Tumor size and lymph node status determined by imaging are reliable factors for predicting advanced cervical cancer prognosis

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Abstract. The aim of the present study was to investigate the prognostic role of a number of clinical factors in advanced cervical cancer patients. Patients (n=157) with stage IIA-IIB cervical cancer treated at four Hallym Medical Centers in South Korea (Hallym University Sacred Heart Hospital; Kangnam Sacred Heart Hospital; Chuncheon Sacred Heart Hospital; and Kangdong Sacred Heart Hospital) between 2006 and 2010 were retrospectively enrolled. Univariate analysis identified significant predictive values in the following eight factors: i) Cancer stage (P<0.0001); ii) tumor size (≤4 vs. 4-6 cm, P=0.0147; and ≤4 vs. >6 cm, P<0.0001); iii) serum squamous cell carcinoma antigen level (≤2 vs. >15 ng/ml; P=0.0291); iv) lower third vaginal involvement (P<0.0001); v) hydronephrosis (P=0.0003); vi) bladder/rectum involvement (P=0.0015); vii) pelvic (P=0.0017) or para-aortic (P=0.0019) lymph node (LN) metastasis detected by imaging vs. no metastasis; and viii) pelvic LN metastasis identified by pathological analysis (P=0.0289). Furthermore, multivariate analysis determined that tumor size (≤4 vs. 4-6 cm, P=0.0371; and ≤4 vs. >6 cm, P=0.0024) and pelvic LN metastasis determined by imaging vs. no metastasis (P=0.0499) were independent predictive variables. Therefore, tumor size and pelvic LN metastasis measured by imaging were independent predictive factors for the prognosis of advanced cervical cancer. These factors may provide more clinically significant prognostic information compared with the currently used International Federation of Gynecology and Obstetrics staging system.

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Introduction

Cervical cancer is the third most common type of cancer in the United States. Similarly, in Korea, cervical cancer is the sixth most common malignancy in female individuals and, more specifically, the second most common malignancy in females aged 15-44 years (1). The treatment strategy selected for patients with cervical cancer is based on the International Federation of Gynecology and Obstetrics (FIGO) staging system (2). For instance, surgery is the primary treatment strategy for early stage cervical cancer (stages IA-IIA), while concurrent chemoradiotherapy (CCRT) is the primary treatment strategy for more advanced stages of cervical cancer (stages IIB-IVB) (3). Despite the application of CCRT resulting in significant improvements in the disease-free and overall survival rates of patients with advanced cervical cancer, the survival rates in these patients remain unsatisfactory (4-7). Therefore, adjunctive treatment strategies following CCRT may be considered to improve survival rates for patients with poor prognostic factors, although there are currently no definite treatment guidelines. Therefore, it is important to assess individual prognoses to determine the most effective treatment method. The prognoses of patients with cervical cancer

are typically estimated using the FIGO staging system. However, the current FIGO clinical staging system has limited value due to individual variability in physical examinations and a lack of consideration of other important factors, including pathological parameters and lymph node (LN) metastasis (8). Therefore, considering prognostic factors other than the FIGO stage may be required for more accurate prediction of individual prognoses.

At present, numerous prognostic factors, including tumor size, LN involvement, age, pretreatment serum squamous cell carcinoma antigen (SCC-Ag) levels, parametrial invasion and deep stromal invasion (9-17), are used to predict the risk of disease recurrence. However, the majority of previously conducted studies assessed early stage cervical cancer, while only a relatively small number of studies were performed in advanced stage cervical cancer patients.

The aim of the present study was to identify predictors of survival among various clinical variables and identify independent prognostic factors in advanced cervical cancer.

Patients and methods

Patient characteristics. In total, 157 patients diagnosed with stages IIA-IVB cervical cancer, who were treated between January 2006 and December 2010, were retrospectively included in the present analysis. The clinical findings and laboratory results of the included patients were collected from electronic medical records from four Hallym Medical Centers in South Korea (Hallym University Sacred Heart Hospital, Anyang; Kangnam Sacred Heart Hospital, Seoul; Chuncheon Sacred Heart Hospital, Chuncheon; and Kangdong Sacred Heart Hospital, Seoul, Republic of Korea). The study was approved by the Institutional Review Boards of Hallym University Sacred Heart Hospital.

Cases of stage II cervical cancer were subdivided into stages IIA and IIB, according to the FIGO staging system. Although the FIGO staging system was revised in 2009 (2), the number of patients exhibiting cervical cancer of stage IIB or higher was not altered. In addition, tumor size was included as a variable, and cases of revised stage IIA cervical cancer were divided by clinically visible lesion size without affecting the results. The patients were classified into four serum SCC-Ag groups, including the ≤2, 2-5, 5-15 and >15 ng/ml groups. The tumor size was determined as the largest diameter of the primary tumor as measured by computed tomography (CT) or magnetic resonance imaging (MRI), and was categorized as ≤4, 4-6 or >6 cm. Parametrial involvement was determined by physical examination and hydronephrosis by CT scanning or intravenous pyelography. In addition, bladder/rectal invasion was diagnosed by cystoscopic or sigmoidoscopic biopsy, while pelvic/para-aortic LN metastasis was pathologically verified or defined as a nodal size of ≥1 cm using CT or MRI. Patients exhibiting pelvic and para-aortic LN involvement were included in the para-aortic LN-positive group. The number of LN metastases determined from the pathological biopsies was relatively small due to inoperable advanced cervical cancer cases; thus, imaging identification of LN metastases was used as a variable. In addition, high-risk human papilloma virus (HPV) infection was observed using DNA microarray analysis.

Cancer treatment strategies. Of the 157 patients included in the study, 76 were treated with CCRT, 26 with surgery and chemotherapy, 23 with surgery and CCRT and the remaining 32 patients were treated using alternative methods. The patients treated with alternative methods were excluded from the current study due to the low sample number in each treatment group.

Surgical procedures included a radical hysterectomy with pelvic and/or para-aortic LN dissection for patients with stage IIA cervical cancer. Patients receiving CCRT were administered with six weekly infusions of cisplatin (40 mg/m^2). Patients with a glomerular filtration rate of <60 ml/min were treated with carboplatin (120 mg/m^2); however, if the leukocyte count of the patient reduced to <3,000/m^3 or the platelet count decreased to <100,000/m^3, the treatment was terminated. Following the completion of chemotherapy, the patients undergoing CCRT received external beam radiation therapy (EBRT) to the entire pelvis using ≤50.4 Gy with a 10 MeV photon and the four-field box technique. Daily doses of EBRT were administered in five fractions/week at 1.8 Gy per fraction. Following EBRT, the patients undergoing radical CCRT received additional EBRT, as well as high-dose intracavitary brachytherapy with iridium-192, in which the dose to point A was 30 Gy in six fractions. When para-aortic LN metastasis was suspected, the patients received extended field radiation therapy with a total dose of 55-60 Gy. Furthermore, patients receiving chemotherapy were administered combination therapy with paclitaxel (135 mg/m^2, 24 h infusion on day 1) and cisplatin (50 mg/m^2, 1 h infusion on day 2) every three weeks.

Following completion of the therapy, the patients underwent follow-up examinations every three months for the initial two years, every six months for the next three years and annually thereafter. The overall survival was assessed from the point of diagnosis to the point of mortality caused by the specific disease or the date of the final follow-up visit.

Statistical analysis. Kaplan-Meier analysis was used to calculate the disease-specific survival rate from the date of the initial treatment session to the date of disease-specific mortality. Differences in survival rates between the groups were compared using the log-rank test for categorical variables. In addition to the inclusion of age as a continuous covariate, variables identified as significant by univariate analysis were subsequently analyzed using the multivariate Cox proportional hazard model to clarify the association between overall survival and the identified risk factors. $P<0.05$ was considered to indicate a statistically significant difference and all statistical analyses were performed using the SAS software (version 9.2; SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. The clinical characteristics of the patients included in the present multi-institutional study are summarized in Table I. The mean age of the patients at presentation was 57.52±14.06 years.

Univariate analysis of 12 clinical factors. The Cox proportional hazards model was applied to analyze 12 factors,

Table I. Clinical, treatment and outcome characteristics of 157 patients with cervical cancer treated between January 2006 and December 2010.

Characteristic	Value
Age, years (n=157)	
Median (range)	56 (27-85)
Mean ± standard deviation	57.52±14.06
Stage, n (%; n=156)	
IIA	55 (35.26)
IIB	60 (38.46)
IIIA and IIIB	17 (10.90)
IVA and IVB	24 (15.38)
SCC-Ag, ng/ml (%; n=149)	
≤2	42 (28.19)
2-5	33 (22.15)
5-15	36 (24.16)
>15	38 (25.50)
Tumor size, cm (%; n=151)	
≤4	61 (40.40)
4-6	60 (39.74)
>6	30 (19.87)
Parametrial involvement, n (%; n=155)	
(-)	39 (25.16)
(+)	116 (74.84)
Lower third vagina involvement, n (%; n=156)	
(-)	153 (98.08)
(+)	3 (1.92)
Hydronephrosis, n (%; n=156)	
(-)	123 (79.35)
(+)	32 (20.65)
Bladder/rectum involvement, n (%; n=155)	
(-)	124 (80.00)
(+)	31 (20.00)
LN status by imaging, n (%; n=148)	
(-)	75 (50.68)
(+) pelvic	65 (43.92)
(+) para-aortic	8 (5.41)
LN status by pathological analysis, n (%; n=46)	
(-)	31 (67.39)
(+)	15 (32.61)
HPV infection, n (%; n=65)	
(-)	16 (24.62)
(+)	49 (75.38)
Tumor cell type, n (%; n=157)	
SCC	124 (78.98)
Adenocarcinoma/adenosquamous carcinoma	18 (11.46)
Small cell carcinoma	15 (9.55)
Treatment modality, n (%; n=125)	
Surgery + chemotherapy	26 (20.80)
Surgery + CCRT	23 (18.40)
CCRT	76 (60.80)

SCC-Ag, squamous cell carcinoma antigen; LN, lymph node; HPV, human papilloma virus; CCRT, concurrent chemoradiotherapy.

Table II. Cox proportional hazards model for survival of 12 factors considered to have a prognostic value in patients with advanced cervical cancer.

Variable	RR	95% CI	P-value
Age	1.325	0.993-1.768	0.0558
Stage	2.228	1.620-3.063	<0.0001
SCC-Ag, ng/ml			
≤2	1.000		
2-5	0.660	0.207-2.106	0.4823
5-15	0.733	0.250-2.149	0.5715
>15	2.480	1.097-5.607	0.0291
Tumor size, cm			
≤4	1.000		
4-6	3.528	1.282-9.710	0.0147
>6	8.691	3.088-24.461	<0.0001
Parametrial involvement			
(-)	1.000		
(+)	2.635	0.926-7.501	0.0694
Lower third vaginal involvement			
(-)	1.000		
(+)	12.976	3.786-44.472	<0.0001
Hydronephrosis			
(-)	1.000		
(+)	3.740	1.843-7.589	0.0003
Bladder/rectum involvement			
(-)	1.000		
(+)	3.216	1.562-6.621	0.0015
LN metastasis by imaging			
(-)	1.000		
(+) pelvic	3.505	1.604-7.661	0.0017
(+) para-aortic	8.214	2.174-31.036	0.0019
LN metastasis by pathological analysis			
(-)	1.000		
(+)	10.971	1.279-94.104	0.0289
HPV infection			
(-)	1.000		
(+)	1.000	0.282-3.547	1.0000
Tumor cell type			
SCC	1.000		
Adenoca/adenosq	1.309	0.500-3.426	0.5831

RR, relative risk; CI, confidence interval; SCC-Ag, squamous carcinoma cell antigen; LN, lymph node; HPV, human papilloma virus; adenoca, adenocarcinoma; adenosq, adenosquamous carcinoma.

including age, tumor stage, SCC-Ag level, tumor size, parametrial involvement, lower third vaginal involvement, hydronephrosis, bladder/rectal involvement, LN metastasis

detected by imaging, LN metastasis detected by pathology, HPV infection and tumor cell type, which were considered to have a prognostic value. Of these factors, the following eight variables demonstrated significantly high relative risk (RR; Table II), in order of decreasing RR: Lower third vaginal involvement (RR, 12.976), pathological LN metastasis (RR, 10.971), tumor size of >6 cm (RR, 8.691), LN metastasis (para-aortic and/or pelvic) detected by imaging (RR, 8.214), hydronephrosis (RR, 3.740), bladder/rectal involvement (RR, 3.216), SCC-Ag of >15 ng/ml (RR 2.480) and tumor stage (RR, 2.228).

Furthermore, significant predictive roles were identified for the following eight factors: i) Stage (P<0.0001); ii) tumor size (≤4 vs. 4-6 cm, P=0.0147; and ≤4 vs. >6 cm, P<0.0001); iii) SCC-Ag level of ≤2 vs. >15 ng/ml (P=0.0291); iv) lower third vaginal involvement (P<0.0001); v) hydronephrosis (P=0.0003); vi) bladder/rectal involvement (P=0.0015); vii) pelvic (P=0.0017) or para-aortic (P=0.0019) LN metastasis detected by imaging vs. no metastasis; and viii) pelvic LN identified by pathological analysis (P=0.0289).

Multivariate analysis of clinical factors. Of the eight factors identified as significant by univariate analysis, lower third vaginal involvement, hydronephrosis and bladder/rectal involvement were excluded from multivariate analysis as they are included in the FIGO staging system. In addition, LN metastasis detected by pathology was excluded due to the small number of cases available for analysis (n=46). However, age was included due to its marginal significance and clinical relevance.

The results of the multivariate analysis are summarized in Table III. The RR values were found to be 1.233 [95% confidence interval (CI), 0.918-1.686; P=0.1589] for patient age and 1.460 (95% CI, 0.964-2.210; P=0.0739) for tumor stage. Furthermore, the RR values for ≤2, 2-5, 5-15 and >15 ng/ml SCC-Ag were 1.000, 0.519 (95% CI, 0.153-1.760; P=0.2921), 0.458 (95% CI, 0.149-1.402; P=0.1712) and 0.944 (95% CI, 0.378-2.360; P=0.9022), respectively. In addition, the RR values for tumor sizes of ≤4, 4-6 and >6 cm were 1.000, 3.421 (95% CI, 1.077-10.872; P=0.0371) and 6.599 (95% CI, 1.952-22.311; P=0.0024), respectively. In LN metastasis detected by imaging, the RR values were 2.319 (95% CI, 1.000-5.376; P=0.0499) for positive pelvic LN and 3.204 (95% CI, 0.561-18.302; P=0.1902) for positive para-aortic LN.

Of the five factors analyzed, the following two were determined as independent predictive variables by multivariate analysis: i) Tumor size (≤4 vs. 4-6 cm, P=0.0371; and ≤4 vs. >6 cm, P=0.0024); and ii) pelvic LN metastasis detected by imaging vs. no metastasis (P=0.0499). By contrast, para-aortic LN metastasis (P=0.1902), age (P=0.1589), tumor stage (P=0.0739) and serum SCC-Ag level (P>0.1712) were not found to be independent predictive factors.

Survival analysis. In the current study, the median follow-up period was 55 months (range, 12-70 months), the median survival rate was 33.0 months and the mean survival rate was 44.5 months. The Kaplan-Meier method was applied to determine the duration of patient survival according to each of the investigated variables. Significantly different mean survival rates were identified among the various tumor stages (Fig. 1), including 39.91 months for stage IIA, 50.60 months for stage IIB, 14.34 months for stage III and 28.67 months for stage IV (log-rank test, P<0.0001). Although the mean survival duration was significantly different, marked overlapping of the survival durations were observed between stages IIA and IIB, and stages IIIA/B and IVA/B of cervical cancer.

Statistically significant differences in survival were identified according to tumor size and the presence of LN metastasis (Fig. 2). For instance, the mean survival rates of patients with a maximum tumor diameter of ≤4, 4-6 and >6 cm were 66.1, 50.3 and 38.3 months, respectively (log-rank test, P<0.001). Furthermore, the mean survival rates of patients with no LN, pelvic LN and para-aortic LN metastases were 60.9, 49.3 and 22.0 months, respectively (log-rank test, P=0.001). No overlapping in survival duration was identified according to these variables.

Table III. Multivariate Cox proportional hazards model for survival in advanced cervical cancer patients.

Variable	RR	95% CI	P-value
Age[b]	1.244	0.918-1.686	0.1589
Stage[b]	1.460	0.964-2.210	0.0739
SCC-Ag[b], ng/ml			
≤2	1.000		
2-5	0.519	0.153-1.760	0.2921
5-15	0.458	0.149-1.402	0.1712
>15	0.944	0.378-2.360	0.9022
Tumor size[a], cm			
≤4	1.000		
4-6	3.421	1.077-10.872	0.0371
>6	6.599	1.952-22.311	0.0024
LN metastasis by imaging			
(-)	1.000		
(+) pelvic[a]	2.319	1.000-5.376	0.0499
(+) para-aortic[b]	3.204	0.561-18.302	0.1902

[a]Independent and [b]dependent variables. RR, relative risk; CI, confidence intervall; SCC-Ag, squamous cell carcinoma antigen; LN, lymph node.

Discussion

The FIGO staging system is widely used to select the appropriate treatment strategy and predict the prognosis for cervical cancer (2). Accurate staging of cervical cancer is essential for therapeutic decision-making, determining the prognosis and comparing the results of different treatment modalities (2). However, the current FIGO clinical staging system has limited prognostic accuracy and an increased possibility of staging errors in patients with advanced disease (18-20). Thus, the prognosis of patients with advanced cervical cancer appears to be variable, even among patients at the same stage (17,21). In the present study, a significant overlap of survival duration

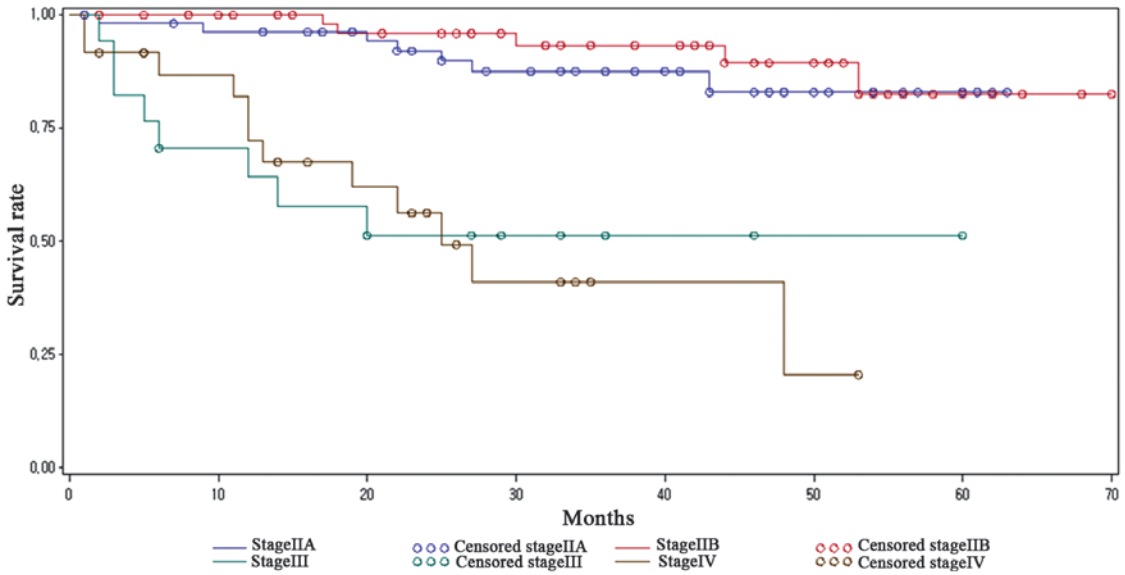

Figure 1. Kaplan-Meier analysis of stage-specific overall survival for all eligible advanced cervical cancer patients. The mean survival rate was 39.91 months for stage IIA, 50.60 months for stage IIB, 14.34 months for stage III and 28.67 months for stage IV cervical cancer. Significant differences in survival rate were identified between the different stages (log-rank test, P<0.0001); however, the survival rates of stage IIA vs. IIB and stage III vs. IV intersected.

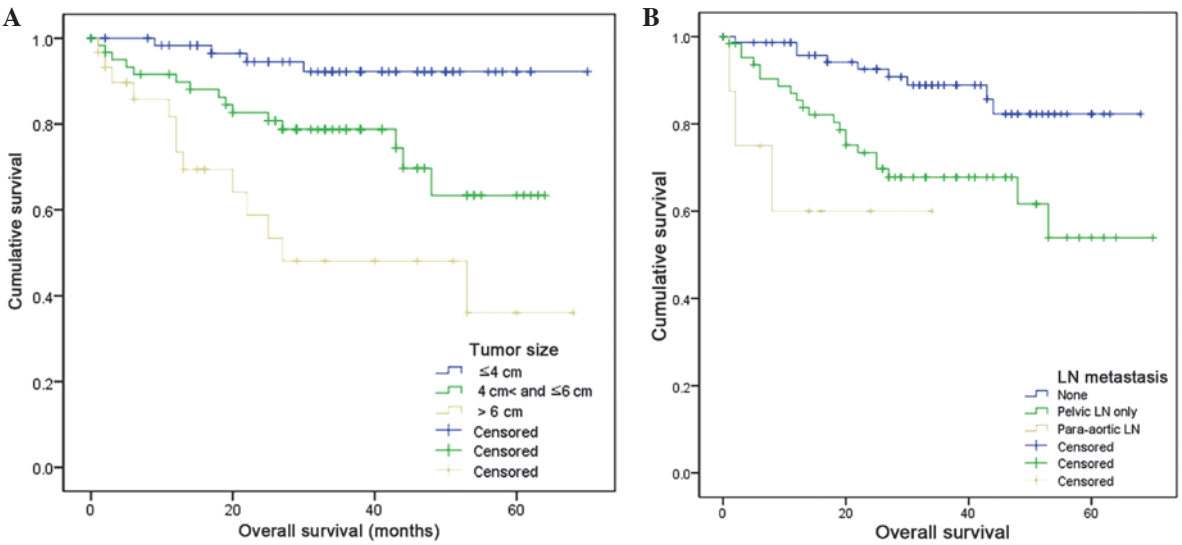

Figure 2. Kaplan-Meier analysis of overall survival according to (A) tumor size and (B) LN metastasis. Statistically significant differences in survival were identified among the various tumor sizes and the presence of LN metastasis detected by imaging. The mean survival rate of patients with tumors measuring a maximum diameter of ≤4, 4-6 and >6 cm were 66.1, 50.3 and 38.3 months, respectively (log-rank test, P=0.000). The mean survival rates of patients with no LN, pelvic LN and para-aortic LN metastasis were 60.9, 49.3 and 22.0 months, respectively (log-rank test, P=0.001). LN, lymph node.

was observed between cervical cancer stages IIA and IIB, as well as stages IIIA/B and IVA/B (Fig. 1), demonstrating the difficulty of accurately predicting survival using stage alone in advanced cervical cancer cases.

Furthermore, the FIGO staging system does not include pathological factors, such as tumor size and LN involvement, which are established prognostic factors (6,13,18-22). Thus, developing a novel tool for accurate prognostic prediction in advanced cervical cancer is essential.

As tumor size is closely associated with prognosis, the preoperative division of stage IIA into substages IIA1 and IIA2 has been attempted based on clinical measurements of the maximum tumor diameter (2). The tumor size is reflected in FIGO stages IA-IIA, but not in stage IIB or higher, from which suffered a number of the subjects in the present study. As a consequence, tumor size was analyzed as a prognostic factor in the current study. Classifying tumors into stages IIB1 and IIB2 based on a tumor size of >6 cm was not found to be appropriate for stage IIB cancer.

The Cox proportional hazards model was used to analyze factors considered to be associated with the prognosis of cervical cancer. Significant variables with high RR were identified as follows: Lower third vaginal involvement (RR, 12.976), pathological LN metastasis (RR, 10.971), LN metastasis (para-aortic and/or pelvic) detected by imaging (RR, 8.214), tumor size of >6 cm (RR, 8.691), hydronephrosis (RR, 3.740), bladder/rectal

involvement (RR, 3.216) and tumor stage (RR, 2.228). Among these variables, lower third vaginal involvement was associated with a greater risk of poor prognosis compared with bladder/rectal involvement, resulting in uncertainty regarding the reliability of lower third vaginal and bladder/rectal involvement as requirements for FIGO stages IIIB and IVA, respectively. Improvements in palliative treatment, including percutaneous nephrostomy, diversion cystostomy/colostomy and neoadjuvant chemotherapy, may have affected these survival results (23-25).

The involvement of HPV in cervical cancer development is well-established; however, attempts to determine the prognostic significance of the presence or absence of HPV DNA in patients with cervical cancer have yielded conflicting results (26-29). HPV-negative cervical carcinoma was associated with poor survival in a number of reports (26-29), but not in other studies (30,31). Furthermore, high-risk HPV infection is an important and well-established risk factor for cancer development, with a previous study identifying high-risk HPV infection as an independent prognostic factor in early stage cervical cancer (32). However, the present study identified no statistically significant correlation between high-risk HPV infection and cervical cancer prognosis (P=1.0000). This indicates that HPV infection may be associated with prognosis in early but not advanced-stage cervical cancer.

The specific tumor cell type of cervical cancer has been investigated (12). Previous studies have demonstrated that early and advanced stage adenocarcinomas are more aggressive and associated with decreased survival rates (33-36). However, the present study indicated that the tumor cell type was not significantly associated with prognosis (P=0.5831).

Based on the results of the present study, the association between the overall survival and prognostic factors in stage IIA or higher cervical cancer patients are as follows: Survival analysis determined that tumor sizes of >6 cm (P=0.0024) and pelvic LN metastasis detected by imaging (P=0.0499) were independent factors of advanced-stage cervical cancer. Preoperative staging or pretreatment evaluation by CT or MRI have previously been demonstrated as predictive factors (36,37) and are commonly performed, indicating that it may be clinically acceptable to investigate tumor size and LN status by imaging. Thus, based on the present data, it is proposed that the inclusion of tumor size and imaging detection of pelvic LN metastasis in a future FIGO staging system may improve the accuracy of survival prediction. In addition, cancer stage has not been previously identified as an independent risk factor in early stage cervical cancer (22). The results of the present study demonstrated that cancer stage is not an independent risk factor in advanced-stage cervical cancer (P=0.0739) and, thus, verifying that the FIGO stage alone is not an accurate method for predicting the prognosis of advanced cervical cancer. Therefore, modification of the currently employed advanced cervical cancer staging system is required. Furthermore, an SCC-Ag level of >15 ng/ml was associated with survival in univariate analysis; however, it was not identified as an independent variable in the multivariate analysis. Previous studies have reported that SCC-Ag levels were associated with FIGO stage, tumor volume and the risk of developing LN metastasis (38,39); therefore, SCC-Ag may not be an independent risk factor, but is associated with survival. In addition, data from the present study did not support that the age at diagnosis is a prognostic factor, contrary to previous studies (11-13,40). The revised FIGO staging system is considered to provide more accurate details for dividing stage IIA cervical cancer into stages IIA1 and IIA2, according to a tumor size of 4 cm. In addition, the present authors consider it necessary for stages III and IV to be divided into substages according to the tumor size.

However, the current study presents a number of limitations. The first limitation is that the LN status was determined by CT or MRI imaging, despite the accuracy of LN metastasis detection by CT or MRI varying between 75-86 and 75-100%, respectively, and thus potentially biasing the current results (41). To eliminate this bias, determination of the LN status by pathological examination is required. However, staging surgery in patients with advanced stage cervical cancer is associated with potential morbidity. Recently, positron emission tomography (PET)-CT has been proven to be a useful tool for detecting LN metastasis with high sensitivity and specificity (42); thus, assessment of LN status using PET-CT may aid in reducing bias. The second limitation is that the present study included 33 patients with small cell carcinoma, adenocarcinoma and adenosquamous cell carcinoma, which are more likely to metastasize compared with other nonsquamous cell carcinoma histological types. Inclusion of these patients may have influenced the estimation of other prognostic variables, including the HPV infection status, SCC-Ag levels and age. Another limitation is the fact that patients underwent various treatment strategies (including, surgery plus chemotherapy, surgery plus CCRT and CCRT alone), which may have potentially influenced the survival analysis in the present study. In addition, the HPV types were not analyzed, since HPV typing was not available at Kangdong Sacred Heart Hospital or Kangnam Sacred Heart Hospital during the study period. Finally, the significance of the present study is limited due to its retrospective nature and small number of patients included. These limitations may be overcome by conducting a large sample size randomized trial.

In conclusion, accurately predicting survival rates in advanced cervical cancer is difficult using the stage alone. In the present study, tumor size and pelvic LN metastasis determined by CT and/or MRI were identified as independent predictive factors for the prognosis of stage II-IV cervical cancer. These factors may provide more clinically significant prognostic data compared with the currently used FIGO staging system.

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