

Carcinoma of the Uterine Cervix Treated with External Beam Irradiation Alone

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A retrospective analysis was performed on 42 patients with carcinoma of the uterine cervix who were treated with external beam (EB) radiation therapy alone at the Department of Therapeutic Radiology, Seoul National University Hospital from March 1979 to December 1988. After whole pelvic field irradiation of 50Gy, all the patients received additional booster dose of 12-22Gy to the primary tumor. Thirty one received EB radiotherapy alone because of poor geometry for intracavitary application, 5 because of medical problems and 6 because of other reasons. Five year locoregional control rate and five year survival rate were 34.5% and 35.4%, respectively. Five year survivals were 66.7%, 36.4%, 32.8% and 25.0% for stage IIA, IIB, IIIB and IVA, respectively. The response one month after treatment well correlated with prognosis. The incidence of grade 2 and 3 complication was 12% and 10%, respectively. There was tendency of increased complication with advanced stage.

Key Words: Uterine cervix cancer, External beam radiotherapy.

INTRODUCTION

A combination of external beam (EB) and intracavitary irradiation is standard treatment method for patients with carcinoma of the uterine cervix treated with radiation alone. Higher dose of radiation can be delivered to the tumor with intracavitary radiotherapy and better local tumor control has been achieved. However, when it is not appropriate to perform an intracavitary radiotherapy, only EB irradiation is given. This study was performed to analyze treatment results in the patients treated with EB irradiation alone.

MATERIALS AND METHODS

Previously untreated 640 patients with carcinoma of the uterine cervix were registered at the Department of Therapeutic Radiology, Seoul National University Hospital from March 1979 to December 1988. Of these, 42 patients were treated with EB irradiation alone. The age of the patients ranged from 30 to 76 years. According to the FIGO staging system, 1 patient was stage IB, 3 were IIA, 12 were IIB, 1 was IIIA, 20 were IIIB and 5 were IVA.

Thirty one received EB radiotherapy alone because of poor geometry for intracavitary application, 5 because of medical problems and 6 because of other reasons (Table 1).

All the patients were initially treated with anterior and posterior parallel opposing fields to whole

pelvis, upto 50Gy. Three of them received 45Gy of paraaortic lymph node (LN) irradiation in addition to whole pelvic irradiation because of paraaortic LN enlargement on CT. After whole pelvic irradiation, additional booster dose of 12 to 22Gy was given to the primary site through three fields (anterior, right posterior oblique and left posterior oblique) or right and left lateral parallel opposing fields. The total dose to primary site ranged from 60.4 to 72.0 Gy (Table 2).

Response was evaluated immediately after completion of radiotherapy and one month later. Treatment failures were classified into locoregional recurrence (cervix, vagina, parametrium, and other intrapelvic sites) and distant metastasis. Survival

Table 1. Reasons for Treatment with External Beam Irradiation Alone

Reason	No. of patients
Poor geometry	31
tumor necrosis	25
narrow vagina	5
perforated uterus	1
Medical problem	5
Liver cirrhosis	3
COPD*	1
pancytopenia	1
Old age	2
Patient's refusal	2
Intestinal obstruction	1
Pelvic inflammatory disease	1

*chronic obstructive pulmonary disease

rates were calculated with Kaplan-Meier method¹¹. The significance of survival differences was measured by the log rank test²¹.

All the complications of treatment were carefully assessed. They were classified according to grade defined by Perez³³ as: Grade 1; Minor symptoms, self-limited or responding to simple outpatient management, Grade 2; Major symptoms, repeated occurrences which often required hospitalization for diagnosis and for nonsurgical management, Grade 3; Complication which required major surgery for correction or was life threatening.

RESULTS

The five year locoregional control and survival of the entire group of patients were 34.5% and 35.4%, respectively. The actuarial five year local control rates by stage were 66.7%, 38.9%, 27.0% and 20.0% for stage IIA, IIB, IIIB and IVA, respectively (Fig. 1). The five year survivals by stage were 66.7%, 36.4%, 32.8% and 25.0%, respectively (Fig. 2).

The response of tumor evaluated at the completion of treatment had prognostic significance. The responders (CR+PR) had better locoregional control and survival. When the response was evaluated one month after completion of radiotherapy, it had higher prognostic significance (Table 3).

The patients treated with EB irradiation alone

Table 2. Dose of Radiation Therapy

	Dose (cGy)
Whole pelvis	4550-6000 (median : 5040)
Tumor boost	1200-2160 (median : 1840)
Point B boost (N=4)	600-900
Paraaortic LN irradiation (N=4)	4500
Total dose to tumor	6040-7200 (median : 6850)

because of poor geometry had worse five year locoregional control rate (31.0% vs 53.3%) and survival rate (30.0% vs 49.1%) than the patients with other reasons. But the difference was not statistically significant.

A total of 15 patients (35%) had treatment complications. Rectal bleeding and hematuria were the most common (Table 4). There were four patients with grade 3 complication: 1 rectovaginal fistula, 2 vesicovaginal fistula and 1 uterine rupture with hemoperitoneum during radiation therapy. The

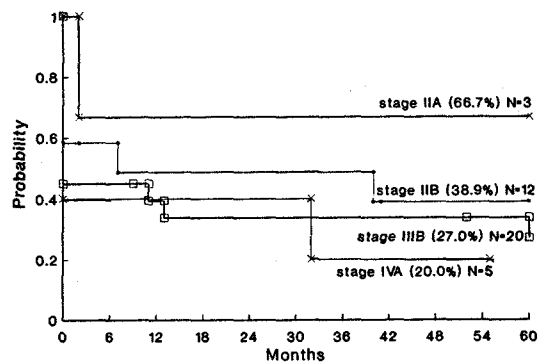


Fig. 1. Actuarial locoregional control by stage.

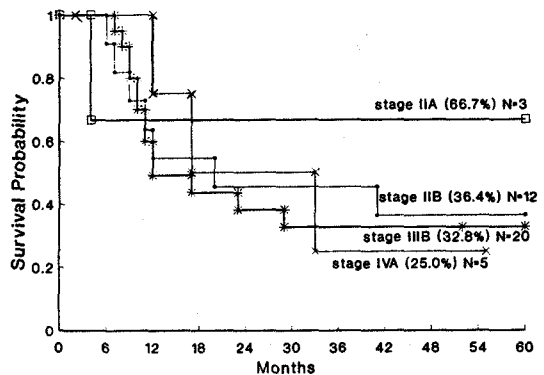


Fig. 2. Actuarial survival by stage.

Table 3. Five Year Locoregional Control and Survival by Response

Time of evaluation	Response	No.	5 yr LRC (%)		5 yr survival (%)	
immediately after RT	CR+PR	27	45.3	p=0.04	43.5	p=0.17
	NR	15	17.8		23.1	
1 Month after RT	CR+PR	26	53.8	p=0.0002	51.3	p=0.001
	NR	11	0		9.1	

Table 4. Type of Complication

	Incidence
Rectal bleeding	7
Hematuria	3
Dysuria	1
Urinary incontinence	1
Rectovaginal fistula	1
Vesicovaginal fistula	2
Uterine perforation	1
Total	16

one patient had 2 symptoms, rectal bleeding and hematuria.

Table 5. The Grade of Complication by Stage

stage	No. of pts	Grade			Total
		1	2	3	
IB	1	0	0	0	0 / 1
IIA	3	0	0	0	0 / 3
IIB	12	2	1	0	3 / 12
IIIA	1	0	0	0	0 / 1
IIIB	20	4	4	2	10 / 20
IVA	5	0	0	2	2 / 5
Total	42	6	5	4	15 / 42

incidence of complication was higher in advanced stage and all the grade 3 complication appeared in advanced stage patients (Table 5).

DISCUSSION

The local control and survival for the patients treated with EB radiotherapy alone were poorer than those for patients treated with standard combination of EB and intracavitary radiotherapy. Our previous local controls⁴⁻⁶ of patients treated with standard treatment in stage IB, IIA, IIB, IIIA, IIIB, and IVA were 79%, 78%, 70%, 58%, 51%, and 27%, respectively. The survival rates were 82%, 72%, 67%, 67%, 51% and 33%, respectively.

The locoregional control and survival of patients treated with EB radiotherapy only because of poor geometry were poorer than those of patients with other reasons although the difference was not statistically significant. This may come from the fact that patients with poor geometry had more advanced disease and/or the response to whole pelvic irradiation was so poor that intracavitary radiation could not be applied.

Variable results of external beam treatment has been reported. Koeck et al⁷, Ulmer et al⁸, and Kakehi⁹ reported that in patients with carcinoma of

the uterine cervix, the results of treatment with EB irradiation alone were comparable with those of treatment with a combination of intracavitary and external irradiation. But the patients in these reports could have been treated with intracavitary irradiation. In other studies^{10,11}, the survival and local control of patients treated with EB irradiation alone were poorer than those of patients treated with combination treatment. Kramer's study¹¹ revealed that there was a substantial difference in survival based on treatment techniques in advanced cases. Of the 35 patients with stage IVA treated with EB plus intracavitary radiation, 8 patients (23%) remained free of disease. None of the 12 patients treated with EB alone was alive. One patient treated with preoperative EB radiotherapy plus exenteration had no evidence of disease 10 years following treatment. The superior results of EB plus intracavitary irradiation to EB alone in patients with advanced disease are not surprising. Most patients treated with combination treatment received a total dose of 12000 cGy or more to uterine cervix compared to 6040-7200 cGy in patients treated with EB irradiation.

Incidence of complication was higher in this group compared to that in patients treated with standard method in our hospital. A crude incidence of grade 2 or 3 rectal and bladder complication was 4.5% and 1.6%, respectively and the cumulative incidence was 6.7% and 2.5%, respectively¹². But in this series 9 (22%) out of 42 patients experienced grade 2 or grade 3 complications. This can be expected because larger area of rectum and bladder is usually included in high dose volume. Perez³ reported that in patients treated with a combination of EB and two intracavitary insertions, the total incidence of grade 2 complication was 10% and that of grade 3 was 9%. The incidence of grade 2 and grade 3 complication (12% and 10%) of this study may be comparable to that results.

The incidence of grade 3 complication was higher in patients with advanced stage (stage IIIB, IVA) in our study as in other reports. Thar et al¹³ reported a severe complication rate of 22% and Park et al¹⁴ reported a severe complication rate of 25% in their stage IVA patients. Kramer et al¹¹ reported severe complication rate of 22% in their stage IVA patients treated aggressively. The severe complication rate was 40% (2/5) in our stage IVA patients. But it must be emphasized that such complication in advanced cases is due not only to the method of treatment but also to the locally advanced nature of this disease; cancer invasion of

bladder or rectum and lysis of tumor after treatment hence causing fistula.

The response of tumor had a dramatic impact on local control and survival. Radiation induced tumor regression as a prognostic factor in cervical cancer has been evaluated by a number of investigators¹⁵⁻¹⁷. These investigators noted that early tumor regression was generally indicative of radiosensitive tumor which could be permanently controlled by radiation therapy. Patients with complete tumor regression by the end of EB therapy had a 77% three-year survival compared to 31% in patients whose tumor did not regress¹⁷. But Fletcher¹⁸ emphasized that even if, 6 weeks to 3 months after completion of irradiation, there seemed to be clinically residual central disease, it did not necessarily mean that those cells were clonogenic. In our study, the regression within 1 month after radiation therapy was closely correlated with tumor control and survival. In patients with no response at 1 month after radiation, further regression was not seen at longer follow-up. Five year local control in patients whose tumors had no response at one month after treatment was 0. Also these patients had significantly poorer survival rates (9.1% vs 51.3%). The response at the end of treatment was also a significant indicator for local control.

In patients with uterine cervical cancer treated with EB radiation therapy, the local control and survival were poor and the incidence of complication was high. When the patients cannot tolerate anesthesia needed for low dose rate intracavitary radiotherapy, high dose rate intracavitary radiotherapy is indicated. When the patients can not receive intracavitary radiation in any form because of poor geometry or when the response is poor, surgery should be considered if possible.

REFERENCES

1. American Joint Committee on Cancer: Reporting of cancer survival and end results. In Manual for Staging of Cancer, 4th ed, JB Lippincott Co, Philadelphia, 1992, pp 155-157
2. Peto R, Pike MC, Armitage P, et al: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 35:1-35, 1977
3. Perez CA, Breaux S, Bedwinek JM, et al: Radiation therapy alone in the treatment of carcinoma of the uterine cervix. II. Analysis of complications. *Cancer* 54:235-246, 1984
4. Kim MS, Ha SW: Pretreatment prognostic factors in early stage carcinoma of the uterine cervix. *J Korean Soc Ther Radiol* 10:59-67, 1992
5. Shin KH, Ha SW, Yoo KY: Analysis of pretreatment prognostic factors in stage IIB carcinoma of the uterine cervix. *J Korean Soc Ther Radiol* 10:227-236, 1992
6. Oh DH, Ha SW, Lee MS: Analysis of prognostic factors in locally advanced carcinoma of the uterine cervix. *J Korean Soc Ther Radiol* 10:69-76, 1992
7. Koeck GP, Jacobson LE, Hillsinger WR: Results of cobalt 60 rotation therapy in carcinoma of the cervix. *AJR* 96:81-91, 1966
8. Ulmer HU, Frischbier HJ: Treatment of advanced cancers of the cervix uteri with external irradiation alone. *Int J Radiat Oncol Biol Phys* 9:309-312, 1983
9. Kakehi M: Radiotherapy of carcinoma of the uterine cervix by the external irradiation using conformation technique. *Jap J Med Radiol* 35:16-27, 1975
10. Akine Y, Hashida I, Kafiura Y, et al: Carcinoma of the uterine cervix treated with external irradiation alone. *Int J Radiat Oncol Biol Phys* 12:1611-1616, 1986
11. Kramer C, Peschel RE, Goldberg N, et al: Radiation treatment of FIGO stage IVA carcinoma of the cervix. *Gynecol Oncol* 32:323-326, 1989
12. Ha SW, Chung WK, Kim JH: Bowel complication after radiotherapy of uterine cervix carcinoma. *J Korean Soc Ther Radiol* 10:237-245, 1992
13. Thar TL, Million RR, Daly JW: Radiation treatment of carcinoma of the cervix. *Semin Oncol* 9:299-311, 1982
14. Park TL, Kong JS, Gersheason DM, et al: Definitive radiotherapy in the treatment of carcinoma of the cervix with bladder invasion. *Int J Radiat Oncol Biol Phys* 12:96, 1987 (Abstract)
15. Marcial VA, Bosch A: Radiation-induced tumor regression in carcinoma of the uterine cervix: prognostic significance. *Amer J Roent* 108:113-123, 1970
16. Grossman I, Kurohara Ss, Webster JH, et al: The prognostic significance of tumor response during radiotherapy in cervical carcinoma. *Radiology* 107:411-415, 1973
17. Hong JH, Chen MS, Lin FJ, et al: Prognostic assessment of tumor regression after external irradiation for cervical cancer. *Int J Radiat Oncol Biol Phys* 22:913-917, 1991
18. Fletcher GH: Textbook of Radiotherapy. 3rd ed, Philadelphia, Lea & Febiger 1980, pp 720-773

국문초록 =

자궁경부암의 외부방사선 치료 성적

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자궁경부암의 방사선 치료중 외부방사선조사로만 치료한 환자에서 생존율, 합병증, 예후인자를 알아보기 위하여 본 연구를 시행하였다. 1979년 3월부터 1988년 12월까지 서울대학교병원 치료방사선과에서 근치적 방사선 치료를 시행받은 총 650명의 자궁경부암 환자 중 외부방사선 조사만 시행한 42명을 대상으로 후향적 분석을 실시하였다. 방사선치료는 45 Gy내지 50 Gy의 전골반 조사후 3 내지 2 조사야를 사용한 축소야로 12 Gy에서 22 Gy의 추가조사를 시행하였다. 외부방사선조사만 시행한 이유는 심한 종양괴사로 인한 경우 25예, vaginal vault가 좁은 경우 5예, 외부방사선 치료 중 자궁강의 파열 1예등 강내조사용기구삽입이 불가능한 경우(poor geometry) 31명, 내과적 문제 5명, 고령 2명, 환자의 거부 2명, 장관 유착과 골반질환이 각각 1명이었다. FIGO 병기 IB, IIA, IIB, IIIA, IIIB, IVA의 환자수는 각각 1명, 3명, 12명, 1명, 20명, 5명이었다. 병기 IIA, IIB, IIIB, IVA에 따른 5년 국소치유율은 각각 66.7%, 38.9%, 27.0%, 20.0%이었고 5년 생존율은 각각 66.7%, 36.4%, 32.8%, 25.0%으며 1명씩의 IB와 IIIA의 환자는 무병생존했다. 방사선 치료가 끝난 후 치료반응 판정에서 완전관해와 부분관해를 보인 환자군이 그렇지 않은 환자군보다 5년 국소치유율은 의미있게 높았으나 (45.3% vs 17.8% p=0.04) 5년 생존율의 의미있는 차이는 없었다(43.5% vs 23.1% p=0.17). 방사선 치료후 1개월에서 완전관해와 부분관해를 보인 환자군은 그렇지 않은 환자군보다 5년 국소치유율 (53.8% vs 0% p=0.0002)과 5년 생존율 (51.3% vs 1.0% p=0.001)이 의미있게 높았다. Grade 2와 Grade 3의 합병증은 각각 12%와 10%였다. 진행된 경우일수록 합병증의 빈도가 증가하는 경향이였다. 따라서 자궁경부암 환자의 방사선 치료에 가장 적합한 방법은 외부조사와 강내 치료를 병행하는 것이나 강내 치료가 불가능한 환자군에 대해서는 적극적 수술방법의 도입을 고려해야하겠다.