# Comparison of the Result of Radiation Alone and Chemoradiation in Cervical Cancer

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=Abstract=

Purpose : This analysis was to compare the result of radiation alone and chemoradiation in cervical cancer in terms of response, survival, failure, and complication.

Materials and Methods : A retrospective analysis of 135 cervical cancer patients treated with definitive radiotherapy from November 1985 to December 1991 was performed. Fifty-six patients were treated with radiation alone and 79 patients were treated with cisplatin-based chemotherapy plus radiation. Follow-up period ranged from 5 to 105 months with a median 47 months. According to the FIGO classification, the patients were subdivided into 18 (13.3%) stage IB, 7 (5.2%) stage IIA, 97 (71.9%) stage IIB, and 9 (6.7%) stage IIIB.

Results : A complete response was noted in 51 patients (91.1%) of the radiation alone group, and 68 patients (86.1%) of the chemoradiation group. There was no statistical difference in complete response rate between the two groups.

Overall survival rate at 5 years was 73.3%. According to stage, overall survival rates at 5 years were 88.9% in stage IB, 85.7% in stage IIA, 73.8% in stage IIB, and 37.5% in stage IIIB, respectively. According to treatment modality, overall survival rates at 5 years were 81.9% in the radiation alone group, 67.0% in the chemoradiation group ($p=0.22$). Disease-free survival rate at 5 years were 70.4% in the radiation alone group, 68.5% in the chemoradiation group ($p=0.85$). Locoregional control rates at 5 years were 76.1% in the radiation alone group, 73.8% in the chemoradiation group ($p=0.70$). Distant disease-free survival rates at 5 years were 83.9% in the radiation alone group, 90.3% in the chemoradiation group ($p=0.59$). Treatment-related bone marrow suppressions were noted in 3 (5.4%) patients of the radiation alone group, 14 patients (17.7%) of the chemoradiation group ($p<0.05$). Grade 2 vesical complications were noted in 14 patients of the radiation alone group, and 10 patients of the chemoradiation group. Grade 2 rectal complications were noted in 2 patients of the radiation alone group, and 3 patients of the chemoradiation group. One case of rectal perforation was noted in the chemoradiation group, and grade 2 small bowel

**obstructions were noted in 2 patients of the radiation alone group. There were no statistical differences in the incidence of vesical, rectal, and small bowel complicaions between the two groups.**

**Conclusion : No statistical difference was found between the radiation alone group and the chemoradiation group in terms of response, survival, and failure, but the incidence of bone marrow suppression was higher in the chemoradiation group.**

**Key Words : Cervical cancer, Chemoradiation**

## INTRODUCTION

In spite of the success of definitive radiotherapy for cancer of the uterine cervix, some patients present with metastatic disease and there is a subset of patients who will not be cured with radiotherapy alone even in early stages. In fact, nearly a third of patients with invasive cervical cancer still die of their disease[1]. Thus, there is a potential role of chemotherapy of the carcinoma of the uterine cervix.

The use of chemotherapy as initial treatment before pelvic radiotherapy would be theoretically advantageous as the vascular supply to the tumor is not compromised, allowing a higher local tissue concentration of chemotherapeutic agents, thereby improving the effectiveness of chemotherapy. Chemotherapy and radiotherapy theoretically interact by sensitization, normal tissue protection, or by spatial cooperation, i.e., radiation therapy for local disease and chemotherapy for subclinical metastasis[2]. Unfortunately, the results of chemotherapy still fall short of what is needed. Although dramatic responses occur in some patients, the results tend to be brief, inconsistent, and not reproducible[1].

Of many chemotherapeutic agents, cisplatin has been regarded as the most active chemotherapeutic agent in cervical cancer[3], and is recognized as having radiosensitizing effect when used concomitant with radiation in in vitro studies. Extensive in vivo and in vitro studies have shown an increased cytotoxicity of cisplatin and radiation therapy. Although the precise mechanism of action has not been defined, inhibition of the repair of sublethal damage and hypoxic cell sensitization have been postulated[4].

We studied retrospectively for the effect of cisplatin-based chemotherapy plus radiotherapy on cervical cancer by comparing with the result of radiotherapy alone.

## MATERIALS AND METHODS

A retrospective analysis of 135 cervical cancer patients treated with definitive radiotherapy at Kyungpook University Hospital from November 1985 to December 1991 was performed.

Patient characteristics are shown in Table 1. Fifty-six patients were treated with radiotherapy alone and 79 patients were treated with cisplatin-based chemotherapy plus radiotherapy. Follow-up period ranged from 5 to 105 months with a median 47 months. According to the FIGO classification, the patients were subdivided into 18 (13.3%) stage IB, 7 (5.2%) stage IIA, 97 (71.9%) stage IIB, and 9 (6.7%) stage IIIB. All patients were ambulatory.

All patients were treated with external whole pelvic irradiation of 45 Gy (1.8 Gy per fraction, 5 times a week) without midline shielding. Stage IIIB patients were boosted 16 Gy on parametrial area.

After two-week interval, high dose rate intracavitary irradiation (Cobalt-60 in tandem, Cesium-137 in ovoids) of 39 Gy (3 Gy per fraction, 3 times a week) was delivered to point A.

Neoadjuvant chemotherapy regimens were as follows: bleomycin, vincristine, mitomycin, and cisplatin in 60 patients, cisplatin and mitomycin in 5 patients, cisplatin and 5-fluorouracil in 1 patient,

**Table 1. Patient Characteristics**

| | Radoatopm alone group (N=56) | Chemoradiation group (N=79) |
|---|---|---|
| Stage | | |
| IB | 11 | 7 |
| IIA | 4 | 3 |
| IIB | 36 | 61 |
| IIIB | 5 | 8 |
| Histology | | |
| Squamous cell carcinoma | 54 | 73 |
| Adenocarcinoma | 2 | 6 |
| Age (years) | | |
| Range | 30-78 | 28-73 |
| Median | 53 | 52 |
| Follow-up (months) | | |
| Range | 5-105 | 11-91 |
| Median | 62 | 42 |
| Performance status | all ambulatory (0,1) | |

**Table 2. Response according to Treatment Modality and Stage**

| | Radeation group | | Chemoradiation group | |
|---|---|---|---|---|
| | CR | Non-CR | CR | Non-CR |
| IB | 11 | 0 | 6 | 1 |
| IIA | 4 | 0 | 3 | 0 |
| IIB | 33 | 3 | 54 | 7 |
| IIIB | 3 | 2 | 5 | 3 |
| Total | 51 | 5 | 68 | 11 |

CR : Complete Response
Non-CR : cases with any residual desease

cisplatin, adriamycin and bleomycin in 1 patient. Concurrent cisplatin was administered in 12 patients. The range of chemotherapy cycles was 1-3 (median 2).

Responses were evaluated 1 month after all treatment. A complete response (CR) was defined as clinically no evidence of disease by physical examination and non-CR as any residual disease. If any suspicious lesions were noted, a pathologic evaluation was performed at least 3 months after treatment.

Survival was calculated by Kaplan-Meier method and analyzed by logrank test[5]. Overall survival, disease-free survival, local control, and distant disease-free survival rate were calculated from the beginning of the first treatment to the date of death, the date of the first failure, the date of locoregional relapse, and the date of distant metastasis, respectively.

Complications were estimated according to the RTOG and EORTC scale[6]. Complications of only grade 2 or more were evaluated.

All contingency tables were evaluated by chi-square test[7].

## RESULTS

A complete response was noted in 51 patients (91.1%) of the radiation alone group, and 68 patients (86.1%) of the chemoradiation group (Table 2). There was no statistical difference in complete response rate between the two groups.

Overall and disease-free survival rate at 5 years were 73.3% and 69.1%, respectively (Fig. 1). According to stage, overall survival rates at 5 years were 88.9% in stage IB, 85.7% in stage IIA, 73.8% in stage IIB, and 37.5% in stage IIIB, respectively. According to treatment modality, overall survival rates at 5 years were 81.9% in the radiation alone group, and 67.0% in the chemoradiation group (Fig. 2, p=0.22). Disease-free survival rates at 5 years were 70.4% in the

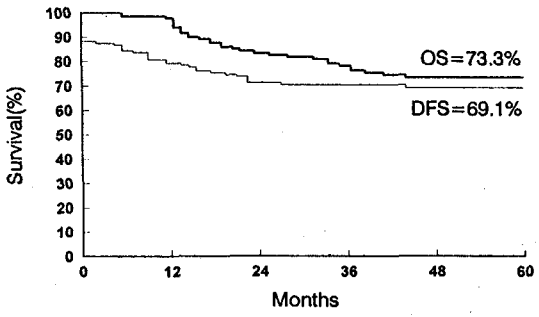


Fig. 1. Overall survival (OS) and desease-free survival rates (DFS).

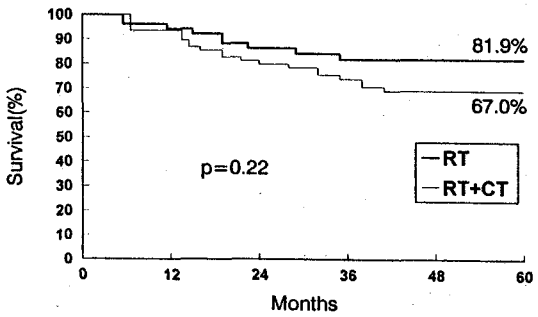


Fig. 2. Comparison of overall survival rate following radiation alone (RT) and chemoradiation (RT+CT).

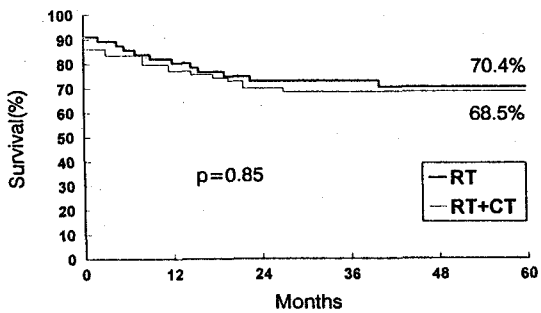


Fig. 3. Comparison of desease-free survival Rate following radiation alone (RT) and chemoradiation (RT+CT).

radiation alone group, and 68.5% in the chemoradiation group (Fig. 3, p=0.85). Locoregional control rates at 5 years were 76.1% in the radiation alone group, and 73.8% in the chemoradiation group (Fig. 4, p=0.70). Distant disease-free survival rates at 5 years were 83.9% in the radiation alone

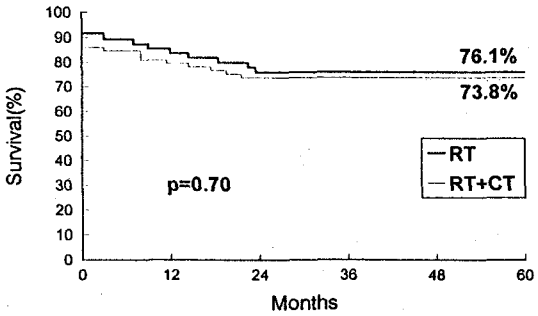


Fig. 4. Comparison of locoregional control rate following radiation alone (RT) and chemoradiation (RT+CT).

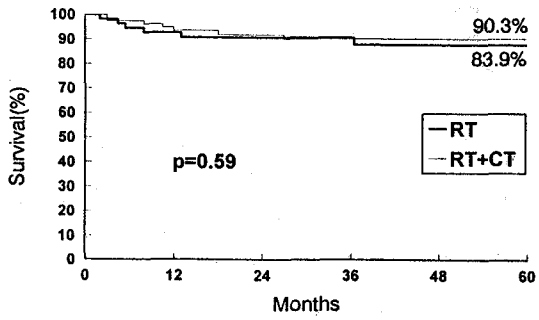


Fig. 5. Comparison of distant disease-free survival rate following radiation alone (RT) and chemoradiation (RT+CT).

group, and 90.3% in the chemoradiation group (Fig. 5, p=0.59).

There were 5 cases of locoregional failure, 4 cases of distant failure, and 1 case of locoregional and distant failure in the radiation alone group. In the chemoradiation group, there were 6 cases of locoregional failure, 4 cases of distant failure, and 3 cases of locoregional and distant failure. There was no statistical difference in the pattern of failure between the two groups (Table 3).

Treatment-related bone marrow suppressions were noted in 3 (5.4%) patients of the radiation alone group, and 14 patients (17.7%) of the chemoradiation group and the difference was statistically significant ($p<0.05$). All cases of bone marrow suppression were estimated as grade 2. Grade 2 vesical complications were noted in 14 patients of the radiation alone group, and 10 patients of the chemoradiation group. All cases of

**Table 3. Failure Pattern according to Treatment Modality and Stage**

| | Radiation group | | | Chemoradiation group | | |
|---|---|---|---|---|---|---|
| | LR | DM | LR+DM | LR | DM | LR+DM |
| IB | 1 | 1 | - | - | - | - |
| IIA | - | - | - | - | - | - |
| IIB | 4 | 2 | 1 | 6 | 3 | 3 |
| IIIB | - | 1 | - | - | 1 | - |
| Total | 5 | 4 | 1 | 6 | 4 | 3 |

LR : Locoregional
DM : Distant Metastasis

**Table 4. Incidence of Complications of Grade 2 or More**

| | Radiation group | Chemoradiation group | p-value |
|---|---|---|---|
| Rectal | 2 | 4* | NS |
| Vesical | 14 | 10 | NS |
| Small bowel | 2 | 0 | NS |
| Bone marrow | 3 | 14 | p<0.05 |

NS : not significant
All of the cases were grade 2 except one case of rectal perforation jn the chemoradiation guoup*

vesical complication were controlled with appropriate medications. Grade 2 rectal complications were noted in 2 patients of the radiation alone group, and 3 patients of the chemoradiation group. One case of rectal perforation was noted in the chemoradiation group and was treated with low anterior resection. Grade 2 small bowel obstruction was noted only in 2 patients of the radiation alone group and was treated with conservative management. There were no statistical differences in the incidence of vesical, rectal, and small bowel complicaions between the two groups (Table 4).

## DISCUSSION

It has been argued whether carcinoma of the cervix should be treated with radiation alone or with chemoradiation. So far, randomized studies[8-10] failed to show an improvement in response rate or survival rate with the addition of neoadjuvant chemotherapy. Although 12 cases of concurrent cisplatin treatment was included, most patients of the chemoradiation group in our analysis were given a cisplatin-based regimen neoadjuvantly. There was no statistical difference between radiation alone group and chemoradiation group in terms of response, survival, and failure.

The reason for this disturbing finding is not entirely clear. All patients in the chemoradiation group completed pelvic radiotherapy plus brachytherapy and therefore inadequate irradiation dosage cannot explain the non-superior results of the chemoradiation group. In a randomized trial of three cisplatin dose schedules, Bonomi et al[11] noted only a minimal increase in complete response rate and no improvement in response duration, progression-free interval, or survival by increasing the dosage of cisplatin. Because every patient of the chemoradiation group in our study was given a cisplatin-based regimen and cisplatin is considered as the most active drug in cervical cancer, inadequate drug dosage neither explain the non-superior results of the chemoradiation group. Then it is possible to state that chemotherapy was ineffective in controlling pelvic or extrapelvic disease in carcinoma of the cervix.

One possible explanation for the non-superior results of the chemoradiation group is that delay in definitive radiotherapy and prolongation of overall duration of treatment might mask the gain in survival. Retrospective analysis of clinical trials in both gynecologic and head and neck cancers have shown that prolonging the radiotherapy treatment course leads to lower local control and worse overall survival. The head and neck data showed a median loss of 10% to 14% per week of prolongation of radiotherapy[12,13]. A somewhat smaller rate of loss, averaging 7% to 9% per week of prolongation of the radiotherapy, is reported for carcinoma of the cervix[14-16]. In our data, median duration of treatment of the chemoradiation group was 19.1 weeks, and 12.6 weeks for the radiation alone group. The difference of median duration of treatment between the two groups was 6.5 weeks. So even if there had been a real gain in survival in the chemoradiation group, it might have been masked

by a loss in survival due to prolongation of the duration of treatment.

The second possible explanation for the non-superior results of the chemoradiation group in this analysis is the enhancement of accelerated tumor cell proliferation during treatment. Withers et al[17] have shown that clonogenic repopulation in squamous cell carcinoma of the head and neck region accelerates after about 4±1 weeks after initiation of radiotherapy. Since repopulation by surviving tumor clonogens is not a specific response to radiotherapy but rather results from killing of tumor cells, these authors have suggested that chemotherapy, which is able to kill cells, could also lead to an accelerated regrowth of surviving clonogens, decreasing the effect of subsequent radiotherapy. This may explain why in spite of satisfactory rate of response following neoadjuvant chemotherapy, there was no improvement in local tumor control, and survival was adversely affected. The mechanisms by which this increased cell proliferation occurs are not entirely clear, although, it may result from improved nutrition of surviving cells following shrinkage of the tumor due to previous therapy[18].

The third possible explanatory mechanism for our non-superior results of the combined treatment modality may be the development of cross-resistance between radiation and certain antineoplastic agents. The mechanisms responsible for such cross-resistance remain to be determined. Recent studies have shown significant similarity between the cytotoxicity of irradiation and antineoplastic agents and that tumor cells may develop a resistance capable of decreasing the cytotoxic effects of some antineoplastic drugs as well as radiation.

In our study, the incidences of vesical, rectal, and small bowel complications were not different significantly between the two groups. Only the incidence of bone marrow suppression was higher in the chemoradiation group. The two groups in this analysis received essentially the same dose of radiation so radiation dose could not be considered as a primary factor in the comparison of the rate of complications. Vesical, rectal, and small bowel complications are late events. Urinary tract complications are known to occur 3 to 4 years after irradiation and gastrointestinal tract complications within 2 years after irradiation[19]. The follow-up period (median 47 months) in our study is somewhat short for full occurrence of late tissue reactions. If we wait more, the chance of these late tissue reactions probably will increase. However, regarding bone marrow which is considered as an acutely responding tissue, it is postulated that all incidence of marrow suppression has been evaluated and the possibility of further incidence is low.

Although cisplatin is known to have limited bone marrow toxicity, the possibility that cisplatin-based chemotherapy affected marrow adversely couldn't be excluded. Although whether increased incidence of bone marrow suppression was contributed from cisplatin or other marrow-toxic agents was not clear, the fact is that decreased tolerance for marrow-toxic agents exhibited by some patients after combined therapy may contribute to the non-superior results of the chemoradiation group.

That chemoradiation had no gain in CR rate, overall survival, disease-free survival, locoregional control, and distant disease-free survival and had even higher incidence of marrow suppression in this study suggest that we may exclude the routine use of chemotherapy in the treatment of cervical cancer and the current enthusiasm for chemoradiation of cervical cancer should be reserved until properly analyzed randomized studies will be completed.

## CONCLUSION

In a retrospective analysis of 135 cervical cancer patients, following conclusions were derived.

1) Cisplatin-based chemotherapy had no effect in response, survival, and failure compared with the radiation alone group.

2) The incidence of bone marrow suppression was higher in the chemoradiation group than that of the radiation alone group.

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=국문초록=

## 자궁 경부암에서 방사선 단독치료와 방사선 및 화학요법 병행치료의 비교

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**목 적** : 자궁경부암의 치료에 있어 방사선 단독치료와 비교하여 방사선 및 화학요법 병행치료가 치료에 대한 반응, 생존율, 재발양상, 원격전이 및 부작용의 빈도 등에 영향를 주는가를 보고자 하였다.

**방 법** : 경북대학교병원 치료방사선과에서 1985년 11월부터 1991년 12월까지 자궁경부암으로 근치적 방사선치료를 받은 135명의 환자를 대상으로 치료에 대한 반응, 생존율, 재발양상, 원격전이 및 부작용의 빈도에 대하여 후향적 분석을 하였다. 방사선 단독으로 치료한 환자는 56명이었고, cisplatin을 포함한 화학요법을 병행한 환자는 79명이었다. 대상 환자들의 추적조사기간은 5개월에서 105개월이었다 (중간값: 47개월). FIGO 병기별 분류에 의하면, IB가 18명 (13.3%), IIA가 7명 (5.2%), IIB가 97명 (71.9%), IIIB가 9명 (6.7%)이었다.

**결 과** : 방사선 단독치료군 중 51예 (91.1%), 병행치료군 중 68예 (86.1%)에서 완전관해가 관찰되었다. 전체 환자의 5년생존율은 73.3%였고, 병기별 5년생존율은 IB가 88.9%, IIA가 85.7%, IIB가 73.8%, IIIB가 37.5%였다. 치료방법에 따른 5년생존율은 방사선 단독치료군에서 81.9%였고, 병행치료군에서 67.0%였다(p=0.22). 5년무병생존율은 방사선 단독치료군에서 70.4%였고, 병행치료군에서 68.5%였다 (p=0.85). 5년국소제어율은 방사선 단독치료군에서 76.1%였고, 병행치료군에서 73.8%였다(p=0.70). 5년원격제어율은 방사선 단독치료군에서 83.9%였고, 병행치료군에서 90.3%였다(p=0.59). 치료에 따른 골수억제는 방사선 단독치료군에서 3예 (5.4%), 병행치료군에서 14예 (17.7%)가 관찰되었다(p<0.05). 내과적 치료로 호전되었던 방광염이 방사선 단독치료군에서 14예, 병행치료군에서 10예 관찰되었다. 내과적 치료로 호전되었던 직장염이 방사선 단독치료군에서 2예, 병행치료군에서 4예 관찰되었고, 외과적 치료를 요했던 직장천공이 병행치료군에서 1예 관찰되었다. 보존적 치료로 해결되었던 장폐쇄의 부작용은 방사선 단독치료군에서만 2예 관찰되었다. 양 군간의 방광염, 직장염, 소장폐쇄의 빈도에는 유의한 차이가 없었다.

**결 론** : 방사선 단독치료군과 비교할 때 cisplatin을 포함한 화학요법의 병행은 치료에 대한 반응, 생존율, 재발양상, 원격전이에 영향을 미치지 않았고, 병행치료군에서 골수억제의 빈도가 더 높게 나타났다.