Nodal stage-oriented adjuvant chemotherapy in breast cancer

Byoung Chul Cho

Department of Medicine

The Graduate School, Yonsei University

Nodal stage-oriented adjuvant chemotherapy in breast cancer

Directed by Professor Hyun Cheol Chung

The Master's Thesis

submitted to the Department of Medicine

the Graduate School of Yonsei University

in partial fulfillment of the requirements for the

degree of Master of Medical Science

Byoung Chul Cho

June 2005

This certifies that the Master's Thesis of

Byoung Chul Cho is approved.

Thesis Supervisor : Hyun Cheol Chung

Thesis Committee Member : Kunhong Kim

Thesis Committee Member : Sun Young Rha

The Graduate School

Yonsei University

June 2005

감사의 글

본 논문이 완성되기까지 깊은 애정과 자상한 지도로 이끌어 주신 정현철 교수님께 진심으로 감사드리며, 연구 계획 수립 과 논문 작업에 각별한 조언을 아끼지 않으신 라선영 교수님, 김건홍 교수님께 깊은 감사를 드립니다. 아울러 쉽게 풀리지 않는 문제들에서 언제나 열정적인 토의를 해 주신 정희철 교수님, 손주혁교수님께 감사드립니다. 항상 옆에서 힘이 되어준 모든 내과 의국원들에게 감사합니다. 마지막으로 뒤에서 힘이 되어 주시는 부모님, 정은이(색동이)와 현빈이에게 고마운 마음을 전합니다.

저자씀

<TABLE OF CONTENTS>

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Nodal stage-oriented adjuvant chemotherapy in breast cancer

Byoung Chul Cho

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Hyun Cheol Chung)

Background. The role of adjuvant chemotherapy in various axillary nodal stages has not been clearly defined. We evaluated the efficacy of adjuvant chemotherapy (CMF or FAC) on survival of breast cancer patients according to nodal stages.

Methods. Over a 9-year period, 665 women undergoing curative surgery for breast cancer were stratified with respect to axillary node involvement (≤3 versus ≥4), and treated with either CMF (cyclophosphamide 500 mg/m2 i.v. day 1, 8, methotrexate 50 mg/m^2 i.v. day 1, 8 and 5-fluorouracil 500 mg/m^2 i.v. day 1, 8) every 4 weeks for six cycles if they had three or less positive nodes or FAC (5-fluorouracil 500 mg/m^2 i.v. day 1, 8, doxorubicin 40 mg/m^2 i.v. day 1 and cyclophosphamide 500 mg/m^2 i.v. day 1, 8) every 4 weeks for six cycles if they had four or more positive nodes. The 5-year results were retrospectively analysed according to nodal status (node-negative, 1 to 3 positive nodes, and 4 or more positive nodes).

Results. Five hundred and ten patients (76.7 %) and 155 patients (23.3 %) were treated with CMF and FAC, respectively. The relative dose intensities

(RDI) of CMF and FAC were 0.97 (range, 0.32-1.00) and 0.94 (range, 0.63-1.00) of planned doses, respectively. The RDI of each nodal group was 0.98 (range, 0.60-1.00) in node-negative group (LN 0), 0.92 (range, 0.32-1.00) in 1-3 positive nodes (LN 1-3), 0.94 (0.63-1.00) in 4 or more positive nodes (LN ≥ 4). With a median follow-up duration of 68 months (range, 14-142 months), 140 (21.1 %, 45 in LN 0, 51 in LN 1-3, 44 in LN ≥ 4) of total patients have disease recurrence, whereas 81 patients (12.2 %, 20 in LN 0, 30 in LN 1-3, 31 in LN ≥ 4) have died. 5-year overall survival (OS) rate and disease free survival (DFS) rate of all patients was 89.5 % and 80.1 %, respectively. The 5-year OS rates of each nodal group were 94.6 % in LN 0, 87.3 % in LN 1-3, 83.3 % in LN ≥ 4, respectively (*P*= 0.0003). The 5-year DFS rates of each nodal group were 85.1 % in LN 0, 78.4 % in LN 1-3, 73.5 % in LN ≥ 4, respectively (P= 0.0066). When treatment outcome was compared according to nodal status, a significant difference in OS and DFS existed between LN 0 and LN 1-3 group. However, no significant difference was found between LN 1-3 and LN ≥ 4 group. The patterns of first relapse was mainly in distant sites (64.3 %), followed by locoregional relapses (22.1 %). The incidences of first relapse in distant viscera and soft tissue were significantly different among three nodal groups (*P*= 0.002 and *P*= 0.004, respectively). Chemotherapy was fairly well tolerated and devoid of life-threatening toxicity.

Conclusions. Considering the favorable 5-year results achieved in this study at the expense of minimal toxicity, we suggest that CMF regimen is the adjuvant chemotherapy of choice for patients with node-negative or one to three positive nodes. Although FAC regimen was still a reasonable choice in patients with four or more nodes, more active regimens including taxanes would be required to obtain better long-term results.

Key words: breast carcinoma; adjuvant chemotherapy; nodal stage; survival.

Nodal stage-oriented adjuvant chemotherapy in breast cancer

Byoung Chul Cho

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Hyun Cheol Chung)

I. Introduction

In 1976, Bonadonna et al presented that combination chemotherapy regimen of cyclophophamide, methotrexate, and fluorouracil (CMF) was effective in node-positive breast cancer.[1] With a follow-up of 20 years, this trial provides unequivocal evidence that CMF increases disease-free survival (DFS) and overall survival (OS) in these patients.[2] Results of similar studies have confirmed that adjuvant CMF improves DFS as well as OS in all subsets of patients with operable breast cancer.[3-4] Since these early studies, CMF-like protocols have been considered as the gold standard for adjuvant chemotherapy in operable breast cancer.

In an attempt to increase the efficacy of adjuvant therapy, anthracyclines, which are still considered to be the most effective drugs for metastatic breast cancer, were introduced in adjuvant chemotherapy regimens.[5] Adjuvant chemotherapy with anthracyclines, such as doxorubicin or epirubicin, induced a small but statistically significant improvement in survival compared with CMF regimens.[4,6] This superiority is smaller than expected, and it is, therefore,

still debatable if this strategy is safe and offers a benefit as far as long-term survival. In clinical practice, the decision to use an anthracycline in an individual patient should consider the potential survival benefits versus the specific concern about additional toxicity.[7]

Unfortunately, our current understanding of the optimal selection of the adjuvant chemotherapy regimen for the individual patient is still very limited. Although several randomized trials reported superiority of anthracycline-based regimen over CMF regimen, this only provides average treatment benefits in the global clinical trial populations studied.[7] In a very heterogenous disease such as breast cancer, a large difference in the magnitude of the treatment effect for subpopulations of patients according to clinicopathologic characteristics of tumors, examplified by axillary nodal status, may exist. For example, anthracycline-based chemotherapy is associated with a 4 % absolute advantage over CMF in node positive disease, whereas 1.7 % in node-negative disease.[4] However, treatment efficacy of CMF or anthracycline-based regimen in different nodal stages has not been adequately addressed because most clinical trials comparing the two regimens included both node-negative and node-positive patients.

Since 1994, we stratified women undergoing curative surgery for breast cancer with respect to axillary node involvement (node-negative, 1-3 positive nodes, 4 or more positive nodes), and treated with either CMF regimen if they had three or less positive nodes or FAC regimen if they had four or more positive nodes. Indeed, our institute had adopted the strategy of adjuvant chemotherapy for breast cancer according to number of positive nodes after observing the following results of randomized trials; firstly, adjuvant chemotherapy appeared to produce survival benefit for patients with node-negative disease, although its benefit was smaller than for patients with node-positive disease.[4] Secondly, CMF adjuvant chemotherapy provided a clear survival benefit in patients with one to three positive nodes, but showed limited benefit for patients with more than three nodes.[2,8] Thirdly,

anthracycline-containing regimen had well-known efficacy in advanced and metastatic breast cancer.[7,9]

The purpose of this study was to evaluate the treatment efficacy of each regimen according to the nodal stages. To evaluate relative efficacy, we compared treatment outcomes of each regimen in two different nodal groups.

II. Patients and Methods

1. Patient population

The study population consisted of 665 consecutive patients who underwent surgery for breast cancer between January 1994 and December 2002 at the Yonsei Medical Center. Clinicopathologic data and follow-up information were retrieved from medical records. Primary treatment consisted of either modified radical mastectomy or partial mastectomy followed by radiotherapy. All patients received a complete axillary lymph node dissection. The median number of lymph nodes examined for patients was 22 (range, 6 -51). Patients were stratified according to the nodal stages; node-negative (LN 0), one to three positive axillary node (LN 1-3), four or more positive axillary node (LN ≥ 4).

Estrogen (ER) and progesterone receptor (PgR) status was defined by immunohistochemistry (IHC) or enzyme immunoassay, and were available for 91.3 % and 91.4 % of eligible patients, respectively. For all patients, ER values of ≥15 fmol per mg of cytosol protein and PgR value of ≥10 fmol per mg of cytosol protein were considered positive. Tumor size was taken to be the largest diameter as determined on pathologic analysis. Histologic grade was assessed using the Elston-Ellis modification of the Bloom-Richardson grading system.

2. Adjuvant treatment

All patients were begun on treatment within 4 weeks after mastectomy. Among lymph-node negative patients, treatment was given only to the followings; T1b tumor (size between 0.5 cm and 1 cm) with histologic grade 2-3, and T1c tumor (size > 1 cm).

Patients stratified according to axillary node status were received either CMF if they had three or less positive nodes or FAC if they had four or more positive nodes, according to the following schedules. CMF: cyclophosphamide 500 mg/m2 *i.v.* day 1, 8, methotrexate 50 mg/m2 *i.v.* day 1, 8 and 5-fluorouracil 500 mg/m2 *i.v.* day 1, 8, every 4 weeks for six cycles. FAC: 5-fluorouracil 500 mg/m2 *i.v.* day 1, 8, doxorubicin 40 mg/m2 *i.v.* day 1 and cyclophosphamide 500 mg/m2 *i.v.* day 1, 8, every 4 weeks for six cycles.

In patients undergoing either partial mastectomy or modified radical mastectomy with LN ≥ 10 or LN 4-9 with large tumors (> 5 cm), adjuvant radiotherapy was mandatory. Adjuvant tamoxifen was administered concurrently or sequentially for 5 years in patients with positive ER and/or PgR.

3. Follow-up

Assessment of patients were required every 6 months until the end of the fifth year, and yearly thereafter. Routine follow-up consisted of physical examination, laboratory tests (including estimation of CA 125 and CA 15-3 levels), chest radiography, mammography, breast sonography, liver sonography, and bone scan. LVEF measurement by radionuclide scan was performed in patients treated with FAC before administration of doxorubicin, at the end of the adjuvant treatment and yearly thereafter upto 5 years.

Relapse was classified as follows: locoregional sites that included ipsilateral axillary adenopathy, chest wall, and the ipsilateral breast in patients treated with breast-conserving surgery; distant sites that were sub-classified as soft tissue, viscera, and bone; contralateral breast.

4. Evaluation of efficacy and toxicity

The primary endpoints of the study were 5-year DFS and OS, and

secondary endpoints were dose intensity and toxicity.

OS was calculated from the day of surgery to death from any cause. DFS was calculated from the day of surgery until locoregional, distant, contralateral breast relapse, or appearance of second primary cancer.

Hematologic toxicity was evaluated on day 1 and 8 of each cycle. A general biochemistry was mandatory immediately before each new cycle. Non-hematologic toxicity was evaluated on each outpatient visit. The parameters evaluated were emesis, mucositis, diarrhea, amenorrhea (in premenopausal patients), and weight gain. Toxicity was graded according to the NCI-CTC version 2.0.

5. Statistical analysis

Comparisons of clinicopathologic characteristics were made using a Chi-square test for discrete variables, and an independent two sample t-test for continuous variables. The role of each chemotherapy regimen and the usefulness of other pathologic markers as prognostic indicators were investigated in terms of disease-free survival and overall survival. Calculation of survival was based on all-cause mortality and breast cancer-specific mortality, respectively. In terms of DFS, all disease recurrence, including second primary cancers, and breast cancer-specific DFS were calculated, respectively. For second breast cancers, in which it is difficult to differentiate between second primary cancers and contralateral recurrences, diagnosis of any contralateral breast disease during the first 3 years following primary diagnosis was considered as contralateral recurrence, with diagnosis of a second breast cancer after 3 years treated in the same way as second primary cancer.[10] Survival curves were estimated using the Kaplan-Meier method and the differences in survival between the groups were assessed by a log-rank test. To make adjustments for any confounding variables and to assess the relative importance of potential prognostic factors, univariate and multivariate

analyses were performed using the Cox proportional hazards regression model. Data were analyzed using SPSS (version 11.5) software, and *P*-value < 0.05 was considered statistically significant.

III. Results

1. Patient characteristics

Table 1 displays the clinicopathologic characteristics of the study population according to axillary lymph node involvement. The median follow-up was 68 months (range, 14-142). Two hundred and eighty seven patients (43.2 %) was in LN 0, 223 (33.5 %) in LN 1-3, and 155 (23.3 %) in LN ≥ 4 group. Therefore, 509 patients (76.7 %) of total patients received CMF chemotherapy, whereas 155 (23.3 %) received FAC chemotherapy. The median age of overall patients was 44 years (range, 21 to 74) with slightly more patients with age of ≥ 60 years in LN ≥ 4 group.

In terms of menopausal status, premenopausal women accounted for 73.9 % of entire patients with higher proportion of premenopausal women in LN 0 group. Overall, 40.4 % of patients had ER-positive tumors, whereas 43.1 % had PgR-positive tumors. ER or PgR-positive tumors were more likely to be present in LN ≥ 4 group. Histologic grade II-III tumors accounted for approximately two third of each nodal group. Tumor size of 2-5 cm was dominant in each nodal group. TNM stage was mainly IIA-B in node-negative and LN 1-3 group, whereas IIIA-C in LN ≥ 4 group. There was no significant difference among nodal groups in terms of type of surgery, with most patients undergoing radical mastectomy. Finally, patients with LN ≥ 4 were more likely to be treated with adjuvant hormonal and radiation therapy than patients with node-negative or LN 1-3. Forty-three (68.2 %) of 63 patients with 10 or more positive nodes did not go on to receive radiotherapy because of patients' refusal. Adjuvant tamoxifen was administered concurrently (85.3 %) or sequentially (14.7 %) for 5 years in patients with positive ER and/or PgR. Bilateral breast cancer occurred in 12 patients (1.8 %), among whom 3

Table 1. Patients characteristics according to axillary lymph node involvement

Characteristics	CMF, n (%)		FAC, n (%)	*P* value[a]
	LN 0	LN 1-3	LN ≥ 4	
All patients	287 (43.2)	223 (33.5)	155 (23.3)	
Age (yrs)				0.024
< 60	276 (96.2)	206 (92.4)	139 (89.7)	
≥ 60	11 (3.8)	17 (7.6)	16 (10.3)	
Menstrual status				0.006
Pre-/peri-menopausal	224 (78.0)	153 (68.6)	64 (69.6)	
Postmenopausal	63 (22.0)	70 (31.4)	28 (30.4)	
ER				0.060
Positive	104 (36.2)	102 (45.7)	76 (49.0)	
Negative	159 (55.4)	97 (43.5)	69 (44.5)	
Unknown	24 (8.4)	24 (10.8)	10 (6.5)	
PgR				0.029
Positive	116 (40.4)	104 (46.6)	86 (55.5)	
Negative	148 (51.6)	95 (42.6)	59 (38.1)	
Unknown	23 (8.0)	24 (10.8)	10 (6.5)	
Histologic grade				0.456
2-3	179 (62.4)	157 (70.4)	103 (66.5)	
1	50 (17.4)	37 (16.6)	34 (21.9)	
Unknown	58 (20.2)	29 (13.0)	18 (11.6)	
Tumor size (cm)				0.095
T1	21 (7.3)	30 (13.5)	17 (11.0)	
T2	233 (81.5)	168 (75.3)	108 (69.7)	
T3	33 (11.5)	25 (11.2)	30 (19.4)	
Stage				0.0001
I	44 (15.4)	0 (0.0)	0 (0.0)	
IIA-B	240 (83.6)	210 (94.2)	3 (1.9)	
IIIA-C	3 (1.0)	13 (5.8)	152 (98.1)	

Type of surgery				0.117
Radical mastectomy	228 (79.4)	175 (78.5)	134 (86.5)	
Partial mastectomy	59 (20.6)	48 (21.5)	21 (13.5)	
Adjuvant hormonal therapy				0.0001
Yes	123 (42.9)	118 (52.9)	99 (63.9)	
No	164 (57.1)	105 (47.1)	56 (36.1)	
Radiotherapy				0.0001
Yes	60 (20.9)	56 (25.1)	85 (54.8)	
No	227 (79.1)	167 (74.9)	70 (45.2)	

[a]ANOVA was performed among three nodal groups.

patients had simultaneous bilateral disease at the time of diagnosis.

2. Dose intensity

Table 2 depicts the actual and relative dose intensity of drugs received by the patients. Ninety-eight percent of patients were known to have completed six courses of chemotherapy; this repreresents 500 (98 %) of 510 patients allocated to CMF regimen (280/287 in LN 0 and 220/223 in LN 1-3 group) and 154 (99.4 %) of 155 patients allocated to FAC regimen (LN ≥ 4 group). Two patients (1 in LN 0 and 1in LN 1-3 group) refused further treatment after first cycle. Three patients (2 in LN 0 and 1 in LN ≥ 4 group) refused further treatment after four cycles. Six patients (4 in node-negative and 2 in LN 1-3 group) stopped after five cycles: one in LN 0 group stopped for aggravation of her underlying Behcet disease and five refused further treatment. Overall, patients received nearly 97 % of planned doses of CMF (both LN 0 and LN 1-3 group) and nearly 94 % of FAC (LN ≥ 4 group). The median relative dose intensities (RDIs) of cyclophosphamide were 0.96 (range, 0.57-1.00) for LN 0, 0.96 (range, 0.32-1.00) for LN 1-3, and 0.94 (range, 0.56-1.00) for LN ≥ 4 group, respectively.

Table 2. Actual and Relative Dose Intensity of drugs

Drug	CMF (median, mg/m^2/week)		FAC(median, mg/m^2/week)
	LN 0	LN 1-3	LN ≥ 4
Cyclophosphomide	241.0 (0.96)	239.1 (0.96)	235.7 (0.94)
5-Fluorouracil	241.0 (0.96)	239.1 (0.96)	237.6 (0.95)
Methotrexate	24.0 (1.00)	23.9 (0.99)	
Doxorubicin			9.4 (0.94)
CMF	(0.97)	(0.97)	
FAC			(0.94)

Figures in parenthesis are relative dose intensities of the drugs.

LN 0, node-negative; LN 1-3, one to three positive nodes; LN ≥ 4, four or more positive nodes.

The median RDIs of 5-fluorouracil were 0.96 (range, 0.25-1.00) for LN 0, 0.96 (range, 0.32-1.00) for LN 1-3, and 0.94 (range, 0.61-1.00) for LN ≥ 4 group, respectively. The RDIs of agents that were common to both regimens (cyclophosphomide and 5-fluorouracil) were higher in node-negative and LN 1-3 group than those in LN ≥ 4 group (*P*= 0.0001 for cyclophophamide, *P*= 0.001 for 5-fluorouracil). The median cumulative doses of methotrexate and doxorubicin were 576 mg/m^2 (range, 145-600 mg) and 225 mg/m^2 (range, 150-240 mg), respectively. There were more dose reduction or delay in chemotherapy schedule in the FAC group than in the CMF group (8.2 % in CMF vs. 25.2 % in FAC, *P*= 0.0001). The causes of dose reduction or schedule delay in each group are as follows: 30 (5.9 %) leukopenia, 4 (0.8 %) patients' wish, 3 (0.6 %) mucositis, 2 (0.4 %) wound dehiscence, 1 (0.2 %) 5-FU hypersensitivity, 1 (0.2 %) local recurrence (after wide excision of recurrent mass on chest wall, the patient continued on CMF chemotherapy), 1 (0.2 %) cerebrovascular accident in CMF group. 37 (23.9 %) leukopenia, 1 (0.6 %) wound dehiscence, 1 (0.6 %) emesis in FAC group.

3. Survival

Overall survival and disease free survival curves according to TNM stages and nodal groups are shown in Figures 1, 2, and 3. After a median follow-up of 68 months, 140 (21.1 %, 45 in LN 0, 51 in LN 1-3, 44 in LN ≥ 4) of total patients had disease recurrence, whereas 81 patients (12.2 %, 20 in LN 0, 30 in LN 1-3, 31 in LN ≥ 4) have died. Table 3. depicts the corresponding 5-year and 8-year survival parameters of all study population according to each nodal groups. Overall, 5-year DFS and OS rates of all study population were 80.2 % and 89.5 %, respectively. 5-year DFS and OS rates for each nodal group were estimated to be as follows; 85.3 % and 94.6 % in LN 0 group, 78.4 % and 87.3 % in LN 1-3 group, and 73.5 % and 83.3 % in LN ≥ 4 group, respectively.

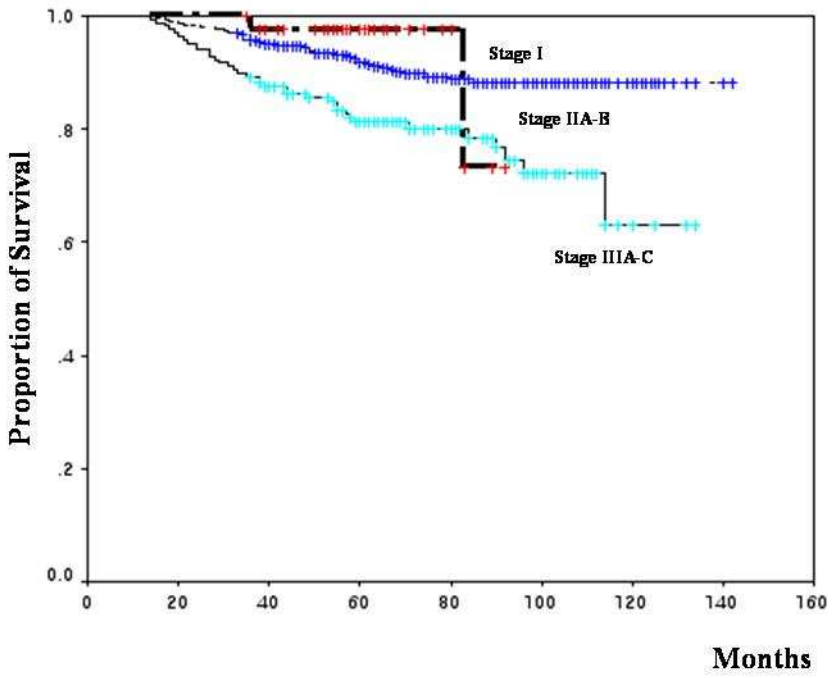

Figure 1. Overall survival curves according to TNM stages.

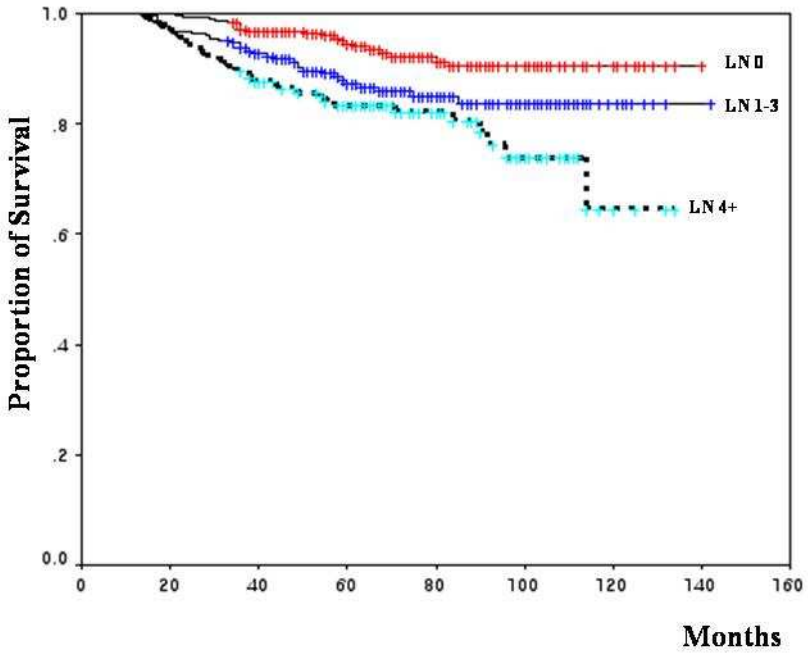

Figure 2. Overall survival curves according to nodal status

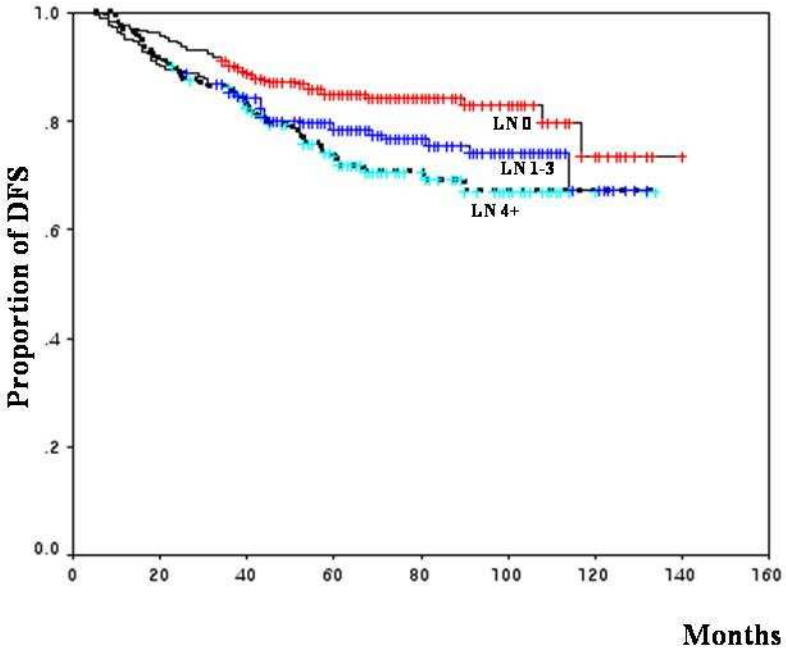

Figure 3. Disease-free survival curves according to nodal status

5-year breast cancer-specific DFS and OS rates for each nodal group were estimated to be as follows; 89.2 % and 95.7 % in LN 0 group, 81 % and 89.2 % in LN 1-3 group, and 76.4 % and 84.4 % in LN ≥ 4 group, respectively. 5-year locoregional and distant DFS rates were 95.2 % and 87.0 %, respectively. 5-year distant DFS rates were significantly different among nodal groups (92.3 % in LN 0 *vs.* 84.5 % in LN 1-3 *vs.* 79.2 % in LN ≥ 4, *P*= 0.0002), whereas 5-year locoregional DFS rates were not (96.1 % in LN 0 *vs.* 94.3 % in LN 1-3 *vs.* 94.7 % in LN ≥ 4, *P*= 0.502). Median OS of patients with locoregional and distant relapse were 96 months and 54 months, respectively.

When analyses were performed between two adjacent nodal groups, a significant difference in terms of DFS and OS was found in between LN 0 and LN 1-3 (DFS, *P*= 0.029; OS, *P*= 0.012), but not in between LN

Table 3. Survival parameters (%) at 5-year and 8-year follow-up according to nodal stage

Follow-up	CMF		FAC
	LN0	LN1-3	LN ≥ 4
Disease-free survival (%)			
5-year	85.3	78.4	73.5
8-year	83.2	74.2	67.0
Overall survival (%)			
5-year	94.6	87.3	83.3
8-year	90.4	83.6	73.7

Table 4. Univariate and Multivariate Analysis of Factors affecting DFS and OS in all population

Factors	DFS		OS	
	Univariate	Multivariate	Univariate	Multivariate
Number of positive nodes	0.006	0.002	0.0003	0.0001
Tumor size	0.027	NS	0.0049	0.002
Histologic grade	0.061	NS	0.103	NS
ER status	0.015	NS	0.0096	NS
PgR status	0.002	NS	0.0034	NS
Menopausal status	0.029	NS	0.0011	0.009
Chemotherapy regimen	0.013	NS	0.0008	NS
RDI of chemotherapy (<90 % vs.≥90 %)	0.0176	NS	0.625	NS
Type of surgery	0.466	NS	0.471	NS
Hormonal therapy	0.031	0.016	0.040	0.009
Radiation therapy	0.361	NS	0.474	NS
Amenorrhea during chemotherapy	0.223	NS	0.456	NS
Weight gain during chemotherapy	0.882	NS	0.897	NS

1-3 and LN ≥ 4 (DFS, *P*= 0.278; OS, *P*= 0.103). When a Cox proportional hazards model was performed, number of positive nodes and hormonal therapy were independent prognostic factors for DFS and number of positive nodes tumor size, menopausal status, and hormonal therapy for OS (Table 4).

4. Recurrence and further treatments

Table 5 summarizes the sites of first recurrence (defined as the organ in which the first signs of recurrence were observed). There were no significant differences among three nodal groups in the incidence of locoregional relapse, distant bone recurrence, relapse in the contralateral breast, and occurrence of second primary cancer. Although incidences of overall distant and soft tissue recurrence were significantly different among 3 nodal groups, analyses between two adjacent nodal groups showed a difference only in between node-negative and LN 1-3 group. The incidences of visceral recurrence were similar between two adjacent nodal groups, although overall comparison of 3 nodal groups demonstrated significant differences. In about one third of patients, multiple sites were observed to be involved at the time of recurrence. Thirty-one patients have experienced a second primary cancer- all solid tumors (Table 6). Twenty-three of these cases occurred in the CMF group and seven patients in FAC group (*P*= 0.513). Contralateral breast cancer was reported in 8 patients. Eleven cases of thyroid carcinomas were reported. Other primaries were less frequently reported; 2 stomach cancers, 2 colorectal cancers, 1 hepatocellular carcinomas, 2 pancreatic cancers, 1 lung cancer, 2 ovarian cancer, and 1 schwanoma. No hematologic malignancy occurred. After breast cancer recurrence, subsequent treatments were given in 90 patients in previous CMF group and 43 in previous FAC group, respectively (Table 7).

Table 5. Sites of first recurrence, *n* (%)[a]

Site	N 0	N 1-3	N ≥ 4	*P* value[b]
Loco-regional only	7 (15.6)	7 (13.8)	3 (6.8)	0.756
Distant (± loco-regional ± contralateral breast)[c]	22 (48.9)	35 (68.6)	33 (75.0)	0.0001
Viscera[d]	12 (26.7)	17 (33.3)	20 (45.5)	0.004
Bone[e]	16 (35.6)	21 (41.2)	11 (25.0)	0.252
Soft tissue[f]	9 (20.0)	23 (45.1)	15 (34.1)	0.003
Contralateral breast only	2 (4.4)	0 (0.0)	1 (2.3)	0.466
Second primary	14 (31.1)	9 (17.6)	7 (15.9)	0.855
Contralateral breast cancer	4 (8.8)	3 (5.9)	1 (2.3)	0.565
Other cancers	10 (22.3)	6 (11.7)	6 (13.6)	0.662

[a]Some patients had recurrence in more than one site.

[b]*P* value were obtained using χ^2 test among 3 nodal groups.

[c]*P*= 0.004, N 0 *vs.* N 1-3; *P*= 0.164, N 1-3 *vs.* N ≥ 4.

[d]*P*= 0.096, N 0 *vs.* N 1-3; *P*= 0.089, N 1-3 *vs.* N ≥ 4.

[e]*P*= 0.121, N 0 *vs.* N 1-3; *P*= 0.459, N 1-3 *vs.* N ≥ 4.

[f]*P*= 0.001, N 0 *vs.* N 1-3; *P*= 0.864, N 1-3 *vs.* N ≥ 4.

Table 6. Occurrence of second primary cancer

Type of malignancy	Number of cases		
	CMF	FAC	*P* value
Contra-lateral breast	7	1	
Stomach	2	0	
Colorectal	1	1	
HCC[a]	1	0	
Pancreas	1	1	
Lung (NSCLC[b])	1	0	
Thyroid	8	3	
Ovary	1	1	
Schwannoma	1	0	
Total (%)	23	7	0.513

[a]HCC, hepatocellular carcinoma; [b]NSCLC, non-small-cell lung cancer

Table 7. Subsequent treatments after recurrence of breast cancer

Treatment[a]	CMF (*n*)	FAC (*n*)
No treatment	6	1
Surgery	12	4
Chemotherapy	53	18
Paclitaxel	4	15
Doxorubicin-based combination	48	0
CMF	1	1
5-FU+DDP+VP-16	0	2
Radiotherapy	37	16
Hormonal therapy	15	10
Multimodality[b]	41	17

[a]Some patients received more than one type of treatment.

[b]Any combination of surgery, chemotherapy, radiotherapy, or hormonal therapy.

Surgical treatments of curative purpose for local recurrence were given in 12 patients in previous CMF group and 4 in previous FAC group, respectively. Systemic chemotherapies were given in 53 patients in previous CMF group and 18 in previous FAC group, respectively. Forty-eight (91 %) of 53 previous CMF group received doxorubicin-based combination chemotherapy, whereas 15 (83 %) of 18 previous FAC group received paclitaxel. Radiotherapies, either with palliative purpose for brain or bone metastasis or with curative purpose for locoregional recurrence, were given in 37 patients of previous CMF group and 16 of previous FAC group, respectively. Hormonal treatment with tamoxifen or anastrozole were given in 15 in previous CMF group and 10 in previous FAC-treated group, respectively. Forty-one (51 %) of previous CMF group and 17 (77 %) of previous FAC group were treated with multimodality approach. Of the patients who have died, 72 (89 %) died of metastatic disease, four of second primary cancer (1 stomach cancer, 1 cervix

Table 8. Cause of death by lymph node stage

	CMF		FAC	
Cause of death	LN 0, *n* (%)	LN 1-3, *n* (%)	LN 4-9, *n* (%)	LN ≥10, *n* (%)
Breast cancer	17 (3.3)	26 (5.1)	13 (8.4)	16 (10.3)
Other cancer	1 (0.2)	3 (0.6)	0 (0)	0 (0)
Treatment-related complication[a]	2 (0.4)	1 (0.2)	2 (1.3)	0 (0)
Total	50 (9.8)		31 (20.0)	

[a]Pneumonia during or after palliative chemotherapy after recurrece

cancer, 1 ovarian cancer, and 1 hepatocellular carcinoma), and five of pneumonia during palliative chemotherapy after the diagnosis of multiple metastasis.

5. Toxicity

The hematologic and non-hematologic toxicities are summarized in Table 9 and 10. For hematologic toxicity, the incidence of grade III/IV leucopenia was significantly higher in FAC group (P= 0.0001). Myelotoxicity was mild and no patients had severe infection due to myelosuppression. For non-hematologic toxicities, FAC treatment induced significantly more emesis, mucositis, and weight gain. Amenorrhea, defined as absence of three or more consecutive menses, occurred significantly more in CMF group than FAC group. In addition to chemotherapy regimen, age was the primary determinant of chemotherapy-induced amenorrhea. Median age of patients with chemotherapy-induced amenorrhea (CIA) was significantly higher than those without CIA (45 years, range 25-74 vs. 44 years, range 21-60; P= 0.001). Cardiotoxicity was not seen in our patients. No toxic deaths occurred in this study.

Table 9. Hematologic toxicities (percentage of patients with grade III/IV toxicity)

Toxicity	CMF (%)	FAC (%)	*P*
Leukopenia	13.0	32.9	0.0001
Anemia	2.0	2.6	NS
Thrombocytopenia	0	0	NS

Table 10. Non-hematologic toxicities

Toxicity	CMF	FAC	*P*
	Grade I-II/III-IV(%)	Grade I-II/III-IV(%)	
Emesis	7.1/0.0	18.1/0.0	0.0001
Mucositis	4.7/0.0	9.0/0.0	0.049
Diarrhea	1.4/0.0	1.3/0.0	NS
Amenorrhea[a]	51.0	41.0	0.039
Weight gain[b]	26.5	35.5	0.033
AST/ALT elevation	0.2/0.0	0.0/0.0	NS

[a]Amenorrhea was defined as absence of three or more consecutive menses, regardless of reversibility

[b]Figures in the table correspond to considerable weight gain (> 10 % of baseline)

IV. Discussion

Most patients with breast cancer who appear to be disease-free after surgery eventually relapse and die with overt metastases. It is thought that occult micrometastases present at the time of diagnosis are responsible.[1] Adjuvant chemotherapy has been shown to substantially improve the long-term disease-free survival and overall survival in both premenopausal and postmenopausal women with lymph node-positive or lymph node-negative disease.[1-4]

Regarding adjuvant chemotherapy, one of the most important and challenging tasks of the medical oncologist is to select optimal chemotherapy regimen that will work best for the individual patient.[5-7] Injudicious use of more active agent, such as anthracyclines, might increase the risk of severe or permanent toxicities, and be no better than waste of a valuable agent reserved for possible relapse later on. Thus, it would be reasonable to choose chemotherapy regimen on the basis of number of positive axillary nodes, which has been shown to be one of the most powerful predictor of poor prognosis among other biologic markers.[11,12]

Although chemotherapy are currently considered to be the treatment of choice for node-negative patients, no specific recommendation for chemotherapy regimen has not been made so far. In overview analysis, the absolute advantage of anthracyclines over CMF was only 1.7 % at 5 years in node-negative patients.[4] Another randomized trial supporting the superiority of FAC over CMF in node-negative patients was subject to criticism for being conducted with post hoc stratification with respect to axillary lymph node status.[13] At this time, there are insufficient data to recommend the use of doxorubicin in women with node-negative breast cancer.[8,9,13]

Our study suggests that in node-negative patients, adjuvant chemotherapy with CMF regimen yields excellent DFS and OS rates, both of which were at least comparable to previously reported rates with anthracycline-containing

regimens.[13-15] The superior results achieved in this subset of patients might be, in part, due to improved compliance for cyclophosphamide given intravenously, instead of orally. Previous reports have found that lack of compliance due to use of oral cyclophosphamide impaired outcome by reducing actual dose intensity of adjuvant chemotherapy.[2] Adjuvant chemotherapy with intravenous cyclophosphamide was well tolerated, as exemplified by high RDI of drugs in our study.

Few randomized trial comparing CMF and anthracycline-containing regimen has been performed in the specific subset of patients with LN 1-3.[8] However, considering the good 5-year results achieved in this study and relatively lower baseline risk of recurrence of this subset of patients than that of patients with LN ≥ 4, we would suggest CMF remain, at present, as the adjuvant chemotherapy for patients with one to three positive nodes.

DFS and OS were not significantly different between patients with one to three nodes and patients with four or more nodes, although there was a non-significant trend towards better results in patients with one to three nodes. Because there has been clear evidence of poorer outcome associated with advanced nodal stage, our results indirectly showed that FAC was efficacious regimen.[16] Because RDIs of cyclophosphamide and 5-fluorouracil were higher in LN 1-3 group than in LN ≥ 4 group, the benefit from doxorubicin would be possible explanation for the similarity of outcome in two different nodal groups. Thus, the substitution of the cumulative dose of 225 mg/m^2 of doxorubicin for methotrexate appeared to overcome more advanced nodal stage doomed to poorer prognosis. By this indirect comparison of different regimens in different nodal stages, we could draw conclusion that FAC regimen had good efficacy enough to compensate for more advanced nodal stage. It is interesting to note, however, that the differences between two nodal groups augmented in the latter parts of the survival curves. This might suggest that an advantage of FAC regimen persist only for a while after surgery, and therefore use of more active regimens be

warranted in the patients with four or more nodes.

Although statistically significant difference was detected in the pattern of overall distant and distant soft tissue recurrences among nodal groups, the pairwise comparisons demonstrated differences only in between LN0 and LN 1-3 group. No differences were found in recurrence patterns between LN 1-3 and LN ≥ 4 group. Therefore, we concluded that the main therapeutic effect of doxorubicin was to reduce the incidence of overall distant and distant soft tissue recurrence.

Initial reluctance to use doxorubicin in the adjuvant treatment of breast cancer was due to the potential risk of late cardiac damage.[17] However, in several long-term follow-up studies, no such delayed cardiac events have been noted in women treated with doxorubicin at the cumulative doses utilized in adjuvant chemotherapy for breast cancer.[18] Consistently, we documented no case of congestive heart failure during the follow-up.

In our study, as well as in others, a close relationship between chemotherapy-induced amenorrhea (CIA) and age of patient was evident; the older the patient the greater the incidence of CIA.[19] With CMF adjuvant chemotherapy given for more than 3 months, approximately 70 % of women develop amenorrhea.[20] In our study, CIA occurred in 43.8 % (291/665) of patients, in 28.4 % of women 40 years or younger and 49.9 % of those older than 40. CMF regimen caused amenorrhea more frequently than FAC in our study. This was not only because cyclophosphamide among other drugs had most effect on causing ovarian failure, but because significantly lower dose of cyclophosphamide was administered in FAC group. Weight gain is common side effect during adjuvant chemotherapy of breast cancer.[21] The postulated cause of weight gain include decreased physical activity due to fatigue, increased food consumption, and reduced basal metabolic rate.[22] This side effect occurred more frequently in FAC-treated group, partly because of more frequent administration of prednisone to prevent emesis.

In conclusion, our study emphasizes strategy of adjuvant chemotherapy

according to the risk of recurrence, which was stratified by axillary nodal status. We suggest that CMF regimen, at present, was the adjuvant chemotherapy of choice for patients with node-negative or one to three positive nodes. Although FAC regimen was still a reasonable choice in patients with four or more nodes, more active regimens including taxanes were required to obtain better long-term results. Confirmation of our hypothesis requires randomized comparative trial of CMF versus FAC to be conducted with prospective stratification with respect to axillary lymph node status.

V. Conclusion

Considering the good 5-year results achieved in this study at the expense of minimal toxicity, we suggest that CMF regimen, at present, is the adjuvant chemotherapy of choice for patients with node-negative or one to three positive nodes. Although FAC regimen was still a reasonable choice in patients with four or more nodes, more active regimens including taxanes would be required to obtain better long-term results.

VI. References

1. Bonadonna G, Brusamolino E, Valagussa P, Rossi A, Brugnatelli L, Brambilla C, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 1976;294:405-410.
2. Bonadonna G, Valagussa P, Angela M, Zaambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: The results of 20 years of follow-up. N Engl J Med 1995;332:901-906.
3. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomized trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Lancet 1992;339:1-15.
4. EBCTCG. Polychemotherapy for early breast cancer: an overview of the randomized trials. Lancet 1998;352:930-942.
5. Roy JA, Piccart MJ. Adjuvant systemic chemotherapy for breast cancer. Curr Opin Oncol 1995;7:517-522.
6. Cardoso F, Atalay G, Piccart MJ. Optimizing anthracycline therapy for node positive breast cancer. Am J Cancer 2002;1:257-268.
7. Cardoso F, Piccart MJ. The best use of chemotherapy in the adjuvant setting. The Breat 2003;12:522-528.
8. Moliterni A, Bonadonna G, Valagussa P, Ferrari L, Zambetti M. Cyclophosphamide, methotrexate, and fluorouracil with and without doxorubicin in the adjuvant treatment of resectable breast cancer with one to three positive axillary nodes. J Clin Oncol 1991;9:1124-1130.
9. Buzdar AU, Kau SW, Smith TL, Hortobagyi GN. Ten-year results of FAC adjuvant chemotherapy trial in breast cancer. Am J Clin Oncol 1989;12:123-128.
10. Coombes RC, Bliss JM, Wils J, Morvan F, Espie M, Amadori D, et al.

Adjuvant cyclophosphamide, methotrexate, and fluorouracil versus fluorouracil, epirubicin, and cyclophophamide chemotherapy in premenopausal women with axillary node-positive operable breast cancer: results of a randomized trial. J Clin Oncol 1996;14:35-45.
11. Quiet CA, Ferguson DJ, Weichselbaum RR, Hellman S. Natural history of node positive breast cancer: the curability of small cancer with a limited number of positive nodes. J Clin Oncol 1996;14:3105-3111.
12. Michaelson JS, Silverstein M, Sgroi D, Cheongsiatmoy JA, Taghian A, Powell S, et al. The effect of tumor size and lymph node status on breast carcinoma lethality. Cancer 2003;98:2133-2143.
13. Martin M, Villar A, Sole-Calvo A, Gonzalez R, Massuti B, Lizon J, et al. Doxorubicin in combination with fluorouracil and cyclophosphamide (i.v. FAC regimen, day 1,21) versus methotrexate in combination with fluorouracil and cyclophsphamide (i.v. CMF regimen, day 1, 21) as adjuvant chemotherapy for operable breast cancer: a study by the GEICAM group. Ann Oncol 2003;14:833-842.
14. Hutchins L, Green S, Ravdin P, et al. CMF versus CAF with and without tamoxifen in high-risk node-negative breast cancer patients and natural history follow-up study in low-risk node-negative patients. First results of Intergroup trial INT 0102. Proc Am Soc Clin Oncol 1998;17:1a (Abstr).
15. Mouridsen HT, Andersen J, Andersson M, et al. Adjuvant anthracycline in breast cancer. Improved outcome in premenopausal patients following substitution of methotrexate in the CMF combination with epirubicin. Proc Am Soc Clin Oncol 1999;18:68a (Abstr).
16. Carter CL, Allen C, Henson DE. Relation of tumor size, nodal status, and survival in 24,740 breast cancer cases. Cancer 1989;63:181-187.
17. Shapiro CL, Recht A. Side effects of adjuvant treatment of breast cancer. N Engl J Med 2001;344:1997-2008.
18. Zambetti M, Moliterni A, Materazzo C. Long-term cardiac sequelae in operable breast cancer patients given adjuvant chemotherapy with or

without doxorubicin and breast irradiation. J Clin Oncol 2001;19:37-43.
19. Bianco AR, Mastro LD, Gallo C, Perrone F, Matano E, Pagliarulo C, et al. Prognostic role of amenorrhea induced by adjuvant chemotherapy in premenopausal patients with early breast cancer. Br J Cancer 1991;63:799-803.
20. Goodwin PJ, Ennis M, Pritchard KI, Trudeau M, Hood N. Risk of menopause during the first year after breast cancer diagnosis. J Clin Oncol 1999;17:2365-2370.
21. Huntington MO. Weight gain in patients receiving adjuvant chemotherapy for carcinoma of the breast. Cancer 1985;56:472-474.
22. Levine EG, Raczynski JM, Carpenter JT. Weight gain with breast cancer adjuvant treatment. Cancer 1991;67:1954-1959.

ABSTRACT(IN KOREAN)

유방암 환자에서 근치적 수술후 림프절 병기에 따른 보조약물요법

<지도교수 정현철>

연세대학교 대학원 의학과

조병철

배경. 각각 다른 액와 림프절 병기에 따른 보조약물요법의 역할은 명확히 정해지지 않았다. 저자등은 유방암 환자에서 근치적 수술후림프절 병기에 따른 보조약물요법의 효과를 알아보고자 하였다.

방법. 본원에서 유방암으로 수술받은 665명의 환자를 대상으로 전이 액와 림프절의 개수에 따라 치료 방침을 정하였다. 전이 액와 림프절이 3개 이하인 경우는 CMF요법 (cyclophosphamide 500 mg/m2 i.v. day 1, 8, methotrexate 50 mg/m^2 i.v. day 1, 8 and 5-fluorouracil 500 mg/m^2 i.v. day 1, 8), 전이 액와 림프절이 4개 이상인 경우는 FAC요법 (5-fluorouracil 500 mg/m^2 i.v. day 1, 8, doxorubicin 40 mg/m^2 i.v. day 1 and cyclophosphamide 500 mg/m^2 i.v. day 1, 8)으로 매 4주간격으로 6주기를 보조화학요법으로 시행하였다. 5년 무병 생존율과 전체 생존율을 전이 림프절 개수 (림프절 음성, 1-3 림프절 양성, 4개 이상 림프절 양성)에 따라 후향적으로 분석하였다.

결과. 510명 (76.7 %)의 환자와 155명 (23.3 %)의 환자가 각각 CMF와 FAC요법으로 치료받았다. CMF와 FAC의 상대용량강도는 각각 0.97 (범위, 0.32-1.00)와 0.94 (범위, 0.63-1.00)이었다. 각 림프절군에 따른 상대용량강도는 림프절 음성군은 0.98 (범위, 0.60-1.00), 1-3 림프절 양성군은 0.92 (범위, 0.32-1.00), 4개 이상 림프절 양성군은 0.94 (0.63-1.00)이었다. 68개월 (범위, 14-142

개월)의 중앙 관찰기간동안 140명의 환자가 재발을 경험하였고 81명의 환자가 사망하였다. 5년 전체생존율과 무병 생존율은 각각 89.5 %와 80.1 %이었다. 각 림프절군에 따른 5년 전체 생존율은 림프절 음성군은 94.6 %, 1-3 림프절 양성군은 87.3 %, 4개 이상 림프절 양성군은 83.3 %이었다 (*P*= 0.0003). 림프절군에 따른 5년 무병 생존율은 림프절 음성군은 85.1 %, 1-3 림프절 양성군은 78.4 %, 4개 이상 림프절 양성군은 73.5 %이었다 (*P*= 0.0066). 치료 성적을 림프절군에 따라 비교하면, 전체 생존율과 무병 생존율에서 림프절 음성군과 1-3 림프절 양성군사이에는 유의한 차이가 있었으나, 1-3 림프절 양성군과 4개 이상 림프절 양성군에는 차이가 없었다. 재발의 유형은 원격 재발이 가장 많았고 (64.3 %), 국소 재발 (22.1 %)이 두번째로 많았다. 원격 장기 전이와 연조직 전이는 각 림프절군에 따라 유의한 차이가 있었다 (각각 *P*= 0.002와 *P*= 0.004). 대부분의 환자들은 보조화학요법을 잘 견뎠고 생명을 위협하는 독성은 나타나지 않았다.

결론. 좋은 5년 생존율과 미미한 독성을 감안할 때, CMF요법은 림프절 음성 또는 1-3 림프절 양성환자군에서 우수한 보조화학요법이다. 비록 FAC요법은 4개 이상의 림프절 양성환자군에서 사용할 수 있겠으나, 좀 더 좋은 장기 생존율을 위하여 taxanes을 포함한 더 효과적인 약제의 사용이 필요하리라 생각된다.

핵심되는 말 : 유방암; 보조약물요법; 림프절 병기; 생존율