RESEARCH ARTICLE

Comparisons of Radiotherapy Outcomes in Cervical Squamous Cell Carcinoma Stage IIIB with and without Lymph Node Enlargement

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Abstract

Aim: Cervical cancer is the second rank as the most common cancer worldwide. Squamous cell carcinoma (SCC) is the most common histopathology type for cervical cancers. The radiotherapy prognostic and survival rate becomes important information for patients and clinicians.

Materials and methods: This is a historical cohort study in patients with stage IIIB cervical SCC at RSUPN Dr Cipto Mangunkusumo or RSCM from 2016 to 2017. Patients are grouped into two: stage IIIB cervical SCC with lymph node enlargement (LNE) and stage IIIB cervical SCC without LNE. Univariate, bivariate, and multivariate analyses were performed. The 1-year survival rate was analyzed using the Kaplan–Meier method.

Results: Research subjects were divided into two groups of which 36 patients (47.4%) with LNE and 40 patients (52.6%) without LNE. The radiotherapy response for patients with stage IIIB cervical SCC with LNE is worse than those without LNE, RR 4.26 (1.96–9.27, 95% IK). Sociodemographic and clinicopathologic descriptions were comparable between the two groups. The 1-year survival of patients with stage IIIB cervical SCC without LNE is better than those with LNE, hazard ratio (HR) 9.57 (3.28–27.88 95% IK). Predictor score of ≥2.1 as the cutoff point to determine negative response on radiotherapy was chosen (LR + 2.31, sensitivity 96.3%, specificity 58.3%, and accuracy 77.3%).

Conclusion: There was a significant difference in radiotherapy response between the patients with stage IIIB cervical SCC with LNE and without LNE.

Clinical significance: To improve the prognosis and efficacy of radiotherapy in patients with LNE, consideration should be given to further studies on the removal of the LNE prior to undergoing radiotherapy.

Keywords: Lymph node enlargement, Magnetic resonance imaging, Radiotherapy, Stage IIIB SCC.

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Introduction

Incidence of cervical cancer is growing in the developing countries. It is caused by the higher life expectancy of women and a variety of risk factors that trigger cancer in daily life. Cervical cancer is the second most common cancer worldwide for women after breast cancer. In 2012, there were about 528,000 new cases of cervical cancer, of which 266,000 ended with a patient's death.[1] While in Indonesia, cervical cancer is the most prevalent gynecological malignancy with a prevalence of 75% of all gynecological malignancies. Based on the International Federation of Gynaecology and Obstetrics (FIGO) 2009, most of the cervical cancers were found in the advanced stage (±50% were found at stage IIIB). The predominant histopathological features of cervical cancer are squamous cell carcinoma (SCC) and adenocarcinoma. Most of the cases of cervical cancers are of SCC types (95%).[2]

Management and survival of cervical SCC will largely depend on the variety of clinical findings, especially in stages when it is diagnosed, size of tumors, histopathologic type, differentiation type, kidney involvement, lymph node enlargement (LNE), and metastasis.[3] Advances in medical technology, especially magnetic resonance imaging (MRI), have made it possible to examine many noninvasive prognostic factors. MRI has been increasingly used in the staging of cervical cancer, because in the early stages and advanced stages, it can show superiority in clinical evaluation when compared to intra-operative findings. MRI also can be used to evaluate the success rate of therapy. Increased use of MRI allows early detection of recurrence and accurate identification of prognostic factors so as to contribute to the decision-making process and the results of therapeutic predictions with excellent cost-effectiveness. The radiotherapy prognostic and survival rate of cervical SCC becomes important information for patients and clinicians.[4]

The main purpose of this study was to improve prognostic and radiotherapy responses from cervical SCC. The other purposes were to get the prevalence rate and description of sociodemographic, the radiotherapy response, clinicopathologic differences, and 1-year survival rate after radiotherapy.

It is expected that the results of this study will be able to provide information to the clinician as a consideration in making decisions regarding the effective treatment of stage IIIB cervical SCC patients.

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This study is also expected to be the beginning of further researches to obtain the best management method.

Materials and Methods

This is a historical cohort study determined to assess the radiation therapy responses in patients with SCC stage IIIB who have LNE and not having one. This study uses 5% error bound and 95% confidence interval limit; the power of the test is considered to be 90%. Among all patients with stage IIIB SCC cervical cancer in Dr. Cipto Mangunkusumo National General Hospital, 76 subjects were matched with inclusion criteria. Patients are grouped into stage IIIB cervical SCC with and without LNE.

The inclusion criteria were patients with stage IIIB SCC cervical cancer who have undergone complete radiation therapy. The study was approved by the Faculty of Medicine, University of Indonesia. All human studies have been approved by the Research Ethics Committee on ethical approval letter numbered 0332/UN2.F1/ETIK/2018.

Results

From January 2016 to December 2017, 76 patients with stage IIIB cervical SCC who received complete radiotherapy and perform MRI examination before and after radiotherapy were identified. Through MRI examination, LNE was found in 36 patients (47.4%). A large proportion of sociodemographic characteristics are relatively balanced at patients with stage IIIB cervical SCC with LNE compared to those without LNE. The clinicopathological characteristics also showed a relatively balanced proportion at patients with stage IIIB cervical SCC with LNE compared to those without LNE.

Based on the bivariate analysis on sociodemographic and clinicopathologic characteristics, it was seen that the first sexual intercourse was the only variable affecting LNE, with p <0.05 and relative risk 1.68 (1.1–2.5, 95% IK). The other variables in patients did not affect the incidence of LNE. Bivariate analysis was also performed to examine the relationship between variable characteristics of patients with the patient's treatment response, and it was seen that the histopathological type was the only variable that affecting the response of radiotherapy, p <0.05 and relative risk (RR) 0.45 (0.25–0.80, 95% IK). The other variables in patients did not affect the response of radiotherapy. The Chi-square test was used to evaluate the relationship between LNE in stage IIIB cervical squamous cell carcinoma (SCC) with radiotheraphy response. The p value was <0.001, and the RR score was 4.26 (1.96–9.27, 95% IK). Bivariate analysis results are shown in Tables 1 to 3.

Kaplan–Meier method was used to determine the survival rate in 1 year since patient completed her radiotherapy. One-year survival rate of patients with stage IIIB cervical SCC without LNE is higher than those with LNE. It is 86% compared to 19%, as shown in Figure 1. Cox survival analysis was performed to determine the risk of death in LNE patients with stage IIIB cervical SCC. The results showed that patients with stage IIIB cervical SCC with LNE had a hazard ratio (HR) of 9.57 (95% IK: 3.28–27.88) compared to the patients without LNE.

Table 1: Bivariate analysis between patient characteristics and LNE incidence

Variable	*p*	*RR*
Age	0.27	
Parity	0.71	
First sexual intercourse	**0.04**	**1.68 (1.1–2.5, IK 95%)**
Cervical cancer size	0.81	
Differentiated type	0.18	
Histopathological type	0.18	

The bold values are the only variable affecting LNE, with p<0.05 and relative risk 1.68

Discussion

In this study, LNE became an important prognostic factor for predicting survival in patients with stage IIIB cervical SCC who will undergo radiotherapy. Patients with LNE will have the higher probability in negative radiotherapy response than those without LNE. This result is suitable with research conducted by Park et al. in several educational hospitals in Korea in 2006 to 2016.[5] Research conducted on other types of cancer obtained LNE is also a risk factor that can determine the success of therapy and survival of patients. As the research was done in 2017 by Barbosa et al. in Rio Janeiro, Brazil, obtained LNE in the neck is a risk factor that can worsen the patient's treatment response to thyroid cancer.[6]

The prevalence of LNE in stage IIIB cervical SCC patients at RSCM from 2016 to 2017 was 47.4%. Previously, there were no similar studies with the same population. In a population characteristic study conducted by Kasuya et al. in Japan from 1985 to 2004, the prevalence of cervical cancer patients with LNE was 41.8%.[7] Research by Horn et al. in Germany in 2008 obtained the prevalence of cervical cancer with LNE is 30.9%.[8] Generally, the prevalence of LNE in stage IIIB cervical SCC patients at RSCM from 2016 to 2017 is slightly higher than similar studies in various centers. This may be due to a sample of studies in these countries taken from all patients with cervical cancer, while in this study, the sample was taken from the patients with stage IIIB cervical SCC. Demographic characteristics were quite comparable between the patients with stage IIIB cervical SCC with and without LNE. Average patient age of about 50 years; these data are consistent with research data conducted by Zhou et al. in 2017 in China, but the average age of the patient is about 43 years.[9]

Based on the significance test conducted on each demographic characteristic of the patient, the age of first sexual intercourse was one of the risk factors for LNE with a value RR 1.68 (1.01–2.45, 95% IK). Previously, it was known that the age of first sexual intercourse under 20 years was one of the risk factors for cervical cancer itself, according to previous studies that were conducted by Aziz in 2009 which showed an eightfold risk to get cervical cancer in women who have had her first sexual intercourse at under 20 years.[2]

This study also conducted a 1-year survival analysis of patients with the Kaplan–Meier method. In the analysis, the results of patients without LNE had a better 1-year survival rate of 86% compared to 19% in patients with stage IIIB cervical SCC without LNE. There was no study that evaluate 1-year survival rate in patients with stage IIIB cervical SCC with LNE. Based on the cancer research registry, the 1-year survival rate in stage IIIB cervical SCC is about

Table 2: Bivariate analysis between patient characteristics and radiotherapy response

Variable	*p*	*RR*
Age	0.07	
Parity	0.22	
First sexual intercourse	0.43	
Cervical cancer size	0.32	
Differentiated type	0.08	
Histopathological type	**0.03**	**0.45 (0.25–0.80, IK 95%)**

The bold values are the only variable affecting the response of radiotheraphy, p<0.05 and relative risk (RR) 0.45

Table 3: Chi-square test of LNE status with post-radiotherapy response in patients with stage IIIB cervical SCC

		Response				
		Negative	*Positive*	*Total*	*p*	*RR*
LNE	Positive	23 (63.9%)	13 (36.1%)	36 (47.4%)	<0.001	4.26 (1.96–9.27, IK 95%)
	Negative	6 (15%)	34 (85%)	40 (52.6%)		
	Total	29 (38.2%)	47 (61.8%)	76 (100.0%)		

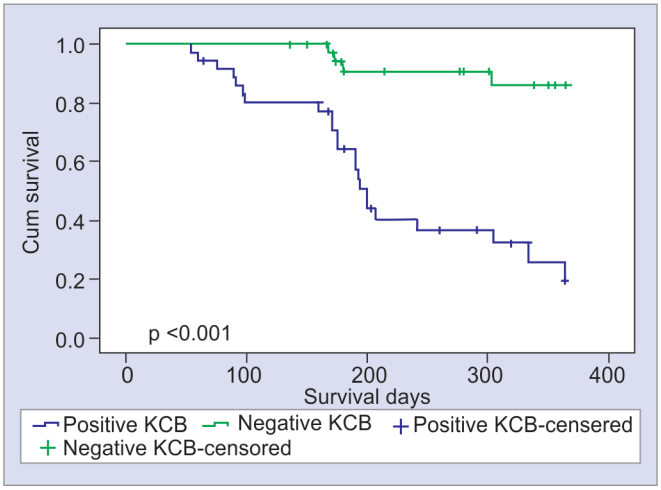

Fig. 1: Survival rate in 1 year since patient completed her radiotherapy by Kaplan–Meier method

74.4%,[10] but it does not evaluate LNE status in patients. Likewise, in a research conducted by Nuranna et al. in 2005 to 2006 at RSCM, patients with stage IIIB cervical cancer had a 5-year survival of 36%.[10] Bivariate testing using Cox survival was performed to determine HR in Lymph Nodes enlargement variables. The results showed that patients with LNE had HR 9.57 (95% IK: 3.28–27.88) compared to the patients without LNE.

This is the first study that compared the relationship between stage IIIB cervical SCC with LNE and without LNE, using MRI as imaging to describe LNE at RSCM as a national tertiary referral hospital in Indonesia. The data obtained in this study can also be used as the prevalence data of patients with stage IIIB cervical cancer. To improve the prognosis and the efficacy of radiotherapy in patients with LNE, consideration should be given to further studies on the removal of the LNE prior to undergoing radiotherapy.

Conclusion

Positive response on post-radiotherapy in stage IIIB cervical SCC patients with LNE is lower when compared to those without LNE. There was a significantly different relationship between the patients with stage IIIB cervical SCC with LNE and those without LNE who received radiotherapy (RR value 4.26). The prevalence rate of LNE in patients with stage IIIB cervical SCC at RSCM from 2016 to 2017 was 47.4%. Demographic characteristics are quite balanced between the patients with and without LNE. Cervical cancer diameter and differentiation type are not associated with LNE events. Histopathologic types of cancer cells affect the incidence of LNE. Patient with LNE had a better 1-year survival rate (86%) when compared to those without LNE (19%), HR 9,57 (95% IK: 3.28–27.88).

Clinical Significance

The data obtained in this study can be used as the prevalence data of patients with stage IIIB cervical cancer. To improve the prognosis and efficacy of radiotherapy in patients with LNE, consideration should be given to further studies on the removal of the LNE prior to undergoing radiotherapy.

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