

Analysis of Treatment Failures in Early Uterine Cervical Cancer

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One hundred and twenty six patients with early uterine cervical cancer who had been treated at Department of Radiation Oncology of Korea University Hospital from Jan. 1981 to Dec. 1988 were analysed retrospectively by the treatment result and pattern of failures.

All patients had stage Ia to IIa disease and were grouped whether they had combination of operation and postop irradiation or radiation therapy alone.

1) Sixty six patients belonged to the combination treatment group and 60 patients to the radiation alone group.

2) Combination group consisted of 18.1% (12/66) stage Ia, 71.2% (47/66) stage Ib and 10.6% (7/66) stage IIa patients.

There were no stage Ia, 18.8% (11/60) stage Ib and 81.6% (49/60) stage IIa patients for RT alone group.

3) There were total 23% (29/126) treatment failures, 13 patients in combination group and 16 patients in RT alone group.

In 66 patients of combination group, they were found to have 5 locoregional failures, 7 distant failures and 1 at both sites.

In 60 patients of RT alone group, 9 locoregional failure and 7 distant failures occurred.

Eighty six percent (25/29) of total failures appeared within 18 month after completion of treatment.

About 60% of the patients with regional recurrences which were located at pelvic side wall or pelvic lymph nodes presented their recurrent disease after 1 year of completion of treatment, whereas same percent of distant failures appeared within 6 month.

5) In RT alone group, the first sites of distant failure were mostly para-aortic lymph node and / or left supraclavicular lymph node (71.4%, 5/7).

In combination group, various sites such as inguinal lymph node, mediastinal lymph node, liver, lung and bone appeared first or at the same time with para-aortic and supraclavicular lymph node metastasis.

6) Logistic regression analysis was done for multivariate analysis of the factors contributing to locoregional and distant failures. In combination group, adequacy of the resection margin and the presence of positive pelvic node were found to be the most significant factors ($p=0.0423$ & 0.0060 respectively).

In RT alone group, less than complete regression of the tumor at the end of treatment was the only significant contributing factor for the treatment failures ($p=0.0013$) with good likelihood ratio.

Key Words: Early uterine cervical cancer, Treatment failures

INTRODUCTION

Early uterine cervical cancer is known as a curative disease which has the survival rate of up to 90% when properly treated. But treatment failures about 10~20% either at locoregional or distant sites are reported in many literatures¹⁾. The prognosis of the patients with treatment failure is very poor even though salvage treatment is given^{2,3,4)}.

We have published the overall treatment result of uterine cervical cancer previously⁵⁾. In this arti-

cle, pattern of failures exclusively for the early lesion were analysed by treatment methods. Multivariate analysis was done for several clinicopathologic risk factors to find out how they correlates with treatment failures.

MATERIALS AND METHODS

All patients were confirmed to have primary carcinoma of the uterine cervix by biopsy or cytologic examination. All patients were staged according to the current FIGO classification by

pelvic examination and works-up like IVP, barium enema, proctoscopy and cystoscopy. Since 1987, pelvic CT scan replaced most of above procedures on outpatient base. Of the three hundred thirty seven patients with uterine cervical cancer referred to our department since 1981 through 1988, only one hundred twenty six patients with stage Ia to IIa disease were included in this study.

Patients with previous history of any operation or radiotherapy for cervical cancer were excluded from the study.

Of the one hundred and twenty six patients, there were 12 stage Ia, 58 stage Ib and 56 stage IIa patients (Table 1).

Sixty six patients have been treated by the combination of the surgery and postop radiation therapy and sixty patients by primary radiation therapy.

1. Surgery

Operation of curative aim was given to 66 patients, 37 of which were radical hysterectomy with pelvic lymphadenectomy and 29 of which were total abdominal hysterectomy with or without lymph node dissection.

Eighteen patients were those who had been referred to our department from other community hospitals. Informations about their preoperative findings and fully descriptive permanent pathologic report were sometimes not available.

2. Radiation Therapy

Standard radiation therapy for unoperated cervical cancer consisted of external radiation therapy to a dose of 5,400 cGy delivered in 180 cGy fractions followed by one or two times of brachytherapy applications.

External radiation therapy was given by Cobalt 60 teletherapy unit usually by four oblique portals to the whole pelvis. At 5040 cGy, the field was shrunk from the top to avoid small bowel irradiation.

Table 1. Distribution of the Patients by Clinical Stage and Treatment Mode

	Combination treatment (%)	RT alone (%)	Total
Stage Ia	12 (18.1)	0 (0)	12
Stage Ib	47 (71.2)	11 (18.3)	58
Stage IIa	7 (10.6)	49 (81.6)	56
Total	66 (100)	60 (100)	126

tion.

Brachytherapy was done by low dose rate intracavitary radiation using Fletcher-Suit-Delclos applicator with 137 cesium source. 1440 to 2880 mg-hr dose was given through the ICR. At the end of radiation therapy, total dose to point A and B reached minimal dose of 8000 to 9000 cGy and 6000 to 7000 cGy respectively.

Postoperative irradiation was given to the patients whose final pathologic specimen revealed over 4 mm stromal invasion, presence of lymphovascular invasion, positive pelvic lymph node and poor resection margin.

We used ICR in addition to the external radiation therapy for every operated patients with positive or inadequate resection margin.

In those cases, vaginal mucosal dose through ICR alone exceeded 10,000 cGy in rate of 140 cGy per hour.

3. Follow up

Median follow up period was 78 month, ranging from 30 to 126 months. Every patients had follow up check at 1 month and 4 month after completion of treatment. Routine Pap smear was done at 4 month follow up day. After then, follow up check was done by every three month during the first year, by four month during second and third year and by every six month until the fifth year. The patients were seen yearly after fifth year.

4. Statistical Analyses

To find out factors that contributes to the treatment failures, several parameters were selected for analyses in each group (Table 2 and Table 3).

Multivariate analysis was done by Logistic regression model (Table 4 and Table 5).

Table 2. Correlation of In-Field Failure with Initial Histopathologic Risk Factors in 66 Patients of Combination Group

Risk factor	In-field recurrence	
	Number	Percent
Insufficient or positive resection margin	5/40	12.5
Positive pelvic node	1/ 9	11.1
Deep stromal invasion	3/34	8.8
Lymphovascular invasion	0/15	0
Endometrial extension	1/10	10.0
Adenocarcinoma histology	1/ 5	20

RESULTS

Of the 126 patients, there was 23% (29/126) treatment failure. Local pelvic recurrences were defined as failures confined to the area of the vaginal cuff, cervix and parametrium. Regional

Table 3. Correlation of In-Field Failure with Risk Factors in 60 Patients of RT Alone Group

Risk factor	In-field recurrence	
	Number	Percent
Bulky tumor size over 5cm in diameter	7/26	26.9
Infiltrating gross morphology	2/17	11.7
Adenocarcinoma histology	0/ 2	0
Partial tumor regression	8/11	72.7

Table 4. Maximum Likelihood Analysis of Variance Table in 66 Patients of Combination Group

Source	DF	Chi-Square	Prob
Intercept	1	8.88	0.0029
Poor RM*	1	4.12	0.0423
Pelvic node positive	1	7.55	0.0060
Deep str. invasion	1	0.18	0.6677
Lymphovasc. invasion	1	1.06	0.3039
Endomet. extension	1	0.53	0.4646
Adenoca. histology	1	.	.
Age	1	2.78	0.0957
Stage	1	0.19	0.6614
Likelihood ratio	18	26.64	0.0860

* resection margin

recurrences consisted of isolated tumor mass at the pelvic side wall and pelvic lymphadenopathy. Parametrial disease extended to the pelvic side wall (frozen pelvis) was also included in this category. Distant failures included all tumor recurrences outside the pelvis.

In combination threatment group, 19.7% (13/66) of failure developed. In RT alone group, there was 26.6% (16/60) of treatment failure (Table 6).

The initial pattern of clinical recurrence is diagrammed in Fig 1 and 2.

1. Locoregional Failures

In combination treatment group, 5 of 12 patients who developed recurrence had failures within the irradiated volume as a component of initial pattern of failure. In each instance, the in-field site of recurrence had absorbed a minimum dose of 5000 cGy in 5-5.5 weeks. 3 cases among the 5 locoregional failure showed recurrent mass or positive Pap smear at vaginal stump on 4 month follow up. All they had positive vaginal resection margin on the examination of the operative specimen.

Table 5. Maximum Likelihood Analysis of Variance Table in 60 Patients of RT Alone Group

Source	DF	Chi-Square	Prob
Intercept	1	2.13	0.1447
Tumor size over 5cm	1	0.20	0.6520
Partial regression	1	10.37	0.0013
Adenoca histology	1	0.53	0.4682
Infiltrating type	1	2.00	0.1573
Age	1	1.75	0.1861
Stage	1	0.01	0.9171
Likelihood ratio	14	7.64	0.9073

Table 6. Treatment Failures by Treatment Mode and Stage

	Combination group (13)		RT alone group (16)	
	LRF (%)	DM (%)	LRF (%)	DM (%)
Ia	0/12 (0)	0/12 (0)	0	0
Ib	5/47 (10.6)	5/47 (10.6)	1/11 (9.0)	0/11 (0)
IIa	1/ 7 (14.2)	2/ 7 (28.5)	8/49 (16.3)	7/49 (14.2)
Total	6/66 (9.0)	7/66 (10.6)	9/60 (15)	7/60 (11.6)

* LRF : locoregional failure DM : distant metastasis

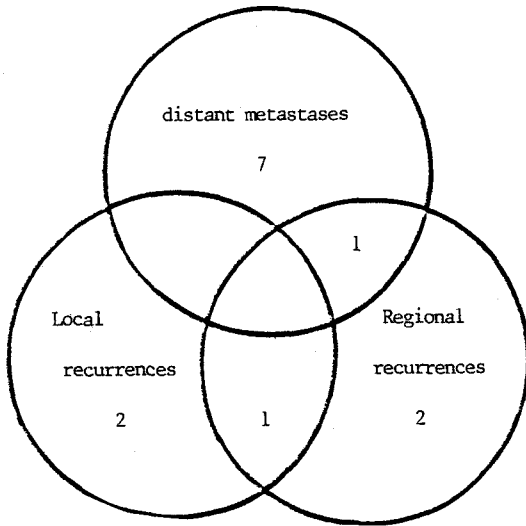


Fig. 1. Pattern of recurrence in 13 patients in combination group.

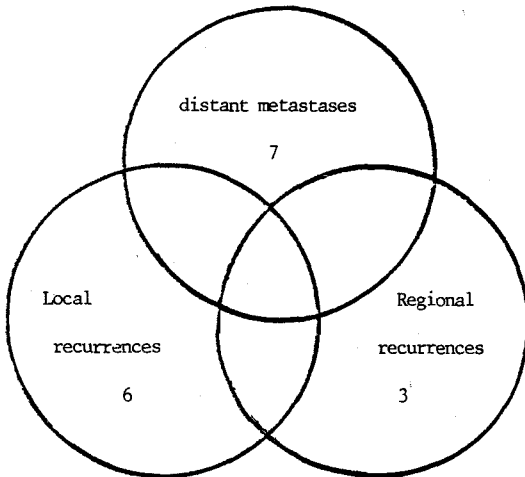


Fig. 2. Pattern of recurrence in 16 patients in RT alone group.

In RT alone group, 9 patients showed locoregional failure. Six of them had persistent disease at the end of radiation therapy.

Four of the five regional recurrences presented as soft tissue mass involving pelvic side wall and one patient as pelvic lymphadenopathy at the time between 8 month and 29 month. Correlation of in-field failure with initial histopathologic and clinical risk factors is seen in Table 2 and 3.

2. Distant Failures

15 patients have failed at sites remote from the

Table 7. Sites of Distant Metastases in 15 Patients by Treatment Mode

	Combination group (8) (No. of initial metastatic site)	RT alone group (7) (No. of initial metastatic site)
Nodes		
supraclavicular	1 (1)	4 (3)
para-aortic	2 (1)	4 (2)
inguinal	1 (1)	
mediastinal	1 (1)	
axillary		1
submaxillary		1 (1)
Lung	2 (1)	2
Bone	3 (2)	2 (1)
Liver	1	

* para-aortic and/or supraclavicular LN as the first site of metastasis ; 5/7 (71.4%) in RT alone group & 2/8 (25%) in combination group.

irradiated volume, of which 8 in combination treatment group and 7 in RT alone group.

In combination group, 6 of 8 patients showed single organ metastasis whereas all seven patients showed multiple organ metastasis.

In RT alone group, 6 of 7 patients with distant metastases have developed para-aortic and/or left supraclavicular lymph node metastases. In 5 of that 6 patients, that was the first site of metastasis. The other one patient initially presented with submaxillary lymphadenopathy but she soon has been found to have para-aortic disease.

In combination treatment group, only 2 of 8 patients (25%) showed the first and the only metastasis in para-aortic and left supraclavicular lymph node chain.

Frequent metastatic sites are shown in Table 7.

3. Time of Appearance of Failures

Time to distant failure was shorter than that of regional recurrence. 53% (8/15) of the distant failures occurred in 6 month. Mean time of appearance of distant metastasis and regional recurrence was 11 month and 17 month respectively. Time of appearance of failures are shown in Table 8.

4. Statistical Significance

There was no statistically significant difference in locoregional & distant failure rate by treatment group both in stage I and II.

Table 8. Time of Appearance of Failures After Completion of Treatment in 29 Patients

	Combination group (13)			RT alone group (16)			Total
	Local	Regional	Distant	Local	Regional	Distant	
< 6 mo	2†	1⊙	3	6*		5	17 (58.6%)
6 – 12 mo		1★			1⊙		2 (6.8%)
12 – 18 mo	1†	1⊙Δ	3		2⊙	1	8 (27.5%)
> 18 mo			1			1	2 (6.8%)

† : recurrence at the vaginal stump

* : persistent gross disease at the end of RT

⊙ : pelvic mass, solitary or with parametrial disease

★ : pelvic node

Δ : pelvic node + para-aortic nodes

Distribution of site of distant failures between the combination group and RT alone group showed statistically significant difference 0.0361.

In combination group, poor resection margin and positive pelvic lymph node were found to be the most significant factors contributing to the treatment failure ($p=0.042$ and 0.006 respectively).

In RT alone group, partial tumor regression at the end of treatment was revealed as the most significant factor ($p=0.001$).

DISCUSSION

Either radical hysterectomy and pelvic lymphadenectomy or primary radiation therapy is an effective modality for the treatment of early, uterine cervical cancer.

However, approximately 10 to 20% of the patients will develop recurrent cancer after treatment.

In most of the patients who fail primary surgical therapy or primary radiation therapy, recurrence is said to be initially within the pelvis with or without distant metastases^{15,16,18,19,20}.

The treatment failures of early cervical cancer in our hospital during last eight years were analysed in this study.

The patients were grouped either they had combination of surgery and postop irradiation or primary radiation therapy but comparison of the result between these two groups by the stage couldn't be done properly for uneven distribution of the patients.

89% (59/66) of the patients in combination treatment group belonged to stage Ia and Ib, whereas 81.6% (49/60) of the patients in RT alone group to stage Ia.

Locoregional failure was seen in 9.2% (6/66) of the patients in combination treatment group, of

which 5 were stage Ib.

15% (9/60) of the patients in RT alone group failed locoregionally and 8 of them had stage IIa disease.

Three patients who showed recurrence at the vaginal stump who had positive vaginal resection margin had received 5400 cGy of external radiation and over 10,000 cGy vaginal stump dose through the ICR.

It may suggest that surgical procedure itself may create zones of poorly vascularized tissue harboring microscopic foci of hypoxic and therefore, radioresistant cancer cells¹⁸.

The possibility exists that some patients referred for adjuvant pelvic radiation may harbor more than microscopic residual disease because we had no full pathologic description of the two patients among the three vaginal stump failures.

In fact, of the 13 failures in combination treatment group, there were five patients who had been referred to our department from other community hospitals. They had only TAH as a surgical procedure and full pathologic evaluation was not done. We are not sure that they had true stage Ib disease initially.

Of the 9 patients with locoregional failure in RT alone group, 6 patients had gross residual lesion at the cervix or vagina at the end of radiation therapy. All had initially bulky mass measured about 7–8 cm in diameter. Tumor morphology did not show any difference either they were fungating or infiltrating type. All had squamous cell histology.

Some authors have suggested that there are radioresistant squamous cell ca of the cervix which should be managed surgically rather than by radiotherapy to prevent central recurrence^{6,14,17}. Others have been less willing to accept the concept of "radioresistance" and have suggested that local failures are related to other factors including in-

adequate treatment such as poor ICR geometry^{10,11,12,13}). Possibly, above two factors would contribute to some extent⁹).

In our series, tumor bulk itself might be an important factor. Since 1989, we have been trying extrafascial hysterectomy for the patient with central residual disease.

We expect that it may work to reduce local failure in the treatment of early cervical cancer.

In both treatment group, regional failures have occurred more often in the parametrial tissue than in the regional lymphatics. This finding is in accordance with that of Samuel et al¹⁰).

Many institutes report distant failure rate of stage Ib and Ila disease as 5 to 15%^{6,7,8}).

The failure rate in distant sites in this study was 12.1% (8/66) in combination treatment group and 11.6% (7/60) in RT alone group. It may be a measure of the biologic behavior of the tumor rather than the adequacy of surgical resection⁹), but we have found some difference in the distribution of sites of distant failure in this study, that is, contiguous node chain outside the treatment volume in RT alone group and other distant organs such as lung, bone and liver in combination treatment group.

It is also likely that vascular invasion or lymphatic infiltration occurs to some degree in all patients, either before or during radical surgery. Viable tumor cells might stay behind in which case the individual prognosis is a function of specific tumor aggressivity and host response⁹).

Prospective randomized study will have to be done to find out factors useful in predicting which patient is likely to fare better with radiation therapy than with radical surgery.

SUMMARY

1) There were total 23% (29/126) treatment failures, 13 in combination group and 16 in RT alone group.

2) There was no statistically significant difference in the incidence of locoregional and distant failures between the two treatment arms, but there seems to be a trend that among the patients with the same stage, lesser failures are expected for the RT alone group.

3) About 60% of the patients with regional recurrences presented their recurrent disease after 1 year of completion of treatment, whereas same percent of distant failures appeared within 6 month.

4) Main site of the first metastasis was para-aortic and/or left supraclavicular lymph nodes in

RT alone group whereas most of the patients with distant failures in combination treatment group initially failed at non-contiguous node or other distant organs such as lung, bone and liver ($p=0.0361$).

5) Logistic regression analysis was done for multivariate analysis of the factors contributing to the treatment failures.

In combination group, adequacy of resection margin and the presence of positive pelvic node were most significant factors ($p=0.0423$ and 0.0060 respectively).

In RT alone group, less than complete regression of tumor at completion of treatment was shown to have good causality with the treatment failure and highly significant value in predicting treatment failure ($p=0.0013$).

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== 국문초록 ==

조기 자궁경부 악성종양의 치료실패에 대한 분석

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1981년 1월부터 1988년 12월까지 고려대학교 의과대학 치료방사선과에서 제1기에서 2기초까지의 자궁경부악성종양으로 방사선치료를 받았던 126명의 환자를 수술과 방사선치료의 병행요법군(66)과 단독방사선치료(60)군의 두군으로 나누어 그 치료실패의 양상과 요인을 분석하였다.

총 126명 중 29명인 23%의 환자에서 국소재발이나 원격전이를 보였으며 각 군 사이에 병기별로 의미있는 차이를 보이지는 않았다.

29명 중 25명인 86%의 환자에서 치료종결후 18개월 이내에 치료실패를 보였으며 원격전이의 평균 시기는 국소적인 재발보다 빨라 약 60%의 원격전이가 6개월 이내에 발생되었다.

첫 원격전이의 장소로는 단독방사선군에서는 주로 복부임파절이나 쇄골 상부임파절이 많았던 반면 병행요법군에서는 이를 제외한 원격임파절, 폐, 간 및 골전이가 많았던 것으로 나타났으며 이는 통계학적인 유의성이 있었다.

각 군에서 치료실패에 기여하는 요소를 알아내기 위해 조직병리학적, 또는 임상적인 위험요소들에 대해 다변수 분석을 시행한 결과 병행요법군에서는 불충분한 제거범위($p=0.0423$) 및 전이성 골반임파절($p=0.0060$)의 존재가, 단독요법군에서는 치료 종결시 종양의 불완전관해($p=0.0013$)가 가장 의미있는 요소로 관찰되었다.