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

Nintita Sripaiboonkij Thokanit a, Pope Kosalaraksa b, Pornsuda Jitkasikorn a, Tanapol Thonkamdee a, Sopit Promchana a, Sarikapan Wilailak c, *

a Tumor Registry, Ramathibodi Comprehensive Cancer Center, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
b Department of Pediatrics, Faculty of Medicine, Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand
c Department of Obstetrics and Gynaecology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand

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 (Insamran 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 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.

* Corresponding author at: Department of Obstetrics and Gynaecology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand, 270 Rama VI Road, Ratchatewi, Bangkok 10400, Thailand.
E-mail address: sarikapan.wil@mahidol.ac.th (S. Wilailak).

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
2352-5789/© 2020 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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, immunochromatography 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 for patients without HIV/AIDS was 63.2% (95%CI: 60.2–66.2%), 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 survival rates 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: 54.9–63.7%), 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
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 CSMSB and a bachelor’s degree or higher were significant prognostics. Women who were covered under the CSMSB 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; Vincerzevskiene et al., 2017) showing that the level of education affects survival. Highly educated patients may have a better understanding of their disease and higher access to treatment (Suphanchaimat et al., 2019). Consistent with these conclusions, we show here that survival outcomes were significantly associated with a patient’s education, consistent with the findings of previous studies (Robbins et al., 2014; Ford et al., 2017).
The difference may explain why there was no significant difference in overall 5-year survival rates of patients with HIV/AIDS, which were 74.2% vs 87.4%, respectively, and 63.6% vs 63.7%. However, we found that the 1- and 3-year survival rates of 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 is contributing 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., 2019). Here we did not find such a difference. Thus, patients with HIV/AIDS survived as long as those without.

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**            |                  |         |                      |         |
| 20–44                 | Reference        | 0.138   | Reference            |         |
| 45–54                 | 0.86             | <0.001  | 0.68 (0.46–1.01)     |         |
| 55–64                 | 0.87             | 0.99    | 0.79 (0.51–1.23)     |         |
| ≥65                   | 1.59             | 0.001   | 1.02 (0.63–1.56)     | 0.514   |
| **Marital status**    |                  |         |                      |         |
| Single                | Reference        | 0.039   | Reference            | 0.001   |
| Married               | 0.95             | 0.82    | 0.95 (0.54–1.60)     |         |
| Separate              | 1.22             | 0.97    | 0.97 (0.60–1.67)     |         |
| Divorced              | (0.90–1.66)      |         |                      |         |
| **Healthcare scheme** |                  |         |                      |         |
| UCS                   | Reference        | 0.001   | Reference            | 0.001   |
| CSMB                 | Reference        |         | 0.71 (0.49–1.02)     |         |
| SSS                  | 0.70             | 1.17    | 1.17 (0.75–1.83)     |         |
| Education level       |                  |         |                      |         |
| Primary               | Reference        | 0.001   | Reference            | 0.001   |
| Secondary             | 1.01             | 0.77    | 0.77 (0.49–1.22)     |         |
| Bachelor and higher   | (0.94–0.74)      |         |                      |         |
| **FIGO staging**      |                  |         |                      |         |
| Stage I               | Reference        | 0.001   | Reference            | 0.001   |
| Stage II              | 2.35             | 4.01    | 4.01 (2.41–6.62)     |         |
| Stage III             | (1.80–3.07)      |         |                      |         |
| Stage IV              | 4.28             | 7.24    | 7.24 (4.38–11.97)    |         |
| Stage V               | (3.28–5.57)      |         |                      |         |
| **HIV/AIDS infected** |                  |         |                      |         |
| Un-infected           | 9.40             | 20.59   | 20.59 (11.60–36.56)  |         |
| Infected              | (6.85–12.89)     |         |                      |         |
| **HRV/AIDS un-infected** | 0.831    |         | 0.831                |         |
| **HIV/AIDS un-infected** | Reference   |         | Reference            |         |
|                       | 0.94             | 1.70    | 1.70 (0.73–3.94)     |         |
|                       | (0.53–1.66)      |         |                      |         |

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 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.

Declarations 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).

References

Chambuso, R.S., Shadrack, S., Lidenge, S.J., Mwekibete, N., Medeiros, R.M., 2017. Influence of HIV/AIDS on cervical cancer: a retrospective study from Tanzania. J Glob Oncol. 3 (1), 72–78.

Coghill, A.E., Newcomb, P.A., Madeleine, M.M., Richardson, B.A., Mutyaba, I., Okuku, F., et al., 2013. Contribution of HIV infection to mortality among cancer patients in Uganda. AIDS 27 (18), 2933–2942.

Coghill, A.E., Shiel, M.S., Sunesa, G., Engels, E.A., 2015. Elevated cancer-specific mortality among HIV-infected patients in the United States. J. Clin. Oncol. 33 (21), 2376–2383.

Medeiros RC da SC de, Medeiros JA de, Silva TAL da, Andrade RD de, Medeiros DC de, Araújo J de S, et al., 2017. Quality of life, socioeconomic and clinical factors, and physical exercise in persons living with HIV/AIDS. Rev Saúde Pública [Internet], vol. 51, no. 0.

de Pokomandy, A., Burchell, A.N., Salters, K., Ding, E., O’Brien, N., Bakombo, D.M., et al., 2019. Cervical cancer screening among women living with HIV: a cross-sectional study using the baseline questionnaire data from the Canadian HIV Women’s Sexual and Reproductive Health Cohort Study (CHWOS). cmajo 7 (2), E217–E226.
Dryden-Peterson, S., Bvochora-Nsingo, M., Suneja, G., Efstathiou, J.A., Grover, S., Chiyapo, S., et al., 2016. HIV infection and survival among women with cervical cancer. J. Clin. Oncol. 34 (31), 3749–3757.

Ferreira, M.P., Coghill, A.E., Chaves, G.C., Bergmann, A., Thuler, L.C., Soares, E.A., et al., 2017. Outcomes of cervical cancer among HIV-infected and HIV-uninfected women treated at the Brazilian National Institute of Cancer. AIDS 31 (4), 523–531.

Ford, N., Wilson, D., Chaves, G.C., Lotrowska, M., Kijtiwatchakul, K., 2007. Sustaining access to antiretroviral therapy in the less-developed world: lessons from Brazil and Thailand. AIDS 21 (Suppl 4), S21–S29.

Ghebre, R.G., Grover, S., Xu, M.J., Chuang, L.T., Simonds, H., 2017. Cervical cancer control in HIV-infected women: past, present and future. Gynecol Oncol Rep. 21, 101–108.

Grabar, S., Hleyhel, M., Belot, A., Bouvier, A.-M., Tattevin, P., Pacanowski, J., et al., 2019. Invasive cervical cancer in HIV-infected women: risk and survival relative to those of the general population in France. Results from the French Hospital Database on HIV (FHDD)-Agence Nationale de Recherches sur le SIDA et les Hepatites Virales (ANRS) CO4. HIV Med. 20 (3), 222–229.

Grover, S., Bvochora-Nsingo, M., Yeager, A., Chiyapo, S., Bhatia, R., MacDuffie, E., et al., 2018. Impact of human immunodeficiency virus infection on survival and acute toxicities from chemoradiation therapy for cervical cancer patients in a limited-resource setting. Int. J. Radiat. Oncol. Biol. Phys. 101 (1), 201–210.

Himakalasa, W., Grisurapong, S., Phuangpaichit, S., 2015. Access to antiretroviral therapy among HIV/AIDS patients in Chiang Mai province, Thailand. HIV, vol. 205.

Imsamran, W., Pattatang, A., Namthaisong, K., Supattagorn, P., Chiawiriyabunya, I., Wongsema, M., et al., 2018. Cancer in Thailand Volume IX: 2013-2015. National Cancer Institute, Ministry of Public Health: Bangkok, Thailand, vol. 88.

Jung, K.-W., Won, Y.-J., Oh, C.-M., Kong, H.-J., Lee, D.H., Lee, K.H., et al., 2017. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2014. Cancer Res Treat. 49 (2), 292–305.

Miller, T.A., 2016. Health literacy and adherence to medical treatment in chronic and acute illness: a meta-analysis. Patient Educ. Couns. 99 (7), 1079–1086.

Robbins, H.A., Shiel, M.S., Pfeiffer, R.M., Engels, E.A., 2014. Epidemiologic contributions to recent cancer trends among HIV-infected people in the United States. AIDS 28 (6), 881–890.

Suphancharimate, R., Kunpeuk, W., Phaiyarom, M., Nipaporn, S., 2019. The effects of the health insurance card scheme on out-of-pocket expenditure among migrants in Ranong Province, Thailand. Risk Manage. Healthcare Policy 12, 317–330.

Vencrizevskienė, I., Jasiliūnienė, D., Austys, D., Stukas, R., Kacėniene, A., Smaliute, G., 2017. Education predicts cervical cancer survival: a Lithuanian cohort study. Eur. J. Publ. Health ckv261.

Yamagami, W., Nagase, S., Takahashi, F., Ino, K., Hachisuga, T., Aoki, D., et al., 2017. Clinical statistics of gynecologic cancers in Japan. J Gynecol Oncol [Internet] 28 (2),