Adenocarcinoma of the Uterine Cervix

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Survival data, prognostic factors, and patterns of failure were retrospectively analyzed for a total of 76 patients with adenocarcinoma of the uterine cervix treated between January 1981 and December 1987, which represents 4.1% of all primary cervical carcinomas treated, at Department of Radiation Oncology, Yensei Cancer Center, Yonsei University College of Medicine. The mean age of the patients was 49 years (range, 27~79 years) and the peak incidence was in the group 50 to 59 years of age. More half of the patients were postmenopausal (46/76=60.5%). Most patients (76%) had abnormal vaginal bleeding either alone or in combination with other symptoms. The proportion of stage IIb was 43.4%. There were 4 major histologic subtypes: pure adenocarcinoma (48/76=63.2%), adenosquamous carcinoma (20/76=26.3%), papillary (5/76=6.6%) and clear cell carcinoma (3/76=3.9%). Of the many clinicopathologic variables evaluated for prognosis, the most significant prognostic factors were stage of disease and the size of tumor.

The overall 5-year survival rate was 68%, and the 5-year survival rates for stage Ib, II and III were 90%, 66% and 54%, respectively. Control of pelvic tumors was achieved in 93.8%, 90.2% and 50.0% of cases of stage Ib, II and III disease, respectively. In present study, treatment modalities (radiation therapy alone/combined operative and radiation therapy) did not affect the local control of tumor and the survival.

Key Words: Adenocarcinoma of cervix, Tumor size, Stage of the disease

INTRODUCTION

Adenocarcinoma of the uterine cervix is the second most frequent histologic classification of cervial malignancies, accounting for 3~34% of all cervical carcinoma[1~11]. The relative frequency of these tumors appears to be increasing in recent years as compared to the squamous carcinoma[5~11]. Among many gynecologic and radiation oncologists, controversy exists regarding the relative values of radiation therapy versus radical surgery in the treatment of these patients.

Although several investigators have achieved similar results with either treatment modalities combined[3,10,12,13], most reports have showed improved survival with radical surgery or combined modalities as compared with radiation alone[1,2,14~16]. Rutledge et al[14] showed a significant survival advantage in stage II adenocarcinoma of the uterine cervix with radiation plus extrafascial hysterectomy, compared to radiation alone.

In spite of the multiplicity of reports examining cervical adenocarcinoma, only recently have investigators focused on such prognostic factors as tumor grade, histologic subtype, lesion size, depth of invasion or lymph node involvement in analysing survival data[2,10,13,16~18].

In the current report, we analyzed retrospectively 76 cases of cervical adenocarcinoma treated at our department from 1981 to 1987.

MATERIALS AND METHODS

1. Patients Characteristics

Clinical characterictics of patients are listed in Table 1. Their ages ranged from 27 to 79 years and the most prevalent age was the sixth decade (50%). Diagnosis was confirmed by punch biopsy. All patients had routine base-line work up including pelvic examination, CBC, urinalysis, liver function profiles, electrolyte, chest X-ray, IVP, cystoscopic and colonoscopic examination, CT scan. Staging was determined by FIGO staging system.

Forty six (60.5%) patients were postmenopausal. The main symptom was abnormal vaginal bleeding (76.4%). Vaginal discharge was the only symptom in seven (9.2%) of the patients and 8(10.5%) had both abnormal bleeding and

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Table 1. Patient Characteristics (No. of patients : 76, 1981–1987)

		No. of patients (%)
Age (years)	20–29	1 (1.3)
	30–39	7 (9.2)
	40–49	24 (31.6)
	50–59	38 (50.0)
	60–69	5 (6.6)
	70–79	1 (1.3)
Menopause status		
	premenopause	30 (39.5)
	postmenopause	46 (60.5)
Histologic Subtype		
	adenoca. WD, MD	37 (48.7)
	adenoca. PD	11 (14.5)
	adenosquamous	20 (26.3)
	papillary	5 (6.6)
	clear cell	3 (3.9)
Differentiation		
	WD & MD	47 (61.8)
	PD & Undiff.	29 (38.2)
Stage		
	Ib	16 (21.0)
	IIa	8 (10.5)
	IIb	33 (43.4)
	IIIa	0 (0.0)
	IIIb	14 (18.4)
	IVa	5 (6.6)
Size of tumor		
	< 3 cm	11 (14.5)
	3 – 6 cm	49 (64.5)
	> 6 cm	16 (21.0)
Shape of tumor		
	exophytic	33 (43.4)
	Infiltrative	43 (56.6)
Pelvic LN status		
	negative	71 (93.4)
	positive	5 (6.6)
Treatment modality		
	RT alone	59 (77.6)
	OP + RT	17 (22.4)

vaginal discharge. Only three (3.9%) of the patients were totally asymptomatic. The histologic pattern was pure adenocarcinoma in 48(63.2%) patients and adenosquamous carcinoma in 20(26.3%). The size (the greatest diameter) of the tumor was estimated roughly in the first clinical examination. Fifty-nine patients received primary radiotherapy and the other 17 patients had operation and postoperative adjuvant radiotherapy.

In operative patients, the size of the tumor was estimated in the pathologic specimen. In eleven (14.5%) patients the size of tumor was under 3 cm, in 49(64.5%) it was 3 to 6 cm, and 16(21.0%) it was over 6 cm. No correlation between the size and differentiation of the tumor was seen.

The proportions of stage I, II, III and IV were 21.1% (16 patients), 53.9% (41 patients), 18.4%(14 patients) and 6.6% (5 patients), respectively. Diagnosis of lymph node metastases were made by CT scan or lymphangiography, and operative pathologic specimen in the operative cases. Because of the lack of the operative case (only 17 patients) lymph node metastases were found in only 5 of 76 patients (6.6%).

2. Treatment Methods

External pelvic irradiation by conventional fractionation was performed with a 10 MeV linear accelerator X-ray or Co-60 teletherapy unit using four fields box technique or AP/PA parallel opposing ports. The total external pelvic dose was equal to or greater than 4400~4500 cGy.

In forty six patients, HDR ICR (high-dose-rate intracavitary irradiation) was performed with a Co-60 remotely controlled afterloading system (Ralstron, manufactured by Toshiba, Japan), and in 18 patients LDR ICR (low-dose-rate intracavitary irradiation) was perfomed with a Henschke applicator using radium sources. When radiotherapy was delivered with postoperative adjuvant aim, an ICR was indicated in case that the vaginal resection margin was involved by tumor or that risk for vaginal recurrence was high. So only 5 of 17 postoperative cases were treated with ICR. The dose of whole pelvis irradiation and ICR was altered according to the stage of disease.

3. Follow-up and Statistical Analysis

The patients were followed up every three months during the first two years and every six months thereafter. In the cases lost of follow-up even by telephone calls to patients' relatives, we could confirm their vital status from the family registration in their local and hometown addresses.

Sixty seven patients among 76(89.5%) were followed for more than four years or until death by the clinical assessment and/or telephone or mail. Survival rates were calculated by the Kaplan-Meier

method, and prognostic factors were evaluated with univariate analysis (log-rank test). But multivariate analysis was not performed because of small size of the analyzed data.

RESULTS

Initial response to radiotherapy was assessed at three months after the completion of radiotherapy. The overall comlete response rate was 85.5% and the CR rate by the stage were outlined in Table 2.

The overall 5-year survival rate was 68%(Fig. 1). Several prognostic factors affecting survival were analyzed in the patient group treated with radiotherapy. For the univariate analysis, patients were categorized by size of tumor, tumor characteristics (shape of tumor), pathologic subtype, cell differentiation and treatment modalities, and survival rates according to each factor were analyzed by log-rank test (Table 3. and Fig. 2, 3).

The best prognostic factors were the size of the tumor and the stage of the disease. When the primary tumor size was under 3 cm, the 5-year survival rate was 91%, in tumors of 3 to 6 cm the

Table 2. Initial CR Rate After Radiotherapy

Stage	Total No.	No. of CR	(%)
Ib	16	16	100.0
II	41	39	95.1
III	14	9	64.3
IVa	5	1	20.0
Total	76	65	85.5

Table 3. Univariate Analysis of Prognostic Factors in the Patients of Cervical Adenocarcinoma

Variables	No. of pts	5 YSR (%)	p-value
Histologic subtype			
adenoca. WD & MD	37	65.4	
adenoca. PD	11	66.7	
adenosquamous	20	68.3	>0.1
papillary	5	75.0	
clear cell	3	45.0	
Size of tumor			
> 3 cm	11	91.0	
3 – 6 cm	49	66.3	<0.05
< 6 cm	16	47.1	
Shape of tumor			
Exophytic	33	67.9	>0.05
Infiltrative	43	72.8	
Differentiation			
WD & MD	47	73.5	>0.05
PD & UD	29	64.2	
Stage			
Ib	16	90.9	
II	41	66.0	<0.05
III	14	54.2	
IVa	5	0.0	
Treatment modality			
RT alone	59	64.0	>0.1
RT + op	17	71.0	

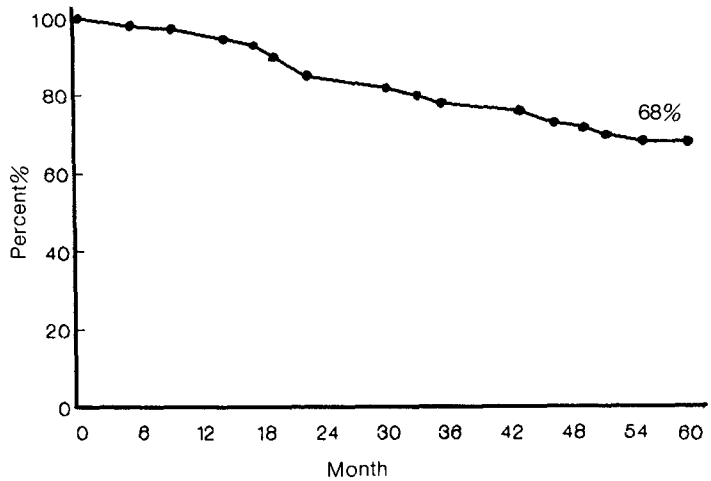

Fig. 1. Overall 5–YSR in adenocarcinoma of cevix.

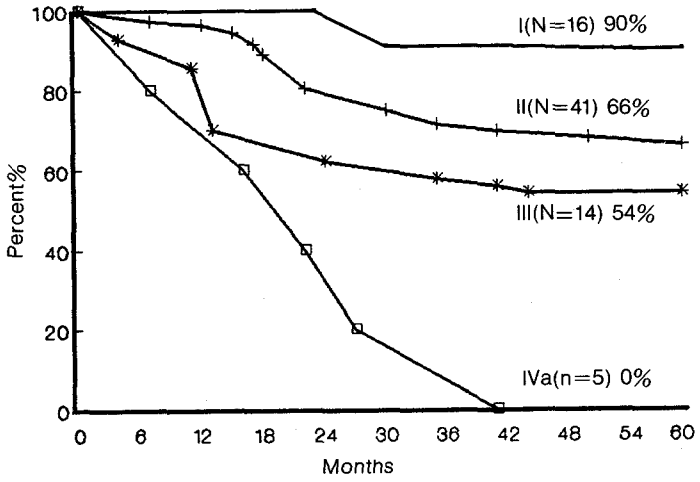

Fig. 2. 5–YSR by stage.

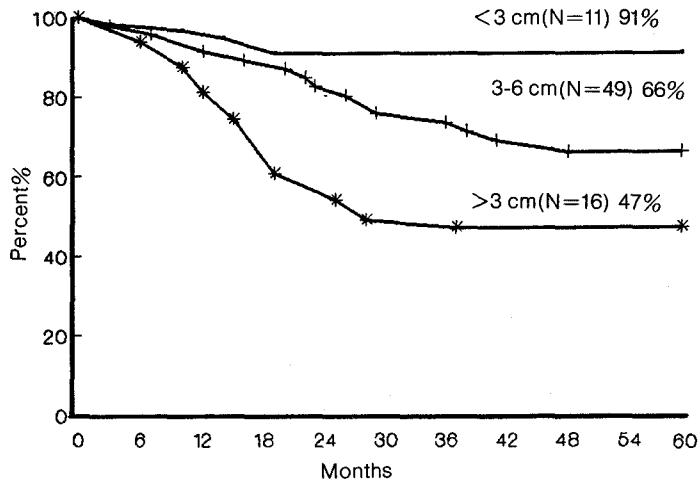

Fig. 3. 5–YSR by tumor size.

corresponding rate was 66%, and in tumors over 6 cm it was 47%, respectively. The difference of survival among these 3 groups was statistically significant ($p<0.05$). The 5-year survival rates for stage I to III were 90%, 66%, and 54% ($p<0.05$), respectively. There was no 5-year survivor in stage IV diasese.

The gross characteristics of tumor (shape of tumor), the differentiation of cell and the histologic subtype of the tumor did not correlate with the survival. The 5-year survial rate of patients treated by operation and radiotherapy was 71% and 64% among patients who were treated by radiation therapy alone, there was no significant difference($p>0.1$).

The pattern of recurrence as a function of stage is shown in Table 4. Pelvic control was achieved in 93.8% of stage I and 90.2% of stage II, but only 50% of stage III patients. Only one patient with stage Ib disease had local recurrence (1/16=6.3%), and it was noted at 15 months of diagnosis. Distant metastasis in the absence of pelvic tumor was observed in four patients, all of whom were stage IIb disease. The distant metastasis sites are follow as lung;1, paraaortic;1, bone;1.

Late bowel complications following radiotherapy were noted in 6.6% (5/76) of all patients. One patients with stage IIb disease required surgical management (transverse colostomy) due to severe rectal complication. The incidence of bladder com-

Table 4. Patterns of Failure by Stage of Disease

Stage	No. of pts	No. of F.	LF	LF + DF	Total LF (%)	DF
Ib	16	1	1	0	1/16 (6.3)	0
II	41	8	3	1	4/41 (9.8)	4
III	14	7	5	2	7/14 (50.0)	0
IVa	5	4	2	2	4/ 5 (80.0)	0
Total	76	20	11	5	16/76 (21.1)	4

LF : local failure, DF : distant failure

plication was 2.6% (2/76).

DISCUSSION

Adenocarcinoma of the uterine cervix account for 4.1% (76/1850) of the primary invasive cervical carcinoma treated at our department during this time period, similar to the 4~8% relative incidence reported in the literature[1~4]. Tasker and Collins[6] and later Tamini and Figge[11] reported an increasing relative incidence of adenocarcinoma compared to squamous lesions over the periods they studied, supporting the premise that this disease is becoming more common.

Berkowitz et al[19] reported that this lesion is becoming more common in the younger age group. This may, however, merely represent a relative increase as a result of the reduction of squamous lesions secondary to more widespread screening practices. Peter[8] reported that the overall increasing incidence of cervical adenocarcinoma in Los Angeles County was due to an increased incidence in women under the age of 35, and suggested that oral contraceptives might have a carcinogenic effect on cervical glandular cells.

In our present study, only 6.6% (5/76) of the patients were under 35 years of age, the mean age at diagnosis was 49 years, which is similar to that reported in the literature, 47 to 56.4 years[4,13,18,19], and not significantly different from the mean age of patients with squamous lesions.

The stage, tumor size, lymph node metastases and grade of differentiation are all well-known prognostic factors[2,10,11]. However, in our study only the size of the tumor and the disease stage did correlate with the survival whereas the other factors did not.

The actuarial 5-year survival rate for adenocarcinoma of the uterine cervix was 68%: for clinical stage Ib it was 90%, stage II, 66%, and stage III, 54%. The same figures for all cervical cancers treated in the same hospital according to a similar treatment protocol in 1979 to 1981 were 77.6%, 68.2%, and 50.9%, respectively[20].

Although these two investigations did not cover an identical period of time, the prognosis of adenocarcinoma seems to be equal or slight more favorable than that of squamous cell carcinoma[29]. In stage II adenocarcinoma the survival rate after radiotherapy was 66%. It was slight higher than other reports[21,29]. The reason for the good prognosis was slight higher than other reports[21,29]. The reason for the good prognosis was the tendency to overstaging in our department. These survival rates contrast with the findings of several investigators who have reported an inferior prognosis for adenocarcinoma compared with squmaous lesions[6,22,23].

As in previous studies histologic differentiation of adenocarcinoma was important in predicting survival[1,2,11,14,21,22]; well differentiated tumors tend to have better prognosis than poorly differentiated ones. However, in this series, well to moderately well differentiated and poorly differentiated or undifferentiated ones did not differ significantly in respect to survival rate.

Also in the present work, no significant differences between histologic subtypes of cervical adenocarcinoma were noted. Adenosquamous carcinoma accounted for 26.3% of all cervical adenocarcinoma and these lesions have at the least response to treatment similar to that of pure adenocarcinoma. This finding was in agreement with other series[11,13,21], and refuted by others reported[4,18,21,23,29]. Other small numbers of patients had poorly differentiated pure adenocarcinoma (11/76=14.5%), clear cell (3/76=3.9%), and papillary carcinoma (5/76=6.6%). Clear cell adenocarcinoma of the cervix had a prognosis comparable to that of other histologic type[21,29].

In previous reports, the frequency of lymph node metastases seems to be higher in adenocarcinoma[24~26]. The high frequency of lymph node metastases, however, indicates that adenocarcinoma are in fact more widely disseminated than squamous cell carcinoma. This suggests that the clinical staging proposed by FIGO does not accurately reflect the real extent of adenocarcinoma of the cervix. Also Doderlein[27] reviewed the literature and concluded that adenocarcinoma of the cervix has a greater tendency to lymphatic spread than squamous cell carcinoma and that it spreads to parametria as small streaks which cannot be palpated on bimanual pelvic examination. Too few patients had positive lymph nodes (5/76) to allow any statistical valid comparison to be drawn in our analysis. However, Saigo et al[18] observed lymphatic space invasion to be a strong predictor of poor outcome.

When the primary tumor size was under 3 cm the 5YSR was 91%, in tumors of 3 to 6 cm the corresponding rate was 66%, and in tumors over 6 cm it was 47%, respectively. We observed the similar results in many literatures[10,13]. The difference among these groups was statistically significant ($p<0.05$). But there was no significant difference according to the gross appearance of tumors (exophytic/infiltrative endophytic) and treatment modality.

The overall survival for the present group of patients is shown to be similar to that reported for squamous carcinoma of the uterine cervix[20,29]. Control of pelvic disease may be a better measure than survival in evaluating the relative radiosensitivity of adenocarcinoma compared to squamous carcinoma. If given equivalent radiotherapy techniques, adenocarcinoma are less responsive than their squamous counterparts, lower radiosensitivity should translate into higher pelvic recurrence rates (Table. 4).

Within the stage Ib disease, only one of the 16 patients treated with radiation alone (10 pts) or combined therapy (6 pts) recurred, yielding a pelvic control rate of 93.8%. Within stage II, three patients treated with radiation alone (31 pts) recurred, pelvic failure alone 2, pelvic & distant failure 1, were noted, yielding a pelvic control rate 90.3%. With more advanced disease such as stage III and IV, pelvic control was rarely achieved (8 out of 19). Perez et al[28] reported pelvic control in 94% of stage Ib, 83% of stage II, and 64% stage III patients. Goodman et al[13] reported similar results of 100% in stage Ib & 75% in stage II disease, respectively.

The pelvic control rate with early stage tumors reported in the literature is similar to that observed here. This agreement in ability to control pelvic disease, in conjunction with the excellent survivals observed, indicates a similarity in radioresponsiveness between squamous and glandular tumors. Differences in reported survival rates may therefore be attributable to differences in tumor volume, which has been shown to have an inverse relationship with tumor radiosensitivity[16].

Pure distant recurrences without loco-regional failure were unusual[13], noted in only 4 of 76 patients, all with stage IIb disease. Distant failures in this patients were noted in the lung(2), the bone(1) and the paraaortic nodes(1) and these distant metastases were developed within 3 years after radical radiotherapy. None of the patients with advanced disease recurred distantly.

In summary, 76 women with histologically confirmed adenocarcinoma of the uterine cervix were treated between 1981 and 1987. With univariate analysis, the stage of the disease and the tumor size were predictors of survival. Other possible well-known prognostic factors did not have any impact on survival.

Survival data and pelvic control rates were similar to those reported in the literature[29] for squamous cell carcinoma, suggesting a similarity in tumor biology and radiosensitivity between these two histologic types. In conclusion, this retrospective study suggests that the prognosis of patients with adenocarcinoma or squamous tumors treated by radical radiotherapy are for all practical purpose identical.

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= 국문초록 =

자궁경부선암의 방사선 치료

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1981년 1월부터 1987년 12월까지 연세대학교 의과대학 치료방사선과에서 침윤성 자궁경부암으로 방사선치료를 받은 총 1850명의 환자들중 조직학적 분류상 선암인 환자 76명(4.1%)을 대상으로 후향적인 임상분석을 하였다. 대상환자의 연령분포는 27세에서 71세까지로 평균 49세였고, 50~59세가 가장 많았다. 환자들의 주소는 대부분 이상자궁출혈(76%)이었으며, 병기의 분포는 FIGO 병기 Ⅰb, Ⅱa, Ⅱb, Ⅲa, Ⅲb 및 Ⅳa가 각각 16, 8, 33, 14, 5명으로 병기 Ⅱb가 43.4%로 가장 많이 차지했다. 조직학적 아형은 크게 4종류로 나눌 수 있었는데, 순수선암이 48명으로 가장 많았고, 선암과 편평상피암이 섞여있는 아형이 20명이었다. 방사선 치료후 3개월에 분석한 골반내 완전 관해율은 병기 Ⅰb, Ⅱ, Ⅲ에 대해 각각 100%, 95.1%, 64.3%였다. 선암의 조직학적 아형과 분화도, 자궁경부 종양의 크기 및 모양, 병기, 임파절 전이 여부, 치료방법(방사선 단독 및 수술과 방사선 병합요법)등에 따라 생존율을 분석한 결과 병기와 종양의 크기만이 생존율에 영향을 미치는 유의한 예후인자로 밝혀졌다.

전체 환자군의 5년 생존율은 68%였고 병기별로는 Ⅰb기(N=16)가 90%, Ⅱ기(N=41)가 66%, Ⅲ기(N=14)가 54%였으며 Ⅳa기(N=5) 환자군에는 5년 생존자가 없었다. 직장 합병증은 6.6%(5/76)로 이중 한명에서 수술요법을 시행하였고 방광의 합병증은 2례로 2.6%를 보였다. 이상의 결과로서, 자궁경부 선암은 편평상피암에 비해 그 치료성적이 나쁘지 않으므로 치료요법을 결정함에 있어 수술 및 방사선치료등 자궁경부 편평상피암과 같은 치료원칙에 따른다면 좋은 치료결과를 보일 수 있으리라 생각한다.