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Prediction model for para-aortic lymph node metastasis in patients with locally advanced cervical cancer

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HIGHLIGHTS

- 245 consecutive LACC patients undergoing para-aortic lymphadenectomy before definitive treatment were analyzed.
- Using tumor size and PET/CT features, a risk prediction model for predicting PALN metastasis was developed.
- The model displayed good discrimination and calibration (concordance index = 0.886; 95% confidence interval = 0.825–0.947).

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ABSTRACT

Objective. Concurrent chemoradiotherapy is usually administered to patients with locally advanced cervical cancer (LACC). Extended-field chemoradiotherapy is required if para-aortic lymph node (PALN) metastasis is detected. This study aimed to construct a prediction model for PALN metastasis in patients with LACC before definitive treatment.

Methods. Between 2009 and 2016, all consecutive patients with LACC who underwent para-aortic lymphadenectomy at two tertiary centers were retrospectively analyzed. A multivariate logistic model was constructed, from which a prediction model for PALN metastasis was developed and internally validated. Before analysis, risk grouping was predefined based on the likelihood ratio.

Results. In total, 245 patients satisfied the eligibility criteria. Thirty-four patients (13.9%) had pathologically proven PALN metastases. Additionally, 16/222 (7.2%) patients with negative PALNs on positron emission tomography/computed tomography (PET/CT) had PALN metastasis. Moreover, 11/105 (10.5%) patients with both negative PALNs and positive pelvic lymph nodes on PET/CT had PALN metastasis. Tumor size on magnetic resonance imaging and PALN status on PET/CT were independent predictors of PALN metastasis. The model incorporating these two predictors displayed good discrimination and calibration (bootstrap-corrected concordance index = 0.886; 95% confidence interval = 0.825–0.947). The model categorized 169 (69%), 52 (22%), and 23 (9%) patients into low-, intermediate-, and high-risk groups, respectively. The predicted probabilities of PALN metastasis for these groups were 2.9, 20.8, and 76.2%, respectively.

Conclusion. We constructed a robust model predicting PALN metastasis in patients with LACC that may improve clinical trial design and help clinicians determine whether nodal-staging surgery should be performed.

1. Introduction

Since cytological screening was introduced, the incidence of cervical cancer has decreased remarkably. However, this disease remains a sizeable health problem that accounted for an estimated 528,000 new cases and for 266,000 deaths worldwide in 2012 [1]. In Korea, it is the most common female genital malignancy, and the age-standardized incidence rate is 9.5 per 100,000 persons in 2013 [2].

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Based on five phase III randomized trials demonstrating that concurrent chemoradiotherapy (CCRT) improves overall survival in patients with locally advanced cervical cancer (LACC), the current guidelines recommend CCRT as the standard treatment for these patients [3,4]. Nodal metastasis is among the most important prognostic factors for survival in patients with LACC. In patients with para-aortic lymph node (PALN) metastasis, extended-field radiotherapy should be considered [5]. Accurate pretreatment evaluation of PALN involvement is therefore of paramount importance in selecting radiation fields.

The use of fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) may aid in detecting extrapelvic disease compared with conventional imaging modalities such as pelvic magnetic resonance imaging (MRI) or CT [6,7]. Although PET is valuable for detecting extrapelvic disease, the reported false-negative rate of PALN metastasis on PET/CT ranged 9–22%, which is ascribable to small-volume metastases [5,7]. Consequently, nodal-staging surgery is possibly beneficial for patients with negative PALN involvement on PET/CT [8–10]. However, considering potential morbidity and the cost of staging surgery, nodal-staging surgery needs to be individualized in these patients [11]. Thus, it would be useful to develop an individualized prediction model for PALN metastasis before definitive treatment. Furthermore, individualized risk stratification of PALN metastasis may be advantageous in clinical trial design.

Thus, this study aimed to develop and internally validate a prediction model for PALN metastasis in patients with LACC and identify potential candidates for PALN staging surgery using the model.

2. Methods

2.1. Patients

Two tertiary medical centers participated in this retrospective study. After obtaining institutional review board approval from both the participating institutions, patients were identified from a computerized database of patients with cervical cancer between March 2009 and February 2016. The inclusion criteria were as follows: pathologically proven cervical cancer; a clinical diagnosis of FIGO stage IB2, IIA2, IIB, III, or IVA disease; age > 18 years and <80 years; para-aortic lymphadenectomy before definitive treatment; pelvic MRI and PET/CT performed within 3 weeks before lymphadenectomy; absence of distant metastatic disease on imaging or physical examination; and no history of chemotherapy or radiotherapy prior to para-aortic lymphadenectomy.

2.2. Preoperative assessment

Patients received exact staging, including physical examination, chest X-ray, serum squamous cell carcinoma antigen (SCC Ag) analysis, urinalysis, intravenous pyelography, and sigmoidoscopy before para-aortic lymphadenectomy. To identify variables predicting PALN metastasis, the following factors were tested on the basis of previously reported results [8,12–14]: age, body mass index (BMI), parity, FIGO stage, histology, parametrial invasion, tumor size, pelvic lymph node (PLN) metastasis on PET/CT, PALN metastasis on PET/CT, and pretreatment serum SCC Ag content. Tumor size and parametrial invasion were determined by MRI. The settings and conditions of the PET/CT scanning process are described in the Supplementary data (online only). Scans were interpreted based on the criteria of the International Harmonization Project in Lymphoma [15]. The results of MRI and PET/CT were interpreted blindly without knowledge of lymph node metastasis by radiologists and nuclear medicine physicians, respectively. All clinicopathologic and radiologic data were obtained from the medical records of each institution, and no central review was performed.

2.3. Para-aortic lymphadenectomy

In both institutions, the indications for para-aortic lymphadenectomy are as follows: a clinical diagnosis of FIGO stage IB2, IIA2, IIB, III, or IVA disease; age > 18 years and <80 years; and the absence of distant metastatic disease on imaging or physical examination. Para-aortic lymphadenectomy was performed as previously described [16]. Briefly, para-aortic lymphadenectomy was performed via laparoscopy or laparotomy. All of lymphatic tissue from the aorta, aortocaval space, and vena cava were completely removed. The boundaries of the para-aortic lymphadenectomy were defined as the bifurcation of the aorta caudally and the inferior mesenteric artery cranially. If the PALN at this level was enlarged or positive for metastasis, PALN dissection was extended to the left renal vein level. All harvested lymph nodes were grouped according to the name of the adjacent vessel (venacaval, aortocaval, aortic below the inferior mesenteric artery, and aortic above the inferior mesenteric artery). Each lymph node was sliced perpendicular to its long axis, stained with hematoxylin and eosin, and examined microscopically by a pathologist. Each pathology report included the number of lymph nodes retrieved from each area, the presence or absence of metastases, the largest size of lymph node metastases, and the presence or absence of extracapsular extension. Pelvic lymphadenectomy was not routinely performed as part of surgical nodal staging because the pelvic area is covered by the conventional radiation field. However, pelvic lymphadenectomy was performed to remove enlarged or suspicious pelvic nodes at the surgeon's discretion. In both institutions, for patients with negative results on frozen section of para-aortic lymphadenectomy, radical hysterectomy was considered in selected younger patients (especially those under 45 years old) and FIGO stage IB2 or IIA2.

2.4. Concurrent chemoradiotherapy

The uterine cervical cancer treatment protocol has been described previously [17]. A brief description is available in the Supplementary data (online only).

2.5. Statistical analysis

Age, BMI, parity, tumor size, and serum SCC Ag levels were considered continuous variables. FIGO stage, histology, parametrial invasion, and lymph node metastasis determined by imaging studies were considered categorical variables. The histological subtype was classified as squamous cell or non-squamous cell carcinoma.

The prediction model was developed as described previously [18]. To construct a robust and well-calibrated model predicting the risk of PALN metastasis, a logistic regression model was built using the entire cohort of 245 patients and internally validated using a bootstrap procedure. A multivariable logistic regression model with penalized maximum likelihood estimation was created to predict PALN metastasis. First, the bivariate relationship between risk factors and PALN metastasis was assessed via logistic regression in the enrolled cohort. Next, the candidate variables with a P-value < 0.5 on univariate analysis were tested by bootstrap resampling, in which a logistic regression model with a backward elimination procedure was performed with 1000 repetitions. The criterion for inclusion of predictors in the final logistic model was a 50% relative frequency of selection by bootstrap resampling. The final model was presented as a score chart to facilitate practical application. The score chart was derived from the multivariable regression coefficients. To score tumor size, the patients were categorized into three groups: ≤4 cm, 4.01–5 cm, and >5 cm. For simple application, the coefficients were divided by the effect of a 1-cm increase in tumor size and rounded.

The performance of the model was assessed with respect to discrimination and calibration. To measure discrimination, the concordance index was determined by calculating the area under the receiver operating characteristics curve (AUC). To assess calibration, which means