

Nasopharyngeal carcinoma: A new synthesis of literature data (Review)

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Abstract. Nasopharyngeal carcinoma (NPC) is an epithelial tumor, which develops most frequently from the lateral

pharyngeal recess and holds some complex epidemiological characteristics. Its unusual race and geographic distribution suggests that not only the environmental factors are a contributing factor to the development of this rare cancer type, but also the genetic traits play an important role, along with nitrosamine-containing food consumption and Epstein-Barr virus infection. The signs and symptoms which a patient can present and suffer from are various and include nasal, otic, neurological as well as general ones; the way this tumor manifests being dependent on the stage of the tumor. The therapeutic management applicable in NPC needs to be established according to the case of the patient and include radiotherapy, chemotherapy, surgery, immune therapy, targeted therapy or combined treatment. The main objective of the treatment is local and regional tumor control; relapse is an important factor for future development of distant metastases. New therapeutic concepts are always sought of, current research focusing on precision medicine, meaning systemic treatment with a personalized radiotherapy approach according to the characteristics of the tumor.

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Abbreviations: 2D-RT, two-dimensional radiotherapy; AJCC, American Joint Committee on Cancer; anti-IL-6R mAb, anti-human IL-6R monoclonal antibody; DNA, deoxyribonucleic acid; EBER, EBV-encoding region; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HNC, head and neck cancers; HPV, human papilloma virus; HT, helical tomotherapy; IL-6, interleukin-6; IMRT, intensity-modulated radiation therapy; LMP1, latent membrane protein 1; MMP-2, matrix metalloproteinase 2; MMP-9, matrix metalloproteinase 9; NPC, nasopharyngeal carcinoma; ORL, otorhinolaryngology; WHO, World Health Organization

Key words: nasopharyngeal carcinoma, Epstein Barr virus, histopathology, radiotherapy, chemotherapy, surgery, genetic modification

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1. Introduction

At present, epidemiological data supports the fact that head and neck tumors are a major public health problem due to their continuously rising incidence, prevalence and death rate. Head and neck cancers (HNC) account for over 550,000 cases and 380,000 cancer-related deaths worldwide, annually (1). Most otorhinolaryngology (ORL) tumors have an insidious, asymptomatic development, thus being either an incidental finding, or a late diagnosis of advanced, therapeutically unmanageable tumors (2,3).

The region of the body usually known as 'head and neck' includes the superior aero-digestive tract, which incorporates the oral cavity, paranasal sinuses, pharynx, larynx, cervical esophagus, thyroid, associated lymph nodes, soft tissues and bones. The various tissues from this anatomical region give rise to a large spectrum of tumors and tumor-like conditions (4). One of the most unusual malignant tumors among HNC is the nasopharyngeal carcinoma (NPC).

The nasopharynx is part of the upper airway system and an anatomical element connecting the nasal cavities with the larynx and trachea, through the oropharynx. It is the most superior part of the pharynx, having as a superior anatomical limit the skull base and as an inferior one, the soft palate. It comprises important local and regional anatomic elements such as the pharyngeal orifice of the Eustachian tube, Rosenmüller fossae and Gerlach's tubal amygdala. The most frequent malignant tumor found at this level is NPC, an epithelial tumor which develops from Rosenmüller's fossa (5).

2. Materials and methods

The present review is the result of a thorough literature research which included studies from 1979 to 2021, using databases such as Web of Science and Google Scholar with the help of keywords such as 'nasopharyngeal carcinoma' alone or associated with others key words such as 'treatment' or 'etiology'. Other articles and means of information were selected, after they had been deemed useful for our research, such as the World Wide Web, using sites as WebMD or NCBI. In total, 58 studies were included in the present review.

3. Epidemiology and etiology

A distinctive entity among HNC, NPC is characterized by a distinct worldwide distribution (6), being considered endemic in the southern region of China where the incidence is ~15-50/100,000 inhabitants, and also in Indonesia, Malaysia and South-East Asia (7).

Causal factors for NPC development include: tobacco, alcohol and nitrosamine-containing food consumption. Alcohol, especially when it is combined with tobacco, has an increasing effect as regards the risk of developing this type of cancer. The aforementioned factors have a multiplying, synergistic effect on the risk for oral cavity, pharyngeal and

laryngeal cancer development (8,9). Similarly, other incriminating factors in the development of these cancer types are considered to be a rich diet in salt preserved fish and meat (9), host genetics (HLA gene on the 6p21 chromosome), environmental factors (such as chemical substances or carcinogens) as well as the Epstein-Barr virus (EBV) or human papilloma virus (HPV; the high-risk subtypes: 16, 18, 31, 33 and 35) infection. Extremely rare cases have been also linked to the human immunodeficiency virus (HIV) infection; one case presented the patient as being co-infected with EBV. Much as the Koebner phenomenon in skin disorders, NPC develops in a prior set environment, with certain characteristics which support malignant growth (5,10-15).

A first step in NPC development is considered to be the stable infection with EBV in the nasopharyngeal epithelium. Similarly, at the epithelial cell level, EBV infection manifests through lithic replication; in NPC development, slow replication appears to be the dominant infective manner (16). EBV slowly infects epithelial cells at this level, and sporadically enters the productive lithic viral infection. In this manner, type II latency is maintained, and EBV gene expression is limited to mRNA which is coded by these oncogenes: BNA1, LMP1, LMP2, EBER and BART (17). The expression of lithic EBV genes has been detected along with the latent membrane protein 1 (LMP1) which can induce genomic instability and stimulate immune-suppressive cytokine release in order to evade immune recognition of the viral infected cells. As such, latent genes and lithic ones are involved in the malignant transformation of the nasopharyngeal epithelium (16).

One of the most studied oncoproteins is LMP1; it is considered to be the main EBV oncoprotein, which on the one hand can induce important genetic and epigenetic alterations, and on the other hand can promote cellular mobility, invasion and cervical lymph node metastasis, a unique characteristic of NPC (18,19).

In short, the oncogenic activity of EBV is revealed by the important effects exerted on the host genome, modifying its genetic profile, inducing genomic instability, evading host immunity and promoting cell survival through LMP1 activity. Another important fact stems from the activity of EBV; being able to induce stem-cell like properties in NPC tumor cells (16).

Inflammation is a key player in the cytokine release phenomena, and also in tumor development, progression and migration. Literature data suggests that malignant cells use chemokine gradients in order to metastasize to other body sites. Interleukin-6 (IL-6) appears to have a role in NPC progression, as it has the capacity of promoting malignant behavior. It is involved in NPC and also other types of malignant tumors: pancreatic, breast, prostate and lung cancers; it influences the capacity of invasiveness and migration of NPC cells by increasing it through mediation of matrix metalloproteinases 2 and 9 (MMP-2 and MMP-9). IL-6 and its receptors are highly expressed in NPC cells (20-23). Chow *et al* revealed that NPC patients have higher IL-6 levels as compared with the average, healthy individuals, and have stated that NPC tumor cells may be also a source for IL-6 (23). Targeting its receptor could be at least an associated treatment in NPC; the monoclonal, anti-human IL-6R antibody (anti-IL-6R mAb) having inhibitory effects on the malignant cell proliferation, and on the migrating and invasive capacities of NPC cells (20-23).

4. Histogenesis

NPC develops from the surface of crypt epithelium found in the mucous layer of the nasopharynx. In some cases, this tumor can stem from the basal layers of the stratified squamous epithelium, a fact supported still by the strong immune reactivity for p63, both in the tumor and the normal basal cells (16).

5. Signs and symptoms

The signs and symptoms that NPC patients can present with are according to the stage and extension of the tumor, and can be grouped as follows:

The nasal level: unilateral nasal obstruction, epistaxis, nasal voice, olfactory acuity decrease, and olfactory disorders which can range even as severe as cacosmia. Almost 80% of patients suffer from nasal signs and symptoms (7,24).

The otic level: recurrent middle ear infections with ototubal dysfunction, hypoacusis to cophosis, ear fullness sensation, otorrhea, otorrhagia, middle ear effusion and tinnitus (7,24).

Neurological signs and symptoms develop in accordance to the tumor extension and implicitly, to the nerve structures which it involves: vestibule-cochlear nerve, facial and abducent nerve, with certain sensibility loss (7,24).

Lymph node enlargement can also accompany the evolution of NPC, localizing at the cervical or submandibular level, or even at distant sites (7,24).

General signs and symptoms which the NPC patient can develop are: headaches, low fever, anemia and weight loss (7,24).

In the early stages of NPC development the signs and symptoms are nonspecific, setting in slowly and the most frequent ones are otic, nasal or ocular. The following time frame is characterized by an increase in the intensity and persistence of symptoms, this especially taking place as the tumor expands and as it extends intracranially.

Having in mind the characteristics presented earlier, NPC appears to have a propensity for distant metastasis, with a higher frequency than other types of HNC. In the order of their frequency, metastases can be localized in the bones, liver, lungs and distant lymph nodes (25).

6. Classification, staging and diagnosis

The World Health Organization (WHO) classifies NPC by its histopathological characteristics in the following types: keratinizing type (up to 25%), non-keratinizing differentiated type (almost 15%) and non-keratinizing undifferentiated (up to 65%) (7).

EBV-associated, undifferentiated NPC has certain special characteristics such as: invasiveness, distant metastases, and sensitivity to both radiotherapy and chemotherapy. Differentiated NPC, which is not associated with EBV, is similar to other ORL cancers, having a mostly local and regional development (a distant one to a lesser extent), and is less sensitive to chemo- and radiotherapy (17).

NPC staging is conducted according to the eighth edition of the American Joint Committee on Cancer (AJCC) staging (26,27).

The primary tumor can range from an *in situ* one (Tis), to an extensive infiltrating one (with intracranial, orbital, hypopharyngeal, parotid or soft tissue involvement) (T4). Lymph node involvement (N) can range from absent regional lymph node metastases (N0), to uni-/bilateral cervical lymph node metastases (over 6 cm) and/lymph node metastases extending under the cricoid cartilage (N3). Distant metastases can be absent (cM0), present (cM1) or present and with microscopic confirmation (pM1). The anatomic stage and prognostic groups stem from the earlier characterization of the tumor and its behavior, ranging from stage 0 to stage IVC (7).

It has already been established that the terms pM0 and Mx are not taken into consideration for tumor staging; these are frequently used in the pathologic (p) or clinical (c) classification, which are useful in those cases where surgical intervention is the most suitable therapeutic option (26).

In order to diagnose this type of cancer which is mostly a late finding, it is necessary to perform an elaborate local examination with the help of a posterior rhinoscopy or endoscopy, associated with a biopsy obtained from key-tissue changes. Imaging techniques can help in rhinopharyngeal tumor diagnosis by accurately describing the tumor diameter, its precise location and whether there is extension to the neighboring structures (5). As a plus, EBV detection can be a useful marker for diagnosis (28).

The most simple and reliable method of diagnosing the presence of EBV is by using the *in situ* hybridization for the EBV-encoding region (EBER), which is present in abundance in the latent-infected EBV cells. Less reliable is the use of the polymerase chain reaction in order to search for EBV in the tumor cells, due to the fact that even low numbers of EBV-positive lymphocytes can generate a false-positive result (29).

The latest medical research has accentuated the need for plasma EBV deoxyribonucleic acid (DNA) liquid biopsy in population screening (30).

7. Genetic components

Genetic factors in NPC development are considered co-factors, along with EBV infection and food consumption containing nitrosamines. Some genes that are considered to play a role in the development of this type of cancer are: HLA class I genes, TP53 and MDM2 (cell cycle control genes), MMP2 (cell adhesion/migration gene) and RAD51L1 (DNA repair gene). There is a great deal of research required in finding a genetic background for NPC, although the specialty literature has consistent findings with regard to the aforementioned genes (31).

8. Relation to other associated pathologies and medication

Statins are an already well-known class of drugs having the capacity to induce pro-apoptotic and anti-proliferative activities in cancer cells, being thus able to act as anticancer drugs. In NPC, the molecular mechanism and the possible effects of statins are yet unknown, although research conducted by Ma *et al* (2019) has revealed promising results (32). Simvastatin, an inactive prodrug before being hydroxylated in the gastrointestinal system, used as a chemotherapy treatment agent, had

positive effects on an NPC cell line by reducing the viability of the cell line (in a dose-dependent manner), increasing enzymatic activity (caspase-3), and also inducing apoptosis through cell-arresting effects in the G1 cycle phase (32,33).

Chronic ORL diseases have been associated with an increased risk for NPC. Patients who used nasal drops or even aspirin were revealed to have a two-fold risk of developing this type of cancer. These chronic diseases, along with the related drugs had no significant effect concerning NPC development if more than 5 years has passed since their occurrence. Important factors appear to be the untreated, chronically evolving nasal polyps, the uncured, chronic ORL diseases, the younger patients at first diagnosis and the recent or even first-time aspirin use. Another medication which is positively involved in cancer development is hydrochlorothiazide, a diuretic or saluretic which is associated with squamous cell carcinoma located on the lip (34,35).

Beta-blockers, mainly used for heart failure, hypertension, intention tremors, but also for dermatologic diseases including hemangiomas, Kaposi sarcoma, melanoma, or pemphigus are generally considered safe. Their activities are exerted by blocking the β -adrenergic receptors in the body, where they are abundant in numerous organs or tissues. Some research has revealed that these receptors are also expressed by malignant cells or immune cells, and by activating them, consequent changes could take place with regard to the tumor microenvironment. This indicates that they influence tumor proliferation, migration and also invasion. That, being said, some studies revealed that beta-blocker use did not in fact influence the incidence of head and neck cancer, while another study reported that propranolol reduced the viability of head and neck cancer, inducing apoptosis and decreasing production of VEGF (36-39). Further studies need to be conducted in order to find the precise implications and consequences that beta-blockers have on NPC.

Tetracycline, a drug which also possesses anti-inflammatory properties, with TNF- α inhibition, is used either alone or in combination with other drugs and it has the capacity to decrease the synthesis of energy in a cell, and thus, block cell division. It therefore has a potential therapeutic ability in cancer cases, possibly used as a carrier for various medications towards the cancerous cells or even by coupling them with radionuclides for use in local radiotherapy. Tetracycline appears to have cytostatic effects in NPC or laryngeal cancers and a study conducted by Leezenberg *et al* in 1979, revealed that patients suffering from these types of cancers, when administered tetracycline in association with other therapies, had a longer survival (40,41).

Concerning diseases that are associated with NPC, studies have revealed that connective tissue diseases, such as scleroderma or dermatomyositis, are found in patients suffering from such a malignancy. Connective tissue diseases, similarly to diabetes, are a burden for the organism in terms of prevalence and impairment. The mechanism by which NPC and connective tissue diseases are linked remains unknown, but there are hypotheses that state that one may influence the development of the other; dermatomyositis being occasionally diagnosed as paraneoplastic. Furthermore, another hypothesis is the possible immune dysregulation with abnormal recognition of tissues. The fact that malignant tumors develop from normal

cells of the body that suffer various genetic alterations, may be the link between NPC development and autoimmune diseases such as connective tissue ones. This could also explain the association between two or more autoimmune diseases (such as the association between thyroiditis, vitiligo and alopecia aerata or multiple autoimmune syndrome type 3). Diabetes is known to act both as a risk and prognostic factor in malignancy development; it is a disease which favors infection and inflammation, with important medical and social consequences. In NPC, Peng *et al* revealed that diabetes mellitus patients had a poorer prognosis, with lower disease-free survival rates, more frequent loco-regional relapse and lower overall survival rates (42-45).

9. Management

The therapeutic approach of NPC should be personalized for each patient, according to some factors such as the time of diagnosis (early or late diagnosis), tumor stage, tumor grade and histopathology type, depth of tumor invasion, performance status, local expertise availability, the general health state of patients, associated pathology, and preferences.

The therapeutic possibilities that can be applied according to the case of the patient, are: radiotherapy, chemotherapy, surgery, immune therapy, targeted therapy or combined treatment. The main objective of the treatment is a favorable local and regional control of the tumor, as it was found that relapse is an important factor in the development of distant metastases (18).

Most NPC are radiosensitive, this being an important treatment factor. Although conventional two-dimensional radiotherapy (2D-RT) can successfully control T1-T2 tumors in 75-90% of cases, and T3-T4 in 50-75% of cases (without distant metastases), there is a great deal of inconvenience.

Due to its positioning, the nasopharynx is surrounded by a series of anatomical elements which are extremely radio-sensitive including the medulla oblongata, spinal cord, eyes, middle and internal ear, parotid gland, temporal lobes and the hypothalamus-pituitary axis. The main characteristic of NPC is the fact that it infiltrates rapidly in the neighboring structures, and thus the radiation volumes are irregular, with multiple toxicities to the elements involved by the tumor (18).

In the latest years, techniques have evolved, going from conventional 2D or 3D, to intensity-modulated radiation therapy (IMRT). IMRT is an advanced form of RT which modulates radiation in order to closely target the tumor; it adapts the radiation dose according to the shape of the tumor, its center receiving the highest dose of radiation and decreasing its intensity towards the periphery. It allows a local tumor control in 90% of patients, being the new standard therapy for NPC. That being said, helical tomotherapy (HT) is another innovative type of RT, that similar to IMRT, is based on inverse planning, but it uses a rotational gantry system and not fixed numbers of beam angles. Chen *et al* reported important dosimetric outcomes with improved patient outcomes with the use of HT, but further studies need to be performed in this direction (18,46).

Another innovative RT treatment is brachytherapy, which uses removable implants that are placed in the tumor area and that are extracted after the adequate dose has been

administered. Frequent radioactive substances used are iridium 192, cesium, radium or cobalt. Some studies which researched the dose response found that higher radiation doses determine improved local tumor control, but also increase the rate of severe complications (palate and/or sphenoid floor perforation and nasopharynx necrosis). Brachytherapy has favorable outcomes for primary and recurrent NPC, it is well tolerated and has minimal morbidity (47-49).

Radiotherapy is also used when other therapies have failed, or when the tumor has relapsed (7). A recent concept is adaptive radiotherapy which uses one or more sessions with the purpose of correcting some variables that are patient-derived and that can develop during treatment, this in order to optimize the dose distribution in every patient. The beneficial roles of this new concept are toxicity decrease and local control improvement in advanced carcinomas, however time is required in order for it to be introduced as routine practice (50).

NPC was determined to also be sensitive to chemotherapy, and radiotherapy sensitivity is correlated highly with chemotherapy sensitivity. The standard of care in locally and regionally advanced cases of NPC is concomitant platinum-based chemotherapy (7,18,51). That being said, induction chemotherapy appears to be superior to concomitant chemotherapy alone (30). Administered before chemotherapy treatment, concomitant radiotherapy has the benefit of maintaining a good local, regional and distant control, results comparable to IMRT (52).

Over time, various treatment combinations have been studied, however, cisplatin is at the basis of NPC treatment, in doses of 100 mg/m² every 3 weeks (7). The main manner by which platinum-based chemotherapy works is by damaging the cancer cell DNA through the inducement of apoptosis. Although it is considered to be the treatment basis, cisplatin can have important toxicities including ototoxicity, nephrotoxicity, nausea, vomiting, liver enzyme increases, peripheral neuropathy, or bone marrow inhibition; if it is administered concurrently with radiotherapy, it can exacerbate acute toxicities such as mucositis or dermatitis (53).

New research studies are awaited with regard to the efficacy of gemcitabine administered in association with cisplatin as induction chemotherapy treatment in local and regional advanced NPC (52).

Other chemotherapeutic agents that can be used are: cetuximab, 5-fluorouracil or docetaxel. Monoclonal antibodies that are newly approved are: nivolumab and pembrolizumab (53). As it is already known, immune therapy uses agents that have the capacity to block immune control check-points; it is considered as a revolution in treating advanced metastatic and recurrent cancers. The current research focuses on the efficacy of ipilimumab which mainly targets CTLA-4 and is used in combination with nivolumab in the treatment of rare tumors which also include NPC (30).

In treating NPC, surgical intervention is considered to be a safe option (7). As an anatomical region which is difficult to approach surgically, the nasopharynx is rarely a surgically approached region; it is located close to some vital vascular and nerve structures such as foramen ovale, foramen lacerum, foramen spinosum, foramen jugulare and the carotid canal. That being said, when necessary and recommended, the

nasopharynx can be surgically treated through a trans-palatine-maxillary-cervical approach, a trans-mandibular approach, a transcervical-mandibular-palatine approach, through the infratemporal fossa, a lateral temporal approach (although with a significant failure rate of 15.6-58%), or an endoscopic approach (7,54).

The main treatment approach of NPC is radiotherapy, more importantly, IMRT, which is frequently administered in association with chemotherapy; for recurrent tumors, brachytherapy is the main treatment method, with the risk of skull base radiotherapy necrosis development (47,55). Stereotactic radiosurgery can also be used (24). Although radical dissection of cervical lymph nodes is indicated in recurrent or persistent NPC cases, numerous patients only receive palliative chemotherapy (18).

In addition to the aforementioned IL-6R blockers, recent research has focused on melatonin, a compound with oncostatic properties which modulates the angiogenic, proliferative and metastatic properties of some cancers, including the HNC. Stanciu *et al* (2020) found that patients with oral squamous cell carcinoma had decreased levels of melatonin and that this hormone can be used in the assessment of cancer progression, being a predictive biomarker for metastatic spread; they also stipulated that melatonin could be used as a possible therapeutic agent for preventing tumor progression (56).

NPC treatment is multidisciplinary. Irrespective of the selected therapeutic approach, the main treatment purpose is tumor eradication with minimization of adverse effects, the improvement of the quality of life of the patient and relapse prevention. At present, new concepts are introduced with regard to anticancer treatment, including the use of precision medicine, which refers to administering a systemic treatment and personalized radiotherapy according to tumor characteristics (57).

10. Conclusions

NPC is an epithelial tumor with one of the most aggressive behaviors among HNC, having high rates of invasion and metastasis and frequent failure of treatment. It is a radiosensitive malignant tumor and radiotherapy remains the basis for treatment; combined treatments, also using chemotherapy, have yielded improved disease-free survival rates. With more accurate radiotherapy techniques, local and regional tumor control has been improved, while new treatment options are necessary for metastatic spread management (such as IL-6R blockers).

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Availability of data and materials

The information generated and analyzed during the current study is available from the corresponding author on reasonable request.

Authors' contributions

DJS, EN, ALT, ML, SF, FB, CO and LR contributed to the acquisition, analysis and interpretation of data. DJS, EN, ALT, ML, SF, FB, DV and LB made substantial contributions to the conception and design of the work, while DJS, EN, ALT, ML, SF, FB, MIS and RM supervised and substantially revised this work. DJS and EN confirm the authenticity of all the raw data. All authors have read and approve the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare they have no competing interests.

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