

RESEARCH COMMUNICATION

Nasopharyngeal Carcinoma - a Clinico-pathological Study in a Regional Cancer Centre of Northeastern India

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Abstract

Objectives: To study the clinico-pathological pattern of nasopharyngeal carcinoma (NPC) with dietary, smoking and tobacco consumption habits in the Northeastern region of India. **Methods:** This is a retrospective study on 200 patients with nasopharyngeal carcinoma who were registered in Regional Cancer Centre, Regional Institute of Medical Sciences, Manipur from July 2004 to July 2009. **Results:** There were 139 males and 61 females (ratio 2.2:1), with a mean age of 49.7±15.9 years. The commonest presenting symptoms were neck swelling (78.0%) followed by nasal obstruction (35.5%) and epistaxis (27.5%). Histopathologically, undifferentiated carcinoma type (Type III, WHO) was the commonest (75.0%) followed by differentiated non-keratinizing squamous cell carcinoma (15.0%) and keratinizing squamous cell carcinoma (10.0%). 25% of total patients had cranial nerve (CN) involvement, the commonly involved CN being V (28.8%) followed by VI (26.9%) and X (25.0%). Of the total 200 patients, 88.0% had history of regular intake of smoked meat, 62.0% admitted regular intake of poorly preserved fermented foods, only 19.0% consumed fresh fruits (at least 4 times a month). Majority of patients (47.0%) chewed tobacco in different forms and (51.0%) smoked at least for 15 years. 186 patients (93.0%) lived in poorly ventilated houses with history of exposure to household smoke from burning firewood. **Conclusion:** High incidence of NPC in Northeastern India is highlighted in this study. Early detection and early treatment to reduce the morbidity and mortality associated with NPC in addition to imparting awareness on how to prevent the disease to general population is needed in this region.

Keywords: Nasopharyngeal carcinoma - keratinizing squamous cell carcinoma - North-East India

Asian Pacific J Cancer Prev, 12, 1583-1587

Introduction

Nasopharyngeal carcinoma (NPC) is a rare cancer worldwide except in South East Asia, Southern China and North Africa. In spite of the high incidence of cancer of the oral cavity and other parts of pharynx, NPC is uncommon in the Indian subcontinent except in the Northeastern part of the country (Kataki et al., 2011). The Mongoloid race in this region has shown an increase in NPC incidence (Singh et al., 2010; Kumar et al., 2003). The latest National Cancer Registry programme (NCRP), 2006-2008 has reported the highest age-adjusted incidence rates (AARs) of NPC in Aizawl district (6/100000) followed by Manipur State (5/100000) excluding Imphal West district and Nagaland state in males in Northeastern India. As per earlier report of NCRP 2002, Nagaland state had the highest AARs followed by Manipur and Mizoram in this region. The district-wise distribution of the age-adjusted incidence rates (AARs) of NPC in Kohima district in Nagaland states was 19.4/100000, among the highest AARs reported in the world.

In our departmental cancer registry report, total cases of

NPC accounts for approximately 6.5% of all malignancies over the 5 years. NPC has been the 2nd most common malignancy in males for the past decade contributing approximately 11% of all malignancies in the same sex. NPC has a remarkable racial and geographical distribution with complex interaction of genetic, viral (Epstein Barr Virus), environmental and dietary factors which may be associated with the etiology of these disease.

The significant difference in geographical, ethnicity and dietary habits within our country could predispose people of Northeastern India for high incidence of NPC. One study from this region reveals an association of this cancer with consumption of smoked meat and herbal nasal medicine (Chelleng et al., 2000). Another study on smoked meat of this region has shown the presence of volatile nitrosamine which is already known as strong carcinogen (Sarkar et al., 1989; Kumar et al., 1992). NPC has a tendency to affect the relatively young population more than most other cancers; the loss of working life due to NPC is substantial. Neck mass, nasal obstruction, epistaxis and diplopia are the common presenting symptoms. In endemic region of the world like Southern China, Hong

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Kong, Taiwan etc, non-keratinizing carcinoma (Type III, WHO) particularly the undifferentiated type is the commonest type (Wei et al., 2007). Nasopharynx being not easily accessible, diagnosis is often delayed and the disease is in advanced stage at the time of presentation. Since complete surgical resection is impossible due to close proximity to base of skull, radiation therapy has been the mainstay of primary treatment and chemoradiation is the preferred approach for advanced stages. A concrete study on clinico - pathology of NPC with dietary, smoking and tobacco consumption history from this region has not been reported till date to the best of our knowledge.

The purpose of this study was to analyze the clinico-pathological pattern of NPC with dietary, smoking and tobacco consumption habits in the Northeastern region of India.

Materials and Methods

Regional Cancer Centre (RCC), Regional Institute of Medical Sciences (RIMS) is situated in Manipur state. It is the biggest referral Centre for the neighbouring Northeastern states in India i.e. Nagaland, Mizoram, and bordering Myanmar.

An approval from the institutional Ethics Committee for Research Involving Human Subjects was obtained before the study was conducted. Case notes of 200 patients who were registered as nasopharyngeal carcinomas(NPC) after histopathological confirmation in the RCC, RIMS during the period from July 2004 to July 2009 were reviewed for demographic data, findings of clinical history including dietary habit, smoking, consumption of tobacco in any form, physical examination, histopathological diagnosis, investigation reports, disease staging and follow-up records. All NPC were regrouped into three histopathological types according to the WHO 1991 classification. This classification consisted of Type I (Keratinizing squamous cell carcinoma), Type II (Differentiated non-keratinizing carcinoma) and Type III (Undifferentiated non-keratinizing carcinoma). Cases without histopathological biopsy confirmation were excluded. The treatment and presence of distant metastasis were noted. Treatment outcomes were assessed via hospital records and telephone interviews. The data were analyzed using SPSS14 and results were presented in percentage and simple frequency.

Results

There were 139 males and 61 females with male to female ratio 2.2:1. The ages ranged from 26 to 76 yrs. The mean age of presentation was 49.7 ± 10.7 yrs. The peak incidence in the males was in the 50 – 59 years age group (30.2 %) and in the 40 – 49 yrs age group (29.5%) in females. The number of patients begins to increase after age of 30years, reaches a peak between 50 and 59 years, then begins to decline, as shown in Figure 1.

In majority of patients (48.2%), presentation was within 3 months from onset of symptoms. The frequency of different presenting symptoms is listed in Table 1. The commonest presenting symptoms were neck swelling

Table 1. Presenting Symptoms and their Frequencies (n = 200)

Symptoms	No (%)	
Neck Swelling	156 (78.0)	
Nose	Bleeding	55 (27.5)
	Obstruction	71 (35.5)
	Discharge	11 (5.5)
Aural	Impairment of hearing	49 (24.5)
	Tinnitus	10 (5.0)
Headache	46 (23.0)	
Eye	Blindness	7 (3.5)
	Diplopia	5 (2.5)
	Squint	2 (1.0)
Facial Pain	7 (3.5)	
Dysphagia	16 (8.0)	
Hoarseness	6 (3.0)	
Others	20 (10.0)	

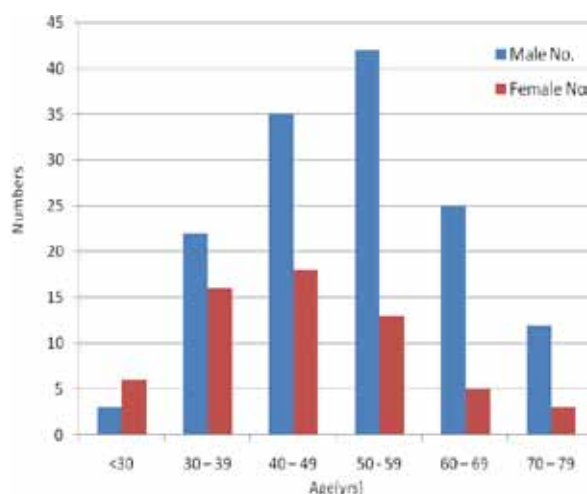


Figure 1. Age Distribution of NPC Cases

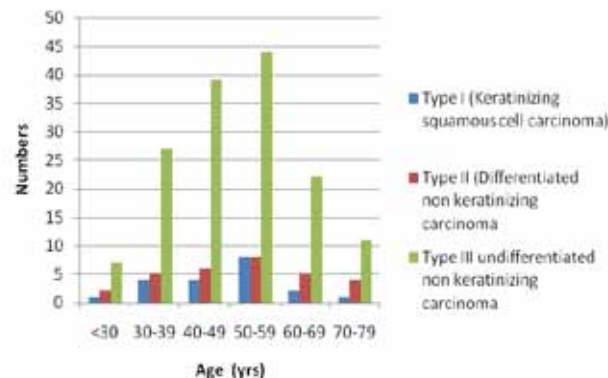


Figure 2. Age and Histopathology after the WHO Classification

(78.0%) followed by nasal obstruction (35.5%) and epistaxis (27.5%). The neck swellings were unilateral in 45% and bilateral in 42% of patients. Other symptoms were impairment of hearing (24.5%), headache (23.0%), dysphagia (8.0%) and nasal discharge (5.5%) respectively. The primary growth was found locating more frequently on the right lateral wall (23.0%) and left lateral wall (22.5%) compared with other subsites. The locations of the primary growths were not documented on the remaining 20 patients. The commonest histopathology observed was undifferentiated carcinoma (Type III, WHO) accounting for approximately 75.0 % of all histological types affecting

both young and elderly patients as shown in Figure 2. No patient had other histological types.

52 cases (25.0% of total patients) had cranial nerve (CN) lesions. One of 52 cases had bilateral VI and VII CNs involvement. Commonly the cranial nerve V was affected upto 28.8 % followed VI (26.9 %) and X (25.0%) cranial nerves respectively. The patients were staged according to the Tumor, Node, Metastasis (TNM) staging system. Only 28.5% of total patients presented in early stages and remaining patients (71.5%) in advanced stages. 46.7% of males and 36.0% of females were diagnosed in stage IV. 176 patients (88.0%) had history of regular intake of smoked meat while 124 patients (62.0%) admitted regular intake of poorly preserved fermented food. The minimum number of patients (19.0%) consumed fresh fruits (at least 4 times / month) but 47.0% of patients used tobacco in different forms. 102 patients (51.0%) were smoker at least for 10 years. 186 patients (93.0%) lived in poorly ventilated room with history of exposure to household smoke from burning fire wood. Of these 200 patients, only 180 patients (90.0%) completed curative treatment. We treated our patients with Cobalt-60 teletherapy machine. Cases in early stages (I-IIA) were treated by radiotherapy alone. Cisplatin and 5FU based chemotherapy was administered as adjuvant chemotherapy in addition to cisplatin 40mg/m² or carboplatin 150mg weekly as radiosensitizers during radiotherapy in locally advanced stages (IIB-IVA). No patient had surgery as definitive treatment except for residual neck node dissection after chemoradiation. 18 patients (10.0%) were lost to follow-up despite all attempts to trace them. 26 patients (15.9%) developed distant metastasis. The distant metastatic sites were in liver (46.1%), skeleton (30.7%) and lungs (23.0%) respectively. The mean follow-up was 45 months (range, 20- 68 months). The disease- free survival rate, survival with disease rate and overall survival rate were 41.0%, 13.0% and 54.0% respectively.

Discussion

The pattern of bimodal age distribution with peaks in age groups of 15-24yrs and 65-74yrs has been reported in low-risk populations (Bray et al., 2008). However, the pattern of age distribution in our study doesn't show any such bimodal pattern like earlier studies in this region (Kumar et al., 1996). Number of patients begins to increase after age of 30years, reaches a peak between 50 and 59 years, then begins to decline after 60 years in our present study similarly with studies in high-incidence areas in China (Parkin et al., 2005; Zong et al., 1983). One intriguing characteristic of North African NPC, concerning its bimodal age distribution with a secondary peak of incidence in the range of 15-25 years, is not observed in Asian NPC (Ayadi et al., 2010).

In different parts of the world, male preponderance over the females in most studies has been reported (Wei et al., 2007). Likewise, our study gives a male to female ratio of 2.2:1 similarly to those observations in Northeast states population based cancer registries 2006-2008 of National Cancer Registry program, India.

The mean duration of symptomatology before

presentation was 6 months (range: 15 days – 36 months) in our patients. Neck swelling (78.0%) followed by nasal obstruction (35.5%) were the common presenting symptoms in our patients. Percentages of neck swelling and epistaxis (27.5%) were similar to those findings of one study in Malaysia (Tiong et al., 2005). In that study, 17.0% and 36.0% of the patients had nasal block and hearing loss whereas in our present study, 35.5% and 24.5% of the patients presented the symptoms (Ayadi et al., 2010). Less number of our patients (10.0%) had neuro-ophthalmic manifestation compared to findings of a study in Nigeria where 60.0% of the patients presented the same manifestation (Tiong et al., 2005).

Non-keratinizing type particularly undifferentiated squamous cell type was the most common histopathological type in 75.0% of our patients followed by differentiated non-keratinizing carcinoma (15.0%) and keratinizing type (10.0%) which agrees with findings from high - incidence region of China where 84.6% of all histopathological types was non-keratinizing and keratinizing type was only in 5.8% of all NPC (Wei et al., 2007). The non-keratinizing type particularly undifferentiated histopathological type has the strongest association with EBV infection (McDermott et al, 2001; Zong et al., 2001; Chinese Cancer Registry, Annual report, 2006) and it is the dominant type found in children and adolescent. But, none of our patient is adolescent despite evidence reveals the association of EBV infection with NPC in patients of this region (Kumar et al., 2001). The undifferentiated type is more radiosensitive and less aggressive in behavior compared to other types.

More number of our patients (25.0%) had cranial nerve (CN) involvement in contrast to findings of one study by Huang W et al where involvement was in few patients (9.6%) (Huang et al., 2009). Cranial nerves V (28.8 %), VI (26.9%) and X(25.0%) were commonly found to be affected respectively in our patients which are different from findings of one study from China where cranial nerves V, VI and XII were involved in 38.0%, 26.0%, and 11.0% respectively (Li et al., 2006). Neuroophthalmic manifestation with symptoms such as ocular pain, double vision and loss of vision were also encountered similar to a study in Nigeria (Dunmade and Ademola-Popoola, 2008). The poorer neurologic outcome associated with a longer duration of CN symptoms may be related to a more severe long term CN compression that results in irreversible damage. Timely diagnosis and treatment are therefore critical to improving the neurologic outcome. Periods of cranial nerve involvement and the level of the recovery of cranial nerve involvement were significantly correlated with prognosis (Huang et al., 2009).

The commonest site for NPC to arise is the lateral wall (45.5%) followed by the roof with lateral wall (14.0%). Majority of our patients were diagnosed in advanced stages: N2 and N3 Nodal diseases in 26.0% and 27.5 % of patients respectively. Moreover, T3 and T4 primary diseases were presented in 20.0% and 26.5% of patients. This reflects lack of awareness about the disease in general population of this region. There lies the role of effective awareness programmes in our region for early diagnosis and early treatment. 24.3% of our patients had family

history of cancer. The primary sites were nasopharynx (8.1%), nasal cavity (2.7%), paranasal sinus (1.3%), lungs (2.7%), stomach (2.7%), unknown site (6.7%) respectively. The proportion of our patients with a family history of NPC is higher compared to those findings in the high-incidence areas Hong Kong (7.2.0%) and Guangzhou (5.9.0%) (Yu et al., 1986; Yu et al., 1990). More females (39.2%) were diagnosed in early stages compared to males (23.6%) in our study. The fact could be due to more cancer awareness and self-care among females than males.

In Northeastern region, smoked meat and smoked fish are widely eaten as main source of protein like salted fish in South East Asia. Few studies already had shown the carcinogenicity of smoked meat which contains nitrosamines like in salted fish. Moreover, association of regular smoked meat intake and NPC in this region has been reported. Maximum number of our patients (88.0%) had been taking smoked meat regularly since childhood. Therefore, in our patients, possibly regular intake of smoked meat could be a risk factor in majority of the patients.

Some 180 patients (90.0%) were found living in poorly ventilated overcrowded houses and they used firewood for cooking and warming the room thereby leads to daily exposure to smokes. Significant association of occupational exposure to smoke with NPC has already been reported (Armstrong et al., 1983). 102 patients (51.0%) were smokers and while 94 patients (47.0%) consumed tobacco in different forms. Though cigarette smoking and snuff (tobacco powder with additives) intake were significantly associated with NPC (differentiated squamous cell carcinoma) (Feng et al., 2009), percentage of patients (15.0%) with this type is less in our study despite high percentage of smoker and consumption of tobacco in different forms. Regular intake of fermented foods being a risk factor of NPC has been shown in one study (Yu et al., 1988). Majority of patients (62.0%) had history of taking poorly preserved fermented food regularly. The inefficiency of the preservation method might result in putrefaction accumulating carcinogens like nitrosamines, bacterial mutagens and EBV-reacting substances. Our study showed poor habit of fresh fruit intake among patients; never taken fruits in 16.0%, taken rarely in 40.0%, 1-4 times/month in 25.0% and at least 4 times/month in 19.0%. Findings has been reported how consumption of fresh fruit can significantly reduce the risk of NPC with a dose-dependent relationship (Jia et al., 2010; Farrow et al., 1998). More studies are needed to confirm more risk factors in this region.

Poor survival rate in our study could be due to more number of patients in advanced stage (71.5%), bigger nodal size >5cm (40.0%), multiple neck nodes (42.5%) at the time of presentation. Further studies to develop techniques for screening and early detection based on genetic, environmental and dietary factors are highly needed in this region.

In conclusion, this retrospective study shows high-incidence of NPC in Northeastern India. Age distribution, sex ratio, presenting symptoms and pattern of histopathology in our patients are similar to those findings in high-incidence areas of world. By improving

the awareness of this leading cancer, any further delay in presentation could be minimized. Early detection and early treatment to reduce the morbidity and mortality associated with NPC in addition to imparting awareness on how to prevent the disease to general population is the need of this region.

References

- Armstrong RW, Armstrong MJ, Mimi C Yu, Henderson BE (1983). Salted fish and inhalants as risk factors for nasopharyngeal carcinoma in Malaysian Chinese. *Cancer Res*, **43**, 2967-70.
- Ayadi W, Khabir A, Hadhri-Guiga B, et al (2010). North African and Southeast Asian nasopharyngeal carcinomas: between the resemblance and the dissemblance. *Bull Cancer*, **97**, 475-82.
- Bray F, Haugen M, Moger TA, et al (2008). Age-incidence curves of nasopharyngeal carcinoma worldwide: Bimodality in low-risk populations and aetiologic implications. *Cancer Epidemiol Biomarkers Prev*, **17**, 2356-65.
- Chelleng PK, Narain K, Das HK, Chetia M, Mahanta J (2000). Risk factors for cancer nasopharynx: a case-control study from Nagaland, India. *Natl Med J India*, **13**, 6-8.
- Chinese National office for Cancer Prevention and Control, Chinese National Cancer Registration Center, Bureau of Disease Prevention and Control of Chinese Health Ministry (2009), Chinese Cancer Registry Annual report (cancer incidence and mortality in Chinese cancer registration areas in 2006) [M]. Beijing: Military Medical Science Press, 15.
- Dunmade AD, Ademola-popoola DS (2008). Neuro-ophthalmic manifestation of nasopharyngeal carcinoma at Llorin: a five years review. *Negir J Clin Pract*, **11**, 376-8.
- Farrow DC, Vaughan TL, Berwick M, et al (1998). Diet and nasopharyngeal cancer in a low-risk population. *Int J Cancer*, **78**, 675-9.
- Feng BJ, M Khyatti, Ben-Ayoub W, et al (2009). Cannabis, tobacco and domestic fumes intake are associated with nasopharyngeal carcinoma in North Africa. *Br J Cancer*, **101**, 1207-12.
- Huang W, Mo H, Deng M, et al (2009). Relationship between cranial nerve involvement in nasopharyngeal carcinoma and the prognosis. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*, **23**, 964-7.
- Jia W, Luo X-Y, Feng B-J, et al (2010). Traditional Cantonese diet and nasopharyngeal carcinoma risk: a large-scale case-control study in Guangdong, China. *BMC Cancer*, **10**, 44.
- Kataki AC, Malcolm J, Simons et al (2011). Nasopharyngeal cancer in the Northeastern states of India. *Chinese J Cancer*, **30**, 106-12.
- Kumar S, Zinyu R, Chetia M, Dutta LP (1992). Genotoxic effect of smoked-dried meat extract in swiss albinos mice using sperm head shape abnormality test. *Cancer Lett*, **64**, 51-3.
- Kumar S, Zinyu R, Singh IKK, et al (1996). Studies on nasopharyngeal carcinoma with reference to the Northeastern region of India. *Ann Natl Acad Med Sci (India)*, **32**, 199.
- Kumar S, Wairagker NS, Mahanta J (2001). Demonstration of Epstein-Barr virus antibodies in serum of patients with nasopharyngeal carcinoma. *Indian J Cancer*, **8**, 72-5.
- Kumar S (2003). Epidemiological and etiological factors associated with nasopharyngeal carcinoma. *ICMR Bull*, **33**, 1-9.

- Li JC, Mayr NA, Yuh WT, Wang JZ, Jiang GL (2006). Cranial nerve involvement in nasopharyngeal carcinoma: response to radiotherapy and its clinical impact. *Ann Otol Rhinol Laryngol*, **115**, 340-5.
- McDermott AL, Dutta SN, Watkinson JC (2001). The aetiology of nasopharyngeal carcinoma. *Clin Otolaryngol*, **26**, 82-92.
- Parkin DM, Bray F, Ferlay J, et al (2005). Global cancer statistics, 2002. *CA Cancer J Clin*, **55**, 74-108.
- Sarkar S, Nagabhushan M, Soman CS, Tricker AR, Bhide SV (1989). Mutagenicity and carcinogenicity of smoked meat from Nagaland, a region of India prone to a high incidence of nasopharyngeal cancer. *Carcinogenesis*, **10**, 733-6.
- Singh I, Lyngdoh NC (2009-2010). Nasopharyngeal carcinoma-our experience in Regional Institute of Medical Sciences, Manipur. *Ann Otolaryngol Head Neck Surg*, **18**, 10-5.
- Tiong TS, Selva KS (2005). Clinical presentation of nasopharyngeal carcinoma in Sarawak Malaysia. *Med J Malaysia*, **60**, 624-8.
- Wei K, Xu Y, Liu J, Zhang W, Liang Z (2010). No incidence trends and no change in pathological proportions of nasopharyngeal carcinoma in Zhongshan in 1970-2007. *Asian Pacific J Cancer Prev*, **11**, 1595-9.
- Yu MC, Ho JH, Lai SH, et al (1986). Cantonese-style salted fish as a cause of nasopharyngeal carcinoma: report of a case-control study in Hong Kong. *Cancer Res*, **46**, 956-61.
- Yu MC, Mo C-C, Chong W-X, et al (1988). Preserved foods and nasopharyngeal carcinoma: A case-control study in Guangxi, China. *Cancer Res*, **48**, 1954-9.
- Yu MC, Garabrant DH, Huang TB, et al. Occupational and other non-dietary risk factors for nasopharyngeal carcinoma in Guangzhou, China. *Int J Cancer* 1990; 45(6):1033-39.
- Zong YS, Zhang RF, He SY, et al (1983). Histopathologic types and incidence of malignant nasopharyngeal tumors in Zhongshan country. *China Med J*, **96**, 511-6.
- Zong YS (2001). Advanced of research on nasopharyngeal carcinoma pathology. *Shi Yong Zhong Liu Za Zhi*, **16**, 1-3.