Journal of the Formosan Medical Association (2015) 114, 231–237

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journal homepage: www.jfma-online.com

ORIGINAL ARTICLE

# The prognostic factors for locally advanced cervical cancer patients treated by intensity-modulated radiation therapy with concurrent chemotherapy

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Received 26 January 2012; received in revised form 23 June 2012; accepted 30 October 2012

**KEYWORDS**
cervical cancer;
concurrent chemotherapy;
IMRT;
prognostic factors

*Background/Purpose:* To identify the prognostic factors for locally advanced cervical cancer patients treated by intensity-modulated radiotherapy (IMRT) and concurrent cisplatin-based chemotherapy.
*Methods:* A total of 125 patients with stage IB2–III cervical carcinoma were treated with IMRT and concurrent cisplatin-based chemotherapy, plus high dose rate (HDR) brachytherapy between January 2004 and November 2010, in our institution. All patients received external irradiation of 45–54 Gy with the IMRT technique and concurrent cisplatin-based chemotherapy monthly or weekly. HDR brachytherapy of 20–30.5 Gy was prescribed to point A, as a local boost. Prognostic factors including age, histology, stage, lymph nodes metastasis, pretreatment hemoglobin level, serum squamous cell carcinoma antigen (serum SCC-Ag), chemotherapy regimens and the cumulative dose of weekly cisplatin, were analyzed. The endpoints were overall survival (OS), local failure-free survival (LFFS) and disease-free survival (DFS).
*Results:* The median follow-up time was 42 months. The 4-year OS, LFFS and DFS were 73.8%, 77.9% and 67.2%, respectively. Four (3.2%) patients developed ≥grade 3 acute gastrointestinal (GI) toxicity and 29 (23.2%) patients developed ≥grade 3 acute hematological toxicity. Five (4.0%) patients developed ≥grade 3 late GI toxicity and seven (5.6%) patients developed ≥grade 3 late genitourinary system toxicity. On univariate analysis, adenocarcinoma was a poor prognostic factor for OS ($p = 0.05$), LFFS ($p = 0.01$) and DFS ($p = 0.006$). Patients with lymph nodes metastasis at diagnosis had worse OS ($p = 0.02$). The high cumulative dose of cisplatin (>180 mg/m$^2$) had better OS ($p = 0.03$) and tended to have better survival on LFFS ($p = 0.13$) and DFS ($p = 0.10$). On multivariate analysis, adenocarcinoma was a significant independent

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http://dx.doi.org/10.1016/j.jfma.2012.10.021

prognostic factor for OS ($p = 0.001$), LFFS ($p = 0.005$) and DFS ($p < 0.001$). Initial lymph nodes metastasis was an independent predictor of OS ($p = 0.013$). Cumulative dose of weekly cisplatin significantly affected OS ($p = 0.041$), and high cumulative dose of cisplatin tended to have better LFFS ($p = 0.083$). Higher pretreatment hemoglobin level had better LFFS ($p = 0.034$).
*Conclusion:* Adenocarcinoma and lymph nodes metastases were poor prognostic factors for patients with locally advanced cervical cancer. Lower pretreatment hemoglobin level had poorer local control. Chemotherapy with a high cumulative dose of cisplatin tended to result in better survival.


## Introduction

Five randomized studies[1–5] demonstrated that concurrent chemoradiotherapy (CCRT) improved overall survival (OS) and progression-free survival in patients with locally advanced cervical cancer. The use of radiotherapy with concurrent cisplatin-based chemotherapy has become the mainstay treatment in locally advanced cervical cancer.

Previous studies[6,7] on other pelvic malignancies found that intensity-modulated radiation therapy (IMRT) helped to achieve adequate target organ and lymph nodes coverage and decreased the dose to the small bowel, bladder and rectum. Traditional radiation therapy techniques, including three-dimensional conformal radiation therapy (3DCRT) with uniform radiation intensity and/or with simple beam fluence modifying devices, such as wedges, do not provide a method for sparing critical structures that push into and are partially or fully surrounded by a target or combination of targets. IMRT dose plan and treatment delivery used inverse or forward planning techniques for modulated beam delivery, and used a binary collimator, or with a conventional multileaf collimator (MLC) system, either sliding window (dynamic MLC) or step and shoot (segmented MLC) modes. IMRT had more conformal dose distributions of the radiation fields and reduction in the volume of critical organs. These advantages may diminish acute and late toxicity. However, the IMRT treatment had a longer treatment time than conventional radiotherapy and the possibility of organ motion. In our study,[8] we demonstrated that IMRT achieved good outcomes and was well tolerated, with favorable acute and late toxicity in locally advanced cervical cancer patients. In this retrospective study, we reviewed more patients and all patients received IMRT and high dose rate (HDR) brachytherapy; patients also had a longer follow up time. One purpose of our study was to demonstrate the longer treatment outcomes, including survival and toxicity, of IMRT with concurrent chemotherapy.

Many studies[9–15] have shown that some prognostic factors, such as concurrent cisplatin dose, histology, advanced stage, age, and anemia, have an effect on survival. Another purpose of this study was to identify the prognostic factors of cervical cancer and find the patients who need more aggressive treatment.

## Methods and materials

### Patients

A total of 125 stage IB2-III cervical cancer patients met the inclusion criteria, which were: (1) biopsy confirmation of adenocarcinoma or squamous cell carcinoma (SCC) of the cervix; (2) no evidence of distant metastasis initially; (3) completion of IMRT and concurrent cisplatin-based chemotherapy plus HDR brachytherapy boost; and (4) no previous surgery, chemotherapy or radiotherapy. All patients received definitive CCRT at the radiation oncology department of Taichung Veterans General Hospital in Taiwan, between January 2004 and November 2010. The pretreatment staging workup included a comprehensive medical history, clinical physical examination, bimanual pelvic and rectal examinations, cervical biopsy, a chest X-ray, diagnostic abdomen and pelvic computed tomography (CT) scan, complete blood cell count, blood chemistry profiles and serum SCC antigen (serum SCC-Ag). A positron emission tomography (PET) scan was elective for 20 patients with equivocal lymph node metastasis at CT scan. Magnetic resonance imaging was used for workup in two selected patients. The lymph node metastasis criteria including: (1) enlarged lymph node $\geq$0.8 cm and/or central necrosis on CT scan; (2) 2-deoxy-2-fluoro-D-glucose (FDG) increased uptake in the PET scan and compatible with the equivocal lymph node region by CT scan; and (3) the enlarged lymph node $\geq$0.8 cm and/or heterogeneous enhanced signal intensity on T1-weighted image, were considered as having clinical lymph node metastasis. Cystoscopy or proctoscopy was indicated if bladder or rectal invasion was suspected clinically. Clinical staging was defined according to the International Federation of Obstetrics and Gynecology (FIGO) staging system. Written informed consent was obtained from each patient before treatment. The study was approved by the Institutional Review Board at Taichung Veterans General Hospital.

### IMRT technique and brachytherapy

All patients were scheduled to undergo IMRT and HDR intracavitary brachytherapy. The treatment planning system of Eclipse (Varian Medical Systems, Palo Alto, CA, USA) software program was used for treatment planning of IMRT. The IMRT treatment planning was delivered using a dynamic multileaf linear accelerator with photon energy of 10 MV. In general, a vacuum fixed pad was used to immobilize the patient and bladder filling was arranged before taking a CT image and daily treatment. The contrast-enhanced CT scan images were obtained using a radiopaque marker, to define the cervix and upper vagina before contouring. We checked the patients' position and V-films before IMRT treatment. If the patients could not fit the vacuum fixed pad, we would recheck the treatment centers and/or arrange repeat CT images and another IMRT plan.