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Preoperative nomogram for prediction of microscopic parametrial infiltration in patients with FIGO stage IB cervical cancer treated with radical hysterectomy

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HIGHLIGHTS

- Preoperative nomogram was established to predict microscopic parametrial infiltration in FIGO stage IB cervical cancer.
- Tumor volume and disruption of the cervical stromal ring on MRI, SCC-Ag, and menopause were incorporated into the model.
- The nomogram is useful for accurate and individual prediction of microscopic parametrial infiltration.

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ABSTRACT

Objective. This study aimed to establish a nomogram to predict microscopic parametrial infiltration (PMI) by combining preoperative clinicopathologic factors in FIGO stage IB cervical cancer patients treated by radical hysterectomy (RH).

Methods. We retrospectively analyzed clinicopathologic data of 298 patients with FIGO stage IB cervical cancer treated by RH between February 2000 and March 2015. The nomogram was developed based on multivariate logistic regression analysis of preoperative clinicopathologic data. The accuracy and discriminative ability of the nomogram were evaluated by a concordance index and calibration curve. The low-risk group was predefined as having a predicted probability of PMI <10%.

Results. Multivariate analysis identified diameter-based tumor volume and disruption of the cervical stromal ring on magnetic resonance imaging, serum squamous cell carcinoma antigen level, and menopausal status as independent prognostic factors associated with PMI. The concordance index of the nomogram was 0.940 (95% CI, 0.908–0.967), and calibration plots revealed good agreement between the observed probabilities and nomogram-predicted probabilities (Hosmer Lemeshow test, $p = 0.574$). The nomogram classified 200 out of 298 patients (67.1%) as low risk. In the low-risk group, the predicted probability of PMI was 3.5% and the actual PMI rate was 2.5% (5 out of 200).

Conclusions. We developed a preoperative nomogram predicting microscopic PMI in surgically treated FIGO stage IB cervical cancer patients. The probabilities derived from this nomogram may have the potential to provide valuable guidance for physicians regarding the primary management of FIGO stage IB cervical cancer patients.

1. Introduction

International Federation of Gynecology and Obstetrics (FIGO) stage IB cervical cancer can be cured by radical hysterectomy (RH) or radiotherapy (RT), but both treatments have different rates and types of complications (RH, 28% vs. RT, 12%; $p = 0.004$) [1]. As the two treatment modalities show similar survival rates, physicians must consider treatment-related quality of life issues when selecting the best treatment

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for each patient. Recently, Katanyoo et al. [2] performed a cost-utility analysis of primary treatment in patients with FIGO stage IB cervical cancer. They found that primary radical surgery was less cost-effective when postoperative adjuvant chemoradiation was added. Thus, the use of postoperative chemoradiation as adjuvant therapy should be minimized and a predictive model for high-risk pathologic features including microscopic parametrial infiltration (PMI) and lymph node (LN) metastasis would be of great benefit in limiting the use of postoperative chemoradiation.

Parametrial invasion is the most important factor in cervical cancer staging and treatment because it is associated with poor prognoses. Previous authors have demonstrated that preoperative magnetic resonance imaging (MRI) can help identify patients at a low risk for PMI; simple or modified RH may be performed in patients with FIGO stage IB1 cervical cancer [3–6]. However, approximately 5% to 10% of patients with FIGO stage IB1 cervical cancer had microscopic PMI [4,7–9]. Moreover, microscopic PMI is detected in approximately 35% (range, 32.3%–36.4%) of patients with FIGO stage IB2/IIA cervical cancer [7,10]. Thus, it is difficult to preoperatively predict microscopic PMI in cases where less radical surgery is used to treat patients with FIGO stage IB cervical cancer, using only tumor size on clinical examination/MRI or cone specimens.

Our institution has suggested a predictive model for PMI using tumor size on MRI and tumor biomarkers according to the menopausal status [11]. To develop more objective criteria for PMI, we used a specific MRI method to identify PMI that includes diameter-based tumor volume and the presence of a dark band around the uterine cervix on axial T2-weighted MRI [12–15]. In particular, preservation of the low signal intensity cervical stromal ring has a negative predictive value of 94% to 100% in virtually excluding PMI [13–15]. Using all possible risk factors for PMI, we constructed a preoperative nomogram for individualized prediction of PMI in patients with FIGO stage IB cervical cancer treated with RH.

2. Material and methods

We retrospectively analyzed clinicopathologic data of 360 patients with FIGO stage IB cervical cancer treated by Piver type III RH with retroperitoneal lymphadenectomy between February 2000 and March 2015 at Ajou University Hospital. The inclusion criteria were as follows: patients who were diagnosed with invasive squamous cell carcinoma, adenosquamous cell carcinoma, and adenocarcinoma on cervical punch biopsy; patients with FIGO stage IB cervical cancer with no definite evidence of parametrial invasion or LN metastasis during preoperative gynecologic examination, MRI, and positron emission tomography-computed tomography (PET-CT); and those without underlying disease that would have influenced survival. Specifically, a definite evidence of parametrial invasion was defined as a full-thickness loss of normal low signal intensity cervical stroma on T2-weighted axial MRI. We excluded 46 patients who had received conization before MRI, 14 patients in whom tumor biomarkers had not been measured and no pelvic MRI was done pretreatment, and 2 patients who were diagnosed with non-squamous cell carcinoma or non-adenocarcinoma (Fig. 1). A total of 298 patients were enrolled in this study. Clinicopathologic data were obtained from medical records after getting approval from the center's institutional review board.

All patients underwent pelvic examination and the clinical tumor size of the uterine cervix was evaluated as described previously [9]. RH with retroperitonal lymphadenectomy was performed via laparotomy or laparoscopy as described in a previous report [9]. When choosing the primary surgical approach, the patient's age, personal preferences, and comorbidities as well as the surgeon's experience were considered. Pathologic characteristics were evaluated as described previously [9]. In addition, pathologic specimens of the uterine cervix and parametrium were processed as follows. In the gross examination of RH specimens, the parametrial margins were identified and conventional microscopic evaluation was performed with hematoxylin-eosin staining. After identification of the parametrial wing, the parametrium was searched for any palpable nodes and contiguous full-thickness sections of the uterine cervix and parametrium were evaluated microscopically using hematoxylin-eosin staining. Microscopic PMI was defined as direct tumor infiltration or nodal spread through the lymphatic or vascular systems.

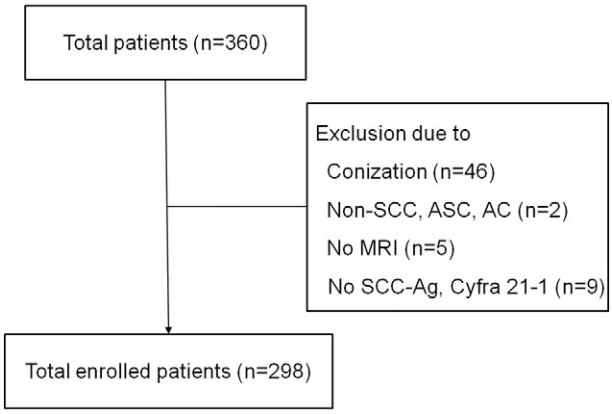

Fig. 1. Inclusion criteria. SCC, squamous cell carcinoma; ASC, adenosquamous cell carcinoma; AC, adenocarcinoma; MRI, magnetic resonance imaging; SCC-Ag, squamous cell carcinoma antigen; Cyfra 21-1, an enzyme immunoassay measuring serum fragments of cytokeratin 19.

MRI was performed in all patients using 3.0T machines (Achieva; Philips Medical Systems, Best, The Netherlands) with body coils or phased-array coils. Details of the MRI protocols were described in a previous report [11]. In our institution, staging of uterine cervical cancer is based on clinical FIGO criteria and MRI/PET-CT remains an ancillary tool in the evaluation of patients with cervical cancer. The diameter-based tumor volume was computed with the formula $d1 \times d2 \times d3 \times \pi/6$ for the ellipsoid as described previously [12]. Specifically, the longitudinal diameter (d1) along the long axis of the uterine cavity was measured in the sagittal plane, the anteroposterior diameter (d2) was obtained perpendicularly to the longitudinal diameter (d1) in the sagittal plane, and the largest lateral diameter (d3) was measured in the axial plane. In addition, we evaluated the radiological signs of PMI including focal disruption of the cervical stromal ring on oblique axial T2-weighted MRI [16,17].

Patients were assigned to two groups according to the presence of microscopic PMI in postoperative pathologic results. Pre- and post-operative clinicopathologic factors including diameter-based tumor volume and disruption of the cervical stromal ring on MRI, serum squamous cell carcinoma antigen (SCC-Ag), and cytokeratin-19 fragments (Cyfra 21-1) were compared between the two groups. A Kolmogorov–Smirnov normality test was performed to evaluate whether data were normally distributed. Continuous variables were analyzed using the Student's *t*-test and the Mann-Whitney *U* test according to normality, and categorical variables were compared between the two groups using the Pearson chi-square test and Fisher's exact test. Preoperative risk factors for microscopic PMI were determined based on multivariate logistic regression analysis with a backward elimination method. Data were analyzed using SPSS ver. 20.0 (IBM Co., Somers, NY, USA). The preoperative nomogram for microscopic PMI was constructed based on the results of the multivariate analysis with the aid of the rms package in R version 3.2.1 (https://www.r-project.org/) as described previously [18,19]. The accuracy and discriminative ability of the nomogram were evaluated by a concordance index and calibration curve, which were derived based on the regression analysis. The Hosmer-Lemeshow test was employed to assess calibration. The low-risk group was predefined as having a predicted probability of PMI <10%. A *p*-value (from two-sided tests) <0.05 was used to indicate a statistically significant difference.