FACTORS THAT HAVE PROGNOSTIC VALUES IN THE MANAGEMENT OF NASOPHARYNGEAL CARCINOMA PATIENTS

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Abstract

Introduction: The survival rate of Nasopharyngeal carcinoma (NPC) patients is influenced by several prognostic factors, such as patient factors, tumor factors and therapeutic interventions carried out as well as the quality of care. Tumor factors in the form of spread of local invasion, regional lymphatic involvement and metastasis that is reflected in the TNM stage (Tumor, Nodule and Metastatic) are the most important prognostic factors of NPC. Study data on NPC prognostic factors is very important to develop better management while NPC prognostic factors are very different.

Objective: To determine the prognostic factors that affected survival rate of nasopharyngeal carcinoma patients. **Material and methods:** Analytic observational study with particular design of survival analysis. Data was taken from medical records and then performed survival analysis on the studied factors. Factors investigated in this study are age, sex, staging, T size, N size, Metastasis, WHO classification and treatment. Sample of this study were all patients who were initially diagnosed with NPC in RSUP. Dr. Mohammad Hoesin Palembang from January 2013 until December 2013. A total of 52 patients fulfilled the inclusion and exclusion criteria.

Results: From a total of 52 patients, 50% died and 50% survived. Survival was worse in the 30-39 year age group (30.8%), male sex (47.2%), Stage IV (44.4%), T4 size (40%), N1 size (23.1%), Distant metastases (40%), WHO type III (48.5%), and chemoradiation (48.9%). In multivariate analysis, it was found that the variables that most influenced the survival of NPC patients based on $P < 0.05$ and based on hazard ratio strength were T-size, N-size categories and Metastasis with 95% CI.

Conclusion: Prognostic factors that affected the survival of NPC patients in RSUP. Dr. Mohammad Hoesin Palembang are T size, N size, and Metastasis.

Article Info

Keywords:

Nasopharyngeal carcinoma, survival rate, prognostic factors

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1. INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignant tumor that grows in the nasopharyngeal area with predilection in the fossa Rossemuller and nasopharyngeal roof, which is a transitional area of the cuboidal epithelium transforms into a squamous epithelium [1]. Based on a report from the Global Burden of Cancer (GLOBOCAN) in 2012, there were 87,000 new cases of nasopharyngeal carcinoma that appeared annually (61,000 new cases of men and 26,000 new cases of women), out of 51,000 deaths due to nasopharyngeal carcinoma (36,000 men and 15,000 female). The incidence of nasopharyngeal carcinoma in Indonesia turns out to be quite high, which is about 4.7 new cases per year per 100,000 population or estimated at around 7000-8000 cases per year in Indonesia [2]. Data in O.R.L.H.N.S. Medical Faculty Universitas Indonesia RSCM in 2013 to 2016 showed 506 cases [3]. Data in O.R.L.H.N.S. Medical Faculty Universitas Sriwijaya RSMH in 2013 to 2017 showed 284 cases.

The prognosis of NPC is affected by several factors including tumor factors, patient factors and therapeutic interventions carried out as well as the quality of care. Tumor factors such as spread of local invasion, regional lymphatic involvement and metastasis reflected in the TNM stage (tumor, node and Metastatic) are the most important prognostic factors of NPC. In general, advanced T size is associated with poor local control and survival rates, advanced N size increases the risk of distant metastases and patients with distant metastases usually have low survival rate. The histopathological classification of NPC based on the World Health Organization (WHO) also influences the prognosis. Patient factors are age and gender. Therapeutic interventions consisting of radiotherapy, chemotherapy and chemoradiotherapy are included in the prognostic factor, concurrent chemoradiation at an advanced local stage has a better prognosis than radiotherapy alone. The quality of care in the form of providing care for NPC patients with comorbidities such as performance status, anemia and nutritional status also affects the prognosis. Performance status was assessed using ECOG (Eastern Cooperative Oncology Group) scores [4]. Decreased hemoglobin levels will cause tumor hypoxia and increased hypoxic cells,

thereby affecting the effectiveness of radiotherapy. Nutritional status with weight loss of more than 10% has a local control of 5 years 85.6% compared to 90.9% in patients with weight loss of less than 10% [5].

Survival is the percentage of individuals living in a group with a certain disease in a specified period. The overall survival period can be assessed with a survival period of 2 years, 5 years or 10 years [6]. Medical studies often used survival as a method in assessing the effectiveness of treatments that can affect the prognosis and survival rate [7]. Overall survival is the gold standard in evaluating the outcome of treatments carried out in the field of oncology but does not directly measure the benefits of treatment and the cause of death for individuals [8]. Survival was analyzed by a particular design that is using survival analysis. The survival rate of NPC is affected by several prognostic factors, such as patient factors, tumor factors and therapeutic interventions carried out as well as the quality of care. In a retrospective study by Wu et al (2017), 10-years survival rate in NPC patients receiving radiotherapy was 100%, 87.1%, 75.5% and 55.6% for stages I, II, III and IV respectively [8]. According to the 2010 AJCC, 5-years relative survival rate in patients with Stage I to IV NPC in a sequence of 72%, 64%, 62%, and 38% [9].

Study data on NPC prognostic factors is very important to develop better management while NPC prognostic factors are very different. Study on the prognostic factors of NPC in RSUP. Dr. Mohammad Hoesin has never been done and data regarding the survival rate of NPC patients is not available, while NPC cases in RSUP. Dr. Mohammad Hoesin are quite high. This study was intended to determine the prognostic factors that affect the survival rate of nasopharyngeal carcinoma patients in RSUP. Dr. Mohammad Hoesin Palembang.

2. MATERIAL AND METHODS

This study is an observational analytic study with a particular design of survival analysis. The study sample was all patients who were first diagnosed with NPC from January 2013 until December 2013 who came for treatment at the Department of O.R.L.H.N.S RSUP Dr. Mohammad Hoesin

Palembang. Inclusion criteria are patients initially diagnosed with Nasopharyngeal Carcinoma (NPC), NPC patients who have undergone radiotherapy, chemotherapy or combination chemoradiotherapy, and complete Medical Record. Exclusion Criteria were NPC patients who had not received treatment. Sampling in this study was conducted by total sampling. The subjects were 52 patients.

Data was obtained through medical records, such as age, sex, clinical stage, T size, N size, histopathology and treatment of patients initially diagnosed with NPC from January 2013 until December 2013. Then, the patient or family was contacted to find out the patient's last condition whether if they survived or died. Univariate analysis was performed on the characteristics data of the subjects.

The data from the univariate analysis were analyzed furtherly using survival analysis by the Kaplan Meier method. To test the strength of the correlation between the dependent variable (survival rate) with the independent variables (age, sex, clinical stage, T size, N size, histopathology and therapy), a multivariate analysis was performed. The p value is considered significant if $P < 0.05$ with a 95% confidence interval.

Validation test for factors is considered related in the cox regression analysis, if the sensitivity and specificity $> 80\%$ then these factors are considered as valid prognostic factors. Data processing and results using SPSS software for Windows version 21.0. Data from the results of statistical analysis are displayed in tables, graphs and textures..

3. RESULT

This study was conducted on 52 NPC patients who were initially diagnosed from January 2013 until December 2013 in the O.R.L.H.N.S. RSUP Dr. Mohammad Hoesin Palembang who met the inclusion and exclusion criteriaceritria.

Table 1. Life Table

Time (Year)	Cumulative Death (%)	Survival rate (%)
1	3.8	96.2
2	28.8	71.2
3	36.5	63.5
4	40	59.6
5	50	50.0

In the first year, subjects who died were 3.8% and survivors were 96.2%. In the second year, subjects who died became 28.8% and survivors became 71.2%. In the third year, subjects who died increased to 36.5% and those who experienced survival decreased to 63.5%. In the fourth year the subjects who died became 40% and the survivors became 59.6%. In the fifth year, 50% of subjects died and 50% experienced survival. The distribution of subjects by age found that the age group of more than 50 years was more dominant, as many as 21 people. (Table 1, Picture 1).

Picture 1. Kaplan Meier's For patients with NPC RSUP Dr. Mohammad Hoesin based on overall survival rate

Overall survival rate based on age, less than 20 years, 20-29 years, 30-39 years, 40-49 years and more than 50 years respectively 33.3%, 100%, 30.8%, 54.5% and 52.4%. The distribution of subjects with male more than women is 36 people and 16 people with overall survival rate based on male and female gender is 47.2% and 56.3%. From this study, it was shown that 27 NPC patients who came were diagnosed with stage IV. Overall survival rate based on clinical stages I, II, III and IV were 66.7%, 66.7%, 46.2% and 44.4% respectively (table 2).

Table 2. Distribution of patients based on prognostic factors

Prognostic Factors	n=52	Percentage (%)	Survival Rate (%)
Age			
<20	3	5.8	33.3
20-29	4	7.7	100
30-39	13	25	30.8
40-49	11	21.1	54.5
>50	21	40.4	52.4
Sex			
Males	36	69.2	47.2
Females	16	30.8	56.3
Stage			
Stage I	3	5.8	66.7
Stage II	9	17.3	66.7
Stage III	13	25	46.2
Stage IV	27	51.9	44.4
T Size			
T1	5	9.6	60
T2	12	23.1	58.3
T3	15	28.8	53.3
T4	20	38.5	40
N Size			
N0	19	36.5	63.2
N1	13	25	23.1
N2	11	21.2	63.6
N3	9	17.3	44.4
Metastasis			
M0	47	90.4	51.1
M1	5	9.6	40
Histopathology			
WHO type I	3	5.8	66.7
WHO type II	16	30.8	50
WHO type III	33	63.4	48.5
Therapy			
Radiotherapy	3	5.8	66.7
Chemoradiotherapy	49	94.2	48.9

The relationship between age and survival, based on the results of statistical analysis p value is 0.151 (P-value > 0.05), meaning no statistical significance. This shows that there is no statistically significant relationship between the age variable with survival based on life and death groups. The hazard ratio value of 7.254 shows that death is faster in the age category above 50 years. The relationship between sex and survival, based on the results of statistical analysis, resulted in a p value is 0.947 (P-value > 0.05), meaning not statistical significance. This shows that there is no statistically significant relationship between gender variables with survival based on life and death group. Based on the hazard ratio value of 3,077, it shows that each time of death is faster in the male group compared to the female.

The relationship between stage and survival, the results of statistical analysis revealed p value of 0.413 (P-value > 0.05), meaning that it was not significant or not statistically significant. This shows that there is no statistically significant relationship between stage variables with survival based on life and death groups. Stage I has a better survival. Based on the value of the hazard ratio, stage IV has the highest value of 2,691 each time death is faster at stage IV.

The relationship between T Size and survival, based on the results of statistical analysis p value is 0.020 (P-value < 0.05), meaning significant or statistically significant. This shows that there is a statistically significant relationship between T Size variables with survival based on life and death groups. Based on the hazard ratio value of 2,691, it shows that each time of death is faster in the group of NPC patients with T4 size. The relationship between N size and survival, based on the results of statistical analysis, it is known that p value is 0.027 (P-value < 0.05), meaning that it is significant or statistically significant. This shows that there is a statistically significant relationship between N Size variables on survival based on life and death groups. Based on the hazard ratio value of 1,474, it shows that death is faster in the NPC group of N2 patients. The relationship between Metastasis and survival, based on the results of statistical analysis, it is known that the p value is 0.013 (P-value < 0.05), meaning that it is significant or statistically significant. This shows that there is a statistically significant relationship between the Metastasis variable on survival based on life and death groups. Based on the value of the hazard ratio of 0.081 shows that death is faster in the group of NPC patients with Distant Metastasis.

The relationship between the types of histopathology with survival, based on the results of statistical analysis known p value of 0.618 (P-value >0.05), meaning that it is not significant or statistically significant. This shows that there is no statistically significant relationship between histopathological type variables on survival based on life and death groups. Based on the hazard ratio value of 2,119, it shows that death is faster in the group of NPC patients with a hazard ratio value of 2.119 which indicates that type I WHO death is faster than WHO type III. The relationship between therapy with survival, based on the results of statistical analysis using statistical tests known p value of 0.872 (P-value >0.05), meaning that it is not significant or statistically significant. This shows that there is no statistically significant relationship between therapeutic variables on the survival of a statistically significant relationship between therapeutic variables on survival based on life and death groups. Based on the hazard ratio, chemoradiation therapy has a value of 0.893 times, which indicates that each time of death is faster in patients with radiotherapy. (Picture 2)

Picture 2. Kaplan Meier's For patients with nasopharyngeal carcinoma RSUP Dr. Mohammad Hoesin based a. Tumor size, b. nodule size, c. metastasis, d. stage

Multivariate analysis is used to assess the correlation between variables with a 5-year survival, in which a P-value for each variable is less than 0.05 (P<0.05) shows significance or meaningful for each variable by looking at the ratio hazard based on statistical analysis. In the second step of multivariate analysis, it will be seen that multivariate effects can be explained that the variables that most influence the survival of NPC patients based on P<0.05 and the sequence of hazard ratio strength are T-size, N-size and Metastasis with 95% IK. The sensitivity and specificity of the size of T2 to T1 were 66.7% and 27.3%, respectively. The sensitivity and specificity of T3 size to T1 are 66.7% and 21.4%, respectively. The sensitivity and specificity values of T4 to T1 are 85.7% and 27.3%, respectively. to T1 are 85.7% and 27.3%, respectively.

Table 3. Multivariate analysis between independent variables and survival

variable	Hazard Ratio	P Value
	B Value	Exp. B
T size		
T1		0.020
T2	0.520	0.095
T3	0.765	0.127
T4	2.355	2.691
N size		
N0		0.027
N1	0.911	0.402
N2	0.388	1.474
N3	2.090	0.124
Metastasis		
M0		0.013
M1	2.516	0.081

4. DISCUSSION

The most dominant patient age variable is the age group of more than 50 years, as many as 21 people. The results of this study are in line with the study conducted by Sukri Rahman et al. (2015) from Andalas University, Padang, that the incidence of nasopharyngeal carcinoma began to increase after the age of 30 years with the highest peak at the age of 45 - 55 years [10]. Ferdinand Maubere's study (2014) at the Sanglah Central General Hospital in Denpasar found that of the 68 patient samples obtained by the age group with the highest incidence of nasopharyngeal carcinoma was the 30-50 year age group with a total of 35 people or 51.5%. More men than women, with 36 men (69.2%) and 16 women (30.8%). Liu et al found more men than women, 70 men (84%) and 13 women (16%). Xiao et al reported that there were more men diagnosed with NPC than women, respectively 213 men (71.2%) and 86 women (28.8%). [11] All of these studies have occurred because male lifestyles are different from women, such as smoking where the number of smokers in men is higher than in women. [12, 13]

The most common type of histopathology was WHO type III, undifferentiated carcinoma of 33 people (63.4%) compared to WHO types I and II. These results are in accordance with Adham et al who reported WHO type III was found to be around 85% while WHO type II was found to be around 2.3%. [14] El-Sherbieny et al. reported that type III WHO was more dominant than WHO type II, 106 people (67%) and 53 people (33%), respectively [15]. All of these studies are due to the most type III WHO in Southeast Asia and in other countries with a high incidence of KNE, besides that undifferentiated carcinoma is closely related to VEB and the high expression of p53 is associated with high tumor cell proliferation [16].

The stage IV NPC patients were 27 people (51.9%) compared to stages I, II, and III of 3 (5.8%), 4 (7.7%), 13 (25%), and 11 (21.1%). These results are in accordance with the research of Adham et al. That more advanced stage NPC cases compared to early stage, 40 cases and 8 cases. Liu et al reported that the highest stage IV was 32 people (39%) compared to stages I, II, III each with 6 people (7%), 25 people (30%), 20 people (24%) [14]. All existing research showed that more NPC patients come at an advanced stage [16], this is due to inadequate health services, delays in NPC patients coming to the hospital due to lack of knowledge, delays in early detection of early symptoms of NPC even by experts because NPC has non-typical clinical symptoms, similar to an upper respiratory tract infection and on endoscopic examination resembles normal in the submucosa in the nasopharynx [17].

The relationship between the Size of T, N, and M with survival rate found that there was a statistically significant relationship between survival of the life and death group [18]. Based on the T size, the higher T size the faster the death in the NPC group patients, based on the N size also shows the faster mortality in the N2 group, whereas based on

metastasis also shows more deaths in the NPC group with distant metastases [18]. Based on the results by Hasanov R et al and El-Sherbieny showed that the size of T and N at the time of diagnostic is a poor prognosis factor in patients the relationship between therapy with survival using a statistical test known p value of 0.872 (P-value >0, 05), the meaning is not significant or statistically significant for survival based on life and death groups. NPC patients undergoing radiotherapy have a better survival than chemoradiation. Kong et al. reported that the 5-year survival rate of NPC patients who underwent radiotherapy reached 50%-80%. Chua et al. reported that 141 people in stages I and II had very good results, 10 years survival rate reaching 98%. [19]. Based on the hazard ratio the combination therapy of radiotherapy and chemotherapy has a value of 0.893 times which shows that at any time of death faster in patients with radiotherapy. Therapy on NPC is given with the aim of reducing tumor progressivity. Therapy is also closely related to staging. Radiotherapy is a therapeutic modality for NPC at an early stage, whereas a combination therapy for radiotherapy and chemotherapy is given at an advanced stage. The results of therapy will be bad if the primary tumor is large, infiltrative, ulcerative, intracranial extension, large neck tumor, and distant metastases. So it can be concluded that survival in NPC patients with combination therapy with radiotherapy and chemotherapy will be worse than radiotherapy [20].

Based on multivariate analysis, the variables that most influence the survival of NPC patients based on P-value <0.05 and the order of strength of hazard ratios are the categories of size T, size N and then Metastasis with 95% CI. Based on the results of the validity test of the T size, the highest sensitivity value is the sensitivity value of the T4 size to the T1 size that is 85.7% but the specificity value is only about 27.3%, if the sensitivity and specificity >80% then the factor is considered a prognostic factor valid, so the T size factor in this study cannot be considered as a valid prognostic factor because of the low specificity value.

There are limitations in this study, such as data from the medical record did not get comorbid disease in NPC patients which can aggravate general conditions such as diabetes, hypertension, and myocardial infarction. Another limitation is the limited number of NPC patient samples that can have an impact in analyzing data on morbidity and mortality

5. CONCLUSION

Prognostic factors that affected the survival rate of NPC patients in RSUP. Dr. Mohammad Hoesin Palembang is a category of size T, N, and Metastasis. Suggestions need to be carried out study regarding the survival rate of NPC patients with a larger number of samples and follow-up within a period of 5 years.

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