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Long-term Results of Breast-conserving Surgery and Radiation Therapy in Early Breast Cancer

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Purpose: To evaluate the long-term results after breast-conserving surgery and radiation therapy in early breast cancer in terms of failure, survival, and cosmesis.

Materials and Methods: One hundred fifty-four patients with stage I and II breast cancer were treated with conservative surgery plus radiotherapy between January 1992 and December 2002 at the Keimyung University Dongsan Medical Center. According to TNM stage, 93 patients were stage I, 50 were IIa, and 11 were IIb. The affected breasts were irradiated with 6 MV photons to 50.4 Gy in 28 fractions over 5.5 weeks with a boost irradiation dose of 10~16 Gy to the excision site. Chemotherapy was administered in 75 patients and hormonal therapy in 92 patients with tamoxifen. Follow-up periods were 13~179 months, with a median of 92.5 months.

Results: The 5- and 10-year overall survival rates were 97.3% and 94.5%, respectively. The 5- and 10-year disease-free survival (5YDFS and 10YDFS, respectively) rates were 92.5% and 88.9%, respectively; the ultimate 5YDFS and 10YDFS rates after salvage treatment were 93.9% and 90.2%, respectively. Based on multivariate analysis, only the interval between surgery and radiation therapy ($\leq$6 weeks vs. $>$6 weeks, p=0.017) was a statistically significant prognostic factor for DFS. The major type of treatment failure was distant failure (78.5%) and the most common distant metastatic site was the lungs. The cosmetic results were good-to-excellent in 96 patients (80.7%).

Conclusion: Conservative surgery and radiation for early stage invasive breast cancer yielded excellent survival and cosmetic results. Radiation therapy should be started as soon as possible after breast-conserving surgery in patients with early breast cancer, ideally within 6 weeks.

Key Words: Early breast cancer, Breast-conserving surgery, Radiation, Survival, Failure

Introduction

Breast conserving surgery combined with radiotherapy is a standard therapeutic procedure for patients with early breast cancer. Several phase III randomized trials have shown that survival after breast conserving treatment (BCT) consisting of local excision and whole breast irradiation was equal to the survival rate after radical mastectomy.[1~3] In 1992, the Journal of National Cancer Institute published a monograph stating that breast conservation treatment is an appropriate method of primary therapy for most women with stage I or II breast cancer.[4] According to a 2002 annual report of the Korean Central Registry, breast cancer is the most common cancer of women and comprises 16.8% of all reported cancers in Korea.[5] In Korea, the incidence of early stage breast cancer is increasing with the use of screening mammography. The proportion of breast conserving treatment is also increasing with 18.7% in 1996, 27% in 2000 and 41.9% in 2004.[6] Our institution started team approach for breast conservation treatment in early breast cancer in 1992. We have previously reported preliminary results of breast conserving treatment in early breast cancer.[7] We here report long term results of our experiences in terms of survival, prognostic factors, failure, and cosmetic results.

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Materials and Methods

From January 1992 through December 2002, one hundred fifty four patients with early stage I and II breast cancer were treated with breast conserving surgery and radiotherapy at Keimyung University Dongsan Medical Center. Patient characteristics are presented in Table 1. Age distribution was 25 to 72 years old with median age of 44. According to TNM stage, ninety three patients were stage I, fifty were IIa, and eleven were IIb. There were 122 patients of N0, 26 of N1 (1～3) and 6 of N2 (≥4). The most common pathology was invasive ductal carcinoma with one hundred twenty two patients (79.2%). In ninety patients (58.4%), the lesions were located in the left breast. The most common site was upper outer quadrant (UOQ, 92 patients) followed by upper inner quadrant (UIQ, 32), lower outer quadrant (LOQ, 14), lower inner quadrant (LIQ, 8), and central area (8).

All patients underwent excision of all gross tumors in the procedure that attempted to achieve histologically negative surgical margins. Several patients were referred from local surgeons after biopsy and we performed removal of the most of tumor as much as possible. In these patients, re-excisions were performed when feasible if surgical margins were involved or if they could not be assessed. One patient with positive surgical resection margin didn't receive re-excision. In addition, all but 7 patients underwent level I-II axillary lymph node dissection for staging. Median number of dissected node was 20 (Table 2). In some cases, radio-opaque hemoclips were placed at the margin of resection to assist the radiation oncologist in treatment planning of boost fields to the tumor bed. Radiation therapy was performed at 1.5～32.8 weeks (median, 3.6 weeks) after surgery. All patients had ipsilateral breast treated with radiation. Radiation therapy to ipsilateral breast was delivered through medial and lateral tangential fields of 6 MV photons to 50.4 Gy in 28 fractions over 5.5 weeks. Medial margin was 1 cm over the midline of anterior chest. Upper margin of the portals was placed at the head of the clavicle to include the entire breast. Lateral margin was placed 2 cm beyond all palpable breast tissue, which is usually near the mid-axillary line. Inferior margin was drawn 1 cm below the inframammary fold. Compensating wedge filter was used to whole breast irradiation in most patients.

Table 1. Patient Characteristics

Characteristics		No. of patients
Age (yr)	<40	42
	≥40	112
Pathology	Invasive ductal carcinoma	122
	Mucinous carcinoma	9
	Papillary carcinoma	5
	Medullary carcinoma	6
	Tubular carcinoma	3
	Other	9
T-stage	T1a	3
	T1b	23
	T1c	90
	T2	37
	T3	1
N-stage	N0	122
	N1 (1～3)	26
	N2 (≥4)	6
Stage	I	93
	IIa	50
	IIb	11
Resection margin	−	131
	+	1
	Close	9
	Unknown	13
ER	−	44
	+	48
	Unknown	62
PR	−	44
	+	47
	Unknown	63
Site	Left	90
	Right	64
Location	UOQ*	92
	UIQ†	32
	LOQ‡	14
	LIQ§	8
	Central	8
Total		154

*upper outer quadrant, †upper inner quadrant, ‡lowerouter quadrant, §lower inner quadrant

Margins, in general, were 2～3 cm from the scar, depending on the size of the lesion and the adequacy of the surgical margins. A boost of 10 Gy in 5 days was delivered through reduced fields with electrons of appropriate energy (6～12 MeV). If the margins contained tumor or if the status of the margins were close or unknown, electron beam boost was escalated to deliver 16 Gy. In fourteen patients with axillary node involve-

Table 2. Treatment

Surgery		No.	Radiation therapy	Dose (Gy)
Wide excision		147	Ipsilateral breast	45～50.4 (median 50.4)
Axillary LN dissection		140	Tumor bed boost	10～16 (median 10)
Sentinel LN biopsy		7	Supraclavicular LN[§]	45～50.4 (median 50)
Chemotherapy		**No.**	**Hormonal therapy[‖]**	**No.**
Yes		75	Yes	92
Regimen:	CMF*	58	No	62
	AC[†]	9		
	FEC[†]	6		
	AC-Taxol	2		
No		79		

*cyclophosphamide+methotrexate+5-fluorouracil, [†]adriamycin+cyclophosphamide, [‡]5-FU+epirubicin+cyclophosphamide, [§]18 patients among N (+), [‖]tamoxifen

ment, ipsilateral supraclavicular node and level III axillary node was treated up to 45 to 50 Gy over five weeks. Adjuvant chemotherapy was administered in seventy five patients with several regimens such as CMF (cyclophosphamide, methotrexate, 5-fluorouracil), AC (adriamycin®, cyclophosphamide), FEC (5-FU, epirubicin, cyclophosphamide). Adjuvant hormonal therapy was administered in ninety two patients with tamoxifen.

Cosmetic results were assessed by questionnaire to patients grading from excellent, good, fair to poor.

Follow-up period was 13 to 179 months with median 92.5 months. The time to local failure and distant metastases were analyzed from primary surgery. Five year- and ten year-disease free survival rate (5YDFS, 10YDFS) were also evaluated from the day of surgery. We used Kaplan-Meier method for overall and disease free survival, log-rank test for prognostic significance, and Cox-proportional hazard model for multivariate analysis. We used p-value below 0.05 which was statistically significant. We also used Pearson correlation coefficient to analyze the relation between factors which were statistically significant by univariate analysis.

Results

1. Survival rates and prognostic factors

Five year- and ten year-overall survival rate (5YOS, 10YOS) were 97.3% and 94.5% (Fig. 1). 5YDFS, 10YDFS were 92.5% and 88.9% (Fig. 1). After salvage treatment, ultimate 5YDFS and 10YDFS were 93.9% and 90.2%. To

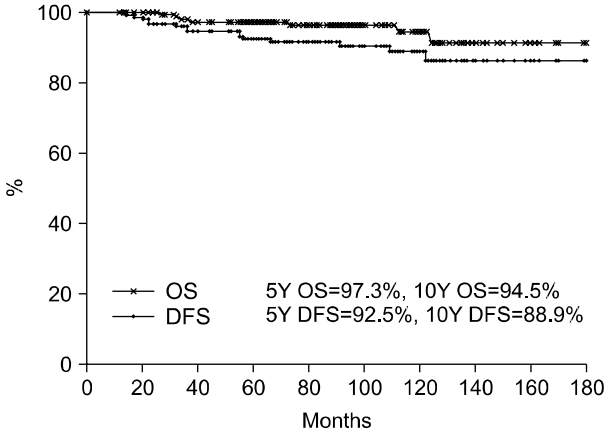

Fig. 1. Overall survival (OS) curve & disease free survival (DFS) curve.

evaluate prognostic factors affecting overall and disease free survival, we analyzed prognostic factors such as age, surgical margin, estrogen receptor, progesterone receptor, stage including T-stage and N-stage, hormonal therapy, chemotherapy and interval between surgery and radiation therapy. There was no statistically significant prognostic factor for overall survival by univariate analysis. N-stage, chemotherapy and interval between surgery and radiation therapy were statistically significant prognostic factors affecting disease free survival by univariate analysis (Table 3). There were statistically significant differences in disease free survival by interval between surgery and radiation therapy (5YDFS 96.7% vs. 76.7%, 10YDFS 93.1% vs. 63.6%, ≤6 weeks vs. >6 weeks, p=0.000)(Fig. 2), N-stage (5YDFS 94.1%, 87.8%, 83.3%, 10YDFS 92%, 77.65%, 0% in N0, N1, N2 respectively, p=0.047)(Fig. 3), and

Table 3. Univariate Analysis of Prognostic Factors for Disease-free Survival

Factors		5YDFS*	p-value
Age	<40	85.7	0.42
	≥40	93.7	
Surgical margin	Close/positive	100	0.56
	Negative	92.9	
	Unknown	84.6	
Estrogen receptor	Positive	95.3	0.61
	Negative	90.9	
	Unknown	91.7	
Progesterone receptor	Positive	93.1	0.30
	Negative	90.6	
	Unknown	93.6	
T-stage	T1a	100	0.82
	T1b	94.1	
	T1c	89.7	
	T2	94.3	
	T3	100	
N-stage	N0	94.1	0.047
	N1	87.8	
	N2	83.3	
Hormonal therapy	Yes	93.1	0.33
	No	92.2	
Chemotherapy	Yes	87.4	0.026
	No	97.4	
Interval between surgery and radiation therapy	≤6 wk	96.7	0.000
	>6 wk	76.7	

*5 yr disease-free surviral

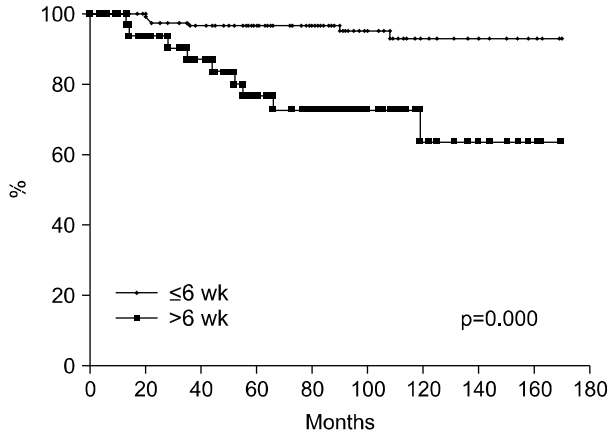

Fig. 2. Disease free survival curve by the interval between surgery and radiotherapy.

chemotherapy (5YDFS 87.4% vs. 97.4%, 10YDFS 85.5% vs. 92.8%, with chemotherapy vs. without chemotherapy, p=0.026) (Fig. 4). According to stage, 5YDFS and 10YDFS was 93.3% and 90.6%, 91.7% and 89%, 90% and 75% in stage I, IIa and IIb (Fig. 5), respectively. By multivariate analysis of chemotherapy, N-stage and the interval between surgery and radiation therapy which were statistically significant in univariate analysis, only the interval between surgery and radiation therapy was a significant prognostic factor for disease free

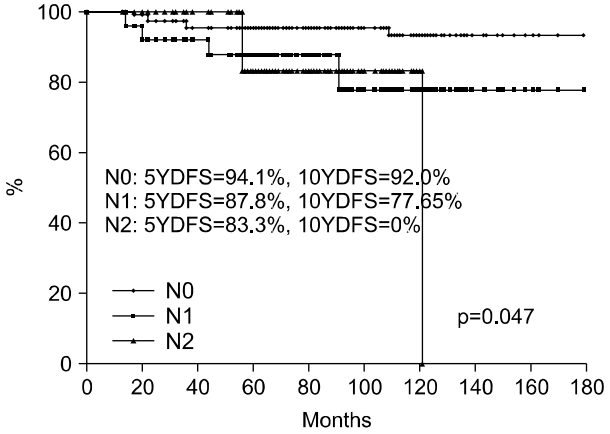

Fig. 3. Disease free survival (DFS) curve by N-stage.

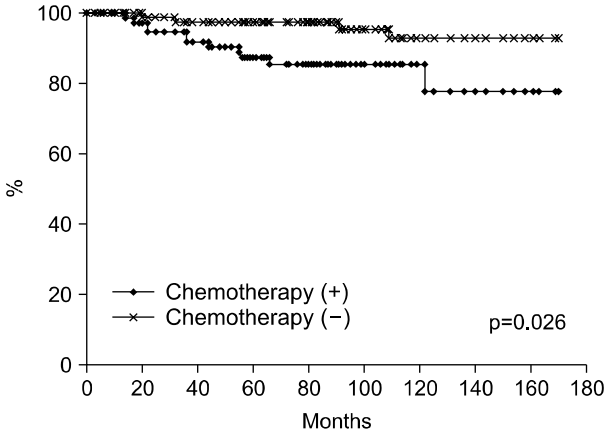

Fig. 4. Disease free survival curve by chemotherapy.

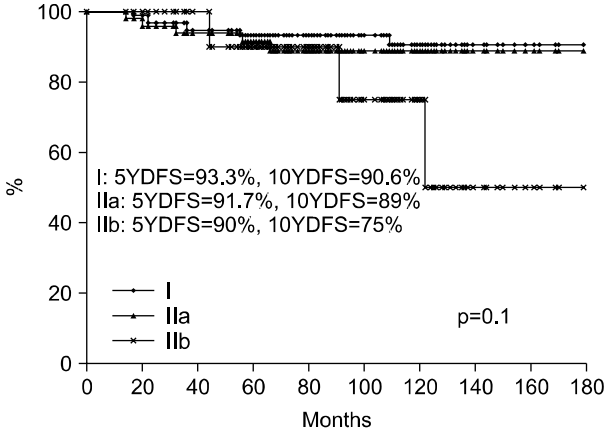

Fig. 5. Disease free survival (DFS) curve by stage.

survival (≤6 weeks vs. >6 weeks; HR, 0.21; 95% CI, 0.058 to 0.756; p=0.017). There was strong correlation between N-stage and interval between surgery and radiation therapy (Pearson correlation coefficient=0.513).

2. Patterns of failure

Fourteen patients out of one hundred fifty four had treatment failure (9.1%). Ten patients had distant metastasis and one had local and distant failure and three had ipsilateral local failure. Local failure developed after 17, 22 and 50 months and they were treated by surgery, chemotherapy and hormonal therapy. One of them had tumor bed relapse and the rest two had local failure in elsewhere. The patient with tumor bed recurrence was salvaged by wide excision and hormonal therapy so one of three with local recurrence has conserved the breast after salvage treatment. The major type of failure was distant failure (78.5%) and most patients with distant metastasis had multiple metastatic sites with 55.5 months of median time. The most common distant metastatic site was lung. Patients with distant metastasis received chemotherapy, supportive care or surgery (Table 4). The status of patients with treatment failure is presented in Table 5.

3. Complication and cosmesis

Four patients (2.5%) had an arm edema more than NCI CTCAE grade II with 57 months of median time. They had radiation therapy to only ipsilateral breast and mean numbers of dissected axillary lymph node were 11.5. One of them had local failure and received total mastectomy. One patient had doxorubicin induced cardiac failure. She had recurrent tumor in left breast 44 months after primary treatment. She underwent neoadjuvant chemotherapy with doxorubicin containing regimen and total mastectomy. She died from doxorubicin induced cardiac failure 59 months after the primary treatment (Table 6). One hundred nineteen patients answered our cosmetic result questionnaire and the results were good to excellent in ninety six patients (80.7%)(Fig. 6). There was no significant effect of tumor location and tumor size to cosmesis.

Table 4. Patterns of Failure

Type of failure	No. (%)
Distant metastasis*	10/14 (71.4)
Local failure alone	3/14 (21.4)
Local failure & distant metastasis	1/14 (7.1)

*median time to distant metastasis: 55.5 months

Table 6. Complications

	No. (%)
Arm edema*	4 (2.5)
Adriamycin induced cardiac failure†	1 (0.6)

*median time to radiation: 57 months, †recurrent breast cancer (patient 13 in Table 5)

Table 5. Status of Failed Patient

Patient	Initial stage	Failure (months)	Treatment after failure	Status (months)
1	T2 N2 M0	Lung, Bone, SCL* (122)	CHT†	DOD‡ (127)
2	T1c N1 M0	Lung, SCL (20)	Supportive care	DOD (32)
3	T2 N2 M0	Bone (91), SCL (144)	CHT, Excision	DOD (137)
4	T1c N0 M0	Lung, Liver, SCL (109)	CHT	DOD (130)
5	T1c N1 M0	Lung (55), Bone (76)	CHT	DOD (73)
6	T1b N1 M0	Lung (66)	CHT	DOD (88)
7	T1c N2 M0	Liver, Ovary, Kidney (56)	CHT	DOD (87)
8	T1c N0	Lung (36)	CHT	DOD (79)
9	T1c N0	Lung (36), Bone (40)	CHT	DOD (53)
10	T2 N0 M0	Liver (32)	HRT§	DOD (38)
11	T1c N1 M0	Breast (14), Lung (19)	TM‖, CHT	DOD (34)
12	T1c N0 M0	Breast (22)	TM, CHT, HRT	NED¶ (81)
13	T2 N1 M0	Breast (50)	TM, CHT	DI** (59)
14	T1c N0 M0	Breast (17)	Wide excision, HRT	NED (95)

*supraclavicular lymph node, †chemotherapy, ‡dead of disease, §total mastectomy, §hormone therapy, ‖total mastectomy, ¶no evidence of disease, **die of intercurrent disease (adriamycin induced cardiac failure)

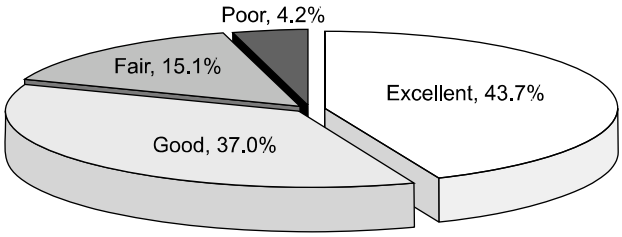

Fig. 6. Cosmetic results.

Discussion and Conclusion

Over the past two decades, we knew that mastectomy is not needed for most small tumors and does not improve prognosis for more extensive disease. Therefore, as many as 80% of the patients with invasive breast cancer may benefit from breast conserving treatment (BCT), offering good cosmesis and identical disease control and survival compared to modified radical mastectomy. The number of patients suitable for BCT might even further increase as patients are now diagnosed at earlier stage. This trend is reinforced through the implementation of mass screening for breast cancer.[8] In the USA, 58% of patients with stage I breast cancer and 36.2% of patients with stage II breast cancer underwent BCS according to one report.[9] In our institute, we have performed breast conserving treatment in early breast cancer since 1992. Our results of 5YOS and 10YOS in early breast cancer were 97.3% and 95.8%. 5YDFS and 10YDFS were 92.5% and 88.9% and ultimate 5YDFS and 10YDFS were 93.9% and 90.2%. These results were compatible to other nonrandomized studies.[10~16] Chie et al.[14] reported that five year overall survival and disease free survival after breast conserving treatment in breast cancer were 93.1% and 88.7%. Kim et al.[15] also reported that the 5YOS and 5YDFS after breast conserving treatment in early breast cancer were 95.3 and 88.5%.[16]

Recently many randomized studies reported long term results.[2,17~21] Researchers have shown that local failure rates were in the range of 3~22%. However local failure rates were about 10% excluding two studies with high local failure rate.[19,20] In our study, the local relapse occurred in five patients (3.2%). This is very low compared with other studies and comparable to randomized study of Danish Breast Cancer Cooperative Group.[21] Our study shows that main failure pattern was distant metastasis. In early stage breast cancer, distant metastasis was more frequent than local failure, which means there was micro-metastasis developed in early stage. Therefore, we believe that the more effective combined chemotherapy is needed to improve survival in high risk group.

There were so many prognostic factors affecting overall survival and disease free survival. Some researchers have reported that patients with positive surgical margin had high local failure.[22~25] In this study, eight patients had close resection margin, whereas one patient had positive resection margin. However we didn't have statistically significant difference by margin status. We believe this was due to small number of patients with close or positive margin.

Young age (<35 or 40 years) has been associated with an increased risk of breast recurrence in a number of series.[26,27] In our study, age was not prognostic factor affecting survival. The proportion of young patients (<40 years) was 27.2% and higher than that of American series, which was 7%.[27] Therefore, we should make an effort to improve treatment results in young patients. N-stage, chemotherapy and interval between surgery and radiation therapy were statistically significant prognostic factors affecting disease free survival by univariate analysis in this study. Patients who received chemotherapy had inferior disease free survival compared to those who did not. After multivariate analysis, the statistical significance of chemotherapy was not shown. This means that patients with more advanced disease received chemotherapy. Only the interval between surgery and radiation therapy was a statistically significant prognostic factor by multivariate analysis. Clinical trials and clinical practice guidelines have variously recommended that intervals between breast conserving surgery (BCS) and radiation therapy (RT) should be less than 6 weeks to less than 16 weeks. The available meta-analyses of the effect of BCS-to-RT intervals on breast cancer outcomes have yielded disparate results. Olivotto et al.[28] showed that intervals longer than 20 weeks from BCS-to-RT are associated with inferior outcome for women with early-stage breast cancer who are not receiving chemotherapy. But they had improved local control compared with no RT at all (HR, 2.32; p=0.08). They suggested that RT should not be withheld, even if the elapsed time from surgery is greater than 20 weeks. Also Huang et al.[29] found that BCS-to-RT intervals of 8 weeks and longer were associated with a higher risk of local recurrence (odds ratio, 1.62; 95% CI, 1.20 to 2.16) but with no significant

difference in distant recurrence or breast cancer death. Chen et al.[30] found an increased risk of local recurrence (relative risk, 1.11 per month of delay; 95% CI, 0.94 to 1.33) but found no difference in distant recurrence or survival with longer BCS-to-RT intervals. In contrast, Hebert-Croteau et al.[31] reported no significant associations between the BCS-to-RT interval and local recurrence or breast cancer death. Therefore, we considered that radiation therapy need to be started after breast conserving surgery as soon as reasonably achievable, especially within 6 weeks according to our results.

There were four patients with arm swelling more than NCI CTCAE grade II. Powell et al.[32] have shown that nodal irradiation was the only significant risk factor for arm lymphedema in patients receiving breast conservation therapy for early-stage breast cancer in meta-analysis. Bar Ad et al.[33] suggested that mild arm lymphedema, generally considered to be a minor complication after breast conservation treatment for breast cancer, was associated with a risk of progression to a more severe grade of arm lymphedema in a substantial fraction of patients. Therefore we should pay attention to mild arm edema in breast cancer patients.

We experienced doxorubicin induced cardiac failure. She had a stage IIb left breast cancer. She received breast conserving treatment with six cycles of CMF chemotherapy and recurred at left breast after 44 months. She underwent neoadjuvant doxorubicin containing chemotherapy and total mastectomy. She died of doxorubicin induced cardiac failure 59 months after primary treatment. We believe that physician should be careful in treating patients with doxorubicin containing chemotherapy for patients with left breast cancer with previous medical history of radiation and chemotherapy.

Cosmetic results were reported as good or excellent in more than 80 percent in MD Anderson report but good in 50 percents in European report.[34] Other series reported excellent cosmetic results of 86% and good to excellent of 93%, which were usually physician assessment cosmetic score.[35,36] Arenas et al.[37] have shown that 73% of patients rated cosmesis as excellent or good, while the percentage was 71% when rated by radiation oncologists. Our cosmetic result was patient's opinion. Our patients had a good to excellent cosmetic result in 80.7%.

Breast conserving treatments in early breast cancer was excellent in local control and survival. It takes about 6 weeks for radiation therapy and patients may have difficulty to reach hospital if it is far from their residential area.[38] Therefore many attempt have been made to identify subgroups of patients who might avoid radiation therapy after breast conserving surgery in early breast cancer. However, Veronesi et al.[39] reported that local recurrence was significantly higher in patients treated with surgery alone (59 cases out of 273; 10-year crude cumulative incidence of 23.5%) than in patients treated with surgery plus radiotherapy (16 cases out of 294; 10-year crude cumulative incidence of 5.8%) in spite of quadrantectomy in small breast cancer. Radiation therapy may not be necessary after conservative surgery in selected elderly patients (over 70 years) with small endocrine responsive cancer whose tumor excision was complete and who receive tamoxifen, although long-term follow up is not yet available.[40] Recently, accelerated partial breast irradiation (APBI) to reduce the treatment period has been investigated for patients with early stage breast cancer who are expected to have a good prognosis.[41] The results of APBI are consistent and successful, but selecting patients who are appropriate for APBI is very difficult and controversial.

In conclusion, ten year-overall survival rate was 95.8%, ten year- disease free survival rate was 88.9% after receiving breast conserving treatment in early breast cancer at Keimyung University Dongsan hospital. After salvage treatment, ultimate ten year disease free survival rate was 90.2%. Only the interval between surgery and radiation therapy was a statistically significant prognostic factor affecting disease free survival in multivariate analysis. We have shown that breast conservative operation and radiation therapy for early stage invasive breast cancer have excellent local control, survival and cosmetic results. We also considered that radiation therapy need to be started after breast conserving surgery as soon as reasonably achievable, especially within 6 weeks according to our results.

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국문초록

초기 유방암의 유방보존수술과 방사선치료의 장기추적결과

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목 적: 초기 유방암에서 유방 보존 수술과 방사선치료 후 실패양상과 생존율 및 미용효과를 알아보고자 하였다.
대상 및 방법: 1992년 1월부터 2002년 12월까지 계명대학교 동산의료원에서 유방보존수술과 방사선치료를 받은 초기 유방암환자 154명을 대상으로 하였다. TNM 병기는 1기 90명, IIa기 50명, IIb기 11명이었다. 모든 환자는 유방의 부분절제술과 동측 액와림프절 곽청술을 시행하고 방사선치료를 하였다. 유방의 방사선치료는 동측 전체 유방에 6 MV 광자선으로 50~54 Gy를 5주에서 6주간에 조사하였고 원발병소에 추가 방사선은 전자선으로 10~16 Gy를 조사하였다. 항암화학요법은 75명에서 방사선치료 전후에 시행하였고 호르몬치료는 92명에서 Tamoxifen을 사용하였다. 추적관찰기간은 13개월에서 179개월로 중앙값이 92.5개월이었다.
결 과: 전체환자의 5년, 10년 생존율은 97.3%, 94.5%이었다. 5년, 10년 무병생존율은 92.5%, 88.9%이었고 구제치료후 5년, 10년 무병생존율은 93.9%, 90.2%이었다. 다변량 분석상 수술 후 방사선치료까지의 기간이(≤6 weeks vs. >6 weeks, p=0.017) 무병생존율에 있어서 통계적으로 유의한 예후 인자였다. 주된 실패양상은 원격전이였고 다발성으로 치료 후 중앙값 55.5개월에 전이를 하였다. 원격전이의 호발부위는 폐였다. 미용결과는 80.7%에서 좋음에서 매우 좋음으로 나타났다.
결 론: 초기 유방암에서 유방보존수술과 방사선치료는 우수한 생존율과 미용결과를 보인다고 생각된다. 또한 유방보존수술 후 방사선치료는 가능한 한 빨리, 6주 이내에 시행되는 것이 좋을 것으로 생각된다.

핵심용어: 초기 유방암, 유방보존수술, 방사선치료, 생존율, 실패양상