

# High Versus Low Dose Rate Intracavitary Irradiation for Adenocarcinoma of the Uterine Cervix

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**Background:** Traditionally, low dose rate (LDR) brachytherapy has been used as a standard modality in the treatment of patients with carcinoma of the uterine cervix. The purpose of this work was to evaluate the effects of high dose rate (HDR) brachytherapy on patients with adenocarcinoma of the uterine cervix and to compare them with the effects of LDR brachytherapy.

**Methods:** From January 1971 to December 1992, 104 patients suffering from adenocarcinoma of the uterine cervix were treated with radiation therapy in the Department of Radiation Oncology, Yonsei University. LDR brachytherapy was carried out on 34 patients and HDR brachytherapy on 70 patients. In the LDR group, eight patients were in stage IB, six in IIA, 12 in IIB, three in IIIA and five in IIIB. External radiation therapy was delivered with 10 MV X-rays, 2 Gy fraction per day, total dose of whole pelvis 36–52 Gy (median 46 Gy). LDR radium intracavitary irradiation was performed with a Henschke applicator, 37–59 Gy targeted at point A (median 43 Gy). In the HDR group, there were 16 patients in stage IB, six in IIA, 32 in IIB and 16 in IIIB. The total whole pelvis dose of external radiation was 40–50 Gy (median 44 Gy), daily 1.8–2.0 Gy. HDR Co-60 intracavitary irradiation was performed with a remotely controlled after-loading system (RALS), 30–48 Gy (median 39 Gy) targeted at point A, three times per week, 3 Gy per fraction.

**Results:** The 5-year overall survival rate in the LDR group was 72.9, 61.9 and 35.7% in stage I, II and III, respectively and the corresponding figures for HDR were 87.1, 58.3 and 43.8% ( $p > 0.05$ ). There was no statistical difference between the HDR group and the LDR group in terms of the 5-year overall survival rate from adenocarcinoma of the uterine cervix. There was a late complication rate of 12% in the LDR group and 27% in the HDR group. The incidence of late complications in stages II and III was higher in the HDR group than in the LDR group (31.6 vs 16.7% in stage II, 37.3% vs 12.5% in stage III,  $p > 0.05$ ). No prognostic factors were evident in the comparison between the two groups.

**Conclusion:** There was no difference in terms of 5-year survival rate in the patients with adenocarcinoma of the uterine cervix between those treated with HDR and those treated with LDR brachytherapy. Even though late complication rates were higher in the HDR group, most of them were classified as grade I. This retrospective study suggests that HDR brachytherapy may be able to replace LDR brachytherapy in the treatment of adenocarcinoma of the uterine cervix.

*Key words:* adenocarcinoma – cervix uteri – radiotherapy – brachytherapy

## INTRODUCTION

Traditionally, low dose rate (LDR) brachytherapy has been used as a standard modality in the treatment of patients with

carcinoma of the uterine cervix. However, there has been increased interest in high dose rate (HDR) brachytherapy for such treatment. Until now, only three prospective randomized trials comparing HDR with LDR intracavitary brachytherapy in the management of uterine cervical carcinoma have been reported (1–3), in all of which the 5-year survival rate and failure rate were similar. Numerous retrospective trials (4–10) have also demonstrated similar results. However, almost all patients in these previous reports had squamous carcinoma

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**Table 1.** Patients' characteristics with adenocarcinoma of the uterine cervix

Characteristic	LDR (%) (n = 34)	HDR (%) (n = 70)	p Value
Age (years):			
Range	26–66	32–79	
Mean	48	51	
Stage:			
IB	8 (23.5)	16 (22.9)	0.992
IIA	6 (17.6)	6 (8.6)	
IIB	12 (35.3)	32 (45.7)	
IIIA	3 (8.8)	–	
IIIB	5 (14.7)	16 (22.9)	
Pathology:			
Endocervical	30 (88.2)	53 (75.7)	0.418
Endometrioid	1 (2.9)	2 (2.9)	
Clear cell	–	2 (2.9)	
Adenosquamous	3 (8.8)	13 (18.6)	
Differentiation:			
Well	10 (29.4)	19 (27.1)	0.840
Moderate	5 (14.7)	12 (17.1)	
Poor	3 (8.8)	10 (14.3)	
Unknown	16 (47.1)	29 (41.4)	

with only a few cases of adenocarcinoma. Therefore, these previously reported similar LDR and HDR results for the squamous histology cannot be considered representative of the results for adenocarcinoma.

Adenocarcinoma of the uterine cervix demonstrates heterogeneous histology, with complex growth patterns and different biological behavior, and accounts for 6–20% of all cervical cancers (11–15). The relative incidence of these tumors appears to have been increasing in recent years compared with squamous carcinoma (16,17). Although the natural history of squamous cell carcinoma has been studied extensively, that of adenocarcinoma of the cervix has not yet been fully elucidated because of its uncommon incidence. The overall survival rate for patients with adenocarcinoma of the uterine cervix has been reported with varying results. Several investigators (12–14,18,19) have reported similar survival rates between adenocarcinoma of the uterine cervix and that of squamous carcinoma, and a few (11,20) have reported a difference in survival rates between them when the treatment consisted of LDR intracavitary irradiation combined with external radiation therapy. Little attention has been paid to the treatment results for patients with adenocarcinoma of the uterine cervix treated with HDR brachytherapy. Nakano et al. (21) suggested that the local control rate with HDR therapy was significantly lower than that with LDR therapy for adenocarcinoma of the uterine cervix, probably owing to the radiation-resistant nature of adenocarcinoma to HDR treatment. However, they mentioned

some limitations in drawing a definite conclusion about the difference in radiation effects on adenocarcinoma of the uterine cervix because of the small number of patients. Further investigations of radiation effects on adenocarcinoma will be needed.

The aim of the present study was to compare the results for adenocarcinoma patients treated with either HDR or LDR brachytherapy for the evaluation of dose rate effects.

## PATIENTS AND METHODS

### PATIENTS

Between January 1971 and December 1992, a total of 146 patients, 4.1% of all primary cervical carcinomas over the period (22,23), with pathologically proven adenocarcinoma of the uterine cervix who had not undergone radical surgery presented at the Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University. Eighteen patients who had been treated with combined chemotherapy, 14 treated with intracavitary radiation therapy using HDR with an Ir-192 source, four in stage IV and six who had received incomplete radiation therapy were excluded. The remaining 104 patients were analyzed retrospectively. Before 1980, 34 patients with adenocarcinoma of the uterine cervix were treated with LDR with radium intracavitary irradiation combined with external radiation. After 1980, the remaining 70 patients were treated with HDR with Co-60 intracavitary irradiation with external radiation therapy. The patients' characteristics of both groups are shown in Table 1. All patients underwent clinical staging according to the International Federation of Gynecology and Obstetrics (FIGO) classification. In terms of stage, pathological subtype and tumor differentiation, the distribution was not significantly different in either group.

### RADIATION THERAPY TECHNIQUE

In both groups, external radiation therapy was performed with 10 MV X-rays using either the anterior and posterior parallel opposing field technique or the four-field box technique. Five fractions weekly, with 1.8 or 2.0 Gy per fraction, were delivered to the mid-plane of the pelvis. The volume of external radiation therapy included both the primary tumor and the regional lymph nodes. The fraction size was 1.8–2 Gy and total dose to the whole pelvis was 36–52 Gy (median 48 Gy) in the LDR group, whereas in the HDR group the fraction size was 1.8–2 Gy and the total 40–50 Gy (median 45 Gy), with midline shielding at 20–45 Gy (median 43 Gy). In the LDR group, we delivered the intracavitary irradiation either before or after external radiation therapy using a Henschke applicator with a 65–80 mg radium source (mean 5140 mg/h), 37–59 Gy per 1 or 2 fractions to point A (median 43 Gy). In the HDR group, intracavitary irradiation was delivered after external irradiation using a Modified Manchester Applicator, a Co-60 source with a remotely controlled after-loading system (RALS) without general anesthesia. Three times per week, 3 Gy per fraction,

**Table 2.** Patterns of failure according to stage after HDR and LDR intracavitary radiation therapy in patients with adenocarcinoma of the uterine cervix

Stage	LDR (n = 34)			HDR (n = 70)		
	LF (%)	DF (%)	LF + DF (%)	LF (%)	DF (%)	LF + DF (%)
I	1/8 (12.5)	1/8 (12.5)	1/8 (12.5)	–	1/16 (6.3)	–
II	3/18 (16.7)	2/18 (11.1)	1/18 (5.6)	8/38 (21.1)	4/38 (10.5)	1/38 (2.6)
III	2/8 (25.0)	–	–	4/16 (25.0)	1/16 (6.2)	1/16 (6.2)
Total	6/34 (17.6)	3/34 (8.8)	2/34 (5.9)	12/70 (17.1)	6/70 (8.6)	2/70 (2.9)

LF, local failure; DF, distant failure; HDR, high dose rate; LDR, low dose rate.

total 30–48 Gy was delivered to point A (median 39 Gy). Orthogonal films were taken with dummy sources after insertion of the tandem and ovoids. The bladder neck was identified using a Foley catheter balloon filled with 7 ml of Hypaque and the rectum was filled with barium. The degree of weighting of the sources was decided by several model plans according to the length of the tandem and distance between the two ovoids.

#### FOLLOW-UP AND STATISTICAL ANALYSIS

After completion of the radiation therapy, regular follow-up every 3 months was done during the first 2 years and every 6 months thereafter. Treatment failure was detected from physical examination and computed tomography (CT) and biopsy in cases of central failure. Para-aortic lymph node metastasis was considered to be distant metastasis. Of the 104 patients, 102 were followed for more than 5 years or until death. The median follow-up period was 41 months. The severity of late complications was classified according to the RTOG/ECOG grading system (24). Comparison of patient distribution and failure rates was made by the chi-squared test, survival analysis was carried out by the Kaplan–Meier method and comparison of the survival rates was performed by the log-rank test.

**Table 3.** Prognostic factors in adenocarcinoma of the uterine cervix

Factor	5-year survival rate (%)		p Value
	LDR	HDR	
Age (years):			
<50	62.4	69.9	0.7301
≥50	53.0	55.1	0.5354
Differentiation:			
Well	51.4	78.8	0.4147
Moderate	66.7	68.6	0.8625
Poor	25.0	44.4	0.1487
Stage:			
I	72.9	87.1	0.4569
II	61.9	58.3	0.8813
III	35.7	43.8	0.9424

## RESULTS

#### PATTERNS OF FAILURE

The local and distant failure rates for the patients with stage I lesions treated with LDR were both 12.5%. These rates were greater than those in the HDR group, which were 0 and 6.3%, respectively, but this was not statistically significant. In stage II and III diseases, the local failures occurred more frequently in the HDR group (21.1 and 25.0%) than in the LDR group (16.7 and 25.0%), but the difference was not statistically significant (Table 2).

#### PROGNOSTIC FACTORS

An attempt was made to look at the possible factors that may be responsible for the observed survival rates; such as patient age, cellular differentiation and stage according to the treatment modalities (Table 3). However, no statistically significant prognostic factors correlating with survival rates were found.

#### OVERALL SURVIVAL RATE

For the purpose of comparison, the 5-year overall survival rates of patients treated by either HDR or LDR are presented in Figs 1 and 2. The HDR group showed a survival rate of 87.1% for stage I, 58.3% for stage II and 43.8% for stage III disease. The 5-year overall survival rate of the LDR group was 72.9% for stage I, 61.9% for stage II and 35.7% for stage III disease. Having compared the survival data from both groups of treatment, stage by stage, the survival rate of stage I disease was found to be better in the HDR than in the LDR group, even

**Table 4.** Late complication rates after HDR and LDR intracavitary radiation therapy in the patients with adenocarcinoma of the uterine cervix

Stage	Complication rate (%)		p Value
	LDR (n = 34)	HDR (n = 70)	
I	0/8 (0)	1/16 (6.3)	0.47
II	3/18 (16.7)	12/38 (31.6)	0.239
III	1/8 (12.5)	6/16 (37.3)	0.204
Total	4/34 (11.8)	19/70 (27.1)	0.076

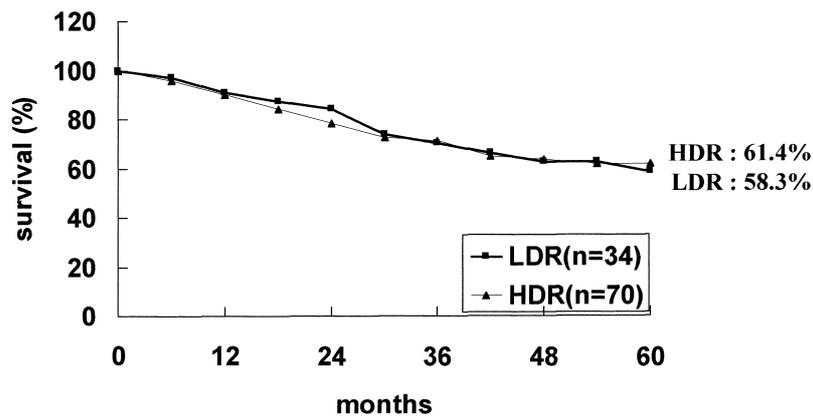


Figure 1. Five-year survival rates after HDR and LDR intracavitary radiation therapy in patients with adenocarcinoma of the uterine cervix.

though the difference was not statistically significant. However, there was no difference in the survival rate of patients treated by either method in stage II or III disease.

COMPLICATIONS

The incidence of late complications is shown in Table 4. The overall late complication rate in the HDR group was higher than that in the LDR group (27.1 vs 11.8%). In stages II and III, the complication rate tended to be higher in the HDR group (31.6 and 37.3%) than in the LDR group (16.7 and 12.5%) ( $p > 0.05$ ). However, most of the complications were classified as grade I. Grade II or IV complication rates in the HDR group were only 4.3 and 1.4%, respectively. Rectal complications occurred more frequently than bladder complications in the HDR group (Table 5).

DISCUSSION

The biology and prognosis of adenocarcinoma of the uterine cervix have been shown to be different from those of squamous

cell carcinoma by some investigators (11,13). A possible explanation for the biological difference is that it is partly due to different radiosensitivity, based on LDR brachytherapy combined with external radiation therapy. The question of whether adenocarcinoma shows a different radiosensitivity to HDR therapy still remains unanswered. Even though the treatment results of HDR and LDR brachytherapy in squamous carcinoma were not different, it is not appropriate to apply these results to adenocarcinoma of the uterine cervix. Unfortunately, there have been no published reports on adenocarcinoma of the uterine cervix treated with HDR brachytherapy, except for a paper by Nakano et al. (21), who reported that adenocarcinoma of the uterine cervix showed more radiation resistance to HDR than to LDR brachytherapy. However, the present study shows that the 5-year overall survival rate of patients with adenocarcinoma of the uterine cervix was not different between the LDR and HDR groups. There were also similar local failure rates and distant metastasis rates in both groups. Hence, according to our results, we could not detect any evidence of greater radiation resistance to HDR brachytherapy for adeno-

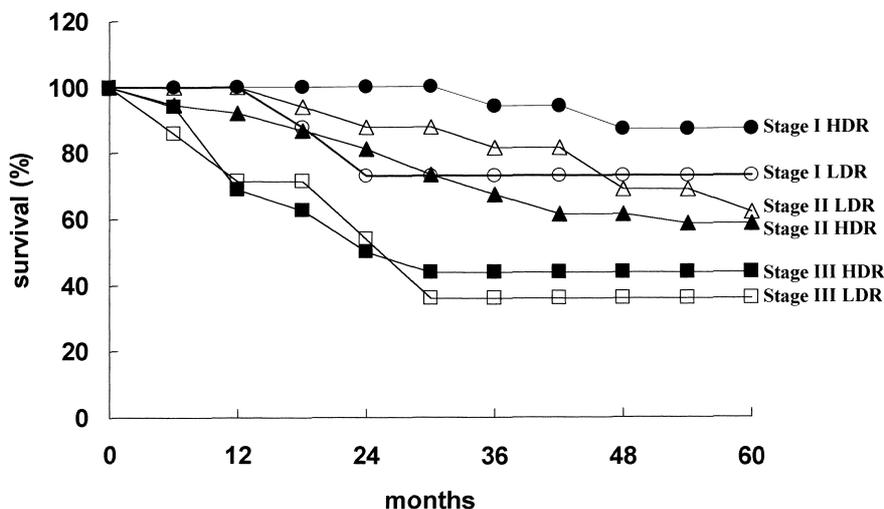


Figure 2. Five-year survival rates related to HDR and LDR intracavitary radiation therapy by stage.

**Table 5.** Grade and site of the late complications after HDR and LDR intracavitary radiation therapy in patients with adenocarcinoma of the uterine cervix

	LDR (n = 34)				HDR (n = 70)			
	GI	GII	GIII	GIV	GI	GII	GIII	GIV
Rectum	1/34	–	–	–	10/70	3/70	–	–
Bladder	2/34	–	–	–	4/70	–	–	–
Combined	1/34	–	–	–	1/70	–	–	1/70
Total	4/34 (11.8)	–	–	–	15/70 (21.4)	3/70 (4.3)	–	1/70 (1.4)

carcinoma of the uterine cervix. Nakano et al. reported that the local control rates for stage I, II and III with low and mixed dose rates were 50, 100 and 62.5%, respectively, and with high dose rates 60, 40 and 41.7%, respectively. We speculated that the difference in the local control rates resulted from the high local control rate in the low and mixed dose rate groups, not from the low local control rate in the high dose rate group. According to two reports that tested the radiosensitivity of tumor biopsies from patients with cervical cancer, adenocarcinoma of the uterine cervix was not on average more radioresistant than squamous cell carcinoma to HDR treatment (25,26). The radioresistance for patients with adenocarcinoma of the cervix who were treated with HDR brachytherapy must be defined.

The stage, tumor size, lymph node metastasis and tumor grade are well-known prognostic factors in adenocarcinoma of the uterine cervix (12–14,27–31). Several prognostic factors were evaluated in this study by both modalities. None of the factors evaluated were found to influence the prognosis.

One problem with this study appears to be the large difference in the number of patients between the two groups. LDR treatment was discontinued in 1980 owing to the failure of the LDR machine so no LDR-treated patients were enrolled in this study after 1980. Furthermore, the FIGO staging system was changed in 1985 during the course of this study period. Some patients originally staged as IC, IIA and IIIA before 1985 had to be categorized as stage IB, IIB and IIIB, respectively, according to the updated staging system. However, there is no possibility that the data was misinterpreted because the patients were analyzed by stage I, II and III.

The late complication rate was significantly higher in the HDR group. Various authors have reported that the incidence of severe late complications when the patients were treated with HDR brachytherapy was 3–11% (4–8), a range comparable to that with LDR brachytherapy (32–34). However, some authors (3,35) emphasized the higher incidence of late complications of HDR therapy than that of LDR brachytherapy. Teshima et al. (3) reported a higher complication rate with HDR brachytherapy of carcinoma of the uterine cervix. They stated that the difference between the treatment position in the LDR and HDR groups might be the reason for the higher incidence of complications in the HDR group. We consider that the higher late complication rate in the HDR group may be due to the higher rectal or bladder point dose. We did not apply

vaginal packing, which played an important role in increasing the incidence of late complications, in every patient treated with HDR brachytherapy. It was unfortunate, however, that we could not calculate the point dose or volume in the LDR group, so we could not compare the point dose in the two groups. We could not confirm the reason why the late complication rate was higher in the HDR group than in the LDR group. A well-planned control study should answer this question in the future.

Another problem in the use of HDR brachytherapy was the lack of established fraction size, fraction number and total dose (36–40). Usually most institutes used 3–10 fractions, each delivering 3–10 Gy to point A (4–10). Koga et al. (10) recommended that 5–6 Gy once per week or 3 Gy twice per week is a proper schedule. Ogino et al. (41) reported that the regimen in HDR treatment based on 5–6 Gy per fraction planned at point A for 5–6 fractions is adjusted by rectal point dose and clinical tumor regression. Brenner (39) suggested that when the dose to the dose-limiting critical normal tissue is less than about 75% of the prescribed dose, about five fractions are probably optimal. However, Orton (36,40) asserted that when HDR treatment is indicated, increased fractionation plays a very significant role in decreasing the risk of late complications. As for fraction size, Arai et al. (42) reported that the optimal dose fractionation schedules for intracavitary irradiation were for HDR 28 + 3 Gy in 4–5 fractions or 34 + 4 Gy in 8–10 fractions or 40 + 5 Gy in 12–14 fractions at point A and for LDR 51 + 5 Gy in 3–4 fractions at point A. From our data, 3 Gy to point A, three times per week, total 39 Gy may be effective when HDR brachytherapy is used. The number of fractionations seems to be important in reducing the late complication rate of HDR brachytherapy and vaginal gauze packing is also important because with increasing source-to-organ distance, the radiation dose decreases. Further studies, with modification of the fraction size and fraction number or searching for the proper combination of external radiation dose and brachytherapy dose, will be required to reduce the late complication rates. A well-planned prospective randomized trial will also be required to confirm the effect of HDR brachytherapy on adenocarcinoma of the uterine cervix carcinoma.

In conclusion, there was no difference in terms of 5-year survival rate and failure pattern between the patients with adenocarcinoma of the uterine cervix treated with either HDR or LDR brachytherapy. Even though late complication rates were higher in the HDR group, it was within an acceptable range.

This retrospective study suggests that HDR brachytherapy may be suitable to replace LDR brachytherapy for adenocarcinoma of the uterine cervix. However, further studies will be required to refine the dose rate effect and fraction size.

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