

자궁경부암 병기 IB, IIA, IIB에서 방사선 단독치료성적 : I 생존기간 및 재발양상에 관한 분석

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Irradiation Alone in Stage IB, IIA, and IIB Cervix Cancer : I Analysis of Survival and Failure Patterns

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Purpose : We analyzed the survival and failure patterns of cervix cancer patients treated with irradiation alone to evaluate our treatment method and to compare with the others.

Methods and Materials : Two hundred and twenty cervical cancer patients, Stage IB, IIA, and IIB who completed the planned treatment between May 1987 and December 1991 were analyzed retrospectively. The Stage IB patients were restaged to the Stage IB1 and IB2 by the recently revised FIGO classification. Patients were treated with a combination of external irradiation and the intracavitary brachytherapy. Determination of the tumor control was done at the time of 6 months postirradiation. The follow-up time was ranged from 3 to 115 months and the mean was 62 months and the follow-up rate was 93.6%(206/220).

Results : The overall 5-year survival rate of Stage IB1(N=50), IB2(N=15), IIA(N=58), and IIB(N=97) was 94%, 87%, 69%, and 56%, respectively. In the univariate analysis of prognostic factors, stage(0.00), initial Hg level (p=0.00), initial TA-4(tumor-associated) antigen level(p=0.02), initial CEA level(p=0.02), barrel-shaped tumor(p=0.02), whole cervical involvement (0.00), pelvic lymphadenopathy(LAP) in CT(p=0.04), and post-irradiation adjuvant chemotherapy(p=0.00) were statistically significant in survival analysis. In a while, multivariate analysis showed that the stage was the most powerful prognostic indicator and the post-irradiation chemotherapy factor also showed the statistical significance. The overall local control rate was 81% and by the stage, 100% in Stage IB1, 86.7% in Stage IB2, 84.5% in Stage IIA, and 68.1% in Stage IIB, respectively. The overall tumor recurrence rate was 15.5%(27/174) and by the stage, 8%(4/50) in

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Stage IB1, 0%(0/13) in Stage IB2, 22.4%(11/49) in Stage IIA, and 19.4%(12/62) in Stage IIB, respectively.

Conclusions: We obtained the similar treatment results to the other's ones in early stage cervical cancer patients. But in Stage IIB, the local control rate was lower than that of the other institutes and also the survival was poorer. So it seems to be necessary to reevaluate the treatment method in advanced cervical cancer patients.

Key Words: Survival, Failure patterns, Radiotherapy, Cervical cancer

INTRODUCTION

Throughout the many published articles on the results of the tumor control and survival in uterine cervix cancer patients, it is the well-known consensus that definitive radiotherapy or radical surgery is comparable treatment modality in stage I and IIA disease and definitive radiotherapy is the main modality in over stage IIB rather than surgery¹⁻⁴⁾. The combination of brachytherapy and the external irradiation increased the radiocurability of cervix cancer and radiation therapy has firmly established its role in the treatment of carcinoma of the uterine cervix for any clinical stage.

The goal of therapy in cancer patients is to obtain the highest possible tumor control and survival with the lowest incidence of major complications and minimal interference with anatomical and functional integrity. And it is apparent that the adequacy of the treatment program, whether it would be surgical or radiotherapeutic, is crucial to the control of the tumor and the survival of the patient. In a while, the therapeutic strategies and radiation therapy technique is variable among the institutes and especially the brachytherapy, which is very important treatment modality in cervix cancer treatment, is performed with different devices and different methods. So it is necessary process to review their own programs. Our own treatment program also must be tested in the aspect of its efficacy. We analyzed the cervix cancer patients treated with radiotherapy alone at the Department of Radiation Oncology, Chonnam University Hospital, retrospectively and compared the results

such as survival, local control rate, and failure patterns with the others.

MATERIALS AND METHODS

Total 227 patients diagnosed histologically as cervical cancer with Stage IB to IIB and referred for definitive radiotherapy were enrolled in the Tumor Registry of the Department of Radiation Oncology, Chonnam University Hospital, between May 1987 and December 1991. Of those, 7 cases with incomplete treatment were excluded in this analysis and the remaining 220 cases were the basis of this retrospective analysis.

A routine physical examination were performed on all patients and complete blood count, chemistry profile, serologic tumor marker study, chest X-ray, intravenous pyelogram, cystoscopy, rectosigmoidoscopy and pelvic CT were obtained as staging work-up study.

The patients were staged according to the FIGO classification and the Stage IB was restaged to the Stage IB1 or IB2 at the time of analysis according to the recently revised FIGO classification⁵⁾.

Patients were treated with a combination of external-beam radiation therapy and brachytherapy. External-beam radiotherapy was delivered with a 6MV photons(MEVATRON, Siemens Co) from the linear accelerator. Initially, the external beam irradiation was done to the whole pelvis through the parallel opposing AP and PA fields or four-field box technique and we used the conventional size of ports. After the 2000-4000cGy was given to the whole pelvis, the brachytherapy was per-

formed. And then, the AP and PA port with rectangular midline block of 4cm width was applied to the whole pelvic dose of 4500–5000cGy and if necessary, the parametrial boost dose 540–900cGy was used. A midline depth dose of 180cGy was administered daily in five fractions a week.

The intracavitary irradiation(ICR) was done with the Buchler system(Germany). The radioactive isotope of tandem and ovoids is Cobalt-60 and Cesium-137, respectively and the dose rate is 50 cGy per minute and the daily fractionation dose is 500cGy to the point A. ICR is delivered twice in a week, usually Monday and Thursday and the total prescription dose to the point A is usually 3000–4000cGy according to the tumor size and the external whole pelvic dose.

Tumor control was assessed by periodic pelvic examinations and tumor control was defined when complete response sustained over 6 months. Whenever a recurrence was suspected in accessible sites, such as the cervix, vagina, or parametrium, an attempt was made to confirm it by biopsy. Failures were classified as pelvic failure when there was evidence of recurrent tumor within the true pelvis such as cervix, parametrium, vagina, pelvic LN area and distant metastasis when there was evidence of tumor dissemination beyond the true pelvis. If there were sciatic or obturator pain, leg edema, and/or hydronephrosis or progressive parametrial nodular induration associated with any of the above symptoms, these findings were recorded as a pelvic recurrence, even if not confirmed by biopsy.

All patients were followed for unlimited time (minimum of five years), until death or, or until lost to follow-up. The follow-up time was ranged from 3 to 115 months and the mean value was 62 months. Survival information was obtained in 93.6%(206/220) of the patients either from our own records or by letter or telephone contact with the patients or relatives.

The statistical significance was tested using the BMDP software program and we used the Log-rank test(1L) and Cox-proportional hazard test(2L) in the univariate and multivariate survival

Table 1. Patients Characteristics(N=220)

Parameters	No. of Patients(%)
Age(yrs)	
range	27–78
mean	56
median	57
Histology	
squamous cell ca.	213(96.8)
nonsquamous cell ca.	7(3.2)
adenoca.	5
adenosquamous cell ca.	1
glassy cell ca.	1
Stage	
IB1	50(22.7)
IB2	15(6.8)
IIA	58(26.4)
IIB	97(44.1)
Pelvic CT as work-up study	
Yes	175(79.5)
No	45(20.5)
Local Tumor Control	
Evaluable	214(97.3)
No information	6(2.7)

analysis, respectively⁶⁾.

RESULTS

The patients' characteristics were shown in Table 1. The age ranged from 27 to 78 years old with the median 57. Almost of the patients(96.8%) in this study had the histologic type of squamous cell carcinoma.

The overall 5-year survival rate of Stage IB1, IB2, IIA, and IIB was 94%, 87%, 69%, and 56%, respectively(Fig. 1). We analyzed various factors affecting survival rate such as the age, hypertension, diabetes mellitus, Hg level and tumor marker level at the time of diagnosis, tumor ulceration, barrel type, whole cervical involvement, LAP in the pelvic CT, adjuvant chemotherapy(Table 2). In the univariate analysis of factors, Hg level($p=0.00$), TA-4 level($p=0.02$), CEA level($p=0.02$), barrel tumor($p=0.02$), whole cervical tumor($p=0.00$), pelvic LAP in CT($p=0.02$), and post-irradiation adjuvant chemotherapy($p=0.00$) were statistically significant prognostic factor affecting to the survival. In a while, multivariate analysis showed that the stage was the most significant prognostic indicator and the post-irradiation adjuvant chemotherapy also showed the statistical significance.

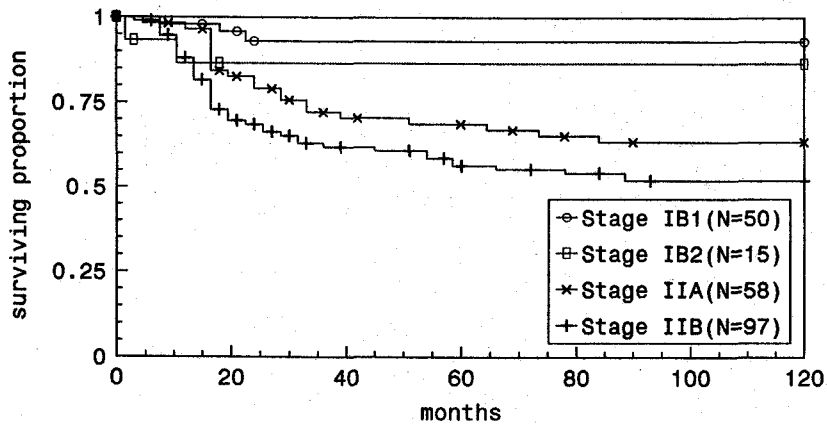


Fig. 1. The overall 5-year survival rate of uterine cervix cancer treated with definitive radiotherapy.

Table 2. Survival Analysis in Cervical Cancer Patients, Stage IB, IIA, and Stage IIB, Treated with Definitive Radiotherapy

Variables	Group (No. of Pts.)	5YSR(%)	p value*
Age(yrs)	Below 45 Above 45	69 66	0.62
Hypertension	No (199) Yes(21)	67.3 76.2	0.50
Diabetes Mellitus	No (205) Yes(15)	67.8 73.3	0.53
Hemoglobin	12.0 or less(65) over 12.0 (154)	50.8 75.3	0.00
TA-4	1.0 or less(25) over 1.0 (82)	88.3 63.2	0.02
CEA	20 or less(172) over 20 (16)	69.8 43.8	0.02
Ulceration	No (169) Yes(49)	69.8 61.2	0.57
Barrel	No (199) Yes(19)	69.4 52.6	0.02
Whole Cervix	No (94) Yes(124)	81.9 57.3	0.00
Pelvic LAP* in CT	No (143) Yes(32)	72.7 59.4	0.04
Neoadjuvant Chemotherapy	No (196) Yes(24)	67.9 70.8	0.99
Post-irradiation Chemotherapy	No (181) Yes(39)	71.8 51.3	0.00

* : univariate analysis

#LAP : lymphadenopathy

Table 3. Local Control Rate

Stage (No.of Pts)	No. of Persistent Tumor	Local Control Rate(%)
IB1 (50)	0	100.0
IB2 (15)	2	86.7
IIA (58)	9	84.5
IIB (91)	29	68.1
Total(214)	40	81.0

The local control rate of all 214 patients of whom we could evaluate the radiation response was 81%. The local control rate by the stage was 100% in Stage IB1, 86.7% in Stage IB2, 84.5% in Stage IIA, and 68.1% in Stage IIB, respectively(Table 3).

Twenty-seven patients(15.5%) of 174 who initially obtained the complete tumor response showed tumor recurrence(Table 4). In Stage IB1, the failure rate was 8%(4/50), 2 patients in pelvis and the others 2 patients in distant organs. In Stage IB2, there was no tumor recurrence. In Stage IIA, the recurrence rate is 22.4%(11/49) and 6 patients in the pelvis only and the other patients in the distant organs. In Stage IIB, the tumor recurrence rate is 19.4%(12/62) and 5 patients in the pelvis and 7 patients in the distant organs, respectively.

The site of distant metastasis was relatively evenly distributed to the bone, lung, liver(Table 5). The interval between the completion of radiothe-

Table 4. Failure Patterns in Complete Responders After Definitive Radiotherapy

Failure pattern \ Stage	IB1	IB2	IIA	II B	Total(%)
No. of patients	50	13	49	62	174
Pelvic only	2(4%)	0	6(12.2%)	5(8.1%)	13(7.5%)
Distant Metastasis	2(4%)	0	5(8.2%)	7(11.3%)	13(7.5%)
PA* only	0		0	2	2
DM# only	2		2	4	8
Pelvic+PA	0		1	1	2
PA+DM	0		1		1
Combined			1(2%)		1(0.5%)
Total	4(8%)	0(0%)	12(22.4%)	12(19.4%)	27(15.5%)

*PA : paraaortic LN
 #DM : distant metastasis

Table 5. Sites of Distant Metastasis

Site	No. of Patients
Bone	2
Liver	3*
Lung	2
Supraclavicular LN	2
Carcinomatosis Peritonei	2

* : combined with lung metastasis in one case

rapy and the detection of distant metastasis was ranged from 1 month to 56 months and median was 18 months. In the long-term survivors, two patients were diagnosed to have the metachronous second primary cancer, one was breast cancer and the other was endometrial cancer.

DISCUSSIONS

Numerous nonrandomized and a few randomized studies document similar survival and recurrence patterns in selected patients with Stage IB and IIA carcinoma of the uterine cervix treated with irradiation alone or radical hysterectomy with lymphadenectomy^{1-4, 7-11)}. In general, in patients with Stage IB cervical cancer, there is a tendency to treat patients with lesions that are less than 4cm in diameter by radical operation. Those patients who have lesions that are between 4 and 6cm in diameter are treated by radiation therapy and bulky tumors such as barrel-shaped tumors or in case of tumor extension to the en-

dometrial cavity are treated with a combination of preoperative radiation therapy and surgery.

In patients treated with irradiation alone(external-beam irradiation and brachytherapy), the usual 5-year survival rate for Stage IB is 86 to 92%, for Stage IIA, about 75%, and for Stage II B, 72%, respectively⁷⁻¹¹⁾. In our analysis, the overall 5-year survival rate of Stage IB1, IB2, II A and II B was 94%, 87%, 69%, and 56%, respectively. The survival rate of our data was similar to others except for stage II B which was poor than other's.

There are many studies on the effect of various prognostic parameters to the survival in cervical cancer patients¹²⁻¹⁸⁾. But the effect of the age, tumor grade, hypertension and diabetes mellitus is still controversial¹²⁻¹⁵⁾ and our analysis do not also show any statistically significant association between age, hypertension, DM and survival. The patient with glassy cell type in our cases showed poor tumor response to radiation and showed the multiple distant organ metastasis and was accompanied with SVC syndrome, obstructive uropathy, and malignant ascites during the radiation therapy. In the effect of hemoglobin concentration, Girinski et al.¹⁴⁾ reported the positive effect of the hemoglobin to both of radiation response and patient's survival. Our study showed the similar finding that patients with Hg level greater than 12g/dl showed better survival rate than those with Hg level below it.

The tumor volume of the cervix cancer was

also known to affect to the survival as well as local control, although the method of tumor measurement was variable and has not been standardized and do not always implicate the real tumor volume. Bulky disease tended to decrease the disease-free survival and the local control rate¹⁶⁻¹⁸⁾. In our analysis, the tumor volume was not clearly described, so we analyzed the volume effect indirectly by the colposcopic findings of the whole cervical involvement or barrel type of the tumor and there was statistical significance in the univariate survival analysis. Pelvic LAP in the CT finding also showed statistical significance in univariate survival analysis. In a while, multivariate analysis showed that the only stage was the most powerful prognostic factor.

The local control of the tumor in the pelvis was correlated with better survival and a lower incidence of distant metastasis¹⁹⁾. This is an important end-point, because the salvage rate in patients who fail to isolated pelvic recurrence is not optimal even after pelvic exenteration. In our analysis, the local control rate of all patients was 81% and by the stage 100% in Stage IB1, 87% in IB2, 85% in IIA, and 68% in IIB, respectively. The results of our study, except that of stage IIB, showed similar to those of others'. We considered that the poor local control of stage IIB patients of this study resulted in the poor survival rate. Only one patient with persistent disease received the radical hysterectomy and pelvic lymphadenectomy has survived until now with no evidence of disease recurrence for 105 months. It is evident that in advanced disease over Stage IIA, the inability to local control of the tumor in the pelvis is still a significant concern. As the radiation dosage is increased, there has been a diminution in the incidence of pelvic failure, but along with this, an increase in complications. Refinement in treatment planning with current techniques, the judicious combination of irradiation and surgery in selected patients and search for biological enhancers of irradiation response of tumor, such as chemical modifiers, hypoxic cell sensitizers, hyperthermia or high LET irradiation should be con-

tinued in an effort to enhance pelvic tumor control. Brady et al.²⁰⁾ analyzed the failure patterns in gynecological cancer and reported the results that the pelvic and distant metastatic failure rate was 8.6% vs. 7% in stage I, 18% vs. 12% in stage IIA, and 25% vs. 13% in stage IIB, respectively. In our analysis the results were 4% vs. 4% in stage IB1, 0% vs. 0% in IB2, 12.2% vs. 8.2% in stage IIA, and 8.1% vs. 11.3% in stage IIB, respectively. The one who had the local recurrence 29 months after radiotherapy received the pelvic exenteration and is in the disease-free state for 98 months.

The magnitude of distant dissemination in the long-term survivors without evidence of locoregional recurrent disease should be emphasized, since this points out the need for identifying effective systemic therapy which control micrometastasis. Through this study we obtained the result that patients with post-irradiation chemotherapy showed poorer survival rate than those without chemotherapy with the statistical significance. We may suppose the explanation that patients with persistent disease and poor tumor response was mainly indicated post-irradiation chemotherapy without any initial treatment planning. The development of a combined integrated program of definitive radiation therapy and/or surgery with adjuvant systemic chemotherapy, in those patients at high risk for distant micrometastatic disease, would have a significant impact on improving the potential for long-term control.

In conclusion, we obtained the similar treatment results to the other's in early stage cervical cancer patients by radiation alone. But in Stage IIB, the local control rate was lower than that of the other institutes and also the survival was poorer. So we need to reevaluate the treatment method in advanced cervical cancer patients.

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= 국문 초록 =

Irradiation Alone in Stage IB, IIA, IIB에서 방사선 단독치료성적 : I 생존기간 및 재발양상에 관한 분석

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목적 : 본병원에서 방사선 단독치료를 받은 자궁경부암 환자의 생존율 및 재발 양상을 분석하고 이에대한 결과를 비교 분석함으로써 치료방법에 대한 평가를 하고자 하였다.

대상 및 방법 : 1987년 5월부터 1991년 12월까지 자궁경부암병기(FIGO) IB, IIA, IIB 로 근치목적의 방사선치료를 완료한 220명의 환자를 대상으로 후향적 분석을 시행하였다. 이중 병기 IB환자는 1995년에 개정된 FIGO 분류법에 의해서 분석당시 IB1과 IB2로 재분류를 시행하였다. 방사선치료는 외부방사선치료와 강내조사를 병용하였으며 방사선치료 후 6개월에서 국소종양의 치유여부를 판정하였다. 추적기간은 3개월에서 115개월까지 였으며 평균 62개월이었고 추적율은 93.6%(206/220) 였다.

결과 : 병기별 5년 생존율은 IB1(N=50), IB2(N=15), IIA(N=58), IIB(N=97)에서 각각 94%, 87%, 69%, 56%였다. 생존과 관계있는 예후인자로는 병기(p=0.00), 진단시 혈색소치(p=0.00), 진단시 종양표지자 수치(p=0.02), 종양의 크기(0.00), 골반단층촬영에서의 임파선전이(p=0.04) 등이 통계적인 유의수준을 보였으나 다요인 분석에서는 병기만이 유일하게 통계적인 유의수준의 차이를 보였다. 판정이 가능한 214명의 방사선치료에 따른 국소종양제어율은 81%였으며, 병기별로 보면, IB1, IB2, IIA, IIB 각각 100%, 86.7%, 84.5%, 68.1%의 결과를 보였다. 치료 후 재발율은 15.5%(27/174)였으며, 병기별로 보면 IB1, IB2, IIA, IIB 각각 8%, 0%, 22.4%, 19.4%였다.

결론 : 초기 자궁경부암 환자의 치료결과는 이미 보고되어 있는 다른 결과와 비교시 비슷한 수준을 보이나 진행된 IIB 환자에서는 낮은 생존율의 결과를 보이고 있으며 이에대한 원인분석과 치료방법의 개선이 필요하다 하겠다.