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Nasopharyngeal Carcinoma: an Enigmatic Tumor*

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Abstract

Tay W-L, Tan P-H, Yip GW-C, Bay B-H. *Nasopharyngeal Carcinoma: an Enigmatic Tumor. ARBS Annu Rev Biomed Sci* 2008;10:27-35. Nasopharyngeal cancer (NPC) is endemic in Southern China and South East Asia but is rare in the West. Men have a two to three times higher risk of developing the disease than women. NPC has been classified by the World Health Organization (WHO) into three categories based on the degree of differentiation, with WHO Type 3 being the most common histopathological type in endemic areas. The multifactorial etiologies of NPC include genetic predisposition, Epstein-Barr virus (EBV) infection, and environmental and dietary factors. Genetic linkage or association studies have demonstrated a correlation between the human Histocompatibility Leukocyte Antigen (HLA) haplotype and NPC susceptibility. Higher EBV antibody titers have been observed in most patients with undifferentiated NPC compared with normal controls. Consumption of salted fish containing volatile nitrosamines, especially during childhood, has been implicated as a possible factor contributing to NPC. The most common presenting symptom is enlarged cervical lymph nodes and patients may also have nasal, otological and neurological symptoms. Radiotherapy remains the main modality of treatment for this cancer.

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Keywords: nasopharyngeal cancer, etiology, epidemiology, histopathology, clinical management

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1. Introduction

The nasopharynx is a thumb sized space located behind the nasal cavity and above the oropharynx, which is lined by pseudostratified ciliated respiratory epithelium (Fig. 1).

Nasopharyngeal carcinoma (NPC), a tumor of epithelial origin, typically originates in the pharyngeal recess of the nasopharynx (also known as fossa of Rosenmuller). NPC is an enigmatic tumor with a great disparity in incidence throughout the world and a distinct multifactorial etiology, which include genetic predisposition, Epstein-Barr virus (EBV) infection, and exposure to environmental and dietary carcinogens. This mini-review will explore the different facets of NPC such as histopathology, epidemiology, etiology, clinical presentation, diagnosis and therapy.

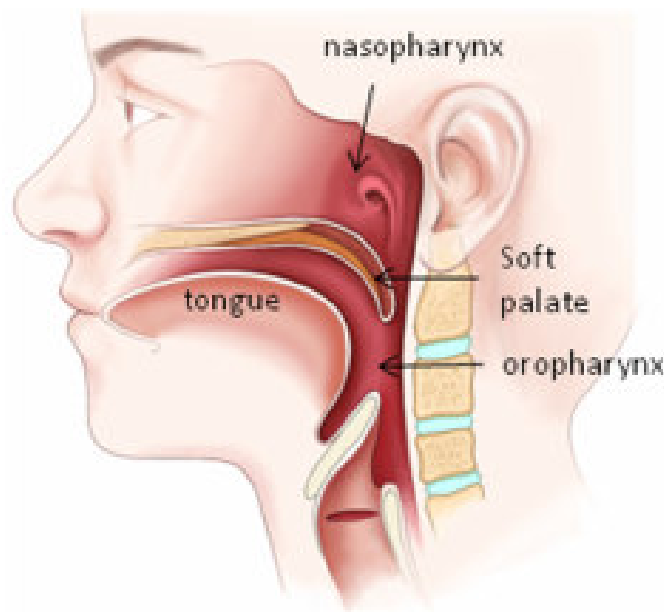


Figure 1. Anatomical location of the human nasopharynx and surrounding structures.

2. Histopathological Classification of NPC

NPC has been classified by the World Health Organization (WHO) into three categories based on the degree of differentiation, *viz* keratinizing squamous cell carcinoma (WHO Type 1), and nonkeratinizing carcinoma that is further subdivided into the differentiated subtype (WHO Type 2) and undifferentiated subtype (WHO Type 3). WHO Type 3 NPC, the most common histopathological type in endemic areas such as Southern China where it accounts for more than 97% of NPC cases, is also

known as lymphoepithelioma because of a prominent lymphocytic infiltrate (Fig. 2). On the other hand, WHO Type 1 NPC is more prevalent in Western countries where it accounts for up to 50% of NPC diagnosed but less than 5% in endemic areas (Marks *et al.*, 1998; Lo *et al.*, 2004).

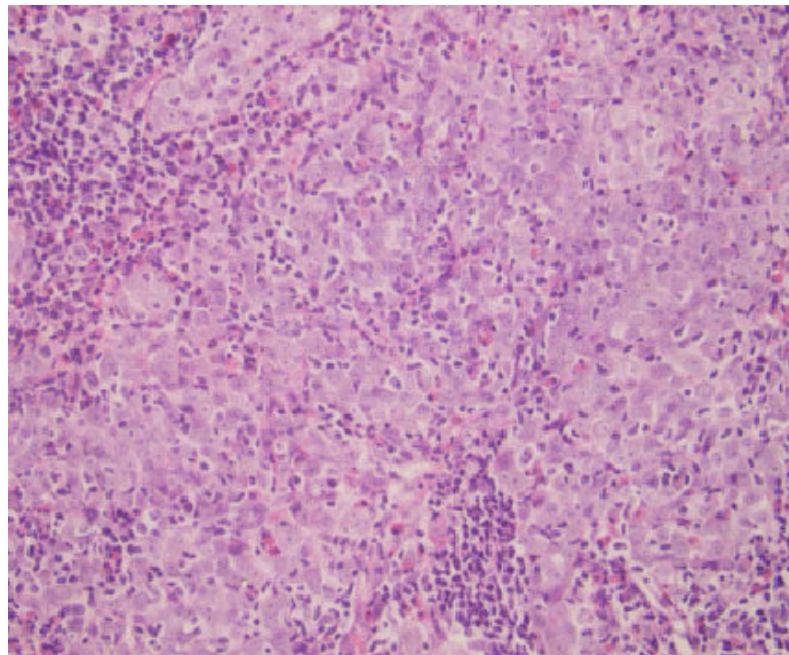


Figure 2. Nonkeratinizing nasopharyngeal carcinoma, undifferentiated subtype (WHO Type 3) characterized by a lack of keratinization and the presence of nests of cells with large, round to oval vesicular nuclei and prominent nucleoli and a rich lymphocytic infiltrate. (H & E stain, Magnification 400X.)

3. Epidemiology

In 2000, 64,798 new NPC cases and 38,000 NPC-related deaths were reported worldwide, with more than 80% of patients from China, Southeast Asia and other Asian countries (Ferlay *et al.*, 2001). WHO Types 2 and 3 NPC are endemic in southern parts of China, especially in people of Cantonese origin. Areas with intermediate incidences of NPC include Southeast Asia, North Africa, Alaska, Greenland and the Mediterranean basin (Chan *et al.*, 2002; Yu & Yuan, 2002). Within the high-risk populations, there is a significant heterogeneity among ethnic lineages. NPC is rare in other parts of the world, with sporadic cases occurring in America and Europe. These cases are usually WHO Type 1 NPC and are related to exposure to risk factors such as alcohol and tobacco (Henderson *et al.*, 1976).

Early age of onset of NPC is observed in endemic regions and men have a two to three times higher risk of the disease than their female counterparts (Yu & Yuan, 2002). The sex ratio differs in various populations, with a male: female ratio of 2.8:1 in Singaporean Chinese and 2.5:1 among the Chinese in Hong Kong (Ho, 1967; Seow *et al.*, 2004). There has been a decrease in NPC incidences in countries such as Hong Kong, which could be attributed to changes in environmental risk factors (Lee *et al.*, 2003).

4. Etiology

4.1. Epstein-Barr virus (EBV)

The EBV is known to infect nasopharyngeal epithelial cells through cell-cell contact with B lymphocytes carrying EBV or via a polymeric IgA-mediated mechanism (Speck *et al.*, 2000). Higher

antibody titers, especially IgA, against the EBV diffuse form of the early antigen, viral capsid antigen, membrane antigen, virus-encoded DNase and DNA polymerase have been observed in most patients with undifferentiated NPC compared with normal controls (Chan *et al.*, 2005b). Furthermore, the EBV genome in the form of a clonal episome is detected in the nuclei of all malignant cells of undifferentiated NPC and in cells of preinvasive nasopharyngeal lesions but seldom in the adjacent normal nasopharyngeal epithelium or in low-grade dysplastic lesions (Pathmanathan *et al.*, 1995). It would appear that EBV infection occurs early in NPC development (Raab-Traub, 2002). The expression of EBV latent genes may alter multiple signaling pathways and thus play a role in malignant transformation of nasopharyngeal epithelial cells (Dolcetti & Menezes, 2003).

4.2. Genetic susceptibility

NPC incidence is characterized by a distinct geographical distribution which suggests the contribution of genetic predisposition to this disease. Familial clustering has also been frequently reported (Zhang & Zhang, 1999). Furthermore, the risk of developing NPC in migrants originating from high-incidence areas does not diminish (Li *et al.*, 1983; Grulich *et al.*, 1995). Linkage or association studies have demonstrated a correlation between the HLA haplotype and NPC susceptibility (Lu *et al.*, 1990, 2003). It has been hypothesized that certain HLA antigens have lower efficiency in activating the cytotoxic T cell recognition and host immune response to EBV infection (Lo *et al.*, 2004). In particular, HLA-A2, Aw19, A2-B46, B17, and haplotypes A2-B17, A2-B38, A2-B16 and Aw19 B17 are associated with increased risk of NPC while A11, B13 and B22 have a negative correlation with the risk of NPC (Chan *et al.*, 1983; 1985; Wu *et al.*, 1989; Lu *et al.*, 1990; 2003; Hildesheim *et al.*, 1997; Goldsmith *et al.*, 2002). Hirunsatit *et al.* (2003) have also reported that a single nucleotide polymorphism (SNP) (1739C → T) on exon 7 at position 1739 correlates with increased risk of NPC by altering the efficiency of releasing IgA-EBV complex and thus increasing the possibility of infection of nasopharyngeal epithelial cells with EBV. (The polymeric immunoglobulin receptor on nasopharyngeal epithelial cells mediates entry of EBV into the nasopharyngeal epithelium by endocytosis and transcytosis of IgA-EBV complexes). A recent finding has shown that polymorphisms or haplotype in the MMP2 promoter could possibly play a role in mediating susceptibility to NPC in Chinese populations (Zhou *et al.*, 2007). As for the observation that NPC is more common in males than females, a gender association between exon5 of the MICA gene which increases susceptibility to NPC has been observed (Tian *et al.*, 2006).

4.3. Environmental factors

The consumption of Cantonese-style salted fish especially during childhood has long been implicated as a possible factor contributing to NPC in South China (Henderson *et al.*, 1976; Yu *et al.*, 1986; Yu & Yuan, 2002). Several carcinogenic volatile nitrosamines have been detected in salted fish which may induce genetic damage in nasopharyngeal epithelial cells (Lo *et al.*, 2004). The use of Chinese medicinal herbs has been proposed to increase the risk for NPC by reactivating EBV infection in the host or through a direct promoting effect on EBV-transformed cells (Hildesheim *et al.*, 1992; Lo *et al.*, 2004). Cigarette smoking, occupational exposure to smoke, chemical fumes, wood dust, formaldehyde and exposure to radiation are other purported risk factors (Yu *et al.*, 1990; Armstrong *et al.*, 2000; Hildesheim *et al.*, 2001). Although formaldehyde has been classified as a carcinogen and linked with NPC, this has been challenged by some investigators (Marsh & Youk, 2005; Marsh *et al.*, 2007).

5. Clinical presentation

The most common presenting symptom is cervical lymphadenopathy, which is largely due to the abundant drainage by regional lymphatic vessels from the nasopharynx to the cervical lymph nodes. Clinically, nasal and otological symptoms include nose bleed, stuffy nose with blood drainage, serous otitis media, tinnitus and hearing loss (Vokes *et al.*, 1993; Altun *et al.*, 1995). The disease may also spread locally to the oropharynx giving rise to blood tinged sputum or to the skull base resulting in

cranial nerve paralyses. The most common sites of haematogenous deposits are the bone, lung, liver and distant nodes in decreasing order of frequency (Teo *et al.*, 1996).

6. Diagnosis and Staging

Diagnosis and staging methods include a thorough physical examination with direct visualization of the nasopharynx using a fiber optic nasopharyngoscope followed by endoscopy under anesthesia with biopsy sampling from gross lesions. Computed tomography (CT) scans and magnetic resonance imaging (MRI) are used to define the extent of primary tumor and lymph node involvement. Distant metastasis is detected via liver ultrasound and/or CT scan, thoracic CT scan, isotope bone scan and positron emission tomography coupled with CT (PET-CT). EBV serology has been proven useful in detecting preclinical NPC in endemic regions and prediction of recurrences after therapy (Zeng *et al.*, 1985; Dolcetti & Menezes, 2003; Lo *et al.*, 2004). IgA against viral capsid antigen and IgG/IgA against early antigens are used most widely, with detection rates ranging from 69-93% (Chan *et al.*, 2005b). Another approach is to assay for elevated levels of circulating EBV DNA or RNA in the plasma or serum by quantitative PCR with a reported sensitivity of up to 96% (Lo *et al.*, 1999; Shotelersuk *et al.*, 2000; Chan & Lo, 2002). Quantification of plasma EBV DNA has been found to be useful for monitoring NPC patients and predicting treatment outcome. (Lin *et al.*, 2004). Development of EBV serological markers for seropidemiological screening are actively in progress (Fachiroh *et al.*, 2006).

The American Joint Committee on Cancer (AJCC) Nasopharynx Staging System has been developed specifically for NPC and is the most common classification used in most countries. Using the AJCC system which incorporates the TNM classification (T1-T4, N0-N3 and M0-M1 where T is primary tumor, N is regional lymph node involvement and M is distant metastasis), NPC is staged as Stage I-IV.

7. Treatment

Radiation therapy is the mainstay of treatment for locally and regionally confined stages of NPC (Lee, 2003). A dose of 70 to 75 Gray units is administered to most patients over a period of 7 to 8 weeks to the primary tumor and regional lymph nodes. Both WHO Type 2 and 3 NPCs are generally more radiosensitive and have a higher local control rate after radiotherapy than WHO Type 1, but they are also more likely to undergo distant metastasis (Reddy *et al.*, 1995). Although NPC has remarkable radiosensitivity and chemosensitivity at the early stages of treatment due to p53 functionality and retention of clonality, there is usually resistance to these treatment modalities in more advanced stages of NPC. Intensity-modulated radiotherapy (IMRT) provides superior local control and delineation of tumor target volume, sparing the adjacent vital organs. Thus, it has replaced conventional radiotherapy in centers where the technology is available (Teo & Chan, 2002). In addition, intracavitary radiation and external-beam therapy may improve local control (Wang, 1991). Interestingly, a recent report showed that Chinese NPC patients had lower risks of overall mortality compared with non-Hispanic White patients after controlling for factors which include histology grade, tumor stage and use of radiotherapy (Sun *et al.*, 2007).

Radiotherapy has been integrated with chemotherapy to improve survival rates in patients with large primary tumors (T3 or T4) or nodal involvement (N1-N3) but without systemic metastasis (Chan *et al.*, 2005a). Cisplatin, a cytotoxic agent and radiation sensitizer, is often used in combination with fluorouracil or bleomycin and an anthracycline (Vokes *et al.*, 1993; Altun *et al.*, 1995). Kawashima *et al.* (2004) have reported that concurrent platinum-based chemoradiotherapy is superior over radiotherapy alone in patients with node-positive or T3/4 disease in terms of survival. Chua *et al.*, (2005) observed that addition of cisplatin-based induction chemotherapy to radiotherapy was associated with a significant reduction in the relapse rate but not overall survival in patients with advanced-stage NPC. In another study by Wee *et al.* (2005), chemotherapy in conjunction with radiotherapy was found to improve the distant metastasis control rate in NPC patients,

In general, radiotherapy is used for early disease and concurrent chemotherapy-radiotherapy in locally advanced NPC (Teo & Chan, 2002). However, it must also be borne in mind that severe acute

adverse events and poor patient compliance may occur during concurrent chemoradiotherapy protocol (Isobe *et al.*, 2003). Plasma EBV DNA has recently been found to be the most valuable prognostic factor for NPC patients receiving concurrent chemoradiotherapy (Lin *et al.*, 2007). Most patients with metastatic or recurrent NPC are usually treated with cisplatin-based combination chemotherapy for symptom control and extension of survival time (Boussen *et al.*, 1991; Altun *et al.*, 1995).

Due to the complex anatomical location of the disease, surgery is usually not used. However, lymph node dissection in the neck can be performed in patients with bulky N2 or N3 disease (Busson *et al.*, 2004) or if the cancer persists or recurs in the cervical lymph nodes after radiotherapy (Wang, 1987; Lee *et al.*, 1997). If the residual or recurrent tumor in the nasopharynx is too large or has invaded into the paranasopharyngeal space, nasopharyngectomy may be performed.

8. Concluding Remarks

As NPC occurs in selective populations and is mostly absent in the West, much is still not known about this enigmatic cancer. However, research has intensified with regard to improving early diagnosis and therapy for this cancer. This tumor frequently affects individuals who are actively contributing to the economy and who often have young families. Therefore, the challenges facing Ear, Nose and Throat surgeons, pathologists, medical and radiation oncologists are early diagnosis of NPC before the onset of cervical lymphadenopathy (indicating regional spread) and improvement in treatment modalities so as to reduce radioresistance especially in the more advanced cases.

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