Nutritional Status of Patients with Nasopharyngeal Carcinoma

Yussy Afriani Dewi*, Arief Fakhrizal, Shinta Fitri Boesoirie, Ayu Hardianti Saputri

Department of Otorhinolaryngology, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin Hospital, Bandung, West Java, Indonesia

Abstract

BACKGROUND: Nasopharyngeal carcinoma (NPC) is the most common malignant tumor found in the otorhinolaryngology department of the head and neck. On the other hand, malnutrition is common problems among patients with cancer.

AIM: The objective of the study was to determine the relationship between NPC stage and nutritional status.

METHODS: Data were obtained retrospectively through medical records of NPC patients at Hasan Sadikin General Hospital Bandung and Santosa Hospital Bandung Kopo who were examined in the first examination between 2016 and 2020. Data collection included age, gender, NPC stage, and body mass index (BMI) of all patients. To analyze the association among variables, Mann–Whitney, Chi-square test with alternative Kolmogorov–Smirnov test and Fisher’s exact for categorical data, and multivariate analysis with binary logistic regression were performed.

RESULTS: Patients who were included in this study found 554 people, mostly malnourished. There was a significant difference between the NPC stage and the level of malnutrition with \( p = 0.001 \), but there was no significant difference between the NPC stage and age (\( p = 0.353 \)), the NPC stage and gender (\( p = 0.074 \)), BMI and age only (\( p = 0.194 \)), early stage only (\( p = 0.464 \)), and late stage only (\( p = 0.368 \)); BMI and gender in early and late stage (\( p = 0.411 \)), early stage only (\( p = 0.583 \)), and late stage only (\( p = 0.731 \)).

CONCLUSION: At an advanced stage of NPC, the BMI value will be lower.

Introduction

Nasopharyngeal carcinoma (NPC), cancer of the nasopharyngeal epithelial cells, is a less common malignancy [1]. NPC is highly endemic to South China, Malay, and Indonesian population along with people from Southeast Asia. The rate varies from a minuscule value of <1/100,000 individuals in non-endemic areas to a high value of 25–30 and 15–20 males and females per 100,000 individuals in endemic areas, respectively [1]. NPC patients at the otolaryngologia-head-and-neck surgery department. Dr. Hasan Sadikin General Hospital, Bandung, is 3.8% in 2010–2017 [2]. There was higher instance in middle age, and older men and elementary school educated with major histopathology finding were undifferentiated carcinoma [1].

Nutrition is an important aspect of cancer management. It determines the patient’s functional status, tolerance to therapeutic interventions, and overall prognosis [3]. There is no convention regarding the definition of malnutrition, which results from a situation where food intake does not meet energy requirements. This can be caused by increased metabolism, malabsorption, or insufficient food intake. Malignant cell transformation alters its metabolism to support the metabolic needs of the tumor. This involves a shift from mitochondrial oxidative phosphorylation to aerobic glycolysis, an inefficient process [4]. This results in a rapid depletion of glucose stores and a shift toward gluconeogenesis of fat and protein stores in muscle. The body’s metabolic and immunological responses to cancer also promote malnutrition through anorexia [1].

Malnutrition and wasting in cancer are common conditions and their incidence ranges from 30% to 80% [1]. In patients with head-and-neck cancer, malnutrition is further exacerbated by dysphagia, odynophagia, pain, and depressed mood [1]. Malnutrition increases the risk of infection, treatment toxicity, and health care costs. It also adversely affects quality of life and prognosis [1].

There are several factors that may associate with the treatment of NPC, including malnutrition and cachexia. Malnutrition and cachexia are common problems among cancer patients. They can affect quality of life and affect life. Malnutrition and cachexia can occur because of serotonin and bombes in secreted by tumor cells [5]. So that it can suppress appetite and increase psychological factors such as depression and anxiety. These factors, together with the effects of the treatment itself, such as chemotherapy, radiotherapy, or surgery can lead to malnutrition and cachexia. Furthermore, due to reduced oral intake, the immune system will decrease and eventually can result in weight loss and...
an increased risk of secondary infection. About 50% of cancer patients experience weight loss and decreased nutritional status at the time of diagnosis. Therefore, the initial nutritional status and needs of the patient at this stage are very important. Body mass index (BMI) is one indicator in determining nutritional status. BMI is expressed as body weight in kilograms divided by the square of height in meters. According to Asia Pacific, classification of nutritional status is divided into several categories such as poor nutrition if BMI <18.5, normal if 18.5–22.9, overweight ≥23, risk if 23–24.9, obese 1 if BMI 25–29.9, and obese 2 if BMI ≥30 [6].

Staging is a very important indicator in decision-making for treatment management as well as in predicting prognosis. The more advanced the cancer, the more complex the treatment and the worse the prognosis. Unfortunately, nutritional status is found more frequently in advanced stages [7], [8]. Several questions related to these facts, including the relationship between NPC stage and anemia and nutritional status. Finally, this study will analyze the independent effect of nutritional status on NPC stage.

### Material and Methods

#### Subject

This study was approved by the Research Ethics Committee Padjadjaran University in June 2020. The number of ethical exemption is 542/UN6.KEP/EC/2020. Patients with a histologic diagnosis of NPC were submitted to the study. Written informed consent was obtained from all study participants. Analytic study was done to analyze the association among the variables. Data were obtained retrospectively through medical records of patients with NPC in the Hasan Sadikin General Hospital and Santosa Hospital Bandung Kopo who examined at the first of examination between 2016 and 2020.

#### Methods

Several data including the age, gender, stage of NPC, and BMI of all patients would be collected. The stage of NPC would be categorized according to 8th edition of NCCN. The BMI will be calculated through the weight (kg) and height (m) data and will be categorized according to Standard Asia Pacific. A Shapiro–Wilcoxon and Kolmogorov–Smirnov test was done to know the normality distribution of the data. To analyze the comparison between the variable, the unpaired T test was used if normally distribution data and Mann-Whitney test if it was not normally distributed. Chi-square test with alternative Fisher’s Exact for categorical data. Multivariate analysis with binary logistic regression was carried out to find the relationship between variables.

### Results

In the early-stage patient group, the patient’s age had an average of 48.42 ± 12.105, consisting of 60 male patients or 56.1% and 47 female patients or 43.9%. For BMI, patients have an average of 21.81±2.166. In the late-stage patient group, the patient’s age had an average of 49.37 ± 13.359 consisting of 292 male patients or 65.3% and 155 female patients or 34.7%. For BMI, patients have an average of 19.49 ± 2.957 (Table 1).

For the analysis of numerical data, it was tested using the Mann–Whitney test, namely, the variables of age and BMI. The results of the statistical test in the research group above obtained information on the p-value of the age variable greater than 0.05 (p > 0.05) which means that it is not statistically significant, thus it can be explained that there is no statistically significant mean difference between the age variable in early-stage and late-stage patient groups.

For the analysis of the categorical data, gender in the table above was tested using the Chi-square test. The results of the statistical test in the research group above obtained information on the p-value of the gender variable greater than 0.05 (p > 0.05) which means that it is not statistically significant. Thus, it can be explained that there is no statistically significant difference in percentage between the variables of gender in early-stage and late-stage patient groups.

While the p-value on the BMI variable is less than 0.05 (p < 0.05) which means statistically significant, it can be explained that there is a statistically significant mean difference between the BMI variable in the early-stage and late-stage patient groups.

From the comparative analysis result of the characteristics of the two groups above, it can be concluded that the two groups are the same or there is no difference in characteristics at the beginning of the examination. It shows that both groups are the same or homogeneous except for the BMI variable (Table 2).

After the bivariate analysis in the table above, it was followed by a multivariate analysis of the association between several independent variables and stage. The independent variables included in the model are gender and BMI which of the two independent variables have the most dominant influence on the stage with the results of the analysis in the table above. From the multivariate analysis in the initial model, the p value of gender was greater than 0.05 (p > 0.05) this indicates that simultaneously gender does not affect the stage but p-value of BMI was smaller than 0.05 (p < 0.05) this indicates that simultaneously, BMI affects
the stage. Based on the final model which can be seen from the two initial model variables after going through two stages, the best model is in the final model. It can be concluded that statistically only the BMI variable is strongly related in predicting stage.

In the male patient group, the BMI of the patient had an average of 19.87 ± 2.864. In the female patient group, the patient’s BMI had a mean of 20.06 ± 3.136. For the analysis of numerical data, it was tested using the Mann–Whitney test, namely, the BMI variable. The results of statistical tests in the research group above obtained information on the p-value of the BMI variable greater than 0.05 (p > 0.05) which means that it is not statistically significant, thus it can be explained that there is no statistically significant difference in the mean between BMI and gender variables in the early and late stages of patients (Table 3).

**Table 3: Comparison of BMI according to gender in patient with nasopharyngeal carcinoma at the early and late stage**

| Variable | Group    | p-value | Early stage | Late stage |
|----------|----------|---------|-------------|------------|
| BMI      | Man      | 0.411   | 19.87 ± 2.864 | 20.06 ± 3.136 |
|          | Woman    |         | 19.97        | 20.54      |

For numerical data, p value is tested by unpaired t-test if the data are normally distributed with the alternative of Mann–Whitney test if the data are not normally distributed. Categorical data p value is calculated based on the Chi-square test with the alternative of Chi-square–Fisher test and Fisher’s exact if the Chi-square requirements are not met. The significance value is based on P < 0.05. The * sign indicates p < 0.05, meaning significant or significant statistically. NPC: Nasopharyngeal carcinoma, BMI: Body mass index.

**Table 4: Table of age correlation analysis with BMI at the early and late stage**

| Variable Correlation | r       | p-value |
|----------------------|---------|---------|
| Age correlation with BMI early stage | Spearman | -0.072 | 0.464 |
| Age correlation with BMI late stage | Spearman | -0.043 | 0.368 |

The *sign indicates statistically significant or significant. r: Correlation coefficient. BMI: Body mass index.

Correlation of age and BMI in late stage using Spearman’s statistical analysis, the R-value for the correlation value between Age and BMI is -0.043; p-value = 0.368; This shows that there is not significant correlation with the direction of the negative correlation and a very small and can be ignored between Age and BMI.

**Discussion**

Similar to previous reports, in this study, NPC is often found in the fourth decade of life, men are more affected by women and especially at an advanced stage [7]. In this study, the data show that men are more affected than woman but in the analysis have no significant correlation to staging of NPC. The male predominance in the incidence of NPC may be partly explained by differences between the sexes in some environmental risks, such as smoking and hazardous occupational exposure. It is also possible that some intrinsic exposures, such as sex hormones, may explain the observed male predominance with the protective effects of endogenous estrogens that are rarely examined [9]. According to age, the incidence of nasopharyngeal cancer has a peak incidence at the age of 50–60 years. In this study, the median age value was 49 years in early stage and 51 years in late stage. This is due to the fact that these groups are exposed to carcinogenic agents in the early stages of life. Nasopharyngeal cancer takes decades to develop into malignant cells and then signs appear. Therefore, exposure to carcinogens early in life may have a significant effect on the incidence of these cancers [10].

Approximately 10% of patients with non-metastatic NPC are underweight at diagnosis; overall relapse, metastasis, and death rates, underweight patients had worse outcomes than normal weight patients [11]. There are several factors that may associate with the treatment of NPC, including malnutrition, cachexia, and anemia. In this study, the independent variable that has the most dominant influence is BMI or nutritional status. Based on statistics, only BMI variable has a strong correlation in predicting
NPC stage. Malnutrition and cachexia are common problems among cancer patients. Cachexia is not only caused by malnutrition due to anorexia. The condition of cachexia is a more complex condition, including the occurrence of reduced, metabolic dysfunction, and increased energy requirements. The process involves various inflammatory cytokines in cancer cells, changes in protein and lipid metabolism, and a balance in the processes of muscle protein production and degradation. Dysfunction in the regulation of the human inflammatory process is observed in several diseases, including cancer. Several studies have shown that an increase in inflammatory cytokines such as TNF and interleukin-6 (IL-6) has an important role in the nutritional metabolism of cancer patients. TNF is a cytokine associated with cachexia that causes loss of skeletal muscle mass. In addition, TNF activates other cytokines and can cause symptoms associated with cachexia, such as anorexia. IL-6 is also believed to play a very important role in cancer-associated cachexia. In cancer patients, IL-6 increases acute-phase reactants such as CRP through signal transducer and transcription activator 3, and by muscle wasting. However, in a study of lung cancer patients, administration of a humanized anti-IL-6 antibody was effective in reducing anorexia-like symptoms but did not cause weight gain. Therefore, it was observed that cancer-associated cachexia is not only associated with a single cytokine but also is influenced by the interaction of various signaling substances. In catabolic disease, various hormones and cytokines regulate protein production and degradation through the ubiquitin-proteasome pathway, autophagy, and transformation of growth factor-beta family ligands. Upregulation of the ubiquitin-proteasome pathway by catabolic stress in several animal tumor models has muscle wasting. The myofibrillar component of the protein is destroyed in the ubiquitin-proteasome pathway, and this causes a decrease in muscle strength. In addition, stress hormones and inflammatory cytokines increase autophagy and mitochondrial dysfunction, leading to muscle atrophy. This process is regulated by androgens and transcription factors, such as NFkB and Forkhead box protein O. Especially in cancer patients, the cancer itself and malabsorption by chemotherapy complications, such as mucositis, can directly cause muscle wasting [12].

The mechanism of malnutrition is low intake of food containing macro- and micro-nutrients and impaired absorption will cause malnutrition. Low food intake may be related to low appetite, psychology, and the effects of cancer treatment itself [13]. Cancer-associated malnutrition can result from local effects of a tumor, the host response to the tumor, and anticancer therapies. Although cancer patients often have reduced food intake (due to systemic effects of the disease, local tumor effects, psychological effects, or adverse effects of treatment), alterations in nutrient metabolism and resting energy expenditure may also contribute to nutritional status. Several agents produced by the tumor directly, or systemically in response to the tumor, such as pro-inflammatory cytokines and hormones, have been implicated in the pathogenesis of malnutrition and cachexia [14]. The consequences of malnutrition include impairment of immune functions, performance status, muscle function, and quality of life. Therefore, it is logical that nutritional deficiencies will often be found in cancer patients, including NPC. But even so, not all patients experience malnutrition because the occurrence of cancer can even be triggered by obesity. The study of Efranto et al. explained that a large BMI is associated with an increased incidence and mortality of several cancers, such as esophageal adenocarcinoma, breast cancer, and colon cancer, and causes problems with the diagnosis and treatment of HNSCC. Several studies have shown a stronger association between obesity and death in smokers. Smoking is known to trigger the development of NPC, increasing the risk of treatment failure and death in NPC patients. Adipocytes can accelerate tumor growth and progression through insulin resistance, hyperinsulinemia, hyperglycemia, and low-grade chronic inflammation [15].

The stage of cancer is very important not only for making treatment decisions but also for predicting prognosis. In this study, the results of statistical analysis showed that there was a correlation between BMI and NPC stage which the more severe the NPC stage, the risk of nutritional decline would be higher but the mean value indicates that the patient has a normal BMI. The decrease in BMI in cancer patients can be caused by several things, including impaired metabolic function due to cancer and due to treatment in the form of chemotherapy which can damage healthy cells. Processes caused by cancer cells themselves involve various inflammatory cytokines in cancer cells, changes in protein and lipid metabolism, and balance in the production and degradation of muscle protein. In addition, weight loss at the start of chemotherapy is known to occur in approximately 85% of patients with advanced cancer [16]. Therefore, it can be concluded that this study may be biased when cross-sectional examination is performed. A cross-sectional study is an observational study that assesses exposure and outcome at a particular point in time in the sample population. There was no prospective or retrospective follow-up as evidenced by no further examination on BMI measurements, only BMI examination was carried out at the time of the patient’s initial examination. In this case, the researcher did not conduct a follow-up examination after being given treatment so that the results showed that the patient had a normal BMI value. In addition, it can be caused by not assessing history of BMI, so the researcher does not know whether the patient has experienced a decrease in BMI or not and does not know whether the patient’s BMI value is included in the overweight, obese 1, or obese 2 categories. If the patient has decreased, it is possible for the patient to reach normal values even though at that time, the patient is experiencing changes or metabolic dysfunction which is
one of the signs of cancer so that it can cause a decrease in BMI although not yet reached malnutrition.

The analysis conducted in this study showed that there was a significant correlation between BMI and NPC stage, but for gender and age, the values were not statistically significant. However, the results obtained show that there is no significant correlation, either between BMI and gender or BMI and age. Although several studies have shown that there is a significant relationship between BMI and age, the greatest changes in BMI occur at younger ages. This young adult represents a critical period during which accelerated weight gain occurs, possibly lifestyle changes involving energy expenditure and food intake. In addition, there are studies that state that the prevalence of overweight is higher in women than men [17].

Some research found no significant relationship between stage and nutritional status, but malnutrition was more common in advanced cancers [8]. This result can be explained because malnutrition occur not only due to the stage of cancer but also by other factors such as tumor type, organ affected, treatment given, and occurrence of other diseases in later life. Even so, it is possible that people with nasopharyngeal cancer have a high BMI or obesity which is one of the risk factors for nasopharyngeal cancer [15]. The better research should be done to increase the validity of this study.

The limitations of this analysis are insufficient or missing information, as well as input data collected from only two hospitals so that not all the population. Certain variables such as smoking history which were closely related to NPC in some of the studies mentioned could not be studied further. In addition, the assessment of nutritional status to determine the patient had obesity, underweight or normal assessment is only through BMI, while other tests such as waist ratio, body fat proportion, skinfold thickness, and intra-abdominal fat assessment are not available.

Conclusion

From this study, it can be concluded that there is a close relationship between BMI and NPC stage. At an advanced stage of NPC, the BMI value will be lower.

Acknowledgments

We thank you to Nurvita Trianasari, S.Si, M.STAT(NVT), PhD who have made great efforts for statistical calculation, and Ifiq Budiyan Nazar as our manuscript editor.

References

1. Basit SA, Zulfikar H, Nagalli S. Nasopharyngeal Cancer. Treasure Island, FL: StatPearls; 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554588. [Last accessed on 2021 Jun 09].
2. Handayani R, Afriani Dewi Y, Madani DZ. Prevalence of nasopharyngeal carcinoma patients in department of ORL-HNS Hasan Sadikin general hospital 2010-2017. Int J Nasopharyngeal Carcinoma. 2020;2(1):1-3. https://doi.org/10.32734/jnpc.v2i01.3191
3. Irungu CW, Oburra HO, Ochola B. Prevalence and predictors of malnutrition in nasopharyngeal carcinoma. Clin Med Insights Ear Nose Throat. 2015;8:512119. https://doi.org/10.4137/ment.s12119 PMid:26056508
4. Icard P, Coquerel A, Wu Z, Gilgorov J, Fuku D, Fournel L, et al: Understanding the central role of citrate in the metabolism of cancer cells and tumors: An update. Int J Mol Sci. 2021;22(12):6587. https://doi.org/10.3390/ijms22126587 PMid:34205414
5. Ohnnuma T, Ali MA, Adigun R, Anoreksia and Cachexia. Treasure Island, FL: StatPearls; 2021.
6. Lim JU, Lee JH, Kim JS, Hwang YI, Kim TH, Lim SY, et al. Comparison of World Health Organization and Asia-Pacific body mass index classifications in COPD patients. Int J COPD. 2017;12:2465-75. https://doi.org/10.2147/copd.s14129
PMid:28860741
7. Kadiryan H, Sulaksana MA, Lestarini IA, Susilawati NK, Punagi AQ, Pieter NA, et al. Incidence and Characteristics of Anemia Among Patients with Nasopharyngeal Carcinoma in Lombok, Indonesia. Vol. 2199. United States: AIP Conference Proceedings; 2019. https://doi.org/10.1063/1.5141329
8. Trijayanti E, Probosari E. Hubungan asupan makan dan status gizi pada pasien kanker serviks post kemoterapi. J Kedokt Diponegoro. 2016;5(4):751-60.
9. Hamid GA. Epidemiology and Outcomes of Nasopharyngeal Carcinoma. In: Pharynx-diagnosis and Treatment. India: IntechOpen; 2021. Available from: https://www.intechopen.com/online-first/epidemiology-and-outcomes-of-nasopharyngeal-carcinoma. [Last accessed on 2021 May 22]. https://doi.org/10.5772/intechopen.96802
10. Salehniya H, Mohammadian M, Mohammadian-Hafshejani A, Mahdavifar N. Nasopharyngeal cancer in the world: Epidemiology, incidence, mortality and risk factors. World Cancer Res J. 2018;5(1):1-8. https://doi.org/10.15419/bmrat.v5i02.415
11. Li W, Shen LJ, Chen T, Sun XQ, Zhang Y, Wu M, et al. Overweight/obese status associates with favorable outcome in patients with metastatic nasopharyngeal carcinoma: A 10-year retrospective study. Chin J Cancer. 2016;35(1):75. https://doi.org/10.1186/s40880-016-0139-6 PMid:27507261
12. Kim DH. Nutritional issues in patients with cancer. Intest Res. 2019;17(4):455-62. PMid:31597414
13. PERKENI. Surabaya Diabetes Workshop 7: Diabetes and Nutrition RSU Dr.Soetomo. Surabaya, Indonesia: PERKENI; 2020.
14. van de Worp WR, Schols AM, Theys J, van Helvoort A, Langen RC. Nutritional interventions in cancer Cachexia: Evidence and perspectives from experimental models. Front Nutr. 2020;7:601329. https://doi.org/10.3389/fnut.2020.601329 PMid:33415123
15. Efranto BH, Handoko E. Correlation of nodule with body mass index and Karnofsky status in nasopharyngeal carcinoma chemotherapy. 2021;51(1):20-30. https://doi.org/10.32637/orli.v51i1.412

16. Kang J, Lee SH, Son JH, Lee JW, Choi YH, Choi JH, et al. Body mass index and weight change during initial period of chemotherapy affect survival outcome in advanced biliary tract cancer patients. PLoS One. 2018;13(4):1-15. https://doi.org/10.1371/journal.pone.0195118

PMid:29608578

17. Harbuwono DS, Pramono LA, Yunir E, Subekti I. Obesity and central obesity in Indonesia: Evidence from a national health survey. Med J Indones. 2018;27(2):53-9. https://doi.org/10.13181/mji.v27i2.1512