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CLINICAL INVESTIGATION **Cervix**

IS ADJUVANT CHEMORADIOTHERAPY OVERTREATMENT IN CERVICAL CANCER PATIENTS WITH INTERMEDIATE RISK FACTORS?

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Purpose: To determine whether adjuvant chemoradiotherapy (CRT) improves the outcome of cervical cancer patients with intermediate risk factors.

Methods and Materials: Between January 2000 and June 2006, the medical records of 735 patients who had undergone radical surgery for Stage IB-IIA cervical cancer were reviewed retrospectively. Of the 735 patients, 172 with two or more intermediate risk factors (*i.e.,* lymphovascular space involvement, deep stromal invasion, and tumor size ≥2 cm) were grouped as follows according to the adjuvant treatment received: 34 patients, no further treatment; 49 patients, RT; and 89 patients, CRT. The significance of the clinical parameters and recurrence-free survival of each group were analyzed.

Results: Of the 172 patients with any of the intermediate risk factors, 137 (79.6%) had two or more intermediate risk factors. Of the 172 patients, 12 developed recurrences (6.4%)->(7.0%), with 6 in the pelvis and 6 in distant sites. All 12 recurrences occurred in those who had two or more intermediate risk factors (sensitivity, 100%); however, only six recurrences were detected in patients who met the Gynecologic Oncology Group criteria for the intermediate-risk group (sensitivity, 50%; Z test, $p < .05$). A statistically significant difference was found in the 3-year recurrence-free survival rate among the no further treatment, RT, and CRT groups (67.5%, 90.5%, and 97.5%, respectively; $p < .05$). The incidence of Grade 3-4 hematologic and gastrointestinal toxicities was not signficantly different statistically between the RT and CRT groups (6.1% and 13.4%, respectively; $p > .05$).

Conclusion: Postoperative adjuvant CRT can improve the outcome of cervical cancer patients with intermediate risk factors, with low increase in toxicity. © 2011 Elsevier Inc.

Cervical cancer, adjuvant chemoradiotherapy, intermediate risk factors, recurrence-free survival.

INTRODUCTION

Early cervical cancer has a relatively favorable prognosis, with a >80% survival rate (1). Most early-stage cervical cancer is treated with radical hysterectomy and pelvic lymph node dissection. However, additional adjuvant treatment is considered according to the presence or absence of risk factors for recurrence. Several clinicopathologic risk factors for recurrence have been identified, and their clinical significance in early-stage cervical cancers has been investigated (2–7).

Factors, such as lymph node metastasis, parametrial invasion, and positive resection margins, are well-known high-risk factors that increase the recurrence rate ≤40% in postoperative cervical cancer (8, 9). However, the prognostic significance of intermediate risk factors, such as lymphovascular space involvement, deep stromal invasion, and tumor size ≥2 cm, remains controversial (3–5, 7, 10–13).

Currently, many physicians are reluctant to treat the intermediate-risk group with adjuvant therapy because of concerns regarding overtreatment. The reluctance has been because the intermediate-risk group has a favorable prognosis (85–90% survival rate) without adjuvant treatment (14). However, several studies have shown that intermediate risk factors are present in as many as 25% of patients with Stage IB cervical cancer and increase the risk of recurrence to 31% in patients with multiple intermediate risk factors, suggesting the need for adjuvant treatment (11, 12, 15).

In a Gynecologic Oncology Group (GOG) study that attempted to investigate the role of adjuvant radiotherapy (RT) in the intermediate-risk group, 277 cervical cancer patients with intermediate risk factors were randomized to the no further treatment (NFT) or RT group. In those who met the GOG criteria, which defined the intermediate-risk group

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using a three-factor model of a combination of intermediate-risk factors (capillary lymphatic space involvement, stromal invasion depth, and tumor size), a statistically significant reduction of risk of recurrence and an increase in recurrence-free survival was found in the RT group compared with the NFT group (3, 11, 12).

Two practical debates still remain regarding the adjuvant treatment of the intermediate-risk group. First, is whether concurrent chemoradiotherapy (CRT), which has been established as a standard treatment of locally advanced cervical cancer, is beneficial for an intermediate-risk group. Second, is whether the eligibility criteria used to define the intermediate-risk group select those with the greatest risk of relapse. However, no randomized prospective trials have been done to compare the RT group with the CRT group in patients with intermediate-risk factors. Furthermore, no standard criteria are available to define the greatest risk group in cervical cancer patients with intermediate risk factors.

The aim of the present study was to study the outcome of adjuvant treatment and investigate the feasibility of two criteria for risk factor grouping in cervical cancer patients with intermediate-risk factors.

METHODS AND MATERIALS

Between January 2000 and June 2006, the medical records of 735 patients who had undergone radical hysterectomy with pelvic lymphadenectomy at the Korea Cancer Center Hospital for International Federation of Gynecology and Obstetrics Stage IB-IIA cervical cancer were reviewed. A total of 172 patients who had any of the following intermediate risk factors were analyzed retrospectively for the prognostic significance of the following clinicopathologic factors: greater than one-third stromal invasion, lymphovascular space involvement, or tumor size ≥2 cm. Patients who had high-risk factors, such as positive pelvic lymph nodes, parametrial involvement, or positive surgical margins, were excluded. Those patients who had received neoadjuvant chemotherapy, had metastatic cancer to the cervix, or had rare histologic disease types, such as melanoma and lymphoma, were also excluded.

All patients were examined preoperatively under general anesthesia, and the clinical tumor diameter was assessed by inspection and palpation. The pathologic criteria were determined and reviewed by 3 pathologists, with agreement of ≥2 pathologists' opinions. The stromal invasion depth was measured by the fractional thickness of the cervical wall divided in thirds. Lymphovascular involvement was determined by the presence or absence of tumor cells in the lymphovascular space on the surgical specimen.

The grouping of the intermediate-risk factors were done using two criteria regimens (the classic criteria and GOG criteria). The classic criteria group used the two-factor model, which defined the intermediate-risk group as those with two or more intermediate risk factors (*e.g.,* lymphovascular space involvement, greater than one-third stromal invasion, or tumor size ≥2 cm). The GOG criteria used a three-factor model, which defined the intermediate-risk group as follows: category 1, positive capillary lymphatic space, deep one-third stromal invasion, and tumor of any size; category 2, positive capillary lymphatic space, middle one-third stromal invasion, and tumor size ≥2 cm; category 3, negative capillary lymphatic space, deep or middle one-third stromal invasion, and tumor size ≥4 cm; and category 4, positive capillary lymphatic space, superficial one-third stromal invasion, and tumor size ≥5 cm (11).

Adjuvant RT was started within 4–6 weeks postoperatively. Patients underwent external beam RT to whole pelvis, but no brachytherapy. Pelvic RT was given with a four-field technique with a megavoltage beam, although ^{60}Co was allowed if the source-to-surface distance was >80 cm. The radiation dose was from 40 Gy in 23 fractions to 50.4 Gy in 28 fractions (five fractions weekly). Each patient was to be given daily fractions of 1.80–2.00 Gy within 4.5–6 weeks.

The cisplatin-based concurrent chemotherapy regimen was weekly cisplatin (40 mg/m^2) or cyclophosphamide (500 mg/m^2) plus cisplatin (50 mg/m^2) every 3 weeks.

The patients were followed up by physical examination and Papanicolaou smear every 3 months for 2 years and every 6 months for the next 3 years. Chest radiography and imaging studies, such as pelvic computed tomography, positron emission tomography, or positron emission tomography/computed tomography were performed annually.

Recurrence was defined as the appearance of clinical, radiologic, or histologic evidence of disease after study entry. In the case of suspicion, at least a 20% change in size on the close follow-up computed tomography scan within 3 months was defined as recurrence. Recurrence-free survival was defined as the period from study entry until disease recurrence, death, or the date of last examination.

The survival duration was determined as the interval from the date of primary surgery to the date of death, confirmed at both the National Statistical Office and the National Registry Program in Korea, or the date of last follow-up if the patient was alive at the last follow-up visit.

The chi-square test, Student *t* test, and Fisher exact test were used for statistical analysis of the patient characteristics, and a Z test was used to compare sensitivities. The Kaplan-Meier method and the log–rank test were used for determining the survival distribution and the differences in each group. The Cox regression model was used for univariate and multivariate analyses of prognostic factors. The Statistical Package for Social Sciences (SPSS, Chicago, IL) was used for the analysis, with statistical significance defined as $p < .05$.

RESULTS

The mean patient age was 49.8 years (range, 19.6–72), and most patients had Stage IB1 disease (62.2%) and squamous cell histologic type (75.1%; Table 1).

Of the 172 patients with any of the intermediate-risk factors, 137 (79.6%) met the classic criteria, and 70 patients met the GOG criteria (40.7%; Table 1). Using the classic criteria, the most frequent intermediate-risk factor was stromal invasion of more than one-third (80% or 28 of 35 patients) as a single factor and stromal invasion of more than one-third and tumor size ≥2 cm (80.2% or 81 of 101 patients) as a combination of two factors. Category 1 (capillary lymphatic space involvement, deep stromal invasion, and tumor of any size) was the most common category among the GOG criteria (54.3%, 38 of 70 patients; Table 1).

Of the 172 patients, 12 developed recurrence (7.0%), of which six were in the pelvis and six were in distant sites (Table 2). No recurrence was found in the 35 patients who had any one of the intermediate-risk factors (0%). The recurrence rate in those who met the classic criteria was 27.3%,