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Treatment outcomes in patients with FIGO stage IB–IIA cervical cancer and a focally disrupted cervical stromal ring on magnetic resonance imaging: A propensity score matching study

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HIGHLIGHTS

- FIGO stage IB-IIA cervical cancer patients may have a focal disruption of the hypointense cervical stromal ring on MRI.
- Primary CCRT showed comparable survival outcomes, but fewer treatment-related complications, compared to radical surgery.
- Primary radical surgery should be done more cautiously in these patients.

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ABSTRACT

Objective. The aim of this study was to compare treatment outcomes of primary concurrent chemoradiation therapy (CCRT) versus radical hysterectomy (RH) followed by adjuvant RT or CCRT in patients with FIGO stage IB–IIA cervical cancer with focal disruption of the cervical stromal ring on magnetic resonance imaging (MRI).

Methods. We retrospectively analyzed the clinicopathological data of 156 patients with FIGO stage IB–IIA cervical cancer showing a focal disruption of the stromal ring on MRI between March 2000 and March 2015. Treatment outcomes were compared between the RT-based (n = 54) group and RH-based group (n = 54) after propensity score matching of each of the patients using a logistic regression model, including age, tumor size on MRI, pelvic lymph node enlargement on MRI, and histology.

Results. Five-year disease-free survival rate was 83.1% for the RT-based group and 77.4% for the RH-based group ($p = 0.228$). Five-year disease-specific survival rate was 84.3% for the RT-based group and 83.5% for the RH-based group ($p = 0.434$). Incidence rates of late grade 3 genitourinary adverse reactions (14.8% vs. 0.0%, $p = 0.006$) were significantly higher in the RH-based group than those in the RT-based group.

Conclusions. Primary CCRT might be the preferred treatment for FIGO stage IB–IIA cervical cancer patients with focal disruption of cervical stromal ring on MRI given that no difference in patient's survival was found, but higher incidence of treatment-related complications was observed in the RH-based group. Also, primary radical surgery should be done more cautiously in these patients.

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1. Introduction

The National Cancer Comprehensive Network guidelines category 1 recommendation for treating International Federation of Gynecology and Obstetrics (FIGO) stage IB2 cervical cancer is concurrent chemoradiation therapy (CCRT). The surgical option only has a category 2B recommendation status in these patients. However, the optimal management strategy for patients with FIGO stage IB2 cervical cancer is controversial [1–3]. The choice of primary management for FIGO stage IB2 cervical cancer usually depends on the availability of treatment facilities, physician preference, costs, and the patient's performance status and age [4,5]. Both treatment modalities have demonstrated acceptable disease control rates [6–8]. However, previous studies have shown conflicting results for treatment-related morbidities and cost-effectiveness [6–11].

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Clinical tumor size is one of the most important factors in treatment planning. However, the accuracy of clinical measurements compared with magnetic resonance imaging (MRI) is controversial [12,13]. Furthermore, mean uterine cervical size increases according to parity and decreases after menopause [14]. Therefore, criteria for parametrial invasion may differ according to uterine cervical size and menopausal status [15]. In addition, patients with FIGO stage IB1 cervical cancer with tumors < 3–4 cm have a focal disruption of the low signal intensity cervical stromal ring on axial T2-weighted MRI, which cannot be estimated by palpation of the parametrial tissues, but may imply microscopic parametrial invasion [16–20].

Several authors have compared primary radical hysterectomy (RH) plus adjuvant therapy to primary CCRT in patients with FIGO stage IB2 or IB2–IIA2 cervical cancer [3,21–23]. However, no randomized studies have compared primary RH plus adjuvant therapy to primary CCRT in these patients, which would help inform physician decisions regarding CCRT or RH. The aim of this study was to compare treatment outcomes and treatment-related morbidities of RH followed by adjuvant therapy and primary CCRT in patients with FIGO stage IB–IIA cervical cancer and a focal disruption of the cervical stromal ring on MRI after propensity score matching of all patients.

2. Material and methods

We retrospectively analyzed the clinicopathological data of patients with FIGO stage IB–IIA cervical cancer showing a focal disruption of the stromal ring on MRI between March 2000 and March 2015 at Ajou University Hospital. Inclusion criteria were patients diagnosed with invasive squamous cell carcinoma, adenosquamous cell carcinoma, and adenocarcinoma on cervical punch biopsy or conization; patients with FIGO stage IB–IIA cervical cancer without obvious parametrial involvement according to a bimanual rectovaginal examination; patients who had a focal disruption of cervical stromal ring on T2-weighted axial MRI (Fig. S1-B); and those without underlying disease that could influence survival. A total of 162 patients were enrolled in this study. The clinicopathological data were obtained from medical records after obtaining approval from the center's institutional review board.

MRI was performed in all patients using 3.0 T machines (Achieva; Philips Medical Systems, Best, The Netherlands) with body coils or phased-array coils. Details of the MRI protocols were described previously [15]. Focal parametrial involvement was diagnosed on oblique axial T2-weighted MRI when (a) there was a focal disruption of the cervical stromal ring and protrusion of the tumor (Fig. S1-B), and (b) there was no full-thickness loss of normal low signal intensity cervical stroma [16,18,19]. A definite evidence of parametrial involvement was defined as a full-thickness loss of normal low signal intensity cervical stroma on T2-weighted axial MRI (Fig. S1-C). Thus, FIGO stage IIB patients who showed a full-thickness loss of hypointense cervical stroma on T2-weighted axial MRI with nodular or irregular mass extending into the parametrium were not included in this study.

RH with pelvic and/or para-aortic lymphadenectomy was performed via laparotomy (n = 41) or laparoscopy (n = 13), as described previously [24]. The patient's age, personal preferences, and comorbidities as well as the surgeon's experience were considered when choosing the primary surgical approach. Histopathological characteristics were evaluated as described previously [24]. Patients who had two or more intermediate-risk pathological features, including lymphovascular invasion, large tumor diameter ≥ 4 cm, or stromal invasion of more than one half the depth of the cervical stroma received adjuvant RT [25]. Adjuvant CCRT using a 5-fluorouracil and cisplatin regimen was given to patients who had one or more high-risk pathological features, including microscopic parametrial invasion, lymph node (LN) metastasis, or involvement of the resection margin [26]. Postoperative RT was given as whole pelvis external-beam radiation therapy (EBRT) with or without cylinder brachytherapy to the vaginal vault, with a total median pelvic dose of 4930 cGy (range, 4500–6100 cGy) over 6 weeks. Brachytherapy boosts, in combination with EBRT, were considered for patients with tumor extension to the vaginal cuff margin. Primary CCRT was administered as described previously, with a total median pelvic dose 8150 cGy (range, 6840–9100 cGy) [27].

Patients were classified into the including primary CCRT (106 in the RT-based group) and RH (59 in the RH-based group). We excluded 6 patients (5 in primary CCRT group and 1 in RH plus adjuvant therapy group) because they did not complete the planned RT. Failure to complete RT was related to acute hematological and/or gastrointestinal toxicities. Clinicopathological data and treatment outcomes were compared between the two groups (102 in the RT-based group and 54 in the RH-based group). To balance the covariates in the two groups and reduce the effect of selection bias, estimated propensity scores were used to match the RT-based group to the RH-based group. Propensity score matching was computed for each of the patients using a logistic regression model, including age, tumor size on MRI, pelvic LN enlargement on MRI, and histology. The propensity score model was well-calibrated (Hosmer–Lemeshow goodness-of-fit test, $p = 0.304$) with good discrimination (c-statistic = 0.772) (Fig. 1-B). Based on the propensity scores, 54 patients who underwent primary CCRT were matched with 54 patients who received RH plus adjuvant therapy. Recurrence rate, disease-free survival rate, disease-specific survival rate, and late treatment-related complications were compared between the two groups. The Common Terminology Criteria for Adverse Events ver. 4.0 were used to classify treatment-related adverse events.

The Kolmogorov–Smirnov normality test was performed to determine whether the data were normally distributed. Clinicopathological data, recurrence pattern, and treatment-related adverse events were compared between the two groups with Pearson chi-square test and Fisher's exact test for categorical data, and Student's *t*-test and the

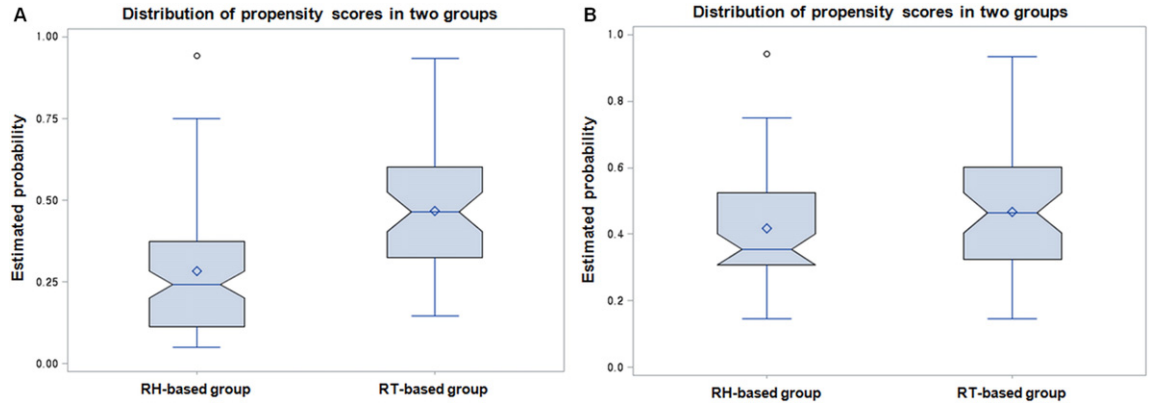

Fig. 1. Distribution of the propensity score in the RH- and RT-based group before (A) and after (B) 1-to-1 matching based on individuals' propensity score. RH, radical hysterectomy; RT, radiation therapy.

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