Radiotherapy of Recurrent Uterine Cervical Cancer

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Forty seven patients with locally recurrent uterine cerival cancer after surgery were treated with radiation during the 6 year period from 1979 through 1984 at the Department of Therapeutic Radiology of Seoul National University Hospital. In 30 out of the 47 patients, recurrence was diagnosed within 2 years after surgery. Site of recurrence was vagina in 19 patients, vagina and parametrium in 21 patients and parametrium only in 7 patients. Complete tumor control was achieved in 35 patients (74.5%); the complete response rates were 94.7% (18/19) in vaginal recurrences, 57.1% (12/21) in combined vaginal and parametrial recurrences and 71.4% (5/7) in parametrial recurrences. Overall and disease free survival rates at 4 years were 55.2 and 50.1 percent, respectively, for entire group. Overall 4 year survival rates were 77.0% for vaginal recurrences, 44.1% for vaginal and parametrial recurrences and 42.9% for parametrial recrrences. When the disease extent was classified in the same way as the staging system of FIGO, the 4 year survival was 80.4, 73.0, 25.0 and 0 percent for stage IIa, IIb, IIIb and IVa, respectively.

Key Words: Locally recurrent uterine cervical cancer, Radiotherapy, Survival.

INTRODUCTION

It is generally accepted that appropriate initial treatment of cancer offers best chance for cure and once it recurs, the prognosis is grave. But this may be a little different in case of uterine cervical cancer. In almost half of patients with uterine cervical carcinomas, the disease is limited in pelvic cavity even at late stage[1,2]. And so salvage of these recurrences limited to pelvic cavity might be possible with treatment of local modality such as radiation. And in patients without previous irradiation to pelvis, a very high dose of radiation can be delivered to the tumor relatively safely. Forty seven locally recurrent uterine cervical cancer patients were treated with radiation and the results were analyzed.

MATERIALS AND METHODS

During the 6 year period from 1979 to 1984, 56 patients were referred to our department for radiation treatment of locally recurrent uterine cervical cancer after previous surgery. The recurrent cancer was diagnosed in less than 6 months after initial surgery in 8 patients and one patient did not receive complete treatment. Remaining 47 patients were analyzed as of December 31st, 1986.

Recurrence was diagnosed histopathologically in 35 patients. In the remaining 12 patients, diagnosis was based on clinical evidences such as palpable mass in parametrium and/or pelvic side wall, newly developed hydronephrosis, mass on computed tomography, and etc.

The histopathological diagnosis at initial surgery was squamous cell carcinoma in 44 patients (Table 1). The stage at the time of inital surgery was stage 0 in 5 patients, stage I in 21 patients and stage II in 17 patients. Fifteen patients had been treated with simple hysterectomy and 32, with radical surgery (Table 2). The interval between the initial surgery and diagnosis of recurrence was less than 2 years in 30 patients (63.8%) and was less than 6 years in 42 patients (89.4%) (Table 3).

The recurrence was limited to vagina in 19 patients, involved vagina and parametrium or side wall in 21 patients and involved parametrium or side wall in 7 patients (Table 4). The tumor volume was relatively small in the vagina only group, being larger than 3 cm in diameter in only 2 patients out of 19. In contrast, the tumor was bigger in vagina and parametrium or pelvic side wall group, being larger than 3 cm in diameter in 12 patients out of 21.

Curative dose radiotherapy was performed in every patients. 4,500 to 5,040 cGy was delivered to

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whole pelvis through AP and PA parallel opposed portals or 4 field box technique, using 10 MV X-ray or gamma ray from Co^{60} teletherapy unit. Then intracavitary radiotherapy using vaginal applicator or small field external beam irradiation was performed depending on the site of recurrence and response of tumor to whole pelvic irradiation.

All but 6 patients were followed to the time of analysis or to the time of death. Median follow-up period for the survivors was 41 months. Of the 6 patients who were lost to follow up, 4 patients were lost at 5, 7, 31 and 44 months each, without evidence of disease. One patient was lost at 2 months with residual disease and the last at 23 months with pelvic re-recurrence.

RESULTS

Complete tumor regression was achieved in 35 patients (74.5%). Complete response rate was highest in cases of recurrences limited to vagina being 94.7% (18/19). Complete response was more frequent in the group treated with combined external whole pelvic irradiation and intracavitary radiotherapy (Table 5). Of the 35 patients with complete tumor regression, tumor re-recurred locally in 5 patients, one patient had pelvic re-recurrence and distant metastasis, and another had distant failure only. In one of the patients with local failure, salvage pelvic excentration was performed, but the patient died of pelvic re-recurrence 6 months after salvage surgery.

Of the 12 patients with incomplete tumor regression, 10 patients died of disease 6 to 25 months after start of radiotherapy. One patient is alive at 32 months and one patient was lost at 2 months.

Of the total of 47 patients, 14 had local failure, 4 had local and distant failure, and 1 had distant failure only; the local control was achieved in 29 out of 47 patients (61.7%) (Table 6).

Disease free and overall survival at 4 years was 50.1 and 55.2 per cent, respectively, for the entire group (Fig. 1). The survival was highest in the patients with vaginal recurrences, being 77.0% compared to 44.1% in combined vagina and parametrium or pelvic side wall recurrences and 42.9 % in parametrium and/or pelvic side wall recurrences. When the latter two groups were combined, the difference in survival was statistically significant ($p<.05$). When the extent of recurrent disease was classified according to the equivalent FIGO staging system, the 4 year survival was 80.4, 73.0, 25.0 and 0 per cent for stage IIa, IIb, IIIb and IVa, respectively

Table 1. Distribution of Histopathologic Type

Histopathology	No. of patients	Percent
Squamous	44	93.6
large non-keratinizing	17	36.2
large keratinizing	18	38.3
small cell	0	0
not sepcified	9	19.1
Adenocarcinoma	1	2.1
Adenosquamous	1	2.1
No inofrmation	1	2.1

Table 2. Initial Surgery and Stage

Initial stage	TAH ± BSO*	Wertheim's operation	Total
0	5	0	5
Ia	2	1	3
Ib	6	12	18
IIa	1**	10	11
IIb	0	6	6
No information	1	3	4
Total	15	32	47

* Total abdominal hysterectomy ± bilateral salphingo-oophorectomy

** Trachelectomy

Table 3. Time to Recurrence

Time to recurrence (yr)	No. of patients	Percent
0.5 – 2	30	63.8
2 – 4	6	12.8
4 – 6	6	12.8
6 – 8	2	4.2
8 – 10	3	6.4

Table 4. Site of Recurrence

Recurrent site	No. of patients	Percent
Remnant vagina	19	40.4
Vagina + PM*/side wall	21	44.7
Parametrium/side wall	7	14.9

* PM : Parametrium

(Fig. 2) (Table 7).

The survival rate was higher in patients with histopathology of large cell non-keratinizing type. The difference was statistically significant in stage II equivalent extent but not in more advanced disease (Table 7).

Age of patients, stage at inital surgery and interval to diagnosis of recurrence did not affect survival (Table 7).

Radiation complication developed in a total of 8 patients. Two patients had transient hematuria and four had transient rectal bleeding and all these subsided spontaneously without specific treatment. Rectal bleeding of large amount develped in one patient and this patient had to be managed under hospitalization. Small bowel obstruction

Table 5. Complete Response after Radiotherapy

Recurrent site	External RT only (%)	External RT + ICR* (%)	Total (%)
Remnant vagina	3/3 (100.0)	15/16 (93.8)	18/19 (94.7)
Vag + PM/side wall	4/9 (44.4)	8/12 (66.7)	12/21 (57.1)
Parametrium/side wall	5/7 (71.4)	–	5/ 7 (71.4)
Total	12/19 (63.2)	23/28 (82.1)	35/47 (74.5)

* ICR : intracavitary radiotherapy

Table 6. Overall Treatment Failure

Recurrent site	LF * (%)	LF + DM** (%)	DM (%)	Total
Remnant vagina	3/19 (15.8)	1/19 (5.3)	1/19 (5.3)	5/19 (26.3)
Vag + PM/side wall	9/21 (42.9)	3/21 (14.3)	0/21 (0)	12/21 (57.1)
Parametrium/side wall	2/ 7 (28.6)	0/ 7 (0)	0/ 7 (0)	2/ 7 (28.6)
Total	14/47 (29.8)	4/47 (8.5)	1/47 (2.1)	19/47 (40.4)

* LF : locoregional failure
** DM : distant metastasis

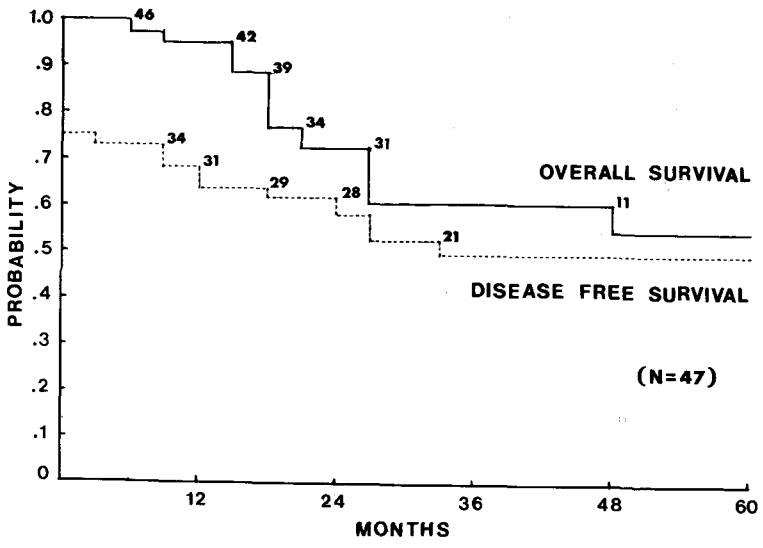

Fig. 1. Actuarial overall and disease free survival.

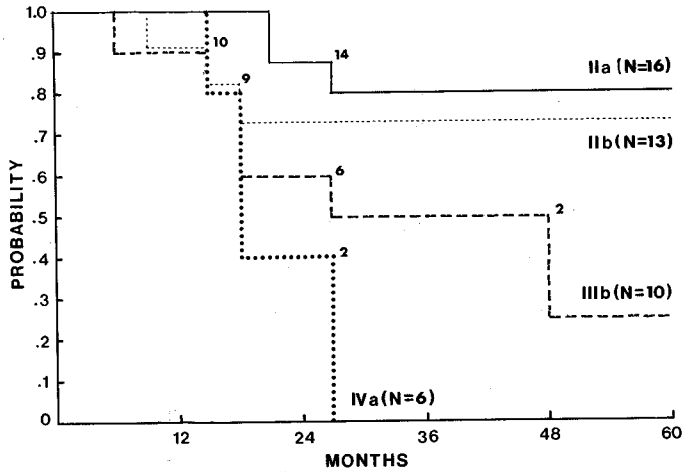

Fig. 2. Actuarial overall survival according to equivalent FIGO stage.

Table 7. 4 Year Actuarial Survival Rate According to Various Factors

Factors (No. of patients)		4 year survival rate (%)	P-value
Age			
Over 50 years	(29)	55.2	
Under 50 years	(18)	47.1	0.62
Initial stage (FIGO classification)			
0, Ia, Ib	(26)	50.2	
IIa, IIb	(17)	64.1	0.38
Interval to recurrence			
Over 24 month	(17)	55.2	
Within 24 month	(30)	52.9	0.38
Recurrent site			
Remnant vagina	(19)	77.0	
Vagina + PM/side wall	(21)	44.1	Vag vs. PM & PM + Vag (0.01)
Parametrium/side wall	(7)	42.9	
Equivalent FIGO stage			
IIa	(16)	80.4	
IIb	(13)	73.0	IIa vs. IIb (0.66)
IIIa	(2)	50.0	IIa vs. IIIb + IVa (0.002)
IIIb	(10)	25.0	IIb vs. IIIb + IVa (0.002)
IVa	(6)	0.0	
Histopathology			
IIa, IIb extent			
squamous			
large non-keratinizing	(10)	100.0	0.0002
large keratinizing	(11)	50.5	
III, IVa extent			
squamous			
large non-keratinizing	(7)	33.8	0.84
large keratinizing	(7)	28.5	

developed in one patient and this patient was treated surgically.

DISCUSSION

Radical hysterectomy with pelvic node dissection is a well accepted mode of therapy for uterine cervical cancer of FIGO stage Ib and IIa and the treatment result is comparable to that after radiotherapy. Recurrence develops in 10 to 20% of the patients, and the recurrence is limited to the pelvic cavity in 15 to 35% of the cases[1~3]. These group of patients can be candidates for intensive local radiotherapy and relatively good rate of salvage can be expected.

The reported results of radiotherapy for locally recurrent uterine cervical carcinomas after surgery varies widely. Barber et al analyzed 222 patients with recurrent uterine cervical carcinomas after definitive surgery. Of the 23 patients with localized pelvic recurrences who were treated with radiation, only 4 patients (17.3%) were alive at 5 years following radiation[4]. Krebs et al reported 15.8% 5-year survivors out of 19 such patients[1]. Deutsch et al reported 15.7% disease free survival at 2.5 years among 38 such patients[5]. In contrast to these poor results, Friedman et al reported 42% 5-year disease free survival in 38 patients[6]. These wide variation of reported results of radiotherapy for localized recurrent uterine cervical cancer is due probably to wide variation in distribution of tumor volume and site of recurrences. It is clear that site of recurrence is a very important prognositic factor. Recurrences limited to central portion or vagina is favorable over recurrences involving other portion of pelvic cavity. Krebs reported 18% and 13%[1], Deutsch reported 38% and 4%[5], and Friedman reported 50% and 17%, for central recurrences and others, respectively[6]. In our study the 4 year survival was 77% and 43% for the two groups. This marked difference seems to be due to early detection and smaller volume of vaginal recurrences and more adequate radiotherapy with combined external beam and intracavitary or interstitial radiation. This is reflected in the survival rate along the equivalent FIGO stage classification. This method of classification looks quite useful as well as the classification by Munnell and Bonney[2]. They classified into 6 groups: central pelvic recurrence limited to vagina, deep pelvic recurrence in lateral parametrium and/or pelvic node, bladder or rectal wall invasion, peripheral pelvic recurrences (inguinal nodes, pelvic bone, lumbosacral vertebrae), distant metastasis with pelvic recurrence, and distant metastasis. The classification along the equivalent FIGO staging system is actually not much different from this and is easier to use and memorize. And moreover, the result of each stage in this study is not much different from that of equivalent stage in our previous report on radiotherapy result of primary uterine cerivcal carcinomas[7].

Better survival of patients with large cell nonkeratinizing squamous cell carcinoma compared to keratinizing variety after radiotherapy has been reported, especially in earlier stage diseases[8~10]. In this study of recurrent carcinoma the same tendency could be demonstrated.

Whole pelvic irradiation followed by brachytherapy or small field external beam irradiation seems to be adequate in most cases. Evans, in the analysis of unresectable recurrent disease, found very high incidence of para-aortic node metastasis and suggested the need of irradiation of para-aortic node region[11]. But in our study, no instance of para-aortic node metastasis was detected on computed tomographic study performed in 8 patients. Further, distant metastasis develped only in 5 patients. And so, inclusion of para-aortic node in radiation field does not seem to be justified.

In summary, locally recurrent uterine cervical cancers after surgery can be controlled in relatively good proportion by well planned radiotherapy along the site and extent of the recurrent disease. And the survival might be comparable to that of initial radiation treatment of uterine cervical carcinomas when compared by equivalent stages.

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=국문초록=

수술후 재발된 자궁경부암의 방사선 치료

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수술후 골반강내에 국소재발된 자궁경부암의 진단하에 1979년부터 1984년까지 6년간 서울대학교 병원 치료방사선과에서 방사선치료를 시행한 47명의 환자에 대하여 후향적 분석을 시행하여 다음과 같은 결과를 얻었다.

1. 방사선치료후 완전관해를 보인 환자는 35명으로 완전관해율은 74.5%이었다.
2. 완전관해를 보인 35명중 7명에서 국소재발 또는 원격전이를 보여 전체적으로 19명(40.4%)의 환자에서 치료실패를 나타내었다.
3. 4년 무병생존율 및 전체생존율은 각각 50.1 및 55.2%이었다.
4. 병소의 범위를 자궁경부암에 적용되는 FIGO병기 결정기준에 의하여 분류한 결과 각 병기에 따른 4년 생존율은 IIa기에서 80.4%, IIb기에서 73.0%, IIIb기에서 25.0%, IVa기에서 0%이었다.

따라서 수술후 골반강내에 국소재발된 자궁경부암의 경우 적절한 방사선치료를 시행함으로써 좋은 결과를 얻을 수 있음을 알 수 있었다.