RESEARCH ARTICLE

Prognostic Model in Patients with Early-stage Squamous Cell Carcinoma of the Uterine Cervix: A Combination of Invasive Margin Pathological Characteristics and Lymphovascular Space Invasion

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Abstract

Background: This study aimed to develop a prognostic model in patients with early-stage cervical squamous cell carcinoma based on clinicopathological features, including invasive margin characteristics. Materials and Methods: Clinicopathological features and outcomes of 190 patients with FIGO stage IB-IIA cervical squamous cell carcinoma treated by surgery were collected and analyzed for factors associated with tumor recurrence. In addition to well-recognized pathological risk factors, the pathological characteristics of invasive margin (type of invasive pattern and degree of stromal desmoplasia and peritumoral inflammatory reaction) were also included in the analysis. Multiple scoring models were made by matching different clinicopathological variables and/or different weighting of the score for each variable. The model with the best performance in the prediction of recurrence and decreased survival was selected. Results: The model with the best performance was composed of a combined score of invasive pattern, lymphovascular space invasion (LVSI), and degree of inflammatory reaction and stromal desmoplasia (total score =10). Compared to those with score ≤8, the patients with score 9-10 had a significantly higher recurrence rate in the overall group ($p<0.001$) and the subgroup without adjuvant therapy ($p<0.001$), while the significance was marginal in the subgroup with adjuvant therapy ($p=0.069$). In addition, the patients with score 9-10 had a higher rate of tumor recurrence at distant sites ($p=0.007$). The disease-free survival was significantly lower in the patients with score 9-10 than those with score ≤8 among the overall patients ($p<0.001$), in the subgroup without adjuvant therapy ($p<0.001$), and the subgroup with adjuvant therapy ($p=0.047$). Conclusions: In this study, a prognostic model based on a combination of pathological characteristics of invasive margin and LVSI proved to be predictive of tumor recurrence and decreased disease-free survival in patients with early-stage cervical squamous cell carcinoma.

Keywords: Cervical cancer - squamous cell carcinoma - prognostic model - pathology - invasive margin

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Introduction

Pathologic examination of specimens from radical surgery in patients with early-stage cervical cancers provides information that has predictive prognostic potential. Several pathologic features have been extensively studied and recognized as standard prognostic features such as extent of tumor invasion, presence of lymphovascular space invasion (LVSI), parametrial involvement, and lymph node metastasis (Biewenga et al., 2009; 2011; Suprasert et al., 2010). The pathologic characteristics at the invasive margin (tumor front) were found to provide prognostic information in several types of cancers, including the uterine cervix (Bryne et al., 1998; Kristensen et al., 1999; Horn et al., 2006a; Eggen et al., 2007). The major characteristics of invasive margin include invasive pattern, stromal desmoplasia, and peritumoral inflammatory reaction (Horn et al., 2006a; 2006b; Fregnani et al., 2007).

The invasive pattern of cervical squamous cell carcinoma may be divided into 3 types: closed, finger-like, and spray-like (Horn et al., 2006a). The spray-like invasive pattern has been demonstrated to be predictive of poor clinical outcomes (Horn et al., 2006a; Khunamornpong et al., 2013). In our previous study, the recurrence rate in early-stage patients with a spray-like pattern was significantly higher than the rate in those with other invasive patterns (14% *vs* 3%) (Khunamornpong et al., 2013). Since a spray-like pattern was found in the majority (almost 60%) of cases (Horn et al., 2006a; Khunamornpong et al., 2013), it would be of greater benefit if the prognostic predicting performance could be

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improved by a combination of spray-like invasive pattern with other clinicopathologic features.

Stromal desmoplasia may enhance the invasive and metastatic potential of tumors (Tsujino et al., 2007), whereas peritumoral inflammatory reaction may be associated with a favorable prognosis in cancer patients, including those with cervical cancer (Kainz et al., 1994; Fregnani et al., 2007; Jass et al., 2007). In our previous study, stromal desmoplasia and peritumoral inflammatory reaction were not predictive of the prognosis in early-stage cervical cancer patients (Khunamornpong et al., 2013). However, the recurrence rate gradually increased with the degree of stromal desmoplasia, whereas the patients with marked inflammatory reaction had a lower recurrence rate than those without (Khunamornpong et al., 2013). Furthermore, there were independent correlations between each characteristic of invasive margin and the associations between these characteristics and other potential prognostic features in cervical cancer (Khunamornpong et al., 2013).

This study aimed to develop a potential model for prognostic prediction in patients with early-stage cervical squamous cell carcinoma based on the combination of spray-like invasive pattern and other clinical or pathologic features.

Materials and Methods

The study was approved by the Institutional Ethics Committee. This study was based on the patients with FIGO stage IB1-2 to IIA cervical squamous cell carcinoma who were treated by radical hysterectomy with pelvic lymph node dissection at Chiang Mai University Hospital between January 2003 and December 2006 and had available medical records with known follow-up results. Regarding the policy for post-operative adjuvant therapy, adjuvant radiation and/or chemotherapy was justified in patients with high pathological risk factors (lymph node metastasis, parametrial involvement, or positive vaginal margin involvement) or in patients who had a combination of residual uninvolved stromal thickness <3 mm and extensive LVSI (>10 foci in all tumor sections).

The histological criteria of each characteristic of the invasive margin (invasive pattern, stromal desmoplasia, and peritumoral inflammatory reaction) were previously described in detail (Khunamornpong et al., 2013). Briefly, the characteristics of invasive margin were evaluated in all tumor slides in each case. The invasive patterns were classified based on the predominant pattern that occupied >50% of margin areas as closed, finger-like, and spray-like pattern (Horn et al., 2006a; Khunamornpong et al., 2013). Stromal desmoplasia was classified into 3 grades: grade 1 - absent or minimal, grade 2 - moderate, and grade 3 - marked. Peritumoral inflammatory reaction was classified into 3 grades: grade 1 - absent or minimal, grade 2 - moderate, and grade 3 - marked. The other clinical and pathologic characteristics of cervical cancer included patient age, clinical stage, tumor size, tumor grade, deep stromal invasion (outer third of wall thickness), residual uninvolved cervical stromal thickness <3 mm, LVSI or extensive LVSI, parametrial involvement, positive vaginal margin, lymph node metastasis, and post-operative adjuvant treatment.

The data were analyzed using STATA software version 11. The association between tumor recurrence and variables was evaluated by Fisher exact test. Multivariate analysis was performed by logistic regression using the variables with p value <0.1 in univariate analysis. Five-year disease-free survival was calculated by Wilcoxon test. Disease-free survival was estimated by Kaplan-Meier method and log-rank test for equality of survivor function. A p value <0.05 was considered as statistically significant.

Multiple models were made by matching of different clinicopathological variables and/or different weighting of the score in each variable, including modifications of previously reported models or predicting systems for early-stage cervical cancer (Delgado et al., 1990; Yuan et al., 1998; Sedlis et al., 1999; Grisaru et al., 2003; Van de Putte et al., 2005; Biewenga et al., 2009; 2011). Each variable was scored ranging from 1 to 3; score 1 representing one end with the lowest adverse probability, and score 2 or 3 for the other end with the higher adverse probability. In each model, the difference in recurrence rate between the patient groups stratified by combined variables or scores was tested. The models with statistically significant performance were compared for the prediction of disease-free survival. The model with the best performance (lowest p value) in the prediction of recurrence and decreased survival in the overall patients and in the patient subgroups with and without adjuvant therapy was selected.

Results

Among 190 cases included in the study, 109 patients (57%) received adjuvant therapy including concurrent chemoradiation therapy in 76 (40%) and either radiation or chemotherapy in 33 (17%). Tumor recurrence was observed in 18 of the 190 patients (9%); 6 of 81 patients without adjuvant therapy (7%) and 12 of 109 patients with adjuvant therapy (11%). The median follow-up period was 73 months (range 3-120). Table 1 shows the association between clinicopathologic variables and tumor recurrence. Spray-like invasive pattern was the only variable significantly associated with recurrence (p=0.005), whereas a marginal association was observed for LVSI (p=0.079). The presence of extensive LVSI was not significantly associated with recurrence (p=0.214). In multivariate analysis, the spray-like pattern was the only variable independently associated with recurrence (p=0.015, odds ratio 6.5, 95% CI 1.4-29.5), whereas LVSI had only marginal association (p=0.085, odds ratio 6.1, 95%CI 0.8-47.7).

Further subgroup analysis in the patients without and with adjuvant therapy was performed. Among the patients without adjuvant therapy (81 cases), a spray-like invasive pattern had a significant association with recurrence (100% *vs* 51%, p=0.029), whereas LVSI had a marginal association (100% *vs* 56%, p=0.076). No significant association of recurrence with other clinicopathological variables was identified, with p values ranged from 0.345 (stage IB2-IIA) to >0.999 (grade 2-3). In patients with

adjuvant therapy (109 cases), a spray-like pattern was the variable with the least p value for recurrence, but the difference was not statistically significant (83% *vs* 59%, p=0.124). The other clinicopathological variables had no significant association with tumor recurrence including parametrial involvement (p=0.369), lymph node metastasis (p=0.762), LVSI (p>0.999), and vaginal margin involvement (p>0.999).

As spray-like invasive pattern and LVSI were the two variables related with recurrence; the model based on both features was tested. The recurrence rate in the patients with a combination of both features was compared with those without. Tumor recurrence was observed in 15 of 85 patients (18%) with combined spray-like pattern and LVSI compared with 3 of 105 patients (3%) without this combination (p<0.001). Considering the group of patients who did not receive adjuvant therapy (81 cases), 6 of 26 patients (23%) with the combined features had recurrence, compared with none of 55 patients (0%) without (p=0.001). Among 109 patients with adjuvant therapy, the recurrence rate in the patients with combined spray-like invasion and LVSI (9 of 59 cases, 15%) was higher than that of the patients without this combination (3 of 50, 6%), however, the difference was not significant (p=0.218).

When multiple scoring models were created based on various combinations of the clinicopathological variables, a spray-like pattern and LVSI appeared to be the two most influential variables. The model that produced the best predictive performance for tumor recurrence in the overall patients and in the subgroups with and without adjuvant therapy was composed of an invasive pattern (3 scores: 3 for spray-like pattern and 1 for the other patterns), LVSI (3 scores: 3 for positive and 1 for negative), inflammatory reaction (2 scores; 2 for grade 1-2 and 1 for grade 3), and desmoplasia (2 scores: 2 for grade 2-3 and 1 for grade 1), with a total score of 10.

Table 2 shows the performance of this scoring model among overall patients and in the subgroups with and without adjuvant therapy. A strong association between score 9-10 and tumor recurrence was observed in the overall group (p<0.001) and the subgroup without adjuvant therapy (p<0.001), although the significance was only marginal in the subgroup with adjuvant therapy (p=0.069). Among 114 cases with score ≤8, the recurrence rate was comparable between the group with score 7-8 (2 of 75 cases, 3%) and the group with score 4-6 (1 of 39 cases, 3%). The recurrence rate in the group with score 7-8 was significantly lower than the group with score 9-10 (p=0.001). Distant tumor recurrence was observed in 7 of 76 patients (9%) with score 9-10 compared with only one of 114 patients (1%) with score ≤8, the difference was statistically significant (p=0.007).

Table 1. Association of Clinicopathological Variables with Tumor Recurrence

Variables	Recurrent cases, n=18 (%)	Non-recurrent cases, n=172 (%)	p value
Spray-like invasive pattern	16 (89)	95 (55)	0.005
LVSI	17 (94)	127 (74)	0.079
Extensive LVSI	10 (56)	68 (40)	0.214
Parametrial involvement	7 (39)	42 (24)	0.255
Stage IB2-IIA	8 (44)	53 (31)	0.290
Age>45	6 (33)	76 (44)	0.458
Adjuvant therapy	12 (67)	97 (56)	0.461
Deep stromal invasion	17 (94)	145 (84)	0.481
Size >4 cm	4 (22)	27 (16)	0.502
Desmoplasia grade 2-3	14 (78)	118 (69)	0.592
Inflammation grade 1-2	14 (78)	120 (70)	0.594
Residual stroma <3 mm	12 (67)	103 (59)	0.623
Tumor grade 2-3	14 (78)	138 (80)	0.762
Positive vaginal margin	2 (11)	21 (12)	>0.999
Lymph node metastasis	5 (28)	48 (28)	>0.999

*LVSI: lymphovascular invasion

Table 2. Recurrence Rates of Patients Stratified by the Scoring Model (±deep stromal invasion) in Different Patient Groups

		No. of recurrence (%)	p value
Score 9-10			
Among overall cases (n=190)	Yes, n=76	15 (20)	<0.001
	No, n=114	3 (3)	
Among cases without adjuvant therapy (n=81)	Yes, n=23	6 (26)	<0.001
	No, n=58	0 (0)	
Among cases with adjuvant therapy (n=109)	Yes, n=53	9 (17)	0.069
	No, n=56	3 (5)	
Score 9-10 and deep stromal invasion			
Among overall cases (n=190)	Yes, n=67	14 (21)	<0.001
	No, n=123	4 (3)	
Among cases without adjuvant therapy (n=81)	Yes, n=20	6 (30)	<0.001
	No, n=61	0 (0)	
Among cases with adjuvant therapy (n=109)	Yes, n=47	8 (17)	0.076
	No, n=62	4 (6)	

Table 3. Comparison of 5-year Disease-free Survival of Patients Stratified by 5 Methods in Overall Patients (n=190), in Patients Without Adjuvant Therapy (n=81), and in Patients with Adjuvant Therapy (n=109)

		DFS, overall patients (95% CI)	p value	DFS, patients without adjuvant therapy (95% CI)	p value	DFS, patients with adjuvant therapy (95% CI)	p value
Spray-like pattern	Yes, n=111	83% (74-90)	0.004	85 %(68-93)	0.019	83% (71-91)	0.093
	No, n=79	97% (89-99)		100%		95% (80-99)	
Spray-like+LVSI	Yes, n=85	80% (69-87)	<0.001	73% (49-88)	<0.001	83% (69-91)	0.139
	No, n=105	97% (90-99)		100%		93% (81-98)	
Spray-like+LVSI+DSI	Yes, n=74	78% (66-87)	<0.001	70% (43-86)	<0.001	82% (68-91)	0.130
	No, n=116	96% (90-99)		100%		92% (80-97)	
Score 9-10	Yes, n=76	77% (65-86)	<0.001	71% (46-86)	<0.001	80% (66-89)	0.053
	No, n=114	97% (91-99)		100%		94% (83-98)	
Score 9-10+DSI	Yes, n=67	76% (63-85)	<0.001	67% (39-84)	<0.001	81% (65-90)	0.066
	No, n=123	96% (90-99)		100%		93% (82-97)	

*DFS: 5-year disease-free survival; DSI: deep stromal invasion; LVSI: lymphovascular invasion

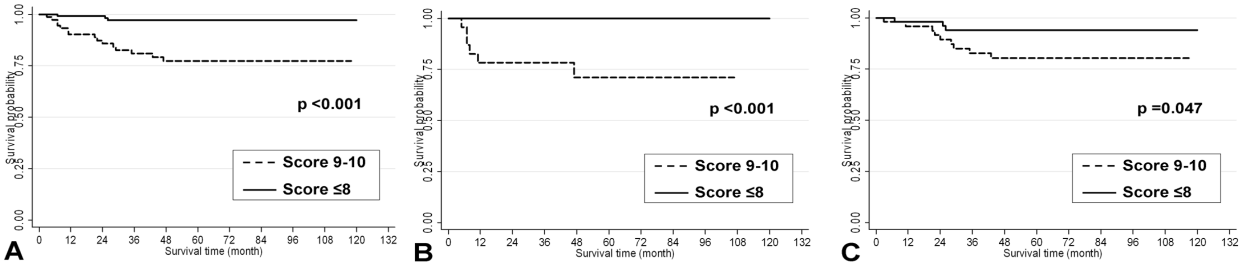

Figure 1. Kaplan-Meier Plots of Disease-free Survival Stratified by Combined Score. A) in the overall patients (n=190); **B)** in the patients without adjuvant therapy (n=81); and **C)** in the patients with adjuvant therapy (n=109)

Additions of other variables to the model did not improve the performance in prediction of recurrence of the model. Replacement of desmoplasia or inflammatory reaction with other variables resulted in a lowered performance of the model in overall patients. A combination of spray-like pattern, LVSI, and deep stromal invasion had the same predicting performance as that of the score 9-10 among the patients without adjuvant therapy, but a lower performance among the patients with adjuvant therapy (p=0.220). Compared with the score 9-10 alone, a combination of score 9-10 and deep stromal invasion improved the predicting performance among the patients without adjuvant therapy by an increase in recurrence risk (30% *vs* 26%), but not for the patients with adjuvant therapy (p=0.076 *vs* p=0.069) (Table 2).

Five-year disease-free survivals calculated by Wilcoxon test were compared between patients stratified by 5 methods based on various combinations of invasive pattern, LVSI, and deep stromal invasion (including the scoring model), in overall patients and the subgroups with and without adjuvant therapy (Table 3). The differences in 5-year survival of patients stratified by all 4 combined methods were highly significant (p<0.001) among the overall group and the subgroup without adjuvant therapy. In the subgroup with adjuvant therapy, the survival differences by all methods did not reach statistical significance. However, the combined scoring model had the best performance in this patient group (p=0.053).

Kaplan-Meier survival analysis showed similar results with a better performance of combined scoring model compared with the other methods in Table 3 (data not shown). The scoring model was the only method that stratified patients with significantly different disease-free survival in overall patients (p<0.001), in the subgroup without adjuvant therapy (p<0.001), and the subgroup with adjuvant therapy (p=0.047) (Figure 1). The performance of disease-free survival prediction among the patients with adjuvant therapy by combined score was better than those of the other methods (including the combination of deep stromal invasion with score 9-10, p=0.070).

Discussion

The pathologic characteristics of invasive margin are interrelated (Khunamornpong et al., 2013). Spray-like invasive pattern and low inflammatory reaction (grade 1-2) had an independent correlation with marked stromal desmoplasia (Horn et al., 2006b; Khunamornpong et al., 2013). The invasive margin characteristics are also associated with other pathological variables with prognostic potential. Low inflammatory reaction and a spray-like pattern was associated with a higher rate of LVSI or extensive LVSI (Horn et al., 2006a; Khunamornpong et al., 2013). Both stromal desmoplasia and low inflammatory reaction was also associated with aggressive pathological features in cervical carcinoma such as parametrial involvement and deep cervical wall invasion in univariate analysis (Khunamornpong et al., 2013). While the spray-like invasive pattern is reflective of an intrinsic property of cancer cells for dissociation and dissemination (Horn et al., 2006a), inflammatory reaction could represent a host response against tumor cells (Kainz et al., 1994; Fregnani et al., 2007) and may have a role in limiting direct extension of tumor or LVSI (Khunamornpong et al., 2013). As an inflammatory reaction seems to prevent stromal desmoplasia (Khunamornpong et al., 2013), it might help reduce one of the factors that promote tumor growth and spread (Tsujino et al., 2007). It is possible that the interaction of these features of invasive margin would contribute to the prognosis in individual patients.

In this study, a spray-like pattern and LVSI are the two variables with highest impact on tumor recurrence when compared with the other clinicopathological variables which have been recognized as potential prognostic factors in early-stage cervical cancer (Delgado et al., 1990; Yuan et al., 1998; Sedlis et al., 1999; Suprasert et al., 2010). The lack of prognostic values of several well-recognized high-risk pathological variables (e.g. parametrial involvement and lymph node metastasis) in our patient population might be due to the effectiveness of adjuvant therapy tailored in each individual patient based on these recognized risk factors (Khunamornpong et al., 2013). In this study, the combination of spray-like pattern and LVSI identified a group of patients with a significantly increased recurrence risk, particularly in the subgroup without adjuvant therapy. This finding is in keeping with the high capacity for dissociation and spread of carcinoma cells with a spray-like invasive pattern (Horn et al., 2006a) and its association with extensive LVSI (Khunamornpong et al., 2013). When these cancer cells invade the lymphovascular spaces, they may easily spread outside the uterus which could be an explanation for an increased recurrence risk.

Although the degree of desmoplasia and inflammatory reaction was not significantly associated with tumor recurrence in our study, addition of both variables into the combined scoring model based on spray-like pattern and LVSI led to an improved predictive performance in the

disease-free survival analysis regardless of adjuvant therapy. In the patients without adjuvant therapy, combined score 9-10 may be classified as an intermediate to high risk factor, with a 5-year disease-free survival of 71%. Despite only a marginal statistical significance, a p value by combined scoring model in the prediction of tumor recurrence in patients with adjuvant therapy was improved compared with the use of spray-like pattern with or without combination of LVSI (p=0.069 *vs* 0.124-0.218). In addition, the combined scoring model stratified the patients with a significantly higher risk for distant recurrence of disease (p=0.007). It should be noted that replacement of desmoplasia or inflammatory reaction with other variables did not improve the performance of this scoring model. The finding supports the possible contribution of desmoplasia and inflammatory reaction to the prognostic determination, in combination with spray-like pattern. Among the patients without adjuvant therapy, it is interesting that those with a combination of deep stromal invasion with score 9-10 had the lowest 5-year disease-free survival of only 67%. Therefore, adjuvant therapy should be indicated in this patient group based on such a high risk of tumor recurrence.

Several scoring systems for prognostic prediction in patients with early-stage cervical squamous cell carcinoma have been proposed (Stendahl et al., 1979; Kristensen et al., 1999; Eggen et al., 2007). Invasive pattern and inflammatory reaction have been included in the grading systems of early stage squamous cell carcinoma focusing on the pathologic evaluation of the invasive front (Stendahl et al., 1979; Kristensen et al., 1999; Eggen et al., 2007). These grading systems were also based on additional 2 to 6 pathologic features of tumor such as architectural pattern, degree of keratinization (comparable with tumor grade in our study), nuclear polymorphism (degree of pleomorphism), mitotic count, extent of stromal invasion, and LVSI (Stendahl et al., 1979; Kristensen et al., 1999; Eggen et al., 2007). Although these scoring systems are found to be predictive of recurrence risk or disease-free survival, they are rather complex and some constituting scores are closely related or overlapping (Horn et al., 2008).

A prognostic predicting system of cervical squamous cell carcinoma has been proposed by the Gynecologic Oncology Group (GOG) and validated in previous studies (Delgado et al., 1990; Sedlis et al., 1999; Van de Putte et al., 2005). This system is based on tumor size, depth of cervical wall invasion in fractional thirds, and presence of LVSI. Among our cases, the recurrence rate in patients with a combination of tumor size >4 cm, deep stromal invasion, and LVSI (16%) was not significantly higher than that of the remaining patients (8%, p=0.265) or that of the patients with LVSI alone or with LVSI and either size >4 cm or deep stromal invasion (12%, p=0.519). In another study, a prognostic predicting system composed of a combination of lymph node metastasis, deep stromal invasion, and tumor grade 3 (Yuan et al., 1998). This system stratified patient groups with different 5-year survival rate, which was as low as 25% when all 3 features were present. LVSI was not significantly associated with survival in the study (Yuan et al., 1998). However, such model could not stratify the patients with significantly higher recurrence risk in our study population (12% *vs* 9%, p=0.554). Furthermore, the model that includes lymph node metastasis could not be applied to the patients who did not receive adjuvant therapy because lymph node metastasis is an indication for adjuvant treatment.

Many predicting systems for patients with early-stage cervical carcinoma of various histologic types (including adenocarcinoma and adenosquamous carcinoma) have also been proposed. These models represent various combinations of 3 to 7 prognostic features which were found to be significant in the multivariate analysis in each study, including the clinical variables (i.e. age or stage), the pathological variables (i.e. histologic type, histologic grade, tumor size, depth of stromal invasion, LVSI, venous invasion, parametrial involvement, lymph node metastasis, vaginal involvement, or invasive pattern), or ancillary investigation results (i.e. DNA index by flow cytometry or HPV18 detection) (Kamura et al., 1992; Sevin et al., 1996; Lai et al., 1999; Trattner et al., 2001; Takeda et al., 2002; Grisaru et al., 2003; Ayhan et al., 2004; Ho et al., 2004; Shinohara et al., 2004; Lai et al., 2007; Metindir and Bilir, 2007; Sartori et al., 2007; Behtash et al., 2009; Biewenga et al., 2009; 2011). When applied to our patient population, only two of these prognostic models by Shinohara et al. (2004) and Ho et al. (2004) could identify the patient group with a significantly higher recurrence rate than the remaining cases (p<0.05).

In Shinohara prognostic model (Shinohara et al., 2004), the high-risk group with a recurrence risk of 52% was classified by the presence of at least 3 of 5 pathologic features including deep stromal invasion, venous invasion, parametrial involvement, nodal metastasis, and an infiltrative tumor border. Adaptation of this model to our cases also identified a patient group with a significantly increased recurrence risk than the remaining patients (20% *vs* 7%, p=0.028). In Ho model (Ho et al., 2004), the presence of deep stromal invasion and LVSI classified a high-risk group among patients with squamous cell carcinoma. Using this model in our cases, a higher recurrence rate was also observed in the high-risk group than in the remaining cases (13% *vs* 3%, p=0.037). However, the performance of these two models did not reach the high level of significance (p<0.001) as obtained by the combined scoring model in the present study.

Biewenga et al. (2011) recently proposed a prognostic model for survival which was composed of multiple combined features including histological type, tumor size, lymph node metastasis, parametrial involvement, LVSI, and fractions of stromal invasion, with differently weighted scores. When applied to the patients in our study, there was no difference in the recurrence rate between cases stratified into low, intermediate, and high risk groups by this model system among the patients with LVSI (p>0.999). The patients without LVSI but scored as 'high risk' by the other features using this system (n=11) had no recurrence. This supports our finding that LVSI is an important prognostic determinant. Variation in the histological types of cases, in the patient selection criteria for adjuvant therapy, or in the selection of adjuvant treatment modality (radiation and/or chemotherapy) between each study may be an explanation for the difference in the results when the prognostic predictive systems are evaluated in different institutions (Sedlis et al., 1999; Van de Putte et al., 2005; Biewenga et al., 2009; 2011).

In conclusion, patients with early-stage cervical squamous cell carcinoma who had a combination of spray-

like invasive pattern and LVSI have an increased recurrence risk and decreased disease-free survival. Addition of the assessment of stromal desmoplasia and peritumoral inflammatory reaction may improve the performance in the prognostic prediction based on spray-like pattern and LVSI.

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