Review of nasopharyngeal carcinoma

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Abstract

We review the literature on nasopharyngeal carcinoma that has been published within the past 5 years. Nasopharyngeal carcinoma is a highly morbid disease, and survival is poor. Its management remains extremely difficult, not just for otolaryngologists but for radiation oncologists and medical oncologists, as well. A clear understanding of its etiology is still lacking, but nasopharyngeal carcinoma is widely suspected to be the result of both a genetic susceptibility and exposure to environmental factors or Epstein-Barr virus infection. With no clear cause, treatment is controversial. For example, an optimal radiation regimen has not been determined, reports in the literature regarding the role of chemotherapy for advanced disease are conflicting, and treatment of local recurrences is unsettled. Still, advances in immunologic research and chemotherapy offer hope for better control of the disease. We hope that our assessment of the recent literature will provide otolaryngologists with a more clear understanding of the etiology and management of nasopharyngeal carcinoma.

Introduction

Nasopharyngeal carcinoma is a rare tumor that arises in the epithelium of the nasopharynx. It accounts for more than 95% of nasopharyngeal malignancies in adults and 20 to 35% of nasopharyngeal malignancies in children. It is often misdiagnosed early because of the vagueness of the presenting symptoms and the difficulty of the nasopharyngeal examination.

Anatomy

The nasopharynx is a trapezoid chamber located posterior to the nasal choanae; it extends inferiorly to the lower border of the soft palate. The superior border is formed by the basisphenoid and basiocciput. The posterior border is made up of the prevertebral fascia of the atlas and axis.

Histology

At birth, the nasopharynx is lined with a predominantly pseudostratified columnar epithelium. Over the first 10 years of life, this epithelium gradually transforms into a predominantly stratified, nonkeratinizing squamous epithelium, except in a few areas (transition zones).

Epidemiology

The incidence of nasopharyngeal carcinoma in the United States and Europe is only about 1 per 100,000 population, but in Taiwan, Hong Kong, and southern China (especially Guangdong province), the incidence is approximately 30 times higher. The risk of nasopharyngeal carcinoma in any given area rises when Chinese genes are introduced into the area. The incidence among Africans and Filipinos is approximately 2 to 4 per 100,000 population. Nasopharyngeal carcinoma is more common in males by a margin of about 2 to 1. Its incidence peaks at 50 to 60 years of age; a small peak also occurs during late childhood.

Genetic analysis of endemic populations has revealed that the association of HLA-A2, HLA-B17, and HLA-Bw26 doubles the risk of nasopharyngeal carcinoma. These HLA associations are not seen in North America.

Another important etiologic factor in some types of nasopharyngeal carcinoma is the Epstein-Barr virus (EBV). The detection of the EBV nuclear antigen and viral DNA in nasopharyngeal carcinoma has revealed that EBV can infect epithelial cells and that it is associated with their transformation to cancer. Clonal EBV DNA has been found in some preinvasive lesions, suggesting a relationship to the transformation process.

Other associations include chronic nasal infections, poor hygiene, poor ventilation of the nasopharynx, and exposure to nitrosamines and polycyclic hydrocarbons in salt-preserved foods.
Clinical presentation
Nasopharyngeal carcinoma rarely comes to medical attention before it has spread to regional lymph nodes. Skinner et al found that a unilateral neck mass was the most common presenting sign, occurring in 36% of cases. Other authors have reported rates as high as 80%. Other presenting symptoms include blood-stained nasal discharge (18% of cases), unilateral hearing loss (12%), and unilateral nasal obstruction (5%). Cranial nerve involvement subsequent to invasion of the skull base is seen in 25% of cases. The two principal cranial nerve syndromes associated with nasopharyngeal carcinoma are retroparotid syndrome (involving cranial nerves IX, X, XI, and XII) and petrophenoid syndrome (involving cranial nerves III, IV, V, and VI). Occasionally, cranial nerve II becomes involved through the foramen lacerum.

Typically, nasopharyngeal carcinoma carries a poor prognosis because of its proximity to vital structures, its invasiveness, the subtlety of its symptoms, and the difficult nature of the examination, especially for primary care physicians. Rates of distant metastasis at presentation are 3% in the United States and up to 6% in endemic areas of the world.

Pathology
In 1979, the World Health Organization (WHO) defined three types of nasopharyngeal carcinoma on the basis of findings on light microscopy.

Type I. This keratinizing squamous cell carcinoma is characterized by the presence of intracellular bridges and prominent keratin formation. Type I tumors account for approximately 25% of all nasopharyngeal carcinomas in North America but only 1% of cases in endemic areas. Patients with type I disease have the worst prognosis, as the 5-year survival rate is only 35%.

Type II. This tumor exhibits the maturation sequence characteristic of squamous cell carcinoma but no keratin formation. This is the least common of the three types, and it is often classified as type III. The 5-year survival rate is 61%.

Type III. This undifferentiated carcinoma is made up of cells of varying morphology, and it frequently contains clumps of benign T cells intermixed within the tumor mass; as a result, it is also called a lymphoepithelioma. Type III tumors account for 95% of all cases in endemic areas and 60% of cases in North America. The 5-year survival rate is 61%.

Rates of distant metastasis are higher in patients with type II or III tumors than in patients with type I tumors. On the other hand, type II and III tumors are more easily controlled, owing to their greater degree of radiosensitivity, and therefore patients with type II or III disease have a better prognosis.

Diagnosis
The diagnosis of nasopharyngeal carcinoma is based primarily on the history and physical examination. Obviously, a definitive diagnosis requires a biopsy of the lesion, either in the office or in the operating room. The preferred imaging modalities are computed tomography (CT) with contrast and magnetic resonance imaging (MRI) with enhancement. Most oncology texts appear to favor MRI over CT because it provides more details on extension and intracranial involvement. On the other hand, CT demonstrates more evidence of bony erosion. These factors are all important in the staging of the disease.

Staging
Approximately 20 different staging systems for nasopharyngeal carcinoma have been reported in the literature since the early 1950s. John Ho, a preeminent radiation oncologist, developed a staging system in the late 1960s that was used for many years. Ho's system, which is based on the natural history of the disease and autopsy observations, is still used in China, but it has been replaced by more standardized systems elsewhere. Even so, the systems that have replaced Ho's have various inadequacies of their own. In 1989, for example, Neel and Taylor used Cox regression methods to identify five disease-related characteristics that were significantly associated with survival, but their system was not adopted by many institutions because its criteria were completely different from existing systems that had been used to stage nasopharyngeal cancers. The major drawback of the system published by the American Joint Committee on Cancer (AJCC) in 1992 was the unevenness of the patient distribution—specifically, too many patients were pooled into stage IV. The AJCC subsequently improved the distribution of patients and adopted some of Ho's prognostic criteria (e.g., the involvement of the supraclavicular fossa), and in 1997 and 2002, it published updated guidelines that are standard in most institutions. The widespread acceptance of the newest AJCC system (tables 1 and 2) has made it much easier to compare outcomes in different centers.

Molecular markers
Most tumor markers are proteins found in plasma or serum that have some degree of specificity for a particular tumor. Proteins are used as markers partly because of their relatively high concentrations in serum and plasma and because of the ready availability of immunologic methods (e.g., radioimmunooassay and enzyme-linked immunosorbent assay) that provide rapid and accurate quantification of markers. With a potentially superior therapeutic index, molecular markers represent an exciting advance in that they can be used to generate immunotherapy that will complement conventional chemotherapy.

Markers for nasopharyngeal carcinoma include p53,
patients with metastatic disease, had detectable levels of radiation.

Of note, no large randomized trial comparing EBV DNA in plasma; none of the disease-free controls had detectable EBV DNA. The role of immunotherapy based on EBV latent membrane proteins is under study.

Table 1. The 2002 AJCC criteria for staging nasopharyngeal carcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor is confined to the nasopharynx</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor extends to the soft tissue of the oropharynx and/or nasopharynx</td>
</tr>
<tr>
<td>T2a</td>
<td>No extension to the parapharyngeal space is present</td>
</tr>
<tr>
<td>T2b</td>
<td>Extension to the parapharyngeal space is present</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor has invaded bone and/or the paranasal sinuses</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor extends intracranially and/or involves the cranial nerves, hypopharynx, infratemporal fossa, or orbit</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis is present</td>
</tr>
<tr>
<td>N1</td>
<td>Unilateral node metastasis is present above the supraclavicular fossa; node is 6 cm or smaller</td>
</tr>
<tr>
<td>N2</td>
<td>Bilateral node metastasis is present above the supraclavicular fossa; node is 6 cm or smaller</td>
</tr>
<tr>
<td>N3</td>
<td>Node metastasis is present</td>
</tr>
<tr>
<td>N3a</td>
<td>Node is larger than 6 cm</td>
</tr>
<tr>
<td>N3b</td>
<td>Metastasis to the supraclavicular fossa is present</td>
</tr>
</tbody>
</table>

Table 2. The 2002 AJCC staging system

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>N1</td>
<td>II</td>
<td>II</td>
<td>III</td>
<td>IV</td>
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<tr>
<td>N2</td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>N3</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
</tbody>
</table>

Epidermal growth factor receptor (EGFR), angiogenic factors, EBV, proliferating cell nuclear antigen, Ki-67, and c-erbB2. Genc et al showed that although p53 positivity correlated with the presence of lymph node disease, it was not a significant factor in predicting outcome. Studies by Chua et al and Leong et al showed that expression of EGFR was increased in nasopharyngeal carcinoma. This finding paved the way for a phase II study of cetuximab in combination with carboplatin. The overall response rate was 17%, and the rate of partial response or stable disease was 66%. EGFR may be a viable target for further clinical trials.

Vascular endothelial growth factor (VEGF) is an angiogenic factor. Guang-Wu et al reported that VEGF was expressed in 10% of subjects who had a normal nasopharynx, in 40% of patients who had a benign tumor of the nasopharynx, and in 80% of those who had nasopharyngeal carcinoma. They also reported that expression of VEGF was seven times higher in patients with advanced nasopharyngeal carcinoma. Despite these findings, the role of VEGF as a potential target has yet to be explored.

EBV DNA in plasma; none of the disease-free controls had detectable EBV DNA. The role of immunotherapy based on EBV latent membrane proteins is under study.

Treatment

Radiotherapy. It was not until the 1920s that radiation therapy was considered for nasopharyngeal carcinoma. The early reluctance to irradiate the nasopharynx was attributable to its proximity to other radiation-sensitive structures, such as the eye and spinal cord, as well as to the poor depth of penetration of x-rays at that time. In the early 1920s, the first intercavitary treatment with radium was performed at the Institut Curie in Paris. This brachytherapy continues to be used in some places today for the treatment of primary T1 and T2 tumors thinner than 10 mm, although radium has been replaced by iridium 192. Until 1977, the standard of care for nasopharyngeal carcinoma in North America was standard fractionated radiation therapy.

Typical radiation fields encompass the adjacent skull base and the nasopharynx. Fields are bilaterally directed and include the retropharyngeal drainage pathway and the anterior and posterior cervical chains. Patients with stage I or II nasopharyngeal carcinoma have a high rate of cure with radiotherapy alone, but the prognosis for those with distant metastasis is poor. Tumor control has been highly correlated with the amount of radiation delivered to the tumor. In a review of 13 randomized trials with similar dosing by Agulnik and Siu, most of the studies involved the use of a split-field technique, with two lateral opposed facial fields and an anterior field if necessary. In order to achieve tumor control, a dose of more than 67 Gy is required; local control can be further improved by maintaining technical accuracy during radiation delivery.

In 1998, the use of EBV DNA in plasma; none of the disease-free controls had detectable EBV DNA. The role of immunotherapy based on EBV latent membrane proteins is under study.

In 1998, the use of three-dimensional intensity-modulated radiation therapy (IMRT) was initiated at Memorial Sloan-Kettering Cancer Center for the treatment of nasopharyngeal carcinoma. A 2-year follow-up of 39 of these patients revealed a local relapse-free survival rate of 97%, compared with a rate of only 78% among historical controls. Similar studies in San Francisco and Hong Kong demonstrated the local benefits of IMRT, as well as its favorable toxicity profile. Of note, no large randomized trial comparing IMRT with conventional two- or three-dimensional radiation techniques has been completed.

Table 2. The 2002 AJCC staging system

<table>
<thead>
<tr>
<th>Stage</th>
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<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>N1</td>
<td>II</td>
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<td>IV</td>
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</table>
To help us determine the optimal radiation regimen, authors must clearly report total radiation doses, doses per fraction, and target volume dose variations.

Chemotherapy. Chemotherapy was first used in the 1970s as a component of primary curative treatment.\textsuperscript{14} Chemotherapy is classified into three categories based on when it is delivered in relation to radiotherapy: neoadjuvant, concurrent, and adjuvant. Chemotherapy acts as a radiosensitizer, and it helps decrease the rate of distant metastasis.

In 1998, Intergroup study 0099 was published by Al-Sarraf et al.\textsuperscript{21} This study showed that patients who were treated with radiation alone had a significantly lower 3-year survival rate (46\%) than did patients who received radiation with concurrent cisplatin chemotherapy followed by additional chemotherapy with cisplatin and 5-fluorouracil (76\%). This study changed the standard of care in the United States, even though it has been criticized because (1) the investigators used the 1992 AJCC staging criteria and therefore treated some early-stage nasopharyngeal carcinomas; (2) only about 45\% of patients had WHO stage III cancer; (3) the radiotherapy techniques used at different institutions were not uniform, which accounted for the poor results seen in the radiotherapy-alone arm; and (4) compliance with chemotherapy was poor (only 55 to 73\%).\textsuperscript{20} Furthermore, prior to 2004, 13 phase III randomized comparisons of radiotherapy alone with concurrent and/or adjuvant chemotherapy had been published in the literature, and Intergroup study 0099 was the only one to show that combined therapy resulted in a positive outcome.\textsuperscript{20}

As a result of these criticisms, combined-modality treatment for advanced nasopharyngeal carcinoma has not been accepted to a significant extent in endemic southeastern Asia. However, some of these 13 previously published trials had shortcomings of their own. For example, Rossi et al included many patients who were at low risk for distant metastasis while using a less-active combination of vincristine, cyclophosphamide, and doxorubicin.\textsuperscript{24} Chietal used adjuvant cisplatin, 5-fluorouracil, and leucovorin and noted no benefit in survival, but their patients experienced an unusually high number of treatment-related deaths in the combination arm and an intermediate risk of relapse in one of their cohorts.\textsuperscript{25} Hareyama et al found no benefit to using neoadjuvant chemotherapy, but their study was small, they included patients with early-stage disease, and their chemotherapeutic dosages were low.\textsuperscript{26} Finally, an Asian-Oceanian Clinical Oncology Association study\textsuperscript{27} involved a relatively low dose of cisplatin, and an International Nasopharynx Cancer Study Group trial\textsuperscript{28} was marked by a significant number of patients who refused radiotherapy and a large number of chemotherapy-related deaths.

The first study to show any benefit to concurrent chemotherapy in an endemic area was the 2003 study by Lin et al.\textsuperscript{20} The structure of this study was similar to that of Intergroup study 0099.\textsuperscript{21} Patients received concurrent cisplatin and a lower dose of 5-fluorouracil. The 5-year disease-free survival rate was 89\% in the combination arm, compared with 73\% in the radiation-only arm—a statistically significant difference.\textsuperscript{20}

In summary, the conflicting results in the literature make it difficult to develop a chemotherapeutic regimen—or even to determine that chemotherapy confers any benefit at all. The difficulty is compounded by the use of different staging systems and study protocols. For example, some studies are not randomized, and some have small sample sizes. In many published series, authors have not specified rates of distant metastases or indicated whether the metastasis was the first or only site of failure; it is important that these data be interpreted in relation to the WHO classification because types II and III are associated with higher rates of distant metastasis. Finally, we have not identified the optimum number of chemotherapy cycles. We do know that the timing of chemotherapy appears to have an impact on clinical outcome and that the dose intensity is best maintained in the induction setting. In the 13 randomized trials reported by Agulnik and Siu, the disparity in dose intensities may partially explain the lack of benefit associated with adjuvant chemotherapy.\textsuperscript{13} More trials on chemoradiation are required to determine the optimum chemotherapeutic agents and schedule that can be used with radiation therapy to achieve better treatment results.

Surgery. Surgery has a limited role in the treatment of nasopharyngeal carcinoma because of the tumor’s high degree of radiosensitivity and the anatomic barriers to surgical access. The role of the surgeon is usually limited to obtaining tissue for diagnosis, occasionally resecting residual adenopathy after definitive radiotherapy, and providing symptomatic relief (e.g., placement of tympanostomy tubes).

Various surgical approaches have been described in the literature, including transpalatal, transmaxillary, midline mandibulotomy, facial degloving, infratemporal fossa, and endoscopic approaches.\textsuperscript{29} Surgery is associated with slightly better control and a lower rate of complications than repeat irradiation in patients with limited disease. Surgery is typically contraindicated for patients with any evidence of extension into the parapharyngeal space, skull base, paranasal sinuses, or carotid artery because of surgery’s high degree of morbidity and the low probability of effecting a cure.

Fee et al described a combination transpalatal, transmaxillary, and transcervical approach in 33 patients with recurrent nasopharyngeal carcinoma.\textsuperscript{30} They achieved a 5-year local control rate of 67\% and an overall survival of 60\%. Fisch et al\textsuperscript{13} described the infratemporal approach, and Panje et al\textsuperscript{22} described the lateral temporal approach; although both resulted in excellent tumor exposure on the
ipsilateral side, contralateral exposure was poor, making complete excision of the tumor difficult in cases of tumor extension. Othersurgical approaches have been described, but regardless of the choice, the nature of nasopharyngeal carcinoma demands that the operation be tailored to the individual patient.

Nasopharyngectomy is an alternative treatment for local recurrent and residual nasopharyngeal carcinoma.\textsuperscript{33}

Treatment complications

Complications of radiotherapy are fairly well documented. Xerostomia is the most common; others include pituitary dysfunction, temporal bone necrosis, dysphagia, cranial nerve palsy, hearing loss, carotid artery stenosis, hypothyroidism, dry eye syndrome, myelitis, encephalopathy, hypopituitarism, and severe trismus, to name a few.\textsuperscript{29,34} Repeat irradiation has been associated with long-term problems with necrosis of the central nervous system, bone, and soft tissue.

Most of the complications associated with cisplatin-based chemotherapy are bone marrow suppression, hearing loss, and renal impairment.\textsuperscript{14} Experience with chemotherapy is still limited, and studies with longer follow-up are required.

Surgical complications can be divided into two categories: those associated with nasopharyngectomy and those associated with neck dissection.\textsuperscript{29} Because surgery is usually performed after radiation has been delivered, complications related to poor wound healing are common; they include palatal fistula, nasopharyngeal wound infection, osteonecrosis, nonunion or malunion of osteotomy sites, and flap necrosis. The most serious potential complications associated with resection of recurrent disease are death, carotid artery rupture, and violation of the dura.\textsuperscript{29} Other possible complications are specific to the surgical approach; among them are maxillary necrosis, choanal stenosis, saddle-nose deformity, and trismus.

Follow-up

The roles of direct and indirect nasopharyngoscopy, CT, MRI, and molecular markers still need to be fully determined with respect to survival and cost-effectiveness. Frequent follow-up with biopsy of any suspicious residual or recurrent disease is necessary.

References


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