Research Article

Effect of Smoking on Advanced Stage Cervical Cancer Patient Survival

Pengaruh Merokok pada Kesintasan Pasien Kanker Serviks Stadium Lanjut

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Abstract

Objective: The researchers aim to investigate the relationship between smoking habit and other factors as prognostic factors of cervical cancer.

Method: We performed a retrospective and prospective cohort study with subjects that are stage IIB-IVB cervical cancer patients in Dr. Cipto Mangunkusumo Hospital followed up from August 2009 to April 2014. The subjects'medical records were reviewed, and patients were interviewed about their current condition by telephone. Questions asked include smoking habit, spouse's smoking habit, and mortality status. Patients that could not be contacted by phone were excluded from the study. Statistical analysis was done using Stata 10.

Result: Out of 390 cervical cancer patients stage IIB-IVB in 2009, there were 270 patients (69.2%) that were included in the inclusion criteria. Most of the patients are 40-59 years old (82.2%) and are non-smokers (91.8%). The most frequent clinicopathological characteristic is IIIB (63.3%) and squamous cell carcinoma (71.9%). The 5-year survival rate is 22.6%. There is no statistical significance between advanced stage cervical cancer survival with the patients' or patients' husbands' smoking habit.

Conclusion: In our study, smoking habits do not aggravate survival rate of advanced stage cervical cancer patients but further research must be done with more sample. Stage, and tumor size both by physical examination and ultrasound can be used as the prognostic factor.

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Keywords: Brigmann Index, cervical cancer, smoking, survival

Abstrak

Tujuan: *Mengetahui pengaruh merokok terhadap faktor prognosis kanker serviks serta faktor-faktor lain yang berhubungan sehingga dapat membantu memberikan gambaran mengenai prognosis kanker serviks.*

Metode: *Penelitian ini adalah kohort retrospektif. Sampel penelitian adalah pasien kanker serviks stadium IIB-IVB di RS Dr. Cipto Mangunkusumo mulai dari Agustus 2009 sampai April 2014. Kondisi terakhir pasien di follow up menggunakan telepon. Kondisi yang dinilai adalah pasien masih hidup atau tidak, pasien merokok atau tidak, dan suami pasien merokok atau tidak. Pasien yang tidak dapat dihubungi akan dieksklusi dari penelitian. Analisa data menggunakan Stata 10.*

Hasil: *Dari 390 pasien kanker serviks stadium IIB-IVB, hanya 270 pasien (69,2%) yang memenuhi criteria inklusi dan eksklusi. Sebagian besar pasien berusia 40-59 tahun (82,2%), tidak merokok (91,8%), suami merokok (73,3%). Karakteristik kliniko patologis yang terbanyak adalah stadium IIIB (63,3%), jenis karsinoma skuamosa (71,9%). Kesintasan 5 tahun pasien kanker serviks adalah 22,6%. Hubungan antara kebiasaan merokok pasien dan suami dibandingkan dengan kesintasan pasien kanker serviks menunjukkan hasil yang tidak signifikan.*

Kesimpulan: *Dalam penelitian kami, kebiasaan merokok tidak memperburuk tingkat kelangsungan hidup penderita kanker serviks stadium lanjut, tetapi penelitian lebih lanjut harus dilakukan dengan jumlah sampel lebih besar. Stadium, dan ukuran tumor baik dengan pemeriksaan fisik dan USG dapat digunakan sebagai faktor prognostik.*

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Kata kunci: *kanker serviks, merokok, Indeks Brigmann, kesintasan*

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INTRODUCTION

The mortality and morbidity rate of cervical cancer globally is 275.000 and 529.000, respectively, making it the third leading cancer globally and the first leading cancer in developing country.[1-4] Smoking has been a well-known risk factor for cervical cancer. According to the WHO in 2008, Indonesia is the third leading country in number of smoker globally, with 59.8 million smokers (approximately 225 billion cigarettes per year), and 2.7% of them are women. It is estimated that each year there are 2,3 million Indonesian women who are active smokers while another 1.6 million women are non-cigarette tobacco users. Tobacco contains carcinogenic material; burned tobacco produces polycyclic aromatic hydrocarbon heterocyclic nitrosamines, which gives negative effects to people who consume it.

The role of smoking habit as prognostic factor for cervical cancer patients in Dr. Cipto Mangunkusumo Hospital has not been established yet. The

most well known prognostic factor for cervical cancer patient is its stage. Other prognostic factors contributing to cervical cancer patient outcome is important to be investigated. Therefore, the study aims to investigate the relationship between smoking and other factors as prognostic factors of cervical cancer.

METHODS

The study uses cohort retrospective method. Subjects are patients from Dr. Cipto Mangunkusumo Hospital with advanced stage (Stage IIB-IVB) cervical cancer from August 2009 - April 2014. Demographic and clinicopathological characteristics were obtained from medical record. Patients were contacted via telephone, from numbers listed on the medical record, and asked their mortality status, smoking habit and husband's smoking habit. Exclusion criteria include patients who could not be contacted by telephone. Patients' survival rate was calculated by finding the interval (in days) between date of death and date of diagnosis. Outcome measure is survival rate, which is determined by months after diagnosis. The follow up period is 58 months, therefore survival until the end of the follow up period is considered as 5-year survival rate. Statistical analysis was done using Stata 10.

RESULTS

Among 390 patients with cervical cancer stage IIB-IVB in RSCM since August 2009, 270 (69.2%) patients were successfully interviewed by phone. Sixty five percent of these patients were referred by rural hospital, 28.1% patients were referred by gynecologist and rest of them were referred by primary health care centers. Occupation of the subjects was mostly (85.2%) housewives. Patients were divided into ages above 60 years old (10.4%), between 40-59 years old (82.2%) and below 40 years of age (7.4%). While, the age of cervical cancer onset were found mostly in the 40-59 age group with 65% belonging to this group. Most of the patients (41.1%) has an undergraduate degree, and 64.1% had 3 children or more. 89.3% of the patients never had a pap smear examination before.

The physical examination showed that most of the subjects (80%) had tumors sized 4-8 centimeters, and rest (15.2%) had tumors less than 4 cm. On ultrasonography findings, only 66.7% of the patients had 4-8 centimeters tumor. Patients were also classified into The International Federation of Gynecology and Obstetrics (FIGO) stages, results were as follows: IIB: 22.2%, IIIA: 4.8%, IIIB: 63.3%; and IVA: 9.6%. 85% patients didn't have any pelvic lymph node enlargement. From histopathology findings, most patients (71.9%) were found to have squamous cell carcinoma (SCC) histological subtype; with 66.6% of them being moderately differentiated and 16.7% being well differentiated. 81.3% of the subjects' tumor cells were not keratinized, and no lymphovascular invasion was found in 86.7% of patients. Therapy modalities were mostly radiotherapy (42.2%) and chemoradiation with cisplatin-ifosfamide (30%).

The patients were then divided into the light, moderate and heavy smoker based on the Brigmann's Index. Only 8.2% (n=8) of patients admitted to be a smoker while the rest claim to not smoke; 73.3% of the subjects' spouses were smokers.

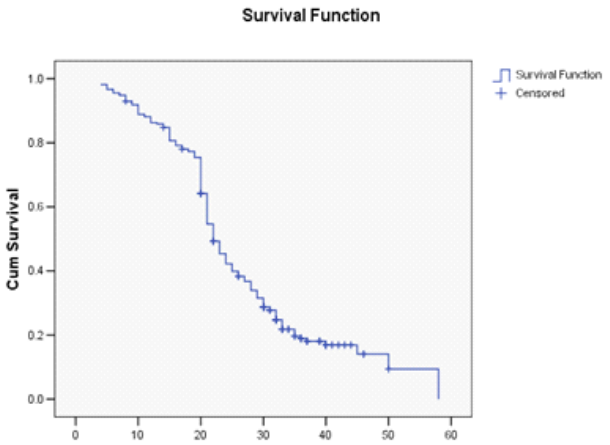

Figure 1. Advance Stage Cervical Cancer 5-years Survival Rate.

The average survival rate amongst patients was 22 months (SD= 4-58). While those who made it until the end of the follow up period (5-year survival rate) of advanced stage cervical cancer patients was 22.6%. The study showed that survival in the first year was 86.3%, decreasing to half in the second year to 43.3%, and kept decreasing to 24.4%, 23.3%, and 22.6% for the third, fourth, and fifth year, respectively.

Bivariate analysis showed no statistically significant relationship between the size of the tumor, lymphadenopathy, cell differentiation, lymphovascular invasion, keratinization stage of cervical cancer, and response to therapy with smoking status of both the patient and the husband.

Table 1. Bivariate Analysis of the Relationship between Prognostic Factor and Survival

	B	p	HR	95%CI	
				Lower limit	Upper limit
Age	-0.161	0.317	0.852	0.622	1.167
Parity	-0.059	0.599	0.942	0.755	1.176
Pap Smear	0.144	0.504	1.155	0.757	1.762
Tumor size	0.247	0.104	1.281	0.950	1.726
Tumor size USG	0.561	<0.001	1.752	1.354	2.267
Cancer stage	1.518	<0.001	4.564	3.527	5.906
Pelvic lymph node	-0.148	0.458	0.863	0.584	1.274
Histopathology	0.054	0.486	1.056	0.906	1.229
Cell differentiation	0.152	0.008	1.164	1.041	1.302
Lymphovascular invasion	0.251	0.220	1.285	0.860	1.919
Brigmann Index	-0.029	0.874	0.972	0.679	1.389
Brigmann Index Patient Husband	0.072	0.282	1.075	0.942	1.227
Keratinization	0.192	0.236	1.212	0.882	1.666
Therapy response	0.261	0.066	1.299	.982	1.717

Table 1 shows that there is a significant relationship between cervical cancer survival rate with the prognostic factors: tumor size, cell differentiation, lymphovascular invasion, keratinization, stage of cervical cancer, and response to therapy based on p-value<0.25. thus, a multivariate analysis was done revealing that stage and tumor size has a statistically significant relationship with survival of cervical cancer.

Table 2. Multivariate Analysis of the Relationship between Prognostic Factors and Survival

	B	p	HR	95%CI	
				Lower limit	Upper limit
Tumor size < 4 cm		0.122			
Tumor size 4-8 cm	0.366	0.043	1.441	1.011	2.054
Tumor size > 8 cm	0.337	0.272	1.400	0.768	2.555
Cell diff Good		0.885			
Cell diff Medium	-0.075	0.726	0.928	0.612	1.409
Cell diff Bad	0.041	0.900	1.042	0.551	1.970
Cell diff Good + Medium	0.164	0.580	1.178	0.659	2.107
Cell diff Medium + Bad	-0.113	0.706	0.894	0.498	1.604
Lymphovascular invasion	-0.096	0.675	0.908	0.580	1.423
Keratinization	0.235	0.220	1.265	0.869	1.841
Stad IIB		<0.001			
Stad IIIA	3.182	<0.001	24.084	7.420	78.174
Stad IIIB	3.704	<0.001	40.607	14.757	111.740
Stad IVA	5.113	<0.001	166.128	55.508	497.202
Therapy response Complete		0.419			
Therapy response Partial	0.154	0.307	1.167	0.868	1.568
Therapy response Progressive	0.379	0.313	1.461	0.700	3.051

The Kaplan-Meier's curve supports the result of the multivariate analysis. The curve shows that tumor size and stage of cervical cancer are associated with 5-year survival. Patients with 4-8 centimeters sized tumors were 1.441 times less likely to survive than tumors sized <4 centimeters. A confidence interval of 99.5% shows that there is a statistically significant association between cervical cancer stage and 5-year survival rate.

There is no significant difference in the correlation between active and passive smokers status (based on Briggman index) with 5-year survival rate analyzed using the Cox regression. This was shown every year during the follow-up period (first to fifth year).

DISCUSSION

In Indonesia, most cases of cervical cancer is found in its advanced stage, most commonly stage III.[5] Based on INASGO Cancer Registry Reports, advanced stage cervical cancer (IIB-IVA) cases in Dr. Cipto Mangunkusumo Hospital has reached 71.2% of all cases of cervical cancer in 2013.[6] Cervical cancer survival rate is mainly influenced by the size of the tumor and metastatic organ involvement.[7] Overall, cervical cancer survival rate will worsen as cancer stage increases, regardless of other prognostic factors such as type of therapy or comorbidities.[8-10]

Five-year survival rate in cervical cancer based on stage is as follows: IA: 93%, IB: 80%, IIA: 63%, IIB: 65.8%, IIIA: 39.7%, IIIB: 41.5%, IVA: 22.0%, and IVB: 9.3%.[8-10] This is consistent with our study (p<0.001). The method used in this study was a retrospective and prospective cohort. Patients were phoned to obtain smoking status and were followed up for 58 months using a prospective cohort method to calculate survival rate.

Aside from being a risk factor for cervical cancer, smoking also contributes to lower survival rate.[11,12] The mechanism of the detrimental effects of smoking on the incidence of cervical cancer still remains unclear. However, it is believed, cigarettes suppresses the immune system against HPV infection making patients more prone to infection.[13,14] In addition, smoking causes remodeling of cervical epithelium[13] and disrupts tissue oxygenation which impacts the usage of radiation therapy.[12] Waggoner et al, stated that the prognosis of cervical cancer patients who underwent chemoradiation therapy are poorer in smoking patients compared to non-smokers patients.[12] However, in this study, smoking did not show significant differences on cervical cancer survival rate. Supporting our study, Fyles et al argues that there is no significant difference between smoking and levels of tissue oxygenation in patients with cervical cancer.[15] Our study showed the proportion of cervical cancer patients who smoke is 8.2% compared to 91.8% who do not smoke. The low amount of patients who smokes could be a contribution to why our study shows that there is no significant relationship between smoking and cervical cancer survival rate.

The effect of being a passive smoker on the survival rate of cervical cancer is still debatable. A research in China by Cheng et al. concluded that

Table 3. Correlation Patient Smoking Status with 5-years Survival of Cervical Cancer

	B	p	HR	95%CI	
				Lower limit	Upper limit
Brigmann Index 0		0.828			
Brigmann Index 1 - 200	0.097	0.720	1.102	0.649	1.872
Brigmann Index 200-600	-0.245	0.628	0.783	0.291	2.107

Table 4. Correlation Patient Husband Smoking Status with 5-years Survival of Cervical Cancer

	B	p	HR	95%CI	
				Lower limit	Upper limit
Brigmann Index 0		0.382			
BrigmannIndex 1-200	0.254	0.198	1.289	0.876	1.899
BrigmannIndex 200-600	0.300	0.096	1.350	0.948	1.924
BrigmannIndex > 600	0.135	0.577	1.144	0.713	1.836

smoking women have a 73% increased risk for cervical cancer.[16]

Furthermore, this is clarified by Louis et al in their study which described that the risk only occur to women with active smoking habits.[17] Their research concluded that passive smoking factor could not be the only deciding factor on whether one could have cervical cancer. 73.3% of subjects in our research are passive smokers. However, a flaw in our method was that the passive smoker patients were not asked the amount of exposure to cigarette smoke. Currently, the authors could not find any other researches investigating the correlation between passive smoking and cervical cancer survival rate and further research with a larger sample size is needed.

Various studies reveal that age is one of the prognostic factors for cervical cancer survival rate, but the significance of age as the sole determinant remains unknown.[17-20] In this study, age shows no significant association (p=0.317) with the prognosis of advanced stage cervical cancer. This is consistent with Kumari et al,[21] which showed that the age of patients has no significant correlation as a prognostic factor of cervical cancer. This could be due to most of our subjects (82.2%) are between the ages 40-59 years old. According to literature, age only affects survival rate of cervical cancer in patients younger than 35 years old and older than 70 years old.[20-23]

Another factor investigated in our study is the association of multiparity with the incidence of cervical cancer. We found significant relationship between parity and cervical cancer survival rate (p-value = 0.599). However, studies have shown that it is highly correlated.[24,25] According to a multicenter study, by Muñoz et al[25] and Liao et al,[26] the relationship between multiparity and cervical cancer survival rate is statistically significant (n = 1673; p <0.0001). The reason for discrepancy between our study and other studies could be contributed to the uneven distribution of subjects in our study. At our study, 64.1% of subjects have parity ≥ 3 in a sample of only 270, while Muñoz et al conducted a multicenter study with 1673 subjects and equal distribution (53.1% were multiparity). Another factor could be the cut-off point of multiparity in our study (>3 births) are low compared to Muñoz et al, which is >5 births.

Coldman et al reported that women with a history of dysplasia, even with three consecutive negative Pap tests, evidently still have an increased risk of cervical cancer compared with women with no history of dysplasia found with Pap smear screening.[27] Mählcket alstated that the pap smear is the key in reducing the number of deaths from cervical cancer (n=6799; p=0.003).[28] In this study it was found that a history of pap smear does not provide a significant association with cervical cancer survival rate (p=0504). This could be due to fewer numbers of subjects (n=270), compared with studies of Mählck et al (n=6799).

Studies have shown that tumor size of cervical cancer affects survival rate. Smaller tumors have a better prognosis compared to larger ones.[29,30] Various publications reveal that tumor size cervical cancer stage is a prognostic factor.[21,30-33] This is in line with our results, which indicates size of mass correlates significantly to survival rate of cervical cancer (p-value<0.001).

Lymph node involvement is known to be poor prognostic factors for recurrence and survival rate in patients with cervical cancer. Lymph node involvement is also the basis for determining the schedule of adjuvant therapy in early-stage cervical cancer who received surgical therapy management.[34-36]

Locally advanced cervical cancer, which includes adenosquamous lymph node involvement post-operatively and involvement of pelvic lymph node, shown to be a poor prognostic factor as it lowers survival rate as well as increase incidence of recurrence.[37] In this study, the presence of metastasis in the pelvic lymph nodes showed no significant relationship with cervical cancer survival rate. This can be explained by the differences in the proportion of cases with pelvic lymph node involvement and without the involvement of pelvic lymph nodes (14.1% vs 85.9%).

Squamous cell carcinoma is the most common type of cervical cancer.[38-41] Prognostic significance of histologic types of cervical cancer cells is still debated. Adenocarcinoma has a worse prognostic value when compared to squamous cell carcinoma in predicting cervical cancer survival rate.[38-41] In this study, the prevalence of squamous cell carcinoma is similar to various reports on the proportion of cases of cervical cancer by histology types.[42,43] However, in this study, although the patients with squamous cell carcinoma have a lower survival rate, the relationship between the two is proven insignificant.

Keratinization is a prognostic factor in determining the survival rate of squamous cell carcinoma. In our study, there is no significant association between keratinized squamous cell carcinoma with cervical cancer survival rate (p=0.236). This is in contrast to the study by Kumar et al,[44] which revealed that keratinized squamous cell carcinoma provides a lower survival rate compared with non-keratinized squamous cell carcinoma. This difference could be explained by the number of subjects (n = 270) in our study compared to Kumar et al, as well as unbalanced ratio between subjects with keratinized and non-keratinized squamous cell carcinoma (18.7% vs 81.3%). Kumar et al,[44] reported total number of subjects was 68543, showed a balanced ratio between the two groups of subjects (45.3% vs 54.7%). According to Crissman et al[45] and Reagan et al,[46] tumor differentiation as a prognostic factor for survival rate of cervical cancer is still controversial. The data from our study showed no significant relationship found between cell differentiation to cervical cancer survival rate. (p=0.008).

CONCLUSION

The survival rate of advanced staged cervical in the first year to fifth was 86.3%, 43.3%, 24.4%, 23.3%, 22.6% respectively and the average survival rate in our study was 22 months (SD = 4-58 months). There is no statistically significant relationship between patients and patients' husbands smoking status to advanced stage cervical cancer survival rate. Furthermore, there is no association between the patient's severity of smoking to tumor size, stage of cervical cancer, response to therapy, cell differentiation and keratinization. A bivariate analysis was done and showed that tumor size, cell differentiation, lymphovascular invasion, response to therapy, keratinization and stage of the cervical cancer has a statistically significant effect on survival rate. However, the multivariate analysis done showed that only tumor size and stage of cervical cancer had a statistically significant impact on survival rate.

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