Pretreatment Prognostic Factors in Carcinoma of the Uterine Cervix

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To identify pretreatment prognostic factors in carcinoma of the uterine cervix, a retrospective analysis was undertaken of 510 patients treated with curative radiation therapy in Seoul National University Hospital during the 7 year period, from March 1979 through December 1986. According to FIGO classification, 35 patients were stage I B, 89 were stage II A, 232 were stage II B, 8 were stage III A, 134 were III B, and 12 were stage IV A. Five year locoregional control (LRC) rates in stage I B, II A, II B, III A, III B, and IV A were 79%, 78%, 70%, 58%, 51% and 27%, respectively. Five year disease free survival (DFS) rates were 76%, 67%, 60%, 57%, 40%, and 25%, respectively. Overall survival (OS) rates at five years were 82%, 72%, 67%, 67%, 51%, and 33%, respectively. In univariate analyses, stage, age, initial hemoglobin level, type of histology, tumor size, and several CT findings including pelvic lymph node (LN) status, paraaortic lymph node (PAN) status, extent of parametrial invasion, bladder invasion, and rectal invasion were significant factors in terms of LRC. All these factors and elevation of BUN or creatinine were associated with DFS. In terms of overall survival, stage, initial hemoglobin level, type of histology, tumor size, elevation of BUN or creatinine, and five CT findings associated with LRC were prognostically significant. In multivariate analysis excluding CT findings, stage IV disease, non-squamous histology, and tumor size $\geq$ 4 cm were associated with poor LRC and DFS. Stage IV disease and tumor size significantly affected OS. In multivariate analysis including CT findings, histology, tumor size, and pelvic LN status on CT were uniformly significant in terms of LRC, DFS, and OS. PAN status on CT affected overall survival only.

Key Words: Cervix cancer, Prognostic factor, Radiation therapy

INTRODUCTION

Three consecutive studies on analysis of prognostic factors in patients with early stage, stage II B, and locally advanced carcinoma of the uterine cervix were previously reported[1~3]. The purpose of this analysis is to identify the prognostic significance of pretreatment factors in patients with cervical carcinoma treated with radiation therapy alone as a whole and to update the results of our previous study[4].

METHODS AND MATERIALS

The records of 600 patients with histologically proven carcinoma of the uterine cervix who were treated with curative radiation therapy in Seoul National University Hospital from March 1979 through December 1986 were reviewed. Of them, 90 patients who had not undertaken the planned radiotherapy completely were excluded from the analysis.

All the patients were initially evaluated with physical examination and the majority of patients had undergone pretreatment 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 and was performed in 100 patients as an ancillary study thereafter. All the patients were staged according to the recommendations of the International Federation of Gynecology and Obstetrics (FIGO) classification system[5].

Patients were usually treated with external beam radiotherapy followed by one or two courses of

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intracavitary radiation with Fletcher-Suit afterloading applicator. In 38 patients, brachytherapy was impossible or seemed to be not appropriate because of poor geometry and/or extensive residual tumor after whole pelvis irradiation. They received additional external beam radiotherapy with reduced fields. Treatment details have been previously reported[4]. The distribution of patients according to stages and treatment modalities is shown in Table 1.

Treatment failures were classified as locoregional recurrence (cervix, vagina, parametrium, and other intrapelvic sites) or distant metastasis (inguinal node, PAN, and other distant sites). Period of locoregional control was measured from date of initation of treatment to the date of first locoregional recurrence or the date of last follow-up. Period of disease free survival was the time interval to the date of first recurrence or the date of

Table 1. Treatment Modality by Stage

Treatment modality	Stage						
	I B	IIA	IIB	IIIA	IIIB	IVA	Total
Ext. RT*	1	3	11	1	18	4	38
Ext. RT+ICR							
1 course**	19	53	135	5	90	6	308
2 course	15	33	86	3	26	2	164
Total	35	89	232	8	134	12	510

* External beam radiotherapy
**Number of intracavitary applications

Table 2. Prognostic Factors, Univariate Analysis (I)

Factor	No. of patients (%)	5-year LRC (%)	p-value	5-year DFS (%)	p-value	5-year OS (%)	p-value
Stage			0.0001		0.0001		0.0001
I B	35(7)	79		76		82	
IIA	89(17)	78		67		72	
IIB	232(46)	70		60		67	
IIIA	8(2)	58		57		67	
IIIB	134(26)	51		40		51	
IVA	12(2)	27		25		33	
Age (years)			0.01		0.01		0.07
< 50	194(38)	62		51		61	
≥ 50	316(62)	69		60		66	
ECOG score			0.06		0.08		NS
0~1	376(90)	69		58		66	
2~4	40(10)	55		49		59	
No. of pregnancies			NS		0.07		NS
< 5	136(37)	61		53		61	
≥ 5	227(63)	68		59		67	
History of diabetes			NS		NS		NS
absent	422(94)	67		58		66	
present	27(6)	64		58		63	
History of hypertension			NS		0.08		NS
absent	371(86)	65		57		64	
present	62(14)	73		67		73	
Hemoglobin (mg/dL)			0.001		0.0003		0.02
< 10	54(11)	48		36		48	
≥ 10	446(89)	68		59		66	
Neutrophil count (/mm³)			0.09		NS		NS
< 4000	128(41)	68		59		66	
≥ 4000	188(59)	60		52		60	
Lymphocyte count (/mm³)			NS		NS		NS
< 2000	162(51)	66		57		66	
≥ 2000	154(49)	60		52		60	
BUN or creatinine			0.07		0.002		0.008
normal	425(98)	67		58		66	
elevated	9(2)	43		22		29	

last follow-up. Overall survival was measured from date of initiation of treatment to the date of death from cervix cancer or date of last follow-up. Death from intercurrent disease was censored. Follow-up ranged from 2 to 146 months (median 80 months).

Various factors which have been reported to be associated with prognosis in other reports were included for univariate analyses and factors chosen from the results of univariate analyses were included for multivariate analyses.

Survival rates were estimated by the life table method. Statistical test for equality of survival curves across striata was done by the generalized Wilcoxon test[6] in PC-SAS system. Cox proportional hazard model[7] was used to estimate the adjusted relative risk of each prognostic factor in multivariate analyses.

RESULT

Five year locoregional control (LRC) rates in stage I B, IIA, IIB, IIIA, IIIB, and IVA were 79%, 78%, 70%, 58%, 51% and 27%, respectively. Five year disease free survival (DFS) rates were 76%, 67%, 60%, 57%, 40% and 25%. Overall survival (OS) rates at five years were 82%, 72%, 67%, 67%, 51%, and 33%. FIGO stage at the time of diagnosis was a significant prognostic factor in terms of LRC ($p=0.0001$), DFS ($p=0.0005$), and OS($p=0.0001$).

The results of univariate analyses are summarized in Table 2 and Table 3. The patients younger than 50 years of age had poor LRC and DFS. Those with initial hemoglobin of less than 10 g% had worse LRC, DFS, and OS. The elevation of BUN or creatinine adversely affected DFS and OS. Squamous histology and small size of the primary tumor (less than 4 cm) were associated with better LRC, DFS, and OS. Several CT findings including pelvic LN status, PAN status, extent of parametrial invasion, and presence or absence of bladder or rectal invasion were prognostically significant in terms of LRC, DFS, and OS. ECOG performance

Table 3. Prognostic Factors, Univariate Analysis (II)

Factor	No. of patients (%)	5-year LRC (%)	p-value	5-year DFS (%)	p-value	5-year OS (%)	p-value
Histology			0.002		0.02		0.003
squamous	479(95)	67		57		65	
non-squamous	23(5)	35		34		36	
Tumor shape			NS		NS		NS
infiltrative	423(87)	66		57		66	
non-infiltrative	63(13)	63		54		57	
Tumor size (cm)			0.0001		0.001		0.0003
< 4	207(45)	76		64		74	
≥ 4	258(55)	58		51		58	
CT findings							
pelvic LN			0.002		0.001		0.007
normal	254(76)	70		60		68	
enlarged	81(24)	52		43		53	
paraaortic LN			0.02		0.005		0.003
normal	310(93)	68		58		66	
enlarged	25(7)	40		29		34	
parametrium			0.0003		0.0001		0.0002
normal	134(40)	71		63		72	
involved	171(51)	66		55		63	
to sidewall	30(9)	39		27		36	
uterine body			NS		NS		NS
invasion (−)	320(96)	65		55		64	
invasion (+)	15(4)	73		66		71	
bladder			0.02		0.04		0.02
invasion (−)	294(88)	67		57		66	
invasion (+)	41(12)	55		47		54	
rectum			0.0001		0.001		0.0001
invasion (−)	296(88)	69		58		68	
invasion (+)	39(12)	42		40		40	

Table 4. Prognostic Factors, Multivariate Analysis Excluding CT Findings (N=495)

Factor	Relative risk		
	LRC	DFS	OS
Stage			
I B	1.00	1.00	1.00
II A	0.82	0.83	1.18
II B	1.11	1.12	1.36
III A	1.76	1.77	1.43
III B	1.93	1.98	2.10*
IV A	3.44**	3.46**	3.60**
Age (years)			
<50/≥50	1.23	1.23	1.15
Hemoglobin (gm/dl)			
<10/≥10	1.27	1.30	1.24
Histology			
non-squamous/ squamous	1.76**	1.73**	1.48
Tumor size (cm)			
≥4.0/<4.0	1.61**	1.59**	1.76**

* $0.05<p<0.1$
** $p<0.05$

Table 5. Prognostic Factors, Multivariate Analysis Including CT Findings (N=327)

Factor	Relative risk		
	LRC	DFS	OS
Stage			
I B	1.00	1.00	1.00
II A	1.11	1.12	1.87
II B	1.47	1.48	2.30
III A	3.32	3.34	4.80
III B	2.48	2.53	3.52*
IV A	3.79*	3.72*	5.47*
Age (years)			
<50/≥50	1.04	1.04	1.11
Hemoglobin (gm/dl)			
<10/≥10	1.34	1.40	1.28
Histology			
non-squamous/ squamous	2.67**	2.62**	2.38**
Tumor size (cm)			
≥4.0/<4.0	1.56**	1.56**	1.81**
CT findings			
pelvic LN (+)/(−)	1.63**	1.66**	1.58**
PAN (+)/(−)	1.30	1.27	1.95**

* $0.05<p<0.1$
** $p<0.05$

score, number of pregnancies, history of diabetes or hypertension, neutrophil count, lymphocyte count, shape of primary tumor, and uterine body invasion on CT were not significantly related to LRC, DFS, or OS.

Five variables including FIGO stage were selected from the results of univariate analyses and put into multivariate analyses; excluded were factors which did not have prognostic significance in univariate analyses and owed their prognostic significance to intrinsic association with FIGO stage. Because abdomino-pelvic CT was not done in all patients, we carried out multivariate analysis with 5 variables excluding CT findings in 495 patients and with 7 variables including CT findings in 327 patients.

In multivariate analysis excluding CT findings, histology was a significant factor in terms of LRC and OS and size of primary tumor was proved to be signifcant in LRC, DFS, and OS. In regard to stage, only stage IVA showed significantly higher relative risk over stage I B (Table 4). When CT findings were included, histology, size of primary tumor, and pelvic LN status on CT were significant factors in terms of LRC, DFS, and OS. PAN status was significantly associated with OS, but not with LRC and DFS (Table 5).

DISCUSSION

Many pretreatment factors have been reported to be associated with survival in patients with carcinoma of the uterine cervix. But most of them are analyses of results in patients treated in several institutions or in patients treated over a long period of time at one institution possibly in various protocols. Our patients were treated in a fairly uniform way in one institute in a relatively short time interval and this may allow more valuable informations.

1. Age

Young age, in univariate analysis, was associated with decreased LRC and DFS and it was marginally significant in OS. But its prognostic significance disappeared in multivariate analysis. Several reports[8~12] describing the effect of age on prognosis showed conflicting results. Dattoli et al[8] suggested that patients less than or equal to 40 years of age had lower five year survival and higher local and distant failures independent of potentially confounding variables in stage I B cervical cancer. Lanciano et al[9], in their patterns of care study, reported that young age was not associated with decreased survival, but there was a significant

decrease in pelvic control for younger patients with stage I and II. Kapp et al[10] reported that older patients had lower survival rate because of death of other causes than cervical cancer but lower incidence of loco-regional failures in multivariate analysis for all stages of cervival cancer. In our previous study[1] young age was significantly associated with poor LRC in group of patients with stage I B and II A. On the contrary, van der Graaf et al[11] and Meanwell et al[12] indicated a signficant advantage for younger patients. Although the prognostic significance of age can not be defined clearly yet, our study suggests that old age does not affect survival adversely when it is corrected for intercurrent deaths and older patients shows a tendency of better LRC and DFS.

2. Anemia

Hypoxia may be one of the factors that contribute to local failures in some tumors treated by radiation therapy alone. Low hemoglobin concentrations before and/or during treatment could cause tumor hypoxia which would lead to increased local failures. There are several published studies supporting that hemoglobin concentration is important for several tumors including uterine cervix cancer[13~15], some tumors of the head and neck[16], and endometrial cancer[17].

In this study low hemoglobin concentration before treatment had adverse effect on LRC, DFS, and OS in univariate analysis. Its effect was not verified in multivariate analysis. Hemoglobin levels during treatment were not considered in this analysis because high hemoglobin level was maintained after start of radiotherapy by transfusion as needed. Animal experiments[18] showed that there is an important difference between acute and chronic anemia in their influence on the radiosensitivity; while acute anemia consistently causes radioresistance, this effect is lost as the duration of the anemia prior to irradiation is prolonged. And the role of transfusion is still controversial: for some authors it could be beneficial[13,15] for others[19] it could be detrimental especially if whole blood or large quantities of red blood cell units are given to patients. Our data suggested that low hemoglobin concentration before treatment might not be a prognostic indicator if adequate monitoring and correction of hemoglobin level before and during treatment should be performed. Girinski et al[20] demonstrated that hemoglobin concentrations were prognostically significant only during treatment and patients with at least one value below the threshold of 10 g% had a higher risk of locoregional failure than the patients with all their values above the threshold. Kapp et al[10] noted a significant effect of anemia on LRC, DFS, and OS despite of transfusion prior to initiation of radiation therapy. They did not evaluate the effect of hematocrit during treatment.

3. Histology

Excluding eight patients whose histologic cell type was not specified, 479 (95%) patients had squamous cell carcinomas and 23 (5%) patients had non-squamous histologies. Of the 23 patients with non-squamous histologies, 14 had adenocarcinomas and 9 adenosquamous carcinomas. In our study, non-squamous histology was a strong predictor of poor outcome.

Many reports attempting to define prognostic significance and optimal management of the adenocarcinoma of the uterine cervix have produced conflicting conclusions. Moberg et al[21] reported lower survival rate for patients with stage II and III adenocarcinoma than for patients with squamous carcinoma treated during same period. Eifel et al[22] reported that 5-year relapse free survival of patients with stage II disease was only 32% which is much lower than what they had observed after treatment of comparable stage squamous carcinoma. In contrast, some investigators indicated that the survivals of patients with adenocarcinomas and squamous cell carcinomas were comparable. Grigsby et al[23] reported that the 5-year disease free survival was similar for epidermoid carcinoma and adenocarcinoma (68.0% vs 64.9%) within all stages and types of therapy. In Shingleton et al's study[24] which used matched squamous cell carcinoma controls, there was no difference in survival between adenocarcinomas and controls, and rates of metastases to pelvic nodes in the two groups were identical. Stehman et al[25], in their multivariate analysis, reported that cell type was not associated with progression free survival and overall survival.

Gallup et al[26] found an overall survival rate of 20% in 20 patients with adenosquamous carcinoma. The survival rate for patients with stage I B squamous cell carcinoma (91%) was much better than for adenosquamous carcinoma (27%). Other investigators[27,28] also observed that, stage by stage, adenosquamous carcinomas of the cervix had a poorer 5-year survival.

4. Tumor Size

Prognostic significance of tumor size and its correlation with lymph node metastasis was reported previously by several authors[29~31]. Most of these studies included only patients with stage I B and II A disease who had undergone radical hysterectomy. Also it has been identified to be strongly correlated with prognosis following radiotherapy[25,32]. Stehman et al[25] noted that tumor size had linear relationship with progression free interval and survival for the assessment by centimeter measurement. In our previous studies[1,3], tumor size was a significant prognosticator in early and locally advanced stage disease. In this study, its effect on LRC, DFS, and OS was confirmed in univariate analysis and multivariate analysis.

5. CT Finding

CT have been widely applied to the evaluation of patients with carcinoma of the uterine cervix. The main value of CT is in detecting enlarged pelvic and paraaortic lymph node and in identifying local invasion to adjacent organ. The importance of pelvic LN status as a prognostic indicator has been clarified by many investigators[29,30] especially in patients with early stage disease treated by radical surgery. But its prognostic significance is controversial in patients treated with radiation therapy alone. Moreover, variety of patient population and methods for evaluation of pelvic LN status make it difficult to interpret several clinical studies. Sinistrero et al[32], in accordance with this study, reported that patients without evidence of nodal involvement on lymphography and/or CT had better pelvic control and survival. In contrast, Girinski et al[20] reviewed 386 patients with stage II B or III cervical cancer treated with radiation therapy and found that LN status on lymphangiogram was not correlated to locoregional and distant failure in multivariate analysis.

Many authors[33~35] consistently demonstrated that patients with PAN metastasis had a substantially higher risk of extrapelvic failure and significantly lower survival, although extended field irradiation may occasionally be curative for patients with PAN metastasis. Stehman et al[25], in a study from Gynecologic Oncologic Group, reported that presence of metastatic involvement of PAN was the most significant predictor of recurrence and death and positive pelvic node was only significant when PAN was negative in 626 patients who underwent operative assessment of lymph node status. Podczaski et al[36] found that tumor histology, PAN status, tumor size, and presence of peritoneal disease were significant prognostic factors in patients who underwent selective paraaortic lymphadenectomy and exploratory laparotomy prior to initiation of radiotherapy. In this study, PAN status was statistically significant for only OS, not LRC and DFS in multivariate analysis. This finding may have resulted from relatively lower incidence of enlargement of PAN on CT compared with the reported rate of biopy confirmed PAN metastasis.

Extent of parametrial invasion, rectal invasion, and bladder invasion on CT were significnat in terms of LRC, DFS, and OS in univariate analysis. These factors were not included in multivariate analysis because of inherent relation to stage. CT has some limitation in evaluation of adjacent organ invasion. Walsh[37] reported that CT was not sufficiently accurate to differentiate I B and II B lesion and that CT staging of IVA tumors was problematic since tumor involvement of the serosa and muscularis without mucosal penetration could escape cystoscopic or sigmoidoscopic detection. We previously reported that CT had much lower positive predicitive value than negative predictive value in the evaluation of adjacent organ invasion[38]. But positive findings on CT may suggest more advanced disease which is not reflected in clinical stage.

6. Other Factors

Elevation of BUN or creatinine adversely affected DFS and OS in univariate analysis. But its significance resulted from influence of stage. Actually we previously noted that it was not a significant prognostic factor in the subgroup analysis confined to locally advanced cervical cancer[3].

Additional factors reported previoulsly to be of prognostic significance in carcinoma of the cervix, including performance status, number of pregnancies, history of diabetes or hypertension, neutrophil count, lymphocyte count, shape of primary tumor, did not prove to be of significance in our study.

CONCLUSION

To identify pretreatment prognostic factors in carcinoma of the uterine cervix, a retrospective analysis was undertaken of 510 patients treated with curative radiation therapy. We used Cox proportional hazard model to exclude impact of confounding varibles.

In univariate analysis, stage, age, initial hemo-

globin, histology, tumor size, pelvic lymph node (LN) status on CT, several CT findings including paraaortic lymph node (PAN) status, extent of parametrial invasion, bladder invasion, and rectal invasion were significant factors in LRC. All these factors and elevation of BUN or creatinine were associated with DFS. In terms of OS, stage, initial hemoglobin, histology, tumor size, elevation of BUN or creatinine, and CT findings above mentioned were prognostically significant.

In multivariate analysis excluding CT findings, stage IV disease, non-squamous histology, and tumor size ≥ 4 cm were associated with poor LRC and DFS and Stage IV disease and tumor size significantly affected OS. In multivariate analysis including CT findings, histology, tumor size, and pelvic LN status on CT were uniformly significant in terms of LRC, DFS, and OS. PAN status on CT affected overall survival only.

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═ 국문초록 ═

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자궁경부암에 있어서의 예후인자를 알아보기 위해 1979년 3월부터 1986년 12월까지 서울대학교 병원에서 근치적방사선치료를 시행받은 510명의 환자를 대상으로 후향적분석을 시행하였다. FIGO 병기 I B, II A, II B, III A, III B, IV A의 환자 수는 각각 35, 89, 232, 8, 134, 12명이었고 병기에 따른 5년 국소치유율은 각각 79%, 78%, 70%, 58%, 51%, 27%이었으며 5년 무병생존율은 각각 76%, 67%, 60%, 57%, 40%, 25%, 5년 생존율은 각각 82%, 72%, 67%, 67%, 51%, 33%이었다. 단변수분석에 의하면 병기, 연령, 혈색소치, 병리조직학적 소견, 원발병소의 크기와 전산화단층촬영상 골반림프절 비대, 대동맥림프절 비대, 자궁방조직 침윤의 정도, 방광의 침윤 및 직장의 침윤소견이 국소치유율에 영향을 미치는 인자이었고 상기 인자와 혈중요소질소나 혈중 크레아티닌의 증가가 무병생존율에 영향을 미치는 인자이었으며 생존율에 영향을 미치는 인자는 병기, 혈색소치, 혈중요소질소나 혈중 크레아티닌의 증가, 병리조직학적 소견, 원발병소의 크기와 전산화단층촬영상 골반림프절 비대, 대동맥림프절 비대, 자궁방조직 침윤의 정도, 방광의 침윤 및 직장의 침윤 소견이었다. 전산화단층촬영 소견을 포함하지 않은 다변량분석에 의하면 IVA병기, 병리조직학적 소견, 원발병소의 크기가 국소치유율 및 무병생존율에 영향을 미치는 인자이었고 생존율에 영향을 미치는 인자는 IVA 병기와 원발병소의 크기이었다. 전산화단층촬영 소견을 포함한 다변량분석에 의하면 병리조직학적 소견, 원발병소의 크기, 전산화단층촬영상 골반림프절 비대가 국소치유율, 무병생존율, 생존율에 영향을 미치는 인자이었고 이들 세가지 인자와 전산화단층촬영상의 대동맥림프절 비대가 생존율에 영향을 미치는 인자이었다