INTRODUCTION
Cancer begins when cells in a part of the body start to grow out of control. There are many kinds of cancer, but they all start because of out-of-control growth of abnormal cells. Cancer cell growth is different from normal cell growth. Instead of dying, cancer cells continue to grow and form new, abnormal cells. Cancer cells can also invade other tissues, something that normal cells cannot do. In most cases, the cancer cells form a tumor. Some cancers, like leukemia, rarely form tumors. Instead, these cancer cells involve the blood and blood-forming organs and circulate through other tissues where they grow. Metastasis happens when the cancer cells get into the bloodstream or lymph vessels of our body. No matter where a cancer may spread, it is always named for the place where it started. Nasopharyngeal cancer is a cancer that starts in the nasopharynx, the upper part of the throat behind the nose and near the base of the skull. Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma (SCC) that usually develops around the ostium of the Eustachian tube in the lateral wall of the nasopharynx. The World Health Organization classifies NPC into three histopathological types based on the degree of differentiation. In endemic regions, NPC presents as a complex disease caused by an interaction of the oncogenic gamma herpes virus EBV chronic infection, environmental, and genetic factors, in a multistep carcinogenic process. The most common presenting symptom is cervical lymphadenopathy, followed by nasal, aural and neurological symptoms. Once the diagnosis is suspected on clinical grounds, histological confirmation of the diagnosis is mandatory. Radiotherapy is the mainstay treatment for early disease and concurrent cisplatin/radiotherapy has been demonstrated to prolong survival in locoregionally advanced disease. Ongoing studies of targeting agents and immunotherapeutic approaches may further improve treatment results.

HISTOLOGICAL SUBTYPES OF NPC
The World Health Organization classifies NPC into three histopathological types based on the degree of differentiation. Type 1, SCC, is seen in 5%–10% of cases of NPC and is characterized by well-differentiated cells that produce keratin and demonstrated the presence of intracellular bridges when observed under the electron microscope. Type 2, nonkeratinizing squamous carcinoma, varies in cell differentiation but does not produce keratin. Type 3 or undifferentiated NPC constitutes the bulk of the tumors seen in patients with NPC, is also nonkeratinizing, but is less differentiated, with highly variable cell types.
2. Types 2 and 3 NPC are Epstein–Barr virus (EBV) associated and have better prognoses than type 1; EBV infection is generally absent in type 1, especially in nonendemic areas. However, more recent data suggest that almost all NPC tumors in the endemic areas, regardless of histologic subtype, have comorbid EBV infections, which is a strong evidence for EBV as the etiology of NPC. Undifferentiated NPC or type 3 was frequently characterized as lymphoepithelioma owing to the heavy infiltration of the primary tumor with lymphocytes.

ETIOLOGIES AND PATHOGENESIS
In endemic regions, NPC presents as a complex disease caused by an interaction of the oncogenic gamma herpes virus EBV chronic infection, environmental, and genetic factors, in a multistep carcinogenic process.

GENETIC FACTORS
While nasopharyngeal carcinoma is a rare malignancy in most parts of the world, it is one of the most common cancers in Southeast Asia including areas such as Southern China, Hong Kong, Singapore, Malaysia, and Taiwan. The familial risk of NPC is among the highest of any malignancy. The described relative risk of NPC in first-degree relatives is about 8.0. An important characteristic of familial cancers is the early age onset of NPC. Several linkage analyses studies suggested the association of susceptibility human leukocyte antigen (HLA) haplotypes with NPC development. The finding of translocation, amplification, and deletion of 3p, 5p, and 3q indicates that a minimal region of breakpoints is possible for contributing to NPC. Breakpoints have been frequently observed in 1p11–31, 3p12–21, 3q25, 5q31, 11q13, 12q13, and Xq25. Inactivation of tumorsuppressor genes on 3p, 9p, 13q, 14q, and 16q and alteration of oncogenes on chromosomes 8 and 12 are important in the development of NPC. Some studies suggested that genetic polymorphisms in genes that metabolize carcinogens are associated with NPC susceptibility.

ENVIRONMENTAL FACTORS
A large number of case-control studies conducted in diverse populations (Cantonese, other Southern Chinese, Northern Chinese, and Thais) residing in different parts of Asia and North America have confirmed that Cantonese-style salted fish and other preserved foods containing large amounts of nitrosodimethyamine (NDMA), N-nitrospyrrolidene (NPR), and N-nitropriperidine (NP) may be carcinogenic factors for NPC. Moreover, cigarette smoking and occupational exposure to formaldehyde and wood dust are recognized risk factors as well. Several studies conducted in high- and low-risk populations during the past decade have obviously implicated the nasopharynx as a tobacco susceptible cancer site.

EPSTEIN–BARR VIRUS
It was in 1966 when Old et al. first discovered the relationship between EBV and NPC, using in situ hybridization and the anti-complement immune fluorescent assay. Subsequent studies by others demonstrated the expression of EBV latent genes – Epstein–Barr virus nuclear antigen, latent membrane protein-1 (LMP-1), LMP-2, and EBV-encoded small RNAs (EBER) – in NPC cells confirming the infection of tumor cells by EBV. Intriguingly, expression of EBV early antigen (EA) is positively correlated with the consumption of salted and preserved food, suggesting that development of EBV-positive NPC could be related to dietary habits, and provides another link to the epidemiological studies with NPC.

PRESENTATION, IMAGING AND STAGING
The most common presenting symptom is cervical lymphadenopathy, followed by nasal, aural and neurological symptoms. Only 5% of patients present with distant metastases in series from Southern China. Once the diagnosis is suspected on clinical grounds, histological confirmation of the diagnosis is mandatory. The technique of biopsy under local anesthesia has been found to have a diagnostic sensitivity comparable to that obtained by examination under general anesthesia. The biopsy is facilitated by direct visualization of the nasopharynx with a fiberoptic nasopharyngoscope. However, since the biopsy may cause soft tissue swelling and/or hematomata, computed tomography scan and magnetic resonance imaging of the nasopharynx and the skull base should be undertaken before the biopsy. The primary tumor extent should be evaluated by both CT scan and MRI. The latter is more sensitive than CT scan for the detection of the primary tumor, its direct soft tissue extent, regional nodal metastasis and perineural extension. Blood vessels are clearly shown by MRI even without the use of intravenous contrast. On the other hand, although MRI can also demonstrate erosion...
into the base of the skull by virtue of the change in signal of fatty bone marrow, CT scan is generally considered a better tool for defining bone erosion. The role of positron emission tomography scanning in NPC remains to be defined, although preliminary reports indicate that it can be useful in detecting both local failures after treatment and distant metastases.

Prior to 1997, several different stage classifications were used but that described by Ho\textsuperscript{10} was found to be superior to the others in its ability to predict prognosis and treatment outcome\textsuperscript{11}. However, Ho’s classification was not ideal as an international system because it comprised five overall stages, there were only three T-stages and it did not take into account CT scan evidence of tumor infiltration of the parapharyngeal region, a factor of considerable prognostic significance.

The demonstration that tumor-derived DNA is detectable in the plasma and serum of cancer patients raised the possibility that non-invasive detection and monitoring of NPC may be feasible. Using real-time quantitative PCR, cell-free EBV-DNA was found in the plasma of 96% of NPC patients and 7% of controls. Advanced-stage NPC patients had higher plasma EBV-DNA levels than tumors with early-stage disease\textsuperscript{12}. Further studies have demonstrated that EBV-DNA may be a valuable tool for monitoring NPC patient response during radiotherapy and chemotherapy, as well as early detection of tumor recurrence.

**MANAGEMENT**

With advances in technology, the modern radiotherapy for NPC should be that of three-dimensional conformal or intensity-modulated with inverse radiotherapy planning. Researchers at the University of Californian at San Francisco, Stanford University, University of Texas M.D. Anderson and Memorial Sloan–Kettering Cancer Centers have reported superior local control using such techniques when compared with standard 2D methods. First, the success of 3DCRT or IMRT depends on better delineation of the tumor target by CT scan and MRI, images of which can be co-registered, such that ‘geographical misses’ are largely avoided. Second, there is a clear definition of the vital organs in the vicinity of the NPC such that these organs are spared a heavy radiation dose, thus minimizing complications. In general the clinical target volume should include the whole GTV and the structures in the vicinity of the tumor, which are at substantial risk of subclinical infiltration. The sphenoid floor, the medial aspect of the greater wings of the sphenoid, the vomer, the posterior choanae, the pterygoid plates, the pterygopalatine fossa, the posterior wall of the maxillary sinus, the parapharyngeal spaces bilaterally\textsuperscript{13} and the prevertebral muscles and fascia are all at risk of tumor infiltration and should be included in the CTV.

**ALTERED FRACTIONATION**

In addition to improved radiotherapy techniques, use of altered fractionation and radiation dose escalation have been reported to improve the local control. Although a Radiation Therapy Oncology Group trial has proved the superiority of both concomitant boost and hyperfractionation over the conventional daily fractionation for head and neck cancers in general, the benefit for NPC has not been addressed specifically. Subgroup analysis for NPC was not possible in the RTOG trial due to the small numbers of NPC cases.

**COMBINED MODALITY TREATMENT FOR LOCO REGIONALLY ADVANCED DISEASE**

Although the initial remission rate is substantial with radiotherapy alone even in locoregionally advanced, UICC stages III and IV disease, the subsequent rates of both local and distant failures are high. Since NPC is highly chemosensitive, efforts have been made to incorporate chemotherapy into the primary treatment of the disease.

**CONCURRENT CHEMORADIOThERAPY**

Complete remission rates of locoregionally advanced disease to concurrent cisplatin radiotherapy in head and neck cancers, including NPC, were high and the early relapse-free survival rates were promising.\textsuperscript{14} Cisplatin acts both as a cytotoxic agent and as a radiation sensitizer. The optimal scheduling of cisplatin and radiation has not yet been established, but daily low dose, weekly intermediate dose or 3-weekly high doseregimens have all been used.

**TREATMENT FOR DISTANT METASTASES**

The median survival for patients with distant metastases is around 9 months. Several chemotherapeutic agents have been used in the treatment of patients with locally recurrent and metastatic NPC. Older agents including methotrexate, bleomycin, 5-FU, cisplatin and
carboplatin are the most active agents, with response rates varying from 15% to 31%. Newer active agents include paclitaxel and gemcitabine with single agent response rates of 22 and 49%, respectively.

CONCLUSION
Nasopharyngeal carcinoma is a squamous cell carcinoma that usually develops around the ostium of the Eustachian tube in the lateral wall of the nasopharynx. In endemic regions, NPC presents as a complex disease caused by an interaction of the oncogenic gamma herpesvirus EBV chronic infection, environmental, and genetic factors, in a multistep carcinogenic process. Radiotherapy is the mainstay treatment for early disease and concurrent cisplatin/radiotherapy has been demonstrated to prolong survival in locoregionally advanced disease. Ongoing studies of targeting agents and immunotherapeutic approaches may further improve treatment results.

REFERENCES

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