

ORIGINAL ARTICLE

An Analytical Study: Survival Rate of Laryngeal Carcinoma Patients Among Indonesian Population

PUTU ADITYA BAWA¹, NUR AKBAR AROEMAN¹, YUSSY AFRIANI DEWI¹

¹ Department of Dr. Hasan Sadikin Hospital, Faculty of Medicine, Padjadjaran University, Indonesia
Corresponding author: Putu Aditya Bawa, Email: putuaditya.tht@gmail.com

ABSTRACT

Introduction: Laryngeal carcinoma is a malignant squamous metaplasia of the overlying epithelial surface of larynx. Several factors are believed to affect the survival of laryngeal carcinoma. This study aims to identify the survival of patients with laryngeal carcinoma.

Materials and Methods: This was a retrospective cohort study using Cox Regression analysis for the survival analysis design. Patients were included if they were diagnosed with laryngeal cancer, had radiotherapy, chemotherapy, surgery or combination therapy and had a complete medical record. Data were collected retrospectively from medical records, such as smoking, alcohol consumption, genetic, tumor location, stadium, and therapy.

Result: The results shows that from the 149 patients with laryngeal carcinoma who came to Head and Neck Surgery oncology outpatient clinic and had received therapy in the period January 2009 to December 2014, it was founded that smoking, alcohol, genetic, staging, surgery, and chemotherapy had a significant relationship to the laryngeal carcinoma survival (p value <0.05). While the location of the tumor and radiation did not show a significant relationship (p value > 0.05). Based on multivariable analysis of Cox Regression obtained smoking, alcohol, and surgery which provides a significant influence on survival. Patients who smoke have a risk of death 23.9 times. Suffering from consuming alcohol has a risk 2.41 times of death. Patients who do surgery can reduce the risk of death about 54%. Conclusion: The 5-year survival of patients with laryngeal carcinoma is 56.4%.

Keywords: Patient Factors, Prognostic Factors, Tumor Factors, Laryngeal Carcinoma, Survival

INTRODUCTION

Laryngeal carcinoma is a malignant squamous metaplasia of the overlying epithelial surface of larynx.^{1,2} Globally in 2018, there were 177,422 cases.³ Data in 2018 in the United States shows 13,150 new cases of laryngeal carcinoma.⁴ Smoking and alcohol consumption are the main factors of laryngeal carcinoma occurrence.^{5,6} Other prognostic factors for laryngeal carcinoma are genetic factors.⁷ Patients who undergo surgery show an increased risk of recurrence.⁸ Survival is the percentage of individuals living in a group with a certain disease in a specified period.⁹ Several factors are believed to affect the survival of laryngeal carcinoma, including patient and tumor factors.¹⁰ This study aims to show the survival of patients with laryngeal carcinoma in Indonesia.

MATERIAL & METHOD

This was a retrospective cohort observational study with a special design of survival rate analysis in patients diagnosed with laryngeal cancer in the period January 2009 until December 2014 in the Otorhinolaryngology-

Head and Neck Surgery Department at the Hasan Sadikin General Hospital and met the inclusion criteria. Patients were included if they were diagnosed with laryngeal cancer, had radiotherapy, chemotherapy, surgery or combination therapy and had a complete medical record. Data were collected retrospectively from medical records, such as smoking, alcohol consumption, genetic, tumor location, stadium, and therapy. Then the patient or family were contacted by the researcher to find out the patient living status. Survival rates were analyzed using the Cox Regression test. A $p \leq 0.05$ was regarded as statistically significant.

RESULTS

During the period January 2009 to December 2014 the patients with laryngeal carcinoma were selected from 251 medical records, of which 75 patients had incomplete medical data and 27 patients were unreachable, only 149 patients were included in the study. The demographic characteristics are summarized in Table 1.

Table 1. Demographic Characteristics of Laryngeal Carcinoma Patients in RSHS

Characteristics	Total, n=149	
Sex, n (%)		
Men	128 (85.9)	
Women	21 (14.1)	
Age (year)		
Mean±SD	57±12	
Range	22–84	
Education, n (%)		
No history	1	(0.7)
Primary School	2	(1.3)
Junior High School	74	(49.7)

Senior High School	72	(48.3)
Occupation, n (%)		
Civil worker	6	(4.0)
Private	84	(56.4)
Entrepreneur	29	(19.5)
Laborer	8	(5.4)
Housewife	22	(14.8)

Table 1 shows that laryngeal carcinoma in Hasan Sadikin General Hospital were suffered by men (85.9%) compared to women (14.1%), with an average age of 57 years old and lowest age of 22 years old, while the oldest age was 84 years.

Table 2. Five Years Survival of Laryngeal Carcinoma Patients in RSHS

Outcome	n=149	Mean Survival Time In Month (95% CI)	Survival Rate (%)		
			1 Year	3 Years	5 Years
Survival					
Life	65 (43.6)	53.8 (51.91 – 55.69)	98.0%	84.6%	56.4%
Death	84 (56.4)				

Table 2 shows that 65 out of 149 people (43.6%) with laryngeal carcinoma in Hasan Sadikin General Hospital died over a period of five years and 85 people survive (56.4%). Mean Survival Time within 5 years is 53.8 months. Figure 1 shows the overall survival rate of patients with laryngeal carcinoma less than 5 years of observation. Within 1-5 years the survival rate of patients with laryngeal carcinoma was 98.0%, 93.3%, 84.6%, 72.5% and 56.4%.

Table 3 Relationship of Factors to the Survival of Laryngeal Carcinoma

Table 3 shows the role of factors that affect the survival of patients with laryngeal carcinoma.

Variable	Total	Life	Death	Mean Survival Time in Month (95% CI)	5 Years Survival Rate (%)	p - value
	n = 149 n (%)	n = 84 n (%)	n = 65 n (%)			
Smoking						
Smoking	87 (58.4)	23 (26.4)	64 (73.6)	49.38 (46.49 - 52.27)	26.4%	<0.001*
Non-smoking	62 (41.6)	61 (98.4)	1 (1.6)	60.00 (60.00 - 60.00)	98.4%	
Alcohol Consumption						
Alcohol Consumption	55 (36.9)	1 (1.8)	54 (98.2)	45.60 (41.82 - 49.38)	1.8%	<0.001*
Non-alcohol Consumption	94 (63.1)	83 (88.3)	11 (11.7)	58.60 (57.32 - 59.87)	88.3%	
Genetic						
With Family History	21 (14.1)	2 (9.5)	19 (90.5)	48.00 (42.13 - 53.87)	9.5%	<0.001*
No Family History	128 (85.9)	82 (64.1)	46 (35.9)	54.75 (52.81 - 66.69)	64.1%	
Tumor Location						
Supraglottic	16 (10.7)	11 (68.8)	5 (31.3)	51.00 (43.65 - 58.35)	68.8%	0.174
Glottic	54 (36.2)	36 (66.7)	18 (33.3)	55.11 (51.97 - 58.25)	66.7%	
Subglottic	4 (2.7)	2 (50.0)	2 (50.0)	51.00 (29.40 - 72.60)	50.0%	
Transglottic	75 (50.3)	35 (46.7)	40 (53.3)	53.60 (51.17 - 56.03)	46.7%	
Stage						
III	38 (25.5)	25 (65.8)	13 (34.2)	56.53 (54.13 - 58.92)	65.8%	<0.001*
IVA	104 (69.8)	59 (56.7)	45 (43.3)	54.81 (52.90 - 56.72)	56.7%	
IVB	7 (4.7)	0 (0)	7 (100.0)	24.00 (11.43 - 36.57)	0.0%	
Surgery						
Yes	95 (63.8)	81 (85.3)	14 (14.7)	58.48 (57.38 - 59.59)	85.3%	<0.001*
No	54 (36.2)	3 (5.6)	51 (94.4)	45.56 (41.55 - 49.56)	5.6%	
Chemotherapy						
Yes	59 (39.6)	15 (25.4)	44 (74.6)	48.81 (45.04 - 52.59)	25.4%	<0.001*
No	90 (60.4)	69 (76.7)	21 (23.3)	57.07(55.45 - 58.69)	76.7%	
Radiotherapy						
Yes	141 (94.6)	81 (57.4)	60 (42.6)	53.87(51.93 - 55.81)	57.4%	0.305
No	8 (5.4)	3 (37.5)	5 (62.5)	52.50 (43.28 - 61.72)	37.5%	

Smoking, alcohol consumption, genetic history, stadium of laryngeal carcinoma, surgery and chemotherapy have a significant relation to the survival of patients with laryngeal carcinoma, while the location of the tumor and radiation did not. The mortality rate of patients with laryngeal carcinoma who smoked was 73.6%. The five-year survival rate in non-

smoking patients with laryngeal carcinoma was 60 months with a survival rate of 98.4% while those who smoked were shorter at 49.38 months with a survival rate of 26.4%. The mortality rate of patients with laryngeal carcinoma with history of alcohol consumption is higher, which is 98.2%. The five-year survival rate in laryngeal carcinoma patients

who did not drink alcohol was 58.6 months and the survival rate were 88.3% and those who drank alcohol were 45.6 months with a survival rate of 1.8%.

The mortality rate of patients with laryngeal carcinoma with genetic history was 90.5%, higher than patients who did not have a genetic history. The five-year survival rate of patients with a genetic history was 48 months with a survival rate of 9.5%. The results show that the highest number of patients with laryngeal carcinoma was in stage IVA, but the highest five-year survival rate was in stage III that is 56.53 months with a survival rate of 65.8%. Patients with stage IVB laryngeal carcinoma have a 100% mortality rate in 5 years. The mortality rate of patients who

underwent surgical treatment (14.7%) was lower than those who did not (94.4%). The five-year survival rate for patients with laryngeal carcinoma who underwent surgical treatment was 58.48 months with a survival rate of 85.3% and those who did not was 45.56 months with a survival rate of 5.6%. In this study, the mortality rate of patients who received chemotherapy treatment was higher at 74.6%. The five-year survival rate for patients with laryngeal carcinoma who underwent chemotherapy was 48.81 months with a survival rate of 25.4% and those who did not was 57.07 months with a survival rate of 75.6%.

Table 4. The Output of the Cox Regression Analysis of Laryngeal Carcinoma Survival

Variable	Univariable			Multivariable		
	Crude HR	95% CI	p-value	Adjusted HR	95% CI	p-value
Smoking						
Non-smoking	1			1		
Smoking	66.46	9.21 – 479.46	<0.001*	23.90	2.99 – 190.86	0.003*
Alcohol						
Non-alcohol consumption	1			1		
Alcohol consumption	14.44	7.50 – 27.79	<0.001*	2.41	1.08 – 5.38	0.031*
Genetic						
No family history	1					
With family history	3.30	1.93 – 5.65	<0.001*			
Tumor location						
Supraglottic	1					
Glottic	0.95	0.35 – 2.54	0.910			
Subglottic	1.58	0.31 – 8.14	0.585			
Transglottic	1.63	0.64 – 4.12	0.305			
Staging						
III	1					
IVA	1.33	0.72 – 2.47	0.365			
IVB	12.84	5.03 – 32.74	<0.001*			
Surgery						
No	1			1		
Yes	0.10	0.05 – 0.17	<0.001*	0.46	0.21 – 0.98	0.045*
Chemotherapy						
No	1					
Yes	4.20	2.49 – 7.07	<0.001*			
Radiation						
No	1					
Yes	0.64	0.26 – 1.60	0.344			

Table 4 shows that smoker's mortality rates are nearly 23.9 times greater than those of non-smokers (HR = 23.9, 95% CI: 2.99-190.86, p = 0.003.) Likewise, patients who consumed alcohol also have a higher mortality rate (HR = 2.41, 95% CI: 1.08 - 5.38, p = 0.031). Laryngeal carcinoma patients who undergo surgery can reduce the risk of death (HR = 0.46, 95% CI: 0.21 - 0.98, p = 0.045), which means surgery can reduce mortality rate in the amount of 54% compared to those who not doing surgery. Based on multivariable analysis of the three factors that have a significant influence on survival, the most dominant factor related to death is smoking with HR = 23.90.

DISCUSSION

Most of the patients with laryngeal carcinoma in Hasan Sadikin General Hospital were men (85.9%). It was also found in the study of Abrahao et al. which showed more men (87.1%) than women.¹¹ This happened because smoking and alcohol consumption is likely done more by men.¹²

The average age of patients with laryngeal carcinoma is 57 years old, in general, laryngeal carcinoma affects patients over 50 years old. This statement is also suitable to Du et al study which states that laryngeal carcinoma in China affects patients over 45 years and peaks at the age of 75-79 years.¹³ This result showed that cigarette and alcohol exposure needs a long time until the onset of cancer.¹² Also in older patients who are exposed to carcinogens for longer, there is an accumulation of cells, decreased DNA repair function, and decreased immune system.¹⁴

The results show that alcohol consumption can worsen the condition and lower the survival of patients with laryngeal carcinoma. The study of Abrahao et al. supports this, which states that 5-year survival in laryngeal and hypopharyngeal carcinoma patients with drinking habits before and after being diagnosed with carcinoma were 57.3% and 58.8% respectively whereas in patients who do

not were 66.7%.¹¹ The habit of drinking alcohol can cause increased complications, comorbid conditions, and side effects of treatment in patients with laryngeal carcinoma so the mortality rate is higher. One mechanism of drinking alcohol that affects the development of cancer cells in laryngeal carcinoma is the MDM2 gene polymorphism which is a proto-oncogene which is able to extend the time of cells to live, cause DNA damage and trigger the proliferation of cancer cells so that the growth and development of cancer cells will be faster.¹⁵

Patients who have a genetic history show a 5-year survival that is lower than patients who have not. Renkonen et al. stated that patients with a similar family history of head and neck carcinoma, including laryngeal carcinoma, had 1.3 times higher risk of death compared to patients without a family history of head and neck carcinoma.¹⁶ This is thought to occur because of inherited genetic factors that are susceptible to triggers of laryngeal carcinoma and play a role in the incidence of laryngeal carcinoma.¹⁵

The location of the tumor in laryngeal carcinoma patients with the highest survival rate of 5 years is supraglottic while the lowest 5-year survival is transglottic. In this study, mortality rates in laryngeal carcinoma patients were higher in carcinomas in transglottic sites. Transglottic laryngeal carcinoma has a poor survival due to the location of the tumor which includes supraglottic, glottis, and subglottis.^{15,17}

The results of this study were most laryngeal carcinoma patients were diagnosed at stage IVA 69.8%, even the mortality rate of patients at the stage IVB reached 100%. This shows that patients with laryngeal carcinoma with stage III show a five-year survival higher than stage IV. Some studies suggest that the higher the stage of laryngeal carcinoma, the lower life expectancy or survival. The higher the degree of the tumor, the spread of the tumor to other body parts such as the lungs, liver and bones add to the deterioration in the patient, then the higher the stage, the smaller the five-year survival rate of the patient.¹⁵ Previous study explained that the time period for clinical upstaging from stage III to stage IV is 4.4 to 23.4 months (median 8.5 months).¹⁸ However, This study still has not included the time period of clinical upstaging while investigating for mortality and 5-years survival rate due to data limitation.

Surgical therapy can increase the survival of patients with laryngeal carcinoma because it can reduce the risk of death. Laryngeal carcinoma patients with stages III and IV who undergo surgical treatment have a higher survival than those who do not. Surgery is still the first choice for treatment of laryngeal carcinoma because it can stop the spread of cancer cells by removing the source of damaged cells.¹⁹ Surgical treatment of laryngeal carcinoma patients with higher stages are still likely to be offered. The surgical resection margin can be an important impact on the prognosis of patients who undergo surgical treatment.⁸ A negative surgical margin affects the improvement of patient survival rate.⁸ Nowadays, surgical treatment shows better survival rate as it combined with other treatment options, such as radiotherapy.⁸ However, this study still has not explained the survival rate for any combinations of therapeutic approach which is needed for explain the better survival rate for surgical therapy than other therapeutic

approach. Surgical resection of the tumor can provide locoregional control of the primary tumor. Locoregional control is the elimination of neoplastic processes so that the possibility of tumor recurrence can be minimized.²⁰

Chemotherapy is used as a modality to regulate tumor cell growth, especially with a disease that has spread locally, to reduce the size of primary cancer to increase the likelihood of total resection at the time of surgery, especially in cases of the advanced stage with resectable lesions.²¹ Patients who received neoadjuvant chemotherapy were statistically better than those who did not, with a five-year survival of 21%:8%. Patients who received chemotherapy had significantly decreased metastases compared to those who did not.²¹

This study shows that with radiation therapy, the five-year survival rate of patients with laryngeal carcinoma is higher than those who did not. However, five-year survival in patients who received radiation therapy compared with those who did not were not differ significantly. This is due to many factors, including the patient's physical condition, hemoglobin level, therapy compliance, and depending on the carcinoma volume and stage of the tumor, besides that radiotherapy can also have an impact on healthy cells around the tumor. Large tumor volume and poor condition of the patient's body are the main sources of radiation therapy failure.²²

Based on multivariable analysis, it can be explained that the factors that most influence the survival of patients with laryngeal carcinoma are smoking, alcohol, and surgery. The same as study of Ramroth et al., smoking and alcohol consumption are proven to be factors that influence the progression of laryngeal carcinoma and also increase its mortality.¹⁰ Multivariate analysis from Menach et al. shows logistic regression in people who still smoke and long smoking duration are a significant component of significant risk factors for laryngeal carcinoma events.²³ Ceachir et al. stated that there was a reduction in mortality of more than 50% in patients with laryngeal carcinoma who were treated surgically.²⁴ Based on research by Li et al. smoking and alcohol factors are still the biggest risk factors of laryngeal cancer and also as a prognostic factor, Li also explained the influence of the importance of surgery on recurrence and survival in laryngeal cancer patients.¹⁹

Based on multivariable analysis, genetic factors, staging, and chemotherapy were not significant. Genetic factors play an important role in the development of laryngeal carcinoma, but they are also influenced by the lifestyle of individuals, such as smoking, alcohol consumption, healthy lifestyle, food consumption, exposure to carcinogenic substances, and health awareness.¹⁶ Based on Daneshi et al. research, it was found that the nodal stage was an important factor in univariate laryngeal cancer patient survival and showed that laryngeal cancer patients with more lymph node involvement had lower survival.²⁵ The success of chemotherapy is inseparable from the patient's health status and lifestyle such as smoking, alcohol consumption, dietary, also the conditions of the development of laryngeal carcinomas such as staging and spread of metastases. Chemotherapy will be bad if the patient's condition is worse, there are smoking behaviours, alcohol consumption and primary tumors are large, infiltrative, ulcerative, intracranial extension, large

neck tumors, and distant metastases.²⁶ Chemotherapy is associated with a disease that is getting more severe, other than that the use of chemotherapy drugs can reduce the condition of the patient's body.²⁶

CONCLUSION

The survival rate of patients with laryngeal carcinoma in Hasan Sadikin General Hospital in five year was 56.4%. Smoking, alcohol consumption, genetic, cancer stadium, surgery of the cancer and chemotherapy have a significant influence to the survival of patients with laryngeal carcinoma, with the factors that most influence it being smoking, alcohol consumption and surgery of the cancer. In this study, tumor location and radiation therapy have no significant influence to the survival of patients with laryngeal carcinoma.

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