REVIEW ARTICLE

RECENT UPDATES IN THE MANAGEMENT OF NASOPHARYNGEAL CARCINOMA

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Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor arising from the nasopharyngeal mucosal lining.[1] Nasopharyngeal carcinoma and other epithelial head and neck tumors differ significantly, despite originating from similar cell lineages.

NPC is a rare kind of cancer compared to other cancers, and it has a very unusual geographic distribution. NPC is rare in the Western world and more prevalent in Asia, with more than 70% of new cases being recorded in East and Southeast Asia.[2]

In order to provide the best oncological and functional outcomes for our patients, this article will provide an overview of the care of nasopharyngeal cancer, discussing current developments and the critical role of multidisciplinary teams.

Nasopharyngeal cancer has a distinctive racial and geographic distribution, which points to a multifactorial cause. There are currently at least three key etiologic variables identified by epidemiologic and experimental data: Genetic susceptibility, environment, and virus. NPC is an uncommon tumor in most parts of the world. With around 3,200 cases annually in the United States (0.5-2 per 100,000). It is endemic in South China, Hong Kong, Southeast Asia, North Africa with rates around 25 per 100,000. It is relatively more core common in males (2.3:1 ratio).[3]

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A bimodal age distribution is observed in low-risk populations. The first peak incidence arises between 15 and 25 years of age, with the second peak at 50 and 59 years of age. 4 In endemic areas, incidence is shown to peak at 50 to 59 years of age Nasopharyngeal cancer is quite prevalent in Southern Chinese and populations of Southern Chinese ancestry, which may be due in part to a hereditary vulnerability. Several HLA Haplotypes are associated with increased genetic susceptibility; HLA Haplotypes (A2, B46 and B17).[5]

The high consumption of salted fish in Southern China has been implicated as an important environmental factor.[6] Salted fish releases volatile nitrosamines that are carried by steam and distributed over the nasopharyngeal mucosa.

Other environmental etiologic factors include alcohol consumption and exposure to dust, fumes, formaldehyde, and cigarette smoke, diet low in fruits/vegetables

Regardless of ethnicity or location, the Epstein-Barr virus (EBV) has been linked to nasopharyngeal cancer, especially the nonkeratinizing variety.[7]

EBV levels are higher in premalignant lesions of the nasopharyngeal epithelium, which suggests that EBV infection may have an impact on the early stages of carcinogenesis in NPC.

PATHOLOGY:

WHO classification divides NPC into three groups:[8]
Keratinizing squamous cell carcinoma which correlates to WHO type I and is associated with smoking and occasionally HPV
Non-keratinizing which is further subdivided into

Differentiated:
WHO type II (transitional cell carcinoma)

Undifferentiated:
WHO type III (lymphoepithelial carcinoma)
Endemic
Associated with EBV
Most favorable prognosis

Basaloid squamous cell carcinoma which has an aggressive clinical course and poor survival.
A miscellaneous group of malignant tumors includes melanoma, plasmacytoma, juvenile angiofibroma, carcinosarcoma, sarcomas, nonchromaffin paragangliomas and minor salivary gland tumors.

CLINICAL PRESENTATION:

A neck mass is the most common presenting symptom. Other symptoms include epistaxis, nasal obstruction and discharge. Serous otitis media and hearing loss, headaches, diplopia, or numbness in the face due to CN V and VI palsy.[9]
Cervical lymphadenopathy is present in up to 87% of patients.[10]
There are several syndromes that are associated with NPC due to invasion of critical structures in proximity. These include:

JACODS SYNDROME: Due to cavernous Sinus invasion leading to CN II to VI compression causing ophthalmoplegia, blindness and trigeminal neuralgia.

HORNERS SYNDROME: Cervical sympathetic chain involvement leading to ptosis, anhidrosis and miosis.

VILLARET SYNDROME: Lateral RPN compression on CN IX to XII. Dysphonia, dysphagia, paralysis of soft palate

VERNET SYNDROME / JUGULAR FORAMEN SYNDROME: Invasion of jugular foramen leading to paresis of CN IX to XII. Leading to Shoulder pain, aspiration, loss of gag reflex, vocal cord paralysis, trapezius atrophy, deviation of uvula and tongue on protrusion.

TROTTER S TRIAD: Sinus of Morgagni invasion leading to Ipsilateral palatal paralysis, conductive deafness and temporo-parietal Neuralgia.

DIAGNOSTIC WORKUP:

History and Physical examination: With comprehensive neck palpation, cranial nerve testing, auscultation of the chest, palpation of the abdomen for potential liver involvement, and percussion of the spine and bones for potential bone metastasis should all be included in a thorough physical examination.
Followed by Pan-endoscopy and Biopsy.
Pre-treatment routine labs include CBC and CMP. EBV DNA titers have a prognostic implication.[11]
Pre-Treatment Workup include dental, nutritional, speech and swallowing, and audiology, ophthalmologic and endocrine evaluation as clinically indicated.
The three imaging modalities that are currently most

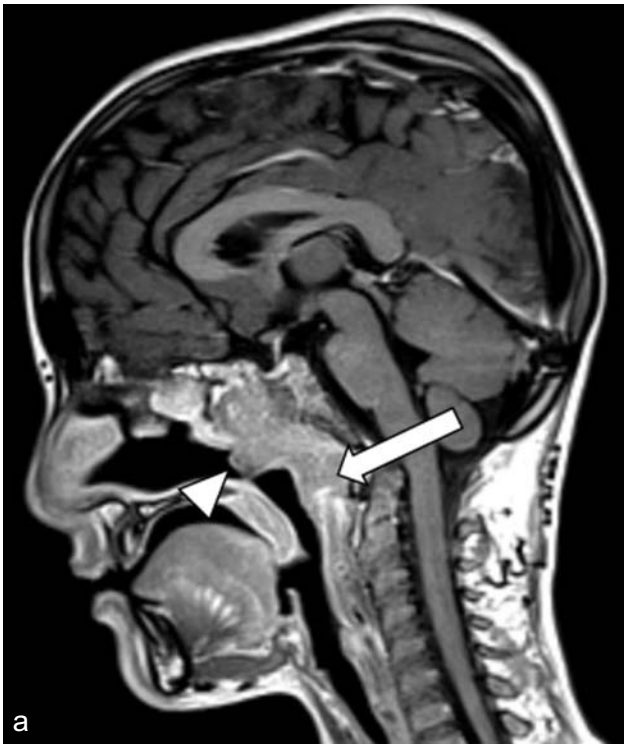


Figure 1a: Sagittal T1-weighted image after IV gadolinium administration through the head and neck showing enhancing soft tissue thickening (arrow) almost completely obliterating the nasopharynx (arrowhead).

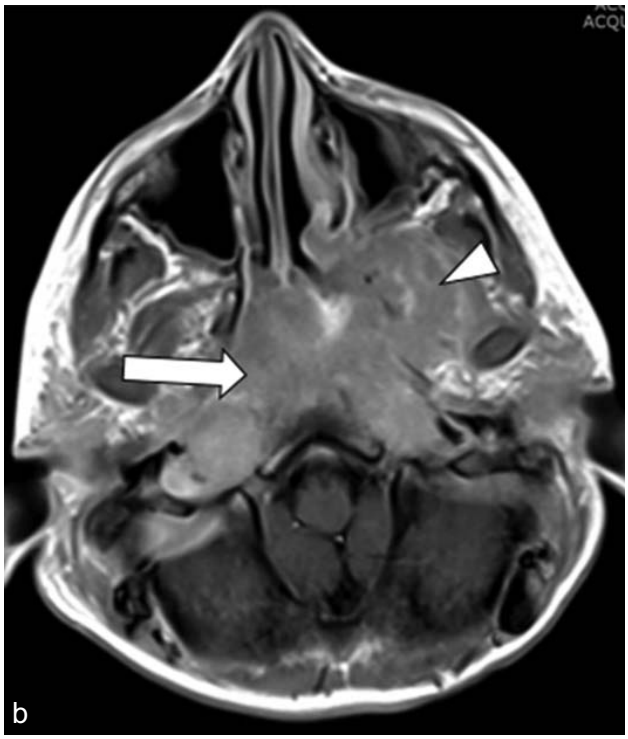


Figure 1b: Axial T1-weighted image after IV gadolinium administration through the skull base showing enhancing soft tissue infiltrating the base of skull (arrow) and left infratemporal fossa (arrow head).

frequently utilized for nasopharyngeal cancer staging and treatment are MRI, CT, and ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET/CT.

High soft-tissue resolution in MRI makes it superior to CT for assessing original tumor extension and retropharyngeal lymph node metastasis, but they share similar accuracy in detecting cervical lymph node metastasis.

Magnetic resonance imaging (MRI) of the nasopharynx, skull base, and neckwith cranial nerve imaging is indicated to assess for skull base involvement.

ROLE OF PET SCAN IN NPC:

FDG PET/CT is a valuable imaging tool in the diagnosis and management of nasopharyngeal carcinoma. It helps in accurate staging which enables the treating oncologists to devise an appropriate treatment plan.[12] Moreover, it helps in radiation therapy planning, provides valuable prognostic information, and is useful in the evaluation of therapy response and in detecting disease recurrences.

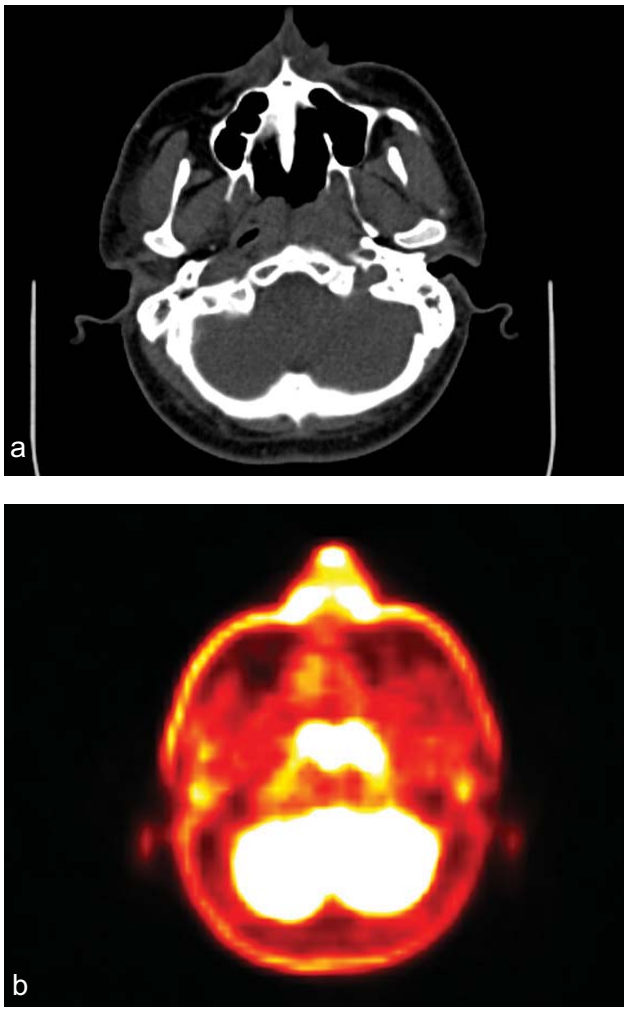
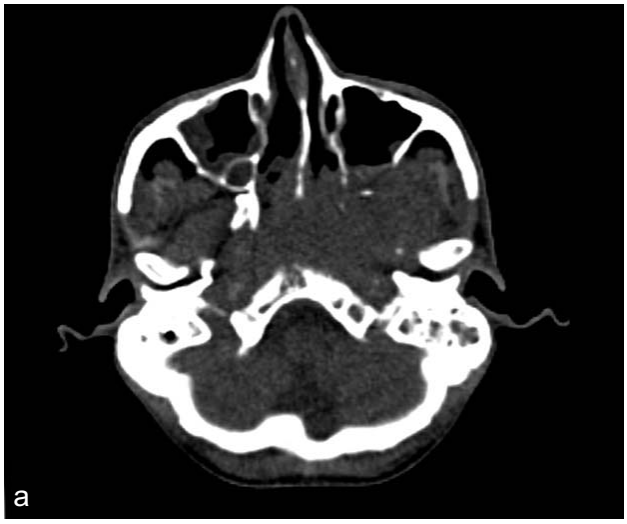


Figure 2a,b: Depict axial PET CT scan images showing a fluorodeoxyglucose (FDG) avid mass lesion arising from the left nasopharyngeal wall and anteriorly extending to involve the fossa of Rosenmuller, infiltrating in the left para-nasopharyngeal region. SUV max of 5.22.



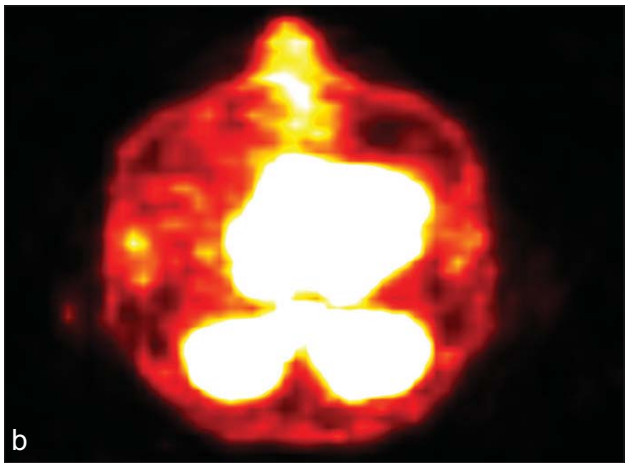


Figure 3a,b: Illustrate axial PET CT scan images demonstrating a FDG avid infiltrative nasopharyngeal mass lesion with a SUV max 12.73 involving the infratemporal fossa.

MANAGEMENT:

The management should commence with multidisciplinary tumor board discussion.[13] Aim of treatment is functional preservation of organs that helps in respiration, swallowing and speech.

Management depends upon the stage group of the patient.

Early stage disease is treated by definitive radiation, while for locoregional disease concurrent chemoradiation is the standard of care. At locally advanced stages neoadjuvant chemotherapy followed by concurrent chemoradiation is the mainstay of treatment algorithm.

Due to the anatomical location and proximity to critical structures, surgical intervention and tumor removal with adequate margins has proven to be highly difficult and can be highly morbid. NPC is a radiosensitive tumor and cannot be approached surgically due to neurovascular structures so definitive management is concurrent chemoradiotherapy.

Surgery is designated as a salvage option for a small percentage of patients and is not routine in the upfront scenario. Neck dissection may be used to treat nodal disease after primary treatment or after nodal recurrence.

A critical advancement in the treatment of locoregionally progressed illness is the use of chemotherapy in conjunction with radiotherapy. While early stage NPC can be managed only via radiotherapy, locoregionally advanced stage requires treatment with concurrent chemoradiotherapy

ROLE OF RADIATION:

Radiotherapy is the mainstay treatment option because nasopharyngeal carcinoma is extremely sensitive to ionizing radiation. Nasopharyngeal carcinoma due to its critical anatomic location and advanced stages at presentation poses a unique challenge for the treating radiation oncologist.

From traditional two-dimensional (2D) radiotherapy to 3D conformal radiotherapy, and finally to intensity-modulated radiotherapy, photon-based radiotherapy techniques have advanced over time.[1] IMRT is associated with significant decrease in late xerostomia, trismus and temporal lobe injury as compared with older RT techniques.[16] Not only this, conformal techniques like IMRT and 3DCRT enables uniform delivery of higher doses to the target volume while reducing the dose to surrounding normal structures.[17]

International consensus guidelines have been suggested for delineating the CTV and OARs in order to ensure maximal target coverage and reduce adverse effects.[15]

Acute toxicities include mucositis & odynophagia, xerostomia, dysphagia, skin hyperpigmentation and desquamation. Serious late toxicities include webbing of the pharynx, laryngeal edema, trismus, xerostomia, temporal lobe necrosis.[19,20]

FOLOW-UP:

Follow up includes history and physical examination as a core component. First follow up with imaging (CT scan) after 2 months or PET CT scan after 3 months from last fraction of Radiation Therapy. Along with fiberoptic pan-endoscopic evaluation which is the modality of choice for ENT follow up.[21]

RECURRENT OR RESIDUAL DISEASE:

In the IMRT era, 10% patients have recurrent or persistent disease at the primary and/or regional location.[22,23]

It is widely accepted that patients with primary treatment option for isolated regional failure is salvage neck dissection. Tumor that recurs within a year are regarded as radioresistant; if they are resectable, surgery is advised.

PROGNOSIS:

The prognosis depends upon the extent of local invasion, lymphatic spread and distant metastases.

In general, advanced T category is linked to worse overall local control and advance N category suggests a higher chance of distant metastases and overall lower survival.

Other prognostic indicators include age of the patient, WHO classification, EBV titers. EBV levels both before and after treatment are predictive for survival since it is the principal etiologic agent in the development of NPC. Numerous studies have demonstrated that the presence of detectable EBV following negative RT may act as a poor prognostic indicator.[14,15]

Conclusion

To conclude our discussion about NPC, it is an uncommon tumor arising from the Nasopharyngeal epithelial lining with a unique geographical distribution. Management revolves around chemoradiotherapy. Early stage can be managed via definitive radiotherapy, while locoregional stage may be treated with concurrent chemoradiotherapy. Locally advanced stage is treated with neoadjuvant chemotherapy followed by concurrent chemotherapy.

Conflict of interest: None

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