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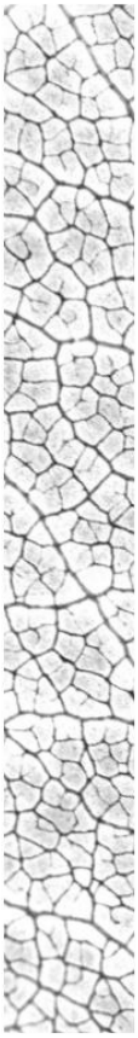

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Disease-free survival and overall survival of cervical cancer patients after radical hysterectomy and pelvic lymph-node dissection

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Abstract

Introduction: Radical Hysterectomy and Pelvic Lymph-Node Dissection (RH-PLND), with or without Neoadjuvant Chemotherapy (NAC) nor Adjuvant Therapy (AT), is still the treatment of choice in stages IB-IIB of cervical cancer due to limited access to concurrent chemoradiotherapy. This study aimed to find out the 3-year Disease-Free Survival (DFS) and Overall Survival (OS) in post-RH-PLND for cervical cancer patients.

Methods: This was a restrospective descriptive observational study. Sample was divided into 4 groups [group 1: RH-PLND and group 2: RH-PLND + AT (operable group); group 3: NAC + RH-PLND + AT and group 4: NAC + RH-PLND (inoperable group)].

Results: Total of eight recurrences and six mortalities, with the highest 3-years DFS and OS in group 2 (91.7%) and 1 (100%), respectively. Group 3 had the lowest 3-years DFS and OS compared to other groups (67.4 and 65.6%, respectively). Most recurrence and mortality occured in the inoperable group (five and four patients).

Conclusion: The highest DFS and OS among all groups was post RH-PLND cervical cancer patients who get adjuvant therapy group and post-RH-PLND without parametric infiltration pre-operation and positive prognosis factors group, respectively.

Keywords: cervical cancer, radical hysterectomy, pelvic lymph node dissection, recurrence, mortality, survival

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INTRODUCTION

Cervical cancer is still a big problem in the world for cases of malignancy in women. In developing countries including Indonesia, cervical cancer is a gynecological malignancy and the second leading cause of death for all types of cancer in women after breast cancer (Hafiz et al. 2019, Mursyidah et al. 2019, Torre et al. 2015). In 2017, cervical cancer was the most common incident cancer for women in 50 countries (Fitzmaurice et al. 2019). Whereas, in developed countries, cervical cancer is relatively rare. This is because cervical cancer screening using Papaniculaou smear is well known and has a wide scope in developed countries, so early detection of cervical cancer or commonly called cervical cancer pre lesions is very good (Sherris et al. 2001). Previous study revealed there is better technique than is needed to identify the true cervical malignancy process using cancer molecular marker (Zulham et al. 2011). The most common histological types in cervical cancer are squamous cells (69%) and adenocarcinomas (25%) (Siegel et al. 2014). The knowledge of Human Papilloma Virus (HPV) as the main cause of cervical cancer makes experts recommend HPV serology examination as a screening method. If the results of screening, physical examination, laboratory, and radiology show abnormalities and suspicion of cervical cancer is very strong, then colposcopy and biopsy are the main choices for establishing a diagnosis of cervical cancer (Frederick et al. 2009).

Cancer have impact to economic-social consequences for individuals and household sufferers (Razak et al. 2018; Mohiuddin, 2019). A study showed 84% of cervical cancer cases found throughout the world were in developing countries, including Indonesia, with most (80%) in advanced or locally advanced stages, of

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which half came in stages III and IV (Torre et al. 2015). The high incidence of cervical cancer in developing countries is largely due to lack of access to adequate health facilities, such as screening for cervical cancer, awareness of patients for treatment, and lack of access to radiotherapy. This may be prevented by empowerment of women (Surbakti et al. 2018). The most common indications for radical hysterectomy and pelvic lymphadenectomy are early-stage cervical cancer and locally advanced cancer (stages IB to IIB according to FIGO). In cervical cancer stages IB1 to IIA, radical hysterectomy accompanied by lymphadenectomy of pelvic lymph nodes or often called Radical Hysterectomy - Pelvic Lymph-Node Dissection (RH-PLND) has a five-year overall and Disease-Free Survival (DFS), which is comparable with cervical cancer patients who received radiotherapy alone (83% and 74%) (Harrington et al. 1997, Kokka et al. 2015, Landoni et al. 2017).

Whereas, the administration of neoadjuvant chemotherapy (NAC), which is then followed by radical hysterectomy operations especially in stage IIB, has a better Overall Survival (OS) and Progression-Free Survival (PFS) compared to those receiving radiotherapy alone, but not significantly different in terms of recurrence and survival (Benedetti-Panici et al. 2002, Rydzewska et al. 2012). Treatment recommendations for IB1 stage are radiotherapy only or with RH-PLND. Whereas, in stages IB2 to IIB, concurrent chemoradiation is a therapeutic choice (Wiebe et al. 2012). Prognostic factors such as the presence of lymph nodes involved, parametrial infiltration and Lympho-Vascular Space Invasion (LVSI) influence the incidence of recurrence and prognosis. These prognostic factors take into consideration the need for adjuvant therapy (AT) in postoperative patients. The histopathologic type of adenocarcinoma is known to have a high recurrence rate and a poor prognosis compared to squamous types (Lee et al. 2015, Marchiolè et al. 2005, Sevin et al. 1996, Zreik et al. 1996).

During this time at the Dr. Soetomo General Hospital, an indication of RH-PLND, whether with or without NAC and AT, is cervical cancer stages IB to IIB. Radical hysterectomy is the treatment of choice in Dr. Soetomo General Hospital against cervical cancer stages IB to IIB because access to radiotherapy facilities are still limited and the number of patients is very large, which impacts on the very long radiotherapy queue (Grizanchuk A.M et al ., 2019). There is an early marker for radiation therapy response in cervical cancer, which has important role in maintaining cell, such as p53 expression (Pasaribu et al. 2018). Until now, there have been no data regarding patient outcomes both recurrence and survival in cervical cancer after radical hysterectomy as evaluation material. This study aimed to find out the 3-year Disease-Free Survival (DFS) and Overall Survival (OS) in post-RH-PLND for cervical cancer patients.

METHODS

This was a retrospective observational descriptive study of post-RH-PLND cervical cancer patients with clinical stages IB1 to IIB in which we then conducted a survival analysis of recurrence and mortality. The medical records which could not be read and missing were excluded. This study was conducted at Dr. Soetomo General Hospital, Surabaya, Indonesia started in April to August 2018. The sample was divided into four groups: the first group was post-RH-PLND as control negative, the second group was post-NAC + RH-PLND, the third group was post-NAC + RH-PLND + AT, and the fourth group was post-RH-PLND + AT. Each group was then searched for recurrence and whether the patient was still alive or dead, and then counted for DFS and OS. The subjects who were loss to follow-up would be automatically censored from this study. Ethical feasibility had been obtained from the Ethics Commission for basic science/clinical research at Dr. Soetomo Hospital/Faculty of Medicine, Universitas Airlangga, Surabaya, number 0441/KEPK/VII/2018.

Descriptive analysis was performed for existing data, then survival analysis was carried out using the Kaplan-Meier method. The ultimate goal of this study was to obtain DFS and OS for an observation period of three years or 36 months. Univariate analysis was also performed on the characteristics and prognostic factors of patients and presented in tables (Jafarzadeh et al, 2018).

RESULTS

Of the total 76 postoperative RH-PLND patients during 2012-2014 according to the patient register in the operating room, 16 medical records were not found, so we included them in the exclusion criteria, and the remaining 60 patients were able to find their medical records. Sixty patients consisted of 15 post-RH-PLND patients (group 1), 13 post-RH-PLND + AT patients (group 2), 21 post-NAC + RH-PLND + AT patients (group 3), and 11 post-NAC patients + RH-PLND (group 4).

Table 1 presents the characteristics of patients. The mean age of patients was 52.6 years (range 32-71 years), 18 patients were found with post-operative parametrial infiltration, 12 patients with positive lymph node status, and 5 patients with positive LVSI. Of the histopathological types, most patients had squamous cell carcinoma with 37 (61.7%) cases. Most clinical stages were found in stage IIB as many as 31 patients (51.7%). The length of time required from the diagnosis to the operation had a median of 32 days (range 8-103 days). In this study, we found 26 patients who experienced loss to follow-up, either because they were not able to be contacted, could not be visited, or because there were no telephone numbers and addresses listed on the medical record. Patients who were loss to follow-

Table 1. Characteristics of patients (n = 60)

Characteristics	n	(%)
Age (years)	52.6±7.93*	
<40	4	6.7
>40	56	93.3
Parametrium		
Positive	18	30.0
Negative	42	70.0
Lymph gland		
Positive	12	20.0
Negative	48	80.0
LVSI		
Positive	5	8.3
Negative	55	91.7
Histopathology		
SCC	37	61.7
Keratinizing	16	
Non Keratinizing	19	
Small Cell	2	
Adenocarsinoma	19	31.7
Adenosquamous Ca	4	6.7
Clinical stage		
IB1	17	28.3
IB2	5	8.3
IIA1	4	6.7
IIA2	3	5.0
IIB	31	51.7
Length duration of queue (days)	32 (8 – 103)**	
<30	28	
>30	32	46.7
Diagnosis-NAC[1]	13 (3 – 50)**	53.3
Diagnosis-Radiotherapy[2]	146 (48 – 86)**	
Duration of surgery (minutes)	*251±59.76	
<240	17	28.3
>240	21	35.0
No data	22	36.7
Outcomes		
Recurence	8	13.3
Death	6	10.0

LVSI: Lympho-Vascular Space Invasion
*Mean±SD
**Median (min-max)
[1]n = 32
[2]n = 35

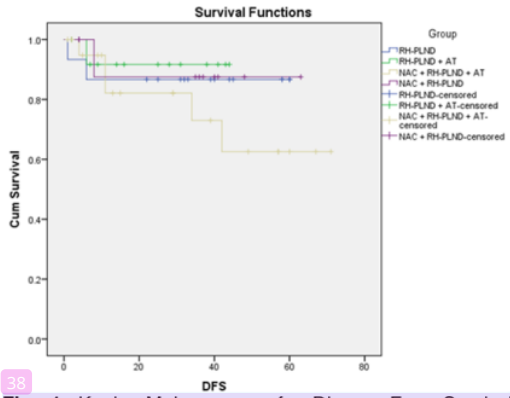

Fig. 1. Kaplan-Meier curves for Disease-Free Survival respectively – each group

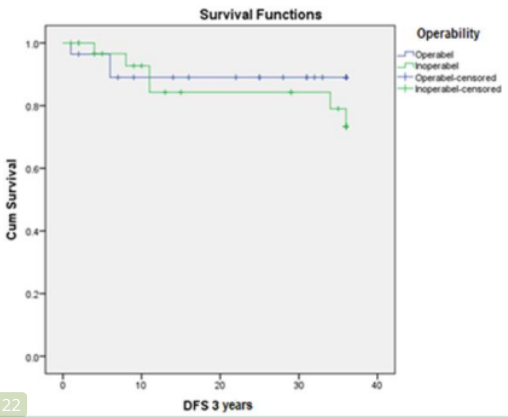

Fig. 2. Kaplan-Meier curves for Disease-Free Survival of operable and inoperable groups

up on survival analysis using Kaplan-Meier were automatically censored.

We performed the survival analysis of each group (total 4 groups) and the analysis of the operable and non-operable groups, as listed in **Fig. 1** and **Fig. 2**. The 3-year DFSs for Groups 1, 2, 3 and 4 were 86.7%, 91.7%, 67.4% and 79.5%, respectively (**Fig. 1** and **Table 2**). The operable and inoperable groups, as well as the DFS results are shown in **Fig. 2** and **Table 3**. The 3-year DFS in the operable group was 89.0% and in the inoperable group was 73.4%.

Table 2. Disease-Free Survival of each group

Group	Number of patients (n = 60)	Median (min – max) (Months)	3-year DFS
Operable group			
Group 1 (RH-PLND)	15	36 (6 – 36)	86.7%
Group 2 (RH-PLND + AT)	13	25 (4 – 36)	91.7%
Inoperable group			
Group 3 (NAC + RH-PLND + AT)	21	29 (5 – 36)	67.4%
Group 4 (NAC + RH-PLND)	11	36 (4 – 36)	79.5%

Table 3. Disease-Free Survival in operable and inoperable groups

Group	Number of patients(n = 60)	Median(min – max) (months)	3-year DFS
Operable groups			
(groups 1 and 2)	28	31.5 (4 – 36)	89.0%
Inoperable groups			
(groups 3 and 4)	32	31.5 (4 – 36)	73.4%

Table 4. Characteristics in six patients died

Characteristics	Group				n
	1	2	3	4	
Experiencing recurrence					
Yes	-	1	-	1	2
No	-	1	2	-	3
No data	-	-	1	-	1
Histopatologycal type					
Squamous Cell Ca	-	1	3	-	4
Adenocarcinoma	-	-	-	-	0
Adenosquamous Ca	-	1	-	1	2
Stadium					
IIA	-	2	-	-	2
IIB	-	-	3	1	4
Prognosis factors*					
Parametrium	-	1	2	-	3
Lymph	-	2	1	-	3
LVSI	-	1	-	-	1
Negative	-	-	1	1	2

* One patient can be obtained several factors prognosis

Table 5. Overall Survival of each group

Group	Number of patients (n = 60)	Median(min – max) (Months)	3-year OS
Operable group			
Group 1 (RH-PLND)	15	36 (7 – 36)	100%
Group 2 (RH-PLND + AT)	13	25 (4 – 36)	72.9%
Inoperable group			
Group 3 (NAC + RH-PLND + AT)	21	29 (5 – 36)	65.6%
Group 4 (NAC + RH-PLND)	11	36 (4 – 36)	88.9%

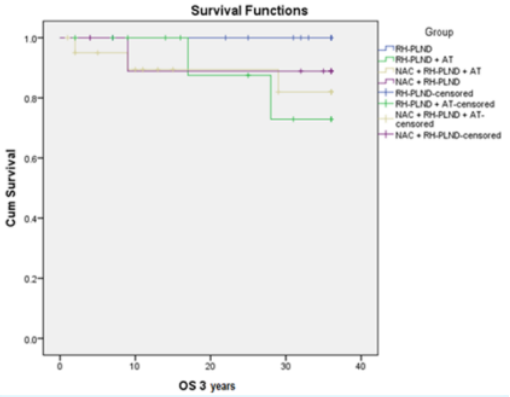

Fig. 3. Kaplan-Meier curves for the respective Overall Survival – each group

We found six patients died out of a total of 60 patients (10%) in this study, with a median death of 13 (5-29) months postoperatively with suspected causes of death directly related to cervical cancer or direct complications of cervical cancer. From observations on the characteristics of patients who died in this study, we found two patients in Group 2, three patients in Group 3, and one patient in Group 4, as seen in **Table 4**.

We carried out a survival analysis for the OS for each group in **Fig. 3** and **Table 5**. The 3-year OSs in Groups 1, 2, 3 and 4 were 100%, 72.9%, 65.6% and 88.9%, respectively. Whereas, **Fig. 4** and **Table 6** display the 3-year OS of operable and inoperable groups. The 3-year OS in the operable group was 90.2% and in the inoperable group was 84.9%.

DISCUSSION

Based on results comparing the four groups, we obtained the highest 3-year DFS for Group 2 (RH-PLND + AT) and the lowest in Group 3 (NAC + RH-PLND + AT). The highest 3-year OS was in Group 1 (RH-PLND) and the lowest in Group 3. In theory, Group 1 should have better DFS and OS than other group because the pre- and post-operative are not found to have positive risk factors in either parametrium, lymph node status, or

Table 6. Overall Survival in the operable and inoperable group

Group	Number of patients (n = 60)	Median(min – maks) (Month)	3-year OS
Operabel (group 1 and 2)	28	32.5 (4 – 36)	90.2%
Inoperabel (group 3 and 4)	32	35.5 (4 – 36)	84.9%

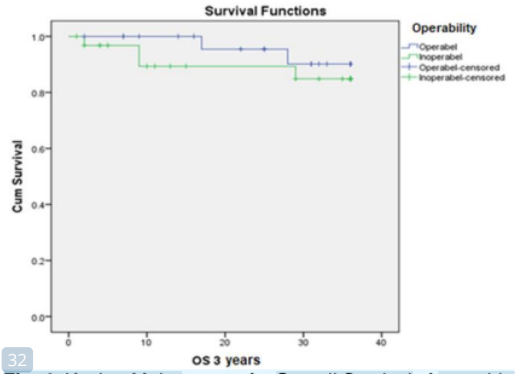

Fig. 4. Kaplan-Meier curves for Overall Survival of operable and inoperable groups

LVSI. In this study, we obtained two recurrences in Group 1 without the prognosis factor compared to one patient in Group 2 that had positive prognosis factor in all three parameters (Parametrium, lymph node status, and LVSI). The two patients in the Group 1 had clinical IB1 and IB2 stages and had their respective recursions in the vulva and abdominal wall during the 6-month postoperative, which was then planned to palliative radiotherapy but the loss to follow-up in the observational occurred. There were recurrence cases in Group 1 compared to Group 2 which might cause DFS in Group 2 better than that in Group 1. Further explanation on this is discussed in the sub-chapter of analysis in the Operable group. A longer average observation period and a larger number of patients in Group 1 may statistically provide lower DFS results than Group 2 due to the possibility of being censored more.

Recurrence at IB stage is most likely due to many other factors that can determine a patient's prognosis. Until now, FIGO still recommends determining cervical cancer staging clinically to make it easier for cancer centers, especially in developing countries to determine cervical cancer therapy with existing facilities and infrastructure. According to Amin et al., Stage IB itself has a 5-year OS of 80% postoperatively (Amin et al. 2017).

The best of 3-year OS was obtained in Group 1. Whereas, Group 3 had most unfavorable clinical pre- and post-operative conditions because there was parametric infiltration before performing the surgery, thus the administration of NAC was needed to obtain operability. Furthermore, positive prognosis factors was found after post-operative that requires adjuvant therapy. The process to obtain adjuvant therapy is also often not easy because of the limited radiotherapy facilities in our institutions that cause radiotherapy queue to be very long. This is in accordance with other literatures that parametrium infiltration, lymph node status, and LVSI are significant prognostic factors for survival, as well as the length of radiotherapy queuing related to external patients and progressive diseases (Amin et al. 2017, Lee et al. 2015, Marchiolè et al. 2005, Sevin et al. 1996, Zreik et al. 1996).

Three-year DFS in inoperable groups was worse than in operable groups. This is related to the mass of tumors that are bulky, so it requires NAC. The discovery of post-operative prognosis factors such as parametric infiltration, lymph node status, and LVSI makes patients require adjuvant therapy and can influence the number of recursive events (Shen et al. 2012, Singh et al. 2004, Zreik et al. 1996). Clinically, DFS and 3-year OS of operable groups is better than DFS and 3-year OS of inoperable groups. The existence of the prognosis pre-operative factor in the form of a positive parametric infiltration affects DFS and 3-year OS in this category.

Three-year DFS in a Group 2 was better due to a shorter observation period on this group. A shorter observation period in Group 2 is likely due to the number of patients with a loss to follow-up. In addition to the Group 2, adjuvant therapy in the form of radiotherapy previously administered Cisplatin chemotherapy while awaiting radiotherapy may have a "protective effect" on the recurrence event so that clinically, Group 2 had better DFS than Group 1. The "protective effect" in post-operative patients was similar to the outcome of a study in the United States in 2012 by Rogers et al., which mentions that there is no meaningful difference in DFS from cervical cancer patients and IIA stage that undergo RH-PLND only and RH-PLND followed by radiotherapy, but clinically, a group that gets post-operative radiotherapy has a 5-year DFS better than the one who gets the surgery (Risk Ratio 0.58; 95% CI 0.37 - 0.91). Suspected administration of radiotherapy is able to eliminate cells - cancer cells remaining after surgery, while in patients without adjuvant therapy, the microscopic cancer cells that are still left in the patient may continue to grow and ultimately lead to recursive (Rogers et al. 2012).

Whereas, 3-year OS of Group 1 was the highest OS among 4 groups. This findings is supported by previous study. This group did not obtain parametrium, lymph node status or a positive LVSI infiltration both pre- and post-surgery. The two patients in this group had a recursive reaction to the vulva and abdominal wall, another factor allegedly played a role in the group's

recurrence, e.g. how many lymph node status were taken, micrometastasis, or patient compressive (Hoffman 2004).

Analysis in inoperable groups showed that the 3-year DFS in Group 3 was lower than Group 4. There were positive prognosis factors after surgery, thus it requires adjuvant therapy. The presence of parametrium infiltration, lymph node status, or LVSI is a significant prognosis factor in the recurrence and survival events (Singh et al. 2004, Zreik et al. 1996). Concurrent chemoradiation is a therapeutic choice in cases like this, and it gives better results than surgery alone or surgery and radiotherapy alone (Liu et al. 2013, Peters III et al. 2000, Wiebe et al. 2012).

This study has limitations. This study has a small amount of sample, and there are incomplete medical record data. In this study, we did not evaluate the radicality of surgery. In addition, the number of patients who were loss to follow-up certainly influenced the results of this study. Comparing the four groups at once in this study is actually not quite right because the backgrounds of each group were different, and we realize that this condition is a weakness of our study, so we then sort out again to try to uniform the background of each group based on the therapy obtained.

CONCLUSION

The highest DFS among all groups was post RH-PLND cervical cancer patients who got adjuvant therapy and the highest OS among all groups post-RH-PLND without parametric infiltration pre-operation and positive prognosis factors group.

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