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# Treatment outcomes of concurrent weekly carboplatin with radiation therapy in locally advanced cervical cancer patients

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ABSTRACT

*Objective.* To evaluate treatment outcomes of locally advanced cervical cancer patients who received concurrent weekly carboplatin with radiation therapy.

*Methods.* Patients with locally advanced cervical cancer who had primary radiation treatment in concurrent with weekly carboplatin (100 mg/m$^2$ or AUC 2) from 1997 to 2008 were identified. Demographic data, chemotherapy cycles, total treatment time, toxicities, and treatment outcomes were recorded.

*Results.* One hundred and forty-eight patients with stage IIB (50.7%), IIIB (48.0%) and IVA (1.3%) cervical cancer patients were included in the study. Median total treatment time was 53.5 days (range, 45–100 days). Carboplatin was given for a median number of 6 cycles (range, 3–6 cycles). Complete response was achieved in 142 patients (95.9%) while six (4.1%) had persistent diseases. Among the 142 responders, 36 experienced recurrences: pelvic recurrences in seven (4.7%), distant failure in 25 (16.9%), and both pelvic and distant in four (2.7%). The 2-year and 5-year progression-free survival rates were 75.1% and 63.0%, respectively with the corresponding 2-year and 5-year overall survival rates of 81.9% and 63.5%. No grade 3 or 4 hematologic and non-hematologic toxicities were observed during treatment in any patients. Late grade 3–4 gastrointestinal or genitourinary toxicities were 10.1% and 0.7%, respectively.

*Conclusion.* Concurrent weekly carboplatin with radiation therapy yields high response rate with modest progression-free and overall survivals in locally advanced cervical cancer. The regimen is feasible with minimal toxicities.



## Introduction

Cervical cancer is the third most common cancer in women worldwide with global estimates of 529,800 new cases and 275,100 deaths in 2011 [1]. In Thailand, cervical cancer is the second most common gynecologic cancer with an average age standardized incidence rate (ASR) of 18.1 per 100,000 [2]. In most developing countries, including Thailand, one major impediment in cervical cancer reduction is a suboptimal screening coverage. This leads to a higher overall incidence of cervical cancer and a higher proportion of advanced stage compared to those found in developed countries [3]. Thus, any means to increase screening coverage to detect preinvasive or early stage cancer as well as methods to improve treatment outcomes in advanced or locally advanced stage cervical cancer patients are crucial for a mortality rate reduction.

For locally advanced cervical cancer (stage IIB-IVA), a standard primary treatment is concurrent chemoradiation (CCRT) which was proven to have superior activity over radiation alone [4–6]. Cisplatin is the most common fundamental drug used in this concurrent setting, either alone or in combination with other agents e.g. 5-fluorouracil (5-FU) or hydroxyurea [4–7]. One limitation of cisplatin given concurrently with radiation therapy is hematotoxicity and gastrointestinal toxicity when compared to radiation therapy alone [4–9]. Other chemotherapeutic agents which were also tested as radiosensitizers [10,11] were found to have beneficial effect when used concurrently with radiation [12]. Another platinum compound which was also tested was carboplatin. Although carboplatin was found to have inferior efficacy than cisplatin in various types of solid tumors [13], it induced less gastrointestinal and renal toxicities. In cervical cancer, carboplatin showed a synergistic effect in both in vitro and in vivo experiments when used in concurrent with radiation [14–16]. The activity of carboplatin given concurrent with radiation therapy for cervical cancer was reported in a few studies [17–22]. Only one large randomized study, involving 469 cervical cancer patients, reported preliminary results of concurrent radiation with carboplatin alone versus carboplatin with Tegafur-Uracil. No significantly

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differences between the two treatment arms were observed in terms of response rates and toxicities [11].

Despite emerging data suggesting that carboplatin might be useful in concurrent with radiation therapy in locally advanced cervical cancer, a limited number of studies as well as a small number of patients in each study preclude a definite conclusion regarding its activity. Furthermore, most studies provided only short-term outcomes without a long term follow-up for survival or chronic toxicities evaluation. The objective of this study was to determine short- and long-terms treatment outcomes of concurrent chemoradiation therapy with weekly carboplatin in locally advanced cervical cancer.

## Methods

After an approval from the Ethics Committee for Research involving Human Subjects of the institution, we searched the archives of the Radiation Oncology Unit, Department of Radiology to identify cervical cancer patients treated between January 1997 and December 2008. We included patients who had locally advanced cervical cancer (the International Federation of Gynecology and Obstetrics or FIGO stage IIB to IVA) with histopathology of squamous, adenocarcinoma or adenosquamous cell carcinoma. All patients had concurrent weekly carboplatin and radiation therapy as a primary treatment in the institution. Exclusion criteria were patients who had received partial treatment elsewhere or had incomplete medical records.

The following data were collected: age, histopathology, stage, tumor size, pre-treatment and at completion of treatment hemoglobin (Hb) levels, total duration of treatment, number of chemotherapy cycles, toxicities, and tumor response. Tumor response was evaluated according to WHO criteria as complete response, partial response, and progressive diseases. Progression-free survival (PFS) and overall survival (OS) were determined. PFS was defined as interval from the first date of treatment to the time of recurrence, disease progression, or dead. For the patients who were lost to follow-up, PFS data was right censored at the time of the last evaluation, or contact when the patients were known to be progression-free. OS was defined as the time from the first date of treatment to the date of death. For the patients who were alive at the time of the study, survival data were right-censored at the date of last follow-up visit.

As a general practice in the institution, all cervical cancer patients received standard pretreatment evaluation which consisted of complete physical including pelvic and bimanual rectal examination to obtain clinical staging, tumor diameters, and extent of diseases. The examination was performed by a radiation oncologist and two gynecologic oncologists together in the clinic. Metastatic survey was achieved by chest x-ray, cystoscopy, proctoscopy, and intravenous pyelogram. Radiation treatment composed of external beam pelvic radiotherapy at a total dose of 54–60 Gy applied in daily fractions of 1.8–2.0 Gy. Three to five fractions of intracavitary high dose-rate brachytherapy were applied on weekly fractions of 6.0–7.2 Gy each to point A, depending on tumor volume. Carboplatin was given with radiation at a weekly dosage of 100 mg/m$^2$ or AUC 2. Complete blood count and renal function were obtained before each cycle of carboplatin. Any patients with Hb level $<10$ g/dL received red blood cell transfusion before further treatment.

Treatment and follow-up evaluation for individual patient were recorded for patient status, response, and toxicity prior to each cycle of chemotherapy and at 3 months after completion of treatment. Post-treatment surveillance was conducted by complete physical examination every 3 months during the first 2 years, every 6 months for another 3 years, and annually thereafter. Imaging study was done only if indicated by abnormal physical findings. Acute hematologic and non-hematologic toxicities were recorded according to the Common Toxicity Criteria (CTC) Version 2.0. Acute and late toxicity of gastrointestinal (GI) and genitourinary (GU) tracts were recorded using RTOG/EORTC Late Radiation Morbidity Scoring Criteria.

Data were analyzed using SPSS statistical software, version 11.5 (SPSS Inc., Chicago, IL). Descriptive statistic was used to analyze clinicopathological data, which was summarized as number and percentage. OS and PFS were analyzed by the Kaplan-Meier method and compared between groups with log-rank test. The Cox proportional hazards model was used to adjust for all prognostic factors in multivariable analysis. A two sided p-value $<0.05$ was considered statistically significance.

## Results

### *Patients' characteristics and treatment*

During the study period, 148 locally advanced cervical cancer patients were included in the study. Mean age of patients was $50.9 \pm 11.1$ years. Except two patients with stage IVA, almost of all patients had stage IIB and IIIB. Majority had squamous cell carcinoma. More than half (60.1%) received carboplatin for 6 cycles. Ten patients (6.7%) had 3–5 cycles due to toxicities from treatment, while the remaining had a variation in practice of the individual radiation oncologists of the institution. Median total treatment time (TTT) in this study was 53.5 days (range, 45–100 days). Basic characteristic features of cervical cancer patients treated with concurrent chemoradiation are shown in Table 1.

### *Outcome of treatment*

Evaluation at completion of treatment showed that 142/148 (95.9%) had complete response. Six patients (4.1%) who were in stage IIB (two patients) and IIIB (four patients) had persistent diseases (having partial response as the best response) and received further chemotherapy or palliative care for their symptoms. Unfortunately, all of the six non-responders were dead of their diseases within 3–25 months (median survival of 10.8 months). From a median follow-up of 55.6 months (range, 25–166 months), 36 out of 142 responders (25.4%) experienced recurrences: pelvic recurrence in seven (4.7%), distant failure in 25 (16.9%), and both pelvic and distant in four (2.7%). The two most common sites of distant metastases were

**Table 1**
Patients' characteristics and treatment factors (N = 148).

| Characteristics | Number | (%) |
|---|---|---|
| Stage | | |
| IIB | 75 | (50.7) |
| IIIB | 71 | (48.0) |
| IVA | 2 | (1.3) |
| Histology | | |
| Squamous cell carcinoma | 122 | (82.4) |
| Adenocarcinoma | 26 | (17.6) |
| Tumor size | | |
| ≤4 cm | 66 | (44.6) |
| >4 cm | 82 | (55.4) |
| Hb level at baseline | | |
| ≥10 g/dL | 119 | (80.4) |
| <10 g/dL | 29 | (19.6) |
| Cycle of carboplatin | | |
| 3 cycles | 7 | (4.7) |
| 4 cycles | 12 | (8.1) |
| 5 cycles | 40 | (27.1) |
| 6 cycles | 89 | (60.1) |
| Total treatment time | | |
| ≤56 days | 94 | (63.5) |
| >56 days | 54 | (36.5) |
| Hb level at last week of treatment | | |
| ≥10 g/dL | 124 | (83.8) |
| <10 g/dL | 24 | (16.2) |