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ORIGINAL ARTICLE



# Postoperative nomogram for the prediction of disease-free survival in lymph node-negative stage I–IIA cervical cancer patients treated with radical hysterectomy

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**ABSTRACT**

The purpose of this study was to develop and validate a nomogram for individual prediction of recurrence and disease-free survival (DFS) among lymph node (LN)-negative early-stage (I–IIA) cervical cancer (CC) patients treated with Type B or Type C2 hysterectomy. Data were collected from patients diagnosed with CC between 1995 and 2017 at the Gynecological Oncology Department, Tepecik Training and Research Hospital. A total of 194 cases with stage IA2–IIA CC were evaluated retrospectively. Patients with stage IA2–IIA CC who underwent radical (Type C2) or modified radical (Type B) hysterectomy and pelvic ± paraaortic LN dissection with LN negativity were included in the study. The relationships between prognostic factors such as stage, tumour size, parametrial involvement, vaginal cuff margin, endomyometrial infiltration, and lymphovascular space invasion status and DFS were compared using a univariable Cox regression model. When the nomogram was prepared, the scores of the risk factors were collected, and we observed that scores were at least 0 to a maximum of 414 points. The concordance-index for the nomogram was 0.895 (95% confidence interval, 0.79–0.99). The nomogram based on the indicated prognostic factors yielded excellent results in predicting recurrence in early-stage CC patients without LN metastasis who underwent radical hysterectomy.

**KEYWORDS**

Disease-free survival; lymph node; cervical cancer; radical hysterectomy

**IMPACT STATEMENT**

- **What is already known on this subject?** Pathology of radical hysterectomy specimens in patients with early-stage cervical cancer provides information that has predictive prognostic potential. In addition to FIGO stage, other important prognostic factors are lymph node status, tumour size, parametrial involvement, vaginal cuff margin status, endomyometrial infiltration, histological type, patient age, lymphovascular space invasion, histological grade, and depth of cervical stromal invasion.
- **What do the results of this study add?** In this study, patients with early-stage cervical cancer who underwent radical and modified radical hysterectomy without retroperitoneal lymph node involvement were evaluated, and recurrence development and factors affecting disease-free survival were investigated. A nomogram consisting of factors influencing disease-free survival was constructed. The total score was determined according to the status of all risk factors. This allowed clear definition of the risk for each patient. A nomogram predicting recurrence in patients with stages IA2–IIA cervical cancer with radical hysterectomy without lymph node involvement has not previously been published.
- **What are the implications of these findings for clinical practice and/or further research?** Our study investigated early-stage cervical cancer (CC) patients without lymph node (LN) metastasis. Cox regression analysis was performed with six prognostic factors: FIGO stage, tumour size, parametrial margin infiltration, vaginal cuff margin involvement, endomyometrial infiltration, and LVSI positivity. The nomogram was constructed based on the results of Cox regression. The C-index for the nomogram was 0.895 (95% CI, 0.79–0.99). These results can be considered excellent. The higher concordance index in our study indicates that these six factors may be more valuable in predicting recurrence development in CC patients.

## Introduction

The strongest prognostic parameter in cervical cancer (CC) is stage based on the International Federation of Gynaecologists and Obstetricians (FIGO) system (Polterauer et al. 2012). Pathology of radical hysterectomy specimens in patients with early-stage CC provides information that has predictive prognostic potential. In addition to FIGO stage, other important prognostic factors are lymph node (LN) status, tumour size, parametrial involvement, vaginal cuff margin status,

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endomyometrial infiltration, histological type, patient age, lymphovascular space invasion (LVSI), histological grade, and depth of cervical stromal invasion (Polterauer et al. 2012).

Despite the infrequency of metastasis at the time of initial diagnosis of cervical cancer (CC), 15–61% of patients develop metastases (Ries et al. 2006). In general, metastases progress in the first two years after initial diagnosis. Approximately 67% of all metastases are diagnosed within 1 year of a primary CC diagnosis, and 75% of patients die within 1 year of a diagnosis of metastasis (Li et al. 2016). The most common metastatic sites are the vaginal apex (22–56%), lateral walls of the pelvis (28–37%), and distant organ metastases (15–61%) (Rintala et al. 1997). Metastases to distant organs are characterised by haematogenous spread and a poor prognosis (Thanapprapasr et al. 2010). The most common sites of distant metastases are the lungs, liver and bone (Thanapprapasr et al. 2010).

The aim of this study was to develop and validate a nomogram for individual prediction of recurrence and disease-free survival (DFS) in LN-negative early-stage (I–IIA) CC patients treated with Type B or Type C2 hysterectomy.

## Patients and methods

Data were collected from patients diagnosed with CC between January 1995 and January 2017 at the Gynecological Oncology Department, Tepecik Training and Research Hospital. A total of 194 cases with stage IA2–IIA CC were evaluated retrospectively. Patients with FIGO stage IA2–IIA CC who underwent radical (Type C2) or modified radical (Type B) hysterectomy and pelvic ± paraaortic LN dissection with LN negativity were included in the study. Patients with local advanced stage (IIB–IVA) and metastatic stage (IVB) CC, those who had undergone type 1 hysterectomy or surgery without lymphadenectomy, or who had CC with LN involvement were excluded. Figure 1 presents a flowchart of the recruitment of study patients. Staging was performed according to the FIGO 2018 staging system (Bhatla et al. 2018) by examination under general anaesthesia, and patients were evaluated using imaging modalities. In patients treated before 2018, the stage was determined retrospectively based on surgical and pathological assessments. The study was approved by the local ethics committees of the participating institutions and was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Clinical data were obtained from the patient files. Patient age, menopausal status, type of surgery, adjuvant therapy, DFS, and overall survival were investigated. Surveillance consisted mainly of a physical examination and questioning the patients about their symptoms. Tumour recurrence was confirmed via clinical pelvic exam or imaging studies during a regular visit or following the occurrence of symptoms such as vaginal spotting or abdominal discomfort.

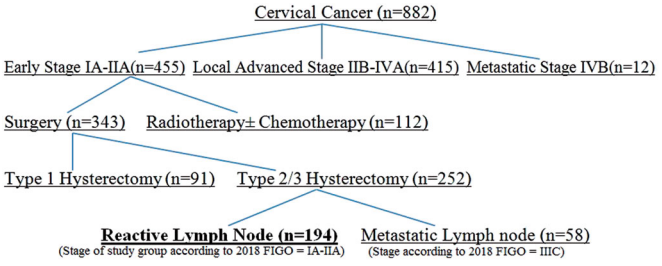


Figure 1. Flowchart of patient recruitment to the study (according to 2009 FIGO clinical staging).

All surgical specimens were evaluated by specialised gynecological pathologists. Tumour size, grade, histological type, depth of stromal invasion (DOI), LVSI, LN status, endomyometrial invasion, vaginal cuff margin status, and parametrial margin status were analysed in accordance with the pathology reports. The numbers of pelvic and paraaortic LNs and LN involvement were evaluated from the pathology reports. DOI was defined as the measurement of the tumour from the epithelial–stromal junction of the adjacent most superficial epithelial papilla to the deepest point of invasion. LVSI was defined as the presence of tumour cells inside the capillary lumens of either the lymphatic or microvascular drainage systems within the primary tumour.

Radical hysterectomy (type C2) consisted of removal of the uterus and adjacent parametrium to its most lateral extent along the paracolpium and the upper portion of the vagina and the proximal uterosacral ligaments. Modified radical hysterectomy (type B) included removal of the uterus, cervix, upper one-fourth of the vagina, 1 cm of the ventral parametrium, 1–1.5 cm of the lateral parametrium, and 1–2 cm of the dorsal parametrium. Pelvic lymphadenectomy consisted of removal of the lymphatic tissue over the external and common iliac vessels and in the obturator fossa. Paraaortic LN dissection was performed by removing the lymphatic tissue over the inferior vena cava and aorta, beginning at the bifurcation and proceeding to the inferior mesenteric artery if necessary.

The patients completed follow-up evaluations every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Computed tomography or magnetic resonance imaging was performed annually. DFS was defined as the interval from the date of primary surgery to the detection of recurrence or the latest observation. Overall survival was defined as the interval from the date of primary surgery to death or the latest observation.

### *Statistical analyses*

Data were analysed using standard descriptive statistics. The Chi-square test and Student's *t*-test were used for unpaired data comparisons. Survival was analysed using the Kaplan–Meier method, and the results were compared using the log-rank test. Logistic regression analysis was used to define predictive factors. The results are presented as odds ratios (OR) and 95% confidence intervals (CI). Cox regression analysis was used to determine the factors affecting survival, with the results presented as hazard ratios (HR). β value shows the average change that a unit change in the independent variable will create in the dependent variable. The nomogram was constructed based on the results of the Cox regression. The nomogram was internally validated by discrimination and calibration. The prediction accuracies of the

nomograms were measured using the concordance index (C-index). The C-statistic is a measure of the model's ability to discriminate between high-risk and low-risk subjects. It varies from 0.0 (the model's predictions are no better than chance) to 1.0 (perfect predictive power). Calibration curves were drawn by plotting corresponding nomogram-predicted survival probabilities and observed probabilities. The obtained life probabilities were compared with the nomogram using Deming regression (orthogonal regression), Bland-Altman plot, or Kendall's W concordance correlation coefficient (CCC) methods. All statistical analyses were performed using MedCalc software version 14.0 for Windows (MedCalc Software, Mariakerke, Belgium). In all analyses, $p < .05$ was considered to indicate statistical significance.

## Results

The study was performed with 194 early-stage (stage IA2–IIA) patients who underwent radical and modified radical hysterectomy and had no retroperitoneal LN involvement. Table 1 lists the clinical and demographic characteristics of the study population. Pelvic LN dissection was performed in 194 patients (100%) and paraaortic LN dissection was performed in 158 patients (81.4%). The mean of the collected pelvic LN was 26.8 (95% CI =25.0–28.5) and the mean of the paraaortic LN was 9.6 (95% CI =8.4–10.6). Serious morbidities observed during and after surgery were: 1 patient (0.5%) with bladder laceration, 1 patient (0.5%) with rectum laceration, and 1 patient (0.5%) with pulmonary embolism. During the study period, the mean rate of DFS was 82.0% (95% CI =74.0–89.9). Table 2 lists the primary treatments given for CC. After primary treatment, 18 patients (9.3%) experienced recurrence. Recurrence and developmental areas were as follows: 1 (0.5%), vagina; 2 (1.0%), vertebra; 2 (1.0%), lungs; 1 (0.5%), pelvic mass; 1 (0.5%), liver; 1 (0.5%), retroperitoneal LN; and 3 (1.5%), multiple solid organ metastases. In total, 38.9% of the recurrences developed in the first year, and 55.6% within the first 3 years.

**Table 1.** Demographic characteristics and clinical characteristics of patients.

| Characteristic | Patients ($n = 194$) |
|---|---|
| Stage [*n* (%)] | |
| IA2 | 22 (11.3) |
| IB1 | 40 (20.7) |
| IB2 | 80 (41.2) |
| IB3 | 45 (23.2) |
| IIA | 7 (3.6) |
| Size of tumour [*n* (%)] | |
| <2 | 62 (32.0) |
| 2–3.9 | 80 (41.2) |
| ≥4 | 52 (26.8) |
| Histological type [*n* (%)] | |
| SCC | 146 (75.3) |
| Non-SCC | 48 (24.7) |
| Parametrial margin involvement [*n* (%)] | 16 (8.2) |
| Vaginal cuff margin involvement [*n* (%)] | 16 (8.2) |
| Endomyometrial infiltration [*n* (%)] | 17 (8.8) |
| LVSI + [*n* (%)] | 83 (42.8) |
| Age [*n* (%)] | |
| <40 | 41 (21.1) |
| 40–59 | 130 (67.0) |
| ≥60 | 23 (11.9) |
| Size of tumour (mean ± SD) | 2.6 ±1.6 |

SCC: squamous cell carcinoma; LVSI: lymphovascular space invasion; SD: standard deviation

The relationships between prognostic factors such as stage, tumour size, parametrial involvement, vaginal cuff margin, endomyometrial infiltration, and LVSI status with DFS were compared using the univariable Cox regression model (Table 3). From the univariable penalised Cox regression model, we computed nomogram points for each predictor by dividing the shrunk coefficients by the largest shrunk coefficient obtained in the analysis, and multiplying by 100 (Figure 2). When the nomogram was prepared, the scores of the risk factors were collected and we observed that scores were at least 0 to a maximum of 414 points. Based on the nomogram score, DFS was evaluated by CCC analysis. The C-index for the nomogram was 0.895 (95% CI, 0.79–0.99). The scatter diagram revealed good agreement between the nomogram predictions and the observations, as shown in Figure 3.

## Discussion

In this study, patients with early-stage CC who underwent radical and modified radical hysterectomy without retroperitoneal lymph node involvement were evaluated, and recurrence development and factors affecting DFS were investigated. A nomogram consisting of factors influencing

**Table 2.** Primary therapies for the study groups.

| | Patients ($n = 294$) |
|---|---|
| Therapy [*n* (%)] | |
| Surgery | 60 (30.9) |
| Surgery + Adjuvant radiotherapy | 72 (37.1) |
| Surgery + Chemoradiotherapy | 62 (32.0) |
| Surgery [*n* (%)] | 18 (9.2) |
| Type 2 Hysterectomy | 176 (90.8) |
| Type 3 Hysterectomy | |
| Type of adjuvant radiotherapy [*n* (%)] | |
| Adjuvant internal radiotherapy | 89 (45.9) |
| Adjuvant external radiotherapy | 95 (49.0) |
| Radiotherapy dose range (Gy) | |
| Adjuvant internal radiotherapy | 5–9.25 |
| Adjuvant external radiotherapy | 36–54 |
| Adjuvant chemotherapy [*n* (%)] | |
| Cisplatin | 53 (27.3) |
| Cisplatin + Ifosfamide | 6 (3.1) |
| Cisplatin + Paclitaxel | 2 (1.0) |
| Carboplatin + Paclitaxel | 1 (0.5) |

**Table 3.** Cox hazard ratios for disease-free survival for the predictors used in the nomogram.

| | β | HR | 95% CI | *p* |
|---|---|---|---|---|
| Stage | | | | |
| IA2 | | 1 (ref) | | |
| IB1 | 0.470 | 1.3 | 0.2–10.4 | .468 |
| IB2 | 0.824 | 2.2 | 0.4–16.3 | .658 |
| IB3 | 1.250 | 3.5 | 0.4–29.7 | .252 |
| IIA | 2.192 | 9.0 | 0.8–102.2 | .078 |
| Size of tumour (cm) | | | | |
| < 2 | | 1 (ref) | | |
| 2–3.9 | 1.134 | 3.1 | 0.7–14.7 | .151 |
| ≥4 | 1.651 | 5.2 | 1.1–24.7 | .038 |
| Parametrial margin Involvement | 1.311 | 3.7 | 1.1–11.5 | .023 |
| Vaginal cuff margin Involvement | 1.376 | 4.0 | 1.2–12.3 | .017 |
| Endomyometrial infiltration Positive | 1.337 | 3.8 | 1.2–11.8 | .021 |
| LVSI Positive | 1.211 | 3.3 | 1.2–9.5 | .023 |

LVSI: lymphovascular space invasion; HR: hazard ratio; CI: confidence interval

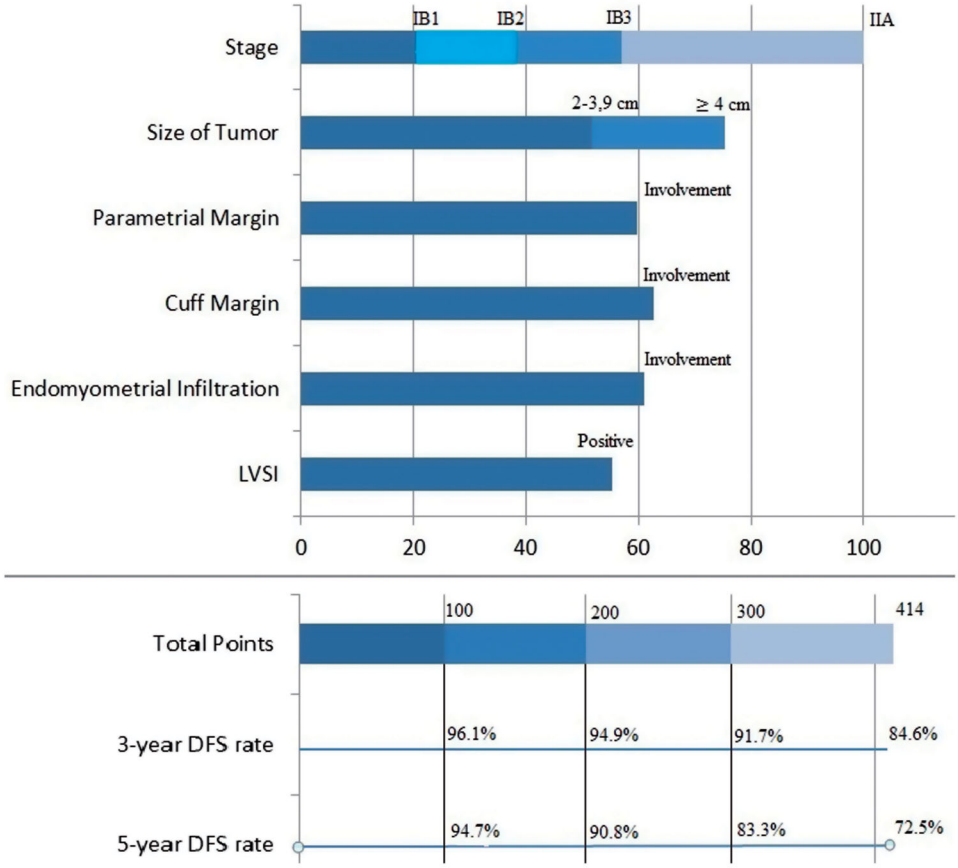


Figure 2. Nomogram for predicting 3- and 5-year disease-free survival (DFS) using six easily available clinical characteristics. To use the nomogram, locate a patient's variable on the corresponding axis, then draw a line to the points axis, sum the points, and draw a line from the total points axis to the 3- and 5-year DFS probability axis.

DFS was constructed. The total score was determined according to the status of all risk factors. This allowed clear definition of the risk for each patient. A nomogram predicting recurrence in patients with stages IA2–IIA CC with radical hysterectomy without LN involvement has not previously been published. The incidence of recurrence in early-stage CC patients is 9% (Khunamornpong et al. 2013). Recurrence progression is observed most frequently in the first 2 years after diagnosis of CC (Li et al. 2016). Survival after recurrence is poor, and post-recurrence 1- and 3-year survival rates are 75.1 and 41.9%, respectively (Yoshida et al. 2018). One of the most important issues affecting survival after recurrence is the site of recurrence (Yoshida et al. 2018). There is no generally accepted treatment method for recurrence, and treatment is mostly individualised as it is influenced by the initial treatment method. Because prognosis is poor and treatments are non-curative, it is vital to identify patients who are most likely to develop recurrence in their primary CC follow-up. In our study, we determined that 9.3% of early-stage CC patients without LN involvement who underwent modified radical or radical hysterectomy developed recurrence. We found that 38.9% of recurrences developed in the first year and 55.6% within the first 3 years.

Prognostic factors that increased the risk of recurrence in early-stage CC patients who underwent radical hysterectomy were stage, older age, deep stromal invasion, large tumour diameter, non-squamous histology, LN involvement, vaginal

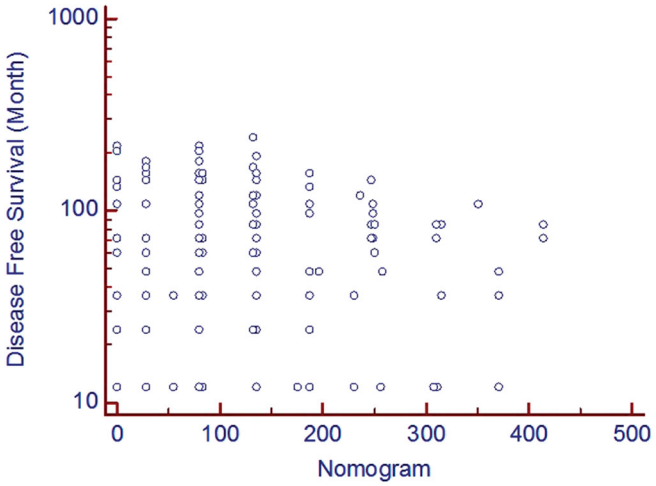


Figure 3. Scatter diagram between nomogram-predicted values and observed values.

margin involvement, parametrial involvement, LVSI, and less radical surgery. The 5-year DFS rate for the whole group was 81.1–93.6% (Escande et al. 2017; Je et al. 2017; Derks et al. 2018). The same prognostic factors have also been shown to influence the DFS rate in other studies, according to Cox regression analysis (Kim et al. 2010; Derks et al. 2018). In the past, factors affecting recurrence and DFS have been studied, and statistically significant factors were revealed. However, no single factor was found to predict recurrence

development with high sensitivity and specificity. Some studies have also found that some of these factors are not significant (Khunamornpong et al. 2013; Chandeying and Hanprasertpong 2017). Therefore, a nomogram of a few statistically significant risk factors was developed to create a model to strongly predict recurrence. Nomograms are graphical representations of prognostic models that facilitate the prediction of prognosis directly from individual case characteristics without requiring complex calculations.

Several nomogram studies have predicted recurrence in early-stage CC patients (Kim et al. 2010; Je et al. 2014, 2017). A nomogram incorporating the prognostic factors stage, number of positive LN, parametrial involvement, and depth of invasion appeared to be accurate, and predicted outcomes better than the FIGO stage alone in patients with stage I–IIA CC who underwent radical hysterectomy (C-index, 0.858 vs. 0.719; $p = .001$) (Kim et al. 2010). Another nomogram model including histological type, pelvic LN involvement, depth of stromal invasion, and parametrial invasion demonstrated good calibration and discrimination, with an internally validated C-index of 0.71 and an externally validated C-index of 0.65 (Je et al. 2014). A study with a nomogram of the prognostic factors pelvic LN metastasis, histological type, parametrial invasion, LVSI, and tumour size also demonstrated a good discrimination performance, with a C-index of 0.72 (Je et al. 2017). Our study investigated early-stage CC patients without LN metastasis. Cox regression analysis was performed with six prognostic factors: FIGO stage, tumour size, parametrial margin infiltration, vaginal cuff margin involvement, endomyometrial infiltration, and LVSI positivity. The nomogram was constructed based on the results of Cox regression. The C-index for the nomogram was 0.895 (95% CI, 0.79–0.99). These results can be considered excellent. In our cohort, comparison of single prognostic factors that exhibited a broad range in terms of recurrence yielded a nomogram that accurately predicted individualised risks based on individual risk factors. The higher concordance index in our study indicates that these six factors may be more valuable in predicting recurrence development in CC patients. Additionally, the fact that the study was performed in a group without LN involvement, which is a more specific subset of early-stage CC patients, also distinguishes it from other studies.

Nonetheless, there were some limitations to this study. First, the study utilised a retrospective design. Second, the sample size was relatively small. Third, significant improvements in surgical approaches over the 23 years of the study may have affected the results. Despite these limitations, the similarities of the demographic characteristics in the study population and the reports of expert pathologists increased the validity of our results and diminished weaknesses. The availability of good follow-up data also increased the validity of the results and mitigated the weaknesses.

In conclusion, a nomogram based on the prognostic factors of tumour size, parametrial margin infiltration, vaginal cuff margin involvement, endomyometrial infiltration, and LVSI positivity yielded excellent results in predicting recurrence in early-stage CC patients without LN metastasis who underwent radical hysterectomy.

## Author contributions

Data collecting: İlker Çakır
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Editing: Muzaffer Sancı, Kemal Güngördük
Literature research: Kemal Güngördük, Mustafa Kocaer
Statistical analysis: Varol Gülseren
Idea and design: İsa Aykut Özdemir

## Disclosure statement

The authors have no conflicts of interest to report.

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