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BRIEF COMMUNICATION

Challenges in the Management of Nasopharyngeal Carcinoma: A Review

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Abstract

Nasopharyngeal carcinoma (NPC) is a non-lymphomatous, squamous cell carcinoma that occurs in the epithelial lining of the nasopharynx, an area that shows varying degrees of differentiation. Although relatively rare worldwide, NPC has substantial incidence and mortality in populations in Southeast Asia and in people with Southern Chinese ancestry. In Malaysia, NPC is a leading cancer type. In the clinic, NPC presents on a very wide spectrum. Therefore, a high degree of suspicion on the part of the clinician and an increased awareness by the patient is essential for the recognition of an early lesion. Early detection of the cancer is important as it affects the patient's prognosis and the mode of treatment. Managing patients with NPC is very challenging as patients usually present late when the cancer is already in an advanced stage. Here, we review the challenges in the management of NPC.

***Keywords*:** *nasopharyngeal carcinoma, management, challenges, medical sciences*

Introduction

Nasopharyngeal carcinoma (NPC) manifests itself in multiple forms and may present to different medical specialists. Many patients with NPC present with an advanced stage of the disease, resulting in a poor prognosis. Reasons why patients present with such a late stage of NPC include the following: a delay in seeking medical advice; the confusing nature of the presenting symptoms, which are misleading to the clinician; the difficult nature of a clinical examination of the nasopharynx, even for experienced clinicians; and the spread of a silent submucosal lesion with a normal appearance during examination of the nasopharynx.

The average time between the appearance of NPC symptoms and the first consultation is about six months (1). The patient's symptoms often include epistaxis, nasal obstruction, decreased hearing, tinnitus, neck masses, headache, diplopia, facial numbness, hypoaesthesia, trismus, ptosis or hoarseness. NPC is often diagnosed due to Trotter's triad, a combination of conductive deafness, elevation and immobility of the ipsilateral soft palate, together with pain on the side of the head, which represents symptoms of local invasion (1). A study conducted in Hospital University Sains Malaysia (2), found that the most common presentations of NPC in patients are neck masses (commonly unilateral), followed by headache and epistaxis. Other symptoms may include unilateral nasal obstruction, tinnitus, diplopia, otalgia, bilateral deafness, blindness and dysphagia. Besides the above symptoms, cranial nerves are also commonly affected. The most common cranial nerve affected is the sixth, followed by maxillary division of the fifth and twelve nerve palsies.

Diagnosis and screening

With such a wide spectrum of clinical presentations, it is important to have a high index of suspicion for early diagnoses of NPC. Early identification of NPC is important for patient treatment and prognosis. To establish the correct diagnosis, thorough patient history and physical examination are important. The clinical examination must include a complete examination of the head and neck, including all levels of the neck and cranial nerve function. A nasoendoscopy

is mandatory during diagnosis of NPC. The nasoendoscope and postnasal mirror may reveal an exophytic tumour. Unfortunately, many tumours remain submucosal and difficult to diagnose.

Laboratory investigations, including full blood count and erythrocyte sedimentation rate (ESR), are essential because repeated epistaxis may cause anaemia and a raised ESR increases the possibility of an underlying lymphoma. In addition, hearing assessment using audiometry may indicate a compromised eustachian tube function due to tumour compression that leads to hearing impairment. Visual test, visual acuity and visual field are also important during diagnosis of NPC, especially for patients presenting with visual symptoms or eye signs.

Radiological examination remains one of the most important approaches for NPC diagnosis, evaluation and staging. The density of NPC tissue is often similar to that of soft tissue. Therefore, detection of a tumour depends on the displacement or erosion of the normal anatomy and the uptake of the iodinated intravenous product by the tumour. Most often, computerised tomography (CT) is the investigation method of choice. CT seems to be better at detecting cortical bone erosion, whereas magnetic resonance imaging (MRI) appears superior at clearly delineating the tumour edge, determining the vascular nature of the lesion and identifying intracranial extension. With the modern spiral CT scan, it is possible to examine the skull base down to the abdomen to visualise the presence of any metastasis (1). As this technology is still not widely available in Malaysia, the other imaging modalities, such as chest X-ray and abdomen ultrasound are sufficient. The tumour can then be staged based on the International Union Against Cancer/American Joint Committee on Cancer (UICC-AJCC) system (1997) (3). Histopathological examination of the biopsy material obtained from the nasopharynx will confirm the diagnosis of NPC. Based on histopathological examination, NPC can be divided into three categories, World Health Organization (WHO) type 1, type 2 and type 3 (WHO classification) (4). All of the above examinations are the standard diagnostic practice locally and internationally.

Several studies have been conducted to determine a screening method for NPC (5–10). In Southern China, where NPC is endemic, Epstein-Barr virus (EBV) serology has been used for population screening for NPC. Identification of EBV genomic latent membrane protein-1 (LMP-1) by a nasopharyngeal swab is able to diagnose NPC with an 87.3% sensitivity and a 98.4% specificity (11). Use of an nasopharyngeal brush biopsy has also demonstrated the presence of EBV DNA with a sensitivity of 90% and a specificity of 99% (7). The high cost involved in this diagnosis method means that it is still not justifiable to do in every patient suspected of having NPC. In our centre, we use a nasopharyngeal brush biopsy in situations that are difficult to interpret by other diagnostic modalities.

Treatment

The majority of NPC patients are treated radically with the goal of curing the patients in the early stages of the disease. Patients with distant metastases at the time of presentation and those medically unfit for treatment receive palliative treatment and symptomatic care. Radiotherapy is the primary treatment modality for NPC at all disease stages (12). The primary tumour and the neck are treated even in patients without palpable nodal disease. However, the treatment area must be extended to include the base of skull if there is evidence of cranial nerve involvement. Standard radiotherapy doses are more than 7000 cGy. The lower aspect of the neck and supraclavicular region receive 5000 cGy through the use of an anterior field. The brain stem and spinal cord are blocked, so that they do not receive more than 4500 cGy and the optic chiasm does not receive more than 5000 cGy.

Intensity-modulated radiotherapy has achieved excellent locoregional control of NPC (13). A study that prospectively assessed salivary functions confirmed the gradual recovery of parotid function within two years after the completion of intensity-modulated radiotherapy. Satisfactory dosimetric results were also achieved with this treatment approach for recurrent NPC, and the degree of short-term control was encouraging. Other attempts to enhance the biological effects of radiotherapy have been reported. These attempts include accelerated fractionation, accelerated hyperfractionation, and a combination of one or more of these treatment approaches with chemotherapy. However, hyperfractionation radiotherapy for NPC should be used with care. A study of accelerated hyperfractionation by 2D radiotherapy planning reported an increase in radiation damage to the central nervous system without an improvement in tumour control.

Surgical therapy has a secondary role and is generally considered for patients with residual cervical lymphadenopathy after radiation therapy, or for patients that develop cervical metastases after radiation therapy. Due to its location, the nasopharynx has traditionally been considered unresectable. Wei et al. (14) popularised the

maxillary swing procedure for nasopharyngectomy in the treatment of recurrent NPC post-radiotherapy. This technique is now the current practice locally and worldwide. In this procedure, the maxillary antrum with the hard palate attached to the anterior cheek flap is turned laterally as an osteocutaneous flap. After removal of the recurrent tumour by nasopharyngectomy, the maxilla is repositioned to its original location and anchored by plates and screws.

Alternatively, nasopharyngectomy can be performed via the infratemporal approach (15). For this surgical technique, an extended radical mastoidectomy is initially carried out followed by the transection of the external auditory canal. The facial nerve is displaced inferiorly, and the temporalis muscle is retracted. Bone in the skull base is removed, starting at the glenoid fossa and continuing to the infratemporal fossa, to expose the eustachian tube and the tissue of the parapharyngeal space. The internal carotid artery is exposed from the middle ear to the foramen lacerum, and the middle meningeal artery and the mandibular branch of the fifth cranial nerve are separated. Tumours in the nasopharynx can be removed en bloc, with the surrounding tissue extending to the contralateral nasopharyngeal wall. The mobilised temporalis muscle is used to fill the surgical defect, after which the middle ear cavity and temporal area are filled with abdominal fat.

For patients with advanced locoregional disease (stages III and IV), a combination of chemotherapy and radiation is given. Prasad showed a combination of radiotherapy and CT prolonged the survival rate of patients at a late stage of NPC (16). Chemotherapy can be given neoadjuvantly, concurrently, adjuvantly, or in a combination of these approaches. A study examining the three basic approaches to chemotherapy (neoadjuvant, concurrent, and adjuvant) showed that concurrent chemoradiotherapy is the most efficacious. The chemotherapy agents (anti-neoplastic agents) commonly used to treat NPC patients include cisplatin and 5-fluorouracil.

Residual or recurrent disease in the nasopharynx used to be managed with a second course of external radiotherapy (17). The treatment dosage is normally greater than the initial radiation dose. Although a salvage rate of 32% has been achieved, the cumulative incidence of late sequelae after re-irradiation is 24% with a treatment mortality of 1.8%. To avoid the high incidence of complications resulting from re-irradiation, stereotactic radiotherapy and brachytherapy have been used for patients with small localised tumours in the nasopharynx where surgery is not warranted, or is undesirable. Stereotactic radiotherapy, when used for the management of a residual or recurrent tumour, is associated with a two year local tumour control rate of 72%. Intracavitary or interstitial bracytherapy may allow a high radiation dose to be delivered to the tumour within the nasopharynx while sparing the normal tissue that would be irradiated beyond tolerance limits by the external beam treatment. Brachytherapy is of little value when the disease extends much beyond the nasopharynx (18) .

Circulating free EBV DNA has been reported in patients with NPC (13,19). The quantity of free plasma EBV DNA as measured by real-time quantitative polymerase chain reaction is related to the stage of the disease. The number of copies of EBV DNA before and after treatment is significantly related to the rates of overall and disease-free survival (20). A study has reported that the level of post-treatment EBV DNA compared with pre-treatment EBV DNA is a good predictor of progression-free survival (21).

Of note, survivors of NPC have an impaired, health-related quality of life (22). Patients who survive the disease have several late complications, many of which result from the effects of radiation on the dose-limiting organs adjacent to the nasopharynx and neck nodes. The most debilitating sequelae are neurological complications. These complications can include serious disorders, such as temporal lobe necrosis, cranial nerve palsies and dysphagia. Also, less obvious effects include memory loss, cognitive dysfunction and neuropsychological dysfunction. Despite the effectiveness of radiation and chemotherapy on the management of NPC, local or regional failure presenting as a persistent or recurrent tumour still occur. With modern advances in techniques and combined modalities of therapy, these morbidities could be minimised and preferably prevented altogether.

Prognosis

As with most tumours, the extent of NPC, as embodied in the TNM staging system, is the most important prognostic factor. A report in 1990 (23) showed that besides the T and N stages, other prognostic factors include the size and degree of fixation of neck nodes, the patient's sex and age, the presence of cranial nerve palsy and ear symptoms at the time of presentation. The size of the lymph node and the extent of the ear symptoms likely suggest the lack of recognition of nodal size and paranasopharyngeal extension

in the T and N staging system used at that time. In 1992, a study (24) reported that the tumour's histological type and the radiotherapy dose and coverage were significant independent prognostic factors. Paranasopharyngeal extension was an independent prognostic factor correlated with adverse local tumour control and increased distant spread (25). A large variation in tumour volume is present in T stages of different staging systems, and primary tumour volume represents an independent prognostic factor of local control. The validity of tumour volume has been confirmed in patients with T3 and T4 tumours. There is an increased risk of approximately 1% in local failure for every cubic centimetre increase in the primary tumour volume (26,27).

Conclusions

NPC presents clinically on a wide spectrum. Therefore, a high index of suspicion on the part of the clinician and an increased awareness by the patient are essential for recognition of an early lesion. Advances in treatment techniques and combined modalities of therapy are necessary to improve the patient's outcome and prognosis.

Author's contributions

All authors contributed equally to the design, data analysis and interpretation, drafting of the article, critical revision and final approval of the article.

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