REVIEW ARTICLE

CONTEMPORARY LITERATURE REVIEW ON NASOPHARYNGEAL CANCER

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Introduction

In most regions of the world, nasopharyngeal carcinoma (NPC) is a rare head and neck (H&N) cancer with variable geographical distribution, higher incidence is seen in Southern Chinese population.[1] Nasopharyngeal carcinoma is a non-lymphomatous squamous-cell cancer that originates in the epithelial membrane of the nasopharynx. Diverse levels of differentiation are present in this tumor. The most prevalent origin of nasopharyngeal malignancies is the lateral walls, including the pharyngeal recess (fossa of Rosenm ller). Nasopharyngeal carcinoma has various etiological factors like genetic, environmental, and viral factors.

Certain environmental exposures, such as consumingsalt-preserved fish, smoking, and insufficient consumption of raw fruits and vegetables, are commonly known cancer risk factors. Both high-and low-incidence areas patients with nasopharyngeal malignancy have repeatedly demonstrated Epstein-Barr virus (EBV) as a risk factor.[2] Additionally, EBV has been detected in premalignant lesions of the nasopharyngeal epithelium, which shows that the infection happens before the development of cancer. EBV-DNA in circulation has been shown to improve patient monitoring and prognosisfor NPC patients. Nasopharyngeal tumors exhibit a significant frequency of metastasis, ranging from 5% to 41%, when compared to other H&N cancers both localized and distant metastasis. The most frequent locations for metastasis in this form of cancer are nodes, bones, lungs, and liver.[1] Because they are radiosensitive, nasopharyngeal tumors are rarely amenable to surgery. The combination of radiation therapy and concurrent chemotherapy has improved methods (such intensity-modulated radiotherapy) and boosted survival. The most recent modifications are covered in this review article.

EPIDEMIOLOGY ANDETIOLOGY:

In most parts of the globe, the incidence of nasopharyngeal carcinoma is low. Age-adjusted incidence rates for men (per 100,000 persons per year) varies 0.6 in the US and Japan, 5.4 in Algeria, 5.8 in the Philippines, 11.0 in Singapore, 17.2 among Eskimos, Indians, and Aleuts in Alaska, and 17.8 and 26.9 in Hong Kong and Guangdong province in Southern China, respectively.[3,4] Observed bimodal Age distribution with peaks at 15-25 and 50-59 years. Male to female ratios range from 2:1 to 3:1.[5] A significant environmental issue has been linked to Southern China's widespread eating of salted fish due to carcinogen dimethyl nitrosamine, which is present in salted fish. Other environmental etiologic factors connected to nasopharyngeal cancer include alcohol consumption and exposure to dust, gases, formaldehyde, and cigarette smoke.[3] Regardless of racial or geographical origin, The Epstein-Barr virus (EBV), particularly the nonkeratinizing strain, has been associated to nasopharyngeal cancer. Premalignant nasopharyngeal epithelial lesions had increased

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EBV levels, which maydemonstrate that EBV infection influences the early stages of NPC carcinogenesis.[3,5]

GENETICS:

Southern Chinese ancestry populations point to a genetic sensitivity factor. Linkage research that discovered that a gene closely related to the (Human Leukocyte Antigen) HLA locus imparted a significantly increased risk of this disease was validated by the results of a genome-wide susceptibility loci study. In addition, the development of nasopharyngeal carcinoma is associated with several HLA haplotypes, including A2, B46, and B17(12-13). Genetic polymorphisms in cytochrome P450 2E1 (CYP2E1), CYP2A6, glutathione S-transferase M1 (GSTM1) and GSTT1 are also under discussion.[6,7]

PATHOLOGY:

Majority of NPC cases (85%) are SCC.10% of the malignant tumors are lymphomas. Histochemical analyses and electron microscopy have proven its epidermoid lineage. The usual appearance of NPC is frequently enough to confirm the diagnosis even when looking at a lymph node metastasis.[8]

WHO Classification: (2005)	Description
Type I	Keratinizing Squamous Cell Carcinoma Associated with smoking / HPV
Type II	Non-keratinizing • Differentiated • Undifferentiated: Associated with EBV. Good prognosis • Lymphoepithelial
Type III	Basaloid Squamous Cell Carcinoma Aggressive course

NATURAL HISTORY:

The mucosa surrounding the Rosen muller fossa is usually where the malignant transformation of NPC first takes place. When there is no clinically apparent or imaging-confirmed macroscopic tumor but NPC is suspected, this location produces the majority of positive biopsies. It is typical for tumors to extend into the nasal passages and infiltrate them anteriorly. Tumors can directly enter the clivus, sphenoid sinus, and base of the skull superiorly. Inferiorly, Oropharynx extension is not unusual. TheTumors can enter the cavernous sinus and the middle cranial fossa via the foramen lacerum, which is positioned directly above the pharyngeal recess (Rossenmuller fossa) and invade cranial nerves II to VI. The invasion of the levator and tensor veli palatini muscles into the lateral parapharyngeal area occurs early in lateral extension. Pterygoid muscle invasion can be shown in more advance settings. The Eustachian tube (pharyngotympanic tube) is a direct pathway for tumor to enter the middle ear. Because the nasopharynx is in a deep anatomical site, NPC is typically discovered after it has spread to the lymph nodes.[9] Up to 85% to 90% of patients have lymphatic dissemination to ipsilateral nodal areas, with 50% having bilateral metastatic spread.Levels II, III, and IV are the principal tiers of retropharyngeal lymph nodes.[9,10]

CLINICAL FEATURES:

Patients with nasopharyngeal carcinoma typically experience symptoms from at least one of the three following clinical scenarios: (1) neck masses, which typically manifest in the upper neck; (2) a tumor mass in the nasopharynx (epistaxis, nasal obstruction, and discharge); and (3) erosion of the cranium base and palsy of cranial nerves V and VI due to superior tumor extension (headache, diplopia, facial pain, and numbness). Up to 87 percent of patients exhibit cer-vical lymphadenopathy. Cranial nerve palsy occurs less frequently. While cranial nerves I, VII, and VIII are seldom affected, nerves V and VI are frequently affected.1,2

JACODS SYNDROME: Cavernous sinus invasion that causes trigeminal neuralgia, ophthalmoplegia, and blindness by compressing CN II to VI.

HORNERS SYNDROME: Involvement of the cervical sympathetic chain resulting in ptosis, anhidrosis, and miosis.

VILLARET SYNDROME: Lateral RPN compression on CN IX to XII causing dysphagia, dysphonia, and soft palate paralysis.

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

TROTTER S TRIAD (Sinus of Morgagni): Three conditions: conductive hearing loss, temporal-

parietal neuralgia, and ipsilateral pharyngeal paralysis.

DIAGNOSTIC AND STAGING WORKUP:

A comprehensive physical examination must include neck palpation, cranial nerve examination, auscultation of the thorax, palpation of the abdomen for the possibility of liver involvement, and percussion of the vertebrae and bones for the possibility of bone metastasis. For the diagnosis of NPCs, pan endoscopy and biopsy are required. CT and MRI of the head and neck can be used to evaluate tumor erosion into the bony structures of the base of the cranium, as well as retropharyngeal and cervical lymphadenopathy. Magnetic resonance imaging (MRI) is the primary imaging technique for staging evaluation of nasopharyngeal cancer.[10,11,12]

MRI is superior to CT when evaluating the base of the skull and defining muscle and soft tissue involvement.

PET-CT scanning has increasingly supplanted CT, bone scans, and ultrasound in staging procedures. PET demonstrated optimal sensitivity and 90.1% specificity in the research.[13] Plasma EBV DNA levels over time can be used for therapy-related follow-up monitoring based on initial diagnosis results.

STAGING SYSTEM:

Staging is based on American Joint Committee on Cancer (AJCC) staging system 8th edition.

(Tab.1a,b,c,d): Definitions for T, N, M AJCC Cancer Staging Manual, Eighth Edition (2017).[14]

(a) T Primary Tumor

T-Stage	Description
T0	No tumor identified, but EBV positive node
Tis	In situ
T1	Limited to nasopharynx or extension to oropharynx or nasal cavity without parapharyngeal extension
T3	Infiltration of: • Medial Pterygoid • Lateral Pterygoid • Prevertebral Muscles
T4	Involves • Intracranial Extension • CN involvement • Hypopharynx • Orbit • Parotid • Extensive infilteration beyond lateral surface of lateral pterygoids

(b) N-Stage

N-Stage	Description
N1	• Unilateral Metastasis in Cervical lymph nodes • Unilateral / Bilateral in Retropharyngeal lymph nodes • 6 cm or smaller above caudal border of cricoid
N2	• Bilateral in Cervical lymph nodes • 6 cm or smaller above caudal border of cricoid
N3	• Uni / bilateral in Cervical lymph nodes • Larger than 6 cm • Extension below caudal border of cricoid

(c) Distant metastasis:

MO	No distant metastasis
M1	Distant metastasis

(d) Prognostic group staging:

Stage	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T0 - T1	N1	M0
	T2	N0, N1	M0
Stage III	T0, T1, T2	N2	M0
	T3	N0, N1, N2	M0
Stage IVA	T4	N0, N1, N2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

PROGNOSTIC FACTORS:

The extent of local invasion, regional lymphatic spread, and distant metastasis is the single most critical factor in determining prognosis and evidence of distant metastasis, as demonstrated by TNM staging. Non-keratinizing and undifferentiated carcinomas, formerly referred to as lymphoepitheliomas, are more radiosensitive and have a more favorable prognosis than keratinizing squamous cell carcinoma.[1] EBV DNA levels were significantly correlated with tumor burden. High levels before treatment were associated with poor prognosis and advanced disease.[15]

GENERAL TREATMENT PARADIGM:

The general treatment paradigm of nasopharyngeal cancer typically involves a multidisciplinary approach, which according to current guidelines, can include surgery, radiation therapy, chemotherapy, and targeted therapy.

Radiotherapy is the primary treatment for non-small-

cell lung cancer, with chemotherapy added for advanced disease. Surgical intervention is restricted to extremely small primary lesions or small recurrences, as the morbidity of large-scale surgical resection is frequently substantially greater than the morbidity associated with regional radiotherapy.

The specific treatment modalities and sequence depends on various factors, including stage of the cancer, extent of spread, overall health of the patient, and individual preferences.

This review article will present a general overview of the different treatment modalities for nasopharynx cancer.

SURGERY:

In the initial setting, surgery is not routine, but rather reserved as a salvage option for select patients. Salvage neck nodal excision may be utilized to treat persistent nodal disease following primary therapy or nodal recurrence.

Surgery is not used as the initial treatment for primary site due to the relative lack of surgical access to the deep anatomical location of the nasopharynx and its proximity to critical neurovascular structures which is associated with significant morbidity if proceeding surgically.[16]

Surgical exposure, and tumor removal with adequate margins has proven to be quite difficult. Surgical interventions are used mostly for biopsy to get histologic confirmation and salvage therapy for chronic or recurring malignancy.

RADIOTHERAPY:

Nasopharyngeal cancer has traditionally been treated with radiation therapy as it is a radiosensitive tumor, and its anatomic location precludes surgical intervention, therefore radiotherapy remains the mainstay treatment for patients with nasopharyngeal cancer.

The main treatment for nasopharyngeal canceris external beam radiotherapy with or with concurrent chemotherapy depending upon the stage of the disease. The precision of radiation treatment has substantially increased in the past decade due to the development of intensity-modulated radiotherapy (IMRT) and improvements to various imaging modalities, leading to good tumor control and toxicity results in modern cohorts.[17]

Non-keratinizing NPC accounts for about 95% of cases and is responsive to radiation and chemotherapy. As a result, RT serves as the primary treatment for non-metastatic NPC, whereas concomitant chemotherapy is advised for locally or regionally progressed NPC.[18]

In selected cases, RT can be proposed also in the setting of recurrent disease. According to the dose-limiting constraints and to the dose delivered during the primary treatment, the technique of choice is, if feasible, GTV debulking and interventional radiotherapy on the residual local disease or surgical bed (brachytherapy, IRT). In this scenario, such also in the primary treatment of NPC, a promising impact has been shown for proton beam RT even if results of large-scale experiences are still needed.[19]

RADIOTHERAPY TECHNIQUES:

Traditional two-dimensional (2D) radiotherapy has evolved over the years into three-dimensional (3D) conformal radiotherapy and then intensity-modulated radiotherapy (IMRT).[20]

3D CRT provides adequate PTV radiation coverage as measured by the isodose line at 95%. For adequate PTV coverage, however, advanced T stage, intracranial extension, and a large target volume require advanced methods such as IMRT.[21]

Intensity-modulated RT (IMRT) modulates the radiation beams so that a high dose can be delivered to the tumor while the dose to the normal tissues is reduced.

Intensity-modulated radiation therapy (IMRT) is the radiation technique of choice as demonstrated in RTOG 0225. The purpose of RTOG 0225 was to evaluate the viability of IMRT in a multi-institution setting. 70 Grey in 33 fractions were given to gross disease, while 59.4 Grey in 33 fractions were given to subclinical volume.

Acute grade 4 mucositis occurred in 4.4%, and the worst late grade 3 toxicities were as follows: esophagus, 4.7%; mucous membranes, 3.1%; and xerostomia, 3.1%.

Hence it was concluded that IMRT is the treatment technique of choice with minimization of treatment related toxicities.[22] However, radiation planning for NPC is quite challenging and a robust intra departmental peer review process at each step pf planning and delivery of radiation is a mandatory requirement.[23]

As mentioned before, in the setting of recurrent

disease after a primary RT treatment, IRT should be considered in order to adequately spare organ at risk (OAR). Only a few experiences are described in scientific literature, therefore doses and fractionations should be evaluated also considering previously received RT dose. An IRT schedule of 30 Gy in 12 fractions of 2.5 Gy twice a day in 6 days is proposed.[19]

TREATMENT TOXICITY:

The risks of radiation-induced toxicities are significant due to the anatomic proximity of the nasopharynx to vital tissues, the requirement for high radiation doses, and proper field coverage. Severe sequelae including temporal lobe necrosis, hearing loss, xerostomia, neck fibrosis, cranial nerve dysfunction, endocrine dysfunction, soft tissue necrosis, osteonecrosis, and transverse radiation myelitis.[24]

In 90% of patients, cutaneous, salivary gland, mucosal, pharyngeal, esophageal, and laryngeal reactions were observed following radiotherapy.[25]

In the era of IMRT, OARs sparing protocols are usually proposed to avoid main and common toxicities; in parallel, multiple tools to correctly detect and progressively measure during treatment and follow-up are proposed such as quality of life (QoL) questionnaire to assess toxicity through patient-reported outcomes (PROs).[26] Such a tools can be used in traditional or digital ways and, according to the even higher diffusion of digital technologies and to the relevant toxicity, the electronic patient monitoring represents an interesting field of interest for future studies since in large non-cancer-specific randomized clinical trials, it has shown to be superior to traditional evaluations allowing better outcomes.[27,28] This interesting future perspective, where digital health could be integrated with cancer treatments from diagnosis to segmentation and treatment planning and to patient s follow-up, should be tested and evaluated in dedicated disease-specific studies before to be proposed as routine by adequately trained multidisciplinary teams.[29]

INDUCTION CHEMOTHERAPY:

Neoadjuvant chemotherapy followed by radiation alone has been unable to show an advantage in survival in clinical trials. Recent interest in combining neoadjuvant chemotherapy and concurrent chemoradiation has been substantial.

Compared to adjuvant sequencing, induction chemotherapy is better tolerated and eradicates micro metastases more rapidly; consequently, induction chemotherapy followed by concurrent chemoradiotherapy may represent a promising treatment strategy for nasopharyngeal carcinoma in the era of IMRT.[30]

In a phase 3 multicenter, randomized, controlled trial involving 10 Chinese institutions. Patients with locally advanced nasopharyngeal carcinoma were evaluated for the inclusion of induction chemotherapy (cisplatin, fluorouracil, and docetaxel every three weeks for three cycles) to concurrent chemoradiation without induction chemotherapy.

The eligibility criteria included stages III IVB (excluding T3-4N0). Chemotherapy was administered concurrently as cisplatin 100 mg/m^2 every three weeks for three cycles. Principal purpose FFS. MFU 45 months, 3-year FSS rose from 72% to 80% (p =.034) in favor of chemotherapy induction. Induction of CHT was associated with increased grade 3/4 toxicity: 42% neutropenia as compared to 17% neutropenia, 41% leukopenia as compared to 17% leukopenia, and 41% stomatitis as compared to 35% stomatitis. Induction CHT significantly improved 3-year FFS compared to concurrent chemoradiation alone.[31]

In conclusion, induction chemotherapy plays an increasingly important role in the management of locoregionally advanced nasopharyngeal carcinoma in the IMRT era, helping to improve distant control and consequently survival; patients at high risk of distant metastasis may benefit from additional induction chemotherapy over concurrent chemoradiotherapy alone.

CONCURRENT AND ADJUVANT CHEMOTHERAPY:

Patients with stage I NPC are amenable to definitive radiation therapy alone. In locoregionally advanced nasopharyngeal carcinoma, several studies have demonstrated the survival advantage of concurrent chemoradiotherapy with or without adjuvant chemotherapy versus radiotherapy alone.

A phase III randomized control trial studied 230 patients with stage II nasopharyngeal cancer. They were randomly assigned to receive concurrent chemoradiotherapy with weekly cisplatin (30 mg/m^2) or radiation alone. With concurrent chemoradiotherapy,

5-year overall survival was enhanced, but acute toxicity was exacerbated.[32]

Multiple trials have demonstrated the benefit to concurrent chemoradiotherapy in locally advanced nasopharyngeal cancer.[33,34]

Therefore, concurrent chemoradiotherapy is deemed the mainstay treatment in locoregionally advanced disease.

Furthermore, in a recent randomized clinical trial, adjuvant capecitabine following definitive chemo-radiation was found to be beneficial in terms of failure-free survival with an acceptable toxicity profile for patients with locally advanced disease and high-risk disease.[35]

RECURRENT DISEASE:

Approximately 10% of patients have residual or recurrent disease at the primary and/or regional site in the time of IMRT. With a 5-year survival rate of 41%, it is generally recognized that neck dissection is the treatment of choice for patients with isolated regional failure.[36]

Local nasopharyngeal failure is salvageable with radiotherapy or surgery, typically, tumors that recur within a year are radioresistant; if they are resectable, surgery is advised. Reirradiation is preferable to systemic therapy for patients with larger (cT3 to T4) locoregionally recurrent nasopharyngeal tumors, unresectable disease, or who are ineligible for surgery or wish to avoid it. Although reirradiation and systemic therapy have not been directly compared, reirradiation has extended follow-up on OS outcomes in this population. Patients who are ineligible for reirradiation or who wish to avoid the potential late toxicities associated with reirradiation may be administered systemic therapy employing a similar strategy as patients with metastatic disease. Candidates for reirradiation are those with no history of substantial RT toxicity and at least a one-year gap between initial RT and reirradiation. In a randomized trial, reirradiation with hyper-fractionated IMRT increased OS and decreased severe late radiation-related side effects.[37]

Other techniques for reirradiation have been studied in this context, such as endoscopy guided IRT, but clinical trials have not directly compared them. These methods include:

3D Conformal radiation, intracavitary and interstitial brachytherapy, including radioactive gold grain implantation, stereotactic radiosurgery, fractionated stereotactic radiation, proton beam radiation.

Conflict of Interest: None

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