Survival Rate of Cervical Cancer in National Referral Hospital in 2012 - 2014

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ABSTRAK

Latar belakang: *kanker serviks menduduki peringkat ke tiga di seluruh dunia sebagai penyebab kematian perempuan dan merupakan penyebab kematian utama perempuan di negara berkembang. Diperlukan evaluasi kesintasan berkala yang secara tidak langsung menjadi cermin tatalaksana. Penelitian ini bertujuan mengetahui kesintasan pasien kanker serviks di Rumah Sakit Cipto Mangunkusumo sebagai rumah sakit rujukan nasional di Indonesia.* ***Metode:*** *penelitian ini menggunakan desian kohort retrospektif terhadap data rekam medis pasien kanker serviks pada tahun 2012-2014 dengan metode total population sampling. Analisis data dilakukan menggunakan kurva Kaplan Meier, uji Log Rank dan Regresi Cox untuk mencari kemaknaan hubungan antarvariabel.* ***Hasil:*** *terdapat 1,303 subjek penelitian dengan angka kesintasan kanker serviks hingga tahun ke-5 sebesar 76%, 65%, 59%, 43% dan 34% dengan median kesintasan sebesar 1,316 hari secara keseluruhan. Terdapat perbedaan hazard bermakna pada variabel stadium kanker ($p<0.001$). Analisis regresi cox menunjukkan faktor yang berpengaruh terhadap kesintasan adalah stadium kanker.* ***Kesimpulan:*** *kesintasan 5 tahun kanker serviks di RSCM tahun 2012-2014 sebesar 34%.*

Kata kunci: *kanker serviks, kesintasan, rumah sakit nasional.*

ABSTRACT

Background: *cervical cancer is the third leading cause of female deaths worldwide, and it is the leading cause of female deaths in developing countries. A routine survival evaluation is required to imply the result of the treatment. The aim of this study was to determine the cervical cancer patient survival rate at the Cipto Mangunkusumo hospital as national referral hospital in Indonesia.* ***Methods:*** *our retrospective cohort study utilized the medical records of cervical cancer patients from 2012 to 2014 using total population sampling method. The data analysis was conducted using the Kaplan-Meier curve, log rank test and Cox regression to determine significant associations between variables.* ***Results:*** *there were 1,303 subjects with overall survival rates of cervical cancer up to the fifth year of 76%, 65%, 59%, 43% and 34%, respectively, with a median survival of 1,316 days. There were significant differences of hazard ratio for cancer stage variables ($p<0.001$), and the Cox regression analysis showed that the factor affecting survival was cancer stage.* ***Conclusion:*** *the 5-year cervical cancer survival rate at the Cipto Mangunkusumo hospital from 2012 to 2014 was 34%.*

Keywords: *cervical cancer, survival rate, national hospital.*

INTRODUCTION

Cervical cancer is one of the most common malignancies worldwide. Globally, it is the third leading cause of female deaths and the seventh leading cause of death in the total population. Moreover, it is the leading cause of female deaths in developing countries. According to the Global Cancer Incidence, Mortality and Prevalence database, there were 530,000 new cervical cancer cases in 2008, with more than 85% of these occurring in developing countries. Overall, cervical cancer causes 275,000 deaths annually and the cervical cancer mortality in Indonesia reached 7,493 deaths in 2008.[1]

However, there are discrepancies in the cervical cancer 5-year survival rates among countries. In a study by Sankaranarayanan et al. conducted from 1990 to 2000, various survival rates were reported: 46.4% in India, 65.7% in Singapore, 37.4% in the Philippines, 63.5% in China, 79.5% in Hong Kong and 54% in Thailand. In European countries, the survival rates were 59.1% in the United Kingdom, 64% in Denmark, 63.7% in Austria, 51.5% in Poland, 65% in Belgium and 60.5% in Germany.[2]

In Indonesia, a study was conducted at the Cipto Mangunkusumo Hospital in Jakarta in 1997. During the 5-year follow up, 47.9% of the subjects died, 14.6% survived and 37.6% dropped out.[3] The 5-year survival rate in that study was 30.3%, with a median survival of 934 days. Another study in 2001 examined the survival rate among patients grouped according to their cancer stages. The 5-year survival rates of the patients with cervical cancer stages I, II, III and IV were 50%, 40%, 20% and 0%, respectively.[3] A study in another Indonesian hospital in 1996 reported a 40.3% 5-year survival rate. The grouping based on the cancer stages revealed that the survival rates were 56.6% for stage I, 56.0% for stage II, 23.7% for stage III and 0 for stage IV. The study also examined different therapies received by the patients. Those who were treated with surgery alone had a 35% survival rate, with a median survival of 1,236 days; while those treated with radiation had a 38% survival rate, with a median survival of 1,127 days. The patients who were treated with chemotherapy had a median survival of 273 days. Among the patients receiving combined therapy, those who underwent surgery and chemotherapy had a median survival of 123 days, those who underwent surgery and radiation had a 61% survival rate, with a median survival rate of over 50%, and those who were treated with radiation and chemotherapy had a median survival of 509 days.[4]

A paper published by Andrae et al. reported 567 cervical cancer cases in Sweden between 1999 and 2001. They found that the stage IA cases had a survival rate of 94%, the stage IB cases had a survival rate of 81% and the stage IA or higher cases had a 40% survival rate. They also examined the survival rate based on cancer histopathology and found the following results: the survival rate among patients with squamous cell carcinoma was 71%, the rate for patients with adenocarcinoma was 68%, for those with adenosquamous carcinoma, it was 73% and for those with small cell carcinoma, it was 44%.[5] In a study conducted in Bologna, Italy, Syrjanen et al. reported that the median survival among the patients with squamous cell carcinoma was 13 months in those cases with tumour sizes larger than 2 cm, and it was 37 months in those cases with tumour sizes of less than 2 cm.[6]

With regard to cervical cancer, there has been a consistent decline in the mortality rate over the last 40 years and a consistent rise in the 5-year survival rate due to the introduction of screening programs in many countries.[7] The most important prognostic factors include the cancer stage, tissue histopathology, screening history, degree of tissue differentiation, metastasis and response to therapy.[3,5] However, there have not been adequate studies addressing the cervical cancer survival rate based on histopathology and response to therapy. Reliable data regarding these prognostic factors may be essential for clinicians to determine and evaluate the treatment options for their cervical cancer patients. The aim of this study was to determine the cervical cancer patient survival rate at the Cipto Mangunkusumo hospital as national referral hospital in Indonesia

METHODS

Our study was a retrospective cohort study. Data was collected from the medical records of

cervical cancer patients at Cipto Mangunkusumo Hospital from 1 January 2012 to 31 December 2014. The inclusion criteria were patients in the OBGYN Oncology Division who were diagnosed during the aforementioned duration of study with reliable medical records. No exclusion criteria were set for this study. This study has been approved by the Ethics Committee of Faculty of Medicine Universitas Indonesia, reference number 655/UN2.F1/ETIK/2017.

Data collected in this study were age, parity children, marriage age, FIGO staging, histopathology, type of treatment, and outcome (die or alive). The total number of samples needed was 249 subjects. The subjects were enrolled in this study using a consecutive sampling technique. Data collection and input were conducted by trained physicians and medical students. Statistical analysis was conducted using Stata 10 (StataCorp LLC, College Station, TX, USA) and data analysis was performed using the Kaplan-Meier curve, log-rank test and Cox regression to determine the associations between variables.

RESULTS

A total of 1,651 patients with cervical cancer were found in the registry between 2012 and 2014. Data validation was conducted for all of necessary variables and this resulted in 1,303 valid subjects. Any missing data were completed using the imputation method. With regard to the missing data, 3 subjects had missing age data, 236 had missing marriage age data, 250 had missing cancer staging data, 208 had missing tissue histopathology data, 452 had missing treatment option data and 169 had missing outcome data. There were 368 (28.2%) deaths that were counted as events. Of the 1,303 cervical cancer patients included in this study, the mean age was 53 years old, the youngest was 27 years old, and the oldest was 87 years old. The demographic characteristics of all of the subjects are presented in **Table 1**.

There were 1,303 subjects with overall survival rates of cervical cancer up to the fifth year of 76%, 65%, 59%, 43% and 34%, respectively, with a median survival of 1,316 days. An analysis was performed to compare survival rates of the subjects grouped by their demographic and clinical characteristics. However, in the further bivariate analysis using the log rank Cox regression, we found no significant difference in the survival rates of the subjects when they were grouped by age (p=0.59), parity (p=0.75), duration of marriage (p=0.92), tissue histopathology (p=0.16) and treatment (p=0.65).

The only variable associated with a significant survival rate difference was the cancer staging (p<0.005). Based on cancer staging of our subjects, we found that the median survival time for patients with stages II, III and IV were 1,900

Table 1. Demographic and clinical characteristics of the study subjects

Variables	Value (n = 1,303)
Age (years), Mean (SD)	53.18 (9.5)
Parity [children, n (%)]	
- Nulliparous	135 (10.4)
- Primiparous	90 (6.9)
- Multiparous	921 (7.7)
- Grand multiparous	157 (12.0)
Marriage age [years, n (%)]	
- < 20 years old	882 (67.7)
- 20 – 30 years old	402 (30.8)
- > 30 years old	19 (1.5)
FIGO staging [n (%)]	
- Stage I	137 (10.5)
- Stage II	335 (25.7)
- Stage III	707 (54.3)
- Stage IV	124 (9.5)
Histopathology [n (%)]	
- Squamous cell carcinoma	1009 (77.4)
- Adenocarcinoma	172 (13.2)
- Adenosquamous	122 (9.4)
Treatment [n (%)]	
- Surgery	48 (3.7)
- Surgery + chemotherapy	19 (1.5)
- Surgery + radiation	90 (6.9)
- Radiation	867 (66.5)
- Chemotherapy	39 (3.0)
- Radiation + chemotherapy	240 (18.4)
Outcome [n (%)]	
- Die	368(28.2)
- Live	935 (71.8)

SD: standard deviation; FIGO: International Federation of Gynaecology and Obstetrics

days, 1,243 days and 328 days, respectively. The survival rates for these subjects were 58% (stage I), 76% (stage II), 23% (stage III) and 0 (stage IV). The median survival is shown in the Kaplan-Meier survival curve in **Figure 1**.

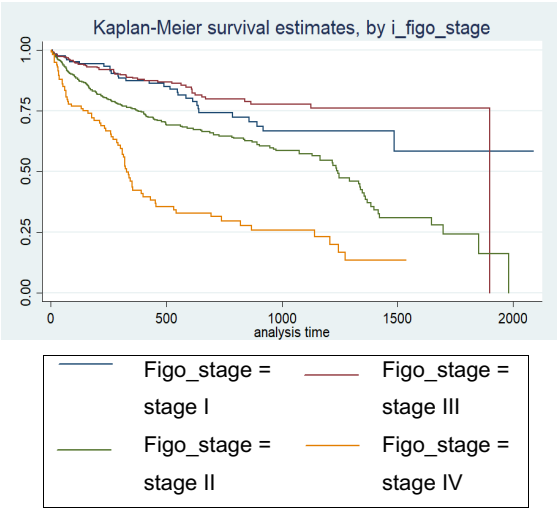

Figure 1. Kaplan-Meier survival curve classified by cancer staging.

The bivariate analysis with reference to stage I revealed that patients with stage III cervical cancer had a hazard ratio (HR) of 1.68 [95% confidence interval (CI): 1.05–2.68] and those with stage IV cervical cancer had an HR of 3.93 (95% CI: 2.39–6.47). The complete results of the bivariate analysis are shown in **Table 2**.

We performed further analysis using multivariate Cox regression to determine the effects of certain variables in relation to others. The variables with p values of less than 0.25 in the bivariate analyses, those that did not satisfy the proportional hazard assumption and those that were theoretically important were included. The variables that fulfilled these criteria were parity (primiparous), cancer staging (stages I, II, III and IV), adenocarcinoma and surgery + radiation. The results of the multivariate analysis are shown in **Table 3**.

The multivariate analysis showed that only cancer stages III and IV significantly affected the 5-year survival rates of cervical cancer patients with adjusted HRs of 1.68 (95% CI: 1.05–2.68) and 3.93 (95% CI: 2,39 – 6.47), respectively. However, based on our clinical judgment, several other variables, such as the age, histopathology and therapy were also essential for predicting patient survival rates.

Table 2. Cox regression bivariate analysis of the 5-year cervical cancer survival rate.

Variables	HR	95% CI
Age (Ref. 0 – 30 years)		
- 30 – 50	1.877	0.259 – 13.587
- > 50	1.814	0.251 – 13.101
Parity (Ref. Nulliparous)		
- Primiparous*	1.402	0.836 – 2.351
- Multiparous	0.992	0.676 – 1.457
- Grand multiparous	0.837	0.516 – 1.356
Marriage age (Ref. <20 years old)		
- 20 – 30 years old	1.877	0.259 – 13.587
- > 30 years old	1.814	0.251 – 13.108
Staging** (Ref. I)		
- II	0.700	0.418 – 1.171
- III**	1.681	1.053 – 2.684
- IV**	3.936	2.392 – 6.475
Histopathology* (Ref. Squamous cell carcinoma)		
- Adenocarcinoma*	0.773	0.542 – 1.101
- Adenosquamous carcinoma	1.041	0.726 – 1.493
Treatment (Ref. Surgery)		
- Surgery + chemotherapy	0.860	0.309 – 2.387
- Surgery + radiation*	0.626	0.285 – 1.374
- Radiation	1.079	0.549 – 2.119
- Chemotherapy	0.934	0.385 – 2.268
- Radiation + chemotherapy	0.868	0.425 – 1.773

HR: hazard ratio, CI: confidence interval; *p value of less than 0.25; **p value of less than 0.05.

Table 3. Cox regression multivariate analysis of the 5-year cervical cancer survival rate.

Variables	Adjusted HR	95% CI on the HR
Staging (Ref. I)		
- II	0.700	0.418 – 1.171
- III	1.681	1.053 – 2.684
- IV	3.936	2.392 – 6.475

CI: confidence interval, HR: hazard ratio

DISCUSSION

The demographic characteristics of our study subjects are not much different from those of the study conducted by Sirait et al[6] at the Dharmais Cancer Hospital in Jakarta in 2003.

In their study, the mean age was 50 years old, with the youngest patient was 21 years old and the oldest was 80 years old. However, the results of our study are different when compared to a previous study that was conducted at the Cipto Mangunkusumo Hospital by Nuranna et al.[8] in 2012, which reported a mean age of 47.5 years old, with the youngest patient was 24 years old and the oldest was 73 years old. In general, the age characteristic of our study subjects was older than those of the other studies.[9] According to the 2001–2009 National Cancer Institute Surveillance, Epidemiology and End Result report, the average age of cervical cancer patients was 49 years old with 62% of them under 55 years old and 38% of them over 55 years old.[10]

Our results showed that the overall 5-year survival rate was 34%, with a median survival of 1,316 days. The number was lower than that in the 2012 study conducted by Nuranna et al. that found a 5-year survival rate of 52%, with a median survival of 1,916 days, and it was only slightly higher than the results reported by Sirait et al.[9] in 1997 that found 30% survival rate and a median survival of 934 days. All of these studies were conducted in Jakarta, and the results were lower than those in a report released by FIGO in 2006.[5] The survival rate for that large study, which included 11,775 subjects, was 69.6%. The discrepancy in the results may have been caused by the fewer subjects with early cancer stages.

Based on the staging diagnosis, the median of survival in our study were consistent with previous results regarding the overall analysis; our findings were lower than those reported by Nuranna et al.[8], but they are slightly better than those reported by Sirait et al.[9] It is important to note that these findings may have been caused by the higher proportion of subjects who had more advanced clinical stages.

There was no survival difference between the subjects with stage I cervical cancer and those with stage II cervical cancer.[8] In our study, there was no significant relationship between the histopathology and the cervical cancer survival rate ($p>0.05$). However, based on the hazard ratios, it was determined that adenocarcinoma (HR=0.73) was more protective than squamous cell carcinoma (HR=1.00); moreover, adenosquamous carcinoma (HR=1.04) did not differ significantly from squamous cell carcinoma in relation to the survival. Regarding the histopathological survival reported by Nuranna et al.[8], patients with squamous cell carcinoma had worse prognosis, followed by adenosquamous carcinoma and adenocarcinoma. In one previous study involving 703 hospitals with a total of 11,157 cases, there was no significant difference in the 5-year survival among patients with squamous cell carcinoma, adenocarcinoma and adenosquamous carcinoma, except with regard to metastases to lymph nodes.[11]

CONCLUSION

Our study shows that the 5-year cervical cancer patient survival rate at the Cipto Mangunkusumo Hospital in Jakarta from 2012 to 2014 was 34%, and it was significantly affected by the cancer staging at the time of the diagnosis. Subjects with stage III and stage IV cervical cancer had lower chances of survival (adjusted HRs: 1.68 and 3.93, respectively) when compared to those with stage I cancer.

Our study was conducted for a longer duration and it involved a larger sample size than the prior studies conducted in a similar setting. Our results also offered data on a prediction of the disease outcome and its clinical progression. However, we are aware that a retrospective cohort design is highly prone to informational bias in the data collection, and there were difficulties accessing certain medical records, which resulted in numerous incidences of incomplete data.

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CONFLICT OF INTEREST

The authors declare that there were no conflicts of interest with regard to this study.

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