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Recurrence Rate of Cervical Cancer in Jakarta

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Abstract. *Introduction:* Cervical cancer is one of the ten most commonly diagnosed cancer in the world population. It is estimated there are around 570.000 new cases, with 3.3% deaths in 2018. The recurrence rate for cervical cancer ranges from 8% to 26% and usually appears within 2-3 years after the first treatment. The recurrence rate of cancer is one quality service in healthcare.; thus, the authors decide to evaluate this issue. *Materials and Methods:* This multicenter and retrospective study reporting 262 patients of all stage cervical cancer who met inclusion criteria from 2015 to 2019 in national reference teaching hospitals in Jakarta, Indonesia. Patients were treated with radical hysterectomy, radiation, and chemotherapy and observed for five years period. Univariate and multivariate analyses were performed to investigate the recurrence of cervical cancer. *Results:* The recurrence rate over all stages after primary treatment is 21.4%. The recurrence rate early stage and advanced stage is 20% and 38%, respectively. Univariate and multivariate analysis revealed parity, cancer stage, tumor size, histotype, and differentiation affecting the recurrence of the disease. Cox multivariate modeling determined the significant factors are parity (Hazard Ratio (HR) = 0.5, *p*-value <0.01), cancer stage (Hazard Ratio (HR) = 1.6, *p*-value 0.013), tumor size (Hazard Ratio (HR) = 2.08, *p*-value 0.018), histotype (Hazard Ratio (HR) = 2.6, *p*-value <0.01), and differentiation (Hazard Ratio (HR) = 0.5, *p*-value 0.01). *Conclusion:* The recurrence rate of cervical cancer is related to the cancer stage. The higher cancer stage resulted in a higher recurrence rate.

Key words: Cervical cancer, Recurrence, Radical Hysterectomy, Histopathology

Introduction

Globally, Cervical cancer is in the ten most commonly diagnosed cancer in the world population. It is estimated there are 570.000 new cases with 3.3% deaths in 2018. Of all the reported cases worldwide, most cases are from Asia, with 55% of the total new cases and have 826.000 for 5-year prevalence cases (56.1%). However, in low-middle income countries, cervical cancer is still ranked in second place for the new cases and ranked fourth for the death cases with a 5-year prevalence estimation of about 34% of all reported cases. In Indonesia, cervical cancer is ranked in second place for 32.000 (9.3%) new cases and ranked in third place for 8.8% death cases in 2018 (1-3). The national data from the Indonesian Society of Gynecologic Oncology showed that cervical cancer is still the leading cause of all gynecology cancer cases. The most prevalent patients came from the middle age group (36-55), in which the majority stage is IIIB and for the histotype is squamous cell carcinoma (4).

Among all cervical cancer stages, the estimation for stage I disease is approximately 50%. The five-year survival rate for cervical cancer is 67.9% for all stages, where the stage I disease exceeds 90% 5-year survival rate[5]. The cure rate of primary treatment for cervical cancer in patients diagnosed with early-stage is 80% to 95% while in stage III disease is 60%[6]. According to which stage the disease was in, the recurrence rate for cervical cancer ranges from 8% to 26%. Within 2-3

years after the first treatment, most recurrences will occur during follow-up examination with or without symptoms. The presentation of symptoms ranging from 46% to 95% includes pelvic pain, leg symptoms such as pain or lymphedema, vaginal bleeding or discharge, urinary symptoms, cough, and weight loss (5). The common sites of distant recurrence are lung, paraaortic lymph nodes, abdominal cavity, and supraclavicular nodes, which of 90% of those will die of their disease within five years (6).

In that high recurrence in an advanced stage, it needs to do screening and early detection to reduce the advanced stage incidence.

To our knowledge, the recurrence rate of cancer is one of the quality services in healthcare. Thus, the authors decide to investigate this issue.

Methods

We conducted a multicenter retrospective study and retrieved the data from Dr. Cipto Mangunkusumo National Center General Hospital's medical records in Jakarta, and Fatmawati Hospital, Jakarta. We enrolled patients diagnosed with all cervical cancer stages from January 1, 2015, to December 31, 2019. We collected demographic details, clinical profiles, and treatment details. The recurrence of cervical cancer was confirmed by biopsy. Surgical staging and grading followed the International Federation of Gynecology and Obstetrics (FIGO) standards.

Statistical software that we use to analyze the data is SPSS, using the Kaplan-Meier method. Logistic regression analysis was also performed where indicated. The Cox proportional hazards regression model was used for univariate and multivariate analyses. The multivariate analysis, which was used to determine prognostic factors, was compared using a log-rank test. All statistical analyses were considered significant at $p< 0.05$.

This study was reviewed and approved by the Institutional Review Board and Ethical Committee Dr. Cipto Mangunkusumo, a national reference and teaching hospital. Patient medical records were maintained under applicable medical ethical standards.

Results

We collected 262 all cervical cancer stage patients from January 2015 to December 2019. The majority of patients were ≥ 50-year-old (51.9%), multipara (59.2%), Stage I (48.1%), squamous cell carcinoma histotype (76%), Grade II differentiation (53.4%). The lymph node was examined in 25% of patients. Patient characteristics are shown in Table 1.

The median recurrence rate was 363 days (1 year, 3 days). The shortest recurrence rate was one month, and the longest recurrence rate was five years. The overall survival was measured using Kaplan-Meier where the survival rate in early stage is 76.7% while in advanced stage is 73.5% (*p-value* 0.006)- (table 3). Recurrence rates, across all stages, five years post-primary treatment diagnosis is 21.4% (Table 2). Log-rank analysis with chi-square analysis determines the factors which significantly correlated with patient recurrence. These are parity, cancer stage, tumor size, histotype, and differentiation (Table 2). We analyze

Table 1. *Descriptive Cervical Cancer Patient Characteristics.*

Characteristics	Patients n = (%)
Age (y)	
<50	123 (46.9)
≥50	136 (51.9)
Parity	
Nuliparity	83 (31.7)
Primiparity	20 (7.6)
Multiparity	155 (59.2)
Cancer Stage	
Early stage	220 (84)
Advanced stage	42(16)
Tumor size	
<4 cm	165 (63)
≥ 4 cm	97 (37)
Histotype	
SCC	199 (76)
Adenocarcinoma	49 (18.7)
Adenosquamous	9 (3.4)
Differentiation	
1	78 (29.8)
2	140 (53.4)
3	44 (16.8)
Lymph Node extraction	
(mean±SD)	5.5±8.83
Min-Max	0 47

the data using Cox multivariate modeling to determine the significant factors affecting cervical cancer recurrence rate. The significant factors are parity (Hazard Ratio (HR) = 0.5, *p*-value <0.01), cancer stage (Hazard Ratio (HR) = 1.6, *p*-value 0.013), tumor size (Hazard Ratio (HR) = 2.08, *p*-value 0.018), histotype (Hazard Ratio (HR) = 2.6, *p*-value <0.01), and differentiation (Hazard Ratio (HR) = 0.5, *p*-value 0.01) (Table 4). These results showed that cancer stage, tumor size, and histotype had a higher likelihood to cause recurrence in cervical cancer. From analysis, focusing on cancer stage, the data showed that advanced cervical cancer is more likely to cause reccurence over time (Figure 1).

From patient characteristics, the age category was distributed evenly. The most patients are multiparity women (59.2%) and diagnosed at early stage with tumor size less than four centimetres (63%). For the histotype we got most of the patient in SCC category (76%) while the differentiation mostly came from grade 2 (53.4%) while the lymph node extraction was done based on the indications (Table 1).

The recurrence rate showed in the table 2 showed a significant value in parity, stage, tumor size, histotype, and differentiation. The recurrence rate in nuliparity women is the most likely (51.2%) compared to primiparity (20%) and multiparity women (16.8%). The recurrence rate in early stage and advanced stage are 20% and 38%, respectively, while for tumor size the recurrence rate is higher in tumor size bigger than four

Table 2. *Recurrence rate of all stage cervical cancer patients (days)*

Factors	Recurrence Rate After Primary Treatment*	p-value
All	21.4%	0.02
Age (y)		
<50	15.2%	0.67
≥50	30.7%	
Parity		
Nuliparity	51.2%	<0.001
Primiparity	20%	
Multiparity	16.8%	
Cancer Stage		
Early stage	20%	0.011
Advanced stage	38%	
Tumor size		
<4 cm	20.8%	0.008
≥ 4 cm	38.2%	
Histotype		
SCC	21.4%	0.03
Adenocarcinoma	45%	
Adenosquamous	37.1%	
Differentiation		
1	22%	0.02
2	25.3%	
3	26%	
Lymph Node extraction		0.19
Yes	30%	
No	25%	

**Data are % (95% confidence interval); +log rank test*

Table 3. *Survival rate of all stage cervical cancer patients (days)*

Factors	Survival Rate *	p-value+
Age (y)		
<50	79.9%	0.10
≥50	69.5%	
Parity		
Nuliparity	44.4%	<0.001
Primiparity	88.9%	
Multiparity	80.7%	
Cancer Stage		
Early stage	76.7%	0.006
Advanced stage	73.5%	
Tumor size		
<4 cm	75.1%	0.77
≥ 4 cm	75.0%	
Histotype		
SCC	73.5%	0.69
Adenocarcinoma	79.5%	
Adenosquamous	59.3%	
Differentiation		
1	79.9%	0.67
2	74.4%	
3	70%	

**Data are % (95% confidence interval); *Data are % (95% confidence interval); +log rank testlog rank test*

Table 4. Estimated Hazard Ratio of Cervical cancer

Characteristics	Adjusted HR	95% CI HR	p-value*
Age (y)	1.1	0.61 – 1.89	0.812
Parity	0.5	0.39 – 0.75	0.00
Cancer Stage	1.6	1.11 – 2.43	0.013
Tumor size	2.08	1.13 – 3.83	0.018
Histotype	2.6	1.68 – 4.08	0.00
Differentiation	0.5	0.33 – 0.86	0.01
Lymph Node extraction	1.1	0.97 – 1.03	0.96

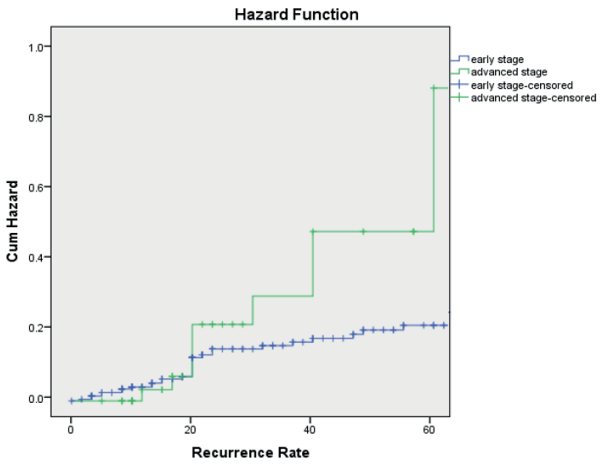

Figure 1. Five-year recurrence by stage

centimetres. For histotype and differentiation category, the recurrence rate are almost the same.

Discussion

Recurrent cervical cancer is a problem in clinical settings because of the poor outcome. It is essential to do a routine follow-up after the initial treatment to identify the recurrence while the disease is still responsive to the curative therapy (6). Some studies stated Guidelines recommendation for follow-up evaluation should be made within the next two years. The National Comprehensive Cancer Network (NCCN) guidelines recommend following-up evaluations every 3-6 months in the next two years, and then every six months for the next three years. From Society of Gynecologic Oncologists (SGO) recommends to divide the follow-up based on the risks; 6 months for the first two years, then yearly for lower-risk women; every three months in the first two years, followed by every six months evaluation for another three years and then evaluate annually for the high-risk women (5,7).

A previous study conducted by Duyn, et al. reported that the recurrence rate for cervical cancer is 17% with at least 3 months of disease-free interval. This DFS could be a prognostic factor to recurrent disease (8). A systematic review by Elit, et al. showed a result recurrence rate of 8% to 26% within two years after primary treatment. The recurrence could reach 62% to 89% of all cases, while in year three, it became 85%, and in year five, it reached 99% recurrent disease detected (6). Currently, the International Federation of Gynecology and Obstetrics staging system is still the main prognostic factor in cervical cancer. With a survival rate between 5% to 15%, patients with recurrent cervical cancer disease have a very poor prognosis, and the treatment remains palliative9. Another study conducted by Hanprasertpong, et al. showed the recurrence rate three years after the primary treatment is 5.9%. This study also showed that only lymph node metastases and deep stromal invasions are independent predictors for recurrent cervical cancer (10).

In this multi-institutional retrospective study, still within the range of the previous study, which is 8% - 26%, we got the recurrence rate of all stages of cervical cancer is 21.6% after the primary treatment, and the median of the recurrence rate is still within two years after initial treatment. Following previous results, our study showed that cancer stage correlates with cervical cancer recurrence. We also found that age and lymph node extraction did not significantly correlate with the event of recurrence in cervical cancer. Although the result is not statistically significant (log-rank test, p-value=0.19), lymph node examining has a significant clinical correlation. In contrast with previously reported studies, our study showed other factors such as parity, tumor size (<4cm, and ≥4cm), histotype, and differentiation are significantly proven to correlate with cervical cancer recurrence.

This study has limitations due to the retrospective design, and the data rely on medical records and lack of patient follow-up. Aside from the limitation, we collected a large sample size, and we conducted this study in a multicenter referral hospital. To our knowledge, there are only a few numbers of study on this topic, so we suggest that this study could be a novel reference for future studies.

Conclusion

This multi-institutional retrospective study from a national reference and teaching hospital in Indonesia found that cervical cancer recurrence is correlated with cancer stage. Advanced stage cervical cancer has a high recurrence rate.

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