

## Results of Postoperative Irradiation in Patients with Carcinoma of Uterine Cervix Stage IB and IIA

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### = Abstract =

**Purpose:** The adjuvant postoperative radiotherapy has been usually applied to the patients with unfavorable prognostic factors after radical operation in early cervical cancer. We focused on the evaluation of the survival status and failure patterns of the patients with postoperative radiotherapy.

**Materials and Methods:** We retrospectively analyzed ninety patients with FIGO stage IB and IIA cervix cancer who received postoperative pelvic irradiation at Chonnam University Hospital between August 1985 and December 1988. Seventy-eight patients had adequate follow-up information for survival analysis. Median follow-up time of these patients was 64 months.

**Results:** The 5 year overall and disease free survival rate of ninety patients was 80.0% and 80.2%, respectively. The prognostic significance to the survival was determined by multivariate analysis. Adequacy of resection margin( $p=0.005$ ) and lymph node status( $p=0.005$ ) appeared to be independent prognostic factors. Recurrence occurred in 13 patients, 5 in the pelvis and 8 at distant sites. The median time to recurrence was 19 months(range;3-39 months). The pelvic recurrence was more prevalent in the group of patients with adenocarcinoma, depth of stromal invasion more than 10mm and use of chemotherapy. The distant failure was more prevalent in the group of positive resection margin or positive lymph node with statistical significance.

**Conclusion:** Patients with pelvic lymph node or surgical margin involvement clearly constitute a high risk group in this analysis and should be considered as candidates for some form of adjuvant therapy.

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**Key Words :** Uterine cervix, Carcinoma, Postoperative irradiation

### INTRODUCTION

The early cervix stage IB and IIA(FIGO) cancer can be effectively treated by either radical surgery or radical radiation therapy. Data from prospective and retrospective studies have

shown comparable survival rates for both treatment modalities<sup>1,2</sup>. The attending physicians usually recommend operation to the younger patients to avoid radiation induced sequelae. But, the presence of postoperative findings such as pelvic node metastases, positive resection margin, and deep stromal inva-

sion has been correlated with the increased risk of treatment failure<sup>3-10</sup>. Several adjuvant therapeutic approaches have been proposed in an attempt to decrease recurrences and thus increase patient's survival. An example of such therapy has been postoperative pelvic irradiation.

We retrospectively reviewed the medical records of patients who received postoperative irradiation after radical operation at Chonnam University Hospital from August 1985 to December 1988. Throughout this analysis we aim to understand the natural course of the early cervical cancer patients with combined modality therapy.

## MATERIALS AND METHODS

Between August 1985 to December 1988, 137 patients with stage IB and IIA cervical cancer received postoperative irradiation with or without adjuvant chemotherapy at the Department of Therapeutic Radiology, Chonnam University Hospital. Of those, 16 cases with incomplete radiotherapy and 31 cases who received operation at other hospital were excluded from this analysis. Staging was done according to FIGO classification<sup>11</sup>). Prior to surgery, clinical staging was done by using pelvic examination, routine blood chemistry, chest x-ray, intravenous pyelogram, cystoscopy, proctosigmoidoscopy, and pelvic CT scan. Pelvic examination was done without anesthesia. All patients underwent radical hysterectomy and pelvic lymph node dissection and their surgical specimens were pathologically evaluated. The usual indications for radiation therapy after radical hysterectomy in our hospital were shown in Table 1.

Postoperative external beam radiation therapy was given to the whole pelvis by 6MV X-rays (Mevatron, Siemens Co. Germany) using two opposing anterior and posterior parallel fields or four field box technique with or without intracavitary insertions. The median

**Table 1. Indications for Postoperative Radiotherapy**

Parameters	No. of patients
Positive lymph node	25
Negative lymph node	64
positive resection margin	1
close resection margin	11
stromal invasion	52
> 10mm	37
< 10mm	15
Unknown lymph node status with stromal invasion(8mm)	1

**Table 2. Patients Characteristics (N=90)**

Characteristics	No. of patients(%)
Age	
range 30-64	
median 47	
< 40	28(31.1)
> 40	62(68.9)
Stage	
IB	70(77.8)
IIA	20(22.2)
Histology	
squamous	81(93.1)
adenoca.	6( 6.9)
unproven	3
Lymph Node	
negative	64(71.9)
positive	25(28.1)
1-3	22
above 3	3
unknown	1

midplane dose of pelvic irradiation was 5040 cGy in 5 and a half weeks. In that case combining with brachytherapy, the midline block was placed after 3060 cGy external beam irradiation. Intracavitary irradiation was used in 49 patients(54 %) and done by remote afterloading system with <sup>60</sup>Co source (Buchler, Germany). The prescription dose per insertion was 2000 cGy to the vaginal mucosal surface and total dose was 6000 cGy in one and a half

**Table 3. Summary of Survival according to Patient Characteristics**

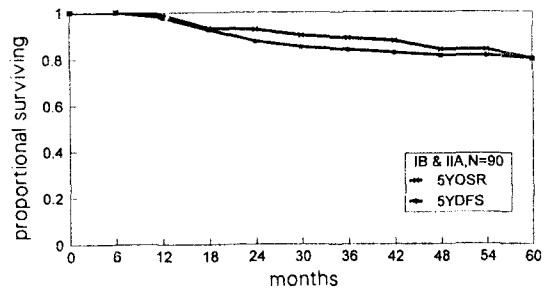
Characteristic	No. of patient	5-yr survival	p*	p <sup>#</sup>
Age				
<40	28	74		
>40	62	82	0.709	0.124
Stage				
IB	70	79		
IIA	20	84	0.713	0.902
Histology				
squamous	81	80		
adenoca.	6	82	0.849	0.340
Parity				
3 or less	31	82		
over 3	56	80	0.904	0.063
Preop. CEA				
5 or less	53	82		
over 6	17	74	0.569	0.395
Tumor Diameter				
3cm or less	72	80		
over 3cm	13	92	0.353	0.426
Tumor Gross Finding				
ulcerative	25	72		
no	61	82	0.691	0.783
Lymph Node(LN)				
negative	64	87		
positive	25	72	0.016	0.005
Common iliac LN				
positive	5	40		
negative	84	82	0.0013	
Periaortic LN				
positive	4	32		
negative	85	82	0.0059	
Resection Margin				
negative	78	85		
positive	12	50	0.0013	0.005
Stromal Invasion Depth				
10mm or less	25	87		
over 10mm	61	82	0.6452	0.459

\* Log-rank test

# Multivariate analysis by Cox proportional hazard model

weeks with 3 insertions.

Follow-up was obtained by review of the patients' record, by written or telephone correspondence, or by review of the death certificate. Follow-up ranged from 3 to 95 months



**Fig. 1.** The 5 year overall and disease free survival rates in stage IB and IIA cervix cancer patients treated by postoperative radiotherapy.

(median 64 months). Complete follow-up information was obtained in 86.7%(78/90). Survival was measured from the date of initial therapy to death or to last follow-up. Survival rates were estimated by a life table method and the statistical significance was verified by the log-rank test. T-test was also utilized to compare recurrence rates between two groups. The statistical program, BMDP, was used for the multivariate analysis(survival analysis with covariates-Cox Model)<sup>12)</sup> of various potential prognostic factors.

## RESULTS

The ninety patients' characteristics are shown in Table 2. Twenty five patients were found postoperatively to have pelvic nodal metastasis. The 5 year overall and disease free survival rate of all 90 patients are 80.0% and 80.2% respectively(Fig. 1). Survival difference according to the prognostic parameters was compared(Table 3). The 5 year overall survival rate of metastatic node group was 72 % and that of node negative group was 87% (p=0.016). When we compared survival difference according to the level of metastatic lymph node, positive group of common iliac and periaortic lymph node showed poorer survival rates(40% and 32%) than negative group (82% and 82%). To determine which prognostic factors had a significant independent value

**Table 4. Pattern of Treatment Failures(N= 13)**

Time to Recurrence(months)	
range	3-39
median	19
Site(No.)	
Pelvic only	5
vaginal stump	4
vagina	2
urethral	2
pelvic node	1
Distant metastases only	8
lung	4
bone	3
Periaortic LN	2
supraclavicular LN	1
soft tissue	1

for survival, a multivariate analysis was carried out. The following covariates were entered in the statistics: age, stage, histology, parity, pre-operative CEA value, tumor diameter, gross finding of tumor, lymph node status, resection margin, depth of stromal invasion, time interval between diagnosis and operation and between operation and radiotherapy, radiotherapy technique and chemotherapy. In 25 patients, some information concerning one of the covariates was missing so that 65 patients remained definitively in the stepwise analysis. Only resection margin( $p=0.005$ ) and lymph node status( $p=0.005$ ) appeared to be independent prognostic indicators. Treatment failure was occurred in 13 patients(14.4%); the median time to failure was 19 months, 13 months for pelvic recurrence and 24 months for distant metastases(Table 4). Sites of failure were pelvic alone in 38%(5/13) and distant metastases alone in 62%(8/13). The pelvic recurrence was more prevalent in the group of patients with adenocarcinoma( $p=0.034$ ), depth of stromal invasion more than 10mm( $p=0.02$ ) and chemotherapy( $p=0.003$ )(Table 5). On the other hand, positive resection margin( $p=0.003$ ) and positive lymph node( $p=0.000$ ) affect the rate of distant metastases(Table 6).

**Table 5. Comparison of Pelvic Recurrence rates according to Prognostic Clinical Variables**

Clinical variables	No. of pts	recurrence rate(%)	p
Age			
40 or less than	1/28	3.6	0.268
over 40	4/62	6.5	
Stage			
IB	3/70	4.3	0.057
IIA	2/20	10.0	
Histology			
squamous	4/81	4.9	0.034
adenoca	1/ 6	16.7	
Parity			
3 or less	2/31	6.5	0.679
Over 3	3/56	5.4	
Preop. CEA			
5 or less	3/53	5.7	0.946
over 5	1/17	5.9	
Tumor Diameter			
3cm or less	3/72	4.2	0.287
over 3cm	1/13	7.7	
Tumor Gross Finding			
ulcerative	2/25	8.0	0.279
no	3/61	4.9	
Resection Margin			
negative	4/78	5.1	0.384
positive	1/12	8.3	
Lymph Node			
negative	3/64	4.7	0.234
positive	2/25	8.0	
Stromal Invasion Depth			
10mm or less	0/25	0.0	0.020
over 10	3/61	4.9	
Chemotherapy			
yes	4/42	9.5	0.001
no	1/48	2.1	

The complication rate was 16.7%(15/90). All of them had mild or moderate degree of discomfort and did not need surgical correction or hospitalization(Table 7).

## DISCUSSION

The treatment results of cervix cancer stage

**Table 6. Comparison of Distant Failure Rates according to Prognostic Clinical Variables**

Clinical variables	No. of pts	recurrence rate(%)	p
Age			
40 or less	3/28	10.7	
over 40	5/62	8.1	0.424
Stage			
IB	6/70	8.6	
IIA	2/20	10.0	0.698
Histology			
squamous	8/81	9.9	
adenoca.	0/6	0.0	0.075
Parity			
3 or less	3/31	9.7	
Over 3	5/56	8.9	0.819
Preop. CEA			
5 or less	4/53	7.5	
over 5	2/17	11.8	0.298
Tumor Diameter			
3cm or less	8/72	11.1	
over 3cm	0/13	0.0	0.005
Tumor Gross Finding			
ulcerative	1/25	4.0	
no	7/61	11.5	0.023
Resection Margin			
negative	5/78	6.4	
positive	3/12	25.0	0.003
LN			
negative	4/64	6.3	
positive	4/25	16.0	0.000
Stromal Invasion Depth			
10mm or less	2/25	8.0	
over 10mm	6/61	9.8	0.596
Chemotherapy			
yes	5/42	11.9	
no	3/48	6.3	0.061

IB and IIA by radical operation or radiotherapy alone have been accepted<sup>1,2</sup>. Irrespective of therapeutics there now appears to be a group of patients with poor prognostic factors among the early stage cervical cancer that show a proclivity for loco-regional failure and decreased survival. In the group of patients who underwent operation, careful histological

**Table 7. Pattern of Complication(N= 15)**

Type	Cases
blood-tinged stool	8
hematuria	6
NVK*	3
lymphocyst	2
abdominal pain	2
lymphedema	2

\* Nonvisualization of Kidney

evaluation of the surgical specimen reveals characteristics of high risk for recurrence.

Many investigators are convinced that the major underlying cause of death in the cervix cancer is the lymph node metastases in the presence of morpho-histologic poor prognostic factors<sup>10,13</sup>. Gonzalez et al reported that the 5 - and 10-year survival rate of the patients with negative pelvic lymph node were 85% and 85% and that of positive node group were 60% and 51%, respectively<sup>13</sup>. While postoperative radiation has been advocated and widely used, there have been controversies about effectiveness until now<sup>4,14-16</sup>. No controlled studies are available showing improved survival with postoperative pelvic irradiation in the presence of positive pelvic nodes. In this report the 5 year overall survival rate in patients with positive pelvic node was 72%.

But, many reports showed the benefit of postoperative irradiation in the positive pelvic nodal metastases patients in the aspect of local recurrence rate<sup>4,15,17</sup>. Kinney et al reported that adjuvant radiotherapy decreased the proportion of recurrences occurring in the pelvis alone-27% compared with 67% in the surgery-only group( $p=0.01$ )<sup>4</sup>. Park et al also reported higher distant failure rate(14.3%) than local recurrence rate(8.4%) in the early cervical cancer patients treated by postoperative radiotherapy<sup>18</sup>. In this analysis the pelvic recurrence rate of positive node group was 8.0% compared to the negative group, 4.7% ( $p=0.234$ ).

There are many reports that lymphovascular invasion, tumor diameter, and tumor histopathology influence the frequency of lymph node metastases<sup>7,10,16,17</sup>. Nahhas et al described a greater incidence of metastatic lymph nodes in the presence of deep stromal invasion or lymphatic permeation and showed that these patients had a lower 2-year relapse free survival rate and a greater incidence of recurrence<sup>17</sup>. Burke et al reported that patients whose tumors contained vascular lymphatic space invasion or adenomatous histologic components recurred more frequently than patients whose tumors did not ( $p < 0.05$ )<sup>7</sup>. In this analysis, pelvic recurrence rate was higher in the group of deep stromal invasion more than 10mm (4.9% vs 0%,  $p = 0.02$ ) although the difference of the 5 year survival rate and distant failure rate between two groups were not statistically significant. In the results according to the histopathology, we observed that the survival was not affected by the cell type (82% vs 80%) although pelvic recurrence was more prevalent in the adenomatous type (10.0% vs 4.9%).

Burghardt et al and Piver et al have shown a greater incidence of lymphatic and distant metastasis, and also lower survival rate in patients with bulky and barrel-shaped Stage IB and IIA tumors treated by radical hysterectomy<sup>10,16</sup>. But we obtained controversial result in that the 5 year survival rate was lower and distant metastases was higher in the group of tumor size less than 3cm than the group of larger tumor size (80% vs 92%,  $p = 0.426/11.1\% vs 0.0\%$ ,  $p = 0.005$ ). One of possible explanations for this result is the result from inappropriate colposcopic measurement of cervical tumor mass, especially in case of endocervical lesions.

Many reports illustrated that age has a profound influence on survival in women with Stage IB cervical cancer independent of potentially confounding variables<sup>9,19,20</sup>. In this analysis, the younger women were shown to have

poorer results in the survival and distant metastases rate than older ones, but, there was no statistical significance.

It is clear that Stage IB carcinoma of cervix as defined by FIGO represents a wide spectrum of disease with considerable variation in prognosis. Rotman et al. have proposed a clinical-pathological subclassification of Stage IB carcinoma, IB1 and IB2. Stage IB1 includes patients with stromal invasion of up to 10mm and IB2 those patients have more than 10mm stromal invasion, corpus involvement, tumor size of more than 2cm endocervical lesion, vascular invasion and more than two quadrant involvement of cervix with tumor<sup>21</sup>. Poor prognostic subgroups of early cervical cancer patients therefore need to be identified so that appropriate alterations are made in their therapeutic management. If the adjuvant radiotherapy was indicated due to the metastatic pelvic lymph node 5000 cGy to the whole pelvis by external irradiation is enough<sup>14,15</sup>. Although there were complaints of rectal-urinary or abdominal discomfort such as abdominal pain, blood-tinged stool, and hematuria, we did not experience the severe sequelae by the irradiation. Because vascular supply may be affected by the surgical procedure, and adhesion can prevent mobilization of small bowel loops that occasionally may be fixed in the pelvis, radiation therapist must be careful in the design of radiation field and prescription of radiation dose. Without an control group, it is impossible to estimate the contribution of pelvic irradiation to the complication rate in our series. We are planning to compensate this aspect in the next analysis.

In conclusion, postoperative pelvic irradiation can be performed to the early cervical cancer patients with poor prognostic factors without significantly increased morbidity and more intensive therapeutic plan are needed for the selective patients with positive lymph nodes and positive resection margin.

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=국문초록=

### 자궁경부암 IB와 IIA 환자의 수술후 방사선치료 결과

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**목 적 :** 조기 자궁경부암 환자에서 보조적 방사선치료요법은 근치적수술을 시행하고 재발의 위험이 높은 불량한 예후를 갖는 환자에서 시행되고 있다. 이에 저자는 수술후 방사선치료를 받았던 환자의 생존과 치료실패에 영향을 주는 예후인자를 분석하고자 하였다.

**대상 및 방법 :** 전남대학교병원 치료방사선과에서 1985년 8월부터 1988년 12월까지 수술후 방사선치료를 받았던 자궁경부암 병기 IB와 IIA환자 106명중 기록이 충분한 90명을 대상으로 후향적 분석을 시행하였다. 추적율은 88%(78/90)였고 추적기간의 중간값은 64개월이었다.

**결 과 :** 90명에 대한 5년 생존율 및 5년 무병생존율은 각각 80.0%, 80.2%였다. 다변량생존분석에서 65명을 대상으로 환자의 연령, 병기, 조직학적 분류, 수술전 혈중 CEA 농도, 출산력, 경부침윤정도, 종양의 육안적 크기, 종양의 궤양성 유무, 임파선 전이 유무, 수술절단면의 소견, 항암제치료 유무를 변수로 분석결과 수술절단면의 조직학적인 소견( $p=0.005$ ), 임파선전이유무( $p=0.005$ )가 통계학적으로 의미있는 예후인자였다. 추적기간중 13명에서 재발이 확인되었고 부위별로 보면 골반내 국소재발이 5명, 원격전이가 8명 이었으며 수술후 3개월에서 39개월사이에 발견되었으며 중간값은 19개월이었다. 골반내 전이는 선암( $p=0.034$ )과 경부침윤 10mm 이상( $p=0.02$ ) 그리고 항암제치료( $p=0.023$ )를 시행하였던 환자군에서, 원격 전이에 있어서는 임파선전이와 수술절단면에서 암세포가 양성을 보였던 환자군에서 각각 더 높은 전이율을 보였다. 치료에 의한 합병증을 호소하였던 환자는 15명이었으며 가장 흔한 증상은 혈변이나 혈뇨였고 중증의 합병증을 보인 환자는 없었다.

**결 론 :** 이에 저자는 조기자궁경부암 IB와 IIA환자에서 수술병리학적소견중 임파선전이와 불충분한 수술적절제가 예후에 있어서 가장 큰 영향을 보임을 알수 있었으며 이러한 소견을 보인 환자는 보다 적극적인 보조치료가 필요하리라 사료된다.