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# 20 year experience of postoperative radiotherapy in IB-IIA cervical cancer patients with intermediate risk factors: Impact of treatment period and concurrent chemotherapy ☆

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ABSTRACT

*Objective.* To compare the long-term clinical outcomes of adjuvant radiotherapy (RT) versus concurrent chemoradiotherapy (CCRT) in cervical cancer patients with intermediate risk factors.

*Methods.* Between 1990 and 2010, 110 cervical cancer patients with 2 or more intermediate risk factors (deep stromal invasion, lymphovascular space invasion, and large tumor size) underwent adjuvant RT (n = 56) or CCRT (n = 54) following radical surgery. Because CCRT had been performed since 2000, patients were divided into 3 groups regarding treatment period and the addition of chemotherapy, RT 1990–1999 (n = 39), RT 2000–2010 (n = 17) and CCRT 2000–2010 (n = 54). Majority of concurrent chemotherapeutic regimens were carboplatin and paclitaxel (n = 48).

*Results.* Five-year relapse-free survival (RFS) rates for RT 1990–1999, RT 2000–2010 and CCRT 2000–2010 were 83.5%, 85.6% and 93.8%, respectively. CCRT 2000–2010 had a significant decrease in pelvic recurrence ($p = 0.012$) and distant metastasis ($p = 0.027$). There were no significant differences in overall survival and RFS between RT 1990–1999 and RT 2000–2010. Acute grade 3 and 4 hematologic toxicities were more frequently observed in CCRT 2000–2010 ($p < 0.001$). However, acute grade 3 and 4 gastrointestinal (GI) and chronic toxicities did not differ between the groups.

*Conclusions.* This study shows that the addition of concurrent chemotherapy to postoperative RT in cervical cancer patients with intermediate risk factors may improve RFS without increasing acute GI and chronic toxicities, although hematologic toxicities increased significantly.



## Introduction

Stage IB and IIA uterine cervical cancer has been associated with an excellent tumor control rate and favorable prognosis after either radiotherapy (RT) or radical hysterectomy and pelvic lymph node dissection, with a 5-year overall survival rate of 80–90% [1,2]. In Korea, these patients are usually treated via radical hysterectomy and pelvic lymph node dissection. Certain clinicopathologic findings have been previously identified as risk factors for recurrence after radical surgery. These findings include pelvic lymph node metastasis, positive resection margin, parametrial involvement, deep stromal invasion (DSI), lymphovascular space invasion (LVSI), and large tumor size [3–8]. Pelvic lymph node metastasis, positive resection margin, and/or parametrial invasion are all regarded as high risk factors for recurrence [7], and DSI, LVSI, and large tumor size, when found in combinations of two or more, are regarded as intermediate risk factors for recurrence [6,8].

With regard to high risk patients, the results of a Gynecologic Oncology Group phase III study (GOG 109) showed that the addition of concurrent fluorouracil/cisplatin to postoperative RT significantly improved relapse-free (RFS) and overall survival (OS) [9]. Another GOG prospective trial (GOG 92) evaluated the role of postoperative RT in patients exhibiting intermediate risk factors [10,11]. This study demonstrated that the addition of postoperative RT to surgery improved RFS. However, no randomized prospective trials have yet

☆ Condensed abstract for use in the Table of Contents: The survival benefit of adjuvant concurrent chemoradiotherapy (CCRT) has thus far been confirmed only in early stage cervical cancer patients with high risk factors. This study retrospectively analyzed the outcomes of 110 patients with intermediate risk factors who were treated with CCRT or RT alone, and determined that CCRT is also beneficial for patients with intermediate risk factors.

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been conducted to compare postoperative concurrent chemoradiotherapy (CCRT) with postoperative RT alone for intermediate risk patients. Only three retrospective studies conducted in Korea or Japan including previous result of our institution have addressed the role of postoperative CCRT in intermediate risk patients [12–14]. However, retrospective nature of these studies has limitation to interpret the results. Because several randomized multicenter trial demonstrated superiority of CCRT over RT alone at the end of twentieth century, patients who received CCRT in these studies tend to have been treated in twenty first century. In contrary, most patients treated with RT alone in these studies received treatment before 2000. Therefore, confounding factors by difference of treatment period could affect the outcome. To overcome this weakness of previous report from our institution, we conducted larger retrospective analysis during 2 different periods of treatment, before (1990–1999) and after (2000–2010) the introduction of CCRT, to evaluate not only the impact of CCRT but also the effect of treatment period.

## Materials and methods

### *Patients*

We retrospectively reviewed the records of 817 patients who were treated with postoperative RT at the Seoul National University Hospital between January 1990 and December 2010. According to our institutional policy, the patients who had 2 or more intermediate risk factors (DSI, defined as an invasion into >half the thickness of the cervical wall; LVSI; tumor size≥4 cm) were classified as intermediate risk group and recommended to received postoperative RT or CCRT. Of the 154 patients, those who had received neoadjuvant chemotherapy or had double primary cancer were excluded from this analysis. The remaining 110 patients constituted the subject of this study.

### *Radiotherapy*

Pelvic RT was delivered using a 6, 10, or 15 MV photon through 4-field box technique. Brachytherapy was not given to any patient. The upper border of radiation field was placed on the L5–S1 junction or L4–L5 junction, and the lower border was set to at least 2 cm below the vaginal cuff. The lateral border was set to 1.5 cm lateral to the lateral margin of bony pelvic wall. The anterior and posterior edges of lateral field were the anterior aspect of the symphysis pubis and the S2–S3 interspace, respectively. External irradiation was delivered to the whole pelvis at 1.8 or 2.0 Gy per fraction once daily, 5 days per week. The median dose to the whole pelvis was 50.4 Gy (range, 45.0–50.4 Gy).

### *Chemotherapy*

From February 2000, most of patients received CCRT. Patient selection was performed on basis of clinical decision reflecting personnel preference of gynecology oncologist. Two Patients received weekly cisplatin (40 mg/m$^2$). Two cycles of fluorouracil (1,000 mg/m$^2$ over 12 h infusion on d 1–5) and cisplatin (60 mg/m$^2$ slow bolus injection on d 1) every 4 weeks were given in 4 patients. The other 48 patients received paclitaxel and carboplatin. Paclitaxel 135 mg/m$^2$ diluted in 500 ml of 5% dextrose water was administered over 3 h followed by carboplatin which dosage was given by an area under the time–concentration curve of 4.5 mg min/ml (based on calculated creatinine clearance) diluted in 500 ml of 5% dextrose water administered over 30 min. Both drugs were given on day 1. Two cycles of paclitaxel/carboplatin were administered at 4-week interval during RT. Sixteen patients received additional paclitaxel/carboplatin with 1 to 4 cycles (median; 1 cycle) according to the gynecologist's preference.

### *Follow-up and evaluation*

During adjuvant therapy, complete blood cell count was performed weekly, and serum BUN, creatinine, liver function test and urinalysis every 4 weeks. Complications that occurred within 90 days of the start of therapy were considered to be acute toxicities. Acute toxicities were scored according to the Common Terminology Criteria for Adverse Events, version 3.0 [15]. Chronic toxicities were graded according to the Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) radiation morbidity criteria [16]. After the completion of treatment, patients were followed up regularly checking a pelvic and digital rectal examination, a Papanicolaou smear, laboratory studies and radiographic studies.

### *Interpretation and statistical consideration*

Patients were categorized into 3 groups according to treatment period and whether or not the use of concurrent chemotherapy in addition to RT (RT 1990–1999 group, n = 39, RT 2000–2010 group, n = 17, CCRT 2000–2010 group, n = 54). Because CCRT was started after February 2000, RT group was divided into 2 groups, before and after the introduction of CCRT in practice. Statistical analysis was performed using SPSS software (release 12.0.1, SPSS Inc., Chicago, IL). The $\chi^2$ test or Fisher's exact test was used to compare discrete variables among groups. Survival curves were generated using the Kaplan–Meier method, and the comparisons between curves were performed using a log-rank test. In terms of the multivariate survival analysis conducted to identify independent predictors of OS and RFS, a Cox proportional hazards model was developed by backward, stepwise regression. It was assumed that the observed differences were statistically significant if the probability of chance occurrence was $<0.05$.

## Results

### *Patient and tumor characteristics*

Table 1 shows the patient and tumor characteristics of 110 patients. There was no difference in terms of age, performance status, histology, stage, mean tumor size, DSI, or the duration of RT. However, patients during 2000–2010 period had a significantly increased proportion of patients with LVSI. Median time to RT completion was 43 days (range, 37–52 days) during 1990–1999 and 41 days (range, 35–61 days) for 2000–2010.

### *Treatment outcomes*

The median follow-up time of patients during 1990–1999 and 2000–2010 were 16.8 and 6.3 years, respectively. No significant difference in survival was noted over period ($p = 0.160$). However, the addition of concurrent chemotherapy resulted in marginally improved OS. While the 5-year OS rate was 92.9% for CCRT 2000–2010 group, the 5-year OS rates were 84.6% and 83.0% for RT 1990–1999 and RT 2000–2010 group, respectively. ($p = 0.053$ between CCRT 2000–2010 and RT 1990–1999, $p = 0.030$ between CCRT 2000–2010 and RT 2000–2010; Fig. 1). RFS of CCRT 2000–2010 group was also significantly better than those of RT 1990–1999 and RT 2000–2010 groups ($p = 0.050$ between CCRT 2000–2010 and RT 1990–1999, $p = 0.003$ between CCRT 2000–2010 and RT 2000–2010; Fig. 2). By multivariate analysis, CCRT was the only significant risk factor for RFS ($p = 0.010$; Table 2).

Notably, no one developed pelvic recurrence in the CCRT 2000–2010 group. For the RT 1990–1999 and 2000–2010 group, 2 of 39 and 2 of 17 patients developed pelvic recurrences. The log-rank test was statistically significant ($p = 0.012$). Distant metastases developed in 2 of 54 patients for the CCRT 2000–2010 group. For the RT 1990–