Original Article

Treatment Outcomes of Cervical Carcinoma in HIV-infected Patients

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Objective: To evaluate treatment outcomes, treatment toxicities and determine prognostic factors of treated cervical cancer in human immunodeficiency virus [HIV]-infected patients.

Materials and Methods: A retrospective analysis of cervical cancer in HIV-infected patients who were treated in Radiation oncology Unit, Department of radiology, Faculty of Medicine Vajira Hospital between 2003 and 2017. The Kaplan-Meier method was used for survival analysis. The authors analyzed association of patients and tumor characteristics with survival using the log-rank test and Cox models.

Results: A total of 131 cervical cancers in HIV-infected patients were included. Eighty-one patients (61.8%) were previously diagnosed with acquired immune deficiency syndrome [AIDS] and treated with antiretroviral therapy [ART], the rest of the patients (38.2%) were diagnosed to AIDS and commenced an ART at the diagnosis of cervical cancer. The 2-year and 5-year DFS were 88.2% and 79.5%, respectively. The corresponding 2-year and 5-year overall survival were 83.8% and 78.7%, respectively. Characteristics associated with a decrease of survival which is statistically significant include grade, stage and a lack of ART during cancer treatment. Treatment toxicities ranged from 0.8% to 8.2%. Majority of the complications were mainly grade 1 or 2. Severe late toxicity (2.3%) was found only in Genito-urinary system.

Conclusion: Cervical cancer in HIV-infected patients who were treated with ART and cancer treatment had a favorable survival outcome and toxicity. Grade and stage of cancer significantly affect the survival outcome.

Keywords: Cervical cancer, AIDS, HIV, Treatment outcome, Antiretroviral

J Med Assoc Thai 2018; 101 (Suppl. 8): S137-S143
Website: http://www.jmatonline.com

Cervical cancer is a significant global health burden being the 9th most common cause of cancer related death in women worldwide and is the leading cause of cancer death among women with human immunodeficiency virus (HIV)-infection[1]. In Thailand, it is the 2nd most common women cancer and is the most common acquired immune deficiency syndrome [AIDS]-defining cancer[2]. Cervical cancer incidence is seven times greater among HIV-seropositive women than the general population[3]. HIV-seropositive women have a higher prevalence of infection with human papilloma virus [HPV] and are likely to develop persistent infection with multiple HPV types, resulting in higher incidence and prevalence of cervical intraepithelial neoplasia [CIN] lesion and a more likely rapid progression to invasive cervical cancer [ICC][4-6]. The three modes of treating cervical cancer are surgery, radiotherapy and chemotherapy either single or in combination to maximize survival opportunity. Cervical cancer in HIV-infected patients not only have more frequent interruptions of radiation treatment and lower rate of treatment completion, but also receive concurrent chemotherapy less often[7]. Cervical cancer in HIV-infected patients have worse survival outcome compared with those who are non-HIV-infected[8]. This high mortality can be explained by further advanced stage, biologically aggressive cancer phenotype, decreased efficacy or increased toxicity from cancer therapy and AIDS-related mortality[8,9] which derive from

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How to cite this article: Rongsriyam K, Tantivatana T. Treatment Outcomes of Cervical Carcinoma in HIV-infected Patients. J Med Assoc Thai 2018;101;Suppl.8: S137-S143.

immune dysregulation (rapid progression, frequent metastases, high rate of relapse and poor therapeutic response). Nowadays, the combination antiretroviral therapy [cART] has improved the survival in HIV-infected patients with cervical cancer[10,11].

The objectives of the present study were to investigate a survival rate after a diagnosis of cervical cancer in HIV-infected patients and to obtain preliminary data of the clinical course, response to therapy, prognostic factors and treatment toxicity at the department of radiation oncology, faculty of Medicine Vajira Hospital, Navamindrahiraj University.

Material and Methods

In this retrospective descriptive study, 131 cervical cancer in HIV-infected patients treated at the department of radiation oncology, faculty of Medicine Vajira Hospital from 2003 to 2017 were included. The authors categorized patients by excluding patients who have previous cervical treatment or the other cancers except melanoma. Prior to commencing the study, hospital institutional ethical committee clearance was sought and obtained (COA98/2559). Data were accumulated from the medical record. Corrected variables included patient characteristics, tumor characteristics, treatment parameters, treatment outcome, antiretroviral treatment, and complications of treatment.

The primary outcome was 2-year and 5-year overall survival [OS]. The secondary outcomes were 2-year and 5-year disease-free survival [DFS], response rate, complication rate and prognostic factors. OS was obtained from the 1st date of treatment to date of death from all causes or last follow-up. DFS was calculated from the 1st date of treatment until date of disease progression or recurrence. Patients who lost a follow-up, DFS data were right-censored at the time of the last follow-up. Tumor response was evaluated at 3 months after completion of treatment.

Acute complication for gastrointestinal system [GI] and genitourinary system [GU] were graded by the radiation oncologist during a course of treatment until 6 months after the completion of therapy. Late complications were graded after 6 months of treatment. Using the RTOG/EORTC toxicity criteria[12].

All data was statistically analyzed by SPSS statistical for Windows (version 22.0. Armonk, NY: IBM Corp). The Kaplan-Meier method was used for survival analysis, and the log-rank test to analyze the survival rate between two groups. Variable achieving significant level of $p<0.05$ were entered to COX proportional hazards regression model to complete multivariable analyses.

Results

A total of 131 patients with HIV-infected cervix cancer were included in this study. Baseline patient characteristics are shown in Table 1. Median age of the patients was 41 years (range, 22 to 64 years). All patients had a performance status equivalent to ECOG 0 to 1 at the beginning of the study. The majority (61.8%) of

Table 1. Patient and tumor characteristic

Characteristic	No. of patients	%
All patients	131	100
Median age (range), years	41 (22 to 64)	
<45 years	88	67.2
≥45 years	43	32.8
Performance status		
ECOG 0 or 1	131	100
Initiated ART before cancer diagnosis	81	61.8
Median CD4 cell count (range), cells/µ	241 (5 to 700)	
Mean CD4 cell count, cells/µ	288	
<200 cells/µL	62	47.3
200 to 500 cells/µL	51	38.9
>500 cells/µL	18	13.7
HIV-RNA viral load copies/mL		
<400	62	47.3
400 to 75,000	8	6.1
>75,000	1	0.8
Unknown	60	45.8
Histology		
Squamous cell carcinoma	100	76.4
Adenocarcinoma	26	19.8
Adenosquamous	5	3.8
Tumor grade		
Well differentiated	46	35.1
Moderate differentiated	68	51.9
Poorly differentiated	17	13.0
Stage		
IA	11	8.4
IB	24	18.3
IIA	17	13.0
IIB	64	48.9
IIIA	0	0
IIIB	12	9.2
IVA	3	2.3

ECOG = Eastern Cooperative Oncology Group; ART = antiretrovial therapy; CD4 = cluster of differentiation 4; HIV = human immunodeficiency virus; RNA = ribonucleic acid; FIGO = the International Federation of Gynecology and Obstetrics

patients with HIV had previously received ART before diagnosis. Median cluster of differentiation 4 (CD4) count is 241 cells/µL (5 to 700 cells/µL) and patients whose CD4 counts less than 200 cells/µL were 47.3%. Patients with HIV viral load <400 copies/mL, >75,000 copies/mL and unknow data was found in 47.3%, 0.8% and 45.8%, respectively. Squamous cell carcinoma was the most common histopathological subtype, accounting for 76.45%, followed by adenocarcinoma and adenosquamous carcinoma, 19.8% and 3.8%, respectively. Most tumors were in stage IIA (48.9%).

Treatment modality which 131 HIV-infected cervix cancer patients received are shown in Table 2. The patients who received ART during cancer treatment were 92.1%. All patients underwent initial therapy with radiation therapy, of which 96 cases (73.3%) received radiotherapy alone and 35 patients (26.7%) were treated with combined chemotherapy. The median total treatment time was 56 days (range, 48 to 107 days). The average external beam radiotherapy [EBRT] dose delivered was 54 Gy (range, 50 to 56 Gy) with 2 Gy/fraction schedules. For brachytherapy treatment, patient received mean total point A dose, bladder point dose and rectal point dose were, 25.87 Gy, 15.42 Gy and 16.42 Gy, respectively.

Table 2. Treatment delivered

Characteristics	No. of patients	%
ART during cancer treatment	122	93.1
Concurrent chemotherapy		
No	96	73.3
Yes	35	26.7
Cisplatin	3	2.3
Carboplatin	32	24.4
Median RT duration (days), range	56 (48 to 107)	
≥56	72	55.0
>56	59	45.0
Mean total EBRT dose (Gy), range	54 (50 to 56)	
ICRT		
Mean total point A dose (Gy), range	25.87 (21 to 32.50)	
Mean bladder point dose (Gy), range	15.42 (10.12 to 23.66)	
Mean rectal point dose (Gy), range	16.42 (11.04 to 24.21)	

ART = antiretrovial therapy; RT = radiation therapy; EBRT = external beam radiation therapy; ICRT = intracavitary radiation therapy

The median follow-up was 46 months (range, 5 to 158 months). All 131 patients achieved complete response and the overall response rate was 100%. There is a cervical cancer recurrence of 29 patients (22.1%). Among these, 25 patients (19.1%) had a systemic metastasis, while 4 patients (3%) had a loco-regional recurrence. The results are summarized in Table 3. The 2-year and 5-year DFS were 88.2% and 79.5%.

During the follow-up period, 102 patients survived (77.9%), 29 deaths occurred (22.1%) due to tumor recurrent. The 2-year and 5-year OS were 83.8% and 78.7%, respectively (Figure 1).

Table 4 shows the overall survival according to various factors. The factors that significantly correlated with lower rate of survival were as follows: CD4 count less than 200 cell/µL, viral load more than >75,000 copies/mL, higher tumor grade, higher tumor stage and non-ART during cancer treatment.

Table 3. Treatment outcomes

	No. of patients	%
Complete response	131	100
Recurrence		
No	102	78
Loco-regional	0	0
Systemic	25	19
Supracalvicular lymph node	2	1.5
Lung	8	6.1
Abdomen	8	6.1
Multiple	7	5.3
Combined loco-regional and systemic	4	3

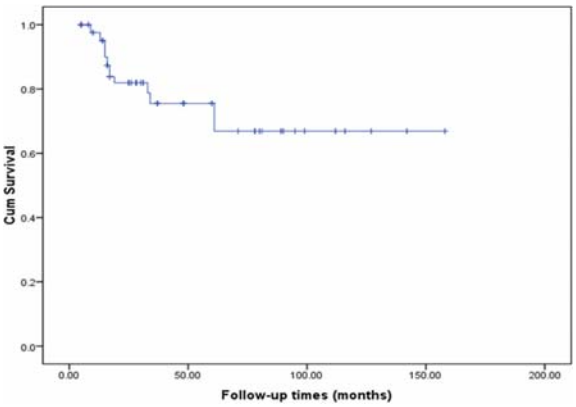

Figure 1. Overall survival of HIV-infected cervix cancer patients.

Table 4. Univariate and multivariate Cox analysis of characteristic associated mortality

Factor	5-year OS (%)	Univariate analysis	Multivariate analysis	
		p-value	HR	95% CI
Age (years)		0.272		
<45	69.5			
≥45	86.5			
CD4 count (<200cells/ µL vs. others)		0.036	0.96	0.42 to 1.75
<200 cells/µL	71			
200-500 cells/µL	79.4			
>500 cells/µL	100			
HIV-RNA viral load copies/mL		0.017	1.02	0.67 to 1.26
<400	82.6			
400-75,000	37.5			
>75,000	0			
Histology type (SCCvs.ACC/ASC)		0.072		
Squamous cell carcinoma	81.5			
Adenocarcinoma	53.8			
Adenosquamous carcinoma	68.7			
Tumor grade (grade 1-2 vs. grade 3)		0.013	1.82	1.18 to 3.77
Well differentiated	100			
Moderate differentiated	66			
Poorly differentiated	0			
Initiated ART before cancer Dx		0.272		
No	68.7			
Yes	78.2			
FIGO Stage (I&II vs. III&IV)		<0.001	2.5	1.88 to 3.67
Stage I	95.7			
Stage II	72.7			
Stage III	16.7			
Stage IV	0			
ART during cancer treatment		<0.001	1.62	1.23 to 3.07
No	37.6			
Yes	74.8			
Concurrent chemotherapy		0.194		
No	74.7			
Yes	69.3			

CI = confidence interval; FIGO = the International Federation of Gynecology and Obstetrics;; HR, hazard ratio; OS = overall survival; CD4 = cluster of differentiation 4; HIV = human immunodeficiency virus; RNA = ribonucleic acid; ART = antiretrovial therapy

These factors which achieve significant level of $p<0.05$ were entered in a multivariable analysis. Tumor grade, tumor stage and ART during cancer treatment provided statistically significant factors effect survival.

The GI and GU toxicity profile presented in Table 5, 21 (16%) patients had only grade 1 acute toxicity. For late complication, patients with grade 1, 2 and 3 toxicities were 7 (5.3%) patients, 11 (8.4%) patients and 3 (2.3%) patients, respectively.

Discussion

In the present study, the authors found that cervical cancer is likely to occur in younger age range, which is like other publications. Cervical cancer has been noted to occur in younger women with HIV infection more than those who is non-HIV, and the peak incidence has been reported to be a decade younger[4,13]. HIV-infected women are also noted to have a cervical cancer at higher CD4 counts compared with the low CD4 counts, associated with other AIDS related

Table 5. Gastrointestinal and urologic adverse events

	No. of patients	%
Acute toxicity		
Gastrointestianl grade 1	11	8.4
Genitourinarytract grade 1	10	7.6
Late toxicity		
Gastrointestianl grade 1	4	0.8
Gastrointestianl grade 2	10	7.6
Gastrointestianl grade 3	3	2.3
Genitourinarytract grade 1	3	2.3
Genitourinarytract grade 2	1	0.8

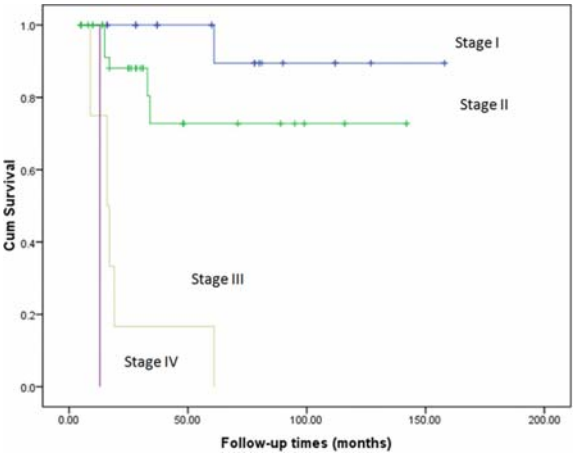

Figure 2. Overall survival by stage of disease.

malignancies like Kaposis' sarcoma and lymphoma[14] which indicated the similar pattern in the present study. Eighty-one patients (61.8%) were previously treated with ART and the rest of the patients (38.2%) received ART before radiothearpy. For this reason, the authors found that most patients had low HIV viral load.

Most patients were in the early stages, patients in stage I, II, III and IV are 35, 81, 12 and 3, respectively. This result possibly came from the effective screening program (pap test) for cervical cancer in HIV seropositive patients. Screening for cervical cancer is an effective strategy for early detection and reducing the incidence and mortality of cervical cancer[15].

The main modalities of cervical cancer management are surgery, chemotherapy and radiotherapy. Nevertheless, a combination therapy is required for most patients. These treatment modalities reduced immunity in patients who have HIV infection which leads to a lower rate of treatment completion, poor treatment outcome and higher treatment toxicity[4,7]. In present study, all patients were treated with radiation, with only 26.7% of patients received concurrent chemotherapy because of the immune status. However, everyone had completed a radiation treatment. Interaction between chemotherapy and ART drugs are quite favorable, combining the treatment modalities in HIV positive patients can be tolerated by most of them.

The previous studies in diffuse large B-cell lymphoma[16], anal carcinoma[17-19] and hepatocellular carcinoma[16] demonstrates similar survival rate between patients with and without HIV infection and cancer in the modern ART era. In the present study, all patients achieved complete response of cervical cancer after their treatment. The 5-year OS and DFS of cervical cancer in HIV-infected patients were 78.7% and 79.5%, respectively, in line with HIV-uninfected cervical cancer patients. Five-year OS for stage I, II, III and IV of cervical cancer in HIV-infected patients were 95.7%, 72.7%, 16.7% and 0% respectively. The survival outcome is favorable compared with 5-year OS for stage I, II, III and IV of 80 to 93%, 58 to 63%, 32 to 35%, 16%, respectively as report by the AJCC[20] in HIV-uninfected cervical cancer patients. Characteristics associated with a decrease of survival which is statistically significant include grade, stage and a lack of ART during cancer treatment. Severe late toxicity (2.3%) was found only in GU system.

The factor's effects are the enhancement of treatment tolerance and optimal outcome in HIV-infected cervix cancer patients. The factor mentioned were early commencement of ART (at diagnosis) based on WHO recommendation of ART in WHO HIV stage IV patients[21,22], most patients who are in the early stage and new radiation techniques which improve the therapeutic outcome.

The present study had limitations. Firstly, in any retrospective observation study, unobserved confounders that are correlated with receipt of the invitation and with the outcome of interest may introduce bias. Secondly, the study with relatively small numbers appeared in only certain subgroups. Finally, there is missing data regarding treatment of AIDS, CD4 cell count and viral loads assay during cancer treatment.

Conclusion

HIV-infected cervix cancer patients who were treated with ART and cancer treatment had a favorable survival outcome and toxicity. Grade and stage of cancer

significantly affect the survival outcome. These results point to a role for an intact immune system in controlling tumor among treated cervical cancer patients. To extend our finding, future investigations which could explain observed survival difference should include prospective evaluation of cancer-specific outcomes and active mortality follow-up, the collection of more sensitive and longitudinal HIV-related measures such as HIV viral load and CD4 counts which may identify characteristics of HIV-infected cancer patients.

What is already known on this topic?

cervical cancer in HIV-infected patients have more frequent interruptions of radiation treatment, lower rate of treatment completion and receive concurrent chemotherapy less often. Cervical cancer in HIV-infected patients have worse survival outcome compared with their non HIV-infected cervical cancer counterparts. The combination ART has improved the survival rates in HIV-infected patients with cervical cancer.

What this study adds?

Cervical cancers in HIV-infected patients who received appropriate ART before and during cancer treatment had a favorable survival outcome and toxicity compared with HIV-uninfected cervical cancer patients. Characteristics associated with a decrease of survival which is statistically significant include grade, stage of tumor and a lack of ART during cancer treatment.

Acknowledgements

The present study was granted from the Faculty of Medicine Vajira Hospital, Navamindradhiraj University research fund.

Potential conflicts of interest

The authors declare no conflict of interest.

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