported. Nowadays, we perform a treatment planning through computerized tomography-based simulation in the same position to the real treatment. Through the CT image, we can identify the real thickness of chest wall or the depth of axilla and internal mammary node, which we realized that there was great individual variance in the thickness of chest wall or the location of lymphatics. We hope the better outcomes by this treatment planning with CT simulation.

The efficacy of adjuvant chemotherapy in reducing the risk of LRF after mastectomy is not well established. Some studies have shown a reduction in LRF by more than 40%,[30] but others have failed to demonstrate such an advantage.[31] NSABP B-13 trial showed that CMF chemotherapy, especially 5-fluorouracil, was effective in decreasing the incidence of local-regional or distant metastases and intrabreast tumor recurrence after therapy.[32] Of notes, the combination of chemotherapy with PMRT was one of the most significant prognostic factor affecting overall survival in our analysis. Our results favored chemotherapy in that the combination of chemoradiation decreased the LRFR and also improved overall survival with the statistical significance.

With the increasingly important role of chemotherapy and radiotherapy in the management of node-positive breast cancer patients, determination of the optimal sequence of combined modality treatments in patients in need of both chemotherapy and radiation has become one of practical considerations. We can suppose the delay of radiotherapy may result in decreased locoregional disease control. Buchholz et al reported that delayed radiation for a period of 6 months or greater led to a statistically inferior local control rate despite the use of immediate postoperative aggressive chemotherapy.[10] In the Dana-Farber/Beth Israel trial, with a median follow-up of 58 months, local recurrence was greater with delayed RT and distant recurrence was greater with delayed chemotherapy.[13] However, with longer follow-up of median 135 months, there was no statistically significant difference between the CT-first and RT-first arms in time to failure, time to distant metastasis, or time to death.[33] The overall actuarial rate of distant failure was higher in the RT-first arm (37% vs. 25%; p=0.05), thus suggesting chemotherapy-first policy. Throughout our analysis, patients with delayed PMRT more than 6 months showed the tendency of higher LRFR and lower overall survival rate without statistically significant difference. With respect to sequence, overall survival of RT first or chemotherapy first group was 64% and 53%, respectively (p=0.45) and local control of both group was 82% in RT first group and 84% in chemotherapy first group, respectively (p=0.90). Our data failed to prove the importance of sequence of chemoradiation in the aspect of survival, local control and distant failure.

Several randomized studies testing the value of PMRT that started in the 1950s to early 1970s, such as Manchester trial[9] and the British trial,[18] had a lower long-term survival rates in the radiotherapy group than in non-irradiated patients. However, based on the encouraging reports of recent trials, we believe that it is appropriate to recommend PMRT in patients with high-risk factors of LRF and this probably result in improved survival rates. However careful attention must be paid to the morbidity of treatment. In this series, in which 96% of all patients were treated with "hockey- stick" technique consisting of a direct photon field for axilla, supraclavicular, and internal mammary lymphatics, which is now discarded technique.[34] With follow-up more than 5 years, we did not find any patients with late cardiac morbidity. In patients irradiated for carcinoma of breast, death from myocardial infarction is the primary event reported, occurring 10 to 15 years after radiation therapy.[35] So we may have the chance to observe the possible heart morbity with longer follow-up.

In conclusion, we find through this analysis that the combination of PMRT with chemotherapy results better overall survival and local control than PMRT alone.

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국문초록

유방절제술을 시행한 유방암 환자에서 방사선과 항암제 치료성적

전남대학교 의과대학 방사선종양학과

안성자 · 정웅기 · 남택근 · 나병식 · 송주영 · 박승진

목 적: 유방절제술 후 방사선치료와 항암화학요법을 시행한 유방암 환자의 치료성적을 연구하고자 하였다.

대상 및 방법: 1989년부터 1995년까지 유방절제술 후 여성 유방암 병기 II-III로 방사선치료를 받았던 83명의 환자를 대상으로 후향적 분석을 시행하였다. 연령 분포는 23~77세였고 중앙 연령은 46세로 77명은 변형된 근치적유방절제술을, 5명은 근치적 유방절제술을, 1명은 단순유방절제술을 받았다. 80명(96%)의 환자에서 액와림프절 전이 소견을 보였고 병리학적 병기상 11명이 2기초, 23명이 2기말, 44명은 3기초, 5명은 3기말이었다. 방사선치료는 80명의 환자에서 "hocky-stick 조사문"을 사용하였고 방사선치료 선량의 중앙값은 일일 1.8 Gy, 총 50.4 Gy였다. 74명(89%)의 환자에서 항암화학요법이 병행되었으며, 54명(65%)의 환자에서 CMF 혹은 doxorubicin이 포함된 약제가 투여되었다. 추적기간은 8~171개월로 중앙값은 82개월이었다.

결 과: 5년 및 10년 전체생존율은 각각 65%와 49%이었다. 생존율에 대한 단변량 및 다변량분석에서 병기 2기와 항암화학요법을 병행한 환자군에서 유의한 생존율의 증가를 보여 주었다. 국소재발률은 16%였으며, 방사선치료 후 4~84개월(중앙값: 20개월) 사이에 발생하였다. 국소재발을 보인 13명 중 6명은 국소 재발 단독으로, 그 외 7명은 원격전이와 동시에 국소재발이 발생하였다. 방사선 치료시기와 관련하여 수술 후 6개월 이내에 방사선치료를 받았던 환자군에서는 국소재발률이 14%인 반면 6개월 이후에 방사선치료를 시행한 경우는 27%였다(p=0.24). 국소재발과 관련하여 시행한 단변량 및 다변량 분석에서는 항암화학요법의 병행 유무가 가장 유의한 예후인자 였다. 그러나 방사선과 항암제의 병행 방법에 따른 생존율이나 국소재발률의 차이는 보이지 않았다. 전체 환자의 약 1/3에서 방사선치료 후 2~92개월(중앙값: 21개월) 사이에 원격전이가 관찰되었고 가장 흔히 침범되는 장기는 골이었다. 17명(20%)의 환자에서 방사선폐렴이 확인되었고 방사선 완료 후 2~7개월(중앙값: 3개월) 사이에 발생하였다. 이중 65% (11/17)의 환자에서는 단순흉부촬영상 폐섬유화 소견이 잔존하였다.

결 론: 본 연구를 통하여 유방절제술 후 방사선치료가 필요하였던 유방암 환자에서 항암제의 병행 치료는 방사선 단독치료에 비해 종양의 국소제어율과 생존율이 향상됨을 알 수 있었다.

핵심용어: 방사선치료, 항암화학요법, 유방절제술, 유방암