

RESEARCH ARTICLE

Profile of Nasopharyngeal Carcinoma in Dr. Cipto Mangunkusumo National Hospital, 2010

Vito F. Jayalie,^{1*} Maria S. Paramitha,¹ Jessica,¹ Cindy A. Liu,¹ Adhitya S. Ramadianto,¹ Trimartani,² Marlinda Adham²

¹Medical Science Program FM Universitas Indonesia

²Department of Otorhinolaryngology, FM Universitas Indonesia-
Dr. Cipto Mangunkusumo National Hospital

*Correspondence: v_lie@hotmail.com

Received 13th June 2016; Accepted 7th December 2016

Abstract

Nasopharyngeal carcinoma (NPC) is the most common head and neck malignancy in Indonesia. NPC presents numerous challenges from non-specific signs and symptoms until lack of awareness from general practitioners (GP), which lead to late or missed diagnosis. Early diagnosis and prevention are proposed as the best solutions for this problem. In order to do that, we need a complete and well-managed patients' data. This study aims to reveal the demographic, clinical and histopathologic characteristics of NPC in Indonesia. A cross-sectional study was conducted by collecting medical records of all NPC patients in 2010 from Otorhinolaryngology Department of Dr. Cipto Mangunkusumo National Hospital. The extracted data were then analyzed to describe the problem of NPC in Indonesia. Out of 167 patients, 68.3% of the patients are male and most of them are Sundanese and Javanese. Palpable lump in the neck is the most common complaint in presentation (58.1%), followed by nasal congestion (49.1%). Salted fish consumption was the most prevalent risk factor (29.9%). Based on the histopathologic findings, 75.4% of the cases were classified as WHO-3 and around half of the patients (51%) were in stage IV upon diagnosis. Studying demographic and clinical characteristics of NPC patients is the first step to overcome problems caused by NPC in Indonesia.

Keywords: head and neck cancer, nasopharyngeal carcinoma, epidemiology.

Profil Karsinoma Nasofaring di RSUPN Dr. Cipto Mangunkusumo, 2010

Abstrak

Karsinoma nasofaring (KNF) merupakan keganasan kepala leher yang paling sering di Indonesia. Tanda dan gejala KNF tidak spesifik dan dokter umum kurang waspada sehingga diagnosis terlambat atau gagal. Untuk mengatasi hal tersebut, diperlukan upaya pencegahan dan deteksi dini yang didasari profil KNF. Studi ini bertujuan untuk mengetahui gambaran demografi, gejala klinis dan karakteristik histopatologi pasien KNF di RSUPN Dr. Cipto Mangunkusumo. Penelitian menggunakan desain potong lintang dengan sumber data rekam medis Departemen Telinga Hidung dan Tenggorokan RSUPN Dr. Cipto Mangunkusumo tahun 2010. Dari 167 data, 68.3% pasien adalah laki-laki dan suku terbanyak Sunda dan Jawa. Sebagian besar pasien datang dengan keluhan terdapat massa di leher (58,1%) dan hidung tersumbat (49,1%). Faktor risiko terbanyak adalah konsumsi ikan asin (29,9%). Berdasarkan hasil histopatologis, 75,4% kasus digolongkan sebagai WHO-3 dan 51% kasus didiagnosis stadium IV. Karakteristik demografi dan gejala klinis pasien KNF merupakan langkah pertama untuk penyelesaian masalah KNF.

Kata kunci: kanker kepala leher, karsinoma nasofaring, epidemiologi.

Introduction

Indonesia is an archipelagic country with more than 13.000 islands and 240.000.000 ethnically-diverse inhabitants. The country is considered as a lower-middle income country by the World Health Organization (WHO) in which targeted prevention will be more effective economically. In 2010, cancers comprised 13% of all mortality in the country. The death rate from cancer in males and females are 135.9 and 108.9 per 100.000 people, respectively.¹

Nasopharyngeal carcinoma (NPC) is the most common malignancy in the head and neck, placing it as the fourth most common among all malignancies in Indonesians. Estimates put the incidence of NPC at 6.2 per 100.000 population or 12.000 new cases per year, with all the cases associated with Epstein Barr virus (EBV).²

NPC is a malignancy with distinct geographical distribution.³ While considered rare in most parts of the world, NPC cases are frequently found in southern China and southeast Asia. Additionally, smaller numbers of cases are also found in north Africa and the Arctic. Males are three times more likely to be affected by NPC compared to females,⁴ and incidence peaks around the age of 45-60 years,² which is still considered productive age range. Environmental risk factors of NPC include EBV infection, consumption of salted fish, and family history of NPC; consumption of preserved food and tobacco smoking may also increase risk of NPC.^{2,3}

Similar with other chronic diseases, NPC presents numerous challenges that go beyond simply treating the disease. The malignancy is manifested with various non-specific signs and symptoms and despite its high incidence, general practitioners' awareness of NPC is inadequate, potentially leading to many late or missed diagnosis.^{2,5} Many cases are referred to hospitals in advanced stages. Early detection techniques such as nasopharyngeal brushing, blood tests, and adjuvant laboratory examinations are available and affordable for everyone, but the practice of early detection is still need to be socialized among practitioners.² Reaching hospital is also a challenge

especially for Indonesians in rural areas who suffer from lack of access to adequate basic medical care and molecular diagnostics such as EBV serology and DNA load. Nationally, the country does not yet have a proper cancer registry.^{2,4}

Once diagnosed, treatment may cause heavy socioeconomic burden to the patient and his/her family, especially considering that NPC affects individuals in productive age. NPC also puts a significant burden on healthcare resources of the country. Additionally, diagnosis of cancer may impact the patient's psychological well-being, which, in turn, plays a role in deciding whether the patient will get an optimal treatment or not.⁶

Realizing the enormous challenge of NPC, early detection and prevention are proposed as the best ways to overcome problems related to NPC. In order to do that, we should have data about risk factor and target of intervention in the population. To answer those challenges, we conducted a study on NPC patients in Dr. Cipto Mangunkusumo National Hospital (CMNH), Jakarta to learn more about the epidemiological, clinical, and histopathological characteristics of NPC.

Methods

This cross-sectional study collected medical records of NPC patients in the Otorhinolaryngology Department of Faculty of Medicine Universitas Indonesia–CMNH. CMNH is the national referral hospital in Indonesia therefore, patients' from all regions in Indonesia are referred to this hospital. This study used total sampling method; the necessary data from all NPC patients in year 2010 were extracted and then analyzed to describe the demographic, clinical and histopathologic characteristics of NPC in Indonesia. The use of medical record in the study is compliant to the university and hospital regulations. The confidentiality of subject identity was guaranteed.

Results

In 2010, there were 167 medical records of NPC patients in CMNH. During data extraction, we found many records were filled incompletely but these records are still included in analysis.

Table 1. Sociodemographic Characteristics and Risk Factors of NPC in CMNH, 2010

Characteristics and risk factors	n	%
Characteristics		
Sex		
Male	114	68.3
Female	53	31.7
Age (Mean ± SD = 43.53 ± 13.796)		
1-15	5	3
16-30	21	12.6
31-45	60	35.9
46-60	56	33.5
>60	18	10.8
Ethnicity		
Javanese	31	18.6
Sundanese	37	22.2
Sumatra	21	12.6
Betawi	19	11.4
Others (Chinese, Bima, Manado, etc)	10	6
Risk factors		
Family		
Yes	13	7.8
No	22	13.2
Active smokers		
Yes	39	23.4
No	41	24.6
Passive smokers		
Yes	14	8.4
No	30	18
Betel consumption		
Yes	2	1.2
No	59	35.3
Alcohol consumption		
Yes	6	3.6
No	64	38.3
Salt fish consumption		
Yes	50	29.9
No	21	12.6
Sunlight exposure		
Yes	22	13.2
No	35	21

As much as 68.3% of the NPC patients are male and most of them (80.2%) are older than 30 years old. The patients come from various ethnicities in Indonesia; the most common are Sundanese (22.2%) and Javanese (18.6%). Among

the known environmental risk factors, the most prevalent is salted fish consumption, identified in 29.9% of patients. Smoking and passive smoking are also prevalent. Betel and alcohol consumption are identified as the two lowest risk factors (1.2% and 3.6% respectively) as shown in Table 1.

Table 2. Symptoms and Duration of NPC in CMNH, 2010

Symptoms and Durations	n	%
Neck lump		
Yes	97	58.1
≤ 6 months	37	22.2
7-12 months	24	14.4
≥ 13 months	14	8.4
No	11	6.6
Nasal congestion		
Yes	82	49.1
≤ 6 months	23	13.8
7-12 months	13	7.8
≥ 13 months	2	1.2
No	24	14.4
Bloody discharge		
Yes	60	35.9
No	41	24.6
Epistaxis		
Yes	59	35.3
No	45	26.9
Post nasal drip		
Yes	38	22.8
No	54	32.3
Diplopia		
Yes	38	22.8
No	62	37.1
Hearing defect (unilateral)		
Yes	66	39.5
≤ 6 months	24	14.4
7-12 months	9	5.4
≥ 13 months	2	1.2
No	34	20.4
Hearing defect (bilateral)		
Yes	15	9
No	59	35.3
Tinnitus		
Yes	57	34.1
No	36	21.6
Pain		
Yes	21	12.6
No	67	40.1
Fluid from ear		
Yes	10	6
No	74	44.3
Unilateral headache		
Yes	63	37.7
No	30	18
Cranial nerve paresis		
Yes	19	11.4
No	42	25.1

As shown in Table 2 palpable lump in the neck is the most common complaint at presentation, found in 58.1% of patients, followed by nasal congestion (49.1%) and unilateral hearing defect (39.5%). The majority of patients have felt these complaints for 6 months or less. However, there are patients who tolerated the complaints for more than a year before going to a physician.

Table 3. Histological Findings and Stages of NPC Patients in CMNH, 2010

Histological findings and NPC stages	n	%
Tumor type		
WHO-1	3	1.8
WHO-2	11	6.6
WHO-3	126	75.4
Others	5	3
NPC stages		
1	0	0
2A	1	0.6
2B	8	4.8
3	22	13.2
4A	31	18.6
4B	32	19.2
4C	22	13.2

Based on the histopathological findings, 75.4% cases were classified as WHO-3. WHO classification is not available in 3% of cases, which is then classified into 'others'. Clinically, 51% patients were already in stage IV upon diagnosis in CMNH (Table 3).

Discussion

Characteristics of the Patients

Male patients make up 68.3% of NPC cases found in 2010. This distribution is consistent with previous findings indicating dominant male predisposition among NPC patients in North America, Middle East/North Africa, Arctic, Southeast Asia, and China and East Asia.³ The predisposition can be found in developing and developed countries alike.⁷

More than 80% of NPC patients are older than 30 years old. This finding follows the general age trend of NPC that starts to rise after age 30. Incidence peaks in the age 31-60 years group, with 69.4% of patients in this age group. This peak concurs with many previous findings which found the peak in age 31-50 years old in North Africa, the peak is around

50 years of age, in China, the majority of patients come in the fifth and sixth decades of life.² NPC in Singapore peaks in age 41-50 years old.⁸

The majority of patients in this study are Sundanese, Javanese, Sumatrans, or Betawi descent. Compared to other ethnicities, these ethnicities have the largest population in Indonesia hence, this distribution may simply reflect the general population and not genetic risk factor. People of Javanese descent are most prevalent in NPC cases.² Nevertheless, other ethnicities are also affected by NPC and thus, there might be no strong relation between risk factors of NPC and ethnicities.

Sign and Symptoms

Most patients developed symptoms such as neck lump, nasal congestion, bloody discharge, epistaxis, hearing defect, tinnitus and unilateral headache. The common early signs and symptoms of NPC is unilateral hearing loss from effusion in a middle ear or a mass on the neck caused by regional spread. Nasal obstruction can be a result of large or exophytic lesions. Adjacent cranial nerves paralysis can be caused by tumor growth and manifests into various symptoms such as facial pain due to involvement of trigeminal nerve, diplopia accompanying injury on abducens nerve, ophthalmoplegia due to the involvement of cranial nerves III, IV, and VI, and xerophthalmia due to the involvement of greater superficial petrosal nerve.⁹

From a study conducted by Cu CY and Lui CC,¹⁰ extension of NPC towards paranasopharyngeal space is considered frequent, signaled by neck masses, auditory symptoms (unilateral or bilateral), bloody nasal discharge, and cranial nerve palsy. The most common cranial nerve palsy to be found is trigeminal neuropathy caused by perineural invasion to trigeminal nerve of the intracranial segment. Facial pain or paresthesia is also found a lot at the time of diagnosis, especially when the tumor has invaded the intracranial paracavernous region. In the early stage of the diseases, these symptoms are still tolerable for the patients. However, the worst possible outcomes for the patients are nerve dysfunction and sensory impairment of ophthalmic division.

For duration of the symptoms, most of the patients come to seek a medical advisor within 6 months after the occurrence of neck lump, nasal congestion and unilateral hearing defect. But unfortunately, there were still a lot of patients who came to seek medical advice after more than 6 months, even years. Combination of lack of awareness, knowledge about NPC and

unspecific early signs and symptoms often lead to worsened prognosis. Therefore, the role of health professional is to be an educator about an early detection system and ensuring the patients to perform healthy behavior in their daily lives.

Risk Factors

Increased risk of NPC has been associated with numerous factors. While an overwhelming majority of NPC is tested positive for EBV, other factors still play a role in oncogenesis. Certain ethnic groups may be healthy carriers of EBV. Genetic risk factors include p53 mutations and polymorphism in genes encoding metabolic enzymes.⁹ Environmental factors such as carcinogens and nutrition may affect NPC in epigenetic level.²

Having a multifactorial etiology, there are several factors related to NPC, such as smoking and salted fish consumption.² This study shows that smoking may not establish risk factor of head and neck malignancy. In previous study, tobacco smoking was not a strong risk factor to undifferentiated nasopharyngeal carcinoma (WHO-3).¹¹ Besides, salted fish, a common food with nitrosamine as its component, may be a risk factor of nasopharyngeal carcinoma. Nitrosamine has been proven to cause NPC in many studies such as study by Zheng et al¹² which stated that there were a strong association between salted fish consumption and EBV with NPC. Another study led by Armstrong,¹³ found that salted marine fish was shown to be a strong and significant risk factor for NPC incidence in Chinese populations. Lau et al¹⁴ also showed that there was a strong correlation between salted fish consumption and NPC in Hongkong ($p < 0.05$). The involvement of salted fish and the development of NPC is believed to be related to its component, nitrosamine.¹⁵ Although betel consumption was associated with 70% increased risk of NPC in Taiwan, Indonesia shows a different pattern as betel consumption was one of the lowest risk factors. Therefore, even though betel consumption might be strongly associated with NPC in some countries, its clear involvement in Indonesia is still yet to be studied.³

Histologic Findings

Histopathologically, there are many types of malignancy in nasopharynx: squamous cell carcinoma as the most common type, lymphoma, salivary gland malignancy, and sarcoma.⁹ Squamous cell carcinoma is further divided by WHO

classification into WHO type 1 (keratinizing form with poor prognosis within 10% survival rate after 5 years), WHO type II (non-keratinizing and poorly differentiated) and WHO type III (non-keratinizing and undifferentiated). The highest prevalence in Southeast Asia, including Indonesia as shown in our research, is patients with WHO Type III.²

A serologic examination showed that in small and submucosal tumors, which are difficult to be identified, more specific signs and symptoms were found in each WHO classifications. In WHO type 1 tumors, squamous cell carcinomas can be located within head and neck regions. This type of tumors appeared to be more persistent and had higher recurrence rate. Although WHO type 2 and 3 tumors usually occur earlier and possess higher survival rate post treatment, early and advanced neck metastasis commonly happen. The tumors in these types were found to be small, submucosal, and not easily detectable. These types of tumors also appeared to be more sensitive towards radiation compared with WHO type 1 tumors.¹⁶

The classification of others (3%) was due to the difference between hospitals in Indonesia. Pathologists in CMNH classified NPC based on WHO classification, but others may not. Patients who came to CMNH with pathologic findings are directly treated based on the findings. The reason for not performing another diagnostic evaluation is to decrease the expenses of the patients as Indonesia is still a developing countries.

Staging of NPC

Since most patients were diagnosed in the late stage, this may indicate that early detection system in Indonesia is not yet established. Doctors and other health providers should give a better understanding on increasing awareness among both patients and medical staff, especially doctors as a primary health care provider.

NPC as A Chronic Disease

Dealing with NPC in Indonesia cannot be considered to be easy since there are major problems such as: low medical awareness towards this chronic disease and its effect, lack of hospital and medical facilities especially in rural areas, and improper nationwide cancer diagnostic and registration system.⁴ Lack of awareness and knowledge about NPC, especially in rural areas, can also add more obstacles to perform early detection. Moreover, most of the early signs and

symptoms are not specific which often lead to situations where NPC is considered as the most commonly misdiagnosed disease.²

Simple, regular, and affordable techniques for early detection of NPC such as nasopharyngeal brushing, blood tests, and adjuvant laboratory examinations are still necessary to be socialized. As a developing country, Indonesia only has few facilities for molecular testing, especially in rural areas. This is unfortunate since molecular examinations such as EBV-IgA serology and EBV-DNA load testing are very promising for early diagnosis and down-staging of NPC. Health workers in rural areas must be educated further in sample-taking technique and how to transport the samples.²

Challenges to deal with NPC also come from the patients. Anxiety and depression has become the most prominent psychopathological comorbidities especially when the patients undergo uncomfortable therapies.⁶ Patients may become reluctant to follow the treatment or even to consult with medical professionals about their conditions. Lack of awareness about the outcome of this disease can also be the reason on why some people do not want to do further confirmation when they are diagnosed with NPC. Confirming the diagnosis with radiological examinations such as CT-Scan contributes to the improvement of this disease since by knowing the staging and the extent of the metastasis can help the medical professionals to determine the appropriate treatment for the patients. Moreover, insufficient knowledge of GP, especially in primary medical healthcare to deliver the information for patients, results into problems to deal with. Previous studies show that the knowledge of GPs were declining after two-weeks period of NPC awareness education to them. Therefore, education of the GPs in endemic areas should be done regularly to reduce mortality rate of NPC patients and to increase the quality of life of the patients.^{5,17}

Since NPC mostly affects individuals in productive ages (begins in 20 years old until 40-50 years old) NPC has created a socio-economic problem for the country especially in the terms of occupation and health system. Thus, multidimensional and multidisciplinary approach from the government, medical doctors and other health providers are also needed to be done. Until now, medical doctors have done numerous approach towards better treatment and prevention of NPC such as educating the medical doctors in primary medical health care.¹⁷

The data of this research is obtained from the medical records of all NPC patients in CMNH in 2010. As the national referral hospital in Indonesia, CMNH has patients from all over Indonesia. Therefore, the data in this study represent the characteristics of all NPC patients in Indonesia. However, not all NPC patients come to CMNH hence there may be bias.

A major obstacle in this study is the lack of data with adequate quality. Several medical records are incompletely filled thus creating a problem in data extraction. This obstacle may be caused by several factors, including human error and not having the records computerized. Therefore, to aid NPC patients further and to nurture a healthy research environment, medical records should be filled as completely as possible and should be computerized.

In conclusion, the characteristic of 167 patients who came to Dr. Cipto Mangunkusumo National Hospital in 2010 showed the same sex and age distribution compared with other studies. In this study, most NPC patients presented with neck lump, nasal congestion, bloody discharge, epistaxis, hearing defect, tinnitus and unilateral headache. We also found that medical seeking behavior of the NPC patients in Indonesia is still low as many patients were diagnosed after 6 months of symptoms. In addition, the most prominent risk factor is salted fish consumption. Regarding to the diagnosis of this disease, WHO-3 was found in almost all cases, and half of the patients came at stage 4 upon diagnosis.

NPC is one of the iceberg phenomenons in Indonesia needing to be solved. Studying the demographic and clinical characteristics of NPC patients is the first step in tackling NPC. A multidimensional approach and collaboration should be carried out by government with their policies and medical providers by sharing information and knowledge about NPC properly to patients. Moreover, a better cancer registration such as using a computerized system will ease the research and study regarding to NPC in Indonesia. Finally, by knowing the risk factors of the development of NPC and understanding what and how certain contributing factors affect the journey of this chronic disease, ultimately we can create a better healthcare system in Indonesia. Nevertheless, further study is necessary especially about the applicable screening method for NPC in countries with limited diagnostic resources such as Indonesia.

Conflicts of Interest

The authors affirm no conflict of interest in this study.

Acknowledgment

We would like to acknowledge Otorhinolaryngology Department Dr. Cipto Mangunkusumo National Hospital-Faculty of Medicine Universitas Indonesia for giving chance to conduct a research in this department.

References

1. World Health Organization. Noncommunicable diseases country profiles 2011. Geneva: WHO; 2011.
2. Adham M, Kurniawan AN, Muhtadi AI. Nasopharyngeal carcinoma in Indonesia: epidemiology, incidence, signs, and symptoms at presentation. *Chin J of Cancer*. 2012;31(4):185-96.
3. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. *Cancer Epidemiology Biomarkers Prev*. 2006;15:1765-77.
4. Angel I, Anghel AG, Dimitru M, Soreanu CC. Nasopharyngeal carcinoma: Analysis of risk factors and immunological markers. *Chirurgia*. 2012;107:640-5.
5. Fles R, Wildeman MA, Sulistiono B, Haryana SM, Tan IB. Knowledge of general practitioners about nasopharyngeal cancer at the Puskesmas in Yogyakarta, Indonesia. *BMC Med Educ*. 2010;10:81.
6. Frick E, Tyroller M, Panzer M. Anxiety, depression and quality of life of cancer patients undergoing radiation therapy: a cross-sectional study in a community hospital outpatient centre. *Eur J Cancer Care*. 2006;16:130-6.
7. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61(2):69-90.
8. Loh KS, Goh BC, Lu J, Hsieh WS, Tan L. Familial nasopharyngeal carcinoma in a cohort of 200 patients. *Arch Otolaryngol Head Neck Surg*. 2006;132(1):82-5.
9. Weber GF. Molecular mechanisms of cancer. New York: Springer; 2007.
10. Cu CY, Lui CC. Perineural invasion of the trigeminal nerve in patients with nasopharyngeal carcinoma. *Cancer*. 1996;78(10): 2063-9.
11. Polesel J, Franceschi S, Talamini R. Tobacco smoking, alcohol drinking, and the risk of different histological types of nasopharyngeal cancer in a low risk population. *Oral Oncol*. 2011;47(6):541-5.
12. Zheng X, Yan L, Nilsson B, Eklund G, Drettner B. Epstein-barr virus infection, salted fish and nasopharyngeal carcinoma. *Acta Oncol*. 1994;33(8): 867-72.
13. Armstrong RW, Imrey PB, Lye MS, Armstrong MJ, Yu MC, Sani S. Nasopharyngeal carcinoma in Malaysian Chinese: salted fish and other dietary exposures. *Int J Cancer*. 1998; 77(2): 228-35.
14. Lau HY, Leung CM, Chan YH, Lee AW, Kwong DL, Lung ML, et al. Secular trends of salted fish consumption and nasopharyngeal carcinoma: A multi jurisdiction ecological study in 8 region from 3 continents. *BMC Cancer*. 2013;13:298.
15. Ward MH, Pan WH, Cheng YJ. Dietary exposure to nitrite and nitrosamines and risk of nasopharyngeal carcinoma in Taiwan. *Int J Cancer*. 2000;86(5):603-9.
16. Neel HB. Nasopharyngeal carcinoma: clinical presentation, diagnosis, treatment, and prognosis. *Otolaryngol Clin North Am*. 1985;18(3):479-90.
17. Wildeman MA, Fles R, Adham M. Short-term effect of different teaching methods on nasopharyngeal carcinoma for general practitioners in Jakarta Indonesia. *PLOS One*. 2012. DOI: 10.1371/journal.pone.0032756.