

## Research Article

## Postradiotherapy Outcome on Cervical Cancer Stage IIIB Patients with and without Paraaortic Lymph Nodes Enlargement

### Hasil Pascaradioterapi pada Pasien Kanker Serviks Stadium IIIB dengan dan tanpa Pembesaran Nodus Paraaorta

Fitriyadi Kusuma<sup>1</sup>, Sahat B. Matondang<sup>2</sup>, Laila Nuranna<sup>1</sup>, Gatot Purwoto<sup>1</sup>,  
Oni Khonsa<sup>1</sup>, Purnomo Hyaswicaksono<sup>1</sup>

<sup>1</sup>Department of Obstetrics and Gynecology

<sup>2</sup>Department of Radiology

Faculty of Medicine Universitas Indonesia

Dr. Cipto Mangunkusumo General Hospital

Jakarta

#### Abstract

**Objective:** To determine whether there are differences in clinical response after radiotherapy and 1 year survival in patients with advanced cervical cancer with and without enlargement of PALN.

**Methods:** An observational analytic study using a retrospective cohort method was done using consecutive sampling. The subjects of this study were all women with a primary diagnosis of stages IIB to IVB cervical cancer who came to the gynecological oncology clinic of Dr. Cipto Mangunkusumo National General Hospital and underwent MRI examination before undergoing treatment in January 2016 to May 2017.

**Results:** Among 76 subjects studied, there were 4 (5.1%) subjects who had enlarged PALN. There were no significant differences between the enlargement status of PALN and age ( $p = 0.829$ ), age of first sexual intercourse ( $p = 0.33$ ), parity ( $p = 0.642$ ), mass diameter ( $p = 0.777$ ). Patients with PALN enlargement have 2.13 times risk of having negative radiotherapy outcome ( $p = 0.02$ , OR 2.13, CI95% 1.12 – 4.07). There was no difference in 1-year survival between patients with and without enlargement of PALN (median 201 vs. 293,  $p = 0.072$ ).

**Conclusions:** Patients with PALN enlargement have increased risk of having negative radiotherapy outcome ( $p < 0.05$ ). There were no differences in 1 year survival between patients with advanced cervical cancer with enlargement PALN.

**Keywords:** cervical cancer, lymph node enlargement, paraaortic, radiotherapy.

#### Abstrak

**Tujuan:** Mengetahui adakah perbedaan respon klinis pascaradioterapi dan kesintasan 1 tahun pada pasien kanker serviks stadium lanjut dengan pembesaran KGB paraaorta dibandingkan tanpa pembesaran KGB paraaorta.

**Metode:** Penelitian ini merupakan penelitian analitik observasional dengan menggunakan metode kohort retrospektif. Pengambilan sampel dilakukan dengan cara pengambilan sampel berturut-turut. Subyek penelitian ini adalah semua perempuan dengan diagnosis primer kanker serviks stadium IIB hingga IVB yang datang ke poliklinik Onkologi Ginekologi RSUPN Dr. Cipto Mangunkusumo dan menjalani pemeriksaan MRI sebelum dilakukan terapi pada bulan Januari 2016 hingga Mei 2017.

**Hasil:** Dari 76 subjek yang diteliti, didapatkan sebanyak 4 (5,1%) subyek yang mengalami pembesaran KGB paraaorta. Tidak didapatkan perbedaan yang bermakna antara status pembesaran KGB paraaorta dan usia ( $p = 0,829$ ), usia hubungan seksual pertama ( $p = 0,333$ ), paritas ( $p = 0,642$ ), dan diameter massa ( $p = 0,777$ ). Pasien dengan pembesaran KGB paraaorta memiliki risiko 2,13 kali lipat ( $p = 0,02$ , OR 2,13, IK95% 1,12-4,07) memiliki risiko respon terapi negatif. Tidak terdapat perbedaan kesintasan 1 tahun antara pembesaran KGB paraaorta dan tidak (median 201 vs. 293,  $p = 0,072$ ).

**Kesimpulan:** Pasien dengan pembesaran KGB paraaorta memiliki risiko lebih tinggi mengalami respon radioterapi negatif. ( $p < 0,05$ ). Tidak terdapat kesintasan 1 tahun antara pasien kanker serviks stadium lanjut dengan dan tanpa pembesaran KGB.

**Kata kunci:** kanker serviks, paraaorta, pembesaran KGB, radioterapi.

Correspondence author. Fitriyadi Kusuma. fitriyadikusuma@gmail.com

## INTRODUCTION

Cervical cancer is the third leading cause of morbidity and mortality in women worldwide<sup>1-3</sup>. GLOBOCAN survey results in 2018 showed that 569,847 women diagnosed with cervical cancer with new cases with a mortality rate of 311,365 worldwide<sup>2</sup>. The Ministry of Health of the Republic of Indonesia estimates that the incidence of cervical cancer is 100 / 100,000 women per year and ranks second in the ranking of cancer cases in Indonesian women.<sup>3</sup> Previous study data in 2007 stated that 75% of gynecological cancers originated from the cervix, and more than 50% of which were diagnosed with advanced stage<sup>3</sup>. This data shows that cervical cancer needs to be highlighted as one of the female main causes of fatalities in Indonesia<sup>4</sup>.

Determination of staging in cervical cancer is very important because it is very influential, not only on its management but also on the patient's prognosis<sup>5,6</sup>. Life expectancy will decrease as the stage increases of which cervical cancer is diagnosed. The development of medical technology in recent decades, especially imaging technology, created a paradigm of imaging technology as a vital part of cancer management. In 2018, FIGO had revised its guidelines of cervical cancer, recommending imaging modalities as an additional examination to further guide clinician in diagnosis and treatment choice<sup>7,8</sup>.

Along with time advancement and the development of various medical diagnostic tools, there are some addition of new categories in the FIGO scoring system, namely in stage 3C which is now separated into 3C1 and 3C2. Stage 3C states that metastasis has occurred to pelvic and/or paraaortic lymph nodes, whereas at stage 3C1 there is only pelvic metastasis and stage 3C2 metastasis has occurred to the paraaortic lymph nodes<sup>8</sup>. In patients without metastasis to lymph nodes, the 5-year overall survival rate (5-YSR) is about 85-90%. However, when metastases to lymph nodes are obtained, 5-YSR decreases between 20-75%.<sup>8</sup>

Although it is known that enlargement of paraaortic lymph nodes has a worse effect on patient outcomes, there has never been a study in Indonesia on how worse the effects exerted on the radiotherapy response and overall survival. Therefore, this study seeks to provide an overview of the effect of paraaortic enlarged lymph nodes on the success of therapy and patient survival.

## METHODS

Analytic observational research with retrospective cohort method was done in Gynecologic Oncology clinic in National General Hospital Dr. Cipto Mangunkusumo, Jakarta, Indonesia on March 2018 to June 2019. The study population were women diagnosed with primary cervical cancer stage IIIB to IVB, undergoing magnetic resonance imaging (MRI) before and after treatment, and completed treatment with radiotherapy. Patients with another malignancy or having incomplete medical record were excluded in this study.

Consecutive sampling method was done in this study. Patients were then divided into paraaortic lymph node (PALN) enlargement group and control group. PALN enlargement was determined using MRI and examined by radiology consultant. Baseline characteristics were then analyzed and compared. Bivariate analysis between subjects' characteristics and was done. Survival analysis using Kaplan-Meier was done to all subjects and overall survival between study groups were compared. Ethical clearance was issued from health research and ethical committee in Faculty of Medicine, Universitas Indonesia.

## RESULTS

During the time of the study, a total of 118 subjects were recruited. However, 39 patients met the exclusion criteria and were excluded from the study. Among 79 patients included in this study, 1 patient did not come for follow up after treatment. Among 78 subjects of this study, 4 patients was known to have PALN enlargement, while 74 patients did not have PALN enlargement. Baseline characteristics of subjects can be found on Table 1.

**Table 1.** Baseline Characteristics of Subjects

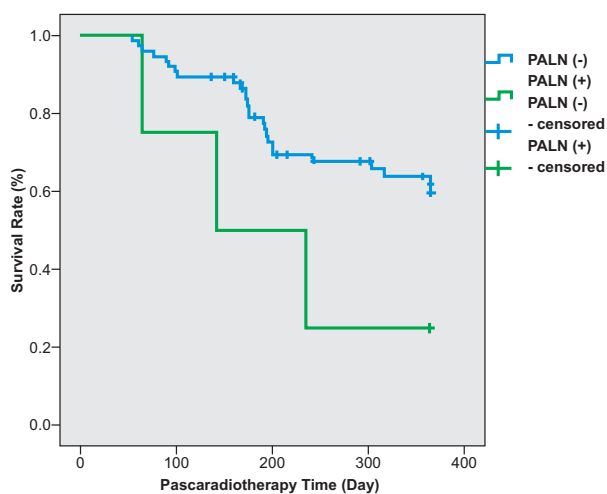
Characteristics	N = 78
Age	50.51 (8.493)
<b>First sexual intercourse age</b>	
< 20	44 (56.4)
> 20	34 (43.6)
Parity	3 (0 -8)
Mass diameter	5.25 (1.9 – 15.0)
<b>Mass differentiation</b>	
Good	19 (24.4)
Poor	59 (73.6)
<b>PALN enlargement status</b>	
Positive	4 (5.1)
Negative	74 (94.9)
<b>Radiotherapy response</b>	
Positive	49 (62.8)
Negative	29 (37.2)
Survival time (days)	242 (18 – 1.460)

In order to determine the differences between study groups, bivariate analysis between groups was done. Result of bivariate analysis in this study can be found in Table 2.

**Table 2.** Result of Bivariate Analysis

Variables	Study groups		P-value	RR	CI 95%
	PALN (+) (n = 4)	PALN (-) (n = 74)			
Age	51.50 (12.3)	50.46 (8.35)	0.829		
<b>First sexual intercourse age (years)</b>			0.333	0.43	0.08-2.37
< 20	1 (25)	43 (58.1)			
> 20	3 (75)	31 (41.9)			
Parity	3 (3 – 4)	3 (0 – 8)	0.643		
Mass diameter	5.0 (3.9 – 6.6)	5.35 (1.9 – 15)	0.777		
<b>Mass differentiation</b>					
Good	4 (100)	55 (74.3)	< 0.0001	3.89	2.64-5.74
Poor	0	19 (25.7)			
<b>PALN enlargement status</b>					
Positive	3 (75)	26 (35.1)	0.02	2.13	1.12-4.07
Negative	1 (25)	48 (64.9)			

In order to compare overall survival rate of patients, 1 year survival analysis using Kaplan-Meier was done in this study. The Kaplan-Meier graph for this study can be found on figure 1.



**Figure 1.** Kaplan-Meier Graph between Study Groups

It was known from the Kaplan Meier analysis that the median survival days for PALN enlargement group was 201 days, while median survival days for PALN negative group was 293 days. However, the result was not statistically significant (p = 0.072).

**DISCUSSION**

In this study, 78 research subjects fitting the inclusion and exclusion criteria of the study were successfully followed up until the end of the study period. On these subjects, the average age was

50.51 years (standard deviation 8.493 years). The mean age obtained in this study is higher than the average age of diagnosis of cervical cancer in both developed countries such as the United States (47 years) and in developing countries such as South Africa (40-49 years old). Previous studies have shown that older women tend to be diagnosed with more advanced cervical cancer while also having a higher mortality rate than younger patients.<sup>9,10</sup>

Cancer differentiation was generally poor in the study subjects (73.6%). The result is reasonable considering the inclusion criteria in this study were patients who have been diagnosed with advanced cervical cancer, thus having worse differentiation. However, the percentage of poor differentiation patient is higher than a similar study conducted in cervical cancer patients with paraaortic lymph node involvement in 2015 in Belgium which had 33% subjects having poor mass differentiation.<sup>11</sup> Another study in Korea only had 1% research subjects who had poor cancer differentiation.<sup>12</sup> In enlarged paraaortic lymph nodes group, it was found that 100% subjects had poor mass differentiation (p <0.001, RR = 3.89 CI95% 2.65-4.07).

In this study, only 4 people (5.1%) of 76 study subjects experienced enlargement of the paraaortic lymph nodes. In the analysis between paraaortic lymph node enlargement and radiotherapy response, a significant relationship was found (p = 0.02, RR = 2.13, CI95% 1.12 - 4.07). In addition, the median survival of 1 year

for subjects with enlargement of the paraaortic lymph nodes was 201 days, while 1 year survival for subjects without enlarged lymph nodes was 293 days. The P value was 0.072, meaning that there were no statistically significant differences of survival rate between the study groups. Although data obtained was not statistically significant, the median survival of patients obtained was judged to be clinically meaningful. In a previous study conducted specifically on cervical cancer patients with enlarged paraaortic lymph nodes in 2001, it was found that the estimated survival at 2 years was 46% and 4 years survival was 29%.<sup>13</sup>

Various factors influence the survival of cervical cancer patients with lymph node involvement. Some risk factors beyond lymph node involvement that have been proven to affect survival are ethnicity, tumor size, treatment performed, age, and nutritional status.<sup>3</sup> A large amount of attempts have been made to improve overall survival in cervical cancer patients with enlarged paraaortic lymph nodes. Previous study assessed that the survival of cervical cancer patients with enlarged paraaortic lymph nodes that carried out radiotherapy extension until the paraaortic lymph nodes is similar compared to patients undergoing standard radiotherapy, despite having a much lower incidence of distant metastasis<sup>14</sup>. Another attempt to perform paraaortic lymphadenectomy before chemoradiotherapy in late cervical cancer is considered effective to improve survival only in patients who have not had an enlarged paraaortic lymph node. However, it has little to no difference in patients with enlarged paraaortic lymph nodes<sup>15</sup>.

### CONCLUSIONS

Patients with PALN enlargement have increased risk of having negative radiotherapy outcome ( $p < 0.05$ ). There were no differences in 1 year survival between patients with advanced cervical cancer with enlargement PALN.

### REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA. Cancer J Clin.* 2015;65(2):87-108.
2. Aziz MF. Masalah pada Kanker Serviks. *Cermin Dunia Kedokteran.* 2001:5-7.
3. Aziz MF. Gynecological cancer in Indonesia. *J Gynecol Oncol.* 2009;20(1):8-10.
4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA. Cancer J Clin.* 2018;68(6):394-424.
5. Benard VB, Saraiya MS, Soman A, Roland KB, Yabroff KR, Miller J. Cancer screening practices among physicians in the national breast and cervical cancer early detection program. *J Womens Health (Larchmt).* 2011;20(10):1479-84.
6. Hopkins MP, Morley GW. Prognostic factors in advanced stage squamous cell cancer of the cervix. *Cancer.* 1993;72(8):2389-93.
7. Rigon G, Vallone C, Starita A, Vismara MFM, Ialongo P, Putignani L, et al. Diagnostic Accuracy of MRI in Primary Cervical Cancer. *Open J Radiol.* 2012;02(01):14-21.
8. Bhatla N, Berek JS, Cuello Fredes M, Denny LA, Grenman S, Karunaratne K, et al. Revised FIGO staging for carcinoma of the cervix uteri. *Int J Gynecol Obstet.* 2019;145(1):129-35.
9. Waggoner SE. Cervical cancer. *Lancet.* 2003;361(9376):2217-25.
10. Fedewa SA, Cokkinides V, Virgo KS, Bandi P, Saslow D, Ward EM. Association of insurance status and age with cervical cancer stage at diagnosis: National Cancer Database, 2000-2007. *Am J Public Health.* 2012;102(9):1782-90.
11. Hansen EK, Roach M. *Handbook of evidence-based radiation oncology.* 2018.
12. Park SG, Kim JH, Oh YK, Byun SJ, Kim MY, Kwon SH, et al. Is Prophylactic Irradiation to Para-aortic Lymph Nodes in Locally Advanced Cervical Cancer Necessary? *Cancer Res Treat.* 2014;46(4):374-82.
13. Grigsby PW, Heydon K, Mutch DG, Kim RY, Eifel P. Long-term follow-up of RTOG 92-10: cervical cancer with positive para-aortic lymph nodes. *Int J Rad Oncol Biol Phys.* 2001;51(4):982-7.
14. Sapienza LG, Gomes MJL, Calsavara VF, Leitao MM, Jr., Baiocchi G. Does para-aortic irradiation reduce the risk of distant metastasis in advanced cervical cancer? A systematic review and meta-analysis of randomized clinical trials. *Gynecol Oncol.* 2017;144(2):312-7.
15. Lee JY, Kim Y, Lee TJ, Jeon YW, Kim K, Chung HH, et al. Cost-effectiveness of para-aortic lymphadenectomy before chemoradiotherapy in locally advanced cervical cancer. *J Gynecol Oncol.* 2015;26(3):171-8.