Original article

Radiotherapy for cervical carcinoma in human immunodeficiency virus-infected patients: A retrospective study

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This was a retrospective study on the results of curative radiotherapy (with or without chemotherapy) for the treatment of cervical carcinoma patients who were infected with human immunodeficiency virus. This study was carried out in the Division of Therapeutic Radiology and Oncology, Department of Radiology, Faculty of Medicine, Chiang Mai University. Fifty-four patients were studied retrospectively from 2004 to 2009 and the $CD4^+$ T cell count was assessed in 29 patients. According to FIGO staging, 25, 19, 9 patients and 1 patient were stage I, II, III and IV, respectively. The 2-year local control, disease-free survival and distant metastasis-free survival rates were 92.6%, 87% and 83.3%, respectively. During treatment, four (7.4%) and three (5.5%) patients developed grade 3-4 anemia and leucopenia, respectively. Serious late toxicity was observed in two patients with grade 3 hematuria. **Chiang Mai Medical Journal 2012;51(2):45-50.**

Keywords: radiotherapy, cervical carcinoma, human immunodeficiency virus

Introduction

Cervical carcinoma is the second most common cancer in women worldwide [1]. AIDS (acquired immunodeficiency syndrome) occurs in patients who have been infected with human immunodeficiency virus (HIV), which causes lowering of the immune system and, consequently, risk of serious opportunistic infection. This condition can be spread by direct sexual contact. Both AIDS and cervical carcinoma share the same risk factors (multiple sexual partners), and the latter has been one of the AIDS-defining cancers since 1993 [2].

Treatment of cervical cancer in an HIV-infected host is the same as in normal patients. Surgery or radiotherapy is an option for early stage cervical cancer and concurrent chemo-radiation for advanced stage. However, some evidence suggests that HIV-infected women with cervical cancer are more likely to have advanced disease at presentation, and a higher recurrence rate than

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non-HIV-infected women [3-5]. However, HIV-infected patients have not been evaluated in detail for their radiation response, toxicities, compliance and survival rate. Therefore the optimal treatment for HIV-infected patient has not been defined [6-7]. HIV-infected women may be at risk of increased complications and shortened life expectancy. It has not been clear whether the benefit of radiotherapy in this group is different from that of normal patients.

This study was a retrospective study on treatment of HIV-related cervical carcinoma patients who were treated with radiotherapy (with or without chemotherapy) during 2004-2009 in the Division of Therapeutic Radiology and Oncology, Department of Radiology, Faculty of Medicine, Chiang Mai University.

Methods

Patients

Eighty-one patients, who were proven to have HIV infection by the enzyme-linked immunosorbent assay (ELISA) method, were treated from 2004 to 2009 by radiotherapy in the Division of Therapeutic Radiology and Oncology, Department of Radiology, Faculty of Medicine, Chiang Mai University. Twenty-seven patients were excluded from the study, due to poor cooperation and palliative goal, leaving only 54 patients for evaluation and treatment with a curative aim. $CD4^+$ T cell counts were evaluated in 29 patients (54%), with a mean $CD4^+$ T cell level in assessable patients of 290 cells/cm^3 (range; 19 to 720 cells/cm^3), and 22 patients had a $CD4^+$ T cell count of more than 200 cells/cm^3. Twenty-three patients (42%) received anti-retroviral drug therapy (ARV). Staging was performed with the International Federation of Gynecology and Obstetrics (FIGO) system. Sixteen patients (28%) received concurrent chemoradiation with weekly cisplatin (40 mg/m^2) or mitomycin-C (10 mg/m^2) at week 1 and 6 of radiation. Characteristic data are shown in Table 1.

Radiotherapy schedules

Radiation therapy with radical intent was given by external beam radiotherapy, with standard AP/PA portals or the four-field box technique, using 6 or 10 MV x-rays or Co-60 rays to a dose of 50-56 Gy in conventional fractionation. Two patients received hypofractionation, due to a problem with the machine. Weekly complete blood count and serum creatinine were prescribed to evaluate toxicity status in patients who received chemotherapy. Appointments were made for patients to make weekly visits in order to estimate their condition and toxicity. Complete blood count was performed weekly in non-chemotherapy patients, and additional blood urea nitrogen/serum creatinine tests were performed in patients with indications for concurrent chemotherapy. The common toxicity criteria were used to evaluate acute toxicities during treatment. High-Dose rate brachytherapy was applied after the 4^{th} week of external beam radiation therapy. A dose of 4 x 6 Gy or 3 x 7.2 Gy was prescribed at point A at 3 and 7 day intervals.

Follow-up program

After completing the treatment, appointments were made for the patients to follow-up in the clinic. History was taken per vaginal examination by physicians and evaluated, and the World Health Organization response criteria also were used to analyze tumor responsiveness. For toxicities, the late morbidity criteria of the Radiotherapy and Oncology Group and European Organization for Research and Treatment of Cancer (RTOG/EORTC) were used by physicians to evaluate late toxicity.

Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) software (version 17.0, Chicago, IL, USA). The Kaplan-Meier method and log-rank test were used to calculated local control and survival rates [8-9].

Ethicical approval

This study was approved by the Ethical Committee of the Faculty of Medicine, Chiang Mai University with the code number of 10SEP010374.

Results

At the median follow-up time of 25 months (range; 2 to 71 months), there were 25, 19, 9 patients and 1 patient at stages I, II, III and IV, respectively. The most common pathological finding was squamous cell carcinoma (81%). The

Table 1. Characteristic data

Parameters	Data
Age (years)	41 (28-67)
Pathological results (n)	
Squamous cell carcinoma	44
Adenocarcinoma	8
Others	2
FIGO stages (n)	
I	25
II	19
III	9
IV	1
$CD4^+$ T cell counts (n)	
More than 200 cells/cm^3	22
Up to 200 cells/cm^3	7

2-year local control, disease-free survival and distant metastasis-free survival rates were 92.6%, 87% and 83.3%, respectively. The 2 years disease-free survival rate for stages I, II and III was 88%, 84.2% and 88.9%, respectively, (Fig. 1) and for CD4 evaluable versus non-evaluable group, 85% versus 88%, respectively. In terms of ARV, the 2-year disease-free survival rate for ARV receivers versus non-ARV receivers was 95.7% versus 80.6%, respectively (Fig. 2). Thirty-eight patients had no evidence of disease. Eight patients developed metastasis and 7 had locoregional recurrence. Twenty-three patients (42.6%) were followed-up for at least 24 months.

CD4 count was evaluated in 29 patients. The 2-year disease-free survival rate of CD4 evaluable versus non-evaluable group was 85% versus 88%, respectively. (p=0.89) Twenty-three patients (42.6%) had a follow-up time of at least 24 months.

Regarding acute toxicity, no patient showed grade 3-4 diarrhea or cystitis. Four (7.4%) and three (5.5%) patients developed grade 3-4 anemia and leucopenia, respectively. With regard to late toxicities, only two patients (3.7%) showed grade 3 hematuria. Toxicity data are shown in Table 2.

Discussion

Nowadays, cervical carcinoma is an AIDS-related malignancy. With immunodeficiency status, patients confront many special situations. Many studies report that the incidence of most cervical cancer emerges in patients who are 5 to 10 years younger than the average population [10]. In our setting, the median age of cervical cancer in HIV-positive patients was 41 years. This confirms the observation in other parts of the world and points towards the hypothesis that HIV infection shortens the latent period seen in progression

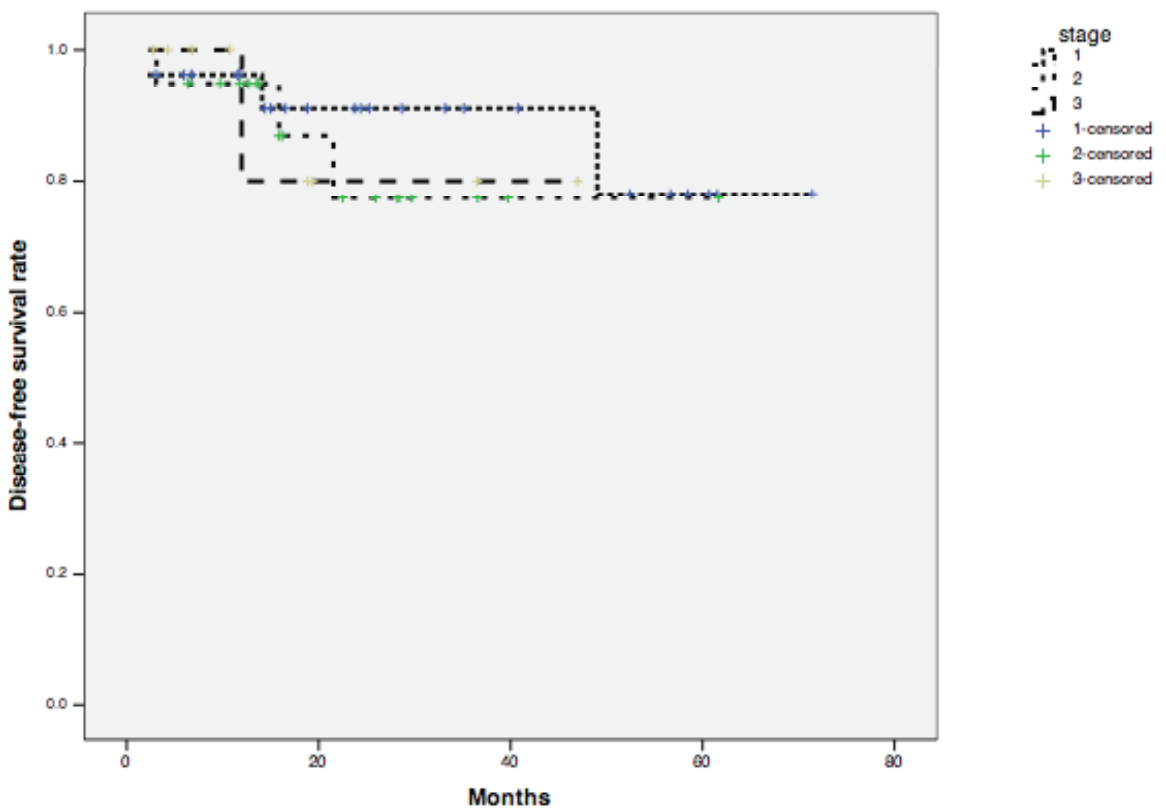

Figure 1. The 2-year disease-free survival rate according to stage.

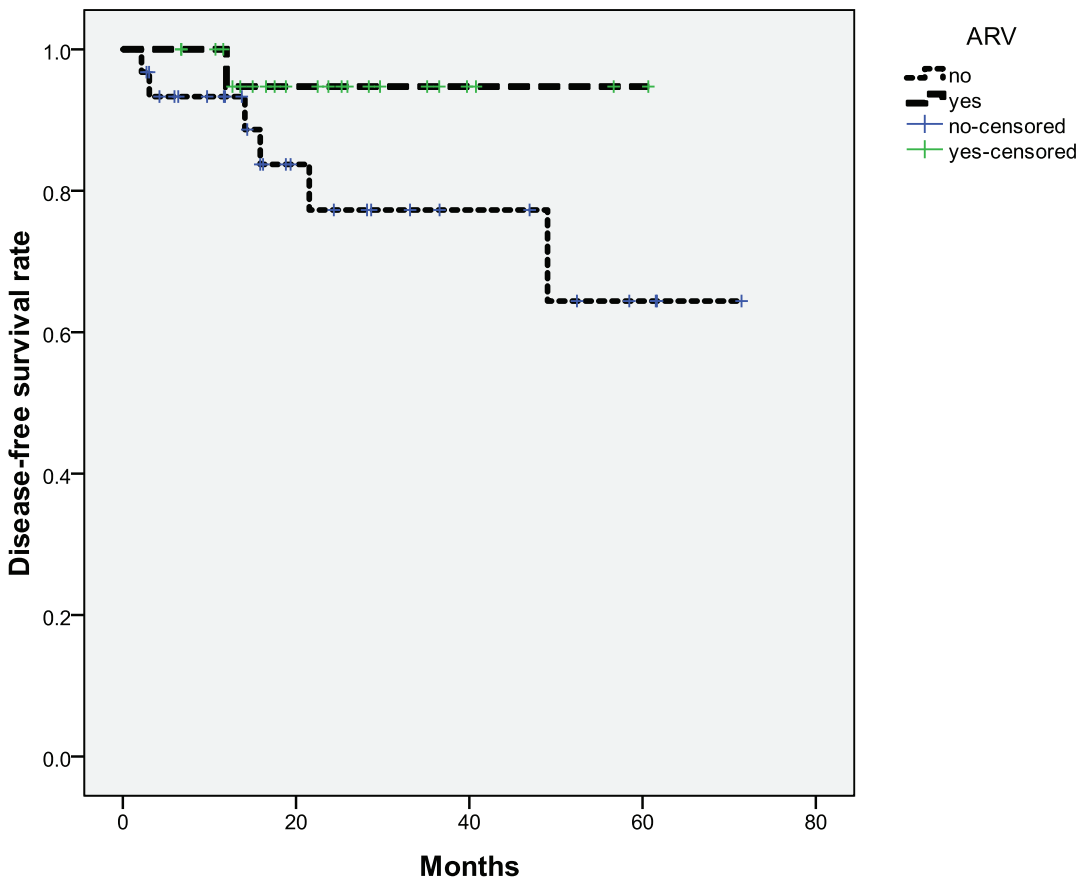

Figure 2. The 2-year disease-free survival rate according to ARV status.

Table 2. Toxicity profiles in treated patients

Toxicities	Grade	N
Acute		
Skin	1-2	6
Gastrointestinal toxicity	1-2	10
Genitourinary toxicity	1-2	3
Anemia	1-2	28
	3-4	4
Leucopenia	1-2	12
	3-4	3
Thrombocytopenia	1-2	3
Late		
Skin	1-2	5
Subcutaneous tissue	1-2	5
Gastrointestinal toxicity	1-2	1
Genitourinary toxicity	1-2	3
	3-4	2

of pre-malignant cervical lesions to invasive disease [11-12]. In the study from Tata Memorial Hospital, Mumbai, India, the mean age of HIV-positive cervical cancer patients was 41 years compared with 48 years in non-HIV positive patients [13]. Cervical cancer was more aggressive in patients with HIV infection than in normal populations [11]. HIV-positive cervical cancer is known to have a poor response to radiotherapy, and early recurrence resulting in poorer overall survival rates. The study of Maiman et al, found that HIV-related cervical cancer patients achieved poor treatment results, and their recurrence rate was up to 88% [12,14]. According to the study of Kigula-Mugambe et al, HIV seropositive patients showed a two-year survival probability of 40% and 0% at the fourth year [15]. In the study of Shrivastava et al, 42 HIV-positive patients, who

were diagnosed with cervical carcinoma, were reviewed retrospectively and 76% of them were treated with curative intent. Compliance to radiation therapy was poor, with 24% of patients discontinuing after a few fractions of radiotherapy. Twenty-two patients completed radical radiotherapy, and 50% of these had complete response. Grade 3-4 gastrointestinal toxicities were seen in 14% of the patients and 27% developed grade III skin toxicity [13].

In conclusion, radiation therapy showed promising results in the treatment of cervical carcinoma in HIV-positive patients. In our series, it yielded 92.6% of local control rate, 87% of disease-free survival rate and 83.3% of distant metastasis-free survival rate. The two-year disease-free survival rate of ARV receiver versus non-ARV receiver was 95.7% versus 80.6%, respectively. There were some differences in treatment results from other studies, due to the high number of stage I in ours, in which radiotherapy was an option for producing good results and less invasiveness.

Acknowledgement

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Conflict of interests: None

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รังสีรักษาในการดูแลรักษาผู้ป่วยมะเร็งปากมดลูกที่ติดเชื้อเอชไอวี: การศึกษาแบบย้อนหลัง

เอกสิทธิ ธราวิจิตรกุล, พ.บ., ภูริวัฒน์ เมืองวงศ์, พ.บ., สมวิไล จักรพันธุ์, พ.บ.,
พิชญาภรณ์ กลั่นกลิ่น, พ.บ., นันทกา ภู่กันหพันธ์, พ.บ., และอิ่มใจ ชิตาพนารักษ์, พ.บ.
หน่วยรังสีรักษาและมะเร็งวิทยา ภาควิชารังสีวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

การศึกษานี้เป็นการศึกษาย้อนหลัง โดยทำการเก็บรวบรวมข้อมูลผู้ป่วยมะเร็งปากมดลูกที่มีภาวะติดเชื้อเอชไอวีเพื่อรายงานผลการรักษาผู้ป่วยมะเร็งปากมดลูกที่ได้รับรังสีรักษา (และ/หรือ) เคมีบำบัด) เพื่อการควบคุมโรค ในระหว่างปี 2547-2552 ภายในหน่วยรังสีรักษาและมะเร็งวิทยา ภาควิชารังสีวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่ โดยได้ทำการศึกษาทั้งสิ้น 54 ราย มีผู้ป่วยระยะที่ I 25 ราย ระยะที่ II 19 ราย ระยะที่ III 9 รายและระยะที่ IV 1 ราย ในผู้ป่วยที่ทำการศึกษาพบว่ามี 29 รายที่มีผลการตรวจ $CD4^{+}$ T cell อัตราการควบคุมโรคเฉพาะที่อัตราการปลอดจากโรค อัตราการปลอดจากการแพร่กระจายของโรคที่ 2 ปี มีค่าเท่ากับร้อยละ 92.6, ร้อยละ 87 และร้อยละ 83.3 ตามลำดับ ในระหว่างการรักษามีผู้ป่วย 4 ราย และ 3 รายที่เป็นภาวะซีดและเม็ดเลือดขาวต่ำระยะที่ 3-4 ตามลำดับ หลังการรักษาผู้ป่วยจำนวน 2 รายมีภาวะปัสสาวะเป็นเลือดที่มีความรุนแรงระดับที่ 3 **เชียงใหม่เวชสาร 2555;51(2):45-50.**

คำสำคัญ: รังสีรักษา มะเร็งปากมดลูก เชื้อไวรัสเอชไอวี