ORIGINAL ARTICLE

Distant Metastases of Nasopharyngeal Carcinoma

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Abstract

Aim: This study aims to review the nasopharyngeal carcinoma patients with distant metastases.

Materials and methods: This is an analytic case-control study. The populations of this study are patients with distant metastases of nasopharyngeal carcinoma as the case group and patients without distant metastases as the control group. The data, such as general characteristics and risk factors, were taken from medical records of two cancer referral hospitals in West Java between 2016 and 2020 with a consecutive sampling method. Categorical data will be analyzed with Chi-square or exact Fisher's test. While numerical data will be analyzed using unpaired *t* test.

Results: Forty-two patients showed distant metastases based on biopsy and imaging studies. Most of both case and control groups were male (73.8 and 81.0%), aged more than 45 years old (69.0 and 64.3%). The most frequently found risk factors in the case group were salted fish (85.7%) and instant noodle (83.3%) consumption. The age of salted fish consumption started, the usage of mosquito coils, and family history are significantly associated with distant metastases of nasopharyngeal carcinoma.

Conclusion: The initiation age of salted fish consumption, usage of mosquito coils, and family history are significantly associated with distant metastases of nasopharyngeal carcinoma. Special attention should be given to these populations to decrease the incidence of distant metastases and improve the outcome.

Clinical significance: The knowledge of general characteristics may increase the awareness of distant metastases and decrease the mortality rate due to metastases.

Keywords: Case-control study, Distant metastases, Nasopharyngeal carcinoma, Risk factors.

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Introduction

Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma arising from the nasopharyngeal epithelium. This carcinoma is frequently found in the fossa of Rosenmuller where the transition of columnar epithelium to the squamous epithelium occurs.[1] This carcinoma is the fourth most common cancer with an incidence of 6.2/100,000 populations per year. A study in Indonesia reported distant metastases in 13.4% of all cases.[2] While another study in China reported 12.0% of distant metastases.[3]

The 5-year survival rate of NPC is 45%, worsened by several factors, such as age more than 40, advanced stage, gender, and distant metastases. The prognosis of patients with distant metastases of NPC was reported to be poor with a 5-year survival rate of 22.3%.[4] The knowledge of general characteristics may increase the awareness of distant metastases and decrease the mortality rate due to metastases. This study aims to review NPC patients with distant metastases.

Materials and Methods

This is an analytic case-control study. The data were taken from medical records with convenient sampling method. The populations of this study are patients with distant metastases of nasopharyngeal carcinoma as case group and patients without distant metastases as control group diagnosed based on biopsy and imaging in Hasan Sadikin General Hospital and Santosa Hospital Kopo between January 2016 and December 2020. Patients with incomplete data were excluded.

General characteristics, risk factors, and site of metastases were obtained from medical records. General characteristics taken include age, gender, education, occupation, and chief complaint. Risk factors, such as consumption of a well-known carcinogen, such as alcohol, salted fish, instant noodle, canned food, soft drinks, and grilled food; smoking status; and exposure to mosquito coils, insecticide, and wood dust, were recorded.

Categorical data will be analyzed using Chi-square test or exact Fisher's test and presented as frequency and percentage, while numerical data will be analyzed using unpaired *t* test and presented as mean, median, standard deviation, and range. This study was approved by Dr. Hasan Sadikin General Hospital Ethical Committee with Register Number: 542/UN6.KEP/EC/2020.

Results

Between 2016 and 2020, there were 554 patients with NPC. Distant metastases was diagnosed in 45 patients (8.1%) based on biopsy and imaging studies. However, three subjects were excluded due to

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incomplete data. Control group was picked randomly to minimize bias. General characteristics of participants are described in Table 1. The majority of the 17 participants were male (77.4%) aged <45 years old (33.3%). Most of the participants were senior high school graduates (44.0%), working as employees (33.3%). Neck lump (81.0%) was the most chief complaint reported.

In both groups, many of the participants were older than 45 years old. However, patients with distant metastases showed a higher average of age than patients without distant metastases. However, there were no significant characteristically differences between both groups in this study as seen in Table 2.

Risk factors were described in Table 3. Most of both groups did not consume alcohol. However, patients with distant metastases showed higher alcohol consumption rate (21.4%), amount of alcohol consumed (11.9% consumed more than a glass per day), and duration of consumption (19.0% consumed for more than 12 months) than patients without. The history of tobacco smoking was higher in the case group (81.0%). This group also reported higher cumulative tobacco exposure based on the number of cigarettes smoked per day.

Salted fish consumption is slightly higher in patients with distant metastases (85.7%). There was a significant difference between both groups in the duration of salted fish consumption based on the age of the consumption started. The usage of mosquito coils in patients with distant metastases was doubled

Table 1: General characteristics of participants

Characteristics	*N = 84*
Age	
<45 years old	28 (33.3%)
≥45 years old	56 (66.7%)
Mean ± Std	49.82 ± 12.712
Median	50
Range (min–max)	20.00–80.00
Gender	
Male	65 (77.4%)
Female	19 (22.6%)
Last education	
Did not attend school	2 (2.4%)
Elementary school	22 (26.2%)
Junior high school	15 (17.9%)
Senior high school	37 (44.0%)
Bachelor	8 (9.5%)
Occupation	
Unemployed	5 (6.0%)
Housewife	11 (13.1%)
Entrepreneur	16 (19.0%)
Employee	28 (33.3%)
Labor	15 (17.9%)
Health worker	1 (1.2%)
Student	1 (1.2%)
Retired	2 (2.4%)
Others	5 (6.0%)
Chief complaint	
Malaise	5 (6.0%)
Neck lump	68 (81.0%)
Bloody discharge	1 (1.2%)
Epistaxis	1 (1.2%)
Diplopia	1 (1.2%)
Headache	4 (4.8%)
Tinnitus	4 (4.8%)

Categorical data were presented by frequency and percentage, while numerical data were presented by mean, median, standard deviation, and range

Table 2: The comparison of characteristics in patients with or without distant metastases

	Distant metastases		
	M0	*M1*	
Variable	*N = 42*	*N = 42*	*p value*
Age			0.643
<45 years old	15 (35.7%)	13 (31.0%)	
≥45 years old	27 (64.3%)	29 (69.0%)	
Mean ± Std	49.17 ± 12.927	50.48 ± 12.615	
Median	49.5	50	
Range (min–max)	20.00–80.00	24.00–79.00	
Gender			0.434
Male	34 (81.0%)	31 (73.8%)	
Female	8 (19.0%)	11 (26.2%)	
Last education			0.604
Did not attend school	1 (2.4%)	1 (2.4%)	
Elementary school	8 (19.0%)	14 (33.3%)	
Junior high school	7 (16.7%)	8 (19.0%)	
Senior high school	22 (52.4%)	15 (35.7%)	
Bachelor	4 (9.5%)	4 (9.5%)	
Occupation			0.785
Unemployed	1 (2.4%)	4 (9.5%)	
Housewife	6 (14.3%)	5 (11.9%)	
Entrepreneur	6 (14.3%)	10 (23.8%)	
Employee	17 (40.5%)	11 (26.2%)	
Labor	8 (19.0%)	7 (16.7%)	
Health worker	1 (2.4%)	0 (0.0%)	
Student	1 (2.4%)	0 (0.0%)	
Retired	0 (0.0%)	2 (4.8%)	
Others	2 (4.8%)	3 (7.1%)	
Chief complaint			0.991
Malaise	2 (4.8%)	3 (7.1%)	
Neck lump	34 (81.0%)	34 (81.0%)	
Bloody discharge	0 (0.0%)	1 (2.4%)	
Epistaxis	0 (0.0%)	1 (2.4%	
Diplopia	1 (2.4%)	0 (0.0%)	
Headache	1 (2.4%)	3 (7.1%)	
Tinnitus	4 (9.5%)	0 (0.0%)	

Categorical data were analyzed using Chi-square test with alternative of Kolmogorov-Smirnov and exact Fisher's test if the requirements of Chi-square test were not fulfilled. Numerical data with normal distribution were analyzed using unpaired *t* test, while data not normally distributed were analyzed using Mann-Whitney test. A *p* value less than 0.05 is statistically significant

Table 3: Risk factors in patients with NPC

	Distant metastases		
	M0	*M1*	
Risk factors	*N = 42*	*N = 42*	*p value*
Alcohol			
Consumption			0.242
Yes	5 (11.9%)	9 (21.4%)	
No	37 (88.1%)	33 (78.6%)	
Frequency			0.242
1–3x/week	5 (11.9%)	9 (21.4%)	
None	37 (88.1%)	33 (78.6%)	
Amount			0.991
<1 glass/day	4 (9.5%)	4 (9.5%)	
>1 glass/day	1 (2.4%)	5 (11.9%)	
None	37 (88.1%)	33 (78.6%)	
Duration			0.991
<12 months	2 (4.8%)	1 (2.4%)	
>12 months	3 (7.1%)	8 (19.0%)	
None	37 (88.1%)	33 (78.6%)	
Smoking status			0.306
Yes	30 (71.4%)	34 (81.0%)	
No	12 (28.6%)	8 (19.0%)	
Amount			0.323
None	12 (28.6%)	8 (19.0%)	
<12 cigarettes	12 (28.6%)	8 (19.0%)	
12–24 cigarettes	13 (31.0%)	21 (50.0%)	
>24 cigarettes	5 (11.9%)	5 (11.9%)	
Salted fish			
Consumption			0.175
Yes	31 (73.8%)	36 (85.7%)	
No	11 (26.2%)	6 (14.3%)	
Age started			0.033*
<10 years old	10 (23.8%)	22 (52.4%)	
10–18 years old	16 (38.1%)	8 (19.0%)	
>18 years old	5 (11.9%)	6 (14.3%)	
None	11 (26.2%)	6 (14.3%)	
Mosquito coils			
Usage			0.002*
Yes	13 (31.0%)	27 (64.3%)	
No	29 (69.0%)	15 (35.7%)	
Frequency			0.009*
<3/day	12 (28.6%)	25 (59.5%)	
3–5/day	0 (0.0%)	2 (4.8%)	
>5/day	1 (2.4%)	0 (0.0%)	
None	29 (69.0%)	15 (35.7%)	
Wood dust			0.057
Yes	5 (11.9%)	12 (28.6%)	
No	37 (88.1%)	30 (71.4%)	
Insecticide >1 year			0.265
Yes	2 (4.8%)	6 (14.3%)	
No	40 (95.2%)	36 (85.7%)	
Instant noodle			0.763
Yes	36 (85.7%)	35 (83.3%)	
No	6 (14.3%)	7 (16.7%)	
Canned food			0.653
Yes	27 (64.3%)	25 (59.5%)	
No	15 (35.7%)	17 (40.5%)	
Soft drink			0.801
Yes	32 (76.2%)	31 (73.8%)	
No	10 (23.8%)	11 (26.2%)	
Grilled food			0.321
Yes	29 (69.0%)	33 (78.6%)	
No	13 (31.0%)	9 (21.4%)	
Family history			0.004*
Yes	4 (9.5%)	15 (35.7%)	
No	38 (90.5%)	27 (64.3%)	

*Categorical data were analyzed using Chi-square test with alternative of Kolmogorov-Smirnov and exact Fisher's test if the requirements of Chi-square test were not fulfilled. A *p* value less than 0.05 is statistically significant

than in patients without (64.3%). There was a significant difference between the two groups and the frequency of usage per day.

Wood dust exposure, insecticide exposure, and grilled food consumption were higher in patients with distant metastases. However, there was no significant difference between these groups. Family history was reported higher in the case group with statistically different proportions between the case and control group.

Discussion

Most distant metastases were reported in male. This finding is in line with another study conducted in Yogyakarta and Palembang, Indonesia, that stated that males are more vulnerable to distant metastases due to higher exposure to carcinogenic materials, such as tobacco smoking, alcohol consumption, and wood dust. In this study, all patients consuming alcohol and exposed to wood dust were male.[2] Hormonal factors, such as higher androgen levels, are also reported to induce proliferative changes and promote tumorigenesis. Men also report VEGF-2578 expression associated with larger tumor size and advance cancer stage.[5] While estrogen exhibit as a negative regulators of cancer cell growth.[2,6]

Nasopharyngeal carcinoma (NPC) is a chronic condition in which normal cells turn into cancer cells due to mutation or exposure to carcinogen. This mechanism may explain the reason of the higher prevalence of distant metastases in the older population as seen in this study and another study by Indrasari et al. which reported that the peak age of distant metastases in NPC occurs in the 40–50 years old group. However, there was no significant differences between older and younger group to the presences of distant metastases.[2]

Regarding the education level, many of the participants had 9–12 years of formal education. Dantas et al. reported the same result that the low education level is associated with reduced access to information about diagnosis and treatment. This result is seen in other head and neck carcinoma, such as oral cancer.[7,8] Lower education level also influences their lifestyle, hence resulting in higher level of metastases.[9]

Several factors may increase the risk of NPC. In this study, most risk factors reported are consumption of salted fish (85.7%), instant noodle (83.3%), and smoking history (81.0%). Salted fish and preserved goods, when added with genetic susceptibility,

are well-known risk factors of NPC especially in endemic areas as reported by Handayani et al.[9] These preserved foods, either with salt or fumigation, contain N-nitrosamines, a carcinogenic substance. In processed meat, nitrate is added as it is toxic to the bacteria. Nitrosamine is formed by the interaction of the heat of the sun and nitrates.[6,10] However, this mechanism is also influenced by genetic susceptibility in nitrosamine metabolism, such as cytochrome P450 mutation and human leukocyte antigen (HLA) haplotype associated with NPC, such as HLAA1, AW19, BW46, and B17. This genetic susceptibility may explain the statistically difference between patients with and without family history of NPC as seen in this study.[9]

Another frequently reported risk factor, tobacco smoking, is also reported by a study by Hardianti et al. This study stated that smoking can increase the risk of developing NPC by 5.8 times higher than nonsmoker population.[10] A meta-analysis in 2017 reported that smoking is a major risk factor for NPC and the risk of NPC increases parallel to the number of tobaccos smoked. In our study, most participants in both groups smoked 12–24 cigarettes per day with a higher proportion in the case group. Tobacco may act as mutagen which results in DNA damage and tumorigenesis.[11,12]

Alcohol also exhibits a dose-dependent relationship with NPC risk development as seen in tobacco smoking. A study in 2019 reported that drinking >7 drinks a week is an independent risk factor of NPC. The main compound of alcohol, ethanol, does not directly act as a carcinogen. However, the first metabolite of ethanol, acetaldehyde, is a local carcinogen interfering with the repair site of genes and the synthesis of genes resulting in cancer cell development. Alcohol also increases the activity of mucosal cytochrome P450 enzyme resulting in the formation of free radicals and cell damage.[13]

The least risk factors reported were wood dust (28.6%) and insecticide exposure (14.3%). The wood dust exposure was mainly associated with occupational risk which does not frequently occur in our participants. Alcohol consumption is generally low in Indonesia due to religious and cultural restrictions.[14] Wood dust may accumulates and causes irritation and inflammation in nasopharyngeal epithelium, inducing mucociliary work and change of epithelial cells.[4] A study conducted in Nigeria showed the genotoxicity effects of agricultural chemicals, such as insecticides, herbicides, and chemical fertilizer. These substances contain nitrates which is a well-known carcinogenesis inducer in nasopharyngeal epithelium of farmers.[15]

Grilled food is cooked using a very high temperature of more than 400°C. During this process, heterocyclic amines or polycyclic aromatic hydrocarbons can be formed. Heterocyclic amines are formed when the meat is burnt incompletely, whereas polycyclic aromatic hydrocarbons are formed due to the dripping of fat to the hot fire and sticking to the surface of food.[16] These substances have been linked to the cell damage and disruption leading to mutation and carcinogenesis.[17]

Moore MA reported that mosquito coils are the most common risk factor of NPC in Indonesia and Malaysia. In this study, mosquito coils showed a significant difference between the user and nonuser and also the frequency per day. Hardianti et al. reported that the mosquito coils contain formaldehyde and acetaldehyde. Both substances exhibit carcinogenic effects. Formaldehyde is related to DNA damage which induces DNA damage, oxidative stress, and apoptosis, while acetaldehyde toxicity is related to the promotion of crotonaldehyde-deprived propano-dGs which promote cell mutation and inhibit DNA synthesis.[10,18,19]

The limitation of this study is the small number of the participants and does not include the odds ratio of each variable. Further analysis can be designed to associate each variable to the risk of NPC with distant metastases.

Conclusion

The initiation age of salted fish consumption, usage of mosquito coils, and family history are significantly associated with distant metastases of nasopharyngeal carcinoma. Special attention should be given to these populations to decrease the incidence of distant metastases and improve the outcome.

Clinical Significance

The knowledge of general characteristics may increase the awareness of distant metastases and decrease the mortality rate due to metastases.

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