Gynecologic Oncology Reports 34 (2020) 100669

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

A prognostic study of patients with cervical cancer and HIV/AIDS in Bangkok, Thailand

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ARTICLE INFO

Keywords:
HIV/AIDS
Survival
Cervical cancer
Healthcare system
Hospital-based registry
Thailand

ABSTRACT

Cervical cancer is one of the most common cancers of women. In Thailand, the incidence and death rate of cervical cancer are 18.1 and 5.7 per 100,000 women, respectively. Disease progresses faster in patients infected with human immunodeficiency virus (HIV) with acquired immune deficiency syndrome (AIDS). However, limited data are available for Thailand. Here we determined the prevalence of HIV/AIDS and identified factors affecting survival. We reviewed medical records of women infected with HIV with cervical cancer treated at Ramathibodi Hospital from 2007 through 2014. Demographic and clinical data were collected upon diagnosis. We used the Kaplan–Meier method and a Cox proportional hazards model to evaluate the association of overall survival (OS) with risk factors. The mean, median and range of ages at diagnosis of the 1,362 subjects were 53.9 years, 53.0 years and 20–94 years, respectively. The prevalence of HIV/AIDS in patients with cervical cancer was 2.3% and 5-year survival was 61.2%. Multivariable analysis revealed that favourable prognostic factors were a civil servant medical benefit plan and higher education. Advanced cervical cancer was a poor prognostic factor. Prognosis of women with stage III and IV cervical cancer was extremely poor (HR = 7.25 (95%CI: 4.39–11.98)) in stage III and HR = 20.57 (95%CI: 11.59–36.53) in stage IV). The 1-, 3-, and 5-year survival rates of patients with (74.2%, 67.6%, and 63.6%, respectively) or without (87.4%, 71.3% and 63.7%, respectively) HIV/AIDS were not significantly different.

1. Introduction

Cervical cancer is the third most common cancer in women worldwide. Age-standardized rates (ASR) per woman per year are high in Eastern Africa (42.7), Melanesia (33.3), Southern Africa (31.5) and Central Africa (30.6) and low in Australia and New Zealand (5.5) and Western Asia (4.4) (Ferlay et al., 2019; Jung et al., 2017). In Thailand, cervical cancer is the second most common (11.7 per 100,000) malignancy of women after breast cancer (21.8%). The mortality rates of cervical cancer steadily increased from 2012 to 2016 from 5.9 to 6.6 per 100,000 women, respectively (Imsamran et al., 2018).

Human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) is associated with high-grade intraepithelial neoplasia and is a major cause of mortality and diminished quality of life (da Medeiros, et al., 2017). Women with HIV/AIDS are at higher risk of cervical cancer compared with women without HIV/AIDS. Several studies convincingly demonstrate the increased in risk of pre-invasive cervical lesions among HIV-infected women, but incidence rates of invasive cervical cancer are not significantly increased in those with HIV/AIDS (Chambuso et al., 2017; Dryden-Peterson et al., 2016; Ghebre et al., 2017; Grover et al., 2018). However, such data are limited for the population of Thailand.

We therefore conducted a retrospective cohort study of patients with cervical cancer who were diagnosed and treated at Ramathibodi Hospital to determine the prevalence of HIV/AIDS and its effects, along with other prognostic factors, on the survival of patients with cervical cancer.

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https://doi.org/10.1016/j.gore.2020.100669
Received 19 June 2020; Received in revised form 5 September 2020; Accepted 27 October 2020
Available online 4 November 2020

2. Materials and methods

2.1. Study population

We analysed the records of women with cervical cancer diagnosed and/or treated at the Faculty of Medicine, Ramathibodi Hospital, Mahidol University between 2007 and 2014. Patients were covered by one of the three main healthcare systems of Thailand as follows: (1) Civil Servant Medical Benefit Scheme (CSMBS) for government employees, (2) Social Security Scheme (SSS) for employees of private organizations and (3) Universal Coverage Scheme (UCS) for Thai citizens not covered by the CSMBS or SSS. Data were gathered from the hospital's medical electronic record system using the ICD-10 coding system and patients' files, along with databases of these three healthcare systems, to ensure that the information was correct. Patients' baseline characteristics were reviewed.

Cancer histopathology, tumour site, and extent of disease were assessed according to the International Classification of Disease for Oncology: Third Edition. (ICD-O-3); and FIGO staging was applied. Clinicians ascertained that cervical cancer patients were diagnosed as having HIV/AIDS infection through their clinical history and, if needed, HIV serology testing (Enzyme-linked immunosorbent assay: ELISA, agglutination assay, immonochromatography and dot immunoassay). All patients received treatments appropriate for their stage according to FIGO guidelines. Overall survival (OS) was defined as time from the date of diagnosis to the date of death or the date of the last follow-up. Follow-up examinations were completed in June 2019. The status of each patient was verified using the records of the Bureau of Registration Administration (BORA). The Ethics Committee of Ramathibodi Hospital approved this study.

2.2. Statistical analysis

Patients' baseline characteristics were summarized using descriptive statistics, and patients' clinical characteristics were defined as categorical variables. Cumulative survival percentages were estimated using the Kaplan–Meier method. The statistical significance of the differences in cumulative survival was evaluated using the log-rank statistic for homogeneity. A Cox proportional hazards model was used to evaluate the significance of the associations between other factors and death, which are represented as hazard ratios (HRs) and the 95% confidence interval (95%CI). $P < 0.05$ indicates a significant difference, and 95%CIs were computed for survival proportions and rates. Statistical analysis was performed using STATA version 15.1 (College Station, Texas, USA).

3. Results

From January 2007 to December 2014, 1362 women were diagnosed with cervical cancer. Most lived in Bangkok and its suburbs (73.2%). The mean (SD) and median (range) ages at first diagnosis were 42.5 years (11.8) and 41 (15–94) years, respectively, and the ages of 50.4% of patients ranged between 45 and 54 years. The most common healthcare system was the CSMBS. By the end of the study, 570 women (41.8%) died, and 31 (2.3%) had HIV/AIDS. The mean (SD) ages of women with or without HIV/AIDS were 54 (12) years and 47 (10) years, respectively ($P = 0.003$). Patients' baseline characteristics are summarized in Table 1.

The total follow-up for all patients was 6451.8 person-years, and the probability of OS was >50% at the end of the study (Fig. 1). The 5-year OS of the entire cohort was 61.2% (95%CI: 58.5–63.8%). The 5-year OS were 48.9% (95%CI: 54.5–49.3%), 46.5% (95%CI: 40.2–52.6%) and 17.7% (95%CI: 10.4–26.5%) of patients who were age at diagnosis >60 years, registered in the UHS and had stage IV, respectively (Fig. 2).

Death rates of patients with or without HIV/AIDS per 100 person-year were 8.8 (95%CI: 8.1–9.6) and 7.8 (95%CI: 4.5–12.9) ($P = 0.831$). The 1- and 3-year OS of women without HIV/AIDS was higher than those of women with HIV/AIDS, although the 5-year overall survivals were not significantly different ($P = 0.827$) (Fig. 3). The 1-, 3-, and 5-year survival rates (95% CI) among women without HIV/AIDS were 87.4% (95%CI: 85.3–89.1%), 71.3% (95%CI: 68.6–73.8%), and 63.7% (95%CI: 60.8–66.5%), respectively, while those of women with HIV/AIDS were 74.2% (95%CI: 54.9–86.2%), 67.6% (95%CI: 48.1–81.1%), and 63.6% (95%CI: 43.8–78.0%), respectively (Table 2).

When we evaluated the data using Cox's proportional hazard ratio, we found that factors predicting favourable prognosis were coverage under the CSMBS and a bachelor's degree or higher. Women covered under the CSMBS experienced hazard ratio (HR) = 0.71 (95%CI: 0.49–1.02) time to death compared with those covered by the UCS. Women who graduated with a bachelor's or higher degree had a 0.57

Table 1
Demographic and clinical characteristics of patients diagnosed with cervical cancer between Octobers 2007 and January 2014.

Characteristics	Group (n, %)		
	Total	HIV/AIDS infected	HIV/AIDS un-infected
Number of patients	**1362 (100)**	**31 (2.3)**	**1331 (97.7)**
Age at diagnosis			
20–44	322 (23.6)	16 (51.6)	306 (23.0)
45–54	433 (31.8)	6 (19.4)	427 (32.1)
55–64	331 (24.3)	7 (22.6)	324 (24.3)
≥65	276 (20.3)	2 (6.5)	274 (20.6)
Mean (sd)	53.9 (12.7)	47.4 (10.3)	54.13 (12.7)
Median (min, max)	53 (20, 94)	44 (33, 69)	53 (20, 94)
Education			
Primary	441 (50.5)	8 (50.0)	433 (50.5)
Secondary	124 (14.2)	4 (25.0)	120 (14.0)
Bachelor and higher	308 (35.3)	4 (25.0)	304 (35.5)
Marital status			
Single	139 (10.2)	4 (12.9)	135 (10.2)
Married	895 (65.9)	15 (48.4)	880 (66.3)
Separate, divorced	324 (23.9)	12 (38.7)	312 (23.5)
Healthcare scheme			
UCS	273 (20.7)	10 (32.3)	263 (20.4)
CSMBS	430 (32.6)	7 (22.6)	423 (32.8)
SSS	133 (10.1)	5 (16.1)	128 (9.9)
Other	484 (36.7)	9 (29.0)	475 (36.9)
FIGO staging			
Stage I	389 (33.9)	8 (29.6)	381 (34.0)
Stage II	374 (32.6)	7 (25.9)	367 (32.7)
Stage III	296 (25.8)	12 (44.4)	284 (25.3)
Stage IV	90 (7.8)	0	90 (8.0)

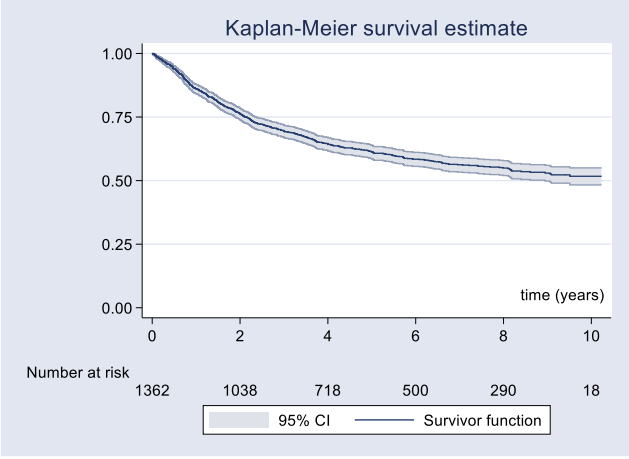

Fig. 1. Overall survival probability of women with cervical cancer during the period of January 2007 – June 2019.

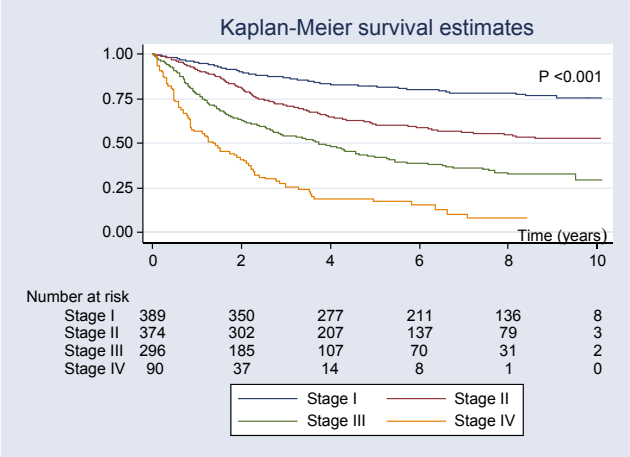

Fig. 2. Overall survival probabilities in women with cervical cancer by stage.

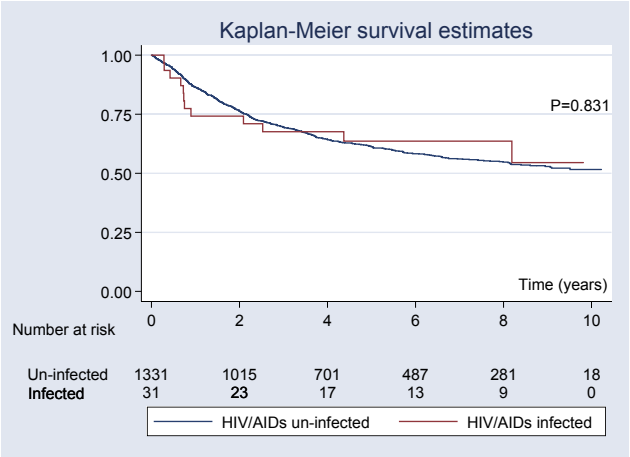

Fig. 3. Overall survival probabilities in women with cervical cancer by self-reported history of HIV/AIDS infected.

(95%CI: 0.39–0.85) risk of death compared with those whose education ended after attending a primary school.

A significant factor for poor prognosis was advanced disease. Thus, cervical cancer stage III and stage IV had 7.25 (95%CI: 4.39–11.98) and 20.57 (95%CI: 11.59–36.53) higher risks of death, respectively, compared that of stage I disease. HIV/AIDS status did not confer a significantly higher risk of death (HR = 1.69-times; 95%CI: 0.73–3.93, P = 0.220) compared with those without HIV/AIDS (Table 3).

4. Discussion

The present study was relatively large and long-term. Among the 1362 patients included, 31 (2.3%) were infected with HIV vs 0.82% in the United States, 19.7% in Kenya, 66.4% in Botswana, 42.4% in Uganda and 20.6% in Brazil (Ferreira et al., 2017; Coghill et al., 2015; Coghill et al., 2013). The 5-year OS of patients studied here was 61.2% compared with United States, 67%; France, 77%; Brazil, 66%; Taiwan, 66% and Korea, 70% (Jung et al., 2017; Yamagami et al., 2017; Grabar et al., 2019). The OS in our study is quite low when compared with other countries. The reason might be the fact that our hospital is a medical school and tertiary referral health care centre, which receives many referrals of advanced cancer cases from the whole country and therefore have a high number of patients with advanced disease in our study.

We found that education and patients' health coverage were significant prognostic factors. Thus, coverage under the CSMBS and a bachelor's degree or higher were significant prognostics. Women who were covered under the CSMBS had a 0.71 time to death compared with those covered by the UCS. Thus, these individuals may have had easier access to treatment (Suphanchaimat et al., 2019).

Our data are consistent with those of previous studies (Miller, 2016; Vincerževskienė et al., 2017) showing that the level of education affects survival. Highly educated patients may have a better understanding of the treatment regimen. Furthermore, patients' medical knowledge and access to health information are associated with their adherence to treatment. Consistent with these conclusions, we show here that survival outcomes were significantly associated with a patient's education. Specifically, patients with a bachelor's degree or higher experienced longer survival vs those who had a primary-school education. Furthermore, there was no significant difference in survival among patients who attended secondary and primary schools (P = 0.262).

Cancer stage was a significant prognostic factor of survival, consistent with the findings of previous studies (Robbins et al., 2014; Ford

Table 2
Kaplan-Meier estimated of overall survival and cause-specific survival by factors.

Characteristics	All women	Person-year	% Death (95%CI)	% 5-year survival rate (95%CI)	P-value
Total	**1320**	**6451.80**	**41.5 (39.2–44.4)**	**61.2 (58.5–63.8)**	
Age, y					<0.001
20–44	322	1568.2	40.7 (35.3–46.2)	60.8 (55.2–66.0)	
45–54	433	2203.5	37.0 (32.3–41.6)	64.5 (59.6–68.9)	
55–64	331	1623.2	36.6 (31.3–41.9)	67.2 (61.6–72.1)	
≥65	276	1056.9	57.2 (51.1–63.1)	48.9 (42.6–55.1)	
Marital status					0.033
Single	139	647.8	40.3 (32.1–48.9)	61.6 (52.8–69.3)	
Married	895	4361.4	40.0 (36.7–43.2)	63.3 (59.9–66.5)	
Separated, divorced	324	1415.6	47.8 (42.3–53.4)	55.1 (49.3–60.5)	
Healthcare scheme					<0.001
UCS	273	1110.3	53.1 (47.0–59.1)	46.5 (40.2–52.6)	
CSMBS	430	2201.4	34.2 (29.7–38.9)	70.1 (65.3–74.3)	
SSS	133	682.5	42.9 (34.3–51.7)	61.2 (52.2–68.9)	
Other	484	2250.4	40.5 (36.1–45.0)	62.4 (57.8–66.7)	
Education level					<0.001
Primary	441	1885.0	44.0 (39.2–48.7)	57.2 (52.2–61.9)	
Secondary	124	497.9	42.7 (33.3–51.9)	57.9 (48.4–66.4)	
Bachelor and higher	308	1555.4	28.2 (23.3–33.6)	72.2 (66.7–77.0)	
FIGO staging					<0.001
Stage I	389	2369.0	20.8 (16.9–25.2)	81.8 (77.5–85.4)	
Stage II	374	1814.0	41.7 (36.6–46.8)	60.5 (55.1–65.4)	
Stage III	296	1073.5	59.8 (53.9–65.4)	42.3 (36.3–48.2)	
Stage IV	90	190.9	85.6 (76.5–92.0)	17.7 (10.4–26.5)	
HIV/AIDs infected					0.831
Un-infected	1331	6299.9	41.9 (39.3–44.6)	63.7 (60.8–66.5)	
Infected	31	151.9	38.7 (21.8–57.8)	63.6 (43.8–78.0)	

Table 3
Results of the multivariable Cox regression models comparing overall survival outcomes in women with cervical cancer.

Characteristics	Crude HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Age, y				0.138
20–44	Reference	<0.001	Reference	
45–54	0.86 (0.68–1.09)		0.68 (0.46–1.01)	
55–64	0.87 (0.69–1.12)		0.79 (0.51–1.23)	
≥65	1.59 (1.27–2.01)		1.02 (0.63–1.56)	
Marital status		0.039		0.514
Single	Reference		Reference	
Married	0.95 (0.72–1.26)		0.82 (0.54–1.26)	
Separate, divorced	1.22 (0.90–1.66)		0.97 (0.60–1.56)	
Healthcare scheme		<0.001		<0.001
UCS	Reference		Reference	
CSMBS	0.53 (0.42–0.67)		0.71 (0.49–1.02)	
SSS	0.70 (0.52–0.96)		1.17 (0.75–1.83)	
Education level		<0.001		<0.001
Primary	Reference		Reference	
Secondary	1.01 (0.75–1.37)		0.77 (0.49–1.22)	
Bachelor and higher	0.57 (0.44–0.74)		0.57 (0.39–0.85)	
FIGO staging		<0.001		<0.001
Stage I	Reference		Reference	
Stage II	2.35 (1.80–3.07)		4.01 (2.41–6.62)	
Stage III	4.28 (3.28–5.57)		7.24 (4.38–11.97)	
Stage IV	9.40 (6.85–12.89)		20.59 (11.60–36.56)	
HIV/AIDs infected		0.831		0.220
Un-infected	Reference		Reference	
Infected	0.94 (0.53–1.66)		1.70 (0.73–3.94)	

et al., 2007). In the present study, the 5-year OS of patients with stage IV was 17.6%, which imposed a 20.6 times higher risk compared with patients with stage I. However, patients with stage IV were only 7.8% of subjects, which may overestimate survival.

Patients with cervical cancer without HIV/AIDS survive longer than those with this disease (Coghill et al., 2013; Himakalasa et al., 2013; de Pokomandy et al., 2019). Here we did not find such a difference. Thus, although the difference was not statistically significant, patients with cervical cancer with HIV/AIDS were at 1.69 times higher risk of death than those without. Interestingly, the average age of patients with HIV/AIDS was lower than those without (47 years vs 54 years). This age difference may explain why there was no significant difference in overall 5-year survival (63.6% vs 63.7%). However, we found that the 1- and 3-year survival rates of patients with HIV/AIDS were 74.2% vs 87.4%, respectively, and 67.6% vs 71.3%, respectively, for patients without HIV/AIDS. Thus, patients with HIV/AIDS survived as long as those without, which may offer them a certain degree of comfort.

Difficulty accessing HIV/AIDS treatment in the past may represent a contributing factor to the high mortality rate of patients with cervical cancer. However, the healthcare system in Thailand provides free antiretroviral medications to patients with HIV/AIDS (since 2002) (Ford et al., 2007; Himakalasa et al., 2013). Such patients may therefore survive longer, or are at lower risk, of developing other cancers. Subgroup analysis of patients receiving antiretroviral medication regarding the compliance and its effect to cancer outcome would be beneficial.

Cervical cancer is AIDS-related, and women must be regularly screened for cervical cancer (de Pokomandy et al., 2019). Data for HIV/AIDS-associated with cervical cancer in Thailand are limited, and most published data are those of patients residing in South America and Africa (Grover et al., 2018; Ferreira et al., 2017; Himakalasa et al., 2013). Thus, robust data of patients with cervical cancer with HIV/AIDS in Thailand are required to demonstrate a definitive natural course and outcomes leading to the successful treatment.

Our study has a number of strengths and limitations. Major strengths include the relatively large number of patients with cervical cancer cases, long follow-up, and the low percentage of cases with an unknown stage at diagnosis. Limitations are the study's retrospective nature, data from a single centre, and the small number of patients with cervical cancer with HIV/AIDS. Despite the small number of HIV/AIDS infected in this study (31 cases), the authors performed a power analysis with a result of power >90% which is sufficient to detail the difference between HIV/AIDS infected and HIV/AIDS un-infected outcome groups. A multicentre case-controlled study will be required for more definitive comparisons of prognostic factors.

In summary, we found a 2.3% prevalence of HIV/AIDS in patients with cervical cancer at a single centre in Thailand. Advanced disease was a significant prognostic factor for shorter survival, and higher education and coverage by the CSMBS were prognostic factors for longer survival. We found that HIV/AIDS status was not a significant prognostic factor for longer survival.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors acknowledge the staff members of Ramathibodi Comprehensive Cancer Centre, Ramathibodi Hospital, Mahidol University for their assistance and providing data; Professor Amnuay Thithapandha for assistance with preparing the manuscript.

Author contributions

Conceptualization: S.W., N.S.T; Data curation: P.J., T.T., SP; Formal analysis: NST; Methodology: P.K., S.W., N.S.T.; Investigations: all authors; Writing original draft: N.S.T.; Writing-review & editing: all authors.

Funding support

This study was supported by a grant from Ramathibodi Comprehensive Cancer Centre (P.J., T.T., SP).

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