The Role of Radiation Therapy in Adenocarcinoma of Endometrium

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From May, 1979 to October, 1987, 38 patients with endometrial carcinoma were treated with radiotherapy at Seoul National University Hospital. Of these, 32 patients received radiotherapy postoperatively, one received radiotherapy preoperatively, and five received radiotherapy only. Relative frequencies of obesity, nulliparity, late menopause, diabetes mellitus, and hypertension were all higher than those reported in normal women in Korea, and those of obesity, diabetes mellitus, and nulliparity were significantly high. The overall actuarial five-year survival rate was 75. 6%. The overall actuarial five year survival rates of stage I (22 cases), stage II (six cases), and stage III (10 cases) were 90.0%, 80.0%, and 44.4%, respectively, and were significantly different from each other. Among various factors, stage only proved to be prognostic by multivariate analysis. There were two local failures, three local failures combined with distant metastasis, and three distant metastasis. Stages I and II could be adequately controlled by local modalities without severe complications, stage III endometrial carcinoma might need more aggressive treatment for better survival.

Key Words: Radiation therapy, Adenocarcinoma of endometrium

INTRODUCTION

Endometrial carcinoma is a relatively rare disease in Korea, but one of the most common gynecologic cancers in Western countries. Unlike Carcinoma of the uterine cervix, carcinoma of the endometrium is more frequently found in nulliparous women and usually occurs in postmenopausal women, especially in women with late menopause. A high proportion of patients with endometrial carcinoma are obese, diabetic, hypertensive, and elderly¹⁾.

Several factors such as histologic type, degree of histologic differentiation, uterine size, stage, depth of myometrial invasion, stage of peritoneal cytology, and lymph node or adnexal metastasis were known to have prognostic value.

Relative frequencies of combined factors, survival patterns, and correlationship of survival with some parameters were analyzed in patients who were treated with radiation at Seoul National University Hospital.

MATERIALS AND METHODS

Thirty-eight patients with endometrial carcinoma completed radiotherapy at the Department of Therapeutic Radiology, Seoul National University Hospital, between February, 1979 and October, 1987. Of 38 patients, 31 (81.6%) were followed up, but seven patients were lost to follow-up.

Characteristics of patients are shown in Table 1. Their ages ranged from 24 to 73 years, and 52.6% of them were in their 50's. Diagnosis was confirmed by fractional dilatation, curretage and biopsy, and the most common histologic subtype was adenocarcinoma (73.7%). Among 26 patients whose histologic differentiation was defined, the number of grades 1,2, and 3 was 8,12, and 6, respectively. For staging, chest PA, IVP, colon study, cystoscopy, sigmoidoscopy, and CT were done, and the number of patients with stage I by FIGO system²⁾ was 22, stage II was six, and stage III was 10. Of stage I patients (22), four (18.2%) had histologic grade 1, nine (40.9%) had grade 2, five (22.3%) had grade 3, but histologic differentiation was not specified in four patients.

Of stage I patients (22), 21 were operated on and received postoperative radiotherapy (RT), while one with diabetes mellitus (DM) received RT only. Of stage II patients (6), one with hypertension received RT only, one received preoperative RT and operation (Op), and four received Op and post-op RT. Of stage III patients (10), three received RT only and seven received Op and post-op RT.

Thus five patients received RT only, 32 received OP and post-op RT, and one received pre-op RT and scheduled TAH six weeks later.

For 32 patients treated with postoperative radiotherapy, the procedures of operation were total abdominal hysterectomy (TAH) and bilateral salpingoophorectomy (BSO) in 14 patients, Wertheim's operation in 12, TAH and lymph node dissection (LND) in one patient, and TAH plus BSO and LND in five patients. According to pathologic examination, the depth of myometrial invasion increased as the histologic grade increased (Table 2). Among 18 patients who had LND during operation, lymph nodes were involved in three (2/3 in stage II, 1/2 in stage III, but 0/13 in stage I). In stage I, one patient with grade 1 without myometrial invasion or lymph node involvement and two other patients with grade 1, with myometrium invasion into the inner 1/3 without lymph node metastasis, were delivered with post-Op RT because surgeons in outside hospitals strongly recommended adjuvant treatment.

External radiotherapy by conventional fractiona-

Table 1. Characteristics of Endometrial Cancer Patients

Feb. 1979- Oct. 1987, SNUH

Characteristics	No. of Patients (%)
Age	
20 – 29	1 (2,6)
30 – 39	4 (10.5)
40 – 49	5 (13,2)
50 — 59	20 (52.6)
60 – 69	6 (15.8)
70 – 79	2 (5.3)
Histology	
Adenocarcinoma	28 (73.7)
Adenosquamous carcinoma	a 7 (18.4)
Adenoacanthoma	3 (7.9)
Histologic Grade	
G1	8 (21.1)
G2	12 (31.6)
G3	6 (15.7)
Unspecified	12 (. 31,6)
Stage	
I .	22 (57.9)
IE.	6 (15.8)
111	10 (26.3)
Total	38 (100.0)

tion was done with a linear accelerator or Co 60 teletherapy unit using AP: PA parallel opposing ports in 33 patients or four fields box technique in five patients. Field included paraaortic node in one patient (45 Gy) and whole abdomen in one patient (20 Gy). The total external pelvic dose was equal to or greater than 50.4 Gy in 31 patients and lower than 50.4 Gy in seven patients. Nineteen patients were also treated with intracavitary radiotherapy (ICR) with Fletcher-Suit apparatus after external radiotherapy (Table 3). When radiotherapy alone was delivered, external RT and ICR were routinely combined (dose to point A was over 85 Gy in two cases and under 85 Gy in two cases), except in one case who refused ICR and received 45 Gy to the paraaortic node area and 50.4 Gy to the whole pelvis. When radiotherapy was delivered with postoperative adjuvant aim, an ICR was indicated when the vaginal resection margin was involved by tumor or when risk for vaginal recurrence was high that is, grade 3, myometrial invasion into the outer 1/3, or long uterine canal (over 8 cm). The total external dose was equal to or greater than 50.4 Gy in 15 out of 17 cases who got post- op radiotherapy without ICR, while the total dose was equal to or greater than 85 Gy at the vaginal surface in 10 out of 15

Table 2. Depth of Myometrial Invasion and Histologic Grade in Endometrial Cancer Patients Who Had Postoperative Radiotherapy

Depth		1	Histolo	gic Grade	
Invasion	1 11		Ш	Unknown	Total
0	2	1	1	2	6
Inner 1/3	4	5	1	1	11
Mid 1/3	. 1	2	1	0 -	4
Outer 1/3	1	3	3	2	9
Unknown	0	1	0	1	2
Total	8	12	6	6	32

Table 3. Methods of Radiotherapy for Endometrial Cancer by Treatment Aim

Radiotherapy Aim	External Alone	External and ICR
Primary	1	4
Postoperative	17	15
Preoperative	1	0
Total	19	19

Table 4. Relative Frequencies of Factors Combined with Endometrial Carcinoma

Factors	No. of Patients (%)				
	Present	Absent	Unknown		
Hypertension	5 (13.2)	6 (15.8)	27 (71.0)		
Menopause	20 (52.6)	6 (15.8)	12 (31.6)		
DM	7 (18.4)	21 (55.2)	10 (26.4)		
Nulliparity	6 (15.8)	19 (50.0)	13 (34.2)		
Obesity	16 (42,1)	16 (42,1)	6 (15.8)		

Table 5. Relative Frequencies of Combined Factors with Endometrial Carcinoma in Comparison with Those from Normal Korean Women

Factors	Relat Fre	ive equency (%)	OMAL - Panal	
	Pati- ents	Normal Women	P Value (###)	
Hypertension	13.2	8.8 (*)	> 0.05	
Late menopause	35.0	12.8 (**)	> 0.05	
DM	18.4	1.0 (***)	< 0.05	
Nulliparity	15.8	1.3 (#)	< 0.05	
Obesity	42.1	2.5 (##)	< 0.05	

(*) Ref. 7, (**) 8, (***) 9, (#) 10, (##) 3, (###) by Student t—test

cases who got post-op RT with ICR.

In this study, DM was defined when a patient was under medical management of the previously diagnosed DM, her level of fasting blood sugar was greater than 140 mg/dl, or her level of random blood sugar was greater than 200. Hypertension was defined when a patient was under medical management of diagnosed hypertension or her blood pressure was greater than 150/100. A patient was considered obese based on a 1977 "ideal body weight chart"3) for Korean women in which height and weight are the major factors in determining ideal body weight. Late menopause was defined as occurring after 52 years of age. Women who had no history of full-term delivery were considered as nulliparous one. We used the life table method4) to get actuarial survival rates, the logrank test5) for univariate analyses and the BMDP package using Cox's proportional hazard model for multivariate analyses6).

Table 6. Actuarial Survival of All Endometrial Cancer Patients by Various Factors

Factors	No. of patients	Five-year Survival Rate (%)	P Value*
Histologic Grade			
G1	8	85.7	>0.05
G2	12	90.9	
G3	6	66.7	
Unspecified	12	58.0	
Histology			
Adenocarcinoma	28	74.7	>0.05
Adenosquamous Ca	7	83.3	
Adenoacanthoma	3	100.0	
Hb Level			
<12 g/dl	20	76.3	>0.05
≥12 g/dl	16	78.1	
Unknown	2	0.0	
Total	38	76.5	

^{*} p value by logrank test 5)

RESULTS

1. Relative Frequencies of Combined Factors

Relative frequencies of hypertension, late menopause, DM, nulliparity, and obesity were 13. 2%, 35.0%, 18.4%, 15.8%, and 42.1% respectively (Table 4). Of 20 women who experienced menopause, seven (35%) had late menopause. Relative frequencies of all factors were higher than those reported in normal women in Korea since 1976 when age and sex were adjusted^{3,7~10}, but the proportional difference of relative frequency was significantly higher in our patients in factors of obestiy, nulliparity, and DM (Table 5).

2. Survival

The overall actuarial surviral rate at five years was 75.6%. Five-year actuarial survival rates of patients with stage I, II, and III were 90.0%, 80.0%, and 44.4%, respectively. Survival differences were significant among stages I, II, and III by logrank test and were also significant between stage I and II and stage III by Cox's proportional hazard model (Fig. 1, 2). In stage I, the survival rate was not influenced by histologic grade; survival rates of four patiens with grade 1, two patients with grade 2, five patients with grade 3, and four patients with unspecified grades were 100.0%, 100.0%, 80.0%, and 75.0%, res-

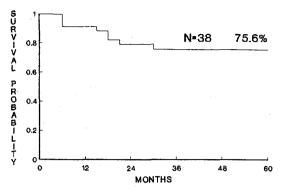


Fig. 1. Overall actuarial survival of endometrial cancer.

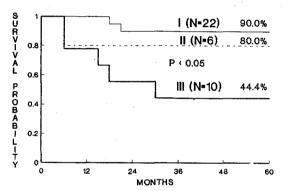


Fig. 2. Actuarial survival of endometrial cancer by FIGO stage.

pectively. The differences of the overall actuarial five-year survival rates according to histologic subtype, histologic grade, and hemoglobin level was not statistically significant as shown in Table 6.

The actuarial survival rate at five years with radiotherapy alone was 50.0%, and the survival difference was not found according to any factors.

A survival rate at five years with postoperative radiotherapy was 82.3% for all patients, 89.5% for stage I, and 67.5% for stages II and III. Survival according to depth of myometrial invasion and LN status are shown in Table 7. When ICR was included in post- op RT (15 cases), the five-year actuarial survival rate was 80.0%, and when ICR was excluded from post- op RT (17 cases), the five year actuarial survival rate was 84.6%. Survival difference by lymph node status was significant by logrank test (p<0.05) but not significant by Cox's proportional hazard model. The depth of myometrial invasion didn't result in a survival difference by both methods.

Table 7. Actuarial Survival of Endometrial Cancer Patients Who Had Postoperative Radiotherapy by Depth of Myometrial Invasion and Lymph Node Metastasis

	No. of Patients	Five-year Survival Rate (%)	P value*
Myometrial Invasion (N=32)			
0	6	71,4	>0.05
Inner 1/3	11	90.5	
Mid 1/3	4	100,0	
Outer 1/3	9	76.5	
Unknown	2	50.0**	
LN Metastasis (N=18)			
Positive	3	33.3	<0.05
Negative	15	100.0	
All Post-Op RT Cases	32	82.3	·

- * p value by logrank test 5)
- ** three-year survival rate

Of eight confirmed failures, the failure pattern was local failure in two cases, distant failure in three cases (liver, PAN, and peritoneal seeding), and local and distant failure in three cases (abdominal wall, peritoneal seeding, and lung) (Table 8).

3. Complications

A total of two complications of rectal bleeding were confirmed, and thus the five-year actuarial complication rate was 8.5%. In one patient with stage II, bleeding appeared 31 months after radio-therapy and disappeared two years after its onset without medical intervention. In another patient with stage I G2, rectal bleeding appeared 19 months after Wertheim's Op and post-op RT and disappeared 31 months after its onset with medical management.

DISCUSSION

When adjusted to age and sex, the relative frequencies of the combined factors in our patients were higher than those reported in normal Korean women since 1976^{3~10}).

In Western countries, the relative frequencies of combined factors showed different patterns. Reported frequencies of nulliparity in endometrial cancer patients ranged from 35~43.5%^{1,11,12)}. The frequency of nulliparity in our series, 13.3%, was

Table 8.	Failure	Pattern	of	all	Endometrial	Cancer
	Patients	by Stag	e ar	nd T	reatment Met	hod

	N	Local Failure	Distant Failure	Local + Distant
Stage				
i	22	0	1	1
11	6	0	1	0
tu tu	10	2	1	2
Methods				
RT	5	1	0	1
OP+RT	32	1	2	2
RT+OP	1	0	1	0
Total	38	2	3	3

lower than those of Western studies, but the possible difference in parity between the Orient and the West must be considered.

There have been suggestions that menopause is delayed in the average cases of endometrial carcinoma. According to Grossen and Hobbs, the frequency of menopause at age 50~55 years is 60% in the endometrial cancer patients, while the frequency is 15% in normal women¹⁾. But in interpreting these results, the fact that irregular vaginal bleeding after menopause may be a result of malignancy and may be misinterpreted by the patients as being a continuation of normal menses must be considered. For this reason, in the cases of endometrial carcinoma, it is very easy to obtain a false history of delayed menopause.

Moss reports a 17% frequency of obesity in his series, and some other series report a 28~35% frequency of obesity. There are suggestions that many patients with endometrial carcinoma are of the lateral-build heavy-weight body type, the so-called "small hands and feet and large hip woman", and someone else implies those are manifestations of endocrine disturbances.

Scheffey et al. reports an 11% incidence of diabetes¹¹⁾, and someone else has suggested a higher incidence of hypertension in endometrial cancer patients¹⁾. These two factors have been noted as hindering operability and may have some relationship to obesity.

From the above discussions and our results, it follows that postmenopausal bleeding in obese, hypertensive women who have a diabetic tendency should be examined more carefully to detect endometrial carcinoma.

Approximately 20~30% of patients with endometrial carcinoma eventually die of the disease. Known poor prognostic groups include patients with stage III and IV disease, recurrent tumors, and clinical stage I and II disease with positive paraaortic or pelvic nodes, deep myometrial invasion, poorly differentiated (high grade) tumors, positive peritoneal cytology, and positive adnexal metastases^{13~30)}. The histologic type is also a prognostic factor in some studies¹⁸⁾. In stage II, some suggest that the extent of cervical involvement is of significant prognostic value, while others do not agree^{26,29)}.

Many studies also report that some of these factors are correlated. For example, stage and lymph node metastasis, and grade and myometrial invasion are known to be correlated.

In our study, grade and myometrial invasion, and stage and lymph node metastasis showed positive correlations.

Stage and lymph node metastasis were correlated with survival, and all three cases with adenoacanthoma, which, known to have a better prognosis than other subtypes, showed better prognosis. However, in a multivariate analysis using Cox's proportional hazard model, stage only proved to be prognostic.

The survival rates of our study were similar to other studies done recently.

In stage I, Wharam et al. report a 90.0% five-year actuarial survival rate in grade 1, 82% in grade 2, and 62% in grade 3¹³⁾. Stokes et al. report 94%, 80%, and 76% for grades 1,2, and 3, respectively¹⁴⁾. Other authors also reported five-year survival rates between 74% and 93%. Bedwinek et al. report 71% for the grade 3 group¹⁵⁾.

In stage II, the reported five-year actuarial survival rates range from $59.5 \sim 92\%$ for the surgery and radiation group and $42.3 \sim 71\%$ for the radiation alone group^{16,17,19)}.

Other authors report from 4.0~30.0% for clinical stage III and 44~59% for pathologic stage III²⁰).

In our series, all two failure cases of RT alone patients had local failure components. Most of the failed cases of the 33 combined treatment cases had distant metastasis components, and local failure alone occurred in one case. These data imply that combined radiotherapy and surgery may result in better local control. But in interpreting these data, the fact that the stage distributions of the two groups—were different must be considered, because the patients who were given radiotherapy alone were, generally, advanced cases or medically

inoperable cases.

Posthysterectomy vaginal vault recurrence is known to be associated with positive resection margin, high grade, deep myometrial invasion, and uterine canal length >8 cm³¹¹. So, in our series, patients with positive vaginal resection margin or patients with multiple high-risk factors received ICR as a part of postoperative radiotherapy. Also in our study, ICR, as a part of radiation therapy in the postoperative radiotherapy group, didn't affect the prognosis significantly, however, because the more risky patients received ICR and the case number was small, so any further suggestions were inadequate.

Stoke reports that in stage I disease, the pelvic failure rate is 2%, simultaneous pelvic and distant failure rate is 2%, and the distant failure rate is 4%, respectively¹⁴). Other studies report a $2.4\sim6\%$ pelvic failure and a $4.5\sim7\%$ distant failure in stage I disease.

In stage II disease, Grigsby reports that pelvic failure, pelvic and distant failure, and distant failure alone occur in 1.1%, 7.8%, and 13.3%, respectively, in the combined radiation and surgery group; while pelvic failure, pelvic and distant failure, and distant failure alone occur in 7.7%, 26.9%, and 11.5%, respectively, in the radiotherapy only group¹⁶⁾. Other studies also report that total pelvis failure is 5~17.5% and total distant failure is 10.5~15% for the radiation and surgery group, total pelvis failure is 18.4~37.5% and total distant failure is 25~34.2% for the radiation alone group.

Danoff et al. report two local failure cases, nine distant failure cases, and five local and distant failure cases from 32 cases with stage III who received radiotherapy as prime treatment²⁰.

In our series, all failures occurred within three years, and most of them occurred within two years (Fig. 1,2). Danoff et al. report the same tendency as our results. They also recommend adjuvant chemotherapy for clinical stage III patients because the onset of recurrence is rapid, and distant metastasis is the main failure pattern20). In advanced endometrial cancer, progestational agents, antiesterogenic tamoxifen, and combination chemotherapy reveal a 20~40% response, respectively, and whether the use of combinations of hormones with chemotherapeutic agents enhances the antitumor effect significantly remains unsolved32~34). It has been recommended to use these agents on an adjuvant basis either prior to and/or following radiotherapy²⁰⁾, but because of the poor response rates of the agents, it is imperative that chemotherapeutic agents useful in endometrial cancer be developed.

In our study, the five year actuarial complication rate was 8.5%, and two complications were radiation colitis after external radiotherapy and ICR with rectal dose of 77.84 Gy and 74.6 Gy; however, surgical intervention was not required to manage them. Stokes et al. show an 8.8% rate of serious complication, such as bowel obstruction in their stage I series with combined operation and external radiotherapy³⁰. Grigsby et al. report a 7% incidence of major complications in the combined surgery and radiotherapy group and 19% for the irradiation alone group¹⁶.

In conclusion, our survival results showed that, in stages I and II, the disease could be adequately controlled by local modalities without severe complications, but stage III might need more aggressive treatment.

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- 국문초록 -

자궁 체부암의 방사선 치료

서울대학교 의과대학 치료방사선과학교실, 산부인과학교실* 윤형근 • 하성환 • 강순범* • 이효표*

1975년 5월부터 1987년 10월까지 38명의 자궁 체부암환자가 서울대학교 병원 치료방사선과에서 근치적 방사선 치료를 받았다. 이 중 32명은 수술 후 방사선 치료를, 1명은 수술 전 방사선 치료를, 5명은 방사선 치료만을 받았다. 전체 환자에서의 비만, 52세 이후의 늦은 월경, 만삭 임신이 없었던 경우, 당뇨병, 고혈압 등의 빈도는 정상 한국 여성들에서의 빈도보다 높았다. 그 중 비만, 당뇨병, 늦은 월경 등의 빈도는 유의하게 높았다. 전체 환자의 5년 생존율은 75.6%였고 FIGO 병기 I, II기 및 III 기에서의 생존율은 각각 90.0%, 80.0% 및 44.4%였고 조기병기(I, II기)와 진행병기(III기)의 생존율은 Cox의 다변량 분석법으로 분석한 결과 유의한 차이가 있었다. 자궁 체부암으로 사망한 것이 확인된 8예 중 원발병소의 치유실패나 재발로 인한 경우가 2예, 원격전이로 인한 경우가 3예, 두 가지 동반된 경우가 3예였다. 자궁 체부암 I, II기는 방사선 치료와 수술등의 국소적 치료방법으로 중중의 부작용없이 양호한 치료 성적을 얻었으나 III기에서는 더 적극적인 치료가 필요할 것으로 생각된다.