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Concurrent chemoradiotherapy followed by adjuvant chemotherapy in uterine cervical cancer patients with high-risk factors

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Abstract

Objectives. To determine whether concurrent chemoradiotherapy (CCRT) followed by adjuvant chemotherapy is better than CCRT alone in the management of FIGO stage bulky IB and IIB uterine cervical cancer.

Methods. Two hundred and five FIGO stage bulky IB and IIB patients with squamous cell carcinoma of the uterine cervix treated with CCRT were divided into 2 groups: (1) CCRT alone ($n=103$, Group A) and (2) CCRT plus adjuvant chemotherapy ($n=102$, Group B), and treatment outcomes were retrospectively compared between the two patient groups.

Results. Only 63% of patients received all three planned cycles of adjuvant chemotherapy, while 16% received only one cycle because of increased treatment-related morbidity or other causes. There were no treatment-related deaths. Although 37 patients experienced failures after completion of treatment, no significant differences were found in patterns of local and regional failures between the two groups. The incidence of distant metastasis, including para-aortic or supraclavicular lymph node metastases, was not reduced in patients of Group B (8% in Group A *vs*. 7% in Group B). Overall five-year actuarial survival rates for Group A and Group B patients were 85% *vs.* 80%, and five-year disease-free survival rates were 83% *vs.* 78%, respectively.

Conclusions. Our data failed to show discernable therapeutic advantage of adjuvant chemotherapy with given after CCRT for the management of FIGO stage bulky IB and IIB uterine cervical cancer patients. A future clinical trial will be necessary to test the clinical efficacy of the adjuvant treatment using newly developed agents in uterine cervical cancer patients.

Keywords: Concurrent chemoradiotherapy; Adjuvant chemotherapy; Uterine cervical cancer

Introduction

Radiotherapy has long been accepted as the most effective treatment in the management of cervical carcinoma. However, patients with high-risk factors such as advanced stage disease [1], bulky disease, and lymph node metastasis [2,3] more often experience treatment failure even after successful completion of planned radiotherapy schedules. The poor outcomes resulting from radiotherapy alone have accelerated the development of novel treatment modalities. With the advent of newer chemotherapeutic agents, chemotherapy has emerged as an additional mode of therapy for patients. Although chemotherapy and radiotherapy can be delivered sequentially or concurrently for the treatment of cervical cancer, there has still been considerable controversy regarding the optimal drugs, dosage, timing, and duration of chemotherapy. Several recent randomized clinical trials have shown a survival benefit from the concurrent use of chemotherapy and radiation therapy (CCRT) in a variety of advanced stage or high-risk settings [4–8]. Based upon data from five randomized trials, the National Cancer Institute (NCI) released a consensus statement declaring

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that the concurrent use of cisplatin-based chemoradiotherapy should be considered as the new standard of care for high-risk patients that require radiotherapy for cervical cancer [9].

Even though CCRT is increasingly becoming accepted as the standard treatment in high-risk cervical cancer, limited data are available regarding the role of adjuvant chemotherapy given after surgery or radiotherapy [10]. Furthermore, it remains unclear whether the addition of adjuvant chemotherapy given after CCRT is superior to CCRT alone. Wong et al. reported the treatment results of epirubicin-based CCRT followed by adjuvant chemotherapy in comparison to those of standard radiotherapy alone. Patients treated with CCRT plus adjuvant chemotherapy demonstrated a better survival rate compared with those treated with radiotherapy alone [11]. However, the relative contributions of CCRT or adjuvant chemotherapy to survival benefits remain unknown because treatment results of CCRT with and without adjuvant chemotherapy were not compared. Recently, Lorvidhaya et al. conducted a phase III multi-center randomized trial to assess the effectiveness of the concurrent use of mitomycin C, oral 5-fluorouracil (5-FU) and radiation, followed by oral 5-FU adjuvant chemotherapy. In their study, 673 patients with predominantly stage IIB and III disease were randomly assigned in a four-arm study design to either standard radiotherapy *vs.* CCRT with or without adjuvant chemotherapy. Although CCRT showed an improved disease-free survival rate in comparison with conventional radiotherapy, there was no significant difference in treatment outcomes with the addition of adjuvant chemotherapy [12]. In trial by the SWOG 8797, two additional cycles of adjuvant chemotherapy were given after the completion of two cycles of CCRT in early-stage, high-risk patients undergoing radical surgery. Higher numbers of chemotherapy courses were favorably associated with both progression-free survival and overall survival, but this study was not designed to allow a subset analysis [6].

We conducted a retrospective study that defined the impact of adding adjuvant chemotherapy after CCRT. This study compared the treatment outcomes of CCRT plus adjuvant chemotherapy versus CCRT alone in uterine cervical cancer patients with FIGO stage bulky IB and IIB. The objective of this study was to determine whether survival rates are higher in patients who are treated with CCRT followed with adjuvant chemotherapy than they are in those receiving CCRT alone.

Materials and methods

Eligibility

Between 1989 and 2002, 263 FIGO stage bulky (≥4 cm) IB and IIB patients with invasive carcinoma of the uterine cervix were treated with CCRT at the Yonsei Cancer Center, Yonsei University, College of Medicine (Seoul, Korea). Of these patients, those with adenocarcinoma and adenosquamous cell carcinomas were excluded to make the study population more homogeneous. Patients having either metastasis of the para-aortic/supraclavicular lymph nodes or hematogeneous metastasis were also eliminated from the analysis. The study was confined to 205 consecutive patients (8 bulky IB, 197 IIB) treated by CCRT with or without adjuvant chemotherapy.

The histological classification of uterine cervical cancer was based on the World Health Organization (Geneva, Switzerland) classifications. The clinical staging was grounded on the FIGO stage classifications. The procedure for staging included a detailed history and a physical examination, as well as common laboratory tests and standard chest radiographs, intravenous pyelograms, barium enemas, X-rays, cystoscopies, and sigmoidoscopies. In the evaluation of lymph node involvement, computed tomography (CT) scans or magnetic resonance imaging (MRI) were performed in all patients. The principal criterion for positive node involvement was based on the axial diameter of the lymph node. Lymph nodes larger than 1 cm in the short-axis dimension were considered abnormal. In addition, central necrosis was also regarded as a useful criterion for metastatic disease within the lymph node [13].

Treatment protocol

The CCRT protocol was composed of three chemotherapy cycles administered at the beginnings of the first, fourth, and seventh weeks of radiotherapy (Fig. 1); details of the protocol have been described elsewhere [14]. The radiotherapy involved a combination of external irradiation and high-dose-rate intracavitary irradiation applied using a remote afterloading system with Ir-192 as its sources (Gamma-Med II). External whole-pelvis irradiation was performed five times per week using a dose of 1.8 Gy/fraction and to a midline dose of 27–36 Gy. This was followed by a high-dose-rate intracavitary irradiation with six insertions (twice per week) and fraction doses from 5 Gy to a total dose of 30 Gy at point A. After completing the intracavitary irradiation, patients were administered a second course of external irradiation with central shielding to a total external beam dose of 45–50.4 Gy. The chemotherapeutic regimens consisted of cisplatin 100 mg/m^2 or carboplatin 400 mg/m^2 followed by five consecutive daily infusions of 5-FU 1000 mg/m^2. One hundred and three patients with old age, poor performance, patient refusal of adjuvant chemotherapy, or comorbid illness were assigned to the Group A, and the remaining 102 patients who received three additional cycles of planned adjuvant

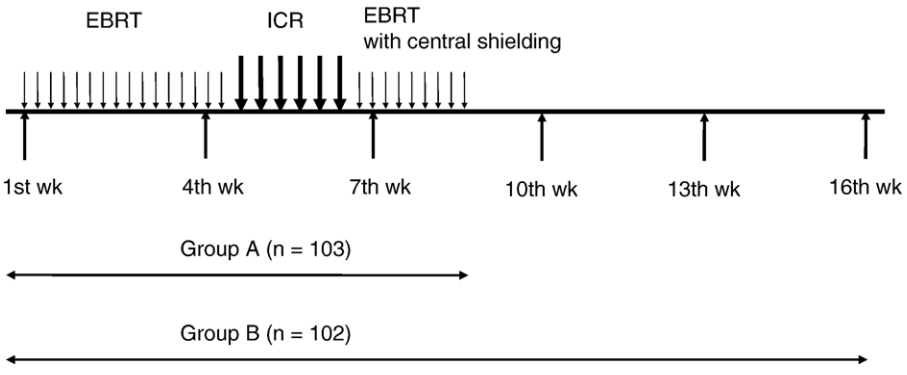

Fig. 1. Treatment scheme. EBRT: external beam radiotherapy. ICR: intracavitary radiation. Group A: concurrent chemoradiotherapy. Group B: concurrent chemoradiotherapy plus adjuvant chemotherapy.