Pretreatment prognostic Factors in Early Stage Caricinoma of the Uterine Cervix

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From March 1979 through December 1986, 124 patients with early stage carcinoma of the uterine cervix received curative radiation therapy. According to FIGO classification, 35 patients were stage IB and 89 were stge II A. In stage IB, five year locoregional control, five year disease free survival, and five year overall survival was 79.0%, 76.4% and 81.8%, respectively. In stage II A, five year locoregional control, five year disease free survival, and five year overall survival were 78.0%, 66.8%, and 72.1%, respectively.

To identify prognostic factors, pretreatment parameters including age, ECOG performance status, number of pregnancies, history of diabetes mellitus and hypertension, histology, size and shape of primary tumor, CT findings and blood parameters were retrospectively analyzed in terms of locoregional control, disease free survival and overall survival using univariate analysis and multivariate analysis. In univariate analysis, tumor size on physical examination and rectal invasion on CT significantly affected locoregional control, disease free survival and overall survival. Parametrial involvement on CT was a significant prognostic factor on locoregional control and disease free survival. Hemoglobin level affected disease free survival and overall survival. Histology and age were significant prognostic factors on locoregional control. In multivariate analysis excluding CT finding, tumor size on physical examination was a significant factor in terms of locoregioal control and overall survival. Hemoglobin level was significant in terms of disease free survival. In multivariate analysis including CT, histology was a prognostic factor on locoregional control and disease free survival. Hemoglobin level and rectal invasion on CT were significant factors on locoregional control.

Key Words: Cervix cancer, Early stage, Prognostic factor, Radiotherapy

INTRODUCTION

Early stage carcinoma of the uterine cervix (stage IB and IIA) can be effectively treated by either radical surgery or radiation therapy. Survival rate obtained with irradiation is comparable to that after surgery or combination of both. But the choice of definitive radiotherapy or radical surgery for stage IB and IIA carcinoma of the cervix remains controversy although surgery is preferred in young women for preservation of vaginal and ovarian function.

Although there have been many reports in the literature describing the prognostic facotrs in patients treated with radical hysterectomy or radiation therapy[1~24], there were few reports demonstrating the prognostic factors controlled for employing multivariate analysis[25~28]. We employed multivariate analysis as well as univariate analysis to evaluate prognostic factors in patients with stage IB and IIA carcinoma of the uterine cervix treated by radical radiation therapy alone.

MATERINALS AND METHODS

Previously untreated 138 patients with stage IB or IIA carcinoma of uterine cervix were registered at the Department of Therapeutic Radiology, seoul National University Hospital from March 1979 through December 1986. Fourteen of them were excluded because of incomplete treatment. Follow-up ranged from 4 to 140 months and median was 84 months.

All the available informations including patient staus during follow-up in the medical records were reviewed and informations of some lost to follow-up patients were updated by mail or on the telephone.

Patients were initially evaluated with physical examination and the pretreatemtn staging work-

ups including complete blood count, blood chemistry, chest X-ray, intravenous pyelography, sigmoidoscopy, and cystoscopy. Abdomino-pelvic CT became available in May 1981. All the patients were staged according to the recommendations of the International Federation of Gynecology and Obstetrics classification system[29]. In physical finding, the tumor size was defined by the widest diameter (Table 1, 2).

Abdomino-pelvic CT was performed in 76 patients. Of CT findings, pelvic lymph node status, paraaortic lymph node status, parametrial involvement, bladder invasion, and rectal invasion were analyzed.

All the patients with exception of four were treated with a combination of external beam radiation therapy and low-dose rate intracavitary radiation, using Fletcher-Suit applicator. Four patients were treated with external beam irradiation alone; 5000 cGy to whole pelvis followed by small field boost, without intracavitary radiation because of poor geometry (1) or medical contraindication to

anethesia (3). Treatment details were reported previously[30,31].

Treatment failures were classified as locoregional recurrence (cervix, vagina, parametrium, and other intrapelvic sites) or distant metastasis. Interval of locoregional control (LRC) was measured from the start of treatment to the date of the first locoregional recurrence or to the date of last follow-up. Disease free survival (DFS) time was measured from start of treatment to relapse or last follow-up for patients who achieved complete response (CR). DFS was defined as zero for patients not achieving CR. Overall survival (OS) was measured from the date of treatment to date of death or date of last follow-up. Intercurrent death was regarded as censoring at that time. Surivival rates were calculated with life table method[32]. Prognostic facotrs were evaluated with univariate analysis using Wilcoxon method first[33]. In multivariate analyses, nine variables were put into analysis; six variables selected from the results of univariate analysis and three others that have been reported to be significant by others[25~28]. Because abdomino-pelvic CT was not done in every

Table 1. Patient Characteristic

Factors	No. of paients (%)
Stage	
IB	35(28)
IIA	89(72)
Age (years)	
<50	49(40)
≥50	75(60)
ECOG performance score	
0~1	100(97)
2~4	3(3)
No. of pergnancies	
<3	14(16)
≥3	71(84)
History of diabetes	
absent	103(90)
present	11(10)
History of hypertension	
absent	87(78)
present	25(22)
Hemoglobin g%	
<10	9(7)
≥10	115(93)
Neutrophil count (/mm³)	
<4000	39(50)
≥4000	39(50)
lymphocyte count (/mm³)	
<2000	38(49)
≥2000	40(51)

Table 2. Patient Characteristic

Facors	No. of paients (%)
Histology	
squamous	117(96)
non-squamous	5(4)
Tumor shape	
infiltrative	106(88)
non-infiltrative	14(12)
Tumor size (cm)	
<4	75(66)
≥4	39(34)
CT findings	
pelvic LN	
normal	67(88)
enlarged	9(12)
paraaortic LN	
normal	71(93)
enlarged	5(7)
parametrium	
normal	49(64)
involved	27(36)
bladder	
invasion (−)	72(95)
invasion (+)	4(5)
rectum	
invasion (−)	69(91)
invasion (+)	7(9)

patients, we carried out multivariate analyses with five variables excluding CT finding in 122 patients and with nine variables including CT finding in 75 patients, respectively. Multivariate analyses were performed using Cox proportional hazard model[34]

RESULTS

Five year LRC rates were 79.0% in satge IB and 78.0% in stage IIA. Five year DFS rates were 76.4% in stage IB and 66.8% in stage IIA. Five year survival rates were 81.8% in stage IB and 72.1% in stage IIA.

The results of univariate analysis of pretreatment factors are summarized in table 3 and table 4. In terms of LRC, the statistically significant factors were age, histology, tumor size, parametrial involvement on CT and rectal invasion on CT. Patients younger than 50 years of age had higher risk of local recurrence than older patients. In terms of DFS, the statistically significant factors were

hemoglobin level, tumor size, parametrial involvement on CT, and rectal invasion on CT. In terms of OS, hemoglobin level, tumor size, and rectal invasion on CT were significant. Age, number of pregnancies, presence of diabetes, presence of hypertension, neutrophil count, lymphocyte count, tumor shape, pelvic lymph node status on CT, paraaortic lymph node status on CT, and bladder invasion on CT were not associated with locoregional control or survival.

The results of multivariate analysis of pretreatment factors excluding CT finding are summarized in table 5. Tumor size was a significant prognostic factor in terms of LRC and OS. Hemoglobin level was significant in terms of DFS. The results of multivariate analysis including CT finding are summarized in table 6. Histology was a prognostic factor on LRC. Among CT findings, rectal invasion was a significant factor in terms of LRC.

Table 3. Prognostic Factors, Univariate Analysis (I)

Factor	5-year LRC*(%)	P value	5-year DFS**(%)	P value	5-year OS***(%)	P value
Stage		NS		NS	OS***(%)	NS
IB	79		76		82	
IIA	78		67		72	
Age (years)		0.05		NS		NS
<50	71		63		71	
≥50	83		74		77	
ECOG score		NS		NS		NS
0~1	81		72		80	
2~4	50		50		33	
No. of pregnancies		0.07		NS		NS
<3	100		81		86	
≥3	78		72		76	
history of diabetes		NS		NS		0.1
absent	80		73		79	
present	68		50		48	
history of hypertension		NS		0.09		NS
absent	75		70		73	
present	87		82		82	
Hemoglobin (g%)		NS		0.02		0.03
<10	53		33		38	
≥10	80		72		77	
Neutrophil count (/mm³)		NS		NS		NS
<4000	77		72		80	
≥4000	86		75		74	
Lymphocytre count (/mm³)		0.07		0.09		NS
<2000	88		80		81	
≥2000	75		67		73	

*LRC: Locoregional control   ***OS: Overall survival   **DFS: Disease free survival

Table 4. Prognostic Factors, univariate Analysis (II)

Factor	5-year LRC(%)	P value	5-year DFS(%)	P value	5-year OS(%)	P value
Histology		0.02		0.052		NS
squamous	80		70		75	
non-squamous	40		40		57	
tumor shape		NS		NS		NS
infiltrative	78		70		75	
non-infiltrative	86		66		57	
tumor size (cm)		0.007		0.02		0.02
<4	86		78		81	
≥4	63		58		61	
CT findigs						
pelvic LN		NS		NS		NS
normal	81		71		76	
enlarged	67		67		78	
paraaortic LN		NS		NS		NS
normal	80		72		78	
enlarged	80		40		50	
parametrium		0.01		0.02		NS
invasion (−)	87		77		80	
invasion (+)	65		55		67	
bladder		NS		NS		NS
invasion (−)	80		70		75	
invasion (+)	100		100		100	
rectum		0.001		0.009		0.003
invasion (−)	85		74		80	
invasion (+)	43		43		43	

Table 5. Prognostic Factors, Multivariate Analysis Excluding CT

Factor	relative		risk
	CRC	DFS	OS
Age (year)			
≥50/<50	0.59	0.70	0.85
Histology			
non-squamous/squamous	2.34	1.79	1.28
Tumor shape			
infiltrative/non-infiltrative	0.87	1.41	1.75
Tumor size (cm)			
≥4.0/<4.0	2.70**	1.73	2.43**
Hemoglobin (gm/dl)			
<10/≥10	2.02	2.63**	2.69*

*0.05<p<0.1 **p<0.05

DISCUSSION

The effects of numerous parameters affecting survival in cervical cancer have been relatively well known in surgical treatment. However, there have been only a few reports regarding prognostic value

Table 6. Prognostic Factors, Multivariate Analysis Including CT

Factor	relative		risk
	CRC	DFS	OS
Age (year)			
≥50/<50	0.42*	0.62	0.69
Histology			
non-squamous/squamous	7.28**	5.28**	4.07
Tumor shape			
infiltrative/non-infiltr	0.29	0.95	1.48
Tumor size (cm)			
≥4.0/<4.0	1.07	0.60	1.13
Hemoglobin (gm/dl)			
<10/≥10	4.60**	4.48*	4.83
CT finding			
perlvic LN positive/negative	1.95	0.70	0.50
paraaortic LN positive/negative	0.50	2.16	1.47
parametrial involvement (+)/(−)	1.28	1.45	1.22
rectal involvement (+)/(−)	6.61**	3.16*	2.76

*0.05<p<0.1 **p<0.05

of pretreatment factors in radiation therapy. This restropective study was carried out to identify the prognostic significance of various pretreatment factors in patients with stage IB and IIA treated with radiotherapy alone.

1. Age

In univariate analyis, our results demonstrated that LRC was higher in patients older than 50 years of age. According to many investigators, the prognosis was the same in both the young and the old patients[1~3]. Some have found a poorer prognosis in the younger age group[4~8] whereas others have found a more favorable outcome in younger patients[9~12]. In our multivariate analysis, age did not show any prognostic significance. By Michael's multivariate analysis[25], age had a profound influence on survival in patients with stage IB cervical cancer independent of potentially comfounding variables. Patients of age ≥ 40 years had better five-year actuarial survival than patients age < 40 years. Also a multivariate analysis of prognostic variables in Gynecologic Oncology Group (GOG)[26] supported the conclusion of advantage for the older population but in conflict with this finding, Daniel's multivariate analysis[27] revealed that older patients had lower survival rates than younger. But this study was not correct for deaths from intercurrent disease.

2. Histology

Some studies reported no difference in survival between patients with adenocarcinoma and those with squamous carcinoma when lesion size and stage were the same[13,14]. Other investigators reported poorer prognosis for patients with adenocarcinoma than for those with squamous carcinoma[15]. In our study, patients with nonsquamous histology had poorer LRC and marginally inferior DFS in univariate analysis. In multivariate analysis including CT, patients with nonsquamous histology had poorer LRC and DFS. Our study could not show certainly a statistically significant adverse prognostic effect of nonsquamous histology for survival. We feel larger numbers of patients for study will help clarify this conflict.

3. Tumor Size

A number of authors have advocated the use of extrafascial hysterectomy as an adjuvant to irradiation in patients with lesion ≥ 6 cm. However the utility of adjuvant hysterectomy remains controversy. Einhorn's study[16] revealed combined

modality gave better results than irradiation alone in tumors of the same size in stage IB. But these results favoring the group treated with combined therapy were retrospective and were apt to be criticized because of selection bias. In a small randomized trial at the M.D. Anderson hospital, no advantage in survival or local control was found for patients treated with a combined approach[35].

In our study, cervical lesion ≥ 4 cm was associated with higher local relapse and with poorer survival. It is suggested that a combined modality of radiation therapy and simple hysterectomy in patients with bulky mass may help decrease central failure and increase survival.

4. Anemia

Generally, tumor hypoxia has been suggested as a potential mechanism of radiation resistance in bulky endocervical tumors. The importance of anemia as an independent prognostic factor and the need for pretreatment transfusion of anmemic patients have been debated. In univariate analysis, our results demonstrated a significant effect of anemia (hemoglobin level < 10 g/dl) on DFS and OS. In multivariate analysis excluding CT, low hemoglobin level affected DFS. In multivariate analysis including CT, it affeted LRC. For patients treated with radiation, it has been argued that oxygen effect was less important when fractionation permitted intertreatment oxygenation[35]. Animal study[18] suggested that although tumors became less senstive to irradiation immediately after phlebotomy, they adapt relatively rapidly to a state of chronic anemia returning to prephlobotomy radiosensitivity within 24 hours. Also clinical trials of hypoxic cell sensitizer (MISO) have failed to demonstrate improved local control. These results may suggest that chronic anemia might not cause chronic radio-resistance. Thus we do not know the mechanism which underlies the clinical association of a chronically low hemoglobin level with an increased risk of relapse after radiation therapy.

We failed to reveal that treansfusion during treatment improved the local control. For some authors blood transfusion was beneficial, for others they were of no value or even detrimental in that they increase the rate of recurrence. By Girinski's multivariate analysis[28] including advanced cervical carcinoma only, only the hemoglobin concentrations during treatment were prognostic and patients with at least one value below the threshold of 10 g% had a significantly higher risk of locor-

egional failure than the patients with all their values above the level. And blood transfusion given during treatment might not have completely offset acute anemia. In analysis of stage IB cervical carcinoma treated with radical hysterectomy, Scott[19] concluded perioperative blood transfusion appeared to be an independent variable predictive of earlier recurrence and diminished survival. They suggested that blood transfusion-induced immunosuppression adversely affected survival.

A prospective study[20] randomized patients with stage IIB and III disease to receive or not to receive transfusion (if anemic) is proved efficiency of transfusion in anemic patients. Patients with a hemoglobin level of 10~12.5 g% who were not transfused had a significantly higher locoregional relapse than either those who were transfused or those who were not anemic. Although the role of blood transfusion in prognosis was unclear and controversial, the preponderance of data strongly suggested that patients who were severely anemic (hemoglobin level<10 g% were benefitted by transfusion. Transfusion was indicated for patients with borderline hemoglobin levels if they continue to be actively bleeding and probably indicated for patients with chronic anemia. Our data also suggested this conclusion.

5. CT Finding

In univariate analysis, rectal invasion was a significant prognostic factor on LRC, DFS and OS. Parametrial involvement was associated with poorer LRC and DFS. Pelvic lymph node enlargement and bladder invasion did not prove to be of significance in our series. Although not statistically significant, paraaortic lymph node involvement was associated with poorer DFS. In multivariate analysis, rectal involvement only was significant in terms of LRC.

Surgical series have long demonstrated the importance of lymph node status as a prognostic indicator and positive pelvic lymph node was associated with a relatively high rates of pelvic faiure[21,22].

But there was controversy about the prognostic value of lymph node in patients treated with radiation therapy. A variety of methods were available for evaluation of lymph node status including CT, MRI, ultrasound, lymphangiography, and surgery. No radiologic study has achieved a sufficient level of accuracy to serve as a substitute for biopsy. Louis Calmilien et al[36] compared the CT imaging with histologic findings in stage I-IIA carcinoma of the cervix. Three of the four enlarged nodes on CT contained metastatic carcinoma. Of 12 patients with metastatic carcinoma in the lymph nodes, only three were identified as enlarged on CT (sensitivity =25%). So enlarged pelvic nodes on CT gave a very high probability of containing metastases, but absence of enlarged nodes correlated poorly with absence of metastases. In case of paraaortic lymph nodes, CT had a relatively high specificity (100%), but a low sensitivity (67%). In our study, pelvic lymph node did not prove to be a significant factor and positive paraaortic lymph nodes had marginal significance on DFS only. These results imply that CT findings about pelvic lymph node or paraaortic lymph ndoe have a relatively high specificity but a low sensitivity, so could not affect survival.

Parametrial involvement on CT was found in 35% of stage IB and IIA patients. In univariate analysis, parametrial involvement was associoated with poorer LRC and DFS. But multivariate analysis failed to reveal any significance. Grumbine et al[37] reported that even fourth-generation CT had an accuracy of only 58% compared with surgical/pathological finding in parametrial tumor extension, whereas physical examination had an accuracy of 92%. Finding of parametrial involvement on CT, though the rate of coincidence with physical examination is not very high[38], might be related with large cervical tumor or deep stromal invasion and this may be the reason why this finding is related with LRC and DFS in univariate analysis.

In our study, rectal invasion was reported in 9% and was a significant prognostic factor in terms of LRC, DFS and OS in univariate analysis. According to review of patients with rectal involvement, tumor extension was relatively wide on both physical examination and CT. All of them were stage IIA. But even in multivariate analysis, it was significant in terms of LRC. Then bladder invasion on CT was reported in 5% and was not significant on any survival. Bladder or rectal involvement in CT was characterized by the obliteration of the fat plane surrounding the above organs and/or nodular indentatioin along the posterior bladder or anterior rectal wall. But it was difficult to distinguish invasion from close contact, especially in rectum[39]. CT staging of IVA tumors was problematic since tumor involvement of the serosa and muscularis without mucosal penetration could escape cystocopic or sigmodioscopic detection. By Botsis's study[40], among 12 patients clinically staged as IV, CT agreed with the clinical stage in 10 cases but in 2 cases did not detect the bladder involvement. In 2

clinical stage III cases, bladder involvement and/or rectal involvement on CT were detected. Lojima reported that CT was superior to conventional diagnostic methods in detecting paravaginal and vesical involvement, and the accuracy of CT in the detection of vesical involvement was 96% in surgically treated cases[41]. But we could not find any literature in which CT findings were analysed on the survival. In Yamada's report[42], CT findfings before treatment were analysed on the basis of the outcome during 5 year follow-up period (75 survivals, and 54 deaths); the incidence of vesical involvement in the two groups were 8.0% in surivivals and 57.4% in deaths. Then our results revealed that the prognostic factor was rectal involvement on CT, not vesical involvement on CT. It is difficult to know whether the suspicous rectal involvement is false positive or true positive because the patients with these findings did not have operation. In our study, suspicious rectal invasion on CT has predictive value, but bladder invasion on CT is rarely detected and has not a good value to predict prognosis in early stage carcinoma of uterine cervix. But if bladder invasion on CT is detected in more cases, the positive findings may affect survival. Further studies to reveal the prognostic value of CT findings would be needed.

6. Other Pretreatment Factors

GOG multivariate analysis[26] revealed that performance status was significantly associated with progression free interval. The Patterns of Care Study (PCS)[23] revealed that in stag I and II, higher Karnofsky performance status was associated with improved pelvic control in multivariate analysis. In our study, patients with ECOG performance scale ≥ 2 had poorer LRC, DFS and OS but there was no statistical significance probably because the number of cases were very small.

Patients with history of 0~2 pregnancies had better LRC than patients having had 3 or more pregnancies though it was marginally significant. In conflilict with this finding, some data[27] suggested advantage of larger number of pregnancies. They suggested that patients with fewer pregnancies had less corpious vagina, so were treated with less dose of ICR than patients with larger number of pregnancies.

In our study, although the patients with history of diabetes mellitus adversely affected OS, it was not statistically significant. This would imply that there was no direct effect of diabetes mellitus on the response to the treatment of cervical cancer.

Hypertension, increased neutrophil count, and decreased lymphocyte count did not prove to be of significance in our study but previously were reported to be of significance in our study but previously were reported to be adversely significant by others[27]. Riesco[24] has examined the effect of pretreatment lymphocyte counts on survival in 370 patients with stage I-III squamous cell carcinoma of the uterine cervix. A statistically significant decrease in disease free survival at 5 years was correlated with depressed lymphocyte counts. They suggested that immunocompetence may be of prognostic importance in the clincal response of patients with gynecological cancer.

SUMMARY

Multivarate anaysis excluding CT showd that tumor size was significant prognostic factor in terms of LRC and OS. Hemoglobin level was significant in terms of DFS. Multivariate analysis inculding CT showed that histology was significant in terms of LRC and DFS. Hemoglobin level and rectal involvement were significant factors in terms of LRC.

In univariate analysis, age, histology, tumor size, and parametrial invasion on CT affected LRC. In terms of DFS, low hemoglobn level, parametrial invasion on CT, and rectal invasion on CT were associated with poorer prognostic factor.

In terms of OS, the statistically significant factors were hemoglobin level, tumor size, and rectal invasion on CT.

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= 국문초록 =

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1979년 3월 부터 1986년 12월까지 초기 자궁 경부암으로 서울대학교병원 치료방사선과에서 방사선 치료를 받은 124명의 환자를 대상으로 치료 결과 및 예후에 영향을 미치는 인자에 대하여 분석하였다. 병기 IB(35명)에서 5년 국소 치료율, 5년 무병 생존율 및 5년 생존율은 각각 79.0%, 76.4%, 81.8%,였다. 병기 IIA(89명)에서는 78.0%, 66.8%, 72.1%였다. 나이, ECOG 수행상태, 임신 횟수, 당뇨 또는 고혈압의 여부, 병리조직학적 소견, 종양의 크기, 종양의 침투 양상, 전산화단층 촬영 소견 및 혈액 검사소견에 대한 후향적 분석을 단변수 분석과 다변수분석을 이용하여 5년 국소 치료율, 5년 무병생존율, 5년 생존율에 따라 실시하였다. 단변수 분석상 종양의 크기와 전산화단층 촬영상 직장 침윤이 5년 국소 치료율, 5년 무병 생존율 및 5년 생존율에 의미 있는 예후 인자이었다. 전산화 단층촬영상 자궁강 결합 조직 침범이 5년 국소치료율, 5년 무병 생존율에 의미가 있었다. 혈색소 치가 5년 무병 생존율 및 5년 생존율에 의미가 있었다. 병리 소견과 환자의 나이가 5년 국소치료율에 의미가 있었다. 전산화 단층촬영결과를 제외한 다변수 분석결과에서 종양의 크기가 5년 국소치료율과 5년 생존율에 의미가 있었다. 혈색소치가 5년 무병생존율에 의미가 있었다. 전산화 단층촬영결과를 포함한 다변수 분석결과에설 병리소견이 5년 국소치료율과 5년 무병생존율에 의미가 있었다. 혈색소치와 전산화단층촬영상 직장침윤이 5년 국소치료율에 의미가 있었다.