Management of Nasopharyngeal Carcinoma- Current Perspectives

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ABSTRACT

BACKGROUND

Nasopharyngeal carcinoma is the most common malignant tumour arising from epithelial lining of nasopharynx and is commonly associated with Epstein Barr virus. It is endemic in South-East Asia, Southern China and North Africa. The diagnosis in early stage is infrequent as the symptoms of nasopharyngeal carcinoma are non-specific and patients usually present in later stages. In high-risk group of patients, plasma EBV-DNA level has become a screening tool for the diagnosis of nasopharyngeal carcinoma in its early stage. Under endoscopic guidance, biopsy is to be taken for confirmation of disease. Imaging modalities like PET scan have been the mainstay for the detection of extent of disease. Nasopharyngeal carcinoma is highly radiosensitive and chemosensitive tumour. For all the stages of nasopharyngeal carcinoma without distant metastasis, radiotherapy remains the mainstay of treatment. Concurrent chemoradiation with adjuvant chemotherapy has been recommended as standard treatment for advanced nasopharyngeal carcinoma. The advent of intensity modulated radiotherapy has reduced the incidence of radiotherapy induced complications. For better results of salvage therapy, the early detection of residual or recurrent tumour at primary site or in neck is essential. The salvage therapy has improved the overall outcome of these patients. The use of targeted therapy has been reported to be efficacious in management of metastatic or recurrent nasopharyngeal carcinoma. The advent of immunotherapy based on pembrolizumab and T4 CAR T-cell therapy has shown promising results in phase I and phase II trials. Further studies and clinical trials are needed to include it as mainstay treatment in the management of nasopharyngeal carcinoma.

KEYWORDS

Nasopharyngeal Carcinoma, Epstein Barr Virus, Radiotherapy, Concurrent Chemoradiation, Targeted Therapy, Immunotherapy

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INTRODUCTION

Nasopharyngeal carcinoma is the most common malignant tumour arising from the epithelial lining of nasopharynx. It is commonly located in the postero-lateral part of the nasopharynx at fossa of Rosenmuller.[1] It is most commonly seen in fifth to seventh decade of life but may involve younger age group. A male preponderance is seen with male to female ratio of approximately 2:1.[2] Nasopharyngeal carcinoma is rare in most parts of the world but the incidence is higher in Southeast Asia, Southern China and North Africa.[3] Nasopharyngeal carcinoma is commonly associated with Epstein-Barr virus infection. Other risk factors are excessive consumption of salt preserved fish, tobacco smoking, alcohol, frequent consumption of preserved or fermented foods and wood dust. The genetic susceptibility to nasopharyngeal carcinoma is higher in Chinese as even after migration to different countries they continue to have higher incidence.[4] Among first degree relatives, positive family history of nasopharyngeal carcinoma has also been reported.[5] This suggest that both environmental and genetic factors might have a significant role in the aetiology of this malignancy.

Presentation of Nasopharyngeal Carcinoma

The symptoms of nasopharyngeal carcinoma are based on the anatomical location of the primary tumour and its metastasis. The common symptoms can be grouped into four categories, firstly nasal symptoms such as nasal obstruction, nasal discharge and epistaxis. Secondly, otologic symptoms such as conductive hearing loss, otitis media and tinnitus due to obstruction of eustachian tube. Thirdly, cervical lymphadenopathy which may be sometimes the only presentation of nasopharyngeal carcinoma. Fourthly, cranial nerve palsies due to superior extension of tumour with skull base erosion. The cranial nerves frequently involved are third, fifth, sixth and twelfth leading to facial pain, numbness and diplopia.[6] Other symptoms are anorexia, weight loss and distant metastasis can occur to lung, bone and liver. The nasal and aural symptoms are non-specific and frequently escape notice. The majority of patients are diagnosed only when the nasopharyngeal carcinoma has progressed to an advanced stage.

Diagnostic Workup

The workup for suspected nasopharyngeal carcinoma includes examination of mouth, nose, pharynx, larynx, ears, neck and routine investigations including complete blood count, liver function test, renal function test and serum uric acid levels. Flexible fiberoptic endoscopic examination of nasopharynx is done as this area is not easily visible and biopsy of primary lesion is taken for definitive diagnosis.[7] The endoscopic examination of nasopharynx does not determine the deep extension of tumour. The biopsy from cervical lymph nodes should be taken by ultrasound guided fine needle aspiration cytology. The histological types of nasopharyngeal carcinoma are classified as per WHO classification. For extent of primary tumour, MRI is preferred over CT head and neck.[8] For distant metastasis, CT chest, CT abdomen, PET scan and bone scan can be done. For detection of persistent and recurrent tumours in the nasopharynx, PET scan is more sensitive than CT and MRI.[9] Other investigation is Epstein-Barr virus serology, which is a screening tool for nasopharyngeal carcinoma and it includes immunoglobulin A (IgA) level against early intracellular antigen (EA) and viral capsid antigen (VCA). The IgA anti-EA has been observed to be more specific while IgA anti-VCA is more sensitive for diagnosis of nasopharyngeal carcinoma.[10] The plasma EBV-DNA levels measured by real time quantitative PCR in pre and post-treatment has also been observed to be of good prognostic value.[11]

In 1978, World Health Organization classified nasopharyngeal carcinoma into three histological types.[12]

1. Type I - Typical keratinizing squamous cell carcinoma.
2. Type II - Non keratinizing squamous carcinoma.
3. Type III - Undifferentiated carcinoma.

In recent years, a new classification was proposed, and it divided nasopharyngeal carcinoma into two main histological types, namely squamous cell carcinoma (SCCs) and undifferentiated carcinomas of nasopharyngeal type (UCNTs). Among these undifferentiated type is most common and studies have reported that undifferentiated carcinoma is associated with high EBV titre as compared to squamous cell carcinoma.[13] Based on EBV serological markers, individuals, who are at high risk can be offered nasopharyngeal endoscopic examination and biopsy with close surveillance for early diagnosis of nasopharyngeal carcinoma.

Staging of Nasopharyngeal Carcinoma

The clinical staging of nasopharyngeal carcinoma is done according to The American Joint Committee on Cancer Staging System (AJCC) for nasopharyngeal carcinoma, eighth edition (2018).

TREATMENT OF NASOPHARYNGEAL CARCINOMA

Radiotherapy

Nasopharyngeal carcinoma is highly radiosensitive and chemosensitive tumour. For all the stages of nasopharyngeal carcinoma without distant metastasis, radiotherapy remains the mainstay of treatment. Stage I nasopharyngeal carcinoma are treated by radiotherapy alone. The success rate of radiotherapy alone in early stage nasopharyngeal carcinoma may exceed 90 percent.[14]

Primary Tumour (T)	TX: Primary tumour cannot be assessed T0: No tumour identified, but EBV-positive cervical node(s) involvement Tis: Carcinoma in situ T1: Tumour confined to nasopharynx or extension to oropharynx and/ or nasal cavity without parapharyngeal extension T2: Tumour with parapharyngeal extension and/or adjacent soft tissue involvement (lateral pterygoid, medial pterygoid, prevertebral muscles) T3: Tumour with infiltration of bony structures (skull base, cervical vertebra) and/or paranasal sinuses T4: Tumour with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland and/or extensive soft tissue infiltration beyond the lateral surface of lateral pterygoid.
Regional Lymph Nodes (N)	NX: Regional nodes cannot be assessed N0: No regional lymph node metastasis N1: Retropharyngeal lymph nodes(regardless of laterality) Cervical lymph nodes: unilateral, <6 cm and above caudal border of cricoid cartilage N2: Cervical lymph nodes: bilateral,<6 cm and above caudal border of cricoid cartilage N3: >6cm and/or below caudal border of cricoid cartilage (regardless of laterality)
Distant Metastasis (M)	M0: No distant metastasis M1: Distant metastasis Pm1: Distant metastasis, microscopically confirmed
Anatomic Stage	I: T1 N0 M0 II: T2 N0-1 M0, T1 N1 M0 III: T3 N0-2 M0,T1-2 N2 M0 IV a: T4 or N3 M0 IV b: Any T, any N, M1

Table 1. Classification Criteria and Stage Grouping According to AJCC Staging System (Eighth Edition)

Nasopharyngeal carcinoma has tendency of early spread to cervical lymph nodes, therefore prophylactic radiation therapy to neck lymph nodes is mandatory.[15] A dose of 65-70 Gy is given to the nasopharyngeal primary tumour and involved neck lymph nodes, while the dose for prophylactic treatment for node-negative neck is 50-60Gy. The advent of intensity modulated radiotherapy (IMRT), which is a more superior form of 3D conformal radiotherapy allows delivery of highly conformed dose of radiation to the main target through optimization of intensity of multiple beams while low dose to normal tissues.[16] The treatment is planned by taking 3D computed tomography (CT) and magnetic resonance images (MRI) of patient along with computerised dose calculations to determine the accurate dose intensity that will best conform according to the tumour shape. The IMRT has reduced the incidence of complications related to radiotherapy such as xerostomia by selectively sparing parotid glands.[17] The success rate of radiotherapy alone in early stage nasopharyngeal carcinoma may exceed 90 percent.[17]

Combined Chemoradiotherapy

Concurrent chemoradiation with adjuvant chemotherapy is the recommended treatment for stage II-IVb nasopharyngeal carcinoma.[18] Radiation dose during concurrent chemoradiation is up to 70Gy. Platinum based concomitant chemotherapy regimen is now the preferred standard treatment for locoregionally advanced nasopharyngeal carcinoma, which provides a benefit in terms of overall survival and on both locoregional and distant control.[19] At least nine randomized studies have compared benefits of concurrent chemoradiotherapy.[20] The Intergroup 0099 trial also showed positive survival benefits with use of concurrent chemoradiotherapy in nasopharyngeal carcinoma.[21] Twu et al. in his retrospective study showed that adjuvant chemotherapy given to patients with detectable plasma EBV DNA levels after concurrent chemoradiotherapy has improved overall 5 year survival along with reduction in distant failure. The overall 5-year survival rate in patients with adjuvant chemotherapy and in patients without adjuvant chemotherapy was reported to be 71.6% and 28.7% respectively (P< 0.0001).[22] Some studies have also reported that induction chemotherapy given before concurrent chemotherapy has improved the overall survival in patients with locoregionally advanced nasopharyngeal carcinoma as compared to chemoradiotherapy alone.[23-24]

Management of Residual or Recurrent Nasopharyngeal Carcinoma

Despite good efficacy of concurrent chemoradiotherapy, still there are some patients with regional and local failure, who present with persistent or recurrent tumours. For salvage therapy to be successful, early detection and treatment is essential. After completion of treatment, follow up imaging at 10-12 weeks is required to document the tumour response. The levels of free EBV-DNA are also useful for detection of relapse, especially in distant metastasis.[25] For residual or recurrent tumours in nasopharynx, FDG-PET scan has been observed to be better than CT or MRI and this is usually confirmed by biopsy on endoscopic examination.[26] Residual or recurrent tumours in cervical group of lymph nodes after radiotherapy is difficult to confirm as there is only cluster of tumour cells present in the lymph nodes.[27] Although the overall survival rate in patients with extensive disease is poor with salvage therapy but it is better as compared to patients receiving symptomatic management.[28]

Metastatic Cervical Lymph Nodes

Following concurrent chemoradiotherapy for nasopharyngeal carcinoma, the incidence of isolated failure in neck lymph nodes has decreased and it is less than 5 percent.[29] Salvage therapy is recommended, if there is clinical progression of lymph nodes or imaging studies suggest residual or recurrence of cancer in cervical lymph nodes. The metastatic cervical lymph nodes are managed by external radiotherapy or surgical salvage in form of radical neck dissection. The overall five year survival rate with external radiotherapy is 19.7% whereas surgical salvage has five year tumour control rate in neck of 66% and a five year actuarial survival of 37%. In cervical lymph node tumour

with extracapsular spread, brachytherapy delivered to tumour bed after radical neck dissection has shown good results. Similar results has been observed with adjuvant brachytherapy in extensive neck diseases as compared to radical neck dissection alone performed in less extensive neck disease.[30]

Disease in the Nasopharynx

The patients with residual or recurrent tumour in nasopharynx are managed by external reirradiation. In view of complications associated with second course of radiotherapy, brachytherapy, stereotactic radiosurgery and surgical resection have been considered for the salvage of localized small tumours in nasopharynx. The selection of treatment modality depends on extent of disease. In stereotactic radiosurgery, the localized small target is irradiated by multiple convergent beams providing a single high dose of irradiation. The local control rate achieved at 2 years with stereotactic radiosurgery for recurrent diseases confined to nasopharynx and adjacent soft tissues was reported to be 72 percent.[31]

Brachytherapy

In brachytherapy, high dose of irradiation is given to the residual or recurrent tumour but a much smaller dose is delivered to surrounding tissue. It is delivered at continuous low dose rate, which gives it a radiobiological advantage over other forms of external radiotherapy. Brachytherapy is indicated mainly for localized tumour in nasopharynx without bone invasion. In Nasopharyngeal carcinoma, intracavitary brachytherapy has also been used in which the radiation source is placed over a mould or either in a tube before insertion into the nasopharynx.[32] The irregular contour of nasopharynx make it difficult to position radiation source accurately in nasopharynx. The advent of radioactive interstitial implants used to treat small localized recurrent or residual tumours in the nasopharynx has overcome this problem. The 5 year local tumour control rate achieved by use of gold grain implants in residual and recurrent tumours after radiotherapy were reported to be 87% and 63% respectively.[33] Radioactive gold grains have been frequently used and these grains can be implanted into the tumour either transnasally under endoscopic guidance or by using the split palate approach.[34]

Nasopharyngectomy

The main indication of nasopharyngectomy is to treat the residual or recurrent tumour, which cannot be managed by brachytherapy as they are too extensive or when the tumour extends to the paranasopharyngeal space. There are number of approaches which can be used for nasopharyngectomy, including infratemporal approach from lateral aspect, transcervical approach from inferior aspect, transmaxillary, transpalatal and an anterolateral approach.[35] The choice of surgical approach for nasopharyngectomy depends on location and extent of tumour in the nasopharynx. The anterolateral or maxillary swing approach is commonly used for residual or recurrent tumours affecting fossa of Rosenmuller.[36] The overall mortality associated with these surgical salvage procedures is low. Patient selection is very important for surgical salvage as nasopharyngectomy is only indicated for tumours located in nasopharynx without infiltration of skull base. For tumours which are too extensive for surgery or infiltrate skull base, stereotactic radiosurgery or IMRT can be given and sometimes can be combined with chemotherapy.[37]

Distant Metastasis

In metastatic nasopharyngeal carcinoma, palliative chemotherapy is recommended treatment. Platinum based combination regimen including cisplatin or carboplatin are commonly used as first line therapy. Other active agents include paclitaxel, docetaxel, gemcitabine, capecitabine and 5-fluorouracil. Polychemotherapy is more effective than monotherapy.

Role of Targeted Therapy in Recurrent Or Metastatic Nasopharyngeal Carcinoma

Targeted therapy acts by targeting the cancer specific genes, proteins and tissue environment, which contribute in cancer growth and survival. The epidermal growth factor receptor (EGFR) is highly expressed in nasopharyngeal carcinoma.[38] The use of EGFR inhibitor like cetuximab, erlotinib, gefitinib have been considered in various clinical trials. In a meta-analysis, cetuximab, a monoclonal antibody against epidermal growth factor when given in combination treatment in advanced nasopharyngeal carcinoma was reported to have more benefits than conventional treatment alone.[39] The vascular endothelial growth factor (VEGF) when bind to its receptor (VEGF-R) it activates various intracellular pathways which are linked to neo-angiogenesis and cell survival. VEGF-R overexpression is associated with poor prognosis.[40] Sunitinib and pazopanib are antiangiogenic drugs which targets VEGF-R. The effect of these drugs have been tested in patients with recurrent or metastatic nasopharyngeal carcinoma under phase II clinical trial but does not show any valuable clinical and survival benefits.[41] Results have been scarce at the cost of toxicity and there are various ongoing studies that are currently investigating angiogenesis inhibition targets.

Role of Immunotherapy in Recurrent or Metastatic Nasopharyngeal Carcinoma

Immunotherapy is another therapeutic strategy used in nasopharyngeal carcinoma which reinforce the immune system to act against cancer cells. It includes various strategies such as immune-check point blockade, Cancer vaccine and adoptive immunotherapy. The immune-check point inhibitors are the drugs which inhibit the interaction of PD-L1 (Programmed cell death ligand-1) highly expressed by

cancer cells to PD-1 (Programmed death-1) present on T cell membrane and allows T cells to kill cancer cells by removing the inhibitory stimuli on cytotoxic T-lymphocytes elicited by tumour microenvironment. The monoclonal antibodies to PD-1 including pembrolizumab and nivolumab are used as check point inhibitors. KEYNOTE-028 is a phase Ib nonrandomized trial of pembrolizumab in patients with PD-L1 positive advanced solid tumour. The cohort study including 27 patients of recurrent or metastatic nasopharyngeal carcinoma showed partial response in 7 patients (25.9%), with stable disease observed in additional 14 patients (51.9%).[42] Epstein Barr virus leads to neoplastic transformation of nasopharyngeal epithelial cells and further induce the expression of immunogenic peptides on the surface of infected cells which can be used as main targets in immunotherapy. The cancer cells express the two EBV antigens EBNA1 and LMP2. A vaccine with recombinant modified vaccinia virus Ankara (MVA-EL) encoding EBNA1/ LMP2 fusion protein is designed to boost T-cell immunity to these antigens. In two Phase I trials this vaccine has been observed to be safe.[43] Vaccines has also been constituted by using dendritic cell pulsed with nasopharyngeal tumour associated antigens. This approach has obtained good results in phase II clinical trials in patients with recurrent nasopharyngeal carcinoma.[44] In EBV specific adoptive immunotherapy, the main aim is to obtain T-cytotoxic lymphocytes which are able to eliminate cancer cells with high selectivity. Various clinical studies have tried to boost anti EBV responses in circulating cytotoxic T lymphocytes through autologous T cell transfer in patients with nasopharyngeal carcinoma.[45-46] A phase I trial evaluated safe intratumoural administration of T4 CAR T-cell in patients of advanced head and neck cancer including nasopharyngeal carcinoma.[47]

CONCLUSIONS

Nasopharyngeal carcinoma is commonly associated with Epstein Barr virus infection. It is highly radiosensitive, chemosensitive and highly curable when detected early. The optimal treatment needs a multidisciplinary approach which involves ENT specialist, medical and radiation oncologist. Radiotherapy is the recommended treatment in early stage nasopharyngeal carcinoma. In locally advanced nasopharyngeal carcinoma, excellent local control can be achieved with concurrent chemoradiation with adjuvant chemotherapy. The advent of intensity-modulated radiotherapy reduces the incidence of radiotherapy-induced complications. The use of molecular targeted therapy and immunotherapy has better outcomes in recurrent and metastatic nasopharyngeal carcinoma. The plasma EBV-DNA measured in pre- and post-treatment has been reported to be of good prognostic value and it is an excellent tool for detection of tumour relapse, especially in distant metastasis.

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