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Submission date: 04-Apr-2023 07:17AM (UTC+0800)

Submission ID: 2055054986

File name: entation_of_Nasopharyngeal_Carcinoma_in_East_Java,_Indonesia.pdf (394.1K)

Word count: 3727

Character count: 19873

Clinical Presentation of Nasopharyngeal Carcinoma in East Java, Indonesia

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ABSTRACT

Background: Nasopharyngeal Carcinoma (NPC) is a rare malignancy throughout most of the world, but the incidence in Southeast Asia is very high. In Indonesia, NPC is the fourth most common malignancy. Among all regions in Indonesia, East Java has the highest incidence. However, there is no detailed study in East Java regarding this malignancy.

Aim: To document the clinical presentation of NPC in East Java.

Methodology: This was a descriptive study using medical record at Dr. Soetomo General Hospital. Samples were newly diagnosed NPC patients who attended radiotherapy outpatient clinic between January – December 2016. Total sampling method was used in this study. Patients' characteristic including presented symptoms, chief complaints, clinical staging, and histological subtypes were assessed and evaluated.

Results: There were 270 NPC patients registered in radiotherapy outpatients clinic at Dr. Soetomo General Hospital in 2016. Two-thirds of the patients were male. More than half of the patients came to the healthcare service with the chief complaint of lump in the neck. Based on the staging, almost all patients were already in the late stage. Histopathologic findings showed that WHO type 3 was the most common subtypes of NPC.

Conclusion: Majority of the NPC patients in East Java were already in the advanced stage. Early diagnosis is important for favorable outcome of this disease. Thus, it is important to understand the chief complaint and symptoms in patients with NPC so that the diagnostic delay could be avoided.

Keywords: Indonesia, Nasopharyngeal carcinoma, Signs and Symptoms

INTRODUCTION

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Nasopharyngeal Carcinoma (NPC) is a rarely occurred malignancy in most areas of the world which emerges from epithelial cells in nasopharynx area. Commonly it arises from the lateral wall, including fossa of Rosenmüller, can expand inside or outside of nasopharynx area (i.e. base of the skull, nasal cavity, and oropharynx), and metastases to lymph nodes in cervical areas¹. Mean incidence of NPC in the world is 1.2 per 100,000 (1.7 per 100,000 in men and 0.7 per 100,000 in women²). Although it is a rare malignancy, it is a prime form of cancer in well-defined populations, including natives of Southern China, Southeast Asia, the Arctic, and the Middle East / North Africa³. Its geographical distribution is very unbalanced, where more than 80% of the new cases worldwide located in Asia, and more than half of the global burden of this cancer is accounted in Southeast Asian Countries⁴.

In Indonesia, NPC is the fourth most common malignancy following breast cancer, cervical cancer, and lung cancer, with the prevalence of 5.66 per 100,000 equaling roughly 1000 new cases per month⁵. However, due to poor cancer registries, it is believed that the real incidence of NPC in Indonesia is not known⁶. Estimated regional incidence of NPC in 2000 showed that East Java was the highest incidence region in Indonesia with the incidence rate of 16.42 per 100,000⁵. However, there was

no detailed study in East Java region regarding this malignancy until now.

To date, almost all patients with NPC are correctly diagnosed after the tumor reached late stage⁷. It is very unfortunate, since early diagnosis is essential to significantly improve the five-year survival rates of the patients⁸. Previous study in Indonesia found that the delay in diagnosis was not merely due to patients lack of awareness to seek for medical attention. The doctors also contribute to the delay because they tend to ignore or misdiagnose the unspecific symptoms⁵.

Considering the fact that East Java region has the highest incidence of NPC, and doctors are also plays a role in the diagnostic delay, this study aimed to scrutinize the clinical presentation of NPC in East Java by using the data from Dr. Soetomo General Hospital as the tertiary referral hospital in this region. By conducting this study, we were hoping to give updated information regarding the common chief complaints and clinical symptoms of patients with NPC in East Java region, so that doctors will be more aware and eventually reduce the diagnostic delay, at least from the clinician sides.

METHODOLOGY

This was a descriptive study using medical record from radiotherapy outpatient clinic at Dr. Soetomo General Hospital. Dr. Soetomo General Hospital is a tertiary referral

hospital for the East Java region, Indonesia. Ethical approval from Research Ethics Committee was received before the study begins (Ethical Approval Number: 639/panke.KKE/XI/2017). This study had been performed in accordance with Declaration of Helsinki. Samples of this study were newly diagnosed NPC patients who attended radiotherapy outpatient clinic for radiotherapy treatment between January – December 2016. Data were collected from medical records by the authors.

Total sampling method was used in this study. Patients' characteristic including identified symptoms, chief complaints, clinical staging, and histological subtypes were assessed and evaluated. The assessed patients' characteristics were gender, age, education level, and occupation. The 7th edition of International Union against Cancer/American Joint Committee on Cancer (UICC/AJCC) was used for NPC staging system⁹. Histological subtypes were classified using 1978 WHO classification¹⁰. Patients' chief complaints and identified symptoms were categorized according to the location of the tumor(7). Acquired data was analyzed with descriptive analysis using SPSS version 17.0¹¹.

RESULTS

In 2016, there were a total of 270 NPC patients registered in radiotherapy outpatients clinic at Dr. Soetomo General Hospital. Based on gender, male: female ratio was 2:1. Based on the patients' age, majority of the patients were aged 51-60 years old. Education level of the patients showed that 39.8% were primary graduate(Table I).

From 270 patients, NPC staging were written in 244 patients' medical records. From 244 patients, 172 patients (70.49%) were in stage 4, while only 1 patient was in stage 1 (table II). Histopathological subtypes were written in 236 out of 270 patients' medical records. From 236 patients, 192 patients' histopathology results showed WHO type 3 classification (81.36%) (Table II).

Chief complaints and identified symptoms were written in 261 out of 270 patients' medical records. From 261 patients, majority seek medical attention because of enlarged lump in their neck area. Around 70% of the

patients had a symptom of lumps in the neck area, 55% had a tinnitus, and 44% had a chronic nasal congestion (table III).

Number of radiotherapy treatment cycles and dose received was determined by radiotherapy specialist. Based on the patients adherence to radiotherapy treatment, 180 out of 270 patients (66.67%) had completed the treatment. Sixteen patients were died during the treatment period, while 74 patients decided to quit the radiotherapy treatment in the middle of the treatment period. There were no data regarding the successfulness of the radiotherapy treatment.

Table I. Characteristic of NPC patients

Characteristics	(n=270)n (%)
Gender	
Male	180 (66.7)
Female	90 (33.3)
Age	
≤ 20 years old	14 (5.18)
21-30 years old	8 (2.96)
31-40 years old	43 (15.93)
41-50 years old	76 (28.16)
51-60 years old	93 (34.44)
>60 years old	36 (13.33)
Area of Residence	
Urban	39 (14.44)
Rural	231 (85.56)
Education level	
No formal education	5 (1.9)
Primary graduates	106 (39.3)
Secondary graduates	45 (16.7)
High Secondary graduates	69 (25.6)
Diploma graduates	45 (16.7)
Occupation	
Doctor	3 (1.1)
Fisherman	3 (1.1)
Farmer	46 (17.04)
Entrepreneur	40 (14.82)
Government employees	24 (8.9)
Private employees	98 (36.3)
Unemployed	56 (20.74)

Table II. Clinical staging and histological subtypes of NPC patients

NPC Staging	N = 244 n (%)	Histological subtypes	N = 236 n (%)
Early Stages			7 (2.97)
1	1 (0.41)	WHO type 1	
2	24 (9.84)	(Squamous Cell Carcinoma)	
Late Stages		WHO type 2	37 (15.68)
3	47 (19.26)	(Non-Keratinizing Carcinoma)	
4a	155 (63.52)		
4b	17 (6.97)		
		WHO type 3 (Undifferentiated Carcinoma)	192 (81.35)

Table III. NPC patients' chief complaints and identified symptoms based on tumor location

Chief complaints	N = 261 n (%)	Identified symptoms	N = 261 n (%)
Nasopharynx		Nasopharynx	
Epistaxis	28 (10.73)	Epistaxis	95 (36.4)
Nasal congestion	23 (8.81)	Nasal congestion	117 (44.83)
Nasal discharge	7 (2.68)	Nasal discharge	77 (29.5)
		Rhinolalia	15 (5.75)
Superior extension		Superior extension	
Headache	12 (4.6)	Headache	115 (44.06)
Facial pain and numbness	3 (1.15)	Facial pain and numbness	69 (26.44)
Blurred vision	3 (1.5)	Blurred vision	30 (11.49)
Diplopia	3 (1.5)	Diplopia	41 (15.71)
Exophthalmos	1 (0.38)	exophthalmos	1 (0.38)
Lateroposterior extension		Lateroposterior extension	
Tinnitus	14 (5.36)	Tinnitus	144 (55.17)
Deafness	2 (0.77)	Deafness	85 (32.57)
Neck masses		Neck masses	
Lumps	163 (62.45)	Lumps	188 (72.03)
Dysphagia	2 (0.77)	Dysphagia	41 (15.71)

DISCUSSION

In our study, we found that the incidence of NPC was twice higher in male than female. This finding was similar with previous studies where the incidence of NPC in male was higher than the female^{5,12}. In this study, incidence of NPC was highest in the age of 51-60 years old. In the areas where NPC was endemic, the incidence of NPC is increased after the age of 30-years old, peaked at the age group of 40–59-years old, and decreased at the older age group¹³. This pattern suggesting that there is an involvement of carcinogenic agents exposure early in life³. In contrary, in areas where NPC incidences is low, the incidences of NPC is increased with age¹³.

Majority of the patients' education level was elementary school graduates, and less than 20% graduated from the university. Previous study in United State showed that people with educational level of less than high school graduates had a higher risk of developing head and neck cancer compare to people with educational level of post graduate (1.98 times higher in men and 1.61 times higher in women)¹⁴. Population-based study in Denmark conclude that people with low educational level were less aware³ cancer than people with high educational level¹⁵. In countries with higher educated individuals, they are typically have healthier habits and more appropriate behaviors when exposed to risk factors compared with those in countries with lower educated individuals¹⁶.

In our finding, occupation of the NPC patients was diverse. Until now, there are no certainty about which occupational hazard is associated with NPC. Previous study in Malaysia found that occupational hazard which associated with NPC was wood dust and industrial heat, but not formaldehyde¹⁷. In contrary, multicenter study from United State found that formaldehyde increase risk of NPC but not wood dust¹⁸. Formaldehyde has been classified as definite human carcinogen for NPC by International Agency for Research on Cancer¹⁹. However, amendment of the International Labor Organization (ILO) guidelines in 2010 did not reach a consensus about whether occupational formaldehyde exposure and NPC is directly linked or not²⁰. Recent study concluded that additional evidence is needed

to understand the correlation between formaldehyde exposure and NPC²¹.

Other than occupational exposure, there are also several risk factors that associated with NPC, i.e. salted fish and other salt-preserved food consumption, Epstein-Barr virus (EBV) infection, inadequate intake of fresh fruits and vegetables, cigarette smoking, alcohol consumption, genetic susceptibility, herbal medicine consumption, low socioeconomic status, and chronic upper respiratory disease^{2,3,13,22}. However, we did not assess the risk factor because the data in the patients' medical records was incomplete.

In this study, we found all histopathologic subtypes of NPC. Majority of it was NPC WHO type 3. This finding is similar with previous study in Indonesia where WHO type 3 was the most frequent histopathologic subtypes, and there were few patients with WHO type 1 NPC⁵. In total, there are 3 subtypes that recognized in the WHO classification, which are: squamous cell carcinoma (WHO type 1), non-keratinizing carcinoma (WHO type 2), and undifferentiated carcinoma (WHO type 3)¹⁰. NPC WHO type 3 was found to be the most common form of NPC in Southeast Asia and other high incidence regions^{3,5}. Theoretically, WHO type 2 and 3 are related with elevated titer of EBV but type 1 is not¹. However, it has been discovered that WHO type 1 can also be associated with EBV but in endemic regions only, while in non-endemic regions it is associated with alcohol and tobacco abuse⁵. There is no reasonable explanation about this unusual finding until now.

Wei et al. (2005) divided presented symptoms in NPC patients into four categories according to the tumor location, which are: (1) tumor mass in the nasopharynx (epistaxis, nasal obstruction, and discharge); (2) lateroposterior extension of the tumor to paranasopharyngeal space (tinnitus and deafness due to eustachian tube dysfunction); (3) superior extension of the tumor to the skull-base (diplopia, numbness, facial pain, and headache because of the skull-base erosion and 5th and 6th cranial nerve palsy); and (4) neck masses⁷. In our findings, the most common presented symptom was due to the presence of the tumor mass in nasopharynx, followed by tinnitus, nasal congestion, and headache. From all presented symptoms found in the NPC patients, lumps in the neck was the most dominant chief complaints of NPC

patients. This finding was similar to previous study where the most common presented symptom and the highest occurrence of presenting complaints in NPC patients was neck mass²³. Other study in Saudi Arabia found that the most common presenting symptoms was neck mass, followed by nasal obstruction and epistaxis²⁴.

Most of the patients in our study were already in the advanced stage. To date, almost all patients with NPC are correctly diagnosed after the tumor reached late stage⁷. Previous studies showed that more than 75% of the patients was already in the late stage NPC at the time they presented in the hospital^{24,25}. Early diagnosis is essential to improve the prognosis of NPC because 5-year survival rates for early-stage patients exceed 90%, while in late-stage patients is less than 50%⁸. Other than the fact that NPC is hard to diagnose clinically because the location is hidden in the nasopharynx, there are other factors that contributes to the diagnostic delay, which are patient-related delay (PRD) and doctor-related delay (DRD). PRD is the time from initial symptoms to the first visit to a doctor, and DRD is the time from the first visit to diagnosis and treatment²⁶.

Study in Saudi Arabia found that PRD contributes to a median of 1-month delay and DRD contributes to a median of 3-month delay. Around quarter of the patients experience delay because of their lack of awareness about the symptoms, and more than half of the patients experience delay because their symptoms are treated as benign condition²⁴. Earlier study in Indonesia found that the diagnostic delay is because either patients or doctors do not give an attention of any presenting symptoms until enlargement of cervical lymph nodes was detected. It is suggested that patients contribute to the delay because of their lack of knowledge about the early sign and symptoms, while the doctors contribute to the delay because they tend to ignore or misdiagnose the unspecific symptoms⁵. Study in Indonesia primary health care found that General Practitioner (GP) had lack of knowledge on all aspect of NPC. They receive lack of education about NPC during their study period at university, and more than half of them gain insufficient knowledge during daily practice as GP⁶. Previous study regarding potential factors that associated with clinical stage of NPC at diagnosis found that accessibility to health facilities, routine physical examination, and knowledge about early symptoms can increase the rate of early diagnosis and improve the prognosis⁸. However, in this study we did not evaluate the PRD and DRD because of the lack of data in the medical records.

There were several limitations in this study. The medical record in the hospital was not an electronic medical record, therefore it took a lot of efforts for the authors to manually retract the data from patients' medical record. Risk factors could not be evaluated because not all known risk factors were written in the medical record. DRD was also not written in the medical record. Nevertheless, this was the first study conducted in East Java region, the region with the highest prevalence of NPC in Indonesia, that scrutinize the clinical presentation of NPC patients.

CONCLUSION

Almost all NPC patients in East Java presented to the tertiary referral hospital in advanced stage. Early diagnosis is critical for favorable outcome of this disease. It is important for clinician to understand the chief complaint and symptoms in patients with NPC, so that the diagnostic delay could be reduced, at least from the clinician sides. Future study needs to be done to assess the risk factors of the NPC patients, so that the society could be informed to avoid those risk factors.

Acknowledgements: The authors would like to thank all staffs from radiotherapy outpatient clinic at Dr. Soetomo General Hospital for their support during the study. The authors received no funding for this work.

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